Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: HMYE NGS POS EXAMPLE,

DOB	
Sex:	Male
Patient Identifiers:	57389
Visit Number (FIN):	57779
Collection Date:	2/20/2024 07:52

Hereditary Myeloid Neoplasms Panel, Sequencing

ARUP test code 3001842

Hereditary Myeloid Neoplasms Specimen	Whole Blood
Hereditary Myeloid Neoplasms Interp	Positive

RESULT
One pathogenic variant was detected in the TP53 gene.
PATHOGENIC VARIANT
Gene: TP53 (NM_000546.6)
Nucleic Acid Change: c.743G>A; Heterozygous
Amino Acid Alteration: p.Arg248Gln
Inheritance: Autosomal dominant
INTERPRETATION
One pathogenic variant, c.743G>A; p.Arg248Gln, was detected in the TP53 gene by massively parallel sequencing. Pathogenic germline variants in TP53 are associated with autosomal dominant Li-Fraumeni syndrome (MIM: 151623), as well as with increased risk for a variety of cancers, including breast (MIM: 114480), brain (MIM: 137800), liver (MIM: 114550), bone (MIM: 259500), colorectal (MIM: 114500), nasopharyngeal (MIM: 607107), and pancreatic cancers (MIM: 260350). This result is consistent with a diagnosis of Li-Fraumeni syndrome; clinical manifestations are variable. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.
Please refer to the background information included in this report for a list of the genes analyzed, methodology and limitations of this test.
Evidence for variant classification:
The TP53 c.743G>A; p.Arg248Gln variant (rs11540652) is reported in the germline of several individuals and families with Li-Fraumeni syndrome and TP53-associated cancers (see Grill 2021, Masciari 2011, Villani 2011, Wu 2011). This variant has occurred de novo (Behjati 2014, Bendig 2004, Toguchida 1992), and at least one case of germline mosaicism has been reported (Behjati 2014). Functional analyses have shown that the variant protein has reduced transcriptional activity and altered function (Barakat 2011, Grill 2021, Monti 2007). This variant is reported in ClinVar (Variation ID: 12356), and classified as pathogenic by an expert panel (Fortuno 2021). This variant is only observed on three alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 248 is highly conserved, located in a hotspot, and computational analyses predict that this variant is deleterious (REVEL: 0.934). 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,

H=High, L=Low, *=Abnormal, C=Critical

may consider testing for the identified pathogenic TP53 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS

Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not included in this report.

Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:

NONE

REFERENCES

Barakat K et al. Effects of temperature on the p53-DNA binding interactions and their dynamical behavior: comparing the wild type to the R248Q mutant. PLoS One. 2011;6(11):e27651. PMID: 22110706.

Behjati S et al. A pathogenic mosaic TP53 mutation in two germ layers detected by next generation sequencing. PLoS One. 2014 May 8;9(5):e96531. PMID: 24810334.

Bendig I et al. Identification of novel TP53 mutations in familial and sporadic cancer cases of German and Swiss origin. Cancer Genet Cytogenet. 2004 Oct 1;154(1):22-6. PMID: 15381368.

Fortuno C et al. ClinGen TP53 Variant Curation Expert Panel. Specifications of the ACMG/AMP variant interpretation guidelines for germline TP53 variants. Hum Mutat. 2021 Mar;42(3):223-236. PMID: 33300245.

Grill S et al. TP53 germline mutations in the context of families with hereditary breast and ovarian cancer: a clinical challenge. Arch Gynecol Obstet. 2021 Jun;303(6):1557-1567. PMID: 33245408.

Masciari S et al. Gastric cancer in individuals with Li-Fraumeni syndrome. Genet Med. 2011 Jul;13(7):651-7. PMID: 21552135.

Monti P et al. Transcriptional functionality of germ line p53 mutants influences cancer phenotype. Clin Cancer Res. 2007 Jul 1;13(13):3789-95. PMID: 17606709.

Toguchida J et al. Prevalence and spectrum of germline mutations of the p53 gene among patients with sarcoma. N Engl J Med. 1992 May 14;326(20):1301-8. PMID: 1565143.

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. PMID: 21601526.

Wu CC et al. Joint effects of germ-line TP53 mutation, MDM2 SNP309, and gender on cancer risk in family studies of Li-Fraumeni syndrome. Hum Genet. 2011 Jun;129(6):663-73. PMID: 21305319.

This result has been reviewed and approved by

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.

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 to confirm reported variants that do not meet acceptable quality metrics. 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. Noncoding 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 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Hereditary Myeloid Neoplasms Specimen	24-051-100925	2/20/2024 7:52:00 AM	2/20/2024 7:52:26 AM	2/20/2024 7:55:00 AM

H=High, L=Low, *=Abnormal, C=Critical

Hereditary Myeloid Neoplasms Interp	24-051-100925	2/20/2024 7:52:00 AM	2/20/2024 7:52:26 AM	2/20/2024 7:55:00 AM

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical