Guide to understanding your Revvity Omics sponsored testing report

At the top of every Revvity Omics test result you will find pertinent information about patient demographics, sample and reporting dates, and the provider who ordered the test.

Test performed and reason for referral

This section includes both the name of the test that was completed by Revvity Omics and the reason it was ordered.

Relevant findings and interpretation

This section includes a summary of reportable sequence and copy number variants (pathogenic, likely pathogenic variants, and variant of uncertain significance, pseudodeficiency alleles) that are identified in this individual.
All findings are listed in a table similar to that below:

Single nucleotide variant (SNV) table

Classification	Gene	Exon / intron	DNA change	Protein change	Zygosity	Inheritance	OMIM	Associated disease

Information Included in the SNV table

1. **Classification:** Defines the specific classification of the variant identified based on ACMG criteria.
2. **Gene:** Defines the specific gene that harbors the variant in the row.
3. **Exon/intron:** Specifies in which exon/intron the variant in this row is located.
4. **DNA change:** Defines the DNA location of the variant as well as the specific base change.
5. **Protein change:** Specifies the amino acid alteration that results from the DNA change identified, if applicable.
6. **Zygosity:** Defines whether the change is heterozygous (patient carries only 1 copy of the variant), homozygous (patient carries two copies of the variant) or is hemizygous (male patient caries only one copy of the variant).
7. **Inheritance:** Specifies the disease-associated inheritance patterns (autosomal dominant, autosomal recessive, X-linked).
8. **OMIM:** Relays the OMIM number for the associated gene(s).
9. **Associated disease:** Lists the specific clinical conditions that have been associated with the affected gene as defined by OMIM and does not necessarily indicate that individual being tested is affected by them. If a patient only carries one copy of the variant in a recessive gene and disease, the patient is likely an asymptomatic carrier. Genetic counseling is recommended.

This section includes a more detailed description of each reported variant and summary of the evidence used by our ACMG board-certified directors to classify the variant as Pathogenic, Likely Pathogenic, Variant of Uncertain Significance, or a Pseudodeficiency Allele.

Copy number variant (CNV) table

Classification	Event	Cytoband/Gene	Genomic location	Size (bp)	OMIM	Associated disease

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1. **Classification:** Defines the specific classification of the CNV event based on ACMG criteria.
2. **Event:** Defines the type of copy number change that was detected (gain/loss).
3. **Cytoband/gene:** Describes the exons, genes, and/or regions included in the CNV event.
4. **Genomic location:** Defines the genomic coordinates of the CNV event.
5. **Size (bp):** Delineates the number of base pairs included in the CNV event.
6. **OMIM:** Relays the OMIM number for the associated gene(s).
7. **Associated disease:** Lists the specific clinical conditions that have been associated with the affected gene as defined by OMIM.
8. **CNV detection limit:** Copy number variant size is approximate for panels and for more accurate breakpoint detection, testing by orthogonal methods may be recommended.

Things to know

Types of variants that are reported:

SNV - A substitution of a single nucleotide for another, or small insertions/deletions.

CNV - Gain or loss that changes the number of copies of a particular DNA segment.

How variant classification is determined: Our team utilizes the ACMG guidelines for review and interpretation of sequence and copy number variants. Some of the factors considered in the variant classification process include:

- Previous literature observations of the variant in affected individuals.
- Population frequency of the variant.
- The type of variant (e.g. missense, nonsense, frameshift, splice site).
- The mechanism of disease.
- Results from functional studies.
- Predictive modeling.

How variants are classified: The American College of Genetics and Genomics (ACMG) has recommended a 5-tier classification system. (PMID: 25741868). Revvity Omics follows these recommendations when classifying variants as described below:

Pathogenic – Variants with sufficient evidence that they are disease-causing. A pathogenic variant is always included in reports.

Likely pathogenic (LP) – Variants with strong evidence (greater than 90% certainty) that they are disease-causing. A LP variant is always included in reports.

Variant of uncertain significance (VOUS) – Changes with limited and/or conflicting evidence regarding their effect on the function of the protein built from the gene.

Information currently available is insufficient to support a more definitive classification of these variants. A VOUS in a gene associated with reported clinical features is routinely included in reports.

Likely benign (LB) – Variants with strong evidence against being disease-causing. A LB variant is not routinely included in reports.

Benign – Variants that do not cause disease. A benign variant is not routinely included in reports.

Recommendations

This section includes correlation of molecular findings with clinical presentations (e.g., consistent with diagnosis), follow-up testing recommendations based on the variant(s) detected, the inheritance pattern, and the clinical information utilized in the interpretation process.

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Things to know

Examples of common recommendations included in our panel reports are listed below:

- If a pathogenic and/or likely pathogenic variant is detected, then targeted testing of at-risk family members is recommended as this may change their medical management.
- If a VOUS is detected, then targeted testing of the parents and appropriate affected or unaffected family members is often recommended. This information can help to provide further interpretation of the results. For example, it can be helpful to understand if a VOUS is new (*de novo*) in the affected individual or if it was inherited from a parent. It can also be helpful to understand if a particular VOUS is found in similarly affected family members.
- Please note that the targeted variant testing for family members may or maynot be covered as part of the sponsored testing program. Please contact your program coordinator for more information.

Notes

This section includes relevant information about Revvity Omics' reporting process and coverage information about each variant in the "variant statistics" table.

Methods and limitations

This section includes a detailed description of the methods utilized by our laboratory to perform the test ordered. It also includes a discussion of the possible limitations of the assay.

Genes Tested

This section provides a list of genes analyzed as part of the panel being tested.

Relevant Revvity Omics policies

Requests for reclassification of variants

With variant reclassification, we have to ensure the classification of a variant holds for every individual who may be referred to our laboratory. Therefore, we have stringent criteria for the types of evidence necessary for reclassification. Factors taken into consideration when reclassification is requested may include but is not limited to:

- New report(s) of genotype-phenotype correlation in the literature.
- New evidence from functional studies.
- Clear evidence of disease-segregation in the family.
- *De novo* inheritance for autosomal dominant genes.

Variants are reviewed periodically by variant analysts and laboratory directors. An updated report will be issued for variants that are upgraded from uncertain significance to likely pathogenic or pathogenic, or from likely pathogenic to pathogenic. Ordering providers are encouraged to check the classification status of a variant, and provide relevant clinical information to aid variant reclassification.

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