Test Definition: PRKSD

PRKAR1A Full Gene Analysis

Overview

Useful For

Aiding in the diagnosis of individuals with suspected Carney complex

Aiding in the diagnosis of individuals with suspected acrodysostosis-1 with hormone resistance

Genetics Test Information

This test uses Sanger sequencing to evaluate for the presence of *PRKAR1A* gene variants associated with Carney complex (CNC), acrodysostosis-1 with hormone resistance, or other *PRKAR1A*-associated conditions. Additionally, quantitative PCR (qPCR) is used to test for the presence of large deletions and duplications of the *PRKAR1A* gene.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- PRKAR1A-Related Disorders Patient Information

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis and qPCR

NY State Available

Yes

Specimen

Specimen Type

Varies

Advisory Information

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for the genes on this panel. See:

-KVAR1 / Known Variant Analysis-1 Variant, Varies

-KVAR2 / Known Variant Analysis-2 Variants, Varies

-KVAR3 / Known Variant Analysis-3+ Variants, Varies

Call 800-533-1710 to confirm the appropriate test for targeted testing.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

1. ***PRKAR1A*-Related Disorders Patient Information (T820) is required**. See Special Instructions. Testing may proceed without the patient information, however, the information aids in providing a more thorough interpretation. Ordering physicians are strongly encouraged to fill out the form.

2. Include physician name and phone number with specimen.

Specimen Required

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 14 days

Specimen Type: DNA

Container/Tube: 2 mL screw top tube

Specimen Volume: 100 mcL (microliters)

Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms

1. ***PRKAR1A*-Related Disorders Patient Information (T820) is required**. See Special Instructions.

2. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

Specimen Minimum Volume

Blood: 1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical and Interpretive

Clinical Information

Carneycomplex (CNC) is an autosomal dominant disorder caused by heterozygous germline pathogenic inactivating variants in the *PRKAR1A* gene. This condition has also been designated by the following acronyms: NAME (nevi, atrial myxomas, ephelides) and LAMB (lentigines, atrial myxoma, blue nevi). CNC is characterized by skin pigmentary abnormalities, myxomas, endocrine tumors, and schwannomas. The most common presenting feature of CNC is unusual skin pigmentation, including brown skin spots called lentigines or blue-black moles called blue nevi. Myxomas are noncancerous (benign) tumors which can occur in the heart (cardiac myxoma), skin, breast, and other internal organs. Cardiac myxomas can occur at a young age, and may block blood flow through the heart, causing serious complications or sudden death. Approximately 25% of affected individuals will develop primary pigmented nodular adrenocortical disease (PPNAD), which can lead to development of Cushing syndrome. Large-cell calcifying Sertoli cell tumors occur in most affected males and may develop in the first decade of life in about one third of cases. Multiple thyroid nodules are present in as many as 75% of affected individuals. Pituitary adenomas resulting in clinically evident acromegaly occur in approximately 10% of adults with CNC. Another 10% of affected individuals have psammomatous melanotic schwannomas, which are typically benign but may be malignant.

PRKAR1A encodes for cAMP-dependent protein kinase type I-alpha regulatory subunit. *PRKAR1A* functions as a canonical tumor-suppressor gene, with biallelic inactivation in tumors resulting in constitutive activation of protein kinase A (PKA). Approximately 70% of individuals with a diagnosis of CNC have an affected parent, while approximately 30% have a de novo pathogenic variant. CNC is a highly penetrant disorder, with approximately 95% of those with a pathogenic *PRKAR1A* variant developing disease by age 50 years. The proportion of probands with a pathogenic variant detectable by sequence analysis is approximately 60%, but can be higher (approximately 80%) in individuals presenting with Cushing syndrome caused by PPNAD. Approximately 10% to 20% of individuals with CNC who test negative for a pathogenic sequence variant may have a large *PRKAR1A* deletion.

While the majority of reported pathogenic *PRKAR1A* gene variants are associated with CNC, this gene is also associated with an autosomal dominant condition called acrodysostosis-1 with hormone resistance. This condition is characterized by multiple hormone resistance, short stature, brachycephaly, and short broad hands with short metacarpals and phalanges, among other features. This phenotype results from pathogenic *PRKAR1A* variants in 1 of the 2 cAMP-binding domains and has a different mechanism of disease than CNC.

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Clinical Correlations:

Some individuals may have a *PRKAR1A* variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of disease. Genomic regions that are not sufficiently covered for analysis and interpretation will be indicated on the laboratory report.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

For predictive testing of asymptomatic individuals, it is often useful to first test an affected family member.

Identification of a pathogenic variant in an affected individual allows for more informative testing of at-risk individuals.

Technical Limitations:

If the patient has had an allogeneic blood or bone marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that have been detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with a genetics professional should be considered for interpretation of this result.

A list of benign and likely benign variants detected for this patient is available from the laboratory upon request.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient's results.

Clinical Reference

1. Maleszewski JJ, Larsen BT, Kip NS, et al: PRKAR1A in the development of cardiac myxoma. Am J Surg Pathol 2014;38:1079-1087

2. Rhayem Y, Le Stunff C, Abdel Khalek W, et al: Functional characterization of PRKAR1A mutations reveals a unique molecular mechanism causing acrodysostosis but multiple mechanisms causing Carney complex. J Biol Chem 2015;290(46):27816-27828

3. Salpea P, Horvath A, London E, et al: Deletions of the PRKAR1A locus at 17q24.2-q24.3 in Carney complex: genotype-phenotype correlations and implications for genetic testing. J Clin Endocrinol Metab 2014;99(1):E183-188

4. Stratakis CA, Raygada M: Carney Complex. In GeneReviews. Updated 2018 Aug 16. Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle WA. 1993-2019. Accessed 8/2018 Available at www.ncbi.nlm.nih.gov/books/NBK1286/

5. Online Mendelian Inheritance in Man. Accessed 6/2019 Â Available at www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM

Performance

Method Description

Polymerase chain reaction (PCR) followed by bidirectional DNA sequence analysis is performed to test for the presence of sequence variants in all coding regions and intron/exon boundaries of the *PRKAR1A* gene. Quantitative PCR (qPCR) using SYBR green fluorescent-dye terminator chemistry is performed to test for the presence of whole exon deletions and duplications.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Varies

Analytic Time

3 days (Not reported Saturday or Sunday)

Maximum Laboratory Time

7 days

Specimen Retention Time

Extracted DNA:2 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

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.

CPT Code Information

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
PRKSD	PRKAR1A Full Gene Analysis	94214-4

Result ID	Test Result Name	Result LOINC Value
605940	Result Summary	50397-9

Result ID	Test Result Name	Result LOINC Value
605941	Result Details	82939-0
605942	Interpretation	69047-9
605943	Additional Information	48767-8
605944	Method	85069-3
605945	Disclaimer	62364-5
605946	Reviewed by	18771-6