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Hereditary Hyperparathyroidism–Jaw Tumor Syndrome: The Endocrine Tumor Gene HRPT2 Maps to Chromosome 1q21-q31

József Szabó,[1] Brett Heath,[1] Virginia M. Hill,[1] Charles E. Jackson,[3] Richard J. Zarbo,[4] Lawrence E. Mallette,[5] Shern L. Chew,[7] Gordon M. Besser,[7] Rajesh V. Thakker,[8] Vicki Huff,[6] Mark F. Leppert,[2] and Hunter Heath III[1]

[1]Section of Endocrinology, Veterans Affairs Medical Center and Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, and [2]Howard Hughes Medical Research Institute, Eccles Institute of Human Genetics, and Department of Human Genetics, University of Utah School of Medicine, Salt Lake City; [3]Department of Medicine and [4]Department of Pathology, Henry Ford Hospital, Detroit; [5]Veterans Affairs Medical Center and Baylor College of Medicine and [6]Department of Experimental Pediatrics, University of Texas M. D. Anderson Medical Center, Houston; [7]Department of Endocrinology, St. Bartholomew's Hospital and [8]MRC Molecular Medicine Group, Royal Postgraduate Medical School, London

Summary

The syndrome of hereditary hyperparathyroidism and jaw tumors (HPT-JT) is characterized by inheritance, in an autosomal dominant pattern, of recurrent parathyroid adenomas, fibro-osseous tumors of the mandible and/or maxilla, Wilms tumor, and parathyroid carcinoma. This syndrome is clinically and genetically distinct from other endocrine neoplasia syndromes and appears to result from mutation of an endocrine tumor gene designated "HRPT2." We studied five HPT-JT families (59 persons, 20 affected); using PCR-based markers, we instituted a genomewide linkage search after excluding several candidate genes. Lod scores were calculated at various recombination fractions (θ), penetrance 90%. We mapped HRPT2 to the long arm of chromosome 1 (1q21-q31). The maximal lod score was 6.10 at $\theta = .0$ with marker D1S212, or $>10^6$ odds in favor of linkage. In six hereditary Wilms tumor families (96 persons, 29 affected), we found no linkage to 1q markers closely linked with HRPT2 (lod scores −15.6 [D1S191] and −17.8 [D1S196], $\theta = .001$). Nine parathyroid adenomas and one Wilms tumor from nine members of three HPT-JT families were examined for loss of heterozygosity at linked loci. The parathyroid adenomas and Wilms tumor showed no loss of heterozygosity for these DNA markers. Our data establish that HRPT2, an endocrine tumor gene on the long arm of chromosome 1, is responsible for the HPT-JT syndrome but not for the classical hereditary Wilms tumor syndrome.

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Address for correspondence and reprints: Dr. Hunter Heath III, University of Utah School of Medicine, Room 4C116 SOM, Salt Lake City, UT 84132

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Introduction

While most primary hyperparathyroidism results from sporadic parathyroid adenomas (Mallette 1994), both adenomatous and hyperplastic hyperparathyroidism may represent any of a number of inherited disorders (Szabó et al. 1993). Hereditary hyperparathyroidism is relatively rare, comprising ≤10% of all cases and occurring as part of multiple endocrine neoplasia types 1 and 2A (MEN 1, MEN 2A) (Friedman et al. 1994; Gagel 1994), possible autosomal recessive parathyroid adenomatosis (Law et al. 1983), and isolated familial parathyroid hyperplasia. The latter can represent a variant of MEN 1; genetic linkage analysis of a large kindred with isolated familial parathyroid hyperplasia mapped the disease to the MEN 1 locus (chromosome 11q13) (Kassem et al. 1992). However, one other family had isolated hyperparathyroidism that did not link to markers on 11q13 (Wassif et al. 1993).

Rarely, patients with any form of primary hyperparathyroidism may develop the classical skeletal disorder, osteitis fibrosa cystica, including lytic lesions termed "brown tumors." These lesions are characterized by abundant multinucleated osteoclasts and heal after correction of hyperparathyroidism. Jackson et al. (1990) reported two families in which fibro-osseous lesions of the maxilla and/or mandible accompanied adenomatous primary hyperparathyroidism but in which the bone lesions differed histologically and clinically from brown tumors. The fibro-osseous jaw lesions had been described earlier under various names (Jackson 1958; Jackson and Boonstra 1967; Kennett and Pollick 1971; Dinnen et al. 1977; Rosen and Palmer 1981; Warnakulasuriya et al. 1985; Mallette et al. 1987) but characteristically lacked multinucleated osteoclasts, occurred asynchronously with parathyroid tumors, and did not heal after removal of parathyroid adenomas. Hyperparathyroidism–jaw tumor (HPT-JT) syndrome has been characterized by an apparent autosomal dominant pattern of inheritance and well-documented recurrence of parathyroid adenomas. Jackson et al. (1990) established by

linkage analysis in two families that HPT-JT syndrome (OMIM 145001) was genetically distinct from MEN 1 and MEN 2A. In two of the families reported below, persons affected with hyperparathyroidism and jaw tumors also had Wilms tumor, a striking concurrence of two rare conditions that has been reported only once before (Kakinuma et al. 1994). In two reported families, affected members had parathyroid carcinoma (Dinnen et al. 1977; Kakinuma et al. 1994).

The gene responsible for HPT-JT syndrome may be of great interest, affecting at least three distinct tissues (parathyroid glands, gnathic skeleton, and kidney) with benign and malignant neoplasms. Therefore, we used five families having HPT-JT for a candidate gene and a general linkage search for the chromosomal location of the mutated gene (HRPT2) (Jackson et al. 1990). We also studied six families with inherited Wilms tumor (Matsunaga 1981) for parallel studies to determine whether hereditary Wilms tumor syndrome would map to the HRPT2 locus. "HRPT1" designates the gene mutated in hereditary isolated primary hyperparathyroidism (OMIM 145000); "HRPT2" designates the gene mutated in the hereditary HPT-JT syndrome (OMIM 145001).

Patients and Methods

Illustrative Case History

A 10-year-old boy was first screened for hypercalcemia in 1980 because his father and paternal uncle had primary hyperparathyroidism and jaw tumors (Warnakulasuriya et al. 1985). The boy was hypercalcemic (10.8–11.4 mg/dl [2.69–2.84 mmol/liter]), and serum immunoreactive parathyroid hormone was elevated. An enlarged right-superior parathyroid gland was removed and proved to be an adenoma; the right-inferior and left-inferior glands were biopsied and were histologically unremarkable; the left-superior gland was not seen. The patient became normocalcemic for nearly 12 years. In December 1992, at age 22 years, he noted painless, nontender swelling in the right mandible; isotopic bone scan, radiographs, and biopsies revealed ossifying fibromas (fig. 1), and he was again hypercalcemic (10.8–11.6 mg/dl [2.70–2.90 mmol/liter]). In July 1993, the serum calcium was 11.4 mg/dl (2.84 mmol/liter), and the serum-intact parathyroid hormone was 8.0 pmol/liter (normal, 0.9–5.4), confirming recurrence of primary hyperparathyroidism. He then underwent parathyroid reexploration, with removal of a left-inferior parathyroid adenoma, at the site of a previously normal parathyroid gland. Postoperatively, he developed permanent hypoparathyroidism. The jaw tumors are clinically stable and have not been removed.

Families

Three HPT-JT families were studied at the Henry Ford Hospital, one family at the Baylor College of Medicine, and one family at St. Bartholomew's Hospital. The five HPT-JT families have been previously reported in part (Jackson 1958; Jackson and Boonstra 1967; Jackson et al. 1990; Warnakulasuriya et al. 1985; Mallette et al. 1987); updated pedigrees are depicted in figure 2. Patients were considered affected if they had current or past primary hyperparathyroidism, with or without characteristic jaw tumors. Ten family members had hyperparathyroidism only, without known jaw tumors (seven of whom were available for study), but no patients had jaw tumors only. For each family except K11689, there was histologic evidence that the jaw tumors were characteristic of HPT-JT rather than hyperparathyroid brown tumors. All six Wilms tumor families were studied at the M. D. Anderson Cancer Center (by V. Huff). The studies were approved by institutional review boards at each of the institutions where blood samples were obtained, and each participant gave informed consent to the studies.

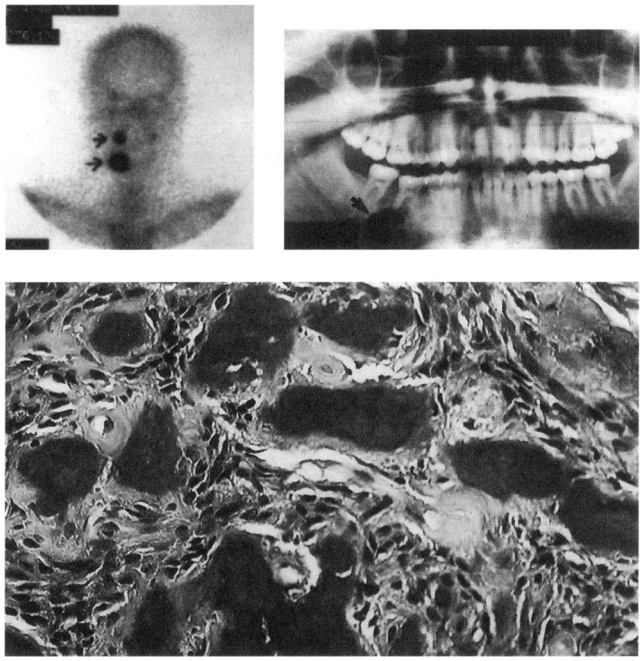

Figure 1 Radioisotopic bone scan, radiographic, and histologic findings for jaw tumors of case presented in text. *Upper left,* bone scan showing two areas of increased uptake in the maxilla and mandible (arrows). *Upper right,* oral pantographic X-ray showing the lytic lesion of the mandible (arrow). *Bottom,* tissue from the mandibular lesion, typical of the syndrome, with islands of woven bone interspersed in a background of fibrous tissue. Note in particular the lack of abundant multinucleated osteoclasts that would be expected for a hyperparathyroid brown tumor.

Genetic Linkage Analysis

Peripheral leukocyte DNA was purified by standard techniques (Heath and Leppert 1992). Two candidate-gene marker loci were tested directly, using an intragenic polymorphism for the cyclin D1 gene locus (PRAD1 and

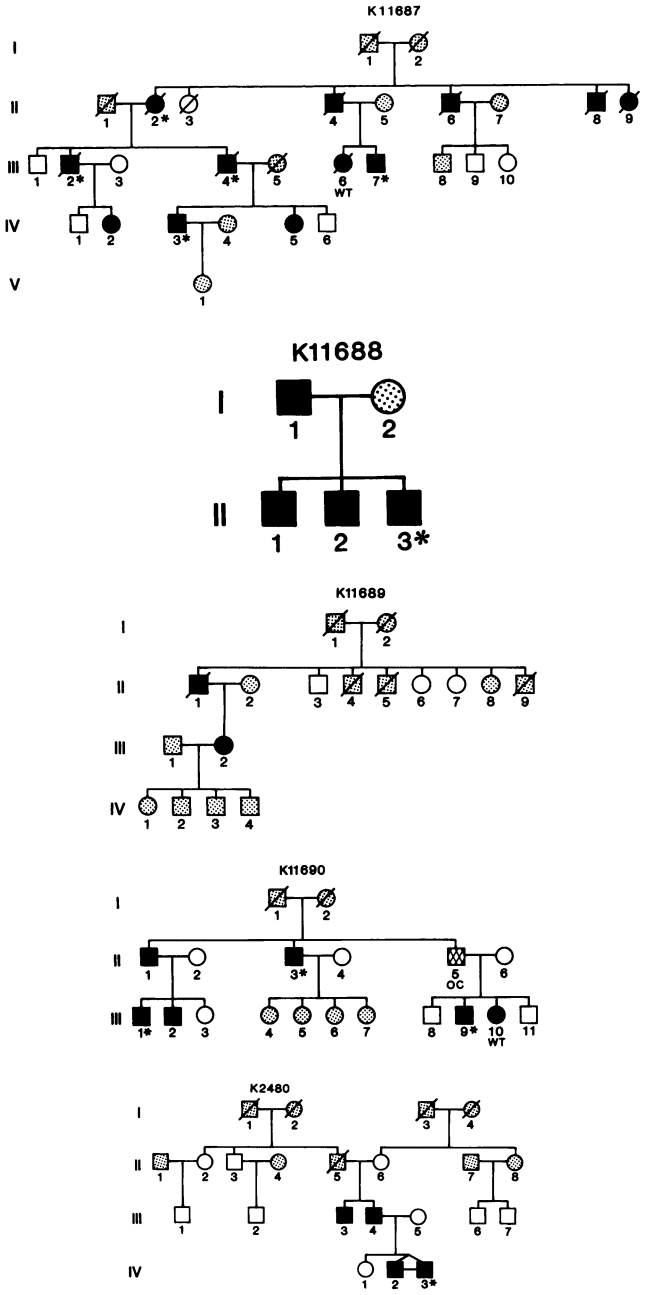

Figure 2 Updated pedigrees of all primary HPT-JT families used for linkage analyses. Each family is shown in its entirety, except for K11688; four unclassified siblings of I-1 and their offspring are omitted (Mallette et al. 1987). Squares, males; and circles, females. Unblackened symbols, unaffected with HPT-JT; blackened symbols, affected; stippled symbols, unclassified; slashes, deceased; WT, Wilms tumor; an asterisk (*), hyperparathyroidism without known jaw tumors; OC, obligate carrier (II-5 in K11690 [coarse cross-hatched symbol] is the single example of nonpenetrance). The individual described in the case history is IV-2 of kindred 2480. Genotypes were not determined for persons shown as deceased (except for II-9 in K11687, who died after sampling). Genotyping information obtained for each pedigree: K2480 (no genotypes for II-1, II-4, II-7, II-8); K11687 (no genotypes for II-7 and IV-4 and their offspring); K11688 (genotypes available for all shown); K11689 (genotypes were determined for II-2, II-3, II-6, II-7, and III-2); K11690 (no genotypes for II-4 and her offspring).

D11S287E) (Heighway 1991; Motokura et al. 1991) and a polymorphism <10 kb from the 5′ end of the p53 tumor-suppressor–gene locus (TP53) (B. Høyheim, personal communication). The remaining candidate-gene loci were the MEN 1 and MEN 2A loci (proxy markers PYGM and UT1466, respectively), the retinoblastoma gene (RB) locus (proxy marker D13S155) (Weissenbach et al. 1992; Cryns et al. 1994), and the gene responsible for familial adenomatous colonic polyposis (APC, proxy marker D5S346) (Spirio et al. 1991). The general linkage search was performed using highly polymorphic, PCR-based DNA markers according to the methods outlined by Heath et al. (1993). We used a systematic screening strategy with selected markers of known reliability, large numbers of alleles, and a high degree of heterozygosity, distributed evenly throughout the genome (approximately every 30 cM). The methods for genotyping at each locus by PCR were described elsewhere (Heath et al. 1993). Radioautographic films were scored independently by two observers then reviewed by two other investigators without reference to the disease status of the patients. Data were stored in the SYBASE program, and linkage calculations were made using the Howard Hughes Medical Institute Research Laboratories computer with the LINKAGE program, version 5.1 (Heath and Leppert 1992; Heath et al. 1993). Family members were classified as affected, unaffected, or unknown (inadequately tested or too young to have manifested disease). The legend to figure 2 designates genotyped family members. An autosomal dominant mode of inheritance and a penetrance of .90 were assumed. We calculated lod scores first using equal allele frequencies. Subsequently, for the markers showing no recombination (D1S196, D1S212, and D1S191), we used population allele frequencies calculated from our studies with a set of 137 unrelated CEPH grandparents. By convention, linkage of a given marker to the disease trait was accepted if the lod score was ≥ 3.0, signifying $\geq 1{,}000{:}1$ odds in favor of linkage and rejected if the lod score were ≤ -2.0 ($\geq 100{:}1$ odds against linkage) (Ott 1991).

Loss-of-Heterozygosity Studies

We obtained original tissue blocks from the parathyroid operations of seven patients from two HPT-JT families and fresh-frozen parathyroid tissue from one patient of a third family. We also obtained Wilms tumor tissue from one person having HPT-JT (III-10 of K11690). DNA was extracted from microdissected 5 μm sections of fixed, paraffin-imbedded parathyroid adenomas, the Wilms tumor, and normal tissue (verified by R. J. Zarbo), and from frozen tissue, by using standard methods (Wright and Manos 1990). Tumor slices contained much less than 20% nonneoplastic tissue by area. Paired somatic and tumor DNA samples were examined for loss of heterozygosity, with each of the three markers shown below to be linked to the HPT-JT phenotype.

Table 1

Total Lod Scores for Chromosome 1q Markers in Five Families with HPT-JT Syndrome

	Total Lod Score at θ =						
Locus	.001	.01	.05	.10	.20	.30	.40
D1S104	−1.94	−.24	.91	1.20	1.11	.73	.29
D1S196	4.51	4.45	4.13	3.68	2.69	1.63	.64
D1S212	6.09	5.99	5.52	4.91	3.59	2.20	.87
D1S191	3.30	3.22	2.89	2.45	1.56	.80	.23
D1S245	−2.71	−2.34	−.89	−.17	.30	.28	.11

Note.—The markers are arranged from centromeric (top) to telomeric (bottom). Map distances in centimorgans between the 1q markers are D1S104–4–19 cM–D1S196–12 cM–D1S212–7 cM–D1S191–28 cM–D1S245. The map location of D1S104 is placed by a confidence interval (4–19 cM) centromeric to D1S196 (Weissenbach et al. 1992).

Results

Candidate Genes

We studied as candidate genes for the HPT-JT trait the MEN 1, MEN 2A, PRAD1, TP53, RB, and APC loci, finding lod scores at recombination fraction (θ) = .001 ranging from −3.29 to −13.75. For the two candidate genes tested directly with intragenic polymorphisms (PRAD1 and TP53), obligate recombinants were obtained (lod scores at θ = .0 of −5.85 and −16.29, respectively). For the four candidate-gene loci tested with tightly linked (θ < .01) markers (PYGM, UT1466, RB, and LNS-CA), we obtained −2.0 lod exclusion regions of >5% recombination from each of the proxy markers. These data firmly exclude all six genes as candidates for the HRPT2 locus.

General Linkage Search in HPT-JT

We found compelling evidence for linkage of the HPT-JT trait to markers on the long arm of chromosome 1 (1q), after analysis of nearly 30 markers. The maximal two-point lod scores were obtained with markers D1S191, D1S196, and D1S212, with which we found no recombination (table 1). The highest lod score (Z_{max}) obtained was 6.10 (θ = .0) with marker D1S212, or odds of >1 million:1 in favor of linkage. Z_{max} also was found at θ = .0 for markers D1S196 and D1S191 (4.52 and 3.30, respectively). Table 2 shows the distribution of lod scores by family, for marker D1S212. We obtained recombination with at least one marker on either side of the three linked markers, restricting the disease locus to the region 1q21-q31 (Weissenbach et al. 1992). The only significantly positive lod scores were obtained with markers in the 1q21-q31 region.

Loss of Heterozygosity for 1q Markers in Parathyroid and Wilms Tumors

Each of the eight individuals for whom we had parathyroid tumors were heterozygous for the markers D1S191, D1S196, and D1S212, and there was no loss of heterozygosity in their tumor tissue (data not shown). Similarly, there was no loss of heterozygosity in the single Wilms tumor examined from a patient having HPT-JT.

Genetic Linkage Analysis in Wilms Tumor Families

Having established linkage of the HPT-JT syndrome to markers on chromosome 1q, we then performed limited genetic linkage analysis in the hereditary Wilms tumor kindreds. None of these patients had any of the characteristics of the HPT-JT syndrome. There was no suggestion of linkage of the Wilms tumor trait with the markers flanking HRPT2. The lod scores at θ = .001 ranged from −15.6 (D1S191) to −17.8 (D1S196), and were not positive at any value of θ.

Discussion

Earlier studies (Jackson et al. 1990) suggested a distinct genetic basis for the HPT-JT syndrome, but without presenting formal segregational analysis. The present data establish beyond reasonable doubt that HPT-JT is inherited in an autosomal dominant fashion and that the endocrine tumor gene HRPT2, on the long arm of chromosome 1, is responsible for the syndrome.

The most common forms of hereditary hyperparathyroidism occur in the multiple endocrine neoplasia (MEN) syndromes, which manifest as pluriglandular disease or parathyroid hyperplasia (Friedman et al. 1994; Gagel 1994). In contrast, HPT-JT syndrome described here presents as early-onset parathyroid adenomatosis (Jackson 1958; Jackson and Boonstra 1967; Jackson et al. 1990; Kennett and Pollick 1971; Dinnen et al. 1977; Rosen and Palmer 1981; Warnakulasuriya et al. 1985; Mallette et al. 1987), remarkable because the peak incidence of sporadic parathyroid adenomas is at age >60 years (Heath et al. 1980).

The HPT-JT syndrome may be underrecognized because the parathyroid disease and gnathic skeletal lesions often occur asynchronously and may be diagnosed

Table 2

Total and By-Family Lod Scores for Marker D1S212 in the Five HPT-JT Families

	Lod Scores at θ =						
Kindred	.001	.01	.05	.10	.20	.30	.40
K2480	1.13	1.11	1.03	.92	.69	.45	.22
K11687	2.53	2.48	2.28	2.02	1.46	.88	.35
K11688	.00	.00	.00	.00	.00	.00	.00
K11689	.18	.18	.18	.16	.11	.06	.02
K11690	2.24	2.21	2.03	1.81	1.33	.81	.29
Totals	6.08	5.98	5.52	4.91	3.59	2.20	.88

Note.—For this marker, only K11688 failed to contribute to the total lod score.

and treated separately by physicians, dentists, and oral surgeons. Moreover, the jaw lesions may be confused with the more commonly occurring osteolytic brown tumors of hyperparathyroidism (Rosenberg and Guralnick 1962).

The clinical characteristics of the HPT-JT syndrome are distinctive. First, the patients often become hypercalcemic in childhood to late teenage years, similarly to patients having MEN 1 (Mallette 1994). However, rather than having parathyroid hyperplasia, the patients manifesting HPT-JT usually have solitary adenomas that often recur (Jackson et al. 1990). The parathyroid adenomas in HPT-JT syndrome are often cystic (Mallette et al. 1987), although cystic lesions are also common in sporadic adenomatous hyperparathyroidism (Zarbo et al. 1993). The bone lesions specific to HPT-JT are restricted to the maxilla and mandible, in contrast to the distribution of classical hyperparathyroid brown tumors, which may occur almost anywhere. The jaw lesions usually present as intraoral tumoral masses that may distort dentition but are more commonly asymptomatic incidental findings on dental radiographs. These lesions appear to run an independent course from the hyperparathyroidism, whereas classical hyperparathyroid bone lesions heal after removal of the parathyroid tumor. Histologically, the fibro-osseous jaw tumors of HPT-JT are composed of trabeculae of woven bone or cementumlike droplets with or without osteoblastic rimming and are set in a cytologically bland fibrocellular stroma. Jaw tumors resembling the lesions of HPT-JT may occur sporadically (Slootweg and Muller 1990), which can further detract from recognition of the syndrome in an individual. A distinguishing point is that sporadic jaw tumors generally occur in the 3d decade and beyond (Eversole et al. 1985), whereas the jaw lesions in HPT-JT occur earlier. Hyperparathyroidism and jaw tumors do not always occur in the same person; we observed seven family members with hyperparathyroidism alone but none with jaw tumors alone. We have also observed one instance of apparent nonpenetrance in an obligate carrier. A family reported elsewhere (Dinnen et al. 1977) had one member with parathyroid carcinoma, but it has not been observed in our families. In the present study, two female members of unrelated families also had Wilms tumor, which was lethal in one, raising the possibility that Wilms tumor may be a component of the HPT-JT syndrome. Further evidence that parathyroid carcinoma and Wilms tumor are part of the HPT-JT syndrome comes from a recently reported small Japanese kindred, in which one sibling had parathyroid carcinoma, a second had parathyroid adenoma plus Wilms tumor, and a third had parathyroid adenoma plus jaw tumor (Kakinuma et al. 1994).

Our studies of five families having the HPT-JT syndrome suggest that the responsible gene, termed "HRPT2" (OMIM 145001), lies on the long arm of chromosome 1 in the region 1q21-q31. Since two affected patients also developed Wilms tumor, the markers linked to the HPT-JT phenotype also were tested in six hereditary Wilms tumor kindreds to determine whether the same locus could be linked to both diseases. Our data establish that HPT-JT and hereditary isolated Wilms tumor (Matsunaga 1981) are different diseases. The nature of the gene mutated in HPT-JT is unknown, but it might be classified as a proto-oncogene, based on our inability to find loss of heterozygosity for 1q21-q31 markers in nine parathyroid tumors from three families and one renal tumor. In this sense, HRPT2 mutations, causing benign and malignant tumors in three distinct tissues, might be analogous to those in the retinoblastoma gene (causing retinal and skeletal tumors) (Cryns et al. 1994) or the RET proto-oncogene (medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia) (Gagel 1994).

The spectrum of diseases associated with hereditary parathyroid neoplasia is remarkably broad, and we emphasize here a little-recognized co-occurrence of parathyroid, renal, and gnathic skeletal lesions. Identifying the gene responsible for hereditary HPT-JT syndrome may provide new insights into the basic nature of endocrine and skeletal tumorigenesis. In any case, physicians, oral surgeons, and dentists should be alert to the possi-

bility of the HPT-JT syndrome in adolescents and young adults presenting with primary hyperparathyroidism and jaw tumors together or separately.

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