Chromosome 4

Description

Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 4, one copy inherited from each parent, form one of the pairs. Chromosome 4 spans about 191 million DNA building blocks (nucleotides) and represents more than 6 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 4 likely contains 1,000 to 1,100 genes that provide instructions for making proteins. These proteins perform a variety of different roles in the body.

Health Conditions Related to Chromosomal Changes

The following chromosomal conditions are associated with changes in the structure or number of copies of chromosome 4.

Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy is caused by genetic changes in the long (q) arm of chromosome 4. This condition is characterized by muscle weakness and wasting (atrophy) that worsens slowly over time.

Facioscapulohumeral muscular dystrophy is a result of changes in a region of DNA known as D4Z4, located near the end of the chromosome at a position described as 4q35. The D4Z4 region consists of 11 to more than 100 repeated segments, each of which is about 3,300 DNA base pairs (3.3 kb) long. The entire D4Z4 region is normally hypermethylated, which means that it has a large number of methyl groups (molecules that consist of one carbon atom and three hydrogen atoms) attached to the DNA.

Facioscapulohumeral muscular dystrophy occurs when the region is hypomethylated, with too few methyl groups attached. In facioscapulohumeral muscular dystrophy type 1 (FSHD1), hypomethylation occurs because the D4Z4 region contains between 1 and 10 repeats instead of the usual 11 to 100 repeats. In facioscapulohumeral muscular dystrophy type 2 (FSHD2), hypomethylation is most often a result of variants (also called mutations) in a gene called *SMCHD1*, which normally hypermethylates the D4Z4 region.

The segment of the D4Z4 region closest to the end of chromosome 4 contains a gene called *DUX4*. Hypermethylation of the D4Z4 region normally keeps the *DUX4* gene turned off (silenced) in most adult cells and tissues. In people with facioscapulohumeral muscular dystrophy, hypomethylation of the D4Z4 region prevents the *DUX4* gene from being silenced. Although little is known about the function of the *DUX4* gene when it is turned on (active), researchers believe that it influences the activity of other genes, particularly in muscle cells. It is unknown how abnormal activity of the *DUX4* gene damages or destroys these cells, leading to progressive muscle weakness and atrophy.

The *DUX4* gene is located next to a regulatory region of DNA known as a pLAM sequence, which is necessary for the production of the DUX4 protein. Some copies of chromosome 4 have a functional pLAM sequence, while others do not. Copies of chromosome 4 with a functional pLAM sequence are described as 4qA or "permissive." Those without a functional pLAM sequence are described as 4qB or "non-permissive."

Without a functional pLAM sequence, no DUX4 protein is made. Because there are two copies of chromosome 4 in each cell, individuals may have two "permissive" copies of chromosome 4, two "non-permissive" copies, or one of each. Facioscapulohumeral muscular dystrophy can only occur in people who have at least one "permissive" copy of chromosome 4. Whether an affected individual has a contracted D4Z4 region or a *SMCHD1* gene variant, the disease occurs only if a functional pLAM sequence is also present to allow DUX4 protein to be produced.

PDGFRA-associated chronic eosinophilic leukemia

PDGFRA-associated chronic eosinophilic leukemia is caused by genetic abnormalities that involve the *PDGFRA* gene, a gene found on chromosome 4. This condition is a type of blood cell cancer characterized by an increased number of eosinophils, a type of white blood cell involved in allergic reactions.

The *PDGFRA* gene abnormalities are somatic variants, which are variants acquired during a person's lifetime that are present only in certain cells. The most common of these abnormalities removes part of chromosome 4 and brings together parts of two genes, *FIP1L1* and *PDGFRA*, creating the *FIP1L1-PDGFRA* fusion gene. Occasionally, genes other than *FIP1L1* fuse with the *PDGFRA* gene. Rarely, variants that change single nucleotides in the *PDGFRA* gene (point variants) cause this condition.

The protein produced from the *FIP1L1-PDGFRA* fusion gene (as well as other *PDGFRA* fusion genes) has the function of the PDGFRA protein, which stimulates signaling pathways inside the cell that control many important cellular processes, such as cell growth and division (proliferation) and cell survival. Unlike the normal PDGFRA protein, however, the fusion protein is constantly turned on (constitutively activated), which means the cells are always receiving signals to proliferate. Similarly, point variants in the *PDGFRA* gene can result in a constitutively activated PDGFRA protein.

When the *FIP1L1-PDGFRA* fusion gene or point variants in the *PDGFRA* gene occur in blood cell precursors, the growth of eosinophils (and occasionally other blood cells) is poorly controlled, leading to *PDGFRA*-associated chronic eosinophilic leukemia. It is unclear why eosinophils are preferentially affected by this genetic change.

Wolf-Hirschhorn syndrome

Wolf-Hirschhorn syndrome is caused by a deletion of genetic material near the end of the short (p) arm of chromosome 4. The signs and symptoms of this condition are related to the loss of multiple genes from this part of the chromosome. 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.

The region of chromosome 4 that is deleted most often in people with Wolf-Hirschhorn syndrome is known as Wolf-Hirschhorn syndrome critical region 2 (WHSCR-2). This region contains several genes, some of which are known to play important roles in early development. A loss of these genes leads to developmental delay, distinctive facial features, slow growth, seizures, and other characteristic features of the condition. Scientists are working to identify additional genes at the end of the short arm of chromosome 4 that contribute to the features of Wolf-Hirschhorn syndrome.

Other chromosomal conditions

Some deletions of genetic material from the short (p) arm of chromosome 4 do not involve the critical region WHSCR-2. These deletions cause signs and symptoms that are distinct from those of Wolf-Hirschhorn syndrome (described above), including mild intellectual disability and, in some cases, rapid (accelerated) growth. People with this type of deletion usually do not have seizures.

Trisomy 4 occurs when cells have three copies of chromosome 4 instead of the usual two copies. Full trisomy 4, which occurs when all of the body's cells contain an extra copy of chromosome 4, is not compatible with life. A similar but somewhat less severe condition called mosaic trisomy 4 occurs when only some of the body's cells have an extra copy of chromosome 4. The signs and symptoms of mosaic trisomy 4 vary widely and can include heart defects, abnormalities of the fingers and toes, and other birth defects. Mosaic trisomy 4 is very rare; only a few cases have been reported.

Other changes in the number or structure of chromosome 4 can have a variety of effects, including delayed growth and development, intellectual disability, distinctive facial features, heart defects, and other medical problems. Changes involving chromosome 4 include an extra piece of the chromosome in each cell (partial trisomy 4), a missing segment of the chromosome in each cell (partial monosomy 4), and a circular structure called 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.

Cancers

Somatic changes in chromosome 4 have been identified in several types of human cancer. For example, rearrangements (translocations) of genetic material between chromosome 4 and several other chromosomes have been associated with leukemias, which are cancers of blood-forming cells.

A specific translocation involving chromosome 4 and chromosome 14 is commonly found in multiple myeloma, which is a cancer that starts in cells of the bone marrow. The translocation abnormally fuses the *WHSC1* gene on chromosome 4 with part of another gene on chromosome 14. The fusion of these genes overactivates *WHSC1*, which appears to promote the uncontrolled growth and division of cancer cells.

Additional Information & Resources

Additional NIH Resources

- National Human Genome Research Institute: Chromosome Abnormalities (https://www.genome.gov/about-genomics/fact-sheets/Chromosome-Abnormalities-Fact-Sheet)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Chromosomes,+Human,+Pair+4%5BMAJR%5D%29+AND+%28%284%5BTI%5D%29+OR+%284p%5BTI%5D%29+OR+%284q%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

References

- Bergemann AD, Cole F, Hirschhorn K. The etiology of Wolf-Hirschhorn syndrome. Trends Genet. 2005 Mar;21(3):188-95. doi: 10.1016/j.tig.2005.01.008. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15734578)
- Buitenhuis M, Verhagen LP, Cools J, Coffer PJ. Molecular mechanisms underlyingFIP1L1-PDGFRA-mediated myeloproliferation. Cancer Res. 2007 Apr 15; 67(8):3759-66.doi: 10.1158/0008-5472.CAN-06-4183. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17440089)
- Chen CP, Chern SR, Lee CC, Chang TY, Wang W, Tzen CY. Clinical, cytogenetic, and molecular findings of prenatally diagnosed mosaic trisomy 4. Prenat Diagn.2004 Jan;24(1):38-44. doi: 10.1002/pd.792. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/14755408)
- Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, Kutok J, ClarkJ, Galinsky I, Griffin JD, Cross NC, Tefferi A, Malone J, Alam R, Schrier SL,Schmid J, Rose M, Vandenberghe P, Verhoef G, Boogaerts M, Wlodarska I, KantarjianH, Marynen P, Coutre SE, Stone R, Gilliland DG. A tyrosine kinase created byfusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib inidiopathic hypereosinophilic syndrome. N Engl J Med. 2003 Mar 27;348(13):1201-14.doi: 10.1056/NEJMoa025217. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12660384)
- Ensembl Human Map View (http://www.ensembl.org/Homo_sapiens/Location/Chromosome?chr=4;r=4:1-190214555)

- Goldfrank D, Schoenberger E, Gilbert F. Disease genes and chromosomes: diseasemaps of the human genome. Chromosome 4. Genet Test. 2003 Winter;7(4): 351-72. doi:10.1089/109065703322783752. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15000816)
- Hayne CC, Winer E, Williams T, Chaves F, Khorsand J, Mark HF. Acutelymphoblastic leukemia with 4;11 translocation analyzed by a multi-modal strategyof conventional cytogenetics, FISH, morphology, flow cytometry and moleculargenetics, and review of the literature. Exp Mol Pathol. 2006 Aug;81(1):62-71.doi: 10.1016/j.yexmp.2006.04.002. Epub 2006 Jun 12. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16765346)
- Hillier LW, Graves TA, Fulton RS, Fulton LA, Pepin KH, Minx P,Wagner-McPherson C, Layman D, Wylie K, Sekhon M, Becker MC, Fewell GA, DelehauntyKD, Miner TL, Nash WE, Kremitzki C, Oddy L, Du H, Sun H, Bradshaw-Cordum H, AliJ, Carter J, Cordes M, Harris A, Isak A, van Brunt A, Nguyen C, Du F, Courtney L,Kalicki J, Ozersky P, Abbott S, Armstrong J, Belter EA, Caruso L, Cedroni M,Cotton M, Davidson T, Desai A, Elliott G, Erb T, Fronick C, Gaige T, Haakenson W,Haglund K, Holmes A, Harkins R, Kim K, Kruchowski SS, Strong CM, Grewal N, GoyeaE, Hou S, Levy A, Martinka S, Mead K, McLellan MD, Meyer R, Randall-Maher J,Tomlinson C, Dauphin-Kohlberg S, Kozlowicz-Reilly A, Shah N, Swearengen-Shahid S,Snider J, Strong JT, Thompson J, Yoakum M, Leonard S, Pearman C, Trani L,Radionenko M, Waligorski JE, Wang C, Rock SM, Tin-Wollam AM, Maupin R, LatreilleP, Wendl MC, Yang SP, Pohl C, Wallis JW, Spieth J, Bieri TA, Berkowicz N, NelsonJO, Osborne J, Ding L, Meyer R, Sabo A, Shotland Y, Sinha P, Wohldmann PE, CookLL, Hickenbotham MT, Eldred J, Williams D, Jones TA, She X, Ciccarelli FD,Izaurralde E, Taylor J, Schmutz J, Myers RM, Cox DR, Huang X, McPherson JD,Mardis ER, Clifton SW, Warren WC, Chinwalla AT, Eddy SR, Marra MA, Ovcharenko I,Furey TS, Miller W, Eichler EE, Bork P, Suyama M, Torrents D, Waterston RH,Wilson RK. Generation and annotation of the DNA sequences of human chromosomes 2and 4. Nature. 2005 Apr 7;434(7034):724-31. doi: 10.1038/nature03466. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15815621)
- Keats JJ, Maxwell CA, Taylor BJ, Hendzel MJ, Chesi M, Bergsagel PL, LarrattLM, Mant MJ, Reiman T, Belch AR, Pilarski LM. Overexpression of transcriptsoriginating from the MMSET locus characterizes all t(4;14)(p16;q32)-positivemultiple myeloma patients. Blood. 2005 May 15;105(10):4060-9. doi:10.1182/blood-2004-09-3704. Epub 2005 Jan 27. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15677557) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1895072/)
- Keats JJ, Reiman T, Belch AR, Pilarski LM. Ten years and counting: so what dowe know about t(4;14)(p16;q32) multiple myeloma. Leuk Lymphoma. 2006Nov;47(11): 2289-300. doi: 10.1080/10428190600822128. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17107900)
- Lemmers RJ, van der Vliet PJ, Klooster R, Sacconi S, Camano P, Dauwerse JG, Snider L, Straasheijm KR, van Ommen GJ, Padberg GW, Miller DG, Tapscott SJ, TawilR, Frants RR, van der Maarel SM. A unifying genetic model for facioscapulohumeralmuscular dystrophy. Science. 2010 Sep 24;329(5999):1650-3. doi:10.1126/science.1189044. Epub 2010 Aug 19. Citation on PubMed (https://pubm

ed.ncbi.nlm.nih.gov/20724583) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677822/)

- Lundin C, Zech L, Sjors K, Wadelius C, Anneren G. Trisomy 4q syndrome: presentation of a new case and review of the literature. Ann Genet. 2002Apr-Jun;45(2):53-7. doi: 10.1016/s0003-3995(02)01117-6. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12119211)
- South ST, Hannes F, Fisch GS, Vermeesch JR, Zollino M. Pathogenic significanceof deletions distal to the currently described Wolf-Hirschhorn syndrome criticalregions on 4p16.3. Am J Med Genet C Semin Med Genet. 2008 Nov 15;148C(4):270-4.doi: 10.1002/ajmg.c.30188. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18932125)
- Tawil R, van der Maarel SM, Tapscott SJ. Facioscapulohumeral dystrophy: thepath to consensus on pathophysiology. Skelet Muscle. 2014 Jun 10;4:12. doi:10.1186/2044-5040-4-12. eCollection 2014. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/24940479) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4060068/)
- UCSC Genome Browser: Statistics (http://genome.cse.ucsc.edu/goldenPath/stats.html)
- Zollino M, Lecce R, Fischetto R, Murdolo M, Faravelli F, Selicorni A, Butte C,Memo L, Capovilla G, Neri G. Mapping the Wolf-Hirschhorn syndrome phenotypeoutside the currently accepted WHS critical region and defining a new criticalregion, WHSCR-2. Am J Hum Genet. 2003 Mar;72(3):590-7. doi: 10.1086/367925. Epub2003 Jan 30. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12563561) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1180235/)
- Zollino M, Murdolo M, Marangi G, Pecile V, Galasso C, Mazzanti L, Neri G. Onthe nosology and pathogenesis of Wolf-Hirschhorn syndrome: genotype-phenotypecorrelation analysis of 80 patients and literature review. Am J Med Genet C SeminMed Genet. 2008 Nov 15;148C(4):257-69. doi: 10.1002/ajmg.c.30190. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18932124)

Last updated May 22, 2023