



CDC73 Germline Mutation in a Family With Mixed Epithelial and Stromal Tumors

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OBJECTIVE

To describe a family in which 3 members presented with mixed epithelial tumor of the kidney (MEST) and were found to possess a germline mutation in *CDC73*, a gene which is associated with hyperparathyroidism-jaw tumor syndrome (HPT-JT).

MATERIALS AND METHODS RESULTS

Blood and tumor DNA from three family members who presented with a primary diagnosis of MEST was subjected to targeted gene sequencing to identify potential genetic components.

A germline start codon mutation (p.M1I) in *CDC73* was identified in all 3 family members who presented with MEST and 2 tumors from 1 patient demonstrated somatic copy-neutral loss of heterozygosity. Patients presented with no evidence of hyperparathyroidism or jaw tumors, but both female patients had hysterectomies at an early age due to excessive bleeding and numerous fibroids, which is common in HPT-JT. A germline p.M1I mutation has been previously reported in a family with clinical features of HPT-JT.

CONCLUSION

Patients with MEST may be at risk for HPT-JT and *CDC73* germline mutation testing of MEST patients should be considered. UROLOGY 124: 91–97, 2019. Published by Elsevier Inc.

Mixed epithelial and stromal tumor of the kidney (MEST or MESTK) is a neoplasm first described by Michal and Syrucek in 1998.¹ MEST is characterized by a biphasic growth pattern with both epithelial and spindle cell stromal components; the spindle cells resemble ovarian stroma. The epithelial component often stains for cytokeratin AE1/3, epithelial membrane antigen, and carcinoembryonic antigen (CEA), while the stromal

component frequently stains for vimentin, desmin, estrogen receptor, and progesterone receptor.² It is a predominantly benign neoplasm, although malignant transformation has been reported (reviewed in Xie *et al.*³). MEST is most often seen in middle-aged women and is associated with estrogen exposure; it occurs rarely in males and is sometimes associated with androgen deprivation.² Rare cases of bilateral MEST have been reported suggesting the possibility of a germline genetic component.⁴⁻⁶

Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a hereditary syndrome first described by Jackson *et al*⁷ and is clinically and genetically distinct from the multiple endocrine neoplasia syndromes. In addition to hyperparathyroidism in 80% of affected patients, 30%-50% of patients develop fibro-osseous lesions of the mandible and maxilla, and 10%-15% develop parathyroid carcinoma.⁸⁻¹⁰ Other lesions that have been observed in HPT-JT patients include renal lesions, uterine leiomyomas, Hurthle cell adenoma of the thyroid, clear cell pancreatic adenocarcinoma, endometrial polyps, papillary thyroid carcinoma, and salivary gland carcinoma (reviewed in Chen *et al*⁸). HPT-JT is associated with germline loss-of-function mutations in *CDC73* (previously known as *HRPT2*), the gene encoding parafibromin.¹¹ Parafibromin is a member of the Paf1 protein complex, which associates with the RNA polymerase II large subunit POLR2A and with a histone methyltransferase complex that methylates

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histone H3 on lysine 4.¹² Parafibromin can also bind directly to β -catenin and synergize with components of the Wnt signaling pathway.¹³ In the kidney, parafibromin is expressed in renal tubules and glomerular cells of mesangial origin.¹⁴

This study reports a family with 3 affected members, a father and 2 daughters, who presented with MEST as their primary manifestation and in which a germline mutation in *CDC73* has been identified. These affected family members are thus at risk for all of the clinical features of HPT-JT.

MATERIALS AND METHODS

Patients: Patients were seen at the Urologic Oncology Branch (UOB) of the National Cancer Institute (NCI), National Institutes of Health (NIH) for clinical assessment, and peripheral blood samples were obtained for DNA extraction. This study was approved by the Institutional Review Board of the National Cancer Institute and all patients provided written informed consent.

DNA sequencing: DNA was extracted from blood and tumor tissue using Promega Maxwell 16 Blood and Tissue DNA Purification Kits (Promega, WI). Blood DNA from patient III:2 was subjected to a custom-capture next-generation DNA sequencing assay, OncoVar. The OncoVar v3 assay captures 240 known cancer genes for targeted sequencing on the Illumina platform, as previously described.^{15,16} The *CDC73* mutation was validated by bidirectional Sanger sequencing using the Big Dye Terminator v.1.1 Cycle Sequencing Kit (Applied Biosystems, CA) according to the manufacturer's specifications and run on an ABI 3130xl or 3730 Genetic Analyzer (Applied Biosystems, CA). Sanger Sequencing was conducted at the CCR Genomics Core at the National Cancer Institute, NIH, Bethesda, MD 20892. Forward and reverse sequences were evaluated using Sequencher 5.0.1 (Genecodes, MI).

ClinOmics analysis: DNAs from a tumor and matched normal kidney tissue from Patient III:2 were subjected to whole exome sequencing and DNA copy analysis as part of a ClinOmics tumor evaluation protocol at the NIH. Single nucleotide variations (SNV) and small insertion/deletion (indel) variants were detected by whole exome sequencing using Agilent SureSelect Clinical Research Exome Kit (V5; Agilent Santa Clara, CA) and 75bp pair-end sequencing on an Illumina NextSeq500 (Illumina, San Diego, CA) following the manufacturers' instruction. The sequences were compared to the human reference genome hg19 using a custom developed bioinformatic pipeline, and mutations were reported according to HGVS nomenclature (www.hgvs.org/mutnomen). Copy number variation was detected using Sequenza¹⁷ on whole exome DNA sequencing data. Tumor cellularity and ploidy of tumor were as estimated, and allele-specific copy number profile was calculated.

Quantitative polymerase chain reaction (PCR): Real-time quantitative PCR analysis was performed on 10 ng DNA from blood and two MEST tumors from patient III:2 using SYBR Green PCR Master Mix (Thermo Fisher Scientific, Waltham, MA) and analyzed using a ViiA 7 Real-time PCR System (Thermo Fisher Scientific, Waltham, MA) using standard RT-PCR conditions. Exons 1, 7, 10, 11, 14 and 17 of *CDC73* were evaluated with normalization to two endogenous controls, human serum albumin (ALB [MIM103600]) on chromosome 4 and Zinc finger protein 80 (ZNF80 [MIM194553]) on chromosome 3. Primer sequences are shown in Table 1.

RESULTS

Clinical Presentation of the MEST Family

Initially, the 2 sisters (III:1 and III:2) were evaluated at the Urologic Oncology Branch (UOB) of the NCI due to their family history of MEST (Fig. 1A). Patient III:1 had previously undergone a CT scan at age 47 at an outside institution, due to her father (II:2)'s prior histologic diagnosis of MEST, revealing several cystic renal masses. She had undergone a left radical nephrectomy at the outside institution revealing 2 midpole solid/cystic tumors measuring 2.8 and 1.4 cm, as well as an upper pole 2.5 cm fluid filled cyst. The 2 solid/cystic tumors were consistent with MEST, containing areas resembling luteinized ovarian stromal cells and areas of spindle cells. There was no cytologic atypia and mitotic activity was not observed. In the stroma, the spindle cells were estrogen receptor (ER) reactive; fascicles were smooth muscle actin and desmin reactive and S100 and HMB45 nonreactive. The Laboratory of Pathology at the NCI confirmed the histologic classification of MEST and the immunohistochemical staining patterns. Upon presentation to the NCI for evaluation at age 52, a 5 cm stable simple cyst was identified in the right kidney. Patient III:1 also has a history of hysterectomy at age 20 for excessive bleeding and uterine fibroids and bilateral oophorectomies at age 46 for a left cystic adenoma and a right benign mucinous cystic tumor.

Patient III:2 underwent an outside CT scan at age 45 due to her father's and sister's prior diagnoses, revealing bilateral renal masses, including several that were well over 3 cm. CT imaging performed at NCI confirmed the presence of bilateral complex renal cysts (Fig. 1B-C). A family history of MEST is currently not sufficient to ensure that an at-risk individual's renal mass is necessarily benign.¹⁸ Due to the concern about potential malignancy, staged bilateral, partial nephrectomies were performed. Five tumors were removed from her left kidney with the largest measuring 12 × 7 × 5.5 cm with a solid component of 5.4 × 3 cm, and the remaining tumors measuring 3.0, 2.5, 0.8, and 0.8 cm in the largest dimension; all were diagnosed as MEST (Fig. 2A, B). The tumors stained positively for cytokeratin 7, CD57, CD10, SMA,

Table 1. Primer sequences for real-time quantitative polymerase chain reaction (PCR)

Gene - Exon	Forward Primer	Reverse Primer	Amplicon Length
CDC73 - Exon 1	ACAAGAGAAGAAGGAGGCAG	TCTCCCTTACCACAATCTC	139
CDC73 - Exon 7	CACTCCAGGAATGCCTGCT	GTCATCATCTAGATCAGTCTTG	149
CDC73 - Exon 10	TCGTAGAAACGGAAGGCTTC	ACTTCAACATGTGCTACTCAC	138
CDC73 - Exon 11	CAGTACCAAGACCAGGTAGA	GTTCAAAGCATTATACGCATAC	125
CDC73 - Exon 14	TCTTCCATTTTCATCACGTG	CGTTGACAACCTTGTTCCTC	101
CDC73 - Exon 17	TGTCAACTGTTTTACATGCA	GATCAATCTGTGACCTTCTTC	110
ALB	ACCAATGCTGCACAGAATCC	CGTATGTTTCATCGACTTCCAGAG	73
ZNF80	CTGTGACCTGCAGCTCATCCT	TAAGTTCTCTGACGTTGACTGATGTG	120

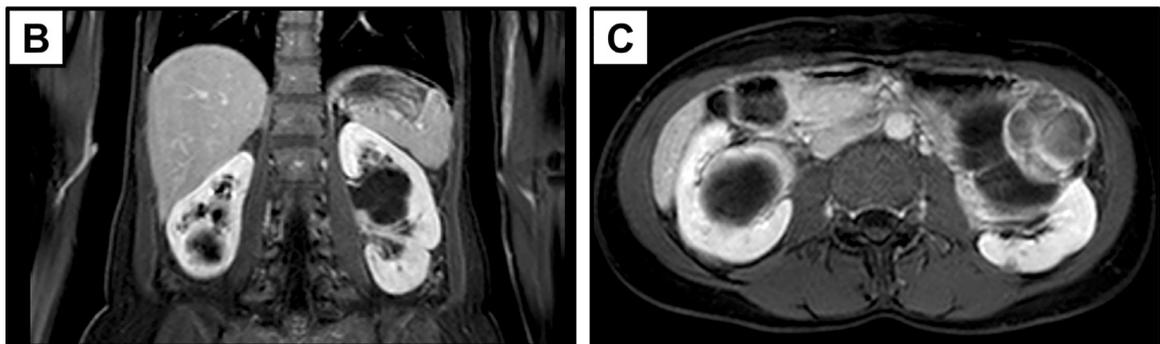
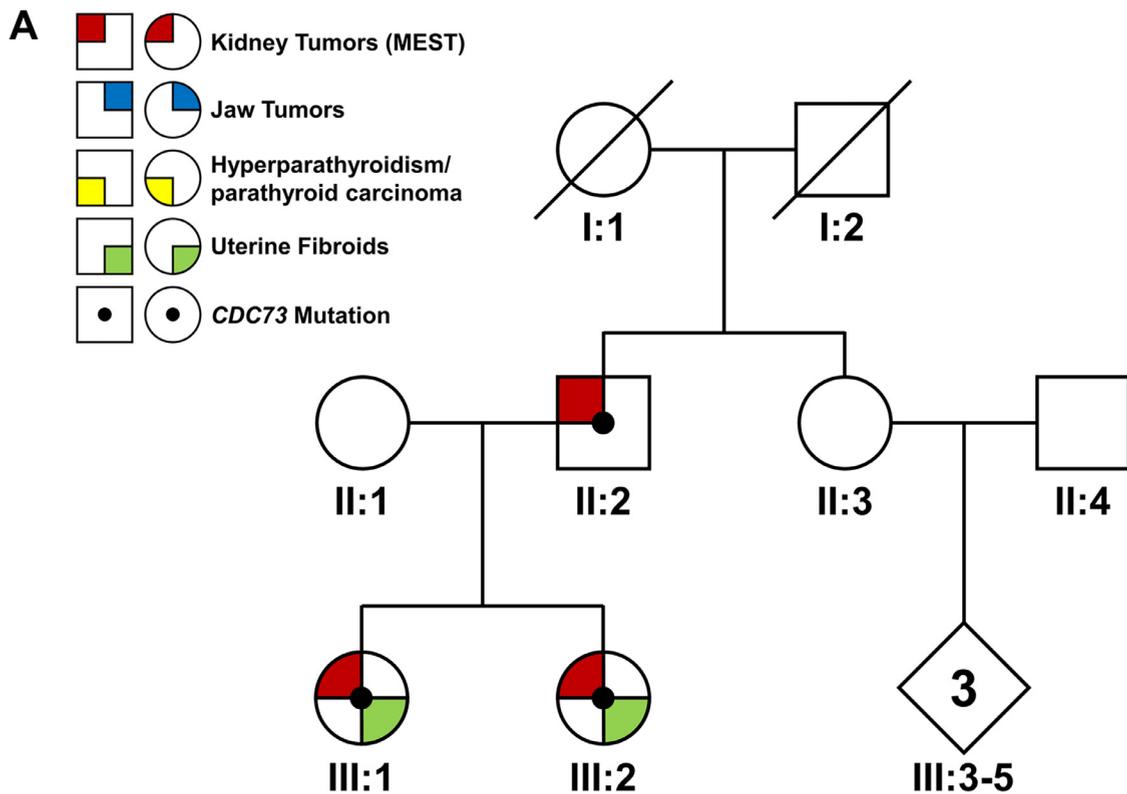


Figure 1. MEST family pedigree and imaging. (A) Patients are designated by generation (Roman numerals) and individual (Arabic numerals). Patients that tested positive for *CDC73* germline mutation are denoted with central black dots; clinical features associated with *CDC73* mutation are indicated in the quadrants as shown. (B) Coronal and (C) Axial CT imaging of patient III:2 demonstrated cystic tumors that were present in both kidneys. MEST, mixed epithelial and stromal tumor of the kidney. (Color version available online.)

desmin, WT-1, ER (Fig. 2C), and PR (Fig. 2D), and showed focal positivity for calretinin. Subsequently, 2 tumors were removed from the right kidney, measuring $6.5 \times 4.5 \times 1.7$ cm and $3.3 \times 3.0 \times 1.8$ cm. Histology and staining features were the same as the tumors from the left kidney, consistent with MEST. The patient also has a history of a hysterectomy at age 19 for excessive bleeding and uterine fibroids.

The patients' father, II:2, was subsequently seen in the NCI for evaluation. This patient had had an abdominal CT at an outside institution at age 70 due to localized pain, resulting in incidental identification of bilateral renal masses: a heterogeneous 3.6 cm right kidney mass with punctate calcifications and a 3.1 cm left midpole kidney mass. A core biopsy of the right kidney mass demonstrated no malignancy and was treated by cryotherapy. A subsequent left partial nephrectomy at the outside

institution resected a 3.4 cm lesion consistent with MEST, with a histology similar to that of the biopsy of the right mass. The Laboratory of Pathology at the NCI confirmed both the histologic classification of MEST for the left tumor (Fig. 2E, F) and the positive staining for ER (Fig. 2G), and PR (Fig. 2H). During his NCI visit 5 years postsurgery, CT imaging revealed a 3 cm lower pole mass with multiple calcifications, a 1.8 cm cyst, and a 1 cm indeterminate mass in the right kidney, as well as two small cysts within the left kidney.

Mutation Analysis of the MEST Family

Blood DNA from patient III:2 was evaluated for germline mutation in a panel of approximately 240 known cancer genes using the OncoVar v3 targeted sequencing assay.^{15,16} A germline mutation in *CDC73* (c.3G>T) was identified, resulting in loss of the

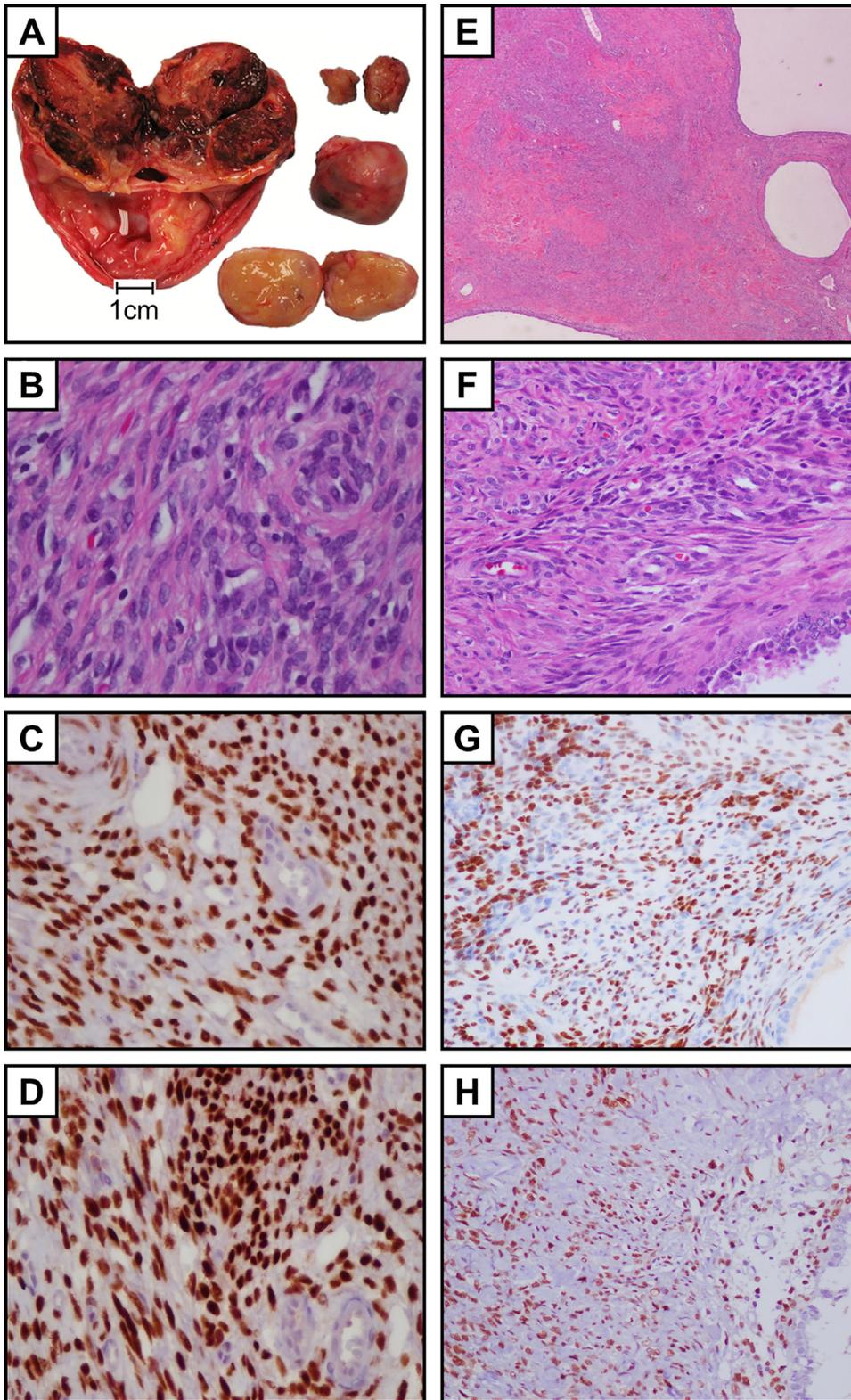


Figure 2. MEST histopathology and immunohistochemistry. (A) The 6 tumors surgically resected from patient III:2 and (B) a representative H&E stain from 1 of the 6 tumors from patient III:2 demonstrating the MEST histology. Positive nuclear IHC staining in the tumor from patient III:2 for (C) ER and (D) PR. (E) and (F) Hematoxylin and eosin (H&E) staining of a tumor from patient II:2 demonstrating a MEST histology. Positive nuclear IHC staining in the tumor from patient II:2 for (G) ER and (H) PR. IHC, immunohistochemical; MEST, mixed epithelial and stromal tumor of the kidney. (Color version available online.)

canonical initiating methionine (p.M1I) and thus precluding translation of the full-length protein product, parafibromin. This variant was not observed in the Exome Aggregation Consortium (ExAC) Database (<http://exac.broadinstitute.org/>) or in the ClinVar Database (<https://www.ncbi.nlm.nih.gov/clinvar/>); Sanger sequencing demonstrated that the germline *CDC73* mutation was carried by all 3 affected family members (Fig. 3). DNA from both tumors from the right kidney of patient III:2 was Sanger sequenced and demonstrated loss of heterozygosity (LOH) (Fig. 3). These results corroborate that the mutation co-segregates with the MEST phenotype, and that these MEST tumors display bi-allelic loss of *CDC73* consistent with a tumor suppressor function.

Whole exome sequencing (WES) was then performed to compare DNA from the largest right-sided kidney tumor to blood DNA from patient III:2. LOH at the *CDC73* locus was confirmed by a variant to total coverage of 84/160 reads (variant allele frequency [VAF] = 0.525) for the blood DNA compared to

a variant to total coverage of 156/169 reads (VAF = 0.923) in the tumor. No additional germline or somatic mutations were identified in any known kidney cancer genes. While copy number loss of chromosome 1 was not detected by WES, allelic imbalance was observed across most of the chromosome 1q arm including the 1q21.1 region encoding *CDC73* (Fig. 4A). This copy-neutral LOH was confirmed in both of the right-sided kidney tumors using quantitative PCR (Fig. 4B). Apart from the q arm of chromosome 1, there were no other genomic areas of gross copy loss or allelic imbalance (Fig. 4C).

Clinical Follow-up for Features Associated With MEST and HPT-JT

Patients III:1 and III:2 were subsequently sent for CLIA-approved testing to confirm their *CDC73* germline mutation. Both patients are continuing surveillance for their renal lesions in the UOB; patient III:1 for a 5 cm simple cyst in the right kidney and patient

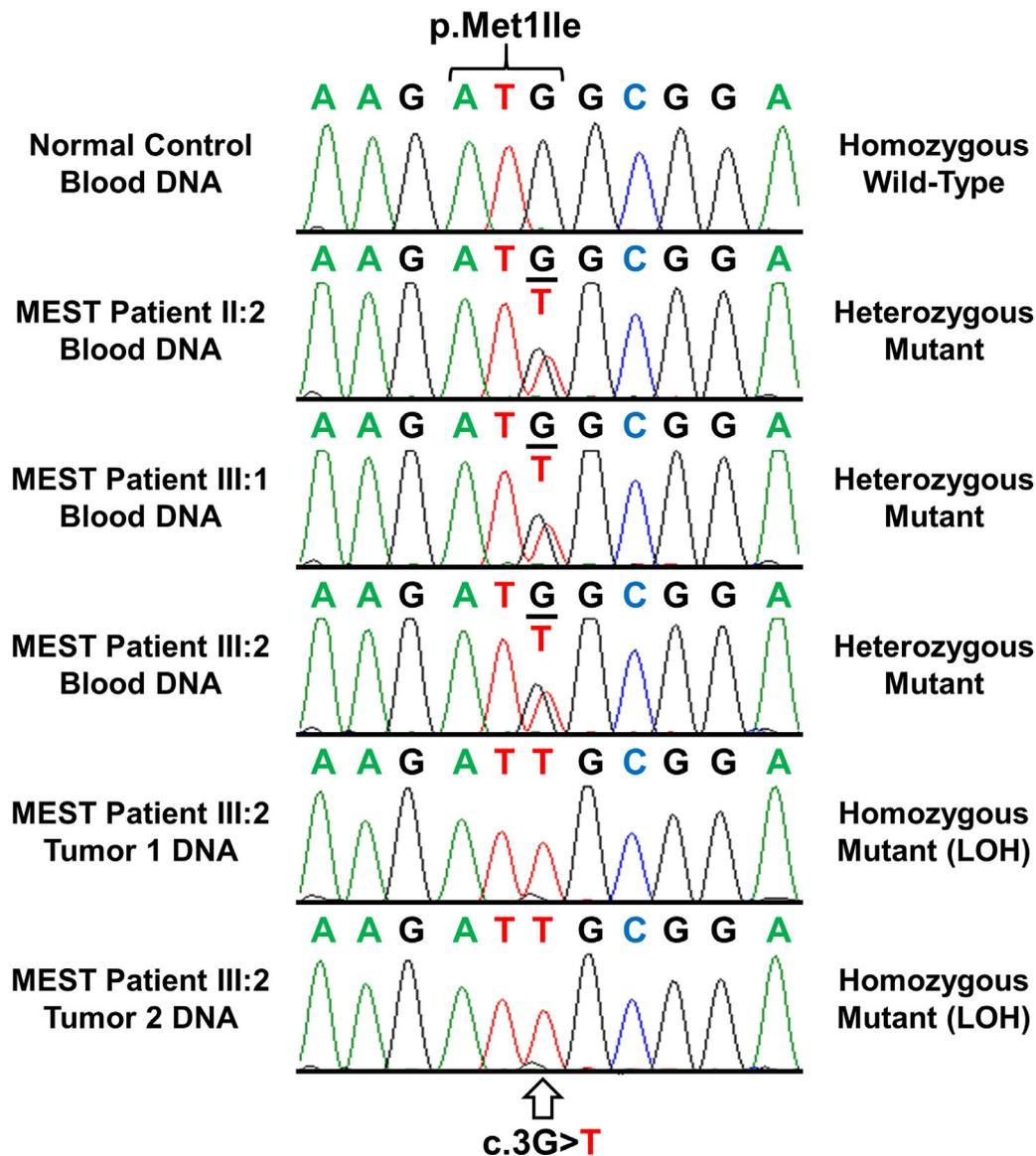


Figure 3. Sanger DNA sequencing of MEST family blood and tumor DNA samples. Chromatographs of *CDC73* sequencing identify the heterozygous germline G to T change resulting in the p.Met1Ile mutation in the blood DNA from patients II:2, III:1 and III:2. Analysis of DNA from 2 tumors excised from patient III:2 demonstrates loss of heterozygosity (LOH) indicative of a somatic second hit. MEST, mixed epithelial and stromal tumor of the kidney. (Color version available online.)

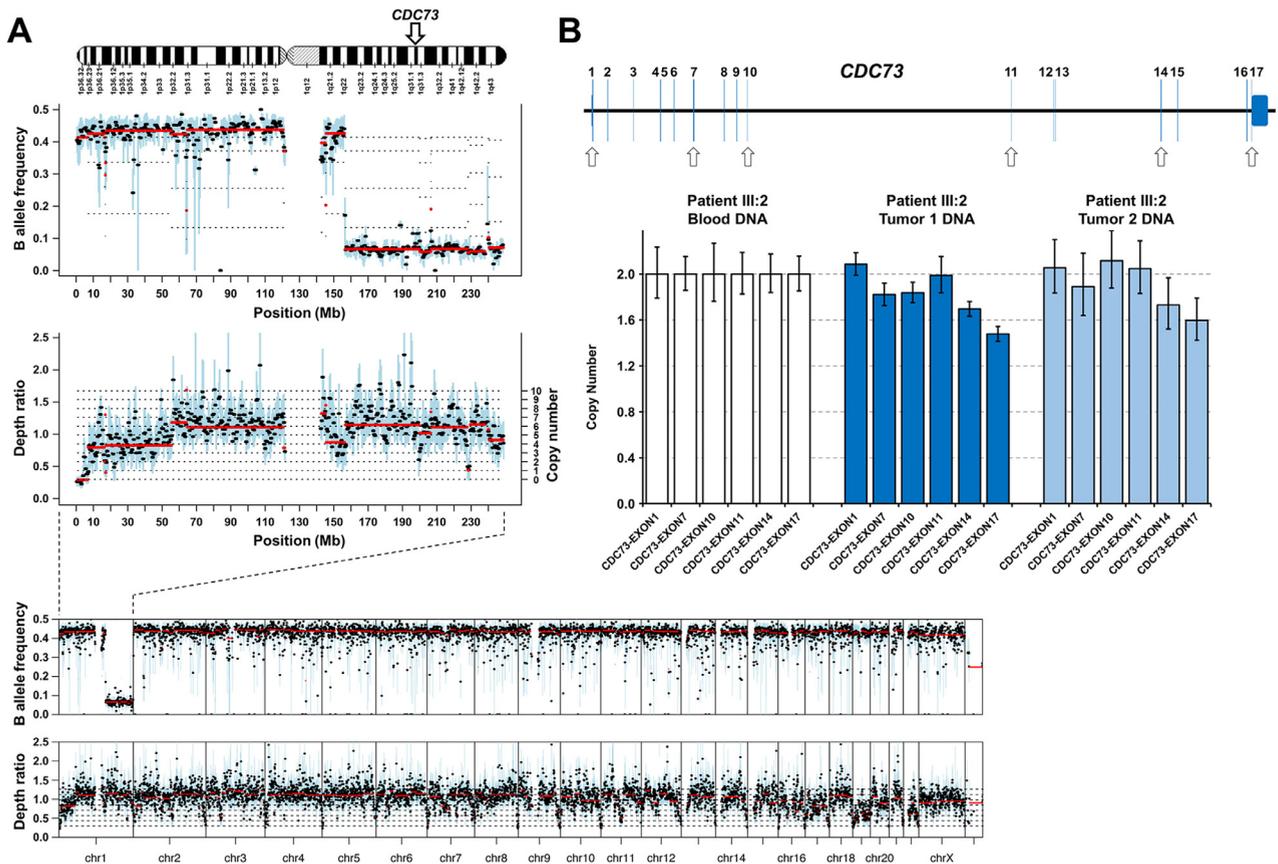


Figure 4. MEST tumor allelic imbalance and copy number. (A) Copy number (Depth ratio) and allelic imbalance (B allele frequency) for chromosome 1 (top) and the entire genome in the largest tumor from patient III:2 were evaluated by whole exome sequencing. While no copy loss for chromosome 1 was observed, the allelic imbalance (B allele frequency) analysis demonstrated a significant loss of allelic variation in most of the qter arm of chromosome 1, including the *CDC73* locus, indicating a copy neutral LOH event. (B) Copy number analysis was confirmed using quantitative PCR of selected exons (1, 7, 10, 11, 14 and 17) spread throughout the length of the *CDC73* gene. The gene structure for *CDC73* and location of the primers is indicated. Copy number was normalized to blood DNA from patient III:2 and a normal copy number pattern was observed in both tumors from patient III:2. LOH, loss of heterozygosity; MEST, mixed epithelial and stromal tumor of the kidney. (Color version available online.)

III:2 for sub-cm simple cysts in both kidneys. Both patients also underwent HPT-JT screening based on their germline mutation. A panoramic radiograph of patient III:1's mandible revealed radiolucency along the distal root of tooth 19, and irregular trabecular patterns behind several teeth, but no distinct jaw lesions were noted. A CT scan of the mandible demonstrated a poorly defined nodule of approximately 0.9 by 0.6 cm posterior to the left thyroid lobe in the expected location of the left parathyroid gland. The lesion was resected and found to be a lymph node with no specific pathological changes, and an attached fragment of normal parathyroid gland. She will be followed closely with repeat imaging of neck, maxilla, and mandible. To date, patients III:1 and III:2 are both asymptomatic and exhibit normal levels of calcium, ionized calcium, vitamin D, and parathyroid hormone.

DISCUSSION

This study evaluated a family of 3 affected individuals, including 1 male that presented with an unusual primary diagnosis of bilateral and/or multifocal MEST. This family

was found to have a germline *CDC73* mutation (c.3G>T, p.M11), predicted to inactivate one copy of the gene encoding parafibromin. Analysis of tumors from one individual demonstrated somatic copy-neutral LOH, in a manner consistent with a tumor suppressor gene. Our family exhibited only MEST kidney tumors and uterine manifestations and, to date, has demonstrated no definitive evidence of hyperparathyroidism or distinct jaw tumors.

The current literature concerning MEST and its connection to HPT-JT and mutation of *CDC73* is very limited. A single report in 1996 by Teh *et al* reported a HPT-JT family with parathyroid adenoma and hyperplasia, mandibular and maxillary ossifying fibromas, and multifocal renal hamartomas.¹⁹ These renal lesions were initially described as well differentiated with 3 components, mesenchymal, blastemic, and epithelial, and displayed loss of heterozygosity of microsatellite markers in the 1q21-q32 region.¹⁹ These hamartomas were subsequently described as MEST¹⁴ following the identification of

CDC73/HRPT2 by Carpten *et al* in 2002¹¹ and a germline CDC73 mutation (c.3G>A, p.M1I) in this HPT-JT Family (identified as Kindred 5 in Table 1; personal communication from Catharina Larsson to W.F.S.).

In general, bilateral MEST is thought to be rare in adults and has only been reported a few times. Lane *et al* observed one case of bilateral MEST, in addition to one case of bilateral cystic nephroma (CN), within a cohort of 21 MEST and 9 CN patients; they believed these to be the first 2 cases of bilateral CN or MEST reported in adults.⁴ While neither patient had family history of kidney tumors, it was speculated that there might be a genetic basis for bilateral MEST or CN. The authors proposed CDC73 (HPRT2) as a putative candidate, but reported that the patients had no evidence of facial bone tumors or calcium abnormality and did not report any mutation in the gene.⁵ Tsai *et al* reported one case of bilateral MEST, but no genetic analysis was performed in that study.⁶

Germline mutation of CDC73 is strongly associated with HPT-JT and the clinical manifestations of HPT-JT are relatively well known.⁸⁻¹⁰ This study suggests that a differential diagnosis of MEST should be considered in HPT-JT patients with germline CDC73 mutations who exhibit kidney lesions. In addition, uterine tumors are considered a frequent event in HPT-JT patients.²⁰ The hysterectomies at the early ages of 20 and 19 in the 2 affected female family members in this study are consistent with this HPT-JT phenotype.

This study also supports the importance of CDC73 germline mutation analysis for patients who present with MEST, particularly those with a family history, or bilateral/multifocal disease. Even if currently asymptomatic, CDC73 mutation-positive patients may be at future risk for manifestations of HPT-JT including jaw tumors, parathyroid carcinoma, papillary thyroid carcinoma, and papillary renal cell carcinoma. Since these patients may be at risk for multiple, bilateral tumors potentially requiring multiple renal surgeries over their lifetime, nephron-sparing surgery rather than radical surgery is advocated, in order to preserve renal function. Due to the potential for MEST to undergo malignant transformation, sarcomatoid differentiation and metastatic spread (reviewed in Xie *et al*³), timely surgical intervention rather than active surveillance would be recommended for these tumors.

Many CLIA-approved renal cell carcinoma gene panels now include CDC73. Therefore, it is very important for any patient with a strong family history and/or bilateral presentation of renal lesions to undergo genetic testing at the earliest opportunity, so that patients can be accurately diagnosed and managed as soon as possible.

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