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HYPERPARATHYROID GENES: SEQUENCES REVEAL ANSWERS AND QUESTIONS

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Abstract

Objective—To review hyperparathyroid syndromes and genes.

Methods—Pertinent original studies from the literature are discussed.

Results—Six main hyperparathyroid syndromes are recognized; 5 are from germline mutations in 4 genes— *CASR*, *MEN1*, *RET*, and *HRPT2*. Each hyperparathyroid syndrome was first described around 1965; the main gene for each syndrome was identified about 30 years later. Gene identification addressed clinical issues. (1) Testing for mutation carriers among affected probands or among unaffected relatives is more robust than prior methods, which were based on syndromal traits such as serum calcium. (2) Interpreting a gene test (*RET*) could guide an important intervention; other gene tests could yield useful information for patients and physicians. (3) Proving the roles of each gene (in particular, *MEN1* somatic mutations) provided insights about contributions to many common tumors. (4) Clarifying molecular pathways and drugs led, for example, to the *CASR*-aided development of calcimimetic and calcilytic drugs. (5) Explaining novel features, such as the *CASR* gene encoding a membrane calcium-sensing receptor and its mutations resulting in nonsuppressed parathyroid hormone secretion uncoupled from proliferation, characterized familial hypocalciuric hypercalcemia. (6) Disclosing probands without an identifiable mutation promoted searches for other syndromal genes. Subsequently, rare multiple endocrine neoplasia type 1-like families were shown to have inactivating germline mutations, first of *p27* and subsequently of *p15*, *p18*, or *p21*.

Conclusion—The next frontier in mutation detection is arriving, with possible sequencing of the whole exome or even the whole genome for 1 case or 1 tumor at an affordable cost.

DEFINITIONS OF HYPERPARATHYROID SYNDROMES AND THEIR GENES

A hyperparathyroid syndrome is a complex of symptoms and signs that include overactivity of the parathyroid glands and its downstream expressions. Most hyperparathyroid syndromes can also express characteristic features outside the parathyroid glands. Hyperparathyroid syndromes are potentially hereditary, although this feature is not obligatory. For example, neck irradiation can cause tumors of the parathyroid glands and the thyroid in a family (1). Furthermore, hyperparathyroidism may be caused by autoantibodies to the extracellular calcium-sensing receptor (Ca-SR); these may coexist with antithyroid autoantibodies (2).

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DISCLOSURE

The author has no multiplicity of interest to disclose.

A hyperparathyroid gene is one that can contribute to overactivity of the parathyroid glands. In this report, I will discuss genes that can contribute to hyperparathyroid syndromes mainly through mutation in the germline. For convenience, genes in several related categories are excluded. For example, genes, most thus far unidentified, with mutation acting somatically only in solitary parathyroid adenoma (such as *CCND1*/cyclin D1) are excluded (3). Also excluded are genes such as the vitamin D receptor (*VDR*) that may contribute only by changes of expression in sporadic tumors (4–6) as well as genes that contribute only to secondary hyperparathyroidism by mutation or expression. In fact, no gene in this last category has yet been identified.

There are 6 main hyperparathyroid syndromes and 4 identified hyperparathyroid genes (Table 1). Among the 6 syndromes, only the main gene for familial isolated hyperparathyroidism (FIH) remains unknown.

DISCOVERIES OF HYPERPARATHYROID SYNDROMES AND SUBSEQUENT DISCOVERY OF THEIR GENES

Ancient Identification of Hyperparathyroid Syndromes in Families

The date of first recognition of a syndrome may be controversial because nomenclature and measurements were at preliminary stages and because recognition might be credited even earlier if based on a sporadic case. Discovery based on involvement of multiple members of a family rather than on a sporadic case (or cases) has made first recognition of a syndrome more secure.

Initial recognition of each hyperparathyroid familial syndrome was between 1954 and 1972, long before genomic approaches to heredity were introduced (Fig. 1). What is now termed multiple endocrine neoplasia type 1 (MEN 1) was described in 2 families in 1954 (7,8). Familial multiple endocrine neoplasia type 2A (MEN 2A) was identified in 1962 and thus separated from MEN 1 (9). The hyperparathyroidism-jaw tumor syndrome (HPT-JT) was reported in a family in 1958 (10). Familial benign hypocalciuric hypercalcemia or familial hypocalciuric hypercalcemia (FHH) was first described in 1972 (11). Neonatal severe hyperparathyroidism (NSHPT) was first described in a single case in 1947 (12) and in 2 members of a family in 1964 (13). A familial relationship of NSHPT and FHH was reported in 1982 (14,15). FIH was reported in a large family in 1964 (16). This family and most other large families reported as having FIH in the 1960s were subsequently found to have MEN 1 (17) or FHH (15); this pattern reflects the very high prevalence of the last 2 diagnoses and the infrequency of their recognition among large families with seemingly isolated hyperparathyroidism.

Typically, each of the hyperparathyroid syndromes has a different form of expression in the parathyroid glands (Table 2). An implication is that each main gene with hyperparathyroid mutations can affect the parathyroid glands in its own relatively specific manner. These variations in tumor expression are sufficient to warrant syndrome-specific differences in management of hyperparathyroidism, as outlined in Table 2.

Recent Identification of Hyperparathyroid Genes

The gene for a hyperparathyroid syndrome was typically identified some 30 years after that syndrome was first reported. Only the main gene for FIH has not yet been identified as of 2011. Each of the 4 known hyperparathyroid genes was identified between 1993 and 2002 (Fig. 1). This short interval for discovery of these 4 genes reflects major progress in genomics; it also reflects large kindreds that had been delineated earlier and that were

informative for narrowing the number of candidate genes, during the gene identification process.

The *CASR* gene was identified in a *Xenopus laevis* oocyte expression system in 1993 (18). It was associated with FHH and NSHPT shortly afterward (19,20). The *RET* proto-oncogene was discovered in 1985 because of a DNA rearrangement in NIH3T3 cells during transfection with lymphoma DNA (21). *RET* is an abbreviation for “REarranged during Transfection.” It was cloned and thus sequenced in 1988 (22). *RET* was not known to cause MEN 2A until its underlying mutations were identified in 1993 (23). Because its name had been assigned 5 years earlier for other properties, nomenclature conventions ruled that it should not be renamed as the *MEN2* gene. The *MEN1* gene was identified by positional cloning in 1997 (24). The *HRPT2* gene for HPT-JT was identified by positional cloning in 2002 (25). The cyclin-dependent kinase inhibitor (*CDKI*) genes are not addressed here as main genes of hyperparathyroidism because of their rare contributions; they are discussed separately (see subsequent material).

PROVISION OF CLINICAL ANSWERS BY HYPERPARATHYROID GENES

Each of the 4 hyperparathyroid genes could cause 1 or a few rare syndromes. Insights into rare syndromes alone would have justified the efforts to identify each gene. Each syndromal gene, however, has also provided clinical benefits relating to other disorders, as discussed in the following paragraphs.

An Answer: Gene Sequencing Ascertains Carriers Who Are Symptomatic or Asymptomatic

In the context of a familial syndrome, a carrier is defined as a case that expresses the syndrome or that has the potential to express it. Either status is similar to carriage of a pathologic syndromal mutation in the germline. In the current genomic era, initial identification of a disease-related gene, such as a hyperparathyroid gene, leads almost immediately to application of that gene sequence for the diagnosis of carriers (26–29).

Carrier identification is sought mainly in 2 different settings. The first is the characterization of a proband affected by a syndrome or a possible phenocopy of it. The second is the characterization of an unaffected relative in a family in which the proband has a known mutation.

An Answer: Gene Information Helps Clinical Management

At its best, a hyperparathyroid carrier test can guide an important intervention, such as prevention or cure of C-cell cancer, guided by the *RET* sequence test (29). More frequently, a hyperparathyroid carrier test does not guide an intervention but yields important information to the patient, physician, and family.

Use of a gene sequence for carrier ascertainment represents a major advance over prior carrier tests, which were based on syndromal traits—such as serum calcium or serum calcitonin levels. The gene sequence test can prove or deny the carrier status, with performance of only a single test for a lifetime. In contrast, a normal trait test cannot exclude the carrier state, and it might have to be repeated numerous times, over many years, without ever revealing abnormal results.

An Answer: A Gene for a Rare Syndrome Can Provide Insights About Some Common Tumors

The *MEN1* gene is mutated in about one-third of the common somatic tumors of the parathyroid glands, gastrin cells, insulin cells, and nonfunctioning islet cells, bronchial

carcinoids, and lipomas. Surprisingly, it is mutated in only about 3% of sporadic pituitary tumors (30).

The *RET* gene has a somatic mutation in about 25% of sporadic C-cell tumors and in about 5% of sporadic pheochromocytomas (29). More important to the patient and family, however, is the finding of a germline *RET* mutation in the cases with seemingly sporadic C-cell tumors or adrenal medullary tumors (31). The germline mutation implies the presence of the MEN 2A syndrome in a seemingly “sporadic” case and possible inheritance of MEN 2A in the family. *RET* also can be an oncogene as a somatic fusion-mutation termed *RET-PTC*; this occurs in a range (3% to 85%) of papillary thyroid cancers, the wide variation mainly reflecting methodologic differences (32).

Preliminary data suggest that the *HRPT2* gene is mutated rarely in sporadic parathyroid adenoma but frequently in sporadic kidney cancer (33). In contrast, *HRPT2* is mutated at both alleles in nearly 100% of parathyroid cancers, and the fraction of these that have *HRPT2* germline mutation in one of those alleles is about 30% (34).

Somatic mutations in the aforementioned hyperparathyroid genes do not have important clinical implications unless they are germline/familial mutations. They carry the important implication for research, however, that a single molecular pathway might shed light on both rare syndromal and common sporadic tumors.

The *CASR* gene is rarely, if ever, mutated in sporadic parathyroid adenoma. Its expression (that is, the Ca-SR protein), however, is downregulated in most parathyroid adenomas and in most parathyroid glands in patients with uremic hyperparathyroidism (35). This downregulation may explain why calcimimetic agents can suppress parathyroid hormone secretion by the parathyroid glands in patients with secondary hyperparathyroidism or parathyroid cancer (36). Similar tumoral defects of gene expression have not been proved for the *MEN1*, *RET*, or *HRPT2* genes.

An Answer: A Gene Can Promote Inroads About Molecular Pathways and Drugs

The discovery of sequences of *MEN1* and *HRPT2* provided minimal insight about a molecular pathway (37,38). In contrast, the sequence of the *RET* gene predicted a transmembrane tyrosine kinase, and the *CASR* sequence predicted a G protein-coupled receptor (18,39,40). Both of these pathways were already under active evaluation at the time of identification of these genes.

There has been a time-tested precedent in pharmacology of using bioassays for drug discovery. For example, propranolol was developed in 1964 (41), almost 30 years before cloning of the beta receptor gene (42). By a similar route and using parathyroid slices, Ed Nemeth developed calcimimetics in 1988 (43), well before Ed Brown cloned the *CASR* gene in 1993 (18). Cloning of the *CASR* gene is presumed to have helped promote the further development of drugs acting in a positive or negative manner on the Ca-SR, but this has been proprietary information.

An Answer: A Gene Can Clarify a Novel Paradigm for Nonsuppression of Hormone Secretion

Signature features of FHH from the parathyroid gland have included onset of hypercalcemia at birth, persistence of hypercalcemia immediately after subtotal parathyroidectomy, and parathyroid pathologic features during hypercalcemia that are normal or mildly hyperplastic (Table 3) (44). Each of these features of FHH suggests a decrease in suppression of parathyroid hormone secretion, mainly uncoupled from an increase of proliferation (Fig. 2). This scenario contrasts with the paradigm of virtually all other causes of

hyperparathyroidism, with increased proliferation and slow development of a monoclonal or oligoclonal neoplasm (or neoplasms) in the parathyroid glands (Table 3).

Mutations of the *CASR* gene helped explain the unusual clinical paradigm of FHH. Identification of the encoded sequence and biologic work afterward established that the *CASR* gene encoded the Ca-SR, a G protein-coupled sensor for extracellular calcium (45). Such a molecule, acting at the plasma membrane and homologous to rhodopsin, was suited for sensing in serum and immediate signal transduction (such as rapid regulation of secretion) rather than for regulation of proliferation.

The paradigm of a dysregulation of hormone secretion disproportionate to proliferation also occurs in several other rare hereditary syndromes (Table 4). Therein, the mutation can underlie dysregulated secretion of insulin (46), thyroid hormones (47), or androgens (48); the mutated *TSHR* and *LHR*, like the *CASR*, encode sensors that are G protein-coupled receptors. This unusual paradigm has clinical implications. In particular, a surgical exploration for an underlying adenoma should not be attempted.

QUESTION: WHY ARE THERE CASES OF MISSING MUTATIONS IN HYPERPARATHYROID SYNDROMES?

FIH can be classified as a syndrome or as a category for leftover nonsyndromal hyperparathyroid kindreds. After causes for a weakly expressed syndrome (MEN 1, FHH, or HPT-JT) have been eliminated, about 70% of kindreds with FIH still do not have an identifiable mutation in a main hyperparathyroid syndromal gene (49–51). One locus of an unidentified FIH gene has been mapped to chromosome 2p (52).

In fact, each of the 4 hyperparathyroid genes fails to show a mutation in 3% to 40% of syndromal cases as well (Table 5). One kindred with FHH showed linkage of its defect to chromosome 19p (*FBHH2*); 2 kindreds showed linkage of the trait to chromosome 19q (*FBHH3*) (53,54). In theory, a gene at these or other loci could also contribute in the hemizygous or homozygous form to NSHPT, but no such cases have been identified. The causes of unidentified mutations have not been clarified for *RET* or *HRPT2*.

Possible causes for unidentified mutations in these or other genes are understood. These factors may be inside or outside the syndromal gene.

A mutation of the main syndromal gene that is outside the zone amplified by polymerase chain reaction will not be seen by the mutation detection method. Such 5', 3', and intronic mutations have been recognized for other genes (55). Promoter methylation has been found for the *MEN1* gene in sporadic pancreatic ductal cancer (56), but no germline promoter mutations have been reported in MEN 1.

A large heterozygous deletion, such as deletion of more than a complete copy of the syndromal gene, will result in amplification by polymerase chain reaction of only the normal copy and failure to detect any mutation. Large deletions have been reported as rare in the *MEN1* gene (57,58).

A syndrome caused by a mutation in an unidentified gene is an important possibility and can justify the search for another gene (or genes) (see subsequent material). An important clue to such a cause can be a haplotype or genetic linkage analysis that excludes causative attribution to the syndromal gene in that family.

Laboratory error at any step, such as sample mislabeling, can result in failure to detect a mutation or assignment of a mutation that is not present in the patient (59).

CDKI GENES IN FAMILIAL HYPERPARATHYROIDISM

The *CDKI* Gene Family

The 7 *CDKI* genes form 2 families that participate in cell cycle regulation (the INK family and the CIP/KIP family). Assignment of a gene to either of the 2 *CDKI* families is based on sequence homology (60). Their role as *CDKI* genes is defined by their ability to bind to a cyclin-dependent kinase and inhibit its kinase activity. Their downstream action is to inhibit phosphorylation of critical proteins, such as the retinoblastoma protein.

Cell Cycle-Related Gene Mutation in Rodents

In the 1990s, knockouts of cell cycle-related genes were explored in mice. An early finding was that knockout of *Rb1* caused a tumor of the intermediate lobe of the pituitary gland. There was a focus on *Rb1*, *p53*, *p18*, *p21*, *p16*, and *p27* (61,62). In 2000, an unexpected phenotype was reported in mice with combined knockouts of 3 of the 4 alleles of *p27* and *p18* (63). The mice had a high penetrance concomitantly for tumors characteristic of both MEN 1 and MEN 2A. In several studies, the Atkinson laboratory (in Neuherberg, Germany) reported a similar phenotype that they termed MENX in a strain of laboratory rats with the additional feature of cataract. Positional cloning revealed a homozygous inactivating mutation of *p27* (64).

CDKI Mutations in Humans

The aforementioned investigative group, at the same time, reported an inactivating heterozygous *p27* mutation in 1 human kindred with MEN 1 and no identified *MEN1* mutation (64). This was confirmed separately by the finding of an inactivating *MEN1* mutation in an apparently sporadic case of MEN 1 (65). The disorder in humans was termed MEN 4 (#610755) by the Online Mendelian Inheritance in Man. It was clearly rare because *p27* mutation testing in several larger MEN 1 series did not identify more mutations (66–68). These results also excluded the possibility that the *p27* mutation would account for the subgroup of MEN 1 cases with parathyroid and pituitary tumors but only a 7% prevalence of *MEN1* germline mutations (67).

Agarwal et al (69) analyzed a larger group, consisting of 196 patients selected as referred because of a MEN 1-like phenotype, each of whom had no identifiable mutation in the *MEN1* gene. They sequenced each of the 7 *CDKI* genes in all cases. Seven cases showed missense mutations, which were classified as pathologic in bioassays. Three mutations were in *p27*. The others were in *p15*, *p18*, and *p21*. The absence of mutations in *p16* or *p57* *CDKI* genes likely reflected the involvement of these genes in familial melanoma and Beckwith-Wiedemann syndrome, respectively. Because the *CDKI* mutations represent about 2% of MEN 1-like cases including FIH, it is likely that other genes will be found to be mutated in this group. There was no recognizable phenotype or bias of tumors distinct from MEN 1, reflecting in part small families and the sampling bias toward MEN 1.

THE NEXT QUESTION: WHAT MAY BE THE BENEFIT FROM IMPROVED SEQUENCING METHODS?

Sequencing of hyperparathyroid syndromal genes has been a fruitful process. One could not have predicted the degree to which these genes are involved in common tumors. Nevertheless, obvious gaps exist in our identification of involved genes. Some of the “main” hyperparathyroid genes probably have not yet been identified. Moreover, it is unclear how many genes contribute to hyperparathyroidism in a “supporting” way. Mutation elsewhere in the same gene or even in a different but tightly linked gene seems a likely process in a

variant of MEN 1 that includes rare gastrinoma and frequent prolactinoma, a phenotype that has been tracked unchanged in several generations of 3 large kindreds (70).

Powerful enhancements of gene sequencing will make mutation identification even more robust in the very near future (71). The speed of sequencing has increased more than 10,000-fold in 10 years, and the cost of sequencing has declined more than 10,000-fold during 10 years. The costs of data processing have not decreased in pace with these changes. Different sequencing technologies are competing, and it is unclear which will become dominant. There is speculation about soon determining the sequence of the complete genome for \$1,000 per case. One shortcut is to sequence exonic regions selectively, representing only 1% of the genome and representing the sequences where most of the interest seems to be focused. Important results have already been derived from whole exome sequencing in somatic tissues: pancreatic islet tumor (72) and aldosteronoma (73).

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Abbreviations

Ca-SR	calcium-sensing receptor
CDKI	cyclin-dependent kinase inhibitor
FHH	familial hypocalciuric hypercalcemia
FIH	familial isolated hyperparathyroidism
HPT-JT	hyperparathyroidism-jaw tumor syndrome
MEN 1	multiple endocrine neoplasia type 1
MEN 2A	multiple endocrine neoplasia type 2A
NSHPT	neonatal severe hyperparathyroidism

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Fig. 1.

Timeline for 5 of the 6 hyperparathyroid syndromes, showing their year of first discovery as a familial syndrome and their year of first association to a germline causative hyperparathyroid gene. Familial isolated hyperparathyroidism is omitted here because its gene (or genes) has not yet been identified. *FHH* = familial hypocalciuric hypercalcemia; *HPT-JT* = hyperparathyroidism-jaw tumor syndrome; *MEN1* = multiple endocrine neoplasia type 1; *MEN2A* = multiple endocrine neoplasia type 2A; *NS HPT* = neonatal severe hyperparathyroidism.

Fig. 2.

Two pathways for cellular cause of hyperparathyroidism. Either pathway can cause a downstream expression of inappropriate secretion of parathyroid hormone (*PTH*) in serum. The proliferation pathway involves a 2-hit process that demonstrates a years-long delay until monoclonal or oligoclonal overgrowth, with consequent expression as a tumor. The pathway with decreased suppression of hormone secretion is expressed from birth in all *PTH* secretory cells and may or may not detectably affect parathyroid pathologic features. *FHH* = familial hypocalciuric hypercalcemia; *HPT* = hyperparathyroidism; *MEN* = multiple endocrine neoplasia.

Table 1**Main Hyperparathyroid Syndromes and Their Main Identified Genes**

Syndrome	Main gene
Familial hypocalciuric hypercalcemia	<i>CASR</i>
Neonatal severe hyperparathyroidism	<i>CASR</i>
Multiple endocrine neoplasia type 1	<i>MEN1</i>
Multiple endocrine neoplasia type 2A	<i>RET</i>
Hyperparathyroidism-jaw tumor syndrome	<i>HRPT2</i>
Familial isolated hyperparathyroidism	Unknown

Table 2

Wide Differences in Parathyroid Gland Pathologic Conditions and in Management of Parathyroid Glands, Stratified by Syndrome^a

Syndrome	Pathologic condition in parathyroid glands	Therapy for parathyroid glands
Familial hypocalciuric hypercalcemia	None (normal)	No parathyroidectomy
Neonatal severe hyperparathyroidism	Early, 4 large glands	Urgent total parathyroidectomy
Multiple endocrine neoplasia type 1	3–4 asymmetric tumors	Subtotal parathyroidectomy, based on severity
Multiple endocrine neoplasia type 2A	1–2 asymmetric tumors	Parathyroid tumor removal, based on severity or incidental to thyroidectomy
Hyperparathyroidism-jaw tumor syndrome	Parathyroid cancer (20%)	Surgical resection of cancer, if present
Familial isolated hyperparathyroidism	All possibilities	Treatment of multigland disease

^aAll entries represent typical features. Each entry is representative of a broad spectrum.

Table 3

Comparison Between Clinical Expressions of Hyperparathyroidism From 2 Types of Defect

Clinical feature	Type of defect	
	Increase in proliferation (example: MEN 1)	Decrease in suppression of PTH secretion (example: FHH)
Delay of hypercalcemia after birth	Yes	No
Tumors	Yes	No
Remit by subtotal removal	Yes	No
Hormone-secreting cancer	Yes	No

Abbreviations: FHH = familial hypocalciuric hypercalcemia; MEN 1 = multiple endocrine neoplasia type 1; PTH = parathyroid hormone.

Table 4

Syndromes of Hormone Oversecretion Due to Mutation in a Sensor of Secretion

Syndrome	Mutated sensor	Ligand detected by sensor	Hormone with decreased suppression of secretion
Familial hypocalciuric hypercalcemia	<i>CASR</i>	Calcium ⁺⁺	Parathyroid hormone
Neonatal severe hyperparathyroidism	<i>CASR</i>	Calcium ⁺⁺	Parathyroid hormone
Persistent hypoglycemic hyperinsulinemia of infancy	<i>SUR1</i>	Glucose	Insulin
	<i>KIR6.2</i>	Glucose	Insulin
	<i>GK</i>	Glucose	Insulin
	<i>GLUD1</i>	Glucose	Insulin
Neonatal thyrotoxicosis	<i>TSHR</i>	Thyroid-stimulating hormone	Thyroxine/triiodothyronine
Testotoxicosis	<i>LHR</i>	Luteinizing hormone	Androgens

Table 5

Missing Mutations, Stratified by Hyperparathyroid Syndrome and Gene

Syndrome	Main hyperparathyroid gene	Missing mutation (%)	Other causal genes	Chromosomal loci of unidentified genes
Familial hypocalciuric hypercalcemia	<i>CASR</i>	40	...	19p, 19q
Neonatal severe hyperparathyroidism	<i>CASR</i>	?? ^a	? ^a	...
Multiple endocrine neoplasia type 1	<i>MEN1</i>	30	p18, p27, p15, p21	...
Multiple endocrine neoplasia type 2A	<i>RET</i>	3 ^b	...	...
Hyperparathyroidism-jaw tumor syndrome	<i>HRPT2</i>	40	...	...
Familial isolated hyperparathyroidism	<i>MEN1</i>			
	<i>CASR</i>	70	...	2p
	<i>HRPT2</i>			

^aToo few cases. In particular, not known whether other genes for familial hypocalciuric hypercalcemia are implicated in neonatal severe hyperparathyroidism.

^bMultiple endocrine neoplasia type 2A rarely, if ever, manifests as familial hyperparathyroidism. *RET* mutations are scored here if they are missing in the full syndrome of multiple endocrine neoplasia type 2A.