Homeobox A1

Alternative Names
HOXA1
Homeobox 1F
HOX1F
Hox-1.6, Mouse, Homolog of
Lab, Drosophila, Homolog of

Record Category
Gene locus

WHO-ICD
N.B.: Classification not applicable to gene loci.

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
142955

Mode of Inheritance
Autosomal recessive

Gene Map Locus
7p15.2

Description
Homeobox genes are expressed during embryonic development in a spatially and temporally regulated manner to control the developing body of an embryo along the anterior-posterior axis. These genes are found in clusters named A, B, C, and D on four separate chromosomes, and they encode a group of transcription factors. The HOXA1 gene belongs to the "A" cluster on chromosome 7 and it encodes a DNA-binding transcription factor, with potential roles in regulating gene expression, morphogenesis, and differentiation. The specific role of this transcription factor is thought to revolve around ensuring the correct placement of hindbrain segments in the proper location along the anterior-posterior axis during development.

Molecular Genetics
The HOXA1 gene spans just over 3 Kb with two exons and two transcript variants encoding two different isoforms. Only one of these isoforms contains the homeodomain region. The larger of the two variants is predicted to be 335 amino acids long and to have a molecular weight of 36-kD.

Many clinically relevant mutations were identified in the HOXA1 gene. Loss of function mutations in HOXA1 gene were implicated in two clinically overlapping autosomal recessive syndromes; the Bosley-Salih-Alorainy Syndrome (BSAS) and the Athabascan Brainstem Dysgenesis Syndrome (ABDS). A guanine insertion (c.175-176insG) in HOXA1 introducing a premature stop codon is associated with BSAS, while ABDS is associated with a 76C>T transition in HOXA1 that introduces a stop codon in the place of an arginine residue (p.R26X).

Epidemiology in the Arab World
Saudi Arabia
Tischfield et al. (2005) reported on eight Saudis belonging to four consanguineous families, who were suffering from BSAS. In those patients, a homozygous truncating mutation in the HOXA1 gene was identified; a guanine insertion (c.175-176insG). This mutation was predicted to cause a reading frameshift and introduce a premature stop codon, thus leading to a loss of HOXA1 function. The identification of a homozygous ~300 kb subregion in 7p15.2 that is haploidentical in the these patients is strongly suggestive of a founder mutation in the Saudi Arabian population. The abovementioned eight patients along with an additional Saudi patient from a different consanguineous family were further characterized clinically by Bosley et al. (2007). All the patients had the same guanine insertion (c.175-176insG) mutation, but exhibited a fair degree of clinical variability. This variability led to the extension of the BSAS phenotype. In a subsequent study, Bosley et al. (2008) highlighted another six Saudi individuals in whom homozygous mutations in the HOXA1 gene were found. One of these six patients harbored a novel homozygous HOXA1 mutation (c.185delG) leading to a frameshift and premature termination and the typical BSAS clinical syndrome. The patient had Duane retraction

anomaly, horizontal gaze restriction, and deafness, but normal cognition. The other five had the previously reported HOXA1 mutation (c.175-176insG). These individuals came from three families, one of which had four patients. The latter family was described as an inbred extended family in which two brothers had married two sisters who were first cousins. Each of these individuals suffered a number of the signs and symptoms of BSAS. For instance, there was a proband from each of the three families and all of these probands suffered severe restriction of horizontal gaze and deafness bilaterally. Importantly, some of these BSAS patients had conotruncal or septal heart defects not previously reported in BSAS, such as tetrology of Fallot and double outlet right ventricle.

References

Bosley TM, Alorainy IA, Salih MA, Aldhalaan HM, Abu-Amero KK, Oystreck DT, Tischfield MA, Engle EC, Erickson RP. The clinical spectrum of homozygous HOXA1 mutations. Am J Med Genet A. 2008; 146A(10):1235-40. PMID: 18412118 [FT]

Bosley TM, Salih MA, Alorainy IA, Oystreck DT, Nester M, Abu-Amero KK, Tischfield MA, Engle EC. Clinical characterization of the HOXA1 syndrome BSAS variant. Neurology. 2007 Sep 18; 69(12):1245-53. PMID: 17875913 [FT]

Tischfield MA, Bosley TM, Salih MA, Alorainy IA, Sener EC, Nester MJ, Oystreck DT, Chan WM, Andrews C, Erickson RP, Engle EC. Homozygous HOXA1 mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development. Nat Genet. 2005; 37(10):1035-7. PMID: 16155570 [FT]

Related CTGA Records

Athabaskan Brainstem Dysgenesis Syndrome

External Links

http://ghr.nlm.nih.gov/gene/HOXA1

Contributors

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