

**Germline Mutations and Phenotypic Associations in Korean Patients With
Pheochromocytoma and Paraganglioma: A Multicenter Study and Literature Review**

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Supplemental Data Table S1. Characteristics of cohort with PPGL (N=59) were obtained from six university hospitals

Characteristics	% (N)
Female sex	67.8% (40)
Age at diagnosis, yrs	52.5±14.3
Family history	6.8% (4)
Type	
PCC	88.1% (52)
PGL	10.2% (6)
PCC & PGL	1.7% (1)
Location	
Adrenal, unilateral	83.1% (49)
Adrenal, bilateral	5.1% (3)
Adrenal and Head & Neck	1.7% (1)
Head & Neck	0% (0)
Other sites	10.2% (6)
Multiple tumors	15.3% (9)
Tumor size, cm	4.3 (2.6–6.0)
Metastasis	6.8% (4)
Recurrence	12.3% (7/57)
Biochemical status	
Adrenergic	5.1% (3)
Noradrenergic	47.5% (28)
Adrenergic/Noradrenergic	40.7% (24)
Silent	6.8% (4)
Presence of other tumors	18.6% (11)

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).

Abbreviations: PPGL, pheochromocytoma and paraganglioma; PCC, pheochromocytoma; PGL, paraganglioma.

RET	c.1891G>T	p.Asp631Tyr	Likely-Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PM1, PM2, PM5, PP3, PP5
RET	c.1900T>C	p.Cys634Arg	Likely-Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PM1, PM2, PM5, PP3, PP5
RET	c.1901G>A	p.Cys634Tyr	Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PM1, PM2, PM5, PP3, PP5
RET	c.1902C>G	p.Cys634Trp	Likely-Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PM1, PM2, PM5, PP3, PP5
RET	c.2753T>C	p.Met918Thr	Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PS3, PM1, PM2, PM5, PP3, PP5
NF1	c.928delC	p.His310Metfs*7	Likely-Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PVS1, PM2
NF1	c.4029dupT	p.Glu1344*	Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PVS1, PM2, PP5
MAX	c.289C>T	p.Gln97*	Pathogenic	J Med Genet 2022 Vol. 59(1):56-64	PVS1, PM2, PP5
RET	c.1900T>C	p.Cys634Arg	Likely-Pathogenic	Endocr J. 1998 Aug;45(4):555-61	PM1, PM2, PM5, PP3, PP5
RET	c.1900T>C	p.Cys634Arg	Likely-Pathogenic	Endocr J. 1998 Aug;45(4):555-61	PM1, PM2, PM5, PP3, PP5
RET	c.1852T>C	p.Cys618Arg	Likely-Pathogenic	Endocr J. 1998 Aug;45(4):555-61	PM1, PM2, PM5, PP3, PP5
RET	c.1901G>A	p.Cys634Tyr	Likely-Pathogenic	Endocr J. 1998 Aug;45(4):555-61	PM1, PM2, PM5, PP3, PP5
RET	c.1901G>A	p.Cys634Tyr	Likely-Pathogenic	Endocr J. 1998 Aug;45(4):555-61	PM1, PM2, PM5, PP3, PP5
SDHB	c.757delT	p.Cys253Valfs*5	Pathogenic	Fam Cancer. 2016 Oct;15(4):601-6	PVS1, PM2, PP5
SDHA	c.778G>A	p.Gly260Arg	Likely-Pathogenic	Endocrinol Metab (Seoul). 2020 Dec;35(4):909-917	PS1, PM2, PP2, PP3, PP5
KIF1B	c.2787-2A>C	p.?	Likely-Pathogenic	Endocrinol Metab (Seoul). 2020 Dec;35(4):909-917	PVS1, PM2
RET	c.2692G>T	p.Asp898Tyr	Likely-Pathogenic	Endocrinol. 2018 Apr 15;2018:8657914	PM1, PM2, PP3, PP5

Several variants (RET p.Gln214His, RET 634 codon mutation without further information, SDHD p.Val111Ile, VHL p.Val114Arg, VHL p.Leu85Phe) from literature review has been reclassified as VUSs and subsequently excluded from the mutation(+) group.

^aPathogenicity of variants from literature review were reclassified according to ACMG/AMP guideline [15].

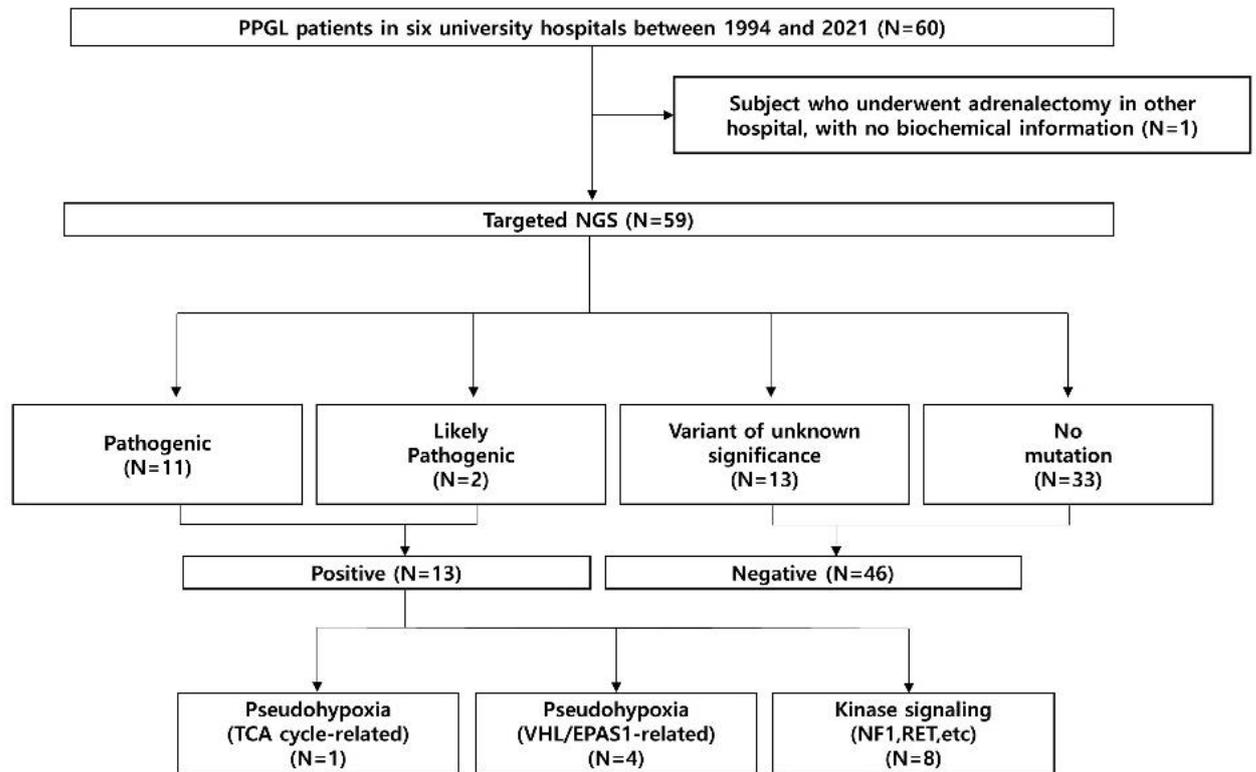
Supplemental Data Table S3. Common genotypic and phenotypic characteristics of all Korean PPGL cases

Characteristic	<i>SDHB</i> (N=16) ^a	<i>VHL</i> (N=30) ^a	<i>NFI</i> (N=8) ^a	<i>RET</i> (N= 31) ^a	<i>P-value</i>
Female sex	30.8% (4/13)	58.3% (14/24)	33.3% (2/6)	81.0% (17/21)	0.050
Age at diagnosis, yrs	40.2 ± 18.4 (13/13)	37.8 ± 16.3 (21/21)	45.5 ± 16.5 (6/6)	48.7 ± 12.6 (21/21)	0.246
Family history	50% (1/2)	52.9% (9/17)	0% (0/4)	73.7% (14/19)	0.055
Type					<0.001
PCC	46.2% (6/13)	91.6% (22/24)	100% (6/6)	100% (26/26)	
PGL	53.8% (7/13)	8.3% (2/24)	0% (0/6)	0% (0/26)	
PCC & PGL	0% (0/13)	0% (0/24)	0% (0/6)	0% (0/26)	
Location					<0.001
Adrenal, unilateral	40% (4/10)	34.8% (8/23)	100% (6/6)	53.3% (8/15)	
Adrenal, bilateral	0% (0/10)	56.5% (13/23)	0% (0/6)	46.7% (7/15)	
Adrenal & Head & Neck	0% (0/10)	0% (0/23)	0% (0/6)	0% (0/15)	
Head & Neck	10% (1/10)	0% (0/23)	0% (0/6)	0% (0/15)	
Other sites	50% (5/10)	8.7% (2/23)	0% (0/6)	0% (0/15)	
Multiple tumors	0% (0/3)	40% (2/5)	0% (0/4)	44.4% (4/9)	0.238
Tumor diameter, cm	4.5 (3.5–9.0; 10/10)	3.5 (2.4–4.3; 10/10)	5.3 (4.3–7.2; 6/6)	4.7 (3.2–6.0; 16/16)	0.014
Metastasis	58.3% (7/12)	36.4% (4/11)	0% (0/6)	0% (0/16)	0.002
Recurrence	25.0% (3/12)	27.3% (3/11)	16.7% (1/6)	6.25% (1/16)	0.290
Biochemical status					0.001
Adrenergic	0% (0/12)	0% (0/11)	0% (0/6)	17.6% (3/17)	
Noradrenergic	83.3% (10/12)	72.7% (8/11)	33.3% (2/6)	17.6% (3/17)	
Adrenergic/Noradrenergic	0% (0/12)	0% (0/11)	50% (3/6)	58.8% (10/17)	
Silent	16.7% (2/12)	27.3% (3/11)	16.7% (1/6)	5.9% (1/17)	
Presence of other tumors	0% (0/10)	40% (4/10)	66.7% (4/6)	92.8% (13/14)	<0.001
Consequences					<0.001
Frameshift	75.0% (12/16)	3.3% (1/30)	50% (4/8)	0% (0/33)	
Missense	25.0% (4/16)	86.7% (26/30)	12.5% (1/8)	100% (33/33)	
Nonsense	0% (0/16)	3.3% (1/30)	25.0% (2/8)	0% (0/33)	
Splicing	0% (0/16)	0% (0/30)	12.5% (1/8)	0% (0/33)	
Stop loss	0% (0/16)	6.6% (2/30)	0% (0/8)	0% (0/33)	

Values are expressed as percentage (%), mean±standard deviation, number (%), or median (interquartile range). Clinical data for all characteristics were collected from available cases only (shown as the number of cases indicated / the number of descriptions of each characteristic).

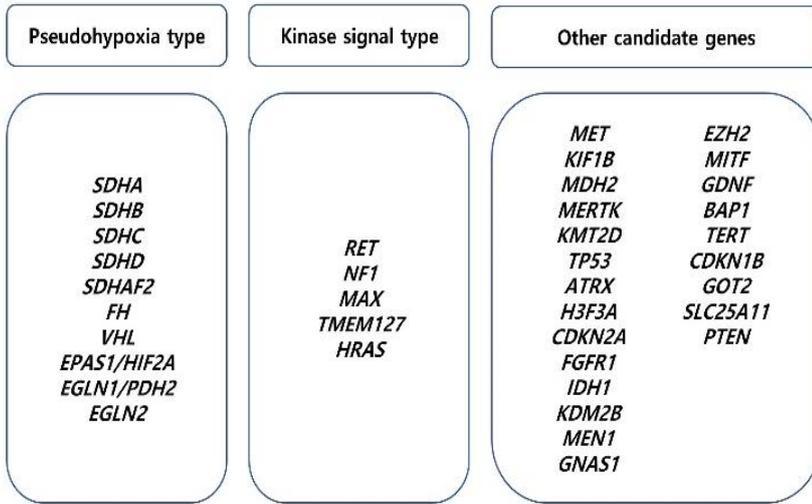
^aNumber of mutation-positive cases, including the literature review.

Abbreviations: PPGL, pheochromocytoma and paraganglioma; *SDH*, succinate dehydrogenase; *VHL*, von Hippel-Lindau; *NFI*, neurofibromatosis type 1; *RET*, rearranged during transformation; PCC, pheochromocytoma; PGL, paraganglioma.



Supplemental Data Fig. S1. Flow chart of this multicenter study.

Abbreviations: PPGL, pheochromocytoma and paraganglioma; TCA, tricarboxylic acid.



Abbreviations

Cluster1 Pseudohypoxia (N=10)	<i>SDHA</i>	Succinate dehydrogenase complex flavoprotein subunit A
	<i>SDHB</i>	Succinate dehydrogenase complex iron sulfur subunit B
	<i>SDHC</i>	Succinate dehydrogenase complex subunit C
	<i>SDHD</i>	Succinate dehydrogenase complex subunit D
	<i>SDHAF2</i>	Succinate dehydrogenase complex assembly factor 2
	<i>FH</i>	Fumarate hydratase
	<i>VHL</i>	Von Hippel-Lindau tumor suppressor
	<i>EPAS1/HIF2A</i>	Endothelial PAS domain protein 1
	<i>EGLN1/PDH2</i>	Egl-9 family hypoxia inducible factor 1
	<i>EGLN2/PDH1</i>	Egl-9 family hypoxia inducible factor 2
Cluster2 Kinase signaling (N=5)	<i>RET</i>	Ret proto-oncogene
	<i>NF1</i>	Neurofibromin 1
	<i>MAX</i>	MYC associated factor X
	<i>TMEM127</i>	Transmembrane protein 127
Other candidate genes (N=23)	<i>HRAS</i>	HRas proto-oncogene, GTPase
	<i>MET</i>	MET proto-oncogene, receptor tyrosine kinase
	<i>KIF1B</i>	Kinesin family member 1B
	<i>MDH2</i>	Malate dehydrogenase 2
	<i>MERTK</i>	MER proto-oncogene, tyrosine kinase
	<i>KMT2D</i>	Lysine methyltransferase 2D
	<i>TP53</i>	Tumor protein p53
	<i>ATRX</i>	ATRX chromatin remodeler
	<i>H3F3A</i>	H3 histone, family 3A
	<i>CDKN2A</i>	Cyclin dependent kinase inhibitor 2A
	<i>FGFR1</i>	Fibroblast growth factor receptor 1
	<i>IDH1</i>	Isocitrate dehydrogenase (NADP(+)) 1, cytosolic
	<i>KDM2B</i>	Lysine demethylase 2B
	<i>MEN1</i>	Menin 1
	<i>GNAS1/GNAS1</i>	GNAS complex locus 1
	<i>EZH2</i>	Enhancer of zeste 2 polycomb repressive complex 2 subunit
	<i>MITF</i>	Melanocyte inducing transcription factor
	<i>GDNF</i>	Gliial cell derived neurotrophic factor
	<i>BAP1</i>	BRCA1 associated protein 1
	<i>TERT</i>	Telomerase reverse transcriptase
	<i>CDKN1B</i>	Cyclin dependent kinase inhibitor 1B
	<i>GOT2</i>	Glutamic-oxaloacetic transaminase 2
	<i>SLC25A11</i>	Solute carrier family 25 member 11
<i>PTEN</i>	Phosphatase and tensin homolog	

Supplemental Data Fig. S2. PPGL molecular clusters and related genes analyzed using NGS in this study.

Abbreviations: PPGL, pheochromocytoma and paraganglioma; NGS, next-generation sequencing.



Supplemental Data Fig. S3. Genotypes of Korean patients with PCC/PGL (N=95) in this multicenter study (N=13) and the literature (N=82).

Abbreviations: PPC, pheochromocytoma; PGL, paraganglioma.