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Tracy I. George, MD, Chief Medical Officer

Patient Report

Patient Age/Gender: 30 years Female

Specimen Collected: 22-Dec-20 10:10

Deletion/Duplication Analysis by MLPA | **Received: 22-Dec-20 10:11** **Report/Verified: 22-Dec-20 11:44**

	Result	Units	Reference Interval
Deletion/Duplication Gene	NF1 DD f1 i1		
Deletion/Duplication Interpretation	**Deletion** * f2		

Result Footnote

f1: Deletion/Duplication Gene

BACKGROUND INFORMATION: Neurofibromatosis Type 1 (NF1), Deletion/Duplication
CHARACTERISTICS: Neurofibromatosis type 1 (NF1) demonstrates extreme clinical variability. Features include: cafe au lait macules, axillary or inguinal freckling, dermal fibromas, Lisch nodules (iris hamartomas), optic glioma, specific osseous lesions such as tibial pseudarthrosis or sphenoid dysplasia, learning disabilities (50 percent), scoliosis, vertebral dysplasia, and somatic overgrowth. Large NF1 locus deletions increase the risk for neurofibroma development, cognitive abnormalities and malignant peripheral nerve sheath tumors (MPNST).
INCIDENCE: 1 in 3000.
INHERITANCE: Autosomal dominant; de novo mutations occur in 50 percent of cases.
PENETRANCE: 100 percent by adulthood.
CAUSE: Pathogenic NF1 mutations.
CLINICAL SENSITIVITY: Approximately 5 percent of NF1 is caused by large NF1 locus deletions and 2 percent due to intragenic deletions.
METHODOLOGY: Multiplex ligation-dependent probe amplification (MLPA) to detect large NF1 locus and intragenic deletions/duplications.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Single base pair substitutions, small deletions/duplications, regulatory region mutations, and deep intronic mutations will not be detected. Large deletions/duplications of exons 11and 20 will not be detected. The breakpoints for large deletions/duplications will not be determined.

f2: Deletion/Duplication Interpretation
TEST PERFORMED - 3003144
TEST DESCRIPTION - Neurofibromatosis Type 1 (NF1) Deletion/Duplication
INDICATION FOR TESTING - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the NF1 gene.

DNA VARIANT
Classification: Pathogenic
Gene: NF1
Nucleic Acid Change: Deletion of exons 1-58 (whole gene); Heterozygous

INTERPRETATION
One copy of a pathogenic variant, deletion of exons 1-58 (whole gene deletion), was detected in the NF1 gene by deletion/duplication analysis. This result is consistent with a diagnosis of neurofibromatosis type 1; clinical manifestations are variable. Offspring of this individual have a 50 percent chance of inheriting the causative variant.

Since this deletion includes the first and last exon of the NF1 gene, and the breakpoints of the deletion cannot be determined, the deletion may extend upstream and/or downstream of the NF1 gene.

Result Footnote

f2: Deletion/Duplication Interpretation
Evidence for variant classification: Deletions including the entire NF1 gene have been reported in patients with neurofibromatosis type 1 (De Raedt 2003, Dorschner 2000, Pasmant 2010). This deletion is considered pathogenic for NF1. NF1 whole gene deletions often occur as part of a contiguous gene deletion known as NF1 microdeletion or 17q11.2 microdeletion syndrome. Individuals with an NF1 microdeletion are more likely to have a severe NF1 phenotype than NF1 patients without a microdeletion. NF1 microdeletions have been associated with facial dysmorphism, overgrowth, more frequent and severe intellectual disabilities, and early appearance and increased numbers of neurofibromas. Such individuals may also be at increased risk for developing malignant peripheral nerve sheath tumors (MPNST) and should be managed accordingly.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered a clinical evaluation for neurofibromatosis type 1. If it is unclear whether or not they are affected, testing for the identified pathogenic variant should be offered (Deletion/Duplication Analysis by MLPA, ARUP test code 3003144).

COMMENTS
Reference Sequence: GenBank # NM_001042492.1 (NF1)

REFERENCES
De Raedt T et al. Elevated risk for MPNST in NF1 microdeletion patients. Am J Hum Genet. 2003. 72(5):1288-92.

Dorschner MO et al. NF1 microdeletion breakpoints are clustered at flanking repetitive sequences. Hum Mol Genet. 2000. 9(1):35-46.

Pasmant E et al. NF1 microdeletions in neurofibromatosis type 1: from genotype to phenotype. Hum Mutat. 2010. 31(6):E1506-18.

This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

Test Information

i1: Deletion/Duplication Gene
This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

Pending Procedures

Deletion/Duplication Analysis by MLPA
Order Date/Time 18-Dec-20 10:37
Status: In-Lab

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H=High, i=Test Information, L=Low, t=Interpretive Text, @=Performing Lab