Familial Exudative Vitreoretinopathy (FEVR) Test

Disorder also known as: Criswick-Schepens Syndrome

FEVR Test Gene List: *FZD4, LRP5, NDP, TSPAN12*

Clinical Features:
Familial Exudative Vitreoretinopathy (FEVR) is a hereditary disorder of retinal blood vessel development.[1] It is characterized by incomplete vascularization of the peripheral retina and poor vascular differentiation.[1] As a result, secondary complications may occur such as retinal neovascularization, dragged macula, subretinal exudation vitreous hemorrhage, retinal fold and retinal detachment.[2] The hallmark of FEVR is the avascular peripheral retina due to premature retinal agenesis.[2] Fundus fluorescein angiography (FFA) examination often reveals a small area of no vascular perfusion around the retina periphery.[4] As the disease becomes more advanced, neovasicularization, intraretinal hemorrhages and exudates, vascularized preretinal membranes leads to retinal folds, macular dragging and retinal detachment. Depending on the degree of ischemia, complications may result in complete blindness.[2] Eyes do not always present with symmetrical findings and, in mild cases, may not cause any symptoms.[1]

The *FZD4, LRP5* and *TSPAN12* genes are associated with autosomal dominant FEVR, whereas *NDP* gene variants result in X-linked FEVR. *LRP5* gene variants also cause autosomal recessive FEVR. The *FZD4* and *TSPAN12* genes have recently been identified in autosomal recessive cases as well.[2-4] There is 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.

Inheritance patterns and expressivity display a heterogeneous course, as do the clinical features and prognosis of the condition.[2] Generally the condition is sporadic, but positive family histories have been reported in approximately 20-40% of cases.[2] Phenotype is generally indistinguishable by gene.[3] One exception is *LRP5* gene variants, which in addition to ocular features, may cause osteopenia and osteoporosis.[1] All at risk individuals should have bone mineral density scans, as initiating treatment can reduce the risk of fractures.[1]

Variants in the X-linked *NDP* gene result in *NDP*-related retinopathies of ranging severities, FEVR being one of the less severe conditions.[5] The most severe is Norrie disease (ND), characterized by congenital blindness due to pseudogliomas (grey-yellow fibrovascular masses) secondary to retinal vascular dysgenesis and detachment.[5] Significant intellectual disability, developmental delay, behavioral issues, psychotic-like features and hearing loss are

present in approximately 25%-50% of individuals.[5,13] Deletion and truncation mutations result in ND, whereas missense mutations may result in ND or FEVR.[5] Rarely, females experience a mild or partial ocular phenotype.[13]

The FEVR panel may clarify a clinical diagnosis or identify a genetic diagnosis for FEVR or a FEVR-related disorder. If a genetic diagnosis is found, genetic testing and recurrence risk information would be available for at-risk family members. In addition, having an identified genetic diagnosis may or may not impact medical management or treatment of the condition.

Genetics:
Autosomal dominant, autosomal recessive, and X-linked recessive inheritances may occur in FEVR, with the autosomal dominant form being the most common.[2]

Test Methods:
Using genomic DNA obtained from the submitted specimen, the coding region and splice junctions of the 4 genes are PCR amplified. Bi-directional sequence is obtained and analyzed to evaluate for variants in these genes. For the genes LRP5 and NDP, concurrent targeted array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or duplication of one or more exons of the genes. Reported variants are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:
Overall, analysis of the FZD4, LRP5, NDP, and TSPAN12 genes is expected to reveal pathogenic variants in about 50% of patients with FEVR, however, detection has ranged from 19-65% of patients.[1,3]

FZD4 gene: Variants are responsible for approximately 20% of patients with FEVR,[6,7] but reports show they have been identified in as low as 3% and as high as 40% of cases.[8,9]

LRP5 gene: Variants have been identified in 10%-25% of individuals with FEVR.[7,9,10]

TSPAN12 gene: Variants are responsible for approximately 3% of FEVR cases and have been identified in 10% of individuals who were negative for variants in other FEVR-related genes.[11,12]

NDP gene: Variants have been reported in approximately 13% of male patients diagnosed with FEVR.[14]

Gene	Protein	Inheritance	Disease Associations
FZD4	FRIZZLED, DROSOPHILA, HOMOLOG OF, 4	AD	FEVR ROP
LRP5	LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 5	AD, AR	FEVR, OPPG
TSPAN12	TETRASPANIN 12	AD	FEVR
NDP	NORRIN	XL	FEVR, Norrie disease

Abbreviations:
AD – Autosomal dominant
AR – Autosomal recessive
XL – X linked
FEVR – Familial Exudative Vitreoretinopathy
ROP – Retinopathy of Prematurity
OPPG – Osteoporosis-pseudoglioma Syndrome

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