



# Cancer Genetics Gazette



A newsletter for specialist clinicians from the Familial Cancer Unit

November 2008 | Issue 6

Welcome to the 2nd edition of the Cancer Genetics Gazette for 2008. The feature article in this edition is '**Genetic assessment of pheochromocytoma**' by Dr Carolyn Petersons and Dr Morton Burt. We hope you find this issue useful and informative.

## In focus

### Genetic assessment of pheochromocytoma

Pheochromocytoma are rare tumours arising from catecholamine-producing chromaffin cells in the adrenal medulla. The term paraganglioma is used to define extra-adrenal tumours arising from sympathetic or parasympathetic ganglia, with only sympathetic paraganglioma producing catecholamines. In addition to a risk of malignancy, excess catecholamine production from pheochromocytoma and paraganglioma can cause debilitating symptoms, hypertensive crises and increased mortality. This article reviews the genetic syndromes associated with pheochromocytoma and catecholamine-producing paraganglioma and suggests an approach to screening for relevant genetic abnormalities.

Recent studies have determined that germline mutations are more frequently associated with pheochromocytoma than originally thought. Historically, 10% of pheochromocytoma were considered familial. However, it is now apparent that up to 30% of all tumours, including 10-25% of apparently sporadic cases, arise secondary to a germline mutation. Recognition of the true incidence of familial pheochromocytoma, coupled with the availability of appropriate genetic analysis, has mandated a greater role for genetic testing in this condition.

Familial catecholamine-producing tumours are associated with von Hippel-Lindau disease (VHL), multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1) and mutations in subunits B and D of the succinate dehydrogenase (SDH) gene. The clinical features associated with each condition are outlined in the Table. These germline mutations have an autosomal dominant mode of inheritance and, with the exception of the RET proto-oncogene in MEN2, all are tumour suppressor genes. Genetic testing is available for VHL, RET and SDH genes, while the diagnosis of NF1 is usually based on clinical criteria.

In addition to the syndromic features, several other factors can suggest a germline mutation. The development of pheochromocytoma at a young age suggests a familial syndrome, with the majority of patients presenting by age 40. The presence of multiple tumours or bilateral adrenal disease occurs more commonly in familial syndromes. Malignant tumours, especially paraganglioma, are frequently associated with SDHB mutations. The presence of one or more of these characteristics should prompt consideration for genetic testing.

The optimal and most cost-effective strategy for genetic testing in pheochromocytoma is still debated. Some recommend that genetic testing be performed in all patients. Others advocate limiting testing to patients at greater risk of a germline mutation,

such as those with associated clinical features, a positive family history, young age at presentation, multiple tumours or malignancy. Clinical features, tumour characteristics and the pattern of catecholamine production can be used to guide appropriate genetic testing. For example, pheochromocytoma in MEN2 are invariably benign and produce adrenaline. Therefore, it is unnecessary to test for a RET mutation in patients with a malignant tumour or one predominantly producing noradrenaline. The First International Symposium on pheochromocytoma recommended an approach to genetic testing, as outlined in the Figure.

Detection of a germline mutation provides important information that enhances clinical management. Firstly, identification of a genetic abnormality can prompt early treatment or screening for associated clinical conditions. This is particularly relevant in MEN2, where prophylactic thyroidectomy can prevent medullary thyroid cancer. Secondly, patients with some genetic syndromes are at greater risk of recurrence, multiple tumours or malignancy. The detection of SDHB mutation is of major prognostic significance, as approximately 50% of these patients develop malignant disease. Most importantly, the discovery of a germline mutation in an index case allows genetic testing of first-degree relatives, which should only be undertaken following appropriate genetic counselling. Genetic testing will provide reassurance for family members without a germline mutation and facilitates early diagnosis and recognition of associated disease in those with a positive result.

In summary, germline mutations underlie the development of pheochromocytoma and catecholamine-producing paraganglioma in up to 30% of cases, including a significant proportion of apparently sporadic cases. Recognition that a patient harbours a germline mutation can promote early diagnosis of associated disorders, provide prognostic information and give relatives an opportunity to have predictive genetic testing to establish their carrier status. Consideration should be given for genetic testing in all patients with catecholamine-producing tumours, especially those with high risk clinical features. Genetic screening should always be performed in close consultation with an appropriate genetic expert.

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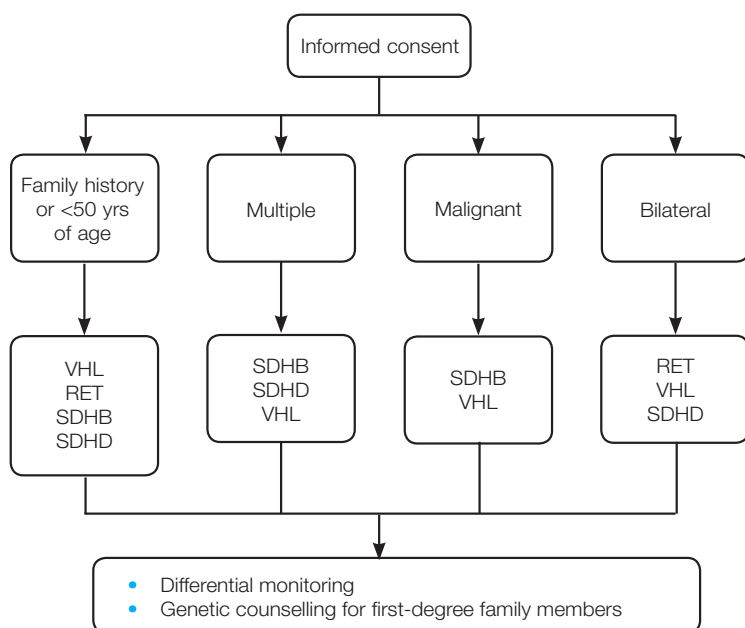
#### Dr Morton Burt MBChB FRACP PhD

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**Table: Familial pheochromocytoma and paraganglioma syndromes**

Gene	Syndrome	Common tumour characteristics	Associated clinical features
VHL	Von Hippel-Lindau disease	Bilateral adrenal	<ul style="list-style-type: none"> <li>• Haemangioblastoma of CNS and retina</li> <li>• Tumours and/or cysts of:               <ul style="list-style-type: none"> <li>• Kidney</li> <li>• Pancreas</li> <li>• Epididymis</li> <li>• Endolymphatic sac</li> </ul> </li> </ul>
RET	Multiple endocrine neoplasia type 2	Bilateral adrenal	<ul style="list-style-type: none"> <li>• Medullary thyroid cancer</li> <li>• Hyperparathyroidism</li> <li>• Ganglioneuroma</li> <li>• Marfanoid habitus</li> </ul>
NF1	Neurofibromatosis type 1	Solitary adrenal	<ul style="list-style-type: none"> <li>• Café-au-lait spots</li> <li>• Neurofibroma</li> <li>• Iris hamartoma</li> <li>• Freckling - inguinal and axillary</li> </ul>
SDHB	Succinate Dehydrogenase B	Extra-adrenal >50% malignant	Renal cell carcinoma
SDHD	Succinate Dehydrogenase D	Multiple intra- and extra-adrenal tumours	

**Figure: Proposed algorithm for genetic testing in patients with catecholamine-producing tumours**



**Reference**

Pacak K et al. Pheochromocytoma: recommendations for clinical practice from the First International Symposium. *Nature Clinical Practice* 2007; 3(2):92-102.

## New resource

**Risk management options for women at increased risk of developing ovarian cancer: Information booklet and decision aid** - this resource was developed by Hereditary Cancer Clinic at Prince of Wales Hospital, Centre for Genetics Education (NSW) and Cancer Council NSW. This booklet provides useful information and a structured decision aid for patients to work through their options (including risk-reducing surgery). Available from **Cancer Council Helpline 13 11 20**.

# How to access genetic testing for familial pheochromocytoma and paraganglioma syndromes

The Familial Cancer Unit offers genetic counselling and genetic testing for familial pheochromocytoma and paraganglioma syndromes in South Australia. Familial Cancer Clinics are held at most major public hospitals in Adelaide and in some regional centres (Port Augusta and Mount Gambier).

The services provided by the Familial Cancer Unit include

- expert cancer risk assessment by a clinical geneticist
- genetic counselling
- information and advice about cancer prevention and early detection
- genetic testing.

At Flinders Medical Centre the service includes a combined appointment with an endocrinologist and a clinical geneticist.

Referral letters should be addressed to Dr Graeme Suthers or Dr Nicola Poplawski and sent to the:

Familial Cancer Unit,  
SA Pathology,  
Women's and Children's Hospital  
72 King William Road, North Adelaide SA 5006  
t 08 8161 6995  
f 08 8161 7984  
e cywhs.famcancer@health.sa.gov.au

Please include the patient's particulars (name, date of birth, address, contact number) and as much information as you have about their personal and family history of cancer.

## Go green

If you prefer to receive the Cancer Genetics Gazette electronically please email your request to [genetics@cancersa.org.au](mailto:genetics@cancersa.org.au)

## Feedback?

If you have any feedback from this edition or suggestions for future editions please send them to Kirsty Stallard, Cancer Genetics Education Project Officer at [genetics@cancersa.org.au](mailto:genetics@cancersa.org.au)

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