

Paroxysmal Paralytic Rhabdomyolysis, Autosomal Recessive via *LPIN1* Gene Sequencing --Test #369

Brief Description of Clinical Features: Familial Paroxysmal Paralytic Rhabdomyolysis with myoglobinuria (OMIM 268200), also known as Childhood Recurrent Acute Myoglobinuria is a rare and life-threatening disease of young children, in which prompt diagnosis and treatment are critical (Tein et al. *Adv Pediatr* 37:77-117, 1990). Early symptoms typically begin before the age of seven years and consist of generalized weakness, inability to walk, myalgia, and dark urine. Recurrent episodes of myoglobinuria are frequent features of the disease. Additional features include cardiac abnormalities, marked sensitivity over the thighs and calf muscles, muscle hypotonia and renal failures. The episodes are triggered by febrile illnesses and persist for several days; they are characterized by concomitant elevated levels of plasma creatine kinase and aspartate aminotransferase (Ramesh and Gardner-Medwin, *Dev Med Child Neurol* 34:73-79, 1992; Zeharia et al. *Am J Hum Genet* 83:489-494, 2008).

Genetics: Familial cases of Paroxysmal Paralytic Rhabdomyolysis with myoglobinuria have been reported (Christensen et al. *Danish Med Bull* 30:112-115, 1983; Ramesh and Gardner-Medwin, *Dev Med Child Neurol* 34:73-79, 1992). In these families, the disease appeared to be transmitted as an autosomal recessive trait. It is caused by mutations in the *LPIN1* gene (Zeharia et al. 2008). Mutations include nonsense, missense, splicing, small deletions or insertions, and one 2-kb deletion that spans exons 18-19. The later deletion appears to be common in patients of European ancestry (Michot et al. *Hum Mutat* 31:E1564-1573, 2010). *LPIN1* mutations were reported in patients from various populations.

Description of This Particular Test: The *LPIN1* gene encodes Lipin-1, phosphatidic acid phosphatase, which catalyzes the conversion of phosphatidic acid to diacylglycerol in the triacylglycerol synthesis pathway. This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *LPIN1* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will sequence any single (Test #100) or double (Test #200) exons in family members of patients with known mutations or to confirm previous results. A specific test for the exon 18-19 deletion is also available (Test #319).

Reference Sequences: Genomic: NC_000002.10 mRNA: NM_145693.1 Protein: NP_663731.1 (CCDS 1682.1)

Indications for Test: Children presenting with recurrent episodes of myoglobinuria, associated with elevated levels of plasma creatine kinase.

Sensitivity of Test: This test may detect mutations in ~60% of patients with a clinical diagnosis as described above.

Turn Around 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 19 coding exons of the *LPIN1* Gene:** **\$1090**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x 21	83898	\$ 340	Sequencing x 21	83904	\$ 510
Separation	83894	\$ 80	Interpretation/Report	83912	\$ 90

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

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