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Hyperparathyroidism–Jaw Tumor Syndrome: The *HRPT2* Locus Is within a 0.7-cM Region on Chromosome 1q

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Summary

Hyperparathyroidism–jaw tumor syndrome (HPT-JT) is an autosomal dominant disease characterized by the development of multiple parathyroid adenomas and multiple fibro-osseous tumors of the maxilla and mandible. Some families have had affected members with involvement of the kidneys, variously reported as Wilms tumors, nephroblastomas, and hamartomas. The HPT-JT gene (*HRPT2*) maps to chromosome 1q25–q31. We describe further investigation of two HPT-JT families (K3304 and K3349) identified through the literature. These two expanded families and two previously reported families were investigated jointly for linkage with 21 new, closely linked markers. Multipoint linkage analysis resulted in a maximum LOD score of 7.83 (at recombination fraction 0) for markers D1S2848–D1S191. Recombination events in these families reduced the *HRPT2* region to ~14.7 cM. In addition, two of these four study families (i.e., K3304 and K11687) share a 2.2-cM length of their (expanded) affected haplotype, indicating a possible common origin. Combining the linkage data and shared-haplotype data, we propose a 0.7-cM candidate region for *HRPT2*.

Introduction

Hyperparathyroidism–jaw tumor syndrome (HPT-JT [MIM 145001]) is an autosomal dominant trait predisposing to the development of parathyroid adenomas and fibro-osseous jaw tumors (Jackson 1958; Warnakulasuriya et al. 1985; Jackson et al. 1990; Zarbo et al. 1993; Inoue et al. 1995) and is distinct from the multiple endocrine neoplasia syndromes MEN 1 and MEN 2A (Jackson et al. 1990; Szabó et al. 1995; Hobbs and Heath 1998). The gene responsible for HPT-JT, *HRPT2*, localizes to a 34-cM region on 1q25-q31 (Szabó et al. 1995; Teh et al. 1996). We report here the expansion of two previously reported families (K3304 and K3349) with HPT-JT (Firat and Stutzman 1968; Kennett and Pollick 1971; Rosen and Palmer 1981).

Sporadic parathyroid adenomas generally occur at age >40 years, as solitary tumors that do not recur, and are more common in women than in men (2:1). In HPT-JT, hypercalcemia has been diagnosed as early as age 10 years (Szabó et al. 1995), with 33 years as the mean age at diagnosis, with men outnumbering women (male:female ratio 1.6:1) (Fujikawa et al. 1998). Patients become normocalcemic after removal of these lesions, but parathyroid adenomas have recurred many years later (Rosen and Palmer 1981; Mallette et al. 1987; Jackson et al. 1990). The risk of parathyroid carcinoma is greatly increased in HPT-JT families, now reported in 6 (including K3304) of 16 HTP-JT families (Dinnen et al. 1977; Kakinuma et al. 1994; Fujikawa et al. 1998; Teh et al. 1998). This is an unusually high prevalence for this rare cancer.

The bone lesions characteristic of HPT-JT are fibro-osseous tumors of the maxilla and mandible, in contrast to classical hyperparathyroid osteoclastic "brown tumors," which may occur elsewhere in the skeleton (Szabó et al. 1995). Sporadic fibro-osseous jaw tumors of this sort generally occur during the 3d decade of life or later (Eversole et al. 1985; Slootweg and Muller 1990), being perhaps 2% of all odontogenic tumors (Regezi et al. 1978). In HPT-JT, however, the tumors often appear in adolescence or young adulthood and are detected in ~50% of affected individuals (18 of 35 in these four families) (table 1).

In addition, renal cysts, hamartomas, mesoblastic nephromas (Teh et al. 1996), or Wilms tumors have been

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Table 1

Frequency of HPT-JT Manifestations

Family	Total No. (Sex) of Affected Individuals	No. (Sex) of Individuals with			
		Hyperparathyroidism	Parathyroid Cancer	Jaw Tumors	Wilms Tumor/ Kidney Cysts
K11687[a]	12 (7 M, 5 F)	12 (7 M, 5 F)		6 (3 M, 3 F)	1 (0 M, 1 F)
K11690[b]	7 (5 M, 2 F)	7 (5 M, 2 F)		3 (2 M, 1 F)	1 (0 M, 1 F)
K3304[c]	8 (5 M, 3 F)	7 (4 M, 3 F)	2 (1 M, 1 F)	5 (3 M, 2 F)	
K3349[d]	8 (2 M, 6 F)	6 (0 M, 6 F)		5 (2 M, 3 F)	
Total	35 (19 M, 16 F)	32 (16 M, 16 F)	2 (1 M, 1 F)	19 (10 M, 9 F)	2 (0 M, 2 F)

[a] Sources: Jackson (1958), Jackson et al. (1990), and Szabó et al. (1995).
[b] Source: Szabó et al. (1995).
[c] Sources: Kennett and Pollick (1971) and Rosen and Palmer (1981).
[d] Source: Firat and Stutzman (1968).

reported in six HPT-JT families (Kakinuma et al. 1994; Szabó et al. 1995; Teh et al. 1996). Sporadic and inherited Wilms tumors generally occur at age <5 years (Matsunaga 1981; Huff and Saunders 1993) but, in HPT-JT, have occurred as late as age 53 years (Kakinuma et al. 1994).

We have analyzed 21 new polymorphic repeat markers in four study families, the two expanded families reported here (K3304 and K3349) and the two most informative families from our previous study (K11687 and K11690) (Szabó et al. 1995). Recombination events in these families further refine the *HRPT2* region to ~14.7 cM. Haplotype analysis in the affected families identified a 2.2-cM region of shared alleles within families 3304 and 11687 (Szabó et al. 1995). Significantly, the recombination data and the shared-haplotype data, when taken together, suggest a 0.7-cM candidate region for *HRPT2*.

Patients and Methods

Patients

Kennett and Pollick (1971) and Rosen and Palmer (1981) reported cases of ossifying fibroma accompanied by primary hyperparathyroidism, in two separate families from Canada. Investigating these reports, we discovered that they represented two branches of one family, K3304 (fig. 1) (Pidwirny et al. 1995). Reinvestigation of another family, K3349 (fig. 2), originally reported by Firat and Stutzman (1968), disclosed further affected individuals in a later generation. Families 11687 and 11690 have been described elsewhere (Szabó et al. 1995). A parathyroid adenoma has since been diagnosed in individual III-4 in family 11690, which we have reported elsewhere (Szabó et al. 1995), and thus should be reclassified as affected.

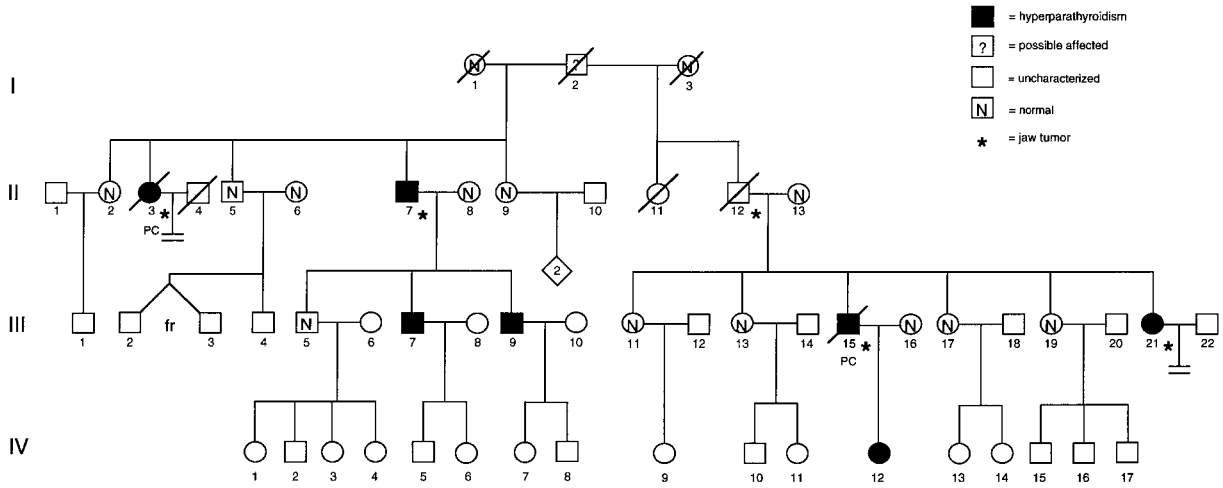

Figure 1 Pedigree for HPT-JT family 3304. Individuals II-3 and II-7 were originally reported as cases IV and V, respectively, by Rosen and Palmer (1981). Individuals III-21 and III-15 were originally reported as cases 1 and 2, respectively, by Kennett and Pollick (1971).

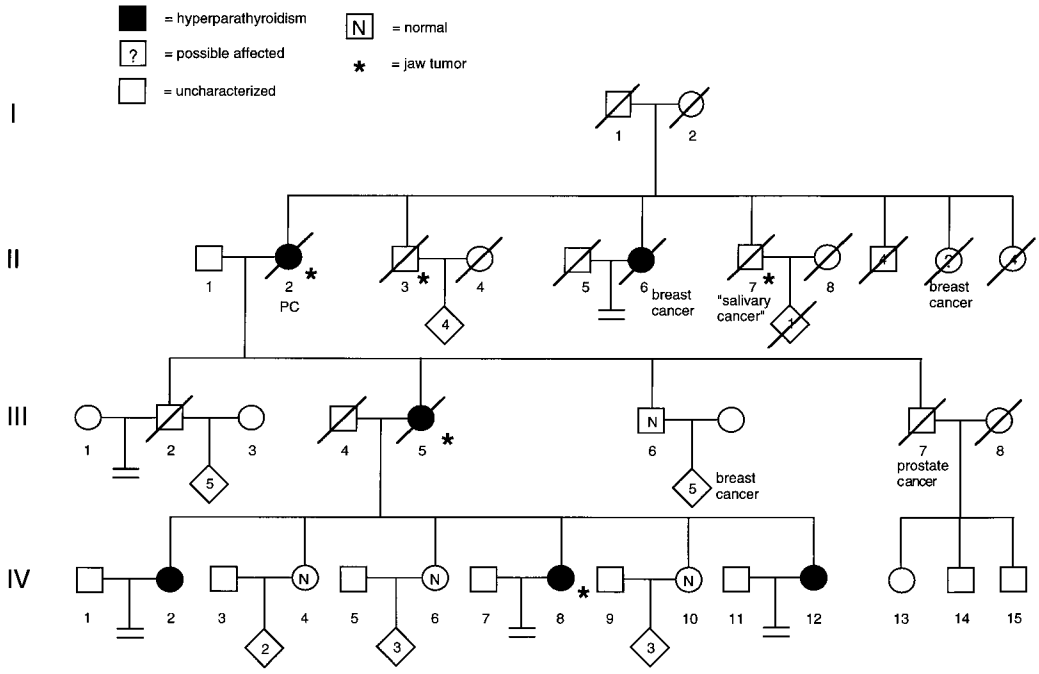

Figure 2 Pedigree for HPT-JT family 3349. Individuals II-2 and III-5 were originally reported as cases 2 and 3, respectively, by Firat and Stutzman (1968).

Informed consent was obtained from all study participants. Blood and serum samples were obtained from each family member, to measure serum calcium levels and to prepare high-molecular-weight DNA for genotyping. Family members were classified as affected if they had a history of one or more of the following disease manifestations: elevated serum calcium levels indicative of hyperparathyroidism, parathyroid adenomas at surgery, fibro-osseous jaw tumors, and/or renal cystic lesions or hamartomas; they were classified as unaffected if their calcium levels were normal (as measured at the time of blood collection for DNA isolation) and they had no history of these manifestations. Those who were either too young to have manifested disease or not available for testing were classified as unknown.

Family 3304.—Individual II-3 was originally reported as case IV, and individual II-7 as case V, by Rosen and Palmer (1981). Individual III-21 was originally reported as case 1, and individual III-15 as case 2, by Kennett and Pollick (1971). Serum calcium levels in affected family members were 11.5–15.5 mg/dl (normal <10.2 mg/dl). Affected women were diagnosed at age 14–15 years, whereas affected males were diagnosed at age 20–40 years. Patients II-3 and III-15 developed parathyroid carcinoma; the carcinoma was metastatic in patient III-15, with a markedly elevated serum parathyroid hormone level (2,060 ng/liter; normal, <65 ng/liter). Family members with jaw tumors underwent two to eight jaw resections for removal of recurrent jaw tumors.

No clinical information is available on patient I-2, although this individual is obviously an obligate heterozygote. Information on patient II-12 indicates that he did have jaw tumors.

Family 3349.—Individual II-2 (fig. 2) was originally reported as case 2, and individual III-5, as case 3, by Firat and Stutzman (1968). Serum calcium levels in affected family members were 11.3–14.8 mg/dl (normal <10.2 mg/dl). Affected women were diagnosed at age 21–35 years. Studies of generation II of K3349 are incomplete; however, patient II-6 had undergone parathyroid surgery, and both II-3 and individual II-7 had some kind of jaw tumor. The HPT-JT lesions of Wilms tumors, kidney cysts, or kidney hamartomas were not found in these two families.

DNA Markers

Twenty-one new microsatellite DNA markers in the *HRPT2* region between D1S212 and D1S245 were evaluated in the four families studied. The total of 22 markers (i.e., one previously analyzed marker [D1S191] plus the 21 new markers) analyzed were (from centromeric to telomeric) D1S215, D1S2883, D1S2640, D1S2619, D1S466, D1S2701, CHLC.GATA12F10, D1S240,

D1S2848, D1S254, D1S444, D1S191, D1S202, D1S2823, D1S2877, D1S422, D1S412, D1S413, D1S2853, D1S2622, D1S373, and D1S306. The map order for these markers was derived from the Généthon map for chromosome 1 (Dib et al. 1996) and from the chromosome 1 map from the Whitehead Institute for Biomedical Research/MIT Center for Genome Research. Allele frequencies used to compute the LOD score were derived from the unaffected individuals marrying into the present study's families that had HPT-JT.

Linkage Analysis

Only the most informative families from our previous study (i.e., K11687 and K11690) (Szabó et al. 1995) and the two new families (K3304 and K3349) were evaluated for this study. Genotyping at each locus by PCR was performed as described elsewhere (Heath et al. 1993). Data were scored independently by two observers, and then the results from each were checked against each other. Linkage calculations were made by FASTLINK (Cottingham et al. 1993), version 2.1, modifications to the LINKAGE software package (Lathrop and Lalouel 1984). Two-point LOD score analysis was completed under the assumptions of an autosomal dominant mode of inheritance with a disease-allele frequency of .0001 and, as reported elsewhere (Szabó et al. 1995), a penetrance of .90. In this genetic model, simulations indicated that these four families could generate an average expected LOD score of 4.71 and a theoretical maximum LOD score of 9.17, if all four had tight linkage to a disease locus (Ott 1989; Weeks et al. 1990). There is one living, as yet unaffected obligate heterozygote in our four study familes, individual II-5 (age 54 years) in K11690, as noted by Szabó et al. (1995).

In addition, the GENEHUNTER program (Kruglyak et al. 1996) was used to generate a multipoint LOD score, with information from all 22 DNA markers (multipoint scores). This analysis assumed the same genetic model parameters as have been described for the two-point analysis. GENEHUNTER was able to analyze all 22 DNA markers simultaneously. Information from 16 unaffected subjects was omitted, to allow the families to fit GENEHUNTER's size constraints. The simultaneous analysis of multiple markers maximizes the information from the DNA markers, ensuring against false-negative results caused by a marker that is less informative in the families (Ott 1996).

Results

Two-point LOD scores generated by FASTLINK for the 22 markers in the region ranged from -1.69 (recombination fraction [θ] 0), at D1S2701, to 8.52 ($\theta =$ 0) at D1S373. D1S373 is a 15-allele marker with heterozygosity of .904 in the four families. This LOD score of 8.52 approximates the theoretical maximum score possible with a marker of this informativeness in these families. Multipoint GENEHUNTER LOD scores (the totals for all four families) are presented in figure 3. The maximum LOD score, 7.83, occurred at markers D1S2848, D1S254, D1S444, and D1S191. Meiotic recombination events occurred in K11690 in individuals III-2 and III-4, placing *HRPT2* centromeric to D1S306 (fig. 4*A*). Furthermore, a recombination event in K3304, in individual III-7, placed the gene telomeric to CHLC.GATA12F10 (fig. 4*A*). We were unable to determine whether the breakpoint in K3304 lies centromeric or telomeric to D1S240, since individual II-7 (the parent of III-7) is homozygous at that marker. This defines an interval for *HRPT2,* between CHLC.GATA12F10 and D1S306 (~14.7 cM).

In addition to the meiotic recombinations that helped narrow the *HRPT2* region, we observed a maximum 2.2-cM region of haplotype shared by families K3304 and K11687 (fig. 4*B*). These two families shared affected-haplotype alleles for six markers: D1S466, D1S2701, CHLC.GATA12F10, D1S240, D1S2848, and D1S254. The multipoint LOD score was never<3.8, for any of these six markers. In view of the allele frequencies for each of these markers (.06, .74, .18, .50, .11, .06, respectively), the random population frequency of this haplotype would be expected to be 1/38,000. This haplotype is not present in either the other two HPT-JT families reported here or any of 30 individuals who married into the HPT-JT families. Significantly, when the shared-haplotype data are combined with the recombination data from K3304, the suggested candidate region for *HRPT2* is further narrowed, to ~0.7 cM (fig. 4*B*).

Discussion

We have narrowed the *HRPT2* region, by linkage analysis in four families, to 14.7 cM. The shared affected haplotype seen in K3304 and K11687 suggests a possible common ancestor for these two families. We are currently conducting a genealogical search to identify any relatedness of these two families. For a disease as rare as HPT-JT, it is reasonable to expect that some families might share a common origin. Significantly, the shared haplotype and the recombination data together suggest that the candidate region for *HRPT2* is only 0.7 cM.

Intriguing candidate genes in the HRPT2 14.7-cM region include those for human cysteine-rich protein (hCRP), regulators of G protein–signaling 2 (RGS2), and cyclooxygenase-2 (Cox-2). The hCRP 1q31–q32 is a potential signal-transduction protein or transcription reg-

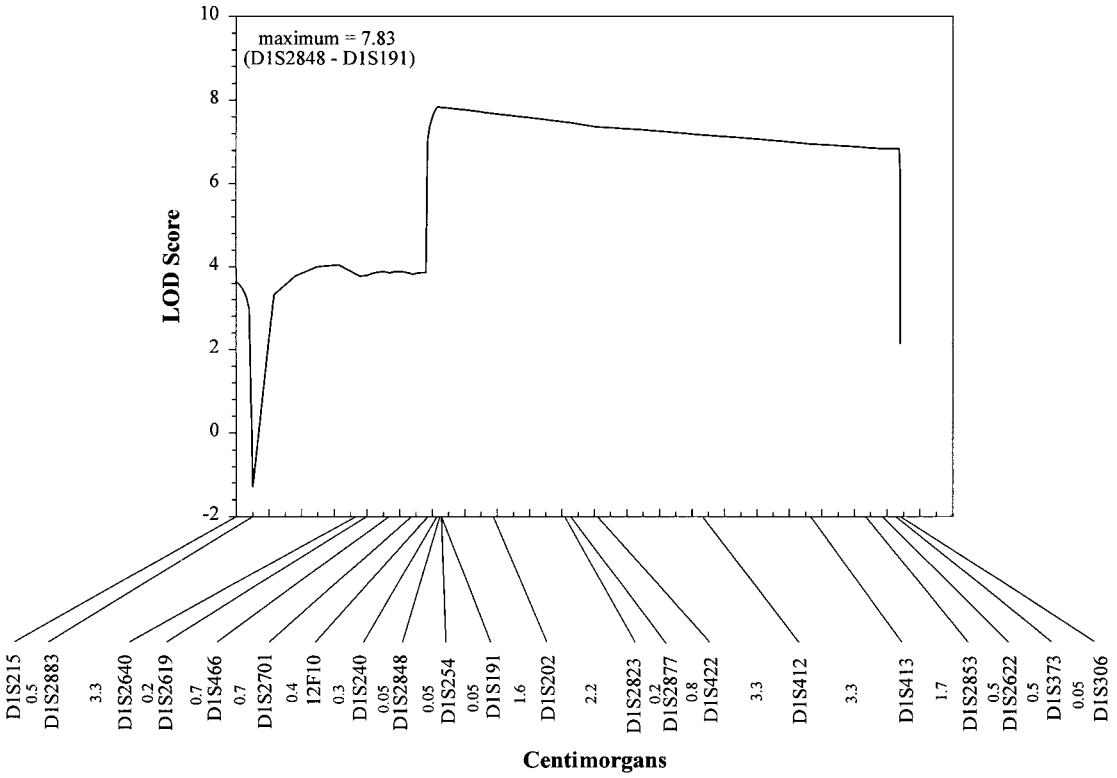

Figure 3 LOD scores obtained over the entire 21-cM region tested. The maximum LOD score of 7.83 ($\theta = 0$) was obtained at markers D1S2848, D1S254, D1S444, and D1S191. Because of space constraints, marker D1S444 is not shown on the centimorgan scale. The LOD scores remain high across the entire linked region of 14.7 cM. The LOD scores sharply decline at CHLC.GATA12F10 (abbreviated as "12F10" on the centimorgan scale) and D1S306, where recombination events occurred.

ulator (Liebhaber et al. 1990). hCRP is expressed in many tissues, including the uterus and kidney (M. R. Hobbs, unpublished data). RGS (Siderovski et al. 1994, 1996) proteins inhibit signaling by heterotrimeric G proteins and are GTP-activating proteins; the parathyroid gland calcium-sensing–receptor (CaR) protein is of the G protein-coupled–receptor type. Mutations in CaR have been shown to give rise to familial benign (hypocalciuric) hypercalcemia (Pearce et al. 1995; Heath et al. 1996). Cox-2 is reportedly overexpressed in colorectal adenomas and adenocarcinomas (Eberhart et al. 1994). Transgenic *Cox-2* −/− mice show abnormal kidney development and infertility in females (Dinchuk et al. 1995). Futhermore, *Cox-2* maps near the shared haplotype region, on the basis of the human transcript map (Schuler et al. 1996).

HPT-JT is a complex disease. The clinical diversity and long time span during which the various manifestations of HPT-JT occur probably result in its being an underrecognized clinical syndrome. Patients may see pediatricians, internists, oncologists, endocrinologists, dentists, gynecologists, and urologists, who may each be managing only one aspect of the disease. In clinical practice, the syndromic nature of these disorders may not be recognized.

HRPT2 may have a significance that extends beyond the HPT-JT families described here. The elucidation of *HRPT2* may point to new pathways of tumorigenesis and may lead to a greater understanding of the processes involved in the initiation and progression of neoplasia in many tumor types.

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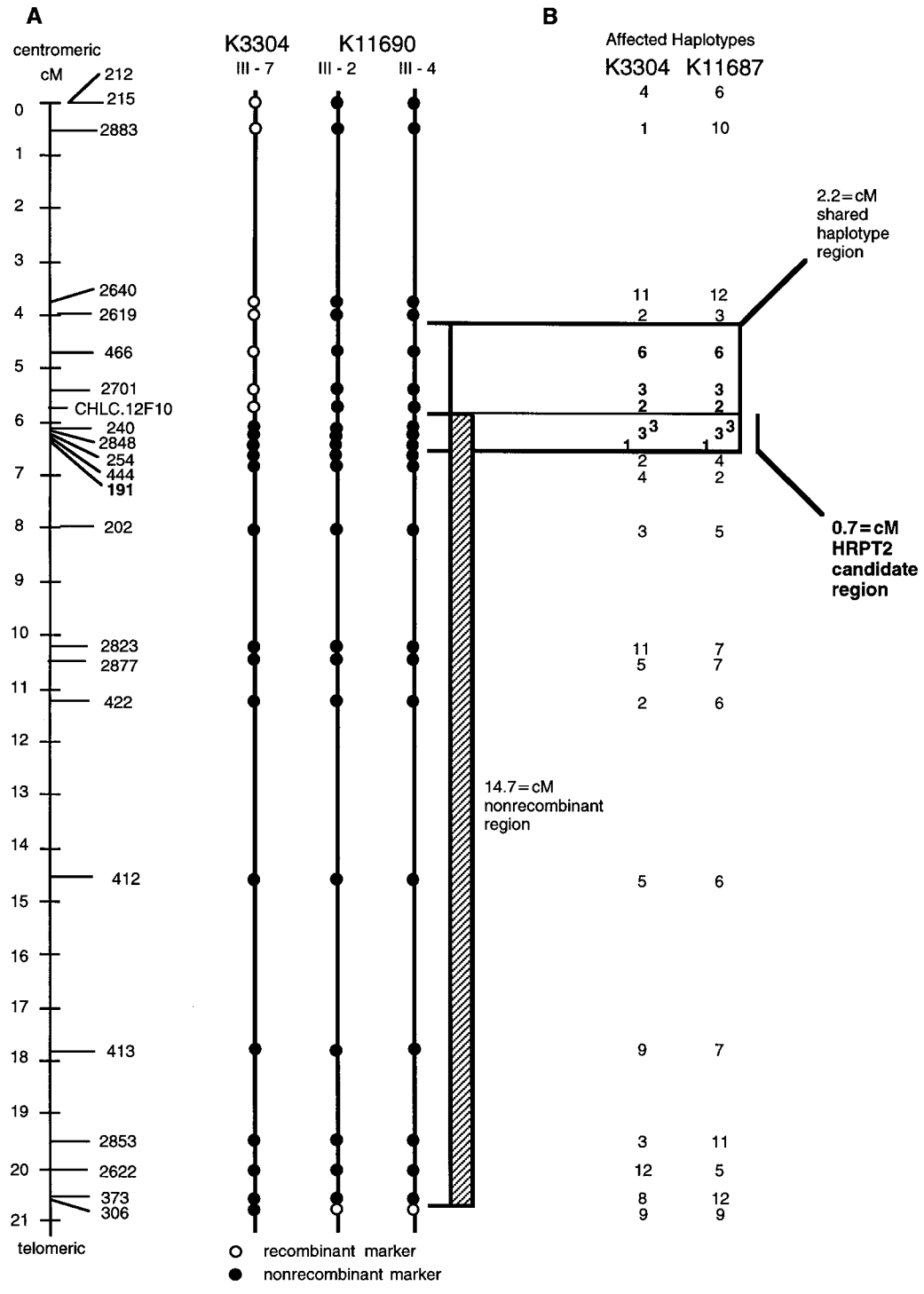

Figure 4 *A*, Diagram illustrating recombination events defining the 14.7-cM region for *HRPT2*. A scale and the approximate locations of markers on chromosome 1q are given on the left. The three thicker vertical lines represent affected chromosomes of the affected individuals in whom recombination events were detected. The blackened circles denote marker alleles inherited by all affected individuals in two families, K3304 and K11690. The unblackened circles denote marker alleles inherited from the unaffected chromosome of the affected parent, thus representing a recombination event. Marker D1S240 in K3304 represents homozygosity at this marker in III-7 and his affected parent. *B*, Alleles composing the affected haplotypes in K3304 and K11687, at the markers listed in *A*. The affected-haplotype region shared by these two families is boxed. The vertical bar on the far right indicates the 0.7-cM candidate region for *HRPT2*, defined by analysis of the recombination data together with the shared-haplotype data.

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Electronic-Database Information

The accession number and URLs for data in this article are as follows:

Généthon, http://www.genethon.fr
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for HPT-JT [MIM 145001)
Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www-genome.wi.mit.edu

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