Toronto Cancer Hospital

Division of Tumor Sequencing and Diagnostics

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Draft PATHOLOGY LABORATORY RESULTS

Patient Info:

Name:
DOB:
Sex:

Patient Information:

Physician Name:
Health Card:
MRN #:
Clinic: Health Sciences North (Sudbury)

Procedure Date	Accession Date	Report Date
2022-07-27	2022-07-28	2022-07-29

Report Details

Genome Reference - NCBI Build 36.1
Sequencing Range - Whole transcriptome sequencing (WTS), Microarray

Referral Reason - Research

Analysis Location - Hamilton Health Sciences (Hamilton)

Table of findings:

Gene	Information	Interpretation
BCL9	17 c.881G>A p.Ser294Asn heterozygous	Variant of uncertain clinical significance

Summary: One variant of uncertain clinical significance 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 variant of uncertain clinical significance was detected in the sample.

Variant 1 of 1

Gene	Variant	Amino	Zygosity
BCL9	c.881G>A	p.Ser294Asn	heterozygous

Variant of uncertain clinical significance

The g.147542381G>A variant occurs in chromosome chr1 , within the BCL9 gene, and it causes c.881G>A change at position 294 in exon 17 , causing the mutation p.Ser294Asn . This mutation has been identified in 40 families. It has a population frequency of 2.59e-04 (135 alleles in 521326 total alleles tested), indicating it is a relatively common variant in the general population. It causes an amino acid substitution, which replaces serine with asparagine . ClinVar and other genomic databases report the BCL9 c.881G>A variant as clinically relevant based on aggregated evidence.

The clinical implications of this variant are not yet fully understood. At present, available data is insufficient to confirm its role in disease.

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

This variant is not currently strongly implicated in specific diseases according to ClinVar records (VCV accession: VCV009878164).

Supporting studies and case reports can be found in the scientific literature. Relevant PubMed references include: 787866390, 332839785, 241707107, 368112509 .

According to ClinVar, the evidence collected to date is insufficient to firmly establish the clinical significance of this variant, therefore it is classified as a variant of uncertain clinical significance .

Test Details:

Genes Analyzed and mRNA sequence (NM_): AKT2 and NM_001626.6. RHBDF2 and NM_001005498.4. PTPN13 and NM_080683.3. H3F3A and NM_002107.4. EGR3 and NM_004430.3. TLX3 and NM_021025.4. PAX5 and NM_016734.3. HNF1A and NM_000545.8. EPHA7 and NM_004440.4. TNR and NM_003285.3. BTK and NM_000061.3. CREB3L1 and NM_052854.4. PRDM16 and NM_022114.4. HOXD13 and NM_000523.4. FOSL2 and NM_005253.4. KIF7 and NM_198525.3. NR4A3 and NM_006981.4. CTNND1 and NM_001085458.2. BCL9 and NM_004326.4. KEAP1 and NM_203500.2. 20 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

Total DNA was sequenced with Whole transcriptome sequencing (WTS) and was analyzed using Microarray 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),

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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: