

IDS Gene Analysis in Mucopolysaccharidosis Type II (MPS II)

CLINICAL FEATURES

Mucopolysaccharidosis Type II (MPS II) or Hunter syndrome is an X-linked lysosomal storage disorder characterized by glycosaminoglycan accumulation with varying age of onset, disease severity and rate of progression in affected males. The diagnosis of Hunter syndrome cannot be made on clinical findings alone, but require molecular diagnosis or enzymatic testing. Early symptoms include upper respiratory tract infections, inguinal and umbilical hernia and joint stiffness. In those with early onset progressive disease, behavioral disturbances, profound intellectual disability, progressive airway disease and cardiac disease usually result in death in the first or second decade of life. Individuals with the slowly progressive form usually preserve normal intelligence and may often survive into adulthood. Additional characteristic findings include short stature, macrocephaly, macroglossia, hoarse voice, hearing loss, hepatosplenomegaly, dysostosis multiplex, spinal stenosis and short neck. Rarely females that are heterozygous for a pathogenic *IDS* variant manifest symptoms.^{1,2}

GENETICS

MPS II is caused by pathogenic variants in the *IDS* gene that is located on chromosome Xp28 and encodes the lysosomal enzyme iduronate 2-sulfatase (IDS). IDS is responsible for the degradation of two extracellular matrix glycosaminoglycans (GAGs), heparin sulfate and dermatan sulfate. Enzyme deficiency results in the accumulation of these GAGs. The continued buildup of GAGs in multiple organs causes the progressive disease. Although urine glycosaminoglycan analysis shows high concentrations of dermatan and heparin sulfate, these findings are also observed in MPS I. In males, enzyme activity can be measured from plasma or fibroblasts however activity may not be elevated in all affected individuals and enzymatic testing requires the measurement of other sulfatases to distinguish from multiple sulfatase deficiency.^{1,3} The severity of MPS II is not correlated with the level of enzyme activity. The birth incidence of MPS II for males is estimated to be from 1/70, 000 to 1/100,000.²

TEST METHODS

Variant analysis of the *IDS* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-9, and corresponding intron/exon boundaries. Concurrent MLPA analysis is included to evaluate for a deletion/duplication of one or more exons of the *IDS* gene. To assess for the presence of *IDS/IDS1P* (pseudogene) recombination events, regions encompassing the known 5' (*IDS* exon 2-intron 3) and 3' (*IDS* intron 7) recombination regions of the *IDS* gene are amplified by long-range PCR, and selectively sequenced.^{3,4} Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing or another appropriate method.

The methods used by GeneDx are expected to be greater than 99% sensitive in detecting variants identifiable by sequencing.

VARIANT SPECTRUM

Approximately 80%-85% of pathogenic variants in the *IDS* gene are detectable by sequence analysis, 7%-9% are large deletions/duplications involving one or more exons of the *IDS* gene and 7%-9% are rearrangements with the *IDS1P* pseudogene.^{1,3} It has been estimated that 23% of pathogenic *IDS* variants occur de novo.³ A pathogenic c.1122 C>T variant has been associated with the slowly progressive form, while males with a deletion or complex rearrangement of the *IDS* gene have the early progressive form.³ Genotype-phenotype correlations cannot be accurately made for point mutations, which are most often unique to a specific family.³

REFERENCES:

1. Froissart et al., (2007) Acta Paediatr. 96 (455):71-7 (PMID: 17391447)
2. Scarpa, M. (Updated [March 26, 2015]). Mucopolysaccharisosis Type II. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2017. Accessed [Dec 2017].
3. Pollard et al., (2013) Journal Of Inherited Metabolic Disease 36 (2):179-87 (PMID: 22976768)
4. Bunge et al., Eur J Hum Genet (1998); 6:492-500, PMID: 9801874