

## Oncology: Renal/Upper Tract/Bladder

### EARLY ONSET HEREDITARY PAPILLARY RENAL CARCINOMA: GERMLINE MISSENSE MUTATIONS IN THE TYROSINE KINASE DOMAIN OF THE MET PROTO-ONCOGENE

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#### ABSTRACT

**Purpose:** Hereditary papillary renal carcinoma (HPRC) is characterized by a predisposition to multiple, bilateral papillary type 1 renal tumors caused by inherited activating missense mutations in the tyrosine kinase domain of the *MET* proto-oncogene. In the current study we evaluated the clinical phenotype and germline *MET* mutation of 3 new HPRC families. We describe the early onset clinical features of HPRC.

**Materials and Methods:** We identified new HPRC families of Italian (family 177), Spanish (family 223) and Cuban (family 268) descent. We evaluated their clinical features, performed *MET* mutation analysis by denaturing high performance liquid chromatography and DNA sequencing, and estimated age dependent penetrance and survival using Kaplan-Meier analysis. We characterized renal tumors by histology and fluorescence in situ hybridization.

**Results:** Identical germline *MET* c.3522G→A mutations (V1110I) were identified in families 177 and 268 but no evidence of a founder effect was found. Affected members of family 223 carried a germline c.3906G→C.3522G→A *MET* mutation (V1238I). Age dependent penetrance but not survival was significantly earlier for the c.3522G→A mutation than for the c.3906G→A mutation in these HPRC families. Trisomy of chromosome 7 and papillary renal carcinoma type 1 histology were detected in papillary renal tumors.

**Conclusions:** HPRC can occur in an early onset form. The median age for renal tumor development in these 3 HPRC families was 46 to 63 years. HPRC associated papillary renal tumors may be aggressive and metastasize, leading to mortality. Median survival age was 60 to 70 years. Families with identical germline mutations in *MET* do not always share a common ancestor. HPRC is characterized by germline mutations in *MET* and papillary type 1 renal tumor histology.

**KEY WORDS:** kidney; carcinoma, renal cell; neoplastic syndromes, hereditary; proto-oncogene protein c-met; mutation

Papillary renal carcinoma (PRC) comprises 10% to 15% of kidney epithelial tumors and it is histologically subdivided into types 1 and 2.<sup>1</sup> Hereditary papillary renal carcinoma

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(HPRC) is an uncommon form of inherited kidney cancer characterized by the predisposition to develop bilateral, multifocal renal tumors with type 1 papillary architecture.<sup>2–4</sup> Tumors show frequent trisomy of chromosome 7<sup>5</sup> and they appear to arise from independent clonal events.<sup>5,6</sup>

The *MET* proto-oncogene encodes a transmembrane receptor tyrosine kinase (TK), which is the receptor for hepatocyte growth factor (HGF).<sup>7</sup> MET/HGF signaling supports a number of biological processes, including embryonic development, cell growth and differentiation.<sup>8</sup> In addition to mediating various normal cellular processes, MET/HGF signaling has also been implicated in tumorigenesis.<sup>9</sup> We and others have identified *MET* proto-oncogene mutations in the germline of affected members of HPRC families.<sup>10,11</sup> All mutations iden-

tified were missense, located in the TK domain of *MET* and constitutively activating.<sup>12,13</sup> Molecular modeling studies suggest that these activating mutations interfere with *MET* TK self-inhibition and facilitate transition to its active form.<sup>14,15</sup>

Previously we have described the novel exon 16 *MET* mutation c.3529A→G (H1112R) in 2 North American HPRC families that share the affected haplotype surrounding the *MET* locus, suggesting that these 2 families may share a common founder.<sup>16</sup> We also reported another exon 16 mutation, c.3522G→A (V11101), in the germline of patient 5946 with multifocal, bilateral papillary renal tumors and a family history of HPRC.<sup>14</sup> Herein we describe the clinical phenotype and *MET* mutation analysis of 1 large Italian HPRC family and an HPRC family of Cuban descent with the identical c.3522G→A *MET* mutation. We also present a Spanish HPRC family with a c.3906G→C.3522G→A *MET* mutation, which has previously been identified in Spanish and French HPRC families.<sup>10</sup> Age dependent penetrance and survival in the HPRC families with different *MET* mutations are presented. The possibility of a common founder among HPRC families that harbor the same disease causing *MET* mutation is examined. These data are discussed relative to the differential diagnosis of HPRC.

#### MATERIALS AND METHODS

**Subjects.** After providing informed consent patients were evaluated at the Clinical Center, National Institutes of Health (NIH) by medical history, physical and dermatological examinations, standard blood chemistry studies, helical computerized tomography (CT) of the abdomen (with/without contrast medium), renal ultrasound and/or magnetic resonance imaging. The diagnosis of papillary renal carcinoma was based on pathology reports, medical records and death certificates. Affection status was determined in asymptomatic individuals by renal CT with/without intravenous contrast administration (130 cc Isovue300, Bracco, Princeton, New Jersey) using 5 mm collimation. Papillary renal tumors are isoechoic and often not visible by ultrasound. An asymptomatic individual was considered affected when 1 or more solid renal tumors of 10 mm or greater were detected. Some members of family 223 were evaluated at Hospital Sant Joan, Reus, Spain.

**Pathological findings.** A renal neoplasm was classified as papillary when at least 50% of the renal tumor had a papillary or tubulopapillary architecture. Papillary type 1 architecture was characterized by delicate fibrovascular cores lined with small cells with basophilic nuclei and scant amphophilic cytoplasm. Foamy macrophages and psammoma bodies were prominent features.

**Fluorescence in situ hybridization (FISH) analysis of HPRC renal tumors.** Touch preparations were taken from patient papillary renal tumors, air dried and prepared for interphase FISH, as previously described.<sup>17</sup> Briefly, a biotin labeled DNA probe was prepared from the *MET* cosmid 182b3 for chromosome 7 and cohybridized with a spectrum orange labeled chromosome 11 centromere enumeration probe (CEP11, Vysis, Downer's Grove, Illinois), as previously described.<sup>18</sup> Image acquisition of greater than 100 cells was performed with Q-FISH software (Leica Microsystems Imaging, Cambridge, United Kingdom) through a charged coupled device camera (Hamamatsu, Tokyo, Japan).

***MET* mutation analysis.** DNA from peripheral blood leukocytes was evaluated for mutations in exons 16–19 of the *MET* proto-oncogene by denaturing high performance liquid chromatography (DHPLC) on a WAVE Nucleic Acid Fragment Analysis System (Transgenomic, Omaha, Nebraska) using previously described primers and PCR conditions.<sup>10,14,19</sup> Amplicons that gave a heteroduplex peak on DHPLC analysis were subjected to double stranded sequenc-

ing using Big Dye chemistry (Applied Biosystems, Foster City, California) and analyzed with Lasergene software (DNASar, Madison, Wisconsin). Cosegregation of mutation with disease was confirmed. Additional mutation testing was performed elsewhere.

**Microsatellite genotyping for common founder.** Affected patients from the 2 families with the c.3522G→A mutation were genotyped using 5 polymorphic microsatellite markers flanking the *MET* gene (D7S1799, D7S1501, D7S523, *MET*, D7S2847 and D7S1809), as previously described.<sup>10,16</sup> The affected haplotype was confirmed by cosegregation with affected status.

**Statistical analysis.** Age dependent penetrance of disease in families with 3 *MET* mutations was estimated using the Kaplan-Meier estimator. Median age at onset was estimated as the earliest age on the Kaplan-Meier curve corresponding to a proportion without the phenotype of 0.5 or less. Median survival was estimated in a similar way. For age dependent penetrance and survival differences among the 3 mutation types were tested with the log rank test. These tests assume independence between outcomes within mutation type group. All values were 2-sided and  $p < 0.05$  was considered statistically significant. All statistical analyses were done using S-Plus Version 6.0 for Windows (Insightful Corp., Seattle, Washington).

#### RESULTS

**Clinical phenotype of HPRC families.** Family 177: We identified a large Italian family with 9 members who had renal carcinoma. There were 4 deceased affected and 5 living affected family members (see table, fig. 1, A). Family members were invited to the NIH Clinical Center for evaluation and blood samples from patients unable to come to NIH were collected in Italy for mutation analysis. Histology slides from Italy were reviewed by the National Cancer Institute (NCI) pathologist (MJM) to confirm the diagnosis of PRC type 1. The parents (subjects II:1 and II:2) died of cirrhosis of the liver and heart attack, respectively, with no history of renal carcinoma. One daughter (subject III:2) died of breast cancer at the age 41 years. Four sons, a daughter and a nephew had previously been diagnosed with renal carcinoma and they are described.

Subject III:3 died at age 37 years with renal carcinoma of uncharacterized histology, which was identified at autopsy. His son, subject IV:1, died at age 45 years with renal carcinoma. A 19-year-old grandson, subject V:1, was evaluated at NIH and found to have several bilateral renal focal lesions. The largest lesion was a 1.6 cm solid renal mass (fig. 2, B). Subject III:5, a brother of III:3, died at age 60 years of metastatic renal cancer of "cystopapillary and sarcomatoid" histology. A son, subject IV:6, was diagnosed with HPRC at age 38 years as a result of clinical evaluation at NCI (fig. 2, A). He underwent right and partial left nephrectomies to remove multiple renal tumors. Altogether 34 tumors of papillary type 1 histology were removed, of which the largest one was 10 cm in diameter.

Subject III:7, another brother of III:3, was diagnosed with kidney stones at age 46 years but metastatic renal carcinoma developed 10 years later, which led to his death at age 56 years. Subject III:13, a sister of III:3, underwent left nephrectomy at age 53 years to remove a 9 cm mass diagnosed as PRC type 1. CT of the abdomen during NIH evaluation showed the right kidney to be normal. Subject III:15, another brother of III:3, underwent bilateral nephrectomy elsewhere at age 51 years to remove multifocal papillary type 1 renal tumors and he is currently on hemodialysis. CT of the abdomen performed in his 27-year-old daughter, subject IV:19, revealed a 3 mm indeterminate lesion in the right kidney.

A maternal cousin of III:3 not seen at NIH (subject III:21) underwent left nephrectomy at age 58 years after a diagnosis

Affected and at risk patients in 3 HPRC families with MET mutations

| Family (mutation)<br>(subject No.) | Seen at<br>NIH | Mutation Carrier Status | Age       |           | Tumors (side/<br>metastasis) | Nephrectomy          |
|------------------------------------|----------------|-------------------------|-----------|-----------|------------------------------|----------------------|
|                                    |                |                         | Diagnosis | Last Scan |                              |                      |
| <b>177 (c.3522G&gt;A):</b>         |                |                         |           |           |                              |                      |
| III:3                              | No             | Obligate carrier        | 37        |           | Unknown                      | None                 |
| IV:1                               | No             | Obligate carrier        | 45        |           | Unknown                      | None                 |
| V:1                                | Yes            | Yes                     | 19        |           | Bilat/none                   | None                 |
| V:2                                | Yes            | Yes                     |           | 16        | None                         | None                 |
| III:5                              | No             | Obligate carrier        | 60        |           | Bilat/yes                    | Lt total, rt partial |
| IV:6                               | Yes            | Yes                     | 38        |           | Bilat/no                     | Lt partial, rt total |
| III:7                              | No             | Obligate carrier        | 56        |           | Bilat/yes                    | None                 |
| IV:10                              | No             | Yes                     | No CT     |           | None                         | None                 |
| III:13                             | Yes            | Yes                     | 53        |           | Bilat/no                     | Lt total             |
| IV:11                              | No             | Yes                     | No CT     |           | None                         | None                 |
| IV:17                              | Yes            | Yes                     |           | 30        | None                         | None                 |
| III:15                             | Yes            | Yes                     | 51        |           | Bilat/no                     | Lt + rt total        |
| IV:19                              | Yes            | Yes                     |           | 27        | None                         | None                 |
| III:20                             | No             | Yes                     | No CT     |           | None                         | None                 |
| III:21                             | No             | Mutation not determined | 58        |           | Unilat/no                    | Lt total             |
| <b>268 (c.3522G&gt;A):</b>         |                |                         |           |           |                              |                      |
| I:1                                | No             | Obligate carrier        | 46        |           | Bilat/yes                    | Lt + rt total        |
| II:1                               | Yes            | Yes                     | 42        |           | Bilat/no                     | Lt partial, rt total |
| II:3                               | Yes            | Yes                     | 38        |           | Bilat/no                     | Lt + rt partial      |
| <b>223 (c.3906G&gt;A):</b>         |                |                         |           |           |                              |                      |
| I:1                                | No             | Obligate carrier        | 70        |           | Unknown                      | Lt total             |
| II:2                               | Yes            | Yes                     | 67        |           | Bilat/no                     | Rt partial           |
| III:3                              | Yes            | Yes                     |           | 30        | None                         | None                 |
| III:4                              | Yes            | Yes                     | 31        |           | Bilat/no                     | Lt + rt partial      |
| II:5                               | No             | Yes                     | 63        |           | Bilat/no                     | Rt total             |
| III:6                              | No             | Yes                     | 34        |           | Bilat/yes                    | Lt + rt total        |
| II:3                               | Yes            | Yes                     |           | 57        | None                         | None                 |
| III:5                              | Yes            | Yes                     | 31        |           | None                         | None                 |
| III:7                              | No             | Yes                     |           | 36        | None                         | None                 |
| III:8                              | No             | Yes                     |           | 28        | None                         | None                 |

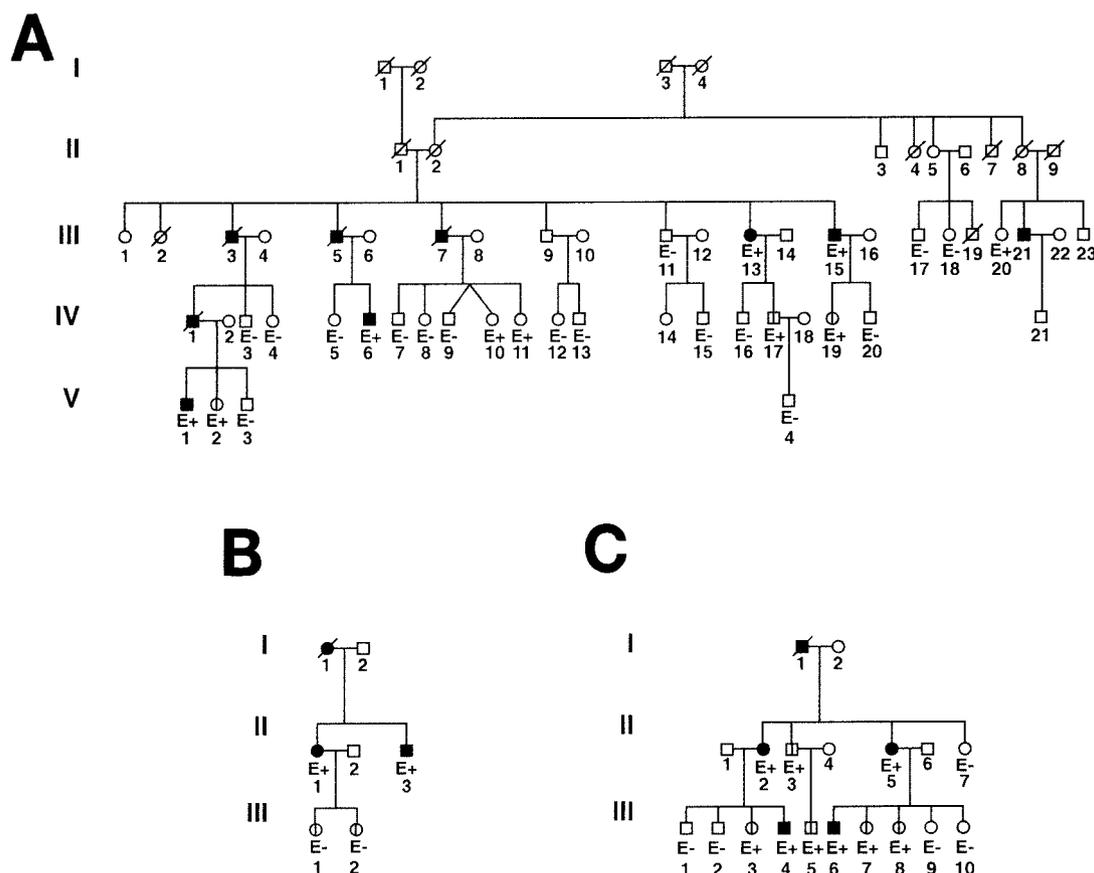


FIG. 1. Pedigrees of 3 HPRC families with mutations in MET proto-oncogene. A, Italian family 177 has 9 affected members and 10 confirmed carriers of c.3522G→C.3522G→A MET mutation. Six asymptomatic mutation carriers were identified. B, family 268 of Cuban descent has 3 affected members with renal carcinoma and 2 confirmed carriers of c.3522G→C.3522G→A MET mutation. C, family 223 from Spain has 9 members who harbor c.3906G→C.3522G→A MET mutation and 5 with renal carcinoma. Five asymptomatic mutation carriers were identified. Vertical line indicates CT negative for renal tumors. Filled symbols indicate renal carcinoma diagnosis. E+, genetic testing positive for mutation. E-, genetic testing negative for mutation.

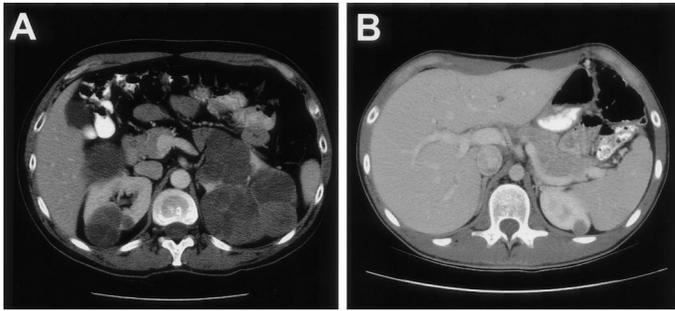


FIG. 2. Abdominal CT reveals early onset PRC in 2 members of HPRC family 177. A, 38-year-old male patient IV:6 had large, bilateral, multifocal papillary renal tumors and underwent staged, bilateral partial nephrectomy. Total of 34 papillary renal tumors were removed. Given relatively slow tumor growth rate it is likely that tumors started growing years before they were detected. B, 19-year-old male patient V:1 at 1 year after detection of bilateral, multifocal renal masses, of which largest was 1.6 cm solid mass. This individual is being treated with careful observation.

of renal cell carcinoma. Histology of the multiple neoplastic lesions was reported as a papillary variant of renal cell carcinoma. Pathological findings of the renal tumors of 3 affected family members were reviewed by the NCI pathologist (MJM) and confirmed as PRC type 1.

Family 268: A family of Cuban descent with renal carcinoma was referred to the NIH (see table, fig. 1, B). Subject I:1 had renal carcinoma at age 46 years and underwent left nephrectomy, followed by right nephrectomy 6 years later. She died of metastatic disease at age 60 years. A 42-year-old daughter, subject II:1, was screened at NIH by CT and found to have bilateral renal masses but she postponed surgical treatment for 1 year. At that time she had gross hematuria and emergency right nephrectomy was performed. Tumors were of papillary type 1 histology and up to 8 cm. She subsequently underwent left partial nephrectomy at NCI. Multiple renal tumors were removed, including 5 and 6 cm lesions. A 38-year-old son, subject II:3, was also screened at the NIH. Occult bilateral renal masses were identified and partial nephrectomies were performed. Tumors were up to 10 cm and all were papillary type 1 histology (fig. 3, A and B).

Family 223: A family with HPRC from Spain was identified by one of us (JB). Five family members were evaluated at the NIH Clinical Center and the remaining members were assessed at Hospital Sant Joan, Reus, Spain (see table, fig. 1, C).

Subject II:2 had previously been diagnosed with multiple tumors in the right kidney at age 67 years. Partial right nephrectomy was performed, followed by complete right nephrectomy. Histological examination of the tumors confirmed papillary type 1 histology. When screened at the NIH two 1 to 2 cm tumor nodules were found in the left kidney. No surgery

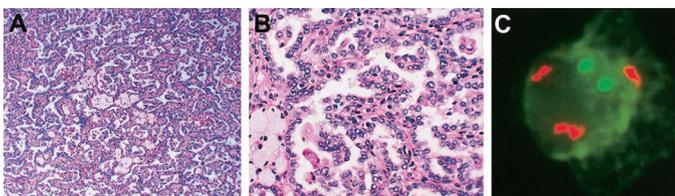


FIG. 3. Characteristics of papillary renal tumors from family 268. A, type 1 PRC histology is characterized by short papillae lined by single layer of cells with regular, small nuclei and inconspicuous cytoplasm. Note some aggregates of foamy macrophages within cores of papillae. H & E, reduced from  $\times 100$ . B, higher magnification shows basophilic nuclei with prominent nucleoli and foamy macrophages. Reduced from  $\times 200$ . C, FISH using *MET* cosmid probe demonstrates chromosome 7 trisomy (red signal) in papillary renal tumors compared with 2 copies of chromosome 11 serving as control (green signal).

was performed but reevaluation in 6 months was recommended. The father (subject I:1) of the patient died of renal cancer at age 70 years.

Subject II:5, a sister of II:2, had tumors in the right kidney at age 63 years and underwent unilateral nephrectomy. Additional small tumors have been noted in the left kidney. Subject III:6, son of subject II:5, also had bilateral multifocal papillary tumors at age 34 years and underwent bilateral nephrectomy. Lung metastases were subsequently detected.

Subject III:3, a 30-year-old daughter of II:2, was born with a single kidney. CT at NIH was negative for renal findings. A 31-year-old son of II:2, subject III:4, was found to have bilateral papillary renal tumors by CT while being evaluated at NIH. Nephron sparing surgery was performed on the 2 kidneys to remove a total of 12 discrete tumor nodules. A 57-year-old brother of II:2, subject II:3, and his 31-year-old son, subject III:5, were screened by CT at NIH and found to be negative for renal findings. Two cousins, subjects III:7 and III:8, were screened by magnetic resonance imaging in Spain and found to be negative for renal findings. Pathological findings of the renal tumors of 2 family 223 members was reviewed by the NCI pathologist (MJM) and confirmed as PRC type 1.

*Pathological phenotype of HPRC families.* Grossly multiple yellow nodules of variable sizes were identified throughout

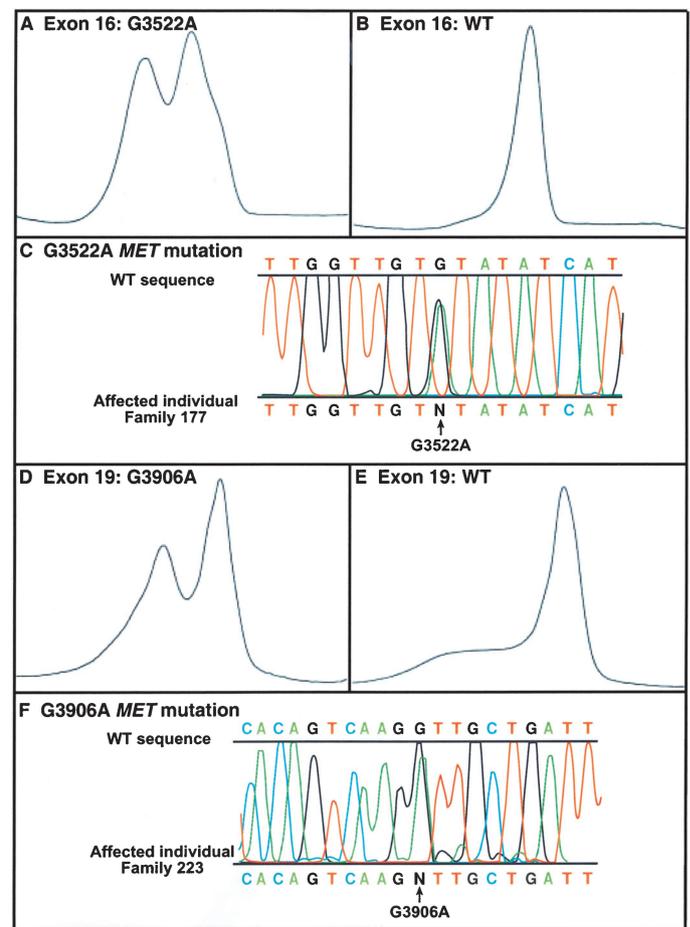


FIG. 4. *MET* mutation analysis of HPRC families 177, 268 and 223. A, unique DHPLC signature for c.3522G→A *MET* mutation present in affected members of HPRC families 177 and 268. B, exon 16 WT DHPLC signature. C, sequence showing germline c.3522G→A *MET* mutation in affected family 177 member. D, unique DHPLC signature for c.3906G→C.3522G→A *MET* mutation present in affected family 223 members. E, exon 19 WT DHPLC signature. F, sequence showing germline c.3906G→A *MET* mutation in affected family 223 member.

the renal parenchyma. Incipient lesions or small adenomas were present in the adjacent kidney parenchyma in all 3 families. Papillary structures were lined by columnar and cuboidal cells with small, low grade nuclei and granular cytoplasm. Histologically while all tumors were classified as papillary type 1, areas of clear cell differentiation were seen in patients from families 268 and 177 with extensive necrosis. Two patients from families 268 and 177 had large masses up to 11 cm with obvious areas of hemorrhage and necrosis.

**MET mutation analysis in HPRC families.** We identified a germline *MET* mutation in the proband of HPRC family 177 (fig. 1, A). The *MET* mutation in exon 16, c.3522G→A, is predicted to substitute isoleucine for valine at codon 1110 (fig. 4, C). Additional family members were screened for the mutation by DHPLC analysis and a characteristic DHPLC heteroduplex profile was identified that cosegregated with affected status (fig. 4, A and B). Two affected members of family 268 were also found to harbor the identical c.3522G→A *MET* mutation (fig. 1, B).<sup>14</sup>

DNA samples from family 223 were analyzed by DHPLC and direct sequencing. A c.3906G→C.3522G→A *MET* mutation in exon 19 was identified in the proband (subject II:2) (fig. 1, C) from this family and subsequently in 3 other affected family members (fig. 4, D to F). This mutation had previously been identified in affected members of French and Spanish HPRC families<sup>10,14</sup> and it was predicted to change valine to isoleucine at codon 1238 of the *MET* proto-oncogene. We were unable to obtain DNA samples from additional French and Spanish HPRC family members who had been previously identified with the G3906 C.3522G→A *MET* mutation and, therefore, we could not evaluate for founder effect in family 223.

**Trisomy 7 in papillary renal tumors.** FISH analysis was performed on renal tumor touch preparations from subject IV:6 of family 177 (data not shown) and subject II:3 of family 268 (fig. 3, C). Hybridization of a chromosome 7 probe from a *MET* containing cosmid revealed 3 copies of chromosome 7 compared with 2 copies of chromosome 11 when the CEP11 probe from chromosome 11 was used as a control.

**Founder effect not found among HPRC families with the same MET mutation.** Since families 177 and 268 harbored the identical germline c.3522G→A *MET* mutation, we considered the possibility that these HPRC families originated from a common ancestor. However, results of genotyping 5 polymorphic microsatellites in affected family members from the 2 families revealed different affected haplotypes, ie a founder effect was not identified. A rare polymorphic allele (11 CA repeats in D7S2847 adjacent to the *MET* gene) cosegregated with affected individuals in family 177 but not in family 268 (data not shown).

**Comparison of age dependent penetrance in HPRC families with different MET mutations.** We compared the age of onset of papillary renal tumors in families 177 and 268 carrying the c.3522G→A *MET* mutation in exon 16 with age at onset of disease in 2 large North American families (HPRC families 150 and 160), which harbor a different exon 16 mutation (c.3529A→G) and share a common founder.<sup>16</sup> We found a significant difference in median age at disease onset for the 2 *MET* mutations (c.3522G→A 46 years and c.3529A→G 57 years,  $p = 0.024$ , fig. 5). In addition, when we compared these values with age at disease onset in family 223 with the c.3906G→C.3522G→A *MET* mutation (median 63 years), we found that age at onset was significantly earlier in affected members of families 177 and 268 carrying the c.3522G→A *MET* mutation compared with affected members of family 223 ( $p = 0.025$ , fig. 5). The differences in age dependent penetrance of PRC may reflect the location of these mutations within the *MET* gene. However, patient numbers were small and evaluation of additional families carrying these 2 mutations is necessary to rule out contributing factors due to environmental or genetic differences. No significant differ-

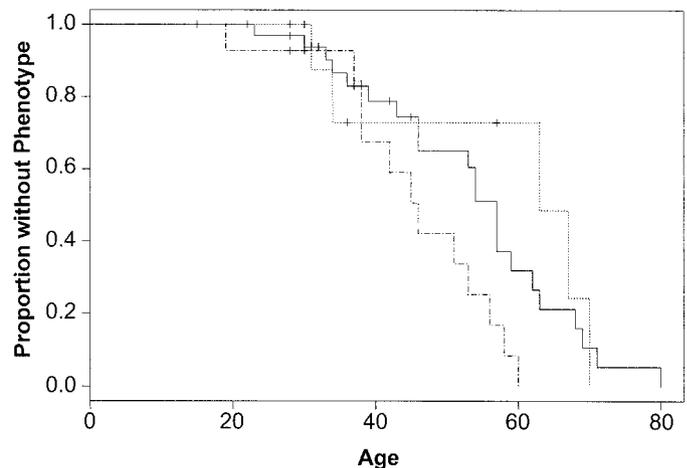


FIG. 5. Age dependent penetrance of different *MET* mutations in HPRC families 177 and 268 (dashed and dotted line), 150 and 160 (solid line), and 223 (dotted line) estimated using Kaplan-Meier estimator. Median age at renal tumor onset in families 177 and 268 with c.3522G→A *MET* was 46 years, significantly earlier than 63 years in family 223 with c.3906G→C.3522G→A *MET*, ( $p = 0.025$ ) and 57 years in families 150 and 160 ( $p = 0.024$ ). Plus signs indicate censored observations.

ence in median survival was seen in patients from families 177 and 268 (60 years), families 150 and 160 (68 years) and family 223 (70 years) (data not shown).

#### DISCUSSION

We present 3 new families clinically affected with HPRC harboring germline missense mutations in the *MET* proto-oncogene, of which 2 (families 177 and 268) share a common mutation and develop papillary renal tumors with an early onset. Patients in HPRC families have previously been reported to have renal cancer on average in the sixth decade of life, later than other inherited renal cancer syndromes such as von Hippel-Lindau disease, which often develops in patients in the third and fourth decades of life. However, individuals in HPRC families are at risk for bilateral, multifocal kidney cancer earlier in life (second decade). In addition, this report emphasizes that HPRC can be a lethal disease since a number of affected individuals in these families died of metastatic kidney cancer. Type 1 papillary renal carcinoma in patients with HPRC is a malignant tumor that can be early onset and metastasize, and which can be lethal if not detected early and treated.

The *MET* proto-oncogene mutations identified in these HPRC families have previously been identified in other HPRC families. Significantly all HPRC causing *MET* mutations identified to date are located within or adjacent to the adenosine triphosphate (ATP) binding pocket or the activation loop of the TK domain. It is possible that *MET* mutations compatible with normal growth and development as well as the development of renal tumors may be restricted to these regions of the *MET* kinase. Additional clustering of identical *MET* mutations within HPRC families may be due to founder effects.<sup>16</sup> However, families 177 and 268 with the identical *MET* mutation did not share the affected haplotype.

Affected members of HPRC families 177 and 268 carry a missense *MET* mutation (c.3522G→A) producing a valine to isoleucine substitution at codon 1110 in the conserved ATP binding pocket of the *MET* TK domain. Computer assisted molecular modeling studies have suggested that replacement of valine 1110 with isoleucine would be incompatible with the self-inhibitory conformation of the activation loop of *MET*.<sup>15</sup> Thus, the V1110I mutation would constitutively activate *MET* kinase independent of ligand. Olivero et al also identified the V1110I *MET* mutation in another Italian HPRC

family.<sup>11</sup> The identification of 3 HPRC families with the V1110I mutation in this uncommon form of inherited renal cancer suggests that it is located in a region of the *MET* gene critical for receptor TK signaling. In fact, this valine is highly conserved among tyrosine kinases, essential for ATP binding and the site of a homologous activating mutation in the v-erbB tyrosine kinase that leads to malignancy.<sup>14</sup>

Mutation of valine 1238 to isoleucine, encoded by the c.3906G→A mutation in family 223, is also predicted to destabilize the self-inhibiting conformation of MET in a more indirect way,<sup>15</sup> promoting conformational transition to an active MET kinase. The indirect effect of the V1238I mutation may explain in vitro assays that show weak oncogenic potential relative to other *MET* mutations found in patients with HPRC.<sup>12</sup>

This report extends previous clinical studies of HPRC families, bringing the number of HPRC families described worldwide to more than 30. HPRC is histologically and genetically distinct from renal tumors seen in other hereditary renal carcinoma syndromes for which disease genes have been identified, such as von Hippel-Lindau disease (clear cell renal cell carcinoma), hereditary leiomyomatosis and renal cell carcinoma (papillary type 2 renal cell carcinoma) and Birt-Hogg-Dubé syndrome (chromophobe and hybrid oncocytic neoplasms).<sup>20</sup> The presence of multiple, bilateral papillary type 1 renal tumors and germline mutations in the tyrosine kinase domain of the *MET* proto-oncogene serve as a basis for making the diagnosis of HPRC. Nephron sparing surgery is often the recommended treatment because it preserves renal function.<sup>21</sup> It is hoped that understanding the genetic basis of this disease and how alteration of this gene causes papillary renal carcinoma will one day lead to the development of disease specific molecular therapeutic approaches for patients with this disease as well as with sporadic, noninherited type 1 papillary renal carcinoma.

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