

Epidemiology, Clinical Features, and Genetics of Multiple Endocrine Neoplasia Type 2B in a Complete Population

Introduction

Multiple endocrine neoplasia type 2 (MEN 2) is a hereditary autosomal dominant endocrine syndrome comprising MEN 2A, MEN 2B, and familial medullary thyroid cancer (MTC) [1, 2]. MEN 2B is characterized by early development of aggressive MTC, and prophylactic total thyroidectomy is advocated by 6 months of age [3–5]. Multiple and bilateral pheochromocytoma occur in 50% of patients, and some with undiagnosed pheochromocytoma may die of cardiovascular crisis perioperatively [4, 6].

MEN 2B may be identified in infancy or early childhood [7] by the presence of mucosal neuromas of the anterior dorsal surface of the tongue, palate, or pharynx. Identification of *RET* gene mutations in MEN 2B in 1994 allowed the possibility of direct DNA-based mutation testing [3]. Before that, linkage testing was available [8, 9]. *RET* molecular genetic testing should be performed as soon as possible after birth in all children known to be at risk or, if no family history exists, as soon as the clinical diagnosis is suspected [2]. Most patients have mutations in codon 918 and, rarely, in codons 883 and 922.

The epidemiology of MEN 2B is unknown. The prevalence of all MEN 2 cases is ~1 in 35,000 [2]. The prevalence of MEN 2B is estimated as between 1 in 600,000 [10] to 1 in 4 million [11], but no figures exist. The annual incidence has been estimated at 4 per 100 million per year [12].

Methods

The Northern Ireland regional genetics service covers a fixed population of ~1.8 million and has a centralized network of genetic clinics covering the entire region, with a single molecular genetics laboratory. The population is stable, with little immigration and emigration, and is ideal for epidemiological studies. Two-thirds of the region is bound by sea and the remainder by a land border with the Republic of Ireland. Prospective records have been maintained for MEN 2 cases since 1988. We interrogated the register of MEN 2B cases to identify cases. Molecular genetic confirmation of diagnoses was carried out in all cases. We included cases with no definite or substantiated family history, all confirmed as MEN 2B on genetic testing, and referred to the genetic clinic between 1988 and 2012. All patients were clinically examined, and a detailed history of symptoms, investigations, and procedures undertaken as well as family history were obtained and validated by medical records.

Inclusion criteria for testing included MTC at an early age, marfanoid body habitus, or presence of mucosal neuromas or other characteristic features of MEN 2B.

For the prevalence calculation, period prevalence and point prevalence were calculated. Point prevalence was

Table 1. Clinical features of the multiple endocrine neoplasia type 2B cases

Feature	Patient 1	Patient 2	Patient 3	Patient 4
MTC, age at diagnosis, years	25	8	37	10
Pheochromocytoma, age at diagnosis, years	26	24	37	n.a.
Presence of mucosal neuroma	+	+	+	+
Marfanoid body habitus	+	+	+	+
Positive family history	–	–	–	–

Abbreviations: +, present; –, absent; MTC, medullary thyroid cancer; n.a., not available.

calculated on the prevalence day of April 21, 2012. Period prevalence was calculated from 1988 to 2012 (average population of 1,689,588 and 4 cases). Period prevalence was defined as persons with a given health indicator during a specified time period in a population during the same time period.

The total population studied was recorded at the last census on April 21, 2012 (1.824 million) [13].

Results

The period prevalence was 0.178×10^{-5} (mean 24 year population: 1,689,588). The point prevalence was 0.219×10^{-5} . Four sporadic cases were identified throughout 24 years. Three patients were alive on the prevalence day, April 21, 2012. Clinical features are shown in Table 1, and family trees are shown in Figure 1.

All of the patients had MTC: two in childhood (aged 8 and 10 years) and two in adulthood (aged 24 and 37 years). Three were diagnosed with pheochromocytoma. The youngest patient remains under thorough screening and remains symptom free to date. All had elongated faces with wide-eyed expressions, large eyebrows, and prominent lips and mucosal neuromas (two patients underwent cosmetic surgery to have neuromas removed from their lips). All had a typical marfanoid body habitus. Three had some gastrointestinal problems including constipation.

Discussion

This paper reports the first published prevalence of MEN 2B. Estimates of the epidemiology of MEN 2B were based on a single population with one centralized genetic clinic.

We sampled a stable population in a defined geographical area, and 100% of cases had the common codon 918 mutation. Ascertainment is fairly close to complete with rigorous register information on cases since 1988, giving minimum prevalence because mild cases may still be missed.

We have excellent relationships with the centralized endocrine medical and surgical teams that refer all cases of medullary thyroid cancer for assessment.

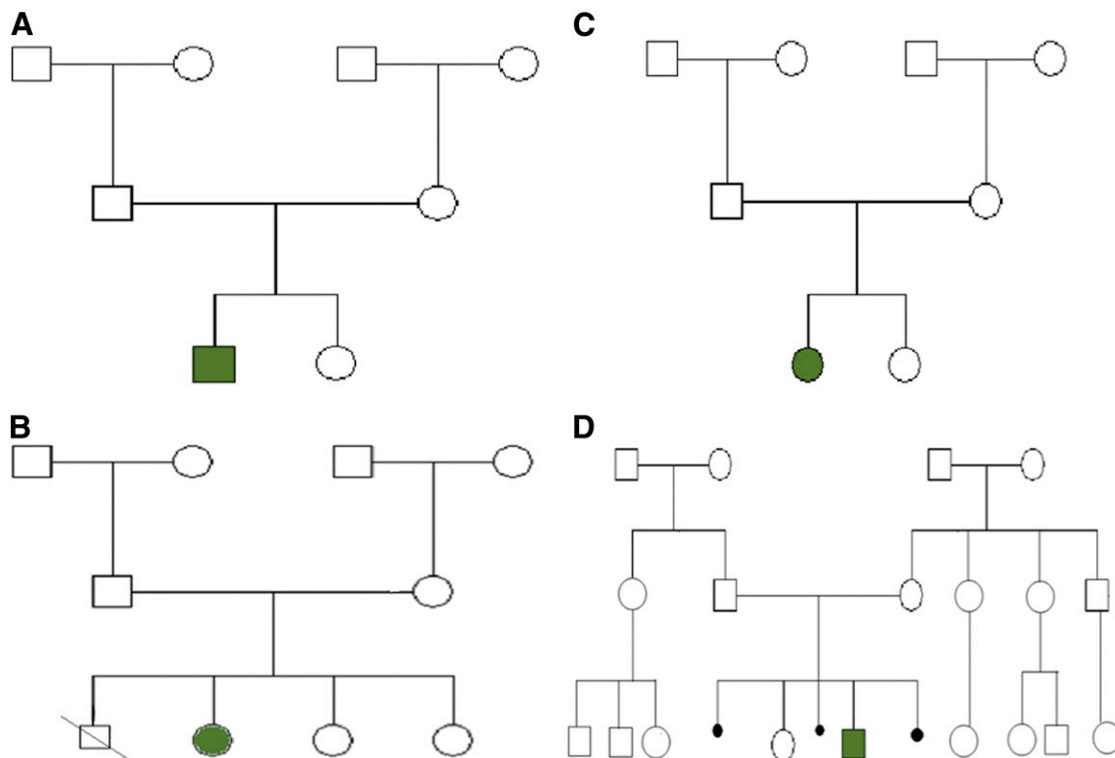


Figure 1. Pedigrees of families with multiple endocrine neoplasia type 2B (A–D). Affected index cases are shown in green shading.

Defining the prevalence of MEN 2B is an important step in determining the public health impact of this condition. Accurate figures allow prediction of numbers of expected cases in populations.

The clinical features of our patients are all consistent with MEN 2B. None of the MEN 2A cases examined in this period had evidence of neuromas or early onset of MTC. The codon 918 mutation was present in all of our patients and is the most common mutation. Cascade screening confirmed the mutation to be de novo in all of our cases. No cases due to the rare codon 883 or 922 mutations were identified, and cases with these codon mutations appear to have a similar phenotype to those with the common 918 mutation. In all cases, early prophylactic thyroidectomy is the treatment of choice before 6 months of age; given the aggressive progression in some cases, consideration should be given to thyroid surgery within the first month of life [14]. Planned surgery after testing of cord blood or prenatal testing may be helpful in offspring of those with diagnosed cases; however, recognition of cases in early life may be difficult because all our cases were de novo mutations.

Conclusion

The prevalence of MEN 2B is $\sim 0.2 \times 10^{-5}$. All MEN 2B cases were new mutations with no positive family history, and all presented classically with MTC, marfanoid body habitus, and mucosal neuromas. All had the common codon 918 mutation in exon 16 of *RET*. MEN 2B remains a relatively rare condition and can be easily missed if the diagnosis has not been considered.

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Disclosures

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<http://dx.doi.org/10.1634/theoncologist.2014-0277>

For Further Reading:

Madhuchhanda Roy, Herbert Chen, Rebecca S. Sippel. Current Understanding and Management of Medullary Thyroid Cancer. *The Oncologist* 2013;18:1093–1100.

Implications for Practice:

Medullary thyroid cancer (MTC) typically accounts for approximately 4% of all thyroid cancers. Of these, 20% of cases are hereditary and can be found in multiple endocrine neoplasia syndrome or as part of familial MTC based on a specific germline mutation in the RET proto-oncogene. This article summarizes the current approaches and guidelines available for the diagnosis, evaluation, and management of patients and their family members with suspected MTC. Surgery is the standard of care, and prophylactic surgeries are performed in genetic carriers. Tyrosine kinase receptor inhibitors vandetanib (ZD6474) and cabozantinib (XL184) were recently approved by the U.S. Food and Drug Administration as promising systemic therapy for advanced MTC.