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Report

Localization of a Susceptibility Gene for Familial Nonmedullary Thyroid Carcinoma to Chromosome 2q21

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The familial form of nonmedullary thyroid carcinoma (NMTC) is a complex genetic disorder characterized by multifocal neoplasia and a higher degree of aggressiveness than its sporadic counterpart. In a large Tasmanian pedigree (Tas1) with recurrence of papillary thyroid carcinoma (PTC), the most common form of NMTC, an extensive genomewide scan revealed a common haplotype on chromosome 2q21 in seven of the eight patients with PTC. To verify the significance of the 2q21 locus, we performed linkage analysis in an independent sample set of 80 pedigrees, yielding a multipoint heterogeneity LOD score (HLOD) of 3.07 ($\alpha = 0.42$), nonparametric linkage (NPL) 3.19, ($P = .001$) at marker D2S2271. Stratification based on the presence of at least one case of the follicular variant of PTC, the phenotype observed in the Tas1 family, identified 17 such pedigrees, yielding a maximal HLOD score of 4.17 ($\alpha = 0.80$) and NPL = 4.99 ($P = .00002$) at markers AFMa272zg9 and D2S2271, respectively. These results indicate the existence of a susceptibility locus for familial NMTC on chromosome 2q21.

Nonmedullary thyroid carcinoma (NMTC [MIM accession number 188550]) is the most common form of thyroid cancer, accounting for as many as 90% of all patients (Schlumberger 1998). The familial form of NMTC (FNMTC) is increasingly recognized as a distinct clinical entity, characterized by multifocality and a higher degree of aggressiveness and mortality with respect to its sporadic counterpart (Grossman et al. 1995). The majority of FNMTC pedigrees are small in size and may present with a variety of additional benign common thyroid disorders such as goiter (Lesueur et al. 1999).

Two loci predisposing to FNMTC have been previously identified: *TCO* (MIM accession number 603386) on 19p13.2, in a French family with an unusual form of NMTC with cell oxyphilia (Canzian et al. 1998), and *PRN1* (MIM accession number 605642) on 1q21, in a U.S. family with the most common from of NMTC, papillary thyroid carcinoma (PTC), and papillary renal neoplasia (Malchoff et al. 2000). However, neither of these loci, nor the *MNG1* (MIM accession number 138800) locus on 14q, identified in a large Canadian family with multinodular goiter and low recurrence of NMTC (Bignell et al. 1997), accounts for a significant

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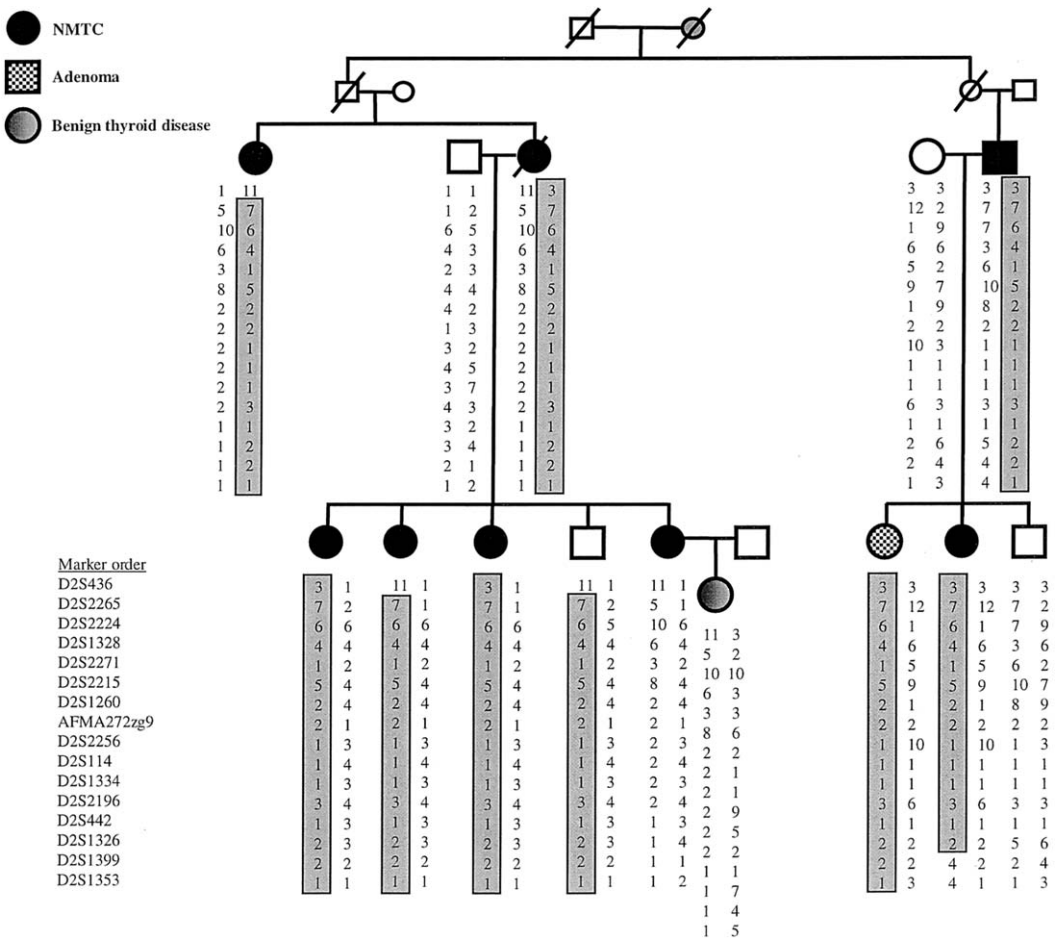

Figure 1 Haplotypes of the eight Tasmanian individuals with PTC. One additional individual affected with neoplastic disease (follicular adenoma) carries the affected haplotype (shown in generation 4 of the pedigree).

Table 1

Description of the NMTC Consortium Family Set Used in This Study

No. of NMTC Patients per Family	NMTC Set[a]		fvPTC Subset	
	No. of Families	No. with BTD[b]	No. of Families	No. with BTD[b]
2	57	14	9	4
3	17	4	5	2
4	4	3	1	1
5	2	2	2	2
Total	80	23	17	9

[a] The complete family set consists of 191 NMTC patients with available DNA (average 2.4 cases/family) and an additional 38 patients with benign thyroid disease.

[b] No. of families with at least one additional member affected with benign thyroid disease (BTD).

fraction of FNMTC pedigrees (Lesueur et al. 1999; authors' unpublished data).

Through the International Consortium for the Genetics of FNMTC, 225 pedigrees have been collected, 81 of which are informative for linkage, with at least one case of PTC and no cell oxyphilia (Canzian et al. 1998) or renal cancer (Malchoff et al. 2000). Blood samples and family histories were obtained from family members after informed consent. DNA was extracted using a cell lysis and precipitation method (Puregene kit; Gentra Systems). The protocol for the study was approved by the French Committee for Protection of Persons in Biomedical Research. For one large Tasmanian family (Tas1) (Burgess et al. 1997; McKay et al. 1999) with recurrence of PTC, an extensive genomewide scan, using a panel of 471 fluorescently labelled microsatellite

Table 2

Liability Classes Based on Estimates of NMTC Risk and Goiter Disease Prevalence in the Tasmanian Population

Category	AA	Aa	aa
Cancer:			
In males	.001	.05	.05
In females	.002	.1	.1
Follicular adenoma	.05	.4	.4
Goiter:			
In females aged:			
<30 years	.1	.3	.3
30–50 years	.15	.375	.375
51–70 years	.2	.4	.4
>70 years	.25	.375	.375
In males aged:			
<30 years	.03	.09	.09
30–50 years	.05	.125	.125
51–70 years	.07	.14	.14
>70 years	.1	.15	.15

NOTE.—AA = wild type; Aa/aa = affected.

markers at an average resolution of 7.6 cM, was completed on a 377 automated sequencer (PE/ABI). Subsequent linkage analysis did not reveal an area of significant linkage either when all individuals with benign thyroid disorders were considered affected, as in previous studies (Bignell et al. 1997; Canzian et al. 1998; Malchoff et al. 2000) or when individuals with neoplastic disease only were considered affected. However, the reconstruction of haplotypes on chromosome 2q21 showed that seven of eight patients with PTC shared a common haplotype extending from D2S436 to D2S1399 (33.8 cM; see fig. 1), with a maximum multipoint LOD score of 1.28 observed for marker D2S1260, using the VITESSE program (O'Connell and Weeks 1995).

Since no other comparable region of linkage or cosegregating haplotype was identified in the Tas1 family, the relevance of this 2q21 locus to FNMTC was tested using 80 additional informative FNMTC pedigrees, for a total of 191 NMTC patients (table 1) collected by the International Consortium for the Genetics of NMTC. Using 80 families as an independent family set, we genotyped 13 microsatellites located on 2q21 (D2S436–11.6 cM–D2S2265–0.57 cM–D2S2224–2.3 cM–D2S1328–1.0 cM–D2S2271–0.9 cM–D2S2215–3.4 cM–D2S1260–4.5 cM–AFMa272zg9–0.8 cM–D2S2256–1.0 cM–D2S114–2.2 cM–D2S1334–1.2 cM–D2S2196–1.2 cM–D2S442). Genetic distances were taken from the Marshfield genetic maps (Broman et al. 1998) or the Genetic Location Database (Collins et al. 1996), and the order was confirmed using the BAC fingerprint map. Allele frequencies were calculated from the data set, using an individual chosen from each family at random. Linkage analysis was performed using the Genehunter plus (v. 1.2) program package (both parametric and NPL) (Kruglyak et al. 1996; Kong and Cox 1997), based on an autosomal dominant model with the disease-allele frequency fixed at .001. The model incorporated different probabilities of disease in noncarriers according to sex-specific rates for NMTC risk (Parkin et al. 1997), familial relative risk (Goldgar et al. 1994), and age- and sex-specific rates for goiter based on estimates of goiter prevalence from Tasmania (table 2). These estimates were taken from an area of high endemicity (Tasmania) (Gibson 1995; Richards 1995), to ensure that any environmental effect on the linkage results is minimized. The linkage analysis of the 80 FNMTC pedigrees achieved a maximum multipoint heterogeneity LOD (HLOD) score of 3.07 at marker D2S2271 ($\alpha = 0.42$; 95% confidence interval [CI] 0.15–0.70), supporting the notion of an NMTC susceptibility gene on 2q21 (table 3, fig. 2).

Stratification by histological subtype has been previously used for genetic studies of FNMTC. Stratification for the cell oxyphilia phenotype observed in the tumors of the original *TCO* family (Canzian et al. 1998; Harach et al. 1999) confirmed linkage to chromosome 19 (Alsanea and Clark 2001; authors' unpublished data). In contrast, large unstratified FNMTC family sets do not support linkage at this locus (Lesueur et al. l999). Similar

Table 3

Multipoint HLOD Scores for 2q21 According to Phenotypic Breakdown

Phenotypic Category	No. of Families	HLOD	Estimated Proportion with Linkage	NPL Score (*P* Value)	Position of Maximum HLOD
All families:	80	3.07	.42	3.19 (.001)	D2S2271
Cancer-only model		2.34	.42	2.53 (.006)	
fvPTC:	17	4.17	.80	4.61 (.00006)[a]	AFMa272zg9
Cancer-only model		3.04	.80	3.66 (.0003)[a]	
PTC only:	48	.52	.38	1.46 (.07)	D2S2224
Cancer-only model		.34	.35	1.27 (.1)	
Unknown histopathology	15	0	0	−.08 (.5)	

[a] NPL and *P* values at marker AFMa272zg9 (the point of maximum HLOD score). Using the 17 families, the maximal NPL score was 4.99 ($P = .00002$); for the cancer-only model, NPL score 4.40 ($P = .00003$) was achieved at marker D2S2271.

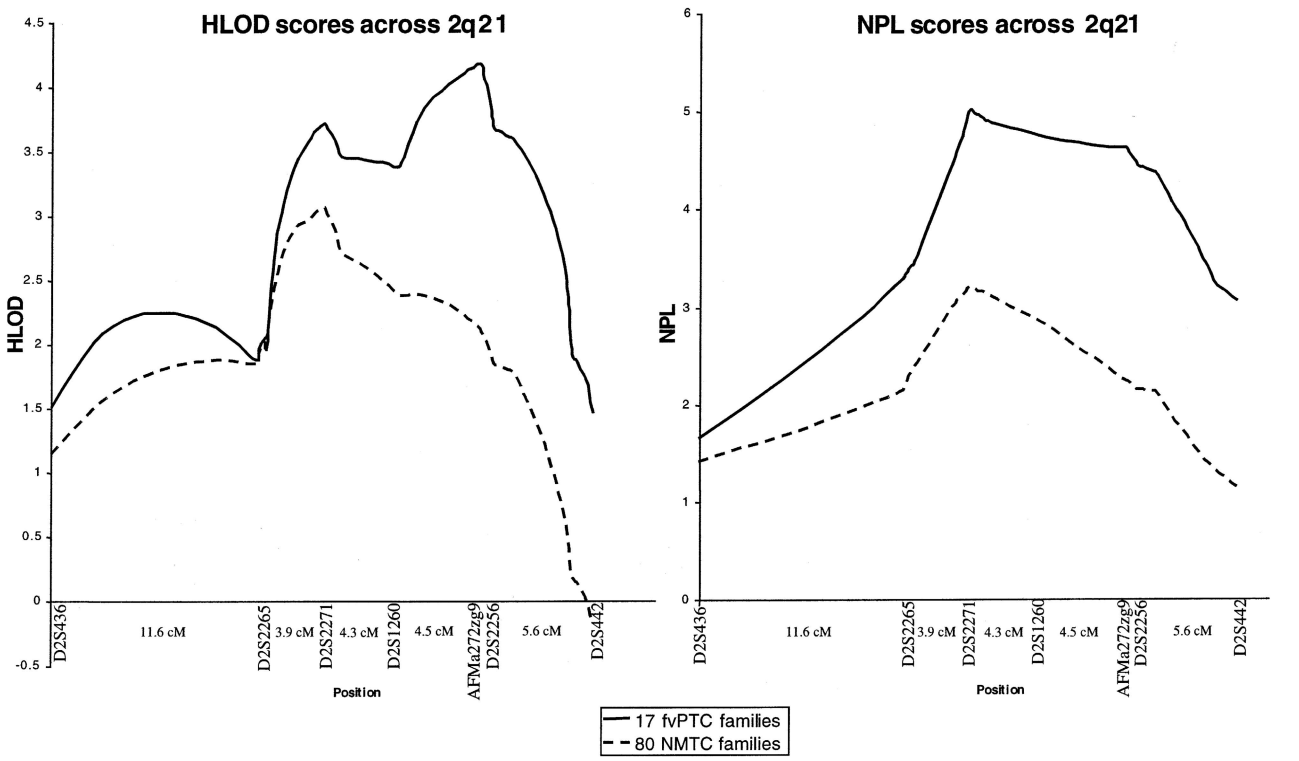

Figure 2 Multipoint HLOD and NPL scores across 2q21, using the complete set of 80 families and the 17 families with at least one case of fvPTC (with heterogeneity held at 0.42 and 0.80, respectively).

studies of testicular cancer and multinodular goiter have used stratification by clinical criteria to detect areas of linkage (Bignell et al. 1997; Neumann et al. 1999; Rapley et al. 2000). A review of the histopathology from the Tas1 family revealed that at least four of the eight PTC patients presented with the follicular variant of PTC (fvPTC) (Burgess et al. 1997; authors' unpublished data), a recognized histological subtype (Hedinger et al. 1988). In a recent survey of thyroid carcinoma in Tasmania in a 21-year period (1978–1998), fvPTC accounted for only 8% of PTC (Burgess et al. 2000). The probability of observing four (or more) follicular variants of eight PTCs in one family, by chance, is low ($P = .002$, assuming a binomial distribution with $p = .08$). By stratifying the 80 FNMTC families according to the presence of at least one case of fvPTC, we identified 17 families that satisfied this criterion. The analysis of this subset of families for the 2q21 region resulted in an HLOD of 4.17 ($\alpha = 0.80$; 95% CI 0.35–1.0) at marker AFMa272zg9, indicating the existence of an FNMTC susceptibility locus in this region (see table 3 and fig. 2 for summary of LOD scores; see fig. 3 for segregating haplotypes in the three largest families).

To avoid overreliance of the LOD score on the assumed genetic model, we performed nonparametric linkage analysis. The 80 unstratified families and the 17 families selected for the presence of a case of fvPTC achieved a maximum NPL score of 3.19 ($P = .001$) and an NPL of 4.99 ($p = .00002$), respectively, at marker D2S2271. These results confirm the parametric linkage analysis, indicating the presence of strong linkage to this region (see table 3 and fig. 2 for summary of NPL scores). Additional analysis was performed, using only those individuals with neoplastic disease (table 3). Using this more conservative cancer-only model, the HLOD scores decreased in all cases. However, the proportion of families with linkage remained constant, indicating that this latter result is due to loss of power caused by the exclusion of the informative individuals, as opposed to a large effect caused by possible phenotype misclassification among individuals with benign thyroid disorders. Informative recombinations among the 17 families that include a case of fvPTC define a critical region of 5.3 cM from D2S1260 and D2S2256.

Contrary to previous studies (Bignell et al. 1997; Canzian et al. 1998; Malchoff et al. 2000), linkage in the Tas1 family was not found when individuals affected with nonneoplastic thyroid disease were included in the analysis. However, this is not surprising, considering that the level of goiter in the average population is estimated to be as much as 30% in Tasmania, probably because of environmental conditions (Gibson 1995; Richards

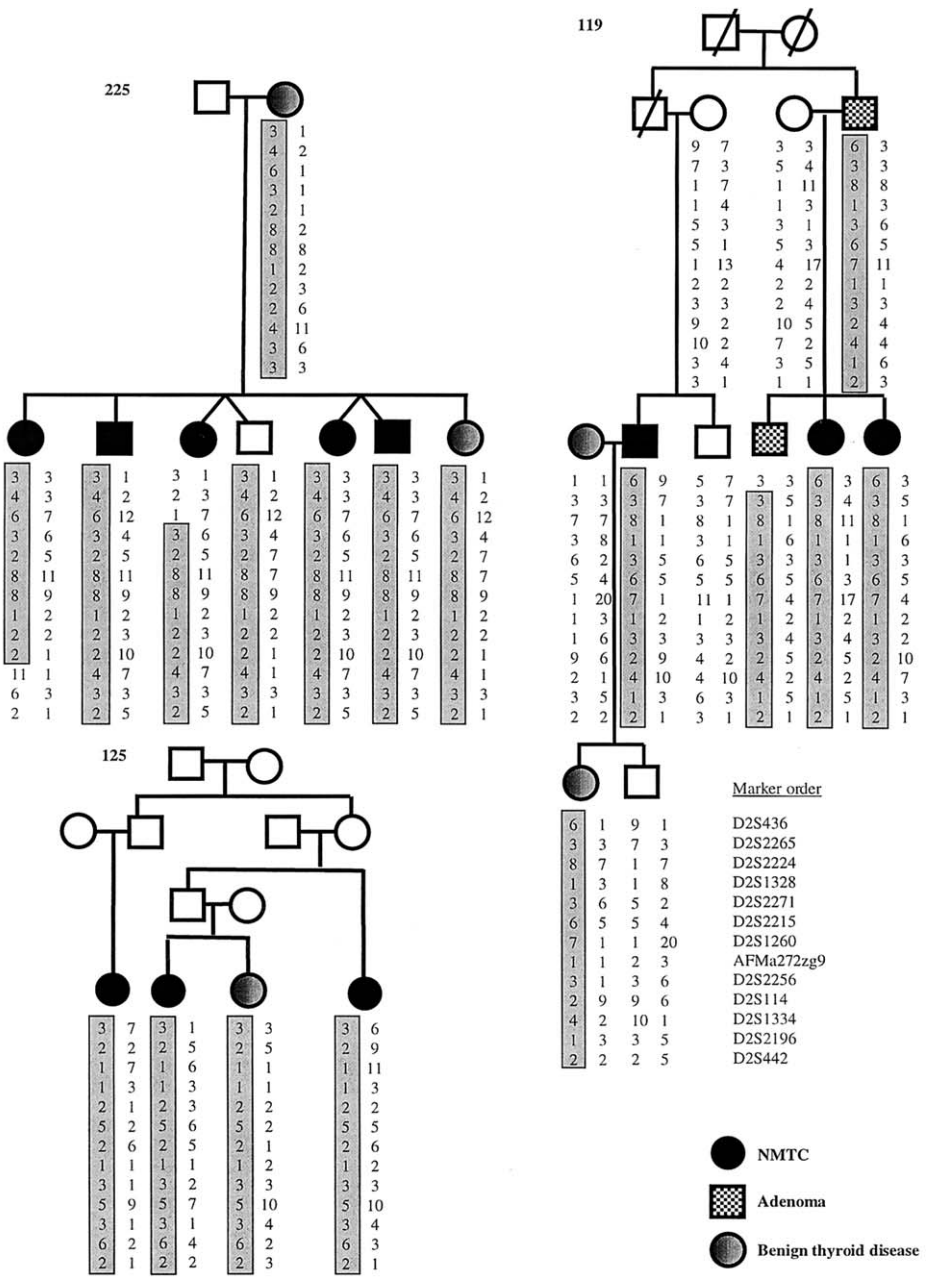

Figure 3 Haplotypes of the three largest pedigrees. The recombinations shown in family 225 allow the exclusion of the *Pax8* gene, which has been implicated in NMTC.

1995). It is also of interest that the Tas1 family contains a member who does not share the affected haplotype and yet presents with PTC. The distances between markers D2S1260 and D2S2256, identified as the critical region, make a double recombination event unlikely. Alternatively, this person may represent a phenocopy. However, the Tasmanian population does not present with an unusually high level of PTC (Parkin et al. 1997), and this patient, who does not have a history of irradiation, presented at an early age (24 years) with the rare form of follicular variant and multifocal disease. In addition, she has a daughter affected with benign thyroid disease. Taken together, these considerations make a phenocopy unlikely. As an alternative to the phenocopy hypothesis, it is possible that the NMTC in this family is caused by multiple environmental and genetic causes that cannot be thoroughly identified yet. Interestingly, a recent study of prostate cancer identified families in

which a haplotype did not segregate in all affected individuals, and yet a potential susceptibility gene was identified (Tavtigian et al. 2001).

Loss of heterozygosity and cytogenetic studies have implicated 2q, and specifically 2q21, in NMTC (Sozzi et al. 1992; Roque et al. 1995; Zedenius et al. 1995; Tung et al. 1997; Bol et al. 1999; Tallini et al. 1999) and in other forms of cancer (Richter et al. 1997; Saretzki et al. 1997; Piao et al. 2001), suggesting the existence of one or more tumor suppressors in this region. Several candidate genes exist in this region, such as *ACVR2,* which has been implicated in thyrocyte growth (Franzen et al. 1999); *RAB6/RALB,* members of the Ras-like family (Hsieh et al. 1990; Rousseau-Merck et al. 1991); and the *LRP-DIT* tumor suppressor (Liu et al. 2000). The *Pax8* gene, which has been found translocated in NMTC (Kroll et al. 2000), should be excluded by recombinations in family 225 (fig. 3) and in other families (data not shown), since it is situated centromeric to marker D2S2265.

In summary, our data provide evidence in favor of the existence of a susceptibility locus for FNMTC at 2q21. This locus appears particularly relevant to—although not confined to—families with at least one case of fvPTC. Considering that this locus appears significant in a larger proportion of FNMTC, identification of critical recombinations should further define the 2q21 region and facilitate the positional cloning of the predisposing gene.

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Electronic Database Information

Accession numbers and URLs for data in this article are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/ (for genetic maps)

Genetic Location Database, http://cedar.genetics.soton.ac.uk/public_html/ldb.html (for genetic distances)

Human Genome Project BAC and Accession Maps, http://genome.wustl.edu/gsc/human/Mapping/ (for marker order)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for FNMTC [MIM 188550], TCO [MIM 603386], PRN1 [MIM 605642], and MNG1 [MIM 138800])

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