

The Role of Genetics in the Surgical Management of Familial Endocrinopathy Syndromes

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Our knowledge of genetics has increased dramatically in recent decades and this has led to important changes in the medical and surgical management of hereditary endocrine diseases. Genetic screening for disease-causing mutations can identify carriers at young ages, which has enabled earlier diagnosis and surgical intervention. For example prophylactic thyroidectomy is now routine in patients with multiple endocrine neoplasia type 2 (MEN2). Appropriately timed surgical intervention will minimize disease-specific morbidity and mortality, but the diagnosis and surgical treatment of disease in pre-symptomatic patients is much more complex than in symptomatic patients with measurable disease. Surgeons must remain conversant with the developments in genetic technology and the established role for genetic counselors in the multidisciplinary management of hereditary endocrine syndromes.

In this article we briefly review the clinically relevant information and indications for genetic testing for the most common hereditary endocrine syndromes including multiple endocrine neoplasia type 1 (MEN1), MEN2, von Hippel-Lindau syndrome (VHL), and hereditary paraganglioma syndrome. We also use several case descriptions to illustrate the impact of genetic counseling on the management of familial cancer. Finally we provide several key genetic counseling resources available for the proper identification and expeditious referral of patients at risk for these familial endocrine syndromes.

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MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

MEN1 is an autosomal dominant disease that demonstrates nearly complete penetrance in the form of various combinations of endocrine tumors involving the parathyroid glands, pancreatic islet cells and duodenum, and pituitary gland (Table 1).^{1,2} Hyperparathyroidism (HPT) is the most prevalent (90% to 97%) and is usually the first manifestation, typically appearing between the ages of 20 and 25 years but sometimes as late as the fifth decade of life.^{1,3,4} Anterior pituitary gland tumors in patients with MEN1 are less common (33%) and may be nonfunctioning or may secrete hormones such as prolactin.^{3,4} Tumors of the pancreatic islet cells and duodenum (pancreatic endocrine tumors, PETs) occur in as many as 30% to 80% of patients.⁵ Some PETs are nonfunctioning, but many secrete one or more pancreatic hormones. With earlier diagnosis and control of hormone-associated complications such as Zollinger-Ellison syndrome, metastatic neuroendocrine tumors of the pancreas are now the leading cause of disease-specific mortality in patients with MEN1. Because PETs in MEN1 patients are multifocal and distributed throughout the pancreas, their proper management remains poorly defined. This issue was summarized in a recent consensus statement in which it was concluded that surgical treatment for MEN1-related PETs is controversial except for patients with hypoglycemia secondary to insulinoma syndrome in whom pancreatic resection is indicated.¹ There is currently no consensus on the timing and extent of surgical treatment for gastrinoma and nonfunctioning PETs in patients with MEN1.

Less prevalent tumors associated with MEN1 include adrenocortical tumors, lipomas, and foregut carcinoid tumors. Foregut carcinoids are found in 2% to 8% of patients with MEN1, but bronchial carcinoids are more common in women and thymic carcinoids are more common in men.^{1,6} The malignant potential of carcinoids, particularly thymic carcinoids, has led to recent

Abbreviations and Acronyms

CLIA	= Clinical Laboratory Improvement Amendments
CNS	= central nervous system
HPT	= hyperparathyroidism
IVF	= in vitro fertilization
MEN1	= multiple endocrine neoplasia type 1
MEN2	= multiple endocrine neoplasia type 2
MTC	= medullary thyroid carcinoma
PET	= pancreatic endocrine tumor
PGD	= preimplantation genetic diagnosis
VHL	= von Hippel-Lindau syndrome

recommendations that patients with MEN1 undergo prophylactic cervical thymectomy at the time of initial parathyroidectomy and subsequently receive serial MRI or CT imaging every 1 to 3 years after the age of 20 years.^{1,6}

The MEN1 gene is a tumor suppressor gene located on chromosome 11q13 and consists of 10 exons.^{7,8} More than 200 mutations have been recognized throughout the MEN1 gene, with no consistent mutation hotspots and no clear relationship between genotype and phenotype.⁹ This makes DNA sequencing the large 9kb MEN1 gene a complicated, time-consuming, and expensive task. Currently genetic testing can successfully identify a mutation in the MEN1 gene in only 75% to 77% of probands from well defined MEN1 families.^{10,11}

Because of the reduced sensitivity of MEN1 genetic analysis, the diagnosis of MEN1 may rely on the clinical definition of sporadic and familial MEN1. A clinical diagnosis of MEN1 requires the presence of tumors in two of the three major involved endocrine glands (parathyroid, pancreas, or pituitary). A diagnosis of familial MEN1 requires a case of MEN1 plus one or more relatives with tumors in at least one of these three endocrine glands.^{1,12} Because of the varying expression of MEN1, many younger patients with MEN1 may express involvement only in a single endocrine gland (usually the parathyroids), so the clinical definition of MEN1 might fail to recognize patients at young ages or those with equivocal family histories.

In addition to MEN1, other autosomal dominant forms of familial HPT include familial isolated HPT, HPT-jaw tumor syndrome, and familial hypocalciuric hypercalcemia. HPT-jaw tumor syndrome is thought to be caused by a tumor suppressor gene on chromosome 1 and is characterized by HPT, ossifying fibromas of the jaw, renal cysts and solid neoplasms, and frequent occurrence of parathyroid carcinoma.^{13,14} Familial hypocalciuric hypercalcemia, which is caused by loss-of-function mutations in the calcium-sensing receptor gene on chromosome 3, is associated with lifelong and generally asymptomatic hypercalcemia, which does not improve after parathyroidectomy.^{15,16} The diagnosis of familial

Table 1. Hereditary Endocrinopathy Syndromes

Disease	Phenotype	Inheritance pattern	Gene (chromosome)	Commercial genetic testing available*
FHH	Hypocalciuria, hypercalcemia, hypermagnesemia	AD	CASR (3q13.3)	Yes [†]
HPT-JT	HPT, ossifying jaw fibromas, renal solid neoplasms and cysts, parathyroid carcinoma	AD	C1orf28 (1q25)	No
MEN1	HPT, PETs, pituitary tumors, foregut carcinoid tumors	AD	MEN1 (11q13)	Yes
MEN2	MTC, HPT (MEN2A), Pheochromocytoma, physical stigmata (MEN2B)	AD	RET (10q11.2)	Yes
Hereditary paraganglioma syndrome	Glomus (nonchromaffin) tumors, extra-adrenal pheochromocytomas, pheochromocytoma	AD	SDHD (11q23) SDHB (1p36.1) SDHC (1q21)	Yes Yes No
VHL	Retinal angioma, CNS hemangioblastoma, renal cell carcinoma, pancreatic and renal cysts	AD	VHL (3p25)	Yes

*Additional information about the availability of commercial laboratories can be found at the GeneTests-GeneClinics website (<http://www.geneclinics.org>).²³

[†]Commercial testing for FHH is currently available at a single laboratory in Canada.

AD, autosomal dominant; FHH, familial hypocalciuric hypercalcemia; HPT, hyperparathyroidism; HPT-JT, hyperparathyroidism-jaw tumor syndrome; MEN1 multiple endocrine neoplasia type 1; MEN2 multiple endocrine neoplasia type 2; PETs, pancreatic endocrine tumors; VHL, von Hippel-Lindau syndrome.

Table 2. CLIA-Certified Laboratories for Genetic Testing of MEN1, MEN2, and VHL*

Gene	Laboratory
MEN1	Boston University School of Medicine; Boston, MA
	GeneDx, Inc.; Gaithersburg, MD
	Yale University School of Medicine; New Haven, CT
RET	All Children's Hospital; St. Petersburg, FL
	Children's Hospital of Philadelphia; Philadelphia, PA
	Dartmouth-Hitchcock Medical Center; Lebanon, NH
	GeneDx, Inc.; Gaithersburg, MD
	Georgetown University Medical Center; Washington, DC
	Henry Ford Hospital; Detroit, MI
	Huntington Medical Research Institutes; Pasadena, CA
	Mayo Clinic; Rochester, MN
	Nichols Institute, Quest Diagnostics, Inc.; San Juan Capistrano, CA
	Ohio State University; Columbus, OH
SDHB	University of Pittsburgh Medical Center; Pittsburgh, PA
	Washington University School of Medicine; St. Louis, MO
	University of Pittsburgh Medical Center; Pittsburgh, PA
SDHD	Boston University School of Medicine; Boston, MA
	Children's Hospital of Philadelphia; Philadelphia, PA
	University of Pittsburgh Medical Center; Pittsburgh, PA
VHL	Boston University School of Medicine; Boston, MA
	Children's Hospital of Philadelphia; Philadelphia, PA
	Johns Hopkins Hospital; Baltimore MD

*Additional information about these and additional testing laboratories can be found at the GeneTests-GeneClinics website (<http://www.geneclinics.org>).²³ CLIA, Clinical Laboratory Improvement Amendments program; MEN, multiple endocrine neoplasia; RET, RET proto-oncogene; SDHB, succinate dehydrogenase subunit B; SDHD, succinate dehydrogenase subunit D; VHL, von Hippel-Lindau syndrome.

hypocalciuric hypercalcemia can often be distinguished from other forms of HPT by a urinary calcium-creatinine clearance ratio below 0.01.¹⁶ In the absence of an obvious syndrome, familial HPT is thought to be secondary to familial isolated HPT. However, commercial genetic testing is currently available only for MEN1 and kindreds with familial isolated HPT may actually represent unrecognized syndromes such as HPT–jaw tumor syndrome, familial hypocalciuric hypercalcemia, allelic variants of MEN1, or occult syndromes yet to be clinically and genetically defined.^{17–19} Importantly a failed operation for HPT or the onset of hypercalcemia before age 10 years should raise the level of concern for familial hypocalciuric hypercalcemia and the presence of parathyroid carcinoma should alert the clinician to the possibility of HPT–jaw tumor syndrome. A careful history of the proband and all affected family members will determine the need for MEN1 genetic testing.

Genetic testing for MEN1 is best performed at commercial laboratories that are certified by the Clinical Laboratory Improvement Amendments (CLIA) program.^{20–22} If genetic testing is not available at a CLIA-

certified laboratory, patients may be eligible for testing as part of a research protocol that has been approved by an institutional review board (as is our practice at The University of Texas MD Anderson Cancer Center). However, results generated in a research laboratory should be confirmed in a CLIA-certified laboratory before such results are used for diagnosis and treatment protocols.

Genetic testing for MEN1 is currently available through several CLIA-certified laboratories in the United States, which are listed in a database accessible through the GeneTests-GeneClinics website (Table 2).²³ Guidelines for MEN1 genetic testing are still being developed; compelling reasons to consider genetic testing include but are not limited to 1) confirmation of a clinical diagnosis or atypical presentation, 2) identification of at-risk relatives through presymptomatic screening, and 3) cessation of clinical screening in relatives who test negative for a mutation previously identified within the kindred.¹ MEN1 genetic testing should be considered in all patients who meet the clinical criteria for MEN1 and in those who present with suspicious findings or atypical

Table 3. Indications for Genetic Testing of MEN1, MEN2, VHL, and Hereditary Paraganglioma Syndrome

Syndrome	Indications
MEN1	Index case:
	Patient who meets the clinical definition of MEN1
	Patient with a highly suspicious or atypical presentation of MEN1
	A member of a family with a known MEN1 mutation:
	A relative at any age who exhibits signs or symptoms of MEN1
	All first-degree relatives* [†]
MEN2	Index case (in the presence or absence of family history):
	Patient with MTC
	Patient with Hirschsprung's disease
	Patient with pheochromocytoma that is bilateral and/or identified before age 18 years
	Patient with physical features or gastrointestinal symptoms suggestive of MEN2B
	A member of a family with a known RET mutation:
	MEN2A and familial MTC: all first-degree relatives before age 5 [†]
MEN2B: all first-degree relatives before age 1	
VHL	Index case:
	Patient who meets the clinical definition of VHL
	Patient with a highly suspicious or atypical presentation of VHL
	Patient with pheochromocytoma that is multifocal, extra-adrenal, and/or identified before age 18 years
	A member of a family with a known VHL mutation:
	All first-degree relatives before age 6 [†]
Hereditary paraganglioma syndrome	Index case (in the presence or absence of family history):
	Patient with paraganglioma (glomus tumor, pheochromocytoma, or extra-adrenal pheochromocytoma) that is multifocal, bilateral, and/or identified before age 18 years
	A member of a family with a known succinate dehydrogenase mutation:
	All first-degree relatives [‡]

Adapted from References 1,35,41,50,53.

*Presymptomatic MEN1 testing in at-risk children remains controversial because of the lack of consensus on prophylactic intervention and the inability to predict onset and extent of future disease.

[†]A second-degree relative may be offered testing if the connecting first-degree relative is deceased or unavailable for screening.

[‡]Specific recommendations for presymptomatic testing of the succinate dehydrogenase genes in children have not yet been determined.

MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; VHL, von Hippel-Lindau syndrome.

features of MEN1 (Table 3).¹ In addition, before any test result is used in a clinical setting, it should be confirmed using a separate blood sample to rule out the possibility of laboratory contamination or sample mix-ups.

When a mutation has been identified in the index patient it is reasonable to consider presymptomatic genetic testing for MEN1 in all first-degree relatives. Presymptomatic genetic testing can identify carrier status as many as 20 years before disease is clinically manifested.²⁴ Because of the lack of consensus on prophylactic intervention and the inability to predict the clinical pattern of future disease, the importance of presymptomatic screening remains controversial.²⁵ We currently recommend that relatives at risk consider presymptomatic genetic analysis at an age when MEN1 manifestations typically first appear (ie, late adolescence or early adulthood) or when the patient develops the maturity to

participate in the informed consent process. Until then children at risk for MEN1 and those from families without an identifiable mutation should be screened biochemically for HPT, insulinoma, and pituitary tumors (parathyroid hormone, ionized calcium, prolactin, fasting glucose, and insulin) annually after age 5 years; biochemical or radiographic screening, or both, for other PETs and carcinoid tumors should begin at age 20 years.^{1,6}

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

MEN2 is an autosomal dominant syndrome characterized by the development of endocrine tumors that include medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid neoplasia (Table 1).²⁶ This triad of tumors constitutes the most common clinical subtype of MEN2 and is known as MEN2A. At least



Figure 1. Mucosal neuromas of the tongue in a patient with multiple endocrine neoplasia type 2B.

two variants of MEN2A have been described: 1) MEN2A with Hirschsprung's disease, and 2) MEN2A with cutaneous lichen amyloidosis.²⁷⁻³⁰ MEN2B is a second, less common subtype and is characterized by the early development of aggressive MTC, pheochromocytoma, an absence of parathyroid neoplasia, and the presence of characteristic physical features such as mucosal neuromas, which are present in nearly all patients with MEN2B (Fig. 1).¹ Familial MTC is a third subtype in which MTC is the sole manifestation. All three clinical subtypes are caused by germline activating mutations in the RET proto-oncogene, which has been mapped to chromosome 10q11.2.^{30,31}

Unlike MEN1 testing, screening the RET gene for MEN2 mutations is more sensitive (approaching 98%) and less challenging because most mutations are located in exons 10, 11, and 16.^{32,33} Many CLIA-certified commercial laboratories now offer RET genetic analysis (Table 2).²³ Because of the sensitivity of the genetic test, the diagnosis of MEN2 is usually made on the basis of genetic testing rather than clinical criteria.

MTC is a rare form of thyroid cancer (comprising 5% to 10% of all thyroid cancers) and is caused by germline RET mutations in as many as 20% to 30% of cases.³⁴ It is not surprising that 1% to 7% of patients with apparently sporadic MTC (ie, negative family history) will test positive for RET mutations.³⁵ We previously confirmed this finding in a series of 101 patients with apparently sporadic MTC.³⁶ Six (6%) of these patients were found to carry germline RET mutations, either inherited or de novo, leading to our current practice of routine RET testing in all patients with apparently sporadic MTC. RET testing is also indicated for some patients with

pheochromocytoma (see Familial Pheochromocytoma) and for all children with presumed sporadic Hirschsprung's disease because of the possible presence of an activating RET mutation associated with MEN2A with Hirschsprung's disease.^{1,28,37} Finally RET testing is indicated for all patients with physical features or gastrointestinal symptoms suggestive of MEN2B regardless of family history, as approximately 50% of all cases of MEN2B are the result of de novo mutations (Table 3).^{38,39} Although RET testing in an index patient will occasionally identify a new MEN2 kindred, the real utility of genetic testing for MEN2 lies in its ability to ascertain carrier status so that prophylactic thyroidectomy can be performed to reduce disease-specific morbidity and mortality.⁴⁰

Clinical subtypes can often be predicted based on the specific RET mutation because of clear genotype-phenotype correlations.^{1,27} For example, pheochromocytoma has been reported in all RET mutations except codons 768 and V804M and is most frequently associated with mutations in codons 634 and 918. HPT is most often associated with codon 634 mutations, less often with codons 609, 611, 618, 620, 790, 791, and never with codon 918 mutations. The established genotype-phenotype correlations have recently allowed stratification of patients with MEN2 into three risk levels according to the aggressiveness of MTC.^{1,27} This information has led to the development of guidelines for the timing of prophylactic thyroidectomy in these patients.¹ Because of the importance of early surgical intervention all first-degree relatives of an affected patient should undergo presymptomatic genetic testing to allow timely thyroidectomy. Testing should be done before age 1 year in those with MEN2B (highest-risk mutations, codons 883 or 918) and before age 5 years in those with MEN2A because of higher-risk mutations (codons 611, 618, 620, or 634). The timing of prophylactic thyroidectomy in patients with mutations in codons 609, 768, 790, 791, 804, or 891 is somewhat debatable because of the variable biological behavior of MTC in these patients.

VON HIPPEL-LINDAU SYNDROME

VHL is a multisystemic autosomal dominant disease that affects approximately 1 in 40,000 live births and displays full penetrance by age 65 years.⁴¹ The phenotype of VHL is highly variable, but it is consistently associated with the abnormal growth of blood vessels

(hemangioblastomas), most commonly in the retina or central nervous system (CNS) (Table 1). Hemangioblastoma of the retina (retinal angioma) is the most frequent and typically the earliest manifestation of VHL, occurring in 50% to 85% of patients at a mean age of 25 years.^{42,43} Common CNS locations of hemangioblastomas include the cerebellum (35% to 59% of patients) and spinal cord (13% to 14% of patients).^{42,43} A clinical diagnosis of VHL requires the presence of a positive family history and one of the following: 1) retinal angioma, 2) CNS hemangioblastoma, or 3) a visceral lesion (eg, renal cell carcinoma, pheochromocytoma, pancreatic or renal cysts, or pancreatic islet cell tumors).⁴¹ In the absence of a positive family history, at least two retinal angiomas or CNS hemangioblastomas or one such angiomatous lesion with a visceral lesion must exist to establish a clinical diagnosis of VHL.⁴¹

VHL has been classified into two main clinical subtypes depending on the presence (type 2) or absence (type 1) of pheochromocytoma.⁴⁴ Type 2 has been subdivided into three categories depending on the presence (type 2B) or absence (type 2A) of renal cell carcinoma, with type 2C being a rare subtype in which pheochromocytoma is the sole manifestation of VHL.⁴⁵ Death from VHL is often caused by CNS hemangioblastoma, renal cell carcinoma, or unrecognized pheochromocytoma, so early diagnosis and screening is critical in these patients.

The VHL gene is a tumor suppressor gene located on chromosome 3p25.⁴⁶ As in MEN2 a clear relationship between the genotype and phenotype has been recognized. Specifically 56% of the mutations associated with type 1 VHL are microdeletions and insertions, nonsense mutations, or deletions, and 96% of the mutations associated with type 2 VHL are missense mutations.⁴⁴ Depending on the laboratory testing methods, which typically include Southern blotting and direct DNA sequencing, genetic testing for the VHL gene can detect 95% to 99% of cases.⁴⁷

VHL can usually be diagnosed on the basis of clinical criteria but genetic testing is now considered to be the definitive diagnostic test for VHL because clinical screening for VHL can often result in misdiagnosis.⁴⁸ Clinical screening is also expensive, can be uncomfortable for young children, and must be repeated because of the varying age of onset of disease.⁴⁹ Conversely genetic testing for VHL is highly accurate; it can be simply done as a single test (which should be repeated as least once for confirmation);

and it is cost-effective. VHL testing can also confirm a suspicious diagnosis in patients who appear to have a solitary hemangioblastoma, who do not meet the clinical criteria for VHL, or who have a history suspicious for familial pheochromocytoma (Table 3).⁴¹ CLIA-certified laboratories in the United States that currently perform VHL genetic testing are listed in Table 2.²³

FAMILIAL PHEOCHROMOCYTOMA

It has long been estimated that only 10% of pheochromocytomas are hereditary, but recent data suggest that up to 24% of unselected cases of apparently sporadic pheochromocytoma are carriers of germline mutations for inherited endocrine syndromes such as MEN2, VHL, and less often MEN1 and neurofibromatosis type 1.⁵⁰ Pheochromocytoma can also occur as an isolated expression of hereditary paraganglioma syndrome.^{1,50-52}

Paragangliomas are highly vascularized tumors arising from neural crest chief cells of the paraganglia neuroendocrine system, which begins at the base of the skull and extends to the pelvic floor. Paragangliomas of the head and neck (glomus tumors) are nonfunctioning and most often occur in the carotid body. Paragangliomas below the head and neck produce catecholamines. They are classified as pheochromocytomas if they arise in the adrenal medulla and they are referred to as extra-adrenal pheochromocytomas or extra-adrenal paragangliomas if they arise in autonomic ganglia outside of the adrenal gland. Hereditary paraganglioma syndrome predisposes to both extra-adrenal (especially carotid body) and adrenal paragangliomas and has recently been associated with mutations in succinate dehydrogenase subunits D, B, and C (SDHD, SDHB, and SDHC, respectively) of mitochondrial complex II.⁵⁰⁻⁵³ Mitochondrial complex II is thought to function as a tumor suppressor as defective mitochondrial complex II results in the overexpression of several hypoxia-inducible genes that are believed to result in proliferation of the paraganglia.⁵²

The risk of intra-abdominal paraganglioma (adrenal and extra-adrenal) in MEN1 and neurofibromatosis type 1 is estimated to be very low (1% or less) in contrast to its incidence in VHL (10% to 20%), MEN2 (50%), and hereditary paraganglioma syndrome (possibly as high as 80%).^{1,50,51,54} Two recent studies have examined these latter genes in patients with apparently sporadic pheochromocytoma. In the first study, Neumann and colleagues⁵⁰ reported that approximately 24% of patients with intra-abdominal paraganglioma (adrenal and

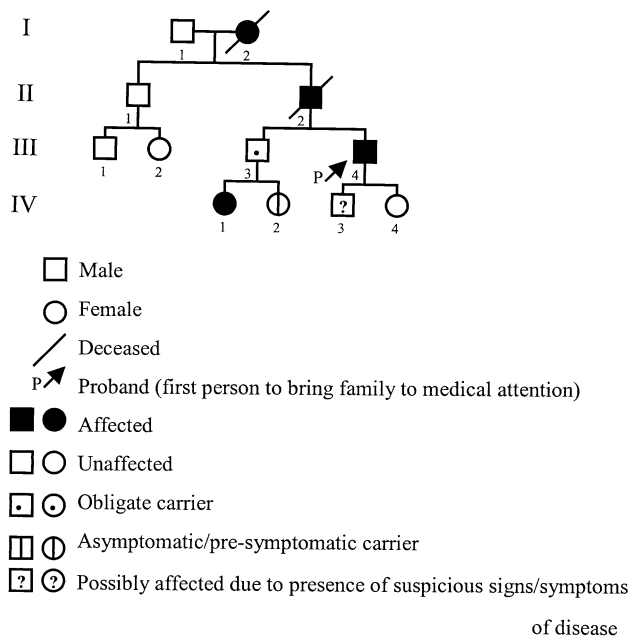


Figure 2. A pedigree illustrating the presence of an autosomal dominant condition using standardized nomenclature.⁵⁹

extra-adrenal) without a positive family history carry mutations in VHL, SDHD, SDHB, and RET. Bauters and colleagues⁵³ found germline mutations in VHL, SDHD, SDHC, and SDHB, and RET in 19% of patients with apparently sporadic paragangliomas (glomus tumors, adrenal and extra-adrenal pheochromocytomas). Both studies concluded that hereditary disease, mutations in VHL in particular, may be predicted by multifocal tumors (including bilateral pheochromocytomas or multiple paragangliomas) and onset before age 18 years.

Genetic analysis of mutations in the B and D subunits of succinate dehydrogenase is available through a limited number of CLIA-certified laboratories (Table 2).²³ Although consensus guidelines have not yet been established, genetic testing of these genes may be justified as part of the etiologic search for familial pheochromocytoma. Clinical clues such as young age, bilateral pheochromocytomas, presence of extra-adrenal paraganglioma, and positive family history should prompt a thorough evaluation for these susceptibility genes (Table 3). It has been proposed that these genes be screened in the following order: VHL, SDHD, SDHB, and RET.⁵³ At MD Anderson Cancer Center, our current screening protocol for patients with suspected familial pheochromocytoma or paraganglioma includes genetic testing of these four susceptibility genes in a sequence dependent

on the presence or absence of other neoplasias such as MTC, renal cell carcinoma, and CNS lesions within the family history.

The absence of metastatic pheochromocytoma in patients with most causes of familial pheochromocytoma and the risk of morbidity and mortality from adrenal insufficiency in patients who undergo bilateral total adrenalectomy support the surgical practice of corticoid-sparing adrenalectomy.²⁷ Our current management of unilateral familial pheochromocytoma is to perform a laparoscopic adrenalectomy. For bilateral disease or contralateral recurrence the main surgical objective is to preserve a portion of the adrenal cortex in situ, which is often facilitated by an open surgical procedure.^{27,55,56}

GENETIC COUNSELING

Although the definition and specific goals of genetic counseling have changed over time, most genetic health care providers agree that genetic counseling is a communication process that includes both educational and therapeutic elements targeted to patients and their families who face the risk of a genetic disorder.⁵⁷

An older, well accepted paradigm of genetic counseling was defined by a subcommittee of the American Society of Human Genetics in 1974, which stated that the process of genetic counseling should ultimately allow the patient to do the following: 1) understand the medical facts of the disorder; 2) understand how heredity influences the risk of disease in other relatives; 3) identify alternatives such as genetic and clinical screening to ascertain more precise risks; 4) choose a course of action to deal with risk and management; and 5) assist the patient and family in making financial and psychological adjustment to a disorder in the family.⁵⁸

A counseling session for patients at risk for a hereditary cancer syndrome typically includes but is not limited to the following: 1) a review of the characteristics and transmission mechanism of the genetic condition; 2) an explanation of the process of genetic or clinical testing, or both, for affected individuals and of carrier ascertainment for their relatives at risk; and 3) a discussion of the potential benefits, risks, and limitations when genetic testing is available. A detailed pedigree is routinely constructed using standardized nomenclature and a properly labeled legend to identify both affected and at-risk individuals (Fig. 2).⁵⁹ Family history data will not only facilitate and confirm the diagnosis of familial disease in the index relative (proband), it will also help to

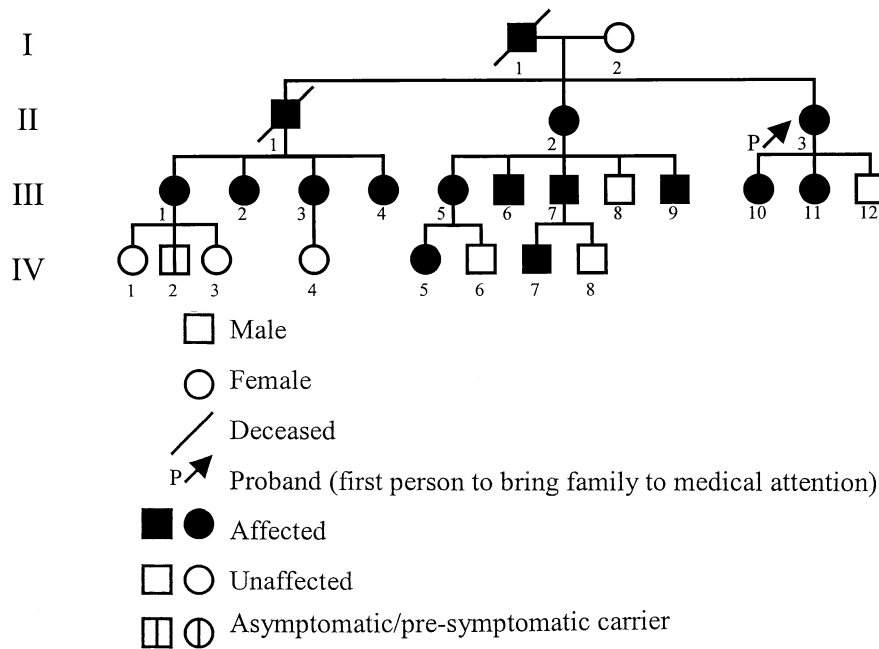


Figure 3. Kindred with multiple endocrine neoplasia type 2A with a C634R RET mutation. Individual III-9 was the first member to undergo genetic counseling, which resulted in risk assessment of all eight children in generation IV. Six of eight children were subsequently tested for the C634R RET mutation and evidence of invasive medullary thyroid carcinoma (MTC) was found in two of three carriers (individuals IV-5 and IV-7, aged 7 years and 5 years, respectively). C-cell hyperplasia without evidence of invasive MTC was found in individual IV-2, who was 5 years old at the time of thyroidectomy.

identify at-risk relatives who require thorough clinical or genetic screening, or both.

Genetic counselors use a nondirective approach to educate patients regarding options such as genetic testing and to determine whether the patient is capable of providing informed consent for genetic testing. Patients must go through the genetic counseling process to give informed consent for genetic testing even if genetic testing is offered on a research basis.⁶⁰ Written documentation by a genetic counselor and a signed consent form are required by most commercial laboratories before they will accept a DNA sample for testing.

Some of the psychological, ethical, and legal risks that may arise during genetic testing include revelation of unexpected information (eg, nonpaternity), psychological and social stress for the patient and family (eg, survivor guilt, burden of knowledge, and social stigmatization), and threat of employment or insurance discrimination.⁶¹ Because of these complex issues that patients face, genetic counseling services should be offered throughout the entire testing process with followup when necessary.

PRENATAL DIAGNOSIS

Prenatal testing for some familial endocrinopathy syndromes is available through some commercial laboratories and is an option for couples in which one member has an identifiable germline mutation. Germline mutation analysis uses fetal DNA acquired either from chorionic villus sampling at 10 to 12 weeks of gestation or amniotic fluid obtained during midtrimester amniocentesis at 16 to 18 weeks of gestation (the number of weeks of gestation is determined from the first day of the last menstrual period rather than the date of conception).⁶² Chorionic villus sampling and amniocentesis are invasive procedures that carry a risk of approximately 1% and 0.5%, respectively, of causing a miscarriage when performed by expert clinicians.^{62,63} Although these prenatal testing procedures are widely available the risk of procedure-related miscarriage and the complex issues surrounding pregnancy termination make prenatal testing unacceptable to some patients.

Preimplantation genetic diagnosis (PGD) is another option for couples in which one partner is a carrier of a

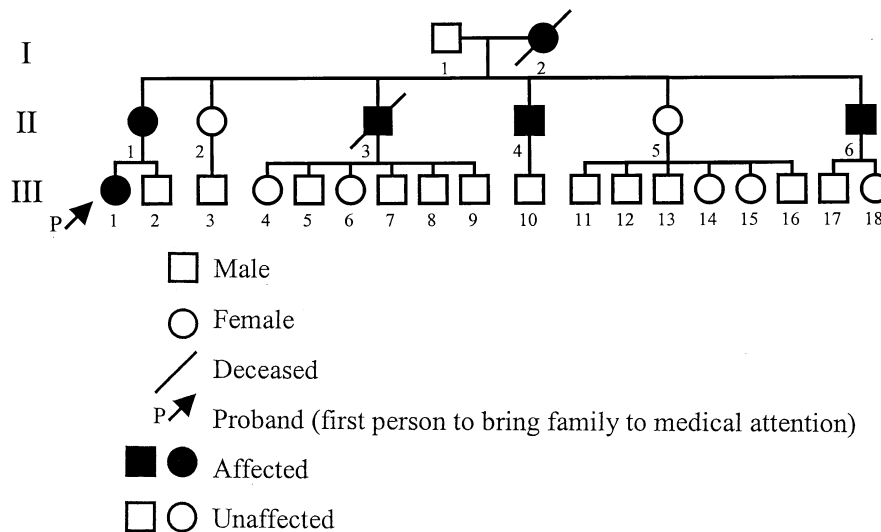


Figure 4. A second kindred with multiple endocrine neoplasia type 2A with a C634R RET mutation. Individual III-1 recently presented at age 14 years with a palpable thyroid nodule in the setting of a suspicious family history. As the first member to undergo RET analysis and genetic counseling she served as the family proband. Identification of the precise RET mutation facilitated diagnosis in her uncle (relative II-4), who was identified as a carrier at age 45 years and subsequently diagnosed with bilateral MTC and bilateral pheochromocytoma. Genetic screening is currently underway for remaining at-risk relatives in this family.

mutated gene for a dominantly inherited disorder. The most common approach is blastomere biopsy, in which one or two blastomeres are removed from in vitro-derived embryos (usually at the 6- to 10-cell stage) followed by transfer and implantation of unaffected embryos.⁶⁴ PGD may be a better option for couples who seek information before conception or who would not terminate an affected pregnancy. However, consideration must also be given to the challenging aspects of in vitro fertilization (IVF), which is generally used with PGD. IVF is expensive and often not covered by insurance, and women undergoing IVF are usually exposed to strong hormonal medications to stimulate superovulation, followed by invasive retrieval of oocytes. Another consideration is the relatively low success rate of IVF. In a 2002 publication of data from 1999, the rate of delivery of a live infant per cycle of IVF was only 25.4% among 370 assisted reproductive technology centers in the United States.⁶⁵ In addition to the technical challenges of IVF alone PGD depends on the availability and testing of numerous embryos to achieve a single successful, unaffected pregnancy. One report estimated that only 2.5% of all eggs collected per PGD cycle will form a viable unaffected PGD pregnancy because of the limited number of embryos suitable for biopsy and trans-

fer.⁶⁶ The potential for PGD to eliminate inherited disorders such as MEN1, MEN2, or VHL from a kindred has tremendous appeal from medical, social, and long-term financial viewpoints. Unfortunately the technical challenges of embryo biopsy, testing, and transfer with IVF currently do not make PGD a realistic solution to eradicate familial endocrinopathies.

DISCUSSION

The clinical and surgical benefits of genetic testing vary among the limited number of familial endocrinopathy syndromes that can be diagnosed through genetic testing. For example the recommendation for early presymptomatic RET testing and prophylactic surgical treatment is perhaps the most striking difference of genetic testing in MEN2 when compared with MEN1. Illustrating this is a large four-generation family with numerous relatives affected by MEN2A (Fig. 3). At the time of referral for genetic counseling we identified eight children in the youngest generation (age range 2 to 9 years) in whom RET screening had not been done and was therefore recommended. Six of eight children were tested (testing has been postponed in two 2-year-old children), and three were found to be carriers of the C634R mutation. All three carriers underwent prophy-

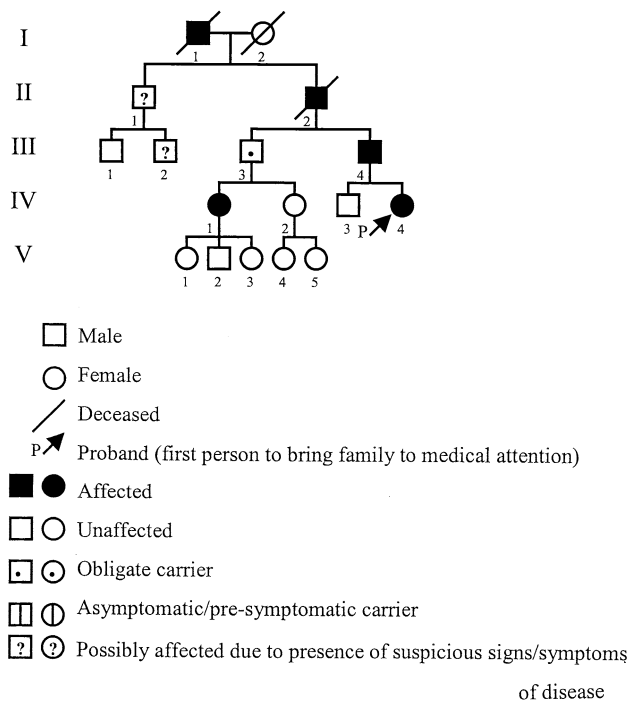


Figure 5. Multiple endocrine neoplasia type 1 (MEN1) kindred with a R460X mutation in MEN1. Individual IV-4 served as the proband for the kindred at age 19 years. Once MEN1 was diagnosed in the kindred, individual III-4, who had a distant history of hyperparathyroidism at age 30 years, was screened at age 53 years and was found to have a metastatic bronchial carcinoid tumor and nonfunctioning tumors of the pancreatic islet cells and duodenum. Individuals II-1 and III-2 have a history of kidney stones but have not pursued formal evaluation. All five individuals in generation V are between the ages of 8 and 16 years, an age group in which genetic testing is not routinely indicated.

lactic thyroidectomy at our institution within 2 months of genetic testing, and pathologic studies revealed microscopic MTC in two patients (aged 5 and 7 years) and C-cell hyperplasia in the third (aged 5 years). This family illustrates two important points. First, genetic counseling, even in a large family that is thought to be well informed, can successfully bring numerous affected family members to medical attention at an age when early treatment is critical to achieve successful outcomes. Second, microscopic MTC in a patient as young as 5 years shows the aggressiveness of the codon 634 mutation and supports the rationale for considering thyroidectomy in all carriers of higher-risk mutations before the recommended age of 5 years.¹ Case reports have documented invasive MTC in codon 634 carriers as young as 2 years.^{67,68} As we discover additional MEN2A families, the age guidelines for testing and prophylactic thyroidectomy may change.

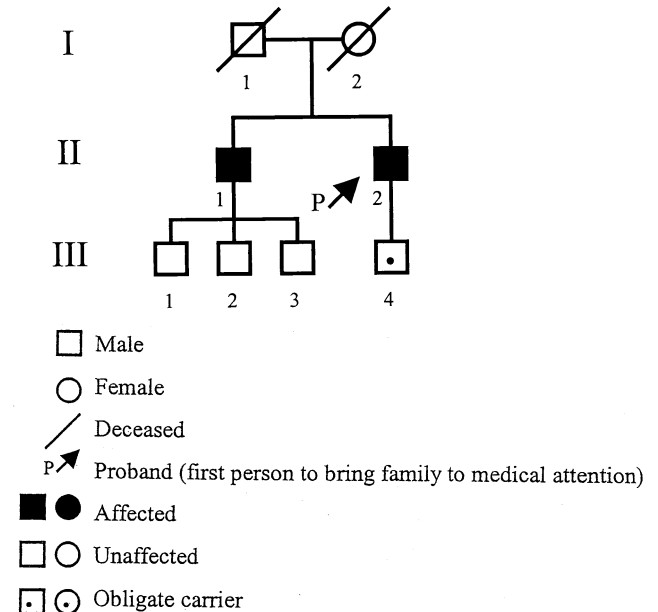


Figure 6. A kindred with familial medullary thyroid carcinoma (MTC) with a V804M RET mutation. It can be dangerous to assume sporadic etiology when family size is small and family history appears unremarkable. At age 54 years individual II-2 was diagnosed with bilateral MTC, prompting additional investigation with RET testing, which revealed a V804M mutation in exon 14. Individual II-1 was then identified as a carrier of the V804M mutation and diagnosed with invasive MTC. Genetic analysis in generation III was negative in individuals 1, 2, and 3 and positive in individual 4, who at age 15 years has electively postponed prophylactic thyroidectomy because of the estimated lower risk of this mutation.

Genetic counseling and thorough pedigree analysis in a young patient can sometimes identify hereditary disease that has been present but unrecognized for many generations. For example a 14-year-old girl who presented with a palpable thyroid mass, a vague family history of thyroid carcinoma, and a history of sudden death in several relatives served as the proband in the third affected generation of a family with MEN2A (Fig. 4). The patient's preoperative basal calcitonin level was 932 pg/mL (normal, 4.6 pg/mL or less) and histopathology following thyroidectomy with central and bilateral neck dissection sonography demonstrated multifocal MTC with regional lymph node metastases. Subsequent RET testing in the patient revealed a C634R mutation. Examination of the pedigree as well as autopsy reports for her uncle (relative II-3) identified several other affected relatives and confirmed the presence of aggressive pheochromocytoma in the family. Recognition of MEN2A in this family has led to additional assessment of other relatives, including another uncle (relative II-4) who

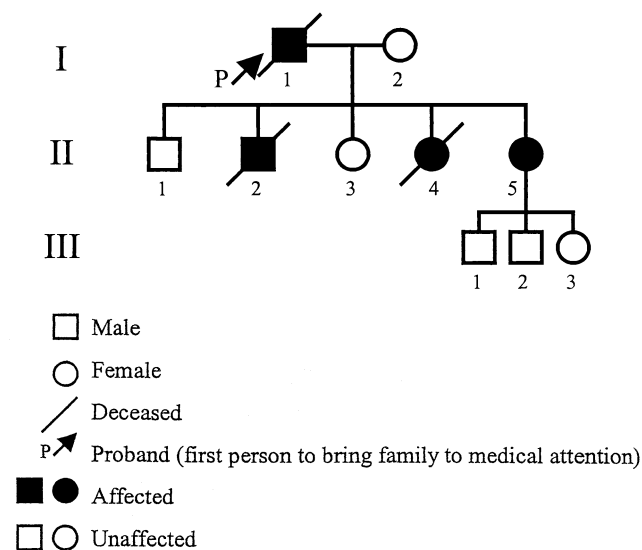


Figure 7. This kindred with von Hippel-Lindau syndrome (VHL) has not elected genetic analysis or early clinical screening. VHL was diagnosed in individual II-5 only after abdominal imaging after an automobile accident demonstrated a large pancreatic mass. Individuals I-1, II-2, and II-4 died from complications related to cerebellar and spinal lesions. Although this family appears to be well informed about their risks for VHL, individuals II-1 and II-3 have not sought screening for VHL.

sought clinical screening at age 45 years and who was subsequently identified as a carrier of the C634R mutation and diagnosed with bilateral MTC and bilateral pheochromocytoma. Genetic screening is currently underway for the remaining at-risk relatives in this family.

Recognition of a familial syndrome in multiple generations can also identify obligate carriers, namely a parent of an affected offspring who by definition must carry a mutation. Obligate carriers may be completely unaware of their status because some signs of disease may be subclinical. This was the case for a 19-year-old woman who was referred to our institution with symptoms of primary HPT. Family history was positive for HPT in her father and pancreatic cancer of uncertain histology in her paternal grandfather (Fig. 5). Because MEN1 was suspected, the patient's asymptomatic father was evaluated at our institution at age 53 years and was

found to have a bronchial carcinoid tumor and a 3.0-cm nonfunctioning PET. The diagnosis of a bronchial carcinoid in this man with MEN1 justifies the recommendation that all men and women with MEN1 be screened for both types of foregut carcinoid tumors despite the gender trends of these tumors.¹ The patient underwent thoracotomy and surgical resection of the carcinoid tumor and received postoperative adjuvant external-beam radiation therapy because of multiple positive regional lymph nodes. After recovering fully he underwent distal subtotal pancreatectomy for the removal of multifocal PETs. Screening in other family members resulted in the diagnosis of MEN1 in two additional symptomatic individuals.

As illustrated by the previous two examples ascertainment of family history should be the first and one of the most critical steps in assessing families for genetic disorders, but one should not be tempted to exclude the possibility of a heritable disease on the basis of a weak or absent family history. Situations that reduce the value of family history include cases with small family size, poor historians, adoption, and de novo mutations. We previously discussed that up to 7% of patients with apparently sporadic MTC are identified as RET carriers during routine genetic screening. This was the case for a man who was diagnosed with MTC at age 54 in 1998 and is a member of a small family with no history of thyroid malignancy or multiple endocrine neoplasia (Fig. 6). Cervical ultrasonography in this patient identified thyroid nodules bilaterally, which were cytologically confirmed as MTC. Despite the unremarkable family history bilateral MTC prompted RET testing, which was negative in exons 10, 11, and 16. Followup testing revealed a V804M mutation in exon 14. Genetic analysis in other relatives identified two additional carriers, a brother with histologically proven MTC and a son who, at age 15 years, has electively postponed prophylactic thyroidectomy because of the mild nature of this mutation. This and several similar cases in our patient population illustrate how family history can help substantiate

Table 4. Genetic Counseling Resources

Organization	Services	Website
National Society of Genetic Counselors (NSGC)	Resource to locate counselors and links to publications	www.nsgc.org
GeneTest-GeneClinics	Directory of genetic clinics and testing laboratories	www.geneclinics.org
Genetic Alliance	Directory of support groups and disease information	www.geneticalliance.org

but should not be used to exclude the indication for genetic testing.

Some families may be aware that a heritable condition is present but do not use clinical or genetic screening services. This was the case for a woman from a family with well documented VHL. At age 26 years she had multiple cystadenomas of the pancreas that were serendipitously found by abdominal imaging to assess injuries sustained in an automobile accident (Fig. 7). A subsequent workup identified multiple spinal and cerebellar lesions in this patient. Despite the established family history and known deaths of three first-degree relatives with VHL, the remaining at-risk relatives have not been motivated to seek diagnostic evaluation for VHL. Several studies have shown that patients at high risk for severe hereditary disease may decline genetic testing because of concerns about high out-of-pocket cost, confidentiality, and the possibility of employment or insurance discrimination.⁶⁹⁻⁷¹ Incomplete dissemination of information and lack of genetic counseling in at-risk populations are also likely explanations for reduced use of clinical and genetic screening services. The attitudes toward genetic testing among families with MEN1, MEN2, and VHL may also differ from those with other hereditary diseases, and additional research is needed to assess this possibility.

The inability to recognize at-risk patients and the limited numbers of trained genetic counselors likely have prevented genetic testing in a significant proportion of cases, but there are many resources available to help locate regional genetic counselors and services, CLIA-licensed laboratories, and support groups for a variety of specific heritable conditions. Several reference tools are identified in Table 4.

The indications and utility of genetic testing may differ depending on the genetic syndrome, but patients with familial endocrinopathies face counseling issues similar to those faced by patients with known familial disease: namely the complexity of the genetic testing process, the possibility of adverse psychological reaction to results, and the rare but possible threat of genetic discrimination. A negative genetic test result (repeated and confirmed) in an at-risk relative from a family with an identifiable mutation in a familial endocrinopathy gene generally eliminates the need for future clinical screening, which can be lengthy, uncomfortable, and expensive. A negative test result will also prevent anxiety related to disease-associated symptoms and will elimi-

nate the need for prenatal counseling for future generations.

In summary, the explosion of research in heritable conditions has led to many advances in the management of genetic diseases. Genetic testing has lowered the age at which carriers with conditions such as MEN1, MEN2, VHL, and hereditary paraganglioma syndrome are recognized. In turn, carriers identified early in the course of their disease can be brought to surgical attention before disease becomes extensive and life-threatening. The more widespread use of genetic testing in the future will likely modify the natural history of these and other heritable conditions.

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