Heparan Sulfate Proteoglycan of Basement Membrane

Alternative Names
HSPG2
Perlecan
PLC

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
142461

Mode of Inheritance
N/A

Gene Map Locus
1p36.1

Description
HSPG2 codes for perlecan protein. Perlecan is a large heparan sulfate proteoglycan, a major component of the basement membrane and other extracellular matrices. This protein is involved in cell growth and differentiation through interactions with growth factors, cell surface receptors, and extracellular matrix molecules. It participates in the orderly assembly of extracellular matrices and functions as a bioactive reservoir for growth factors by stabilizing them against misfolding or proteolysis. Perlecan has an important role in the maintenance of the glomerular filtration barrier. In addition, Perlecan is a potent inhibitor of smooth muscle cell proliferation and is thus thought to help maintain vascular homeostasis.

Molecular Genetics
HSPG2 gene is located on the short arm of chromosome 1 at 1p36.1 and spans at least 120 kb of genomic DNA with a coding sequence consisting of 97 exons. This gene has multiple transcription initiation sites, suggesting that the control of its expression is complex. HSPG2 gene transcription is upregulated by TGF-beta. HSPG2 gene is highly conserved across species and the available data indicate that it has evolved from ancient ancestors by gene duplication and exon shuffling. It is highly expressed in basement membranes and cartilage. The perlecan protein core (HSPG2 gene product) weighs 400 KDa. It has five consecutive domains with only the first domain, the heparan sulfate-binding region, unique to perlecan. The other four domains exhibit homology to molecules involved in the control of cell proliferation, lipoprotein uptake, and adhesion.

Mutations in the HSPG2 gene cause two classes of skeletal disorders: the relatively mild Schwartz-Jampel syndrome (SJS) and the severe neonatal lethal dyssegmental dysplasia, Silverman-Handmaker type (DDSH). It is also found that perlecan levels are decreased in many disease states such as diabetes, atherosclerosis and arthritis.

Epidemiology in the Arab World
Tunisia
Nicole at el. (2000) carried out a molecular study on three consanguineous Tunisias families affected with SJS1, to determine the mutational spectrum in the HSPG2 gene in these families. They detected three additional introns located in exons 7, 18, and 81, giving a total of 97 exons for HSPG2. The first family was found to be homozygous for the splice donor site mutation (IVS64+4 A-toG). The resulting loss of exon 64 in the mRNA introduced a frameshift and a subsequent premature stop codon, predicted to result in a truncated protein lacking 1,595 amino acids. Nicole at el. (2000) calculated the consensus value (CV) at position -2 to +6 which revealed a lower CV for the mutated splic-doner site than for the

wild type equivalent (0.731 compared with 0.839). RT-PCR analysis was carried out in this family and unrelated control, to determine the consequence of this splice-donor mutation. Then, sequencing of the unique product of the RT-PCR in this family was carried out, revealing the absence of exon 46. The second family was found to be homozygous for a silent nucleotide change (4740G-to-A) affecting the last nucleotide of exon 37. The corresponding splice-donor site demonstrated a lower CV (0.702) than that of the wild-type site (0.826). Nicole at el. (2000) summed that this mutation acts in a similar manner to IVS64+4A-to-G. Nicole at el. (2000) suggested that these mutations probably result in loss of function and therefore diminish the integrity of cell basement membranes and cartilage matrix. The third family and 200 control chromosomes were tested by targeting only these two mutations as well as another mutation (C1532Y) also reported in this study. None of the tested individual either from the third family or the control was positive for these three mutations.

References

Nicole S, Davoine CS, Topaloglu H, Cattolico L, Barral D, Beighton P, Hamida CB, Hammouda H, Cruaud C, White PS, Samson D, Urtizberea JA, Lehmann-Horn F, Weissenbach J, Hentati F, Fontaine B. Perlecan, the major proteoglycan of basement membranes, is altered in patients with Schwartz-Jampel syndrome (chondrodystrophic myotonia). Nat Genet. 2000; 26(4):480-3. PMID: 11101850

Related CTGA Records

Dyssegmental Dysplasia, Silverman-Handmaker Type

Schwartz-Jampel Syndrome Type I

External Links

http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=800

Contributors

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