

## Glycogen Storage Disease Type IX via *PHKA2* Gene Sequencing (Test #232)

**Brief Description of Clinical Features:** Glycogen Storage Disease (GSD) resulting from glycogen phosphorylase kinase deficiency (sometimes called GSD Type IX) has several subtypes. This is because the phosphorylase kinase (Phk) enzyme is comprised of four subunits ( $\alpha\beta\gamma\delta$ ) and because there are tissue-specific forms of the subunits. GSD Type IX is one of the most common types of GSD involving ~25% of all GSD patients (Burwinkel et al. *Hum Genet* 102:423-429, 1998; Hendrickx et al. *Am J Hum Genet* 64:1541-1549, 1999). Defects in the liver alpha subunit of Phk (OMIM 306000) are by far the most common cause (~75%) of GSD Type IX. Patients typically present in the first few months of life with hepatomegaly, growth retardation, elevated liver glycogen, and elevated serum triglycerides and cholesterol. For more information see [www.agsdus.org](http://www.agsdus.org).

**Genetics:** The *PHKA2* gene encodes the liver alpha subunit of Phk. *PHKA2* mutations are inherited in an X-linked recessive fashion. Nearly all affected individuals are male. About 50 causative *PHKA2* missense, nonsense, in-frame deletion, frameshift and splicing mutations have been reported (Burwinkel et al. 1998; Hendrickx et al. 1999; Beauchamp et al. *Molec Genet Metab* 92:88-99, 2007). Causative mutations are located throughout the length of the gene; no mutations are predominant. Patients with missense mutations may have normal or even elevated erythrocyte Phk activity (but reduced liver Phk activity). At least one multi-exon deletion has been reported (Fukao et al. *Molec Genet Metab* 92:179-182, 2007).

**Description of This Particular Test:** This test involves PCR amplification from genomic DNA and bidirectional sequencing of all protein coding regions of the 33 *PHKA2* exons along with ~50 bp of flanking non-coding sequence on each side. The test is performed in two tiers. Tier 1 comes first and involves sequencing of exons 1, 4, 6, 9, 26, 32 and 33. These 7 exons have been reported to contain roughly 60% of detectable causative mutations. If no likely causative mutation is found in Tier 1, then sequencing of the remaining 26 exons commences in Tier 2.

**Reference Sequences:** Genomic: NC\_000023.9 mRNA: NM\_000292.1 Protein: NP\_000283.1

**Indications for Test:** Candidates for this test are all patients with symptoms of Type IX GSD and with family history consistent with X-linked recessive inheritance. Male patients with deficiencies in phosphorylase kinase activity are also good candidates. We will sequence single exons in the family members of patients with known mutations to determine carrier status and in patients to confirm research results.

**Sensitivity of Test:** Sensitivity of this test has not been reported.

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

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

**Tier 1: Sequencing of *PHKA2* exons 1, 4, 6, 9, 26, 32, 33** **\$ 490**

**If positive, stop; if negative, then:**

**Tier 2: Sequencing of the remaining 26 *PHKA2* exons** **an additional \$ 1,200** **for a total of \$ 1,690**

**CPT Codes:**

Codes	Description	Tier 1 Only	Tier 1 + Tier 2
83890	Ascertainment	\$ 30 (x1)	\$ 30 (x1)
83891	DNA Isolation	\$ 40 (x1)	\$ 40 (x1)
83898	Amplification	\$116 (x7)	\$ 560 (x31)
83904	Mutation Ident by Sequencing	\$174 (x7)	\$ 840 (x31)
83894	Separation	\$ 45 (x1)	\$ 90 (x1)
83912	Interpretation and Report	\$ 85 (x1)	\$ 130 (x1)
<b>Totals:</b>		<b>\$490</b>	<b>\$1,690</b>

**Single exon sequencing is available for \$190 (Test #100).**

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

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