Brief Communication
Diagnostic Genetics

Ann Lab Med 2024;44:591-597
https://doi.org/10.3343/alm.2023.0376
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

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

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Genetic testing is recommended for all patients with pheochromocytomas and paragangliomas (PPGL) to establish genotype–phenotype associations. We investigated germline mutations in 59 patients with PPGL at six Korean university hospitals using next-generation sequencing (NGS) targeting 38 PPGL-associated genes, including those recommended by the Korean PPGL Task Force. Germline mutations were identified in 13 patients (22%), and affected four genes: *RET*, *NF1*, *VHL*, and *SDHD*. Germline mutations were significantly associated with a family history of PPGL, smaller tumor size, and the presence of other types of tumors. Using 95 Korean PPGL cases with germline mutations identified through a literature review and 13 cases from our cohort, we characterized genotype–phenotype correlations. Mutation hotspots were identified in specific codons of *RET* (codons 631 and 634), *VHL* (157 and 167), and *SDHB* (131 and 253). *NF1* mutations varied, indicating the absence of common hotspots. These findings highlight the efficacy of the recommended NGS panel for Korean patients with PPGL and the importance of genetic testing in establishing clinical management and personalized therapeutic strategies.

Key Words: Genotype, Germline, Korean, Paraganglioma, Phenotype, Pheochromocytoma

Received: September 21, 2023
Revision received: April 17, 2024
Accepted: July 16, 2024
Published online: July 29, 2024

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Pheochromocytomas (PCCs) and paragangliomas (PGLs) (PPGL) are neuroendocrine tumors derived from chromaffin cells that demonstrate notable clinical heterogeneity [1]. While solid tumors have a low incidence of germline mutations [2], PPGL exhibits a high prevalence, with germline mutations detected in up to 40% of cases and somatic mutations in 20%–30% [3-5]. The variability in the mutation prevalence is influenced by variability in factors such as mutation complexity, geographic location, and the patient selection method used [6]. Additionally, genotype–phenotype correlations appear to be race- and genetic background-dependent [7], highlighting the significance of germline mutation analysis in Korean patients with PPGL. Identifying germline mutations in patients with PPGL is crucial for prognosis prediction and genetic counseling, as germline mutations increase the risk of multiple tumors, metastasis, and recurrence [8-10]. While studies on the Korean population have explored these associations, the limited case numbers call for further research to generalize the findings to a broader population [11-13].

This study was approved by the Institutional Review Board of the Catholic University, Seoul, Korea (IRB approval number: XC19TEDI0046), and written informed consent was obtained from all participants. We enrolled 60 unrelated Korean patients diagnosed with PPGL between January 1994 and June 2021 across six university hospitals (Supplemental Data Fig. S1). We assessed clinical characteristics, tumor features, and outcomes, including recurrence and metastasis, by reviewing medical records. Recurrence was defined as the reappearance of PPGL post-surgery, with an elevated catecholamine level [12], whereas metastasis was identified in non-chromaffin organs [13]. One patient was excluded because of an incomplete medical record. Genomic DNA was extracted from peripheral blood and subjected to next-generation sequencing (NGS) using a custom panel (Thermo Fisher Scientific, Waltham, MA, USA) targeting 38 susceptibility genes, including all 10 basic genes and five genes recommended by the Korean PPGL Task Force [7] (Supplemental Data Fig. S2). Genomic mutations in PPGL, categorized into pseudohypoxia and kinase signaling clusters according to The Cancer Genome Atlas (TCGA) [14], alongside various candidate genes, highlight the utility of the NGS panel for efficient genetic analysis.

A total of 59 unrelated patients with PPGL, predominantly women (67.8%), had a mean age of 52.5 yrs at diagnosis. The characteristics of the patients with PPGL are summarized in Supplemental Data Table S1. Germline mutations were identified in 13 patients (22%): four in *RET* and four in *NF1*, both associated with kinase signaling; four in *VHL*, a pseudohypoxic *VHL/EPAS1*-related gene; and one in *SDHD*, a pseudohypoxic tricarboxylic acid (TCA) cycle-related gene (Table 1). We found no actual deletions/duplications at the exon level while checking copy number variation using Integrative Genomics Viewer and Detection of Exon Copy Number (version 2). A genotype–phenotype analysis was performed to explore the clinical characteristics of the 13 Korean patients harboring PPGL germline mutations [mutation (+)] compared with those who lacked germline mutations [mutation (–), N = 46; Table 2]. The mutation (+) group had a higher prevalence of a family history of PPGL and the concomitant presence of other tumor types ($P < 0.001$, each), but their tumors had a significantly smaller diameter ($P < 0.001$). We found no statistically significant differences between the groups in terms of sex, tumor type, recurrence rate, or biochemical status. Although not significant, the mutation (+) group tended to have been diagnosed at a younger age and had higher proportions of bilateral PCCs and multiple PPGL tumors.

Next, we reviewed previous reports on Korean PPGL cases, and mutations of pathogenicity were reclassified according to the ACMG guidelines [15]. We combined potentially overlapping cases from each study's institution into a single case to minimize the possibility of duplication bias in the statistics of mutation prevalence and associated clinical characteristics. In total, 95 Korean PPGL cases with germline mutations were collected, including 82 cases from 12 previous reports, as summarized in Supplemental Data Table S2, and 13 cases from the present study cohort (Supplemental Data Fig. S3). We compared the genotypic and phenotypic characteristics of the following four genes that were common in Korean patients with PPGL according to molecular clustering based on TCGA: *SDHB* (N = 16), *VHL* (N = 30), *NF1* (N = 8), and *RET* (N = 31). Tumor type, tumor location, tumor diameter, metastasis, biochemical status, the presence of other tumors, and the consequences of the germline mutations significantly differed among the four groups (all, $P < 0.05$) (Supplemental Data Table S3). Particularly, *RET* was the most frequently mutated at codons 631 and 634 of exon 11 (Fig. 1). *VHL* mutations were distributed widely across all exons; however, mutations typically occurred after codon 70. *SDHB* was frequently mutated at codons 131 and 253. The frequency of germline mutations in our cohort was 22%, which was significantly lower than the 40% previously reported. A review of Korean and international literature revealed a lower mutation positivity rate in Korean studies (5.6%–32.6%) [6, 11, 12], suggesting that the 40% frequency may be overestimated. Our finding of a 22% positivity rate aligns with those in global studies [16-

https://doi.org/10.3343/alm.2023.0376

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Table 1. Germline mutations and clinical characteristics of patients with PPGL at six university hospitals

Cluster	Gene	No. case	Sex	Age at diagnosis (yrs)	Family history	Clinical diagnosis	Tumor location	Tumor size (max, cm)	Multiple tumors	Metastasis	Recurrence	Biochemical status	Other tumors	cDNA change	Amino acid change	ACMG inter-pretation	Conse-quence	ClinVar accession
Cluster 1. Pseudohypoxia (TCA cycle-related)	SDHD	1	F	44	Yes	PCC/PGL	Rt adrenal, carotid body	2.0	Mu	No	Yes	Nor		NM_003002.3(*SDHD*): c.119delT	p.Ile40ThrfsTer46	P	Frameshift	Not reported
Cluster 1. Pseudohypoxia (VHL/EPAS-1-related)	VHL	2	M	16	No	PCC	Both adrenal	4.0	Mu	No	No	Nor		NM_000551.3(*VHL*): c.208G>A	p.Glu70Lys	P	Missense	VCV000043598.16
	VHL	3	F	49	No	PGL	Retro-peritoneum	3.5	S	No	No	Nor	Lymphoma	NM_000551.3(*VHL*): c.242C>T	p.Pro81Leu	LP	Missense	VCV000036899.24
	VHL	4	F	55	No	PCC	Lt adrenal	7.5	S	No	No	Nor		NM_000551.3(*VHL*): c.499C>T	p.Arg167Trp	P	Missense	VCV000002218.31
	VHL	5	M	70	Yes	PCC	Lt adrenal	2.6	Mu	Yes (bladder)	No	Nor		NM_000551.3(*VHL*): c.640T>A	p.*214Argext*14	LP	Stop lost	VCV000801933.6
Cluster 2. Kinase signaling	NF1	6	M	35	No	PCC	Rt adrenal	4.5	S	No	No	Nor	NF1	NM_001042492.2(*NF1*): c.6596del	p.Leu2199Ter	P	Nonsense	Not reported
	NF1	7	F	56	No	PCC	Lt adrenal	1.6	S	No	No	Nor	NF1	NM_001042492.2(*NF1*): c.1748A>G	p.Lys583Arg	P	Missense	VCV000068306.21
	NF1	8	M	66	No	PCC	Rt adrenal	4.3	S	No	No	Adr/Nor	NF1	NM_001042492.2(*NF1*): c.4800dup	p.Ala1601Serfs Ter21	P	Frameshift	Not reported
	NF1	9	M	40	No	PCC	Lt adrenal	6.0	S	No	Yes	Adr/Nor	NF1	NM_001042492.2(*NF1*): c.7869+1G>A	p?	P	Splice donor	VCV000480091.8
	RET	10	F	64	Yes	PCC	Both adrenal	4.6	Mu	No	No	Adr/Nor		NM_020975.4(*RET*): c.1891G>T	p.Asp631Tyr	P	Missense	VCV000024914.9
	RET	11	F	41	No	PCC	Lt adrenal	6.0	S	No	Yes	Adr/Nor	MTC	NM_020975.4(*RET*): c.1902C>G	p.Cys634Trp	P	Missense	VCV000013918.19
	RET	12	F	52	No	PCC	Lt adrenal	6.5	S	No	No	Adr/Nor	MTC	NM_020975.4(*RET*): c.1902C>G	p.Cys634Trp	P	Missense	VCV000013918.19
	RET	13	F	54	Yes	PCC	Rt adrenal	2.8	S	No	No	Adr/Nor	MTC	NM_020975.4(*RET*): c.1902C>G	p.Cys634Trp	P	Missense	VCV000013918.19

Abbreviations: PPGL, pheochromocytoma and paraganglioma; F, female; M, male; PCC, pheochromocytoma; PGL, paraganglioma; Rt, right; Lt, left; S, single; Mu, multiple; Nor, noradrenergic; Adr, adrenergic; NF1, neurofibromatosis type 1; MTC, medullary thyroid carcinoma; P, pathogenic; LP, likely pathogenic

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Table 2. Characteristics of patients according to the mutation status.

Characteristic	Mutation-negative (N=46)	Mutation-positive (N=13)	*P*
Female sex, N (%)	32 (69.6)	5 (62.5)*	0.588
Age at diagnosis, year, median (IQR)	54.5 (44–63)	52 (41–60)	0.146
Family history	0 (0)	4 (30.8)	<0.001
Type			0.160
PCC, N (%)	41 (89.1)	11 (84.6)	
PGL, N (%)	5 (10.2)	1 (7.7)	
PCC and PGL, N (%)	0 (0)	1 (7.7)	
Location			0.058
Adrenal, unilateral, N (%)	40 (87.0)	9 (69.2)	
Adrenal, bilateral, N (%)	1 (2.3)	2 (15.4)	
Adrenal, head, and neck, N (%)	0 (0)	1 (7.7)	
Head and neck, N (%)	0 (0)	1 (7.7)	
Other sites, N (%)	5 (10.9)	0 (0)	
Multiple tumors, N (%)	5 (10.9)	4 (30.8)	0.081
Tumor diameter, cm, median (IQR)	4.3 (2.5–6.1)	4.0 (2.7–6.0)	<0.001
Metastasis, N (%)	3 (6.5)	1 (7.7)	0.883
Recurrence, N (%)	4 (9.1)	2 (15.4)	0.315
Biochemical status			0.861
Adrenergic, N (%)	3 (6.5)	0 (0)	
Noradrenergic, N (%)	21 (45.7)	7 (53.8)	
Adrenergic/noradrenergic, N (%)	18 (39.1)	6 (46.2)	
Silent, N (%)	4 (8.7)	0 (0)	
Presence of other tumors, N (%)	3 (6.5)	8 (61.5)	<0.001

*The proportion was based on eight parent samples with available gender information.
For all characteristics, clinical data were collected from available cases only.
Abbreviations: PPGL, pheochromocytoma and paraganglioma; PCC, pheochromocytoma; PGL, paraganglioma; IQR, interquartile range

18], challenging the accuracy of the previously reported 40% rate [3, 4]. Pathogenic mutations were found only in the genes recommended for Korean PPGL screening, aligning with the recommendations of the Korean PPGL Task Force [7]. Therefore, these findings support the suitability of the genes recommended by the Korean PPGL Task Force for genetic testing [8].

In our cohort, mutation (+) patients had a family history of PPGL, smaller tumors at diagnosis, and a higher incidence of concurrent tumors. However, metastasis and recurrence rates were not significantly different from those of mutation (–) patients, potentially because of the limited sample size. PPGL germline mutation (+) cases were diagnosed earlier and often had a family history of PPGL and higher incidences of bilateral tumors, multiple tumors, metastases, and non-PPGL tumors, as reported in previous Korean and European studies [9, 12, 16, 17]. Previous studies on the Korean population [11, 12] indicated notable clinical differences among TCGA-based molecular clusters [14]. Furthermore, based on the literature review, we focused on germline mutations in genes with high mutation frequencies, including *RET*, *VHL*, *SDHB*, and *NF1*, and their phenotypic associations. We found high PGL and metastasis rates in *SDHB* mutation (+) cases and significant family history rates in *RET*, *VHL*, and *SDHB* mutation (+) cases. Comparing Korean PPGL cases with *SDHB*, *VHL*, *RET*, and *NF1* mutations with those in international studies revealed parallels and distinctions. Korean *SDHB* mutation (+) cases had a higher PGL frequency, mirroring trends in Asian Indians [18]. *VHL* and *RET* mutations in Koreans were associated with a higher incidence of bilateral PCCs, aligning with findings in previous Korean studies [11, 12]. However, *SDHB* and *VHL* mutations in Koreans exhibited a higher metastasis rate, differing from findings in Europeans [19] and Japanese [8]. Biochemically, pseudohypoxic cases with

https://doi.org/10.3343/alm.2023.0376

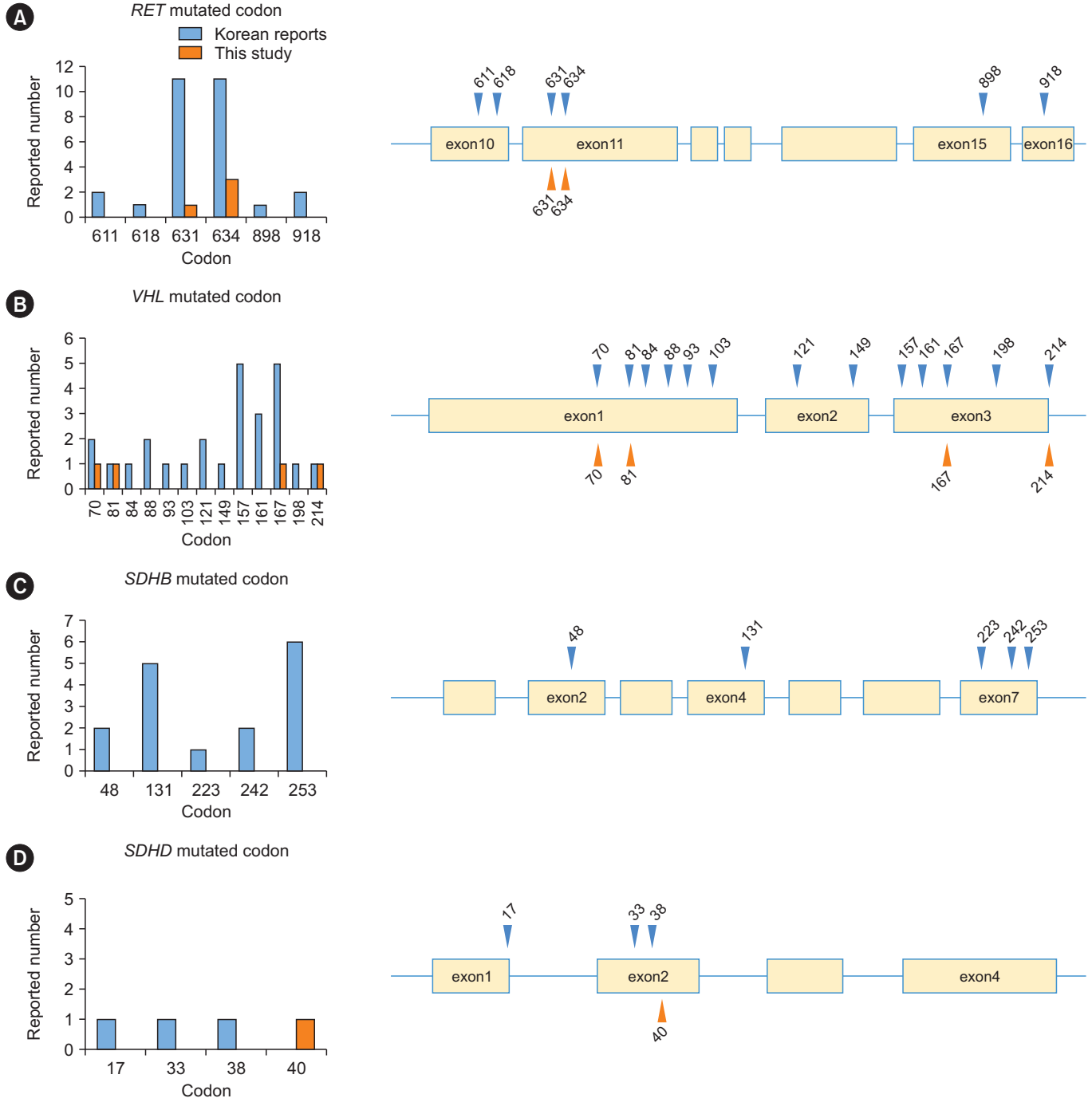

Fig. 1. Locations and frequencies of major causative gene mutations in Korean patients with PPGL) (N=95). Mutated codons and mutation frequencies in *RET* (A), *VHL* (B), *SDHB* (C), and *SDHD* (D). Blue triangles indicate sites of mutations reported previously, and orange triangles indicate sites of mutations detected in patients at six university hospitals in this study.
Abbreviation: PPGL, pheochromocytoma and paraganglioma.

SDHB and *VHL* mutations were mainly noradrenergic or silent, whereas kinase signaling types with *NF1* and *RET* mutations were predominantly adrenergic/noradrenergic. These results highlight mutations among molecular clusters and detailed gene-specific characteristics, indicating that even when genes within a molecular cluster exhibit similar characteristics, the features of individual genes may differ. Therefore, our findings highlight the importance of comparing molecular clusters when ana-

lyzing causative variants associated with PPGL, as well as the necessity for a detailed comparison at the level of individual genes.

Our findings regarding the mutation types and sites in patients with PPGL were largely consistent with the mutation sites previously identified in Korean studies [11, 12]. *SDHB* mutations predominantly involved frameshifts, whereas *VHL* mutations were mainly missense. *RET* mutations were exclusively missense, and *NF1* mutations varied without specific hotspots. Notably, the occurrence of specific *SDHB* mutations (e.g., c.137G>A, c.470delT) was lower in Korean patients than in Japanese patients, suggesting racial differences. *VHL* missense mutations, particularly in exons 1 and 3, were the most frequent across Japanese, Asian Indian, and Korean studies [8, 11, 12, 18]. Korean *RET* mutations primarily occurred in exon 11, consistent with global findings. Our research on mutation sites at the exon level in Koreans offers a foundation for future genotype–phenotype analyses, highlighting the complexity and diversity of PPGL mutations within this population.

The limitations of this study include the reliance on targeted NGS, which does not identify large deletions or duplications despite their reported prevalence in *SDHB*-, *SDHD*-, and *VHL*-related cases. Future research may benefit from whole-exome or whole-genome sequencing for a more comprehensive genetic analysis. Despite being a multicenter effort using a 38-gene panel, the case number was limited, thereby highlighting the need for a broad review of Korean cases to establish genotype–phenotype correlations. To avoid missing or duplicate cases, potentially overlapping cases from each author's institution were combined into one case to minimize the possibility of duplicate bias in the statistics.

In Korea, PPGL is rare, but its clinical features differ depending on the germline mutations involved. Therefore, genetic testing is imperative for patients with PPGL. The genotype–phenotype associations and frequently mutated sites in primary causative genes identified in this study will be useful for understanding the characteristics of PPGL in Korea.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3343/alm.2023.0376

ACKNOWLEDGEMENTS

We thank Seung Jae Lee of the Medical Library, The Catholic University of Korea, Seoul, Korea, for excellent support.

AUTHOR CONTRIBUTIONS

Study conception or design: Lee S, Moon SD; data acquisition, analysis, or interpretation: Jo KH, Kim ES, Han JH, Jang YS, Yun JS, Son JW, Yoo SJ, Lee SH, Kwon HS, Moon SD, Lee S, Lee J, Yoo J, Kim HS, Kim M; drafting or revising the manuscript: Jo KH, Lee J, Lee S, Moon SD; final approval of the manuscript: Lee S, Moon SD. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

RESEARCH FUNDING

This study was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT; 2019R1F1A1058741). The authors acknowledge the financial support of the Catholic Medical Center Research Foundation in the program year 2019.

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