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Familial Nontoxic Multinodular Thyroid Goiter Locus Maps to Chromosome 14q but Does Not Account for Familial Nonmedullary Thyroid Cancer

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Summary

Thyroid goiter is a common condition that is often associated with iodine deficiency. Familial forms of goiter in areas not known to feature iodine deficiency are much less common. We have performed a genomic search on a single large Canadian family with 18 cases of nontoxic multinodular goiter in which 2 individuals also had papillary lesions highly suggestive of papillary carcinoma. A locus on chromosome 14q (*MNG1* [*m*ulti*n*odular *g*oiter 1]) has been identified, with a maximal two-point LOD score of 3.8 at D14S1030 and a multipoint LOD score of 4.88 at the same marker, defined by D14S1062 (upper boundary) and D14S267 (lower boundary). The gene encoding thyroid-stimulating hormone receptor (*TSHR*), which is located on chromosome 14q, is outside the linked region. To determine the role of this gene in familial nonmedullary thyroid cancer (NMTC), we studied 37 smaller pedigrees each containing at least two cases of NMTC. Analysis by both parametric and nonparametric methods indicates that only a very small proportion of familial NMTC (point estimate 0.001, support intervals 0–.6 under a dominant model) is attributable to *MNG1*.

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Introduction

Diffuse enlargement of the thyroid due to the development of multiple nodules (i.e., thyroid goiter) is a common syndrome in many parts of the world. In some geographic areas a high prevalence is attributable to iodine deficiency. However, even in areas without iodine deficiency, multinodular goiter is common. For example, in Framingham, MA, where iodine intake is ample, 1.1% of 5,234 persons examined were found to have palpable multinodular thyroid goiters (Vander et al. 1954), and a smaller study performed in the north of England yielded similar results (Tunbridge et al. 1977). In fact, clinical examination may underestimate the prevalence of mild thyroid enlargement, since as many as a third of all thyroid glands in one autopsy study contained multiple nodules (Mortensen et al. 1955). The female:male ratio is in excess of 5:1.

For a century it has been established that rare inherited disorders of the thyroid gland can result in goiter (Pendred 1896). A role for genetic factors in common multinodular goiter has been supported by a study of Scottish twins, in which the contribution of hereditary factors to nontoxic, simple goiter in females was reported to be ~40% (Greig et al. 1967), and by the existence of multinodular-goiter families with vertical and/or male-to-male transmission (Murray et al. 1966; Couch et al. 1986; Burgess et al. 1997) suggesting an autosomal dominant susceptibility. Although the biochemical and genetic basis of many varieties of thyroid goiter have been elucidated (Medeiros-Neto and Stanbury 1966; Rapoport et al. 1972; De Groot et al. 1984; Ieiri et al. 1991), in most sporadic and familial cases of multinodular-goiter, investigations fail to reveal any specific or consistent biochemical abnormality.

Susceptibility to medullary carcinoma of the thyroid conferred by mutations in *RET* on chromosome 10 is well recognized (Mulligan et al. 1993), but familial pre-

disposition to nonmedullary thyroid cancer (NMTC) has not been the subject of detailed investigation. Evidence in support of susceptibility to NMTC derives from case reports of families with multiple cases of NMTC and from case-control and other population-based studies. In these studies, the observed risk of NMTC in the first-degree relatives of affected cases was elevated five- to ninefold (Stoffer et al. 1986; Ron et al. 1987; Goldgar et al. 1994). Although the population incidence of multinodular goiter far exceeds that of thyroid carcinoma, and although the two conditions have different age-at-onset profiles (De Groot et al. 1984), there is also evidence that genetic susceptibility to multinodular goiter and to NMTC may be related. First, a history of benign thyroid disease is a strong risk factor for the development of thyroid cancer (Preston-Martin et al. 1987; Ron et al. 1987). Second, families with multiple cases of NMTC (reviewed in Houlston and Stratton 1995; Loh 1997) often have probands and relatives with benign thyroid disease including multinodular goiter (Lote et al. 1980; Stoffer et al. 1986; Austoni 1988; Ozaki et al. 1988; Grossman et al. 1995). Finally, families segregating an autosomal dominant trait for multinodular goiter often include cases of NMTC. Therefore, in this study we have used a large Canadian pedigree, Montreal 236, to search for a locus responsible for multinodular goiter and then have assessed the contribution of this locus to NMTC predisposition.

Subjects, Material, and Methods

Subjects

Subjects were recruited into the study from several sources. Probands from Canadian families were recruited via clinicians at McGill University. CRC020 was ascertained in the United States, whereas other CRC families were referred by clinicians in the United Kingdom. The IARC families were recruited through the Consortium for the Genetics of Papillary Thyroid Cancer (details of the families can be obtained at http://www.geocities.com/ResearchTriangle/4485/fnmtc.html).

The clinical features of MON236 have been reported by Couch et al. (1986). In the Couch et al. study, 18 members of this pedigree were found to have adolescent-onset euthyroid multinodular goiter. The pathology of the thyroid glands that were available for examination revealed typical features (multiple adenomata, epithelial hyperplasia, calcification, and hemorrhage). Before treatment, no consistent biochemical abnormalities were present in any affected individual studied. We recontacted the family, and a new branch of the family was identified. By direct questioning of the 57 family members who gave blood, we were able to recheck and update the clinical status of these individuals. Three individuals (individuals 10, 15, and 22) (fig. 1) were of uncertain status on review, on the basis of self-reported absence of goiter (individual 10), disappearance of pregnancy-induced thyroid enlargement (individual 15), and absence of characteristic pathological features of multinodular goiter in the excised thyroid gland (individual 22). These three individuals were assigned to status "uncertain" before the genomic search began.

MON152 is described in more detail by Druker et al. (1997). In brief, the family contains five individuals in two generations who have multinodular goiter. Two individuals, both of whom also had multinodular goiter, developed follicular thyroid cancer. CRC020 was originally described by Stoffer et al. (1986) and contains five individuals with papillary thyroid cancer and seven other individuals with benign thyroid disorders. All pedigrees are summarized in table 1. The study was approved by the relevant institutional review boards.

Molecular Genetic Studies and Computational Analysis

Genome search.—Thirty-four individuals from MON236 (in which there are 12 affected) were typed with 214 markers, giving a resolution of ~20 cM (Gyapay et al. 1994; Dib et al. 1996). The trait was likely to be autosomally inherited, since male-to-male transmission was seen in one pair of father and son (fig. 1), and therefore no X-linked markers were analyzed. After amplification by PCR, fluorescence-labeled products were mixed and electrophoresed on an ABI 377 DNA sequencer. Data were collected and analyzed by use of Genescan collection software (version 1.1), Genescan analysis software (version 2.02), and Genotyper (version 1.1). Regions of possible linkage were evaluated with additional markers.

Haplotype analysis.—Haplotypes were determined for chromosome 14q in the remaining 37 pedigrees by use of 9–14 markers, from centromere to telomere (not all markers were used for all pedigrees). The molecular methods were as described for the genomic search. For MON236 a dense chromosome 14q haplotype was constructed for all tested individuals, by use of 22 markers, with the smallest number of recombination events being assumed (fig. 1).

Statistical analysis.—For the genomic search, we assigned affection status to individuals, on the basis of their status by age 50 years (or, for those <50 years, at their current age). Affected individuals had physician-reported nodular goiter with subsequent thyroid surgery and/or thyroxine replacement. Unaffected individuals reported no thyroid masses, surgery, or therapy by age 50 years (or, for those <50 years, at time of ascertainment). For the other families, affection status was based on

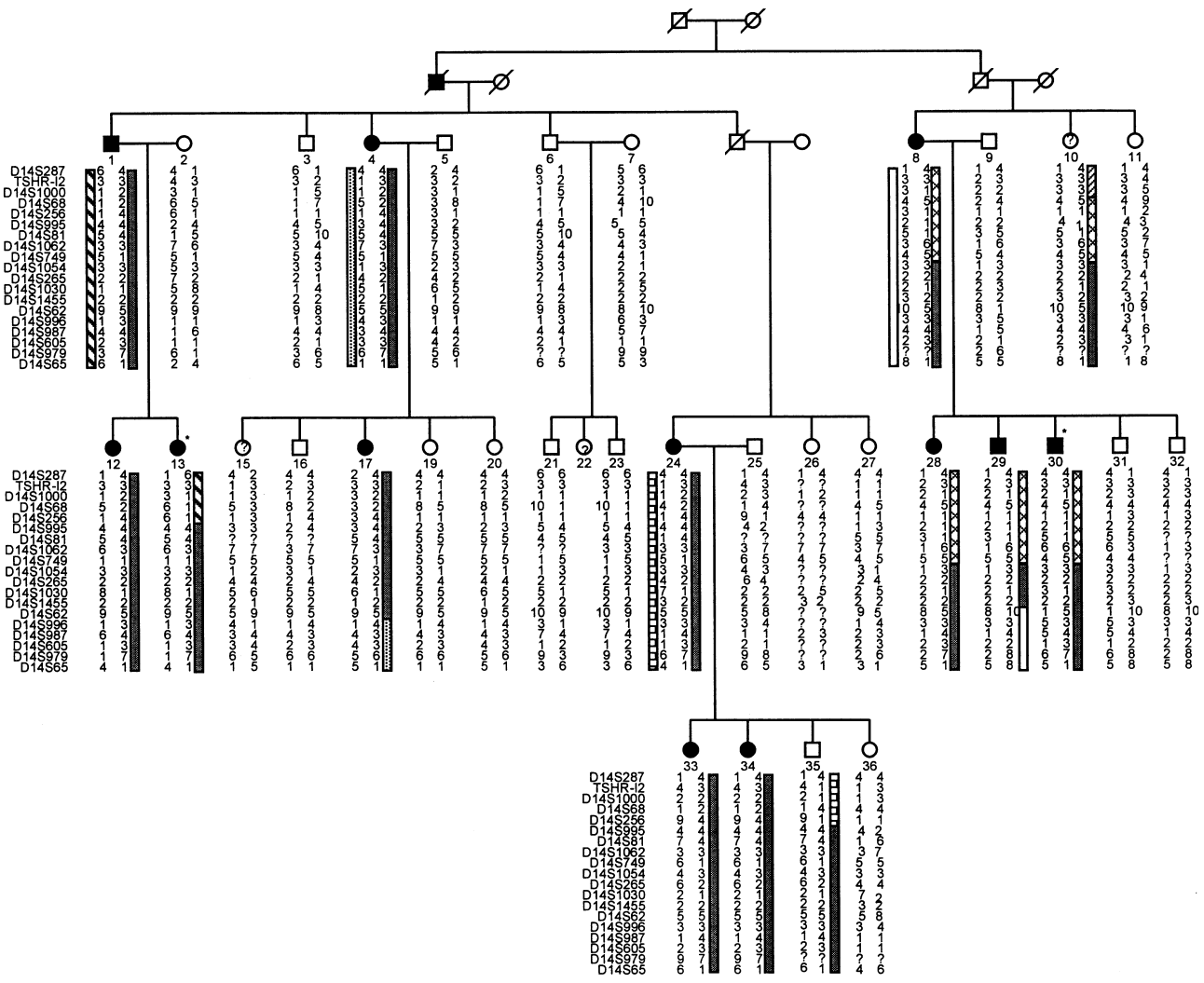

Figure 1 MON236 family. A reduced pedigree is shown with all typed individuals; bars denote all individuals with the at-risk haplotype, together with those required for clarification of recombinations. Blackened symbols denote multinodular goiter; an asterisk (*) indicates those with papillary tumors suggestive of papillary carcinoma; and a question mark (?) inside an unblackened symbol indicates that the individual was assigned to status "uncertain" in the linkage analysis. The alleles for the markers D14S287 (cen) to D14S65 are shown. The segregating haplotype is cen-4-3-2-2-4-4-4-3-1-**3-2-1-2**-5-3-4-3-7-1-tel, with the smallest region of sharing indicated in boldface. These four markers are D14S1054, D14S265, D14S1030, and D14S1455. For individual 29, the only portion of the at-risk haplotype retained is 3-2-1-2. Of the three individuals assigned status "uncertain," individual 10 carriers the at-risk haplotype (3-2-1-2-5-3-4-3-?-1), whereas individual 15 does not; individual 22 is untyped but could not receive the linked haplotype. Individual 35 carries the at-risk haplotype but is unaffected.

clinical and pathological reports and, for unaffected individuals, on personal report.

Two-point LOD scores were calculated for MON236 alone, by use of version 5.1 of the LINKAGE package (Lathrop et al. 1984). The model used assumed an autosomal dominant gene, frequency of .0001 with four liability classes, penetrance .25 by age 20 years, penetrance .5 by age 30 years, and maximum penetrance .70 by age 50 years. Because the mode of inheritance of NMTC is unknown, we analyzed our data from the 37 smaller pedigrees, using both parametric and nonparametric approaches. In the parametric analysis of the smaller families, both dominant and recessive models were constrained to fit both the observed familial relative risk of 8.0 (Goldgar et al. 1994) and a population prevalence of .002 (Parkin 1992). Under the dominant model, we parameterized the gene frequency, penetrance, and phenocopy rate to be .001, .18, and .0016, respectively; under the recessive model, these parameters were fixed at .05, .21, and .0015, respectively. For the multipoint analyses, the map order used was D14S1062–0.08 cM–D14S1030–0.08 cM–D14S267;

Table 1

Clinical Features of Families

Family	Ethnic Origin or Country of Origin	No. of Generations Affected with Goiter or Thyroid Cancer	No. of Affected Individuals[a]	Other Cancer(s) (No. of Cases)
MON236	Canadian/ Germany	3	18 G, 2? PTC	Endometrial (1), bladder (1)
MON152	Canadian/ Ashkenazi Jewish	2	3 G, 2 FTC	Colorectal (1), rhabdomyosarcoma (1)
MON881	Canadian/ Ashkenazi Jewish	1	3 PTC	...
MON883	Canadian/ Ashkenazi Jewish	1	2 PTC	Colorectal (3), breast (1)
CRC019	United Kingdom (unspecified)	1	2 PTC	Colorectal (1), endometrial (1), stom-ach (1), brain (1), lung (1), ovarian (1)
CRC020	United States/Ashkenazi Jewish	3	7 G, 5 PTC	...
CRC127	Sri Lanka	1	1 PTC, 1 FTC	...
CRC180	Anglo-Italian	1	2 PTC	...
CRC238	United Kingdom (unspecified)	1	2 PTC, 1 N	Colorectal (1), leukemia/lymphoma (1)
CRC246	United Kingdom (unspecified)	2	2 PTC, 1 FTC	Breast (1), colorectal (1), primary site other/unknown (1)
CRC306	United Kingdom (unspecified)	2	2 PTC, 1 G	Breast (2), colorectal (1), cervical (1)
CRC360	Maltese	1	2 PTC	...
IARC01.01	France	2	2 PTC, 1 N	Prostate (1), cutaneous melanoma (1)
IARC01.05	Italy	1	2 PTC, 1 N	...
IARC01.06	France	3	2 PTC, 4 G, 1 N	Cutaneous melanoma (1), brain (1), primary site other/unknown (2)
IARC02.08	France	2	2 PTC, 1 G	...
IARC02.10	France	1	3 PTC	Colorectal (2), breast (2), primary site other/unknown (2)
IARC01.12	France	2	2 PTC	Breast (1), primary site other/un-known (1)
IARC02.14	France	2	3 PTC, 1 G	Leukemia/lymphoma(1), pancreatic (2), colorectal (2)
IARC01.16	France	3	2 PTC, 1 G	Primary site other/unknown (1)
IARC01.22	France	1	2 PTC, 1 N	Renal cell (1)
IARC03.37	Spain/France	2	2 PTC	...
IARC04.39	France	1	2 PTC	...
1IARC02.41	France	2	3 PTC	...
IARC07.45	Italy	2	2 PTC, 1 N	...
IARC07.46	Italy	1	2 PTC	...
IARC08.50	France	1	3 PTC	...
IARC1.055	France	2	2 PTC, 1 G	Prostate (1)
IARC1.056	France	2	2 PTC	...
IARC11.61	Italy	1	2 PTC	...
IARC11.62	Italy	1	2 PTC	...
IARC1.063	Italy/France	2	2 PTC, 2 N	Primary site other/unknown (1)
IARC02.65	France	1	2 PTC	Colorectal (1)
IARC04.66	France	2	3 PTC, 1 G	...
IARC14.74	France	2	4 PTC, 6 N	...
IARC17.86	France	3	2 PTC, 1 N	...
IARC02.88	France	2	2 PTC, 1 N	Ovarian (1)
IARC02.89	France	1	2 PTC	...

[a] G = nontoxic goiter only; N = single nodule; PTC = papillary thyroid cancer (with or without other thyroid disease); and FTC = follicular thyroid cancer. Not all affected individuals were analyzed.

published map distances between markers (in cM) were converted to recombination fractions. Multipoint and nonparametric analyses were performed by use of the VITESSE and GENEHUNTER programs, respectively (O'Connell and Weeks 1995; Kruglyak et al. 1996).

Results

Linkage in MON236

After the primary genome search, several markers on chromosome 14q showed LOD scores >1.5, so addi-

Table 2

LOD Scores and Nonparametric-Linkage *P* Values at *TSHR* and *MNG1*

Model	*TSHR*	*MNG1*
Dominant	−2.15	−8.84
Recessive	−8.95	−13.59
Nonparametric-linkage *P* value[a]	.40	.40

[a] Nonparametric-linkage *P* values were generated by the nonparametric method and test the significance of nonrandom sharing of alleles among affected individuals.

tional markers in this region were analyzed (fig. 1). A two-point LOD score of 3.8 at a recombination fraction (θ) of 0 was obtained with marker D14S1030. A multipoint LOD score of 4.88 was achieved with the use of three chromosome 14q markers (D14S1062, D14S1030, and D14S267), with a maximum at D14S1030. Because of the uncertain status of individual 22, who had a single follicular adenoma removed at age 23 years, we reanalyzed the data with this individual included as affected. The multipoint LOD score fell to 4.34, with a maximum 3 cM distal to D14S1030. Construction of haplotypes provided supportive evidence for linkage, and critical recombinants placed *MNG1* within a 1-cM interval bounded by D14S1054 (centromeric) and D14S1455 (telomeric). Individual 35 carries the at-risk haplotype and has not developed multinodular goiter at age 31 years (individual 10 also carries the at-risk haplotype, but her affection status is uncertain; see above). There are no unambiguous phenocopies in this family (see above and fig. 1).

Several other regions showing positive LOD scores were identified (D2S112, LOD score 1.03 at $\theta = 0$; D4S1551, LOD score 1.39 at $\theta = .1$; D7S502, LOD score 1.13 at $\theta = 1.0$; D8S261, LOD score 1.14 at $\theta = .15$; and D15S128, LOD score 1.05 at $\theta = .15$), but all were excluded as candidate loci, on the basis of both examination of additional markers in the vicinity and the nonsharing of haplotypes by affected individuals. As discussed above, because of the uncertain status of individual 22, we recalculated all the two-point LOD scores, assuming her to be affected. The LOD scores did not change substantially for any locus. A new locus, D12S366, did generate a LOD score of 0.8, and the haplotype is shared by many affected family members. However, the two pairs of affected sibs—pair 12 and 13 and pair 33 and 34—do not share haplotypes at this locus, making it unlikely that this locus is segregating with the disease.

TSHR was identified as a strong candidate gene before the genome search began, but no mutations were seen in *TSHR* in four affected individuals from two families, MON236 and MON152 (data not shown). Moreover, recombinations in affected individuals 8, 13, 28, 29, and 30 from MON236 appear to have eliminated this gene genetically.

Linkage Analyses in the Smaller Thyroid Cancer Families

In family MON236, we identified a chromosome 14 region, bounded by D14S1062 and D14S267, that segregated with multinodular goiter. Another family with multiple cases of multinodular goiter, MON152, also showed evidence of linkage to this region. In this family we genotyped seven individuals (four affected) and obtained a maximal two-point LOD score of 0.57 at $\theta = .03$ from D14S1030. This family contains two individuals who, in addition to multinodular goiter, also had follicular thyroid cancer. The segregating haplotype differs from that seen in MON236. For MON152, the haplotype for markers D14S1054, D14S265, D14S1030, and D14S1455 is 3-5-6-2, whereas it is 3-2-1-2 for MON236.

Because both MON236 and MON152 contain cases of NMTC in addition to goiter, and because goiter is a known risk factor for NMTC, we evaluated the contribution of *MNG1* to familial NMTC. We studied 37 NMTC families collected in Europe and North America during the past few years. At least nine chromosome 14q markers were studied in all 37 families, and parametric and nonparametric linkage analyses were performed. In table 2, we present the LOD scores and the *P* values for two locations of interest on chromosome 14: *TSHR* and *MNG1*. Although no evidence for linkage at either region was found, we recognize that there could still be some fraction of NMTC families whose disease is attributable to either of the chromosome 14 loci. To examine this statistically, an analysis was performed under the assumption that a subset of families were linked to the candidate region while the rest were unlinked. Although, for *MNG1,* the point estimate of the linked fraction in these cases were close to zero (.001), we could not, on the basis of our linkage analyses, formally exclude the possibility that a significant fraction of cases were due to these regions (table 3). In addition, we performed a separate analysis using not only NMTC but also goiter or nodule as affection status. No evidence of linkage was detected (results not shown). In conclusion,

Table 3

Point Estimates and 1 − LOD Support Intervals for Estimated Proportion of Linked Families

Model	*TSHR*	*MNG1*
Dominant	.31 (0–.82)	.001 (0–.6)
Recessive	.02 (0–.45)	.001 (0–.65)

both parametric and nonparametric linkage analyses indicate that it is unlikely that either *MNG1* or *TSHR* contributes significantly to susceptibility to NMTC.

Discussion

Multinodular-Goiter Kindreds

In this study, we have presented evidence in favor of linkage of multinodular goiter to a locus on chromosome 14q in a single large family (MON236). Weaker evidence in favor of linkage was obtained in a second family with multinodular goiter. Apart from MON236, four substantial pedigrees with euthyroid multinodular goiter have been reported. A large African American kindred with congenital goiter and follicular carcinoma was reported in 1981 by Cooper et al. (1981). In this kindred, a mother and 7 of her 14 children had goiter, and 2 of those children with goiter also developed metastatic follicular thyroid carcinoma. Biochemical studies showed very rapid rates of iodine turnover, and the authors of that study suggested that an abnormality of thyroid-stimulating hormone (TSH) was likely. The mode of inheritance was uncertain. A five-generation Scottish kindred with adolescent-onset goiter associated with marked age-dependent intrathyroid calcification was reported >30 years ago (Murray et al. 1966). Although there were some abnormalities of thyroid function, these did not fit any known familial disorder. The inheritance pattern was dominant, but a sex-linked trait cannot be excluded from the pedigree published in that article. Recently, two apparently unrelated pedigrees from Tasmania with dominantly inherited multinodular goiter have been reported. One pedigree is very large, containing 17 members (13 females and 4 males) with clinically or screen-detected multinodular goiter, 6 of whom have developed pathologically confirmed papillary thyroid cancer. One individual without goiter had a solitary nodule, within which papillary thyroid cancer was identified after excision. On the basis of historical report, five generations of this family have developed thyroid neoplasia. The other pedigree is smaller, but, interestingly, contains MZ twin males, each of whom has one daughter. All four individuals have developed papillary thyroid cancer with or without multinodular goiter. The daughter of another brother also has multinodular goiter (Burgess et al. 1997).

Candidate Multinodular-Goiter Genes

TSHR is located on chromosome 14q and is a plausible mechanistic candidate for susceptibility to multinodular goiter. Moreover, germ-line mutations in *TSHR* have been reported in two families from France that have numerous cases of goiterous, nonautoimmune autosomal dominant hyperthyroidism (Duprez et al. 1994), and somatic mutations in *TSHR* have been detected in hyperfunctioning thyroid adenomas (Parma et al. 1993). *TSHR* appears to be excluded, however, as a candidate gene for multinodular goiter in the present study, by recombination in five individuals from MON236 and by the absence of mutations in two affected individuals from both MON236 and MON152 (data not shown). Other notable candidates elsewhere in the genome that were excluded by linkage analysis include the thyroglobulin gene on chromosome 8q (which is mutated in nonendemic goiter; Corral et al. 1993) and *RET* and *PTEN,* both located on chromosome 10q (mutations of *PTEN* are responsible for Cowden disease; Liaw et al. 1997) (data not shown). Taken together, the data suggest that a novel locus (designated "*MNG1*") responsible for multinodular goiter is present on chromosome 14q. Further studies will now evaluate whether other families segregating an autosomal dominant trait for multinodular goiter are linked to this locus. Subsequently positional cloning of *MNG1* will allow estimation of the contribution of abnormalities in this gene to multinodular goiter in the general population.

MNG1 *and Familial NMTC*

Because NMTC is present in several families ascertained with multinodular goiter, and vice versa, we have evaluated the contribution of *MNG1* to NMTC susceptibility. Although we cannot completely exclude a contribution by *MNG1,* it is clear that this gene (and also *TSHR*) does not account for most susceptibility to NMTC. Other candidates for susceptibility to NMTC include *RET* and *PTEN,* and assessment of these loci is underway. However, localization of NMTC genes by genomewide search may be problematic, because the number of families available for study is limited, kindreds with multiple cases of NMTC without goiter are exceptionally uncommon, and the degree of genetic heterogeneity is unknown. Nevertheless, the set of NMTC families documented here is the largest reported and provides the basis for further studies to identify NMTC genes.

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