The adrenal gland: an evolution of the roles of genetic counsellors and medical geneticists in endocrine cancers

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Abstract

Endocrine cancers comprise a large proportion of the manifestations of hereditary cancer syndromes. Genetic counselling with a medical genetics assessment is central to the clinical care of such individuals and families. With advances in genetic technologies and the increasing number of known loci, the role of the genetics team is evolving. We discuss these roles by comparing and contrasting two endocrine disorders, pheochromocytoma/paraganglioma and adrenocortical carcinoma.

Keywords adrenocortical carcinoma; genetic counselling; hereditary cancer syndromes; medical genetics; paraganglioma; pheochromocytoma

Introduction

Hereditary cancer syndromes confer an increased risk of developing cancer and tumours due to constitutional alterations in the genome or epigenome. When most recently catalogued in 2008, over 50 such syndromes were described.[1] Endocrine malignancies are either a prominent feature or an associated manifestation of many hereditary cancer syndromes. Frequently affected glands include the thyroid, parathyroid, adrenal, extra-adrenal paraganglia and pituitary, often with involvement of multiple endocrine systems Table 1.[1] Genetic counsellors and medical geneticists frequently play prominent roles in the care of individuals with hereditary cancer syndromes, providing genetic counselling, facilitating molecular genetic testing and interpretation, identifying family members at risk and providing management and surveillance recommendations.

Genetic counselling, management and surveillance can be straightforward for many cancer syndromes. However, patients presenting with endocrine-related cancers can be particularly challenging, due to genetic heterogeneity and pleiotropic extra-endocrine manifestations. This situation is exemplified in hereditary cancer syndromes affecting the adrenal gland and related organs such as pheochromocytoma/paraganglioma (PPGL, Table 2)[2] or adrenocortical carcinoma (ACC, Table 3).[3] The American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counsellors (NSGC) recommend all individuals with an ACC or PPGL be referred for a genetics assessment.[4] Here, we will review a general approach to the patient with a suspected hereditary cancer syndrome and then discuss the evolving role of genetics professionals in these complex hereditary endocrine neoplasms by comparing and contrasting the approach in hereditary ACC and PPGL.

Identification of patients at risk of a hereditary cancer syndrome

Hereditary cancer syndromes should be considered when a number of features are apparent when assessing the family and personal history of an affected individual. Most adult hereditary cancer syndromes follow an autosomal dominant (AD) transmission where multiple individuals are affected in successive generations. Early age of onset, multiple primary cancers, bilateral and multifocal cancers, and multiple benign lesions are all characteristics that can be suggestive of a hereditary cancer syndrome.[5] While single gene testing can be appropriate in some cases, multi-gene cancer panels are now being used to avoid lengthy iterative serial testing of individual genes and in atypical cases which previously would have gone undiagnosed. In addition to these traditional routes of identifying patients at risk of harbouring a germline pathogenic variant/mutation, novel forms of hereditary cancer syndrome identification are emerging due to the clinical application of genomic analyses. For example, patients with advanced cancers are beginning to undergo somatic tumour molecular profiling to guide systemic therapy. These somatic findings are often compared to germline DNA (peripheral blood lymphocytes or other normal tissue), thereby diagnosing a hereditary cancer syndrome in an individual who did not receive formal genetic counselling.[6] Another example is diagnostic whole exome sequencing which is conducted for a number of clinical indications such as neurodevelopmental disorders and congenital malformations. Here, sequencing of the entire coding region of all ~30,000 genes in the human genome is conducted and may inadvertently diagnose a patient or family with a familial cancer syndrome as the result of an incidental or

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Hereditary cancer syndromes with a predominant endocrine phenotype

Syndrome	Gene	Medullary thyroid	Parathyroid	Pituitary	Pheochromocytoma	Gastro-entero pancreatic neuroendocrine
Multiple endocrine neoplasia type 1 [MEN1]	*MEN1*		X	X	X	X
Multiple endocrine neoplasia type 2 [MEN2]	*RET*	X	X		X	
Multiple endocrine neoplasia type 4 [MEN4]	*CDKN1B*		X	X		
Hyperparathyroidism-Jaw Tumour syndrome	*HRPT2*		X			
Familial isolated hyperparathyroidism	*MEN1*		X			
	CaSR					
	HRPT2					
Familial isolated pituitary adenoma	*AIP*			X		

X signifies relevance to the disorder.

Table 1

secondary finding.[7] These examples provide unique legal and ethical challenges regarding genetic counselling and clinical research. We have identified several families with hereditary cancer syndromes in our adult and paediatric clinics through these novel routes, and have found offering an "opting-in" consent successful. Irrespective of the route of ascertainment, a genetics assessment is merited in individuals who are at risk of harbouring a mutation in a cancer predisposition gene and should be offered to all individuals with an ACC or PPGL. Here, we will illustrate evolving practices in genetic counselling and medical genetics using these two endocrine sites as examples.

Genetic counselling in cancer genetics

The NSGC recommends that hereditary cancer risk assessments include several essential elements:[5] intake/information gathering, cancer risk assessment, informed consent, psychosocial assessment, selection of the most appropriate diagnostic investigations (genetic and non-genetic), and disclosure of genetic test results. The intake process should include a personal and three-generation family history with particular attention to manifestations of the suspected hereditary cancer syndromes and gathering of supporting documentation such as pathology reports and other investigations on the proband (affected individual) and family members. A physical examination, additional diagnostic investigations such as radiology, further pathologic analysis of tumour (such as microsatellite instability studies, immunohistochemical analysis of proteins), biopsies of other lesions, and referrals to other specialists may be required for an accurate risk assessment. While empiric calculators are available for a number of hereditary cancer syndromes that can estimate the likelihood of finding a genetic mutation (http://riskfactor.cancer.gov/cancer_risk_prediction/about.html), they should not replace expert clinical suspicion of a hereditary aetiology. Importantly, for certain hereditary cancer syndromes, fulfilment of clinical diagnostic criteria is sufficient to identify patients and families as having a hereditary cancer syndrome regardless of the results of molecular testing. This is due to the limitations of current genetic technologies, non-Mendelian inheritance patterns (e.g. low penetrance or maternal imprinting) and our incomplete understanding of all hereditary cancer loci. Examples related to ACC and PPGL will be further elaborated.

If a formal risk assessment raises the suspicion of a hereditary cancer syndrome, the appropriate genetic test should be selected. This can range from targeted familial mutation testing, founder mutation testing in certain ethnicities, single gene analysis, chromosomal analysis, epigenetic assays, to large multi-gene panels. Whole exome sequencing is also being conducted on cancer cases in many research setting and may be used in hereditary cancer pedigrees in the near future. The American Society of Clinical Oncology recommends offering genetic testing for a cancer predisposition gene only after a number of conditions have been met:[8] 1) the genetic test can be adequately interpreted; 2) testing will influence the management of the patient or other relatives; 3) the potential benefits outweigh the risks; 4) testing is voluntary; and 5) the individual seeking testing or the legal proxy provides informed consent.[5]

A variety of elements are required for pre-test genetic counselling and to establish informed consent. An explanation of the purpose of the test and identification of the appropriate