24. FROM GENES TO DECISIONS

EVOLVING VIEWS OF GENOTYPE-BASED MANAGEMENT IN MEN 2

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INTRODUCTION

The genomic revolution of the past 20 years has led to the identification of the genetic mechanisms that are responsible for a wide variety of human cancers, and has made a huge impact on our ability to recognize, diagnose and, more recently, treat patients with these diseases. Genetic diagnosis of heritable forms of cancer holds out the potential for presymptomatic detection in familial cases and raises the possibility of prophylactic treatments that would decrease morbidity and mortality and improve the quality of life for those affected. While the potential impact of these advances is huge, to date, our understanding of the underlying genetic events that contribute to the familial cancers has only allowed us to significantly modify our management of the disease in a few instances. The paradigm for such genetically based molecular management is the multiple endocrine neoplasia type 2 (MEN 2) syndromes.

Multiple endocrine neoplasia type 2 (MEN 2)

As described in previous chapters (1), MEN 2 is an inherited cancer syndrome characterized by medullary thyroid carcinoma (MTC) and its precursor lesion, C-cell hyperplasia. These phenotypes are clinically recognizable in >90% of all cases (2). Traditionally, MEN 2 has been divided into three disease subtypes, based on the presence of other associated phenotypes. The most common subtype, MEN 2A accounts for about 85% of MEN 2 cases. In addition to MTC, MEN 2A is characterized by pheochromocytoma (PC), tumours of the adrenal chromaffin cells, in about 50% of

cases, and hyperparathyroidism (HPT) in 15–30% of individuals. The most aggressive of the MEN 2 subtypes, MEN 2B, occurs in about 5% of cases and has a median age of tumour onset that is 10 years earlier than other forms of MEN 2 (<10 years) (3, 4). Approximately 50% of MEN 2B are *de novo* cases with no previous family history (5). As in MEN 2A, PC occurs in about 50% of individuals with MEN 2B but HPT is rare and patients also have a variety of other developmental anomalies such as buccal neuromas, marfanoid habitus, ganglioneuromas of the gut, and thickened corneal nerves (3, 6). The final disease subtype, familial MTC (FMTC) is characterized only by thyroid tumors and has no other associated anomalies. This disease form is the least aggressive MEN 2 subtype and may have a lower penetrance and later disease onset (7). As a result, FMTC families are frequently small and may be phenotypically quite difficult to distinguish from MEN 2A families in which cases of PC or HPT have not yet manifested. Because of this, stringent definitions have been suggested in which the diagnosis of FMTC requires a minimum of 4 (8, 9) or even 10 (10) family members with MTC in the absence of other phenotypes.

RET and the genetics of MEN 2

MEN 2 is inherited as an autosomal dominant disease and, as a result, all first-degree relatives of an affected individual are at 50% risk of inheriting the disease causing mutation. Although they differ in phenotype and aggressiveness, all three MEN 2 subtypes are caused by mutations of the *RET* (Rearranged in Transfection) oncogene (8, 9). *RET* encodes a cell surface receptor tyrosine kinase normally required for development of neuroendocrine cell types, the peripheral nervous system, and kidney (1, 11). *RET* mutations are identified in more than 95% of all MEN 2 families and there is no evidence of families in which the MEN 2 phenotype is not linked to *RET*. In each case, RET mutations are single amino acid substitutions that result in inappropriate activation of the RET receptor (12, 13). Mutations are clustered in "hot spots" in the extracellular domain (exons 10 and 11) or in the tyrosine kinase domain (exons 13–16) of the receptor (8, 9) (Figure 1).

Because >99% of mutations occur in only 10 codons of RET, direct DNA testing in MEN 2 is simple, widely available, and very efficient and is recommended for all at-risk individuals (Discussed below).

Although all MEN 2 subtypes are associated with *RET* mutations, specific mutations confer much higher risks for some phenotypes. For example, mutations of *RET* codon 634 are strongly correlated with HPT and PC and thus, not surprisingly, represent 85% of MEN 2A mutations (14, 15). In MEN 2A, mutations generally alter specific cysteine residues in the extracellular domain of RET (residues 609, 611, 618, 620, 634), resulting in a ligand-independent constitutively activated molecule (Figure 1). The mutations found in patients with FMTC have a broader range of functional effects, and may include both the same type of mutations as those seen in MEN 2A as well as mutations in the tyrosine kinase domain (residues 768, 804, 891) that appear to alter ATP binding (16). More than 95% of MEN 2B patients share the same amino acid substitution (Met918Thr) in the binding pocket of the RET kinase