Kleefstra Syndrome

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Kleefstra syndrome is a disorder that involves many parts of the body. Characteristic features of Kleefstra syndrome include developmental delay and intellectual disability, severely limited or absent speech, and weak muscle tone (hypotonia).

genetic conditions

1. Introduction

Affected individuals also have an unusually small head size (microcephaly) and a wide, short skull (brachycephaly). Distinctive facial features include eyebrows that grow together in the middle (synophrys), widely spaced eyes (hypertelorism), a sunken appearance of the middle of the face (midface hypoplasia), nostrils that open to the front rather than downward (anteverted nares), a protruding jaw (prognathism), rolled out (everted) lips, and a large tongue (macroglossia). Affected individuals may have a high birth weight and childhood obesity.

People with Kleefstra syndrome may also have structural brain abnormalities, congenital heart defects, genitourinary abnormalities, seizures, and a tendency to develop severe respiratory infections. During childhood they may exhibit features of autism or related developmental disorders affecting communication and social interaction. In adolescence, they may develop a general loss of interest and enthusiasm (apathy) or unresponsiveness (catatonia).

2. Frequency

The prevalence of Kleefstra syndrome is unknown. Only recently has testing become available to distinguish it from other disorders with similar features.

3. Causes

Kleefstra syndrome is caused by the loss of the *EHMT1* gene or by mutations that disable its function. The *EHMT1* gene provides instructions for making an enzyme called euchromatic histone methyltransferase 1. Histone methyltransferases are enzymes that modify proteins called histones. Histones are structural proteins that attach (bind) to DNA and give chromosomes their shape. By adding a molecule called a methyl group to histones, histone methyltransferases can turn off (suppress) the activity of certain genes, which is essential for normal development and function.

Most people with Kleefstra syndrome are missing a sequence of about 1 million DNA building blocks (base pairs) on one copy of chromosome 9 in each cell. The deletion occurs near the end of the long (q) arm of the chromosome at a location designated q34.3, a region containing the *EHMT1* gene. Some affected individuals have shorter or longer deletions in the same region.

The loss of the *EHMT1* gene from one copy of chromosome 9 in each cell is believed to be responsible for the characteristic features of Kleefstra syndrome in people with the 9q34.3 deletion. However, the loss of other genes in the same region may lead to additional health problems in some affected individuals.

About 25 percent of individuals with Kleefstra syndrome do not have a deletion of genetic material from chromosome 9; instead, these individuals have mutations in the *EHMT1* gene. Some of these mutations change single protein building blocks (amino acids) in euchromatic histone methyltransferase 1. Others create a premature stop signal in the instructions for making the enzyme or alter the way the gene's instructions are pieced together to produce the enzyme. These changes generally result in an enzyme that is unstable and decays rapidly, or that is disabled and cannot function properly.

Either a deletion or a mutation affecting the *EHMT1* gene results in a lack of functional euchromatic histone methyltransferase 1 enzyme. A lack of this enzyme impairs proper control of the activity of certain genes in many of the body's organs and tissues, resulting in the abnormalities of development and function characteristic of Kleefstra syndrome.

3.1. The gene and chromosome associated with Kleefstra syndrome

- EHMT1
- chromosome 9

4. Inheritance

The inheritance of Kleefstra syndrome is considered to be autosomal dominant because a deletion in one copy of chromosome 9 in each cell or a mutation in one copy of the *EHMT1* gene is sufficient to cause the condition. Most cases of Kleefstra syndrome are not inherited, however. The genetic change 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 disorder on to their children. Only a few people with Kleefstra syndrome have been known to reproduce.

Rarely, affected individuals inherit a chromosome 9 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 Kleefstra

syndrome who inherit an unbalanced translocation are missing genetic material from the long arm of chromosome 9.

A few individuals with Kleefstra syndrome have inherited the chromosome 9q34.3 deletion from an unaffected parent who is mosaic for the deletion. Mosaic means that an individual has the deletion in some cells (including some sperm or egg cells), but not in others.

5. Other Names for This Condition

- 9q subtelomeric deletion syndrome
- 9q- syndrome
- 9q34.3 deletion syndrome
- 9q34.3 microdeletion syndrome
- chromosome 9q deletion syndrome

References

1. Iwakoshi M, Okamoto N, Harada N, Nakamura T, Yamamori S, Fujita H, Niikawa N, Matsumoto N. 9q34.3 deletion syndrome in three unrelated children. Am J Med GenetA. 2004 Apr 30;126A(3):278-83. Review.
2. Kleefstra T, Brunner HG, Amiel J, Oudakker AR, Nillesen WM, Magee A, GenevièveD, Cormier-Daire V, van Esch H, Fryns JP, Hamel BC, Sistermans EA, de Vries BB,van Bokhoven H. Loss-of-function mutations in euchromatin histone methyltransferase 1 (EHMT1) cause the 9q34 subtelomeric deletion syndrome. Am J HumGenet. 2006 Aug;79(2):370-7.
3. Kleefstra T, de Leeuw N. Kleefstra Syndrome. 2010 Oct 5 [updated 2019 Mar 21].In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington,Seattle; 1993-2020. Available from http://www.ncbi.nlm.nih.gov/books/NBK47079/
4. Kleefstra T, Smidt M, Banning MJ, Oudakker AR, Van Esch H, de Brouwer AP,Nillesen W, Sistermans EA, Hamel BC, de Bruijn D, Fryns JP, Yntema HG, BrunnerHG, de Vries BB, van Bokhoven H. Disruption of the gene Euchromatin HistoneMethyl Transferase1 (Eu-HMTase1) is associated with the 9q34 subtelomericdeletion syndrome. J Med Genet. 2005 Apr;42(4):299-306.

5. Kleefstra T, van Zelst-Stams WA, Nillesen WM, Cormier-Daire V, Houge G, FouldsN, van Dooren M, Willemsen MH, Pfundt R, Turner A, Wilson M, McGaughran J, Rauch A, Zenker M, Adam MP, Innes M, Davies C, López AG, Casalone R, Weber A, BruetonLA, Navarro AD, Bralo MP, Venselaar H, Stegmann SP, Yntema HG, van Bokhoven H,Brunner HG. Further clinical and molecular delineation of the 9q subtelomericdeletion syndrome supports a major contribution of EHMT1 haploinsufficiency tothe core phenotype. J Med Genet. 2009 Sep;46(9):598-606. doi:10.1136/jmg.2008.062950.
6. Neas KR, Smith JM, Chia N, Huseyin S, St Heaps L, Peters G, Sholler G, TzioumiD, Sillence DO, Mowat D. Three patients with terminal deletions within thesubtelomeric region of chromosome 9q. Am J Med Genet A. 2005 Feb1;132A(4):425-30. Review.
7. Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am JMed Genet C Semin Med Genet. 2007 Nov 15;145C(4):383-92. Review.
8. Verhoeven WM, Egger JI, Vermeulen K, van de Warrenburg BP, Kleefstra T.Kleefstra syndrome in three adult patients: further delineation of the behavioraland neurological phenotype shows aspects of a neurodegenerative course. Am J Med Genet A. 2011 Oct;155A(10):2409-15. doi: 10.1002/ajmg.a.34186.
9. Willemsen MH, Beunders G, Callaghan M, de Leeuw N, Nillesen WM, Yntema HG, vanHagen JM, Nieuwint AW, Morrison N, Keijzers-Vloet ST, Hoischen A, Brunner HG,Tolmie J, Kleefstra T. Familial Kleefstra syndrome due to maternal somaticmosaicism for interstitial 9q34.3 microdeletions. Clin Genet. 2011Jul;80(1):31-8. doi: 10.1111/j.1399-0004.2010.01607.x.