ITGB2 Gene Analysis in Leukocyte Adhesion Deficiency Type 1

Disorder also known as: LAD-1, Deficiency of the common beta chain of LFA-1, Mac-1, and p150,95 antigens

Clinical Features:
Leukocyte adhesion deficiency type 1 (LAD-1) is a phenotypically variable immune deficiency characterized by recurrent bacterial and fungal infections, slow wound healing, periodontitis and impaired pus formation. Delayed separation of the umbilical cord may be the first sign of the disorder in an infant. Patients have absent or severely reduced expression of beta-2 integrin (CD18 antigen) on the surface of their leukocytes. CD18 antigen is involved in adhesion and transmigration of human leukocytes in vivo, and thus patients with LAD-1 have impaired accumulation of myeloid leukocytes at extravascular sites. Treatment by bone marrow transplantation has been successful in several reported cases.

A severe and very rare form of LAD, known as LAD-2, has been identified and linked to a different gene, SLC35C1, in MIM 266265, Congenital Disorder of Glycosylation Type IIc. LAD-2 patients also have growth and mental retardation. This test does not examine SLC35C1.

Genetics:
Leukocyte adhesion deficiency type 1 (LAD-1) has an autosomal recessive pattern of inheritance.

Test Methods:
Analysis is performed by bi-directional sequencing of the coding regions and splice sites of exons 2-16 of the ITGB2 gene (all coding exons). If sequencing identifies a variant on only one allele, focused 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 found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:
All patients with classic LAD-1 identified to date have had variants in the ITGB2 gene. Over 90% of known variants are types readily detected by sequencing, while exon-level array CGH will detect gross deletions that sequencing cannot identify. Thus, over 98% of patients with two ITGB2 variants are expected to have one, and most likely both, variants identified by this test.

Variant Spectrum:

The molecular nature of ITGB2 variants is heterogeneous, with variants for LAD-1 identified in all coding exons of the gene.[1] In particular, frameshift, abnormal splicing events, missense and nonsense variants have all been reported. Deletions of whole exons have been reported in rare cases.[2]

References:

1. Springer, TA, et al., 1984, Inherited deficiency of the Mac-1, LFA-1, p150,95 glycoprotein family and its molecular basis. J. Exp. Med. 160: 1901-1918
2. Roos D et al, 2002, Genetic analysis of patients with leukocyte adhesion deficiency: genomic sequencing reveals otherwise undetectable mutations. Exp Hematol 30:252, 2002.