




OPEN ACCESS

ORIGINAL RESEARCH

# Germline mutations in the new E1' cryptic exon of the *VHL* gene in patients with tumours of von Hippel-Lindau disease spectrum or with paraganglioma

Alexandre Buffet <sup>1</sup>, Bruna Calsina,<sup>2</sup> Shahida Flores,<sup>3</sup> Sophie Giraud,<sup>4,5</sup> Marion Lenglet,<sup>6,7</sup> Pauline Romanet,<sup>8</sup> Elisa Deflorenne,<sup>1</sup> Javier Aller,<sup>9</sup> Isabelle Bourdeau,<sup>10</sup> Brigitte Bressac-de Paillerets,<sup>5,11</sup> María Calatayud,<sup>12</sup> Caroline Dehais,<sup>13</sup> Erwan De Mones Del Pujol,<sup>14</sup> Atanaska Elenkova,<sup>15</sup> Philippe Herman,<sup>16</sup> Peter Kamenický,<sup>17</sup> Sophie Lejeune,<sup>5,18</sup> Jean Louis Sadoul,<sup>19</sup> Anne Barlier,<sup>5,8</sup> Stephane Richard,<sup>5,6,20</sup> Judith Favier,<sup>1</sup> Nelly Burnichon,<sup>1,21</sup> Betty Gardie,<sup>6,7</sup> Patricia L Dahia,<sup>3</sup> Mercedes Robledo,<sup>2</sup> Anne-Paule Gimenez-Roqueplo<sup>1,5,21</sup>

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/jmedgenet-2019-106519>).

For numbered affiliations see end of article.

## Correspondence to

Dr Alexandre Buffet, Université de Paris, PARCC, INSERM, Equipe Labellisée par la Ligue contre le Cancer, F-75015, Paris, France; alexandre.buffet@inserm.fr

BC, SF, SG and ML contributed equally.

Received 22 August 2019  
Revised 3 January 2020  
Accepted 6 January 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Buffet A, Calsina B, Flores S, et al. *J Med Genet* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jmedgenet-2019-106519

## ABSTRACT

**Backgrounds** The incidence of germline mutations in the newly discovered cryptic exon (E1') of *VHL* gene in patients with von Hippel-Lindau (VHL) disease and in patients with paraganglioma or pheochromocytoma (PPGL) is not currently known.

**Methods** We studied a large international multicentre cohort of 1167 patients with a previous negative genetic testing. Germline DNA from 75 patients with a single tumour of the VHL spectrum ('Single VHL tumour' cohort), 70 patients with multiple tumours of the VHL spectrum ('Multiple VHL tumours' cohort), 76 patients with a VHL disease as described in the literature ('VHL-like' cohort) and 946 patients with a PPGL were screened for E1' genetic variants.

**Results** Six different genetic variants in E1' were detected in 12 patients. Two were classified as pathogenic, 3 as variants of unknown significance and 1 as benign. The rs139622356 was found in seven unrelated patients but described in only 16 patients out of the 31 390 of the Genome Aggregation Database ( $p < 0.0001$ ) suggesting that this variant might be either a recurrent mutation or a modifier mutation conferring a risk for the development of tumours and cancers of the VHL spectrum.

**Conclusions** *VHL* E1' cryptic exon mutations contribute to 1.32% (1/76) of 'VHL-like' cohort and to 0.11% (1/946) of PPGL cohort and should be screened in patients with clinical suspicion of VHL, and added to panels for Next Generation Sequencing (NGS) diagnostic testing of hereditary PPGL. Our data highlight the importance of studying variants identified in deep intronic sequences, which would have been missed by examining only coding sequences of genes/exons. These variants will likely be more frequently detected and studied with the upcoming implementation of whole-genome sequencing into clinical practice.

## INTRODUCTION

Von Hippel-Lindau (VHL) disease is an autosomal-dominant renal cancer predisposition syndrome<sup>1</sup>

responsible for the development in affected patients of renal cysts or clear cell carcinomas, and other features as retinal or central nervous system haemangioblastomas, pancreatic cysts or neuroendocrine tumours, endolymphatic sac tumours and pheochromocytomas and/or paragangliomas (PPGLs). A germline mutation (including gross deletion) is identified in one of the three exons of *VHL* in almost all affected patients.<sup>2</sup> Nevertheless, some patients with clinically diagnosed VHL disease, but without identified *VHL* germline mutation, have been reported.<sup>3</sup> One of the tumour types of the VHL tumour spectrum, PPGL, are rare neuroendocrine tumours with a great genetic heterogeneity and the highest heritability rate with about 40% of genetically determined forms.<sup>4,5</sup> Indeed, to date, approximately 17 susceptibility genes have been reported but two thirds of identified mutations are found in *SDHB*, *SDHD* and *VHL* genes.<sup>6,7</sup>

Recently, a cryptic exon of *VHL* gene, named E1', has been discovered. A germline mutation in the first intronic region which results in creation of a cryptic exon designated E1' was found in one large family with a typical VHL disease and without any alteration in the other *VHL* exons.<sup>8</sup> *VHL* gene is one of the major PPGL susceptibility genes but, to date, E1' exon has not been included in PPGL target gene panels.

Hence, our objective was to assess the prevalence of E1' germline mutations in two international cohorts of patients: first, in 221 patients with a single or multiple tumours suggesting a VHL disease and then in 946 with a PPGL but without an identified mutation in the three *VHL* exons or in the main PPGL susceptibility genes, respectively.

## METHODS

### Patient's selection

A total of 1167 patients were analysed, divided into four different groups:

**Table 1** Main clinical and tumour characteristics of the different cohorts

Total patients n=1167	
<i>VHL-like</i> , n=76 patients	
Age at first diagnosis mean (min-max)	45.4 (20–76)
Multiple haemangioblastomas	16 (21%)
Haemangioblastoma with another VHL tumour	28 (37%)
One VHL tumour and family history of VHL tumour	32 (42%)
<i>Multiple VHL tumours</i> , n=70 patients	
Age at first diagnosis mean, (min-max)	55 (11–81)
Three or more VHL tumours	3 (4%)
Two VHL tumours	67 (96%)
<i>Single VHL tumour</i> , n=75 patients	
Age at first diagnosis mean (min-max)	34.6 (11–78)
Clear cell renal cell carcinoma	3 (4%)
Cerebral haemangioblastoma	27 (36%)
Retinal haemangioblastoma	10 (13.3%)
Other tumours	35 (46.6%)
<i>PPGL</i> , n=946 patients	
Age at first diagnosis mean (min-max)	43 (8–94)
Benign PPGL	869 (92%)
Single benign PPGL	771 (82%)
Multiple benign PPGL	98 (10%)
Metastatic PPGL	77 (8%)
Single metastatic PPGL	67 (7%)
Multiple metastatic PPGL	10 (1%)
Familial PPGL	17 (2%)

PPGL, paraganglioma; VHL, von Hippel-Lindau.

- ▶ 946 patients with PPGL but without germline mutation in major PPGL susceptibility genes ('PPGL cohort') (table 1 and online supplementary table S1).
- ▶ 76 patients with a VHL disease as defined in the literature,<sup>2,9</sup> that is, patients with multiple haemangioblastomas, or a single haemangioblastoma with another tumour of the VHL spectrum, or one tumour of the VHL spectrum (excepted epididymal and renal cysts) and family history of VHL tumour but no germline *VHL* gene mutation ('VHL-like' cohort).
- ▶ 70 patients with multiple tumours of the clinical spectrum of VHL disease but who did not fill the definition of a VHL disease and who had no germline *VHL* mutation ('Multiple VHL tumours' cohort).
- ▶ 75 patients with a single tumour of the VHL spectrum without *VHL* mutation occurring at a young age ('Single VHL tumour' cohort) (table 1 and online supplementary table S2).

Germline DNA from 'VHL-like', 'Multiple VHL tumours' and 'Single VHL tumour' cohorts had been previously tested for *VHL* gene by Sanger sequencing or Next Generation Sequencing and large rearrangements by MLPA or QMPSE. The procedures used for PPGL diagnosis were in accordance with international guidelines.<sup>10,11</sup>

Moreover, a control cohort of 198 European subjects without VHL manifestation was analysed in order to determine the frequency of variant in the general population.

Each patient signed a written informed consent for genetic analyses.

## Direct sequencing of the E1' cryptic exon of *VHL* on germline DNA

Sanger sequencing on germline DNA of E1' was performed as previously described.<sup>8</sup> Variants interpretation was performed by using different criterions: ACMG criteria,<sup>12</sup> allele frequency in databases, phenotype of patients and tumour analysis as described below.

## *VHL* gene analysis in tumour

Tumour DNA was extracted from frozen or paraffin embedded tumour by the QIAamp DNA minikit (Qiagen). Loss of heterozygosity (LOH) was evaluated by (1) Sanger sequencing of the E1' cryptic exon of *VHL* by mutation-specific primers and (2) microsatellite analysis on D3S1537, D3S1038, D3S1317 D3S3547, D3S3727 as previously described.<sup>13,14</sup> *VHL* gene deletion on tumour DNA was assessed with the *SALSA MLPA P016 VHL* probemix (MRC-Holland).

## CA9 immunohistochemistry

Immunohistochemistry was performed as previously described on 6 µm slides cut from paraffin-embedded tumours with anti CA9 antibody (1/1500, ab15086, Abcam).<sup>15</sup> Antigen retrieval was performed by boiling slides in Tris-EDTA buffer (pH9) for 45 min. Revelation was performed using Histogreen as a chromogen. Images were acquired with a Leica DM400B microscope with Leica Application Suite software V2.8.1 and a Leica DFC420C camera.

## *PNMT* and *VHL* RT-qPCR

RNA was extracted from paraffin embedded tumours of six control PPGL (3 *NF1*-related, 2 *RET*-related and 1 *TMEM127*-related PPGL), 5 *VHL*- related PPGL (all carrying a missense mutation in *VHL* gene) and patients #3 and #10 PPGL by using the Maxwell 16 LEV RNA FFPE Purification Kit (Promega). RNA was quantified and its purity assessed with a NanoDrop ND-1000 spectrophotometer (Labtech). RT PCR was performed on 1000 ng of RNA with iScript cDNA Synthesis Kit iScript (BioRad). Then, as described in,<sup>16</sup> pre amplification of *PNMT*, *VHL*, *GAPDH* and *18S* on complementary DNA was performed with SsoAdvanced PreAmp Supermix (BioRad). Because of RNA fragmentation, all primers were designed to amplify amplicons smaller than 100 bp. We used two *VHL* primer sets. The first set amplified the *VHL* transcript including exons 1 and 2 (E1-E2) (F: 5'-CATCCACAGCTACCGAGGTC-3' overlapping exons 1 and 2 and R: 5'-GTGTGTCCCTGCATCTCTGA-3' located on exon 2). The second set amplified the *VHL* transcript with exon 1 and the cryptic exon (E1-E1') (F: 5'-GCATCCACAGC-TACCGAGTC-3' overlapping exon 1 and the cryptic exon and R: 5'-AGTCTCCCCAGGAGGAATGT-3' located on the cryptic exon). Quantitative PCR was performed on *VHL* (E1-E2), *PNMT*, *GAPDH* and *18S* by SYBR Green Master MixSybrGreen (BioRad) on the C1000 Touch (BioRad) and *VHL* (E1-E1') was amplified by PCR in parallel with *GAPDH*. All experiments were performed in duplicate three times.

## Statistical analysis

Statistical analysis was carried out with GraphPad software. Differences between allele's frequency in gnomAD and our cohort of patients and relative risk were assessed by  $\chi^2$  tests. A  $p < 0.05$  was considered significant.

## RESULTS

We analysed the germline DNA of 1167 patients from France, Spain, Canada and the USA. We identified a rare germline

Table 2 Patients with a genetic variant in the E1' cryptic exon of VHL gene

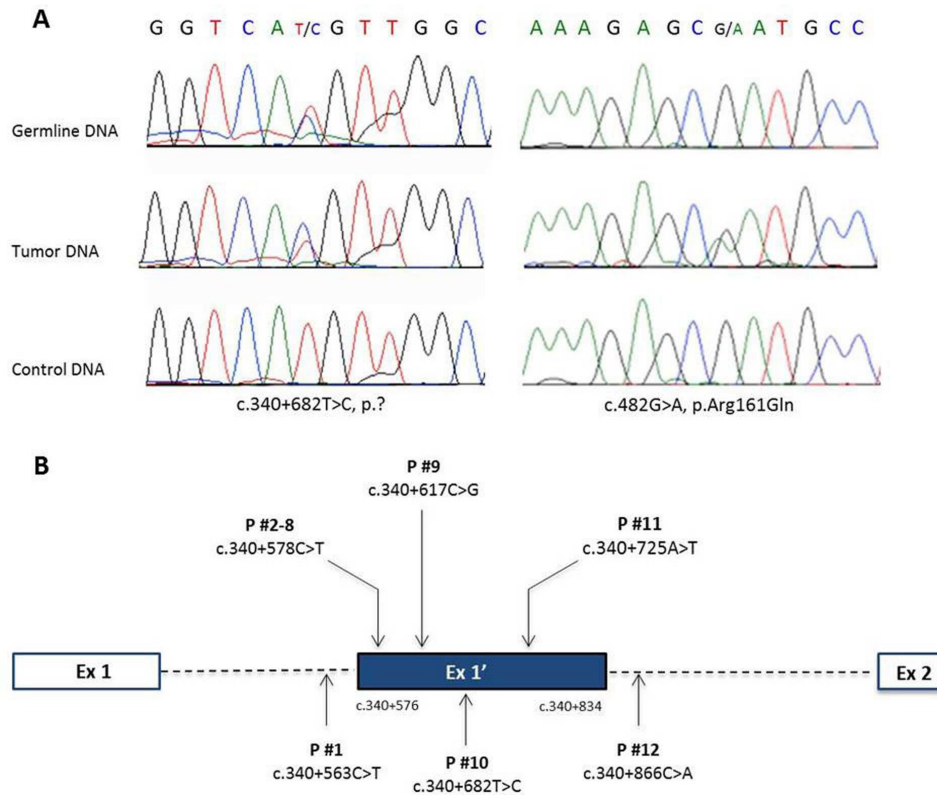
Patient number	Phenotype (age at first diagnosis)	Follow-up duration (years)	Germline genetic variant	dbSNP ID	Allele frequency* (%)	LOH	Somatic VHL mutation	CAIX IHC	PMMT and VHL (E1-E2) expression		Classification of VUS
									VHL (E1-E1' expression)	VHL (E1-E2) expression	
#1	Carotid body PGL (47)	5	c.340+563C>T		NA	Not	ND	Neg	ND	ND	Benign
#2	Carotid body PGL (34)	1	c.340+578C>T	rs139622356	0.05	NA	NA	NA	NA	NA	VUS
#3	PCC (38)	7	c.340+578C>T	rs139622356	0.05	No	No	Neg	Normal	Increase	VUS
#4	Carotid body PGL (74)	1	c.340+578C>T	rs139622356	0.05	NA	NA	NA	NA	NA	VUS
#5	Carotid body PGL (56)	1	c.340+578C>T	rs139622356	0.05	NA	NA	NA	NA	NA	VUS
#6	PGL+ccRCC (81–82)	2	c.340+578C>T	rs139622356	0.05	NA	NA	NA	NA	NA	VUS
#7	bilccRCC (49–51)	NA	c.340+578C>T	rs139622356	0.05	NA	NA	NA	NA	NA	VUS
#8	ccRCC (39)	NA	c.340+578C>T	rs139622356	0.05	NA	NA	NA	NA	NA	VUS
#9	Multiple retinal HMB (36)	32	c.340+617C>G†		NA	NA	NA	NA	NA	NA	Pathogenic
#10	PCC (11)	15	c.340+682T>C		NA	No	c.482G>A p.R161Q	Pos	Decrease	Increase	Pathogenic
#11	Multiple HN PGL (12)	1	340+725A>T		NA	NA	NA	NA	NA	NA	VUS
#12	PCC (34)	10	c.340+866C>A	rs5366931685	0.02	NA	NA	NA	NA	NA	VUS

\*Frequency in gnomAD or 1000 Genomes.

†Loss of the mutated allele.

#Mutation described in Lenglet et al.<sup>8</sup>

bilccRCC, bilateral clear cell renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; HMB, haemangioblastoma; HN, head and neck; LOH, loss of heterozygosity; NA, none available; ND, not done; Neg, negative immunohistochemistry; PCC, pheochromocytoma; PGL, paraganglioma; Pos, positive immunohistochemistry; VHL, von Hippel-Lindau; VUS, variant of uncertain significance.



**Figure 1** *VHL* E1' variants identified: mutations identified in patient #10 on the germline DNA and somatic DNA (A); location of germline variants found in *VHL* E1' (B).

genetic variant (minor allele frequency <1%) in the E1' *VHL* cryptic exon in 12 patients (1%). One of these patients was classified as 'VHL-like' (1 of 76 patients, 1.3%), 2 as 'Multiple VHL tumours' (2/70 patients, 2.9%), 1 as 'Single VHL tumour' (1/75 patients, 1.3%) and 8 belonged to the 'PPGL' cohort (8/946, 0.8%) (table 2). Among these 12 patients, we identified 6 different variants, 4 in the E1' and 2 at the intron-exon junction and we considered only two variants as pathogenic mutations (figure 1). None of these variants was found in a control cohort of 198 European subjects without VHL manifestations.

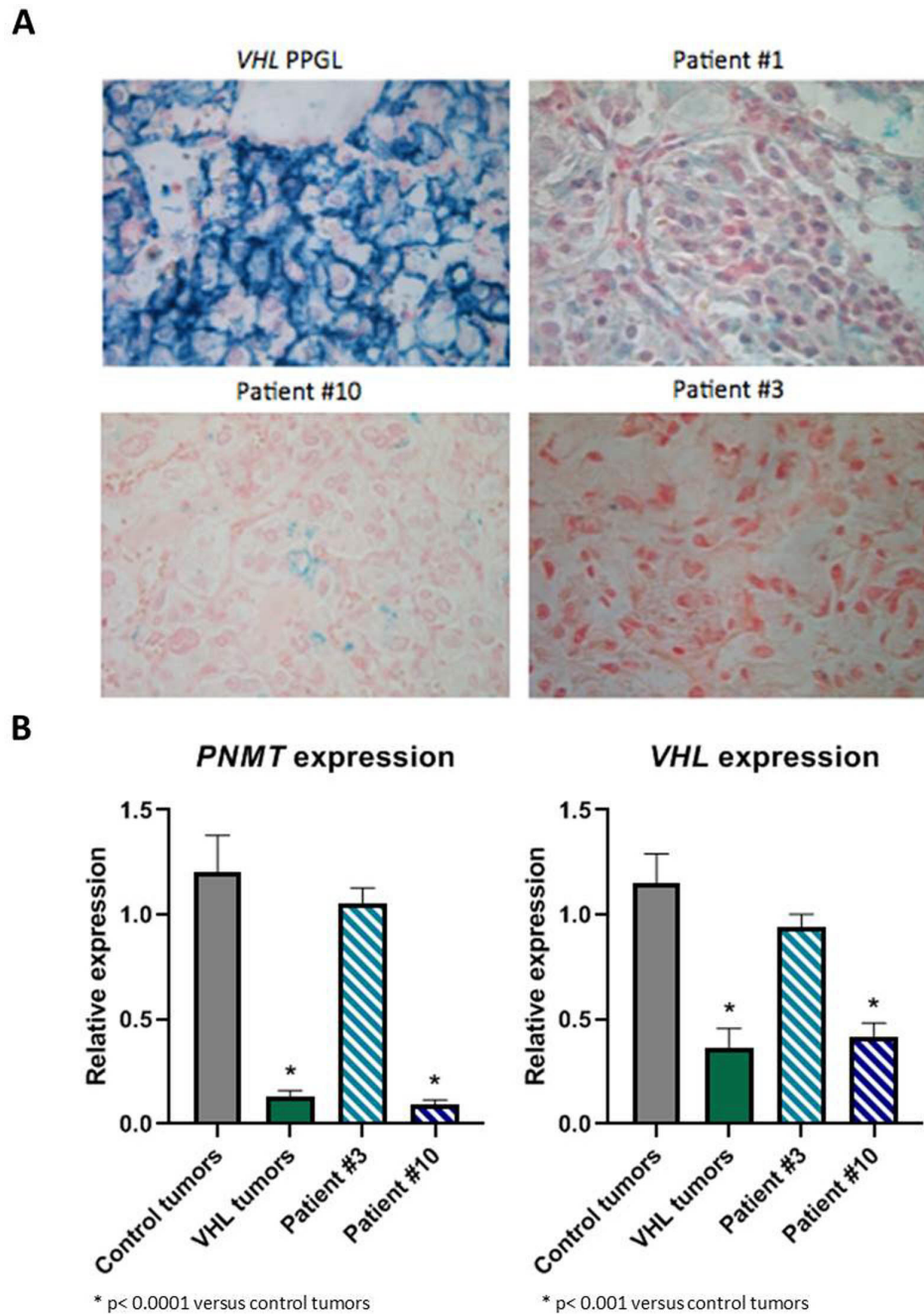
Seven patients (patients #2 to #8) (0.6%) carried the same rare variant of uncertain significance (VUS), c.340+578C>T which is referenced in dbSNP as rs139622356 and has been previously reported in the Genome Aggregation Database (gnomAD). The five remaining patients carried different E1' variants. One of them (patient #9) harbours the c.340+617C>G mutation previously described in the original paper.<sup>8</sup> Patient #12 carried the c.340+866C>A VUS, which is referenced in dbSNP (rs536631685) and 1000 Genomes, but not in the Genome Aggregation Database (gnomAD). Finally, three novel VUS of the E1' *VHL* cryptic exon were discovered in the three remaining patients. None of the four patients with a PPGL and an E1' VUS have developed VHL spectrum tumour(s) during their follow-up and none of them had family history of VHL disease (table 2); however, segregation analysis was only performed in patient #9. The proband's mother did carry the variant and had a pancreatic cyst and multiple vertebral body haemangiomas which both are evocating of VHL disease.<sup>17</sup>

Among the remaining 11 patients, 3 tumours were available, 2 as paraffin embedded samples (patients #1, #10) and 1 as a frozen tumour (patient #3). None of them presented a LOH at *VHL* locus and the mutated allele was lost as determined by

Sanger sequencing in tumour #1. In tumour DNA of patient #10, which harbours the c.340+682T>C variant, we identified a second variant in the exon 3 of *VHL* (c.482G>A; p.Arg161Gln), known to be pathogenic (figure 1). This somatic mutation was previously described in this patient.<sup>18</sup> In the absence of LOH, this exon 3 variant may function as the second *VHL* hit in this tumour. No other mutation of the *VHL* gene was identified in tumour DNA of patient #3.

To validate and classify these different VUS, we carried out different functional studies on available tumour tissues. We first performed immunohistochemistry to study the expression of CA9, known to be expressed at the membrane of tumour cells in case of VHL inactivation.<sup>19</sup> A membranous positive CA9 immunostaining has been previously reported in *VHL*-related PPGL, haemangioblastoma, endolymphatic tumours and ccRCC.<sup>15 20 21</sup> We observed a cluster of tumour cells with a positive membranous CA9 immunostaining only in the PPGL of patient #10 (figure 2A) which can be seen in *VHL*-related PPGL.<sup>15</sup> Then, we assessed the expression of *PNMT* gene, which is one of the most downregulated genes in *VHL*-related PPGL,<sup>22 23</sup> by RT-qPCR. As expected, the PPGL of patient #10 exhibited a significant low expression of *PNMT* mRNA, comparable to the *VHL*-tumours used as controls. On the contrary, the level of *PNMT* expression was equivalent to control tumours in the PPGL of patient #3, which produced both epinephrine and norepinephrine. Finally, we analysed the expression of *VHL* gene by RT-qPCR. We assessed the expression of two different *VHL* mRNA: the mRNA containing the exons 1 and 2 (E1-E2), which will lead with the exon 3 to the expression of the two main VHL proteins (pVHL213 and pVHL160) and *VHL* mRNA containing the exon 1 and E1' (E1-E1'), which was previously described as increased in tumour or in lymphoblastoid cell lines





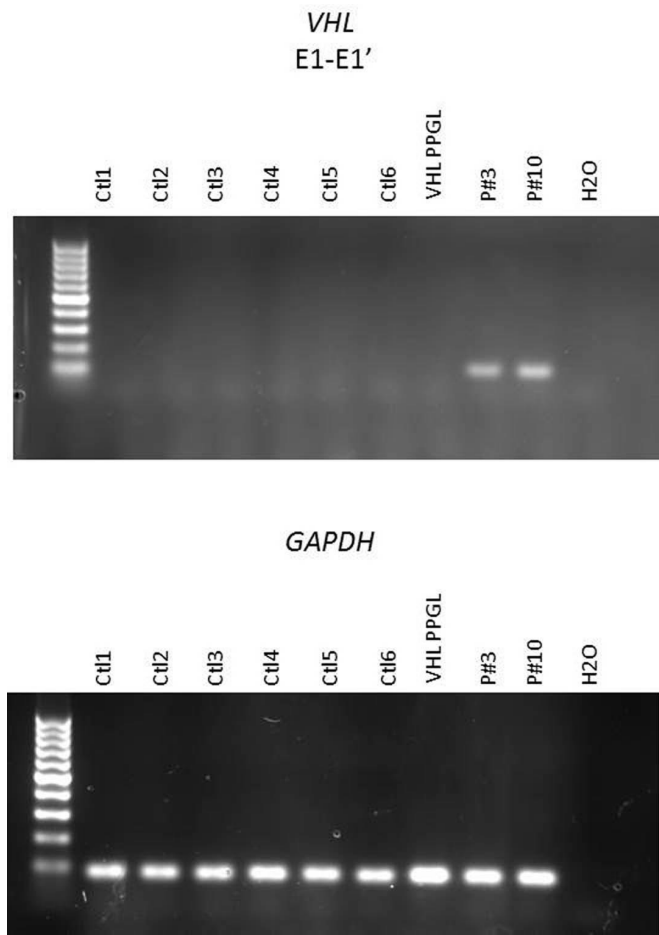
**Figure 2** CA9 immunochemistry in patients tumours with a *VHL* E1' mutation showed a membranous immunostaining on a cluster of cells in patient #10 PPGL (A). *PNMT* and *VHL* (E1-E2 transcript) genes expression by RT-qPCR in patients #3 and #10 showed a low expression of the two genes in patient #10 tumours (B).

of patients with E1' mutation. In normal condition, this *VHL* E1-E1' mRNA is degraded by nonsense-mediated decay (NMD), and in this pathological condition, NMD may be overwhelmed. The PPGL of patients #3 and #10 showed expression of *VHL* E1-E1' mRNA which was absent in controls, suggesting that the two variants change the *VHL* mRNA splicing (figure 3). Moreover, the PPGL of patient #10 showed a low expression of *VHL* E1-E2 mRNA comparable to the *VHL*-related PPGL used as control (figure 2B). Altogether, these data provide evidence that this *VHL* E1' mutation (c.340+682T>C) is a pathogenic mutation that combined with the second mutation (c.482G>A; p.Arg161Gln) induce tumorigenesis.

Finally, 23 patients carry the c.340+648T>C (rs73024533) variant, previously described in dbSNP, at a heterozygous state. The allele frequency of rs73024533 in our cohort is comparable to that of the gnomAD database and of our control cohort of 198 European subjects (1.9% vs 1.3% and 1.3%, respectively,  $p=0.0536$ ).

## DISCUSSION

E1' mutations were previously described by Lenglet *et al* in eight families, either with erythrocytosis or VHL disease. These mutations led to an abnormal *VHL* mRNA with the insertion of the



**Figure 3** Expression of E1-E1' transcript of *VHL* gene showed expression only in patients #3 and #10.

E1' in the transcript and to mRNA degradation by NMD and to global defect in *VHL* protein expression.<sup>8</sup>

In our large international study, we identified four new germline variants in E1' *VHL* gene and we classified two of them as pathogenic, representing 1.3% of 'VHL-like' cohort (1/76 patients) and 0.11% of 'PPGL' cohort (1/946 patients). Our patients did not have all the manifestation of *VHL* disease. However, in the single patient in whom a familial genetic screening was performed (patient #9), the proband's mother had her first screening (cerebral and medullary MRI and abdominal CT scan) at the age of 70 years old, which diagnosed one pancreatic cyst and multiple vertebral body haemangiomas. Interestingly, multiple vertebral body haemangiomas are rare in *VHL* disease but have been described in patients with Chuvash polycythemia, a disease secondary to a recurrent germline biallelic mutation in *VHL* gene (c.598C>T, p.Arg200Trp).<sup>24</sup> Our data suggest incomplete penetrance of E1' *VHL* mutations, as it was previously described for the *SDHA* gene-another PPGL susceptibility gene- mutations that exhibit a relatively high allele frequency in gnomAD.<sup>25</sup>

We have identified the same variant c.340+578C>T (rs139622356) in seven patients, but our tumour analyses were not able to lead to the classification of this variant in a pathogenic variant. Indeed in one tumour with this variant, we identified the E1-E1' mRNA which suggest that the variant is pathogenic. However, epinephrine secretion and *PNMT* expression of this tumour are strong indicator against the diagnosis of *VHL*-related PPGL.<sup>26</sup> Moreover, we identified this variant in 0.6% of our

cohort, which is 10 times more frequent in our cohort than in reference databases. Indeed, this variant is described in 0.05% of gnomAD subjects (7/1167 vs 16/31 390,  $p < 0.0001$ ). It is noteworthy that in Tuscan and Iberian subjects reported in the 1000 Genomes project, the frequency of this rs139622356 is 0.9%. All these data suggest that this variant could be either a pathogenic variant that is not implicated in the PPGL of our patient because of the lack of LOH/second *VHL* mutation, or a modifier variant contributing potentially to an 8.5-fold risk (95% CI 4.4 to 14.3,  $p < 0.0001$ ) for development of PPGL or *VHL* tumours. Hence, more functional analyses and more tumours analyses will be required to achieve a definitive conclusion.

Our study demonstrates that E1' *VHL* variants are rare events in 'VHL-like' and 'PPGL' patients, but nearly as frequent as the *VHL* mutation rate in exons 1 and 2 in patients with PPGL (in the molecular genetic laboratory of Hôpital Européen Georges Pompidou-Paris-France *VHL* mutation rate in exon 1 has been reported to be 0.74% ( $p = 0.062$ ), in exon 2: 0.18% ( $p = 0.99$ ) and in exon 3: 0.92% ( $p = 0.0264$ ),<sup>27</sup> or as frequent as in exons of other PPGL susceptibility genes (for instance, the mutation rate in exon 1 of *SDHD* is 0.43%). However, because patients with well-established *VHL* pathogenic mutations were excluded from our cohort, the current frequency may be an underestimation. As the identification of *VHL* variants has important implications for management and follow-up of patients and relatives, we suggest that E1' cryptic exon should be added to NGS diagnostic panels. Considering the genetic heterogeneity of PPGLs and the high rate of detectable driver mutations in these tumours,<sup>10</sup> a low frequency of variants in any given new gene/exons is not unexpected. However, the interpretation of these E1' variants might be difficult and more functional analyses has to be designed in order to validate these variants. Finally, our study underlines the importance of variants identified in deep intronic sequences, which would have been missed by examining only coding sequences of genes/exomes. These variants will likely be more frequently detected and studied in the next future with the upcoming implementation of whole-genome sequencing into clinical practice.

#### Author affiliations

<sup>1</sup>Université de Paris, PARCC, INSERM, Equipe Labellisée par la Ligue contre le Cancer, F-75015, Paris, France

<sup>2</sup>Hereditary Endocrine Cancer Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain; and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain

<sup>3</sup>Division of Hematology and Medical Oncology, Department of Medicine, Mays Cancer Center, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

<sup>4</sup>Genetics Department, Hospices Civils de LYON (HCL), University Hospital, East Biology and Pathology Center, B-A3, 59 Bld Pinel, 69677, Bron, France

<sup>5</sup>Réseau National pour Cancers Rares PREDIR labellisé par l'Institut National contre le Cancer, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France

<sup>6</sup>École Pratique des Hautes Études, PSL Research University, Paris, France

<sup>7</sup>L'Institut du Thorax, INSERM, Centre National de la Recherche Scientifique (CNRS), Université de Nantes, Nantes, France

<sup>8</sup>Aix Marseille Univ, APHM, INSERM, MMG, Laboratory of Molecular Biology Hospital La Conception, Marseille, France

<sup>9</sup>Endocrinology and Nutrition Service. Hospital Universitario Puerta de Hierro, 28222, Majadahonda, Spain

<sup>10</sup>Division of Endocrinology, Department of Medicine, Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Université de Montréal, Montréal, Quebec, Canada

<sup>11</sup>Gustave Roussy, Université Paris-Saclay, Département de Biopathologie and INSERM U1186, Villejuif, F-94805, France

<sup>12</sup>Department of Endocrinology and Nutrition, Hospital Universitario 12 de Octubre, 28041 Madrid, Spain

<sup>13</sup>Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires La Pitié Salpêtrière-Charles Foix, Service de Neurologie 2-Mazarin, Paris, France

<sup>14</sup>Service ORL, Hôpital Pellegrin, CHU de Bordeaux, Bordeaux, France

<sup>15</sup>Department of Endocrinology, USHATE "Acad. Ivan Penchev", Medical University Sofia, Sofia, Bulgaria

<sup>16</sup>Assistance Publique, Hôpitaux de Paris, Service ORL-CCF, hôpital Lariboisière, université Paris VII, Paris, France

<sup>17</sup>Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse, Le Kremlin Bicêtre, France

<sup>18</sup>Department of Clinical Genetics, Centre Hospitalier Régional et Universitaire de Lille, Lille, France

<sup>19</sup>Service d'Endocrinologie, Hôpital de L'Archet, CHU de Nice, Nice, France

<sup>20</sup>Génétique Oncologique EPHE, INSERM U1186, Gustave Roussy Cancer Campus, Villejuif, France

<sup>21</sup>Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Génétique, Paris, France

**Acknowledgements** We thank Catherine Tritscher for administrative assistance and Caroline Travers, Valentin Adamus and Astrid Ramahefasolo for technical assistance. We also thank Pr Pascal Pigny for his help and the PREDIR and TENGEN networks for their help in patient enrolment. The authors would like to express their gratitude to Sophie Devaux for her help.

**Contributors** APGR conceived and supervised the study. ABu, APGR, MR, PLD and BG designed the study and analysed the results. JF and NB participated to the data analysis. ABu., BC, SF, SG, ML and ED designed and performed the experiments. PR, JA, IB, BbP, MC, CD EdM, AE, PH, PK, SL, JLS, ABa, SR, BG, PLD, MR and APGR collected subjects and clinical parameters. ABu and APGR wrote the manuscript. ABu prepared the figures and the tables. All the authors discussed the results and commented the manuscript.

**Funding** ABu received a financial support from ITMO Cancer AVIESAN (Alliance Nationale pour les Sciences de la Vie et de la Santé, National Alliance for Life Sciences & Health) within the framework of the Cancer Plan and from la Fondation pour la Recherche Médicale (FDT20170436955). SF is currently supported by an NIH-NIGMS individual predoctoral fellowship grant (F31-GM131634-01) and, previously, by an NIH NRSA Institutional Predoctoral Training Grant T32CA148724 and NRSA F31-GM131634-01. PLD receives funding support from NIH-GM114102, Alex's Lemonade Stand Cancer Foundation (Innovation Award) and the NCATS- UL1 TR002645. The Genomic Sequencing Facility at the GCCRI is supported by the P30-CA54174 (CTRC at UTHSCSA) and NIH Shared Instrument grant 1S10DD021805-01 (S10 grant). BC is supported by Rafael del Pino Foundation. MR receives funding support from Instituto de Salud Carlos III (ISCIII), through the 'Acción Estratégica en Salud' (AES) (projects P117/01796), cofounded by the European Regional Development Fund (ERDF), and the Paradifference Foundation.

**Disclaimer** The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All available data are in the article.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Alexandre Buffet <http://orcid.org/0000-0002-4742-2708>

#### REFERENCES

- Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, Stackhouse T, Kuzmin I, Modi W, Geil L. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science* 1993;260:1317–20.
- Lonser RR, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM, Oldfield EH, disease vonH-L. Von Hippel-Lindau disease. *Lancet* 2003;361:2059–67.
- Binderup MLM, Galanakis M, Budtz-Jørgensen E, Kosteljanetz M, Luise Bisgaard M, Prevalence LBM. Prevalence, birth incidence, and penetrance of von Hippel-Lindau disease (vHL) in Denmark. *Eur J Hum Genet* 2017;25:301–7.
- Favier J, Amar L, Gimenez-Roqueplo A-P. Paraganglioma and pheochromocytoma: from genetics to personalized medicine. *Nat Rev Endocrinol* 2015;11:101–11.
- Gimenez-Roqueplo A-P, Dahia PL, Robledo M. An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. *Horm Metab Res* 2012;44:328–33.
- Amar L, Bertherat J, Baudin E, Ajzenberg C, Bressac-de Paillerets B, Chabre O, Chamontin B, Delemer B, Giraud S, Murat A, Niccoli-Sire P, Richard S, Rohmer V, Sadoul J-L, Strompf L, Schlumberger M, Bertagna X, Plouin P-F, Jeunemaitre X, Gimenez-Roqueplo A-P. Genetic testing in pheochromocytoma or functional paraganglioma. *J Clin Oncol* 2005;23:8812–8.
- Currás-Freixes M, Piñero-Yañez E, Montero-Conde C, Apellániz-Ruiz M, Calsina B, Mancikova V, Remacha L, Richter S, Ercolino T, Rogowski-Lehmann N, Deuschlein T, Calatayud M, Guadalupe S, Álvarez-Escolá C, Lamas C, Aller J, Sastre-Marcos J, Lázaro C, Galofré JC, Patiño-García A, Meoro-Avilés A, Balmaña-Gelpi J, De Miguel-Novoa P, Balbín M, Matías-Guiu X, Letón R, Inglada-Pérez L, Torres-Pérez R, Roldán-Romero JM, Rodríguez-Antona C, Fliedner SMJ, Opocher G, Pacak K, Korpershoek E, de Krijger RR, Vroonen L, Mannelli M, Fassnacht M, Beuschlein F, Eisenhofer G, Cascón A, Al-Shahrour F, Robledo M. PheoSeq: a targeted next-generation sequencing assay for pheochromocytoma and paraganglioma diagnostics. *J Mol Diagn* 2017;19:575–88.
- Lenglet M, Robriquet F, Schwarz K, Camps C, Couturier A, Hoogewijs D, Buffet A, Knight SJL, Gad S, Couvé S, Chesnel F, Pacault M, Lindenbaum P, Job S, Dumont S, Besnard T, Cornec M, Dreau H, Pentony M, Kvikstad E, Deveaux S, Burnichon N, Ferlicot S, Vilaine M, Mazzella J-M, Airaud F, Garrec C, Heidet L, Irtan S, Mantadakis E, Bouchireb K, Debatin K-M, Redon R, Beziane S, Bressac-de Paillerets B, Teh BT, Girodon F, Randi M-L, Putti MC, Bours V, Van Wijk R, Göthert JR, Kattamis A, Janin N, Bento C, Taylor JC, Arlot-Bonnemains Y, Richard S, Gimenez-Roqueplo A-P, Cario H, Gardie B. Identification of a new VHL exon and complex splicing alterations in familial erythrocytosis or von Hippel-Lindau disease. *Blood* 2018;132:469–83.
- Maher ER, Neumann HP, Richard S. Von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet* 2011;19:617–23.
- Toledo RA, Burnichon N, Cascon A, Benn DE, Bayley J-P, Welander J, Tops CM, Firth H, Dwight T, Ercolino T, Mannelli M, Opocher G, Clifton-Bligh R, Gimm O, Maher ER, Robledo M, Gimenez-Roqueplo A-P, Dahia PLM, NGS in PPGL (NGSNPPGL) Study Group. Consensus statement on next-generation-sequencing-based diagnostic testing of hereditary pheochromocytomas and paragangliomas. *Nat Rev Endocrinol* 2017;13:233–47.
- Lenders JWM, Duh Q-Y, Eisenhofer G, Gimenez-Roqueplo A-P, Grebe SKG, Murad MH, Naruse M, Pacak K, Young WF, Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:1915–42.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Reh HL, ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical genetics and genomics and the association for molecular pathology. *Genet Med* 2015;17:405–23.
- Hoefling C, Schmidt H, Meinhardt M, Lohse A, Taubert H, Fuessel S, Schmidt U, Schuster K, Baretton G, Wirth MP, Meyer A. Comparative evaluation of microsatellite marker, AP-PCR and CGH studies in primary renal cell carcinoma. *Int J Mol Med* 2004;13:835–42.
- Girolami F, Passerini I, Gargano D, Frusconi S, Villari D, Nicita G, Torricelli F. Microsatellite analysis of chromosome 3p region in sporadic renal cell carcinomas. *Pathol Oncol Res* 2002;8:241–4.
- Favier J, Meatchi T, Robidel E, Badoual C, Sibony M, Nguyen AT, Gimenez-Roqueplo A-P, Burnichon N. Carbonic anhydrase 9 immunohistochemistry as a tool to predict or validate germline and somatic VHL mutations in pheochromocytoma and paraganglioma—a retrospective and prospective study. *Mod Pathol* 2020;33:57–64.
- Zeka F, Vanderheyden K, De Smet E, Cuvelier CA, Mestdagh P, Vandesompele J. Straightforward and sensitive RT-qPCR based gene expression analysis of FFPE samples. *Sci Rep* 2016;6:21418.
- van Asselt SJ, de Vries EG, van Dulleman HM, Brouwers AH, Walenkamp AM, Giles RH, Links TP. Pancreatic cyst development: insights from von Hippel-Lindau disease. *Cilia* 2013;2:3.
- Mircescu H, Wilkin F, Paquette J, Oligny LL, Decaluwe H, Gabouy L, Nolet S, Van Vliet G, Deal C. Molecular characterization of a pediatric pheochromocytoma with suspected bilateral disease. *J Pediatr* 2001;138:269–73.
- Ivanov SV, Kuzmin I, Wei MH, Pack S, Geil L, Johnson BE, Stanbridge EJ, Lerman MI. Down-Regulation of transmembrane carbonic anhydrases in renal cell carcinoma cell lines by wild-type von Hippel-Lindau transgenes. *Proc Natl Acad Sci U S A* 1998;95:12596–601.
- Pinato DJ, Ramachandran R, Toussi STK, Vergine M, Ngo N, Sharma R, Lloyd T, Meeran K, Palazzo F, Martin N, Khoo B, Dina R, Tan TM. Immunohistochemical markers of the hypoxic response can identify malignancy in pheochromocytomas and paragangliomas and optimize the detection of tumours with VHL germline mutations. *Br J Cancer* 2013;108:429–37.
- Stillebroer AB, Mulders PFA, Boerman OC, Oyen WJG, Oosterwijk E. Carbonic anhydrase IX in renal cell carcinoma: implications for prognosis, diagnosis, and therapy. *Eur Urol* 2010;58:75–83.
- Castro-Vega LJ, Letouzé E, Burnichon N, Buffet A, Disderot P-H, Khalifa E, Loriot C, Elarouci N, Morin A, Menara M, Lepoutre-Lussey C, Badoual C, Sibony M, Doussset B, Libé R, Zinzindohoue F, Plouin PF, Bertherat J, Amar L, de Reyniès A, Favier J, Gimenez-Roqueplo A-P. Multi-Omics analysis defines core genomic alterations in pheochromocytomas and paragangliomas. *Nat Commun* 2015;6:6044.

- 23 López-Jiménez E, Gómez-López G, Leandro-García LJ, Muñoz I, Schiavi F, Montero-Conde C, de Cubas AA, Ramires R, Landa I, Leskelä S, Maliszewska A, Inglada-Pérez L, de la Vega L, Rodríguez-Antona C, Letón R, Bernal C, de Campos JM, Diez-Tascón C, Fraga MF, Boulosa C, Pisano DG, Opocher G, Robledo M, Cascón A. Research resource: transcriptional profiling reveals different pseudohypoxic signatures in SDHB and VHL-related pheochromocytomas. *Mol Endocrinol* 2010;24:2382–91.
- 24 Gordeuk VR, Sergueeva AI, Miasnikova GY, Okhotin D, Voloshin Y, Choyke PL, Butman JA, Jedlickova K, Prchal JT, Polyakova LA. Congenital disorder of oxygen sensing: association of the homozygous Chuvash polycythemia VHL mutation with thrombosis and vascular abnormalities but not tumors. *Blood* 2004;103:3924–32.
- 25 van der Tuin K, Mensenkamp AR, Tops CMJ, Corssmit EPM, Dinjens WN, van de Horst-Schrivers ANA, Jansen JC, de Jong MM, Kunst HPM, Kusters B, Leter EM, Morreau H, van Nesselrooij BMP, Oldenburg RA, Spruijt L, Hes FJ, Timmers HJLM. Clinical aspects of SDHA-Related pheochromocytoma and paraganglioma: a nationwide study. *J Clin Endocrinol Metab* 2018;103:438–45.
- 26 Eisenhofer G, Lenders JWM, Timmers H, Mannelli M, Grebe SK, Hofbauer LC, Bornstein SR, Tiebel O, Adams K, Bratslavsky G, Linehan WM, Pacak K. Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. *Clin Chem* 2011;57:411–20.
- 27 Ben Aim L, Pigny P, Castro-Vega LJ, Buffet A, Amar L, Bertherat J, Drui D, Guilhem I, Baudin E, Lussey-Lepoutre C, Corsini C, Chabrier G, Briet C, Faivre L, Cardot-Bauters C, Favier J, Gimenez-Roqueplo A-P, Burnichon N. Targeted next-generation sequencing detects rare genetic events in pheochromocytoma and paraganglioma. *J Med Genet* 2019;56:513–20.



**Supplementary Table S1:** Individual clinical and tumor characteristics of patients in "PPGL" cohort. M: male, F: female, HN: head and neck PPGL, TAP: thoracic, abdominal or pelvic PPGL, PCC: pheochromocytoma, NA: not available.

Number	Age at diagnostic	Sex	Single or multiple PPGL	Malignant PPGL	Localization of PPGL	Family history of PPGL
PPGL1	54	NA	Single		HN	
PPGL2	NA	NA	Multiple		PCC	
PPGL3	16	NA	Single		TAP	
PPGL4	76	NA	Single		PCC	
PPGL5	44	NA	Single		PCC	
PPGL6	47	NA	Single		PCC	
PPGL7	47	NA	Single		PCC	
PPGL8	38	NA	Single		HN	
PPGL9	59	NA	Single		PCC	
PPGL10	74	NA	Single		HN	
PPGL11	42	NA	Single		PCC	
PPGL12	52	NA	Single		PCC	
PPGL13	13	NA	Multiple		TAP	
PPGL14	8	NA	Single		PCC	
PPGL15	45	NA	Single		PCC	
PPGL16	47	NA	Single		PCC	
PPGL17	26	NA	Single		PCC	
PPGL18	45	NA	Single		PCC	
PPGL19	44	NA	Single		PCC	
PPGL20	35	NA	Single	Yes	HN	
PPGL21	44	NA	Single		PCC	
PPGL22	33	NA	Single		PCC	
PPGL23	60	NA	Single		TAP	
PPGL24	48	NA	Single		TAP	
PPGL25	59	NA	Single		PCC	
PPGL26	47	NA	Single		PCC	
PPGL27	22	NA	Single		PCC	
PPGL28	54	NA	Single		PCC	
PPGL29	66	NA	Single		PCC	
PPGL30	24	NA	Multiple		TAP	
PPGL31	42	NA	Single	Yes	TAP	
PPGL32	59	NA	Single		TAP	
PPGL33	59	NA	Single		TAP	
PPGL34	70	NA	Single		HN	
PPGL35	38	NA	Single		TAP	
PPGL36	80	NA	Single		PCC	
PPGL37	57	NA	Single		PCC	
PPGL38	60	NA	Single		PCC	
PPGL39	32	NA	Single		PCC	
PPGL40	75	NA	Single		HN	
PPGL41	64	NA	Single		TAP	
PPGL42	35	NA	Single		PCC	
PPGL43	35	NA	Single	Yes	TAP	
PPGL44	47	NA	Single		PCC	
PPGL45	59	NA	Single		PCC	
PPGL46	51	NA	Single		HN	
PPGL47	30	NA	Single		TAP	
PPGL48	36	NA	Single		PCC	
PPGL49	75	NA	Single		HN	
PPGL50	67	NA	Single		TAP	
PPGL51	62	NA	Single		PCC	
PPGL52	66	NA	Single		PCC	
PPGL53	35	NA	Single		TAP	
PPGL54	69	NA	Single		PCC	
PPGL55	32	NA	Single		PCC	
PPGL56	64	NA	Single		PCC	
PPGL57	38	NA	Single		HN	
PPGL58	67	NA	Single		PCC	
PPGL59	55	NA	Single		PCC	
PPGL60	18	NA	Single		TAP	
PPGL61	36	NA	Single		PCC	
PPGL62	47	NA	Single		HN	
PPGL63	80	NA	Single		HN	
PPGL64	43	NA	Single		HN	
PPGL65	67	NA	Single		PCC	
PPGL66	78	NA	Single		HN	
PPGL67	66	NA	Single		TAP	
PPGL68	78	NA	Single		PCC	
PPGL69	47	NA	Single		PCC	
PPGL70	35	NA	Single		PCC	
PPGL71	64	NA	Single		TAP	
PPGL72	NA	NA	Single		PCC	
PPGL73	44	NA	Single		PCC	
PPGL74	43	NA	Single		PCC	
PPGL75	58	NA	Single		PCC	
PPGL76	75	NA	Single		HN	
PPGL77	51	NA	Single		PCC	
PPGL78	70	NA	Single		PCC	
PPGL79	70	NA	Single		PCC	
PPGL80	46	NA	Single		HN	
PPGL81	36	NA	Single		PCC	
PPGL82	68	NA	Single		HN	
PPGL83	52	NA	Single		PCC	
PPGL84	45	NA	Single		TAP	
PPGL85	47	NA	Single		PCC	
PPGL86	28	NA	Single		HN	
PPGL87	41	NA	Single		PCC	
PPGL88	42	NA	Single		TAP	
PPGL89	52	NA	Single		PCC	Yes

PPGL90	55	NA	Single		PCC
PPGL91	47	NA	Single		PCC
PPGL92	64	NA	Single		TAP
PPGL93	62	NA	Single		TAP
PPGL94	57	NA	Single	Yes	PCC
PPGL95	19	NA	Single		PCC
PPGL96	68	F	Single		HN
PPGL97	43	M	Single		PCC
PPGL98	76	F	Single		NA
PPGL99	63	F	Single		HN
PPGL100	65	M	Single		PCC
PPGL101	65	M	Single		PCC
PPGL102	46	F	Single	Yes	NA
PPGL103	54	F	Single		PCC
PPGL104	66	M	Single		PCC
PPGL105	36	F	Multiple		HN
PPGL106	65	M	Single		PCC
PPGL107	21	M	Single		HN
PPGL108	47	F	Single		NA
PPGL109	45	M	Single		PCC
PPGL110	64	F	Single		PCC
PPGL111	94	F	Single		PCC
PPGL112	70	F	Single		HN
PPGL113	37	F	Single		PCC
PPGL114	64	F	Multiple		TAP/PCC
PPGL115	54	M	Single		PCC
PPGL116	49	M	Single		PCC
PPGL117	71	F	Single		HN
PPGL118	49	F	Single		PCC
PPGL119	47	F	Single		PCC
PPGL120	52	F	Single		HN
PPGL121	73	F	Single		PCC
PPGL122	61	F	Single		PCC
PPGL123	48	M	Single		PCC
PPGL124	72	F	Single		NA
PPGL125	58	M	Single		HN
PPGL126	51	M	Single	Yes	PCC
PPGL127	50	M	Single		NA
PPGL128	78	F	Single		PCC
PPGL129	83	F	Single		NA
PPGL130	65	F	Single		PCC
PPGL131	78	F	Single		HN
PPGL132	61	M	Multiple		NA
PPGL133	55	F	Single		PCC
PPGL134	57	M	Single		PCC
PPGL135	40	M	Single		PCC
PPGL136	60	M	Single		PCC
PPGL137	57	M	Single		PCC
PPGL138	58	F	Single		TAP
PPGL139	58	F	Single		PCC
PPGL140	60	F	Single		PCC
PPGL141	47	F	Single		PCC
PPGL142	48	M	Single		TAP
PPGL143	52	F	Single		PCC
PPGL144	56	M	Single		PCC
PPGL145	38	F	Single		TAP
PPGL146	42	M	Single		PCC
PPGL147	69	M	Single		HN
PPGL148	52	M	Single		NA
PPGL149	61	F	Single		PCC
PPGL150	42	M	Single		HN
PPGL151	49	F	Single		PCC
PPGL152	50	M	Single		PCC
PPGL153	66	F	Single		NA
PPGL154	19	M	Single		PCC
PPGL155	71	F	Single		HN
PPGL156	61	F	Single		PCC
PPGL157	58	F	Single		TAP
PPGL158	56	M	Single		PCC
PPGL159	69	F	Single		PCC
PPGL160	32	M	Multiple		NA
PPGL161	82	F	Single		HN
PPGL162	68	F	Single		PCC
PPGL163	40	F	Single		HN
PPGL164	56	M	Single		PCC
PPGL165	52	F	Multiple		HN
PPGL166	58	F	Single		PCC
PPGL167	68	M	Single		PCC
PPGL168	68	M	Single		HN
PPGL169	73	F	Single		HN
PPGL170	76	M	Single		PCC
PPGL171	38	M	Single		PCC
PPGL172	49	F	Single		HN
PPGL173	66	F	Single		NA
PPGL174	63	M	Single		PCC
PPGL175	84	M	Single		NA

PPGL176	NA	M	Single		PCC	
PPGL177	64	M	Single		PCC	
PPGL178	NA	M	Single	Yes	NA	
PPGL179	57	M	Single		PCC	
PPGL180	67	F	Single		HN	
PPGL181	74	F	Single		HN	
PPGL182	62	M	Single		PCC	
PPGL183	41	F	Single		NA	
PPGL184	70	F	Single		PCC	
PPGL185	41	F	Single		PCC	
PPGL186	21	M	Single		HN	
PPGL187	56	M	Single		TAP	
PPGL188	48	F	Single		PCC	
PPGL189	69	M	Single		HN	
PPGL190	63	F	Single		PCC	
PPGL191	36	M	Single		NA	
PPGL192	77	F	Single		PCC	
PPGL193	50	F	Single		PCC	
PPGL194	67	M	Single		PCC	
PPGL195	55	F	Single		TAP	
PPGL196	71	F	Single		PCC	
PPGL197	62	M	Single		PCC	
PPGL198	70	F	Single		HN	Yes
PPGL199	31	F	Single		PCC	Yes
PPGL200	45	F	Single		HN	
PPGL201	23	M	Multiple		HN	Yes
PPGL202	22	M	Single		PCC	
PPGL203	NA	F	Multiple		HN	Yes
PPGL204	14	M	Single		TAP	
PPGL205	32	M	Multiple		HN/TAP	
PPGL206	69	F	Multiple		HN	
PPGL207	33	F	Single		TAP	
PPGL208	49	M	Multiple		HN	
PPGL209	53	F	Multiple		TAP	
PPGL210	44	M	Multiple		TAP	
PPGL211	35	M	Single	Yes	TAP	
PPGL212	27	F	Single	Yes	TAP	
PPGL213	29	F	Single		HN	
PPGL214	17	M	Single		TAP	
PPGL215	54	F	Multiple		HN	
PPGL216	47	F	Single		HN	
PPGL217	28	F	Single		HN	
PPGL218	46	M	Multiple		HN	
PPGL219	29	M	Single		HN	
PPGL220	32	F	Single	Yes	TAP	
PPGL221	32	F	Single		HN	
PPGL222	24	F	Single		HN	
PPGL223	17	F	Single		HN	
PPGL224	30	M	Single		TAP	
PPGL225	50	F	Multiple		HN	
PPGL226	20	F	Single		TAP	
PPGL227	19	M	Single		TAP	
PPGL228	27	F	Single		TAP	
PPGL229	34	M	Single		HN	
PPGL230	26	F	Single	Yes	HN	
PPGL231	66	M	Multiple		TAP	
PPGL232	31	F	Single		HN	
PPGL233	25	M	Single		HN	
PPGL234	30	F	Single	Yes	HN	
PPGL235	19	F	Multiple		HN	
PPGL236	71	M	Multiple		TAP/PCC	
PPGL237	NA	F	Single		NA	
PPGL238	60	F	Multiple		HN	
PPGL239	39	M	Multiple		HN	
PPGL240	62	F	Single		TAP	
PPGL241	21	M	Multiple		TAP/PCC	
PPGL242	11	M	Single		TAP	
PPGL243	27	F	Multiple		TAP	
PPGL244	43	M	Single		TAP	
PPGL245	28	F	Single		HN	
PPGL246	20	F	Single		TAP	
PPGL247	25	F	Single		HN	
PPGL248	16	F	Single		TAP	
PPGL249	64	F	Multiple		HN	
PPGL250	33	M	Single		HN	
PPGL251	32	F	Single		TAP	
PPGL252	33	M	Single		HN	
PPGL253	17	F	Single		TAP	
PPGL254	32	M	Single		HN	
PPGL255	34	M	Single		HN	
PPGL256	33	F	Single	Yes	HN	
PPGL257	46	M	Multiple		HN	
PPGL258	74	F	Multiple		HN	
PPGL259	53	F	Single		HN	
PPGL260	33	F	Single		HN	
PPGL261	32	F	Single		TAP	
PPGL262	25	F	Single		HN	
PPGL263	30	F	Single		PCC	
PPGL264	33	M	Single		TAP	
PPGL265	32	M	Single	Yes	TAP	

PPGL266	68	F	Multiple		HN	
PPGL267	19	M	Single		HN	
PPGL268	35	M	Single		HN	
PPGL269	80	M	Multiple		TAP/PCC	
PPGL270	NA	M	Single		TAP	
PPGL271	NA	F	Single		TAP	
PPGL272	9	F	Single		HN	
PPGL273	35	F	Single		HN	
PPGL274	34	F	Multiple	Yes	TAP/PCC	
PPGL275	29	F	Multiple		TAP	
PPGL276	29	F	Single		TAP	
PPGL277	55	F	Multiple		HN/TAP	
PPGL278	14	M	Single		HN	
PPGL279	8	M	Single		TAP	
PPGL280	33	M	Single		HN	
PPGL281	15	F	Single		TAP	
PPGL282	22	F	Single	Yes	HN	
PPGL283	32	M	Single		HN	Yes
PPGL284	43	M	Multiple		HN	
PPGL285	33	F	Single		HN	
PPGL286	34	F	Single		HN	
PPGL287	31	M	Single	Yes	HN	Yes
PPGL288	33	M	Single		NA	
PPGL289	16	M	Single		TAP	
PPGL290	35	F	Single		HN	
PPGL291	35	M	Single		TAP	Yes
PPGL292	29	M	Single	Yes	TAP	
PPGL293	45	F	Multiple		HN	Yes
PPGL294	17	M	Multiple	Yes	HN	
PPGL295	22	F	Multiple		HN	
PPGL296	49	F	Multiple		HN	
PPGL297	34	F	Single		HN	
PPGL298	22	M	Single		TAP	
PPGL299	17	F	Single		HN	
PPGL300	31	F	Multiple		HN/TAP	
PPGL301	35	F	Single		HN	
PPGL302	50	F	Multiple		TAP/PCC	
PPGL303	73	F	Multiple		HN	
PPGL304	35	F	Single		HN	
PPGL305	15	F	Multiple		TAP/PCC	
PPGL306	74	F	Multiple		TAP/PCC	
PPGL307	32	F	Multiple		TAP	
PPGL308	32	F	Single		HN	
PPGL309	22	F	Single	Yes	HN	
PPGL310	34	M	Single		HN	
PPGL311	23	F	Single		HN	
PPGL312	35	M	Single		HN	
PPGL313	34	M	Single		HN	
PPGL314	74	M	Multiple		HN/TAP	
PPGL315	22	F	Single		HN	
PPGL316	47	F	Multiple		HN/TAP	
PPGL317	34	F	Multiple		TAP	
PPGL318	22	M	Single		HN	
PPGL319	35	M	Single		HN	
PPGL320	30	F	Single		HN	
PPGL321	30	F	Single		HN	
PPGL322	22	F	Single		HN	
PPGL323	25	F	Single		HN	
PPGL324	27	M	Single		HN	
PPGL325	33	M	Single		HN	
PPGL326	17	F	Single		HN	
PPGL327	54	F	Multiple		TAP	
PPGL328	28	F	Single		HN	
PPGL329	25	M	Single		HN	
PPGL330	27	F	Multiple		HN/TAP	
PPGL331	32	M	Single		HN	
PPGL332	30	F	Single		TAP	
PPGL333	12	F	Multiple		HN	
PPGL334	26	F	Single		HN	
PPGL335	30	F	Single		HN	
PPGL336	34	F	Single		HN	
PPGL337	35	M	Single		HN	
PPGL338	28	F	Single		HN	
PPGL339	35	M	Single		HN	
PPGL340	30	M	Single		HN	
PPGL341	33	F	Single	Yes	TAP	
PPGL342	20	M	Single		HN	
PPGL343	28	F	Single		PCC	
PPGL344	34	M	Single	Yes	PCC	
PPGL345	31	F	Single		PCC	
PPGL346	35	F	Single		PCC	
PPGL347	19	F	Single		PCC	
PPGL348	27	M	Single		HN	
PPGL349	30	F	Single	Yes	PCC	
PPGL350	26	M	Single		PCC	
PPGL351	26	F	Single		PCC	
PPGL352	30	F	Single		PCC	
PPGL353	14	F	Single		PCC	
PPGL354	14	M	Single		PCC	
PPGL355	31	M	Single		PCC	
PPGL356	35	M	Single		PCC	
PPGL357	8	M	Single		PCC	



PPGL358	33	M	Multiple		TAP/PCC
PPGL359	24	M	Single	Yes	TAP
PPGL360	21	M	Single		PCC
PPGL361	16	M	Single		PCC
PPGL362	11	M	Single		PCC
PPGL363	33	F	Single		PCC
PPGL364	28	F	Single		PCC
PPGL365	25	F	Multiple		PCC
PPGL366	32	M	Single		PCC
PPGL367	11	M	Single		PCC
PPGL368	29	M	Single		PCC
PPGL369	22	F	Single		PCC
PPGL370	29	F	Single		PCC
PPGL371	35	M	Single		PCC
PPGL372	29	F	Single		TAP
PPGL373	35	F	Single		PCC
PPGL374	18	F	Single		PCC
PPGL375	35	F	Single		PCC
PPGL376	30	M	Single		PCC
PPGL377	27	F	Single		PCC
PPGL378	14	F	Single		TAP
PPGL379	27	M	Single		PCC
PPGL380	33	F	Single		TAP
PPGL381	27	M	Single		PCC
PPGL382	33	M	Single		PCC
PPGL383	35	F	Single		PCC
PPGL384	47	M	Multiple		HN
PPGL385	11	M	Multiple	Yes	PCC
PPGL386	32	M	Single		PCC
PPGL387	64	F	Single		PCC
PPGL388	21	M	Single		PCC
PPGL389	26	M	Single		PCC
PPGL390	31	F	Single		PCC
PPGL391	21	M	Single		PCC
PPGL392	35	M	Single		PCC
PPGL393	20	M	Single		PCC
PPGL394	27	F	Single		PCC
PPGL395	32	F	Single		PCC
PPGL396	31	M	Single		PCC
PPGL397	21	F	Multiple		PCC
PPGL398	33	M	Single		PCC
PPGL399	38	M	Single		PCC
PPGL400	34	M	Single		PCC
PPGL401	25	M	Single		PCC
PPGL402	29	M	Single		PCC
PPGL403	44	F	Multiple		PCC
PPGL404	28	M	Single		PCC
PPGL405	31	M	Single		PCC
PPGL406	34	M	Single		PCC
PPGL407	35	F	Single		PCC
PPGL408	35	M	Single		PCC
PPGL409	34	F	Single		PCC
PPGL410	24	F	Single		PCC
PPGL411	13	F	Multiple		TAP/PCC
PPGL412	31	F	Single		PCC
PPGL413	33	M	Single		PCC
PPGL414	25	M	Single		PCC
PPGL415	13	F	Multiple		TAP
PPGL416	33	F	Single		PCC
PPGL417	30	F	Single		PCC
PPGL418	30	F	Single		PCC
PPGL419	59	M	Multiple		PCC
PPGL420	30	M	Single		PCC
PPGL421	39	F	Multiple		TAP/PCC
PPGL422	64	F	Multiple		PCC
PPGL423	21	F	Single		PCC
PPGL424	45	M	Single	Yes	PCC
PPGL425	17	M	Single		PCC
PPGL426	34	M	Single	Yes	PCC
PPGL427	54	M	Single	Yes	PCC
PPGL428	39	M	Single	Yes	PCC
PPGL429	13	M	Single		PCC
PPGL430	32	F	Single		PCC
PPGL431	21	M	Single		PCC
PPGL432	28	F	Single		PCC
PPGL433	13	F	Single		TAP
PPGL434	35	F	Single		PCC
PPGL435	62	F	Multiple		TAP/PCC
PPGL436	33	M	Single		PCC
PPGL437	50	F	Multiple		NA
PPGL438	27	M	Single	Yes	PCC
PPGL439	33	M	Single		PCC
PPGL440	33	M	Single	Yes	PCC
PPGL441	26	M	Single		PCC
PPGL442	35	F	Single		PCC
PPGL443	56	F	Single		PCC
PPGL444	35	F	Single		PCC
PPGL445	10	F	Single		TAP
PPGL446	34	F	Single		PCC
PPGL447	28	F	Single		PCC
PPGL448	40	M	Multiple		TAP/PCC
PPGL449	35	M	Single	Yes	PCC

PPGL450	21	F	Single		PCC	
PPGL451	33	M	Single	Yes	PCC	
PPGL452	18	F	Single	Yes	PCC	
PPGL453	15	F	Single	Yes	PCC	
PPGL454	22	F	Single		PCC	
PPGL455	26	M	Single		PCC	
PPGL456	52	F	Single		PCC	
PPGL457	57	M	Single		NA	Yes
PPGL458	18	M	Single		PCC	
PPGL459	28	M	Single		PCC	
PPGL460	55	F	Multiple		PCC	
PPGL461	19	M	Single		TAP	
PPGL462	26	M	Single	Yes	TAP	
PPGL463	26	F	Single		PCC	
PPGL464	31	M	Single		PCC	
PPGL465	13	M	Multiple		PCC	
PPGL466	28	F	Multiple		TAP/PCC	
PPGL467	23	F	Single		TAP	
PPGL468	23	M	Single		PCC	
PPGL469	34	M	Single		PCC	
PPGL470	16	F	Single		TAP	
PPGL471	32	M	Single		PCC	
PPGL472	60	F	Single		PCC	
PPGL473	12	F	Single		PCC	
PPGL474	31	F	Single	Yes	TAP	
PPGL475	46	F	Single		PCC	Yes
PPGL476	54	F	Multiple		TAP/PCC	
PPGL477	36	F	Single	Yes	PCC	Yes
PPGL478	22	F	Single	Yes	PCC	
PPGL479	12	M	Single		PCC	
PPGL480	8	M	Single		PCC	
PPGL481	13	M	Single		PCC	
PPGL482	32	F	Single		PCC	
PPGL483	21	M	Single		PCC	
PPGL484	35	F	Single		PCC	
PPGL485	26	F	Single		PCC	
PPGL486	30	M	Single		PCC	
PPGL487	30	F	Single		PCC	
PPGL488	25	F	Single		TAP	Yes
PPGL489	18	M	Single		PCC	
PPGL490	15	F	Single		PCC	
PPGL491	28	M	Single		PCC	
PPGL492	34	F	Multiple	Yes	PCC	
PPGL493	30	M	Single		PCC	
PPGL494	18	M	Single		PCC	
PPGL495	34	M	Single		PCC	
PPGL496	12	M	Multiple		TAP/PCC	
PPGL497	14	F	Single		PCC	
PPGL498	25	F	Single		PCC	
PPGL499	30	F	Single		PCC	
PPGL500	18	M	Single		PCC	
PPGL501	33	F	Single		PCC	
PPGL502	48	M	Multiple		TAP	
PPGL503	24	M	Single		PCC	
PPGL504	NA	M	Single		NA	
PPGL505	53	F	Single		PCC	
PPGL506	24	M	Single		PCC	
PPGL507	25	F	Single		PCC	
PPGL508	34	F	Single		PCC	
PPGL509	31	M	Single		PCC	
PPGL510	31	M	Single		PCC	
PPGL511	29	M	Single		PCC	
PPGL512	19	M	Single		PCC	
PPGL513	35	F	Single		PCC	
PPGL514	28	M	Single		PCC	
PPGL515	35	F	Single		PCC	
PPGL516	25	F	Multiple		PCC	
PPGL517	32	F	Single		PCC	
PPGL518	33	F	Single		TAP	
PPGL519	35	F	Single		PCC	
PPGL520	40	M	Multiple		TAP/PCC	
PPGL521	32	F	Single		PCC	
PPGL522	31	F	Single		PCC	
PPGL523	35	F	Single		PCC	
PPGL524	30	F	Single		PCC	
PPGL525	44	F	Multiple	Yes	TAP/PCC	Yes
PPGL526	27	F	Single		PCC	
PPGL527	27	M	Single		PCC	
PPGL528	26	M	Single		PCC	
PPGL529	30	M	Single	Yes	PCC	
PPGL530	14	M	Single		PCC	
PPGL531	33	M	Single		PCC	
PPGL532	44	F	Multiple	Yes	PCC	
PPGL533	30	F	Single		PCC	
PPGL534	49	M	Multiple		PCC	
PPGL535	17	F	Single	Yes	PCC	
PPGL536	33	M	Single		PCC	
PPGL537	22	F	Single		PCC	
PPGL538	22	M	Single		PCC	
PPGL539	36	M	Multiple		TAP	
PPGL540	23	M	Single		PCC	
PPGL541	25	M	Single		PCC	

PPGL542	32	M	Single	Yes	PCC	
PPGL543	24	M	Single		PCC	
PPGL544	32	F	Single		PCC	
PPGL545	18	M	Single		PCC	
PPGL546	46	M	Single		PCC	Yes
PPGL547	34	F	Single		PCC	
PPGL548	25	F	Single		PCC	
PPGL549	27	F	Single		PCC	
PPGL550	43	M	Multiple		PCC	
PPGL551	28	F	Single		PCC	
PPGL552	19	M	Single		PCC	
PPGL553	23	M	Single		PCC	
PPGL554	30	M	Single		PCC	
PPGL555	34	M	Single		PCC	
PPGL556	35	M	Single		PCC	
PPGL557	60	M	Multiple		PCC	
PPGL558	10	NA	Multiple		TAP/PCC	
PPGL559	37	NA	Single		PCC	
PPGL560	9	NA	Single		PCC	
PPGL561	54	NA	Single		PCC	
PPGL562	42	NA	Single	Yes	PCC	
PPGL563	28	NA	Single		PCC	
PPGL564	74	NA	Single		PCC	
PPGL565	14	NA	Multiple		PCC/HN	
PPGL566	44	NA	Single		PCC	
PPGL567	32	NA	Single	Yes	PCC	
PPGL568	14	NA	Multiple	Yes	TAP/PCC	
PPGL569	56	NA	Single		PCC	
PPGL570	27	NA	Single		PCC	
PPGL571	25	NA	Single		PCC	
PPGL572	9	NA	Single		PCC	
PPGL573	32	NA	Single		PCC	
PPGL574	43	NA	Single		PCC	
PPGL575	NA	NA	Single		PCC	
PPGL576	55	NA	Single		PCC	
PPGL577	40	NA	Single		PCC	
PPGL578	NA	NA	Single		PCC	
PPGL579	71	NA	Single		PCC	
PPGL580	41	NA	Single		PCC	
PPGL581	42	NA	Single		PCC	
PPGL582	20	NA	Single		TAP	
PPGL583	60	NA	Single		PCC	
PPGL584	63	NA	Single		TAP	
PPGL585	NA	NA	Single		PCC	
PPGL586	NA	NA	Single		PCC	
PPGL587	NA	NA	Single		PCC	
PPGL588	NA	NA	Single		PCC	
PPGL589	NA	NA	Single		PCC	
PPGL590	NA	NA	Single		PCC	
PPGL591	NA	NA	Single		PCC	
PPGL592	NA	NA	Single		PCC	
PPGL593	NA	NA	Single		PCC	
PPGL594	NA	NA	Single		PCC	
PPGL595	NA	NA	Single		PCC	
PPGL596	NA	NA	Single		PCC	
PPGL597	17	NA	Single		TAP	
PPGL598	32	NA	Single		PCC	
PPGL599	30	NA	Single		PCC	
PPGL600	22	NA	Single		TAP	
PPGL601	53	NA	Single		PCC	
PPGL602	21	NA	Single		PCC	
PPGL603	14	NA	Single		PCC	
PPGL604	39	NA	Single		PCC	
PPGL605	53	NA	Single		PCC	
PPGL606	29	NA	Single	Yes	PCC	
PPGL607	47	NA	Multiple		PCC	
PPGL608	50	NA	Single		PCC	
PPGL609	59	NA	Single		PCC	
PPGL610	33	NA	Single		PCC	
PPGL611	46	NA	Single		PCC	
PPGL612	48	NA	Single		PCC	
PPGL613	52	NA	Single		PCC	
PPGL614	48	NA	Single		PCC	
PPGL615	43	NA	Single		PCC	
PPGL616	13	NA	Single		PCC	
PPGL617	45	NA	Single		PCC	
PPGL618	14	NA	Single		PCC	
PPGL619	53	NA	Single		PCC	
PPGL620	8	NA	Single	Yes	TAP	
PPGL621	42	NA	Single		PCC	
PPGL622	51	NA	Single		PCC	
PPGL623	61	NA	Single		PCC	
PPGL624	19	NA	Single		PCC	
PPGL625	39	NA	Single		PCC	
PPGL626	NA	NA	Single	Yes	TAP	
PPGL627	53	NA	Single		TAP	
PPGL628	14	NA	Single	Yes	TAP	Yes
PPGL629	16	NA	Single		TAP	
PPGL630	26	NA	Single		PCC	
PPGL631	55	NA	Single		PCC	
PPGL632	45	NA	Single		PCC	
PPGL633	8	NA	Multiple		TAP	

PPGL634	17	NA	Single	Yes	PCC
PPGL635	71	NA	Single		PCC
PPGL636	30	NA	Single		PCC
PPGL637	59	NA	Single		PCC
PPGL638	43	NA	Single		PCC
PPGL639	76	NA	Single	Yes	TAP
PPGL640	28	NA	Multiple		PCC
PPGL641	47	NA	Single		HN
PPGL642	60	NA	Multiple		HN
PPGL643	48	NA	Single		HN
PPGL644	45	NA	Multiple		PCC
PPGL645	31	NA	Single		PCC
PPGL646	74	F	Single		HN
PPGL647	56	F	Single		HN
PPGL648	29	M	Single		PCC
PPGL649	62	F	Single	Yes	NA
PPGL650	67	F	Single		PCC
PPGL651	57	M	Single		PCC
PPGL652	41	M	Multiple		TAP/PCC
PPGL653	69	F	Single		PCC
PPGL654	52	F	Single		PCC
PPGL655	43	F	Single		PCC
PPGL656	22	F	Single		PCC
PPGL657	37	F	Single		PCC
PPGL658	45	F	Single		PCC
PPGL659	48	F	Single		PCC
PPGL660	16	M	Single		PCC
PPGL661	72	M	Single		TAP
PPGL662	59	F	Single		PCC
PPGL663	56	F	Single		PCC
PPGL664	48	M	Single		PCC
PPGL665	80	F	Single		PCC
PPGL666	62	M	Single		PCC
PPGL667	37	M	Single		PCC
PPGL668	21	F	Single		TAP
PPGL669	57	F	Multiple	Yes	TAP/PCC
PPGL670	59	M	Multiple		PCC
PPGL671	39	F	Single		PCC
PPGL672	37	F	Single		HN
PPGL673	43	F	Single		PCC
PPGL674	71	F	Single		PCC
PPGL675	31	F	Single		PCC
PPGL676	53	F	Single		TAP
PPGL677	35	F	Single		PCC
PPGL678	48	M	Single		PCC
PPGL679	74	F	Single		PCC
PPGL680	39	M	Single		PCC
PPGL681	47	F	Single		PCC
PPGL682	26	F	Single		TAP
PPGL683	26	F	Single		PCC
PPGL684	44	M	Single		PCC
PPGL685	47	M	Single		TAP
PPGL686	36	M	Single		PCC
PPGL687	40	M	Single	Yes	PCC
PPGL688	59	M	Single		HN
PPGL689	59	M	Single		TAP
PPGL690	72	F	Single		TAP
PPGL691	32	M	Single		PCC
PPGL692	56	M	Single		PCC
PPGL693	46	F	Single		PCC
PPGL694	60	F	Single		HN
PPGL695	56	F	Single		TAP
PPGL696	54	M	Multiple		PCC
PPGL697	72	F	Single		TAP
PPGL698	66	F	Single		PCC
PPGL699	36	F	Single		HN
PPGL700	62	F	Single		PCC
PPGL701	60	F	Single		HN
PPGL702	47	F	Single		PCC
PPGL703	65	F	Multiple		PCC
PPGL704	57	M	Single		PCC
PPGL705	32	F	Single	Yes	TAP
PPGL706	61	M	Single		PCC
PPGL707	29	F	Single		HN
PPGL708	24	M	Single		PCC
PPGL709	40	F	Multiple		HN
PPGL710	44	F	Single		HN
PPGL711	37	F	Single		HN
PPGL712	33	M	Single		PCC
PPGL713	41	M	Single		PCC
PPGL714	26	F	Single		PCC
PPGL715	45	F	Single		PCC
PPGL716	51	F	Single		PCC
PPGL717	34	F	Single		PCC
PPGL718	75	M	Single		TAP
PPGL719	55	F	Single		PCC
PPGL720	16	F	Single		TAP
PPGL721	55	M	Single		PCC
PPGL722	44	M	Single		PCC
PPGL723	31	M	Single		TAP
PPGL724	54	M	Single		PCC
PPGL725	66	M	Single		PCC



PPGL726	50	M	Single		PCC
PPGL727	43	F	Single		HN
PPGL728	NA	F	Single		PCC
PPGL729	59	M	Single		PCC
PPGL730	NA	F	Single		PCC
PPGL731	36	M	Single		PCC
PPGL732	47	M	Single		PCC
PPGL733	42	F	Single		PCC
PPGL734	48	M	Single		PCC
PPGL735	74	M	Single		PCC
PPGL736	41	F	Single		PCC
PPGL737	21	F	Single		PCC
PPGL738	35	F	Multiple		HN
PPGL739	33	M	Multiple		PCC
PPGL740	62	F	Single		TAP
PPGL741	43	M	Single		PCC
PPGL742	21	M	Single		PCC
PPGL743	59	F	Single		PCC
PPGL744	45	M	Single		PCC
PPGL745	67	M	Single		PCC
PPGL746	52	M	Single		PCC
PPGL747	28	F	Single		PCC
PPGL748	54	F	Single		PCC
PPGL749	66	M	Single		PCC
PPGL750	40	F	Multiple	Yes	TAP/PCC
PPGL751	77	F	Single		HN
PPGL752	42	M	Single		PCC
PPGL753	63	F	Multiple		HN
PPGL754	16	M	Multiple		PCC
PPGL755	43	M	Single		HN
PPGL756	38	F	Single		HN
PPGL757	69	M	Single		HN
PPGL758	15	M	Single		PCC
PPGL759	57	F	Single		HN
PPGL760	32	M	Single		PCC
PPGL761	47	M	Single	Yes	PCC
PPGL762	9	M	Single		PCC
PPGL763	32	F	Single		PCC
PPGL764	78	F	Single		HN
PPGL765	60	F	Single		HN
PPGL766	44	M	Single		PCC
PPGL767	29	M	Multiple		TAP
PPGL768	48	F	Single		HN
PPGL769	26	M	Single		PCC
PPGL770	70	F	Single		HN
PPGL771	59	F	Single		HN
PPGL772	64	M	Single	Yes	TAP
PPGL773	51	F	Single		HN
PPGL774	74	F	Single		PCC
PPGL775	54	M	Single		HN
PPGL776	47	F	Single		PCC
PPGL777	50	F	Single		TAP
PPGL778	53	F	Single		HN
PPGL779	41	F	Single	Yes	PCC
PPGL780	62	F	Single		PCC
PPGL781	25	F	Single		TAP
PPGL782	26	F	Single		TAP
PPGL783	40	M	Single		PCC
PPGL784	35	M	Single		PCC
PPGL785	53	F	Single		HN
PPGL786	64	F	Single		PCC
PPGL787	41	F	Single		PCC
PPGL788	38	M	Single		PCC
PPGL789	38	M	Single		TAP
PPGL790	38	F	Single		TAP
PPGL791	36	M	Single		PCC
PPGL792	63	F	Single		TAP
PPGL793	64	F	Single		HN
PPGL794	58	F	Single		TAP
PPGL795	52	M	Single		HN
PPGL796	59	M	Single		PCC
PPGL797	42	M	Single		PCC
PPGL798	64	M	Single		TAP
PPGL799	43	F	Single		PCC
PPGL800	55	F	Single		HN
PPGL801	33	F	Single		HN
PPGL802	46	F	Single		HN
PPGL803	45	M	Single		PCC
PPGL804	43	M	Multiple		PCC
PPGL805	52	F	Single		HN
PPGL806	63	F	Single		HN
PPGL807	54	M	Single		HN
PPGL808	70	M	Single		PCC
PPGL809	47	M	Single		TAP
PPGL810	NA	M	Single		PCC
PPGL811	76	F	Single		TAP
PPGL812	45	M	Single		TAP
PPGL813	59	M	Single		HN
PPGL814	60	M	Single		TAP
PPGL815	63	F	Single		PCC
PPGL816	31	M	Multiple	Yes	TAP
PPGL817	48	M	Single		PCC

PPGL818	64	M	Single		PCC
PPGL819	70	F	Single	Yes	PCC
PPGL820	62	F	Single	Yes	HN
PPGL821	39	F	Single		HN
PPGL822	63	M	Single		HN
PPGL823	44	F	Single		PCC
PPGL824	46	F	Single		PCC
PPGL825	42	F	Single		PCC
PPGL826	49	F	Single		PCC
PPGL827	68	M	Single		HN
PPGL828	78	F	Single		PCC
PPGL829	65	F	Single		PCC
PPGL830	50	F	Single		HN
PPGL831	51	M	Single		PCC
PPGL832	45	M	Single		PCC
PPGL833	44	M	Single		PCC
PPGL834	66	M	Single	Yes	PCC
PPGL835	44	F	Single		PCC
PPGL836	59	F	Single		TAP
PPGL837	62	F	Single		HN
PPGL838	58	F	Single		PCC
PPGL839	42	F	Single		PCC
PPGL840	31	F	Single		PCC
PPGL841	NA	F	Single		PCC
PPGL842	64	M	Multiple		TAP/PCC
PPGL843	20	M	Single	Yes	PCC
PPGL844	23	F	Single		PCC
PPGL845	48	F	Single		PCC
PPGL846	35	F	Single		PCC
PPGL847	79	F	Multiple		PCC/HN
PPGL848	39	M	Single	Yes	PCC
PPGL849	43	F	Single		PCC
PPGL850	43	F	Single		PCC
PPGL851	53	F	Single		PCC
PPGL852	49	M	Single		PCC
PPGL853	52	F	Single		PCC
PPGL854	23	F	Single		TAP
PPGL855	56	F	Single		PCC
PPGL856	49	M	Single		TAP
PPGL857	57	M	Single		TAP
PPGL858	29	F	Multiple		PCC
PPGL859	41	F	Single		TAP
PPGL860	70	M	Single	Yes	PCC
PPGL861	NA	F	Single	Yes	NA
PPGL862	86	F	Single		HN
PPGL863	38	F	Single		PCC
PPGL864	35	M	Single		PCC
PPGL865	44	F	Single		PCC
PPGL866	56	F	Single	Yes	TAP
PPGL867	66	F	Single		TAP
PPGL868	46	M	Single		HN
PPGL869	54	F	Single		PCC
PPGL870	51	M	Single		TAP
PPGL871	72	F	Single		HN
PPGL872	65	F	Single		PCC
PPGL873	51	F	Single		PCC
PPGL874	71	M	Single	Yes	TAP
PPGL875	25	F	Single		PCC
PPGL876	82	M	Single		TAP
PPGL877	NA	F	Single	Yes	PCC
PPGL878	33	M	Single	Yes	TAP
PPGL879	56	M	Single		PCC
PPGL880	41	NA	Single	Yes	PCC
PPGL881	56	F	Single		PCC
PPGL882	24	F	Single	Yes	PCC
PPGL883	39	F	Single		PCC
PPGL884	57	F	Single		TAP
PPGL885	30	F	Single		PCC
PPGL886	50	F	Single		HN
PPGL887	40	F	Single		PCC
PPGL888	14	F	Single		TAP
PPGL889	39	F	Single		PCC
PPGL890	40	M	Multiple		PCC
PPGL891	44	M	Single		PCC
PPGL892	45	F	Single		HN
PPGL893	50	F	Single		PCC
PPGL894	43	F	Single		HN
PPGL895	56	F	Single		PCC
PPGL896	59	M	Single		PCC
PPGL897	51	F	Single		HN
PPGL898	70	F	Single		HN
PPGL899	42	M	Single		PCC
PPGL900	78	F	Single		PCC
PPGL901	59	NA	Single		PCC
PPGL902	53	F	Single		TAP
PPGL903	64	F	Single		PCC
PPGL904	64	M	Single		PCC
PPGL905	60	F	Single		TAP
PPGL906	64	F	Single		HN
PPGL907	18	F	Single		TAP
PPGL908	45	F	Single		HN
PPGL909	78	F	Single		HN

PPGL910	60	M	Single		PCC
PPGL911	58	F	Single		TAP
PPGL912	71	F	Single		TAP
PPGL913	31	F	Single		TAP
PPGL914	65	F	Multiple		HN/TAP
PPGL915	65	F	Single		HN
PPGL916	73	M	Multiple		PCC
PPGL917	67	F	Single		TAP
PPGL918	63	F	Single		HN
PPGL919	58	F	Single		HN
PPGL920	15	M	Multiple		PCC
PPGL921	59	M	Single		PCC
PPGL922	47	M	Single		PCC
PPGL923	74	F	Single		HN
PPGL924	60	F	Single		HN
PPGL925	40	M	Single	Yes	PCC
PPGL926	28	M	Single		TAP
PPGL927	70	F	Single		HN
PPGL928	43	F	Single		HN
PPGL929	46	M	Single		HN
PPGL930	25	M	Single		TAP
PPGL931	75	F	Single		TAP
PPGL932	50	M	Single		PCC
PPGL933	62	F	Single		PCC
PPGL934	75	F	Single		HN
PPGL935	74	F	Single		HN
PPGL936	35	F	Single		HN
PPGL937	49	M	Single		TAP
PPGL938	59	M	Single		PCC
PPGL939	24	F	Single		HN
PPGL940	45	F	Single		HN
PPGL941	NA	F	Single		PCC
PPGL942	67	F	Single		HN
PPGL943	50	F	Single		HN
PPGL944	NA	F	Single		PCC
PPGL945	69	F	Single		HN
PPGL946	66	F	Single		PCC

**Supplementary Table S2:** Individual clinical and tumor characteristics of patients in "VHL-like", "Multiple VHL tumors" and "Single VHL tumor" cohorts. M: male, F: female, RCC: renal carcinoma, PET: pancreatic endocrine tumor, CNS hemangioblastoma: central nervous system hemangioblastoma, HN: head and neck PPGL, TAP: thoracic, abdominal or pelvic PPGL, PCC: pheochromocytoma, NA: not available.

Number	Age at diagnostic	Sex	Family history of VHL tumors	Localization (1)	Localization (2)	Localization (3)	Localization (4)
Multiple VHL tumors1	69	NA	No	PCC	RCC		
Multiple VHL tumors2	53	F	No	PCC	PET		
Multiple VHL tumors3	66	F	No	PCC	PET		
Multiple VHL tumors4	44	M	No	RCC	PET		
Multiple VHL tumors5	26	M	No	Multiple RCC			
Multiple VHL tumors6	47	M	No	PCC	RCC		
Multiple VHL tumors7	23	M	No	PCC	RCC		
Multiple VHL tumors8	26	M	No	Multiple RCC			
Multiple VHL tumors9	31	F	No	PCC	RCC		
Multiple VHL tumors10	48	M	No	RCC	Epididymal cystadenoma		
Multiple VHL tumors11	49	NA	No	Multiple RCC			
Multiple VHL tumors12	49	NA	No	Multiple RCC			
Multiple VHL tumors13	48	NA	No	Multiple RCC			
Multiple VHL tumors14	81	NA	No	Multiple RCC	Renal cyst		
Multiple VHL tumors15	53	NA	No	Multiple RCC			
Multiple VHL tumors16	57	NA	No	Multiple RCC			
Multiple VHL tumors17	47	NA	No	Multiple RCC			
Multiple VHL tumors18	44	NA	No	Multiple RCC			
Multiple VHL tumors19	29	NA	No	RCC	Multiple renal cysts	Multiple pancreatic cysts	
Multiple VHL tumors20	63	NA	No	Multiple RCC	Pancreatic cyst		
Multiple VHL tumors21	61	NA	No	PET	Multiple RCC		
Multiple VHL tumors22	NA	F	No	RCC	Multiple pancreatic cysts		
Multiple VHL tumors23	NA	M	No	RCC	Polycythemia		
Multiple VHL tumors24	NA	NA	No	RCC	Polycythemia		
Multiple VHL tumors25	81	M	No	RCC			
Multiple VHL tumors26	65	M	No	PGL TAP	Multiple renal cysts		
Multiple VHL tumors27	39	F	No	PCC	Pancreatic cyst		
Multiple VHL tumors28	47	M	No	PGL TAP	PET		
Multiple VHL tumors29	41	M	No	PCC	RCC		
Multiple VHL tumors30	55	M	No	PCC	Multiple renal cysts		
Multiple VHL tumors31	47	F	No	PCC	PET		
Multiple VHL tumors32	78	F	No	PCC	Multiple renal cysts	PET	Pancreatic cyst
Multiple VHL tumors33	57	F	No	PCC	RCC	PET	
Multiple VHL tumors34	NA	M	No	PCC	PET		
Multiple VHL tumors35	63	M	No	PCC	RCC		
Multiple VHL tumors36	58	M	No	PCC	RCC		
Multiple VHL tumors37	61	F	No	PCC	Pancreatic cyst		
Multiple VHL tumors38	51	M	No	PCC	RCC		
Multiple VHL tumors39	63	M	No	Multiple RCC	PET		
Multiple VHL tumors40	69	M	No	RCC	PET		
Multiple VHL tumors41	43	F	No	Multiple pancreatic cysts			
Multiple VHL tumors42	NA	M	No	Multiple RCC	PET		
Multiple VHL tumors43	NA	F	No	RCC	PET		
Multiple VHL tumors44	58	F	No	Multiple PET			
Multiple VHL tumors45	60	F	No	Multiple PET			
Multiple VHL tumors46	NA	M	No	Multiple renal cysts	PET		
Multiple VHL tumors47	56	M	No	Multiple renal cysts	Multiple PET		
Multiple VHL tumors48	NA	F	No	Multiple pancreatic cysts			
Multiple VHL tumors49	70	F	No	Multiple pancreatic cysts			
Multiple VHL tumors50	64	F	No	Multiple pancreatic cysts			
Multiple VHL tumors51	NA	F	No	PET	Pancreatic cyst		
Multiple VHL tumors52	49	F	No	RCC	PET		
Multiple VHL tumors53	63	F	No	Multiple PET			
Multiple VHL tumors54	58	M	No	RCC	PET		
Multiple VHL tumors55	61	M	No	RCC	PET		
Multiple VHL tumors56	64	M	No	PET	Pancreatic cyst		
Multiple VHL tumors57	79	M	No	PCC	RCC		
Multiple VHL tumors58	NA	M	No	Multiple PET			
Multiple VHL tumors59	59	F	No	Multiple PET			
Multiple VHL tumors60	NA	M	No	Multiple PET			
Multiple VHL tumors61	NA	M	No	Multiple PET			
Multiple VHL tumors62	64	M	No	Multiple PET			
Multiple VHL tumors63	58	F	No	Multiple renal cysts	PET		
Multiple VHL tumors64	NA	F	No	Multiple renal cysts	PET		
Multiple VHL tumors65	61	F	No	Multiple PET			
Multiple VHL tumors66	76	F	No	RCC	Multiple PET		
Multiple VHL tumors67	52	F	No	RCC	PET		
Multiple VHL tumors68	11	F	No	PET	Pancreatic cyst		
Multiple VHL tumors69	69	NA	Yes (Pancreatic cyst)	PGL TAP	Polycythemia		
Multiple VHL tumors70	55	F	No	PGL TAP	Polycythemia		
Single VHL tumor1	51	F	No	CNS hemangioblastoma			
Single VHL tumor2	54	M	No	Multiple renal cysts			
Single VHL tumor3	12	F	No	RCC			
Single VHL tumor4	42	M	No	RCC			
Single VHL tumor5	25	NA	No	Retinal hemangioblastoma			
Single VHL tumor6	14	NA	No	Retinal hemangioblastoma			
Single VHL tumor7	50	NA	No	CNS hemangioblastoma			
Single VHL tumor8	35	NA	No	CNS hemangioblastoma			
Single VHL tumor9	32	NA	No	Medulla hemangioblastoma			
Single VHL tumor10	21	NA	No	CNS hemangioblastoma			
Single VHL tumor11	17	NA	No	CNS hemangioblastoma			
Single VHL tumor12	36	NA	No	CNS hemangioblastoma			
Single VHL tumor13	22	NA	No	CNS hemangioblastoma			
Single VHL tumor14	22	NA	No	CNS hemangioblastoma			
Single VHL tumor15	14	NA	No	CNS hemangioblastoma			
Single VHL tumor16	30	NA	No	CNS hemangioblastoma			
Single VHL tumor17	35	NA	No	CNS hemangioblastoma			
Single VHL tumor18	22	NA	No	Retinal hemangioblastoma			
Single VHL tumor19	33	NA	No	Retinal hemangioblastoma			
Single VHL tumor20	37	NA	No	CNS hemangioblastoma			
Single VHL tumor21	23	NA	No	CNS hemangioblastoma			
Single VHL tumor22	16	NA	No	CNS hemangioblastoma			
Single VHL tumor23	17	NA	No	Retinal hemangioblastoma			
Single VHL tumor24	19	NA	No	CNS hemangioblastoma			
Single VHL tumor25	NA	NA	No	CNS hemangioblastoma			
Single VHL tumor26	29	M	No	Retinal hemangioblastoma			
Single VHL tumor27	NA	F	No	Endolymphatic sac tumor			
Single VHL tumor28	39	M	No	RCC			
Single VHL tumor29	25	F	No	Endolymphatic sac tumor			
Single VHL tumor30	66	F	No	Multiple pancreatic cysts			
Single VHL tumor31	14	F	No	PET			
Single VHL tumor32	41	F	No	Multiple pancreatic cysts			
Single VHL tumor33	22	F	No	Endolymphatic sac tumor			
Single VHL tumor34	34	M	No	CNS hemangioblastoma			
Single VHL tumor35	18	M	No	Pancreatic cyst			
Single VHL tumor36	67	M	No	Multiple pancreatic cysts			
Single VHL tumor37	58	M	No	Multiple renal cysts			
Single VHL tumor38	38	F	No	Retinal hemangioblastoma			
Single VHL tumor39	60	F	No	CNS hemangioblastoma			
Single VHL tumor40	30	F	No	Pancreatic cyst			
Single VHL tumor41	59	M	No	PET			
Single VHL tumor42	40	F	No	Retinal hemangioblastoma			
Single VHL tumor43	27	F	No	Retinal hemangioblastoma			
Single VHL tumor44	71	F	No	Pancreatic cyst			
Single VHL tumor45	59	F	No	CNS hemangioblastoma			
Single VHL tumor46	11	F	No	Retinal hemangioblastoma			
Single VHL tumor47	43	F	No	PET			
Single VHL tumor48	34	F	No	PET			
Single VHL tumor49	23	F	No	CNS hemangioblastoma			
Single VHL tumor50	31	F	No	CNS hemangioblastoma			
Single VHL tumor51	NA	M	No	Medulla hemangioblastoma			



Single VHL tumor52	78	F	No	CNS hemangioblastoma				
Single VHL tumor53	NA	F	No	PET				
Single VHL tumor54	NA	M	No	PET				
Single VHL tumor55	NA	M	No	CNS hemangioblastoma				
Single VHL tumor56	NA	F	No	Multiple pancreatic cysts				
Single VHL tumor57	NA	F	No	Pancreatic cyst				
Single VHL tumor58	42	F	No	CNS hemangioblastoma				
Single VHL tumor59	NA	M	No	Endolymphatic sac tumor				
Single VHL tumor60	35	M	No	CNS hemangioblastoma				
Single VHL tumor61	25	F	No	Multiple pancreatic cysts				
Single VHL tumor62	NA	F	No	PET				
Single VHL tumor63	37	M	No	Endolymphatic sac tumor				
Single VHL tumor64	NA	M	No	Multiple pancreatic cysts				
Single VHL tumor65	45	F	No	PET				
Single VHL tumor66	40	M	No	Pancreatic cyst				
Single VHL tumor67	37	F	No	Multiple pancreatic cysts				
Single VHL tumor68	38	M	No	Multiple pancreatic cysts				
Single VHL tumor69	33	F	No	Pancreatic cyst				
Single VHL tumor70	37	M	No	Epididymal cystadenoma				
Single VHL tumor71	42	F	No	Polycythemia				
Single VHL tumor72	14	F	No	Polycythemia				
Single VHL tumor73	14	M	No	Polycythemia				
Single VHL tumor74	43	M	No	Polycythemia				
Single VHL tumor75	NA	M	No	Polycythemia				
VHL-like1	53	NA	Yes (RCC)	PCC				
VHL-like2	35	F	Yes (CNS hemangioblastoma)	RCC				
VHL-like3	73	F	Yes (RCC)	RCC				
VHL-like4	64	F	Yes (RCC)	RCC				
VHL-like5	34	F	Yes (RCC)	RCC				
VHL-like6	28	F	Yes (RCC)	RCC				
VHL-like7	42	M	Yes (RCC)	RCC				
VHL-like8	55	F	Yes	CNS hemangioblastoma				
VHL-like9	45	M	Yes (RCC)	PET				
VHL-like10	70	F	Yes (RCC)	PCC				
VHL-like11	NA	F	Yes (PET)	PGL HN				
VHL-like12	21	F	Yes (RCC)	Bilateral PCC				
VHL-like13	24	F	No	Retinal hemangioblastoma	RCC			PCC
VHL-like14	35	NA	No	CNS hemangioblastoma	RCC			
VHL-like15	54	NA	No	Medulla hemangioblastoma	Multiple RCC			PGL TAP
VHL-like16	34	NA	Yes (CNS hemangioblastoma)	CNS hemangioblastoma				
VHL-like17	42	NA	No	Multiple medulla hemangioblastomas				
VHL-like18	35	NA	Yes (RCC)	RCC				
VHL-like19	56	NA	Yes (RCC)	RCC				
VHL-like20	56	NA	No	Multiple CNS hemangioblastomas				
VHL-like21	38	NA	No	Multiple CNS hemangioblastomas	RCC			
VHL-like22	67	NA	No	Multiple CNS hemangioblastomas				
VHL-like23	20	NA	No	Multiple CNS hemangioblastomas	PET			
VHL-like24	NA	NA	No	Multiple retinal hemangioblastomas	RCC			Pancreatic cyst
VHL-like25	43	NA	Yes (CNS hemangioblastoma)	CNS hemangioblastoma				
VHL-like26	NA	F	No	CNS hemangioblastoma	Retinal hemangioblastoma			
VHL-like27	NA	F	No	Multiple retinal hemangioblastomas				
VHL-like28	NA	M	No	CNS hemangioblastoma	PCC			
VHL-like29	NA	NA	No	CNS hemangioblastoma	PCC			Renal cyst
VHL-like30	NA	NA	No	Multiple CNS hemangioblastomas				
VHL-like31	NA	NA	No	CNS hemangioblastoma	Retinal hemangioblastoma			Multiple pancreatic cysts
VHL-like32	NA	NA	Yes (RCC)	RCC				
VHL-like33	NA	M	Yes (RCC)	RCC				
VHL-like34	NA	F	Yes (RCC)	RCC				
VHL-like35	NA	NA	Yes	CNS hemangioblastoma				
VHL-like36	NA	F	Yes	CNS hemangioblastoma				
VHL-like37	NA	NA	No	CNS hemangioblastoma	RCC			
VHL-like38	36	F	No	Multiple retinal hemangioblastomas				
VHL-like39	NA	F	Yes	CNS hemangioblastoma	Multiple retinal hemangioblastomas			PCC
VHL-like40	NA	M	Yes	CNS hemangioblastoma	Multiple retinal hemangioblastomas			Multiple RCC
VHL-like41	NA	F	No	CNS hemangioblastoma	Multiple pancreatic cysts			
VHL-like42	NA	F	No	Multiple retinal hemangioblastomas				
VHL-like43	NA	NA	No	CNS hemangioblastoma	Retinal hemangioblastoma			
VHL-like44	NA	NA	No	CNS hemangioblastoma	Retinal hemangioblastoma			PCC
VHL-like45	NA	NA	No	Multiple CNS hemangioblastomas				
VHL-like46	NA	F	No	CNS hemangioblastoma	Multiple retinal hemangioblastomas			Multiple RCC
VHL-like47	37	F	Yes (RCC)	RCC				Multiple pancreatic cysts
VHL-like48	47	M	No	CNS hemangioblastoma	RCC			
VHL-like49	53	M	Yes (RCC)	RCC				
VHL-like50	42	F	No	Medulla hemangioblastoma	RCC			
VHL-like51	NA	F	No	Retinal hemangioblastoma	PCC			
VHL-like52	69	M	No	CNS hemangioblastoma	RCC			
VHL-like53	44	F	No	Retinal hemangioblastoma	Pancreatic cyst			
VHL-like54	78	M	No	CNS hemangioblastoma	PCC			
VHL-like55	55	F	No	CNS hemangioblastoma	RCC			
VHL-like56	50	F	No	CNS hemangioblastoma	PGL TAP			
VHL-like57	36	F	No	CNS hemangioblastoma	PGL TAP			PET
VHL-like58	56	M	No	CNS hemangioblastoma	PGL TAP			Pancreatic cyst
VHL-like59	49	F	No	Medulla hemangioblastoma	PCC			
VHL-like60	59	M	No	CNS hemangioblastoma	PCC			
VHL-like61	59	M	No	CNS hemangioblastoma	PCC			
VHL-like62	66	F	No	Medulla hemangioblastoma	PCC			
VHL-like63	67	F	No	CNS hemangioblastoma	PCC			
VHL-like64	33	M	Yes (RCC)	PCC				
VHL-like65	29	F	Yes (RCC)	PCC				
VHL-like66	15	F	No	CNS hemangioblastoma	RCC			
VHL-like67	NA	M	No	CNS hemangioblastoma	PET			
VHL-like68	NA	M	No	CNS hemangioblastoma	PCC			
VHL-like69	52	F	Yes (RCC)	PGL HN				
VHL-like70	50	M	Yes (RCC)	PCC				
VHL-like71	30	M	Yes (RCC)	PCC				
VHL-like72	48	M	Yes (RCC)	PCC				
VHL-like73	32	F	No	CNS hemangioblastoma	PGL HN			Renal cyst
VHL-like74	42	M	No	CNS hemangioblastoma	PCC			
VHL-like75	38	F	Yes (RCC)	PGL HN				
VHL-like76	20	F	No	CNS hemangioblastoma	PGL TAP			