Toronto Cancer Hospital

Division of Tumor Sequencing and Diagnostics

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Draft MOLECULAR GENETICS LABORATORY RESULTS

Patient Info:

Name:
DOB:
Sex:

Patient Information:

Physician Name:
Health Card:
MRN #:
Clinic: Windsor Regional Hospital (Windsor)

Procedure Date	Accession Date	Report Date
2024-06-15	2024-06-16	2024-06-17

Report Details

Genome Reference - GRCh37
Sequencing Range - Targeted variant testing, Methylation analysis

Referral Reason - Clinical

Analysis Location - Sinai Health System (Toronto)

Table of findings:

Gene	Information	Interpretation
OTOF	7 c.5436G>T p.Glu1812Asp 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
OTOF	c.5436G>T	p.Glu1812Asp	heterozygous

Likely pathogenic

The g.26462638G>T variant occurs in chromosome chr2 , within the OTOF gene, and it causes c.5436G>T change at position 1812 in exon 7 , causing the mutation p.Glu1812Asp . This mutation has been identified in 46 families. It has a population frequency of 0.00e+00 (0 alleles in 375853 total alleles tested), indicating it is a very rare variant in the general population. It causes an amino acid substitution, which replaces glutamate with aspartate . ClinVar and other genomic databases report the OTOF c.5436G>T 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: VCV000920952).

Supporting studies and case reports can be found in the scientific literature. Relevant PubMed references include: 492984350, 246228801, 563728082, 942746831, 956367708 .

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

Test Details:

Genes Analyzed and mRNA sequence (NM_): IL6ST and NM_002184.4. OTOF and NM_194248.3. IGF2R and NM_000876.4. TCF12 and NM_001322159.3. NCKIPSD and NM_016453.4. DAB2IP and NM_001395010.1. MDM2 and NM_002392.6. RAP1GDS1 and NM_001100427.2. 8 total genes tested.

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

ctDNA was sequenced with Targeted variant testing 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: