

Sorsby Fundus Dystrophy, Autosomal Dominant via *TIMP3* Gene Sequencing --Test #699

Brief Description of Clinical Features: Sorsby fundus dystrophy also called hemorrhagic macular dystrophy (SFD, OMIM 136900) is a rare maculopathy. The hallmark of SFD is a sudden reduction in visual acuity presenting in middle age, usually between the third and fifth decades in life. Additional symptoms include night blindness, prolongation of dark adaptation, and color vision deficiency. Clinical findings consist of drusen-like deposits at the level of the Bruch's membrane, subretinal deposits of yellow material, angioid streaks, and exudative lesions of the macula (Sorsby and Mason Br J Ophthalmol 33:67-97, 1949; Jacobson et al. Nat Genet 11:27-32, 1995). Optical coherence tomography (OCT) findings include hyperreflectivity of the retinal pigment epithelium-photoreceptor-choroid complex (Saihan et al. Mol Vis 15:1218-1230, 2009). As the disease progresses, subretinal neovascularization and atrophy of the retinal pigment epithelium may also occur. This results in rapid bilateral loss of central vision in mid age and ultimately loss of peripheral vision later in life. Although rare, SFD has been reported in patients from various populations. See also the Macular Degeneration Foundation (www.eyesight.org/).

Genetics: SFD is a genetic condition that is inherited in an autosomal dominant manner with age-dependant penetrance (Felbor et al. Am J Hum Genet 60:57-62, 1997). It is caused by heterozygous mutations in the *TIMP3* gene (Weber et al. Nat Genet 8:352-356, 1994). Eleven mutations have been reported to date. Two of these are truncating and include a nonsense mutation and a single-nucleotide insertion. All the remaining mutations are of the missense type. The *TIMP3* gene encodes the tissue inhibitor of metalloproteinase-3 protein, which is secreted by the retinal pigment epithelium (RPE) and incorporated into Bruch's membrane (Della et al. Invest Ophthalmol Vis Sci 37:1921-1924, 1996). Accumulation of *TIMP3* protein has been reported in donor eyes of patients affected with SFD (Fariss et al. Br J Ophthalmol 82:1329-1334, 1998).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *TIMP3* gene. The full coding sequence of each exon plus ~50 bp of flanking DNA on either side are sequenced. As indicated, we will sequence one exon (Test #100, \$190) in family members of patients with known mutations or to confirm previous results.

Reference Sequences: Genomic: NC_000022.10 mRNA: NM_000362.4 Protein: NP_000353.1 (CCDS 13911.1)

Indications for Test: Patients presenting with a sudden visual acuity loss in the mid age, accompanied by night and color blindness.

Sensitivity of Test: Unknown at this time.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the *TIMP3* gene \$ 490

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x5	83898 \$ 120	Sequencing x5	83904 \$ 185
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 85

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

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