

Knobloch Syndrome, Type I via *COL18A1* Gene Sequencing (Test #641)

Brief Description of Clinical Features: Knobloch syndrome, type I (KNOI; OMIM 267750) is characterized by major features of ophthalmic abnormalities and occipital encephalocele. While there is variability in clinical presentation both within and between families (Menzel et al., *Hum Mutat.* 23:77-84, 2004), patients are uniformly affected with severe ophthalmic disease leading to vision loss (Sertié et al., *Hum Mol Genet* 9:2051-2058, 2000). Specific findings include high myopia, vitreoretinal degeneration with retinal detachment, and macular abnormalities. Controversy exists regarding the classification of the cranial defect as a true encephalocele or, alternatively, as an occipital scalp defect. Seaver et al. (*Am J Med Genet.* 46:203-208, 1993) have suggested that in some cases the abnormality found associated with Knobloch syndrome is a scalp defect, but that its occurrence should nonetheless alert clinicians to the possibility of a significant underlying midline defect. Patients with Knobloch syndrome have been found to have normal to above normal intelligence (Seaver et al., 1993). Neuronal migration defects have been reported for this disorder in two families (Kliemann et al., *Am J Med Genet* 119A:15-19, 2003). Endostatin is a 20 kDa carboxy terminal proteolytic cleavage product of type XVIII collagen which has been shown to be a potent antiangiogenic and antitumor compound (O'Reilly et al. *Cell* 88:277-285, 1997). An endostatin polymorphism has been shown to be a risk factor for prostate cancer (Iughetti et al., *Cancer Res* 61:7375-7378, 2001).

Genetics: Knobloch syndrome is an autosomal recessive disorder caused by mutations in the *COL18A1* gene (Sertié et al. *Hum Mol Genet* 9:2051-2058, 2000). Evidence has been presented for a second causative locus (Menzel et al. 2004; Suzuki et al. *Am J Hum Genet* 71:1320-1329, 2002), although a second gene has not yet been identified. Almost all *COL18A1* mutations reported are nonsense or splice site mutations. One *COL18A1* missense mutation (p.Asp1437Asn) located within the endostatin region has been reported to be causative for Knobloch syndrome (Menzel et al. 2004). Three isoforms of the alpha chain of collagen type XVIII are coded by exons 1-43 of the *COL18A1* gene (OMIM 120328) located on chromosome 21q22.3. Isoforms 2 and 3, but not 1, are expressed in the retina (Sertié et al., 2000; Suzuki et al. 2002).

Description of This Particular Test: Testing is accomplished by amplifying each coding exon of the three isoforms and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: Genomic: NC_000021.7 mRNA: NM_030582.3 (isoform 1)
 NM_130445.2 (isoform 2)
 NM_130444.2 (isoform 3)

Indication for Testing: Individuals with high myopia, vitreoretinal degeneration with retinal detachment, macular abnormalities, and occipital encephalocele or congenital occipital scalp defect.

Sensitivity of test: Test sensitivity should be high in patients with clinical features consistent with Knobloch syndrome. Suzuki et al. (2002) found two causative alleles in five of eight patients.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *COL18A1* Gene Exons 1-43 \$ 1,990

CPT Codes:

Sample Ascertainment	83890 \$ 30	DNA Isolation	83891 \$ 40
Amplification x43	83898 \$ 680	Sequencing x43	83904 \$1020
Separation	83894 \$ 100	Interpretation/Report	83912 \$ 120

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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