

Proportion of Heritable Paraganglioma Cases and Associated Clinical Characteristics

Carrie M. Drovdlc, MS; Eugene N. Myers, MD; June A. Peters, MS; Bora E. Baysal, MD, PhD;
Derald E. Brackmann, MD; William H. Slattery III, MD; Wendy S. Rubinstein, MD, PhD

Objective/Hypothesis: To determine the heritable proportion of paraganglioma (PGL) and identify clinical features associated with heritable PGL. **Study Design:** Patients diagnosed with head and neck PGLs, identified retrospectively through clinical otolaryngology practices and/or participation in previous PGL research studies, were given a medical and family history questionnaire. **Methods:** Questionnaire information was used to classify participants as having "heritable" or "non-heritable" cases of PGL. Classification of the participants identified through otolaryngology clinics was used to estimate the heritable proportion of PGL. Statistical analysis was performed to identify significant differences in the clinical characteristics of the heritable versus non-heritable groups. **Results:** Among the otolaryngology clinic population, 35% were classified as having heritable PGL. Individuals with heritable PGL were younger on average than those with non-heritable PGL. The majority of non-heritable participants were female, but there was an equal gender ratio among the heritable participants. Individuals diagnosed with a carotid body tumor (CBT) were 5.8 times more likely to be classified as heritable than those diagnosed with PGL

at other anatomic locations. **Conclusions:** Approximately 35% of individuals who present to an otolaryngologist with a head and neck PGL have inherited a predisposition for this growth. Among individuals diagnosed with head and neck PGL, those diagnosed with CBT are 5.8 times more likely to have an inherited predisposition than those diagnosed with PGL at other anatomic locations. **Key Words:** Paraganglioma, carotid body tumor, heritable, non-heritable, imprinting.

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INTRODUCTION

Non-chromaffin paragangliomas (PGL) are mostly benign tumors that originate from paraganglionic cells derived from neural crest tissue. These tumors are located most frequently in the carotid bifurcation (carotid body tumor), along the vagus nerve (glomus vagale), in the jugular foramen (glomus jugulare), in the middle ear space (glomus tympanicum), or in the upper mediastinum.

Although PGL occur sporadically, 7% to 50% of these tumors are considered familial in nature.^{1,2} PGL tumors occurring in families that are linked to the *PGL1* locus follow an autosomal-dominant inheritance pattern, with the exception that children of affected females rarely develop tumors. Van der May et al.² used data from 82 members of 15 large Dutch pedigrees to suggest that genomic imprinting was responsible for the observed inheritance pattern of susceptibility to PGL tumors in these families. Children of female carriers never developed tumors, whereas 50% of the offspring of male carriers developed tumors.

A major gene responsible for these tumors, *PGL1*, is located on chromosome 11q23^{3–6} and was identified as succinate-ubiquinone oxidoreductase subunit D (*SDHD*).⁷ This gene encodes the mitochondrial protein cytochrome b small subunit, or CybS, and has functions in the Krebs cycle and electron transport chain (ETC). Inheritance of this gene is consistent with maternal genomic imprinting.

Another locus, *PGL2*, was linked to chromosome 11q13.1 by Mariman et al.⁸ A third locus was implied by the presence of families that did not link to either the *PGL1* or *PGL2* region and was identified as the succinate-ubiquinone oxidoreductase subunit C (*SDHC*) gene located on chromosome 1q21.^{9,10} *SDHC* and *SDHD* are both

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From the Department of Human Genetics, University of Pittsburgh Graduate School of Public Health (C.M.D., J.A.P., B.E.B., W.S.R.), the University of Pittsburgh Cancer Institute (E.N.M., J.A.P., W.S.R.), the University of Pittsburgh Eye and Ear Institute (E.N.M.), the University of Pittsburgh Department of Psychiatry (B.E.B.), Pittsburgh, Pennsylvania; and the House Ear Institute (D.E.B., W.H.S.), Los Angeles, California, U.S.A.

C.M.D. is currently at the Clinical Cancer Genetics Program, The Ohio State University, Columbus, OH; J.A.P. is currently at the Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD; W.S.R. is currently at the Center for Medical Genetics, Division of Genetics, Evanston Northwestern Healthcare, Evanston, IL.

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Send Correspondence to Carrie M. Drovdlc, MS, Genetic Counselor, Clinical Cancer Genetics, Ohio State University, 410 West 10th Avenue, 303E Doan Hall, Columbus, OH 43210, U.S.A. E-mail: drovdlc-1@medctr.osu.edu

subunits in mitochondrial complex II. Unlike PGL1, predisposition to the development of PGL tumors resulting from the *SDHC* gene (*PGL3*) appears to have a strictly autosomal-dominant mode of transmission without imprinting.

The slow, continuous growth of PGL tumors can result in significant clinical morbidities such as vocal paralysis, dysphagia, facial palsy, and middle ear deafness. If left untreated, these tumors can also metastasize to the lungs or regional lymph nodes. Early treatment of these tumors results in a significant decrease in morbidity and mortality.¹¹ PGL tumors are often effectively treated by surgical resection, and effective surveillance can be achieved through periodic magnetic resonance imaging scans of the head and neck region.^{11,12} Because of the rarity of this condition and the cost of screening, these scans must be targeted to those at increased risk. We propose that PGL surveillance, i.e., secondary prevention, can be efficiently targeted by recognizing hereditary disease and focusing screening efforts on families with previously unrecognized, but significantly increased future risk of developing PGL. A high heritable proportion of PGL tumors will correlate with a greater potential for prevention through genetic screening, making this an important factor to characterize.

The genomic imprinting phenomenon, incomplete penetrance, insufficient acquisition of family histories, and poor syndrome recognition by physicians make patients with hereditary PGL difficult to identify (Fig. 1). We wanted to estimate the heritable proportion of PGL as well as identify clinical features that were significantly associated with heritable cases.

MATERIALS AND METHODS

The participants of this study were living adults and adolescents who had been diagnosed with carotid body tumor (CBT), glomus jugulare (GJ), glomus vagale (GV), and/or glomus tympanicum (GT). Potential participants were identified in two ways: 1) members of the faculty in the Department of Otolaryngology of the University of Pittsburgh School of Medicine Eye and Ear Institute, Pittsburgh, PA (UPMC) and the House Ear Institute (HEI), Los Angeles, CA, contacted patients in their practice diagnosed with PGL of the head and neck irrespective of family history; and 2) participants in the linkage study that identified the *PGL1* gene were invited to participate in this study.

Potential participants were sent a greeting letter describing the study, as well as the consent form(s) for their review. They were subsequently contacted by phone at which time the purpose of the study, the need for family history information, and the procedure for cheek swab were explained. Then voluntary, informed consent was obtained from interested individuals.

Participants completed a mail questionnaire and a structured telephone interview during which a complete medical and family history was obtained. Individuals who consented to the "DNA analysis" section of the study were also sent sterile cheek swabs (Fisher Scientific, Pittsburgh, PA; Cat. No. 22-281-660) with instructions. Participants who had been recruited from the *PGL1* linkage study had previously donated blood samples, so additional cheek swab samples were not needed.

Information from mail and phone questionnaires was entered into a Progeny Enterprise database (Genetic Data Systems, LLC, South Bend, IN). The data were entered into a Microsoft Excel spreadsheet to produce descriptive bar charts, and statis-

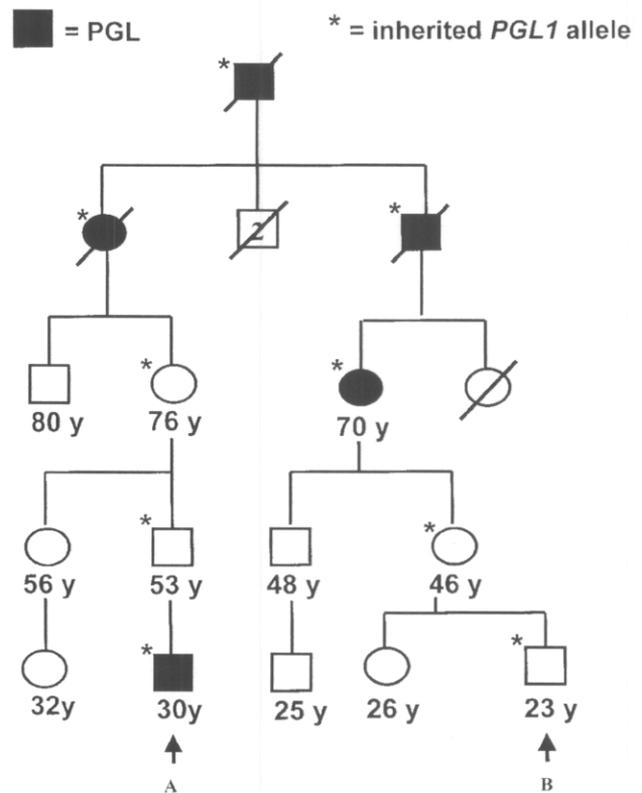


Fig. 1. Family history illustrating the inheritance pattern of PGL1. Circles represent females, squares represent males, and the diagonal slash indicates the individual is deceased. Individuals with PGL tumors are indicated in black and an asterisk indicates individuals who have inherited a mutant PGL-1 allele. Probands are indicated with arrows. Affected proband A inherited a mutant *PGL-1* allele from his unaffected father through his unaffected paternal grandmother. These individuals both inherited this allele from their mother and therefore did not develop tumors. Proband A inherited the allele from his father and developed tumors. In addition, his children are at 50% risk of developing PGL tumors. Unaffected proband B inherited the mutant *PGL-1* allele from his unaffected mother through his affected maternal grandmother. Because he inherited this allele from his mother, he would not be expected to develop PGL tumors. However, his children are at 50% risk to develop a PGL tumor.

tical analyses were implemented using the SAS Institute (Cary, NC) program for Windows. The χ^2 test (χ^2) with one or two degrees of freedom (df), *t* test, Fisher's Exact Test (FET), and logistic regression were performed, as appropriate.

On receipt of the cheek swabs, DNA was isolated using the Puregene D-5000A kit (Gentra Systems, Minneapolis, MN) and protocol for DNA isolation from buccal cells. Each of four exons and corresponding splice sites of the *SDHD* gene was amplified by primers designed from the flanking intronic sequences.⁷ These were subjected to single-strand conformational polymorphism (SSCP) analysis and direct gene sequencing to identify disease-causing mutations.

We wanted to compare individuals with confirmed or likely heritable PGL with those who likely had non-heritable PGL. As outlined in Table I, we classified an affected individual as having hereditary PGL based on the following criteria: a family history of PGL or pheochromocytoma in one or more family members; the presence of bilateral tumors; or the presence of multifocal, non-bilateral tumors. Non-heritable PGL was defined as the absence of family history and bilateral or multifocal tumors.

TABLE I. Criteria by Which Participants Were Classified as Heritable or Non-heritable.	
Classification	Definition
Heritable	At least one family member diagnosed with PGL or pheochromocytoma
	Or
	diagnosis of bilateral PGL
	or
	diagnosis of multifocal PGL
Non-heritable	No family members diagnosed with PGL or pheochromocytoma
	And
	diagnosis of a single, non-bilateral PGL

PGL = paraganglioma.

RESULTS

A total of 182 patients diagnosed with glomus tumor were identified as potential participants for recruitment into the study. Of these, 13 were listed twice from being both a patient of one of the two participating centers and being previously recruited for the *PGL1* linkage study. Thus, there were 169 potential participants in total. Of these, 85 agreed to participate by returning signed consent forms. We were unsuccessful in recruiting the remaining potential participants for the following reasons: 1) inability to contact the potential participant by phone to obtain informed consent (as a result of a change of address/telephone number, or death); 2) the potential participant declined to participate in the study; and 3) the potential participant agreed to participate, but we did not receive consent form(s) and/or questionnaires in time to include the data in the study. Of the 85 participating participants, 82 completed the telephone interview.

Medical and family history information from these 82 participants was used to create a clinical profile that determined the classification of heritable or non-heritable for that participant. Among the 82 respondents, 42 were classified as heritable and 40 were classified as non-heritable.

We considered the study participants recruited from the UPMC and HEI clinics, excluding participants recruited only through the *PGL1* linkage study, to be an unbiased cross-sectional sample of patients presenting to an otolaryngologist with expertise in PGL treatment. There were a total of 60 participants in this group, and among them 21 (35%) were classified as heritable and 39 (65%) were classified as non-heritable as defined in Table I. Of the heritable subjects, six were classified as such based on features other than positive family history (i.e., multifocality). Molecular analysis revealed that several individuals had a germline *SDHD* mutation as assessed by SSCP. The complete results of molecular analysis of *SDHD* will be presented elsewhere.

Among the total 42 heritable participants, 22 were female with an average current age of 51.3 years, and 20 were male with an average current age of 49.2 years. The female to male ratio was 1.1:1. The heritable participants' age distribution and the gender ratio for each age group are illustrated in Figure 2A. The majority of individuals were between the ages of 30 and 59 years, and the gender ratios were equal for the majority of the age groups, with the exception of males outnumbering females in the 50- to 59-year age category, and females outnumbering males in the 40 to 49-year and 70- to 79-year categories.

The non-heritable study group was comprised of 30 females and 10 males, with a female to male ratio of 3:1. The average current age for females was 61 years, and the average age for males was 59.7 years. Illustrated in Figure 2B are the non-heritable participants' age distribution and the gender ratios for each age group. For each cate-

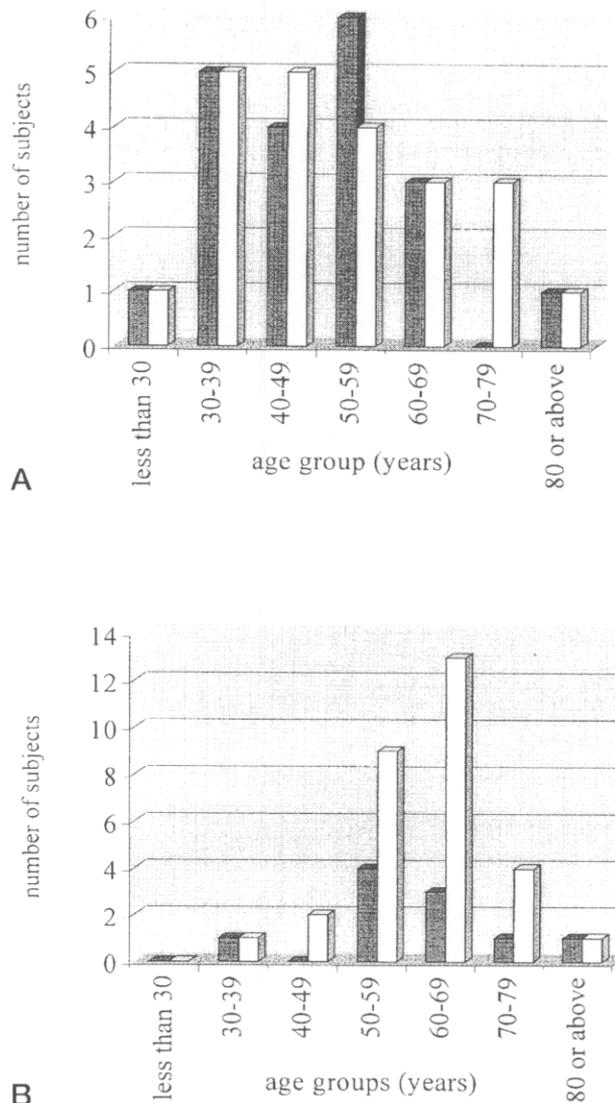


Fig. 2. Age distribution and gender ratios in (A) heritable and (B) non-heritable ■ male and □ female participants.

gory the gender ratio was equal or females predominated, especially in age groups 50 to 59 years and 60 to 69 years, which contained the majority of participants.

During a phone questionnaire, study participants were asked to recall the type of PGL with which they were diagnosed on their first and, when applicable, second diagnosis. Participants who could not remember the type of tumor with which they had been diagnosed, or those who were uncertain, were placed in the general "paraganglioma" (PGL) category.

There was a significant difference in the number of participants diagnosed with CBT ($\chi^2 = 26.04$; $df = 1$; $P < .0001$) and GT ($\chi^2 = 6.55$; $df = 1$; $P = .0105$) between the heritable and non-heritable groups (Table II). There were no significant differences in the number of participants diagnosed with GV tumors (FET $P = .1162$) or GJ tumors ($\chi^2 = 1.72$; $df = 1$; $P = .1895$).

We were intrigued by the observation that CBT is significantly more likely to occur in heritable cases of PGL. We wanted to determine if this finding would still be significant when including only individuals of both subject groups who had non-bilateral CBT on first diagnosis, regardless of family history or subsequent tumor diagnoses.

The number of participants with non-bilateral CBT on first diagnosis in the heritable and non-heritable groups was significantly different ($\chi^2 = 7.98$; $df = 1$; $P = .0047$) (Table III). The approximate odds ratio (OR) of 6.9 had a 95% confidence interval (CI) of 1.82, 26.18.

These data indicate a participant diagnosed with a non-bilateral CBT on first diagnosis was 6.9 times more likely to be considered heritable than an individual diagnosed with a GV, GJ, or GT on first diagnosis.

We analyzed these data further by excluding from the analysis all participants who had been identified through the *PGL1* linkage study only. The remaining participants were the cross-sectional clinic population who had been recruited from the UPMC or HEI clinics and was used to estimate the heritable proportion of PGL. We analyzed this group for a difference in the number of heritable and non-heritable participants whose first PGL diagnosis was that of non-bilateral CBT, regardless of family history or subsequent tumor diagnoses. Table IV indicates there was still a significant difference between the heritable and non-heritable groups ($\chi^2 = 3.90$; $df = 1$; $P = .0483$). The

approximate OR for this analysis was 5.8 with a 95% CI of 1.02, 33.11. These data demonstrate that among participants identified through otolaryngology clinics, an individual diagnosed with a non-bilateral CBT on first diagnosis was 5.8 times more likely to be considered heritable than those diagnosed with GV, GJ, or GT on first diagnosis.

The current average ages and average ages at diagnosis, onset of symptoms, and surgery for heritable and non-heritable participants are summarized in Table V. In every category, the average age of the non-heritable participants was higher than that of the heritable participants. Among heritable participants, the average current age was 50.3 years, the average age at onset of symptoms was 34.1 years, the average age at diagnosis was 36.6 years, and the average age of surgery was 36.1 years. The average age of surgery was lower than the average age of diagnosis because some participants had not undergone surgery. These participants tended to be elderly individuals for whom surgery was avoided because of an increased risk of complications.

Among non-heritable individuals, the average current age was 60.7 years, the average age at onset of symptoms was 45.6 years, the average age at diagnosis was 52.7 years, and the average age at surgery was 52.3 years.

T test analysis revealed that there were no significant differences between individual age comparisons as all *P* values are $>.1000$.

DISCUSSION

The goal of this study was to characterize the clinical characteristics of heritable versus non-heritable PGL based on a definition that incorporates recent advances in understanding the genetics of PGL. With the discovery of at least three PGL-associated loci, one of which is not maternally imprinted, we propose that it is reasonable to diagnose PGL as hereditary if there is a single affected family member, in addition to the proband, within a pedigree that does or does not follow the imprinting rule.

However, the absence of a positive family history does not rule out hereditary PGL resulting from incomplete penetrance, genomic imprinting, and the possibility of silent maternal transmission over several generations. The reported incidence of PGL is 1 in 30,000 individuals.

TABLE II.
Statistical Analysis of PGL Tumor Diagnoses Between Heritable and Non-heritable Participants.

Tumor Type	Diagnosed	Heritable No. (%)	Non-heritable No. (%)	<i>P</i> Value
CBT	Yes	31 (73.8)	3 (7.5)	<.0001
	No	11 (26.2)	37 (92.5)	
GV	Yes	4 (9.5)	0 (0)	.1162
	No	38 (90.5)	40 (100)	
GJ	Yes	12 (28.6)	17 (42.5)	.1895
	No	30 (71.4)	23 (57.5)	
GT	Yes	1 (2.4)	11 (27.5)	.0105
	No	41 (97.6)	29 (72.5)	

CBT = carotid body tumor; GV = glomus vagale; GJ = glomus jugulare; GT = glomus tympanicum.

TABLE III.
Statistical Analysis of First Diagnosis of Non-bilateral CBT Between Heritable and Non-heritable Participants.

CBT	Heritable No. (%)	Non-heritable No. (%)	P Value	Odds Ratio
Yes	15 (38.1)	3 (7.5)	.0047	6.9
No	27 (61.9)	37 (92.5)		

CBT = carotid body tumor.

The probability that an individual would develop two separate PGL tumors by chance (i.e., sporadically) is small. Therefore, we propose that bilateral or multifocal cases of PGL, without a family history of PGL, represent occult genetic transmission of inherited predisposition. The possibility of a de novo germline mutation is also a consideration.

Previous clinical and epidemiologic studies have used varying definitions of heritability. In most cases, patients were classified as having heritable PGL only if they had *familial* PGL, that is, a positive family history. Individuals with bilateral and/or multifocal tumors were typically classified as non-familial and treated as "sporadic" cases. Based on the above proposals, we argue that these definitions have led to misclassification of heritable cases as non-heritable and a falsely decreased estimate of the heritable proportion of PGL. This proportion has been reported to be as low as 7%¹ and as high as 50%.² Our heritable proportion was 35%, which differs significantly from the familial rate of 7% reported by Parry et al.¹ ($\chi^2 = 26.66$; $df = 1$; $P = <.0001$) and that of 9.5% reported by Grufferman et al.¹³ ($\chi^2 = 35.38$; $df = 1$; $P = .0001$). However, our heritable proportion is not statistically different from that of 50% reported by van der Mey et al.² ($\chi^2 = 2.65$; $df = 1$; $P = .1034$), indicating the previous estimates of 7% and 9.5% may be too low.

Despite these differences in classification, many of the findings of this study are consistent with previous studies. For example, within our sample population, females outnumbered males among the non-heritable participants 3 to 1, whereas the gender ratio was approximately equal among heritable participants. This discrepancy has been seen by other groups.^{2,13}

To determine if this difference in gender ratios was the result of a higher participation rate among potential female participants, we calculated the total participation rate of females versus males. Among 108 potential female participants, 55 participated for a rate of approximately 0.51, and among 60 potential male participants, 30 participated for a participation rate of approximately 0.50,

indicating there was no non-response bias between males and females.

According to the most recent estimates of the Centers for Disease Control and Prevention National Center for Health Statistics, the average lifespan of females is 5.8 years longer than that of males (79.4 y vs. 73.6 years, respectively).¹⁴ This may have biased the ascertainment of non-heritable participants (who are, on average, older) and falsely enriched this group with females. Without knowing the precise number and the genders of non-recruited potential participants who were deceased, it is impossible to determine if this potential bias affected the ascertainment of participants in this study. However, previous studies in which the medical records of both deceased and living PGL patients were reviewed also observed this disequilibrium in gender ratios,^{1,13} suggesting it is a real phenomenon.

These data suggest that females in the general population, i.e., who have not inherited a PGL allele, are more likely than males to develop sporadic PGL. Based on the proposed mechanism for PGL formation, this may indicate females are more susceptible to chronic hypoxia or changes in environmental oxygen levels, or to have physiological defects in oxygen sensing.

Other consistent findings include the following. The average age at onset of symptoms, diagnosis, and surgery was lower for heritable participants than for non-heritable participants. None of these differences was statistically significant; however, they are consistently seen across study populations,^{1,2,13} and may represent a real trend which did not achieve statistical significance in this study as a result of sample size.

CBT is often reported as the most common type of PGL to occur among heritable and non-heritable participant populations.^{2,11,15} These findings are consistent with our heritable participant population because CBT was the most common tumor in that group and was diagnosed significantly more often in heritable than non-heritable participants. Lack et al.¹⁵ looked at the clinical and epi-

TABLE IV.
Statistical Analysis of First Diagnosis of Non-bilateral CBT Between Heritable and Non-heritable Participants of the UPMC and HEI Clinics.

CBT	Heritable No. (%)	Non-heritable No. (%)	P Value	Odds Ratio
Yes	5 (23.8)	2 (5.1)	.0483	5.8
No	16 (76.2)	37 (94.8)		

CBT = carotid body tumor; UPMC = University of Pittsburgh School of Medicine Eye and Ear Institute; HEI = House Ear Institute.

TABLE V.
Statistical Comparison of Average Ages of Heritable and Non-heritable Participants.

Average Age	Heritable Years (SD)	Non-heritable Years (SD)	P Value
Current age	50.3 (15.65)	60.7 (11.09)	0.1794
Age at onset of symptoms	34.1 (13.41)	45.6 (11.76)	0.1759
Age at diagnosis	36.6 (12.18)	52.7 (11.66)	0.1036
Age at surgery	36.1 (11.88)	52.3 (11.33)	0.1043

SD = standard deviation.

demographic characteristics of 69 patients diagnosed with glomus tumor divided into categories by glomus tumor type. They found that the gender ratio was approximately equal among those diagnosed with CBT, whereas there was a predominance of females in the groups diagnosed with GV and/or GJ/GT. In addition, those with CBT had a younger age of onset than those with other tumors. This suggests CBT was more likely to be diagnosed among those in the study population with hereditary PGL. These results corroborate our own, suggesting that these findings can be extrapolated to the inherited PGL population as a whole.

CONCLUSION

We have found that approximately 35% of patients who present to an otolaryngologist with PGL have a clinically recognizable hereditary predisposition. Ours is the first report in a non-Dutch population that shows a high proportion of heritable cases. Clinical recognition of heritable PGL currently relies on several criteria, including family history, bilaterality, multifocality, and age of onset. Our study also suggests that tumor type may be used as a criterion of heritability. A patient diagnosed with a single CBT may be at least five times more likely to have heritable PGL than someone with a single GV, GJ, or GT. The presence of any of the above heritable features warrants referral for clinical cancer genetics consultation for identification of at-risk relatives as well as coordination and interpretation of possible predictive genetic testing. Identifying heritable cases of PGL allows targeted screening of affected patients for future PGLs, in addition to their at-risk relatives. We conclude that secondary prevention of a high proportion of paraganglioma tumors can be achieved by assessing all cases for heritable features and focusing screening efforts toward those at genetic risk.

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