Gene Sequencing deletions appear to exhibit a more severe related retinopathies. Sequence analysis identifies disease-causing mutations in about 85% of affected males. Related retinopathy include the following: sequence analysis is recommended as the first step in mutation identification. For patients in related retinopathies are X-linked recessive disorders characterized by very early childhood eye diseases/disorders due to degenerative and proliferative changes of the neuroretina. The spectrum of retinal findings ranges from Norrie disease (ND) to X-linked familial exudative vitreoretinopathy (FEVR), including some cases of persistent hyperplastic primary vitreous (PHPV), Coats disease, and advanced retinopathy of prematurity (ROP). These phenotypes appear to be a continuum of retinal findings with considerable overlap. The ocular findings that permit a presumptive diagnosis of an ND-related retinopathy include the following:

- Bilateral, often symmetric, involvement of the eyes
- Normal-sized eyes, with normal anterior chambers and usually clear lenses at birth
- Vitreous abnormalities (hemorrhage, membranes, detachment, and/or vitreoretinal attachments)
- Presence of fibrous and vascular retinal changes at birth with progressive changes through childhood or adolescence

The most severe phenotype is Norrie disease (ND). Retinal findings include greyish-yellow fibrovascular masses (pseudogliomas), which appear in the first few months of life and result in total blindness. Approximately 50% of individuals with ND show some form of progressive mental disorder, often with psychotic features, and about one-third of patients develop sensorineural deafness in the second decade. In addition, some individuals have more complex phenotypes, including growth failure and seizures.

Less severe phenotypes include: persistent hyperplastic primary vitreous (PHPV), characterized by a fibrotic white stalk from the optic disk to the lens; X-linked familial exudative vitreoretinopathy (XL-FEVR), characterized by peripheral retinal vascular anomalies with or without fibrotic changes; retinopathy of prematurity (ROP); and Coats disease, an exudative proliferative vasculopathy. Phenotypes can vary within families.

The diagnosis of ND-related retinopathies relies upon a combination of clinical findings and molecular genetic testing of NDP (Xp11.4), the only gene known to be associated with ND-related retinopathies. Sequence analysis identifies disease-causing mutations in about 85% of affected males. Approximately 15% of mutations are deletions involving all or part of the NDP gene. Males with NDP deletions appear to exhibit a more severe phenotype than those with non-deletion mutations. In addition to the ocular manifestations of ND, affected individuals with a deletion may also have microcephaly, severe-to-profound mental retardation, seizures, myoclonus, somatic growth failure, and/or delayed puberty.

Rarely, a partial or mild ocular phenotype occurs in carrier females, presumably secondary to non-random X-chromosome inactivation. The majority of mothers of a male proband are carriers of an NDP disease-causing mutation, even when the family history is negative. Rarely, affected males have a de novo mutation. Women who are carriers may have a germline mutation or may have inherited the mutant gene.

For patients with a suspected NDP-related retinopathy, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate. Click here for the GeneTests summary on this condition.

Genes

NDP

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of an NDP-related retinopathy
- Carrier testing in adult females with a family history of an NDP-related retinopathy

Methodology

PCR amplification of 2 exons contained in the NDP gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

Detection

Clinical Sensitivity: Sequence analysis identifies disease-causing mutations in about 85% of affected males. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%
Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Deletion/duplication analysis of the NDP gene by CGH array is available for those individuals in whom sequence analysis is negative (YM).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.