Rady Children's Institute Genomic Medicine | Clinical Genome Center

CLIA ID# 05D2129627
CAP ID# 9487427

Rady Children's Institute for Genomic Medicine – Clinical Genome Center (RCIGM-CGC) Variant Interpretation and Reporting Guidelines

Overview

The Rady Children's Institute for Genomic Medicine – Clinical Genome Center (RCIGM-CGC) reporting workflow focuses on symptom-driven diagnoses for children with suspected genetic disease. Variants classified as likely pathogenic (LP) and pathogenic (P) in genes implicated in human disease are reported to the ordering physician. Selected variants of uncertain significance (VUS) will be reported in accordance with RCIGM-CGC policy (see below). Incidental findings will also be reported if identified if the family does not opt-out of receiving these results. All variants are classified in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines. Reported variants may be confirmed using orthogonal methodologies if variants do not meet RCIGM quality control thresholds.

The current offering includes:

- single nucleotide variants (SNVs)
- small insertions and deletions
- copy number variation (CNV) from 1 kB to whole chromosome abnormalities
- SMN1/SMN2 copy number analysis
- mitochondrial DNA detection
- repeat expansion calling for PHOX2B and DMPK

Classification guidelines and variants to be reported

Variants classified as likely pathogenic and pathogenic per ACMG guidelines for small variants and copy number variation that overlap with the patient's phenotype will be reported. Selected variants of uncertain significance will also be reported. (Richards et al. 2015, Riggs et al. 2019).

- Pathogenic (P): In addition to ACMG guidelines, the variant is report in multiple unrelated cases, with association control data. Functional or expression evidence suggest aberrant gene expression/function. Exceptions may exist for loss of function (LOF) or gain of function (GOF) variants in genes in which the disease mechanism is well established.

- Likely Pathogenic (LP): In addition to ACMG guidelines, the variant is report in a limited number of cases, or in a single family cohort, with or without control data. Limited or no functional evidence is available, but overall biological expectations are suggestive of an aberrant functional effect.

- Variant of Uncertain Significance (VUS) – See "Variants of Uncertain Significance" section below.

Not reported

- Likely Benign: In addition to ACMG guidelines, the variant has been seen in affected individuals, but also in controls. Variant may be present in a high percentage of the population and may be present in a non-conserved region.

- Benign: In addition to ACMG guidelines, the variant is established in the literature or clinical databases as a variant that is not associated with Mendelian (single-gene inherited) disease, or is known to have an allele frequency too high to be compatible with the prevalence of disease, mode of inheritance and penetrance patterns known for that condition.

Reporting Categories

- Primary Findings: Variants in genes associated with patient's reported phenotype with the mode of inheritance in alignment with what is established for gene and disease of interest
- Incidental Findings: Clinically significant variants in genes detected during analysis that are not associated with patient's reported phenotype (if patient does not opt out). Of note, RCIGM-CGC does not purposefully interrogate genes on the ACMG Secondary Findings list, but a pathogenic variant identified in one of these genes would be reported as an incidental finding if revealed during analysis.
- Variants of Uncertain Significance (VUS): See “Variants of Uncertain Significance” section below.
- Genes of Uncertain Significance (GUS): Variants that are suggestive to be disease-causing in genes that have moderate or limited evidence in the literature for the gene-disease association.
- Mitochondrial variants: Mitochondrial DNA variants that may not be related to the patient’s reported phenotype but are established as disease-causing variants in the literature. Mitochondrial variants that may explain the patient’s reported phenotype will be placed in the primary findings section.

What is Not Reported

- Carrier status
- Pharmacogenetic markers
- Polygenic risk scores
- Genome wide association studies risk variants

Variants of Uncertain Significance (VUS)

A variant of uncertain significance is a variant which lacks the evidence required to characterize the variant as pathogenic or benign variation. This may be due to a lack of available evidence or conflicting evidence that currently exists. VUSs may be listed in the primary findings or the VUS table based on the current gene-disease evidence. VUSs may be re-classified as new evidence emerges.

Reporting criteria for VUS include, but are not limited to:

- VUS(s) in a gene that strongly overlaps the phenotype of patient for which the mode of inheritance matches what is known about the gene of interest.
- A P/LP variant is identified in a gene for a recessive condition in trans- with a VUS.
- Compelling VUSs within a gene of uncertain significance – the variants must have supporting information that suggests pathogenicity. What is known about the function of the gene must also have plausibility for the pathophysiology of the condition.

Communication of Results

A final clinical report is provided to the ordering physician once analysis is complete and any orthogonal confirmations that may have been performed are completed. For cases where a likely pathogenic or pathogenic variant has been identified that may explain the patient’s reported phenotype, a preliminary report will be provided prior to any confirmation testing and prior to completion of analysis for the genome. In certain situations, variants of uncertain significance may be reported in a preliminary report if the RCIGM interpretation and clinical teams determine the information should be delivered as soon as possible to potentially inform medical management. The provided contact number will be verbally notified prior to report delivery.

Rady Children's Institute Genomic Medicine | Clinical Genome Center

CLIA ID# 05D2129627
CAP ID# 9487427

All inquiries and questions related to patient results should be sent to **RCIGM_rwgs@rchsd.org** or call 858-966-8127. Laboratory directors and genetic counselors are available at RCIGM to answer questions regarding genomic results and analysis. Direct genetic counseling to families is not provided.

Genome Coverage and Limitations:

Full coverage of the genome is not currently possible due to technically challenging repetitive elements and duplicated regions within the genome. Thus, not all regions of the genome are sequenced and/or uniquely aligned to the reference genome. Mosaic variant detection is limited using whole genome sequencing. Repeat expansion detection is limited to the DMPK and PHOX2B genes. The exact number of repeats cannot be determined by the current methodology and therefore orthogonal confirmation for precise sizing may be required. Non-diagnostic findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable with the current version of this test. False negative results may occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. The chance of false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded. This test is set up to evaluate the potential contribution of rare disease-causing variants in known disease genes. It is not designed to evaluate for common variants in genes that might contribute to disease risk or for disorders that have a multigenic inheritance. Based on current knowledge, potential disease-causing variants may not always be recognized at the time of testing.

References:

Mandelker D, Schmidt RJ, Ankala A, McDonald Gibson K, Bowser M, Sharma H, Duffy E, Hegde M, Santani A, Lebo M, Funke B. Navigating highly homologous genes in a molecular diagnostic setting: a resource for clinical next-generation sequencing. Genet Med. 2016 Dec;18(12):1282-1289. doi: 10.1038/gim.2016.58. Epub 2016 May 26.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. PMID: 25741868.

Riggs ER, Andersen EF, Cherry AM, Kantarci S, Kearney H, Patel A, Raca G, Ritter DI, South ST, Thorland EC, Pineda-Alvarez D, Aradhya S, Martin CL. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med. 2019 Nov 6. doi: 10.1038/s41436-019-0686-8. [Epub ahead of print]