sema4

Sema4 Noninvasive Prenatal Select

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Noninvasive prenatal testing with targeted genome counting

Sema4's Noninvasive Prenatal Testing (NIPT)- Targeted Genome Counting analyzes genetic information of cell-free DNA (cfDNA) through a simple maternal blood draw to determine the risk for common aneuploidies, sex chromosomal abnormalities, and microdeletions, in addition to fetal gender, as early as nine weeks gestation. The test uses paired-end next-generation sequencing technology to provide higher depth across targeted regions. It also uses a laboratory-specific statistical model to help reduce false positive and false negative rates. The test can be offered to all women with singleton pregnancies, including egg donor. The conditions offered include:

Autosomal Trisomy

Condition	Frequency at Birth	Maternal Age Effect	PPV	NPV	Sensitivity[1] (95% CI)	Specificity[1] (95% CI)	Reference Interval Size/Genomic Coordinate in hg19
Trisomy 21 (Down syndrome)	1/800	YES	Patient-specific PPV	>99.9%	>99% (86.8->99.9)	>99% (99.5->99.9)	48 Mb/ Whole chromosome
Trisomy 18 (Edwards syndrome)	1/5,000	YES		>99.9%	>99% (71.6->99.9)	>99% (99.6-99.9)	78 Mb/ Whole chromosome
Trisomy 13 (Patau syndrome)	1/16,000	YES		>99.9%	>99% (66.3->99.9)	>99% (99.7-99.9)	11 5Mb/ Whole chromosome
Trisomy 16	Extremely rare	YES	N/A[3]	N/A[3]	>99% (54.1->99.9)	>99% (99.3->99.9)	90 Mb/ Whole chromosome
Trisomy 22	Extremely rare	YES			>99% (54.1->99.9)	>99% (99.3->99.9)	51 Mb/ Whole chromosome
Trisomy 15	Extremely rare	YES			N/A- Reported when identified[2]		103 Mb/ Whole chromosome

Sex Chromosome Aneuploidy

Condition	Frequency at Birth	Maternal Age Effect	PPV	NPV	Sensitivity[1] (95% CI)	Specificity[1] (95% CI)	Reference Interval Size/Genomic Coordinate in hg19
Monosomy X (Turner syndrome)	1/2,500 females	NO	Patient-specific PPV	>99.9%	>99% (59.0->99.9)	>99% (99.7-99.9)	155 Mb/ Whole chromosome
XXX (Trisomy X)	1/1,000 females	YES		>99.9%	>99% (59.0->99.9)	>99% (99.5-99.9)	155 Mb/ Whole chromosome
XXY (Klinefelter syndrome)	1/1,000 males	YES		>99.9%	>99% (54.0->99.9)	>99% (99.7-99.9)	155 Mb (X); 59 Mb (Y)/ Whole chromosome
XYY	1/1,000 males	NO	N/A[2]	N/A[2]	N/A- Reported when identified[2]		155 Mb (X); 59 Mb (Y)/ Whole chromosome

[1] Sensitivities and specificities are based on analytical calculations.
[2] There is limited data on trisomy 15 and XYY to support performance characteristics. Abnormalities will be reported if detected.
[3] PPVs and NPVs were not calculated for very rare abnormalities.

Microdeletions

Condition	Frequency at Birth	Maternal Age Effect	PPV	NPV	Sensitivity[1] (95% CI)	Specificity[3]	Reference Interval Size/Genomic Coordinate in hg19
22q11.2 deletion	1/4,000	NO	Patient-specific PPV	>99.9 %	78.0% (17.5->99.9)	Estimated >99%	2.7 Mb/ chr22: 18891000-21561000
1p36 deletion	1/5,000	NO		>99.9 %	87.3% (31.6->99.9)	Estimated >99%	3.2 Mb/ chr1: 2700000-5900000
4p16 deletion (Wolf-Hirschhorn syndrome)	1/20,000	NO		>99.9 %	91.9% (46.6- >99.9)	Estimated >99%	3.5 Mb/ chr4: 1500000-5000000
5p15 deletion (Cri-du-chat syndrome)	1/20,000	NO		>99.9 %	97.8% (87.6->99.9)	Estimated >99%	9.8 Mb/ chr5: 1-9800000
15q11.2-q13 deletion (Angelman syndrome)	1/21,000	NO		>99.9 %	88.6% (35.2->99.9)	Estimated >99%	5.8 Mb/ chr15: 22688000-28520000
15q11.2-q13 deletion (Prader-Willi syndrome)	1/23,000	NO					5.8 Mb/ chr15: 22688000-28520000
11q23 deletion (Jacobsen syndrome)	1/100,000	NO		>99.9 %	94.9% (62.7->99.9)	Estimated >99%	6.3 Mb/ chr11: 128739000-135006000
8q24 deletion (Langer-Giedion syndrome)	Extremely rare	NO	N/A[2]	N/A[2]	90.3% (40.5->99.9)	Estimated >99%	2.7 Mb/ chr8: 116420724-119124058

[1] All sensitivities are based on analytical sensitivity.
[2] PPVs and NPVs were not calculated for very rare abnormalities.
[3] Estimated based on other studies using similar technologies (*2015 Prenatal Diagnosis, Clinical outcome of subchromosomal events detected by whole-genome noninvasive prenatal testing*).

Testing methods, sensitivity, and limitations

Circulating cell-free DNA (ccfDNA), which is a mixture of maternal and placental DNA, is purified from the plasma component of anti-coagulated maternal whole blood. ccfDNA is then converted into a genomic DNA library and sequenced by massively parallel sequencing. Sequencing data is quantified for relative amount of chromosomal material across the genome to determine chromosomes 21, 18, 13, 16, 22, 15, X, and Y-representation and to evaluate selected subchromosomal regions (22q11.2, 1p36, 15q11.2-q13, 4p16, 5p15, 11q23, and 8q24). Fetal fraction (percentage of placental DNA present in all cell-free DNA from maternal plasma) is also estimated and reported.

NIPT is a prenatal screening test based on analysis of placental DNA, which may not accurately reflect the status of the fetus. A patient with a positive test result should be offered genetic counseling and invasive diagnostic testing via chorionic villus sampling or amniocentesis for confirmation. A negative test result

does not ensure an unaffected pregnancy. An inconclusive result may be reported due to insufficient fetal fraction, technical difficulties, or other sample-related issues. Fetal sex was classified by Y chromosome representation with >99% accuracy. Given that this test is only intended to identify select conditions, other chromosomal abnormalities and prenatal defects, such as triploidy, balanced rearrangements, and open neural tube defects will not be detected by this test. Please note that this test was not validated for and will not report autosomal monosomies and reciprocal microduplications of targeted microdeletion regions. This test may not detect all the microdeletions within the select subchromosomal regions listed above, including smaller microdeletions and microdeletions with partial overlap with these regions. In addition, this test may not detect all the genetic aberrations associated with the selected conditions tested. Potential causes of inaccurate aneuploidy, microdeletion, or fetal sex prediction include, but are not limited to, low fetal fraction, unreported multiple gestation pregnancy, placental, maternal, or fetal mosaicism, resorbing twin, maternal copy number variants, organ/bone marrow transplantation, recent blood transfusion, and sample misidentification. This test may also lead to unanticipated findings unrelated to the current pregnancy such as maternal aneuploidy, microdeletion, or even neoplasia. The test was validated on singleton pregnancies and is currently not offered for multiple gestation pregnancies.

Positive and negative predictive value

Positive/negative predictive value (PPV/NPV) tells us the chance that a screen positive/negative result is actually a true positive/negative. It is a more accurate way of translating what a positive/negative result actually means for each patient. PPV and NPV depend on the accuracy of the test and the prevalence of the condition, which is impacted by maternal age in most aneuploidies but not in microdeletions. The diagram below is modified from The American College of Obstetricians and Gynecologists (ACOG) to illustrate PPV/NPV calculations.

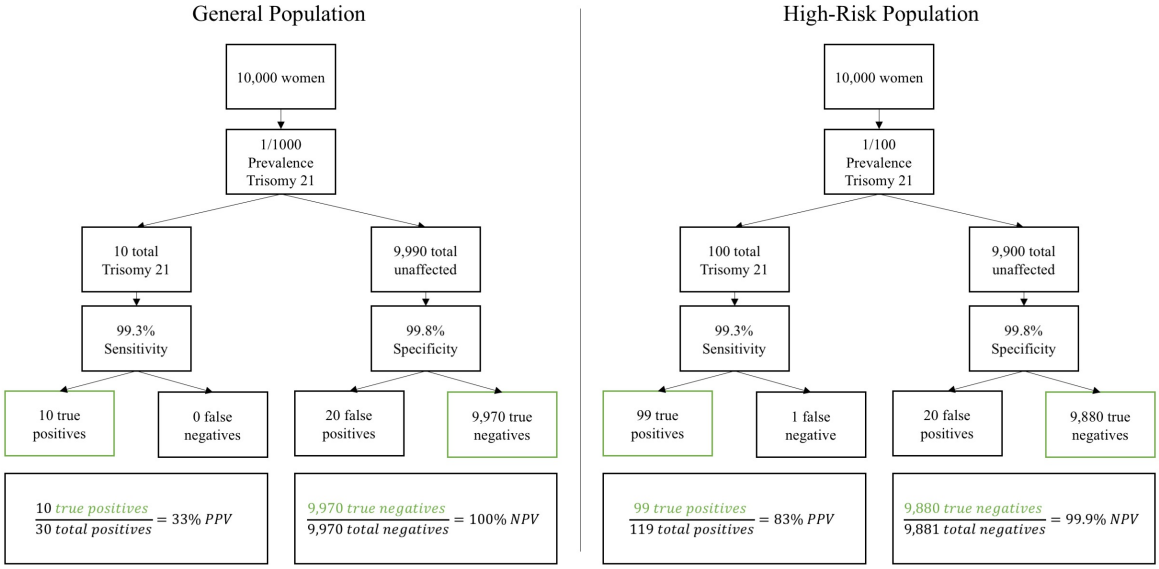

Fig.1. The importance of population prevalence on the predictive value for a screening test: an illustration with cell-free DNA.
Abbreviations: NPV, negative predictive value; PPV, positive predictive value

Cell-free DNA screening for fetal aneuploidy. Committee Opinion No. 640. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;126:e31-7.

Autosomal trisomies

Most cases of autosomal trisomies result from having three copies of a specific chromosome in each cell in the body instead of the usual two copies. The extra genetic material disrupts the normal course of development, causing the characteristic features of the syndrome. However, there are a few other syndrome-specific causes. A very small percentage of people with these syndromes have trisomy in only some of the body's cells; this condition is called a mosaic trisomy. The severity of mosaic trisomy depends on which chromosome is aneuploid and the type and number of cells that have the extra chromosome. The development of individuals with mosaic trisomy may range from normal to severely affected. In addition, trisomy can be caused by chromosome rearrangements (translocations) as discussed below (1-10).

Autosomal trisomies are typically not inherited. The chromosomal abnormality occurs as a random event during the formation of reproductive cells in a parent. The abnormality usually occurs in egg cells, but it occasionally occurs in sperm cells. An error in cell division called nondisjunction results in a reproductive cell with an abnormal number of chromosomes. For example, an egg or sperm cell may gain an extra copy of chromosome 21. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra chromosome 21 in each of the body's cells. The child would be affected with Down Syndrome.

People with translocation trisomy can inherit the condition from an unaffected parent. The parent carries a rearrangement of genetic material between two chromosomes. This rearrangement is called a balanced translocation. No genetic material is gained or lost in a balanced translocation, so these chromosomal changes usually do not cause any health problems. However, as this translocation is passed to the next generation, it can become unbalanced. For example, people who inherit an unbalanced translocation involving chromosome 21 (Robertsonian translocation) may have extra genetic material from chromosome 21, which causes Down syndrome.

Autosomal Trisomy

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References

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Down syndrome; [reviewed 2012 Jun; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/down-syndrome.
2. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Trisomy 18; [reviewed 2012 Mar; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/trisomy-18.
3. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Trisomy 13; [reviewed 2013 Nov; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/trisomy-13.
4. Rieubland C, Francis D, Houben L, Corrie S, Bankier A, White SM. Two cases of trisomy 16 mosaicism ascertained postnatally. Am J Med Genet A. 2009 Jul;149A(7):1523-8. doi: 10.1002/ajmg.a.32925. PMID: 19533780
5. Abdelgadir D, Nowaczyk MJ, Li C. Trisomy 22 mosaicism and normal developmental outcome: report of two patients and review of the literature. Am J Med Genet A. 2013 May;161A(5):1126-31. doi: 10.1002/ajmg.a.35812. Epub 2013 Mar 25. Review. PMID: 23529842
6. Davison EV, Beesley JR. Partial trisomy 16 as a result of familial 16;20 translocation. J Med Genet. 1984 Oct;21(5):384-6. PMID: 6502653
7. Kehinde FI, Anderson CE, McGowan JE, Jethva RN, Wahab MA, Glick AR, Sterner MR, Pascasio JM, Punnett HH, Liu J. 2014. Co-occurrence of non-mosaic trisomy 22 and inherited balanced t(4;6)(q33;q23.3) in a liveborn female: case report and review of the literature. Am J Med Genet Part A 164:3187–3193. PMID: 25257307
8. Slater HR, Voullaire LE, Vaux CE, Bankier A, Pertile M, Choo KH. Confirmation of trisomy 22 in two cases using chromosome painting: comparison with t(11;22). Am J Med Genet. 1993 Jun 1;46(4):434-7. PMID: 8357017
9. Hsu LY, Yu MT, Neu RL, Van Dyke DL, Benn PA, Bradshaw CL, Shaffer LG, Higgins RR, Khodr GS, Morton CC, Wang H, Brothman AR, Chadwick D, Disteche CM, Jenkins LS, Kalousek DK, Pantzar TJ, Wyatt P. Rare trisomy mosaicism diagnosed in amniocytes, involving an autosome other than chromosomes 13, 18, 20, and 21: karyotype/phenotype correlations. Prenat Diagn. 1997 Mar;17(3):201-42. PMID: 9110367
10. Grati FR. Chromosomal Mosaicism in Human Feto-Placental Development: Implications for Prenatal Diagnosis. J Clin Med. 2014 Jul 24;3(3):809-37. doi: 10.3390/jcm3030809. Review. PMID: 26237479

Trisomy 21 (Down syndrome)

Down syndrome is a chromosomal disorder that is associated with intellectual disability, a characteristic facial appearance, and weak muscle tone (hypotonia) in infancy. All affected individuals experience cognitive delays, but the severity varies from mild to moderate intellectual disability. People with Down syndrome may have a variety of birth defects. About half of all affected children are born with a heart defect. Digestive abnormalities, such as a blockage of the intestine, are less common. Individuals with Down syndrome have an increased risk of developing several medical conditions. These include gastroesophageal reflux, which is a backflow of acidic stomach contents into the esophagus, and celiac

disease, which is an intolerance to a wheat protein called gluten. About 15 percent of people with Down syndrome have an underactive thyroid gland (hypothyroidism). The thyroid gland is a butterfly-shaped organ in the lower neck that produces hormones. Individuals with Down syndrome also have an increased risk of hearing and vision problems. Additionally, a small percentage of children with Down syndrome develop cancer of blood-forming cells (leukemia). The life expectancy of individuals with Down syndrome can be over sixty years; however, this can vary greatly depending on the severity of the associated abnormalities.

Delayed development and behavioral problems are often reported in children with Down syndrome. Speech and language develop later and more slowly than in children without Down syndrome, and affected individuals' speech may be more difficult to understand. Behavioral issues can include attention problems, obsessive/compulsive behavior, and stubbornness or tantrums. A small percentage of people with Down syndrome are also diagnosed with developmental conditions called autism spectrum disorders, which affect communication and social interaction. People with Down syndrome often experience a gradual decline in thinking ability (cognition) as they age, usually starting around age 50. Down syndrome is also associated with an increased risk of developing Alzheimer's disease, a brain disorder that results in a gradual loss of memory, judgment, and ability to function. Approximately half of adults with Down syndrome develop Alzheimer's disease. Although Alzheimer's disease is usually a disorder that occurs in older adults, people with Down syndrome usually develop this condition in their fifties or sixties.

Genetics

Down syndrome typically results from trisomy 21 in each cell of the body. Less commonly, Down syndrome occurs when part of chromosome 21 becomes attached (translocated) to another chromosome during the formation of reproductive cells (eggs and sperm) in a parent or very early in fetal development. Affected people have two normal copies of chromosome 21 plus extra material from chromosome 21 attached to another chromosome, resulting in three copies of genetic material from chromosome 21. Affected individuals with this genetic change are said to have Robertsonian translocation Down syndrome. The risk of having a pregnancy affected by trisomy 21 increases with maternal age.

References

1. Covelli V, Raggi A, MeucciP, Paganelli C, Leonardi M (2016). Ageing of people with Down syndrome: a systematic literature review from 2000-2014. International Journal of Rehabilitation Research 39:20-28
2. Glasson EJ, Sullivan SG, Hussasin R, Petterson BA, Montgomery PD,Bittles AH (2002). The changing survival profile of people with Down syndrome: Implications for genetic counseling. Clin Genet 62:390-393
3. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Down syndrome; [reviewed 2012 Jun; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/down-syndrome.

Trisomy 18 (Edwards syndrome)

Trisomy 18, also called Edwards syndrome, is a chromosomal condition associated with abnormalities in many parts of the body. Individuals with trisomy 18 often have slow growth before birth (intrauterine growth retardation) and a low birth weight. Affected individuals may have heart defects and abnormalities of other organs that develop before birth. Other features of trisomy 18 include a small, abnormally shaped

head; a small jaw and mouth; and clenched fists with overlapping fingers. Due to the presence of several life-threatening medical problems, many individuals with trisomy 18 die before birth or within their first month. Five to 10 percent of children with this condition live past their first year, and these children often have severe intellectual disability.

Genetics

Edwards syndrome typically results from trisomy 18 in each cell of the body. Approximately 5 percent of people with trisomy 18 have mosaic trisomy 18. Very rarely, part of the long (q) arm of chromosome 18 becomes attached (translocated) to another chromosome during the formation of reproductive cells (eggs and sperm) or very early in embryonic development. Affected individuals have two copies of chromosome 18, plus the extra material from chromosome 18 attached to another chromosome. People with this genetic change are said to have partial trisomy 18. If only part of the q arm is present in three copies, the physical signs of partial trisomy 18 may be less severe than those typically seen in trisomy 18. If the entire q arm is present in three copies, individuals may be as severely affected as if they had three full copies of chromosome 18. The risk of having a pregnancy affected by trisomy 18 increases with maternal age.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Trisomy 18; [reviewed 2012 Mar; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/trisomy-18.

Trisomy 13 (Patau syndrome)

Trisomy 13, also called Patau syndrome, is a chromosomal disorder associated with severe intellectual disability and physical abnormalities. Individuals with trisomy 13 often have congenital heart defects, brain or spinal cord abnormalities, very small or poorly developed eyes (microphthalmia), extra fingers or toes, an opening in the lip (a cleft lip) with or without an opening in the roof of the mouth (a cleft palate), and weak muscle tone (hypotonia). Due to the presence of several life-threatening medical problems, many infants with trisomy 13 die within their first days or weeks of life. Only five to 10 percent of children with this condition live past their first year.

Genetics

Patau syndrome typically results from trisomy 13 in each cell of the body. A small percentage of people with trisomy 13 have mosaic trisomy 13. Trisomy 13 can also occur when part of chromosome 13 becomes attached (translocated) to another chromosome during the formation of reproductive cells (eggs and sperm) or very early in fetal development. Affected people have two normal copies of chromosome 13, plus an extra copy of chromosome 13 attached to another chromosome. In rare cases, only part of chromosome 13 is present in three copies. The physical signs and symptoms in these cases may be different than those found in full trisomy 13. The risk of having a pregnancy affected by trisomy 13 increases with maternal age.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Trisomy 13; [reviewed 2013 Nov; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/trisomy-13.

Trisomy 16

Trisomy 16 is the most common autosomal trisomy in spontaneous abortions. Most cases of trisomy 16 result in spontaneous abortions at 8 to 15 weeks' gestation, with only a few cases surviving into the second trimester or near-term. Mosaic trisomy 16 fetuses have better chances to survive to term. Affected fetuses could have intrauterine/postnatal growth retardation, congenital heart defects, and other clinical findings. The extra chromosome is of maternal origin, resulting from meiosis I nondisjunction error and is related to maternal age (2).

Genetics

Most cases of trisomy 16 result from having three copies of chromosome 16 in each cell in the body. Full trisomy 16 is well reported in spontaneous abortion and generally results in disorganized embryos with very little evidence of development. Trisomy 16 can also occur when part of chromosome 16 becomes attached (translocated) to another chromosome during the formation of reproductive cells (eggs and sperm) or very early in fetal development. Affected people have two normal copies of chromosome 16, plus an extra copy of chromosome 16 attached to another chromosome. In rare cases, only part of chromosome 16 is present in three copies. Although there is perhaps still insufficient data to attempt to define a syndrome for partial or full trisomy 16, the most notable characteristics are intrauterine growth retardation, particular abnormalities of the face with downward slanting palpebral fissures, abnormal nose and ears, micrognathia, flexion deformities of the limbs and digits, and heart defects. Although many of these anomalies are found in association with other chromosomal aberrations, it is the particular facial appearance which suggests trisomy 16. Due to the presence of several life-threatening medical problems, infants with translocation trisomy 16 typically die within their first days or weeks of life (3). Postnatally ascertained trisomy 16 mosaicism is a rare diagnosis, with only three reported cases to date with no defined clinical phenotype. Trisomy 16 mosaicism diagnosed prenatally is associated with variable pregnancy outcomes ranging from stillbirth with multiple congenital abnormalities to an apparently normal newborn (4). The risk of having a pregnancy affected by trisomy 16 increases with maternal age.

References

1. Hassold T, Abruzzo M, Adkins K, Griffin D, Merrill M, Millie E, Saker D, Shen J, Zaragoza M. Human aneuploidy: incidence, origin, and etiology. Environ Mol Mutagen. 1996;28(3):167-75. Review. No abstract available. PMID: 8908177
2. Dighe M, Cheng E, Dubinsky T. Ultrasound manifestations of unusual trisomies-excluding trisomy 13, 18, and 21: a literature review. Ultrasound Q. 2009 Mar;25(1):15-24. doi: 10.1097/RUQ.0b013e31819eea3a. Review. PMID: 19276932
3. Davison EV, Beesley JR. Partial trisomy 16 as a result of familial 16;20 translocation. J Med Genet. 1984 Oct;21(5):384-6. PMID: 6502653
4. Rieubland C, Francis D, Houben L, Corrie S, Bankier A, White SM. Two cases of trisomy 16 mosaicism ascertained postnatally. Am J Med Genet A. 2009 Jul;149A(7):1523-8. doi: 10.1002/ajmg.a.32925. PMID: 19533780

Trisomy 22

Trisomy 22 is the second most common autosomal trisomy, occurring in 2-5% of all spontaneous abortions. Because of multiple malformations, a low rate of 1 per 30,000 to 50,000 live births and a short life expectancy of infants with this chromosomal aneuploidy are observed. Postnatal and postmortem

examinations revealed clinical features including growth restriction and craniofacial dysmorphisms such as congenital microcephaly, hypertelorism, epicanthal folds, micrognathia, cleft lip and palate, and low-set, malformed ears, often with preauricular tags, pits, or both. Additionally, half of patients with trisomy 22 have complex heart defects and urogenital anomalies such as renal agenesis and dysplasia. Other frequently observed pathologic traits are malformed and malpositioned extremities (2).

Genetics

Most cases of trisomy 22 result from having three copies of chromosome 22 in each cell in the body (3). Trisomy 22 can also occur when part of chromosome 22 becomes attached (translocated) to another chromosome during the formation of reproductive cells (eggs and sperm) or very early in fetal development. The physical signs and symptoms in these cases may be different than those found in full trisomy 22 (5). The severity of mosaic trisomy 22 depends on the type and number of cells that have the extra chromosome. The mosaic form of trisomy 22 is compatible with life. The clinical presentation is variable and may include growth restriction, intellectual disability, cardiovascular abnormalities, dysmorphic features, and hemihyperplasia. The neurodevelopmental outcome ranges from normal to severe developmental delay (4). The risk of having a pregnancy affected by trisomy 22 increases with maternal age.

References

1. Hassold T, Abruzzo M, Adkins K, Griffin D, Merrill M, Millie E, Saker D, Shen J, Zaragoza M. Human aneuploidy: incidence, origin, and etiology. Environ Mol Mutagen. 1996;28(3):167-75. Review. No abstract available. PMID: 8908177
2. Stressig R, Körtge-Jung S, Hickmann G, Kozlowski P. Prenatal sonographic findings in trisomy 22: five case reports and review of the literature. J Ultrasound Med. 2005 Nov;24(11):1547-53. Review. PMID: 16239659
3. Kehinde FI, Anderson CE, McGowan JE, Jethva RN, Wahab MA, Glick AR, Sterner MR, Pascasio JM, Punnett HH, Liu J. 2014. Co-occurrence of non-mosaic trisomy 22 and inherited balanced t(4;6)(q33;q23.3) in a liveborn female: case report and review of the literature. Am J Med Genet Part A 164:3187–3193. PMID: 25257307
4. Abdelgadir D, Nowaczyk MJ, Li C. Trisomy 22 mosaicism and normal developmental outcome: report of two patients and review of the literature. Am J Med Genet A. 2013 May;161A(5):1126-31. doi: 10.1002/ajmg.a.35812. Epub 2013 Mar 25. Review. PMID: 23529842
5. Slater HR, Voullaire LE, Vaux CE, Bankier A, Pertile M, Choo KH. Confirmation of trisomy 22 in two cases using chromosome painting: comparison with t(11;22). Am J Med Genet. 1993 Jun 1;46(4):434-7. PMID: 8357017
6. Jia CW, Wang L, Lan YL, Song R, Zhou LY, Yu L, Yang Y, Liang Y, Li Y, Ma YM, Wang SY. Aneuploidy in Early Miscarriage and its Related Factors. Chin Med J (Engl). 2015 Oct 20;128(20):2772-6. doi: 10.4103/0366-6999.167352. PMID: 26481744

Trisomy 15

A positive trisomy 15 prenatal result is most often due to confined placental mosaicism (CPM). Trisomy 15 is extremely rare in liveborn children and most reported cases are mosaic. Complete trisomy 15 in a fetus is not compatible with life. This chromosomal disorder is characterized by growth delays before and/or

after birth; intellectual disability; and/or distinctive malformations of the head and facial area. Additional abnormalities may involve malformation of the skeleton, spine and neck; fingers and/or toes; genitals (particularly in males); and, in some cases, heart problems. The range and severity of Trisomy 15 varies from case to case.

Genetics

Most reported cases of trisomy 15 in liveborn children are mosaic. The range and severity of trisomy 15 varies from case to case. In addition, trisomy 15 is associated with increased risk for uniparental disomy (UPD) due to trisomy rescue by reduction to disomy. Maternal UPD and paternal UPD of chromosome 15 cause Prader-Willi syndrome and Angelman syndrome, respectively (2,3). The risk of having a pregnancy affected by trisomy 15 increases with maternal age.

References

1. Hassold T, Abruzzo M, Adkins K, Griffin D, Merrill M, Millie E, Saker D, Shen J, Zaragoza M. Human aneuploidy: incidence, origin, and etiology. Environ Mol Mutagen. 1996;28(3):167-75. Review. No abstract available. PMID: 8908177
2. Hsu LY, Yu MT, Neu RL, Van Dyke DL, Benn PA, Bradshaw CL, Shaffer LG, Higgins RR, Khodr GS, Morton CC, Wang H, Brothman AR, Chadwick D, Disteche CM, Jenkins LS, Kalousek DK, Pantzar TJ, Wyatt P. Rare trisomy mosaicism diagnosed in amniocytes, involving an autosome other than chromosomes 13, 18, 20, and 21: karyotype/phenotype correlations. Prenat Diagn. 1997 Mar;17(3):201-42. PMID: 9110367
3. Grati FR. Chromosomal Mosaicism in Human Feto-Placental Development: Implications for Prenatal Diagnosis. J Clin Med. 2014 Jul 24;3(3):809-37. doi: 10.3390/jcm3030809. Review. PMID: 26237479

Sex chromosome aneuploidies

The typical number of chromosomes is 46 chromosomes per cell. Two of the 46 chromosomes, known as X and Y, are called sex chromosomes because they help determine whether a person will develop male or female sexual characteristics. Females typically have two X chromosomes (46, XX), and males have one X chromosome and one Y chromosome (46,XY). Sex chromosome aneuploidy is caused by an atypical number of X or Y chromosomes. Most cases of sex chromosome aneuploidy are not inherited. The chromosomal abnormality occurs as a random event during the formation of reproductive cells (eggs and sperm) in the affected person's parent. An error in cell division called nondisjunction can result in reproductive cells with an abnormal number of chromosomes. For example, an egg or sperm cell may lose a sex chromosome as a result of nondisjunction. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have a single X chromosome in each cell and will be missing the other sex chromosome. This causes Turner syndrome. Mosaic sex chromosome aneuploidy is also not inherited. In an affected individual, it occurs as a random event during cell division in early embryonic or fetal development. As a result, some of an affected person's cells have the usual two sex chromosomes, and other cells have an abnormal number of sex chromosomes. Other sex chromosome abnormalities are also possible in females with X chromosome mosaicism as described below.

Sex Chromosome Aneuploidy

Condition	Frequency at Birth	Maternal Age Effect	PPV	NPV	Sensitivity[1] (95% CI)	Specificity[1] (95% CI)	Reference Interval Size/Genomic Coordinate in hg19
Monosomy X (Turner syndrome)	1/2,500 females	NO	Patient-specific PPV	>99.9%	>99% (59.0->99.9)	>99% (99.7-99.9)	155 Mb/ Whole chromosome
XXX (Trisomy X)	1/1,000 females	YES		>99.9%	>99% (59.0->99.9)	>99% (99.5-99.9)	155 Mb/ Whole chromosome
XXY (Klinefelter syndrome)	1/1,000 males	YES		>99.9%	>99% (54.0->99.9)	>99% (99.7-99.9)	155 Mb (X); 59 Mb (Y)/ Whole chromosome
XYY	1/1,000 males	NO	N/A[2]	N/A[2]	N/A- Reported when identified[2]		155 Mb (X); 59 Mb (Y)/ Whole chromosome

[1] Sensitivities and specificities are based on analytical calculations.
[2] There is limited data on XYY to support performance characteristics. Abnormalities will be reported if detected.

References

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Turner Syndrome; [reviewed 2012 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/turner-syndrome.
2. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Triple X Syndrome; [reviewed 2014 Jun; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/triple-x-syndrome.
3. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Klinefelter Syndrome; [reviewed 2013 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/klinefelter-syndrome.

4. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. 47,XYY Syndrome; [reviewed 2009 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/47xyy-syndrome.

Monosomy X (Turner syndrome)

Turner syndrome is a chromosomal condition that affects female development. The most common feature of Turner syndrome is short stature, which becomes evident by about age 5. An early loss of ovarian function (premature ovarian failure) is also very common. The ovaries develop normally at first, but egg cells (oocytes) usually die prematurely and most ovarian tissue degenerates before birth. Many affected girls do not undergo puberty unless they receive hormone therapy, and most are unable to conceive (infertile). A small percentage of females with Turner syndrome retain normal ovarian function through young adulthood. About 30 percent of females with Turner syndrome have extra folds of skin on the neck (webbed neck), a low hairline at the back of the neck, puffiness or swelling (lymphedema) of the hands and feet, skeletal abnormalities, or kidney problems. One third to one half of individuals with Turner syndrome are born with a heart defect, such as a narrowing of the large artery leaving the heart (coarctation of the aorta) or abnormalities of the valve that connects the aorta with the heart (the aortic valve). Complications associated with these heart defects can be life-threatening. A three-fold increase in mortality exists in individuals with Turner syndrome and overall life expectancy is reduced by up to 13 years. Most girls and women with Turner syndrome have normal intelligence. Developmental delays, nonverbal learning disabilities, and behavioral problems are possible, although these characteristics vary among affected individuals.

Genetics

Turner syndrome is related to the X chromosome, which is one of the two sex chromosomes. People typically have two sex chromosomes in each cell: females have two X chromosomes, while males have one X chromosome and one Y chromosome. Turner syndrome results when one normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered. The missing genetic material affects development before and after birth. About half of individuals with Turner syndrome have monosomy X, which means each cell in the individual's body has only one copy of the X chromosome instead of the usual two sex chromosomes. The chromosome error leading to loss of a sex chromosome is usually paternal. Turner syndrome can also occur if one of the sex chromosomes is partially missing or rearranged rather than completely absent. About one quarter of women with Turner syndrome have a chromosomal change in only some of their cells, which is known as mosaicism. Women with Turner syndrome caused by X chromosome mosaicism are said to have mosaic Turner syndrome. Loss of a sex chromosome from a cell in the early embryo is the likely cause of 45.X mosaicism.

References

1. Elsheikh M, Dunger DB, Conway GS, Wass JAH (2002). Turner's syndrome in Adulthood. Endocrine Reviews 23(1):120-140

2. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Turner Syndrome; [reviewed 2012 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/turner-syndrome.

XXX (Trisomy X)

Trisomy X syndrome, also called triple X syndrome, or 47,XXX, is characterized by the presence of an additional X chromosome than typical in females (47,XXX instead of 46,XX). This is the most common chromosomal abnormality in females. Females with this condition may be taller than average. Most females with trisomy X syndrome have normal sexual development and are able to conceive children. trisomy X syndrome is associated with an increased risk of learning disabilities and delayed development of speech and language skills. Delayed development of motor skills (such as sitting and walking), weak muscle tone (hypotonia), and behavioral and emotional difficulties are also possible, but these characteristics vary widely among affected girls and women. Seizures or kidney abnormalities occur in about 10 percent of affected females. Most individuals with 47,XXX are expected to have a normal life span; however, rare cardiac abnormalities and associated risks have been reported. The risk of having a pregnancy affected by trisomy X increases with maternal age.

Genetics

Trisomy X results from an extra copy of the X chromosome in each of a female's cells. As a result of the extra X chromosome, each cell has a total of 47 chromosomes (47,XXX) instead of the usual 46. An extra copy of the X chromosome is associated with tall stature, learning problems, and other features in some girls and women. Some females with trisomy X have an extra X chromosome in only some of their cells. This phenomenon is called 46,XX/47,XXX mosaicism.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Triple X Syndrome; [reviewed 2014 Jun; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/triple-x-syndrome.

XXY (Klinefelter syndrome)

Klinefelter syndrome is a chromosomal condition that affects male physical and cognitive development. Its signs and symptoms vary among affected individuals. Affected individuals typically have small testes that do not produce as much testosterone as usual. Testosterone is the hormone that directs male sexual development before birth and during puberty. A shortage of testosterone can lead to delayed or incomplete puberty, breast enlargement (gynecomastia), reduced facial and body hair, and an inability to have biological children (infertility). Some affected individuals also have genital differences including undescended testes (cryptorchidism), the opening of the urethra is on the underside of the penis (hypospadias), or an unusually small penis (micropenis). Older children and adults with Klinefelter syndrome tend to be taller than their peers. Compared with unaffected men, adults with Klinefelter syndrome have an increased risk of developing breast cancer and a chronic inflammatory disease called systemic lupus erythematosus. Their chance of developing these disorders is similar to that of women in the general population. Children with Klinefelter syndrome may have learning disabilities and delayed speech and language development. They tend to be quiet, sensitive, and unassertive, but personality characteristics vary among affected individuals. Most individuals with 47,XXY are expected to have a normal lifespan. The risk of having a pregnancy affected by Klinefelter syndrome increases with maternal age.

Genetics

Most often, Klinefelter syndrome results from the presence of one extra copy of the X chromosome than typical in males (47,XXY). Extra copies of genes on the X chromosome interfere with male sexual development, often preventing the testes from functioning normally and reducing the levels of testosterone. Most people with an extra X chromosome have the features described above, although some have few or no associated signs and symptoms. Some people with features of Klinefelter syndrome have more than one extra sex chromosome in each cell (for example, 48,XXXY or 49,XXXXY). These conditions, which are often called variants of Klinefelter syndrome, tend to cause more severe signs and symptoms than classic Klinefelter syndrome. In addition to affecting male sexual development, variants of Klinefelter syndrome are associated with intellectual disability, distinctive facial features, skeletal abnormalities, poor coordination, and severe problems with speech. As the number of extra sex chromosomes increases, so does the risk of these health problems. Some people with features of Klinefelter syndrome have the extra X chromosome in only some of their cells; in these individuals, the condition is described as mosaic Klinefelter syndrome (46,XY/47,XXY). Individuals with mosaic Klinefelter syndrome may have milder signs and symptoms, depending on how many cells have an additional X chromosome.

References

1. Calogero AE, Giagulli VA, Mongioi LMM, Triggiani V, Radicioni AF, Jannini EA, Pasquali D (2017). Klinefelter syndrome: Cardiovascular abnormalities and metabolic disorders. J Endocrinol Invest 40: 705-712
2. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Klinefelter Syndrome; [reviewed 2013 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/klinefelter-syndrome.

XYY

47,XYY syndrome is characterized by an extra copy of the Y chromosome than typical in males. Although males with this condition may be taller than average, this chromosomal change typically causes no unusual physical features. Some individuals develop severe cystic acne during adolescence. Most males with 47,XYY syndrome have normal sexual development and are able to father children. 47,XYY syndrome is associated with an increased risk of learning disabilities and delayed development of speech and language skills. Delayed development of motor skills (such as sitting and walking), weak muscle tone (hypotonia), hand tremors or other involuntary movements (motor tics), and behavioral and emotional difficulties are also possible. These characteristics vary widely among affected boys and men. A small percentage of males with 47,XYY syndrome are diagnosed with autistic spectrum disorders, which are developmental conditions that affect communication and social interaction. Individuals with 47,XYY are expected to have a normal lifespan.

Genetics

47,XYY syndrome is caused by the presence of an extra copy of the Y chromosome in each of a male's cells. As a result of the extra Y chromosome, each cell has a total of 47 chromosomes instead of the usual 46. Some males with 47,XYY syndrome have an extra Y chromosome in only some of their cells. This phenomenon is called 46,XY/47,XYY mosaicism.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. 47,XYY Syndrome; [reviewed 2009 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/47xyy-syndrome.

Microdeletions

People typically have 46 chromosomes in each cell. A microdeletion syndrome is caused by the deletion of a small piece of one of the 46 chromosomes. The signs and symptoms of microdeletion syndromes can vary substantially and are believed to be related to the loss of multiple genes in the deleted region. The size of the deletion may vary among affected individuals. Most cases of microdeletion syndromes are not inherited. They result from a chromosomal deletion that occurs as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family. Rarely, microdeletion syndromes can be inherited due to a chromosomal rearrangement called a translocation or due to an inherited mutation in the region that causes genes to malfunction.

Microdeletions

Condition	Frequency at Birth	Maternal Age Effect	PPV	NPV	Sensitivity[1] (95% CI)	Specificity[3]	Reference Interval Size/Genomic Coordinate in hg19
22q11.2 deletion	1/4,000	NO	Patient-specific PPV	>99.9 %	78.0% (17.5->99.9)	Estimated >99%	2.7 Mb/ chr22: 18891000-21561000
1p36 deletion	1/5,000	NO		>99.9 %	87.3% (31.6->99.9)	Estimated >99%	3.2 Mb/ chr1: 2700000-5900000
4p16 deletion (Wolf-Hirschhorn syndrome)	1/20,000	NO		>99.9 %	91.9% (46.6- >99.9)	Estimated >99%	3.5 Mb/ chr4: 1500000-5000000
5p15 deletion (Cri-du-chat syndrome)	1/20,000	NO		>99.9 %	97.8% (87.6->99.9)	Estimated >99%	9.8 Mb/ chr5: 1-9800000
15q11.2-q13 deletion (Angelman syndrome)	1/21,000	NO		>99.9 %	88.6% (35.2->99.9)	Estimated >99%	5.8 Mb/ chr15: 22688000-28520000
15q11.2-q13 deletion (Prader-Willi syndrome)	1/23,000	NO					5.8 Mb/ chr15: 22688000-28520000
11q23 deletion (Jacobsen syndrome)	1/100,000	NO		>99.9 %	94.9% (62.7->99.9)	Estimated >99%	6.3 Mb/ chr11: 128739000-135006000
8q24 deletion (Langer-Giedion syndrome)	Extremely rare	NO	N/A[2]	N/A[2]	90.3% (40.5->99.9)	Estimated >99%	2.7 Mb/ chr8: 116420724-119124058

[1] All sensitivities are based on analytical sensitivity.
[2] PPVs and NPVs were not calculated for very rare abnormalities.
[3] Estimated based on other studies using similar technologies (*2015 Prenatal Diagnosis, Clinical outcome of subchromosomal events detected by whole-genome noninvasive prenatal testing*).

References

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. 22q11.2 Deletion Syndrome; [reviewed 2013 Jul; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/22q112-deletion-syndrome.
2. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. 1p36 Deletion Syndrome; [reviewed 2014 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/1p36-deletion-syndrome.
3. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Wolf-Hirschhorn Syndrome; [reviewed 2012 Apr; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/wolf-hirschhorn-syndrome.
4. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Cri-du-chat Syndrome; [reviewed 2014 Feb; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/cri-du-chat-syndrome.
5. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Angelman Syndrome; [reviewed 2015 May; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/angelman-syndrome.
6. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Prader-Willi Syndrome; [reviewed 2014 Jun; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/prader-willi-syndrome.
7. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Jacobsen Syndrome; [reviewed 2015 Sep; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/jacobsen-syndrome.
8. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Langer-Giedion Syndrome; [reviewed 2009 Feb; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/langer-giedion-syndrome.

22q11.2 deletion

22q11.2 deletion syndrome (which is also known as DiGeorge Syndrome) is a disorder caused by the deletion of a small piece of chromosome 22. The deletion occurs near the middle of the chromosome at a location designated q11.2.

22q11.2 deletion syndrome has many possible signs and symptoms that can affect almost any part of the body. The features of this syndrome vary widely, even among affected members of the same family. Common signs and symptoms include heart abnormalities that are often present from birth, an opening in the roof of the mouth (a cleft palate), and distinctive facial features. People with 22q11.2 deletion syndrome may experience recurrent infections caused by problems with the immune system, and some develop autoimmune disorders such as rheumatoid arthritis and Graves disease in which the immune system attacks the body's own tissues and organs. Affected individuals may also have breathing problems, kidney abnormalities, low levels of calcium in the blood (which can result in seizures), a decrease in blood platelets (thrombocytopenia), significant feeding difficulties, gastrointestinal problems, and hearing loss. Skeletal differences are possible, including mild short stature and, less frequently, abnormalities of the spinal bones. 22q11.2 deletion syndrome is associated with an increased mortality rate and life expectancy can vary depending on the severity of the abnormalities.

Many children with 22q11.2 deletion syndrome have developmental delays, including delayed motor and speech development, and learning disabilities. Later in life, they are at an increased risk of developing mental illnesses such as schizophrenia, depression, anxiety, and bipolar disorder. Additionally, affected children are more likely than children without 22q11.2 deletion syndrome to have attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder

Because the signs and symptoms of 22q11.2 deletion syndrome are so varied, different groupings of features were once described as separate conditions. Doctors named these conditions DiGeorge syndrome, velocardiofacial syndrome (also called Shprintzen syndrome), and conotruncal anomaly face syndrome. In addition, some children with the 22q11.2 deletion were diagnosed with the autosomal dominant form of Opitz G/BBB syndrome and Cayler cardiofacial syndrome. Once the genetic basis for these disorders was identified, doctors determined that they were all part of a single syndrome with many possible signs and symptoms. To avoid confusion, this condition is usually called 22q11.2 deletion syndrome, a description based on its underlying genetic cause.

Genetics

Most people with 22q11.2 deletion syndrome are missing a sequence of about 3 million DNA building blocks (base pairs) on one copy of chromosome 22 in each cell. This region contains 30 to 40 genes, many of which have not been well characterized. A small percentage of affected individuals have shorter deletions in the same region. This condition is described as a contiguous gene deletion syndrome because it results from the loss of many genes that are close together.

Researchers are working to identify all of the genes that contribute to the features of 22q11.2 deletion syndrome. They have determined that the loss of a particular gene on chromosome 22, *TBX1*, is probably responsible for many of the syndrome's characteristic signs (such as heart defects, a cleft palate, distinctive facial features, hearing loss, and low calcium levels). Some studies suggest that a deletion of this gene may contribute to behavioral problems as well. The loss of another gene, *COMT*, in the same region of chromosome 22 may also help explain the increased risk of behavioral problems and mental illness. The loss of additional genes in the deleted region likely contributes to the varied features of 22q11.2 deletion syndrome. The inheritance of 22q11.2 deletion syndrome is considered autosomal dominant because a deletion in one copy of chromosome 22 in each cell is sufficient to cause the condition. Most cases of 22q11.2 deletion syndrome are not inherited, however. The deletion occurs most often as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family, though they can pass the condition to their children. In about 10 percent of cases, a person with this condition inherits the deletion in chromosome 22 from a parent. In inherited cases, other family members may be affected as well.

References

1. Bassett AS, Chow EWC, Husted J, Hodgkinson KA, Oechslin E, Harris L,Silversides C. (2009) Premature death in adults with 22q11.2 deletion syndrome. J Med Genet 46:324-330
2. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. 22q11.2 Deletion Syndrome; [reviewed 2013 Jul; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/22q112-deletion-syndrome.

1p36 deletion

1p36 deletion syndrome is a disorder that typically causes severe intellectual disability. Most affected individuals do not speak or speak very few words. They may have temper tantrums, bite themselves, or exhibit other behavior problems. Most have structural abnormalities of the brain, and seizures occur in more than half of individuals with this disorder. Affected individuals usually have weak muscle tone (hypotonia) and swallowing difficulties (dysphagia).

People with 1p36 deletion syndrome have a small head that is also unusually short and wide in proportion to its size (microbrachycephaly). Affected individuals also have distinctive facial features including deep-set eyes with straight eyebrows; a sunken appearance of the middle of the face (midface hypoplasia); a broad, flat nose; a long area between the nose and mouth (philtrum); a pointed chin; and ears that are low-set, rotated backwards, and abnormally shaped. People with 1p36 deletion syndrome may have vision or hearing problems. Some have abnormalities of the skeleton, heart, gastrointestinal system, kidneys, or genitalia. The life expectancy of individuals with 1p36 deletion syndrome is not currently known.

Genetics

1p36 deletion syndrome is caused by a deletion of genetic material from a specific region in the short (p) arm of chromosome 1. The signs and symptoms of 1p36 deletion syndrome are probably related to the loss of multiple genes in this region. The size of the deletion varies among affected individuals. Most cases of 1p36 deletion syndrome are not inherited. They result from a chromosomal deletion that occurs as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family.

About 20 percent of people with 1p36 deletion syndrome inherit the chromosome with a deleted segment from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation, in which no genetic material is gained or lost. Balanced translocations usually do not cause any health problems; however, they can become unbalanced as they are passed to the next generation. Children who inherit an unbalanced translocation can have a chromosomal rearrangement with extra or missing genetic material. Individuals with 1p36 deletion syndrome who inherit an unbalanced translocation are missing genetic material from the short arm of chromosome 1, which results in birth defects and other health problems characteristic of this disorder.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. 1p36 Deletion Syndrome; [reviewed 2014 Jan; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/1p36-deletion-syndrome.

4p16 deletion (Wolf-Hirschhorn syndrome)

Wolf-Hirschhorn syndrome is a condition that affects many parts of the body. The major features of this disorder include a characteristic facial appearance, delayed growth and development, intellectual disability, and seizures. Almost everyone with this disorder has distinctive facial features, including a broad, flat nasal bridge and a high forehead. This combination is described as a "Greek warrior helmet" appearance. The eyes are widely spaced and may be protruding. Other characteristic facial features include a shortened distance between the nose and upper lip (a short philtrum), a downturned mouth, a small chin (micrognathia), and poorly formed ears with small holes (pits) or flaps of skin (tags). Additionally, affected individuals may have asymmetrical facial features and an unusually small head (microcephaly).

People with Wolf-Hirschhorn syndrome experience delayed growth and development. Slow growth begins before birth, and affected infants tend to have problems feeding and gaining weight (failure to thrive). They also have weak muscle tone (hypotonia) and underdeveloped muscles. Motor skills such as sitting, standing, and walking are significantly delayed. Most children and adults with this disorder also have short stature. Intellectual disability ranges from mild to severe in people with Wolf-Hirschhorn syndrome. Compared to people with other forms of intellectual disability, their socialization skills are strong, while verbal communication and language skills tend to be weaker. Most affected children also have seizures, which may be resistant to treatment. Seizures tend to disappear with age. Additional features of Wolf-Hirschhorn syndrome include skin changes such as mottled or dry skin, skeletal abnormalities such as abnormal curvature of the spine (scoliosis and kyphosis), dental problems including missing teeth, and an opening in the roof of the mouth (cleft palate) and/or in the lip (cleft lip). Wolf-Hirschhorn syndrome can also cause abnormalities of the eyes, heart, genitourinary tract, and brain. The life expectancy of individuals with Wolf-Hirschhorn syndrome can vary; however, there is an increased mortality rate for children diagnosed with this syndrome.

A condition called Pitt-Rogers-Danks syndrome has features that overlap with those of Wolf-Hirschhorn syndrome. Researchers now recognize that these two conditions are actually part of a single syndrome with variable signs and symptoms.

Genetics

Wolf-Hirschhorn syndrome is caused by a deletion of genetic material near the end of the short (p) arm of chromosome 4. This chromosomal change is sometimes written as 4p-. The size of the deletion varies among affected individuals; studies suggest that larger deletions tend to result in more severe intellectual disability and physical abnormalities than smaller deletions.

Between 85 and 90 percent of all cases of Wolf-Hirschhorn syndrome are not inherited. They result from a chromosomal deletion that occurs as a random (de novo) event during the formation of reproductive cells (eggs or sperm) or in early embryonic development. More complex chromosomal rearrangements can also occur as de novo events, which may help explain the variability in the condition's signs and symptoms. De novo chromosomal changes occur in people with no history of the disorder in their family.

A small percentage of all people with Wolf-Hirschhorn syndrome have the disorder as a result of an unusual chromosomal abnormality such as a ring chromosome 4. Ring chromosomes occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure. In the process, genes near the ends of the chromosome are lost.

In the remaining cases of Wolf-Hirschhorn syndrome, an affected individual inherits a copy of chromosome 4 with a deleted segment. In these cases, one of the individual's parents carries a chromosomal rearrangement between chromosome 4 and another chromosome. This rearrangement is called a balanced translocation. No genetic material is gained or lost in a balanced translocation, so these chromosomal changes usually do not cause any health problems. However, translocations can become unbalanced as they are passed to the next generation. Some people with Wolf-Hirschhorn syndrome inherit an unbalanced translocation that deletes genes near the end of the short arm of chromosome 4. A loss of these genes results in the intellectual disability, slow growth, and other health problems characteristic of this disorder.

References

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Wolf-Hirschhorn Syndrome; [reviewed 2012 Apr; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/wolf-hirschhorn-syndrome.
2. Shannon, NL, Maltby EL, Rigby AS, Quarrell OWJ (2001). An epidemiological study of Wolf Hirschhorn syndrome: life expectancy and cause of mortality. J Med Genet. 38: 674-679

5p15 deletion (Cri-du-chat syndrome)

Cri-du-chat (cat's cry) syndrome, also known as 5p- (5p minus) syndrome, is a chromosomal condition that results when a piece of chromosome 5 is missing. Infants with this condition often have a high-pitched cry that sounds like that of a cat. The disorder is characterized by intellectual disability and delayed development, small head size (microcephaly), low birth weight, and weak muscle tone (hypotonia) in infancy. Affected individuals also have distinctive facial features, including widely set eyes (hypertelorism), low-set ears, a small jaw, and a rounded face. Some children with cri-du-chat syndrome are born with a heart defect. Most individuals with Cri-du-chat syndrome have a normal lifespan; however, individuals with severe defects can have life threatening complications.

Genetics

Cri-du-chat syndrome is caused by a deletion of the end of the short (p) arm of chromosome 5. This chromosomal change is written as 5p-. The size of the deletion varies among affected individuals; studies suggest that larger deletions tend to result in more severe intellectual disability and developmental delay than smaller deletions.

Most cases of cri-du-chat syndrome are not inherited. The deletion occurs most often as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family.

About 10 percent of people with cri-du-chat syndrome inherit the chromosome abnormality from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation, in which no genetic material is gained or lost. Balanced translocations usually do not cause any health problems; however, they can become unbalanced as they are passed to the next generation. Children who inherit an unbalanced translocation can have a chromosomal rearrangement with extra or missing genetic material. Individuals with cri-du-chat syndrome who inherit an unbalanced translocation are missing genetic material from the short arm of chromosome 5, which results in the intellectual disability and health problems characteristic of this disorder.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Cri-du-chat Syndrome; [reviewed 2014 Feb; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/cri-du-chat-syndrome.

15q11.2-q13 deletion (Angelman syndrome)

Angelman syndrome is a complex genetic disorder that primarily affects the nervous system. Characteristic features of this condition include delayed development, intellectual disability, severe

speech impairment, and problems with movement and balance (ataxia). Most affected children also have recurrent seizures (epilepsy) and a small head size (microcephaly). Delayed development becomes noticeable by the age of 6 to 12 months, and other common signs and symptoms usually appear in early childhood. Children with Angelman syndrome typically have a happy, excitable demeanor with frequent smiling, laughter, and hand-flapping movements. Hyperactivity, a short attention span, and a fascination with water are common. Most affected children also have difficulty sleeping and need less sleep than usual.

With age, people with Angelman syndrome become less excitable, and the sleeping problems tend to improve. However, affected individuals continue to have intellectual disability, severe speech impairment, and seizures throughout their lives. Adults with Angelman syndrome have distinctive facial features that may be described as "coarse." Other common features include unusually fair skin with light-colored hair and an abnormal side-to-side curvature of the spine (scoliosis). Most individuals with Angelman Syndrome have a normal lifespan; however, the more severe cases are associated with a shortened lifespan (approximately 10-15 years shorter).

Genetics

Many of the characteristic features of Angelman syndrome result from the loss of function of a gene called *UBE3A*. People normally inherit one copy of the UBE3A gene from each parent. Both copies of this gene are turned on (active) in many of the body's tissues. In certain areas of the brain, however, only the copy inherited from a person's mother (the maternal copy) is active. This parent-specific gene activation is caused by a phenomenon called genomic imprinting. If the maternal copy of the *UBE3A* gene is lost because of a chromosomal change or a gene mutation, a person will have no active copies of the gene in some parts of the brain. Several different genetic mechanisms can inactivate or delete the maternal copy of the *UBE3A* gene. Most cases of Angelman syndrome (about 70 percent) occur when a segment of the maternal chromosome 15 containing this gene is deleted. In other cases (about 11 percent), Angelman syndrome is caused by a mutation in the maternal copy of the *UBE3A* gene.

In a small percentage of cases, Angelman syndrome results when a person inherits two copies of chromosome 15 from his or her father (paternal copies) instead of one copy from each parent. This phenomenon is called paternal uniparental disomy. Rarely, Angelman syndrome can also be caused by a chromosomal rearrangement called a translocation, or by a mutation or other defect in the region of DNA that controls activation of the *UBE3A* gene. These genetic changes can abnormally turn off (inactivate) *UBE3A* or other genes on the maternal copy of chromosome 15.

Most cases of Angelman syndrome are not inherited, particularly those caused by a deletion in the maternal chromosome 15 or by paternal uniparental disomy. These genetic changes occur as random events during the formation of reproductive cells (eggs and sperm) or in early embryonic development. Affected people typically have no history of the disorder in their family. Rarely, a genetic change responsible for Angelman syndrome can be inherited. For example, it is possible for a mutation in the *UBE3A* gene or in the nearby region of DNA that controls gene activation to be passed from one generation to the next. The causes of Angelman syndrome are unknown in 10 to 15 percent of affected individuals. Changes involving other genes or chromosomes may be responsible for the disorder in these cases.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Angelman Syndrome; [reviewed 2015 May; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/angelman-syndrome.

15q11.2-q13 deletion (Prader-Willi syndrome)

Prader-Willi syndrome is a complex genetic condition that affects many parts of the body. In infancy, this condition is characterized by weak muscle tone (hypotonia), feeding difficulties, poor growth, and delayed development. Beginning in childhood, affected individuals develop an insatiable appetite, which leads to chronic overeating (hyperphagia) and obesity. Some people with Prader-Willi syndrome, particularly those with obesity, also develop type 2 diabetes mellitus (the most common form of diabetes).

People with Prader-Willi syndrome typically have mild to moderate intellectual impairment and learning disabilities. Behavioral problems are common, including temper outbursts, stubbornness, and compulsive behavior such as picking at the skin. Sleep abnormalities can also occur. Additional features of this condition include distinctive facial features such as a narrow forehead, almond-shaped eyes, and a triangular mouth; short stature; and small hands and feet. Some people with Prader-Willi syndrome have unusually fair skin and light-colored hair. Both affected males and affected females have underdeveloped genitals. Puberty is delayed or incomplete, and most affected individuals are unable to have children (infertile). There is an increased mortality rate in children with Prader-Willi syndrome, particularly due to complications associated with obesity, cardiac and respiratory issues.

Genetics

Prader-Willi syndrome is caused by the loss of function of genes in a particular region of chromosome 15. People normally inherit one copy of this chromosome from each parent. Some genes are turned on (active) only on the copy that is inherited from a person's father (the paternal copy). This parent-specific gene activation is caused by a phenomenon called genomic imprinting.

Most cases of Prader-Willi syndrome (about 70 percent) occur when a segment of the paternal chromosome 15 is deleted in each cell. People with this chromosomal change are missing certain critical genes in this region because the genes on the paternal copy have been deleted, and the genes on the maternal copy are turned off (inactive). In another 25 percent of cases, a person with Prader-Willi syndrome has two copies of chromosome 15 inherited from his or her mother (maternal copies) instead of one copy from each parent. This phenomenon is called maternal uniparental disomy. Rarely, Prader-Willi syndrome can also be caused by a chromosomal rearrangement called a translocation, or by a mutation or other defect that abnormally turns off (inactivates) genes on the paternal chromosome 15.

Most cases of Prader-Willi syndrome are not inherited, particularly those caused by a deletion in the paternal chromosome 15 or by maternal uniparental disomy. These genetic changes occur as random events during the formation of reproductive cells (eggs and sperm) or in early embryonic development. Affected people typically have no history of the disorder in their family. Rarely, a genetic change responsible for Prader-Willi syndrome can be inherited. For example, it is possible for a genetic change that abnormally inactivates genes on the paternal chromosome 15 to be passed from one generation to the next.

References

1. Butler, MG, Manzardo AM, Heinemann J, Loker C, Loker J (2017) Causes of Death in Prader-Willi Syndrome: Prader -Willi Syndrome Association (USA) 40 Year Mortality Survey. Genet Med.19(6): 635-642
2. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Prader-Willi Syndrome; [reviewed 2014 Jun; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/prader-willi-syndrome.

11q23 deletion (Jacobsen syndrome)

Jacobsen syndrome is a condition caused by a loss of genetic material from chromosome 11. Because this deletion occurs at the end (terminus) of the long (q) arm of chromosome 11, Jacobsen syndrome is also known as 11q terminal deletion disorder.

The signs and symptoms of Jacobsen syndrome vary considerably. Most affected individuals have delayed development, including the development of speech and motor skills (such as sitting, standing, and walking). Most also have cognitive impairment and learning difficulties. Behavioral problems have been reported, including compulsive behavior (such as shredding paper), a short attention span, and easy distractibility. Many people with Jacobsen syndrome have been diagnosed with attention deficit-hyperactivity disorder (ADHD). Jacobsen syndrome is also associated with an increased likelihood of autism spectrum disorders, which are characterized by impaired communication and socialization skills.

Jacobsen syndrome is also characterized by distinctive facial features. These include small and low-set ears, widely set eyes (hypertelorism) with droopy eyelids (ptosis), skin folds covering the inner corner of the eyes (epicanthal folds), a broad nasal bridge, downturned corners of the mouth, a thin upper lip, and a small lower jaw. Affected individuals often have a large head size (macrocephaly) and a skull abnormality called trigonocephaly, which gives the forehead a pointed appearance.

More than 90 percent of people with Jacobsen syndrome have a bleeding disorder called Paris-Trousseau syndrome. This condition causes a lifelong risk of abnormal bleeding and easy bruising. Paris-Trousseau syndrome is a disorder of platelets, which are blood cell fragments that are necessary for blood clotting. Other features of Jacobsen syndrome can include heart defects, feeding difficulties in infancy, short stature, frequent ear and sinus infections, and skeletal abnormalities. The disorder can also affect the digestive system, kidneys, and genitalia. The life expectancy of people with Jacobsen syndrome is unknown, although affected individuals have lived into adulthood.

Genetics

Jacobsen syndrome is caused by a deletion of genetic material at the end of the long (q) arm of chromosome 11. The size of the deletion varies among affected individuals, with most affected people missing 5 million to 16 million DNA building blocks (also written as 5 Mb to 16 Mb). In almost all affected people, the deletion includes the tip of chromosome 11. Larger deletions tend to cause more severe signs and symptoms than smaller deletions.

Most cases of Jacobsen syndrome are not inherited. They result from a chromosomal deletion that occurs as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family, although they can pass the chromosome deletion to their children.

Between 5 and 10 percent of people with Jacobsen syndrome inherit the chromosome abnormality from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation, in which a segment from chromosome 11 has traded places with a segment from another chromosome. In a balanced translocation, no genetic material is gained or lost. Balanced translocations usually do not cause any health problems; however, they can become unbalanced as they are passed to the next generation.

Children who inherit an unbalanced translocation can have a chromosomal rearrangement with some missing genetic material and some extra genetic material. Individuals with Jacobsen syndrome who inherit an unbalanced translocation are missing genetic material from the end of the long arm of chromosome 11

and have extra genetic material from another chromosome. These chromosomal changes result in the health problems characteristic of this disorder.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Jacobsen Syndrome; [reviewed 2015 Sep; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/jacobsen-syndrome.

8q24 deletion (Langer-Giedion syndrome)

Langer-Giedion syndrome is a condition that causes bone abnormalities and distinctive facial features. People with this condition have multiple noncancerous (benign) bone tumors called osteochondromas. Multiple osteochondromas may result in pain, limited range of joint movement, and pressure on nerves, blood vessels, the spinal cord, and tissues surrounding the osteochondromas. Affected individuals also have short stature and cone-shaped ends of the long bones (epiphyses). The characteristic appearance of individuals with Langer-Giedion syndrome includes sparse scalp hair, a rounded nose, a long flat area between the nose and the upper lip (philtrum), and a thin upper lip. Some people with this condition have loose skin in childhood, which typically resolves with age. Affected individuals may have some intellectual disability. Most individuals with Langer-Giedion syndrome are expected to have a normal lifespan.

Genetics

Langer-Giedion syndrome is caused by the deletion or mutation of at least two genes on chromosome 8. Researchers have determined that the loss of a functional *EXT1* gene is responsible for the multiple osteochondromas seen in people with Langer-Giedion syndrome. Loss of a functional *TRPS1* gene may cause the other bone and facial abnormalities. The *EXT1* gene and the *TRPS1* gene are always missing or mutated in affected individuals, but other neighboring genes may also be involved. The loss of additional genes from this region of chromosome 8 likely contributes to the varied features of this condition. Langer-Giedion syndrome is often described as a contiguous gene deletion syndrome because it results from the loss of several neighboring genes. Most cases of Langer-Giedion syndrome are not inherited, but occur as random events during the formation of reproductive cells (eggs or sperm) in a parent of an affected individual. These cases occur in people with no history of the disorder in their family. There have been very few instances in which people with Langer-Giedion syndrome have inherited the chromosomal deletion from a parent with the condition.

Reference

1. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD); the Library; 2017 Apr 18. Langer-Giedion Syndrome; [reviewed 2009 Feb; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/langer-giedion-syndrome.

Turnaround time

- 5-7 calendar days from receipt of the sample

Specimen requirements

Blood samples

- Two 10 mL Streck BCT tubes
- Specimens received >5 days after blood draw will be rejected

Additional requirements

- Gestation age; At least 9 weeks or greater
- Singleton pregnancy
- Please contact the laboratory for options regarding multibirth pregnancies.

Please include the following with each sample

- Completed and signed test requisition form and informed consent
- Billing information or payment (include copy of insurance card)
- Contact information for referring physician
- Testing to be performed
- Indication for testing, patient's family history, ethnic background and prior relevant test results

Send same day or overnight (check for morning delivery) to

Sema4
Atran Laboratory Building
1428 Madison Avenue
Room AB2-25
New York, NY 10029

Contact

gc@sema4.com
Tel: 800-298-6470
Fax: 646-859-6870

Shipping requirements

- Store and ship at room temperature
- Do not freeze

References

1. Gregg AR, Skotko BG, Benkendorf JL, Monaghan KG, Bajaj K, Best RG, Klugman S, and Watson MS. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016;18:1056-65.

2. American College of Obstetricians and Gynecologists. Cell-free DNA screening for fetal aneuploidy. Committee Opinion No. 640. Obstet Gynecol. 2015;126:e31-7.

3. American College of Obstetricians and Gynecologists. Screening for Fetal Aneuploidy. Practice Bulletin No.163. Obstet Gynecol. 2016;127:e123-137.

Please note that this test was developed and its performance characteristics determined by Sema4. It has not been cleared or approved by the US Food and Drug Administration (FDA).

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