

## ABCC6 Gene Analysis in Pseudoxanthoma Elasticum

**Disorder also known as:** PXE; Gronblad-Strandberg Syndrome

### **Clinical Features:**

PXE is associated with dystrophic mineralization of connective tissues and affects multiple organs including the skin, eyes and cardiovascular system. The specific clinical findings include lax and inelastic skin, angioid streaks of the retina, and mineralization of the mid-laminar layer of blood vessels of the gastrointestinal tract and cardiovascular system. Onset is often in late childhood or adolescence when yellowish cutaneous papules are noted, most commonly, on the neck, axillae and antecubital fossae. However, in many cases the initial physical finding is retinal angioid streaks corresponding with breaks in the elastin-rich Bruch's membrane of the choroids. As the disease progresses, fragile new vessels may grow through the angioid streaks and hemorrhage, resulting in central vision loss. Affects on the cardiovascular system may include hypertension, intermittent claudication, gastrointestinal bleeding, and rarely myocardial infarction. Mineralization of elastic structures, the hallmark of PXE, results from altered function of the multidrug resistance associated protein 6 (MRP6), the protein encoded by the ATP-binding cassette family C member 6 (ABCC6) gene.

### **Inheritance Pattern/Genetics:**

Autosomal recessive

### **Test Methods:**

Genetic testing for PXE will be performed in two tiers. Using genomic DNA obtained from the submitted biological material, Tier 1 analysis for the two "common" variants (R1141X and the large deletion of exons 23 to 29), will be performed first. Evaluation for the R1141X variant will be performed by restriction fragment analysis using BsiY1 and for the deletion using gel electrophoresis. In probands in whom no variant is identified but clinical suspicion is high and in probands in whom only a single variant is identified, Tier 2 of testing, comprising bi-directional sequence analysis of the 31 exons and intron/exon boundaries of the ABCC6 gene will be performed. If sequencing identifies a variant on only one allele of ABCC6, 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 this gene. Variants will be confirmed using sequencing, restriction fragment analysis, or another appropriate method.

**Test Sensitivity:**

The method used by GeneDx is expected to have a 90% detection rate given the two-tiered approach and full ABCC6 gene sequencing, with the exception of whole gene deletions. Including ExonArrayDx analysis for deletion/duplication detection, the sensitivity is approximately 97-99%.

**References:**

1. Pfendner et al. (2007) J Med Genet 44:621-628.
2. Le Saux et al., (2001) Am J Hum Genet 69: 749-764.
3. Chassaing et al., (2005) J Med Genet 42:881-892.
4. Laube & Moss, (2005) Arch Dis Child 90:754-756.
5. Bergen et al., (2000) Nat Genet 25(2):228-31.
6. Pfendner et al., (2008) Expert Opin Me. Diagn 2(1):1-17.