Gene Targeting through O-Methylated Catecholamine Metabolite Patterns

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Pheochromocytomas and paragangliomas are rare tumors of neuroendocrine tissue that have a prevalence in postmortem studies of approximately 1 in 2000 (1) and an estimated annual incidence of 500–1100 in the US. They may occur within the adrenal medulla or anywhere in the sympathetic chain. Pheochromocytoma has been called the “10% tumor” because approximately 10% occur outside the adrenal medulla, about 10% are bilateral, and 10% are malignant. The clinical features of pheochromocytomas, which are due to the secretion of catecholamines, include episodes of hypertension associated with symptoms such as headache and palpitations, although sustained hypertension may also occur. The main danger is sudden death through hypertensive crises or arrhythmia, either in the community or in the hospital in situations such as surgery. About 90% of cases can be cured. Paragangliomas are more rare than pheochromocytomas and tend to present as space-occupying lesions, with metastases often present at diagnosis. Both types of tumors are associated with conditions that are inherited in an autosomally dominant manner, such as: multiple endocrine neoplasia type 2 (MEN2),2 which is due to a mutation in the RET3 (ret proto-oncogene) protooncogene; von Hippel–Lindau disease (VHL), which is due to a mutation in the VHL (von Hippel–Lindau tumor suppressor) gene; neurofibromatosis type 1 (NF1), caused by mutation in the NF1 (neurofibromin 1) gene; and mutations in succinate dehydrogenase (SDH) subunits B, C, and D, which are encoded by the SDHB [succinate dehydrogenase complex, subunit B, iron sulfur (Ip)], SDHC (succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa), and SDHD (succinate dehydrogenase complex, subunit D, integral membrane protein) genes. Individuals known to have one of these conditions because of family history or phenotype, or because it had been identified through predictive mutation testing, are offered lifelong surveillance with imaging analysis (e.g., computed tomography or magnetic resonance imaging) and biochemical testing for the presence or development of these tumors so that timely, appropriate surgical management can be offered. Although the majority of patients with pheochromocytomas have no family or medical history suggesting an inherited condition, up to one-third of patients have an identifiable germline mutation in one of these genes, and a pheochromocytoma may be the first or only manifestation of the condition. It is important to the patient that heritable conditions be identified, because other clinical features associated with the condition, such as medullary thyroid cancer and hyperparathyroidism in MEN2, may require management. It also allows the patient’s relatives to undergo predictive testing and thus appropriate surveillance to detect and treat pheochromocytomas and other malignancies if a mutation is present. Screening all the possible genes is not yet practicable, because it is expensive and time-consuming. Interpreting the results of mutation analysis can be problematic, however, because mutations of unknown clinical relevance may be identified. Sometimes it is possible to predict the phenotype from the type of mutation or the particular amino acids involved, but in some situations it will be necessary to study the whole family to discover whether the mutation segregates with the presumed phenotype. At present, therefore, targeted screening is indicated for patients with pheochromocytomas and paragangliomas.

The diagnosis of pheochromocytoma relies mainly on biochemical testing. The major catecholamines—secreted by pheochromocytomas are epinephrine and norepinephrine, although some tumors contain and secrete large amounts of dopamine. Because of the episodic nature of their secretion and the hormones’ short half-lives in the plasma, the concentrations of free catecholamines are extremely variable in both plasma and urine. The main metabolites of these 3 hormones—metanephrine (MN), normetanephrine (NMN), and 3-methoxytyramine (3MT)—have much longer half-lives, are continuously produced, and are

1 Department of Clinical Biochemistry, John Radcliffe Hospital, Oxford, UK.
2 Nonstandard abbreviations: MEN2, multiple endocrine neoplasia type 2; VHL, von Hippel–Lindau disease; NF1, neurofibromatosis type 1; SDH, succinate dehydrogenase; MN, metanephrine; NMN, normetanephrine; 3MT, 3-methoxytyramine.
3 Human genes: RET, ret proto-oncogene; VHL, von Hippel–Lindau tumor suppressor; NF1, neurofibromin 1; SDHB, succinate dehydrogenase complex, subunit B, iron sulfur (Ip); SDHC, succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa; SDHD, succinate dehydrogenase complex, subunit D, integral membrane protein.
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therefore more reliable for identifying the presence of pheochromocytomas. Although other metabolites, such as homovanillic acid and hydroxymethylmandelic acid have been used for diagnosis in the past, it is now agreed that MN, NMN, and 3MT have much better sensitivity and specificity. Although the total metanephrine concentration has been used in the past, the current recommendation is for split metanephrines (MN and NMN) to be reported, because this approach enhances the sensitivity of the test. The sensitivities of measuring these analytes in plasma and 24-h urine samples approach 100% (2, 3), but plasma is now the preferred medium for analysis because it offers better specificity than urine (4). Although the process of collecting plasma requires that the patient be kept supine for at least 20 min, sample preparation, and rapid separation of the sample, collecting 24-h urine samples is even more inconvenient for the patient and is subject to many errors.

In a study reported in this issue of Clinical Chemistry (5), Eisenhofer and colleagues examined the pattern of plasma MN, NMN, and 3MT in patients with known genetic mutations associated with pheochromocytoma. Among 173 patients with pheochromocytomas, those with MEN2 or NF1 had higher plasma MN concentrations than those with VHL or SDH mutations, whereas those with SDH mutations had higher plasma 3MT concentrations than those with VHL. A combination of all 3 plasma markers perfectly discriminated between MEN2 and NF1 patients and patients with VHL and SDH mutations, whereas 3MT results correctly classified VHL and SDH mutations 78% of the time. These results were consistent with the concentrations of catecholamines in the tumors themselves, with epinephrine being the major component in tumors from MEN2 and VHL patients and dopamine being a major component of tumors from individuals with SDH mutations.

This report is important because it suggests that the pattern of O-methylated catecholamine metabolites can help clinicians target the genes to be examined for mutations among patients who present with a pheochromocytoma but with no other clinical features or family history to suggest an underlying inherited condition. This ability is desirable because it may make searching for a cause in pheochromocytoma more cost-effective in cases for which the family history and clinical findings are unhelpful. A problem in generaliz-

ing the data from this report to a diagnostic approach is that the diagnosis was known for all of the cases examined in this series, and so the utility of this approach needs to be confirmed with a series of patients whose mutation status is unknown at the time of diagnosis of the pheochromocytoma. It is likely, as the authors point out, that more genes that confer susceptibility to developing pheochromocytoma will be identified, and thus the pattern of catecholamine metabolites in these cases will also need to be examined. As the costs of mutation analyses fall and turnaround times improve, one may expect the results of a mutation analysis for several genes to be available within a few days of the diagnosis to guide the management of the patient and the predictive testing of relatives. Improving our knowledge of the effects of new mutations will also help us to identify clinically relevant mutations and thus to interpret the results of genetic analyses.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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