

PRKAR1A Gene Analysis in Carney Complex

Disorder Also Known As: NAME Syndrome (Nevi; Atrial myxoma; Myxoid neurofibromata; Ephilides); LAMB Syndrome (Lentigines; Atrial myxoma; Mucocutaneous myxoma; Blue nevi); Isolated Primary Pigmented Nodular Adrenocortical Disease (PPNAD)

Clinical Features:

Carney Complex (CNC) is a multiple endocrine neoplasia syndrome characterized by heart, endocrine, skin, adrenal and neural tumors, and a variety of pigmented lesions of the skin and mucosal surfaces, as well as thyroid cancer. Overall, the clinical manifestations are variable and the full spectrum of disease develops throughout childhood and early adulthood; it has near complete penetrance by age 50.¹

Cutaneous and palpebral lentigines are the most commonly observed feature, occurring in approximately 70-80% of affected individuals with CNC.²⁻⁴ Other skin lesions, including blue nevi, cutaneous myxomas, and café-au-lait spots, are also a common. Cardiac myxomas are the most frequent non-cutaneous lesion, occurring in 20-40% of individuals. Primary Pigmented Nodular Adrenocortical Disease (PPNAD) is the most commonly observed endocrine tumor in CNC occurring in between 25-60% of individuals, with a portion of individuals with *PRKAR1A* pathogenic variants developing only isolated PPNAD.⁵ Benign cystic or nodular thyroid disease and adenomas are also common.^{3,5} Large cell-calcifying Sertoli cell tumors (LCCSCT) occur in 40% of men with Leydig-cell tumors and adrenocortical rest tumors of the testes having also been reported.^{2,3} About 10% of individuals with *PRKAR1A* pathogenic variants develop psammomatous melanotic schwannomas, which primarily occur in the gastrointestinal tract and the paraspinal sympathetic chain. Other benign tumors associated with *PRKAR1A* pathogenic variants include, but are not limited to: myxomas, adenomas and myxoid fibroadenomas of the breast (20% of females); pituitary gland adenomas leading to acromegaly (10-20%); ovarian cysts, teratomas, and cystadenomas (14%); and rarely osteochondromyxomas.^{2,3,5}

Malignant tumors are less common, with the lifetime risk for thyroid cancer (papillary or follicular type) estimated to be up to 10%.³ Pancreatic adenocarcinomas, intraductal pancreatic mucinous neoplasias (IPMNs), and acinar cell carcinomas can also be observed. Risks for other malignancies, albeit rare, include colonic and gastric carcinomas and adrenocortical carcinoma.

Gain-of-function variants in the *PRKAR1A* gene have been reported in association with autosomal dominant acrodysostosis with or without hormone resistance, a skeletal dysplasia with skeletal, endocrine, and neurological features.⁶

Inheritance Pattern:

Carney Complex is inherited in an autosomal dominant manner. At least 30-50% of *PRKAR1A* cases are estimated to be *de novo* (new).³

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *PRKAR1A* are PCR amplified and capillary sequencing is performed. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis *PRKAR1A* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of Carney Complex as outlined above. Sequence analysis is expected to identify pathogenic variants in approximately 60% of individuals with Carney Complex, while large deletions and duplications have been described.^{2,7,8}

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

References:

1. Stratakis, C. A., Kirschner, L. S. & Carney, J. A. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *J. Clin. Endocrinol. Metab.* **86**, 4041–4046 (2001).
2. Bertherat, J. *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.* **94**, 2085–2091 (2009).
3. Correa, R., Salpea, P. & Stratakis, C. A. Carney complex: an update. *Eur. J. Endocrinol.* **173**, M85-97 (2015).
4. Scherthaner-Reiter, M. H., Trivellini, G. & Stratakis, C. A. MEN1, MEN4, and Carney Complex: Pathology and Molecular Genetics. *Neuroendocrinology* **103**, 18–31 (2016).
5. Rothenbuhler, A. & Stratakis, C. A. Clinical and molecular genetics of Carney complex. *Best Pract. Res. Clin. Endocrinol. Metab.* **24**, 389–399 (2010).
6. Linglart, A. *et al.* Recurrent *PRKAR1A* mutation in acrodysostosis with hormone resistance. *N. Engl. J. Med.* **364**, 2218–2226 (2011).
7. Horvath, A. *et al.* Large deletions of the *PRKAR1A* gene in Carney complex. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **14**, 388–395 (2008).

8. Salpea, P. *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.* **99**, E183-188 (2014).
9. Stergiopoulos, S. G. & Stratakis, C. A. Human tumors associated with Carney complex and germline PRKAR1A mutations: a protein kinase A disease! *FEBS Lett.* **546**, 59–64 (2003).
10. Stratakis, C. A., Salpea, P. & Raygada, M. Carney Complex. in *GeneReviews*(®) (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).