Am. J. Hum. Genet. 54:1060–1066, 1994

Mapping the Gene for Hereditary Hyperparathyroidism and Prolactinoma ($MEN1_{Burin}$) to Chromosome 11q: Evidence for a Founder Effect in Patients from Newfoundland

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Summary

An autosomal dominant syndrome of prolactinomas, carcinoids, and hyperparathyroidism was described in four Newfoundland kindreds in 1980 and in one kindred from the Pacific Northwest in 1983. Because this syndrome shares many features with multiple endocrine neoplasia type 1, the gene for which maps to proximal chromosome 11q, we performed linkage studies with chromosome 11 markers in prolactinoma families to determine whether the two genes map to the same location. All proximal chromosome 11q markers gave positive LOD scores, and no recombinants were seen with PYGM (LOD score 15.25, recombination fraction .0). All affected individuals from Newfoundland shared the same PYGM allele, providing evidence for a founder effect. The disease in the Pacific Northwest kindred cosegregated with a different PYGM allele.

Introduction

In 1980, Farid et al. described a syndrome of prolactinomas, carcinoids, and hyperparathyroidism in four large Newfoundland kindreds. This syndrome was later referred to as "$MEN1_{Burin}$" (Bear et al. 1985), reflecting similarity to multiple endocrine neoplasia type 1 and indicating the region of origin of affected individuals, the Burin Peninsula. Unlike typical MEN1, in which pancreatic islet tumors are the second most common feature, $MEN1_{Burin}$ did not manifest this tumor type, and the frequencies of prolactinoma (10/25 affected individuals) and carcinoid tumors (4/25) were higher than those in other MEN1 families. A phenotypically similar but unrelated kindred from the Pacific Northwest, in which six of the seven living affected members had prolactinomas and none had pancreatic islet tumors, was subsequently described (Hershorn et al. 1983).

While genetic linkage studies of $MEN1_{Burin}$ have not revealed the location of the gene (Bear et al. 1985), the gene for typical MEN1 has been mapped to chromosome 11 very close to PYGM (Larsson et al. 1988; Bale et al. 1989; Nakamura et al. 1989). The finding of chromosome 11q allelic loss in MEN1-related pancreatic islet neoplasms and parathyroid adenomas (Larsson et al. 1988; Friedman et al. 1989) provided evidence that the gene functions as a tumor suppressor. There is less evidence that pituitary tumors arise through a tumor-suppressor mechanism involving MEN1 (Byström et al. 1990; Bale et al. 1991). To determine whether $MEN1_{Burin}$ is genetically related to typical MEN1, linkage analysis of the four Newfoundland kindreds and the Pacific Northwest kindred was performed using polymorphic markers from the centromeric region of chromosome 11 and proximal 11q.

Material and Methods

Clinical Data

Blood samples were obtained after informed consent from 216 members of the four Newfoundland kindreds

Received December 20, 1993; accepted for publication February 8, 1994.

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0002-9297/94/5406-0015$02.00

Table 1

Hereditary Prolactinoma Kindreds

Family	Geographic Origin	Generations	Affected	Total (+ spouses)
2876[a]	Pacific Northwest	2	7	9 (10)
2877[b]	Newfoundland	4	21	55 (65)
2878[b]	Newfoundland	3	11	28 (36)
2879[b]	Newfoundland	4	12	28 (32)
F[b]	Newfoundland	3	20	64 (73)

[a] Hershorn et al. 1983.
[b] Farid et al. 1980.

(2877, 2878, 2879, and F) and the Pacific Northwest kindred (2876) including 71 known affecteds, 113 unaffected first-degree relatives, and 32 unrelated spouses (table 1). That <50% of at-risk individuals are affected reflects the age-dependent penetrance of the disease and nonpenetrance in ≤10% of obligate gene carriers. None of these five families was known to be related to any other, but the four Newfoundland kindreds all originated from the same geographically isolated region.

At-risk individuals of all ages were evaluated for parathyroid, pituitary, and pancreatic islet abnormalities by monitoring calcium, parathormone, prolactin, and gastrin levels. In addition, chest radiographs were performed to screen for pulmonary carcinoids. Of 60 affected family members from Newfoundland who underwent extensive screening, 96% had hyperparathyroidism, 39% had prolactinomas, 13% had carcinoids, and 6% had pancreatic islet tumors. One of the seven affected individuals in the Pacific Northwest kindred had developed a pancreatic islet tumor.

Isolation of DNA

DNA was extracted from peripheral blood leukocytes by using the guanidine hydrochloride method (Jeanpierre 1987), modified to include an overnight proteinase K digestion in TNE (10 mM Tris, pH 8, 100 mM NaCl, and 1 mM EDTA) and 1% Sarcosyl, prior to addition of guanidine hydrochloride.

Polymorphism Typing

Three probes detecting RFLPs and four primer pairs that amplify short tandem repeats from proximal chromosome 11 were used in this study (table 2). The order of four of the loci, established by both genetic and physical mapping, is D11S288–PYGM (both RFLP and short tandem repeat used)–D11S146–D11S533 (Julier et al. 1990; Janson et al. 1991; Richard et al. 1991; Fujimori et al. 1992; Gerhard et al. 1992; Larsson et al. 1992; Litt et al. 1992; Tanigami et al. 1992; Petty et al. 1993). The localization of D11S971 (Krebs et al. 1993) and D11S970 (Taggart et al. 1993) to 11q13 was established by radiation hybrids. Preliminary linkage analysis in several MEN1 kindreds indicated that these loci lie between PYGM and D11S146, with one recombinant placing D11S970 distal to D11S971 (E. M. Petty, unpublished data).

For RFLP analysis, DNA samples (5 μg) were digested to completion with restriction enzymes according to the manufacturer's recommendations (Bethesda Research Laboratories) and were size fractionated by electrophoresis in 0.8% agarose. Transfer to nylon membranes (Dupont GeneScreen Plus) was performed, according to the manufacturer's instructions, using high-salt (20 × SSC) capillary transfer. DNA was fixed to the membranes by baking at 80°C for 2 h in a vacuum oven. Fifty nanograms of probe DNA was labeled to a specific activity of ~10^9 CPM/μg, with ^{32}P-dCTP, by the random priming method (Boehringer-Mannheim Random Primed DNA Labelling kit). The probes were hybridized to Southern blots for 15 h at 65°C in a solution containing 0.5 M $NaHPO_4$ (pH 7.2) 7% SDS, 1% bovine serum albumin, 1 mM EDTA, and 200 μg sheared herring sperm DNA/ml. Sheared human placental DNA (500 μg/ml) was added to the hybridization solution when the probe, PMCMP1, was used. Stringent washing was carried out at 65°C in 0.1 × SSC and 0.1% SDS. Blots were subsequently exposed to Kodak X-Omat AR film for 1–14 d at 70°C.

D11S533 was analyzed as described by Litt et al. (1992). The remaining three short tandem repeat polymorphisms—PYGM(AT) (Iwasaki et al. 1992), D11S970, and D11S971—were analyzed using published conditions with several modifications. Each reaction contained 0.25 mM spermidine. The PYGM STR was amplified using the primers CACCAAACTTCCAACCGTG (5′) and AACTGCACATTGAGCATGT-

Table 2

Polymorphic Loci on Chromosome 11

Location	Locus/Clone	Polymorphism	Allele (kb)	Reference
p12–11.2	D11S288/p3C7	*Msp*I	A1 (5.7) A2 (3.1) B1 (10) B2 (7.0)	Williamson et al. 1991
q12–13.2	PYGM/pMCMP1	*Msp*I	≥6 alleles 2.1 (2.4)	Williamson et al. 1991
	PYGM/(AT)rep(VNTR)[a]	PCR	≥6 alleles .427 (.970)	Iwasaki et al. 1992
q13	D11S970/RC29 (CATT)	PCR	A1 (.162) A2 (.158) A3 (.154) A4 (.150)	Taggart et al. 1993
q13	D11S971/RC27 (CATT)	PCR	A1 (.168) A2 (.164) A3 (.160) A4 (.156)	Krebs et al. 1993
q12–13.2	D11S146/pHB159	*Msp*I	A1 (4.3) A2 (3.8, .5)	Williamson et al. 1991
		*Taq*I	B1 (1.2) B2 (.8)	
q13	D11S533/4F7(VNTR)	PCR	10 alleles (.300–.900)	Litt et al. 1992

[a] This AT repeat is one of two variable-length regions within the pMCMP1 clone and is responsible for most of the polymorphism detected by Southern blot analysis with this probe and the enzyme *Msp*I.

ACC (3′), which produce products 218 bp longer than those presented by Iwasaki et al. (1992). A "touchdown" protocol was used with the denaturing step at 94°C for 1 min, the elongation step at 72°C for 2 min, and the 1-min annealing step, varying in temperature from 60°C for the first 2 cycles, to 58°C for the next 4 cycles, to 56°C for the remaining 34 cycles. The PYGM STR polymorphism was visualized on ethidium bromide–stained 3% agarose gels (2% NuSieve and 1% SeaKem LE agarose), and D11S970 and D11S971 were visualized on 5% agarose gels (4% NuSieve and 1% SeaKem LE).

Linkage Analysis

Two-point analyses were performed with the program MLINK from the LINKAGE package (Lathrop and Lalouel 1984). Three liability classes were assigned, based on observations of age at onset in the kindreds studied. Liability class I included all individuals ≤25 years of age in whom the penetrance was assessed to be 5%. A penetrance value of 50% was assigned for individuals 25–45 years of age, and a value of 90% was assigned to individuals >45 years of age. The gene frequency for MEN1 was .0001 on the basis of estimates of population frequency. Allele frequencies for most of the polymorphisms were derived from Williamson et al. (1991) and references for STRs as listed above. For PYGM, population allele frequencies in Newfoundland were derived from analysis of unrelated spouses.

Haplotype Analysis

Affected parent-child pairs from each of the five kindreds studied were analyzed to determine which allele was cosegregating with the disease in each family. Because the PYGM RFLP has many alleles varying in size by small amounts, members from each of the five families were analyzed side by side on the same blot. Likewise, PCR amplification of the complex AT repeat polymorphism at the PYGM locus was run for all families on the same gel.

Results

Linkage Analysis

The Newfoundland kindreds were informative for all seven markers, with the exceptions of kindred 2877, which was uninformative for D11S970 and D11S971, and kindred 2879, which was uninformative with D11S533 (table 3). The two-generation kindred from the Pacific Northwest (2876) was informative only for PYGM, D11S970, and D11S971.

Combining the data from all families gave signifi-

Table 3

Linkage between Hereditary Prolactinoma and Chromosome 11 Loci

Locus and Family	LOD Score at θ =[a]				
	.001	.1	.2	.3	.4
	−1.16	12.28	1.75	5.88	1.37
D11S288:					
2876	NI	NI	NI	NI	NI
2877	1.08	.78	.47	.19	.00
2878	.03	.01	.00	.00	.00
2879	1.12	.99	.75	.48	.21
F	.99	.79	.53	.28	.08
Total	3.22	2.57	1.75	.95	.29
PYGM:					
2876	1.60	1.30	.98	.62	.23
2877	3.50	2.73	1.90	1.04	.27
2878	1.64	1.23	.82	.46	.18
2879	2.65	2.18	1.67	1.13	.55
F	5.86	4.84	3.77	2.63	1.37
Total	15.25	12.28	9.14	5.88	2.60
D11S971:					
2876	1.15	.96	.72	.46	.16
2877	NI	NI	NI	NI	NI
2878	.36	.24	.14	.07	.02
2879	.64	.63	.53	.37	.17
F	−3.31	2.57	2.13	1.49	.69
Total	−1.16	4.40	3.52	2.39	1.04
D11S970:					
2876	1.33	1.09	.83	.51	.19
2877	NI	NI	NI	NI	NI
2878	.70	.53	.36	.20	.07
2879	.30	.20	.11	.05	.01
F	1.82	1.40	1.02	.64	.29
Total	4.15	3.22	2.32	1.40	.56
D11S146:					
2876	NI	NI	NI	NI	NI
2877	−2.83	.11	.13	.08	.03
2878	.64	.48	.33	.21	.10
2879	−.87	.98	.80	.48	.13
F	2.56	2.05	1.50	.93	.38
Total	−.50	3.62	2.76	1.70	.64
D11S533:					
2876	NI	NI	NI	NI	NI
2877	−.45	.20	.26	.21	.12
2878	.31	.23	.16	.11	.07
2879	NI	NI	NI	NI	NI
F	−2.24	1.17	.85	.51	.20
Total	−2.38	1.60	1.27	.83	.39

[a] NI = not informative.

cantly positive LOD scores for linkage of hereditary prolactinoma to the loci D11S288, PYGM, D11S970, D11S971, and D11S146. For D11S533 a maximum LOD score of 1.6 was obtained at θ = .1. All families showed linkage with PYGM, yielding a maximum LOD score of 15.25 at θ = .0. Only two recombinants between D11S971 and the disease gene were detected, both in kindred F (fig. 1). No recombination was seen with D11S970 in these kindreds, but studies in other families place this marker distal to D11S971. D11S146 showed recombination with the disease gene in two families, consistent with the genetic distance of 5 cM distal to PYGM (Nakamura et al. 1989). The lack of recombinants with D11S288, which lies 6 cM proximal to PYGM (Nakamura et al. 1989), most likely reflects the relatively low number of informative meioses. Several recombinants were identified with D11S533, which lies ~12 cM distal to PYGM (Litt et al. 1992).

Evidence for a Founder Effect

Southern blot analysis of the PYGM polymorphism strongly suggested that all affected individuals in the Newfoundland kindreds shared a single allele, but the resolution was not sufficient to determine with certainty whether affected individuals from the Pacific Northwest kindred (2876) also had that allele (fig. 2). PCR analysis with the PYGM AT repeat (see table 2, footnote) of affected parent-child pairs from each of the kindreds showed that all affected individuals from Newfoundland had a 640-bp allele but that an affected member of the Pacific Northwest family did not share this allele (fig. 2). The 640-bp allele was present in only 10% of 62 chromosomes from the unaffected, unrelated spouses married into the Newfoundland families. Although the observations in the Newfoundland kindreds are based on only four independent chromosomes bearing the disease gene, these data strongly sug-

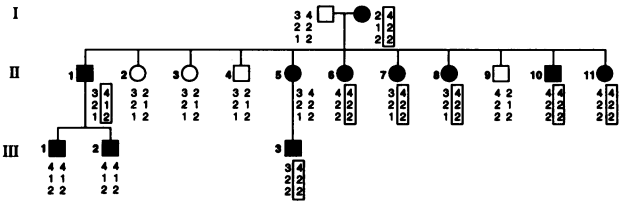

Figure 1 Portion of the F kindred, showing one of the two recombination events between D11S971 and the disease gene. Affected males and females are shown as blackened squares and circles, respectively. Unaffected individuals are shown as unblackened squares and circles. The order of markers is PYGM, D11S971, and D11S970. All of the affected family members have the haplotype 4,2,2, except for individual II-1 and his progeny, who have the haplotype 4,1,2. These data indicate that the gamete transmitted from I-2 to II-1 resulted from a recombination event between PYGM and D11S971, in which the disease gene segregated with PYGM.

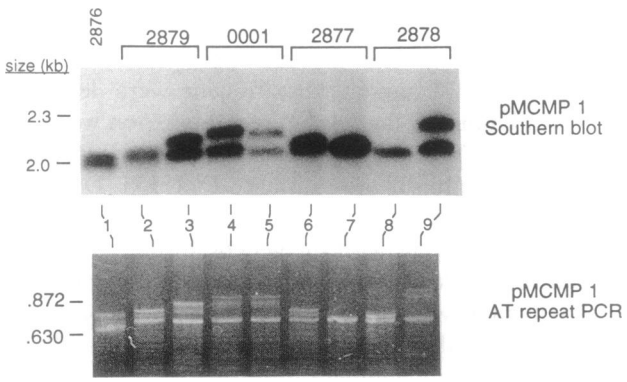

Figure 2 Typing of one individual from the Pacific Northwest kindred and of affected relative pairs from each of the four Newfoundland kindreds, for PYGM. The upper panel shows an autoradiograph resulting from an *MspI* digest probed with pMCMP1, and the lower panel is ethidium bromide–stained products of PCR-based typing of the same polymorphism. Although the resolution of the Southern blot is insufficient to show unambiguously whether all families share the same allele, the PCR-based analysis indicates that affected members of the Newfoundland, but not of the Pacific Northwest, kindred all have a 640-bp allele. Heteroduplexes created during PCR are seen as third bands in lanes 2–6 and 9, reflecting the nondenaturing conditions under which electrophoresis was run.

gest a founder effect ($P < .001$; Fisher's exact test) and argue against a similar origin for the Pacific Northwest kindred.

All affected individuals from Newfoundland also shared the same alleles for D11S970 and D11S971, with the exception of the two recombinants with D11S971 in kindred F. Despite the lack of recombination with D11S288 in any single kindred, the disease gene was not cosegregating with the same D11S288 allele in all of the families, suggesting that recombination had occurred in previous generations. There was no evidence for linkage disequilibrium with D11S146 or D11S533.

Discussion

Three distinct, hereditary forms of multiple endocrine neoplasia have been delineated (Schimke 1984). MEN1 is characterized by hyperparathyroidism, pancreatic islet tumors, pituitary tumors, and, to a lesser extent, carcinoids. In MEN 2A, medullary thyroid carcinoma is the most common tumor type, followed by pheochromocytoma. Hyperparathyroidism is reported occasionally. MEN 2B is similar to MEN 2A but also includes marfanoid habitus, large lips, and mucosal neuromas. An overlap syndrome has been described in which patients have both pheochromocytoma and pancreatic islet tumors, but it is probably a variant of von Hippel-Lindau disease. Both the MEN 2A and MEN 2B loci have been mapped to chromosome 10 (Simpson et al. 1987; Norum et al. 1990), and mutations of the RET oncogene have been identified in MEN 2A (Donis-Keller et al. 1993; Mulligan et al. 1993) and MEN 2B patients (Hofstra et al. 1994). The gene responsible for MEN1 is not yet known.

The syndrome described in the current study more closely resembles MEN1 than it resembles any other disorder involving endocrine neoplasia. In typical MEN1 kindreds, 87%–97% of patients have hyperparathyroidism, 32%–75% have pancreatic islet tumors, 16%–40% have pituitary neoplasms, and 7% have carcinoids (Metz et al. 1994). Of the pituitary tumors, prolactinoma is the most common, although growth hormone– and ACTH-secreting tumors are also seen. $MEN1_{Burin}$ kindreds have a similar incidence of hyperparathyroidism, but approximately twice the usual incidence of carcinoid and pituitary tumors, and all of the reported pituitary tumors have been prolactinomas. The most striking difference between typical MEN1 and $MEN1_{Burin}$ is the very low incidence of pancreatic islet tumors in the latter syndrome. In the initial descriptions, neither the Newfoundland nor the Pacific Northwest kindred had any pancreatic neoplasms, and in 10–13 years of follow-up, very few of these tumors have arisen. That the tumor types observed in these kindreds have changed very little in prospective follow-up studies indicates that the initial observations did not simply reflect random variation in the spectrum of tumors. These kindreds appear to be biologically different from typical MEN1 families.

To determine whether this phenotypic difference is due to interlocus genetic heterogeneity—i.e., that the two syndromes are caused by mutations in different genes—linkage analysis was employed using markers known to be linked to MEN1. The results of this analysis show that $MEN1_{Burin}$ maps to the same region as does typical MEN1. All of the polymorphisms tested gave positive results, and, in particular, no recombination was seen with PYGM, which lies very close to the gene for typical MEN1. Sharing of a relatively uncommon PYGM allele among affected members of all four Newfoundland kindreds strongly suggests a founder effect. It further supports a map location for $MEN1_{Burin}$ very close to PYGM because the apparent linkage disequilibrium with this locus probably reflects lack of recombination through many generations. However, Ozelius et al. (1992) have shown that, in disorders that have arisen relatively recently within a restricted popula-

tion, strong linkage disequilibrium is seen even with polymorphisms 2–4 cM from the disease gene. Linkage disequilibrium in the Newfoundland kindreds may be useful for ordering markers but less so for inferring distances between them.

Allele sharing among all of the Newfoundland kindreds for the markers D11S970 and D11S971 may also reflect linkage disequilibrium, but both markers have only two predominant alleles, and the probability of allele sharing due to chance alone is much higher. Gene ordering by observed recombination events identifies D11S971 as a distal flanking marker. Although no recombination with a proximal marker was observed, the lack of linkage disequilibrium with D11S288 in the Newfoundland kindreds strongly suggests that recombination did occur in previous generations. With the assumption that D11S288 is a flanking marker, the gene for $MEN1_{Burin}$ maps to a region of <11 cM on proximal chromosome 11q.

There are at least three possible explanations for the phenotypic differences between $MEN1_{Burin}$ and typical MEN1. Most likely the differences between the two syndromes reflect intralocus genetic heterogeneity; that is, two different mutations in the same gene lead to related but subtly different phenotypes. If the MEN1 gene transcript is alternatively spliced in different tissues, then the exon bearing the $MEN1_{Burin}$ mutation might be the predominant one in the precursor cells of prolactinomas and carcinoids, but not in the pancreatic islets.

Another possibility is that the two syndromes are caused by two different genes. Even under the best of circumstances, linkage analysis is unlikely to have sufficient resolution to determine whether two diseases are caused by the same gene or by adjacent genes in the same region.

One other explanation is that environmental effects or modifying effects of other genes are responsible for this variant phenotype. This hypothesis seems unlikely because the environments of the Newfoundland and Seattle kindreds are quite different, and, given the lack of linkage disequilibrium, these kindreds probably do not share a similar genetic background of modifying genes. Even within the Newfoundland kindreds, it seems unlikely that a background of modifying genes would have been maintained through the many generations of intermixture, regardless of the relatively small population size on the island. With identification of the MEN1 gene, it will be possible to address these different hypotheses.

Acknowledgments

This work was supported by NIH grant CA50497, the Swibelius Cancer Research Award (Yale University Comprehensive Cancer Center), and the General Hospital Foundation Grant (St. John's, Newfoundland).

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