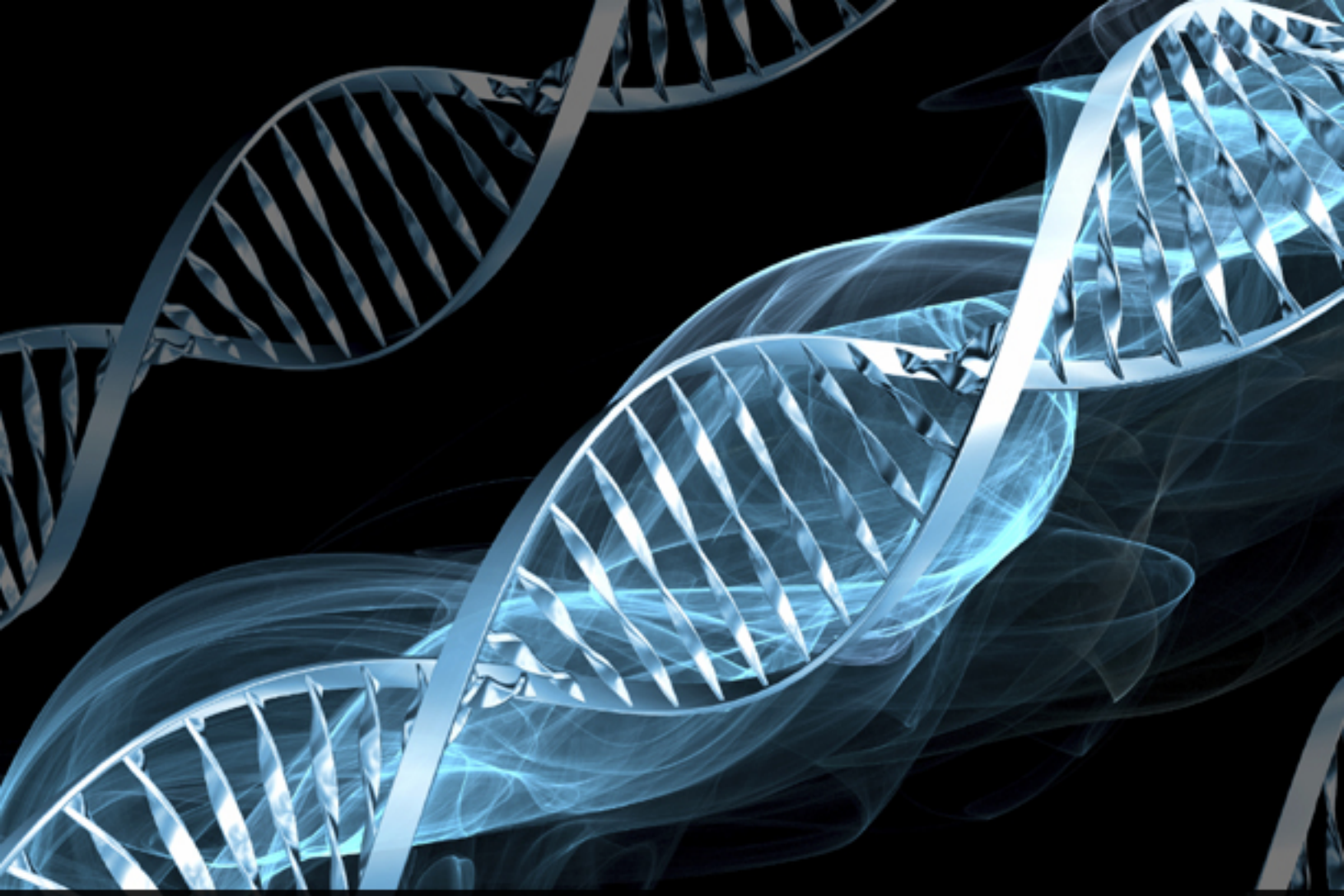

Chromosomal Abnormality Syndromes and Genetic Diseases

Jan Frasier

Ingeborg Durkin

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Chapter 1

Down Syndrome

Down syndrome

Boy with Down syndrome assembling a bookcase

ICD-10	Q90.
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Down syndrome, or **Down's syndrome** (primarily in the United Kingdom), **trisomy 21**, is a chromosomal condition caused by the presence of all or part of an extra 21st chromosome. It is named after John Langdon Down, the British physician who described the syndrome in 1866. The condition was identified as a chromosome 21 trisomy by Jérôme Lejeune in 1959. Down syndrome in a fetus can be identified with amniocentesis (with risks of fetal injury and/or miscarriage) during pregnancy, or in a baby at birth.

Down syndrome is a chromosomal condition characterized by the presence of an extra copy of genetic material on the 21st chromosome, either in whole (trisomy 21) or part

(such as due to translocations). The effects and extent of the extra copy vary greatly among people, depending on genetic history, and pure chance. The incidence of Down syndrome is estimated at 1 per 733 births, although it is statistically more common with older parents (both mothers and fathers) due to increased mutagenic exposures upon some older parents' reproductive cells (however, many older parents produce children without the condition). Other factors may also play a role. Down syndrome occurs in all human populations, and analogous effects have been found in other species such as chimpanzees and mice.

Often Down syndrome is associated with some impairment of cognitive ability and physical growth, and a particular set of facial characteristics. Individuals with Down syndrome tend to have a lower-than-average cognitive ability, often ranging from mild to moderate disabilities. Many children with Down Syndrome who have received family support, enrichment therapies, and tutoring have been known to graduate from high school and college, and enjoy employment in the work force. The average IQ of children with Down syndrome is around 50, compared to normal children with an IQ of 100. A small number have a severe to high degree of intellectual disability.

Many of the common physical features of Down syndrome may also appear in people with a standard set of chromosomes, including microgenia (an abnormally small chin), an unusually round face, macroglossia (protruding or oversized tongue), an almond shape to the eyes caused by an epicanthic fold of the eyelid, upslanting palpebral fissures (the separation between the upper and lower eyelids), shorter limbs, a single transverse palmar crease (a single instead of a double crease across one or both palms), poor muscle tone, and a larger than normal space between the big and second toes. Health concerns for individuals with Down syndrome include a higher risk for congenital heart defects, gastroesophageal reflux disease, recurrent ear infections, obstructive sleep apnea, and thyroid dysfunctions.

Early childhood intervention, screening for common problems, medical treatment where indicated, a conducive family environment, and vocational training can improve the overall development of children with Down syndrome. Education and proper care will improve quality of life significantly, despite genetic limitations.

Signs and symptoms

Down syndrome can result from several different genetic mechanisms. This results in a wide variability in individual signs and symptoms due to complex gene and environment interactions. Prior to birth, it is not possible to predict the symptoms that an individual with Down syndrome will develop.

Individuals with Down syndrome may have some or all of the following physical characteristics: microgenia (abnormally small chin), oblique eye fissures with epicanthic skin folds on the inner corner of the eyes (formerly known as a mongoloid fold), muscle hypotonia (poor muscle tone), a flat nasal bridge, a single palmar fold, a protruding tongue (due to small oral cavity, and an enlarged tongue near the tonsils) or macroglossia,

a short neck, white spots on the iris known as Brushfield spots, excessive joint laxity including atlanto-axial instability, excessive space between large toe and second toe, a single flexion furrow of the fifth finger, and a higher number of ulnar loop dermatoglyphs. Most individuals with Down syndrome have intellectual disability in the mild (IQ 50–70) to moderate (IQ 35–50) range, with individuals having Mosaic Down syndrome typically 10–30 points higher. They also may have a broad head and a very round face.

Language skills show a difference between understanding speech and expressing speech, and commonly individuals with Down syndrome have a speech delay. Fine motor skills are delayed and often lag behind gross motor skills and can interfere with cognitive development. Effects of the condition on the development of gross motor skills are quite variable. Some children will begin walking at around 2 years of age, while others will not walk until age 4. Physical therapy, and/or participation in a program of adapted physical education (APE), may promote enhanced development of gross motor skills in Down syndrome children.

Growth parameters such as height, weight, and head circumference are smaller in children with DS than with typical individuals of the same age. Adults with DS tend to have short stature — the average height for men is 5 feet 1 inch (157 cm) and for women is four feet 9 inches (144 cm). Individuals with DS are also at increased risk for obesity as they age.

Complications

Individuals with Down syndrome have a higher risk for many conditions. The medical consequences of the extra genetic material in Down syndrome are highly variable and may affect the function of any organ system or bodily process. Some problems are present at birth, such as certain heart malformations. Others become apparent over time, such as epilepsy.

Congenital heart disease

The incidence of congenital heart disease in children with Down syndrome is up to 50%. A atrioventricular septal defect also known as endocardial cushion defect is the most common form with up to 40% of patients affected. This is closely followed by ventricular septal defect that affects approximately 30% of patients.

Malignancies

Hematologic malignancies such as leukemia are more common in children with DS. In particular, the risk for acute lymphoblastic leukemia is at least 10 times more common in DS and for the megakaryoblastic form of acute myelogenous leukemia is at least 50 times more common in DS. Transient leukemia is a form of leukemia which is rare in individuals without DS but affects up to 20 percent of newborns with DS. This form of leukemia is typically benign and resolves on its own over several months, though it can

lead to other serious illnesses. In contrast to hematologic malignancies, solid tumor malignancies are less common in DS, possibly due to increased numbers of tumor suppressor genes contained in the extra genetic material.

Thyroid disorders

Individuals with DS are at increased risk for dysfunction of the thyroid gland, an organ which helps control metabolism. Low thyroid (hypothyroidism) is most common, occurring in almost a third of those with DS. This can be due to absence of the thyroid at birth (congenital hypothyroidism) or due to attack on the thyroid by the immune system. Reproduction is also affected by DS.

Gastrointestinal

Down syndrome increases the risk of Hirschsprung's disease, in which the nerve cells that control the function of parts of the colon are not present. This results in severe constipation. Other congenital anomalies occurring more frequently in DS include duodenal atresia, annular pancreas, and imperforate anus. Gastroesophageal reflux disease and celiac disease are also more common among people with DS.

Infertility

There is infertility amongst both males and females with Down syndrome; males are usually unable to father children, while females demonstrate significantly lower rates of conception relative to unaffected individuals. Women with DS are less fertile and often have difficulties with miscarriage, premature birth, and difficult labor. Without preimplantation genetic diagnosis, approximately half of the offspring of someone with Down syndrome also have the syndrome themselves. Men with DS are almost uniformly infertile, exhibiting defects in spermatogenesis. There have been only three recorded instances of males with Down syndrome fathering children.

Neurology

Children and adults with DS are at increased risk for developing epilepsy. The risk for Alzheimer's disease is increased in individuals with DS, with 10-25% of individuals with DS showing signs of AD before age 50, up to 50% with clinical symptoms in the sixth decade, and up to 75% in the 7th decade. This sharp increase in the incidence and prevalence of dementia may be one of the factors driving the decreased life expectancy of persons with Down Syndrome.

Ophthalmology and otolaryngology

Eye disorders are more common in people with DS. Almost half have strabismus, in which the two eyes do not move in tandem. Refractive errors requiring glasses or contacts are also common. Cataracts (opacity of the lens) and glaucoma (increased eye

pressures) are also more common in DS. Brushfield spots (small white or grayish/brown spots on the periphery of the iris) may be present.

Other complications

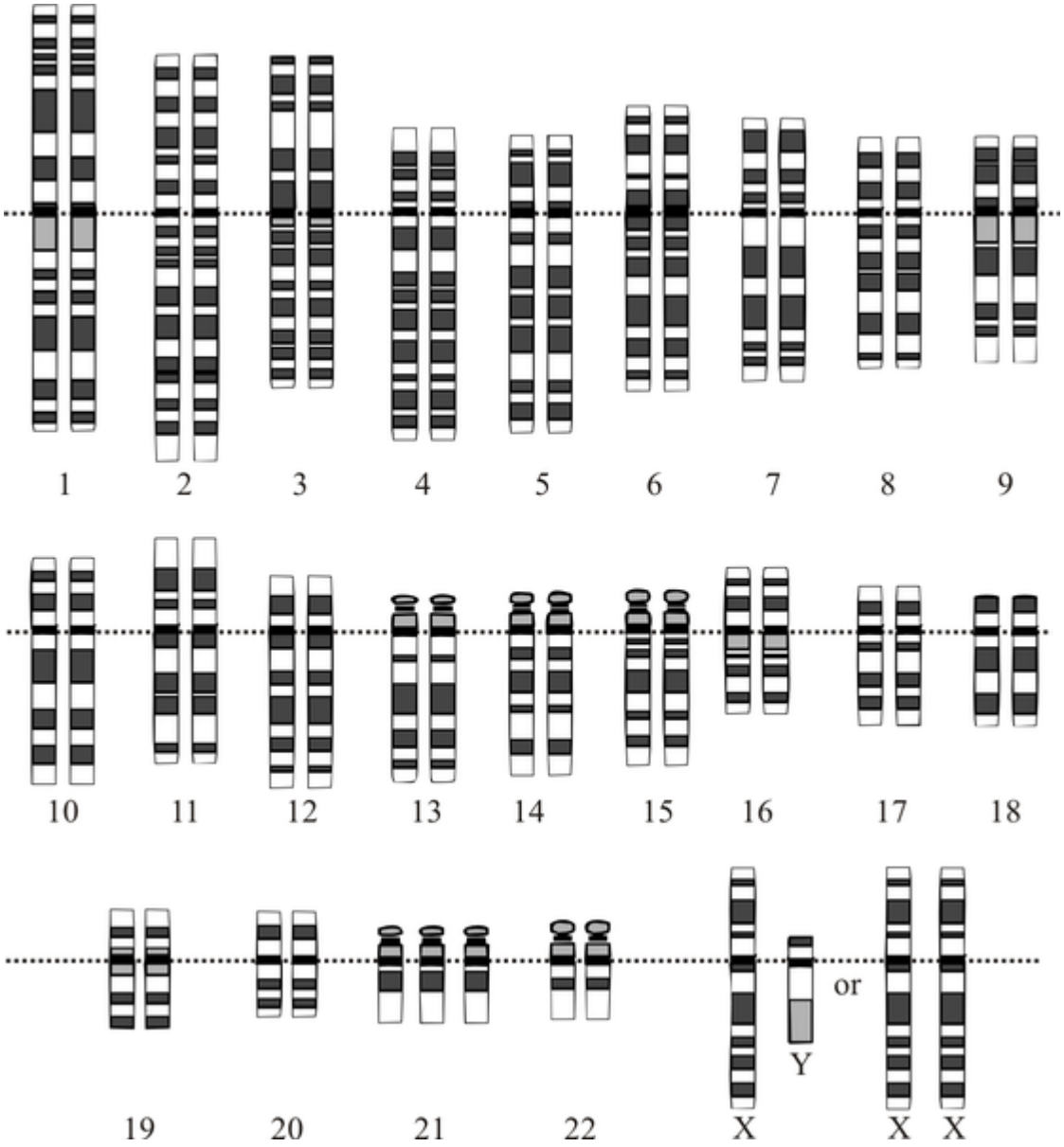
In the past, prior to current treatment, there was a 38-78% incidence of hearing loss in children with Down syndrome. Fortunately, with aggressive, meticulous and compulsive diagnosis and treatment of chronic ear disease (e.g. otitis media, also known as Glue-ear) in children with Down syndrome, approximately 98% of the children have normal hearing levels.

Instability of the atlanto-axial joint occurs in ~15% of people with DS, probably due to ligamental laxity. It may lead to the neurologic symptoms of spinal cord compression. Periodic screening, with cervical x-rays, is recommended to identify this condition.

Other serious illnesses include immune deficiencies.

Decreased incidence of many cancer types

However, health benefits of Down syndrome include greatly reduced incidence of many common malignancies except leukemia and testicular cancer — although it is, as yet, unclear whether the reduced incidence of various fatal cancers among people with Down syndrome is as a direct result of tumor-suppressor genes on chromosome 21, because of reduced exposure to environmental factors that contribute to cancer risk, or some other as-yet unspecified factor. In addition to a reduced risk of most kinds of cancer, people with Down syndrome also have a much lower risk of hardening of the arteries and diabetic retinopathy.



Karyotype for trisomy Down syndrome. Notice the three copies of chromosome 21

Recently, researchers have created transgenic mice with most of human chromosome 21 (in addition to the normal mouse chromosomes). The extra chromosomal material can come about in several distinct ways. A typical human karyotype is designated as 46,XX or 46,XY, indicating 46 chromosomes with an XX arrangement typical of females and 46 chromosomes with an XY arrangement typical of males.

Trisomy 21

Trisomy 21 (47,XX,+21) is caused by a meiotic nondisjunction event. With nondisjunction, a gamete (*i.e.*, a sperm or egg cell) is produced with an extra copy of chromosome 21; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embryo now has 47 chromosomes, with three copies of chromosome 21. Trisomy 21 is the cause of approximately 95% of observed Down syndromes, with 88% coming from nondisjunction in the maternal gamete and 8% coming from nondisjunction in the paternal gamete.

Mosaicism

Trisomy 21 is usually caused by nondisjunction in the gametes prior to conception, and all cells in the body are affected. However, when some of the cells in the body are normal and other cells have trisomy 21, it is called mosaic Down syndrome (46,XX/47,XX,+21). This can occur in one of two ways: a nondisjunction event during an early cell division in a normal embryo leads to a fraction of the cells with trisomy 21; or a Down syndrome embryo undergoes nondisjunction and some of the cells in the embryo revert to the normal chromosomal arrangement. There is considerable variability in the fraction of trisomy 21, both as a whole and among tissues. This is the cause of 1–2% of the observed Down syndromes.

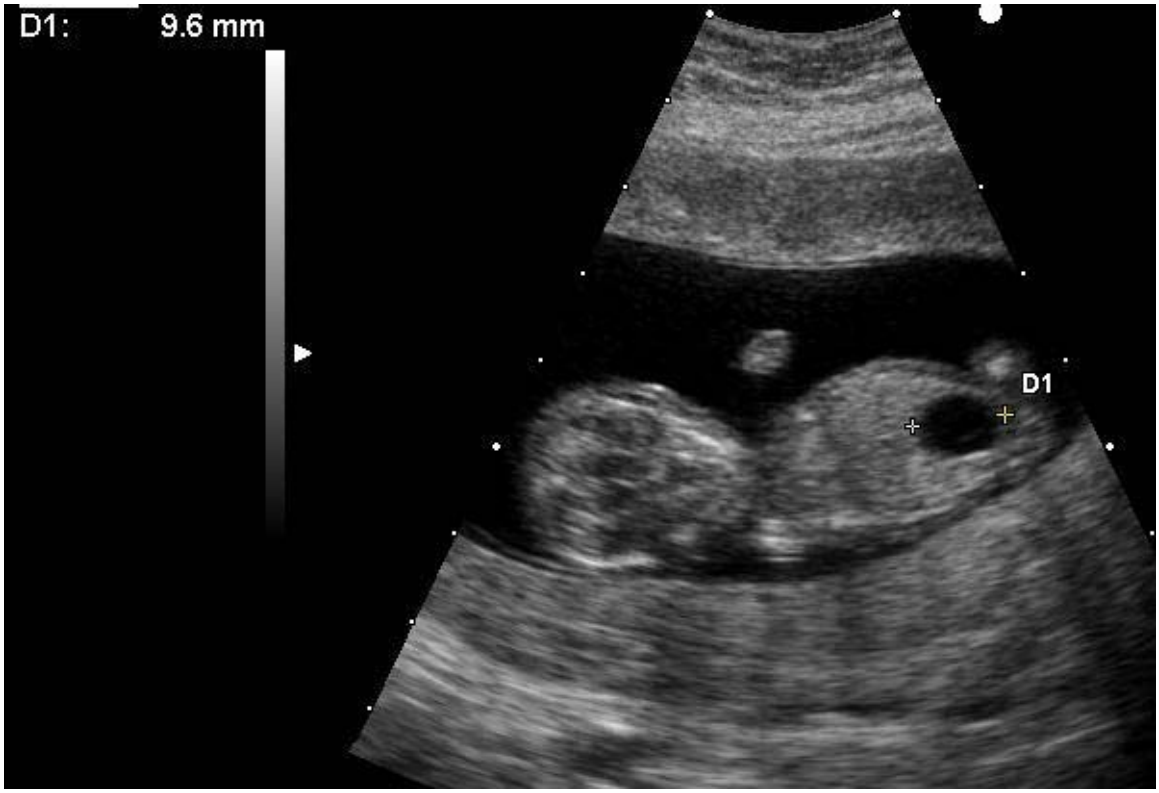
Robertsonian translocation

The extra chromosome 21 material that causes Down syndrome may be due to a Robertsonian translocation in the karyotype of one of the parents. In this case, the long arm of chromosome 21 is attached to another chromosome, often chromosome 14 [45,XX,der(14;21)(q10;q10)]. A person with such a translocation is phenotypically normal. During reproduction, normal disjunctions leading to gametes have a significant chance of creating a gamete with an extra chromosome 21, producing a child with Down syndrome. Translocation Down syndrome is often referred to as *familial Down syndrome*. It is the cause of 2–3% of observed cases of Down syndrome. It does not show the maternal age effect, and is just as likely to have come from fathers as mothers.

Duplication of a portion of chromosome 21

Rarely, a region of chromosome 21 will undergo a duplication event. This will lead to extra copies of some, but not all, of the genes on chromosome 21 (46,XX, dup(21q)). If the duplicated region has genes that are responsible for Down syndrome physical and mental characteristics, such individuals will show those characteristics. This cause is rare and no rate estimates are available.

Screening



Ultrasound of fetus with Down syndrome and megacystis

Pregnant women can be screened for various complications during pregnancy. Many standard prenatal screens can discover Down syndrome. Genetic counseling along with genetic testing, such as amniocentesis, chorionic villus sampling (CVS), or percutaneous umbilical cord blood sampling (PUBS) are usually offered to families who may have an increased chance of having a child with Down syndrome, or where normal prenatal exams indicate possible problems. In the United States, ACOG guidelines recommend that non-invasive screening and invasive testing be offered to all women, regardless of their age, and most likely all physicians currently follow these guidelines. However, some insurance plans will only reimburse invasive testing if a woman is >34 years old or if she has received a high-risk score from a non-invasive screening test.

Amniocentesis and CVS are considered invasive procedures, in that they involve inserting instruments into the uterus, and therefore carry a small risk of causing fetal injury or miscarriage. The risks of miscarriage for CVS and amniocentesis are often quoted as 1% and 0.5% respectively. There are several common non-invasive screens that can indicate a fetus with Down syndrome. These are normally performed in the late first trimester or early second trimester. Due to the nature of screens, each has a significant chance of a false positive, suggesting a fetus with Down syndrome when, in fact, the fetus does not have this genetic condition. Screen positives must be verified before a Down syndrome diagnosis is made. Common screening procedures for Down syndrome are given in Table 1.

Table 1: First and second trimester Down syndrome screens

Screen	When performed (weeks gestation)	Detection rate	False positive rate	Description
Quad screen	15–20	81%	5%	This test measures the maternal serum alpha feto protein (a fetal liver protein), estriol (a pregnancy hormone), human chorionic gonadotropin (hCG, a pregnancy hormone), and inhibin-Alpha (INHA).
Nuchal translucency/free beta/PAPPA screen (aka "1st Trimester Combined Test")	10–13.5	85%	5%	Uses ultrasound to measure Nuchal Translucency in addition to the freeBeta hCG and PAPPA (pregnancy-associated plasma protein A). NIH has confirmed that this first trimester test is more accurate than second trimester screening methods. Performing an NT ultrasound requires considerable skill; a Combined test may be less accurate if there is operator error, resulting in a lower-than-advertised sensitivity and higher false-positive rate, possibly in the 5-10% range.
Integrated Test	10-13.5 and 15–20	95%	5%	The Integrated test uses measurements from both the 1st Trimester Combined test and the 2nd trimester Quad test to yield a more accurate screening result. Because all of these tests are dependent on accurate calculation of the gestational age of the fetus, the real-world false-positive rate is >5% and maybe be closer to 7.5%.

Even with the best non-invasive screens, the detection rate is 90%–95% and the rate of false positive is 2%–5%. Inaccuracies can be caused by undetected multiple fetuses (very rare with the ultrasound tests), incorrect date of pregnancy, or normal variation in the proteins.

Confirmation of screen positive is normally accomplished with amniocentesis or chorionic villus sampling (CVS). Amniocentesis is an invasive procedure and involves taking amniotic fluid from the amniotic sac and identifying fetal cells. The lab work can take several weeks but will detect over 99.8% of all numerical chromosomal problems with a very low false positive rate.

Abortion rates

A 2002 literature review of elective abortion rates found that 91–93% of pregnancies in the United Kingdom and Europe with a diagnosis of Down syndrome were terminated. Data from the *National Down Syndrome Cytogenetic Register* in the United Kingdom indicates that from 1989 to 2006 the proportion of women choosing to terminate a pregnancy following prenatal diagnosis of Down Syndrome has remained constant at around 92%.

Ethical issues

Medical ethicist Ronald Green argues that parents have an obligation to avoid 'genetic harm' to their offspring, and Claire Rayner, then a patron of the Down's Syndrome Association, defended testing and abortion saying "The hard facts are that it is costly in terms of human effort, compassion, energy, and finite resources such as money, to care for individuals with handicaps... People who are not yet parents should ask themselves if they have the right to inflict such burdens on others, however willing they are themselves to take their share of the burden in the beginning."

Some physicians and ethicists are concerned about the ethical ramifications of the high abortion rate for this condition. Conservative commentator George Will called it "eugenics by abortion". British peer Lord Rix stated that "alas, the birth of a child with Down's syndrome is still considered by many to be an utter tragedy" and that the "ghost of the biologist Sir Francis Galton, who founded the eugenics movement in 1885, still stalks the corridors of many a teaching hospital". Doctor David Mortimer has argued in *Ethics & Medicine* that "Down's syndrome infants have long been disparaged by some doctors and government bean counters." Some members of the disability rights movement "believe that public support for prenatal diagnosis and abortion based on disability contravenes the movement's basic philosophy and goals." Peter Singer argued that "neither haemophilia nor Down's syndrome is so crippling as to make life not worth living from the inner perspective of the person with the condition. To abort a fetus with one of these disabilities, intending to have another child who will not be disabled, is to treat fetuses as interchangeable or replaceable. If the mother has previously decided to have a certain number of children, say two, then what she is doing, in effect, is rejecting one potential child in favour of another. She could, in defence of her actions, say: the loss of life of the aborted fetus is outweighed by the gain of a better life for the normal child who will be conceived only if the disabled one dies."

Management

Treatment of individuals with Down Syndrome depends on the particular manifestations of the condition. For instance, individuals with congenital heart disease may need to undergo major corrective surgery soon after birth. Other individuals may have relatively minor health problems requiring no therapy.

Examination at birth

Initial examination of newborns with DS should pay particular attention to certain physical signs which are more commonly found in DS. Evaluation of the red reflex can help identify congenital cataracts. Movement of the eyes should be observed to identify strabismus. Constipation should raise concerns for Hirschsprung's disease and feeding problems should prompt intense education to ensure adequate input and nutrition.

At birth, an ultrasound of the heart (echocardiogram) should be done immediately in order to identify congenital heart disease (this should be carried out by someone with experience in pediatric cardiology). A complete blood count should be done in order to identify pre-existing leukemia. A hearing test using brainstem auditory evoked responses (BAERS) testing should be performed and any hearing deficits further characterized. The thyroid function should also be tested. Early Childhood Intervention should be involved from birth to help coordinate and plan effective strategies for learning and development.

The American Academy of Pediatrics, among other health organizations, has issued a series of recommendations for screening individuals with Down Syndrome for particular diseases. These guidelines enable health care providers to identify and prevent important aspects of DS. All other typical newborn, childhood, and adult screening and vaccination programs should also be performed.

Plastic surgery

Plastic surgery has sometimes been advocated and performed on children with Down syndrome, based on the assumption that surgery can reduce the facial features associated with Down syndrome, therefore decreasing social stigma, and leading to a better quality of life. Plastic surgery on children with Down syndrome is uncommon, and continues to be controversial. Researchers have found that for facial reconstruction, "...although most patients reported improvements in their child's speech and appearance, independent raters could not readily discern improvement...." For partial glossectomy (tongue reduction), one researcher found that 1 out of 3 patients "achieved oral competence," with 2 out of 3 showing speech improvement. Len Leshin, physician and author of the ds-health website, has stated, "Despite being in use for over twenty years, there is still not a lot of solid evidence in favor of the use of plastic surgery in children with Down syndrome." The US National Down Syndrome Society has issued a "Position Statement on Cosmetic Surgery for Children with Down Syndrome", which states that "The goal of inclusion and acceptance is mutual respect based on who we are as individuals, not how we look."

Cognitive development

The identification of the best methods of teaching each particular child ideally begins soon after birth through early intervention programs. Cognitive development in children with Down syndrome is quite variable. It is not currently possible at birth to predict the capabilities of any individual reliably, nor are the number or appearance of physical features predictive of future ability. Since children with Down syndrome have a wide range of abilities, success at school can vary greatly, which underlines the importance of evaluating children individually. The cognitive problems that are found among children with Down syndrome can also be found among other children. Therefore, parents can use general programs that are offered through the schools or other means.

Individuals with Down syndrome differ considerably in their language and communication skills. It is routine to screen for middle ear problems and hearing loss; low gain hearing aids or other amplification devices can be useful for language learning. Early communication intervention fosters linguistic skills. Language assessments can help profile strengths and weaknesses; for example, it is common for receptive language skills to exceed expressive skills. Individualized speech therapy can target specific speech errors, increase speech intelligibility, and in some cases encourage advanced language and literacy. Augmentative and alternative communication (AAC) methods, such as pointing, body language, objects, or graphics are often used to aid communication. Relatively little research has focused on the effectiveness of communications intervention strategies.

In education, mainstreaming of children with Down syndrome is becoming less controversial in many countries. For example, there is a presumption of mainstream in many parts of the UK. Mainstreaming is the process whereby students of differing abilities are placed in classes with their chronological peers. Children with Down syndrome may not age emotionally/socially and intellectually at the same rates as children without Down syndrome, so over time the intellectual and emotional gap between children with and without Down syndrome may widen. Complex thinking as required in sciences but also in history, the arts, and other subjects can often be beyond the abilities of some, or achieved much later than in other children. Therefore, children with Down syndrome may benefit from mainstreaming provided that some adjustments are made to the curriculum.

Some European countries such as Germany and Denmark advise a two-teacher system, whereby the second teacher takes over a group of children with disabilities within the class. A popular alternative is cooperation between special schools and mainstream schools. In cooperation, the core subjects are taught in separate classes, which neither slows down the typical students nor neglects the students with disabilities. Social activities, outings, and many sports and arts activities are performed together, as are all breaks and meals.

Speech delay may require speech therapy to improve expressive language.

Childhood and adulthood follow-up

As children with DS grow, their progress should be plotted on a growth chart in order to detect deviations from expected growth. Special growth charts are available so that children with DS can be compared with other children with DS. Thyroid function testing should be performed at 6 months and 12 months of age as well as yearly thereafter. Evaluation of the ears for infection as well as objective hearing tests should be performed at every visit. Formal evaluation for refractive errors requiring glasses should be performed at least every two years with subjective vision assessments with each visit. After the age of three, an x-ray of the neck should be obtained to screen for atlanto-axial instability. As the child ages, yearly symptom screening for obstructive sleep apnea should be performed.

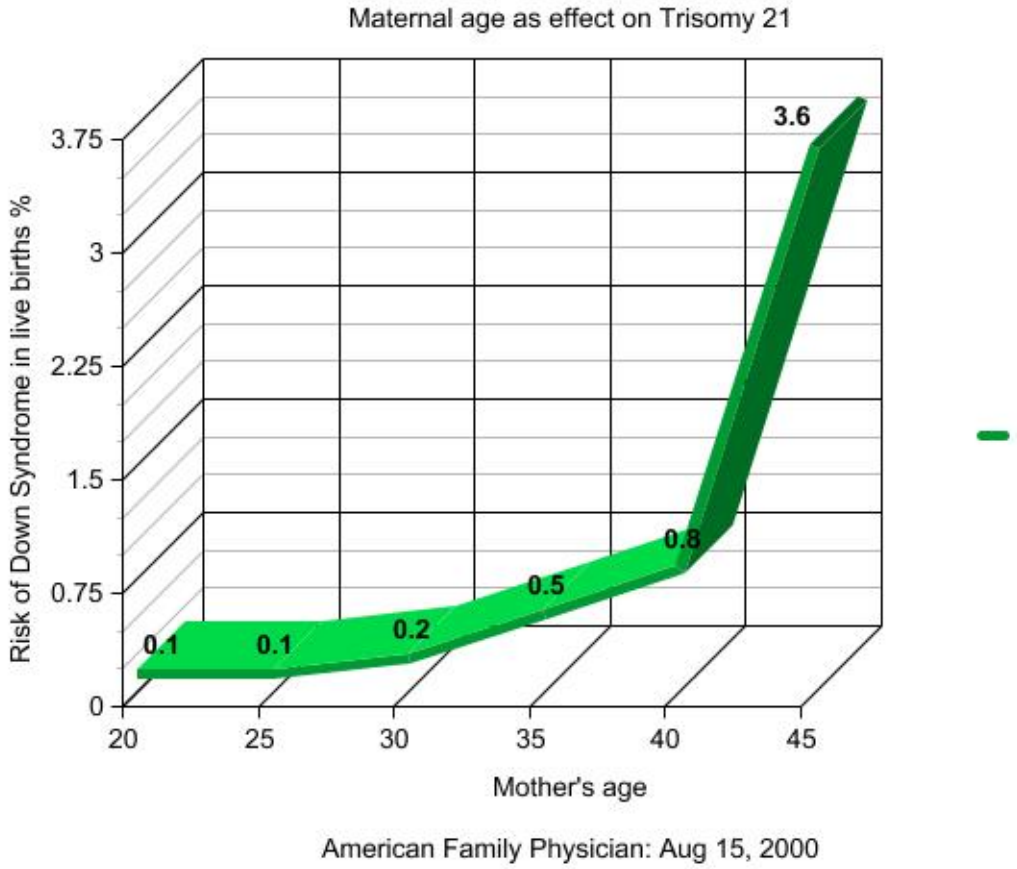
Alternative treatment

The Institutes for the Achievement of Human Potential is a non-profit organization which treats children who have, as the IAHP terms it, "some form of brain injury," including children with Down syndrome. The approach of "Psychomotor Patterning" is not proven, and is considered alternative medicine.

Prognosis

These factors can contribute to a shorter life expectancy for people with Down syndrome. One study, carried out in the United States in 2002, showed an average lifespan of 49 years, with considerable variations between different ethnic and socio-economic groups. However, in recent decades, the life expectancy among persons with Down syndrome has increased significantly up from 25 years in 1980. The causes of death have also changed, with chronic neurodegenerative diseases becoming more common as the population ages. Most people with Down Syndrome who live into their 40s and 50s begin to suffer from an Alzheimer's disease-like dementia.

Epidemiology



Graph showing probability of Down syndrome as a function of maternal age

The incidence of Down syndrome is estimated at one per 800 to one per 1000 births. In 2006, the Centers for Disease Control and Prevention estimated the rate as one per 733 live births in the United States (5429 new cases per year). Approximately 95% of these are trisomy 21. Down syndrome occurs in all ethnic groups and among all economic classes.

Maternal age influences the chances of conceiving a baby with Down syndrome. At maternal age 20 to 24, the probability is one in 1562; at age 35 to 39 the probability is one in 214, and above age 45 the probability is one in 19. Although the probability increases with maternal age, 80% of children with Down syndrome are born to women under the age of 35, reflecting the overall fertility of that age group. Recent data also suggest that paternal age, especially beyond 42, also increases the risk of Down syndrome manifesting.

Current research (as of 2008) has shown that Down syndrome is due to a random event during the formation of sex cells or pregnancy. There has been no evidence that it is due to parental behavior (other than age) or environmental factors.

History

English physician John Langdon Down first characterized Down syndrome as a distinct form of mental disability in 1862, and in a more widely published report in 1866. Due to his perception that children with Down syndrome shared physical facial similarities (epicanthal folds) with those of Blumenbach's Mongolian race, Down used the term *mongoloid*, derived from prevailing ethnic theory. Attitudes about Down syndrome were very much tied to racism and colonialism until as recently as the 1970s.

By the 20th century, Down syndrome had become the most recognizable form of mental disability. Most individuals with Down syndrome were institutionalized, few of the associated medical problems were treated, and most died in infancy or early adult life. With the rise of the eugenics movement, 33 of the (then) 48 U.S. states and several countries began programs of forced sterilization of individuals with Down syndrome and comparable degrees of disability. The ultimate expression of this type of public policy was "Action T4" in Nazi Germany, a program of systematic murder. Court challenges, scientific advances and public revulsion led to discontinuation or repeal of such sterilization programs during the decades after World War II.

Until the middle of the 20th century, the cause of Down syndrome remained unknown. However, the presence in all races, the association with older maternal age, and the rarity of recurrence had been noticed. Standard medical texts assumed it was caused by a combination of inheritable factors which had not been identified. Other theories focused on injuries sustained during birth.

With the discovery of karyotype techniques in the 1950s, it became possible to identify abnormalities of chromosomal number or shape. In 1959, Jérôme Lejeune discovered that Down syndrome resulted from an extra chromosome. The extra chromosome was subsequently labeled as the 21st, and the condition as trisomy 21.

In 1961, eighteen geneticists wrote to the editor of *The Lancet* suggesting that *Mongolian idiocy* had "misleading connotations," had become "an embarrassing term," and should be changed. *The Lancet* supported *Down's Syndrome*. The World Health Organization (WHO) officially dropped references to *mongolism* in 1965 after a request by the Mongolian delegate. However, almost 40 years later, the term ‘mongolism’ still appears in leading medical texts such as *General and Systematic Pathology*, 4th Edition, 2004, edited by Professor Sir James Underwood. Advocacy groups adapted and parents groups welcomed the elimination of the Mongoloid label that had been a burden to their children. The first parents group in the United States, the Mongoloid Development Council, changed its name to the National Association for Down Syndrome in 1972.

In 1975, the United States National Institutes of Health convened a conference to standardize the nomenclature of malformations. They recommended eliminating the possessive form: "The possessive use of an eponym should be discontinued, since the author neither had nor owned the condition." Although both the possessive and non-possessive forms are used in the general population, Down syndrome is the accepted term

among professionals in the USA, Canada and other countries; Down's syndrome is still used in the United Kingdom and other areas.

Notable individuals

Scottish award-winning film and TV actress Paula Sage receives her BAFTA award with Brian Cox.

- Danny Alsabbagh, Australian actor who played Toby in the Australian mockumentary series Summer Heights High
- Chris Burke, American actor who portrayed "Corky Thatcher" on the television series *Life Goes On* and "Taylor" on *Touched By An Angel.*
- Edward Barbanell, played Billy in 2005's *The Ringer*.
- Pascal Duquenne, Belgian film actor, co-starred with Daniel Auteuil in the 1996 film *Le Huitième Jour* (The Eighth Day), both actors won the joint award for Best Actor at the Cannes Film Festival.
- Andrea Friedman: actress who portrayed Corky's girlfriend Amanda in *Life Goes On* and Ellen in the *Family Guy* episode "Extra Large Medium".
- Stephane Ginnsz, actor (*Duo*)—In 1996 was first actor with Down syndrome in the lead part of a motion picture.
- Nigel Hunt, British author (The World Of Nigel Hunt; The Diary Of A Mongoloid Youth—this book was published in 1967, when "mongoloid" was still quite commonly used to refer to people with Down's Syndrome).

- Tommy Jessop, British actor who played Ben in *Coming Down the Mountain*, opposite Nicholas Hoult
- Rene Moreno, subject of "Up Syndrome" - a documentary film about life with Down syndrome.
- Joey Moss, Edmonton Oilers locker room attendant.
- Trig Palin, son of Sarah Palin and her husband Todd.
- Pablo Pineda, Spanish actor who starred in the semi-autobiographical film *Yo También*.
- Isabella Pujols, adopted daughter of St. Louis Cardinals first baseman Albert Pujols and inspiration for the Pujols Family Foundation.
- Paula Sage, Scottish film actress and Special Olympics netball athlete. Her role in the 2003 film *AfterLife* brought her a BAFTA Scotland award for best first time performance and Best Actress in the Bratislava International Film Festival, 2004.

- Hilly, Sam, Lucy and Megan, 4 friends with Down's Syndrome who share a house in Brighton with their friend Lewis who has Williams Syndrome. Their lives are followed in the internet documentary series "The Specials".

Research

Down syndrome is "a developmental condition characterized by trisomy of human chromosome 21" (Nelson 619). The extra copy of chromosome-21 leads to an over expression of certain genes located on chromosome-21.

Research by Arron *et al.* shows that some of the phenotypes associated with Down syndrome can be related to the disregulation of transcription factors (596), and in particular, NFAT. NFAT is controlled in part by two proteins, DSCR1 and DYRK1A; these genes are located on chromosome-21 (Epstein 582). In people with Down syndrome, these proteins have 1.5 times greater concentration than normal (Arron *et al.* 597). The elevated levels of DSCR1 and DYRK1A keep NFAT primarily located in the cytoplasm rather than in the nucleus, preventing NFATc from activating the transcription of target genes and thus the production of certain proteins (Epstein 583).

This disregulation was discovered by testing in transgenic mice that had segments of their chromosomes duplicated to simulate a human chromosome-21 trisomy (Arron *et al.* 597). A test involving grip strength showed that the genetically modified mice had a significantly weaker grip, much like the characteristically poor muscle tone of an individual with Down syndrome (Arron *et al.* 596). The mice squeezed a probe with a paw and displayed a .2 newton weaker grip (Arron *et al.* 596). Down syndrome is also characterized by increased socialization. When modified and unmodified mice were observed for social interaction, the modified mice showed as much as 25% more interactions as compared to the unmodified mice (Arron *et al.* 596).

The genes that may be responsible for the phenotypes associated may be located proximal to 21q22.3. Testing by Olson et al. in transgenic mice show the duplicated genes presumed to cause the phenotypes are not enough to cause the exact features.

While the mice had sections of multiple genes duplicated to approximate a human chromosome-21 triplication, they only showed slight craniofacial abnormalities (688-690). The transgenic mice were compared to mice that had no gene duplication by measuring distances on various points on their skeletal structure and comparing them to the normal mice (Olson *et al.* 687). The exact characteristics of Down syndrome were not observed, so more genes involved for Down Syndrome phenotypes have to be located elsewhere.

Reeves *et al.*, using 250 clones of chromosome-21 and specific gene markers, were able to map the gene in mutated bacteria. The testing had 99.7% coverage of the gene with 99.9995% accuracy due to multiple redundancies in the mapping techniques. In the study 225 genes were identified (311-313).

The search for major genes that may be involved in Down syndrome symptoms is normally in the region 21q21–21q22.3. However, studies by Reeves *et al.* show that 41% of the genes on chromosome-21 have no functional purpose, and only 54% of functional genes have a known protein sequence. Functionality of genes was determined by a computer using exon prediction analysis (312). Exon sequence was obtained by the same procedures of the chromosome-21 mapping.

Research has led to an understanding that two genes located on chromosome-21, that code for proteins that control gene regulators, DSCR1 and DYRK1A can be responsible for some of the phenotypes associated with Down syndrome. DSCR1 and DYRK1A cannot be blamed outright for the symptoms; there are a lot of genes that have no known purpose. Much more research would be needed to produce any appropriate or ethically acceptable treatment options.

Recent use of transgenic mice to study specific genes in the Down syndrome critical region has yielded some results. APP is an Amyloid beta A4 precursor protein. It is suspected to have a major role in cognitive difficulties. Another gene, ETS2 is Avian Erythroblastosis Virus E26 Oncogene Homolog 2. Researchers have "demonstrated that over-expression of ETS2 results in apoptosis. Transgenic mice over-expressing ETS2 developed a smaller thymus and lymphocyte abnormalities, similar to features observed in Down syndrome."

Human chromosome 21 contains five microRNA genes: miR-99a, let-7c, miR-125b-2, miR-155 and miR-802. MiR-155 and miR-802 regulate the expression of the methyl-CpG-binding protein (MeCP2). It has been suggested that the underexpression of MeCP2, secondary to trisomic overexpression of Human chromosome 21 derived miRNAs, may result in aberrant expression of the transcription factors of CREB1 and MEF2C. This in turn may lead to abnormal brain development through anomalous neuronal gene expression during the critical period of synaptic maturation by alterating neurogenesis, neuronal differentiation, myelination, and synaptogenesis.

Chapter 2

1q21.1 Deletion Syndrome

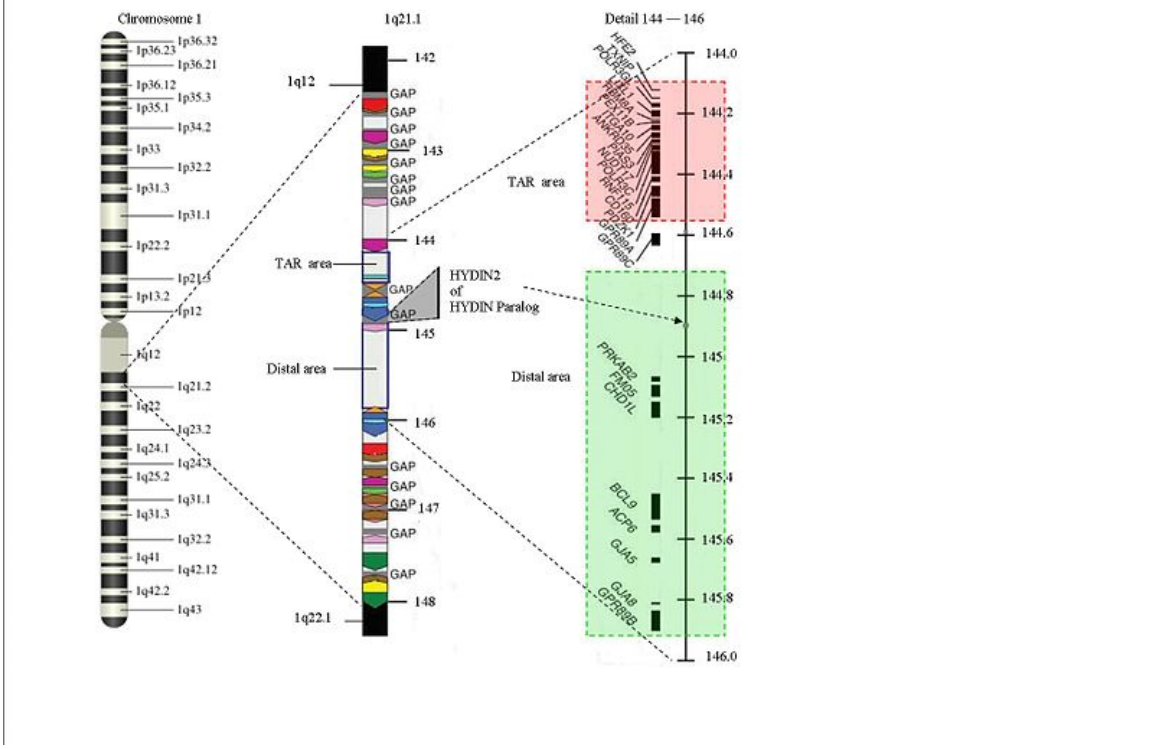
1q21.1 deletion syndrome	
OMIM	612474

1q21.1 deletion syndrome or **1q21.1 (recurrent) microdeletion** is a rare aberration of chromosome 1.

In a common situation a human cell has one pair of identical chromosomes on chromosome 1. With the 1q21.1 deletion syndrome one chromosome of the pair is not complete, because a part of the sequence of the chromosome is missing.

The main symptoms are mental retardation and various physical anomalies. The manifestations in individuals are quite variable. Some people who have the syndrome can function in a normal way.

In 1q21.1, the '1' stands for chromosome 1, the 'q' stands for the long arm of the chromosome and '21.1' stands for the part of the long arm in which the deletion is situated. Next to the deletion syndrome, there is also a 1q21.1 duplication syndrome. While there is a part of the DNA missing with the deletion syndrome on a particular spot, there are two or three copies of a similar part of the DNA on the same spot with the duplication syndrome.



The structure of 1q21.1

The structure of 1q21.1

The structure of 1q21.1 is complex. The area has a size of approximately 6 Megabase (Mb) (from 141.5 Mb to 147.9 Mb). There are two areas where the deletion can be: the TAR-area for the TAR syndrome and the distal area for other anomalies. The area has multiple repetitions of the same structure (areas with the same color in the picture have equal structures) Only 25% of the structure is unique. There are several gaps in the sequence. The gaps represent approximately 700 Kilobase. New genes are expected in the gaps. Because the gaps are still a topic of research, it is hard to find the exact start and end markers of a deletion. The area of 1q21.1 is one of the most difficult parts of the human genome to map.

Typing

A common deletion is restricted to the TAR area or the distal area. This is a Class I-deletion.

In some cases the deletion is so large that both areas are involved, the so called Class II-deletion. There are some complex cases in which both the TAR area and the distal area are affected, while the area in between is normal. There are also some a-typical variants.

Symptoms

Recognised symptoms up till now are:

- Haploinsufficiency
- TAR syndrome
- Mental retardation - mild to moderate
- Autism
- Schizophrenia
- Small head (microcephaly)
- Heart abnormalities and cardiovascular anomalies (30% of the cases)
- Cataracts
- Problems with kidneys (kidney missing or floating kidneys)
- Developmental delay - mild to moderate; milestones like sitting, standing and walking come at a later period in childhood
- Slightly unusual facial appearance
- Neuroblastoma
- Problems with the development of the vagina (Mullerian aplasia)
- epilepsy
- Prominent forehead
- Bulbous nose
- Deep-set eyes
- Broad thumbs
- Broad toes
- Squint (e.g. one eye far left or far right)
- Very flexible joints
- Children show an ataxic gait and fall down a lot
- Clavicular pseudoarthrosis (the collarbone doesn't develop normally) (Class II-deletion)
- Anomalous origin of the coronary artery (Class II-deletion)
- An extra transverse crease of the fifth finger (Class II-deletion))

Symptoms which are not confirmed:

- Families with children who have 1q21.1 deletion syndrome report reflux (GERD)
- There is recent information in which Noncompaction cardiomyopathy has been seen in combination with a ClassII-deletion .
- During a pregnancy increased nunchal translucency and oligohydramnion were detected.

It is not clear whether the list of symptoms is complete. Very little information is known about the syndrome. The syndrome can have complete different effects on members of the same family.

A common deletion is between 1.0-1.9Mb. Mefford states the standard for a deletion is 1.35 Mb. The largest deletion seen on a living human is over 5 Mb.

Heredity

The syndrome may appear in cases where neither of the parents carry the genes. Because of the repetitions in 1q21.1 there is a larger chance on an unequal crossing-over during meiosis. In this situation parts of the chromosome may get lost. Accidental changes appear in the chromosome. In the situation of an unequal crossing-over copy-number variation (CNV's) will appear. These CNV's will lead to deletions or duplications. About 0.4% of the human genome has CNV's and it is a common process. Such an accidental mutation is called a 'de novo'-situation and it appears 75% of the cases.

In 25% of the cases one of the parents is carrier of the syndrome, without any effect on the parent. Sometimes adults have mild problems with the syndrome. To find out if either of the parents carries the syndrome, both parents have to be tested.

In several cases the syndrome was identified with the child, because of an autism disorder or another problem and later it appeared that the parent was affected as well. The parent never knew about it up till the moment that the DNA-test proved the parent to be a carrier.

In families where both parents have been tested negative on the syndrome, chances on a second child with the syndrome are extremely low. If the syndrome was found in the family, chances on a second child with the syndrome are 50%. The effect of the syndrome on the child cannot be predicted.

For parents who have a child with the syndrome, it is advisable to consult a physician before a next pregnancy and to do prenatal screening.

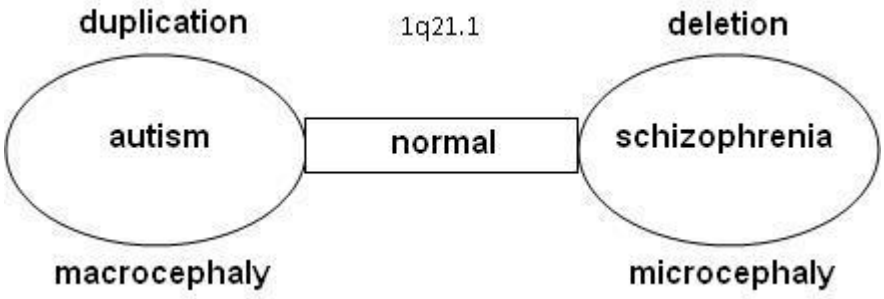
Research

On several locations in the world people are studying on the subject of 1q21.1 deletion syndrome. The syndrome was identified for the first time with people who had heart abnormalities. The syndrome has later been found with patients who had autism and schizofrenia. Research is done on patients who have a symptom of the syndrome, to find more patients who have the syndrome. Due to this research it became clear that 20 out of 1000 autism patients have 1q21.1 deletion syndrome.

It appears there is a relation between autism and schizophrenia. Both autism and schizophrenia are caused by problems of the development of the embryo during the first month of pregnancy. Within 20 to 40 days after the conception something goes wrong in the development of the embryo in both the construction of the body and the brain, which starts a chain reaction. Both diseases have the same cause.

In the genetic area relations have been found between both autism and schizophrenia based on duplications and deletions of chromosomes. Statistical research showed that schizophrenia is significantly more common in combination with 1q21.1 deletion syndrome. On the other side autism is significantly more common with 1q21.1

duplication syndrome. Similar observations were done for chromosome 16 on 16p11.2 (deletion: autism/duplication: schizophrenia), chromosome 22 on 22q11.21 (deletion (Velo-cardio-facial syndrome): schizophrenia/duplication: autism) and 22q13.3 (deletion (Phelan-McDermid syndrome): schizophrenia/duplication: autism). Research on autism/schizophrenia relations for chromosome 15 (15q13.3), chromosome 16 (16p13.1) and chromosome 17 (17p12) on the subject of deletions/duplications are still inconclusive.



Expected relation within 1q21.1

Research is done on 10-12 genes on 1q21.1 that produce DUF1220-locations. DUF1220 is an unknown protein, which is active in the neurons of the brain near the neocortex. Based on research on apes and other mammals, it is assumed that DUF1220 is related to cognitive development (man: 212 locations; chimpanzee: 37 locations; monkey: 30 locations; mouse: 1 location). It appears that the DUF1220-locations on 1q21.1 are in areas which are related to the size and the development of the brain. The aspect of the size and development of the brain is related to autism (macrocephaly) and schizophrenia (microcephaly). It is assumed that a deletion or a duplication of a gene that produces DUF1220-areas, might cause growth and development disorders in the brain

Another relation between macrocephaly with duplications and microcephaly with deletions has been seen in research on the HYDIN Paralog or HYDIN2. This part of 1q21.1 is involved in the development of the brain. It is assumed to be a dosage sensitive gene. When this gene is not available in the 1q21.1 area it leads to microcephaly. The HYDIN2 is a copy of the HYDIN found on 16q22.2.

Chapter 3

1q21.1 Duplication Syndrome

1q21.1 duplication syndrome	
OMIM	612475

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In a common situation a human cell has one pair of identical chromosomes on chromosome 1. With the 1q21.1 duplication syndrome one chromosome of the pair is more than complete, because a part of the sequence of the chromosome is repeated two or three times.

The main symptoms are mental retardation and various physical anomalies. The manifestations in individuals are quite variable. Some people who have the syndrome can function in a normal way.

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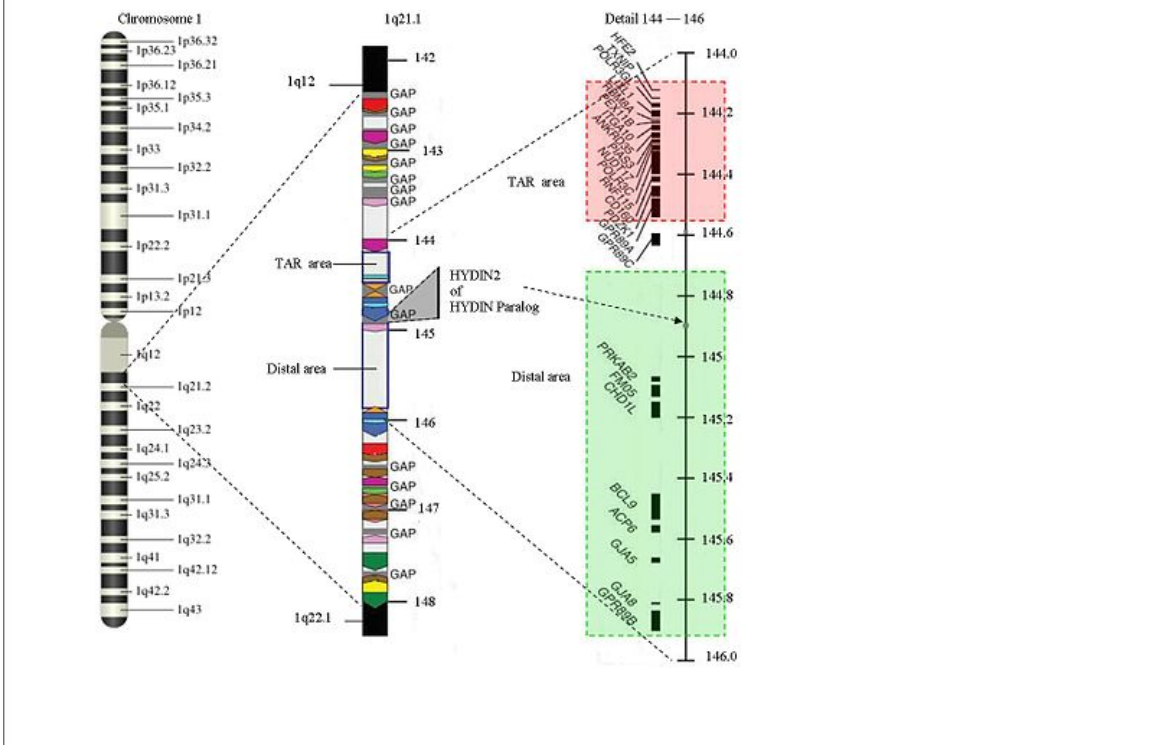

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Symptoms

Recognised symptoms up till now are:

- Autism or autistic behaviors
- ADHD
- Learning disability
- Large head
- Dysmorphic facial appearance - mild

- Prominent forehead
- Wide-set eyes (hypertelorism)
- Schizophrenia
- Underdeveloped parts of brain - corpus callosum and cerebellar vermis

It is not clear whether the list of symptoms is complete. Very little information is known about the syndrome. The syndrome can have complete different effects on members of the same family.

Heredity

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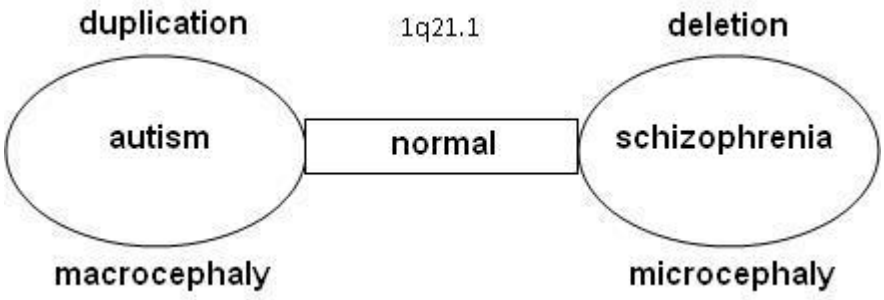

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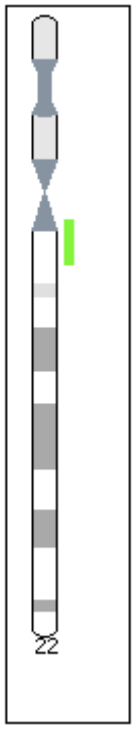
Chapter 4

22q11.2 Duplication Syndrome and 22q13 Deletion Syndrome

22q11.2 duplication syndrome

22q11.2 duplication syndrome



OMIM 608363

22q11.2 duplication syndrome is a rare genetic disorder caused by a duplication of a segment at the end of chromosome 22.

Clinical features

The most frequent reported symptoms in patients with duplication of 22q11.2 duplication syndrome are mental retardation/learning disabilility (97% of patients), delayed psychomotor development (67% of patients), growth retardation (63% of patients) and muscular hypotonia (43% of patients). However, these are common and relatively non-specific indications for cytogenetic analysis, and the extent to which the duplication of 22q11.2 causes these features is currently unknown.

Size of duplication

Duplications of 22q11 vary in size and thereby in gene content. They include the typical common 3-Mb microduplication, 1.5-Mb nested duplication, consistent with non-allelic homologous recombination (NAHR) using distinct low-copy repeats. These microduplications likely represent the predicted reciprocal rearrangements to the microdeletions characterized in the 22q11.2 region. Smaller microduplications may occur within this highly dynamic with frequent rearrangements using alternative low-copy repeats as recombination substrates within and distal to the DiGeorge syndrome region.

Origin of duplication

The majority of 22q11 duplications are [[Mendelian inheritance|inherited often from a parent with a normal or near-normal phenotype. This is in sharp distinction to 22q11 deletion syndrome where about 90% of cases are caused by mutations that occur *de novo*.

22q13 deletion syndrome

22q13 Deletion Syndrome	
OMIM	606232

22q13 Deletion Syndrome (spoken as *twenty two q one three*), also known as **Phelan-McDermid Syndrome**, is a genetic disorder caused by a microdeletion on chromosome 22. The deletion occurs at the terminal end of the chromosome at the location designated q13.3. This microdeletion is rarely uncovered by typical genetic screening, therefore a fluorescence in situ hybridization, or FISH, test is recommended to confirm the diagnosis. Recent work indicates **Phelan-McDermid Syndrome** may also be caused by errors in a single gene (SHANK3/PROSAP2) in the q13.3 region. Errors on the same gene are associated with Autism Spectrum Disorder (ASD), so **Phelan-McDermid Syndrome** is often considered an ASD.

This genetic disorder is characterized by general hypotonia, absent to delayed speech, and global developmental delays. It is estimated that less than 500 people have been diagnosed with this syndrome.

Characteristics

Individuals with a 22q13 deletion can suffer from a range of symptoms, with mild to very serious physical and behavioral characteristics. Possible symptoms are:

Physical

- Absent to severely delayed speech: 99%
- Hypotonia (poor muscle tone): 97%
- Normal to accelerated growth: 95%
- Increased tolerance to pain: 86%
- Thin, flaky toenails: 78%
- Large, fleshy hands: 68%
- Prominent, poorly formed ears: 65%
- Pointed chin: 62%
- Dolichocephaly (elongated head): 57%
- Ptosis (eyelid)(droopy eyelids): 57%
- Poor thermoregulation: 51%

Behavioral

- Chewing on non food items (clothing, bedding, toys):70%
- Teeth grinding: (percent undetermined)
- Autistic behaviors: (percent undetermined)
- Tongue thrusting: (percent undetermined)
- Hair pulling: (percent undetermined)
- Aversion to clothes: (percent undetermined)

Etiology

The deletion affects the terminal region of the long arm of chromosome 22 (the paternal chromosome in 75% of cases), from 22q13.3 to 22qter. Although the deletion is most typically a result of a de novo mutation, there is an inherited form resulting from familial chromosomal translocations involving the 22 chromosome. In the de novo form, the size of the deletion is variable and can go from 130kbp (130,000 base pairs) to 9Mbp (9,000,000 base pairs). While some clinical signs correlate with the size of the deletion, the main traits of the syndrome appear to be independent of the deletion size, and only related to the presence of the Shank3 gene . The haploinsufficiency of Shank3 is thought to be the responsible for the neurological deficits of the syndrome.

The proteins encoded by the Shank genes assemble glutamate receptors with their intracellular signaling apparatus and cytoskeleton at the postsynaptic density. They are important for the formation and stabilisation of synapses:

- Experimentally induced expression of Shank3 has been shown to be sufficient to induce functional dendritic spines in aspiny cerebellar neurons.
- Neural network activity up- or down regulates large groups of postsynaptic proteins through ubiquitin-mediated protein degradation. Shank proteins were identified as one of the few postsynaptic density proteins that can be degraded by ubiquitination

In 2006, a group led by Thomas Bourgeron from the Pasteur Institute in France, found anomalies of the 22q13 locus in five children with diagnosis of autism and Asperger syndrome. While the absence of the Shank3 gene was found in children with the typical characteristics of the Phelan-McDermid syndrome, its duplication was found in one child diagnosed with Asperger syndrome, a type of high-functioning autism.

Van Bokhoven *et al.* (1997) have also assigned the WNT7B gene to 22q13 . Wnt7b acts through Dvl1 to the regulation of dendritic development. found that its overexpression resulted in increased dendritic branching in cultured mouse hippocampal neurons. Knockout mice for Dvl1 are viable, fertile and structurally normal, but show reduced social interaction and abnormal sleeping patterns. Heterozygous knockout mice for Shank3 are viable , but little has been reported yet about the mouse phenotype.

Incidence

The incidence of the 22q13 deletion syndrome is uncertain. The advanced genetic technique essential for diagnosis, fluorescent in situ hybridization (FISH), has only been available since 1998, and currently requires specialized laboratory facilities. Current thinking is that 22q13 deletion syndrome remains largely under-diagnosed, and may be one of the principal causes of idiopathic mental retardation.

Chapter 5

Quadruple X, Pentasomy X and 49, XXXXY Syndrome

Quadruple X

XXXX syndrome	
ICD-10	Q97.1
DiseasesDB	32550

XXXX syndrome (also called **tetrasomy X**, **quadruple X**, or **48, XXXX**) is a rare chromosomal disorder caused by the presence of four X chromosomes instead of two X chromosomes. This condition occurs only in females, as there are no Y chromosomes present. Tetrasomy X was first described in 1961, and since then approximately 100 cases have been reported worldwide. Approximately 60 females have been described in medical literature with this condition.

Causes and diagnosis

Tetrasomy X is a chromosomal aneuploidy, meaning it arises from a defect in meiosis. This can occur when homologous X chromosomes fail to separate in the formation of the egg or sperm. Tetrasomy X is usually suspected based on symptoms present in the individual and is confirmed via karyotyping, which reveals the extra X chromosomes.

Symptoms

Symptoms of tetrasomy X are highly variable, ranging from relatively mild to severe. Physically, tetrasomy X patients tend to have distinctive facial features such as epicanthal folds, flat nasal bridges, upslanting palpebral fissures, midface hypoplasia, small mouths, cleft or high arched palates, delayed or absent teeth, or enamel defects. The majority have also been reported as being longer and taller. Many also show joint and muscle tone abnormalities, including hypotonia and joint looseness in the hips. Skeletal problems may also be present, including abnormal curvatures of the spine. An informal study conducted

by Tetrasomy & Pentasomy X Syndrome Information and Support found that 10% of girls had joint laxity in the hips and 20% had joint limitations in a sample size of 20 tetrasomy and pentasomy patients.

Developmentally, tetrasomy X patients frequently show mild delays in the areas of speech development and articulation, language expression and understanding, and reading skills. Delays in motor development are also present, with walking ages ranging from 16 months to 4.5 years. About 50% of patients undergo puberty normally, whereas the other 50% experiences no puberty, partial puberty without secondary sexual characteristics, or complete puberty with menstrual irregularities and/or early menopause (possibly as early as the teens). Medical literature reports four tetra-X pregnancies, two healthy, one with trisomy 21, one stillborn with omphalocele.

In terms of internal organ systems, tetrasomy X patients may have abnormal vision, hearing, circulatory systems, kidneys, or nervous systems. Disorders of the eye include myopia, nystagmus, coloboma, microphthalmus, or optic nerve hypoplasia. In terms of hearing, patients are more prone to ear infections, sound blockage, or nerve abnormalities. Several cardiac defects have also been reported, including ventricular/atrial septal defects, atresia, hypoplastic right heart syndrome, patent ductus arteriosus, and conotruncal or valvular cardiac defects. Tetrasomy X patients also appear to be more prone to seizure activity, although there is no documented abnormalities in brain function or structure when analyzed using an EEG or MRI.

Treatment and prognosis

The general prognosis for girls with tetrasomy X is relatively good. Due to the variability of symptoms, some tetrasomy X girls are able to function normally, whereas others will need medical attention throughout their lives. Traditionally, treatment for tetrasomy X has been management of the symptoms and support for learning. Most girls are placed on estrogen treatment to induce breast development, arrest longitudinal growth, and stimulate bone formation to prevent osteoporosis. Speech, occupational, and physical therapy may also be needed depending on the severity of the symptoms.

Pentasomy X

49, XXXXX	
ICD-10	Q97.1
DiseasesDB	32625

XXXXX syndrome (also called **pentasomy X** or **49,XXXXX**) is the presence of three additional X chromosomes. Diagnosis is done by karyotyping. Approximately 25 females have been described in medical literature worldwide with this extremely rare condition. The condition was first described in 1963. XXXXX syndrome is a type of aneuploidy (an abnormal number of chromosomes).

Effects

Physical traits

XXXXX syndrome is associated with microcephaly (undersized skull), micrognathia (undersized jaw), and round face. The ears are generally low-set and malformed. Eyes are upslanting and show palpebral fissures, hypertelorism, and strabismus. Usually the nose is shaped with a broad and depressed nasal bridge and epicanthus, with the mouth having a cleft and highly arched palate, dental abnormalities, and thick, furrowed, and everted lips. The neck is webbed, much like the neck of a woman with Turner's syndrome. The hands and feet are small with overlapping toes, camptodactyly, clinodactyly, talipes equinovarus, and metatarsus varus. Scoliosis generally affects the spine and hypotonia affects the muscles.

Internal organs

The heart is usually affected by patent ductus arteriosus, atrial septal defect, ventricular septal defect, and aortic dextroposition. There is abnormal lobulation of the lungs and neonatal asphyxia. The ovaries are abnormally shaped with a small uterus and kidney hypoplasia.

Growth and development

XXXXX syndrome causes mental, growth, and motor retardation. There is occasional delayed puberty. Behavior and performance is affected by opisthotonoid posture. Recent observations have indicated an average of a 10 to 15 IQ point decrease for each extra X chromosome. Thus, the average IQ of XXXXX individuals tends to be between 55 and 70.

49, XXXXY syndrome

49, XXXXY syndrome	
ICD-9	758.81
DiseasesDB	32552

49, XXXXY Syndrome is an extremely rare, aneuploidic sex chromosomal abnormality; its frequency is approximately 1 out of 85,000 to 100,000 males.

Pathophysiology

As its name indicates, a person with the syndrome has one Y chromosome and four X chromosomes on the 23rd pair, thus having 49 chromosomes rather than the normal 46. As is common with aneuploidy disorders, 49, XXXXY syndrome is often accompanied by mental retardation. It can be considered a form of Klinefelter syndrome, or a variant of it.

It is genetic, but not hereditary. This means that while the genes of the parents cause the syndrome, there is a small chance of more than one child having the syndrome. The probability of inheriting the disease is about 1%.

The individuals with this syndrome are males, but 49, XXXXX also exists with similar characteristics as the male version.

Effects

Aneuploidy is often fatal, but in this case there is "X-inactivation" where the effect of the additional gene dosage due to the presence of extra X chromosomes is greatly reduced.

The mental effects of 49, XXXXY Syndrome vary, much like Down syndrome. Impaired speech and behavioral problems are typical. Those with 49 XXXXY syndrome tend to exhibit infantile secondary sex characteristics with sterility in adulthood and have some skeletal anomalies. Skeletal anomalies include:

- Genu valgus
- Pes cavus
- Fifth finger clinodactyly

The effects also include:

- Cleft palate
- Club feet
- Respiratory conditions

- Short or/and broad neck
- Low birth weight
- Hyperextensible joints
- Short stature
- Narrow shoulders
- Coarse features in older age
- Hypertelorism
- Epicanthal folds
- Prognathism
- Gynecomastia (rare)
- Muscular hypotonia
- Hypoplastic genitalia
- Cryptorchidism
- Congenital heart defects
- A very round face in infancy

Chapter 6

Aneuploidy

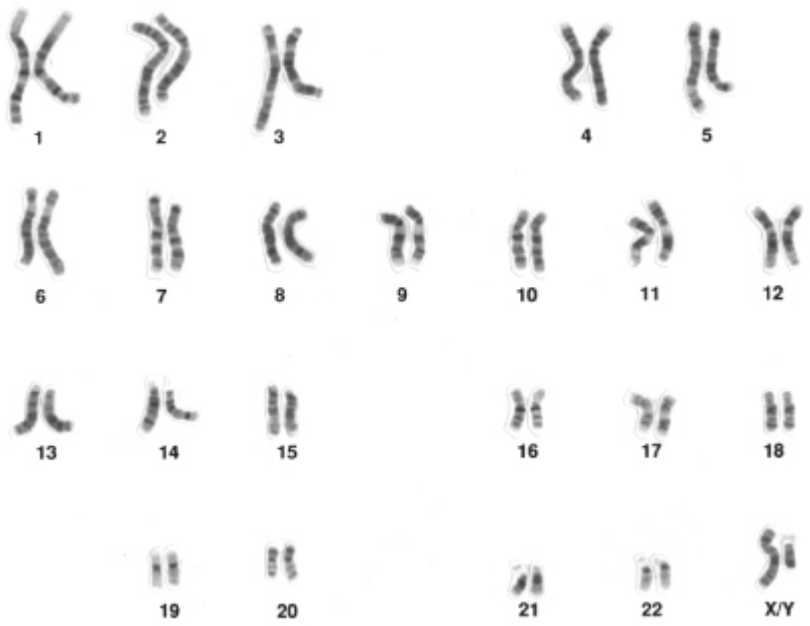
Aneuploidy	
ICD-10	Q90.-Q98.
ICD-9	758
MeSH	D000782

Aneuploidy is an abnormal number of chromosomes, and is a type of chromosome abnormality. An extra or missing chromosome is a common cause of genetic disorders (birth defects). Some cancer cells also have abnormal numbers of chromosomes. Aneuploidy occurs during cell division when the chromosomes do not separate properly between the two cells. Chromosome abnormalities occur in 1 of 160 live births, the most common being extra chromosomes 21, 18 and 13.

Different species have different numbers of normal chromosomes and thus the term "aneuploidy" refers to the chromosome number being different for that species.

Chromosomes

Every cell in the human body, apart from enucleated red blood cells and the haploid gametes, has 23 pairs of chromosomes (for a total of 46). One copy of each pair is inherited from the mother and the other copy is inherited from the father. The first 22 pairs of chromosomes (referred to as autosomes) are numbered from 1 to 22, and are arranged from largest to smallest in a karyotype. The 23rd pair of chromosomes are the sex chromosomes. Normal females have two X chromosomes, while normal males have one X chromosome and one Y chromosome.



During meiosis, when germ cells divide to create sperm and egg (gametes), each half should have the same number of chromosomes. But sometimes, the whole pair of chromosomes will end up in one gamete, and the other gamete will not get that chromosome at all.

Most embryos cannot survive with a missing or extra autosome (numbered chromosome) and are spontaneously aborted. The most frequent aneuploidy in humans is trisomy 16, although fetuses affected with the full version of this chromosome abnormality do not survive to term (it is possible for surviving individuals to have the mosaic form, where trisomy 16 exists in some cells but not all). The most common aneuploidy that infants can survive with is trisomy 21, which is found in Down syndrome, affecting 1 in 800 births. Trisomy 18 (Edwards syndrome) affects 1 in 6,000 births, and trisomy 13 (Patau syndrome) affects 1 in 10,000 births. 10% of infants with trisomy 18 or 13 reach 1 year of age.

Changes in chromosome number may not necessarily be present in all cells in an individual. When aneuploidy is detected in a fraction of cells in an individual, it is called chromosomal mosaicism. In general, individuals who are mosaic for a chromosomal aneuploidy tend to have a less severe form of the syndrome compared to those with full trisomy. For many of the autosomal trisomies, only mosaic cases survive to term. However, mitotic aneuploidy may be more common than previously recognized in somatic tissues, and aneuploidy is a characteristic of many types of tumorigenesis.

Terminology

In the strict sense, a chromosome complement having a number of chromosomes other than 46 (in humans) is considered *heteroploid* while an exact multiple of the haploid chromosome complement is considered euploid.

Number of chromosomes	Name	Description
1	Monosomy	**Monosomy** refers to lack of one chromosome of the normal complement. Partial monosomy can occur in unbalanced translocations or deletions, in which only a portion of the chromosome is present in a single copy. Monosomy of the sex chromosomes (45,X) causes Turner syndrome.
2	Disomy	*Disomy* is the presence of two copies of a chromosome. For organisms such as humans that have two copies of each chromosome (those that are diploid), it is the normal condition. For organisms that normally have three or more copies of each chromosome (those that are triploid or above), disomy is an aneuploid chromosome complement. In uniparental disomy, both copies of a chromosome come from the same parent (with no contribution from the other parent).
3	Trisomy	**Trisomy** refers to the presence of three copies, instead of the normal two, of a particular chromosome. The presence of an extra chromosome 21, which is found in Down syndrome, is called trisomy 21. Trisomy 18 and Trisomy 13, known as Edwards and Patau Syndrome, respectively, are the two other autosomal trisomies recognized in live-born humans. Trisomy of the sex chromosomes is possible, such as in (47,XXX).
4/5	tetrasomy/pentasomy	*Tetrasomy* and *pentasomy* are the presence of four or five copies of a chromosome, respectively. Although rarely seen with autosomes, sex chromosome tetrasomy and pentasomy have been reported in humans, including XXXX, XXXXX, XXXXY and XYYYY.

Mechanisms

Nondisjunction usually occurs as the result of a weakened mitotic checkpoint, as these checkpoints tend to arrest or delay cell division until all components of the cell are ready

to enter the next phase. If a checkpoint is weakened, the cell may fail to 'notice' that a chromosome pair is not lined up on the mitotic plate, for example. In such a case, most chromosomes would separate normally (with one chromatid ending up in each cell), while others could fail to separate at all. This would generate a daughter cell lacking a copy and a daughter cell with an extra copy.

Completely inactive mitotic checkpoints may cause non-disjunction at multiple chromosomes, possibly all. Such a scenario could result in each daughter cell possessing a disjoint set of genetic material.

Merotelic attachment occurs when one kinetochore is attached to both mitotic spindle poles. One daughter cell would have a normal complement of chromosomes; the second would lack one. A third daughter cell may end up with the 'missing' chromosome.

Multipolar spindle: more than two spindle poles form. Such a mitotic division would result in one daughter cell for each spindle pole; each cell may possess an unpredictable complement of chromosomes.

Monopolar spindle: only a single spindle pole forms. This produces a single daughter cell with its copy number doubled.

A *tetraploid intermediate* may be produced as the end-result of the monopolar spindle mechanism. In such a case, the cell has double the copy number of a normal cell, and produces double the number of spindle poles as well. This results in four daughter cells with an unpredictable complement of chromosomes, but in the normal copy number.

Somatic mosaicism in the nervous system

Mosaicism for aneuploid chromosome content may be part of the constitutional make-up of the mammalian brain. In the normal human brain, brain samples from six individuals ranging from 2–86 years of age had mosaicism for chromosome 21 aneuploidy (average of 4% of neurons analyzed). This low-level aneuploidy appears to arise from chromosomal segregation defects during cell division in neuronal precursor cells, and neurons containing such aneuploid chromosome content reportedly integrate into normal circuits. These results suggest the possibility that somatic mosaicism in the brain (and perhaps, by extension, other tissues) may contribute to the diversity between individuals.

Somatic mosaicism in cancer

Somatic mosaicism also occurs in many cancer cells, including trisomy 12 in chronic lymphocytic leukemia (CLL) and trisomy 8 in acute myeloid leukemia (AML). However, these forms of mosaic aneuploidy occur through mechanisms distinct from those typically associated with genetic syndromes involving complete or mosaic aneuploidy.

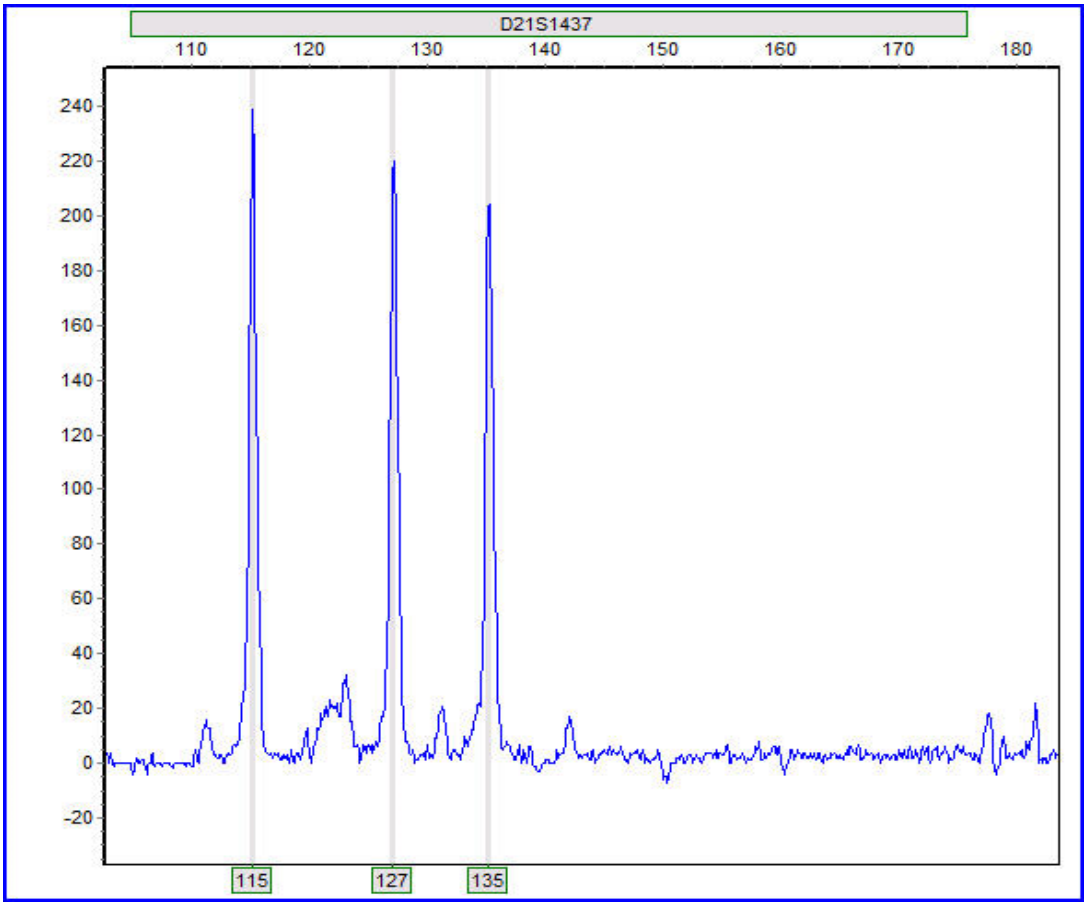
Loss of p53 creates genomic instability that most often results in the aneuploidy phenotype.

In addition, genetic syndromes in which an individual is predisposed to breakage of chromosomes (chromosome instability syndromes) are frequently associated with increased risk for various types of cancer, thus highlighting the role of somatic aneuploidy in carcinogenesis. Studies indicate that aneuploidy directly contributes to carcinogenesis by disrupting the asymmetric division of adult stem cells.

Partial aneuploidy

The terms "partial monosomy" and "partial trisomy" are used to describe an imbalance of genetic material caused by loss or gain of part of a chromosome. In particular, these terms would be used in the situation of an unbalanced translocation, where an individual carries a derivative chromosome formed through the breakage and fusion of two different chromosomes. In this situation, the individual would have three copies of part of one chromosome (two normal copies and the portion that exists on the derivative chromosome) and only one copy of part of the other chromosome involved in the derivative chromosome.

Diagnosis



Example of Trisomy 21 detected via qPCR Short Tandem Repeat assay

Germline aneuploidy is typically detected through karyotyping, a process in which a sample of cells is fixed and stained to create the typical light and dark chromosomal banding pattern and a picture of the chromosomes is analyzed. Other techniques include Fluorescence In Situ Hybridization (FISH), Quantitative Polymerase Chain Reaction (PCR) of Short Tandem Repeats, Quantitative Fluorescence PCR (QF-PCR), Quantitative Real-time PCR (RT-PCR) dosage analysis, Quantitative Mass Spectrometry of Single Nucleotide Polymorphisms, and Comparative Genomic Hybridization (CGH).

These tests can also be performed prenatally to detect aneuploidy in a pregnancy, through either amniocentesis or chorionic villus sampling. Pregnant women of 35 years or older are offered prenatal diagnosis because the chance of chromosomal aneuploidy increases as the mother's age increases.

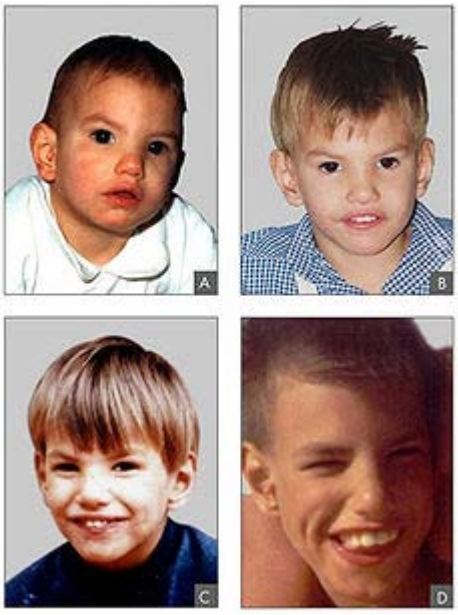
Recent advances have allowed for less invasive testing methods based on the presence of fetal genetic material in maternal blood.

Chapter 7

Cri Du Chat and Edwards Syndrome

Cri du chat

Cri du chat or Cri-du-chat



Facial features of a patient with Cri du Chat syndrome at age of 8 months (A), 2 years (B), 4 years (C) and 9 years (D)

ICD-10	Q93.4
ICD-9	758.31
OMIM	123450
DiseasesDB	29133
MedlinePlus	001593

Cri du chat syndrome, also known as **chromosome 5p deletion syndrome**, **5p minus syndrome** or **Lejeune's syndrome**, is a rare genetic disorder due to a missing part of chromosome 5. Its name is a French term (*cat-cry* or *call of the cat*) referring to the characteristic cat-like cry of affected children. It was first described by Jérôme Lejeune in 1963. The condition affects an estimated 1 in 50,000 live births, strikes all ethnicities, and is more common in females by a 4:3 ratio.

Signs and symptoms

The syndrome gets its name from the characteristic cry of affected infants, which is similar to that of a meowing kitten, due to problems with the larynx and nervous system. About 1/3 of children lose the cry by age 2. Other symptoms of cri du chat syndrome may include:

- feeding problems because of difficulty swallowing and sucking.
- low birth weight and poor growth.
- severe cognitive, speech, and motor delays.
- behavioral problems such as hyperactivity, aggression, tantrums, and repetitive movements.
- unusual facial features which may change over time.
- excessive drooling.
- constipation.

Other common findings include hypotonia, microcephaly, growth retardation, a round face with full cheeks, hypertelorism, epicanthal folds, down-slanting palpebral fissures, strabismus, flat nasal bridge, down-turned mouth, micrognathia, low-set ears, short fingers, single palmar creases, and cardiac defects (eg, ventricular septal defect [VSD], atrial septal defect [ASD], patent ductus arteriosus [PDA], tetralogy of Fallot). People with Cri du chat are fertile and can reproduce.

Less frequently encountered findings include cleft lip and palate, preauricular tags and fistulas, thymic dysplasia, intestinal malrotation, megacolon, inguinal hernia, dislocated hips, cryptorchidism, hypospadias, rare renal malformations (eg, horseshoe kidneys, renal ectopia or agenesis, hydronephrosis), clinodactyly of the fifth fingers, talipes equinovarus, pes planus, syndactyly of the second and third fingers and toes, oligosyndactyly, and hyperextensible joints. The syndrome may also include various dermatoglyphics, including transverse flexion creases, distal axial triradius, increased whorls and arches on digits, and a single palmar crease.

Late childhood and adolescence findings include significant intellectual disability, microcephaly, coarsening of facial features, prominent supraorbital ridges, deep-set eyes, hypoplastic nasal bridge, severe malocclusion, and scoliosis.

Affected females reach puberty, develop secondary sex characteristics, and menstruate at the usual time. The genital tract is usually normal in females except for a report of a bicornuate uterus. In males, testes are often small, but spermatogenesis is thought to be normal.

Genetics

Cri du chat syndrome is due to a partial deletion of the short arm of chromosome number 5, also called "5p monosomy". Approximately 90% of cases results from a sporadic, or randomly-occurring, *de novo* deletion. The remaining 10-15% are due to unequal segregation of a parental balanced translocation where the 5p monosomy is often accompanied by a trisomic portion of the genome. These individuals may have more severe disease than those with isolated monosomy of 5p.

Most cases involve total loss of the most distant 20-10% of the material on the short arm. Fewer than 10% of cases have other rare cytogenetic aberrations (eg, interstitial deletions, mosaicisms, rings and de novo translocations). The deleted chromosome 5 is paternal in origin in about 80% of *de novo* cases.

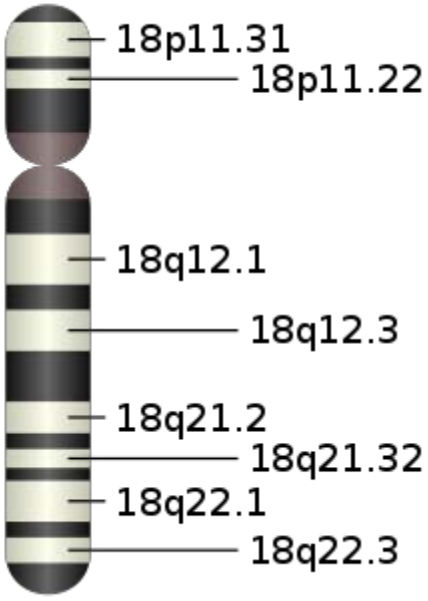
Loss of a small region in band 5p15.2 (cri du chat critical region) correlates with all the clinical features of the syndrome with the exception of the catlike cry, which maps to band 5p15.3 (catlike critical region). The results suggest that 2 noncontiguous critical regions contain genes involved in this condition's etiology. Two genes in these regions, Semaphorine F (SEMA5A) and delta catenin (CTNND2), are potentially involved in cerebral development. The deletion of the telomerase reverse transcriptase (hTERT) gene localized in 5p15.33 may contribute to the phenotypic changes in cri du chat syndrome as well.

Diagnosis and Management

Diagnosis is based on the distinctive cry and accompanying physical problems. Genetic counseling and genetic testing may be offered to families with individuals who have cri du chat syndrome. Children may be treated by speech, sound, and occupational therapists. Cardiac abnormalities often require surgical correction.

Edwards syndrome

Trisomy 18, Edwards Syndrome



Chromosome 18

ICD-10	Q91.0-Q91.3
ICD-9	758.2
DiseasesDB	13378
eMedicine	ped/652

Trisomy 18 (**T18**) (also known as **Trisomy E** or **Edwards syndrome**) is a genetic disorder caused by the presence of all or part of an extra 18th chromosome. It is named after John H. Edwards, who first described the syndrome in 1960. It is the second most common autosomal trisomy, after Down Syndrome, that carries to term.

Trisomy 18 is caused by the presence of three – as opposed to two – copies of chromosome 18 in a fetus or infant's cells. The incidence of the syndrome is estimated as one in 3,000 live births. The incidence increases as the mother's age increases. The syndrome has a very low rate of survival, resulting from heart abnormalities, kidney malformations, and other internal organ disorders.

Prognosis

In England and Wales, there were 495 diagnoses of Edwards' syndrome (trisomy 18) in 2008/2009, of which 92% were made prenatally. There were 339 terminations, 49

stillbirths/miscarriages/fetal deaths, 72 unknown outcomes, and 35 live births. Because approximately 3% of cases of Edwards' syndrome with unknown outcomes are likely to result in a live birth, the total number of live births is estimated to be 37 (2008/09 data are provisional). Only 50% of liveborn infants live to 2 months, and only 5–10% survive their first year of life. Major causes of death include apnea and heart abnormalities. It is impossible to predict the exact prognosis of a child with Edwards syndrome during pregnancy or the neonatal period. The median lifespan is 5–15 days. One percent of children born with this syndrome live to age 10, typically in less severe cases of the mosaic Edwards syndrome. The small percentage of babies with the full Edwards syndrome who survive birth and early infancy may live to adulthood, and children with mosaic or partial forms of this trisomy may have a completely different and much more hopeful prognosis.

Incidence/prevalence

Edwards syndrome occurs in approximately 1 in 3,000 conceptions and approximately 1 in 6,000 live births; 50% of those diagnosed with the condition prenatally will not survive the prenatal period. Although women in their 20s and early 30s may conceive babies with Edwards syndrome, the risk of conceiving a child with Edwards syndrome increases with a woman's age. The average maternal age for conceiving a child with this disorder is 32½.

Genetics

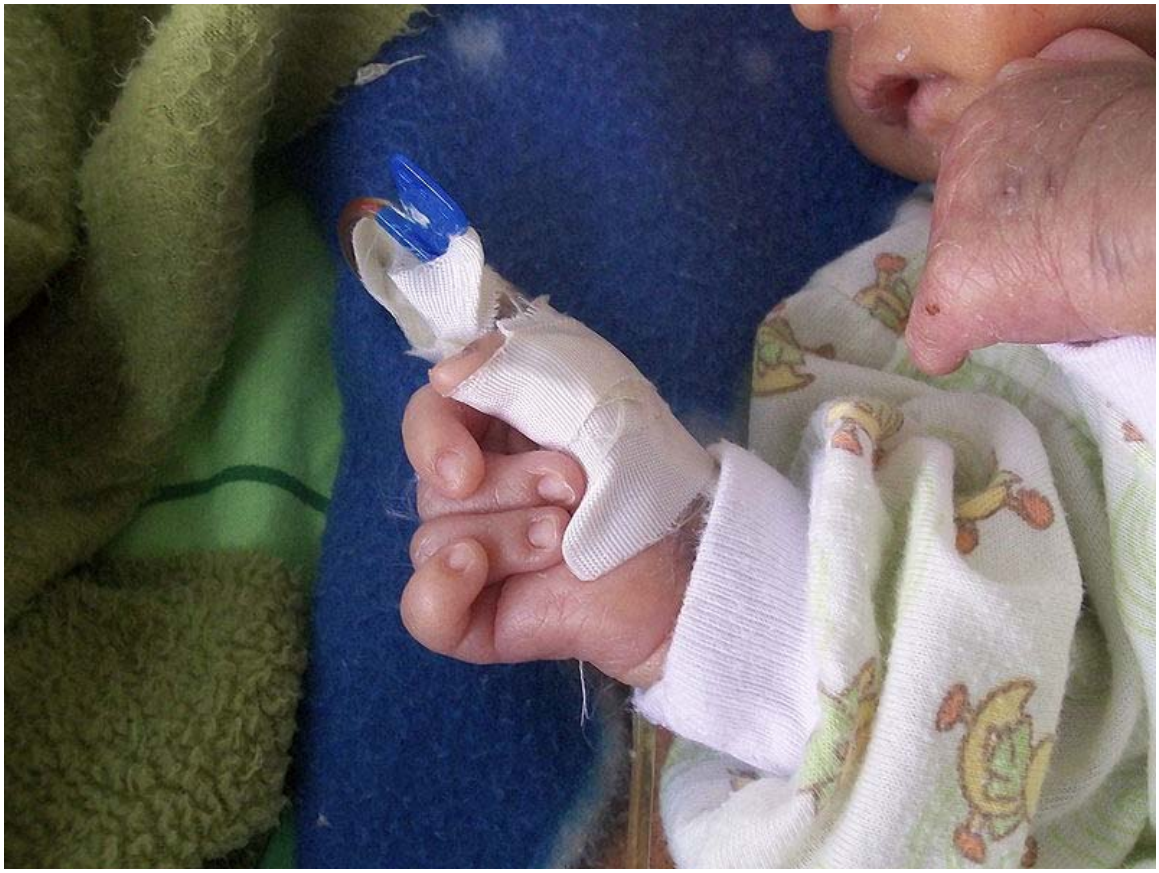
Edwards syndrome is a chromosomal abnormality characterized by the presence of an extra copy of genetic material on the 18th chromosome, either in whole (trisomy 18) or in part (such as due to translocations). The additional chromosome usually occurs before conception. The effects of the extra copy vary greatly, depending on the extent of the extra copy, genetic history, and chance. Edwards syndrome occurs in all human populations but is more prevalent in female offspring.

A healthy egg or sperm cell contains individual chromosomes, each of which contributes to the 23 pairs of chromosomes needed to form a normal cell with a typical human karyotype of 46 chromosomes. Numerical errors can arise at either of the two meiotic divisions and cause the failure of a chromosome to segregate into the daughter cells (nondisjunction). This results in an extra chromosome, making the haploid number 24 rather than 23. Fertilization of eggs or insemination by sperm that contain an extra chromosome results in trisomy, or three copies of a chromosome rather than two.

Trisomy 18 (47,XX,+18) is caused by a meiotic nondisjunction event. With nondisjunction, a gamete (*i.e.*, a sperm or egg cell) is produced with an extra copy of chromosome 18; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embryo has 47 chromosomes, with three copies of chromosome 18.

A small percentage of cases occur when only some of the body's cells have an extra copy of chromosome 18, resulting in a mixed population of cells with a differing number of chromosomes. Such cases are sometimes called mosaic Edwards syndrome. Very rarely, a piece of chromosome 18 becomes attached to another chromosome (translocated) before or after conception. Affected individuals have two copies of chromosome 18 plus extra material from chromosome 18 attached to another chromosome. With a translocation, a person has a partial trisomy for chromosome 18, and the abnormalities are often less severe than for the typical Edwards syndrome.

Features and characteristics



Clenched hand and overlapping fingers: index finger overlaps third finger and fifth finger overlaps fourth finger, characteristically seen in Trisomy 18.

Infants born with Edwards syndrome may have some or all of the following characteristics: kidney malformations, structural heart defects at birth (i.e., ventricular septal defect, atrial septal defect, patent ductus arteriosus), intestines protruding outside the body (omphalocele), esophageal atresia, mental retardation, developmental delays, growth deficiency, feeding difficulties, breathing difficulties, and arthrogryposis (a muscle disorder that causes multiple joint contractures at birth).

Some physical malformations associated with Edwards syndrome include small head (microcephaly) accompanied by a prominent back portion of the head (occiput); low-set,

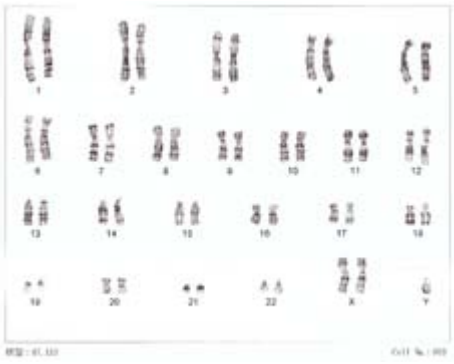
malformed ears; abnormally small jaw (micrognathia); cleft lip/cleft palate; upturned nose; narrow eyelid folds (palpebral fissures); widely spaced eyes (ocular hypertelorism); drooping of the upper eyelids (ptosis); a short breast bone; clenched hands; choroid plexus cysts; underdeveloped thumbs and or nails absent radius, webbing of the second and third toes; clubfoot or *Rocker bottom feet*; and in males, undescended testicles.

In utero, the most common characteristic is cardiac anomalies, followed by central nervous system anomalies such as head shape abnormalities. The most common intracranial anomaly is the presence of choroid plexus cysts, which is a pocket of fluid on the brain that is not problematic in itself but may be a marker for Trisomy 18. Sometimes excess amniotic fluid or polyhydramnios is exhibited.

Chapter 8

Klinefelter's Syndrome

Klinefelter's syndrome



47,XXY

ICD-10	Q98.0-Q98.4
ICD-9	758.7
eMedicine	ped/1252
MeSH	D007713

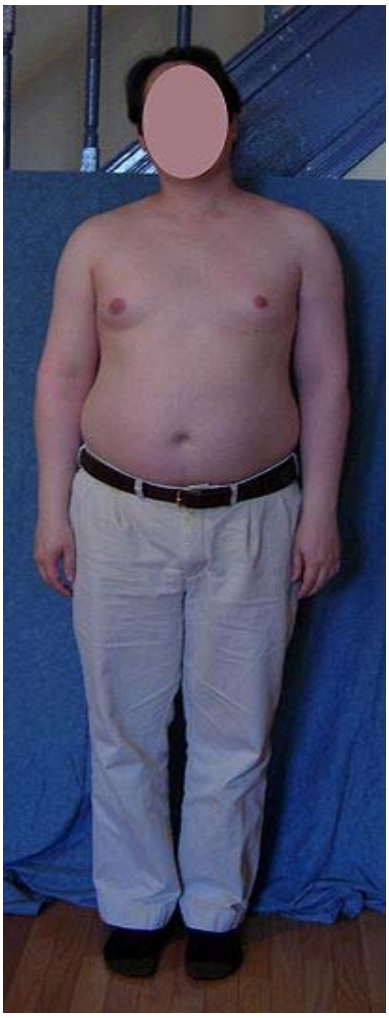
Klinefelter syndrome, 47, XXY, or **XXY syndrome** is a condition in which human males have an extra X chromosome. While females have an XX chromosomal makeup, and males an XY, affected individuals have at least two X chromosomes and at least one Y chromosome. Because of the extra chromosome, individuals with the condition are usually referred to as "XXY Males", or "47, XXY Males".

In humans, Klinefelter syndrome is the most common sex chromosome disorder in males and the second most common condition caused by the presence of extra chromosomes. The condition exists in roughly 1 out of every 1,000 males. One in every 500 males has an extra X chromosome but does not have the syndrome. Other mammals also have the XXY syndrome, including mice.

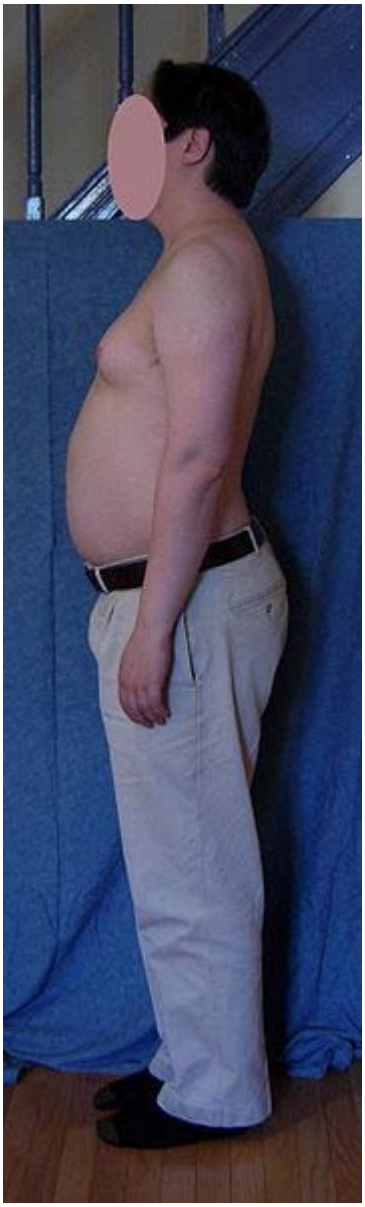
The principal effects are development of small testicles and reduced fertility. A variety of other physical and behavioral differences and problems are common, though severity varies and many boys and men with the condition have few detectable symptoms.

The syndrome was named after Dr. Harry Klinefelter, who in 1942 worked with Fuller Albright at Massachusetts General Hospital in Boston, Massachusetts and first described it in the same year.

Signs and symptoms



Patient with typical untreated (surgery/hormones) Klinefelter 46,XY/47,XXY mosaic, diagnosed at age 19. Scar from biopsy may be visible on left nipple.



Same patient from the side

Affected males are almost always effectively infertile, although advanced reproductive assistance is sometimes possible. Some degree of language learning impairment may be present, and neuropsychological testing often reveals deficits in executive functions. In adults, possible characteristics vary widely and include little to no signs of affectedness, a lanky, youthful build and facial appearance, or a rounded body type with some degree of gynecomastia (increased breast tissue). Gynecomastia is present to some extent in about a third of affected individuals, a slightly higher percentage than in the XY population. About 10% of XXY males have gynecomastia noticeable enough that they may choose to have cosmetic surgery.

The term *hypogonadism* in XXY symptoms is often misinterpreted to mean "small testicles" or "small penis". In fact, it means decreased testicular hormone/endocrine function. Because of this (primary) hypogonadism, individuals will often have a low serum testosterone level but high serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Despite this misunderstanding of the term, however, it is true that XXY men also have microorchidism (i.e. small testicles).

The more severe end of the spectrum of symptom expression is also associated with an increased risk of germ cell tumors, male breast cancer, and osteoporosis, risks shared to varying degrees with females. Additionally, medical literature shows some individual case studies of Klinefelter syndrome coexisting with other disorders, such as pulmonary disease, varicose veins, diabetes mellitus, and rheumatoid arthritis, but possible correlations between Klinefelter and these other conditions are not well characterized or understood.

In contrast to these potentially increased risks, it is currently thought that rare X-linked recessive conditions occur less frequently in XXY males than in normal XY males, since these conditions are transmitted by genes on the X chromosome, and people with two X chromosomes are typically only carriers rather than affected by these X-linked recessive conditions.

There are many variances within the XXY population, just as in the most common 46,XY population. While it is possible to characterise 47,XXY males with certain body types, that in itself should not be the method of identification as to whether or not someone has 47,XXY. The only reliable method of identification is karyotype testing.

Diagnosis

A karyotype is used to confirm the diagnosis. In this procedure, a small blood sample is drawn. White blood cells are then separated from the sample, mixed with tissue culture medium, incubated, and checked for chromosomal abnormalities, such as an extra X chromosome.

Diagnosis can also be made prenatally via chorionic villus sampling or amniocentesis, tests in which fetal tissue is extracted and the fetal DNA is examined for genetic abnormalities. A 2002 literature review of elective abortion rates found that approximately 50% of pregnancies in the United States with a diagnosis of Klinefelter syndrome were terminated.

Cause

The extra X chromosome is retained because of a nondisjunction event during meiosis I (gametogenesis). Nondisjunction occurs with when homologous chromosomes, in the case the X and Y sex chromosomes, fail to separate, producing a sperm with an X and a Y chromosome. Fertilizing a normal (X) egg produces an XXY offspring. The XXY

chromosome arrangement is one of the most common genetic variations from the XY karyotype, occurring in about 1 in 500 live male births.

In mammals with more than one X chromosome, the genes on all but one X chromosome are not expressed; this is known as X inactivation. This happens in XXY males as well as normal XX females. However, in XXY males, a few genes located in the pseudoautosomal regions of their X chromosomes, have corresponding genes on their Y chromosome and are capable of being expressed. These triploid genes in XXY males may be responsible for symptoms associated with Klinefelter syndrome.

The first published report of a man with a 47,XXY karyotype was by Patricia A. Jacobs and Dr. J.A. Strong at Western General Hospital in Edinburgh, Scotland in 1959. This karyotype was found in a 24-year-old man who had signs of Klinefelter syndrome. Dr. Jacobs described her discovery of this first reported human or mammalian chromosome aneuploidy in her 1981 William Allan Memorial Award address.

Variations

The 48, XXYY (male) syndrome occurs in 1 in 18,000–40,000 births and has traditionally been considered to be a variation of Klinefelter syndrome. XXYY tetrasomy is no longer generally considered a variation of KS, although it has not yet been assigned an ICD-10 code.

Males with Klinefelter syndrome may have a mosaic 47,XXY/46,XY constitutional karyotype and varying degrees of spermatogenic failure. Mosaicism 47,XXY/46,XX with clinical features suggestive of Klinefelter syndrome is very rare. Thus far, only about 10 cases have been described in literature.

Treatment

The genetic variation is irreversible. Testosterone treatment is an option for some individuals who desire a more masculine appearance and identity. Often individuals that have noticeable breast tissue or hypogonadism experience depression and/or social anxiety because they are outside of social norms. This is academically referred to as psychosocial morbidity. At least one study indicates that planned and timed support should be provided for young men with Klinefelter syndrome to ameliorate current poor psychosocial outcomes.

By 2010 over 100 successful pregnancies have been reported using IVF technology with surgically removed sperm material from men with Klinefelter syndrome.

Chapter 9

Patau Syndrome

Patau syndrome

Chromosome 13

ICD-10	Q91.4-Q91.7
ICD-9	758.1
DiseasesDB	13373
MedlinePlus	001660
eMedicine	ped/{{{eMedicineTopic}}}

Patau syndrome, also known as **trisomy 13** and **trisomy D**, is a chromosomal abnormality, a syndrome in which a patient has an additional chromosome 13 due to a nondisjunction of chromosomes during meiosis. Some are caused by Robertsonian translocations. The extra chromosome 13 disrupts the normal course of development, causing heart and kidney defects amongst other features characteristic of Patau syndrome. Like all nondisjunction conditions (such as Down syndrome and Edwards syndrome), the risk of this syndrome in the offspring increases with maternal age at pregnancy, with

about 31 years being the average. Patau syndrome affects approximately one in 10,000 live births.

Causes

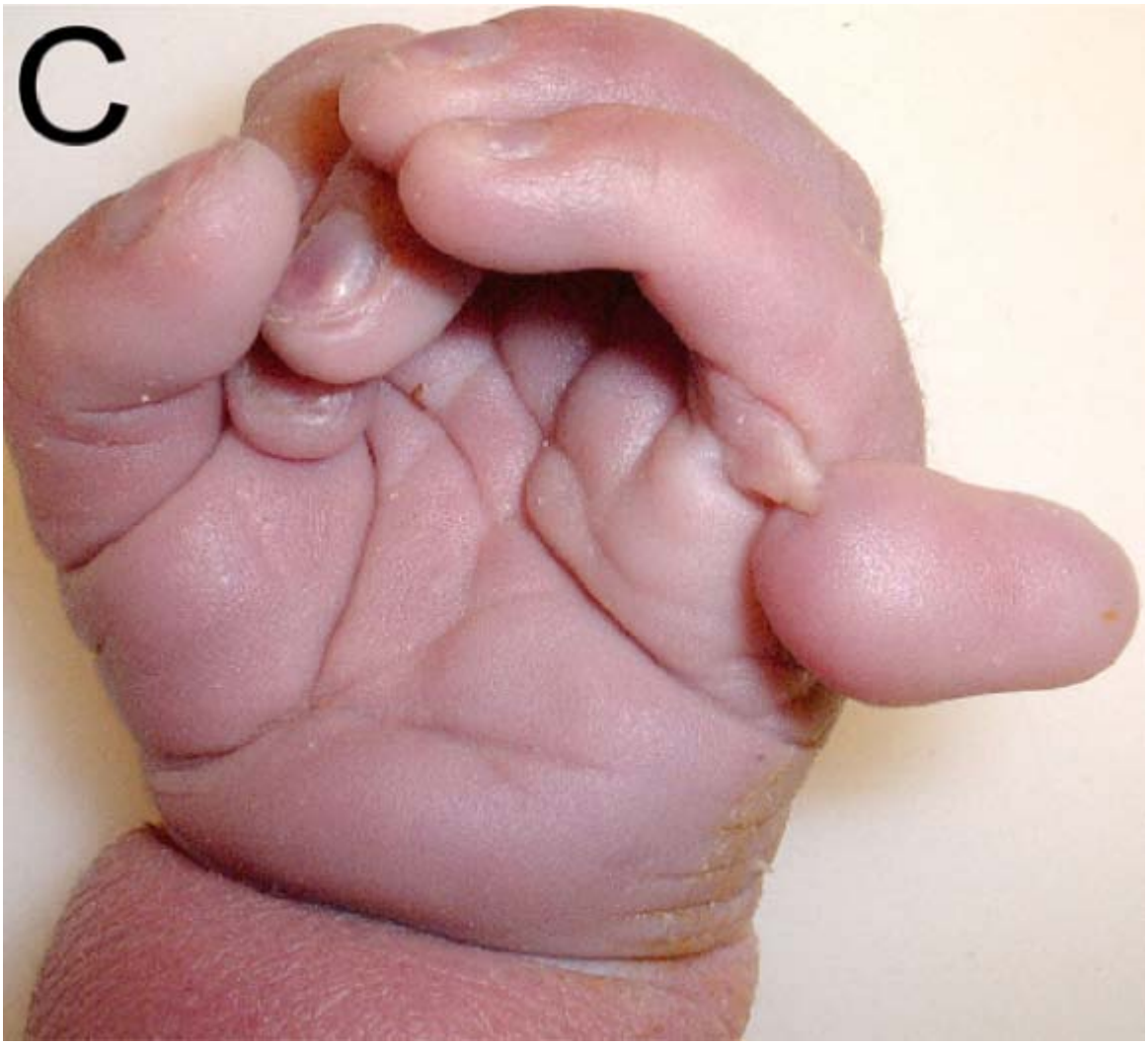
Most cases of Patau's syndrome result from trisomy 13, which means each cell in the body has three copies of chromosome 13 instead of the usual two copies. A small percentage of cases occur when only some of the body's cells have an extra copy, resulting in a mixed population of cells with a differing number of chromosomes; such cases are called mosaic Patau.

Patau syndrome can also occur when part of chromosome 13 becomes attached to another chromosome (translocated) before or at conception. Affected people have two copies of chromosome 13, plus extra material from chromosome 13 attached to another chromosome. With a translocation, the person has a partial trisomy for chromosome 13 and often the physical signs of the syndrome differ from the typical Patau syndrome.

Most cases of Patau syndrome are not inherited, but occur as random events during the formation of reproductive cells (eggs and sperm). An error in cell division called non-disjunction can result in reproductive cells with an abnormal number of chromosomes. For example, an egg or sperm cell may gain an extra copy of the chromosome. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra chromosome 13 in each of the body's cells. Mosaic Patau syndrome is also not inherited. It occurs as a random error during cell division early in fetal development.

Patau syndrome due to a translocation can be inherited. An unaffected person can carry a rearrangement of genetic material between chromosome 13 and another chromosome. This rearrangement is called a balanced translocation because there is no extra material from chromosome 13. Although they do not have signs of Patau syndrome, people who carry this type of balanced translocation are at an increased risk of having children with the condition.

Manifestations and physical findings



A 37 2/7 week gestational age male infant with Patau syndrome demonstrating polydactyly

Of those fetuses that do survive to gestation and subsequent birth, common abnormalites include:

- Nervous system
  - Mental and motor challenged
  - Microcephaly
  - Holoprosencephaly (failure of the forebrain to divide properly).
  - Structural eye defects, including microphthalmia, Peters anomaly, cataract, iris and/or fundus (coloboma), retinal dysplasia or retinal detachment, sensory nystagmus, cortical visual loss, and optic nerve hypoplasia
  - Meningomyelocele (a spinal defect)

- Musculoskeletal and cutaneous
    - Polydactyly (extra digits)
    - Low-set ears
    - Prominent heel
    - Deformed feet known as rocker-bottom feet
    - Omphalocele (abdominal defect)
    - Abnormal palm pattern
    - Overlapping of fingers over thumb
    - Cutis aplasia (missing portion of the skin/hair)
    - Cleft palate

- Urogenital
    - Abnormal genitalia
    - Kidney defects

- Other
    - Heart defects (ventricular septal defect)
    - Single umbilical artery

Recurrence risk

Unless one of the parents is a carrier of a translocation the chances of a couple having another trisomy 13 affected child is less than 1% (less than that of Down Syndrome).

History

Trisomy 13 was first observed by Thomas Bartholin in 1657, but the chromosomal nature of the disease was ascertained by Dr. Klaus Patau in 1960. The disease is named in his honor. Patau syndrome was also described in Pacific island tribes. These reports were thought to have been caused by radiation from atomic bomb tests. The tribes were temporarily moved before and during the test by an *x* amount of distance. They were then put back where they had been taken; all of this occurred before it was known how long, or even if, radiation still lingered on after a nuclear explosion.

In England and Wales during 2008–09 there were 172 diagnoses of Patau's syndrome (trisomy 13), with 91% of diagnoses made prenatally. There were 111 elective abortions, 14 stillbirth/miscarriage/fetal deaths, 30 outcomes unknown, and 17 live births. Approximately 4% of Patau's syndrome with unknown outcomes are likely to result in a live birth, therefore the total number of live births is estimated to be 18. The small percentage of babies with the full Patau's syndrome who survive birth and early infancy may live to adulthood, and children with mosaic or partial forms of this trisomy may have a completely different and much more hopeful prognosis.

Treatment

Medical management of children with Trisomy 13 is planned on a case-by-case basis and depends on the individual circumstances of the patient. Treatment of Patau syndrome focuses on the particular physical problems with which each child is born. Many infants have difficulty surviving the first few days or weeks due to severe neurological problems or complex heart defects. Surgery may be necessary to repair heart defects or cleft lip and cleft palate. Physical, occupational, and speech therapy will help individuals with Patau syndrome reach their full developmental potential.

Chapter 10

Canavan Disease

Canavan disease	
ICD-10	E75.2
ICD-9	330.0
OMIM	271900
DiseasesDB	29780
MedlinePlus	001586
MeSH	D017825

Canavan disease, also called **Canavan-Van Bogaert-Bertrand disease**, **aspartoacylase deficiency** or **aminoacylase 2 deficiency**, is an autosomal recessive degenerative disorder that causes progressive damage to nerve cells in the brain. Canavan disease is also one of the most common degenerative cerebreal diseases of infancy. This disease is one of a group of genetic disorders called leukodystrophies.

Leukodystrophies are characterized by degeneration of myelin in the phospholipid layer insulating the axon of a neuron. The gene associated with the disorder is located on human chromosome 17.

History

Canavan disease was first described in 1931 by Myrtelle Canavan.

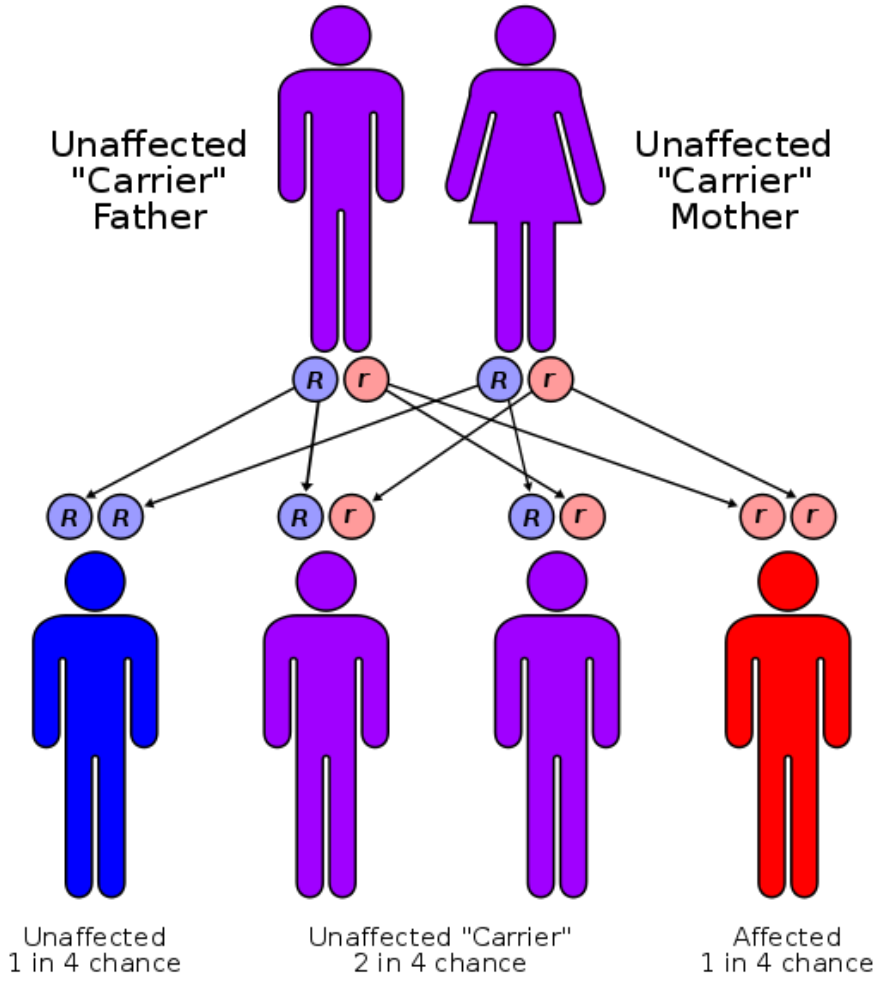
The discovery of the gene for Canavan disease, and subsequent events, generated considerable controversy. In 1987 the Greenbergs, a family with two children affected by Canavan disease, donated tissue samples to Dr Reuben Matalon, a researcher looking for the Canavan gene. He successfully identified the gene in 1993, and developed a test for it that would enable antenatal counselling of couples at risk of having a child with Canavan disease. For a while the Canavan Foundation offered free genetic testing with the test. However, in 1997, Dr Matalon's employer, the Miami Children's Hospital, patented the gene and started claiming royalties on the genetic test, forcing the Canavan Foundation to

withdraw their testing. A subsequent lawsuit brought by the Canavan Foundation against the Miami Children's Hospital was resolved with a sealed out-of-court settlement. The case is sometimes cited in arguments about the appropriateness of patenting genes.

Prevalence

Although Canavan disease may occur in any ethnic group, it affects persons of Eastern European Jewish ancestry more frequently. About 1/40 individuals of Eastern European (Ashkenazi) Jewish ancestry are carriers.

Pathophysiology



Canavan disease has an autosomal recessive pattern of inheritance

Canavan disease is inherited in an autosomal recessive fashion. When both parents are carriers, there is a 25% chance of having an affected child. Genetic counseling and genetic testing is recommended for families with two parental carriers.

Canavan disease is caused by a defective *ASPA* gene which is responsible for the production of the enzyme aspartoacylase. This enzyme breaks down the concentrated brain molecule *N*-acetyl aspartate. Decreased aspartoacylase activity prevents the normal breakdown of N-acetyl aspartate, and the lack of breakdown somehow interferes with growth of the myelin sheath of the nerve fibers in the brain. The myelin sheath is the fatty covering that surrounds nerve cells and acts as an insulator, which allows for efficient transmission of nerve impulses.

Symptoms

Symptoms of Canavan disease, which appear in early infancy and progress rapidly, may include mental retardation, loss of previously acquired motor skills, feeding difficulties, abnormal muscle tone (i.e., floppiness or stiffness), poor head control, and megalocephaly (abnormally enlarged head). Paralysis, blindness, or seizures may also occur.

Treatment

There is no cure for Canavan disease, nor is there a standard course of treatment. Treatment is symptomatic and supportive, but there is an experimental treatment using lithium citrate. When a person has Canavan Disease, his or her levels of N-acetyl aspartate are chronically elevated. The lithium citrate has proven that, in a rat genetic model of Canavan Disease, the lithium citrate significantly decreased the levels of N-acetyl aspartate. When tested on a human, the subject reversed during a two week wash-out period after withdrawal of lithium. The investigation reported that the N-acetyl aspartate levels decreased in regions of the brain tested and magnetic resonance spectroscopic values that are more characteristic of normal development and myelination. With this evidence it is suggested that a larger controlled trial of lithium may be warranted as supportive therapy for children with Canavan disease by significantly decreasing the elevated amounts of N-acetyl aspartate.

In addition, there are experimental trials of gene therapy. A healthy gene is cloned to take over for the defective one that causes Canavan disease.

Prognosis

Death usually occurs before age 4 without treatment. Some children may survive into their twenties via newer gene therapy treatments which have extended their life expectancy. In some cases, this helps to temporarily stop the progression of the disease.

Current research

Research involving triacetin supplementation has shown promise in a mouse model. Triacetin, which can be enzymatically cleaved to form acetate, enters the brain more readily than the negatively charged acetate.

A team of researchers headed by Paola Leone are currently at the University of Medicine and Dentistry of New Jersey, in Camden, New Jersey. The brain gene therapy is conducted at Cooper University Hospital. The procedure involves the insertion of six catheters into the brain that deliver a solution containing 600 billion to 900 billion engineered virus particles. The virus, a modified version of AAV, is designed to replace the aspartoacylase enzyme. Children treated with this procedure to date have shown marked improvements, including the growth of myelin with decreased levels of the n-acetyl-aspartate toxin.

Chapter 11

Color Blindness

Color blindness

An 1895 illustration of normal vision and various kinds of color blindness

ICD-10	H53.5
ICD-9	368.5
DiseasesDB	2999
MeSH	D003117

Color blindness or **color vision deficiency** is the decreased ability to perceive differences between some of the colors that others can distinguish. It is most often of genetic nature, but may also occur because of some eye, nerve, or brain damage, or exposure to certain chemicals. The English chemist John Dalton published the first scientific paper on this subject in 1798, "Extraordinary facts relating to the vision of colours", after the realization of his own color blindness. Because of Dalton's work, the condition was often called **daltonism**, although this term is now used for a type of color blindness called deuteranopia.

Color blindness is usually classed as a mild disability, but in certain situations, color blind individuals have an advantage over those with normal color vision. There are some studies which conclude that color blind individuals are better at penetrating certain color camouflages and it has been suggested that this may be the evolutionary explanation for the surprisingly high frequency of congenital red–green color blindness.

Background

The average human retina contains two kinds of light cells: the rod cells (active in low light) and the cone cells (active in normal daylight). Normally, there are three kinds of cones, each containing a different pigment, which are activated when the pigments absorb light. The spectral sensitivities of the cones differ; one is maximally sensitive to short wavelengths, one to medium wavelengths, and the third to long wavelengths, with their peak sensitivities in the blue, yellowish-green, and yellow regions of the spectrum, respectively. The absorption spectra of all three systems cover the visible spectrum. These receptors are often called S cones, M cones, and L cones, for short, medium, and long wavelength; but they are also often referred to as blue cones, green cones, and red cones, respectively.

Although these receptors are often referred to as "blue, green, and red" receptors, this terminology is not very accurate, especially as the "red" receptor actually has its peak sensitivity in the yellow region. The sensitivity of normal color vision actually depends on the overlap between the absorption spectra of the three systems: different colors are recognized when the different types of cone are stimulated to different degrees. Red light, for example, stimulates the long wavelength cones much more than either of the others, and reducing the wavelength causes the other two cone systems to be increasingly stimulated, causing a gradual change in hue.

Many of the genes involved in color vision are on the X chromosome, making color blindness more common in males than in females because males have only one X chromosome, while females have two. Because this is an X-linked trait about 1% of women have an 4th color cone and can be considered tetrachromats although it is not clear that this provides an advantage in color discrimination.

Classification

By cause

The colors of the rainbow as viewed by a person with no color vision deficiencies

The colors of the rainbow as viewed by a person with protanopia

The colors of the rainbow as viewed by a person with deuteranopia

The colors of the rainbow as viewed by a person with tritanopia

Color vision deficiencies can be classified as acquired or inherited.

- Acquired
- Inherited: There are three types of inherited or congenital color vision deficiencies: monochromacy, dichromacy, and anomalous trichromacy.

    - Monochromacy, also known as "total color blindness," is the lack of ability to distinguish colors; caused by cone defect or absence. Monochromacy occurs when two or all three of the cone pigments are missing and color and lightness vision is reduced to one dimension.

    - Rod monochromacy (achromatopsia) is an exceedingly rare, nonprogressive inability to distinguish any colors as a result of absent or nonfunctioning retinal cones. It is associated with light sensitivity (photophobia), involuntary eye oscillations (nystagmus), and poor vision.
    - Cone monochromacy is a rare total color blindness that is accompanied by relatively normal vision, electoretinogram, and electrooculogram.

    - Dichromacy is a moderately severe color vision defect in which one of the three basic color mechanisms is absent or not functioning. It is hereditary and, in the case of Protanopia or Deuteranopia, sex-linked, affecting predominantly males. Dichromacy occurs when one of the cone pigments is missing and color is reduced to two dimensions.

    - Protanopia is a severe type of color vision deficiency caused by the complete absence of red retinal photoreceptors. It is a form of dichromatism in which red appears dark. It is hereditary, sex-linked, and present in 1% of males.
    - Deuteranopia is a color vision deficiency in which the green retinal photoreceptors are absent, moderately affecting red–green hue discrimination. It is a form of dichromatism in which there are only two cone pigments present. It is likewise hereditary and sex-linked.
    - Tritanopia is a very rare color vision disturbance in which there are only two cone pigments present and a total absence of blue retinal receptors.

    - Anomalous trichromacy is a common type of inherited color vision deficiency, occurring when one of the three cone pigments is altered in its spectral sensitivity. This results in an impairment, rather than loss, of trichromacy (normal three-dimensional color vision).

    - Protanomaly is a mild color vision defect in which an altered spectral sensitivity of red retinal receptors (closer to green receptor response) results in poor red–green hue discrimination. It is hereditary, sex-linked, and present in 1% of males.
    - Deuteranomaly, caused by a similar shift in the green retinal receptors, is by far the most common type of color vision deficiency, mildly affecting red–green hue discrimination in 5% of males. It is hereditary and sex-linked.

- Tritanomaly is a rare, hereditary color vision deficiency affecting blue–yellow hue discrimination. Unlike most other forms, it is not sex-linked.

By clinical appearance

Based on clinical appearance, color blindness may be described as total or partial. Total color blindness is much less common than partial color blindness. There are two major types of color blindness: those who have difficulty distinguishing between red and green, and those who have difficulty distinguishing between blue and yellow.

- Total color blindness
- Partial color blindness
    - Red–green
    - Dichromacy (protanopia and deuteranopia)
    - Anomalous trichromacy (protanomaly and deuteranomaly)
    - Blue–yellow
    - Dichromacy (tritanopia)
    - Anomalous trichromacy (tritanomaly)

Causes

Evolutionary arguments

Any recessive genetic characteristic that persists at a level as high as 5% is generally regarded as possibly having some advantage over the long term. At one time the U.S. Army found that color blind people could spot "camouflage" colors that fooled those with normal color vision. Humans have a higher percentage of color blindness than macaque monkeys according to recent research.

Another possible advantage might result from the presence of a tetrachromic female. Owing to X-chromosome inactivation, females who are heterozygous for anomalous trichromacy ought to have at least four types of cone in their retinae. It is possible that this affords them an extra dimension of color vision, by analogy to New World monkeys where heterozygous females gain trichromacy in a basically dichromatic species.

Genetics

Color blindness can be inherited. It is most commonly inherited from mutations on the X chromosome but the mapping of the human genome has shown there are many causative mutations – mutations capable of causing color blindness originate from at least 19 different chromosomes and 56 different genes (as shown online at the Online Mendelian Inheritance in Man (OMIM) database at Johns Hopkins University).

Some of the inherited diseases known to cause color blindness are:

- cone dystrophy
- cone-rod dystrophy
- achromatopsia (aka rod monochromatism, aka stationary cone dystrophy, aka cone dysfunction syndrome)
- blue cone monochromatism,
- Leber's congenital amaurosis.
- retinitis pigmentosa (initially affects rods but can later progress to cones and therefore color blindness)

Inherited color blindness can be congenital (from birth), or it can commence in childhood or adulthood. Depending on the mutation, it can be stationary, that is, remain the same throughout a person's lifetime, or progressive. As progressive phenotypes involve deterioration of the retina and other parts of the eye, certain forms of color blindness can progress to legal blindness, i.e., an acuity of 6/60 or worse, and often leave a person with complete blindness.

Color blindness always pertains to the cone photoreceptors in retinas, as the cones are capable of detecting the color frequencies of light.

About 8 percent of males, but only 0.5 percent of females, are color blind in some way or another, whether it is one color, a color combination, or another mutation. The reason males are at a greater risk of inheriting an X linked mutation is because males only have one X chromosome (XY, with the Y chromosome being significantly shorter than the X chromosome), and females have two (XX); if a woman inherits a normal X chromosome in addition to the one which carries the mutation, she will not display the mutation. Men do not have a second X chromosome to override the chromosome which carries the mutation. If 5% of variants of a given gene are defective, the probability of a single copy being defective is 5%, but the probability that two copies are both defective is $0.05 \times 0.05 = 0.0025$, or just 0.25%.

Other causes

Other causes of color blindness include brain or retinal damage caused by shaken baby syndrome, accidents and other trauma which produce swelling of the brain in the occipital lobe, and damage to the retina caused by exposure to ultraviolet light. Most ultraviolet light damage is caused during childhood and this form of retinal degeneration is the leading cause of blindness in the world. Damage often presents itself later on in life.

Color blindness may also present itself in the spectrum of degenerative diseases of the eye, such as age-related macular degeneration, and as part of the retinal damage caused by diabetes.

Types

There are many types of color blindness. The most common are red–green hereditary photoreceptor disorders, but it is also possible to acquire color blindness through damage to the retina, optic nerve, or higher brain areas. Higher brain areas implicated in color processing include the parvocellular pathway of the lateral geniculate nucleus of the thalamus, and visual area V4 of the visual cortex. Acquired color blindness is generally unlike the more typical genetic disorders. For example, it is possible to acquire color blindness only in a portion of the visual field but maintain normal color vision elsewhere. Some forms of acquired color blindness are reversible. Transient color blindness also occurs (very rarely) in the aura of some migraine sufferers.

The different kinds of inherited color blindness result from partial or complete loss of function of one or more of the different cone systems. When one cone system is compromised, dichromacy results. The most frequent forms of human color blindness result from problems with either the middle or long wavelength sensitive cone systems, and involve difficulties in discriminating reds, yellows, and greens from one another. They are collectively referred to as "red–green color blindness", though the term is an over-simplification and is somewhat misleading. Other forms of color blindness are much more rare. They include problems in discriminating blues from yellows, and the rarest forms of all, complete color blindness or *monochromacy*, where one cannot distinguish any color from grey, as in a black-and-white movie or photograph.

Congenital

Congenital color vision deficiencies are subdivided based on the number of primary hues needed to match a given sample in the visible spectrum.

Monochromacy

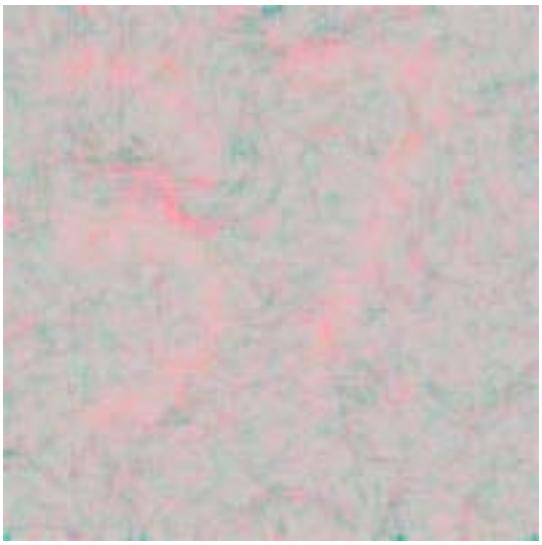
Monochromacy is the condition of possessing only a single channel for conveying information about color. Monochromats possess a complete inability to distinguish any colors and perceive only variations in brightness. It occurs in two primary forms:

1. **Rod monochromacy**, frequently called *achromatopsia*, where the retina contains no cone cells, so that in addition to the absence of color discrimination, vision in lights of normal intensity is difficult. While normally rare, achromatopsia is very common on the island of Pingelap, a part of the Pohnpei state, Federated States of Micronesia, where it is called *maskun*: about 10% of the population there has it, and 30% are unaffected carriers. The island was devastated by a storm in the 18th century, and one of the few male survivors carried a gene for achromatopsia; the population is now several thousand.
2. **Cone monochromacy** is the condition of having both rods and cones, but only a single kind of cone. A cone monochromat can have good pattern vision at normal daylight levels, but will not be able to distinguish hues. **Blue cone monochromacy (X chromosome)** is caused by a complete absence of L and M

cones (red and green). It is encoded at the same place as red–green color blindness on the X chromosome. Peak spectral sensitivities are in the blue region of the visible spectrum (near 440 nm). People with this condition generally show nystagmus ("jiggling eyes"), photophobia (light sensitivity), reduced visual acuity, and myopia (nearsightedness). Visual acuity usually falls to the 20/50 to 20/400 range.

Dichromacy

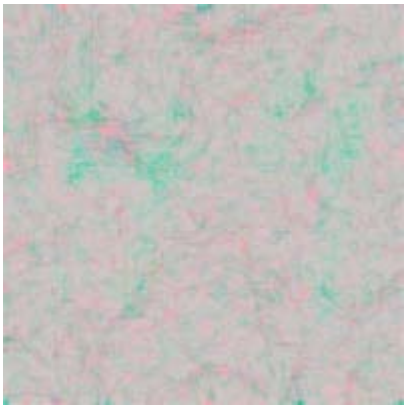
Protanopes, deuteranopes, and tritanopes are dichromats; that is, they can match any color they see with some mixture of just two spectral lights (whereas normally humans are trichromats and require three lights). These individuals normally know they have a color vision problem and it can affect their lives on a daily basis. Protanopes and deuteranopes see no perceptible difference between red, orange, yellow, and green. All these colors, that seem so different to the normal viewer, appear to be the same color for this two percent of the population. The terms protanopia, deuteranopia, and tritanopia come from Greek, and literally mean "inability to see (*anopia*) with the first (*prot-*), second (*deuter-*), or third (*trit-*) [cone]", respectively.



Test for protanopia
This image contains the number 37

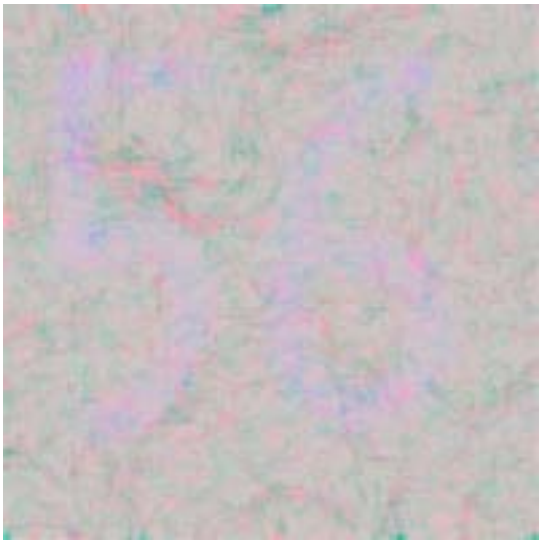
- **Protanopia** (1% of males): Lacking the long-wavelength sensitive retinal cones, those with this condition are unable to distinguish between colors in the green–yellow–red section of the spectrum. They have a neutral point at a greenish wavelength around 492 nm – that is, they cannot discriminate light of this wavelength from white. For the protanope, the brightness of red, orange, and yellow are much reduced compared to normal. This dimming can be so pronounced that reds may be confused with black or dark gray, and red traffic lights may appear to be extinguished. They may learn to distinguish reds from yellows and from greens primarily on the basis of their apparent brightness or

lightness, not on any perceptible hue difference. Violet, lavender, and purple are indistinguishable from various shades of blue because their reddish components are so dimmed as to be invisible. E.g., pink flowers, reflecting both red light and blue light, may appear just blue to the protanope. Very few people have been found who have one normal eye and one protanopic eye. These *unilateral dichromats* report that with only their protanopic eye open, they see wavelengths below the neutral point as blue and those above it as yellow. This is a rare form of color blindness.



Test for deuteranopia
This image shows a number 49, but someone who is deuteranopic may not be able to see it.

- **Deuteranopia** (1% of males): Lacking the medium-wavelength cones, those affected are again unable to distinguish between colors in the green–yellow–red section of the spectrum. Their neutral point is at a slightly longer wavelength, 498 nm. The deuteranope suffers the same hue discrimination problems as the protanope, but without the abnormal dimming. Similarly, violet, lavender, purple, and blue, seem to be too many names to use logically for hues that all look alike to him. This is one of the rarer forms of colorblindness making up about 1% of the male population, also known as *Daltonism* after John Dalton. (Dalton's diagnosis was confirmed as deuteranopia in 1995, some 150 years after his death, by DNA analysis of his preserved eyeball.) Deuteranopic unilateral dichromats report that with only their deuteranopic eye open, they see wavelengths below the neutral point as blue and those above it as yellow.



Test for tritanopia
This image shows the number 56, but someone who is tritanopic may not be able to see it.

- **Tritanopia** (less than 1% of males and females): Lacking the short-wavelength cones, those affected are unable to distinguish colors along the blue–yellow dimension. This form of color blindness is not sex-linked.

Anomalous trichromacy

Those with protanomaly, deuteranomaly, or tritanomaly are trichromats, but the color matches they make differ from the normal. They are called anomalous trichromats. In order to match a given spectral yellow light, protanomalous observers need more red light in a red/green mixture than a normal observer, and deuteranomalous observers need more green. From a practical standpoint though, many protanomalous and deuteranomalous people have very little difficulty carrying out tasks that require normal color vision. Some may not even be aware that their color perception is in any way different from normal.

Protanomaly and deuteranomaly can be diagnosed using an instrument called an anomaloscope, which mixes spectral red and green lights in variable proportions, for comparison with a fixed spectral yellow. If this is done in front of a large audience of males, as the proportion of red is increased from a low value, first a small proportion of the audience will declare a match, while most will see the mixed light as greenish; these are the deuteranomalous observers. Next, as more red is added the majority will say that a match has been achieved. Finally, as yet more red is added, the remaining, protanomalous, observers will declare a match at a point where normal observers will see the mixed light as definitely reddish.

- **Protanomaly** (1% of males, 0.01% of females): Having a mutated form of the long-wavelength (red) pigment, whose peak sensitivity is at a shorter wavelength than in the normal retina, protanomalous individuals are less sensitive to red light

than normal. This means that they are less able to discriminate colors, and they do not see mixed lights as having the same colors as normal observers. They also suffer from a darkening of the red end of the spectrum. This causes reds to reduce in intensity to the point where they can be mistaken for black. Protanomaly is a fairly rare form of color blindness, making up about 1% of the male population. Both protanomaly and deuteranomaly are carried on the X chromosome.

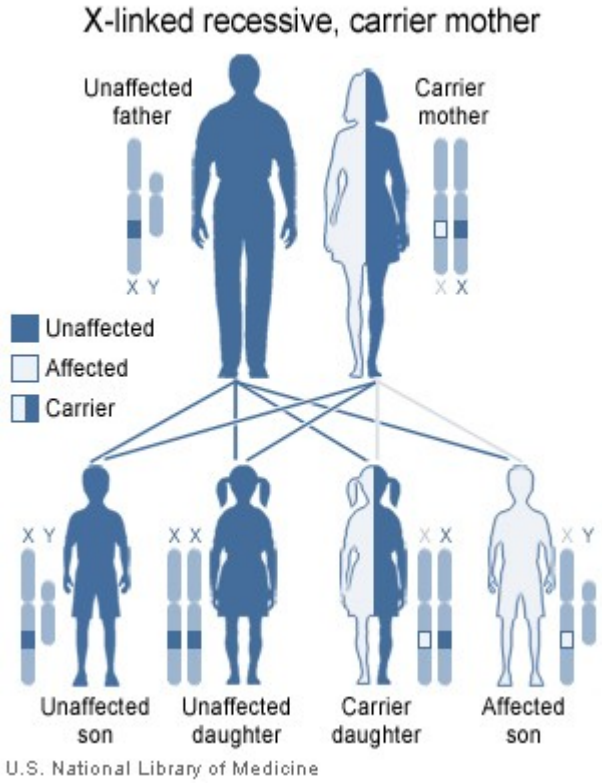
- **Deuteranomaly** (most common — 6% of males, 0.4% of females): Having a mutated form of the medium-wavelength (green) pigment. The medium-wavelength pigment is shifted towards the red end of the spectrum resulting in a reduction in sensitivity to the green area of the spectrum. Unlike protanomaly the intensity of colors is unchanged. This is the most common form of color blindness, making up about 6% of the male population. The deuteranomalous person is considered "green weak". For example, in the evening, dark green cars appear to be black to Deuteranomalous people. Similar to the protanomates, deuteranomates are poor at discriminating small differences in hues in the red, orange, yellow, green region of the spectrum. They make errors in the naming of hues in this region because the hues appear somewhat shifted towards red. One very important difference between deuteranomalous individuals and protanomalous individuals is deuteranomalous individuals do *not* have the loss of "brightness" problem.
- **Tritanomaly** (equally rare for males and females [0.01% for both]): Having a mutated form of the short-wavelength (blue) pigment. The short-wavelength pigment is shifted towards the green area of the spectrum. This is the rarest form of anomalous trichromacy color blindness. Unlike the other anomalous trichromacy color deficiencies, the mutation for this color blindness is carried on chromosome 7. Therefore it is equally prevalent in both male & female populations. The OMIM gene code for this mutation is 304000 “Colorblindness, Partial Tritanomaly”.

Total color blindness

Achromatopsia is strictly defined as the inability to see color. Although the term may refer to acquired disorders such as color agnosia and cerebral achromatopsia, it typically refers to congenital color vision disorders (i.e. more frequently rod monochromacy and less frequently cone monochromacy).

In color agnosia and cerebral achromatopsia, a person cannot perceive colors even though the eyes are capable of distinguishing them. Some sources do not consider these to be true color blindness, because the failure is of perception, not of vision. They are forms of visual agnosia.

Red–green color blindness



X-linked recessive inheritance

Those with protanopia, deuteranopia, protanomaly, and deuteranomaly have difficulty with discriminating red and green hues. It is sex-linked: genetic red–green color blindness affects males much more often than females, because the genes for the red and green color receptors are located on the X chromosome, of which males have only one and females have two. Females (46, XX) are red–green color blind only if *both* their X chromosomes are defective with a similar deficiency, whereas males (46, XY) are color blind if their single X chromosome is defective.

The gene for red–green color blindness is transmitted from a color blind male to all his daughters who are heterozygote carriers and are usually unaffected. In turn, a carrier woman has a fifty percent chance of passing on a mutated X chromosome region to each of her male offspring. The sons of an affected male will not inherit the trait from him, since they receive his Y chromosome and not his (defective) X chromosome. Should an affected male have children with a carrier or colorblind woman, their daughters may be colorblind by inheriting an affected X chromosome from each parent.

Because one X chromosome is inactivated at random in each cell during a woman's development, it is possible for her to have four different cone types, as when a carrier of protanomaly has a child with a deuteranomalic man. Denoting the normal vision alleles by P and D and the anomalous by p and d, the carrier is PD pD and the man is Pd. The daughter is either PD Pd or pD Pd. Suppose she is pD Pd. Each cell in her body expresses

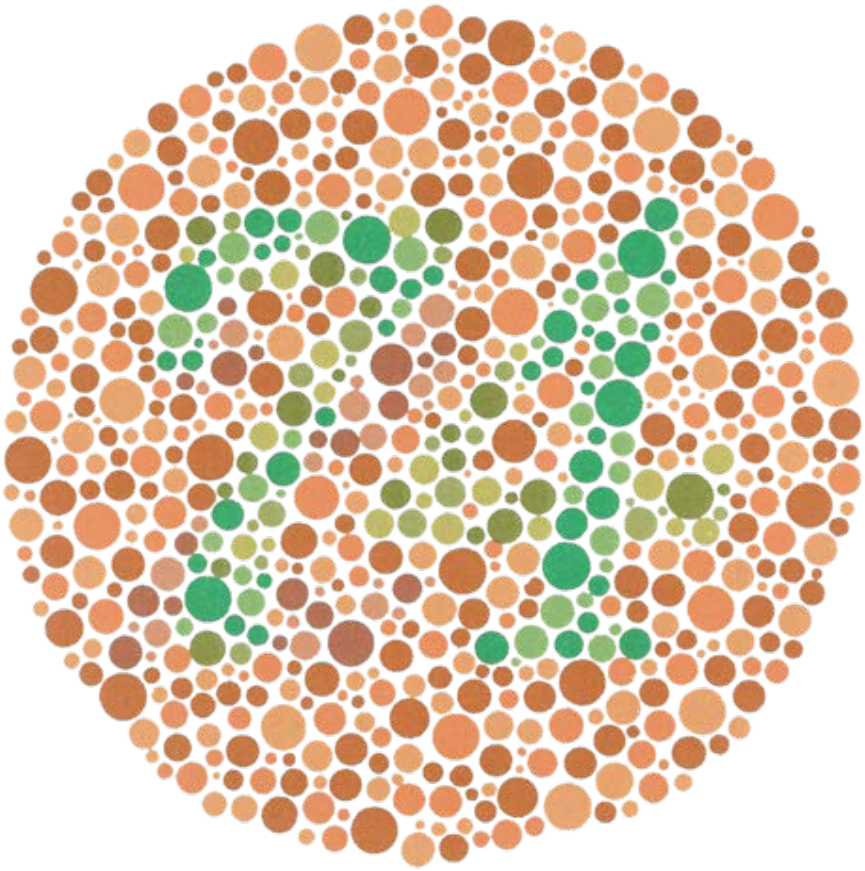
either her mother's chromosome pD or her father's Pd. Thus her red–green sensing will involve both the normal and the anomalous pigments for both colors. Such females are tetrachromats, since they require a mixture of four spectral lights to match an arbitrary light.

Blue–yellow color blindness

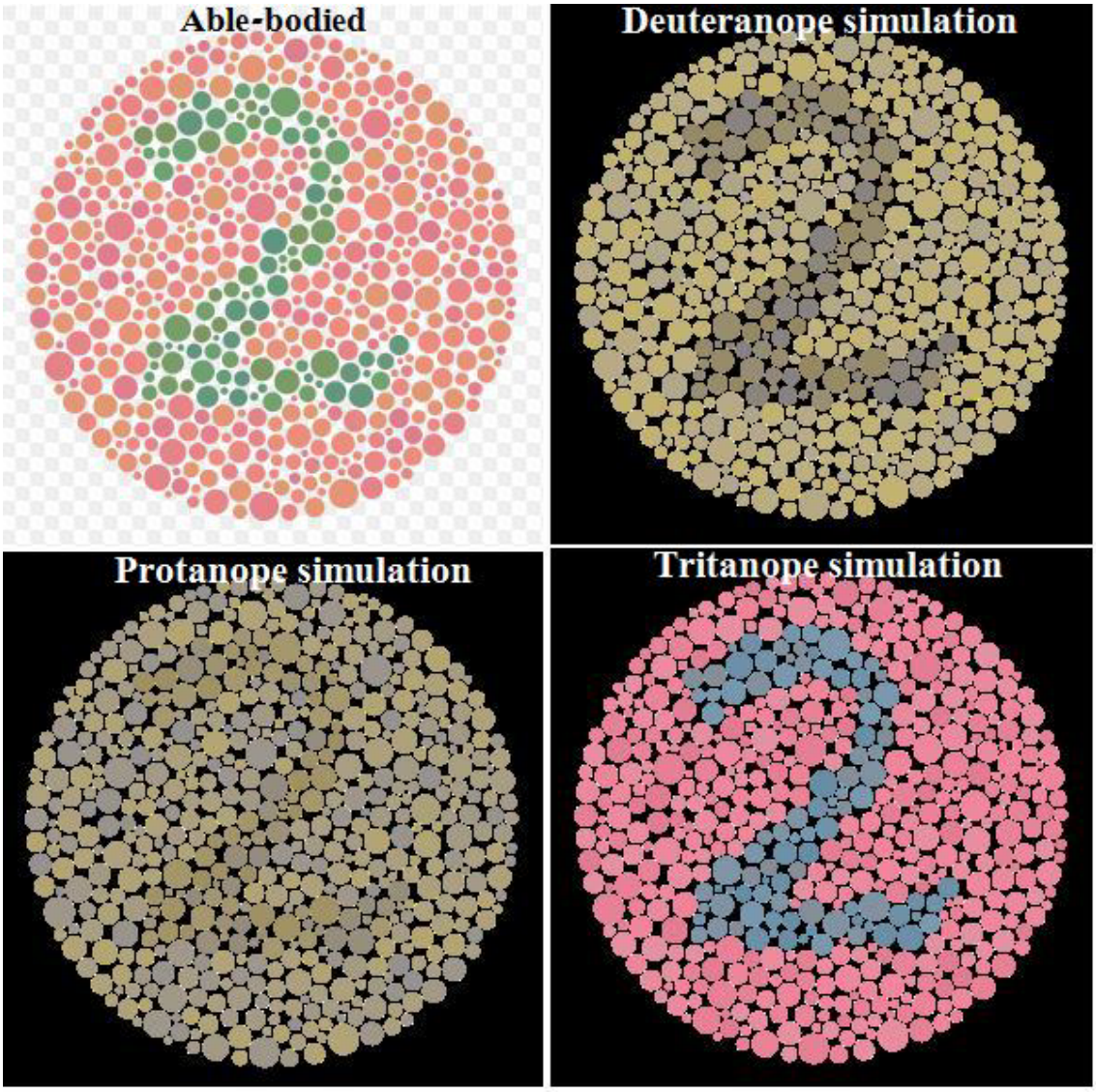
Those with tritanopia and tritanomaly have difficulty discriminating blueish versus yellowish hues.

Color blindness involving the inactivation of the short-wavelength sensitive cone system (whose absorption spectrum peaks in the bluish-violet) is called **tritanopia** or, loosely, blue–yellow color blindness. The tritanopes neutral point occurs near a yellowish 570 nm; green is perceived at shorter wavelengths and red at longer wavelengths. Mutation of the short-wavelength sensitive cones is called **tritanomaly**. Tritanopia is equally distributed among males and females. Jeremy H. Nathans (with the Howard Hughes Medical Institute) proved that the gene coding for the blue receptor lies on chromosome 7, which is shared equally by males and females. Therefore it is not sex-linked. This gene does not have any neighbor whose DNA sequence is similar. Blue color blindness is caused by a simple mutation in this gene.

Diagnosis



Example of an Ishihara color test plate. The numeral "74" should be clearly visible to viewers with normal color vision. Viewers with dichromacy or anomalous trichromacy may read it as "21", and viewers with achromatopsia may not see numbers.



An Ishihara test image as seen by subjects with normal color vision and by those with a variety of color deficiencies

The Ishihara color test, which consists of a series of pictures of colored spots, is the test most often used to diagnose red–green color deficiencies. A figure (usually one or more Arabic digits) is embedded in the picture as a number of spots in a slightly different color, and can be seen with normal color vision, but not with a particular color defect. The full set of tests has a variety of figure/background color combinations, and enable diagnosis of which particular visual defect is present. The anomaloscope, described above, is also used in diagnosing anomalous trichromacy.

Because the Ishihara color test contains only numerals, it may not be useful in diagnosing young children, who have not yet learned to use numerals. In the interest of identifying these problems early on in life, alternative color vision tests were developed using only symbols (square, circle, car).

Besides the Ishihara color test, the US Navy and US Army also allow testing with the Farnsworth Lantern Test. This test allows 30% of color deficient individuals, whose deficiency is not too severe, to pass.

Most clinical tests are designed to be fast, simple, and effective at identifying broad categories of color blindness. In academic studies of color blindness, on the other hand, there is more interest in developing flexible tests to collect thorough datasets, identify copunctal points, and measure just noticeable differences.

Management

There is generally no treatment to cure color deficiencies. However, certain types of tinted filters and contact lenses may help an individual to better distinguish different colors. Optometrists can supply a singular red-tint contact lens to wear on the non-dominant eye. This may enable the wearer to pass some color blindness tests, but they have little practical use. The effect of wearing such a device is akin to wearing red/blue 3D glasses and can take some time getting used to as certain wavelengths can "jump" out and be overly represented. Additionally, computer software and cybernetic devices have been developed to assist those with visual color difficulties such as an eyeborg, a "cybernetic eye" that allows individuals with color blindness to hear sounds representing colors.

The GNOME desktop environment provides colorblind accessibility using the gnome-mag and the libcolorblind software. Using a gnome applet, the user may switch a color filter on and off choosing from a set of possible color transformations that will displace the colors in order to disambiguate them. The software enables, for instance, a color blind person to see the numbers in the Ishihara test.

In September 2009, the journal Nature reported that researchers at the University of Washington and University of Florida were able to give trichromatic vision to squirrel monkeys, which normally have only dichromatic vision, using gene therapy.

Epidemiology

Color blindness affects a significant number of people, although exact proportions vary among groups. In Australia, for example, it occurs in about 8 percent of males and only about 0.4 percent of females. Isolated communities with a restricted gene pool sometimes produce high proportions of color blindness, including the less usual types. Examples include rural Finland, Hungary, and some of the Scottish islands. In the United States, about 7 percent of the male population – or about 10.5 million men – and 0.4 percent of the female population either cannot distinguish red from green, or see red and green differently from how others do (Howard Hughes Medical Institute, 2006). It has been found that more than 95 percent of all variations in human color vision involve the red and green receptors in male eyes. It is very rare for males or females to be "blind" to the blue end of the spectrum.

Prevalence of color blindness

	Males	Females	Total	References
Overall	—	—	—	
Overall (United States)	—	—	—	
Red–green (Overall)	7 to 10%	—	—	
Red–green (Caucasians)	8%	—	—	
Red–green (Asians)	5%	—	—	
Red–green (Africans)	4%	—	—	
Monochromacy	—	—	—	
Rod monochromacy (dysfunctional, abnormally shaped or no cones)	0.00001%	0.00001%	—	
Dichromacy	2.4%	0.03%	1.30%	
Protanopia (red deficient: L cone absent)	1% to 1.3%	0.02%	—	
Deuteranopia (green deficient: M cone absent)	1% to 1.2%	0.01%	—	
Tritanopia (blue deficient: S cone absent)	0.001%	0.03%	—	
Anomalous Trichromacy	6.3%	0.37%	—	
Protanomaly (red deficient: L cone defect)	1.3%	0.02%	—	
Deuteranomaly (green deficient: M cone defect)	5.0%	0.35%	—	
Tritanomaly (blue deficient: S cone defect)	0.01%	0.01%	—	

Society and culture

Design implications of color blindness

Color codes present particular problems for those with color deficiences as they are often difficult or impossible for them to perceive.

Good graphic design avoids using color coding or using color contrasts alone to express information; this not only helps color blind people, but also aids understanding by normally sighted people.

Designers need to take into account that color-blindness is highly sensitive to differences in material. For example, a red–green colorblind person who is incapable of distinguishing colors on a map printed on paper may have no such difficulty when viewing the map on a computer screen or television. In addition, some color blind people find it easier to distinguish problem colors on artificial materials, such as plastic or in acrylic paints, than on natural materials, such as paper or wood. Third, for some color blind people, color can only be distinguished if there is a sufficient "mass" of color: thin

lines might appear black while a thicker line of the same color can be perceived as having color.

When the need to process visual information as rapidly as possible arises, for example in an emergency situation, the visual system may operate only in shades of gray, with the extra information load in adding color being dropped. This is an important possibility to consider when designing, for example, emergency brake handles or emergency phones.

Occupations

Color blindness may make it difficult or impossible for a person to engage in certain occupations. Persons with color blindness may be legally or practically barred from occupations in which color perception is an essential part of the job (*e.g.,* mixing paint colors), or in which color perception is important for safety (*e.g.,* operating vehicles in response to color-coded signals). This occupational safety principle originates from the Lagerlunda train crash of 1875 in Sweden. Following the crash, Professor Alarik Frithiof Holmgren, a physiologist, investigated and concluded that the color blindness of the engineer (who had died) had caused the crash. Professor Holmgren then created the first test using different-colored skeins to exclude people from jobs in the transportation industry on the basis of color blindness.

Driving motor vehicles

Some countries (e.g. Bulgaria, Romania and Turkey) have refused to grant individuals with color blindness driving licenses. In Romania, there is an ongoing campaign to remove the legal restrictions that prohibit colorblind citizens from getting drivers' licenses.

The usual justification for such restrictions is that drivers of motor vehicles must be able to recognize color-coded signals, such as traffic lights or warning lights.

Piloting aircraft

While many aspects of aviation depend on color coding, only a few of them are critical enough to be interfered with by some milder types of color blindness. Some examples include color-gun signaling of aircraft that have lost radio communication, color-coded glide-path indications on runways, and the like. Some jurisdictions restrict the issuance of pilot credentials to persons who suffer from color blindness for this reason. Restrictions may be partial, allowing color-blind persons to obtain certification but with restrictions, or total, in which case color-blind persons are not permitted to obtain piloting credentials at all.

In the United States, the Federal Aviation Administration requires that pilots be tested for normal color vision as part of the medical certification that is prerequisite to obtaining a pilot's license. If testing reveals color blindness, the applicant may be issued a license with restrictions, such as no night flying and no flying by color signals—such a

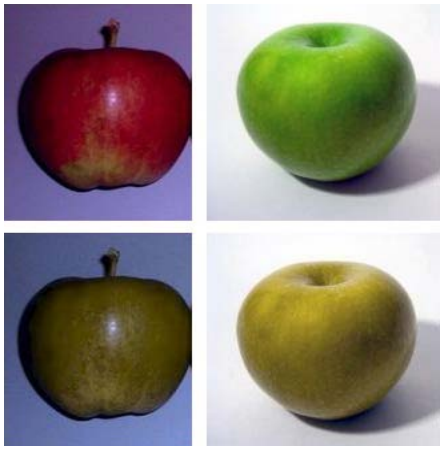
restriction effectively prevents a pilot from working for an airline. The government allows several types of tests, including medical standard tests (*e.g.,* the Ishihara, Dvorine, and others) and specialized tests oriented specifically to the needs of aviation. If an applicant fails the standard tests, he or she will receive a restriction on their medical certificate that states- "Not valid for night flying or by color signal control." He/she may apply to the FAA to take a specialized test, administered by the FAA. Typically, this test is the "color vision light gun test." For this test an FAA inspector will meet the pilot at an airport with an operating control tower, and the color signal light gun will be shone at the pilot from the tower, and he or she must identify the color. If he passes, he may be issued a waiver, which states that the color vision test is no longer required during medical examinations. He will then receive a new medical certificate with the restriction removed. This was once a Statement of Demonstrated Ability (SODA), but the SODA was dropped, and converted to a simple waiver (letter) early in the 2000s.

Research published in 2009 carried out by the City University of London's Applied Vision Research Centre, sponsored by the UK's Civil Aviation Authority and the US Federal Aviation Administration, has established a more accurate assessment of colour deficiencies in pilot applicants' red–green and yellow–blue colour range which could lead to a 35% reduction in the number of prospective pilots who fail to meet the minimum medical threshold.

Art

Inability to distinguish color does not necessarily preclude the ability to become a celebrated artist. The expressionist painter Clifton Pugh, three-time winner of Australia's Archibald Prize, on biographical, gene inheritance and other grounds has been identified as a protanope. Nineteenth century French artist Charles Méryon became successful by concentrating on etching rather than painting after he was diagnosed as having a red–green deficiency.

Misconceptions and compensations



Simulation of the normal (above) and dichromatic (below) perception of red and green apples.

Color blindness is not the swapping of colors by the observer — grass is never red, and stop signs are never green. The color impaired do not learn to call red "green" and vice versa. However, dichromats often confuse red and green items. For example, they may find it difficult to distinguish a Braeburn apple from a Granny Smith and in some cases, the red and green of a traffic light without other clues (e.g., shape or location). The vision of dichromats may also be compared to images produced by a color printer that has run out of the ink in one of its three color cartridges (for protanopes and deuteranopes, the red cartridge, and for tritanopes, the yellow cartridge).

Dichromats tend to learn to use texture and shape clues and so are often able to penetrate camouflage that has been designed to deceive individuals with color-normal vision.

Traffic light colors are confusing to some dichromats as there is insufficient apparent difference between the red/amber traffic lights, and that of sodium street lamps; also the green can be confused with a grubby white lamp. This is a risk factor on high-speed undulating roads where angular cues can't be used. British Rail color lamp signals use more easily identifiable colors: the red is really blood red, the amber is quite yellow and the green is a bluish color. Most British road traffic lights are mounted vertically on a black rectangle with a white border (forming a "sighting board") and so dichromats simply look for the position of the light within the rectangle — top, middle or bottom. In the Eastern provinces of Canada horizontally-mounted traffic lights are generally differentiated by shape to facilitate identification for those with color blindness.

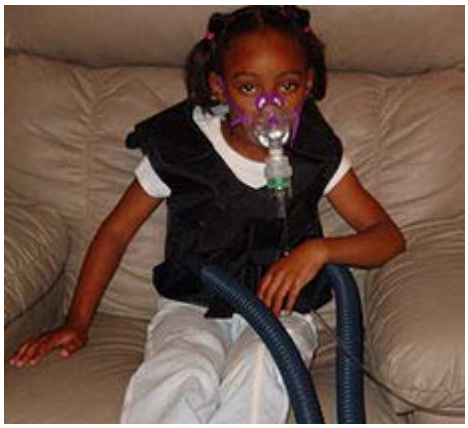
Horizontal traffic light in Halifax, NS Canada

Color blindness very rarely means complete monochromatism. In almost all cases, color blind people retain blue–yellow discrimination, and most color-blind individuals are anomalous trichromats rather than complete dichromats. In practice this means that they often retain a limited discrimination along the red–green axis of color space, although their ability to separate colors in this dimension is severely reduced.

Chapter 12

Cystic Fibrosis

Cystic fibrosis



A breathing treatment for cystic fibrosis, using a mask nebuliser and a ThAIRapy Vest

ICD-10	E84.
ICD-9	277.0
OMIM	219700
DiseasesDB	3347
MedlinePlus	000107
eMedicine	ped/535
MeSH	D003550

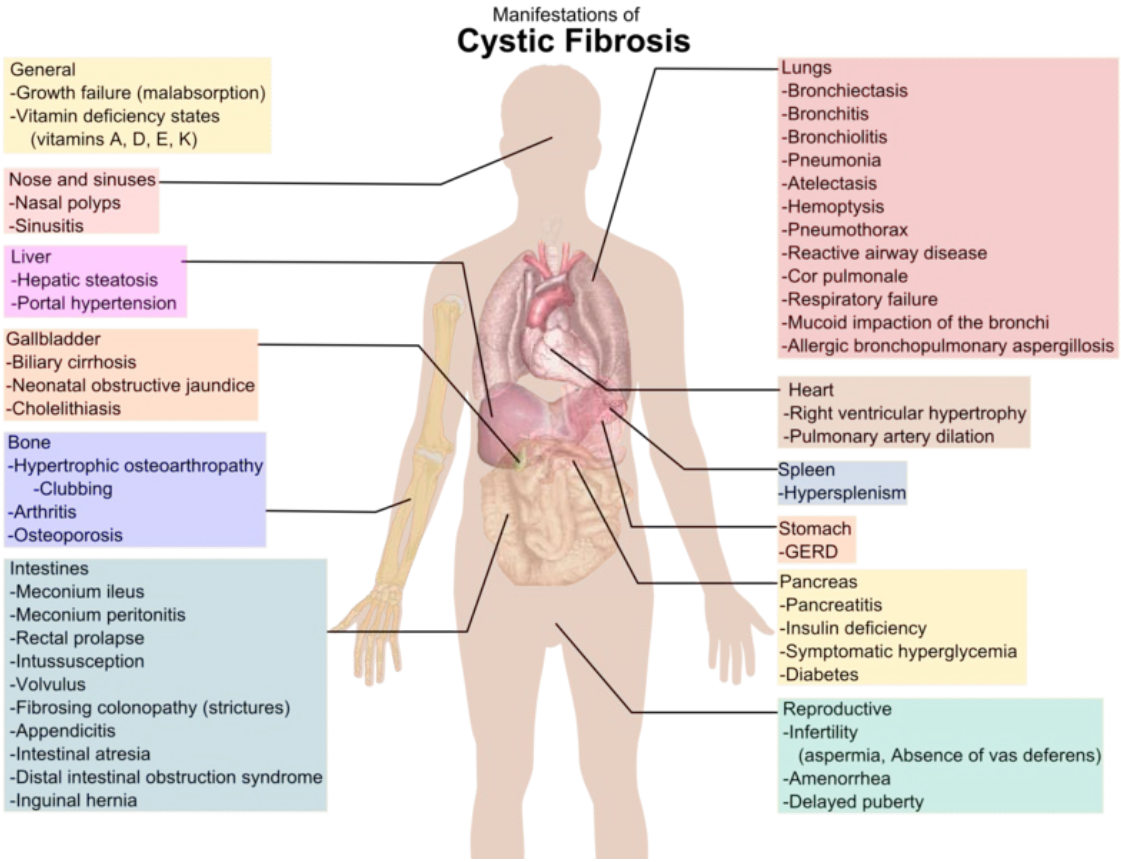
Cystic fibrosis (also known as **CF** or **mucoviscidosis**) is a common recessive genetic disease which affects the entire body, causing progressive disability and often early death. The name *cystic fibrosis* refers to the characteristic scarring (fibrosis) and cyst formation within the pancreas, first recognized in the 1930s. Difficulty breathing is the most serious symptom and results from frequent lung infections that are treated with, though not cured by, antibiotics and other medications. A multitude of other symptoms,

including sinus infections, poor growth, diarrhea, and infertility result from the effects of CF on other parts of the body.

CF is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). This gene is required to regulate the components of sweat, digestive juices, and mucus. Although most people without CF have two working copies of the CFTR gene, only one is needed to prevent cystic fibrosis. CF develops when neither gene works normally. Therefore, CF is considered an autosomal recessive disease.

CF is most common among Caucasians; one in 25 people of European descent carry one gene for CF. Approximately 30,000 Americans have CF, making it one of the most common life-shortening inherited diseases. Individuals with cystic fibrosis can be diagnosed before birth by genetic testing, or by a sweat test in early childhood. Ultimately, lung transplantation is often necessary as CF worsens.

Signs and symptoms



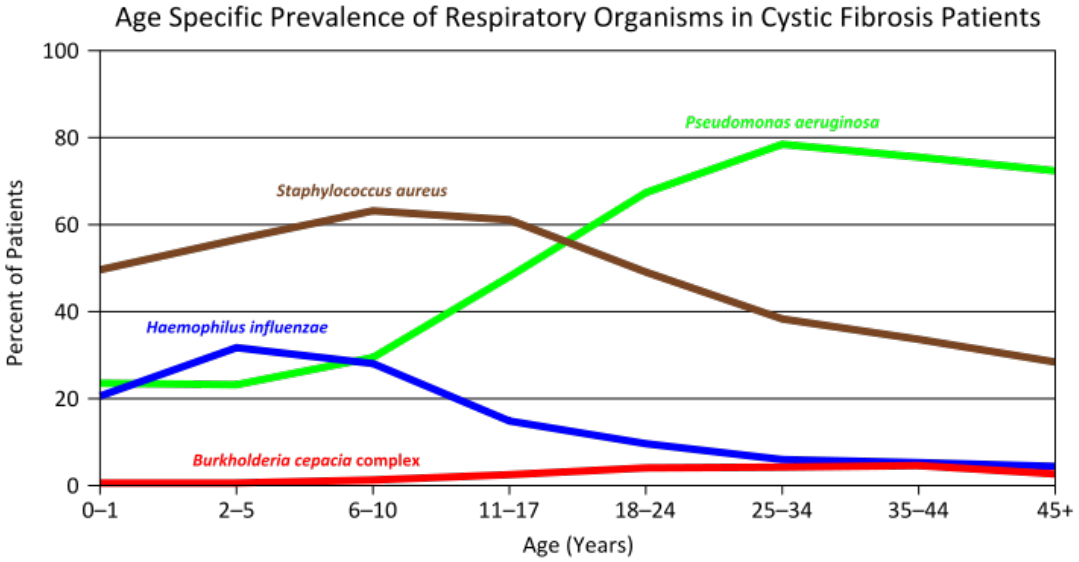
A diagram showing clinical manifestations of cystic fibrosis

The hallmark symptoms of cystic fibrosis are salty tasting skin, poor growth and poor weight gain despite a normal food intake, accumulation of thick, sticky mucus, frequent chest infections and coughing or shortness of breath. Males can be infertile due to

congenital absence of the vas deferens. Symptoms often appear in infancy and childhood, such as bowel obstruction due to meconium ileus in newborn babies. As the child grows, he or she will need to exercise to release mucus in the alveoli. Ciliated epithelial cells in the patient have a mutated protein that leads to abnormally viscous mucus production. The poor growth in children typically presents as an inability to gain weight or height at the same rate as their peers and is occasionally not diagnosed until investigation is initiated for poor growth. The causes of growth failure are multi-factorial and include chronic lung infection, poor absorption of nutrients through the gastrointestinal tract, and increased metabolic demand due to chronic illness.

In rare cases, cystic fibrosis can manifest itself as a coagulation disorder. Young children are especially sensitive to vitamin K malabsorptive disorders because only a very small amount of vitamin K crosses the placenta, leaving the child with very low reserves. Because factors II, VII, IX, and X (clotting factors) are vitamin K–dependent, low levels of vitamin K can result in coagulation problems. Consequently, when a child presents with unexplained bruising, a coagulation evaluation may be warranted to determine whether there is an underlying disease.

Lung and sinus



Respiratory infections in CF patients varies according to age

Green = *Pseudomonas aeruginosa*
Brown = *Staphylococcus aureus*
Blue = *Haemophilus influenzae*
Red = *Burkholderia cepacia* complex

Lung disease results from clogging of the airways due to mucus build-up, decreased mucociliary clearance and resulting inflammation. Inflammation and infection will cause injury and structural changes to the lungs, leading to a variety of symptoms. In the early

stages, incessant coughing, copious phlegm production, and decreased ability to exercise are common. Many of these symptoms occur when bacteria that normally inhabit the thick mucus grow out of control and cause pneumonia. In later stages, changes in the architecture of the lung such as pathology in the major airways (bronchiectasis) further exacerbate difficulties in breathing. Other symptoms include coughing up blood (hemoptysis), high blood pressure in the lung (pulmonary hypertension), heart failure, difficulties getting enough oxygen to the body (hypoxia), and respiratory failure requiring support with breathing masks such as bilevel positive airway pressure machines or ventilators. *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* are the three most common organisms causing lung infections in CF patients. In addition to typical bacterial infections, people with CF more commonly develop other types of lung disease. Among these is allergic bronchopulmonary aspergillosis, in which the body's response to the common fungus *Aspergillus fumigatus* causes worsening of breathing problems. Another is infection with *Mycobacterium avium* complex (MAC), a group of bacteria related to tuberculosis, which can cause a lot of lung damage and does not respond to common antibiotics.

Mucus in the paranasal sinuses is equally thick and may also cause blockage of the sinus passages, leading to infection. This may cause facial pain, fever, nasal drainage, and headaches. Individuals with CF may develop overgrowth of the nasal tissue (nasal polyps) due to inflammation from chronic sinus infections. Recurrent sinonasal polyps can occur in as many as 10% to 25% of CF patients. These polyps can block the nasal passages and increase breathing difficulties.

Cardiorespiratory complications are the most common cause of death (~80%) in patients followed by most CF centers in the United States.

Gastrointestinal

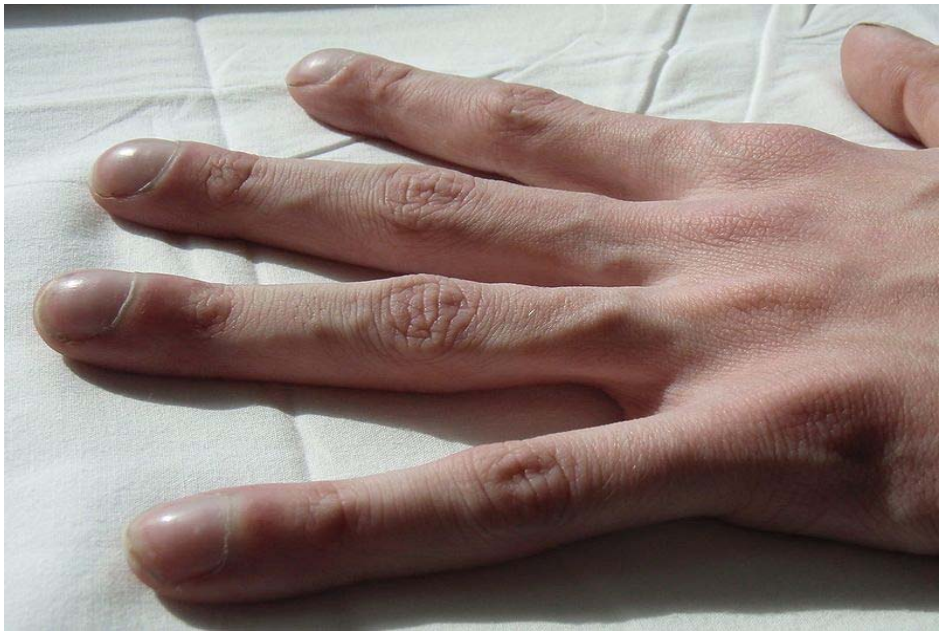
Prior to prenatal and newborn screening, cystic fibrosis was often diagnosed when a newborn infant failed to pass faeces (meconium). Meconium may completely block the intestines and cause serious illness. This condition, called meconium ileus, occurs in 5–10% of newborns with CF. In addition, protrusion of internal rectal membranes (rectal prolapse) is more common, occurring in as many as 10% of children with CF, and it is caused by increased fecal volume, malnutrition, and increased intra–abdominal pressure due to coughing.

The thick mucus seen in the lungs has a counterpart in thickened secretions from the pancreas, an organ responsible for providing digestive juices which help break down food. These secretions block the exocrine movement of the digestive enzymes into the duodenum and result in irreversible damage to the pancreas, often with painful inflammation (pancreatitis). The pancreatic ducts are totally plugged in more advanced cases, usually seen in older children or adolescents. This causes atrophy of the exocrine glands and progressive fibrosis. The lack of digestive enzymes leads to difficulty absorbing nutrients with their subsequent excretion in the feces, a disorder known as malabsorption. Malabsorption leads to malnutrition and poor growth and development

because of calorie loss. Resultant hypoproteinemia may be severe enough to cause generalized edema. Individuals with CF also have difficulties absorbing the fat-soluble vitamins A, D, E, and K. In addition to the pancreas problems, people with cystic fibrosis experience more heartburn, intestinal blockage by intussusception, and constipation. Older individuals with CF may develop distal intestinal obstruction syndrome when thickened feces cause intestinal blockage. Exocrine pancreatic insufficiency occurs in the majority (85% to 90%) of patients with CF. It is mainly associated with "severe" CFTR mutations, where both alleles are completely nonfunctional (e.g. ΔF508/ΔF508). It occurs in 10% to 15% of patients with one "severe" and one "mild" CFTR mutation where there still is a little CFTR activity, or where there are two "mild" CFTR mutations. In these milder cases, there is still sufficient pancreatic exocrine function so that enzyme supplementation is not required. There are usually no other GI complications in pancreas-sufficient phenotypes, and in general, such individuals usually have excellent growth and development. Despite this, idiopathic chronic pancreatitis can occur in a subset of pancreas-sufficient individuals with CF, and is associated with recurrent abdominal pain and life-threatening complications.

Thickened secretions also may cause liver problems in patients with CF. Bile secreted by the liver to aid in digestion may block the bile ducts, leading to liver damage. Over time, this can lead to scarring and nodularity (cirrhosis). The liver fails to rid the blood of toxins and does not make important proteins such as those responsible for blood clotting. Liver disease is the third most common cause of death associated with CF.

Endocrine



Clubbing of the fingers in a person with cystic fibrosis

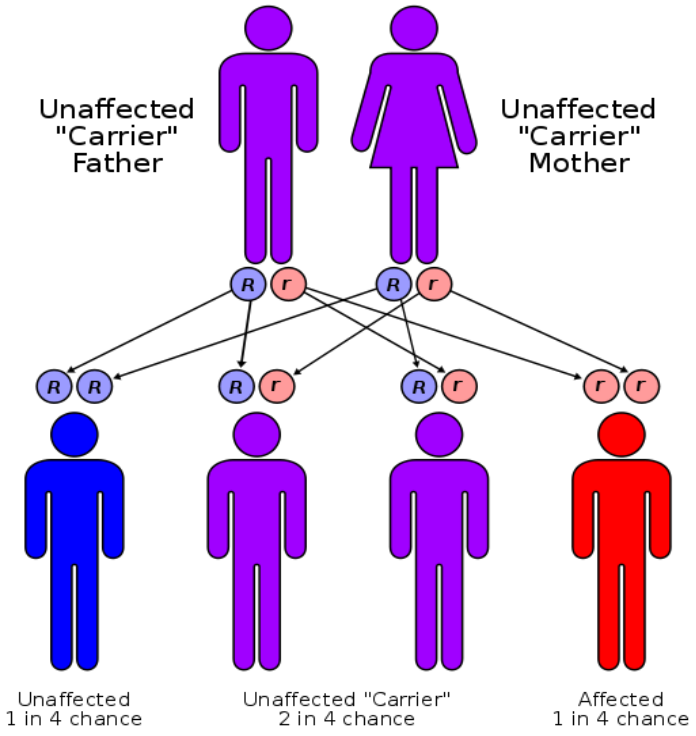
The pancreas contains the islets of Langerhans, which are responsible for making insulin, a hormone that helps regulate blood glucose. Damage of the pancreas can lead to loss of

the islet cells, leading to a type of diabetes that is unique to those with the disease. This cystic fibrosis related diabetes (CFRD) shares characteristics that can be found in Type 1 and Type 2 diabetics, and is one of the principal non-pulmonary complications of CF. Vitamin D is involved in calcium and phosphate regulation. Poor uptake of vitamin D from the diet because of malabsorption can lead to the bone disease osteoporosis in which weakened bones are more susceptible to fractures. In addition, people with CF often develop clubbing of their fingers and toes due to the effects of chronic illness and low oxygen in their tissues.

Infertility

Infertility affects both men and women. At least 97% of men with cystic fibrosis are infertile, but not sterile and can have children with assisted reproductive techniques. These men make normal sperm but are missing the tube (vas deferens), which connects the testes to the ejaculatory ducts of the penis. Many men found to have congenital absence of the vas deferens during evaluation for infertility have a mild, previously undiagnosed form of CF. Some women have fertility difficulties due to thickened cervical mucus or malnutrition. In severe cases, malnutrition disrupts ovulation and causes amenorrhea.

Cause



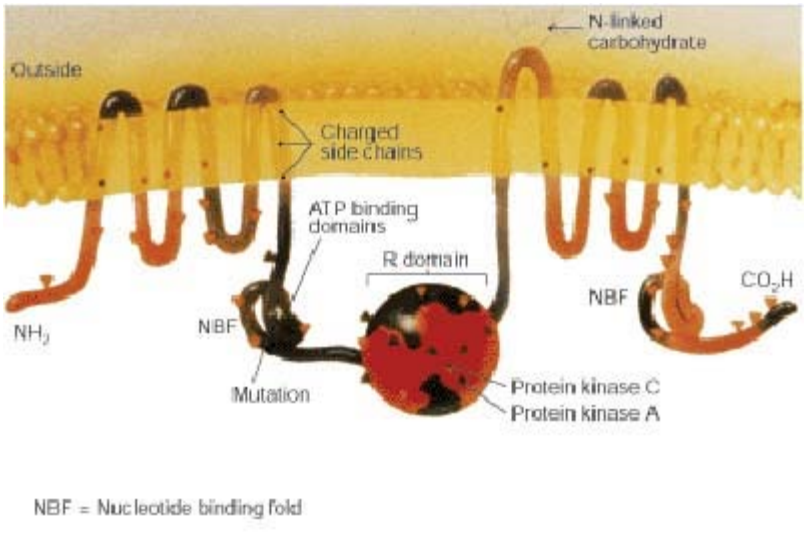
Cystic fibrosis has an autosomal recessive pattern of inheritance

CF is caused by a mutation in the gene cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, ΔF508, is a deletion (Δ) of three nucleotides that results in a loss of the amino acid phenylalanine (F) at the 508th (508) position on the protein. This mutation accounts for two-thirds (66-70%) of CF cases worldwide and 90 percent of cases in the United States; however, there are over 1,400 other mutations that can produce CF. Although most people have two working copies (alleles) of the CFTR gene, only one is needed to prevent cystic fibrosis. CF develops when neither allele can produce a functional CFTR protein. Thus, CF is considered an autosomal recessive disease.

The CFTR gene, found at the q31.2 locus of chromosome 7, is 230,000 base pairs long, and creates a protein that is 1,480 amino acids long. Structurally, CFTR is a type of gene known as an ABC gene. The product of this gene (the CFTR) is a halide anion channel important in creating sweat, digestive juices and mucus. This protein possesses two ATP-hydrolyzing domains which allows the protein to use energy in the form of ATP. It also contains two domains comprising 6 alpha helices apiece, which allow the protein to cross the cell membrane. A regulatory binding site on the protein allows activation by phosphorylation, mainly by cAMP-dependent protein kinase. The carboxyl terminal of the protein is anchored to the cytoskeleton by a PDZ domain interaction.

In addition, there is increasing evidence that genetic modifiers besides CFTR modulate the frequency and severity of the disease. One example is mannan-binding lectin, which is involved in innate immunity by facilitating phagocytosis of microorganisms. Polymorphisms in one or both mannan-binding lectin alleles that result in lower circulating levels of the protein are associated with a threefold higher risk of end-stage lung disease, as well as an increased burden of chronic bacterial infections.

Pathophysiology



Molecular structure of the CFTR protein

There are several mechanisms by which mutations cause problems with the CFTR protein. ΔF508, for instance, creates a protein that does not fold normally and is degraded by the cell. Several different mutations result in proteins that are too short because production is ended prematurely. Less common mutations produce proteins that do not use energy normally, do not allow chloride, iodide and thiocyanate to cross the membrane appropriately, or are degraded at a faster rate than normal. Mutations may also lead to fewer copies of the CFTR protein being produced.

The protein created by this gene is anchored to the outer membrane of cells in the sweat glands, lungs, pancreas, and other affected organs. The protein spans this membrane and acts as a channel connecting the inner part of the cell (cytoplasm) to the surrounding fluid. This channel is primarily responsible for controlling the movement of halogens from inside to outside of the cell; however, in the sweat ducts it facilitates the movement of chloride from the sweat into the cytoplasm. When the CFTR protein does not work, chloride and thiocyanate are trapped inside the cells in the airway and outside in the skin. Then hypothiocyanite, OSCN, cannot be produced by immune defense system. Because chloride is negatively charged, this creates a difference in the electrical potential inside and outside the cell causing cations to cross into the cell. Sodium is the most common cation in the extracellular space and the combination of sodium and chloride creates the salt, which is lost in high amounts in the sweat of individuals with CF. This lost salt forms the basis for the sweat test.

How this malfunction of cells in cystic fibrosis causes the clinical manifestations is not well understood. One theory suggests that the lack of halogen and pseudohalogen (mainly, chloride, iodide and thiocyanate) exodus through the CFTR protein leads to the accumulation of more viscous, nutrient-rich mucus in the lungs that allows bacteria to hide from the body's immune system. Another theory proposes that the CFTR protein failure leads to a paradoxical increase in sodium and chloride uptake, which, by leading to increased water reabsorption, creates dehydrated and thick mucus. Yet another theory focuses on abnormal chloride movement *out* of the cell, which also leads to dehydration of mucus, pancreatic secretions, biliary secretions, etc. These theories all support the observation that the majority of the damage in CF is due to blockage of the narrow passages of affected organs with thickened secretions. These blockages lead to remodeling and infection in the lung, damage by accumulated digestive enzymes in the pancreas, blockage of the intestines by thick faeces, etc.

Chronic infections

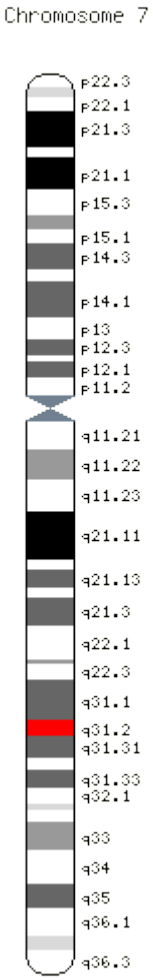
The lungs of individuals with cystic fibrosis are colonized and infected by bacteria from an early age. These bacteria, which often spread among individuals with CF, thrive in the altered mucus, which collects in the small airways of the lungs. This mucus leads to the formation of bacterial microenvironments known as biofilms that are difficult for immune cells and antibiotics to penetrate. Viscous secretions and persistent respiratory infections repeatedly damage the lung by gradually remodeling the airways which makes infection even more difficult to eradicate.

Over time, both the types of bacteria and their individual characteristics change in individuals with CF. In the initial stage, common bacteria such as *Staphylococcus aureus* and *Hemophilus influenzae* colonize and infect the lungs. Eventually, *Pseudomonas aeruginosa* (and sometimes *Burkholderia cepacia*) dominates. By 18 years of age, 80% of patients with classic CF harbor *P. aeruginosa*, and 3.5% harbor *B. cepacia*. Once within the lungs, these bacteria adapt to the environment and develop resistance to commonly used antibiotics. *Pseudomonas* can develop special characteristics that allow the formation of large colonies, known as "mucoid" *Pseudomonas*, which are rarely seen in people that do not have CF.

One way in which infection has spread is by passage between different individuals with CF. In the past, people with CF often participated in summer "CF Camps" and other recreational gatherings. Hospitals grouped patients with CF into common areas and routine equipment (such as nebulizers) was not sterilized between individual patients. This led to transmission of more dangerous strains of bacteria among groups of patients. As a result, individuals with CF are routinely isolated from one another in the healthcare setting and healthcare providers are encouraged to wear gowns and gloves when examining patients with CF to limit the spread of virulent bacterial strains.

CF patients may also have their airways chronically colonized by filamentous fungi (such as *Aspergillus fumigatus*, *Scedosporium apiospermum*, *Aspergillus terreus*) and/or yeasts (such as *Candida albicans*); other filamentous fungi less commonly isolated include *Aspergillus flavus* and *Aspergillus nidulans* (occur transiently in CF respiratory secretions), and *Exophiala dermatitidis* and *Scedosporium prolificans* (chronic airway-colonizers); some filamentous fungi like *Penicillium emersonii* and *Acrophialophora fusispora* are encountered in patients almost exclusively in the context of CF. Defective mucociliary clearance characterizing CF is associated with local immunological disorders. In addition, the prolonged therapy with antibiotics and the use of corticosteroid treatments may also facilitate fungal growth. Although the clinical relevance of the fungal airway colonization is still a matter of debate, filamentous fungi may contribute to the local inflammatory response, and therefore to the progressive deterioration of the lung function, as often happens with allergic broncho-pulmonary aspergillosis (ABPA) - the most common fungal disease in the context of CF, involving a Th2-driven immune response to Aspergillus.

Diagnosis and monitoring



The location of the CFTR gene on chromosome 7

Cystic fibrosis may be diagnosed by many different categories of testing including those such as, newborn screening, sweat testing, or genetic testing. As of 2006 in the United States, 10 percent of cases are diagnosed shortly after birth as part of newborn screening programs. The newborn screen initially measures for raised blood concentration of immunoreactive trypsinogen. Infants with an abnormal newborn screen need a sweat test in order to confirm the CF diagnosis. In many cases, a parent makes the diagnosis because the infant tastes salty. Trypsinogen levels can be increased in individuals who have a single mutated copy of the *CFTR* gene (carriers) or, in rare instances, in individuals with two normal copies of the *CFTR* gene. Due to these false positives, CF screening in newborns can be controversial. Most states and countries do not screen for CF routinely at birth. Therefore, most individuals are diagnosed after symptoms (e.g. sinopulmonary disease and GI manifestations) prompt an evaluation for cystic fibrosis. The most commonly used form of testing is the sweat test. Sweat-testing involves application of a medication that stimulates sweating (pilocarpine). In order to deliver the medication through the skin, iontophoresis is used to, whereby one electrode is placed

onto the applied medication and an electric current is passed to a separate electrode on the skin. The resultant sweat is then collected on filter paper or in a capillary tube and analyzed for abnormal amounts of sodium and chloride. People with CF have increased amounts of sodium and chloride in their sweat. In opposite, people with CF have less thiocyanate and hypothiocyanite in their saliva (Minarowski et al.) and mucus (Banfi et al.). CF can also be diagnosed by identification of mutations in the CFTR gene.

A multitude of tests are used to identify complications of CF and to monitor disease progression. X-rays and CAT scans are used to examine the lungs for signs of damage or infection. The examination of the sputum is required to isolate organisms which may be causing an infection or colonising the lower respiratory tract so that effective antimicrobial therapy can be provided. Culture for organisms such as *Burkholderia (previously Pseudomonas) cepacia* is required for candidates of Lung transplantation as persistent bacterial colonisation reduces the chances of survival.

Pulmonary function tests measure how well the lungs are functioning, and are used to measure the need for and response to antibiotic therapy. Blood tests can identify liver abnormalities, vitamin deficiencies, and the onset of diabetes. DXA scans can screen for osteoporosis and testing for fecal elastase can help diagnose insufficient digestive enzymes.

In individuals with a mild mutation in the CFTR gene the sweat test may be near normal (i.e. a chloride concentration of less than 60mM/L). As an adjunct to diagnosis, the nasal transepithelial potential difference (TEPD) may be used. Due to abnormalities in the CFTR gene in exocrine glands, chloride secretion is reduced and sodium and water reabsorption is increased. The net effect of the preceding is a more negative baseline resulting in a higher than normal TEPD that can be used as an ancillary or necessary form of diagnosis for mild mutations.

People with CF may be listed in a disease registry that allows researchers and doctors to track health results and identify candidates for clinical trials.

Prenatal

Couples who are pregnant or who are planning a pregnancy can themselves be tested for CFTR gene mutations to determine the degree of risk that their child will be born with cystic fibrosis. Testing is typically performed first on one or both parents and, if the risk of CF is found to be high, testing on the fetus can then be performed. The American College of Obstetricians and Gynecologists (ACOG) recommends testing for couples who have a personal or close family history of CF, and they recommend that carrier testing be offered to all Caucasian couples and be made available to couples of other ethnic backgrounds.

Because development of CF in the fetus requires each parent to pass on a mutated copy of the CFTR gene and because CF testing is expensive, testing is often performed initially on one parent. If that parent is found to be a carrier of a CFTR gene mutation, the other

parent is then tested to calculate the risk that their children will have CF. CF can result from more than a thousand different mutations, and as of 2006 it is not possible to test for each one. Testing analyzes the blood for the most common mutations such as ΔF508—most commercially available tests look for 32 or fewer different mutations. If a family has a known uncommon mutation, specific screening for that mutation can be performed. Because not all known mutations are found on current tests, a negative screen does not guarantee that a child will not have CF. In addition, because the mutations tested are necessarily those most common in the highest risk groups, testing in lower risk ethnicities is less successful because the mutations commonly seen in these groups are less common in the general population. These couples may therefore consider testing through labs that offer CF screens with a high number of mutations tested.

Couples at high risk for having a child with CF will often opt to perform further testing before or during pregnancy. In vitro fertilization with preimplantation genetic diagnosis offers the possibility to examine the embryo prior to its placement into the uterus. The test, performed three days after fertilization, looks for the presence of abnormal CF genes. If two mutated CFTR genes are identified, the embryo is not used for embryo transfer and an embryo with at least one normal gene is implanted.

During pregnancy, testing can be performed on the placenta (chorionic villus sampling) or the fluid around the fetus (amniocentesis). However, chorionic villus sampling has a risk of fetal death of 1 in 100 and amniocentesis of 1 in 200; a recent study has indicated this may be much lower, approximately 1 in 1,600. In any case, the benefits must be determined to outweigh these risks prior to going forward with testing. Alternatively, some couples choose to undergo third party reproduction with egg or sperm donors.

Economically, for carrier couples of cystic fibrosis, when comparing preimplantation genetic diagnosis (PGD) with natural conception (NC) followed by prenatal testing and abortion of affected pregnancies, PGD provides net economic benefits up to a maternal age of approximately 40 years, after which NC, prenatal testing and abortion has higher economic benefit.

Management

While there are no cures for cystic fibrosis there are several treatment methods. The management of cystic fibrosis has improved significantly over the past 70 years. While infants born with cystic fibrosis 70 years ago would have been unlikely to live beyond their first year, infants today are likely to live well into adulthood. Recent advances in the treatment of cystic fibrosis have meant that a cystic fibrosis person can live a fuller life less encumbered by their condition. The cornerstones of management are proactive treatment of airway infection, and encouragement of good nutrition and an active lifestyle. Management of cystic fibrosis continues throughout a patient's life, and is aimed at maximizing organ function, and therefore quality of life. At best, current treatments delay the decline in organ function. Because of the wide variation in disease symptoms treatment typically occurs at specialist multidisciplinary centers, and is tailored to the individual. Targets for therapy are the lungs, gastrointestinal tract (including pancreatic

enzyme supplements), the reproductive organs (including assisted reproductive technology (ART)) and psychological support.

The most consistent aspect of therapy in cystic fibrosis is limiting and treating the lung damage caused by thick mucus and infection, with the goal of maintaining quality of life. Intravenous, inhaled, and oral antibiotics are used to treat chronic and acute infections. Mechanical devices and inhalation medications are used to alter and clear the thickened mucus. These therapies, while effective, can be extremely time-consuming for the patient. One of the most important battles that CF patients face is finding the time to comply with prescribed treatments while balancing a normal life.

In addition, therapies such as transplantation and gene therapy aim to cure some of the effects of cystic fibrosis. Gene therapy aims to introduce normal CFTR to airway. Theoretically this process should be simple as the airway is easily accessible and there is only a single gene defect to correct. There are two CFTR gene introduction mechanisms involved, the first use of a viral vector (adenovirus, adeno-associated virus or retro virus) and secondly the use of liposome. However there are some problems associated with these methods involving efficiency (liposomes insufficient protein) and delivery (virus provokes an immune response).

Antibiotics

Many CF patients are on one or more antibiotics at all times, even when they are considered healthy, in order to prophylactically suppress infection. Antibiotics are absolutely necessary whenever pneumonia is suspected or there has been a noticeable decline in lung function, and are usually chosen based on the results of a sputum analysis and the patient's past response. Many bacteria common in cystic fibrosis are resistant to multiple antibiotics and require weeks of treatment with intravenous antibiotics such as vancomycin, tobramycin, meropenem, ciprofloxacin, and piperacillin. This prolonged therapy often necessitates hospitalization and insertion of a more permanent IV such as a peripherally inserted central catheter (PICC line) or Port-a-Cath. Inhaled therapy with antibiotics such as tobramycin, colistin, and cayston is often given for months at a time in order to improve lung function by impeding the growth of colonized bacteria. Oral antibiotics such as ciprofloxacin or azithromycin are given to help prevent infection or to control ongoing infection. The aminoglycoside antibiotics (e.g. tobramycin) used can cause hearing loss, damage to the balance system in the inner ear or kidney problems with long-term use. In order to prevent these side-effects, the amount of antibiotics in the blood are routinely measured and adjusted accordingly.

Other treatments for lung disease

Several mechanical techniques are used to dislodge sputum and encourage its expectoration. In the hospital setting, chest physiotherapy (CPT) is utilized; a respiratory therapist percusses an individual's chest with his or her hands several times a day, to loosen up secretions. Devices that recreate this percussive therapy include the ThAIRapy Vest and the intrapulmonary percussive ventilator (IPV). Newer methods such as

Biphasic Cuirass Ventilation, and associated clearance mode available in such devices, integrate a cough assistance phase, as well as a vibration phase for dislodging secretions. These are portable and adapted for home use. Physiotherapy is essential to help manage an individual's chest on a long term basis, and can also teach techniques for the older child and teenager to manage themselves at home. Aerobic exercise is of great benefit to people with cystic fibrosis. Not only does exercise increase sputum clearance but it also improves cardiovascular and overall health.

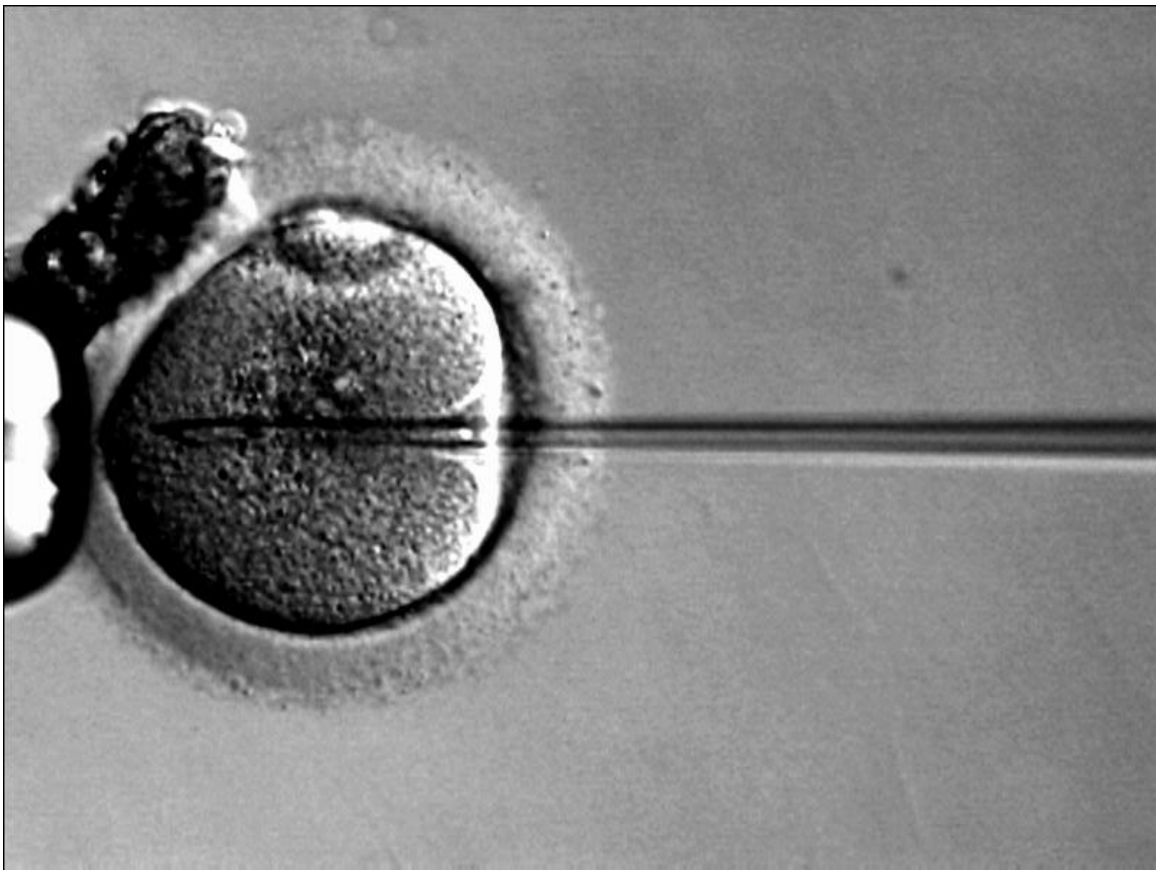
Aerosolized medications that help loosen secretions include dornase alfa and hypertonic saline. Dornase is a recombinant human deoxyribonuclease, which breaks down DNA in the sputum, thus decreasing its viscosity. N-Acetylcysteine may also decrease sputum viscosity, but research and experience have shown its benefits to be minimal. Salbutamol and ipratropium bromide are inhaled to increase the size of the small airways by relaxing the surrounding muscles.

As lung disease worsens, mechanical breathing support may become necessary. Individuals with CF may need to wear special masks at night that help push air into their lungs. These machines, known as bilevel positive airway pressure (BiPAP) ventilators, help prevent low blood oxygen levels during sleep. BiPAP may also be used during physical therapy to improve sputum clearance. During severe illness, a tube may be placed in the throat (a procedure known as a tracheostomy) to enable breathing supported by a ventilator.

Transplantation

Lung transplantation often becomes necessary for individuals with cystic fibrosis as lung function and exercise tolerance declines. Although single lung transplantation is possible in other diseases, individuals with CF must have both lungs replaced because the remaining lung might contain bacteria that could infect the transplanted lung. A pancreatic or liver transplant may be performed at the same time in order to alleviate liver disease and/or diabetes. Lung transplantation is considered when lung function declines to the point where assistance from mechanical devices is required or patient survival is threatened. This point typically occurs when lung function declines to approximately 20 to 30 percent, however there is a small time frame when transplantation is feasible as the patient must be healthy enough to endure the procedure.

Treatment of other aspects



Intracytoplasmic sperm injection can be used to provide fertility for men with cystic fibrosis

Newborns with CF (CYSTIC FIBROSIS) typically require surgery, whereas adults with distal intestinal obstruction syndrome typically do not. Treatment of pancreatic insufficiency by replacement of missing digestive enzymes allows the duodenum to properly absorb nutrients and vitamins that would otherwise be lost in the feces. Even so, most individuals with CF are advised take additional amounts of vitamins A, D, E, and K and eat high-calorie meals. So far, no large-scale research involving the incidence of atherosclerosis and coronary heart disease in adults with cystic fibrosis has been conducted. This is likely due to the fact that the vast majority of people with cystic fibrosis do not live long enough to develop clinically significant atherosclerosis or coronary heart disease.

Diabetes is the most common non-pulmonary complication of CF. It mixes features of type 1 and type 2 diabetes, and is recognized as a distinct entity, cystic fibrosis-related diabetes (CFRD). While oral anti-diabetic drugs are sometimes used, the only recommended treatment is the use of insulin injections or an insulin pump, and, unlike in type 1 and 2 diabetes, dietary restrictions are not recommended.

Development of osteoporosis can be prevented by increased intake of vitamin D and calcium, and can be treated by bisphosphonates, although adverse effects can be an issue. Poor growth may be avoided by insertion of a feeding tube for increasing calories through supplemental feeds or by administration of injected growth hormone.

Sinus infections are treated by prolonged courses of antibiotics. The development of nasal polyps or other chronic changes within the nasal passages may severely limit airflow through the nose, and over time reduce the patient's sense of smell. Sinus surgery is often used to alleviate nasal obstruction and to limit further infections. Nasal steroids such as fluticasone are used to decrease nasal inflammation. Female infertility may be overcome by assisted reproduction technology, particularly embryo transfer techniques. Male infertility caused by absence of the vas deferens may be overcome with testicular sperm extraction (TEST), collecting sperm cells directly from the testicles. If the collected sample contains too few sperm cells to likely have a spontaneous fertilization, intracytoplasmic sperm injection can be performed. Third party reproduction is also a possibility for women with CF.

Prognosis

The improved prognosis of cystic fibrosis, combined with earlier diagnosis through screening, has already started to result in a change in attitude. The hitherto scrawny, ill, infected CF infant who will die before adult life is increasingly being replaced by a fit individual, who has only ever had minimal if any symptoms, who happens to have a problem called CF. Many factors will influence the prognosis of a person with cystic fibrosis. These factors include treatment compliance, efficacy of treatment, and access to health care.

Life expectancy for people with CF depends largely upon access to health care. In 1959, the median age of survival of children with cystic fibrosis was six months. In the United States, the life expectancy for infants born in 2008 with CF is 37.4 years, based upon data compiled by the Cystic Fibrosis Foundation. The median survival age in Canada has increased from 24 in 1982 to 47.7 in 2007, based on data compiled by the Canadian Cystic Fibrosis Foundation.

The U.S. Cystic Fibrosis Foundation compiles lifestyle information about American adults with CF. In 2008, the foundation reported that 92% had graduated from high school and 66% had at least some college education. Employment data revealed 15% of adults were disabled and 7% were unemployed. Marital information showed that 54.8% of adults were single and 40.1% were married or living with a partner. In 2008, 240 American women with CF were pregnant.

Epidemiology

Mutation	Frequency worldwide
ΔF508	66%-70%
G542X	2.4%
G551D	1.6%
N1303K	1.3%
W1282X	1.2%
All others	27.5%

Cystic fibrosis is the most common life-limiting autosomal recessive disease among people of European heritage. In the United States, approximately 30,000 individuals have CF; most are diagnosed by six months of age. Canada has approximately 3,000 citizens with CF. Approximately 1 in 25 people of European descent, and one in 30 of Caucasian Americans, is a carrier of a cystic fibrosis mutation. Although CF is less common in these groups, approximately 1 in 46 Hispanics, 1 in 65 Africans and 1 in 90 Asians carry at least one abnormal CFTR gene.

Although technically a rare disease, cystic fibrosis is ranked as one of the most widespread life-shortening genetic diseases. It is most common among nations in the Western world. An exception is Finland, where only one in 80 people carry a CF mutation. In the United States, 1 in 4,000 children are born with CF. In 1997, about 1 in 3,300 caucasian children in the United States was born with cystic fibrosis. In contrast, only 1 in 15,000 African American children suffered from cystic fibrosis, and in Asian Americans the rate was even lower at 1 in 32,000.

Cystic fibrosis is diagnosed in males and females equally. For unclear reasons, males tend to have a longer life expectancy than females some recent studies suggest this gender gap may no longer exist in younger patients with access to excellent health care facilities., while a recent study from Ireland identified a link between the female hormone oestrogen and worse CF outcomes

The distribution of CF alleles varies among populations. The frequency of ΔF508 carriers has been estimated to be 1:200 in northern Sweden, 1:143 in Lithuanians, and 1:38 in Denmark. No ΔF508 carriers were found among 171 Finns and 151 Saami people. ΔF508 does occur in Finland, but it is a minority allele there. Cystic fibrosis is known to occur in only 20 families (pedigrees) in Finland.

Theories about prevalence

The ΔF508 mutation is estimated to be up to 52,000 years old. Numerous hypotheses have been advanced as to why such a lethal mutation has persisted and spread in the human population. Other common autosomal recessive diseases such as sickle-cell anemia have been found to protect carriers from other diseases, a concept known as

heterozygote advantage. Resistance to the following have all been proposed as possible sources of heterozygote advantage:

- Cholera: With the discovery that cholera toxin requires normal host CFTR proteins to function properly, it was hypothesized that carriers of mutant CFTR genes benefited from resistance to cholera and other causes of diarrhea. Further studies have not confirmed this hypothesis.
- Typhoid: Normal CFTR proteins are also essential for the entry of Salmonella typhi into cells, suggesting that carriers of mutant CFTR genes might be resistant to typhoid fever. No *in vivo* study has yet confirmed this. In both cases, the low level of cystic fibrosis outside of Europe, in places where both cholera and typhoid fever are endemic, is not immediately explicable.
- Diarrhea: It has also been hypothesized that the prevalence of CF in Europe might be connected with the development of cattle domestication. In this hypothesis, carriers of a single mutant CFTR chromosome had some protection from diarrhea caused by lactose intolerance, prior to the appearance of the mutations that created lactose tolerance.
- Tuberculosis: Another possible explanation is that carriers of the gene could have some resistance to TB.

History

National Library of Medicine photo of Dorothy Hansine Andersen. Andersen first described cystic fibrosis in 1938.

Although the entire clinical spectrum of CF was not recognized until the 1930s, certain aspects of CF were identified much earlier. Indeed, literature from Germany and Switzerland in the 18th century warned *Wehe dem Kind, das beim Kuß auf die Stirn salzig schmekt, er ist verhext und muss bald sterbe* or "Woe is the child who tastes salty from a kiss on the brow, for he is cursed, and soon must die," recognizing the association between the salt loss in CF and illness.

In the 19th century, Carl von Rokitansky described a case of fetal death with meconium peritonitis, a complication of meconium ileus associated with cystic fibrosis. Meconium ileus was first described in 1905 by Karl Landsteiner. In 1936, Guido Fanconi published a paper describing a connection between celiac disease, cystic fibrosis of the pancreas, and bronchiectasis.

In 1938 Dorothy Hansine Andersen published an article, "Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: a Clinical and Pathological Study," in the *American Journal of Diseases of Children*. She was the first to describe the characteristic cystic fibrosis of the pancreas and to correlate it with the lung and intestinal disease prominent in CF. She also first hypothesized that CF was a recessive disease and first used pancreatic enzyme replacement to treat affected children. In 1952 Paul di Sant' Agnese discovered abnormalities in sweat electrolytes; a sweat test was developed and improved over the next decade.

In 1988 the first mutation for CF, ΔF508 was discovered by Francis Collins, Lap-Chee Tsui and John R. Riordan on the seventh chromosome. Subsequent research has found over 1,000 different mutations that cause CF.

Because mutations in the CFTR gene are typically small, classical genetics techniques had been unable to accurately pinpoint the mutated gene. Using protein markers, gene-linkage studies were able to map the mutation to chromosome 7. Chromosome-walking and -jumping techniques were then used to identify and sequence the gene. In 1989 Lap-Chee Tsui led a team of researchers at the Hospital for Sick Children in Toronto that discovered the gene responsible for CF. Cystic fibrosis represents the first genetic disorder elucidated strictly by the process of reverse genetics.

Research

Gene therapy has been explored as a potential cure for cystic fibrosis. Ideally, gene therapy attempts to place a normal copy of the CFTR gene into affected cells. Transferring the normal CFTR gene into the affected epithelium cells would result in the production of functional CFTR in all target cells, without adverse reactions or an inflammation response. Studies have shown that to prevent the lung manifestations of cystic fibrosis, only 5–10% the normal amount of CFTR gene expression is needed. Multiple approaches have been tested for gene transfer, such as liposomes and viral vectors in animal models and clinical trials. However, both methods were found to be relatively inefficient treatment options. The main reason is that very few cells take up the vector and express the gene, so the treatment has little effect. Additionally, problems

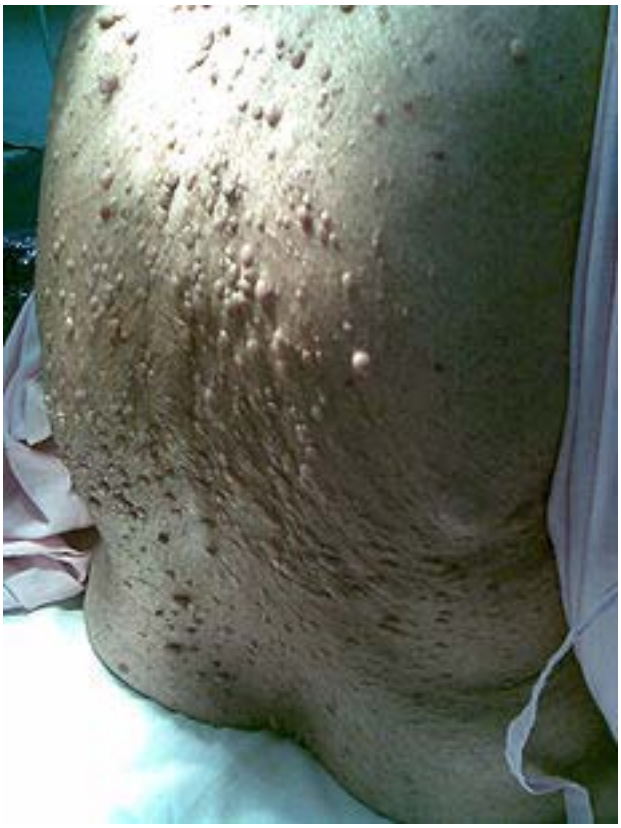
have been noted in cDNA recombination, such that the gene introduced by the treatment is rendered unusable.

Another approach is to develop drugs that will get the ribosome to overcome the stop codon and synthesize a full-length CFTR protein. About 10% of CF result from a premature stop codon in DNA, leading to early termination of protein synthesis and truncated proteins. Aminoglycoside antibiotics interfere with DNA synthesis and error-correction. In some cases, they can cause the cell to overcome the stop codon, insert a random amino acid, and express a full-length protein. The aminoglycoside gentamicin has been used to treat lung cells from CF patients in the laboratory to induce the cells to grown full-length proteins.

Chapter 13

Neurofibromatosis

Neurofibromatosis



Back of an elderly woman with Neurofibromatosis.

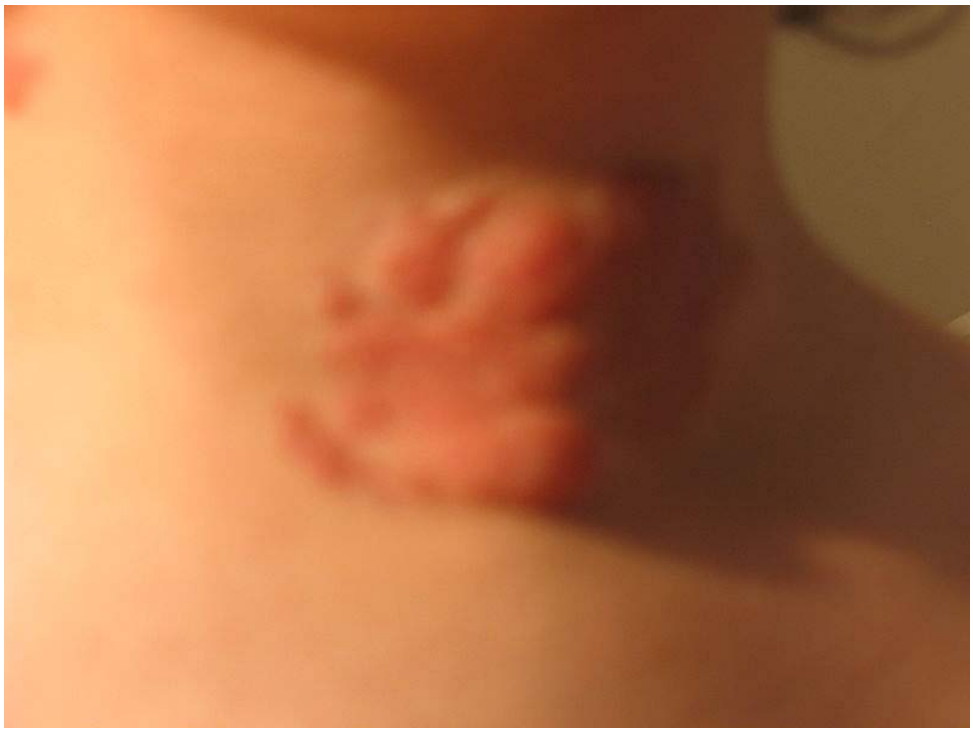
ICD-10	Q85.0
ICD-9	237.7
ICD-O:	9540/0
eMedicine	derm/287
MeSH	D017253

Neurofibromatosis (commonly abbreviated **NF**; neurofibromatosis type 1 is also known as **von Reklinghausen disease**) is a genetically-inherited disorder in which the nerve tissue grows tumors (i.e., neurofibromas) that may be benign or may cause serious damage by compressing nerves and other tissues. The disorder affects all neural crest cells (Schwann cells, melanocytes, endoneurial fibroblasts). Cellular elements from these cell types proliferate excessively throughout the body forming tumors; melanocytes also function abnormally in this disease resulting in disordered skin pigmentation and "cafe-au-lait" spots. The tumors may cause bumps under the skin, colored spots, skeletal problems, pressure on spinal nerve roots, and other neurological problems.

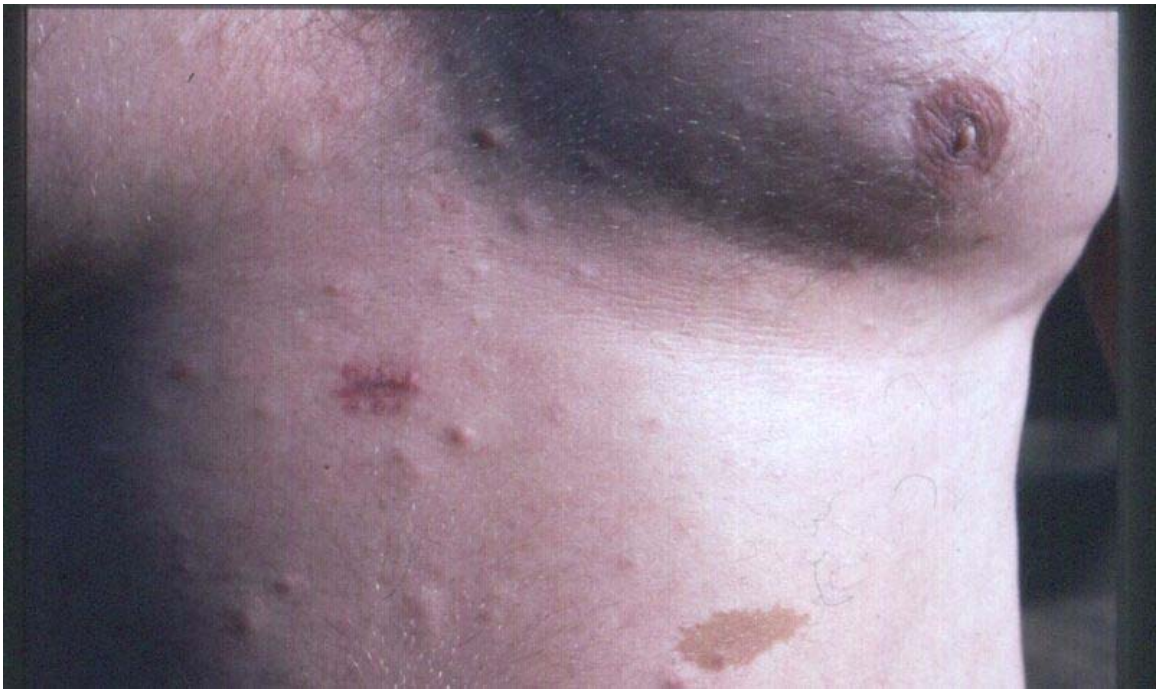
Neurofibromatosis is an autosomal dominant disorder, which means that it affects males and females equally and is dominant (only one copy of the affected gene is needed to get the disorder). Therefore, if only one parent has neurofibromatosis, his or her children have a 50% chance of developing the condition as well. The severity in affected individuals, however, can vary (this is called variable expressivity). Moreover, in around half of cases there is no other affected family member because a new mutation has occurred.

Classification

Neurofibromatosis type 1 (NF 1)



plexiform neurofibroma on the neck of a patient; plexiform neurofibromas are a cause of morbidity in the affected individuals.



Patient with multiple small cutaneous neurofibromas and a 'café au lait spot' (bottom of photo, to the right of centre). A biopsy has been taken of one of the lesions

Neurofibromatosis type 1 (also known as "von Recklinghausen disease") is the most common form of NF, accounting for up to 90% of the cases. NF 1 has a disorder frequency of 1 in 3,000 making it more common than neurofibromatosis type 2, with a frequency of 1 in 45,000 people. It occurs following the mutation of neurofibromin on chromosome 17q11.2. Neurofibromin is a tumor suppressor gene whose function is to inhibit the p21 ras oncoprotein. In absence of this tumor suppressor's inhibitory control on the ras oncoprotein, cellular proliferation is erratic, and uncontrolled resulting in unbalanced cellular proliferation, and tumor development. The diagnosis of NF1 is made if any two of the following seven criteria are met:

- Two or more neurofibromas on or under the skin **or** one plexiform neurofibroma (a large cluster of tumors involving multiple nerves); Neurofibromas are the subcutaneous bumps that are characteristic of the disease and increase in number with age.
- Freckling of the groin or the axilla (arm pit).
- Café au lait spots (pigmented, light brown macules located on nerves, with a smooth edges("coast of California") birthmarks). Six or more measuring 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals.
- Skeletal abnormalities, such as sphenoid dysplasia or thinning of the cortex of the long bones of the body (i.e. bones of the leg, potentially resulting in bowing of the legs)
- Lisch nodules (hamartomas of iris), freckling in the iris.
- Tumors on the optic nerve, also known as an optic glioma.

- Macrocephaly in 30-50% of the pediatric population without any hydrocephalus.
- Epilepsy (seizures)
- Juvenile posterior lenticular opacity

NF 1 also increases the risk of tumor development, particularly, meningiomas, gliomas and pheochromocytomas.

Neurofibromatosis type 2 (NF 2)

Neurofibromatosis type 2 (also called "central neurofibromatosis") is the result of mutation of the Merlin (also known as "schwannomin") in chromosome 22q12. It accounts for only 10% of all cases of NF, and its frequency is lower than NF1. It is also caused by a mutation in a tumor suppressor gene (NF2 or Merlin). The normal function of Merlin is not well understood. The disorder manifests in the following fashion:

- bilateral acoustic neuromas (tumors of the vestibulocochlear nerve or cranial nerve 8 (CN VIII) also known as schwannoma) often leading to hearing loss. In fact, the hallmark of NF 2 is hearing loss due to acoustic neuromas around the age of twenty.
- the tumors may cause:
    - headaches
    - balance problems, and peripheral vertigo often due to schwannoma and involvement of the inner ear.
    - facial weakness/paralysis due to involvement or compression of the facial nerve (cranial nerve 7 or CN VII)
    - patients with NF2 may also develop other brain tumors, as well as spinal tumors.
    - Deafness and Tinnitus.

NF 2 increases the risk of meningiomas and ependymomas.

Schwannomatosis

Schwannomatosis - mutation in both chromosomes 17 and 22

1. Multiple Schwannomas occur.
2. The Schwannomas develop on cranial, spinal and peripheral nerves.
3. Chronic pain, and sometimes numbness, tingling and weakness.
4. About 1/3 of patients have segmental Schwannomatosis, which means that the Schwannomas are limited to a single part of the body, such as an arm, a leg or the spine.
5. Unlike the other forms of NF, the Schwannomas do not develop on vestibular nerves, and as a result, no loss of hearing is associated with Schwannomatosis.
6. Patients with Schwannomatosis do not have learning disabilities related to the disorder.

One must keep in mind, however, that neurofibromatosis can occur in or affect any of the organ systems, whether that entails simply compressing them (from tumor growth) or in fact altering the organs in some fundamental way. This disparity in the disorder is one of many factors that makes it difficult to diagnose, and eventually find a prognosis for.

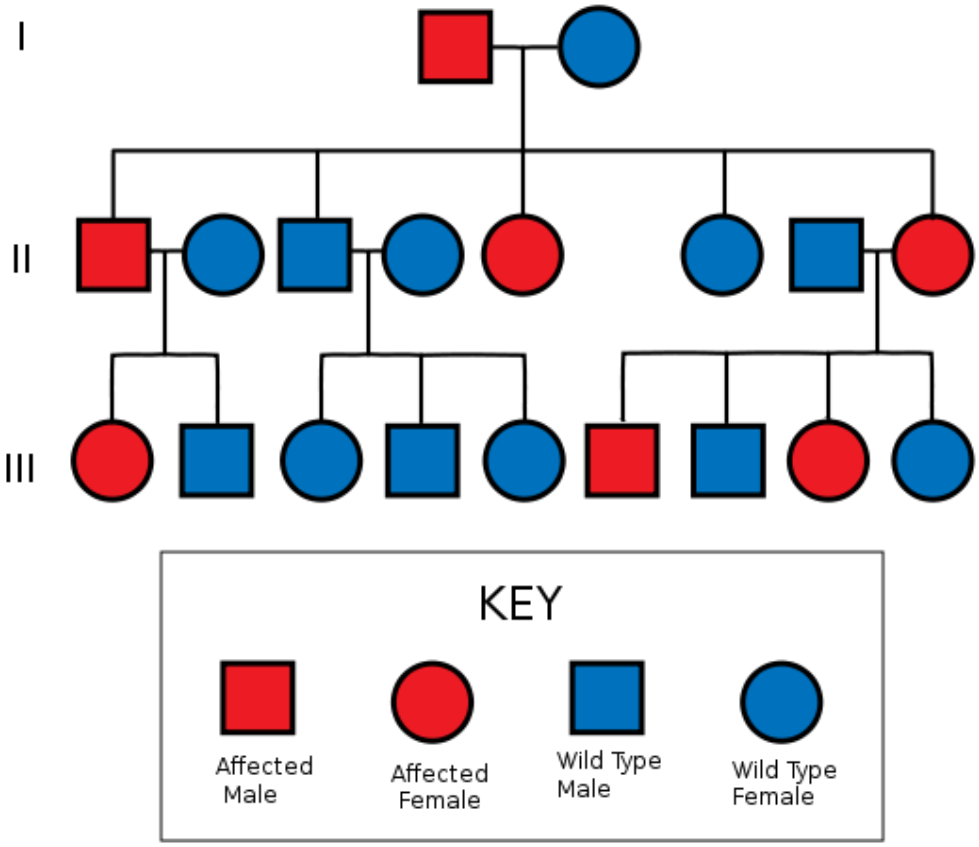
Signs and symptoms

Patients with Neurofibromatosis can be affected in many different ways. Morbidity is often due to plexiform neuromas, optic gliomas, or acoustic neuromas, but mortality can also be associated with malignant transformation of the neuromas such as neurofibrosarcomas (often there is a malignant transformation in less than 3% of the cases of NF1). There is a high incidence of learning disabilities or cognitive deficit in patients with NF, particularly NF-1, however severe retardation is not part of the syndrome. Due to the tumor generating nature of the disorder and its involvement of the nervous system and also due to early onset macrocephaly in the pediatric population, there is often an increased chance of development of epilepsy in those affected. Neurofibromatosis also increases the risk of leukemia particularly in children; Children with NF-1 have 200 to 500 times the normal risk of developing leukemia compared to the general population. Since the tumors grow where there are nerves, they can also grow in areas that are visible causing considerable social suffering for those affected. The tumors can also grow in places that can cause other medical issues that may require them to be removed for the patient's safety. Affected individuals may need multiple surgeries (such as reduction surgery, or Gamma knife surgery), depending on where the tumors are located. For instance those affected with NF 2 might benefit from a surgical decompression of the vestibular tumors to prevent deafness.

Related disorders

Neurofibromatosis is considered a member of the *neurocutaneous syndromes* (*phakomatoses*). In addition to the types of neurofibromatosis, the phakomatoses also include tuberous sclerosis, Sturge-Weber syndrome and von Hippel-Lindau disease. This grouping is an artifact of an earlier time in medicine, before the distinct genetic basis of each of these diseases was understood.

Genetics



NF-1 and NF-2 may be inherited in an autosomal dominant fashion, as well as through random mutation.

Neurofibromatosis type 1 is due to mutation on chromosome 17q11.2 , the gene product being Neurofibromin (a GTPase activating enzyme (GAP)). Neurofibromatosis type 2 is due to mutation on chromosome 22q, the gene product is Merlin, a cytoskeletal protein.

Both NF-1 and NF-2 are autosomal dominant disorders, meaning that only one copy of the mutated gene need be inherited in order to pass the disorder. A child of a parent with NF-1 or NF-2 and an unaffected parent will have a 50%-100% chance of inheriting the disorder, depending on whether the affected parent is heterozygous (*Aa*) or homozygous (*AA*) for the trait ("*A*" depicts the affected dominant allele, while "*a*" depics the recessive allele).

Complicating the question of heritability is the distinction between genotype and phenotype, that is, between the genetics and the actual manifestation of the disorder. In the case of NF1, no clear links between genotype and phenotype have been found, and the severity and the specific nature of the symptoms may vary widely among family members with the disorder. This is a good example of the phenomenon of variable expressivity: the differing severities of disease in different individuals with the same genotype. In the case of NF-2, however, manifestations are similar among family members; a strong genotype-phenotype correlation is believed to exist. Both NF-1 and NF-2 can also appear to be spontaneous de-novo mutations, with no family history. These cases account for about one half of neurofibromatosis cases.

Similar to polydactyly, NF is also a autosomally dominant mutation, that is not prevalent in the society. Neurofibromatosis-1 is found in approximately 1 in 2,500-3,000 live births (carrier incidence 0.0004, gene frequency 0.0002) and is more common than NF-2.

Pathophysiology

The gene affected in NF-1, is located on the long arm of the chromcome 17 (q11.2). It encodes for a protein called Neurofibromin, otherwise known as "the tumor suppressor" protein. This protein is a negative regulator of the Ras kinase pathway (p21 oncoprotein). Neurofibromatosis alters or weakens this protein (due to deletion, missense mutation, or nonsense mutations) allowing rapid, radical growth of cells all over the body, especially around the nervous system. The essential problem is the inability to inactivate GTP due to a defective GTP-ase (Neurofibromin). This leads to the common symptoms for neurofibromatosis - clumpings of the tumors, called neurofibromas and schwannomas. Less is known about the NF-2 linked gene and its product Merlin. However, it is on the long arm of the chromosome 22q(11.1-13.1) and codes for the protein Merlin.

Treatment

Because there is no cure for the condition itself, the only therapy for patients with neurofibromatosis is a program of treatment by a team of specialists to manage symptoms or complications. Surgery may be needed when the tumors compress organs or other structures. Less than 10% of people with neurofibromatosis develop cancerous growths; in these cases, chemotherapy may be successful.

Although there's no cure for NF, the "Neurofibromatosis Association" is optimistic that there will be an effective treatment within the next five to ten years. For families with NF, genetic screening and counselling is available.

History

Neurofibromatosis (or von Recklinghausen disease) was first described in 1882 by the German pathologist, Friedrich Daniel von Recklinghausen (December 2, 1833-August 26, 1910). As a young scientist, Recklinghausen was the student of the then renowned Rudolf Virchow in Berlin. Recklinghausen was successful in generating some of the most

descriptive medical observations of his time, making him the first person to describe and coin the term "hemachromatosis" (*Hämochromatose, Tageblatt der Naturforschenden Versammlung*). Recklinghausen is now known for his contributions to staining methods and most importantly for his important paper on neurofibromatosis published in 1881, to honor Rudolf Virchow's 25 year jubilee in which he describes neurofibromatosis. Recognized as a distinguished histopathologists, and a great scientist to this date, he lends his name to the syndrome, which he himself elucidated.

Chapter 14

Phenylketonuria

Phenylketonuria	
ICD-10	E70.0
ICD-9	270.1
OMIM	261600 261630
DiseasesDB	9987
MedlinePlus	001166
eMedicine	ped/1787 derm/712
MeSH	D010661

Phenylketonuria (**PKU**) is an autosomal recessive metabolic genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH).[:541] This enzyme is necessary to metabolize the amino acid phenylalanine ('Phe') to the amino acid tyrosine. When PAH is deficient, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which is detected in the urine.

Since its discovery, there have been many advances in its treatment. It can now be managed by the patient with little or no side-effects other than the inconvenience of managing the treatment. If, however, the condition is left untreated, it can cause problems with brain development, leading to progressive mental retardation, brain damage, and seizures. In the past, PKU was treated with a low-phenylalanine diet. Latter-day research now has shown that diet alone may not be enough to prevent the negative effects of phenylalanine levels. Optimal treatment involves lowering blood Phe levels to a safe range and monitoring diet and cognitive development. Lowering of phenylalanine levels to a safe range may be achieved by combining a low-phenylalanine diet with protein supplements. There is currently no cure for this disease; however, some treatments are available with varying success rates. In general, PKU is detected through newborn screening and diagnosed by a geneticist. PKU clinics around the world provide care for PKU patients to optimize phe levels, dietary intake, and cognitive outcomes.

History

Phenylketonuria was discovered by the Norwegian physician Ivar Asbjørn Følling in 1934 when he noticed that hyperphenylalaninemia (HPA) was associated with mental retardation. In Norway, this disorder is known as **Følling's disease**, named after its discoverer. Dr. Følling was one of the first physicians to apply detailed chemical analysis to the study of disease. His careful analysis of the urine of two affected siblings led him to request many physicians near Oslo to test the urine of other affected patients. This led to the discovery of the same substance that he had found in eight other patients. The substance found was subjected to much more basic and rudimentary chemical analysis (taste). He conducted tests and found reactions that gave rise to benzaldehyde and benzoic acid, which led him to conclude the compound contained a benzene ring. Further testing showed the melting point to be the same as phenylpyruvic acid, which indicated that the substance was in the urine. His careful science inspired many to pursue similar meticulous and painstaking research with other disorders.

Screening and presentation

Blood is taken from a two-week old infant to test for phenylketonuria

PKU is normally detected using the HPLC test, but some clinics still use the Guthrie test, part of national biochemical screening programs. Most babies in developed countries are screened for PKU soon after birth.

If a child is not screened during the routine newborn screening test (typically performed 6 –14 days after birth, using samples drawn by Neonatal heel prick), the disease may present clinically with seizures, albinism (excessively fair hair and skin), and a "musty odor" to the baby's sweat and urine (due to phenylacetate, one of the ketones produced).

In most cases, a repeat test should be done at approximately 2 weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed.

Untreated children are normal at birth, but fail to attain early developmental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function. Hyperactivity, EEG abnormalities and seizures, and severe learning disabilities are major clinical problems later in life. A "musty or mousy" odor of skin, hair, sweat and urine (due to phenylacetate accumulation); and a tendency to hypopigmentation and eczema are also observed.

In contrast, affected children who are detected and treated are less likely to develop neurological problems or have seizures and mental retardation, though such clinical disorders are still possible.

Pathophysiology

Classical PKU is caused by a mutated gene for the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid phenylalanine to other essential compounds in the body. Other non-PAH mutations can also cause PKU. This is an example of genetic heterogeneity.

Classical PKU

The PAH gene is located on chromosome 12 in the bands 12q22-q24.1. More than four hundred disease-causing mutations have been found in the PAH gene. PAH deficiency causes a spectrum of disorders including classic phenylketonuria (PKU) and hyperphenylalaninemia (a less severe accumulation of phenylalanine).

PKU is known to be an autosomal recessive genetic disorder. This means that both parents must have at least one mutated allele of the PAH gene. The child must inherit both mutated alleles, one from each parent. Therefore, it is not impossible for a parent with the disease to have a child without it if the other parent possesses one functional allele of the gene for PAH. Yet, a child from two parents with PKU will inherit two mutated alleles every time, and therefore the disease.

Phenylketonuria can exist in mice, which have been extensively used in experiments into an effective treatment for PKU. The macaque monkey's genome was recently sequenced, and it was found that the gene encoding phenylalanine hydroxylase has the same sequence that, in humans, would be considered the PKU mutation.

Tetrahydrobiopterin-deficient hyperphenylalaninemia

A rarer form of hyperphenilalaninemia occurs when PAH is normal but there is a defect in the biosynthesis or recycling of the cofactor tetrahydrobiopterin (BH_4) by the patient. This cofactor is necessary for proper activity of the enzyme. The coenzyme (called biopterin) can be supplemented as treatment.

Levels of dopamine can be used to distinguish between these two types. Tetrahydrobiopterin is required to convert phenylalanine to tyrosine, but it is also required to convert tyrosine to L-DOPA (via the enzyme tyrosine hydroxylase), which in turn is converted to dopamine. Low levels of dopamine lead to high levels of prolactin. By contrast, in classical PKU, prolactin levels would be relatively normal. Tetrahydrobiopterin deficiency can be caused by defects in four different genes. These types are known as HPABH4A, HPABH4B, HPABH4C, and HPABH4D.

Metabolic pathways

The enzyme phenylalanine hydroxylase normally converts the amino acid phenylalanine into the amino acid tyrosine. If this reaction does not take place, phenylalanine accumulates and tyrosine is deficient. Excessive phenylalanine can be metabolized into phenylketones through the minor route, a transaminase pathway with glutamate. Metabolites include phenylacetate, phenylpyruvate and phenethylamine. Elevated levels of phenylalanine in the blood and detection of phenylketones in the urine is diagnostic.

Phenylalanine is a large, neutral amino acid (LNAA). LNAAs compete for transport across the blood-brain barrier (BBB) via the large neutral amino acid transporter (LNAAT). If phenylalanine is in excess in the blood, it will saturate the transporter. Excessive levels of phenylalanine tend to decrease the levels of other LNAAs in the brain. However, as these amino acids are necessary for protein and neurotransmitter synthesis, phenylalanine buildup hinders the development of the brain, causing mental retardation.

Treatment

If PKU is diagnosed early enough, an affected newborn can grow up with normal brain development, but only by managing and controlling phenylalanine (Phe) levels through diet, or a combination of diet and medication. When phenylalanine cannot be metabolized by the body, abnormally high levels accumulate in the blood and are toxic to the brain. When left untreated, complications of PKU include severe mental retardation, brain function abnormalities, microcephaly, mood disorders, irregular motor functioning, and behavioral problems such as ADHD.

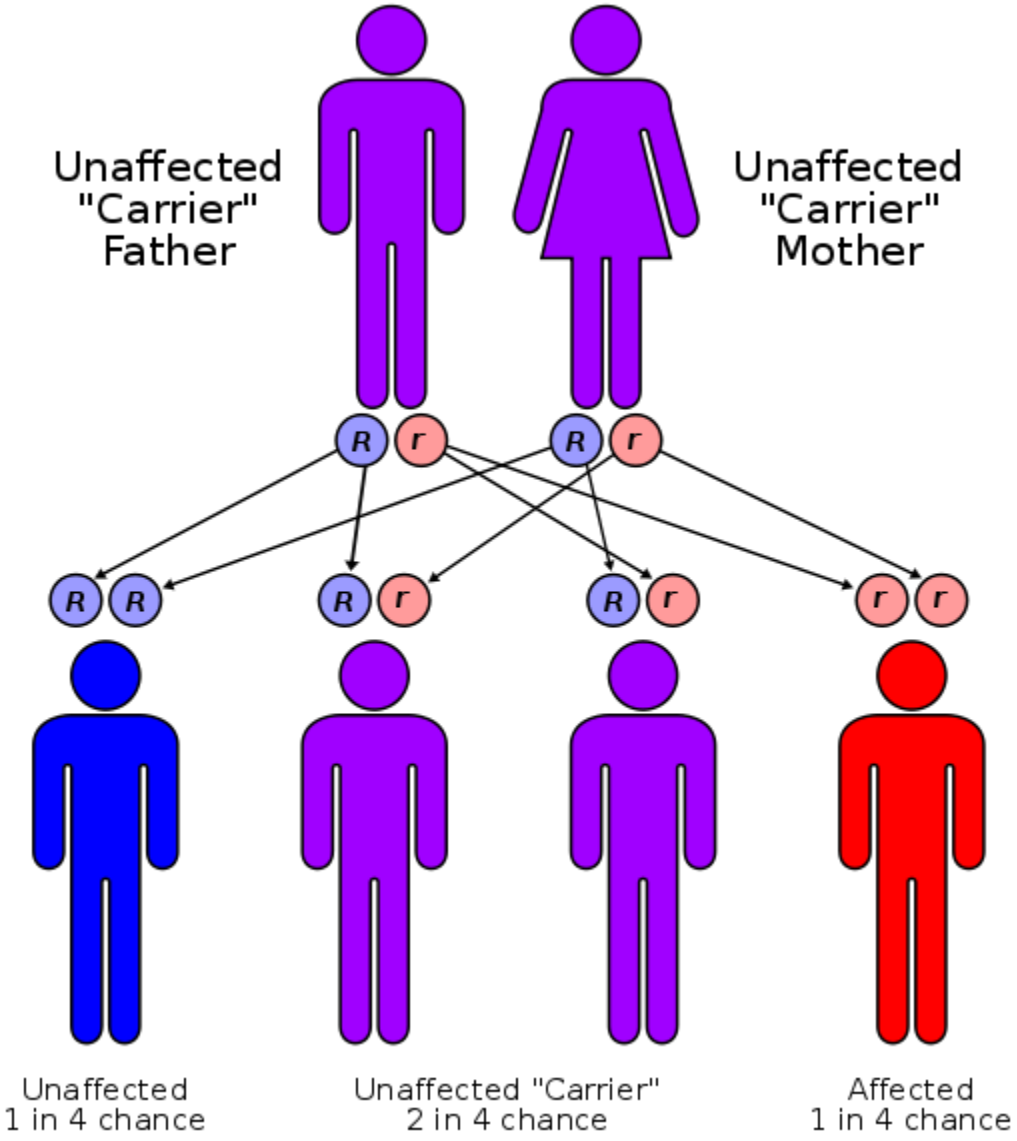
All PKU patients must adhere to a special diet low in phenylalanine for at least the first 16 years of their lives. This requires severely restricting or eliminating foods high in phenylalanine, such as meat, chicken, fish, eggs, nuts, cheese, legumes, cow milk and other dairy products. Starchy foods such as potatoes, bread, pasta, and corn must be monitored. Infants may still be breastfed to provide all of the benefits of breastmilk, but the quantity must also be monitored and supplementation for missing nutrients will be required. Many diet foods and diet soft drinks that contain the sweetener aspartame must also be avoided, as aspartame consists of two amino acids: phenylalanine and aspartic acid.

Supplementary infant formulas are used in these patients to provide the amino acids and other necessary nutrients that would otherwise be lacking in a low-phenylalanine diet. As the child grows up, these can be replaced with pills, formulas, and specially formulated foods. (Since phenylalanine is necessary for the synthesis of many proteins, it is required for appropriate growth but levels must be strictly controlled in PKU patients). In addition, tyrosine, which is normally derived from phenylalanine, must be supplemented.)

The oral administration of tetrahydrobiopterin (or BH4) (a cofactor for the oxidation of phenylalanine) can reduce blood levels of this amino acid in certain patients. The company BioMarin Pharmaceutical has produced a tablet preparation of the compound sapropterin dihydrochloride (Kuvan),which is a form of tetrahydrobiopterin. Kuvan is the first drug that can help BH4-responsive PKU patients (defined among clinicians as about 1/2 of the PKU population) lower Phe levels to recommended ranges. Working closely with a dietitian, some PKU patients who respond to Kuvan may also be able to increase the amount of natural protein they can eat. After extensive clinical trials, Kuvan has been approved by the FDA for use in PKU therapy. Some researchers and clinicians working with PKU are finding Kuvan a safe and effective addition to dietary treatment and beneficial to patients with PKU.

There are several other therapies currently under investigation, including gene therapy, large neutral amino acids, and enzyme substitution therapy with phenylalanine ammonia lyase (PAL). In the past, PKU-affected people were allowed to go off diet after approximately 8, then 18 years of age. Today most physicians recommend that PKU patients must manage their Phe levels throughout life.

Maternal phenylketonuria



Phenylketonuria is inherited in an autosomal recessive fashion

For women affected with PKU, it is essential for the health of their child to maintain low-phenylalanine levels before and during pregnancy. Though the developing fetus may only be a carrier of the PKU gene, the intrauterine environment can have very high levels of phenylalanine, which can cross the placenta. The result is that the child may develop congenital heart disease, growth retardation, microcephaly and mental retardation. PKU-affected women themselves are not at risk from additional complications during pregnancy.

In most countries, women with PKU that wish to have children are advised to lower their blood phenylalanine levels (typically to between 2 and 6 micromol/deciliter) before they

become pregnant, and carefully control their phenylalanine levels throughout the pregnancy. This is achieved by performing regular blood tests and adhering very strictly to a diet, in general monitored on a day-to-day basis by a specialist metabolic dietitian. In many cases, as the fetus' liver begins to develop and produce PAH normally, the mother's blood phenylalanine levels will drop, requiring an increased phenylalanine intake to remain within the safe range of 2-6 micromol/dL. The mother's daily phenylalanine intake may double or even triple by the end of the pregnancy, as a result. When maternal blood phenylalanine levels fall below 2 micromol/dL, anecdotal reports indicate that the mothers may suffer adverse effects including headaches, nausea, hair loss, and general malaise. When low phenylalanine levels are maintained for the duration of pregnancy, there are no elevated levels of risk of birth defects compared with a baby born to a non-PKU mother. Babies with PKU may drink breast milk, while also taking their special metabolic formula. Some research has indicated that an exclusive diet of breast milk for PKU babies may alter the effects of the deficiency, though during breastfeeding the mother must maintain a strict diet to keep their phenylalanine levels low. More research is needed. US scientist have recently announced (June 2010) that they will be conducting thorough investigation on the mutation of genes in the human genome. Their top priority is Phenylketonuria as it has become increasingly common, due to the fact that sufferers often live past the age of sixty and often bear children (carriers of the recessive gene).

Incidence

The incidence of PKU is about 1 in 15,000 births, but the incidence varies widely in different human populations from 1 in 4,500 births among the population of Ireland to 1 in 13,000 births in Norway to fewer than one in 100,000 births among the population of Finland. Turkey, at 1 in 2600, has the highest incidence rate in the world. The illness is also more common in Italy and China, as well as in Yemeni populations.

Chapter 15

Prader–Willi Syndrome

Prader-Willi syndrome

ICD-10	Q87.1
ICD-9	759.81
OMIM	176270
DiseasesDB	104
eMedicine	ped/1880
MeSH	D011218

Prader–Willi syndrome (abbreviated **PWS**) is a rare genetic disorder in which seven genes (or some subset thereof) on chromosome 15 (q 11-13) are deleted or unexpressed (chromosome 15q partial deletion) on the paternal chromosome. It was first described in 1956 by Andrea Prader (1919-2001), Heinrich Willi (1900-1971), Alexis Labhart (1916), Andrew Ziegler, and Guido Fanconi of Switzerland. The incidence of PWS is between 1

in 25,000 and 1 in 10,000 live births. The paternal origin of the genetic material that is affected in the syndrome is important because the particular region of chromosome 15 involved is subject to parent of origin imprinting, meaning that for a number of genes in this region only one copy of the gene is expressed while the other is silenced through imprinting. For the genes affected in PWS it is the paternal copy that is usually expressed, while the maternal copy is silenced. This means that while most people have a single working copy of these genes, people with PWS have no working copy. PWS has the sister syndrome Angelman syndrome in which maternally derived genetic material is affected in the same genetic region.

Signs and symptoms

Clinical features and signs
Holm *et al.* (1993) describe the following features and signs as pretest indicators of PWS, although not all will be present.

In utero:

- Reduced fetal movement
- Frequent abnormal fetal position
- Occasional polyhydramnios (excessive amniotic fluid)

At birth:

- Often breech or caesarean births
- Lethargy
- Hypotonia
- Feeding difficulties (due to poor muscle tone affecting sucking reflex)
- Difficulties establishing respiration
- Hypogonadism

Infancy:

- Failure to thrive (continued feeding difficulties)
- Delayed milestones/intellectual delay
- Excessive sleeping
- Strabismus
- Scoliosis (often not detected at birth)

Childhood:

- Speech delay
- Poor physical coordination
- Hyperphagia (over-eating) from age 2 – 8 years. Note change from feeding difficulties in infancy
- Excessive weight gain

- Sleep disorders
- Scoliosis

Adolescence:

- Delayed puberty
- Short stature
- Obesity
- Extreme flexibility

Adulthood:

- Infertility (males and females)
- Hypogonadism
- Sparse pubic hair
- Obesity
- Hypotonia
- Learning disabilities/borderline intellectual functioning (but some cases of average intelligence)
- Prone to diabetes mellitus
- Extreme flexibility

General physical appearance (adults)

- Prominent nasal bridge
- Small hands and feet with tapering of fingers
- Soft skin, which is easily bruised
- Excess fat, especially in the central portion of the body
- High, narrow forehead
- Almond-shaped eyes with thin, down-turned lids
- Light skin and hair relative to other family members
- Lack of complete sexual development
- Frequent skin picking
- Striae
- Delayed motor development

Neuro-cognitive

Individuals with PWS are at risk of learning and attention difficulties. Curfs and Frym (1992) conducted research into the varying degrees of learning disability found in Prader Willi Syndrome (PWS). Their results were as follows:

- 5%: IQ above 85 (average to low average intelligence)

- 27%: IQ 70 – 85 (borderline intellectual functioning)

- 39%: IQ 50 – 70 (mild intellectual disability)
- 27%: IQ 35 – 50 (moderate intellectual disability)
- 1%: IQ 20 – 35 (severe intellectual disability)
- <1%: IQ <20 (profound intellectual disability)

Cassidy found that 40% of individuals with PWS have borderline/low average intelligence, a figure higher than that found in Curfs and Frym's study (32%). However, both studies suggest that most individuals (50–65%) fall within the mild/borderline/low average intelligence range.

Children with PWS show an unusual cognitive profile. They are often strong in visual organization and perception, including reading and vocabulary, but their spoken language (sometimes affected by hypernasality) is generally poorer than their comprehension. A marked skill in completing jigsaw puzzles has been noted, although this may be an effect of increased practise.

Auditory information processing and sequential processing are relatively poor, as are arithmetic and writing skills, visual and auditory short term memory and auditory attention span. These sometimes improve with age, but deficits in these areas remain throughout adulthood.

Behavioral

Prader–Willi syndrome is also frequently associated with an extreme and insatiable appetite, often resulting in morbid obesity. There is currently no consensus as to the cause for this particular symptom, although genetic abnormalities in chromosome 15 disrupt the normal functioning of the hypothalamus. Given that the hypothalamus regulates many basic processes, including appetite, there may well be a link. However, no organic defect of the hypothalamus has been discovered on post mortem investigation.

Prader–Willi syndrome patients have high ghrelin levels, which are thought to directly contribute to the increased appetite, hyperphagia, and obesity seen in this syndrome. Cassidy states the need for a clear delineation of behavioural expectations, the reinforcement of behavioural limits and the establishment of regular routines.

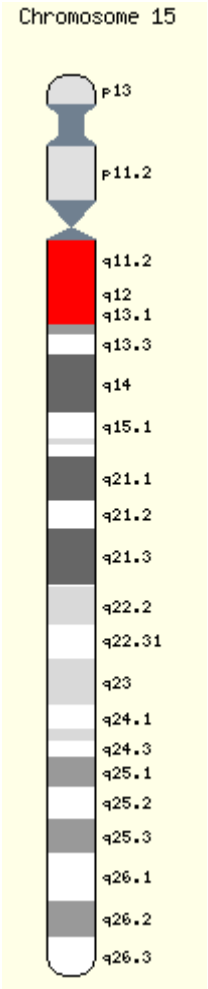
The main mental health difficulties experienced by people with PWS include compulsive behaviour (usually manifested in skin-picking) and anxiety. Psychiatric symptoms, for example, hallucinations, paranoia and depression have been described in some cases and affect approximately 5–10% of young adults. Psychiatric and behavioural problems are the most common cause of hospitalization.

Endocrine

There are several aspects of PWS that support the concept of growth hormone deficiency in individuals with PWS. Specifically, individuals with PWS have short stature, are obese with abnormal body composition, have reduced fat free mass (FFM), have reduced LBM and total energy expenditure, and have decreased bone density.

PWS is characterized by hypogonadism. This is manifested as undescended testes in males and benign premature adrenarche in females. Testes may descend with time or can be managed with surgery or testosterone replacement. Adrenarche may be treated with hormone replacement therapy.

Genetics



PWS is caused by the deletion of the paternal copies of the imprinted SNRPN and necdin genes along with clusters of snoRNAs: SNORD64, SNORD107, SNORD108 and two copies of SNORD109, 29 copies of SNORD116 (HBII-85) and 48 copies of SNORD115 (HBII-52). These are on chromosome 15 located in the region 15q11-13. This so-called PWS/AS region may be lost by one of several genetic mechanisms which, in the majority

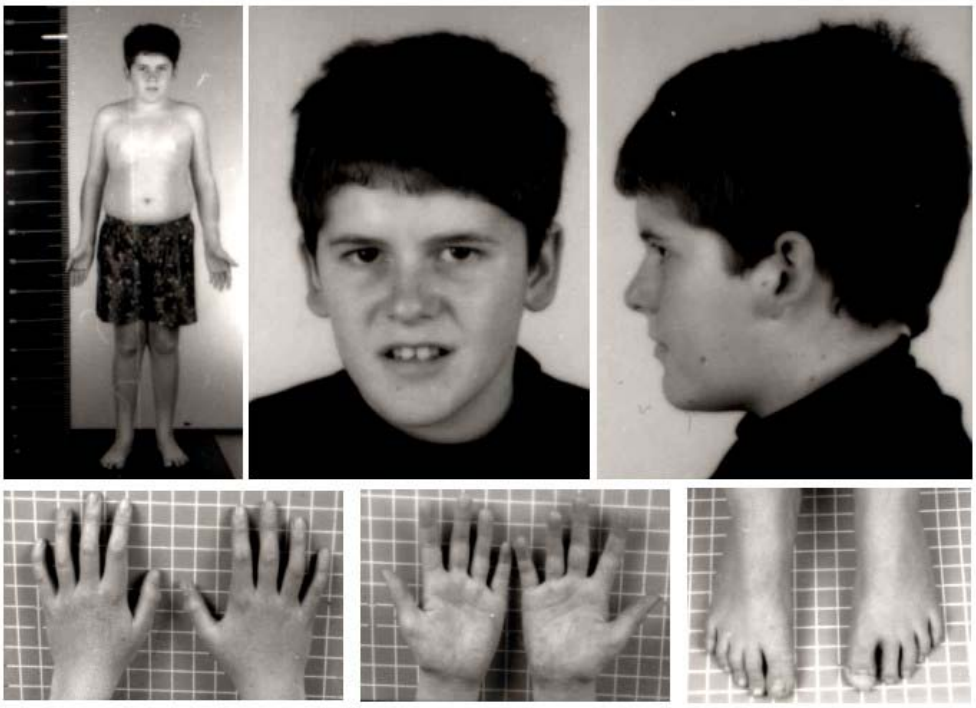
of instances occurs through chance mutation. Other less common mechanisms include; uniparental disomy, sporadic mutations, chromosome translocations, and gene deletions. Due to imprinting, the maternally inherited copies of these genes are virtually silent, only the paternal copies of the genes are expressed. PWS results from the loss of paternal copies of this region. Deletion of the same region on the maternal chromosome causes Angelman syndrome (AS). PWS and AS represent the first reported instances of imprinting disorders in humans.

The risk to the sibling of an affected child of having PWS depends upon the genetic mechanism which caused the disorder. The risk to siblings is <1% if the affected child has a gene deletion or uniparental disomy, up to 50% if the affected child has a mutation of the imprinting control region, and up to 25% if a parental chromosomal translocation is present. Prenatal testing is possible for any of the known genetic mechanisms.

A microdeletion in one family of the snoRNA HBII-52 has excluded it from playing a major role in the disease.

Studies of human and mouse model systems have shown that deletion of the 29 copies of the C/D box snoRNA SNORD116 (HBII-85) has been shown to be the primary cause of Prader–Willi syndrome.

Diagnosis



Prader-Willi syndrome phenotype at 15 years of age. Note absence of typical PWS facial features and presence of mild truncal obesity.

PWS affects approximately 1 in 10,000 to 1 in 25,000 newborns. There are more than 400,000 people who live with PWS around the world. It is traditionally characterized by hypotonia, short stature, hyperphagia, obesity, behavioral issues (specifically OCD-like behaviors), small hands and feet, hypogonadism, and mild mental retardation. However, with early diagnosis and early treatment (such as with growth hormone therapy), the prognosis for persons with PWS is beginning to change. Like autism, PWS is a spectrum disorder and so symptoms can range from mild to severe, and may change throughout the person's lifetime. Various organ systems are affected.

Traditionally, Prader-Willi Syndrome was diagnosed by clinical presentation. Currently, the syndrome is diagnosed through genetic testing; testing is recommended for newborns with pronounced hypotonia. Early diagnosis of PWS allows for early intervention as well as the early prescription of growth hormone. Daily recombinant growth hormone (GH) injections are indicated for children with PWS. GH supports linear growth and increased muscle mass, and may lessen food preoccupation and weight gain.

The mainstay of diagnosis is genetic testing, specifically DNA-based methylation testing to detect the absence of the paternally contributed Prader–Willi syndrome/Angelman syndrome (PWS/AS) region on chromosome 15q11-q13. Such testing detects over 97% of patients. Methylation-specific testing is important to confirm the diagnosis of PWS in all individuals, but especially those who are too young to manifest sufficient features to make the diagnosis on clinical grounds or in those individuals who have atypical findings. Because PWS infants have a higher rate of difficulties at birth (including breech delivery and respiratory delay) birth-related injuries and oxygen deprivation may complicate the genetic handicaps, resulting in atypical PWS.

Differential diagnosis

Prader–Willi syndrome is often misdiagnosed as a variety of other syndromes due to many in the medical community's unfamiliarity with PWS. Sometimes it is misdiagnosed as Down syndrome, simply because of the relative frequency of Down syndrome compared to PWS. Also, marked obesity can occur in Down syndrome due to behavioral problems. Adding to the confusion, parents of children who already carry a diagnosis of Prader–Willi syndrome may tell friends, family, and even physicians and nurses that their child has Down syndrome because more people have heard of that condition. It is thought that 75% of those with PWS are undiagnosed.

Treatment

Prader–Willi syndrome has no cure; however, several treatments are in place to lessen the condition's symptoms. During infancy, subjects should undergo therapies to improve muscle tone. Speech and occupational therapy are also indicated. During the school years, children benefit from a highly structured learning environment as well as extra help. The largest problem associated with the syndrome is severe obesity.

Prescription of daily recombinant growth hormone injections are indicated for children with PWS. GH supports linear growth and increased muscle mass, and may lessen food preoccupation and weight gain.

Because of severe obesity, obstructive sleep apnea is a common sequela, and a positive airway pressure machine is often needed.

Society and culture

Prader–Willi syndrome appeared in the UK media in July 2007 when Channel 4 aired a program *Can't Stop Eating*, surrounding the everyday lives of two Prader-Willi patients, Joe and Tamara.

An individual with Prader-Willi Syndrome featured in the episode entitled "Dog Eat Dog" of the television series *CSI: Crime Scene Investigation* (aired on November 24, 2005).

Another individual with Prader–Willi syndrome, Ethan Starkweather, was on *Extreme Makeover: Home Edition* originally aired on Mothers Day 2010.

Actress and neuroscientist Mayim Bialik wrote a thesis on Prader–Willi syndrome for her Ph.D, which was completed in 2008.

On TLC's *My Deadly Appetite* (aired in December 2010), a patient named Will was treated for the condition (as well as others featured).

Chapter 16

1p36 Deletion Syndrome

1p36 deletion syndrome

A toddler showing facial symptoms of the syndrome.

OMIM	607872
DiseasesDB	34535

1p36 deletion syndrome (also known as **monosomy 1p36**) is a congenital genetic disorder characterized by moderate to severe intellectual disability, delayed growth, hypotonia, seizures, limited speech ability, malformations, hearing and vision impairment, and distinct facial features. The symptoms may vary, depending on the exact location of the chromosomal deletion.

The condition is caused by a genetic deletion (loss of a segment of DNA) on the outermost band on the short arm (p) of chromosome 1. It is one of the most common deletion syndromes. It is estimated that the syndrome occurs in one in every 5,000 to 10,000 births. Knowledge of the disorder has increased a great deal over the last decade, mainly because more patients have been accurately diagnosed and described in international medical literature.

Characteristics

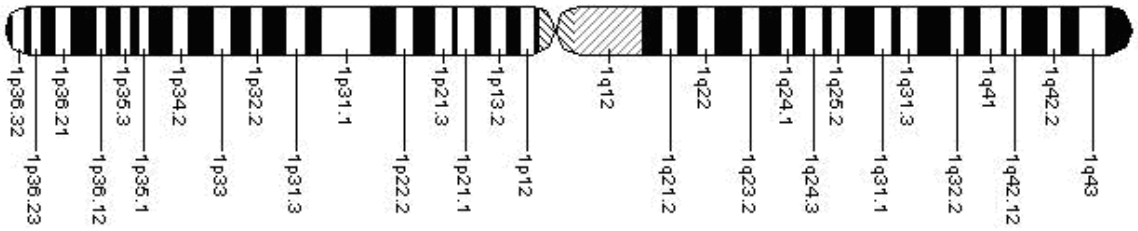
The facial features of 1p36 deletion syndrome have been considered to be characteristic, although few patients have been diagnosed solely on the basis of facial appearance. These features may include microcephaly, small, possibly slanted, deep-set eyes, a flat nose and nasal bridge, anomalous, low-set and small ears, a small mouth with down-turned corners and a pointed chin. Distinguishing features in another study were a large or late-closing anterior fontanelle (up to 85% of patients) and facial asymmetry.

History

The first cases of 1p36 deletion syndrome were described in the 1980s. However, since many of these individuals also had other chromosomal imbalances, symptoms varied widely. The reason it took so long to recognize the condition as a distinct chromosome deletion syndrome is that the deletions causing the disorder are too small to be detected in a routine chromosomal analysis. FISH (fluorescent *in situ* hybridization) and DNA-based technology known as MLPA (multiple ligation probe amplification) used in testing have aided in diagnosing an increasing number of cases since the 1990s.

Genetics

1p36 Deletion Syndrome is a congenital genetic disorder caused by the deletion of the most distal light band of the short arm of chromosome 1. Chromosome 1 is the largest human chromosome and represents about 8 percent of the total DNA in human cells. The "p" stands for the short or 'petite' arm of the chromosome. '36' stands for the location of the deletion on the chromosome.



Human chromosome 1

The breakpoints for 1p36 Deletion Syndrome have been variable and are most commonly found from 1p36.13 to 1p36.33. 40 percent of all breakpoints occur 3 to 5 million base pairs from the telomere. The size of the deletion ranges from approximately 1.5 million base pairs to greater than 10 million. Studies have suggested that the larger the deletion, the more severe the symptoms exhibited in the individual, but this has not been proven definitively.

Most deletions in chromosome 1p36 are new mutations, that occur before fertilization, during the formation of gametes (eggs or sperm). There have also been reports of patients

with 1p36 deletion syndrome whose parents have a balanced or symmetrical translocation. This means a portion of one chromosome is transferred to another chromosome, so the parent has the "36" portion of chromosome 1 attached in an alternate location. When this occurs, cell division creates gametes that are missing a piece of 36.

In new mutations, the mechanism causing chromosome breakage is unknown. Deletions of paternal origin (father) are larger than the deletions deriving from the maternal (mother) chromosome. The majority of deletions are maternally derived. There do not seem to be differences in the clinical manifestations (the symptoms or observable conditions which are seen as a result of 1p36) based on whether the deletion is on the paternal or maternal chromosome.

Health concerns

Developmental delay

Most young children with 1p36 deletion syndrome have delayed development. They sit up, walk and talk later than typical children. Speech is severely affected, with many patients learning only a few words. It was originally thought that the degree of the delay and the ability to acquire complex speech was somewhat dependent on deletion size. Reports of a milder learning disability in children with smaller deletions have suggested that there may be a correlation between deletion size and mental ability; however, this requires further investigation and research. Recent research by Dr Lisa Shaffer has shown however that there is no correlation between deletion size and degree of developmental delay. This suggests that the most genetically potent area of the 1P36 chromosome occurs at the terminal end of the chromosome.

Behavioral differences

Many children with 1p36 deletion syndrome have behavioral problems. Some of these include temper outbursts, banging or throwing objects, striking people, screaming episodes, and self-injurious behavior (wrist biting, head striking/banging). Autistic behavior has also been noted in some children. Also, some parents have described behaviors such as a love of water, although there have not been any studies into this yet.

Feeding difficulties

Many children with 1p36 deletion syndrome have oropharyngeal dysphagia which is characterized by difficulty in initiating a swallow. Some of the other feeding issues include poor sucking and swallowing, reflux, and vomiting in infancy. Many require nasalgastric or gastric tubes to ensure they are receiving sufficient nutrition.

Brain abnormalities

Brain imaging has documented cerebral atrophy, which is a loss of neurons in the brain and the connections between them. Also documented were problems with the ventricular

system in the brain, such as ventricular asymmetry and ventricular enlargement. Hydrocephalus has also been noted in children with 1p36 deletion syndrome. This is basically too much fluid within the brain. Hyperreflexia, which is defined as overactive or overresponsive reflexes in the body, was also found to be common. Many children also have epilepsy which is a disorder of the brain that results in recurrent, unprovoked seizures.

Microcephaly

Microcephaly is a disorder in which the circumference of the head is smaller than average for the person's age and gender. Most children with microcephaly also have a small brain and mental retardation. Some of the most common signs and symptoms associated with microcephaly are seizures, poor feeding, high pitched cry, mental retardation, developmental delay, and increased movement of arms and legs.

Vision problems

Vision abnormalities in children with 1p36 have been wide-ranging, including:

- **Strabismus**: A condition in which the two eyes do not point in the same direction when the patient is looking at a distant object.
- **Sixth nerve palsy**: Double vision
- **Refractive errors**: Refractive errors include nearsightedness, farsightedness, astigmatism (a warping of the curvature of the cornea) and presbyopia (the inability to maintain a clear image or focus as objects are moved closer). These disorders of the eye can be corrected with glasses or contacts.
- **Hypermetropia**: A condition where the eye is too small and eyes have to over focus to see clearly; also called farsightedness.
- **Cataracts**: A cataract is an opacity or cloudiness in the natural lens of the eye.
- **Nystagmus**: A condition characterized by the repetitive oscillations (vibration) of the eyes. Parents of children with nystagmus often refer to this as "jerking" "or "jiggling" eyes.
- **Lacrimal defects**: The lacrimal glands in the eye secrete tears.
- **Visual Inattentiveness**: Defined as an absence of attentive visual behavior such as fixation and following movements.

Distinct facial features

Children with 1p36 deletion syndrome are all unique individuals, but do have some common distinct facial features such as:

- **Large anterior fontanelle/Frontal bossing**: The anterior fontanelle is the "soft spot" towards the front of the top of an infant's head between the growing skull bones. Frontal bossing simply means a prominent forehead.
- **Small and pointed chin**
- **Flat nose and/or nasal bridge**

- **Low-set, small ears/Ear asymmetry**: Ears are abnormally low set on the head and may be small. They may not be the same shape or size, or not lined up.
- **Deep set eyes**
- **Thickened ear helices**: Ear helices are the outer rings of cartilage of the ears.
- **Short, narrow and slanting palpebral fissures**: Palpebral fissures are the gaps between the upper and lower eyelids, or the opening of the eyes.
- **Midface Hypoplasia**: This is where the middle of the face is underdeveloped, leading to a concave-looking face. The bridge of the nose looks sunken in and the eyes are set widely apart and often protrude out of the sockets.
- **Small mouth with down-turned corners**
- **Orofacial clefting**: This is a relatively common birth defect in which the fetus develops with deformities of the upper lip, gum, and roof of the mouth. Children with 1p36 have been noted to have orofacial clefting involving the lip and/or palate or uvula (the small piece of flesh hanging down inside the mouth at the back of the palate).

Growth abnormalities

There are many growth abnormalities associated with 1p36 deletion syndrome. One common problem is delayed growth or difficulty in gaining weight. Even though some of the children may eat well, they still may not grow normally. In contrast, some children may develop hyperphagia, which is overeating, and may become obese. These children clinically resemble children with Prader-Willi syndrome. Developmental delay has also been severe in the patients with the Prader-Willi like characteristics.

- **Hypotonia**: Hypotonia is a decreased or low muscle tone. This may explain the delayed motor skills in children with 1p36.
- **Hypothyroidism**: Hypothyroidism is insufficient production of the thyroid hormone. Symptoms include weight gain, constipation, dry skin, and sensitivity to the cold. Around one third of children with the syndrome have this low thyroid function, which is also called underactive thyroid, and leads to slow metabolism and fatigue.
- **Heart defects**:
    - **Infantile dilated cardiomyopathy**: Dilated cardiomyopathy (DCM) is a disease of the heart muscle that causes the heart to become enlarged, and to pump less strongly. This causes fluid to build up in the lungs, which therefore become congested, and results in a feeling of breathlessness. Children with DCM due to their 1p36 deletion syndrome typically do not worsen over time, though some of them may need to continue taking medication.
    - **Patent ductus arteriosus**: This is the most common structural heart defect in children with 1p36. It is a condition in which the connecting blood vessel between the pulmonary artery and the aorta in fetal circulation stays open in the newborn. The defect often corrects itself within several months of birth, but may require the infusion of chemicals, the placement of "plugs" via catheters, or surgical closure.

    - **Tetralogy of Fallot**: Tetralogy of Fallot is a ventricular septal defect, a hole between the two bottom chambers (ventricles) of the heart. These defects can cause less blood flow to the lungs, the mixing of oxygen-rich and oxygen-poor blood inside the heart, and low levels of oxygen in the blood. When oxygen levels are low, the baby's skin, fingertips, or lips have a bluish tint. This condition is called cyanosis.
- **Increased Risk for Neoplasia**: Chromosome 1p36 alterations, mostly deletions, have been reported to occur in various types of neoplastic growths or tumors which may be benign or malignant. The 1p36 region contains a number of tumor-suppressor genes, which are genes that act to prevent cell growth. The deletion of one or more of these genes can cause malignancy (cancer). Some of the neoplams involved in the 1p36 are neuroblastoma, prostate cancer, lung cancer, melanoma, hepatoma, cervical cancer, breast cancer, colorectal cancer, ovarian cancer, and non-Hodgkin lymphoma. This is not to say that the children with 1p36 deletion syndrome will get these cancers, but this is a theory that has been put forth.
- **Genital hypoplasia**: Genital hypoplasia is the underdevelopment of the genital areas. Some of the genital problems in children with 1p36 are:
    - **Cryptorchidism**: This is the failure of one or both of the testicles to descend into the scrotum.
    - **Shawl Scrotum**: A condition in which the scrotum tends to surround the penis.
    - **Small Genitalia**

Dilation of the renal collecting system

The collecting system is the structure that collects urine directly from the kidney tissue and routes it by way of the ureter to the bladder. Structural renal abnormalities are rare in both sexes.

Hearing loss

Hearing loss affects approximately two thirds of 1p36 deletion patients. It can be of different types. Sensorineural hearing loss is a type of hearing impairment caused by damage that occurs to the inner ear (cochlea) or to the nerve used for hearing (vestibulocochlear nerve). Conductive hearing loss is a hearing loss associated with the functioning of the outer or middle ear. This type is most common in children with 1p36 deletion syndrome. It ranges from mild loss at various frequencies, to severe loss at all frequencies.

Puberty

Puberty in children with 1p36 deletion syndrome can be early, normal, or delayed.

Spinal deformities

Only a few spinal deformities have been seen in children with 1p36. The deformities found are:

- **Kyphoscoliosis**: Spinal deformity combining a sideways curvature with a hunching forward of the upper part of the spine.
- **Postural Kyphosis**: Also called postural "round back". This was found secondary to hypotonia in some children with 1p36.

Treatments and therapy

Although 1p36 Deletion Syndrome can be debilitating in many ways, patients do respond to various treatments and therapies. These include the following:

American Sign Language: Because few individuals with Monosomy 1p36 develop complex speech, an alternate form of communication is critical to development. Most patients can learn basic signs to communicate their needs and wants. This also appears to reduce frustration and may reduce self-injurious tendencies. Children with hearing loss will often qualify for locally sponsored sign language classes.

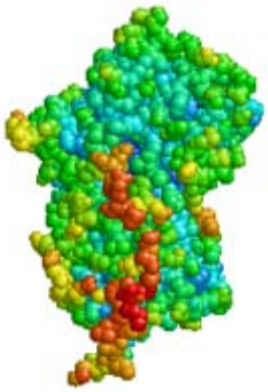
Music: Music has been shown to aid children with 1p36 deletion in various developmental areas. It serves as an excellent auditory stimulus and can teach listening skills. Songs with actions help the child to develop coordination and motor skills.

Physical Therapy: Due to low muscle tone, patients with 1p36 Deletions take a great deal of time to learn to roll over, sit up, crawl and walk. However, regular physical therapy has shown to shorten the length of time needed to achieve each of those developmental milestones.

Chapter 17

Alpha 1-Antitrypsin Deficiency

Alpha 1-antitrypsin deficiency



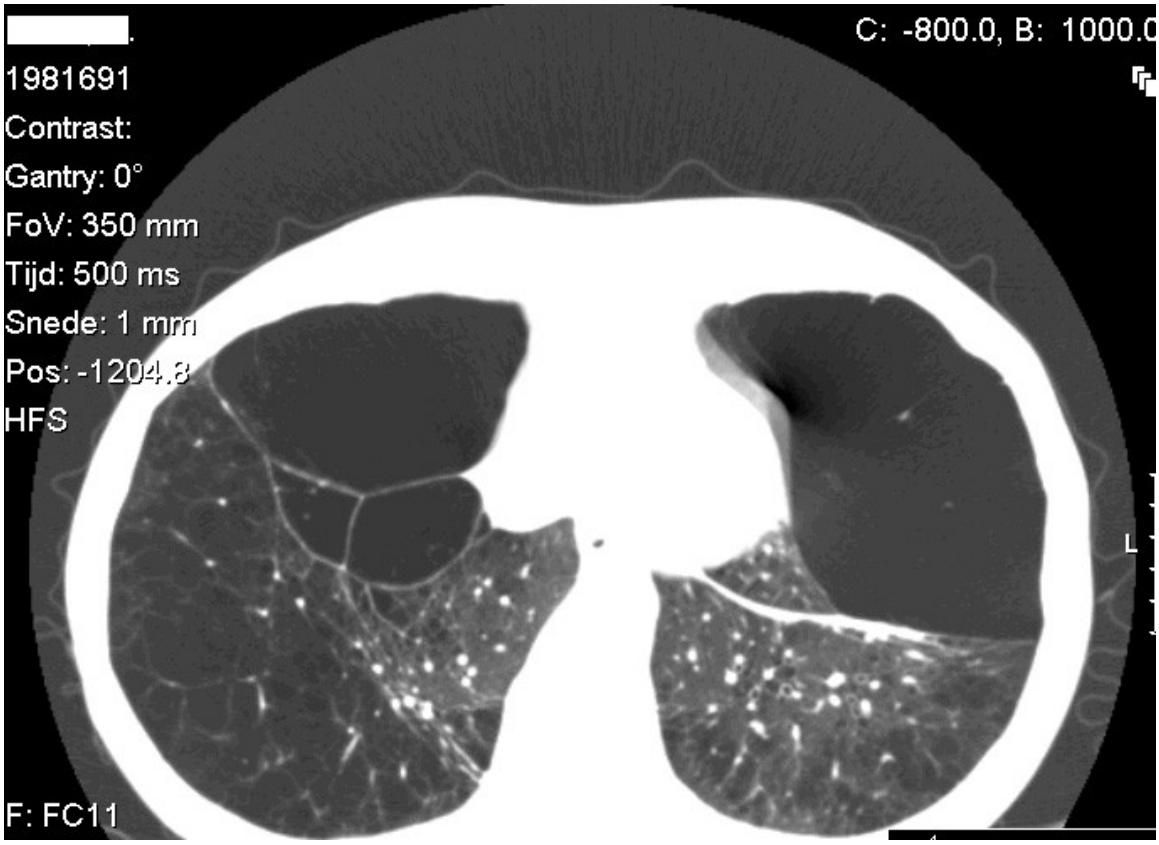
Structure of Alpha 1-antitrypsin

ICD-10	E88.0
ICD-9	273.4
OMIM	107400
DiseasesDB	434
MedlinePlus	000120
eMedicine	med/108
MeSH	D019896
GeneReviews	Alpha1-Antitrypsin Deficiency

Alpha 1-antitrypsin deficiency (**α1-antitrypsin deficiency**, **A1AD** or simply **Alpha-1**) is an autosomal codominant genetic disorder caused by defective production of alpha 1-antitrypsin (A1AT), leading to decreased A1AT activity in the blood and lungs, and deposition of excessive abnormal A1AT protein in liver cells. There are several forms and degrees of deficiency, principally depending on whether the sufferer has one or two copies of the affected gene. Severe A1AT deficiency causes panacinar emphysema or

COPD in adult life in many people with the condition (especially if they are exposed to cigarette smoke), as well as various liver diseases in a minority of children and adults, and occasionally more unusual problems. It is treated by avoidance of damaging inhalants, by intravenous infusions of the A1AT protein, by transplantation of the liver or lungs, and by a variety of other measures, but it usually produces some degree of disability and reduced life expectancy.

Signs and symptoms



Computed tomography of the lung showing emphysema and bullae in the lower lung lobes of a subject with type ZZ alpha-1-antitrypsin deficiency. There is also increased lung density in areas with compression of lung tissue by the bullae.

Symptoms of alpha-1 antitrypsin deficiency include shortness of breath, wheezing, rhonchi, and rales. The patient's symptoms may resemble recurrent respiratory infections or asthma that does not respond to treatment. Individuals with A1AD may develop emphysema during their thirties or forties even without a history of significant smoking, though smoking greatly increases the risk for emphysema. A1AD also causes impaired liver function in some patients and may lead to cirrhosis and liver failure (15%). It is a leading cause of liver transplantation in newborns.

Associated conditions

α_1-antitrypsin deficiency has been associated with a number of diseases:

- Cirrhosis
- COPD
- Pneumothorax
- Asthma
- Wegener's granulomatosis
- Pancreatitis
- Gallstones
- Bronchiectasis
- Pelvic organ prolapse
- Primary sclerosing cholangitis
- Autoimmune hepatitis
- Emphysema, predominantly involving the lower lobes and causing bullae
- Cancer
    - Hepatocellular carcinoma (liver)
    - Bladder carcinoma
    - Gallbladder cancer
    - Lymphoma
    - Lung cancer

Pathophysiology

Alpha 1-antitrypsin (A1AT) is produced in the liver, and one of its functions is to protect the lungs from the neutrophil elastase enzyme, which can disrupt connective tissue. Normal blood levels of alpha-1 antitrypsin are 1.5-3.5 g/l. In individuals with PiSS, PiMZ and PiSZ phenotypes, blood levels of A1AT are reduced to between 40 and 60% of normal levels. This is usually sufficient to protect the lungs from the effects of elastase in people who do not smoke. However, in individuals with the PiZZ phenotype, A1AT levels are less than 15% of normal, and patients are likely to develop panacinar emphysema at a young age; 50% of these patients will develop liver cirrhosis, because the A1AT is not secreted properly and instead accumulates in the liver. A liver biopsy in such cases will reveal PAS-positive, diastase-resistant granules.

Cigarette smoke is especially harmful to individuals with A1AD. In addition to increasing the inflammatory reaction in the airways, cigarette smoke directly inactivates alpha 1-antitrypsin by oxidizing essential methionine residues to sulfoxide forms, decreasing the enzyme activity by a factor of 2000.

Diagnosis

A1AT deficiency remains undiagnosed in many patients. Patients are usually labelled as having COPD without an underlying cause. It is estimated that about 1% of all COPD patients actually have A1AT deficiency. Thus, testing should be performed for all

patients with COPD, asthma with irreversible air-flow obstruction, unexplained liver disease, or necrotizing panniculitis. The initial test performed is serum A1AT level. A low level of A1AT confirms the diagnosis and further assessment with A1AT protein phenotyping and A1AT genotyping should be carried out subsequently.

As protein electrophoresis is imprecise, A1AT is analysed by isoelectric focusing (IEF) in the pH range 4.5-5.5, where the protein migrates in a gel according to its isoelectric point or charge in a pH gradient. Normal A1AT is termed M, as it is migrates toward the center of such an IEF gel. Other variants are less functional, and are termed A-L and N-Z, dependent on whether they run proximal or distal to the M band. The presence of deviant bands on IEF can signify the presence of alpha 1-antitrypsin deficiency. Since the number of identified mutations has exceeded the number of letters in the alphabet, subscripts have been added to most recent discoveries in this area, as in the Pittsburgh mutation described above. As every person has two copies of the A1AT gene, a heterozygote with two different copies of the gene may have two different bands showing on electrofocusing, although heterozygote with one null mutant that abolishes expression of the gene will only show one band. In blood test results, the IEF results are notated as in PiMM, where Pi stands for protease inhibitor and "MM" is the banding pattern of that patient. Other detection methods include use of enzyme-linked-immuno-sorbent-assays in vitro and radial immunodiffusion. Alpha 1-antitrypsin levels in the blood depend on the genotype. Some mutant forms fail to fold properly and are, thus, targeted for destruction in the proteasome, whereas others have a tendency to polymerise, being retained in the endoplasmic reticulum. The serum levels of some of the common genotypes are: PiMM: 100% (normal) PiMS: 80% of normal serum level of A1AT PiSS: 60% of normal serum level of A1AT PiMZ: 60% of normal serum level of A1AT PiSZ: 40% of normal serum level of A1AT PiZZ: 10-15% (severe alpha 1-antitrypsin deficiency) PiZ is caused by a glutamate to lysine mutation at position 342 PiS is caused by a glutamate to valine mutation at position 264 Other rarer forms have been described; in all there are over 80 variants.

Treatment

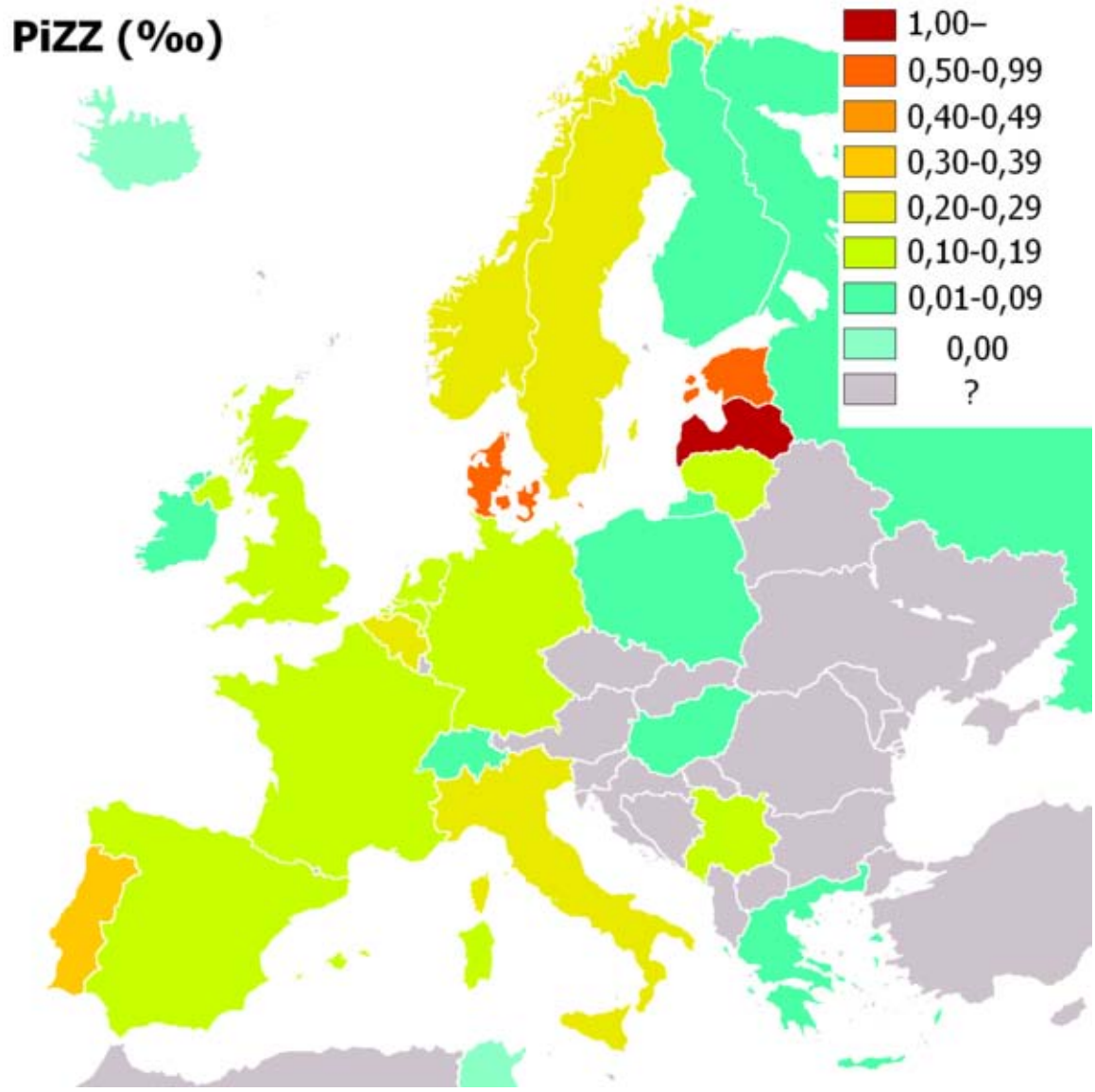
In the United States, Canada, and several European countries, lung-affected A1AD patients may receive intravenous infusions of alpha-1 antitrypsin, derived from donated human plasma. This augmentation therapy is thought to arrest the course of the disease and halt any further damage to the lungs. Long-term studies of the effectiveness of A1AT replacement therapy are not available. It is currently recommended that patients begin augmentation therapy only after the onset of emphysema symptoms.

Augmentation therapy is not appropriate for liver-affected patients; treatment of A1AD-related liver damage focuses on alleviating the symptoms of the disease. In severe cases, liver transplantation may be necessary.

As α_1-antitrypsin is an acute phase reactant, its transcription is markedly increased during inflammation elsewhere in response to increased interleukin-1 and 6 and TNFα production.

Treatments currently being studied include recombinant and inhaled forms of A1AT. Other experimental therapies are aimed at the prevention of polymer formation in the liver.

Epidemiology



Distribution of PiZZ in Europe

People of northern European, Iberian and Saudi Arabian ancestry are at the highest risk for A1AD. Four percent carry the PiZ allele; between 1 in 625 and 1 in 2000 are homozygous.

History

A1AD was discovered in 1963 by Carl-Bertil Laurell (1919–2001), at the University of Lund in Sweden. Laurell, along with a medical resident, Sten Eriksson, made the discovery after noting the absence of the α_1 band on protein electrophoresis in five of 1500 samples; three of the five patient samples were found to have developed emphysema at a young age.

The link with liver disease was made six years later, when Sharp *et al.* described A1AD in the context of liver disease.

Chapter 18

Chronic Granulomatous Disease

Chronic granulomatous disease

Superoxide

ICD-10	D71.
ICD-9	288.1
OMIM	306400 233690 233700
DiseasesDB	2633
MedlinePlus	001239
eMedicine	ped/1590 derm/719
MeSH	D006105

Chronic granulomatous disease (CGD) (also known as "Bridges–Good syndrome," "Chronic granulomatous disorder," and "Quie syndrome") is a diverse group of hereditary diseases in which certain cells of the immune system have difficulty forming the reactive oxygen compounds (most importantly, the superoxide radical) used to kill certain ingested pathogens. This leads to the formation of granulomata in many organs. CGD affects about 1 in 200,000 people in the United States, with about 20 new cases diagnosed each year.

This condition was first discovered in 1954, and in 1957 described as "a fatal granulomatosus of childhood". The underlying cellular mechanism that causes chronic

granulomatous disease was discovered in 1967, and research since that time has further elucidated the molecular mechanisms underlying the disease.

Classification

Chronic granulomatous disease is the name for a genetically heterogeneous group of immunodeficiencies. The core defect is a failure of phagocytic cells to kill organisms that they have engulfed because of defects in a system of enzymes that produce free radicals and other toxic small molecules. There are several types, including chronic X-linked disease, chronic b-negative disease, X-linked cytochrome b-positive disease, x-linked variant disease, and atypical granulomatous disease.

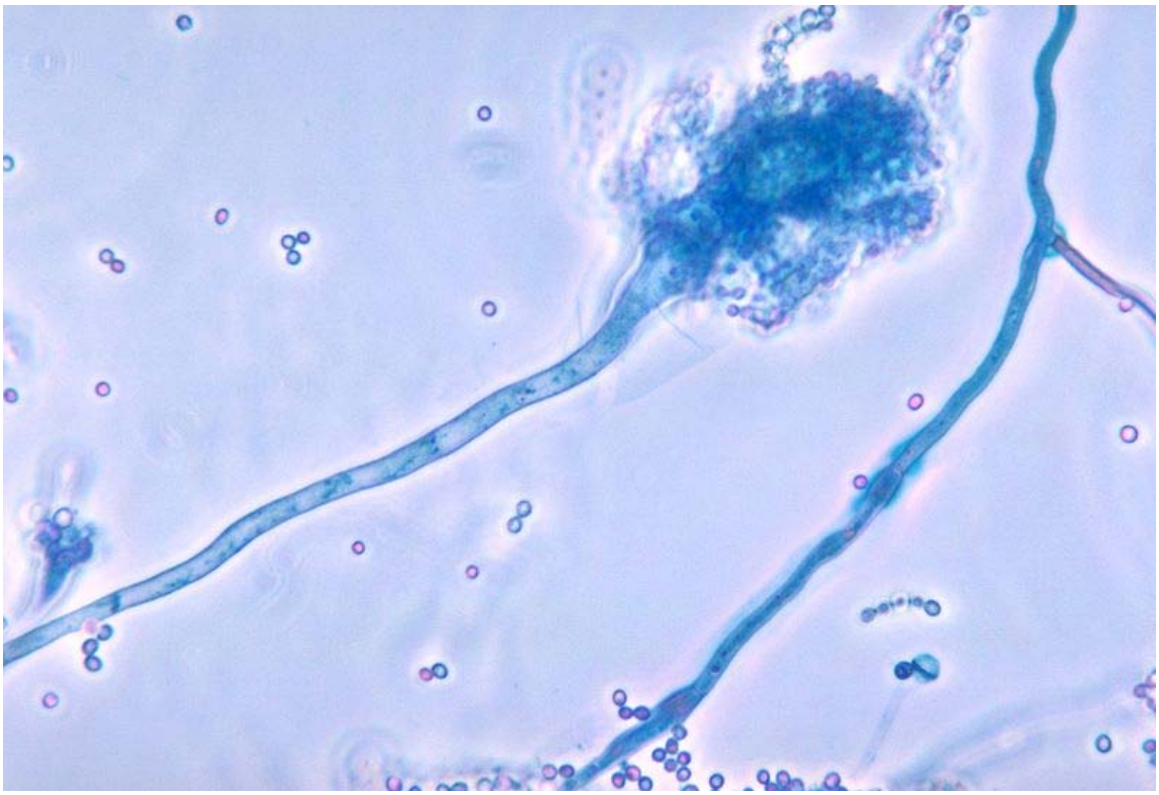
Symptoms

Classically, patients with chronic granulomatous disease will suffer from recurrent bouts of infection due to the decreased capacity of their immune system to fight off disease-causing organisms. The recurrent infections they acquire are specific and are, in decreasing order of frequency:

- pneumonia
- abscesses of the skin, tissues, and organs
- suppurative arthritis
- osteomyelitis
- bacteremia/fungemia
- superficial skin infections such as cellulitis or impetigo

Most people with CGD are diagnosed in childhood, usually before age 5. Early diagnosis is important since these people can be placed on antibiotics to ward off infections before they occur.

Atypical infections



Microscopic image of the fungus, *Aspergillus fumigatus*, an organism that commonly causes disease in people with chronic granulomatous disease.

People with CGD are sometimes infected with organisms that usually do not cause disease in people with normal immune systems. Among the most common organisms that cause disease in CGD patients are:

- bacteria (particularly those that are catalase-positive)
  - *Staphylococcus aureus*.
  - *Serratia marcescens*.
  - *Salmonella* species.
  - *Klebsiella* species.
  - *Pseudomonas cepacia, a.k.a. Burkholderia cepacia.*
  - *Nocardia*.
- fungi
  - *Aspergillus* species. Aspergillus has a propensity to cause infection in people with CGD and of the Aspergillus species, *Aspergillus fumigatus* seems to be most common in CGD.
  - *Candida* species.

Patients with CGD can usually resist infections of catalase-negative bacteria. Catalase is an enzyme that catalyzes the breakdown of hydrogen peroxide in many organisms. In organisms that lack catalase (catalase-negative), normal metabolic functions will cause an

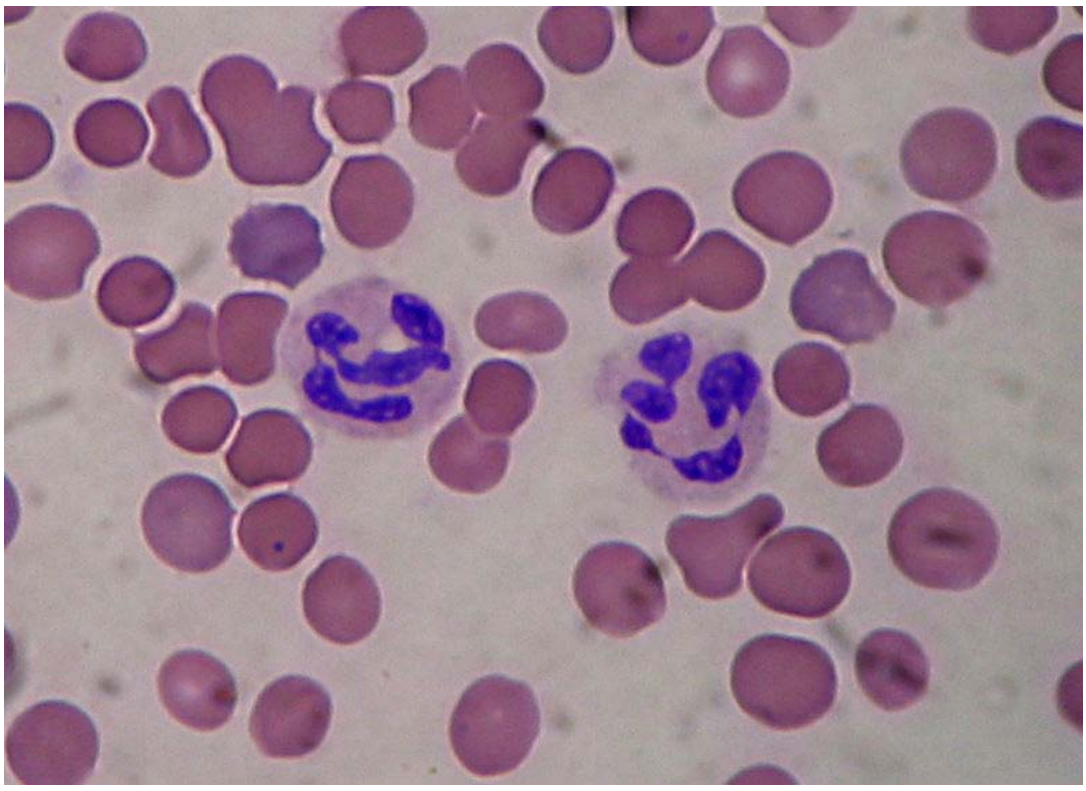
accumulation of hydrogen peroxide which the host's immune system can use to fight off the infection. In organisms that have catalase (catalase-positive), the enzyme breaks down any hydrogen peroxide that was produced through normal metabolism. Therefore hydrogen peroxide will not accumulate, leaving the patient vulnerable to catalase-positive bacteria.

Genetics

Most cases of chronic granulomatous disease are transmitted as a mutation on the X chromosome and are thus called an "X-linked trait". The affected gene on the X chromosome codes for the gp91 protein p91-PHOX (*p* is the weight of the protein in kDa; the *g* means glycoprotein). CGD can also be transmitted in an autosomal recessive fashion (via CYBA and NCF1) and affects other PHOX proteins. The type of mutation that causes both types of CGD are varied and may be deletions, frame-shift, nonsense, and missense.

A low level of NADPH, the cofactor required for superoxide synthesis, can lead to CGD. This has been reported in women who are homozygous for the genetic defect causing glucose-6-phosphate dehydrogenase deficiency (G6PD), which is characterised by reduced NADPH levels.

Pathophysiology



Two neutrophils among many red blood cells. Neutrophils are one type of cell affected by chronic granulomatous disease.

Phagocytes (i.e., neutrophils, monocytes, and macrophages) require an enzyme to produce reactive oxygen species to destroy bacteria after they ingest the bacteria in a process called phagocytosis, a process known as the respiratory burst. This enzyme is termed "phagocyte NADPH oxidase" (*PHOX*). The initial step in this process involves the one-electron reduction of molecular oxygen to produce superoxide anion, a free radical. Superoxide then undergoes a further series of reactions to produce products such as hydrogen peroxide (through the action of superoxide dismutase), hydroxyl radical and hypochlorite (bleach - through the action of myeloperoxidase on hydrogen peroxide). The reactive oxygen species this enzyme produces are toxic to bacteria and help the phagocyte kill them once they are ingested. Defects in one of the four essential subunits of this enzyme can all cause CGD of varying severity, dependent on the defect. There are over 410 known possible defects in the PHOX enzyme complex that can lead to chronic granulomatous disease.

Diagnosis

The nitroblue-tetrazolium (NBT) test is the original and most widely-known test for chronic granulomatous disease. It is negative in CGD, and positive in normal individuals. This test depends upon the direct reduction of NBT by superoxide free radical to form an insoluble formazan. This test is simple to perform and gives rapid results, but only tells whether or not there is a problem with the PHOX enzymes, not how much they are affected. A similar test uses dihydrorhodamine (DHR); whole blood is stained with DHR, incubated, and stimulated produce superoxide radicals which reduce DHR to rhodamin in cells with normal function. An advanced test called the cytochrome C reduction assay tells physicians how much superoxide a patient's phagocytes can produce. Once the diagnosis of CGD is established, a genetic analysis may be used to determine exactly which mutation is the underlying cause.

Treatment

Management of chronic granulomatous disease revolves around two goals: 1) diagnose the disease early so that antibiotic prophylaxis can be given to keep an infection from occurring, and 2) educate the patient about his or her condition so that prompt treatment can be given if an infection occurs.

Antibiotics

Physicians often prescribe the antibiotic trimethoprim-sulfamethoxazole to prevent bacterial infections. This drug also has the benefit of sparing the normal bacteria of the digestive tract. Fungal infection is commonly prevented with itraconazole, although a newer drug of the same type called voriconazole may be more effective. The use of this drug for this purpose is still under scientific investigation.

Immunomodulation

Interferon, in the form of interferon gamma-1b (Actimmune) is approved by the Food and Drug Administration for the prevention of infection in CGD. It has been shown to prevent infections in CGD patients by 70% and to reduce their severity. Although its exact mechanism is still not entirely understood, it has the ability to give CGD patients more immune function and therefore, greater ability to fight off infections. This therapy has been standard treatment for CGD for several years.

Hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation from a matched donor is curative although not without significant risk.

Prognosis

There are currently no studies detailing the long term outcome of chronic granulomatous disease with modern treatment. Without treatment children often die in the first decade of life. Available data indicates that X linked CGD is more severe, with most treated patients dying in the third or fourth decade of life.

Epidemiology

CGD affects about 1 in 200,000 people in the United States, with about 20 new cases diagnosed each year.

Chronic granulomatous disease affects all people of all races, however, little information on prevalence outside of the United States is available. One survey in Sweden reported an incidence of 1 in 220,000 people.

History

This condition was first described in 1954 by Janeway, who reported five cases of the disease in children. In 1957 it was further characterized as "a fatal granulomatosus of childhood". The underlying cellular mechanism that causes chronic granulomatous disease was discovered in 1967, and research since that time has further elucidated the molecular mechanisms underlying the disease. Use of antibiotic prophylaxis, surgical abscess drainage, and vaccination lead to the term "fatal" being dropped from the name of the disease as children survived into adulthood. The oldest person to suffer from Chronic Granulomatos Disease was Mr. Jackie Ray Johnson of Fredericksburg, Virginia who died in 2002 at the age of 63.

Research

Gene therapy is currently being studied as a possible treatment for chronic granulomatous disease. CGD is well-suited for gene therapy since it is caused by a mutation in single gene which only affects one body system (the hematopoietic system). Viruses have been used to deliver a normal gp91 gene to rats with a mutation in this gene, and subsequently the phagocytes in these rats were able to produce oxygen radicals.

In 2006, two human patients with X-linked chronic granulomatous disease underwent gene therapy and blood cell precursor stem cell transplantation to their bone marrow. Both patients recovered from their CGD, clearing pre-existing infections and demonstrating increased oxidase activity in their neutrophils. However, long-term complications and efficacy of this therapy are unknown.