Genetics of Multiple Endocrine Neoplasia Type 1/Multiple Endocrine Neoplasia Type 2 Syndromes

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KEYWORDS

• Multiple endocrine neoplasia type 1 • Multiple endocrine neoplasia type 2 • Hereditary • Genetic testing • Genetic counseling

KEY POINTS

- Genetic testing is an important part of diagnosing, managing, and treating multiple endocrine neoplasia type 1 (MEN1) and multiple endocrine neoplasia type 2 (MEN2) syndromes.
- Approaches to genetic testing for MEN1 and MEN2 have changed, as has understanding of these conditions.
- In some cases, genetic testing for MEN1 and MEN2 can provide uninformative or unclear results that do not necessarily clarify a suspected diagnosis.
- Genetic test results should be carefully interpreted in the context of a patient's personal and/or family history.

INTRODUCTION

The breadth and depth of knowledge about MEN1 and MEN2 are impressive; years of study by many dedicated researchers have allowed characterizing and refining estimates of disease penetrance, expressivity, optimal management, and the spectrum of disease-causing genotypes. This work has permitted risk stratification for medullary thyroid carcinoma (MTC) based on *RET* genotype in MEN2,[1] which has led to genotype-phenotype correlations that are at the crux of management

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recommendations for patients; in cases of MEN1, a better understanding of the age-related penetrance and expression of disease manifestations has helped guide clinicians in determining to whom and when to offer germline *MEN1* testing.[2] For both MEN1 and MEN2 patients and their family members, undergoing genetic testing has expanded understanding of the respective mutation spectrums, while parallel advances in genetic testing technology have also increased the possibility of inconclusive genetic test results (ie, variants of uncertain clinical significance [VUS]). These realities, in the context of certain clinical and/or family histories, can give rise to scenarios that challenge the way of approaching the management of these diseases and the counseling provided to patients and their family members. Examples of such scenarios are discussed to illustrate the evolving understanding of these hereditary conditions.

A HISTORICAL PERSPECTIVE

The recognition of MEN1 and MEN2 as discernable endocrine tumor predisposition syndromes came during the greater first half of the twentieth century. In 1903, Jacob Erdheim,[3] a German pathologist, first described on autopsy an acromegalic man with a pituitary tumor and parathyroid adenomatosis, a constellation of findings that, along with pancreatic islet tumors, was also identified in several related individuals by Paul Wermer,[4] who first suggested that this represented an autosomal dominant, hereditary trait; this syndrome was first named Wermer syndrome but is now known as MEN1. John Sipple[5] was the first, in 1961, to publish on the association of MTC and pheochromocytoma as a second, distinct multiple endocrine neoplasia syndrome; it was only 5 years later that Williams and Pollock published their account of related patients with MTC, gastrointestinal tract ganglioneuromatosis, and mucosal neuromas.[6] Respectively, these syndromes are MEN2A and MEN2B, which were both eventually found to be caused by mutations in the *RET* proto-oncogene.[7,8] Around this same time, mutations in *MEN1* were identified in families affected by MEN1.[9] In the decades that followed these discoveries, the clinical manifestations (both endocrine and nonendocrine) and their molecular etiologies have been well studied and reviewed in the literature, permitting a remarkable understanding of disease penetrance, expressivity, genotype-phenotype correlations, and tumorigenesis.[10–12]

EVOLUTION OF GENETICS TESTING FOR MEN1 AND MEN2

Clinically available genetic testing for MEN1 and MEN2 is now widely available and is an important component of diagnosing affected patients and their family members. Although the diagnoses of MEN1 and MEN2 were, for many years, based on personal and/or family history of endocrine neoplasias, genetic testing to confirm or exclude the presence of a disease-causing mutation can allow for earlier identification of affected family members and can, in some cases, be used to guide management. The American Thyroid Association now recommends that every individual diagnosed with MTC be offered germline *RET* testing to assess for an underlying MEN2-associated gene mutation,[13] and, although there is no similar recommendation for patients suspected to have MEN1, guidelines exist for when genetic testing should be offered based on personal and/or family history of MEN1-associated manifestations.[2,14,15] Consideration of clinical diagnostic criteria for these conditions, however, is still important, particularly in cases of MEN1, where genetic testing sometimes fails to identify a disease-causing mutation in affected individuals and families.[15,16] In these cases, screening recommendations may still be formulated for at-risk family members even in the absence of an identifiable, pathogenic *MEN1* mutation.