Journal of Clinical Endocrinology & Metabolism
jcem.endojournals.org

doi: 10.1210/jc.2005-2758
The Journal of Clinical Endocrinology & Metabolism **March 1, 2006** vol. 91 no. 3 **790-792**

EDITORIAL

Paraganglioma—All in the Family

William F. Young Jr, M.D., M.Sc. and Abbie L. Abboud, M.S., CGC

- Author Affiliations

Division of Endocrinology, Diabetes, Metabolism, and Nutrition (W.F.Y.), Mayo Clinic, Rochester, Minnesota 55905; and Public Health Laboratory, Minnesota Department of Health (A.L.A.), St. Paul, Minnesota 55155

Address all correspondence and requests for reprints to: Dr. William F. Young, Jr., Mayo Clinic College of Medicine, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: young.william@mayo.edu.

Familial paraganglioma is a rare syndrome characterized by slow-growing tumors derived from paraganglia tissue in the head and neck, thorax, abdomen, and pelvis. Recent years have brought significant progress in identifying the genetic etiology of this syndrome. Disease-causing mutations in three genes (*SDHB*, *SDHC*, and *SDHD*) encoding subunits of succinate dehydrogenase (SDH), or mitochondrial complex II, are responsible for most cases of familial paraganglioma (1, 2). SDH has important functions in the Krebs cycle and the mitochondrial respiratory chain. Understanding the relationship between mutations in *SDHB*, *SDHC*, and *SDHD* and the clinical manifestations of familial paraganglioma assists in management, genetic testing, and appropriate genetic counseling.

Of all the clinical aspects of familial paraganglioma, one of the most interesting is that a proportion of the tumors secrete catecholamines. The occurrence of catecholamine hypersecretion depends on tumor location; approximately 5% of head and neck paragangliomas and most abdominal paragangliomas produce clinically significant hormones (3). In both clinical and research settings, catecholamine-secreting tumors should be further defined: pheochromocytomas arise from chromaffin cells of the adrenal medulla, and extraadrenal catecholamine-secreting paragangliomas (extraadrenal pheochromocytomas) arise from the sympathetic ganglia (4). Because the two types of catecholamine-secreting tumors have similar clinical presentations and treatment approaches, many clinicians use the term pheochromocytoma to refer to both adrenal pheochromocytomas and extraadrenal catecholamine-secreting paragangliomas. However, the distinction between a true pheochromocytoma and a paraganglioma is important because the specific diagnosis has implications for associated neoplasms, risk of malignancy, and genetic testing algorithms.

Approximately 15–20% of patients with catecholamine-secreting tumors have germline mutations (inherited mutations present in all cells of the body) in genes associated with disease (5, 6, 7). The most frequent germline mutations identified in patients with pheochromocytoma are in the genes associated with von Hippel Lindau disease, multiple endocrine neoplasia type 2 (MEN type 2), and neurofibromatosis type 1. The most frequent germline mutations found in patients with extraadrenal catecholamine-secreting paragangliomas are in the genes associated with familial paraganglioma, von Hippel Lindau disease, and, rarely, MEN type 2 or neurofibromatosis type 1 (3).

By studying families with *SDHB*, *SDHC*, or *SDHD* mutations, researchers have begun to elucidate differences in the clinical presentation of familial paraganglioma on the basis of the mutated gene present in the family. These distinctions constitute very basic genotype-phenotype correlations. Generally, genotype-phenotype correlations describe the association between a specific gene mutation and particular clinical findings. Some disorders, such as MEN type 2, have very specific genotype-phenotype correlations; for example, any mutation in codon 634 of the *RET* protooncogene results in a higher incidence of pheochromocytoma and hyperparathyroidism than mutations located in other regions of the gene (8, 9). The SDH Mutation Database tool, based on the Leiden Open (source) Variation Database system at http://chromium.liacs.nl/lovd_sdh/, provides an overview of all known *SDH* mutations and the associated tumor types (2). When known, genotype-phenotype correlations can help guide the clinical management of affected and at-risk individuals.

Mutations in *SDHD*, located on chromosome 11q23, have been identified in multigenerational families with primarily head and neck parasympathetic paragangliomas as well as pheochromocytomas and catecholamine-secreting paragangliomas (10, 11). *SDHD* mutations predispose to the development of multifocal paragangliomas (11). In patients with *SDHD* mutations,

penetrance depends on whether the individual inherited the mutation from the mother or the father. The disease is not manifested when the mutation is inherited from the mother, but is highly penetrant when inherited from the father (10, 11). This phenomenon is known as maternal imprinting.

Mutations in *SDHB*, located on chromosome 1p35–36, are primarily associated with paragangliomas in the abdomen, pelvis, and thorax, although head and neck tumors and pheochromocytomas are also observed. In families with *SDHB* mutations, imprinting has not been noted. Patients with *SDHB* mutations are at increased risk for malignant paraganglioma (11, 12, 13) and may be at increased risk for renal cell carcinoma and papillary thyroid cancer (11).

Mutations in *SDHC*, located on chromosome 1q21, have been reported in families with head and neck parasympathetic paragangliomas (14). Inheritance of *SDHC* mutations does not demonstrate the parent of origin effect observed in families with *SDHD* mutations.

Genetic testing for *SDHB*, *SDHC*, and *SDHD* is clinically available, and because of the high prevalence of *SDH* mutations in patients with paraganglioma, stepwise testing should be considered for all affected individuals. The clinician should be aware that large germline deletions of *SDHB* and *SDHD* have been identified in families with paraganglioma (15), but these large deletions are not detected by molecular methodologies that diagnostic laboratories currently offer. Therefore, negative genetic testing of a patient with paraganglioma does not rule out the presence of a disease-causing mutation.

In this issue of the *Journal of Clinical Endocrinology and Metabolism*, Benn *et al*. (16) report clinical findings in a cohort of patients with *SDHB* or *SDHD* mutations. The International *SDH* Consortium (with participants from seven countries) collected data on 116 individuals from 62 families who were evaluated at tertiary referral care centers. Of the index cases, 43 had *SDHB* mutations, and 19 had *SDHD* mutations. Including probands and their family members, 51 *SDHB* carriers and 28 *SDHD* carriers were affected. Family testing also identified 31 *SDHB* carriers and two *SDHD* carriers who were asymptomatic with no clinical evidence of paraganglioma. By evaluating clinical features such as diagnosis, age at onset, results of genetic testing, surgery, pathology, and disease progression, Benn *et al*. (16) endeavored to better define genotype-phenotype correlations in mutation-positive patients.

The median age at initial diagnosis was 34 yr for *SDHB* carriers and 28 yr for *SDHD* carriers, similar to the findings of a published population-based study (11). Benn *et al*. (16) reported a statistically significant age-related penetrance difference for *SDHB* and *SDHD* mutation carriers. By age 30 yr, 29% of *SDHB* mutation carriers and 48% of *SDHD* mutation carriers were diagnosed with paraganglioma; by age 40 yr, 45% of *SDHB* mutation carriers and 73% of *SDHD* mutation carriers were diagnosed with paraganglioma. Of the probands, a familial presentation was evident in only 16 of 43 (37%) *SDHB* patients and 15 of 19 (79%) *SDHD* patients. Thus, absence of a family history of paraganglioma does not exclude genetic disease.

The findings in this report confirm the previous population-based genotype-phenotype studies showing that *SDHB* mutations were mainly associated with abdominal paraganglioma, and *SDHD* mutations were mainly associated with head and neck paraganglioma (11). Adrenal pheochromocytomas were identified in nine of 51 patients with *SDHB* mutations (18%) and two of 28 patients with *SDHD* mutations (7%). In a population-based study, pheochromocytomas were reported to occur in 28% of patients with *SDHB* mutations and 53% of patients with *SDHD* mutations (11). Benn *et al*. (16) found that malignant disease was evident in 19 of 43 families with *SDHB* mutations (44%) and two of 19 families with *SDHD* mutations (11%), a finding that confirms the link between *SDHB* mutations and malignant paraganglioma previously reported (11, 12, 13). In addition, malignant paraganglioma was associated a variety of *SDHB* mutations spread throughout the gene (16). These data suggest that regardless of the specific genotype, all patients with *SDHB* mutations appear to be at increased risk for malignant disease.

Benn *et al*. (16) do not comment extensively on genotype-phenotype correlations based on specific *SDHB* and *SDHD* mutations. However, they did observe a tendency for *SDHD* mutation carriers with nonsense mutations (mutations that prematurely stop the translation of mRNA into protein and result in truncated products) to develop functional paragangliomas.

This report highlights the value of genetic testing for affected patients and at-risk asymptomatic family members. Genetic testing should be considered in all patients with paraganglioma and/or pheochromocytoma. Familial paraganglioma is inherited in an autosomal dominant manner; thus, an affected person has a 1 in 2 (50%) chance of passing the mutation on to each child. In families with *SDHD* mutations, inheritance is further complicated by the maternal imprinting phenomenon. In any clinical scenario, a mutation should be confirmed in an affected individual before genetic testing is offered to at-risk asymptomatic relatives. Genetic testing can be complex; testing one family member clearly has implications for related individuals. Genetic counseling is recommended to help families understand the implications of genetic test results, to coordinate testing of at-risk relatives, and to help families work through the psychosocial issues that may arise before, during, or after the testing process.

The clinician may obtain a list of clinically approved molecular diagnostic laboratories at www.genetests.org. Given the considerable cost of genetic testing, using a stepwise approach when evaluating a patient for the presence of an *SDH* mutation is prudent. Thus, when deciding which

genetic test to order first, the clinician must consider tumor location, tumor hormonal status, presence of malignancy, existence of multifocal tumors, and family history.

The likelihood of identifying an *SDHD* mutation is highest for patients with the following presentations (listed in order of probability): head and neck paraganglioma, chest/abdominal/pelvic paraganglioma, and apparently sporadic pheochromocytoma.

The likelihood of identifying an *SDHB* mutation is highest for patients with the following presentations (listed in order of probability): chest/abdominal/pelvic paraganglioma, apparently sporadic pheochromocytoma, and head and neck paraganglioma.

The likelihood of identifying an *SDHC* mutation is highest for patients with the following presentation: head and neck paraganglioma.

For example, if a patient has catecholamine-secreting abdominal paraganglioma, *SDHB* genetic testing should be ordered first (if negative, follow with *SDHD* genetic testing). If a patient has head and neck paraganglioma, *SDHD* genetic testing should be ordered first (if negative, sequentially order *SDHC* and *SDHB* genetic testing).

Genetic testing should be offered to first degree relatives of patients with *SDH* mutations. Importantly, in this report from Benn *et al*. (16), family testing revealed an additional 39 *SDHB* carriers and 11 *SDHD* carriers. However, subsequent clinical evaluation and testing of these family members showed that 80% of the *SDHB* carriers and 18% of the *SDHD* carriers had no evidence of tumors. As discussed by Benn *et al*. (16), *SDHD* and *SDHB* mutations have an age-related penetrance, and the lifetime risk of developing paraganglioma(s) approaches 100% by age 70 yr (11). Until prospective follow-up studies teach us differently, the surveillance strategy for an *SDH* mutation-positive asymptomatic patient, or a patient who declines genetic testing, but is at 50% risk of being a mutation carrier based on his/her position in the family tree, should begin 10 yr before the earliest age at diagnosis in the family and should include: annual history and physical examination by a clinician experienced with pheochromocytoma and paraganglioma; annual biochemical testing, *e.g.* 24-h urine for fractionated metanephrines and catecholamines and/or fractionated plasma metanephrines; computed imaging every 2 yr taking into consideration the tumor locations typically associated with the mutated gene as well as sites of disease found in affected family members; and [^{123}I]metaiodobenzylguanidine scintigraphy every 3–5 yr. Given the observation that children of female *SDHD* mutation carriers do not manifest the disease when the mutation has been inherited, rigorous clinical surveillance is probably not warranted for these offspring.

The work by Benn *et al*. (16) adds to the body of literature that addresses the differences in the clinical presentation of familial paraganglioma based on which *SDH* gene is mutated. Additional studies may possibly delineate phenotypes more intricately linked to specific mutations in *SDHB*, *SDHC*, and *SDHD*. Knowledge of genotype-phenotype correlations will allow for more patient-tailored management of familial paraganglioma.

Footnotes

Abbreviations: MEN, Multiple endocrine neoplasia; SDH, succinate dehydrogenase.

Received December 19, 2005.
Accepted December 20, 2005.

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