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Review article

Next generation immunohistochemistry: Emerging substitutes to genetic testing?

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BAP1 hereditary cancer predisposition syndrome
HPT-JT
Pancreatic neuroendocrine tumor syndrome
Mahvash disease

ABSTRACT

The identification of at-risk kindreds facilitates screening and risk reduction strategies for patients with hereditary cancer predisposition syndromes. Recently, immunohistochemistry (IHC) has emerged as a cost-effective strategy for detecting or inferring the presence of mutations in both tumors and the germline of patients presenting with tumors associated with hereditary cancer predisposition syndromes. In this review we discuss the use of novel IHC markers, including PRKAR1A, β-catenin, SDHB, fumarate hydratase and 2SC, HRASQ61R, BAP1, parafibromin and glucagon, which have either established applications or show promise for surgical pathologists to complement morphological or clinical suspicion of hereditary cancer predisposition syndromes. Specifically, we focus on Carney complex, familial adenomatous polyposis (FAP)-associated cribriform-morular variant of papillary thyroid carcinoma, familial succinate dehydrogenase-related pheochromocytoma/paraganglioma syndromes, hereditary leiomyomatosis and renal cell cancer (HLRCC), medullary thyroid cancer and Multiple Endocrine Neoplasia 2 (MEN2), BAP1 hereditary cancer predisposition syndrome, Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT), and Pancreatic Neuroendocrine Tumor Syndrome (Mahvash disease).

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Introduction

The identification of at-risk kindreds facilitates screening and risk reduction strategies for patients with hereditary cancer predisposition syndromes. Surgical pathologists play a pivotal role in the recognition of index patients from familial cancer kindreds. Historically many of the initial screening tests initiated by surgical pathologists were based on molecular assays, which are relatively expensive and may not be widely available. More recently, immunohistochemistry (IHC) has emerged as a cost-effective strategy for detecting or inferring the presence of mutations in both tumors and the germline of patients presenting with tumors associated with hereditary cancer predisposition syndromes.

Whilst the role of IHC in screening programs designed to identify patients with Lynch Syndrome presenting with colorectal or endometrial cancer is well established, IHC as a surrogate marker for molecular testing also has a role in the identification of several relatively rare and under-recognized hereditary cancer predisposition syndromes. In this review we discuss the use of novel IHC markers that can aid in the identification of hereditary cancer syndromes other than Lynch syndrome (see Table 1).

Cancer syndrome: Carney complex

Mutated gene: PRKAR1A

First described in 1985 as "the complex of myxomas, spotty pigmentation and endocrine overactivity",[1] Carney complex is a rare hereditary syndrome now characterized by myxomas in many organs, including the heart, skin, and breast; cutaneous pigmented lesions including lentigines and blue nevi; endocrine abnormalities including growth hormone–producing pituitary adenomas and primary pigmented nodular adrenocortical disease; psammomatous melanotic schwannomas; and testicular large-cell calcifying Sertoli cell tumors.[1–5] In the majority of reported cases, the syndrome occurs in an autosomal-dominant pattern with complete penetrance, although a minority of cases result from de novo mutations in the absence of a family history.[4]

The most common clinical manifestations of Carney complex are pigmented skin lesions in the form of lentigines and blue nevi, which occur in up to 80% of Carney complex patients.[6] Cardiac myxomas, occurring in up to 40% of Carney complex patients, represent the most common noncutaneous manifestations of Carney complex. In contrast to sporadic cases of cardiac myxomas, which occur predominantly in the left atrium of older females, cardiac myxomas in the setting of Carney complex can occur anywhere in the heart and affect males and females equally, with a median age of presentation of 20 years, although they have been known to occur as early as infancy.[6,7] Additionally, Carney complex-associated cardiac myxomas tend to have a higher recurrence rate than sporadic cases which typically do not recur following resection,[4,8] and are responsible for more than 50% of the disease-specific mortality of Carney complex due to cardiac outflow obstruction leading to sudden cardiac death, embolic events leading to stroke, and heart failure.[6,7] Considering the morbidity and mortality associated with cardiac myxomas, and their tendency to recur in Carney complex patients, their identification as part of the Carney complex assists both planning treatment for individual patients and counseling at risk kindreds.

In 1998, the syndrome was linked to mutations on chromosome 17,[9] and it was subsequently reported that inactivating germline mutations of the regulatory subunit type 1A (RIα) of cAMP-dependent protein kinase (*PRKAR1A*) gene located on 17q22-24, occur in over 70% of patients.[10,11] *PRKAR1A* functions as a tumor-suppressor gene; inactivating mutations and deletions in *PRKAR1A* result in unchecked cell proliferation and subsequent tumor formation in cAMP-responsive tissues.[6] Over 100 pathogenic mutations have thus far been reported,[7] and historically molecular techniques have been used to detect mutations. However, recently investigators have reported the use of IHC to detect *PRKAR1A* inactivating mutations in cardiac myxomas in Carney complex patients,[12] as well as in melanotic schwannomas.[13]

When originally investigated in the setting of cardiac myxomas, it was reported that *PRKAR1A* mutations were highly specific for Carney complex.[14–18] Maleszewski et al. recently used IHC for PRKAR1A to screen patients presenting with cardiac myxoma for Carney complex.[12] Loss of PRKAR1A expression in neoplastic cells was found in all 7 Carney complex-associated myxomas evaluated. In contrast, retained expression of PRKAR1A was demonstrated in 70 of 103 (68%) sporadic myxomas. However, 9 of 32 (28%) evaluable PRKAR1A IHC negative but apparently sporadic myxomas were found to harbor somatic *PRKAR1A* mutations, and, all four cases with available germline DNA lacked germline mutations, suggesting that the mutations were indeed somatic in nature. That is, the findings indicate that whilst positive staining for PRKAR1A can be used to argue strongly against a diagnosis of Carney complex, loss of PRKAR1A expression by IHC may be observed in cardiac myxomas associated with both germline and somatic mutations and therefore does not confirm Carney complex.

Melanotic schwannomas are also a feature of Carney complex. Grossly, they are black, brown, or blue, well-circumscribed, solid or spongy masses.[19] Histologically, the tumors are circumscribed but incompletely encapsulated and are composed of variably ovoid, short spindled, or epithelioid cells often containing abundant melanin, arranged in a sheet-like and occasionally whorled or palisading pattern, with psammoma bodies in a subset of cases, more common in patients with Carney complex (Fig. 1).[19] By IHC, they are positive for S-100 protein and SOX10.[19] Torres-Mora et al. investigated PRKAR1A expression in melanotic schwannomas and found loss of expression in 7 of 21 (33%) unselected cases not associated with Carney complex.[13] The authors suggested that some of these patients may have a *forme fruste* of Carney complex, but it is also possible that, similar to cardiac myxomas, melanotic schwannomas may be associated with both somatic and germline *PRKAR1A* abnormalities. A more recent study by Wang et al. identified *PRKAR1A* mutations in all 12 melanotic schwannomas evaluated.[20] It therefore seems likely that *PRKAR1A* mutations (and loss of protein expression) are a feature of both sporadic and Carney complex-associated melanotic schwannomas. In summary, whilst the use of IHC for PRKAR1A awaits further validation, this technique shows some promise, particularly in the evaluation of cardiac myxomas to exclude Carney complex.

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