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The Mutation for Medullary Thyroid Carcinoma with Parathyroid Tumors (MTC with PTs) Is Closely Linked to the Centromeric Region of Chromosome 10

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Summary

Two new morphs (F and G) detected by the centromeric alpha satellite probe pα10RP8 and D10Z1 in *Hin*fI digests are linked to the *Pst*I polymorphisms of D10Z1, confirming their chromosome 10 location. The F and G morphs were in strong linkage disequilibrium with each other but were in weak linkage disequilibrium with the A and B morphs defined in *Pst*I digests. Data for haplotypes formed by using the A and F morphs improved the lod score for linkage between the disease locus for multiple endocrine neoplasia type 2A (MEN2A) and D10Z1 (Z = 14.06 at θ = 0) in the six large families studied by Wu et al. Furthermore, the locus that codes for a distinct phenotype, medullary thyroid carcinoma (MTC) with parathyroid tumors (PTs) and no pheochromocytomas (PHEOs) (referred to as MTC with PTs), in one of the families was closely linked to two markers, D10Z1 and RBP3, with lodscores of 2.86 and 3.54, respectively, at θ = 0. A possible allelic association was noted between disease phenotypes and centromeric haplotypes. The phenotype MTC and PHEOs with and without PTs was associated with the same relatively common centromeric haplotype (A+B−F−G−) in the four families in which all four morphs could be determined, while the phenotype MTC with PTs was associated with the rare centromeric haplotype (A−B−F−G+) in one family.

Introduction

The probe pα10RP8 at D10Z1 detects polymorphisms with *Msp*I and *Bcl*I (Devilee et al. 1988), with *Pst*I, *Eco*RV, and *Hinc*II (Wu and Kidd 1990), and with *Hin*fI (Carson and Simpson 1990). These polymorphisms are all dominant, and individuals are scored as either positive or negative for a particular restriction fragment (morph) (Devilee et al. 1988). The probe pα10RP8 has been mapped by in situ hybridization to the centromere of chromosome 10 (Devilee et al. 1988); but it is still necessary to prove that the probe is detecting a new polymorphism on chromosome 10 by linkage, because alphoid sequences are known to occur at centromeres throughout the genome (Willard et al. 1986).

Multiple endocrine neoplasia type 2A (MEN 2A) can be subclassified as (1) medullary thyroid carcinoma (MTC) with pheochromocytomas (PHEOs) and parathyroid tumors (PTs), (2) MTC with PHEOs alone, or (3) MTC with PTs alone. A fourth related phenotype, hereditary MTC alone, has been also described (Farndon et al. 1986). Evidence that the four phenotypes probably map to chromosome 10 has been reported (Mathew et al. 1987; Simpson et al. 1987; Noll et al. 1988; Nakamura et al. 1989; Narod et al. 1989; Sobol et al. 1989). However, the phenotype MTC with PTs alone has not been specifically mapped to chromosome 10, and Nelkin et al. (1989) have suggested that MTC alone may not be on chromosome 10. Furthermore, the locus for the closely related syndrome MEN 2B is likely on chromosome 10 (Norum et al., in press). It is not clear whether the mutation(s) for the MEN 2

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phenotypes are allelic or are at nearby loci or possibly overlapping loci as suggested by Jackson et al. (1989). If the mutations for MEN 2A occur at separate loci, they are likely close to each other, since Narod et al. (1989) were unable to demonstrate linkage heterogeneity by using the RBP3 locus (interstitial retinol binding protein) in their study of families with MTC with and without PHEOs, although they did not separate the data by the occurrence of PTs.

The D10Z1 locus is linked to the locus for MEN2A, with no recombination between the loci detected as yet (Wu et al. 1990; C. G. P. Mathew, personal communication). Given the dominant nature of the D10Z1 polymorphisms, the morphs individually are not particularly informative, and additional polymorphisms in little or no linkage disequilibrium will identify an increased number of informative matings to allow for a clearer understanding of assignments of the MEN2 subclassifications.

We report the linkage of the new *Hin*fI polymorphisms to the *Pst*I polymorphisms; the latter are known to be on chromosome 10 (Wu and Kidd 1990). Using the D10Z1 and RBP3 polymorphisms, we have shown that the locus for the specific MEN 2A phenotype MTC with PTs is linked to the D10Z1 locus. The data suggest an allelic association of one *Hin*fI/*Pst*I haplotype with the phenotypes MTC with PHEOs with and without PTs and of another haplotype with the phenotype MTC with PTs.

Material and Methods

Six MEN 2A families comprising a total of 301 individuals were used in the present study. The families have been described elsewhere (Jackson et al. 1973; Keiser et al. 1973; Birt et al. 1977; Hamilton et al. 1978; Partington et al. 1981; Verdy et al. 1984; Duncan et al. 1986; Kruger et al. 1986). The R and C families have MTC with PHEOs alone, the W, N, and B families have MTC with PHEOs and PTs, and the S family has MTC with PTs alone. The age at onset in the S family appears to be similar to that in the other families. Of more than 30 individuals with either MTC or C-cell hyperplasia who were in the S family, seven have developed PTs and none has developed PHEOs.

Hybridization and washing conditions for the N family have been described elsewhere (Wu and Kidd 1990). For the other five families, the probe pα10RP8 was hybridized under the following high-stringency conditions: 70°C in the presence of 10% dextran sulfate, 1% SDS, 1 M NaCl, and 25 μg sheared human placental DNA/ml. All washes were done at 70°C with a final wash in 0.1 × SSC, 0.1% SDS.

To test for linkage, lod scores (Z) (Morton 1955) were calculated using the program LIPED (Ott 1974) with a straight-line age correction (Hodge et al. 1979) using the parameters described by Farrer et al. (1987). The allele frequencies for the F and G morphs at D10Z1 were based on 52 unrelated individuals, and those for the A and B morphs were based on 94 unrelated individuals (table 1). The frequencies of the FG and the AF haplotypes were determined from the number of individuals missing both morphs and by estimating the other haplotype frequencies, under the assumption of Hardy-Weinberg equilibrium.

Results

In DNAs from most unrelated individuals examined (51 of 52), the F and G morphs were both present or both absent, indicating strong linkage disequilibrium. When the expected and the observed phenotype frequencies were compared, a χ^2 of 48.33 was obtained with 1 df, confirming linkage disequilibrium. The A

Table 1

Frequencies of Polymorphic Restriction Fragments in Alpha Satellite DNA in Human Chromosome 10

Morph	Restriction Enzyme	Size (bp)	No. of Individuals		Allele Frequency	
			+ / + or + / −	− / −	+	−
F.....	*Hin*fI	570	39	13	.50	.50
G	*Hin*fI	280	40	12	.52	.48
A[a]....	*Pst*I	1,100	65	29	.44	.56
B[a]....	*Pst*I	320	10	59	.21	.79

[a] Data are from Wu and Kidd (1990).

Table 2

Z Values between D10Z1 When AF Haplotype and MEN2A Locus Are Used, by Clinical Phenotypes of Families

Family	Syndrome	θ[a] .000	.001	.01	.05	.1	.2	.3	.4
R	MTC + PHEOs	.88	.88	.85	.74	.61	.37	.20	.08
C	MTC + PHEOs	.85	.85	.82	.72	.61	.39	.21	.07
W	MTC + PHEOS + PTs	3.84	3.84	3.82	3.64	3.31	2.50	1.55	.57
B	MTC + PHEOs + PTs	.31	.31	.31	.29	.27	.22	.16	.09
N	MTC + PHEOs + PTs	5.32	5.31	5.22	4.80	4.26	3.12	1.92	.73
Total		11.20	11.19	11.02	10.19	9.06	6.60	4.04	1.54
S	MTC + PTs	2.86	2.86	2.85	2.76	2.59	2.09	1.43	.66
Grand total		14.06	14.05	13.87	12.95	11.65	8.69	5.47	2.20

NOTE.—A allele data Wu et al. (1990).
[a] $\theta_m = \theta_f$.

and F morphs were also in linkage disequilibrium ($\chi^2 = 10.5$ with 1 df).

Linkage analysis between the FG haplotype (*HinfI*) (Carson and Simpson 1990) and the AB haplotype (*PstI*) (table 1) (Wu and Kidd 1990) indicated that F and G define the same locus as the A and B morphs on chromosome 10 (maximum [Z_{max}] = 3.30 at recombination frequency [θ] = 0).

The Z_{max} value for linkage between the AF haplotype at D10Z1 and the disease locus for the phenotypes MTC with PHEOs with and without PTs was 11.20 at $\theta = 0$, and no recombination was observed, although the R, C, and B families were not very informative (table 2). Linkage was of borderline significance ($Z_{max} = 2.86$ at $\theta = 0$; table 2) for the phenotype MTC with PTs when the D10Z1 haplotypes were used but was significant when the haplotypes for the three systems at RBP3 were used ($Z_{max} = 3.54$ at $\theta = 0$) (table 3). From the data used by Wu et al. (1990), the Z_{max} values between the pericentromeric chromosome 10 markers and the disease locus, along with their θ values and confidence limits (table 3), were selected for those families that either were noninformative or had Z_{max} <3.00 for D10Z1.

In all cases in which the genotype of the dominant A, B, F, and G morphs at D10Z1 could be determined, the disease allele in the families with MTC and PHEOs (families C, W, N, and B) was carried on the chromosome with the haplotype consisting of A+B−F−G− (presence of A and absence of B, F, and G) (table 4). This haplotype has an estimated population frequency of .36. In the case of the R family, it could not be determined whether the A+ or A− was associated with the disease allele. However, the B, F, and G morphs were consistent with those in the other families with PHEOs (B−F−G−). In the S family (MTC with PTs alone), how-

Table 3

Z_{max} Values between Chromosome 10 Pericentromeric Loci and Locus for MEN2A, by Clinical Phenotypes of Families

Family	Syndrome	Marker Locus	Z_{max}	θ	Confidence Interval
R	MTC + PHEOs	FNRB	2.30	0	0–.25
C	MTC + PHEOs	FNRB	2.63	0	0–.18
		D10S15	3.55	.05	0–.23
B	MTC + PHEOs + PTs	FNRB	4.42	0	0–.13
S	MTC + PTs	RBP3	3.54	0	0–.18

NOTE.—Positive Z_{max} Values were selected for individual families for the clinical phenotypes that were either noninformative or not >3.00 for D10Z1 and are data that were used by Wu et al. (1990).

Table 4

Haplotypes of Chromosome 10 Pericentromeric Markers in MEN 2A Families, by Clinical Phenotypes of Families

Family	Syndrome	Haplotype of Pericentromeric Markers			
		FNRB[a]	D10Z1[b]	RBP3[c]	D10S15[d]
R[e]	MTC + PHEOs	211	_B-F-G-[f]	212	3
C[g]	MTC + PHEOs	211	A+B-F-G-	211	4
W[e]	MTC + PHEOs + PTs	221	A+B-F-G-	212	1
B[g]	MTC + PHEOs + PTs	221	A+B-F-G-	111	3
N	MTC + PHEOs + PTs	221	A+B-F-G-	_22[f]	0
S	MTC + PTs	221	A-B-F-G+	111	3

[a] Allelic systems—D;A;C; probe—pGEM-32; enzymes—*Bgl*II;*Ban*II;*Hin*fI (Wu et al. 1989).
[b] Morphs—A;B;F;G; probe—pα10RP8; enzymes—*Pst*I;*Hin*fI (Wu and Kidd 1990).
[c] Allelic systems—D;A;B; probe—cTBIRBP9 (D alleles); enzyme—*Taq*I (Nakamura et al. 1988*b*); probe—H.4 IRBP (A and B alleles); enzymes—*Bgl*II;*Msp*I (Liou et al. 1987).
[d] Alleles—VNTR with six alleles; probe—pMCK2; enzyme—*Rsa*I (Nakamura et al. 1988*a*).
[e] Includes one individual with a recombination between the disease and RBP3.
[f] The underbar denotes that the allele could not be determined.
[g] Includes one individual with a recombination between the disease and D10S15.

ever, the disease allele was found to be carried on the chromosome having the haplotype consisting of A-B-F-G+ (absence of A, B, and F and presence of G). The population frequency of this haplotype approaches zero. The alleles and haplotypes for the markers FNRB, RBP3, and D10S15 (from Wu et al. 1990) (table 4) were not associated with the disease phenotypes.

Discussion

The F and G polymorphisms at the D10Z1 locus can provide useful information for determining the disease genotype in MEN 2A families. To test for informative polymorphisms at this locus, we suggest that the A and B morphs (*Pst*I) and the F and G morphs (*Hin*fI) be examined first, as we have found these polymorphisms to be the easiest to interpret.

The F and G morphs at the D10Z1 locus are an example of polymorphisms resulting from the digestion of genomic DNA with restriction enzymes that cleave within the higher-order α satellite repeat unit analogous to the polymorphisms detected by p17H8 at D17Z1 (Willard et al. 1986). The RFLPs cleaved in this manner are due to restriction-site alterations or deletions that occur in most if not all of the repeat units. The resulting hybridization pattern consists of a series of bands all <20 kb in size. In the case of the F and G morphs, the band sizes are all <1.1 kb (Carson and Simpson 1990). Willard et al. (1986) have found substantial disequilibrium among the polymorphisms at D17Z1, and they suggest that strong disequilibrium might be a general feature for these types of RFLPs. The disequilibrium observed for the F and G morphs seems to support this suggestion. In contrast, polymorphisms resulting from the digestion of genomic DNA with restriction enzymes that rarely cleave within the higher-order α satellite repeat unit typically reveal hybridization patterns having a strong hybridization band >20 kb in size (Willard et al. 1986; Devilee et al. 1988). The presence of a large band indicates that not all the repeat units are being cut by the enzyme in question. The different variant bands represent only a proportion of the repeats. The resulting polymorphisms, therefore, could be independent of each other, resulting in little disequilibrium (Willard et al. 1986). As might be expected, therefore, no evidence for linkage disequilibrium was found between the A and B morphs (Wu and Kidd 1990).

Because of the strong disequilibrium observed between the F and G morphs, it is unlikely that the FG haplotype would give more information for linkage analysis than would either the F morph or G morph alone. However, if they were used in combination with the A and B morphs, the chances of detecting informative matings would increase. The families used in the present study had a low frequency of B+, and very little information was obtained from this morph. Therefore, AF haplotypes were used in the linkage analysis.

This combination proved to be more informative than did the AB haplotypes or the FG haplotypes. It should be noted, however, that, since the frequency of the B+ morph is low, the presence of B+ in association with the disease locus would be very informative, as most matings would consist of affected individuals heterozygous at D10Z1 and of spouses homozygous recessive for the B morph.

The phenotype for MTC with PTs alone is linked to the centromeric region of chromosome 10 in the S family, on the basis of the evidence from the data for linkage between the disease locus and both the D10Z1 locus and the RBP3 locus. Our data are consistent with the recent suggestion that the mutations for both MTC with PHEOs and MTC without PHEOs are at a locus or loci close to the centromere of chromosome 10 (Narod et al. 1989), although Narod et al. did not classify their families by the presence or absence of PTs when MTC with no PHEOs occurred. Of our families in which the three tumors developed, two of them (families W and N; table 2) had $Z_{max} > 3.00$ for linkage between the disease and D10Z1 loci, and the B family had $Z_{max} > 4.00$ at $\theta = 0$ (table 3) between the disease and FNRB loci. Although the R and C families with PHEOs and no PTs did not have Z_{max} values significant for linkage when the D10Z1 locus was used (table 2), they did have Z_{max} values that were indicative of linkage near the chromosome 10 centromere (table 3). Thus the data are consistent with the hypothesis that the MEN 2 syndromes are determined by either one locus or adjacent loci, as proposed by Jackson et al. (1989).

Because of the lack of recombination between D10Z1 and the MEN2A locus, an allelic association would be expected if all MEN 2A families had the same mutation by descent (founder effect). In general, the same mutation by descent is unlikely, since the disease has been reported in many ethnic groups (Mathew et al. 1987; Simpson et al. 1987; Sobol et al. 1988; Yamamoto et al. 1989). However, it is interesting that the S family, which has a different phenotype from those of the other families and therefore might be expected to be the result of a different mutation, does not have the same centromeric haplotype as do the families with PHEOs. Another explanation for allelic association is that certain allelic combinations in the centromere predispose to different MEN2A mutations. Finally, of course, our observations may be purely fortuitous and due solely to the small number of families studied.

Recently Narod et al. (1989) reported a possible allelic association between MEN2A and two chromosome 10 markers. Both the A2 allele for RBP3 detected in *Bgl*II digests and the presence of the C VNTR allele for D10S15 detected in the *Msp*I digests were associated, more frequently than expected, with both MTC with PHEOs and MTC without PHEOs, suggesting linkage disequilibrium between the marker loci and the disease allele(s). In our six families the disease gene was associated with the A2 allele for RBP3 in only one family (family N); in all the other families it was associated with the A1 allele (table 4). We also tested for association of haplotypes with the disease phenotypes by using both the *Taq*I RFLP detected by the cTBIRBP9 probe (Nakamura et al. 1988*b*) and the *Bgl*II and *Msp*I RFLPs detected by the H.4IRBP probe (Liou et al. 1987), and we found no evidence for allelic association with RBP3 (table 4). Furthermore, we found no evidence for association of alleles at D10S15 and FNRB (table 4).

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