A Novel Homozygous LRP5 Splice-site Deletion Mutation Causes Syndromic Autosomal Recessive Familial Exudative Vitreoretinopathy.

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Abstract

A consanguineous Saudi Arabian family with two female siblings affected by an autosomal recessive condition resembling Familial Exudative Vitreoretinopathy [FEVR], but also with short stature, bone fragility with thin and wasted appearance was studied by homozygosity mapping and positional candidate gene screening to identify the offending gene and mutation. The gene was mapped to three possible homozygous genomic regions [[2q, 4q, 11q], as the family structure did not allow identification of a single interval with a significant LOD score. Mutations in three genes (FZD4, TSPAN12, NDP and LRP5) have been associated with FEVR. The LRP5 gene localizes within the 11q13.2 homozygosity interval in this family rendering it the positional candidate of choice. Screening by Sanger sequencing identified a novel homozygous one-base splice-site deletion mutation c.3236+1 delG in exon 14. LRP5 is a low-density lipoprotein receptor (LDLR) a transmembrane protein that binds and internalizes ligands in the process of receptor-mediated endocytosis. The cDNA encodes a 1,615-amino acid protein containing conserved modules including a putative signal peptide, four epidermal growth factor (EGF) repeats with associated spacer domains, three LDLR repeats, a single transmembrane-spanning domain, and a cytoplasmic domain. The extracellular domain contains 6 potential N-linked glycosylation sites. LRP5 has a unique organization of EGF and LDLR repeats compared to other LDLR family members and in addition to FEVR, mutations in the gene have been associated with Hyperostosis corticalis OMIM 144750; Osteopetrosis, autosomal dominant 1 OMIM 607634; Osteoporosis-pseudoglioma syndrome OMIM 259770; Osteosclerosis OMIM144750; van Buchem disease, type 2 OMIM 607636; Bone mineral density variability 1 OMIM 601884; Osteoporosis OMIM 166710. Only missense mutations and splice site substitutions in LRP5 have been associated with autosomal dominant and recessive FEVR. This is the first report of an autosomal recessive LRP5 splice-site deletion mutation causing a syndromic form of FEVR.