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Homozygous TMEM127 mutations in 2 patients with bilateral pheochromocytomas


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Pheochromocytoma (PCC) and paraganglioma (PGL) are rare neuroendocrine tumors that are hereditary in up to 50% of patients. The gene encoding transmembrane-protein-127 (TMEM127) is one of the PCC/PGL-susceptibility genes with an autosomal dominant inheritance pattern. Here, we report 2 patients with bilateral PCC who both harbored a homozygous TMEM127-mutation. In a 31-year-old mentally retarded patient, the homozygous c.410-2A > G mutation was discovered during an update of DNA analysis. A 26-year-old mentally retarded patient was found to have a homozygous c.3G > A mutation. The parents of both patients were consanguineous. We reviewed previously reported clinical features of TMEM127 mutation carriers and compared our findings with case descriptions of homozygous mutations in other PGL/PCC-susceptibility genes. Homozygosity for an autosomal dominant inherited disorder is an extremely rare phenomenon and has, to our knowledge, not been reported before for the gene encoding TMEM127. In the present cases, the clinical picture does not seem to be very different from heterozygous TMEM127 mutation carriers, except for a relatively large tumor size and more pronounced plasma metanephrine concentration. It is unclear whether the mental retardation is causally related to homozygosity of the TMEM127 mutations. Updating genetic screening in patients in whom PCC/PGL has been diagnosed in the past should be considered as it might provide clinically relevant information.

KEYWORDS
homozygous, paraganglioma, pheochromocytoma, TMEM127 mutation carriers

1 | INTRODUCTION

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare neuroendocrine tumors that may be hereditary in up to 50% of patients. Genetically determined PCC/PGL should be especially suspected in case of a positive family history, bilateral localization or presentation at a young age.1 The continuous evolving field of clinical genetics has - until today - identified more than 20 different susceptibility genes2 that are classified into 2 clusters depending on their gene expression profile. Cluster 1 mutations are involved with the pseudo-hypoxic pathway and include mutations in the following genes: von Hippel-Lindau (VHL), succinate dehydrogenase complex (SDHx), prolyl hydroxylase domain protein 2 (PHD2), isocitrate dehydrogenase (IDH), hypoxia-inducible factor 2a (HIF2a), malate dehydrogenase 2 (MDH2) and fumarate hydratase (FH). Cluster 2 mutations are associated with abnormal activation of kinase receptor and signaling regulators, including mutations in the following genes; rearranged during transfection (RET), neurofibromin 1 (NF1), kinesin family member 1B (KIF1B), Harvey rat sarcoma viral oncogene (H-ras), myc-associated factor X (MAX) and transmembrane protein 127 (TMEM127).1

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We here describe 2 patients with hereditary bilateral PCC, who were found to have a pathogenic homozygous mutation in the TMEM127 gene. To our knowledge, homozygous TMEM127 germline mutations have not been reported before. In this case report, we aim to review the clinical picture of heterozygous TMEM127 mutation carriers and compare their phenotype with that of the 2 patients encountered by us with homozygous TMEM127 mutations. In addition, we describe the clinical features of homozygous carriers of other PGL-susceptibility genes to gain more insight into the pathophysiological pathways of PCC/PGL tumor development. Informed consent was obtained for both patients. According to the Dutch Medical Research Involving Human Subjects Acts, because we used existing clinical data already collected for regular patient care, no further Institutional Review Board approval was required.

1.1 | Case I

In the year 1997, a mentally retarded Caucasian 31-year-old man was diagnosed with bilateral PCC. He had been admitted to our hospital (the University Medical Center Groningen) because of hypertension (blood pressure 160/90 mmHg, heart rate 100/minute), with symptoms of headache, nausea and dizziness. Laboratory investigations revealed high concentrations of urinary metanephrines: metanephrine 10 948 μmol/mol creatinine (reference range: 33-99 μmol/mol creatinine), normetanephrine 19 089 μmol/mol creatinine (reference range: 64-160 μmol/mol creatinine). An abdominal Computed Tomography (CT) scan identified bilateral adrenal masses (left 4.5 × 3.0 cm, right 7.0 × 6.0 cm). Bilateral adrenalectomy (by laparotomy) was performed after preoperative treatment with α- and β-antagonists. Pathologic examination confirmed the presence of a PCC in the right adrenal gland with a size of 7.0 × 6.0 × 5.0 cm (weight: 120 g) without signs of hyperplasia and 4 small PCC foci in the left adrenal gland. Postoperatively, the excretion of urinary metanephrines normalized. In 2008, the patient was found to have a recurrent PCC localized in the area of the right adrenal gland for which he was successfully operated. Since then, he has been free of recurrent PCC. Despite a negative family history, a hereditary cause of the PCC was suspected because of his young age and the bilateral presentation. In 1998, DNA analysis did not identify a mutation in the RET, VHL, SDHB or SDHD genes. In 2014, an update of the DNA analysis was negative for a mutation in the MAX gene but revealed a mutation in the TMEM127 gene (c.410-2A > G, p?). Remarkably, sequencing results suggested that the TMEM127 mutation, an A-to-G base substitution at nucleotide position c.410-2 where the normal reference nucleotide (A) is replaced by a G, apparently on both TMEM127 alleles. [Color figure can be viewed at wileyonlinelibrary.com]
positive for heterozygous TMEM127 mutations. His father’s DNA could not be examined as he had already died at the age of 56 years, probably due to an aortic dissection. His 79-year-old mother showed no biochemical signs of a PCC or PGL, she declined imaging. Neither his 53-year-old brother nor his 47-year-old sister showed any biochemical or radiological signs (on head and neck and thoracic-abdominal Magnetic Resonance Imaging [MRI]) compatible with PCC/PGL. Two other brothers declined genetic testing as well as any further clinical examinations (Figure 2).

The medical file of the index patient showed that he had distinct dysmorphic features as a child, including microcephaly, hypertelorism, frontal bossing and divergent strabismus diagnosed by the general practitioner. His psychomotor development had been delayed; he could walk by himself at 2 years of age and he spoke his first words at 4 years of age. From the age of 12 years, he experienced short attacks of absence lasting a few seconds, where he turned away his eyes and became pale. Several neurologic examinations including electroencephalograms did not reveal an explanation. Later on, he developed complaints of headache and 2 years before the first diagnosis of bilateral PCC he developed hypertension. It is likely that his mental retardation had contributed to a delayed diagnosis of the PCC, but it is unclear whether the mental retardation is causally related to the homozygous TMEM127 mutation. Further genetic analysis of the other homozygous areas in order to find an explanation for the mental retardation and dysmorphic features was declined by his family.

1.2 | Case II
A mildly mentally retarded 26-year-old Turkish man presented with bilateral PCC in 2013. He had been admitted to another hospital because of episodes of headache, dizziness and profuse perspiration. He was found to have severe hypertension (218/127 mm Hg). Laboratory investigation revealed elevated urinary metanephrines: metanephrine 14 513 μmol/mol creatinine (reference range: 35-150 μmol/mol creatinine), normetanephrine 4749 μmol/mol creatinine (reference range: 60-260 μmol/mol creatinine). CT scan of the abdomen showed a lobulated mass of the left adrenal gland with maximum size of 11 cm and an enlarged right adrenal gland of 2.5 cm. He underwent surgery at the Erasmus Medical Center Rotterdam where a left-sided adrenalectomy and right cortex sparing surgery was performed after preoperative treatment with α- and β-antagonists. Bilateral PCC were confirmed histologically. Pathologic examination revealed a multinodular PCC in the left adrenal gland (14.5 × 11.0 × 7.0 cm) and a PCC in the right adrenal gland (2.1 × 1.8 × 1.4 cm) with signs of hyperplasia of the adrenal medulla. Excretion of urinary metanephrines normalized postoperatively and the patient remained free of recurrent disease during follow-up.

The family history revealed consanguinity of the parents, who were cousins of each other. There were neither other family members with paragangliomas and/or developmental problems nor congenital anomalies (Figure 3). His father had been operated for a parathyroid gland adenoma at the age of 43 years. Because of the patient’s mental retardation and because of the consanguinity of his

FIGURE 3  + = carrier, ++ = double mutation, PCC = pheochromocytoma
parents, an SNP array analysis was performed, showing a normal male profile with large regions of homozygosity. One of the genes in this region was TMEM127. Sanger sequencing of the TMEM127 gene showed a homozygous variant of uncertain clinical significance c.3G > A, p.(Met1?) (chr2:94 900 727-100 417 149 (5 Mb)) (Figure 4). Both parents were recently identified as heterozygous carriers of this variant in TMEM127. They had no suggestive clinical signs or symptoms, diagnostic analysis for PCC was not performed. Immunohistochemistry of the tumor showed normal staining of the SDHA and SDHB proteins. Next-generation targeted sequencing in tumor tissue with a filter for genes involved in PCC and PGL (SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, KIF1B, NF1, RET, HIF2a, MAX, TMEM127 and PHD2) revealed also a homozygous variant in TMEM127 (c.3G > A p. (Met1?)). There were no abnormalities in other genes.

2 | DISCUSSION

The relationship between germline mutations in the TMEM127 gene and the development of PCC/PGL was first described in 2010 by Qin et al. The TMEM127 gene is located at chromosome 2q11.2 and encodes a transmembrane endosomal protein of 238 amino acids. Microarray analysis of TMEM127 mutations revealed a cluster 2 transcriptome, associated with increased kinase receptor signals. This results in inhibition of mammalian target of rapamycin (mTOR), an important regulator of protein synthesis and cell survival. TMEM127 thus acts as a tumor suppressor gene. TMEM127 germline mutations are transmitted in an autosomal dominant fashion. Yao et al already hypothesized a low penetrance since only 1 out of 4 of the cases described, had a clear positive family history, suggesting a penetrance much lower than 100%. Toledo et al estimated a cumulative penetrance varying from 0% at 0 to 20 years to 32% at 51 to 65 years. The parents of both patients here described, as well as the siblings of the first patient, were asymptomatic carriers, which is also compatible with a low penetrance. In the study of Yao et al TMEM127 mutations were identified in 2% (20/990) of the patients with a PCC. Until now, 104 TMEM127 germline mutation carriers have been described in the literature (Table 1). The majority of these mutation carriers develop bilateral PCC, but also adrenal PGL and head and neck paraganglioma (HNPGL) may also occur. According to the current literature, the median age at presentation of disease is 44 years, with a range from 16 to 80 years of age. This is clearly older than the median age at diagnosis in other PCC/PGL-associated germline mutation carriers and is more comparable with the age distribution of sporadic PCC/PGL. Malignant PCC/PGL defined as the presence of metastases, seems to be very rare. Renal cell carcinomas, however, have been described in patients with TMEM127 germline mutations. The optimal follow-up and surveillance for mutation carriers has not been established yet. In the Netherlands, TMEM127 mutation carriers are periodically examined according to the familial paraganglioma surveillance protocol including annual measurement of plasma metanephrines and MRI scanning of head and neck region once every 3 years (Dutch guideline for detecting hereditary tumors 2017, www.stoet.nl). Since the majority of TMEM127 mutation carriers develop a bilateral PCC which is in accordance to patients with multiple endocrine neoplasia type 2, adrenal-sparing surgery should be considered.

Both TMEM127 mutations observed in our patients are predicted to present loss-of-function mutations and are highly likely to have a deleterious character. Either because they lead to a so-called null allele (ie, no TMEM127 protein produced at all) or because they result in the synthesis of a truncated, non-functional TMEM127 protein. The c.410-2A > G p.(?) mutation (Case I) is located near the natural splice donor acceptor site of exon 3. The substitution abolishes this splice site, while strongly activating a nearby cryptic splice acceptor site, located at position c.418 within exon 4. Use of this cryptic splice acceptor site is expected to lead to the deletion of the first 8 bases from exon 4 in the mutant transcript. This deletion creates a frame shift starting at codon Leu138. The new reading frame ends in a stop codon, 11 positions downstream. Because the premature stop codon would be located in the last exon of the TMEM127 gene, non-sense-mediated mRNA-decay is unlikely to occur. We therefore postulate that the splice-site mutation would result in the synthesis of a C-terminally truncated, non-functional TMEM127 protein. The mutant protein could contain the normal N-terminal amino acids 1 until 137, followed by 11 missense amino acids. The shortened, 148-amino acid protein would lack the normal N-terminal amino acids 138 until 238. It is noteworthy that the effect of this c.410-2A > G p.(?) mutation on the natural and cryptic splice sites is predicted by all of the 5 splice prediction programs tested (SpliceSiteFinder-like, MaxEntScan, NNSPLICE, GeneSplicer and Human Splicing Finder). An identical effect on splicing is expected for the proven pathogenic TMEM127 mutation previously reported by others. The mutation c.410-2A > G p.(?) has not been described in literature before, although a mutation in the same nucleotide, but in a different substitution (ie, c.410-2A > C and c.410-1G > C) has been reported in 14 TMEM127 carriers. The clinical features of these carriers are shown in Table 2.
# Studies describing the clinical phenotype of heterozygous TMEM127 mutation carriers

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of carriers</th>
<th>Age in years (range)</th>
<th>PCC (bilateral)</th>
<th>sPGL</th>
<th>HNPGL</th>
<th>Malignant</th>
<th>Other neoplasms</th>
<th>Biochemical profile&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Tumor size (PCC/PGL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qin et al (2010)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>7</td>
<td>43 (25-72)</td>
<td>7 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yao et al (2010)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>43 (21-61)</td>
<td>13 (3)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>Breast carcinoma, papillary thyroid carcinoma</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Neumann et al (2011)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2</td>
<td>34, 51</td>
<td>1 (1)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>AML</td>
<td>13.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Burnichon et al (2011)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1</td>
<td>20</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>4.0 × 2.6 cm and 15.0 × 5.0 cm</td>
<td></td>
</tr>
<tr>
<td>Elston et al (2012)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>1</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>8</td>
<td>2.5</td>
</tr>
<tr>
<td>Takeichi et al (2012)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2</td>
<td>40, 48</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>17</td>
<td>3.7</td>
</tr>
<tr>
<td>Abermil et al (2012)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>6</td>
<td>43 (16-80)</td>
<td>6 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Range: 2.6-18</td>
<td>Range: 1.3-22</td>
<td>-</td>
</tr>
<tr>
<td>Lefebvre and Foulkes (2014)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>5</td>
<td>46 (16-80)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Toledo et al (2015)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>34</td>
<td>43 (22-55)</td>
<td>11 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>Median: 10 cm, range: 0.11-10.5 cm</td>
</tr>
<tr>
<td>Qin et al (2014)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>4</td>
<td>47 (45-67)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>RCC, breast carcinoma, prostate carcinoma</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Welander et al (2014)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>1</td>
<td>55</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>5.5 × 4.0 × 2.5 cm</td>
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</tr>
<tr>
<td>Curras-Freixes et al (2015)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2</td>
<td>28, 33</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hernandez et al (2015)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1</td>
<td>47</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>RCC</td>
<td>2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Patocs et al (2016)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>3</td>
<td>40 (22-51)</td>
<td>3 (2)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Saitoh et al (2017)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>1</td>
<td>42</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>AML, pancreatic adenocarcinoma, melanoma, colon carcinoma</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Bausch et al (2017)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>21</td>
<td>47 (18-76)</td>
<td>20 (10)</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Deng et al (2017)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>1</td>
<td>47</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>RCC</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AML, acute myeloid leukemia; HNPGL, head and neck paraganglioma; MN, metanephrines, NMN, normetanephrines; PCC, pheochromocytoma; RCC, renal cell carcinoma; sPGL, sympathetic paraganglioma.

<sup>a</sup> Median age at diagnosis.

<sup>b</sup> Urinary metanephrines, ratio of measured value divided by upper reference level.

<sup>c</sup> Yao et al without cohort of Qin et al.
The c.3G > A p.(Met1?) mutation (Case II) is located at the first methionine codon in the TMEM127 protein coding sequence, which represents the translation initiation codon in the open reading frame. The G-to-A nucleotide substitution replaces the ATG (methionine) codon by ATA in exon 2, the latter triplet encoding the amino acid isoleucine. Importantly, because the translation initiation codon is lost, no full-length TMEM127 protein is expected to be produced from the mutant allele. Either does this mutation lead to a so-called null allele (no protein synthesized) or to the use of the next ATG (methionine) codon in the normal open reading frame as the translation initiation codon. In the wild-type protein reference sequence, the second in-frame methionine codon is located at amino acid position 85 in exon 3. Use of this methionine would result in the synthesis of an N-terminally truncated TMEM127 protein which lacks the first 84 amino acids. In either case, no full-length, functional TMEM127 protein is likely to be synthesized from alleles harboring the c.3G > A p.(Met1?) mutation. This mutation c.3G > A p.(Met1?) is not described in the ExAC data set which contains more than 60,706 unrelated individuals. This supports a pathogenic nature of the c.3G > A p.(Met1?) mutation, well as the fact that this mutation has been recently described in 4 patients.

To our knowledge, homozygous TMEM127 germline mutations have not been reported before. Our findings raise the question to which extent the phenotype differs between patients harboring a heterozygous or a homozygous TMEM127 germline mutation. The homozygous TMEM127 mutation in these 2 patients did not result in a more severe clinical picture or earlier presentation of PCC/PGL. However, compared to heterozygous TMEM127 mutation carriers, both our cases demonstrated a more markedly elevated excretion of urinary metanephrines and 1 patient harbored a relatively large-sized PCC (Table 1). The age at diagnosis of the present cases was not different from the reported age distribution in heterozygous mutation carriers. Remarkably, both patients suffered from mental retardation. It remains unclear, however, whether mental retardation is causally related to homozygosity of the TMEM127 gene. Mental retardation occurs in up to 50% of the children of consanguineous parents and might therefore also be explained by homozygosity of other DNA regions. The dysmorphic features of the first patient also raise the question whether these might be associated with homozygosity of the TMEM127 mutation. Notably, the second patient did not have any dysmorphic features. Unfortunately, the family of both patients declined further genetic research. The fact that the endocrine phenotype does not differ much from heterozygous mutation carriers could theoretically be explained by imprinting; however, this phenomenon has not been described thus far for mutations of TMEM127. Moreover, chromosomal region 2q11.2 which harbors the TMEM127 locus is not known as an imprinting region. The genealogy of Toledo et al did not support a parent-of-origin inheritance effect. In view of loss of TMEM127 leads to increased mTOR signaling contributing to the pathogenesis of PCC and PGL, one would expect a more severe presentation in our 2 cases. However, a recent study by Oudijk et al showed a relatively low expression of the mTOR1C pathway in tumor tissue, implying that other until now unknown factors are important in the pathogenesis.

In contrast to our patients, homozygous or compound heterozygous carriers of mutations in other PCC/PGL-susceptibility genes demonstrated a severe clinical picture (Table 3). Homozygous mutations of the SDHx and FH genes result in neurodegenerative...

TABLE 2 Clinical features of carriers harboring a heterozygous TMEM127 c.410-2A > C mutation

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at diagnosis (y)</th>
<th>Hypertension</th>
<th>Location PGL</th>
<th>Bilateral</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (index)</td>
<td>F</td>
<td>33</td>
<td>+</td>
<td>PCC</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>43</td>
<td>+</td>
<td>PCC</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>52</td>
<td>+</td>
<td>PCC</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>47</td>
<td>+</td>
<td>PCC</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>54</td>
<td>−</td>
<td>PCC</td>
<td>−</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>37</td>
<td>+</td>
<td>PCC</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>47</td>
<td>+</td>
<td>PCC</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>35</td>
<td>−</td>
<td>PCC</td>
<td>−</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>55</td>
<td>−</td>
<td>PCC</td>
<td>−</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>33</td>
<td>+</td>
<td>PCC</td>
<td>−</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>22</td>
<td>+</td>
<td>PCC</td>
<td>−</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>34</td>
<td>ND</td>
<td>PCC</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>37</td>
<td>ND</td>
<td>PCC</td>
<td>−</td>
</tr>
<tr>
<td>14*</td>
<td>M</td>
<td>45</td>
<td>ND</td>
<td>PCC</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; ND, not described; PCC, pheochromocytoma; PGL, paraganglioma. * c.410-1G > C mutation.

TABLE 3 Clinical presentation homozygous germline mutations in PCC/PGL susceptibility genes

<table>
<thead>
<tr>
<th>Clinical features</th>
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<tr>
<td>SDHA</td>
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<td>SDHB</td>
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<td>SDHD</td>
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<tr>
<td>VHL</td>
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<tr>
<td>FH</td>
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<tr>
<td>RET</td>
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Abbreviations: FH; fumarate hydratase; PCC; pheochromocytoma; PGL; paraganglioma; RET; rearranged during transfection; SDH (A, B, D); succinate dehydrogenase subunit A, B, D; VHL; von Hippel Lindau.
disorders. Homozygous SDHA mutations may result in Leigh syndrome, a progressive neurodegenerative disorder that is characterized by subacute necrotizing encephalomyelopathy during infancy resulting in epilepsy, psychomotor retardation and spasticity. Alston et al reported a patient with a homozygous SDHB mutation (c.143A > T; pAsp48Val) presenting with neurological complications of leukodystrophy with clinical signs of hypotonia due to accumulated succinate demonstrated by magnetic resonance spectroscopy. Homozygous SDHD mutations have been associated with encephalopathy. Furthermore, homozygous mutations in the FH gene may result in neurodegenerative disorders, such as progressive encephalopathy with dystonia and seizures. Homozygous mutations in the VHL-gene have been associated with congenital polycythemia. Lecube et al described 4 patients with homozygous RET mutation, 2 patients presented with medullary thyroid carcinoma. To our knowledge, homozygous mutations in the PHD2, IDH, HIF2a, MDH2, MAX, H-RAS, KIF1B genes have not been described.

In conclusion, homozygosity for an autosomal dominant disorder is an extremely rare phenomenon and has not been reported previously for the gene encoding TMEM127. The clinical picture in these 2 patients seems to be different from heterozygous mutation carriers with respect to biochemical profile and tumor size, but it is not accompanied by a younger age at diagnosis. It is unclear whether the mental retardation in both cases is causally related to the homozygous TMEM127 mutation. The present case furthermore illustrates the importance of updating genetic screening in patients who were diagnosed with a PCC/PGL in the past.

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Conflict of interest
The authors do not have any financial or other conflict of interest to declare.

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REFERENCES


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