Table S2. Variant interpretation.

Gene	Variant	ID patient	Coding effect	Pathogenicity	Public Databases: - ExAC - COSMIC	Methodology to assess mutations as pathogenic: - Pubmed - In silico analysis: SIFT, Mutation Taster and Polyphen2
EPAS1	c.1592C>T, p.Pro531Leu	335 (S), 657 (S) and 967 (S)	Missense	Mutation	Not reported Not reported	- Previously reported in a case with multiple PGL and erythrocytosis [1]. - SIFT: deleterious (score 0.02). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
EPAS1	c.1606C>A, p.Asp536Tyr	344 (S)	Missense	Mutation	Not reported Not reported	- Previously reported: Hidroxilation point described [1]. - SIFT: deleterious (score 0.02). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
EPAS1	c.1599_1604delCCCCAT, p.Ile533_Pro534del	728 (S)	In-frame	Mutation	Not reported Not reported	- Previously reported: Hidroxilation point described [1].
EPAS1	c.1615G>T, p.Asp539Tyr	727 (S)	Missense	Mutation	Not reported Not reported	- Previously reported: Hidroxilation point described [1]. - SIFT: deleterious (score 0.02). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
HRAS	c.181C>A, p.Gln61Lys	167 (S), 379 (S), 587 (S)	Missense	Mutation	Not reported COSM496 and COSM123649.	- Reported 2 times [2, 3]. - SIFT: deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Benign with a score of 0.012
HRAS	c.182A>G, p.Gln61Arg	118 (S), 133 (S), 460 (S), 475 (S), 636 (S), 647 (S), 659 (S) 550 (S), 658 (S), 764 (S)	Missense	Mutation	Not reported COSM244958 and COSM499	- Reported 2 times [2, 3]. - SIFT: deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Benign with a score of 0.008

HRAS	c.37G>C, p.Gly13Arg	62 (S), 396 (S)	Missense	Mutation	Not reported COSM486 and COSM99938	- Reported 2 times [2, 3]. - SIFT: deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 0.997
NF1	c.6855C>A, p.Tyr2285*	145 (S)	Nonsense	Mutation	0.000008251/0 hom COSM33676 and COSM705652.	
RET	c.1900T>C, p.Cys634Arg	103 (S)	Missense	Mutation	0.000008274/0 hom COSM 966	- Described in MEN2 syndrome. First reported 1993 [4, 5]. - SIFT: deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
RET	c.1998G>C, p.Lys666Asn	894 (G)	Missense	Mutation	0.000008242/0 hom Not reported.	- Described mutations in the same amino acid residue in MEN2 syndrome [5]. - Functional studies have demonstrated that p.K666N mutation is associated with a high level of RET and ERK phosphorylation and a high transforming potential [6]. - It has been described in medullary thyroid carcinoma patients [7]. - SIFT: deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 0.999
RET	c.2410G>T, p.Val804Leu	615 (G)	Missense	Mutation	0.00001569/ 0 hom Not reported	- Described in MEN2 syndrome [5]. First described in 1995 [8]. - SIFT: deleterious (score 0.05). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
RET	c.2753T>C, p.Met918Thr	889 (S), 965 (S), 63 (S), 553 (S), 653 (S), 751 (S), 760 (S)	Missense	Mutation	Not reported COSM965	- Described in MEN2 syndrome [5]. First described in 1994 [9]. - SIFT: deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 0.999
SDHA	c.1754G>A,	424 (G)	Missense	Mutation	0.000008282/0 hom	- Negative SDHB- and SDHA-IHC

	p.Arg585Gln				COSM1067147	- LOVD: not reported - SIFT: deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
SDHA	c.457-1G>A, p?	510 (G), 449 (G)	Splice acceptor variant	Mutation	Not reported Not reported	- Negative SDHB- and SDHA-IHC (ID 510) - LOVD: not reported.
SDHAF2	c.362G>A, p.Trp121*	444 (G)	Nonsense	Mutation	Not reported Not reported	- Negative SDHB-IHC - LOVD: not reported.
SDHB	c.166_170delCCTCA, p.Pro56delTyrfs*5	243 (G), 365 (G), 368 (G), 301 (G), 312 (G), 278 (G)	Frameshift	Mutation	Not reported Not reported	- LOVD: Reported 9 times: First time at 2004 [10].
SDHB	c.112C>T, p.Arg38*	671 (G)	Nonsense	Mutation	Not reported Not reported	- LOVD: not described.
SDHB	c.127G>C, p.Ala43Pro	500 (G)	Missense	Mutation	Not reported Not reported	- LOVD: Reported 3 times: First report at 2003 [11]. - SIFT: Tolerated (score 0.19). - Mutation Taster: Disease causing (p-value 0.999) - Polyphen 2: Benign with a score of 0.356
SDHB	c.269G>A, p.Arg90Gln	353 (G)	Missense	Mutation	0.000008315/0 hom Not reported	- LOVD: Reported 3 times: First report at 2006 [12]. - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
SDHB	c.287-3C>G, p?	433 (G)	Splice site	Mutation	- Not reported	- LOVD: Not reported. - Reported 1 time [13]. - We demonstrated the effect on splicing (data not shown).
SDHB	c.423+1G>A, p?	442 (G)	Splice site	Mutation	- Not reported	- LOVD: Reported 9 times: First report at 2003 [14]
SDHB	c.464C>G, p.Pro155Arg	403 (S)	Missense	Mutation	Not reported Not reported	- LOVD: Not reported. - FFPE tumor not available to perform SDHB-IHC. - The second hit was found using SNP array: loss of 1p (data not shown). - SIFT: Deleterious (score 0).

						- Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
SDHB	c.544_550delGGGCTCT, p.Gly182Thrfs*36	413 (G)	Frameshift	Mutation	Not reported Not reported Not ensembl.	- LOVD: Not reported.
SDHB	c.557G>A, p.Cys186Tyr	364 (G)	Missense	Mutation	Not reported Not reported	- LOVD: Reported 4 times. First time at 2007[15]. - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
SDHB	c.725G>A, p.Arg242His	352 (G), 541 (G)	Missense	Mutation	0.00002471/0 hom Not reported	- LOVD: Reported 12 times: First time at 2002 [16]. - SIFT: Deleterious (score 0.01). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
SDHB	c.419T>A, p.Val140Asp	479 (G)	Missense	Mutation (VUS)	Not reported Not reported Not ensembl.	- LOVD: Not reported. - A variant in the same amino acid residue has been described 7 times in LOVD: c.418G>T, p.Val140Phe. - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
SDHB	c.278G>A, p.Cys93Tyr	175 (G)	Missense	Mutation	Not reported. COSM1664073	- LOVD: Reported 1 time. First time at 2009: [17]. - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 1). - Polyphen 2: Probably damaging with a score of 1.000
SDHB	c.424-3C>G, p?	330 (G)	Splice site	Mutation	- Not reported	- LOVD: Reported 3 times: First time at 2005 [18].
SDHB	c.643-2A>C, p?	497 (G)	Splice site	Mutation	- Not reported	- LOVD: Reported 1 time [17].
SDHB	c.540G>C, p.Leu180Leu	815 (G)	Synonymous	Mutation	0.000008237/0 hom Not reported	- LOVD: Not reported. - In silico tools (ESE-finder) predicted this variant affected splicing. We demonstrated by sequencing cDNA the lack of mutant allele (data not shown).
SDHB	exon 1 deletion	400 (G), 430 (G), 487 (G),	Deletion	Mutation	- -	- Previously reported in familial paraganglioma syndrome [19].

		640 (G), 757 (G), 66 (G), 157 (G), 327 (G), 485 (G).				
SDHC	c.43C>T, p.Arg15*	483 (G)	Nonsense	Mutation	Not reported Not reported	- LOVD: Reported 4 times: First time at 2007 [20].
SDHC	c.253-255dupTTT, p.Phe85dup	3 (G)	In-frame	Mutation	Not reported Not reported	- LOVD: Reported 2 times. First time at 2008 [21].
SDHD	c.334_337delACTG, p.Asp113Metfs*21	251 (G), 715 (G)	Frameshift	Mutation	Not reported Not reported	- LOVD: Reported 2 times: First time at 2005 [22].
SDHD	c.191_192delTC, p.Leu64Profs*4	441 (G)	Frameshift	Mutation	Not reported Not reported	- LOVD: Reported 3 times: First time at 2001 [23].
SDHD	c.2T>C, p.Met1?	340 (G)	Missense	Mutation	Not reported Not reported	- LOVD: Not reported. - This mutation affects the first methionine and thus the correct processing of the gene. - Start loss
SDHD	c.168_169delTT, p.Ser57Trpfs*11	307 (G)	Frameshift	Mutation	Not reported Not reported	- LOVD: Reported 2 times. First time at 2005 [17].
SDHD	c.210G>T, p.Arg70Ser	311 (G)	Missense	Mutation	Not reported Not reported	- LOVD. Reported 1 time. First time at 2009 [17]. - LOVD: Mutations affecting the same codon (p.Arg70Met; p.Arg70Gly) have been described. Changes affecting this codon destroy hemo interaction and affect the function of the protein. - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
SDHD	c.112C>T, p.Arg38*	1004 (S)	Non-sense	Mutation	Not reported Not reported	- LOVD: Reported 8 times. First time at 2000 [24].
TMEM127	c.115_118delCTGT, p.Ile41Argfs*39	626 (G)	Frameshift	Mutation	Not reported Not reported	
TMEM127	c.221A>C,	633 (G)	Missense	Mutation	Not reported	- We found LOH involving wild-type allele in the

	p.Tyr74Ser				Not reported	corresponding tumor DNA. - SIFT: Deleterious (score 0.03). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Benign with a score of 0.058
VHL	c.191G>C, p.Arg64Pro	465 (S)	Missense	Mutation	Not reported Not reported	- The UMD-VHL mutations: Request ID: 190515141147-33 - SIFT: Tolerated (score 0.13). - Mutation Taster: Disease causing (p-value0.999) - Polyphen 2: Probably damaging with a score of 1.000
VHL	c.197_211delinsCTCGT, p.Val66_Pro71delinsAlaArgAla	1025 (S)	In-frame	Mutation	Not reported Not reported	- UMD-VHL not reported.
VHL	c.227T>A, p.Phe76Tyr	498 (S)	Missense	Mutation	Not reported COSM14321	- UMD-VHL not reported. - SIFT: Deleterious (score: 0) - Mutation Taster: Disease causing (p-value: 0.974) - Polyphen 2: Probably damaging with a score of 0.935
VHL	c.250G>C, p.Val84Leu	242 (S)	Missense	Mutation	Not reported COSM236660	- The UMD-VHL mutations: Request ID: 190515142416-21 - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value0.549) - Polyphen 2: Benign with a score of 0.017
VHL	c.260T>C, p.Val87Ala	631 (S), 649 (S)	Missense	Mutation	Not reported Not reported	- UMD-VHL not reported. - SIFT: Deleterious (score 0.04). - Mutation Taster: Polymorphism (p-value0.996) - Polyphen 2: Possibly damaging with a score of 0.573
VHL	c.389T>G, p.Val130Gly	480 (S)	Missense	Mutation	Not reported COSM100047	- UMD-VHL not reported. - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 1.000
VHL	c.475A>G, p.Lys159Glu	513 (S)	Missense	Mutation	Not reported COSM144975	- The UMD-VHL mutations: Request ID: 190515142532-25 - SIFT: Deleterious (score 0.03).

						- Mutation Taster: Disease causing (p-value 0.996) - Polyphen 2: Probably damaging with a score of 0.999
VHL	c.482G>A, p.Arg161Gln	616 (G), 581 (S)	Missense	Mutation	Not reported COSM18097	- The UMD-VHL mutations: Request ID: 190515142607-149 - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 0.999) - Polyphen 2: Probably damaging with a score of 1.000
VHL	c.491A>G, p.Gln164Arg	635 (S)	Missense	Mutation	Not reported COSM14283	- The UMD-VHL mutations: Request ID: 190515142653-45 - SIFT: Tolerated (score 0.13). - Mutation Taster: Disease causing (p-value 0.999) - Polyphen 2: Probably damaging with a score of 0.998
VHL	c.496G>T, p.Val166Phe	619 (S)	Missense	Mutation	Not reported COSM17982	- The UMD-VHL mutations: Request ID: 190515142746-49 - SIFT: Deleterious (score 0.03). - Mutation Taster: Disease causing (p-value 0.999) - Polyphen 2: Probably damaging with a score of 0.989
MAX	c.425C>T, p.Ser142Leu	578 (G)	Missense	VUS	0.00001647/0 hom COSM4577970	- Probably non-pathogenic. Although it has been reported two times [25, 26], this variant did not show functional effect on MYC regulation and the aminoacid is located outside the basic helix-loop-helix leucine zipper domain of the MAX protein [27] - SIFT: tolerated (score 0.33). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 0.999
SDHC	c.*90T>C, p?	1017 (G)	Intronic	VUS	Not reported Not reported	- LOVD: Not reported.
SDHB	c.455C>T, p.Ser152Phe	425 (G)	Missense	VUS	0.00005767/0 hom Not reported	- LOVD: Not reported. - FFPE tumor not available to perform SDHB-IHC. - SIFT: Deleterious (score 0). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Benign with a score of 0.167
SDHB	c.49A>G,	619 (G)	Missense	VUS	Not reported	- LOVD: Reported 1 time: Probably no pathogenicity.

	p.Thr17Ala				Not reported Not ensembl	- SIFT: Tolerated (score 0.59) -Mutation Taster: Polymorphism (p-value 1) - Polyphen 2: Benign with a score of 0.000
SDHAF2	c.451C>G, p.Gln151Glu	405 (G)	Missense	VUS	Not reported Not reported	- LOVD: not reported. - This change affects a highly conserved residue in the phylogenetic tree. According to bioinformatic prediction tools, this version is considered as probably pathogenic PolyPhen-probably damaging, and it can affect splicing according to ESEfinder tool. However, two other tools (AGVGD and SIFT-tolerated) classified as a benign variant. Therefore, until we cannot show the effect of the change it should be considered as a VUS. The patient left the follow-up and it was not possible to obtain a new blood sample to retain RNA extract and analyze the potential effect on splicing or FFPE tumor to analyze SDHB-IHC. - SIFT: Tolerated (score 0.37). - Mutation Taster: Disease causing (p-value 1) - Polyphen 2: Probably damaging with a score of 0.982