When should genetic testing be obtained in a patient with phaeochromocytoma or paraganglioma?

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Summary

About 30% of phaeochromocytoma and paraganglioma patients harbour a germline mutation in one of the known susceptibility genes and in more than one-third of these patients there is no family history for these tumours. The genetic classification, risk assessment and specific management of the patients and at risk family members play an important role in preventive medicine. Distinct diagnostic or therapeutic approaches related to the genetic testing results are and will be even more relevant in the future for the detection of mutation carriers. In addition to a positive family history, other clinical features such as young age at time of manifestation, multifocal tumours and specific tumour location are highly associated with the presence of a germline mutation – genetic testing in these cases should be mandatory. Since several genes are involved in the genetics of phaeochromocytoma and paraganglioma, prioritizing which gene(s) to be tested first by using simple clinical information can reduce the efforts and costs of this analysis. The clinicians offering and performing the genetic testing should provide or make available adequate counselling as well as access to preventive and surveillance options to patients. Collaboration with referral centres and research groups in this field can help to coordinate the management of these patients.

Introduction

phaeochromocytomas and paragangliomas form the group of tumours which can occur in any paraganglia from the skull base to the pelvic floor. The World Health Organization (WHO) terminology considers as phaeochromocytoma the paraganglial tumours located in the adrenal medulla and use the term paraganglioma for all other locations. From a clinical point of view, the distinction between sympathetic-derived (‘chromaffin’) paraganglial tumours of adrenal gland or extra-adrenal abdominal, pelvic and thoracic location, and the parasympathetic-derived (‘non-chromaffin’) head and neck paraganglial tumours is more practical. Therefore, we prefer and use here the term ‘phaeochromocytoma’ for the sympathetic-derived paraganglial tumours, which are usually hormonally active and especially pertinent to endocrinologists and visceral surgeons; we assign the term ‘paraganglioma’ to the mainly hormonally inactive tumours and managed by head and neck surgeons. The difference between both types of tumours (phaeochromocytoma and paraganglioma) is also reflected in the genetics.

The ‘classic’ phaeochromocytoma related syndromes (e.g. neurofibromatosis type 1 [NF 1, MIM#162200], multiple endocrine neoplasia type 2 [MEN 2, MIM#171400], and von Hippel-Lindau [VHL, MIM#193300]) are associated almost exclusively with phaeochromocytomas. Only extremely few cases of head and neck paragangliomas have been described within these syndromes.

For paraganglial tumours three other syndromes have been recently clarified genetically: paraganglioma syndrome type 1 (PGL 1, MIM#168000); paraganglioma syndrome type 3 (PGL 3, MIM#605373); and, paraganglioma syndrome type 4, (PGL 4, MIM#115310). The genes involved code for three of the four subunits of the succinate dehydrogenase (SDH) enzyme: SDHD, SDHC and SDHB subunit genes, respectively. While PGL 1 and PGL 4 are associated with both phaeochromocytoma and head and neck paraganglioma, PGL 3 is almost exclusively characterized by head and neck paraganglioma manifestation.

All these syndromes are of autosomal dominant inheritance, but for PGL 1 a parent of origin effect (mimicking imprinting) has been reported by many examples; only children who inherit the mutation from the father are clinically affected.

Genetic testing

The frequency of germline mutations is about 25–30% for phaeochromocytoma (NF1, VHL, RET, SDHB, SDHD genes) and up to 35% for head and neck paraganglioma (SDHB, SDHC, SDHD genes). The NF 1 patients (and in part the MEN 2 and VHL patients) usually have either personal or clear family history for these syndromes at the time of phaeochromocytoma/paraganglioma
diagnosis. Excluding this group of patients with a positive family history, the rate of undetected syndromic cases among patients with apparently sporadic tumour manifestation is still considerable (> 10%). For risk assessment purposes and further patient management it is necessary to detect such patients. In addition, genetic screening of relatives for a given mutation can be used to detect other at-risk probands or already affected asymptomatic subjects.

Who should be tested?

The patients with phaeochromocytoma and/or paraganglioma fulfil the recommendations for testing according to the American Society of Clinical Oncology Policy Statement, and ideally all patients should undergo genetic screening for germline mutations in the susceptibility genes. But the reality is somewhat different. The availability of genetic counsellors and genetic laboratories experienced with these syndromes, especially the PGL syndromes, is restricted in some countries. Furthermore, the costs of such analyses are not always or not completely covered by the health insurance companies. Therefore, whenever possible, simple clinical features could be used for preselection of ‘high-risk for mutations’ patients. For example, it is highly recommended to test patients with positive family or personal history for paraganglial tumours or tumours associated with the related syndromes (Table 1). In addition, patients in which the tumour occurred at a young age (≤ 40), those with multiple tumours, and those with an extra-adrenal located phaeochromocytoma have to be regarded at high risk for germline mutations in the candidate genes. Malignant tumours are not highly associated with the presence of an inherited disorder, but there are some indications that prognosis between the sporadic and the syndromic cases as well as between the different gene-associated syndromes is different and it could be useful to perform a molecular classification for this reason.

For example, there are some indications that malignant tumours in SDHB mutation carriers have a worse prognosis in terms of survival, and, therefore, screening can be helpful for better prognosis assessment. In our experience and based on the published data, the vast majority of the detected mutation carriers harbour one of these clinical ‘predictors’.

When to test the patient?

Currently genetic screening is performed after the diagnosis and primary treatment have been completed. Considering the incomplete knowledge about these syndromes, the variable expression, and the variable tumour penetrance, it is under debate if and how the genetic classification should influence the management of patients with known tumours. Some potential consequences have to be considered.

In the case of a phaeochromocytoma, the genetic classification could drive the clinician to a more meticulous approach in detection of other undetected concomitant paraganglial tumours or tumours related to the respective syndrome before treatment. In addition, a false interpretation of multifocality as malignancy has been observed and here the genetic classification might help to reconsider the correct diagnosis. This information can be potentially useful for the surgeon and impact the surgical approach – for example, this knowledge may affect the number of operations for tumour resection as well as the surgical technique. Further, adrenal-sparing surgery is highly recommended in the syndromic cases because of the risk of future involvement of the contralateral adrenal to prevent a subsequent adrenal insufficiency.

While for phaeochromocytoma tumour removal should be performed whenever possible, for head and neck paraganglioma patients the genetic classification could affect the decision making process between a ‘wait and scan policy’ and surgical removal in patients that are at high risk for post-surgical complications of the diagnosed paraganglioma. Of importance, diagnosis of a concomitant undetected phaeochromocytoma before head and neck paraganglioma surgery might prevent intra-operative complications because of a pharmacologically or stress-induced hypertensive crisis.

Which genes should be tested?

First, a meticulous family history and clinical examination should be performed. If other clinical features or family history for NF 1 are absent, testing for mutations in this gene should not be done.

Phaeochromocytoma patients should be screened for mutations in RET, VHL, SDHB and SDHD genes. For the RET gene, almost

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**Table 1.** Hereditary syndromes associated with phaeochromocytoma and paraganglioma

<table>
<thead>
<tr>
<th>Hereditary syndromes</th>
<th>Gene (chromosome)</th>
<th>Manifestations</th>
</tr>
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<tbody>
<tr>
<td>Multiple endocrine neoplasia 2 (MEN2)</td>
<td>c-RET (10q11.2)</td>
<td>Medullary thyroid carcinoma (95%), phaeochromocytoma (50%), primary hyperparathyroidism (10%)</td>
</tr>
<tr>
<td>Von Hippel-Lindau (VHL)</td>
<td>VHL (3p25–26)</td>
<td>Retinal angiomas (55%), central nervous system haemangioblastoma (55%), phaeochromocytoma (30%), renal cysts (75%), renal cell carcinoma (25%), pancreatic cysts (15%), pancreatic islet-cell tumour (3%)</td>
</tr>
<tr>
<td>Neurofibromatosis type 1 (NF1)</td>
<td>NF1 (17q11.2)</td>
<td>Café-au-lait-spots (70–100%), neurofibroma (≥ 2 or 1 plexiform) (30%), axillary and inguinal freckling, Lisch-nodules (≥ 2) (33–95%), skeletal anomalies, phaeochromocytoma (1–3%), vascular anomalies</td>
</tr>
<tr>
<td>Paraganglioma syndrome type 1 (PGL1)</td>
<td>SDHD (11q23)</td>
<td>Phaeochromocytoma, head and neck paraganglioma, GIST</td>
</tr>
<tr>
<td>Paraganglioma syndrome type 3 (PGL3)</td>
<td>SDHC (1q21)</td>
<td>Phaeochromocytoma, head and neck paraganglioma, GIST</td>
</tr>
<tr>
<td>Paraganglioma syndrome type 4 (PGL4)</td>
<td>SDHB (1p36)</td>
<td>Phaeochromocytoma, head and neck paraganglioma, GIST, renal cell carcinoma</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumour; SDH, succinate-dehydrogenase, subunits B, C and D.
all MEN 2 patients harbour a mutation in exons 10 and 11, but only occasionally in exons 9, 13–16. Consideration about screening for SDHC gene mutations should be restricted for familial cases after exclusion of mutations in the genes VHL, RET, SDHB and SDHD.\textsuperscript{7,24}

In contrast to patients with phaeochromocytoma, patients with head and neck PGL in absence of personal or family history for VHL or MEN 2, should only be screened for mutations in the SDHB, SDHC and SDHD genes.\textsuperscript{5,6}

Prioritizing the gene to be tested might save time and reduce the costs of the screening (Fig. 1). Patients presenting personal or family history for MEN 2 or VHL should be screened for mutations only in RET and VHL, respectively.\textsuperscript{15}

For phaeochromocytoma patients, extra-adrenal location is associated mainly with SDHB, while adrenal location with VHL and RET mutations. Multifocal tumour manifestations are characteristic of the SDHD and VHL mutation carriers. In case of proven malignancy SDHB should be tested first.

Regarding head and neck paraganglioma, the multiple and benign tumours are mainly associated with the SDHD mutations, while SDHB gene carriers rarely develop multiple tumours.

To date, patients have not been described with mutations in more than one gene or several mutations within one gene. Therefore, once the mutation has been found, the screening should be stopped.

Why test?

At the current state of knowledge, consequences of genetic testing have to be drawn mainly for aftercare. Therefore, before performing or offering the genetic testing, physicians should always consider, if they are able to provide or make available adequate genetic education and counselling as well as access to preventive and surveillance options.\textsuperscript{14} Aftercare for these syndromes includes life-long clinical follow-up for appearance of new tumour manifestations in 1–3 years of intervals. Aftercare also includes genetic counselling and screening for the specific mutation in other family members to detect relatives at risk for hereditary tumour, who should receive the same follow-up program as the index patient.

In addition, negative germline testing in young patients and in patients with multiple paraganglial tumours is important. The presence of other yet to be identified genes has been demonstrated in phaeochromocytoma and paraganglioma patients and considerations about aftercare management for ‘at high-risk for mutations’ patients should be taken into account by the physician.\textsuperscript{22–24}

The genetic diagnosis is irreversible and the physician should be aware of the personal and social impact of such a diagnosis.\textsuperscript{14} Currently the risk is thought to be life-long, but some observed data in the follow-up within specific families argue against this assumption. Future long-term follow-up studies will be able to clarify this issue. The consequences, which include benefits as well as negative aspects, of the currently offered clinical screening and management are still under investigation. For this purpose research groups are trying to retrieve retrospective information as well as follow-up data to create a precise risk spectrum and improve the managements of these patients.

Therefore, it is very important for the physician dealing with such patients to be in contact with an experienced referral centre and to collaborate in research projects for these rare syndromes. Only in this way will the knowledge of these syndromes improve and adequate evidence-based overall approach be optimized.

In summary, we believe that practitioners should discuss genetic testing with all patients with phaeochromocytoma and/or paraganglioma, but it is mandatory to recognize and perform testing in the ‘at high at-risk for mutations’ subjects and offer them adequate counselling and consequent management.

References


