Holoprosencephaly 4

Alternative Names
HPE4

Record Category
Disease phenotype

WHO-ICD
Congenital malformations, deformations and chromosomal abnormalities > Congenital malformations of the nervous system

Incidence per 100,000 Live Births
6-10

OMIM Number
142946

Mode of Inheritance
Autosomal Dominant

Gene Map Locus
18p11.31

Description
Holoprosencephaly (HPE) is a condition characterized by the failed or incomplete separation of the forebrain during the early gestation period. This can result in a spectrum of brain malformations that are classified based on severity into alobar, semilobar, lobar, and middle interhemispheric variant (MIHV) type HPE. The condition causes developmental delay and intellectual disability in affected individuals. HPE4, caused by mutations in the TGIF1 gene, presents with facial dysmorphia such as a wide midline cleft lip/palate, hypotelorism, ptosis, a flat nasal bridge, a flattened nasal tip and an absent nasal septum.

Most fetuses with this disorder do not survive the gestation period, and infants often succumb within the first year of life. TGIF1-related HPE4 has a severe phenotype; affected individuals show higher rates of severe facial defects and alobar or semilobar HPE. The overall prevalence of holoprosencephaly is about 1 in 250 embryos, and 1 in 10,000 live births. TGIF1-related HPE is believed to account for less than two percent of these cases.

The condition is diagnosed based on neuroimaging studies. Severe cases are often diagnosed prenatally during ultrasound examinations. There is currently no cure for the disorder and treatment is limited to supportive and symptomatic care. Patients may require cleft lip/palate surgery.

Molecular Genetics
The disorder follows an autosomal dominant pattern of inheritance and is caused by mutations in the TGIF1 gene. This gene encodes a homeobox protein that plays a key role in embryonic development. It competitively binds to RXR responsive elements in the cellular retinol binding protein II promoter, thus inhibiting RXR binding and acting as a transcriptional repressor. Heterozygous mutations in the TGIF1 gene associated with HPE4 include deletions, missense variants, and premature truncations that impair its function.

Epidemiology in the Arab World
Saudi Arabia
Monies et al. (2017) studied the genomic landscape of Saudi Arabia based on the findings of 1000 diagnostic panels and exomes. One patient, an 11-year-old male, suffered from hemimegalencephaly, developmental delay and ADHD. He also had abnormal pigmentation all over his body. Whole exome sequencing helped identify a dual molecular diagnosis in this patient. A heterozygous mutation (c.1557T>G, p.Y519X) was found in exon 8 of the patient's TYRP1 gene, associated with

oculocutaneous albinism type 3, and a heterozygous variant (c.90G>A, p.W30X) was uncovered in exon 1 of the TGIF1 gene, associated with HPE4. Such dual molecular diagnoses were rare and only occurred in 1.5% of the cohort. Further, given the atypical presentation of the patient, this case helped in the phenotypic expansion of the HPE4 disorder.

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

Transforming Growth Factor-Beta-Induced Factor (OMIM 602630)

External Links

https://ghr.nlm.nih.gov/condition/nonsyndromic-holoprosencephaly#

http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=2162

Contributors

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