Hereditary Medullary Thyroid Carcinoma: Genetic Analysis of Three Related Syndromes

Hagay Sobol
Steven A. Narod
Isabelle Schuffenecker
Chris Amos
R. Alan B. Ezekowitz

See next page for additional authors

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol37/iss3/6
Hereditary Medullary Thyroid Carcinoma: Genetic Analysis of Three Related Syndromes

Authors
Hagay Sobol, Steven A. Narod, Isabelle Schuffenecker, Chris Amos, R. Alan B. Ezekowitz, and Gilbert M. Lenoir
Hereditary Medullary Thyroid Carcinoma: Genetic Analysis of Three Related Syndromes

Hagay Sobol,* Steven A. Narod,* Isabelle Schuffenecker,* Chris Amos,* R. Alan B. Ezekowitz,† Gilbert M. Lenoir,* and the Groupe d’Etude des Tumeurs a Calcitonine

Hereditary medullary thyroid carcinoma (MTC) appears in three forms: 1) in association with pheochromocytomas and parathyroid hyperplasia (multiple endocrine neoplasia type 2A [MEN 2A]); 2) with pheochromocytomas, neuromas of the mucous membranes, and a marfanoid appearance (MEN 2B); and 3) without pheochromocytoma. Despite these differences in presentation, age of onset, and clinical severity, limited genetic studies suggest that the three MTC variants may be due to inherited mutations at the same gene locus. We present further data in support of the hypothesis that allelic variation may underlie the diversity of these endocrine neoplasia syndromes. (Henry Ford Hosp Med J 1989;37:109-11)

More than 70 families have been identified in France in which two or more members are affected with medullary thyroid carcinoma (MTC) (1). Pheochromocytomas are also seen in a majority of these families. However, a substantial number of families have only the thyroid tumor. Rare cases of multiple endocrine neoplasia type 2B (MEN 2B) have been documented as well.

The gene for MEN 2A has been assigned by linkage to chromosome 10 (2-4). As part of a national screening effort undertaken in collaboration with the Groupe d’Etude des Tumeurs a Calcitonine (GETC), we have performed linkage analysis on 33 MTC families using a number of polymorphic probes flanking the centromere of chromosome 10. We present the results by MTC subgroup and discuss the issue of genetic heterogeneity in MTC families.

Methods

Thirty-three families suitable for linkage have been identified by the GETC and other collaborating physicians. Diagnosis of MTC and/or pheochromocytoma was based on pathology reports, hospital records, and the results of pentagastrin provocation tests. Details of the polymorphisms used are provided elsewhere (5,6). For the linkage program, penetrance was entered as 10%, 30%, 50%, 80%, and 95% for age groups 0-9, 10-14, 15-19, 20-29, and 30 years and above for the MEN 2A and MTC without pheochromocytoma (MTCWP) families. For MEN 2B, penetrance was set at 50% for ages 5 to 9 and 80% for 10 years and above. The HOMOG program was used to test whether the observed data are consistent with a single recombination fraction for both the MEN 2A and the MTCWP families (7).

Results

Nineteen families with MEN 2A, 13 families with MTCWP, and one family with MEN 2B were suitable for our linkage studies. Lod scores obtained with five informative probes are presented in the Table (8-11).

Because no recombination was found between the MCK2 and IRBP.H4 probes in our data (maximum lod = 15.24; θ = 0.00), we also assessed linkage between the MTC gene and the IRBP.H4/MCK2 haplotype. In the MTCWP families, a maximum lod score of 2.61 was seen at θ = 0.10. Although these results are supportive of a single genetic locus for the three syndromes, the lod scores attained for the MTCWP and MEN 2B families are insufficient to confirm linkage to the region.

The presence of possible genetic heterogeneity among the families was tested in two ways. First, we were unable to reject the hypothesis that all tested families were linked at a single locus. Second, when MEN 2A families were compared with the MTCWP families the recombination distances estimated with any of the five probes used did not vary significantly between the two groups (Table). For the MEN203 probe, the P-value approached significance, but this should be interpreted in view of the number of comparisons evaluated.

Discussion

Several large families have been reported in which MTC has been observed in the absence of pheochromocytoma (12-14). The distinction between the MEN 2A and MTCWP subtypes has been supported statistically (11). Whether the two forms repre-
Table

<table>
<thead>
<tr>
<th>Probes</th>
<th>Number of Informative Families</th>
<th>Maximum Lod Score</th>
<th>Recombination Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRBP.H4 (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN 2A</td>
<td>16</td>
<td>11.76</td>
<td>0.00</td>
</tr>
<tr>
<td>MTCWP</td>
<td>7</td>
<td>1.06</td>
<td>0.13</td>
</tr>
<tr>
<td>MEN 2A versus MTCWP P-value = 0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCK2 (9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN 2A</td>
<td>10</td>
<td>14.18</td>
<td>0.00</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>1</td>
<td>0.59</td>
<td>0.00</td>
</tr>
<tr>
<td>MTCWP</td>
<td>9</td>
<td>1.74</td>
<td>0.08</td>
</tr>
<tr>
<td>MEN 2A versus MTCWP P-value = 0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN203*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN 2A</td>
<td>7</td>
<td>2.98</td>
<td>0.00</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>1</td>
<td>0.58</td>
<td>0.00</td>
</tr>
<tr>
<td>MTCWP</td>
<td>5</td>
<td>0.50</td>
<td>0.17</td>
</tr>
<tr>
<td>MEN 2A versus MTCWP P-value = 0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB14.34 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN 2A</td>
<td>4</td>
<td>1.89</td>
<td>0.00</td>
</tr>
<tr>
<td>MTCWP</td>
<td>4</td>
<td>0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>MEN 2A versus MTCWP P-value = 0.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48.11 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN 2A</td>
<td>7</td>
<td>2.89</td>
<td>0.03</td>
</tr>
<tr>
<td>MTCWP</td>
<td>7</td>
<td>1.43</td>
<td>0.10</td>
</tr>
<tr>
<td>MEN 2A versus MTCWP P-value = 0.53</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


IRBP.H4 is informative with BglII in all families except one in which it is informative with MspI.

The homogeneity test calculates the P-value for rejecting a single recombination fraction for the two MTC subgroups.

---

**Fig 1**—Pedigree of MTCWP family demonstrating possible reduced penetrance in younger individuals. Solid circles (females) and solid squares (males) represent affected individuals.

---

**Fig 2**—Pedigree of MEN 2B family. Letters represent marker alleles. Upper letters = IRBP.H4, middle letters = MCK2, lower letters = MEN203. MEN2B mutation appears linked to AAB haplotype.

---

account for a higher recombination fraction in MTCWP families than in MEN 2A families. One is chance variation. Also, the two different susceptibility loci may be situated close to each other but not at identical sites. Alternatively, if a proportion of the MTCWP families are unlinked (ie, \( \theta = 0.50 \)), the recombination fraction for the entire subgroup will be elevated (7). Finally, if the linkage parameters, which are derived from studies of MEN 2A families, are inappropriate for the MTCWP families, the recombination fraction may be biased. In our data, when the maximum penetrance of the MTCWP families was reduced to a 50% estimate, the recombination fraction for IRBP.H4 became 0.03 (lod = 1.48) in this subgroup. Penetrance studies among MTCWP families should be a priority if the issue of heterogeneity is to be solved.

In contrast to MTCWP, thyroid tumors appear at a very young age in MEN 2B and are often very aggressive (15,18). The median age of MTC diagnosis in one series was 18 years (18). In our family with MEN 2B (Fig 2), the mother, I-2, had surgery for MTC at age 17 and was found to have metastatic disease at age 41. Her affected daughters had MTC diagnosed at 6 and 12 years of age. Pentagastrin test results have been negative to date in the two healthy children (11 and 8 years old). Although segregation of the marker alleles of the probes tested is consistent with linkage in this family, more data are required before the location of the gene for MEN 2B can be assigned with confidence. One report associates the MEN 2B gene to the chromosome 10 centromeric region with a lod score of 2.68 (19). These data do not suggest that different genetic loci may underlie the different MTC syndromes. There were more recombinants observed in the MTCWP families than in the MEN 2A families, but in no individual family could linkage be readily excluded. Epidemiologic studies of MTCWP families will be helpful in determining the linkage parameters with precision so
that the problem of heterogeneity can be addressed with confidence.

Acknowledgments
We thank M. F. Lavoue, C. Bonnardel, S. Pauly, and B. S. Sylla for their helpful advice and technical assistance.
This study was funded in part by the Ligue Nationale Francaise contre le cancer du departamento de l’ Ain and by the Ontario Ministry of Health.

References