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Patient Report

Patient Age/Gender: 41 hours Female

Specimen Collected: 02-Dec-20 17:18

Hereditary Myeloid Neoplasms Panel **|Received: 02-Dec-20 17:18** **Report/Verified: 02-Dec-20 17:57**

	Result	Units	Reference Interval
Hereditary Myeloid Neoplasms Specimen	Skin Punch		
Hereditary Myeloid Neoplasms Interp	Positive f1 i1		

Result Footnote

f1: Hereditary Myeloid Neoplasms Interp
INDICATION FOR TESTING
Suspected hereditary myeloid neoplasm

RESULT
One pathogenic variant was detected in the TP53 gene.

PATHOGENIC VARIANT
Gene: TP53 (NM_000546.5)
Nucleic Acid Change: c.473G>A; Heterozygous
Amino Acid Alteration: p.Arg158His
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.473G>A; p.Arg158His, was detected in the TP53 gene by massively parallel sequencing and confirmed by Sanger sequencing in this cultured skin fibroblasts sample. Germline pathogenic TP53 variants are inherited in an autosomal dominant manner, and are associated with Li-Fraumeni syndrome. This individual’s offspring have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification: The TP53 c.473G>A; p.Arg158His variant (rs587782144), also known as 12407G>A, is reported in the literature in multiple individuals and families affected with Li-Fraumeni syndrome (Morgan 2010, Ruijs 2010, Villani 2011, Shlien 2008) and other TP53-related cancers (Sun 2017, Wasserman 2015). This variant is reported as pathogenic or likely pathogenic by multiple laboratories in ClinVar (Variation ID: 141963), and is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 158 is highly conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Functional analyses of the variant protein show reduced function (Monti 2011, Wasserman 2015, Zerdoumi 2017). Additionally, other amino acid substitutions at this codon (Cys, Gly, Leu, Pro) have been reported in individuals with TP53-related cancers (Curiel-Lewandrowski 2011, Morgan 2010, Parry 2017, Sun 2017). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic and hematologic consultations are indicated, including a discussion of medical screening and management. Close correlation with clinical findings, family history, and laboratory data including hematologic parameters is recommended. At-risk family members, especially potential stem cell donors, should be offered testing for the identified pathogenic TP53 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report, but are available upon request.

Result Footnote

f1: Hereditary Myeloid Neoplasms Interp

REFERENCES
Curiel-Lewandrowski C et al. Multiple primary cutaneous melanomas in Li-Fraumeni syndrome. Arch Dermatol. 2011 Feb;147(2):248-50.

Monti P et al. Dominant-negative features of mutant TP53 in germline carriers have limited impact on cancer outcomes. Mol Cancer Res. 2011 Mar;9(3):271-9.

Morgan JE et al. Genetic diagnosis of familial breast cancer using clonal sequencing. Hum Mutat. 2010 Apr;31(4):484-91.

Parry EM et al. Germline Mutations in DNA Repair Genes in Lung Adenocarcinoma. J Thorac Oncol. 2017 Nov;12(11):1673-1678.

Ruijs MW et al. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. J Med Genet. 2010 Jun;47(6):421-8.

Shlien A et al. Excessive genomic DNA copy number variation in the Li-Fraumeni cancer predisposition syndrome. Proc Natl Acad Sci U S A. 2008 Aug 12;105(32):11264-9.

Sun J et al. Germline Mutations in Cancer Susceptibility Genes in a Large Series of Unselected Breast Cancer Patients. Clin Cancer Res. 2017 Oct 15;23(20):6113-6119.

Villani A et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol. 2011 Jun;12(6):559-67.

Wasserman JD et al. Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study. J Clin Oncol. 2015 Feb 20;33(6):602-9.

Zerdoumi Y et al. Germline TP53 mutations result into a constitutive defect of p53 DNA binding and transcriptional response to DNA damage. Hum Mol Genet. 2017 Jul 15;26(14):2812.

This result has been reviewed and approved by [redacted]

Test Information

i1: Hereditary Myeloid Neoplasms Interp

BACKGROUND INFORMATION: Hereditary Myeloid Neoplasms Panel, Sequencing

CHARACTERISTICS: While the majority of myeloid neoplasms and malignancies occur sporadically due to somatic mutations, a portion are due to inherited or hereditary predispositions. Individuals with an inherited predisposition to myeloid neoplasms may present at a younger age, with more than one first-degree relative with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), solid tumors and/or a family history of physical findings associated with a known cancer predisposition syndrome.

EPIDEMIOLOGY: MDS occurs in approximately 4.5 per 100,000 individuals in the general population. MDS is rare in children and young adults; approximately 50 percent of childhood MDS is associated with an inherited cause. AML occurs in approximately 3.7 per 100,000 individuals in the general population.

Test Information

i1: Hereditary Myeloid Neoplasms Interp

CAUSE: Pathogenic germline variants in genes associated with predisposition to MDS and/or AML.
INHERITANCE: Variable, dependent on gene/condition.
GENES TESTED: ANKRD26*, ATM, BLM, CBL, CEBPA, DDX41, ELANE, ETV6, GATA1, GATA2, KRAS, NBN, PTPN11*, RUNX1, SAMD9, SAMD9L, SRP72*, TERC, TERT, TP53
* One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes (unless otherwise specified in the limitations section below), followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.
ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.
LIMITATIONS: A negative result does not exclude a diagnosis of cancer nor a heritable form of myeloid neoplasm. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified unless specifically targeted for their clinical relevance. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay is not intended to detect somatic variants associated with hematologic malignancy, though such variants may be detected incidentally. Though this test is designed to identify germline variants associated with predisposition to myeloid neoplasms, it cannot definitively determine the germline or somatic origin of detected variants when the patient has a hematologic malignancy and the assay is performed on blood or other tissue that may be contaminated by malignant cells. In addition, this assay may not detect low-level mosaic or somatic variants associated with disease, including variants that have undergone somatic reversion. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
ANKRD26 (NM_014915) exon 19
PTPN11 (NM_002834) exon 9
SRP72 (NM_006947) exon 19

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

Test Information

i1: Hereditary Myeloid Neoplasms Interp

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.

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