Genetic Testing Report

Patient Name:
Date of Birth:
Specimen Type:
Submitters ID No:
Ordered By:

GeneDx Accession No:
Date Specimen Obtained:
Date Specime
Date Test(s) S
Date of Report:

The ordered test and the genes analyzed are clearly identified at the top of the report

Test(s) requested: Diagnostic Testing / Comprehensive Panel for Noonan, LEOPARD, Cardio-Facio-Cutaneous, and Costello Syndromes

Genes Evaluated: BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, SHOC2, and SOS1

Result: **POSITIVE**

Only mutations detected appear

Gene	cDNA	Variant	Zygosity	Classification
RAF1	c.1423 T>C	p.Phe475Leu (F475L)	Heterozygous	Disease-causing mutation

Interpretation: Heterozygous for the F457L mutation in the RAF1 gene, consistent with the diagnosis of a disorder in the Noonan syndrome spectrum

The final diagnosis is made in the Interpretation section.

RAF1 F475L: p.Phe475Leu (TTT>CTT): c.1423 T>C in exon 14 of the RAF1 gene (NM_002880.3)

Expands on the clinical significance of the mutations found

An F475L missense mutation was identified in the RAF1 gene. It has not been published as a mutation, nor has it been reported as a benign polymorphism to our knowledge. However, this mutation has been seen several times previously at GeneDx in one proband and segregating with disease in another unrelated family; all were reported to have phenotypes consistent with the diagnosis of a disorder of the Noonan-CFC-Costello syndrome spectrum. F475L is a semi-conservative amino acid substitution with a non-polar aromatic residue (Phe) being replaced by a non-polar aliphatic residue (Leu). The position at which this mutation occurs is highly conserved across species and is located within 1 of 3 exons where all published mutations have been reported (Pandit et al., 2007 and Razzaque et al., 2007). I
sequence variant is probably damaging to protein structu
disease-causing mutation consistent with the diagnosis in

Outlines follow-up recommendations specific to the particular test result, such as references to management guidelines, risks to family members or recommendations for genetic counseling

Recommendation: Based on the high frequency of hypertrophic cardiomyop
with a RAF1 mutation, an appropriate cardiologic screening protocol is recommended for this patient. Mutation-specific testing of both parents will determine if the F475L mutation was inherited or has arisen de novo. This information can help to address the recurrence risk in future pregnancies. Prenatal molecular diagnostic testing is available, if desired. Genetic counseling is recommended.

Methods: Genomic DNA was PCR amplified and sequenced using a solid-state sequencing-by-synthesis process. Bi-directional sequence was obtained, analyzed and compared to the published gene sequences. This test does not detect large chromosomal aberrations, rearrangements, or deletions and duplications larger than 25bp. This test includes the complete coding region and splice junctions of the following 11 genes currently known to be associated with Noonan, LEOPARD, Cardio-Facio-Cutaneous, and Costello Syndromes: BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, SHOC2, and SOS1. The result was confirmed in a new DNA preparation by conventional dideoxy DNA sequence analysis.

Describes the methodology used by the lab for that particular test

Report electronically signed by:
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Clinical Molecular Genetics

Report electronically signed by:
Elizabeth Kramer M.G.C., C.G.C.
Senior Genetic Counselor

cDNA RefSeq: BRAF: NM_004333.4, CBL: NM_005188.2, HRAS: NM_ 005343.2, KRAS: NM_004985.3, MAP2K1: NM_002755.3, MAP2K2: NM_030662.3, NRAS: NM_002524.4, PTPN11: NM_002834.3, RAF1: NM_002880.3, SOS1: NM_005633.3, SHOC2: NM_007373.3, counting from the ATG initiation codon.

References: Pandit et al., (2007) Nat Genet 39:1007., Razzaque MA et al., (2007) Nat Genet. 39:1013-1017.