

Hyperparathyroidism-Jaw Tumor Syndrome Associated With Large-Scale 1q31 Deletion

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Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare autosomal dominant cause of familial hyperparathyroidism associated with benign, ossifying fibromas of the maxillofacial bones and increased risk of parathyroid carcinoma. The putative tumor suppressor gene *CDC73* has been implicated in the syndrome, with a multitude of inactivating mutations identified; however, HPT-JT due to large-scale deletion of the chromosomal region containing the gene is exceedingly rare, and the clinical significance of this variant remains unclear. We report the case of a 32-year-old woman with a history of mandibular ossifying fibroma who presented with primary hyperparathyroidism and was found to harbor a large-scale, germline deletion on chromosome 1q31, including the *CDC73* locus. HPT-JT is associated with loss of function of the putative tumor suppressor gene *CDC73*. Over 100 mutations and small insertions/deletions have been identified within the gene, the majority of which result in premature truncation of the parafibromin protein product. We report a case of HPT-JT associated with a large chromosomal deletion (4.1 Mb) encompassing the *CDC73* gene locus. In the future, molecular testing in this autosomal dominant disorder should use techniques that allow for the detection of large-scale deletions in addition to the more commonly observed mutations and smaller-scale copy number alterations. Further investigation is needed to determine whether HPT-JT associated with a large-scale deletion carries increased risk of malignancy relative to the more common truncating mutations and what the implications are for genetic counseling.

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Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare autosomal dominant cause of familial hyperparathyroidism associated with benign, ossifying fibromas of the mandible or maxillary facial bones and increased risk of parathyroid carcinoma. The putative tumor suppressor gene cell division cycle protein 73 homolog (*CDC73*) has been implicated in the syndrome, with a multitude of inactivating mutations identified, mostly comprised of point mutations and small insertions and deletions [1]. Historically, primary hyperparathyroidism associated with HPT-JT has been considered a more aggressive entity than its sporadic counterpart, with an increased risk of parathyroid carcinoma. The magnitude of this increased risk ranges from 10% to 15% [2, 3]. A greater understanding of the multitude of potential *CDC73* variants is leading to more accurate estimates of risk that may be specific to certain classes of variant [4]. Here, we report the case of a 32-year-old woman with a history of

Abbreviations: *CDC73*, cell division cycle protein 73 homolog; CT, computed tomography; HPT-JT, hyperparathyroidism-jaw tumor syndrome; PTH, parathyroid hormone.

ossifying mandibular fibroma and primary hyperparathyroidism who carries a previously unreported 4.1-Mb deletion on chromosome 1 encompassing the *CDC73* locus.

1. Case Report

A 32-year-old woman presented with mildly elevated serum calcium (10.4 mg/dL; reference range, 8.4 to 10.2 mg/dL), a parathyroid hormone (PTH) level more than 3 times the upper limit of normal (162.1 pg/mL; reference range, 7.5 to 53.5 pg/mL), normal renal function (creatinine, 0.62 mg/dL; reference range, 0.52 to 1.04 mg/dL), normal 25-hydroxy vitamin D (34.6 ng/mL; reference range, 30.0 to 100.0 ng/mL), normal alkaline phosphatase (80 U/L; reference range, 38 to 126 U/L), and a mildly elevated 24-hour urine calcium (320 mg/24 h; reference range, 100 to 300 mg/24 h), consistent with a diagnosis of primary hyperparathyroidism. Her past history

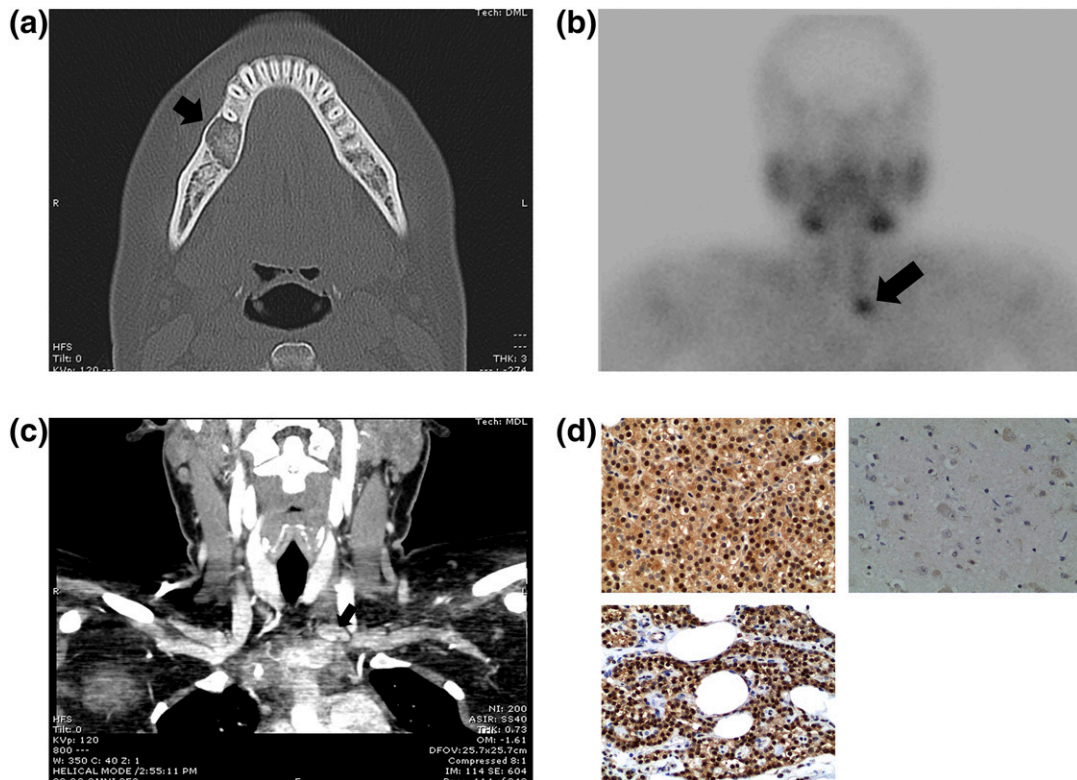


Figure 1. (a) Axial CT scan demonstrating a lucent, well-circumscribed 1.7-cm lesion with homogenous matrix of the right mandible consistent with biopsy-proven ossifying fibroma. (b) Planar image from Tc-99m sestamibi scan demonstrates a focus of delayed radiotracer washout inferior to the left thyroid lobe, at the level of the thoracic inlet, consistent with parathyroid adenoma. (c) Coronal image from four-dimensional, contrast-enhanced CT scan confirming a 2.0-cm lesion in the left inferior position. (d) Immunohistochemistry for parafibromin ($\times 20$ magnification): Tumor (top) demonstrates an admixture of strong nuclear positivity and scattered negative cells, imparting a mosaic pattern of protein expression. Normal parathyroid (bottom) demonstrates strong, diffuse nuclear expression of parafibromin. Brain tissue negative control (right). Paraffin-embedded, formalin-fixed parathyroid gland tissue was used to prepare 4- μ m sections. Dehydration of the sections and a 40-minute epitope retrieval process in Leica Bond ER 1 (catalog no. AR9961) were performed on an automated Leica Bond III stainer. Sections were incubated with the primary mouse monoclonal anti-parafibromin antibody (Research Resource Identification Initiative AB_628102, clone 2H1, SC-33638; Santa Cruz Biotechnology, Santa Cruz, CA) at a dilution of 1:50 for 10 minutes on the automated stainer. This antibody is raised against a peptide corresponding to amino acids 87 to 100 of mouse parafibromin. Antibody detection was achieved using the Leica Bond Polymer Refine DAB Detection Kit (catalog no. DS9800, Leica Biosystems Newcastle, Ltd, Newcastle Upon Tyne, United Kingdom) with diaminobenzidine as the chromogen, and sections were counterstained in hematoxylin.

included resection of a 1.7-cm ossifying fibroma of the mandible 1 year prior [Fig. 1(a)] and a kidney stone several years prior. Thyroid, abdominal, and pelvic ultrasounds were performed, demonstrating normal-appearing thyroid gland, kidneys, uterus, and ovaries. Dual-energy X-ray absorptiometry testing demonstrated bone density within normal range, with *T* scores of -0.33 and -0.2 in the spine and femoral neck, respectively (*z* scores and forearm measures were unavailable). Nuclear medicine scanning utilizing Tc-99m sestamibi was suggestive of parathyroid adenoma inferior to the left thyroid lobe, at the level of the thoracic inlet [Fig. 1(b)], and four-dimensional parathyroid computed tomography (CT) demonstrated a corresponding 2.0-cm lesion [Fig. 1(c)].

The combination of findings was suggestive of HPT-JT, and high-throughput sequencing was undertaken at the Yale Center for Genome Analysis. DNA was extracted and purified from a peripheral blood sample, array capture was performed with Roche/Nimblegen MedExome, and sequencing was performed with the Illumina HiSeq platform. A 4.1-Mb deletion was identified on chromosome 1q31.2-31.3 (chr1:192127840-196227528x1), encompassing the locus of the candidate *CDC73* gene (chr1:193121958-193254815). Additional deleted genes in the region include multiple members of the Regulator of G-protein Signaling Gene family (*RGS1*, *RGS2*, *RGS13*, and *RGS18*) as well as TROVE Domain Family Member 2, Ubiquitin C-terminal Hydrolase L5, and portions of Potassium Sodium-Activated Channel Subfamily Member 2 (*TROVE2*, *UCHL5*, and *KCNT2*). The identified deletion is not documented in the curated International Standards for Cytogenomic Arrays database of pathogenic copy number variations (<http://dbsearch.clinicalgenome.org>). The deletion partially overlaps with known 1q deletions, specifically the intermediate category, which encompass the 1q25-32 region and include the *CDC73* gene locus. The most common clinical manifestation of these intermediate 1q deletions is developmental delay; however, specific causative genes have not been identified [5]. No mutations were detected in the following genes: Multiple Endocrine Neoplasia 1, Ret Proto-Oncogene, Calcium Sensing Receptor, and Cyclin Dependent Kinase Inhibitors 1B, 2B, 2C, and 1A (*MEN1*, *RET*, *CASR*, *CDKN1B*, *CDKN2B*, *CDKN2C*, or *CDKN1A*). Family history is remarkable for two biologic adolescent sons who underwent genetic testing. One was a carrier of the same 4.1-Mb deletion of chromosome 1q31.2-31.3, including the entire *CDC73* gene identified in the index case. The other child was not a carrier of this genotype, and no family members have been diagnosed with hyperparathyroidism and tumors of the jaw, kidney, or uterus.

The patient underwent *en bloc* parathyroidectomy of the preoperatively localized lesion. PTH levels were monitored at 5-minute intervals and fell from a baseline of 154.0 to 12.0 pg/mL 20 minutes post excision. Surgical pathology demonstrated a well-circumscribed parathyroid gland weighing 1.1 gm consisting of an enlarged hypercellular nodule of chief cells devoid of cytologic atypia, invasion, and significant mitotic activity. These findings are consistent with a parathyroid adenoma and rule out atypical adenoma or carcinoma. Immunohistochemistry did demonstrate staining for parafibromin [Fig. 1(d)]. A positive control, a normal parathyroid gland, was reviewed. The test slide was interpreted in a semiquantitative fashion. Nuclear expression of the immunomarker in $>5\%$ of parathyroid cells with a staining intensity approximately equal to that of the control was considered positive staining. Total serum calcium and PTH levels were normal at 9.2 mg/dL and 25.7 pg/mL during follow-up at 4 months.

2. Discussion

HPT-JT is a rare autosomal dominant syndrome with variable penetrance of parathyroid adenoma and carcinoma, benign jaw tumors, and occasional renal and uterine tumors. The syndrome has been linked to the cell division cycle protein 73 homolog gene (*CDC73*), with a multitude of reported variants predicted to result in either truncation or loss of parafibromin expression protein through nonsense-mediated mechanisms. Gross deletions represent only 1% of the mutations found in the *CDC73* gene [1, 6]. Bellido *et al.* report a case of HPT-JT caused by a 24-nucleotide deletion involving the start codon of *CDC73*, presumably leading to

complete loss of transcription, although parafibromin immunohistochemistry was not performed to confirm loss of protein expression [7]. In another HPT-JT kindred, including six patients over two generations, Cascón *et al.* identified a 547-kb germline deletion involving the *CDC73* locus with confirmed loss of parafibromin staining [6].

As part of a cohort of 16 HPT-JT patients, Mehta *et al.* reported seven members from a single family with whole-gene deletion of *CDC73* as detected by array-comparative genomic hybridization; however, the exact size and location of the deletion was not reported [8]. Six of the 16 patients (37.5%) in the cohort were found to have parathyroid carcinoma, which is significantly higher than the reported 15% incidence in the syndrome [2, 3]. Interestingly, of the seven patients harboring whole-gene deletions of *CDC73*, four were among those with malignant lesions, meaning that fully 57% of the patients with this deletion developed parathyroid carcinoma. The remaining two carcinoma patients carried small duplications in exon 7. In total, there were two uterine tumors, three renal lesions, and two jaw tumors reported, all among the parathyroid carcinoma patients. These findings raise the possibility that not all genomic variants confer an equal risk of parathyroid carcinoma or of the other HPT-JT-related lesions. Interestingly, biallelic loss of *CDC73* expression has been reported in cases of sporadic parathyroid carcinoma [9]. Further study is needed to determine if HPT-JT patients with whole-gene deletion of at least one *CDC73* allele may carry a higher risk of carcinoma than those with point mutations or small insertions and deletions.

The case presented here contributes to a relatively small body of literature devoted to HPT-JT, a syndrome with variable penetrance resulting in a spectrum of diseases spanning from the benign to the highly morbid. To our knowledge, this is the first case of HPT-JT arising in a context of large-scale germline chromosomal deletion of the region containing the *CDC73* locus, with a presumed second-hit mutation in the remaining allele rendering it non-functional, yet still immunogenic on immunohistochemistry (fresh tumor material was unavailable to provide DNA for genetic testing of the presumed second-hit mutation). It is important to note that these large variants may not be detected by standard screening methods. High-resolution genomic assessment has become an integral component of the clinical evaluation of our patients, and the growing library of genomic variants in HPT-JT may explain the variable penetrance, severity, and constellation of phenotypes encountered in clinical practice. In the future, it will be critical to elucidate the specific clinical presentation associated with each genomic variant, as well as the impact of a germline heterozygous deletion, to best inform operative planning, surveillance regimens, and genetic counseling for both patients and their families.

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