PRKAR1A Gene Analysis in Carney Complex

Disorder also known as:
NAME Syndrome (Nevi; Atrial myxoma; Myxoid nerutofibromata; Ephilides); LAMB Syndrome (Lentigines; Atrial myxoma; Mucocutaneous myxoma; Blue nevi)

Clinical Features:
Carney Complex is a multiple endocrine neoplasia syndrome characterized by heart, endocrine, skin, and neural tumors, as well as a variety of pigmented lesions of the skin and mucosal surfaces. The disorder may involve multiple endocrine glands, in particular thyroid and adrenal cortex. Carney Complex may include Cushing syndrome and micronodular adrenocortical hyperplasia, acromegaly, breast fibroadenoma, thyroid gland abnormalities and tumors, schwannomas, and/or osteochondromyxomas. Pigmented skin nevi and lentigines occur over the entire body, including lips and conjunctiva. Lesions can be brown-black, blue, or freckles. Myxoid tumors of many types may develop on any skin surface, including eyelids. Myxomas of the heart, especially atrial myxomas, are not uncommon. Carney Complex is due to variants in the PRKAR1A gene on chromosome 17q22-q24, coding for the type 1-alpha regulatory subunit of protein kinase A. Carney Complex overlaps with Cushing disease, Primary Pigmented Nodular Adrenocortical Disease (PPNAD) and other adrenal hyperplasias, which in some patients have been associated with variants in the PDE11A gene involved in cAMP signaling.

Inheritance Pattern/Genetics:
Autosomal dominant, with onset in early childhood

Test Methods:
Using genomic DNA obtained from the submitted biological material, the 10 coding exons and splice sites of the PRKAR1A gene are screened by bi-directional sequence analysis. If no variant is found by sequencing, targeted array CGH analysis with exon-level coverage (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
In approximately 70% of cases of Carney Complex, variants in the PRKAR1A gene can be identified. In adults presenting with Cushing disease and Primary Pigmented Nodular Adrenocortical Disease (PPNAD), the frequency of variant in the PRKAR1A gene was found to be over 80%. Of those individuals without a PRKAR1A variant and PPNAD or other adrenal hyperplasias (but not Carney complex), 3 out of 15 unrelated patients were found to have a

variant in another gene on chromosome 2q31.2, PDE11A, which catalyzes the hydrolysis of cyclic nucleotides.

All of the Carney Complex and Primary Pigmented Nodular Adrenocortical Disease variants in the PRKAR1A gene identified to date are functionally null alleles, and include nonsense, frameshift, and splice-site variants. Large deletions that would not be identified by sequencing have been reported.

References:

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3. Groussin et al., Molecular analysis of the cyclic AMP-dependent protein kinase A (PKA) regulatory subunit 1A (PRKAR1A) gene in patients with Carney complex and PPNAD reveals novel mutations and clue for pathophysiology: Augmented PKA signaling is associated with adrenal tumorigenesis in PPNAD. Am J Hum Genet 71:1433-1442 (2002)
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