THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Marshall-Smith syndrome testing: Mutation Analysis of *NFIX*

Clinical Features:

Sotos syndrome 2 [MIM# 614753] was initially described by Malan et al, (2010), as an overgrowth syndrome that showed resemblance to Sotos syndrome and is also referred to as Sotos-like syndrome. Features include postnatal overgrowth, macrocephaly, advanced bone age, long narrow face, high forehead, slender habitus, scoliosis, and intellectual disability(1).

Marshall-Smith syndrome [MIM#602535] is characterized by accelerated skeletal maturation, relative failure to thrive, unusual facies, motor delay, and intellectual disability (2). The facial features include prominent eyes with shallow orbits, bluish sclerae, small anteverted nares with low nasal bridge and hypoplastic mandibular rami.

Molecular Genetics:

Mutations of the *NFIX* [OMIM #164005] gene have been identified in patients with Sotos-like syndrome. *NFIX* has 10 coding exons and is located at 19p13.2. Malan et al, (2010) identified microdeletions encompassing *NFIX* in two patients with Sotos-like overgrowth features. In addition, a nonsense mutation in *NFIX* was identified in a patient with Sotos-like syndrome (1). Yoneda et al, (2012) identified 2 heterozygous missense mutations in *NFIX* in 2/48 individuals who were suspected of having Sotos syndrome but who did not have abnormalities in *NSD1* (3).

Mutations of the *NFIX* gene have also been identified in patients with Marshall-Smith syndrome. Malan et al, (2010) identified frameshift and splicing mutations in 9 patients with Marshall-Smith syndrome (1).

NFIX belongs to the Nuclear factor one family of transcription factors. Haploinsufficency of *NFIX* leads to Sotos-like features and dominant-negative effects of the truncated NFIX proteins cause Marshall-Smith syndrome (3)

Inheritance:

Mutations in *NFIX* are autosomal dominant and the majority of mutations to date have been *de novo*.

Test Methods:

We offer full gene sequencing of all coding exons and intron/exon boundaries of *NFIX* by direct sequencing of amplification products in both the forward and reverse directions. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

NFIX sequencing and deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405, 81406
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Malan V, Rajan D, Thomas S et al. Distinct effects of allelic NFIX mutations on nonsense-mediated mRNA decay engender either a Sotos-like or a Marshall-Smith syndrome. Am J Hum Genet 2010: 87: 189-198.
2. Adam MP, Hennekam RC, Keppen LD et al. Marshall-Smith syndrome: natural history and evidence of an osteochondrodysplasia with connective tissue abnormalities. Am J Med Genet A 2005: 137: 117-124.
3. Yoneda Y, Saitsu H, Touyama M et al. Missense mutations in the DNA-binding/dimerization domain of NFIX cause Sotos-like features. J Hum Genet 2012: 57: 207-211.

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