

## Retinitis Pigmentosa (Autosomal Dominant or Recessive, Nonsyndromic) via NR2E3 Gene Sequencing -- Test #668

**Brief Description of Disorder:** Nonsyndromic Retinitis Pigmentosa (RP, OMIM 268000) is a large group of inherited degenerative diseases of the retina characterized by abnormalities of the photoreceptors or the retinal pigment epithelium. It is a progressive disease. Symptoms usually begin with night blindness, progressing to constriction of the peripheral visual field and, eventually, to loss of central vision. The age of onset varies from childhood to middle age (Gu et al. J Med Genet 36:705-707, 1999). The clinical hallmarks are abnormal fundus with bone-spicule deposits and attenuated retinal vessels, abnormal electroretinographic findings and reduced visual fields (Daiger et al. Arch Ophthalmol 125:151-158, 2007). RP affects 1 in 3,000 people worldwide (Farrar et al., EMBO J 21:857-864, 2002). Genetic abnormalities are the primary cause of RP.

**Genetics:** RP is genetically and clinically heterogeneous. At least four distinct subgroups are recognized on the basis of the mode of inheritance and age of onset. These include autosomal dominant (AD-RP), autosomal recessive (AR-RP), X-linked, and digenic (Kajiwara et al. Science 264:1604-1608, 1994). In addition, RP can be inherited as a mitochondrial trait (Mansergh et al. Am J Hum Genet 64:971-985, 1999). Genetic heterogeneity is documented within each subgroup. About 50 % of patients with RP are isolated cases with no known affected relatives. It is unclear how many of these are real isolated cases caused by *de novo* mutations or inherited with low penetrance. RP affects all ethnic groups, although mutations in particular genes have been identified in specific populations. Currently, mutations in 18 and 23 genes are known to cause AD-RP and AR-RP, respectively. These include the NR2E3 gene, which is also involved in enhanced S cone dystrophy (ESCS, OMIM 268100, Haider et al. Nat Genet 24:127-131, 2000). Recently, two novel NR2E3 mutations have been implicated in RP. The first, (Gly56Arg), was reported in three families, including two Belgian and one French, with AD-RP (Coppieters et al. Am J Hum Genet 81:147-157, 2007). All affected individuals shared a common disease haplotype. In addition, they shared a similar phenotype, which corresponds to the classic RP phenotype accompanied by specific characteristics of ESCS. Briefly, this phenotype is characterized by decline of rod function followed by that of cone function, as is usually the case in AD-RP, and by three concentric rings of hyperautofluorescence: around the fovea, along the vascular arcades and in the far periphery, with the two more central rings located in the same area as those affected in ESCS (Marmor et al. Am J Ophthalmol 110:124-134, 1990). The second mutation, (c.1038del5bp), was reported in three siblings with AR-RP (Bernel et al. Clin Genet 73:360-366, 2008).

**Description of This Particular Test.** The NR2E3 gene is expressed specifically in the outer layer of the human retina and encodes a retinal nuclear receptor. This test involves bidirectional DNA sequencing of all 8 coding exons and splice sites of the NR2E3 gene. The full coding sequence of each exon plus ~ 50 bp of flanking-coding DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutations and to confirm previous results.

**Reference Sequences:** Genomic: NC\_000015.8 mRNA: NM\_014249.2 Protein: NP\_055064.1

**Indications for Test:** Patients with AD-RP and clinical features described above, patients with AD-RP or AR-RP and no mutations detected in other genes known to cause these diseases. The NR2E3 gene is also a candidate for patients with ESCD.

**Sensitivity of Test:** The Gly56Arg mutation alone accounts for ~ 1-2% of AD-RP (AI Gire et al. Mol. Vis. 13:1970-1975, 2007). However, comprehensive information on sensitivity is not available yet. PreventionGenetics plans to offer Tests for all genes known to cause RP and is committed to add new tests as the remaining RP genes are discovered.

**Turn Around Time:** Maximum of 40 calendar days.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price:** Sequencing of all coding exons of the NR2E3 gene: **\$ 540**

**CPT codes:**

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x8	83898	\$ 140	Sequencing x8	83904	\$ 200
Separation x1	83894	\$ 50	Interpretation/Report x1	83912	\$ 80

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

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