Test Information Sheet

Genetic testing of the FZD4, LRP5, TSPAN12, and NDP genes in Familial Exudative Vitreoretinopathy (FEVR)

Disorder also known as: Criswick-Schepens Syndrome

Clinical Features:
Familial Exudative Vitreoretinopathy (FEVR) is a hereditary disorder characterized by impaired vasculization of parts of the peripheral retina leading to various secondary complications, such as retinal neovascularization, dragged macula, exudation vitreous hemorrhage, retinal fold and retinal detachment. The most serious complications may result in complete blindness. To detect subtle retinal changes, intravenous fluorescein angiography is required. In addition, reduced mass bone density predisposing to bone fractures has been reported in FEVR patients with dominant LRP5 variants\(^2\). FZD4 variants have been reported in 3% of infants diagnosed with severe retinopathy of prematurity\(^10\).

Genetics:
The disease is genetically heterogeneous and may be inherited as autosomal dominant (adFEVR), autosomal recessive (arFEVR), or X-linked recessive trait. Most common is autosomal dominant inheritance. FEVR is usually fully penetrant with clinical variability among patients from the same family or even between the two eyes of an affected individual. LRP5 variants may be inherited as autosomal dominant or recessive trait, while FZD4 and TSPAN12 variants are autosomal dominant. There is also evidence for complex (digenic) inheritance, as missense variants in both genes, FZD4 and LRP5, were identified in a single family with a severe FEVR phenotype.

Test Methods:
Sequencing analysis of the FZD4, LRP5, TSPAN12, and NDP genes for FEVR are offered as separate tests. Using genomic DNA obtained from the submitted biological material, the coding region and splice junctions of FZD4 (exons 1-2), LRP5 (exons 1-23), TSPAN12 (exons 2-8), and NDP (exons 1-3) are PCR amplified. Bi-directional sequence is obtained and analyzed to evaluate for variant(s) in these genes. For NDP gene analysis in females, sequence analysis in combination with targeted array CGH analysis with exon-level resolution (ExonArrayDx) would be performed. Any variant found in the first person of a family to be tested is confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.
Test Sensitivity:
FZD4 variants have been reported in 4-40% of patients diagnosed with FEVR. In one study, 5 of 24 probands (20%) with FEVR (18 familial and 6 simplex cases) were found to have variants in FZD4\textsuperscript{1}, while in another study 2 of 56 patients (4%) with FEVR (31 familial and 25 simplex cases) had a variant in this gene\textsuperscript{8}. A recent study reported a FZD4 variant in 8 of 20 families (20%) with a confirmed diagnosis of FEVR\textsuperscript{11}. LRP5 variants have been identified in 12-18% of the patients with adFEVR. Boonstra et al., have reported that variants in one of the three FEVR genes (FZD4, LRP5, NDP) in 60% of the families studied. More recently, TSPAN12 variants have been reported in 8-10% of patients diagnosed with adFEVR, many of whom previously tested negative for variants in the FZD4, LRP5, and NDP genes\textsuperscript{13,14,12}. Overall, sequence analysis of the FZD4, LRP5, and TSPAN12 genes is expected to reveal pathogenic variants in approximately 19-65% of patients with FEVR. Riveiro et al., have reported variants in the NDP gene in approximately 13% of male patients (2 out of 16) diagnosed with FEVR\textsuperscript{6}.

References: