Kleefstra Syndrome

Alternative Names
Chromosome 9q34.3 Deletion Syndrome
9q- Syndrome
9q Subtelomeric Deletion Syndrome

Record Category
Disease phenotype

WHO-ICD
Congenital malformations, deformations and chromosomal abnormalities > Other congenital malformations

Incidence per 100,000 Live Births
Unknown

OMIM Number
610253

Mode of Inheritance
Autosomal Dominant

Gene Map Locus
9q34.3

Description
Kleefstra syndrome is a rare disorder characterized by moderate to severe intellectual disability, childhood hypotonia, developmental delay and extremely limited speech capabilities. Patients often suffer from distinctive facial dysmorphia, such as brachycephaly, microcephaly, flat face, mid face hypoplasia, hypertelorism, synophrys, a full everted lower lip, a protruding tongue and prognathism. Some patients may also exhibit behavioral problems such as obsessive-compulsive disorder, stereotypic movements and aggressive behavior. Other symptoms may include sleep issues, obesity, brachydactyly and cardiovascular anomalies such as conotruncal heart defects.

Kleefstra syndrome is a rare condition with about 200 affected individuals reported worldwide. Due to its recent discovery and the limited number of cases, the prognosis of the disorder is not completely known. The condition affects men and women equally and does not appear to have a racial or ethnic bias.

The diagnosis can be confirmed by molecular testing of the EHMT1 gene. While there is currently no cure for the disorder, affected individuals benefit from early intervention strategies, including physical and occupational therapy, speech therapy and behavioral therapy. Patients may require medication for sleep issues, behavioral problems and to treat epilepsy.

Molecular Genetics
Kleefstra syndrome follows an autosomal dominant pattern of inheritance and is caused by large heterozygous deletions in the 9q34.3 chromosome region that result in the loss of the EHMT1 gene. This gene encodes a lysine methyltransferase responsible for the methylation of the Lys-9 residue of histone H3. The enzyme is part of the E2F6 complex that negatively regulates gene transcription. In about 25% of Kleefstra cases, patients do not have large deletions but instead have heterozygous point mutations in the EHMT1 gene that result in a non-functioning EHMT1 protein.

Recent studies have identified certain Kleefstra cases with no EHMT1 mutations but with variants in the MBD5, MLL3, SMARCB1 and NR1I3 genes respectively. As these genes all encode epigenetic regulators, their role in Kleefstra syndrome has been speculated. However, a direct causal link between the condition and these gene mutations has not yet been established.

Epidemiology in the Arab World

Saudi Arabia

Monies et al. (2017) investigated the findings of 1000 diagnostic panels and exomes carried out at a next generation sequencing lab in Saudi Arabia. One male patient from a consanguineous family presented with speech and mental delay, learning disability, recurrent fever, seizures and GTC epilepsy. Using whole exome sequencing a heterozygous mutation (c.6589C>A, p.Q2197K) was identified in exon 36 of the patient's KMT2C gene. A mutation in the KMT2C gene had previously been tentatively linked to Kleefstra syndrome, and hence this result was seen to confirm this association.

References

Monies D, Abouelhoda M, AlSayed M, Alhassnan Z, Alotaibi M, Kayyali H, Al-Owain M, Shah A, Rahbeeni Z, Al-Muhaizea MA, Alzaidan HI, Cupler E, Bohlega S, Faqeih E, Faden M, Alyounes B, Jaroudi D, Goljan E, Elbardisy H, Akilan A, Albar R, Aldhalaan H, Gulab S, Chedrawi A, Al Saud BK, Kurdi W, Makhseed N, Alqasim T, El Khashab HY, Al-Mousa H, Alhashem A, Kanaan I, Algoufi T, Alsaleem K, Basha TA, Al-Murshedi F, Khan S, Al-Kindy A, Alnemer M, Al-Hajjar S, Alyamani S, Aldhekri H, Al-Mehaidib A, Arnaout R, Dabbagh O, Shagrani M, Broering D, Tulbah M, Alqassmi A, Almugbel M, AlQuaiz M, Alsaman A, Al-Thihli K, Sulaiman RA, Al-Dekhail W, Alsaegh A, Bashiri FA, Qari A, Alhomadi S, Alkuraya H, Alsebayel M, Hamad MH, Szonyi L, Abaalkhail F, Al-Mayouf SM, Almojalli H, Alqadi KS, Elsiesy H, Shuaib TM, Seidahmed MZ, Abosoudah I, Akleh H, AlGhonaium A, Alkharfy TM, Al Mutairi F, Eyaid W, Alshanbary A, Sheikh FR, Alsohaibani FI, Alsonbul A, Al Tala S, Balkhy S, Bassiouni R, Alenizi AS, Hussein MH, Hassan S, Khalil M, Tabarki B, Alshahwan S, Oshi A, Sabr Y, Alsaadoun S, Salih MA, Mohamed S, Sultana H, Tamim A, El-Haj M, Alshahrani S, Bubshait DK, Alfadhel M, Faquih T, El-Kalioby M, Subhani S, Shah Z, Moghrabi N, Meyer BF, Alkuraya FS. The landscape of genetic diseases in Saudi Arabia based on the first 1000 diagnostic panels and exomes. Hum Genet. 2017 Aug;136(8):921-939. PMID: 28600779.

Related CTGA Records

Lysine-Specific Methyltransferase 2C (OMIM 606833)

External Links

https://ghr.nlm.nih.gov/condition/kleefstra-syndrome#

https://www.genespark.org/id-ks-overview-of-ks/

http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=261494

Contributors

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