Toronto Cancer Hospital

Division of Tumor Sequencing and Diagnostics

123 Main St. West,
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Draft PATHOLOGY LABORATORY RESULTS

Patient Info:

Name:
DOB:
Sex:

Patient Information:

Physician Name:
Health Card:
MRN #:
Clinic: Lakeridge Health (Oshawa)

Procedure Date	Accession Date	Report Date
2022-06-02 02:35:00	2022-06-03 18:29:38	2022-06-04 11:26:50

Report Details

Genome Reference - GRCh38
Sequencing Range - Gene panel, Methylation analysis

Referral Reason - Research

Analysis Location - London Health Sciences Centre (London)

Table of findings:

Gene	Information	Interpretation
TNFAIP3	11 c.1413T>A p.Ser471Arg heterozygous	Likely pathogenic

Summary: One likely pathogenic variant detected.. The details regarding the specific mutations are included below.

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Variant Interpretation:

The interpretation of these variants is as follows: One likely pathogenic variant was detected in the sample.

Variant 1 of 1

Gene	Variant	Amino	Zygosity
TNFAIP3	c.1413T>A	p.Ser471Arg	heterozygous

Likely pathogenic

The g.137868626T>A variant occurs in chromosome chr6 , within the TNFAIP3 gene, and it causes c.1413T>A change at position 471 in exon 11 , forming p.Ser471Arg . This mutation has been identified in 34 families. It has a population frequency of 7.25e-04 (472 alleles in 651297 total alleles tested), indicating it is a rare variant in the general population. causes an amino acid substitution, which replaces serine with arginine . ClinVar and other genomic databases report the TNFAIP3 c.1413T>A variant as clinically relevant based on aggregated evidence.

This variant is classified as likely pathogenic. It is believed to negatively impact protein function and may play a role in disease development in affected individuals.

The affected nucleotide lies within a region that is highly conserved across vertebrate species, which suggests functional importance and evolutionary constraint.

This variant is implicated in oncogenesis and other disease processes according to ClinVar records (VCV accession: VCV004216583).

Supporting studies and case reports can be found in the scientific literature. Relevant PubMed references include: 922610376, 325721135, 464303800, 445498729, 107133198, 250652185, 340317468, 143600442 .

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In accordance with existing evidence, this variant is therefore classified as a likely pathogenic variant.

Test Details:

Genes Analyzed: SS18, total. ACVR1, total. HSP90AA1, total. TNFAIP3, total. RBL1, total. MXRA5, total. NCOA4, total. ASPSCR1, total. 8 total genes tested.

mRNA ref sequences tested NM_...: NM_001007559.3 NM_001111067.4 NM_005348.4 NM_006290.4 NM_002895.5 NM_015419.4 NM_001145263.2 NM_024083.4

Recommendations

A precision oncology approach is advised. These mutations are known oncogenic drivers, linked to constitutive pathway activation. Targeted therapies, including hormone-correcting agents, may be considered, guided by clinical judgment. PI3K inhibitors could be explored in trials for PIK3CA-mutated cases. Germline testing is not indicated, as all mutations are consistent with somatic events. A multidisciplinary tumour board review is recommended to integrate findings into care. Additional testing may be pursued at the physician's discretion.

Methodology

Amplified DNA was sequenced with Gene panel and was analyzed using Methylation analysis covering all coding exons and adjacent intronic regions. Target enrichment was performed with hybrid capture (Twist Bioscience), followed by Illumina NextSeq sequencing. Reads were aligned to GRCh37 using BWA-MEM, and variants called with GATK. Annotation was performed in VarSeq using population databases, predictive algorithms, and ClinVar. CNVs were assessed with CNVkit and confirmed by MLPA when applicable. Regions with pseudogene interference, such as PMS2, were validated using long-range PCR and Sanger sequencing. Mean read depth exceeded 300x, with a minimum threshold of 50x. Analytical sensitivity is >99% for SNVs/indels and >95% for exon-level CNVs. **Only variants classified as pathogenic, likely pathogenic, or variants of uncertain significance (VUS) are reported**, per ACMG/AMP guidelines (PMID: 25741868).

Limitations

This test was developed and validated in a certified clinical laboratory. Limitations include reduced sensitivity in pseudogene regions (e.g., PMS2, CHEK2), and inability to detect certain structural variants (e.g., MSH2 inversions), deep intronic changes, or low-level mosaicism. PMS2 exons 11–15 are not analyzed. Interpretations reflect current knowledge and may be updated as new evidence emerges.

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Report Electronically Verified and Signed by: