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MEN 2A: Update on the Northern Ireland and Australian Family

Patrick J. Morrison,* David R. Hadden,† Colin J. Russell,‡ and Norman C. Nevin*

The Northern Ireland/Australian family with multiple endocrine neoplasia type 2A (MEN 2A) originally described in 1987 is presented with a revised and enlarged pedigree. Four members of the first generation studied have died. A seventh member of the second generation studied has developed medullary thyroid carcinoma and has progressed to surgery. None of the third generation members studied has shown any conclusive abnormality in metabolic screening tests. Each member of the third and fourth generations has had genetic counseling and (if appropriate) DNA analysis with gene probes close to the MEN 2A gene locus on chromosome 10. All members of this highly penetrant family have remained asymptomatic for their disease. (Henry Ford Hosp Med J 1989;37:127-8)

Medullary thyroid carcinoma (MTC) in association with pheochromocytoma was originally described by Sipple (1) with the hereditary nature being recognized by Cushman (2).

Since the first two workshops on multiple endocrine neoplasia type 2 (MEN 2) in 1984 and 1986, the gene for MEN 2A has been localized to chromosome 10. All reports of MEN 2A show autosomal dominant inheritance with a high degree of penetrance.

The G-kindred, originally described in 1987 (3), have been living in County Antrim, Northern Ireland, for many generations. Several members emigrated to Australia in their youth, producing three Australian branches of the pedigree. Initial screening using basal unstimulated plasma calcitonin (CT) and 24-hour urinary catecholamines, followed by adrenal computed tomography and ¹³¹I meta-iodo-benzylguanidine imaging produced positive results in some members of the family. We have updated these results and have used both pentagastrin stimulation CT tests and DNA gene probe analysis to obtain further information in patients whose initially described tests were either uninformative or inappropriate. The updated pedigree is shown in the Figure.

Updated Case Reports

Patients' ages reported are as of 1988.

Case I-3: This patient, initially thought to be deceased, was discovered to be alive and healthy at age 88. She remains clinically euthyroid and asymptomatic. Blood has been taken for DNA analysis.

Case II-1: This patient, the index case, died in 1972. We hope to use histologic tissue for DNA extraction to aid pedigree analysis.

Cases II-2 and II-6: Both remain well after thyroid surgery. Blood has been taken for DNA analysis.

Cases II-3, II-4, II-5: These three Australian brothers all died of MTC.

Case II-7: This member is apparently asymptomatic and has refused metabolic and genetic screening. The thyroid gland was not palpable.

Cases III-1, III-2, III-4, III-5, III-12: All remain clinically asymptomatic. CT basal levels remain unchanged. Blood has been taken for DNA analysis.

Cases III-3, III-6, III-8, III-10, III-11, III-14: All are well following surgery for MTC. Blood has been taken for DNA analysis, but all have refused pentagastrin tests.

Case III-9: This member is clinically asymptomatic. Pentagastrin tests using the intravenous technique as described by Telenius-Berg et al (4) resulted in undetectable CT before and after stimulation.

Case III-13: This member is clinically asymptomatic. Pen-
<0.02 µg/L basal and
0.03 µg/L at two minutes. Blood has been taken for DNA analysis.

Case III-15: This member is clinically asymptomatic. Pentagastrin test results show CT levels of 0.02 µg/L basal and 0.03 µg/L at two minutes. Blood has been taken for DNA analysis.

Case III-7: This 25-year-old man has a barely palpable thyroid gland and no clinical symptoms. Initial basal plasma CT

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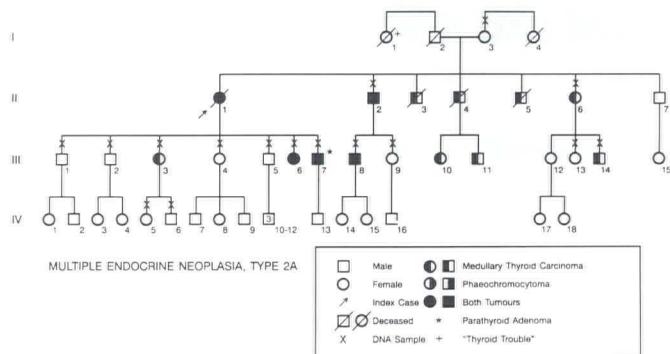
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Figure—Updated pedigree of G-kindred.

was 0.71 $\mu\text{g/L}$; CT remained elevated on subsequent measurements. Although he was initially unwilling to have thyroid surgery, total thyroidectomy done in 1988 showed multiple small foci of MTC, several C-cell adenomas, and a large parathyroid adenoma within the right lobe of the gland. He remains well with normal calcium and CT levels postoperatively. Computed tomography of the adrenals has shown bilateral nodules consistent with pheochromocytomas. Plasma and urinary catecholamines remain normal. Adrenal surgery is currently under consideration. Blood has been taken for DNA analysis.

Cases IV-5 and IV-6: Blood has been taken for DNA analysis. Basal CT levels are marginally elevated.

Remainder of generation IV cases: Basal CT levels remain unchanged. All members under 18 years of age have been screened only for basal CT levels. Pentagastrin testing has not been attempted, and blood has not been taken for DNA analysis.

Discussion

Between 1965 and 1986, 25 cases of MTC were diagnosed histologically in Northern Ireland. Seven of these are from the G-kindred. The remainder have not yet shown any hereditary tendency.

Although we attempted to bring family members together for same-day counseling and screening, we learned that this was inappropriate and inadvisable because of various family member interactions and the reasonable desire for personal discussion. Each member has subsequently been seen by one of us (PJM) on a one-to-one basis, usually in the patient's home. This has allowed the patients to discuss their problems and fear of the disease and has allowed DNA sampling from virtually all the patients over age 18. If the patients do not allow counseling and

screening for their own diagnosis, permission has been obtained for the results to be used to help other members of the pedigree.

Since the ethical guidelines for screening patients under age 18 are uncertain, we have not taken blood for DNA from most patients in generation IV; only two patients were studied with their parents' consent. This approach may change with either clinical concern or from changes in guidelines regarding screening of minors.

Some patients have declined pentagastrin testing but consented to DNA testing. The rationale is that pentagastrin testing is "invasive," ie, it involves injection of a foreign substance with uncomfortable but limited side effects, whereas gene testing is neither physically harmful nor invasive.

Easton et al (5) have suggested that there is an earlier onset of MTC in females and a tendency for pheochromocytoma to cluster in families. Our pedigree does not support the first hypothesis; most of our family members presented at about the same age. The pedigree does, however, show clustering of pheochromocytomas in two branches. The pedigree in general shows that the gene is highly penetrant in character but with a variable expressivity; no individuals diagnosed with MTC have shown symptoms.

We still do not know in whom the mutant gene originated. Patient I-1 was reputed to have a sister who died having had "thyroid trouble." Current genetic tracing using the RBP3, MCK2, and p10 alpha centromere probes may help either to confine or broaden the existing pedigree.

Acknowledgments

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