DNA TESTING FOR MORE SOPHISTICATED CLINICAL MANAGEMENT OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN 2)

DNA testing to predict cancer predisposition currently plays an important role in the clinical management of hereditary cancer. MEN 2 syndromes are autosomal dominant inherited cancer syndromes, and DNA testing is now useful in clinical practice of these diseases. MEN 2 syndromes are subclassified into MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). MEN 2A is characterized by the development of medullary thyroid carcinoma (MTC), pheochromocytoma and hyperparathyroidism (HPT). MEN 2B is associated with MTC and pheochromocytoma but has developmental abnormalities such as marfanoid habitus, mucosal neuromas and ganglioneuromatosis. In FMTC, MTC is the only disease feature. Recently, the RET proto-oncogene has been identified as the susceptibility gene for MEN 2 (1–3). The gene encodes a receptor tyrosine kinase and its physiological ligands are glial-cell-line-derived neurotropic factor (GDNF) and neurturin (NTN) which require the presence of co-receptors of GDNFR-alpha and NTN-alpha for signal transduction to occur, respectively (4,5). In MEN 2A and FMTC cases, the mutations are clustered in the extracellular cysteine rich domain (codons 609, 611, 618, 620, 630 and 634) although they were also found in the intracellular tyrosine kinase domain (codons 768, 790, 791, 804 and 891) as rare cases. In the majority of MEN 2B patients, a mutation has been identified at codon 918 in the extracellular tyrosine kinase domain while a mutation at codon 883 was also found in a few cases.

Mutational analysis of the RET proto-oncogene cannot only confirm diagnosis of MEN 2 but also identify asymptomatic family members at risk of this syndrome. Before DNA testing was available, both affected and unaffected individuals at 50% risk of MEN 2 were required to undergo annual biochemical screening for MTC, pheochromocytoma and HPT from early childhood. These screening tests include a pentagastrin or combined pentagastrin–calcium provocative test which often generated false positive or false negative results in addition to patients' physical discomfort. DNA testing, which is accurate and sensitive and does not give physically adverse effect on patients, has resolved these problems, and has eliminated the need for unnecessary biochemical screening in family members who are not at risk. This diagnostic tool can also allow predisposed family members to have a chance of surgical intervention such as prophylactic thyroidecotomy before the development of MTC. Although MTC occurs in over 95% of patients with MEN 2 and is potentially lethal, it can be prevented by prophylactic thyroidecotomy. The thyroidecotomy is safe when the surgery is performed by an experienced surgeon and thyroid hormone replacement is available.

However, it appears controversial to decide when and on which affected family members the prophylactic surgery should be performed. Skinner et al. recommended that prophylactic thyroidecotomy should be done at the age of five in individuals at risk of MEN 2A, and at an earlier age in those at risk of MEN 2B because of the higher virulence and earlier onset of MTC in this phenotype (6). Lips et al. suggested that the surgery for individuals at risk of MEN 2A can be left until the positive results of the provocative test or age 12–13 (7). For presymptomatic individuals of FMTC, prophylactic thyroidecotomy may be delayed because of its milder phenotype. The clinical features of MEN 2A and FMTC, however, vary among each family. If one can predict clinical features of MTC such as onset of the disease, clinical aggressiveness and extent of MTC by knowing the type of the RET mutation, we may be able to determine the appropriate time and procedure of surgical intervention with a more refined basis for each individual. Previously, genotype-phenotype correlations have been analyzed in several studies, but they were performed to determine whether knowing the nature and position of the mutation can predict the development of pheochromocytoma and hyperparathyroidism. These results demonstrated that mutations at codon 634 were associated with the presence of pheochromocytoma and hyperparathyroidism (8–10). There has been, however, no study which analyzed the relationship between genotype and detailed clinical features including aggressiveness and extent of MTC in these phenotypes.

Egawa et al. in the current issue of the Japanese Journal of Clinical Oncology reported the correlation between types of the RET mutation and clinical features including clinical aggressiveness of MTC in Japanese patients with MEN 2 (11). In this study the authors emphasized the correlation between genetic alteration at codon 634, the most frequent affected codon of the RET proto-oncogene in MEN 2, and clinical features of MTC. They found that, in the cases with C634R, the incidence of lymphatic metastasis in patients whose tumor diameter was smaller than 2 cm was significantly lower than in patients whose tumor diameter was larger than 2 cm, and that no cases with C634R had lymphatic metastasis until the tumor grew larger than 1.2 cm in diameter. In contrast, most patients with a mutation at codon 634, which replaces cysteine to tyrosine (C634Y), had progressive disease regardless of tumor size or age at operation. These results suggest that thyroidecotomy may be delayed in predisposed individuals with C634R until the positive biochemical test is obtained whereas it should be performed for asymptomatic family members with C634Y at an early age. These results also imply that clinical features may differ among the patients with different nature of the mutation even if the position of the mutation is the same. Further accumulation of the data obtained by continuous study is needed to establish the correlation between the genotype and clinical features of MTC in MEN 2. Not only identification of presymptomatic individuals at risk of MEN 2 but also prediction of detailed clinical feature by DNA testing will enable patients and predisposed family members to receive more sophisticated clinical management.
References


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