| Patient ID | Patient Name | | Birth Date | Sex | Age |
|---|---|---|---|---|---|
| SA00154383 | ABNORMAL, PRKSG | | 1986-11-25 | F | 35 |
| **Order Number** | **Client Order Number** | **Ordering Physician** | **Report Notes** | | |
| SA00154383 | SA00154383 | CLIENT,CLIENT | | | |
| **Account Information** | | **Collected** | | | |
| C7028846 DLMP Rochester | | 12 Sep 2022 08:00 | | | |

# PRKAR1A Full Gene Analysis

## Interpretation

MCR

PRKAR1A c.1142_1145del (p.Val381delins58): The heterozygous c.1142_1145del (p.Val381delins58) variant in the PRKAR1A gene (MIM: 188830) is classified as pathogenic. The PRKAR1A gene encodes protein kinase cAMP-dependent type I regulatory subunit alpha, a regulatory subunit of the type I protein kinase A (PKA). The cAMP/PKA signaling pathway is involved in many cellular processes including regulating metabolism and cell proliferation, differentiation, and apoptosis. Pathogenic variants in this gene are primarily associated with autosomal dominant Carney complex (CNC) and autosomal dominant acrodysostosis. This variant has been previously reported in two members of a family diagnosed with Carney complex: a 6-year-old male with Cushing's syndrome and lentigenosis, and a 26-year-old male with large-cell calcifying Sertoli cell tumor and lentigenosis (1,2). Functional studies confirmed that this variant escapes nonsense-mediated mRNA decay (NMD) and results in an elongated protein which is subsequently degraded (2). Finally, this variant has not been observed in exome and/or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (3). Taken together, this result is supportive of a diagnosis of Carney complex or other PRKAR1A-related condition for this individual. Clinical correlation *is recommended*.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1–800–533–1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

## REFERENCES:

1. Bertherat J, Horvath A, Groussin L, et al. Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. J Clin Endocrinol Metab. 2009;94(6):2085–2091. doi:10.1210/jc.2008–2333 (PMID: 19293268)
2. Patronas Y, Horvath A, Greene E, et al. In vitro studies of novel PRKAR1A mutants that extend the predicted RIa protein sequence into the 3'-untranslated open reading frame: proteasomal degradation leads to RIa haploinsufficiency and Carney complex. J Clin Endocrinol Metab. 2012;97(3):E496-E502. doi:10.1210/jc.2011–2220 (PMID: 22205709)
3. gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434–443 (PMID 32461654)

## Result Summary

MCR

Pathogenic Variant Detected

## Result

MCR

The following heterozygous PATHOGENIC variant was detected:
PRKAR1A (NM_002734.4), Chr17(GRCh37):g.66526586_66526589del, c.1142_1145del, p.Val381delins58 (p.V381delins58)

No additional reportable pathogenic variants, likely pathogenic variants, or variants of uncertain significance were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by the assay.

## Test Description

MCR

Evaluation of the PRKAR1A gene associated with Carney Complex (CNC)

## Specimen

MCR

DNA (ul)

## Method

MCR

Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered



**Performing Site Legend**

| Code | Laboratory | Address | Lab Director | CLIA Certificate |
|---|---|---|---|---|
| MCR | Mayo Clinic Laboratories - Rochester Main Campus | 200 First Street SW, Rochester, MN 55905 | William G. Morice M.D. Ph.D | 24D0404292 |

| Patient ID | Patient Name | | Birth Date | Sex | Age |
|---|---|---|---|---|---|
| SA00154383 | ABNORMAL, PRKSG | | 1986-11-25 | F | 35 |
| Order Number | Client Order Number | Ordering Physician | Report Notes | | |
| SA00154383 | SA00154383 | CLIENT,CLIENT | | | |
| Account Information | | Collected | | | |
| C7028846 DLMP Rochester | | 12 Sep 2022 08:00 | | | |

at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS, and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID PRKSG) for details regarding genes with regions not routinely covered.

## Genes Analyzed

MCR

PRKAR1A

## Disclaimer

1 MCR

Clinical Correlations
An online research opportunity called Genome*Connect* (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1–800–533–1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the PRKAR1A Full Gene Analysis in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID PRKSG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.



**Performing Site Legend**

| Code | Laboratory | Address | Lab Director | CLIA Certificate |
|---|---|---|---|---|
| MCR | Mayo Clinic Laboratories - Rochester Main Campus | 200 First Street SW, Rochester, MN 55905 | William G. Morice M.D. Ph.D | 24D0404292 |

MAYO CLINIC LABORATORIES

| Patient ID | Patient Name | | Birth Date | Sex | Age |
|---|---|---|---|---|---|
| SA00154383 | ABNORMAL, PRKSG | | 1986-11-25 | F | 35 |
| **Order Number** | **Client Order Number** | **Ordering Physician** | **Report Notes** | | |
| SA00154383 | SA00154383 | CLIENT,CLIENT | | | |
| **Account Information** | | **Collected** | | | |
| C7028846 DLMP Rochester | | 12 Sep 2022 08:00 | | | |

**Released By** MCR

Linnea M. Baudhuin, Ph.D.

**Received:** 22 Sep 2022 09:19 **Reported:** 28 Sep 2022 21:22



## Laboratory Notes

1 This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

**Performing Site Legend**

| Code | Laboratory | Address | Lab Director | CLIA Certificate |
|---|---|---|---|---|
| MCR | Mayo Clinic Laboratories - Rochester Main Campus | 200 First Street SW, Rochester, MN 55905 | William G. Morice M.D. Ph.D | 24D0404292 |