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# Identification of a pathogenic *SDHD* mutation in a Chinese family with hereditary head and neck paraganglioma: implications for genetic counseling and management

Pu Wang[1], Liming Gao[1], Wenyang Zhang[1], Rui Guo[1] and Yin Xia[1*]

## Abstract

**Background** This study aims to identify a pathogenic *SDHD* mutation associated with hereditary head and neck paraganglioma (HNPGL) in a Chinese family and to explore its implications for genetic counseling.

**Methods** The study involved a family with 15 members spanning three generations. A 31-year-old patient (II-4) was diagnosed with a left parotid gland tumor and a right carotid body tumor, while both the father and elder sister had right carotid body tumors, and the third sister had bilateral carotid body tumors. Whole exome sequencing and Sanger sequencing were employed to identify candidate pathogenic variants. Genetic counseling was conducted for third-generation descendants to assess the likelihood of carrying the mutation and to guide future diagnosis and treatment.

**Results** A nonsense mutation in the *SDHD* gene (NM_001276503:exon2:c.C64T: p.R22X) was identified in the patient and three other affected family members. Genetic counseling for the third generation revealed that only one child (III-4) carried the pathogenic mutation inherited from the patient's third sister.

**Conclusion** We identified a pathogenic mutation in *SDHD* in a Chinese HNPGL family, which is the second reported case of its kind. Our genetic counseling analysis for the third generation provided important information for the family and guidance for future diagnosis and treatment.

**Keywords** *SDHD* mutation, Hereditary head and neck paraganglioma, Genetic counseling, Family study, Whole exome sequencing

*Correspondence:
Yin Xia
xiayin3@163.com
[1]Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tiantan Hospital, Capital Medical University, No. 119, South Fourth Ring Road West, Fengtai District, Beijing 100070, China

## Introduction

Paragangliomas and pheochromocytomas (PPCs) are rare, primarily benign vascular neuroendocrine tumors derived embryologically from neural crest cells associated with the autonomic nervous system. Among these, head and neck paragangliomas (HNPGL) arise from parasympathetic paraganglia, typically located in the carotid, tympanic, jugular, or vagal areas. These tumors present significant surgical challenges due to their proximity to critical vascular and nerve structures. The estimated overall incidence of HNPGLs ranges from 0.3 to 1 per 100,000 individuals, with a notable female predominance, as indicated by a male-to-female ratio of approximately 1:3 to 1:4 [1–3]. Genetic predispositions play a crucial role in the development of these tumors, with mutations in the succinate dehydrogenase complex subunit D (SDHD) gene being among the most commonly implicated [4]. Understanding the epidemiology and genetic underpinnings of HNPGL is crucial for improving early diagnosis and patient management, as timely intervention can mitigate surgical risks and improve outcomes.

Patients with HNPGL typically exhibit a range of symptoms based on the tumor's location and growth [5]. Initial presentations often include painless, gradually enlarging neck masses, which may progress to neurological deficits due to lower cranial nerve involvement. Although most HNPGLs are slow-growing benign tumors, malignancy rates can reach up to 10% [6, 7]. Consequently, when diagnosed, these tumors are often large and intricately associated with vital structures, complicating surgical intervention and increasing the risk of postoperative complications. Therefore, genetic testing holds promise for predicting HNPGL development, enabling earlier detection and more effective management strategies.

Hereditary forms of HNPGL have been linked to mutations in various genes, including succinate dehydrogenase (*SDH)* subunits *SDHD*, *SDHB*, *SDHC*, *SDHAF2*, *SDHA*, *VHL*, *RET*, *TMEM127*, *MAX*, and *NF1* [7]. The *SDH* complex comprised of 4 subunits, *SDHA*, *SDHB*, *SDHC*, and *SDHD*, along with the *SDHAF2* assembly factor, plays a pivotal role in this context. SDH is integral to the Krebs cycle and electron transport chain in mitochondria. Dysfunction in any of the SDH subunits may lead to compensatory adenosine triphosphate (ATP) production via glycolysis, a less efficient metabolic pathway [8–10]. Particularly, mutations in the SDHB subunit have been linked with a heightened risk of malignancy and a worse prognosis; indeed, 50% of patients with metastatic disease possess an SDHB mutation [11, 12]. PGL4 syndrome, arising from autosomal dominant SDHB mutations on chromosome 11p35, frequently presents as sympathetic extra-adrenal PGLs, PCCs, and HNPGLs, with a malignancy rate of up to 70% [7, 13]. Typically located in the abdomen and mediastinum, SDHB mutations also significantly heighten the risk of other cancers, including renal cell carcinoma, gastrointestinal stromal tumors (GIST), breast, and papillary thyroid carcinomas [14–16]. In spite these risks, there are currently no establish guidelines and the patients with metastatic disease are routinely screened for the predisposing SDHB mutation.

Despite established associations between pathogenic variants in the *SDH* subunit genes and specific HNPGL subtypes [17], the understanding of genotype-phenotype correlations remains limited. This gap is partly due to the rarity of the disease and the scarcity of comprehensive genotype-phenotype data. In this study, we identified a pathogenic mutation in the *SDHD* gene (NM_001276503:exon2:c.C64T: p.R22X) within a Chinese HNPGL family, which has parallels with findings from a previously reported French HNPGL family. By analyzing the clinical manifestations of both families, we aim to elucidate the correlation between this specific mutation and phenotypic expression, thereby contributing valuable data to the existing genotype-phenotype knowledge base. Furthermore, we are conducting genetic counseling for the offspring of the affected families to assess the likelihood of mutation transmission and offer guidance for future diagnosis and management.

## Subjects and methods

### Recruitment of family

Genetic counseling was provided to a Chinese family with a documented history of hereditary head and neck paraganglioma (HNPGL). The family pedigree is illustrated in Fig. 1a, encompassing 15 individuals across three generations. The proband (II-4), a 31-year-old male, presented with a left-sided glomus jugulare tumor (Fig. 2) and a right carotid body paraganglioma. His father (I-1) and eldest sister (II-1) were diagnosed with right-sided carotid body tumors, while his third sister (II-3) had bilateral carotid body tumors. Clinical evaluations of subjects I-2, II-2, and the third generation (III:1 to III:5) revealed no tumor manifestations. Prior to blood collection for DNA analysis, written informed consent was obtained from all participants. This study was approved by Ethics Committee of Beijing Tiantan Hospital (No. KY2023-131-01).

### Whole-exome sequencing and sanger sequencing

Peripheral blood samples were collected, and genomic DNA was extracted using the Qiagen Blood Kit (Qiagen, Hilden, Germany) following the manufacturer's protocols. The DNA was fragmented into 250 bp pieces using a TIANamp Blood DNA Kit (Tiangen, Beijing, China). DNA quality was assessed through gel electrophoresis before library construction. Following end repair and

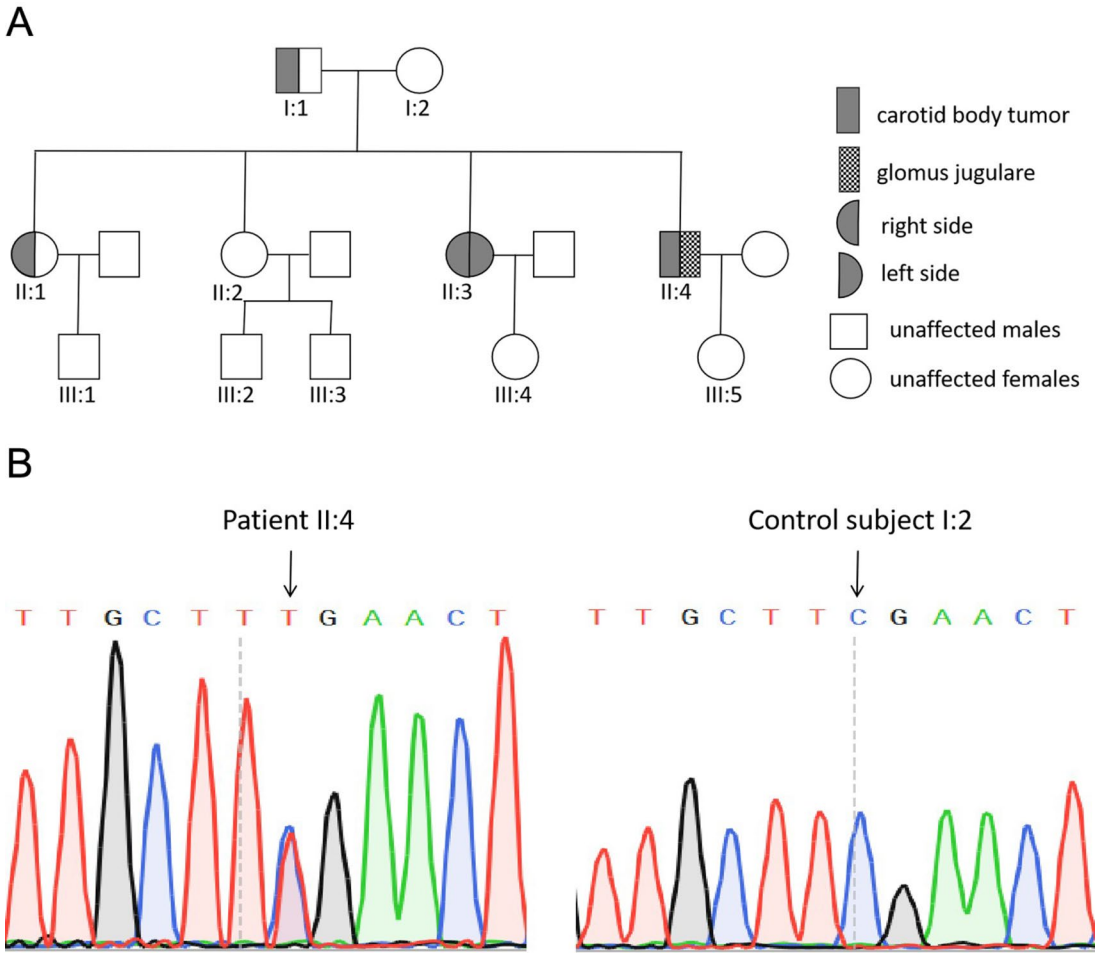


**Fig. 1** Analysis of mutations in the SDHD gene. **A**. Inheritance of Hereditary Non-Canonical Paraganglioma (HNPGL): Diagram illustrating the pedigree of the family under study, highlighting affected individuals (shaded) with the index patient designated as II:4. **B**. Validation of the c.C64T Variant: Sanger sequencing confirmation of the identified heterozygous nonsense mutation (c.C64T: p.R22X) in the *SDHD* gene

A-tailing, sequencing adaptors were ligated to both ends of the DNA fragments. All samples were indexed by amplifying adaptor-ligated products with index-tagged primers, and the amplified products were purified using the QIAquick PCR Purification Kit (QIAGEN).

Sonication (Thermo Fisher, FB705, Waltham, MA, USA) and hybrid capture using the xGen Exome Research Panel v1.0 (Integrated DNA Technologies, Coralville, IA, USA) were employed to enrich and sequence the genomic DNA on the Illumina HiSeq 2500 platform, achieving a coverage depth of 496x across all samples with read lengths of 250 bp. Raw image files were processed using base calling software (Illumina 1.7) with default parameters.

To identify pathogenic variants, whole-exome sequencing (WES) was conducted along with pedigree co-segregation analysis for the nuclear family members (I-1, I-2, II-1, II-2, II-3, and II-4). Additionally, WES was performed for the third generation (III-1 to III-5) to evaluate the presence of pathogenic mutations. Following sequencing, the quality of the raw reads was assessed using FastQC, and low-quality reads were filtered with Fastp (https://github.com/OpenGene/fastp) to obtain clean reads. Subsequently, clean reads were aligned to the human GRCh37/hg19 reference genome using the Burrows-Wheeler Aligner (http://bio-bw.sourceforge.net/, accessed on 04/01/2022). Variant calling, including single nucleotide variants (SNVs) and small insertions/deletions (InDels), was performed, and variants were annotated using ANNOVAR (http://annovar.openbioinformatics.org). Variants classified as missense, nonsense, or splice-site mutations were also characterized alongside other genomic features. Variants with a minor allele frequency < 0.001 in the Exome Aggregation Consortium (ExAC), 1000 Genomes Project, and Exome Sequencing Project (ESP6500) were excluded. Retained variants were focused on exonic regions and splice sites.

For coding or splice-site mutations, conservation of the variant sites and their predicted impacts on protein function were evaluated using in silico tools, including SIFT,

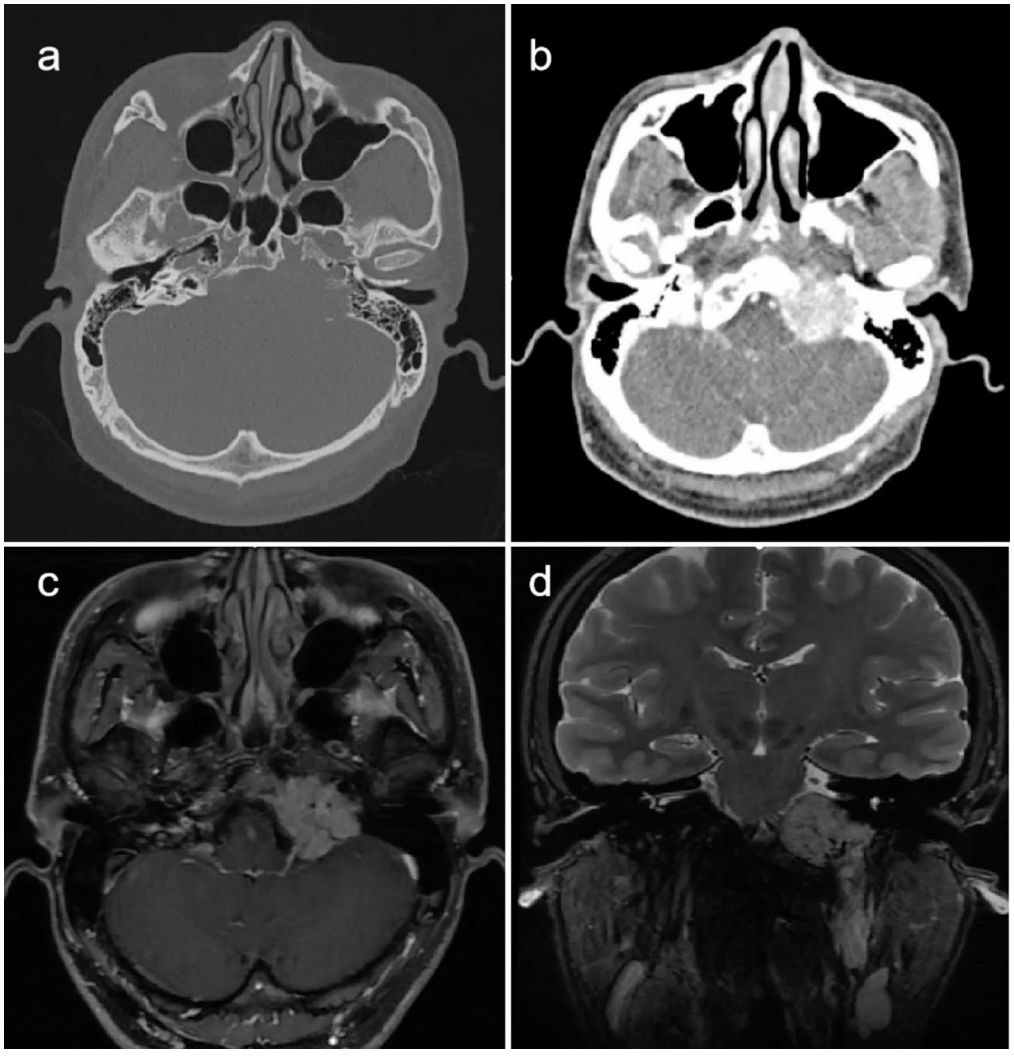


**Fig. 2** Imaging findings of the tumor. CT scans of the temporal bone (**a**, **b**) and enhanced MRI of the head (**c**, **d**) depicting a mass located in the left jugular foramen area, measuring approximately 3.3 cm by 2.6 cm. The imaging shows peripheral bone resorption and destruction, with uniform enhancement on the scans. The lesion extends upward into the foramen lacerum towards the left cavernous sinus, compressing the left cerebellopontine angle posteriorly and medially, and descending along the jugular foramen to the extracranial region

PolyPhen-2, MutationTaster, and CADD (Combined Annotation-Dependent Depletion) [18–21]. The pedigree co-segregation analysis classified I-1, II-1, II-3, and II-4 as the disease group, while I-2 and II-2 served as the control group.

To validate the potential pathogenic variant, Sanger sequencing was performed. PCR primers were designed using Primer-BLAST (National Center for Biotechnology Information) with the following sequences: F-CCCT GGTCTTAACTTCACAG and R-ATAAATGGCATCAT TCAACC. Sanger sequencing data were analyzed using 4Peaks DNA sequence trace viewer software (version 1.8).

### Bioinformatics analysis

Three-dimensional protein structure predictions for the SDHD variant were conducted using AlphaFold (https://www.alphafold.ebi.ac.uk/, accessed on 28/05/2022) and visualized with PyMOL (version 2.5.2).

## Results

### Clinical characterization

The proband, a 31-year-old male, was referred from the Department of Otolaryngology at Beijing Tiantan Hospital, Capital Medical University, presenting with hoarseness and pulsatile tinnitus. Fiberoptic laryngoscopy revealed fixed left vocal cords. Imaging studies, including CT of the temporal bone and enhanced MRI of the head, identified a mass in the left jugular foramen measuring approximately 3.3×2.6 cm. This mass exhibited

peripheral bone resorption and destruction, with significant enhancement on imaging. The lesion extended upward into the foramen lacerum towards the left cavernous sinus, compressing the left cerebellopontine angle, and descended along the jugular foramen into the extracranial space (Fig. 2).

Following diagnosis, the patient underwent resection of the left tumor via an infratemporal fossa type A approach. Post-operative follow-up over 2.5 years indicated no recurrence of the tumor. The proband also had a right carotid-body paraganglioma, which was managed conservatively with ongoing observation, showing no signs of enlargement. Furthermore, familial history revealed that his father (I-1) and eldest sister (II-1) were diagnosed with right carotid body tumors, while his third sister (II-3) exhibited bilateral carotid-body tumors. Clinical evaluations of I-1, II-2, and all individuals in the third generation (III:1, III:2, III:3, III:4, III:5) revealed no evidence of tumors. Given that most hereditary head and neck paraganglioma (HNPGL) patients present symptoms between the fourth and seventh decades of life, it was critical to investigate potential pathogenic mutations in the third generation despite the absence of tumors at this stage. Notably, the third generation was not utilized as normal controls for family segregation analysis.

### Identification of candidate gene

Through whole-exome sequencing, we identified a total of 165,911 unique variants. Following family segregation analysis, 2,213 variants remained. After filtering for non-exonic and synonymous mutations, we retained 555 variants in the exome and splice regions, ultimately narrowing this down to 270 variants. Further analysis excluded variants with a frequency greater than 0.001 in the Exome Aggregation Consortium (ExAC), 1000 Genomes Project, and Exome Sequencing Project (ESP6500), resulting in 22 candidate genes: *DMRTA2*, *LEXM*, *IL17RE*, *EFHB*, *CYP3A43*, *MUC12*, *TMEM123*, *SDHD*, *PLA2G4E*, *NRN1L*, *CLUH*, *RAP1GAP2*, *ZBTB4*, *TRIM16*, *NCOR1*, *KLHL10*, *EFCAB13*, *KIF2B*, *FOXJ1*, *ASCC2*, *IFT27*, and *SREBF2*.

Through functional prediction and literature review, we identified a pathogenic nonsense mutation in the *SDHD* gene (NM_001276503: exon2: c.C64T: p.R22X) as the likely cause of the HNPGL in this family. This heterozygous stop-gain mutation results in premature termination of protein translation, leading to haploinsufficiency of the *SDHD* gene. The pathogenic nature of this variant was confirmed through Sanger sequencing (Fig. 1b).

### In silico analysis of SDHD variant

Prediction of the three-dimensional structure of the *SDHD* protein was conducted using AlphaFold, and visualized with PyMOL. The analysis indicated substantial loss of the amino acid sequence in the mutant protein compared to the wild-type structure (Fig. 3).

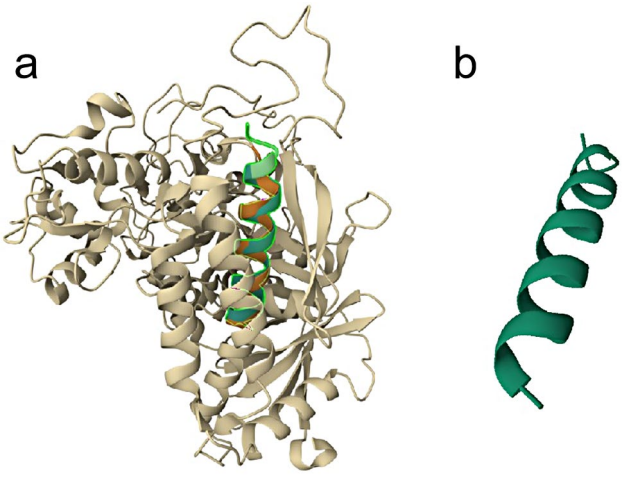


**Fig. 3** Three-Dimensional Structural Prediction of the SDHD Protein. Three-dimensional structural models of the *SDHD* protein generated using AlphaFold and visualized with PyMOL. Panel (**a**) illustrates the wild-type *SDHD* protein structure, while panel (**b**) shows the structural impact of the p.R22X mutation, indicating the significant loss of a portion of the amino acid sequence due to this pathogenic variant

### The impact of the pathogenic mutation on the third generation

As part of our investigation, we performed whole-exome sequencing on the third-generation family members. Notably, only one child (III-4) was found to carry the *SDHD* gene mutation, which was inherited from the proband's sister (II-3), who suffers from bilateral carotid body tumors. Importantly, *SDHD* mutations display distinct genetic imprinting, wherein mutations inherited from the mother do not lead to HNPGL, whereas paternal inheritance does confer risk. Consequently, all third-generation family members are not expected to develop HNPGL, thereby highlighting the significance of parental origin in the manifestation of this hereditary condition.

## Discussion

The prevalence of hereditary non-epithelial paragangliomas (HNPGLs) with a positive family history varies significantly across studies, ranging from 9.5–50% [22, 23]. Among families affected by HNPGL, mutations in the *SDHB*, *SDHC*, and *SDHD* genes have been identified, with *SDHD* mutations being the most prevalent. Reports indicate that *SDHB* mutations are present in approximately 20% of cases, *SDHC* in 10%, and *SDHD* in 50% within families studied in the USA [24, 25]. In the Netherlands, these rates were reported as 6%, 0%, and 94%, respectively, across 32 families consistent with the recent trend [26, 27]. Similarly, an Australian cohort demonstrated rates of 9%, 0%, and 82% for *SDHB*, *SDHC*,

and *SDHD* [28, 29]. In contrast, germline mutations in non-familial HNPGLs show greater variability, with only 11–29% of cases exhibiting SDH mutations [22, 29–31]. In our study, we identified a pathogenic mutation in the *SDHD* gene within a family affected by HNPGL, underscoring the importance of genetic screening in familial cases.

Recent investigations have sought to elucidate the relationship between SDHx gene mutations and clinical phenotypes. However, due to the rarity of HNPGLs and the limited sample sizes in existing studies, findings remain inconclusive. For instance, while *SDHB* mutations are correlated with a higher risk of malignancy, including renal cell carcinoma [32–34], *SDHD* and *SDHC* variants are predominantly associated with HNPGL [35–37]. Notably, mutations in *SDHAF2* have been linked to younger patients presenting with multiple HNPGLs [38, 39]. HNPGL encompasses various tumor types, including glomus jugulotympanicum (GJT) and carotid body tumors (CBTs), indicating that identical mutations can manifest as different tumor phenotypes, ranging from unilateral to bilateral, benign to malignant, and solitary to multifocal. In our family study, along with findings from a previously reported French family [40], we observed that the *SDHD* mutation (NM_001276503: exon2: c.C64T: p.R22X) led to diverse clinical presentations, with CBTs accounting for 75% of cases, GJTs for 16.7%, and an ectopic mediastinal pheochromocytoma for 8.3%. This highlights the mutation's predominant association with CBTs.

The penetrance of SDH gene mutations varies considerably, with *SDHA*, *SDHB*, and *SDHC* exhibiting low penetrance (<25%), while *SDHD* mutations show high penetrance (>80%). The average age of onset for HNPGL patients with *SDHD* mutations is approximately 36 years [41]. Longitudinal studies have revealed that penetrance rates for *SDHD* mutations increase with age, reaching 50% by age 31 and 86% by age 50 [42]. More recent reports indicate that by age 40, 54% of individuals with *SDHD* mutations exhibit HNPGL, rising to 68% by age 60 and 87% by age 70 [43]. In our study, the third-generation family members were significantly younger than 36, prompting their exclusion from direct analysis, although we provided genetic counseling to them.

Among the third-generation family members, we identified one child (III-4) carrying the disease-causing mutation, inherited from their mother, who has bilateral carotid body tumors. Importantly, the *SDHD* gene displays maternal imprinting, meaning that the allele inherited from the mother is transcriptionally silent, while the allele from the father is active [44]. As a result, despite carrying the mutation, III-4 is unlikely to develop HNPGL. This critical information alleviated the family's concerns regarding the potential for disease manifestation in future generations. Our findings emphasize that when a pathogenic mutation in *SDHD* is identified within an HNPGL family, genetic testing for offspring should focus on the male lineage, as maternal inheritance does not confer risk.

### Limitations

Despite the significant findings of our study, several limitations should be acknowledged. First, the sample size of the family under investigation is small, which may limit the generalizability of our results to broader populations. The rarity of hereditary non-epithelial paragangliomas (HNPGLs) presents challenges in recruiting larger cohorts for comprehensive analysis. Additionally, while we identified a pathogenic mutation in the *SDHD* gene, the exact penetrance and expressivity of this mutation within the family remain uncertain due to the limited follow-up of younger family members.

## Conclusion

In conclusion, our study identified a pathogenic mutation in the *SDHD* gene within a Chinese family affected by hereditary non-epithelial paragangliomas, marking it as the second documented family with such a mutation. This research contributes to the understanding of *SDHD*-related pathogenesis and highlights the importance of genetic counseling for affected families. Our findings are invaluable for guiding targeted genetic counseling and informed management strategies to better support individuals at risk of inheriting SDHD mutations.

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None.

#### Author contributions

PW and LG contributed to the conception and design of the study. WZ and RG contributed to the acquisition of data. YX contributed to the analysis of data. PW and LG wrote the manuscript. YX revised the manuscript. All authors approved the final version of the manuscript.

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#### Data availability

Data is provided within the manuscript files.

## Declarations

#### Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Tiantan Hospital (NO.KY2023-131-01). Prior to blood collection for DNA analysis, all Patients and their families participated voluntarily and signed informed consent forms, and the study was performed in accordance with the Helsinki II declaration. Informed consent was obtained from all the study subjects before enrollment.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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