

Leukocyte Adhesion Deficiency Type 2 (LADII) via *SLC35C1* Gene Sequencing, Test # 516

Brief Description of Clinical Features: Leukocyte Adhesion Deficiency (LAD) is characterized by the inability of leukocytes, particularly neutrophils, to adhere to sites of inflammation in response to bacterial-derived attractants, cytokines, and other host-derived signals. Consequently, patients with LAD suffer from recurrent, severe infections. LAD is a consequence of defective adhesion molecule function: LADI (OMIM 116920) and LADIII (OMIM 612840) from defective integrin function, and LADII (OMIM 266265) from defective selectin function (see Wild et al. *Cells Tissues Organs* 172:161-173, 2002). LADII (aka Congenital Disorder of Glycosylation IIc) belongs to a group of hereditary carbohydrate-deficient glycoprotein syndromes (CDGS) which are characterized by impaired glycosylation of newly synthesized glycoproteins. A systemic defect in fucose metabolism results in the loss of fucosylated selectin ligands that under normal conditions are expressed on neutrophils and are required for tethering to the endothelium during the immune response (Tyrrell et al. *PNAS* 88:10372 -10376, 1991). Patients with LADII have high neutrophil counts and normal opsonophagocytic and bactericidal activity, however neutrophil migration is defective (Etzioni et al. *N Engl J Med* 327:1789-1792, 1992). The clinical course of deficient neutrophil adhesion is milder in LADII than in other forms of LAD, however LADII patients present other abnormal features including severe mental and growth retardation, distinctive facial features, and lack the H blood group antigen, a fucosylated carbohydrate (Bombay phenotype), and Lewis blood group antigens Le^a and Le^b (Etzioni et al. 1992). Thus, fucosylated glycoconjugates appear to be important for mental and psychomotor development as well as the immune response. There is some evidence that oral doses of fucose can reverse some effects of LADII (Marquardt et al. *Blood* 94:3976-3985, 1999), but such treatment may not be effective in all LADII patients (Etzioni et al. *Blood* 95:3641-3643, 2000).

Genetics: LADII is caused by recessive mutations in the *SLC35C1* gene which encodes a GDP-fucose transporter located on Golgi vesicles (Lühn et al. *Nat Genet* 28:69-72, 2001; Lübke et al. *Nat Genet* 28:73-76, 2001). To date, three missense mutations represent the only causative mutations found in the *SLC35C1* gene (Lübke et al. 2001; Gazit et al. *J Clin Immunol* 30:308-313, 2010).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the 2 coding exons of the *SLC35C1* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence any single exon (Test #100) or two exons (Test #200) in family members of patients with known mutations, or to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000011.9 mRNA: NM_018389.4 Protein: NP_060859.4 (CCDS 7914.1)

Indications for Test: Patients with recurrent infections and high neutrophil counts, and patients with the Bombay blood type.

Sensitivity of Test: LADII is a rare form of LAD representing a small fraction of all cases.

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

Specimen Requirements: See page 4 of Requisition Form

Price: Sequencing of *SLC35C1* \$ 440

CPT Codes							
Test	83890 x1	83891 x1	83898 x4	83904 x4	83894 x1	83912 x1	Total
<i>SLC35C1</i>	\$30	\$40	\$100	\$150	\$30	\$90	\$440

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

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