

# Characteristics of Pediatric Pheochromocytoma/paraganglioma

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## Abstract

The “rule of 10” used to describe pheochromocytoma/paragangliomas (PCC/PGLs) has been challenged. However, recent studies suggested that pediatric PCC/PGLs may follow a pattern. Hence, we reviewed the available literature to verify the same. We searched PubMed, Scopus, ProQuest, and Google Scholar for studies describing the genotype and/or phenotype characteristics of pediatric PCC/PGL cohorts published after 2000 in English language and those with sample size more than 35 were included in this review. Pediatric PCC/PGLs were malignant in 10%, synchronous bilateral in 20%, extra-adrenal in 30%, among which, 30% were extra-abdominal and familial in 40%. PCC/PGL diagnosed during pediatric age recurs in 50% by 30 years of follow-up and 60% cases occur in boys. Seventy percent of children with PCC/PGL are likely to have sustained hypertension. Germline mutations could be identified in 80% of children with PCC/PGL and 90% are secretory. The review concludes that pediatric PCC/PGLs follow a pattern, which we call “10%–90% rule.” This new rule will help easily remember the characteristics of pediatric PCC/PGLs.

**Keywords:** 10%–90% rule, paraganglioma, pediatric, pheochromocytoma

## INTRODUCTION

The “rule of 10” used to describe pheochromocytoma/paragangliomas (PCC/PGLs) is a good example of axioms that medical students often learn to remember the key characteristics of a disorder. The rule of 10 used to describe PCC/PGLs is as follows: 10% are extra-adrenal, and of those, 10% are extra-abdominal; 10% are malignant; 10% are found in children; 10% of patients are normotensive; and 10% are hereditary.<sup>[1]</sup> However, at the beginning of the 21<sup>st</sup> century, 10% rule was dashed by a study from Neumann *et al.*, which reported germline mutation in 24% of apparently sporadic PCC/PGL patients.<sup>[2]</sup> This study heralded the death of an axiom, as it was aptly called.<sup>[1]</sup>

Data on characteristics, especially of germline mutations in patients with pediatric PCC/PGL were greatly limited till 2013.<sup>[3-5]</sup> Thereafter, few studies have reported genotype and phenotype characteristics of PCC/PGL in pediatric cohorts. From these studies, we appreciated that characteristics of pediatric PCC/PGL follow a pattern.<sup>[3-5]</sup> Hence, we have reviewed the available literature to verify the same.

## METHODS

We searched PubMed, Scopus, ProQuest, and Google Scholar for studies describing the genotype and/or phenotype

characteristics of pediatric PCC/PGL cohorts published after 2000 in English language. A total of twelve studies describing the genotype and/or phenotype characteristics of pediatric PCC/PGL cohorts published after 2000 were identified;<sup>[3-14]</sup> seven cohorts with sample size <35 were excluded to avoid the confounding factors due to smaller sample size and the potential risk of getting replicated in recent larger cohorts.<sup>[8-14]</sup> The five studies had a sample size of more than 35 and included pediatric PCC/PGL cohorts from the National Institute of Health, United States of America, European-American Pheochromocytoma Paraganglioma Registry (EAPPR), Spain, Russia, and Argentina.<sup>[3-7]</sup> The latter study from Argentina was excluded since patients in this cohort were replicated in the EAPPR.<sup>[4,7]</sup> However, the data from Barontini *et al.* and other two smaller studies have been considered for discussion on the prevalence of hypertension since reliable data were not available from other four studies.<sup>[7-9]</sup> Studies published before 2000 were excluded since most of these were of small sample size and

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had the potential risk of being parts of larger cohorts.<sup>[15-25]</sup> Results obtained in this review are discussed in comparison with a review of 100 individual pediatric PCC/PGL cases published in 1963 and data from a review article published in 2000 which collated most of the information available till then.<sup>[26,27]</sup> Data from these two references were considered as a classical description of pediatric PCC/PGL.

## RESULTS AND DISCUSSION

### Proportion of children in pheochromocytoma/paragangliomas cohorts

According to the “10% rule,” 10% of PC/PGL occur in children.<sup>[1]</sup> Pediatric PCC/PGL cases accounted for 9%, 8%, and 8% of the total PCC/PGL cohorts in EAPPR, Spanish, and Russian studies.<sup>[4-6]</sup> Overall, 8.86% of the total PCC/PGL cohort was accounted by pediatric patients [Table 1]. This component of “10% rule” remains unchanged.

### Age at diagnosis

In the review by Stackpole *et al.*,<sup>[26]</sup> in which children up to 15 years were included the mean age of the pediatric PCC/PGL patients was 10.18 years.<sup>[26]</sup> The average age of PCC/PGL in children has been classically described as 11 years.<sup>[27-29]</sup> However, in recent larger pediatric PCC/PGL cohorts, in which children up to 17–18 years are included, mean or median age is between 12 and 14 years [Table 1]. From the data in Table 1, it is apparent that the average age of children with PCC/PGL when children up to 18 years are included will be around 13 years.

### Proportion of boys

Classically, it has been described that ratio of boys to girls in pediatric PCC/PGL cohorts is 2:1.<sup>[27]</sup> It is mainly derived from the review by Stackpole *et al.*<sup>[26]</sup> In this review, 68% of patients were boys. However, in recent studies, the proportion of boys has varied from 52.7% to 65.5%.<sup>[3-6]</sup> The overall proportion of boys in the recently published cohorts was 61.94% [Table 1]. In the review by Stackpole 49 children were 10 years or younger and in this age group ratio 35 (76.5%) were boys whereas in children aged more than 10 years only 31 (60.8%) were boys.<sup>[26]</sup> Higher average age in recent studies might be contributing for relatively less proportion of boys (62%) compared to the classical description (67%).

### Hypertension

According to the 10% rule, 10% of PCC/PGL patients are normotensive. In Bausch *et al.* study (EAPPR), it was mentioned that 94% of patients were symptomatic and had hypertension, palpitations, headache, or profuse sweating; but, it was not distinct whether all these 94% of patients had hypertension. The review by Stackpole *et al.*, identified the presence of hypertension in 100% of pediatric PCC/PGL cases.<sup>[26]</sup> Similar high rates of hypertension have been reported by Barontini *et al.* (100%) and Mishra *et al.* (23/24, 95.83%). However, in cohorts characterized by greater proportion of extra-adrenal PGL such as Pham *et al.* (64%) and Babic *et al.* (37%) have reported hypertension in less number of subjects. In the latter study, a larger proportion of patients identified during family screening (40%) might have also contributed for the lower prevalence of hypertension. It is likely with increasing availability of routine genetic testing and family screening that a greater proportion of PCC/PGL children will be identified before their symptomatic presentation.

It was classically described that the prevalence of sustained hypertension is more common in children (80%–90%) than adults (50%).<sup>[27]</sup> In the review by Stackpole *et al.*, sustained hypertension was reported in 88% of cases.<sup>[26]</sup> In a recent small study by Mishra *et al.*, 62.5% (15/24) of patients had sustained hypertension.<sup>[8]</sup> In another study, 93% of children with PCC/PGL had sustained hypertension.<sup>[7]</sup> However, lower prevalence (31%–64%) of hypertension in other studies, may suggest even lower prevalence of sustained hypertension in those studies.<sup>[3,9]</sup> Considering the data from above-mentioned studies, it is likely that the prevalence of hypertension is not very high as previously thought and approximately only 70% of pediatric PCC/PGL may have sustained hypertension.

### Secretory status

The secretory status can reliably be obtained from only one study. In the EAPPR, secretory status was documented in 89% of patients.<sup>[4]</sup> In the Babic *et al.* study, although, total number of secretory PCC/PGL was not clearly mentioned, it was apparent that at least 70% of patients were secretory.<sup>[3]</sup> It is likely that the proportion of secretory PCC/PGL depends on the proportion of head and neck paraganglioma (HNPG) in the cohort, who are most likely to be nonsecretory and the tests used for evaluating secretory status.<sup>[3,4]</sup>

**Table 1: Contribution of pediatric cases to total pheochromocytoma and paraganglioma cohorts and proportion of boys in pediatric pheochromocytoma and paraganglioma cohorts**

Study	Upper age limit (years)*	Average age (years)	Proportion of children in PCC/PGL cohorts (%)	Proportion of boys in pediatric (%)
Babic <i>et al.</i> <sup>[3]</sup>	21	13.9±5.1 <sup>†</sup>	-	30/55 (55)
Bausch <i>et al.</i> <sup>[4]</sup>	17	12 (12-13) <sup>‡</sup>	177/2001 (9)	116/177 (65.5)
Cascón <i>et al.</i> <sup>[5]</sup>	18	13.8 (12.8-14.8) <sup>‡</sup>	36/447 (8)	19/36 (52.7)
Beltsevich <i>et al.</i> <sup>[6]</sup>	16	12.1±3.1 <sup>†</sup>	50/520 (9.61)	32/50 (64)
Total			263/2968 (8.86)	197/318 (61.94)

\*Upper age limit to define pediatric age group, <sup>†</sup>Mean±SD, <sup>‡</sup>Median (95% CIs). PCC: Pheochromocytoma, PGL: Paraganglioma, SD: Standard deviation, CIs: Confidence intervals

**Table 2: Prevalence of synchronous, metachronous and total bilateral pheochromocytomas in pediatric pheochromocytoma and paraganglioma cohorts**

Study	Synchronous bilateral PCC (%)	Follow-up (years)	Metachronous bilateral PCC	Total bilateral PCC (%)
Babic <i>et al.</i> <sup>[3]</sup>	8/55 (14.54)	2.7±1.1 (1.3-10)	11	19/55 (34.54)
Bausch <i>et al.</i> <sup>[4]</sup>	43/177 (24)	16	21	64/177 (36.16)
Cascón <i>et al.</i> <sup>[5]</sup>	5/36 (13.89)	3-16	3	8/26 (22.22)
Beltsevich <i>et al.</i> <sup>[6]</sup>	10/50 (20)	5.15±2.8 (3-15)	6	16/50 (32)
Total	66/318 (20.75)			105/318 (33.01)

PCC: Pheochromocytoma

### Bilateral pheochromocytoma

Simultaneous diagnosis of PCC in both the adrenal glands is called synchronous bilateral PCC, whereas the subsequent occurrence of PCC in the contralateral adrenal gland after excision of the initial unilateral PCC is called metachronous bilateral PCC. In the EAPPR, 24% (43/177) of children had bilateral PCC at initial presentation, whereas another 13% (21/157) of patients developed contralateral adrenal PCC during follow-up.<sup>[4]</sup> In the Babic *et al.* study eight (14.54%) patients had bilateral PCC at presentation, and during follow-up another 11 patients developed PCC in the contralateral adrenal gland increasing the prevalence of bilateral PCC to 34.54%.<sup>[3]</sup> Less number of synchronous bilateral PCC in this cohort may be due to greater proportion of patients getting diagnosed during screening for family history. In this situation, early diagnosis of these patients may lead to a higher diagnosis of unilateral PCC. A lower percentage of synchronous as well as metachronous bilateral PCC in the Spanish study is probably due to a higher prevalence of extra-adrenal PCC/PGL in the cohort.<sup>[5]</sup> In total, the prevalence of bilateral PCC at initial presentation is 20.75% and overall 33% [Table 2]. It is classically described that in patients with PCC/PGL 20% are bilateral which was also reported in Stackpole *et al.*<sup>[26]</sup> However, it needs to be appreciated that 20% represents the proportion of synchronous bilateral PCC and the overall prevalence of bilateral PCC is as high as 33%. In patients with tumors confined to adrenals, proportions of bilateral PCC were 51.35% (19/37), 41.29% (64/168), 50% (8/16), and 39.02% (16/39) in Babic *et al.*, Bausch *et al.*, Cascon *et al.*, and Beltsevich *et al.* studies.<sup>[3-6]</sup> Overall, the bilateral PCC accounted for 41.15% of total PCC in pediatric cohorts. Hence, it can be remembered that 40% of adrenal-confined PCC will be bilateral in children.

### Extra-adrenal paragangliomas

The prevalence of extra-adrenal PGL varied from 18 to 61.1%, and overall the prevalence of extra-adrenal PCC/PGL cohorts is 32.07% [Table 3].<sup>[3-6]</sup> Similar percentages of extra-adrenal PCC/PGL are also reported by Stackpole *et al.* (31%) and Ross (28%).<sup>[26,27]</sup> High prevalence of extra-adrenal PCC in Spanish study is probably due to founder *SDHB* mutations in the population, which are associated with extra-adrenal PGL. In this study, thoracic and abdominal PGL were reported separately, and out of 22 patients with extra-adrenal PGL, five patients had HNPGL.<sup>[5]</sup> In the EAPPR, 30% of patients

**Table 3: Prevalence of extra-adrenal paraganglioma and malignancy in pediatric pheochromocytoma and paraganglioma cohorts**

Study	Extra-adrenal PGL (%)	Malignant PCC/PGL (%)
Babic <i>et al.</i> <sup>[3]</sup>	18/55 (32.72)	9/55 (16)
Bausch <i>et al.</i> <sup>[4]</sup>	53/177 (30)	16/177 (9)
Cascón <i>et al.</i> <sup>[5]</sup>	22/36 (61.1)	4/36 (11.1)
Beltsevich <i>et al.</i> <sup>[6]</sup>	9/50 (18)	7/58 (12)
Total	102/318 (32.07)	36/318 (11.5)

PCC: Pheochromocytoma, PGL: Paraganglioma

**Table 4: Prevalence of familial or syndromic cases and germline mutations in pediatric pheochromocytoma and paraganglioma cohorts**

Study	Familial/syndromic (%)	Germline mutations (%)
Babic <i>et al.</i> <sup>[3]</sup>	22/55 (40)	44/55 (80)
Bausch <i>et al.</i> <sup>[4]</sup>	72/177 (40.67)	144/177 (81)
Cascón <i>et al.</i> <sup>[5]</sup>	12/36 (33.33)	25/36 (69)
Total	105/268 (39.55)	213/268 (79.47)

PCC: Pheochromocytoma, PGL: Paraganglioma

had extra-adrenal PGL which included 5% with thoracic PGL and 5% with HNPGL.<sup>[4]</sup> In the Barbic *et al.* study, 11% ( $n = 6$ ) were HNPGL, whereas 4% ( $n = 2$ ) of patients had thoracic sympathetic PGL.<sup>[3]</sup> Hence, it is estimated that around 70% extra-adrenal are confined to abdomen, whereas in another 30% of patients, they are extra-abdominal and are located in thorax or head and neck region.

### Nonmetastatic recurrence (occurrence of a second paragangliomas)

Another important issue in children with PCC/PGL is high rates of recurrence. In the EAPPR, overall nonmetastatic recurrence rate during follow-up was around 25% at 10 years, around 40% at 20 years, around 50% by 30 years, and reached around 80% for those with the longest follow-up.<sup>[4]</sup> During a median follow-up of 16 years, occurrence of a second PCC/PGL were 16%, 13%, and 18% in ipsilateral adrenal gland, contralateral adrenal gland, and extra-adrenal ganglia, respectively. In the Spanish study, the recurrence risk was 22.22% (8/36) at 10 years, whereas in the study from the USA, the recurrence rate was around 40% (22/55) over 16 years with

**Table 5: Prevalence of various germline mutations in pediatric pheochromocytoma and paraganglioma cohorts**

Study	Mutation negative	VHL	SDHB	SDHD	NF-1	RET	SDHA	MAX	SDHC
Babic <i>et al.</i> <sup>[3]</sup>	11	21	13	4	1	3	1	1	0
Bausch <i>et al.</i> <sup>[4]</sup>	33	93	25	17	6	1	1	0	1
Cascón <i>et al.</i> <sup>[5]</sup>	11	8	11	4	0	1	0	1	0
Total (%)	55 (20.52)	122 (45.5)	49 (18.28)	25 (9.32)	7 (2.61)	5 (1.68)	2 (0.74)	2 (0.74)	1 (0.37)

27.27% (6/22) of them being ipsilateral, arising from sites of partial adrenalectomy.<sup>[3,5]</sup>

### Malignancy

The prevalence of malignancy varied from 9% to 16% in pediatric PCC/PGL cohorts.<sup>[3-6]</sup> Overall the prevalence of malignancy was 11.5%. Often, it is quoted that the prevalence of malignancy is less (3.5%) in pediatric PCC/PGL than adults.<sup>[27]</sup> However, these figures are derived from studies with no or minimal follow-up. In the Bausch *et al.* study 10 (5.65%) patients had malignancy at initial presentation, whereas another 3.59% of patients developed metastases during follow-up.<sup>[4]</sup> Childhood PCC/PGL have similar malignant potential as adults and should be closely followed-up similar to adults and monitored for metastasis during follow-up. Except the contribution of pediatric patients to total PCC/PGL cohorts, malignancy is the only characteristic of 10% rule which remains still unchanged.

### Familial/syndromic

In the Bausch *et al.* study, 105 patients were apparently sporadic.<sup>[4]</sup> Considering the rest 72 patients to have either family history of PCC/PGL or syndromic associations, familial/syndromic disease occurred in 40.67%. The study also reported extra-paraganglial tumors in 43% of patients with the highest prevalence among children with *VHL* mutations (65%) and *NF-1* (100%). Prevalence of familial disease varied from 30.5% to 40.67% with overall prevalence of 39.2% [Table 4].<sup>[3-5]</sup> Hence, 60% of pediatric PCC/PGL present as apparently sporadic.

### Hereditary (germline mutations)

It is previously believed that only 10% PCC/PGL are hereditary.<sup>[1]</sup> However, recent studies have demonstrated germline mutations in up to 40% of patients with PCC/PGL.<sup>[30]</sup> In the remaining patients with no identifiable germline mutations, one-third contain a somatic mutation in PCC/PGL associated genes. Prevalence of germline mutations in pediatric PCC/PGL cohorts is even higher and varied from 69% to 81% with overall prevalence of 79.4% [Table 4].<sup>[3-5]</sup> Mutations in *VHL* were the most common and seen in 45.5% of the pediatric PCC/PGL patients, whereas *SDHB* and *SDHD* mutations were the second (18.28%) and third (9.32%) most common. Mutations in other genes were significantly less, and altogether these mutations were observed in around 7% of patients [Table 5].<sup>[3-5]</sup>

Even in children with apparently sporadic PCC/PGL prevalence of germline mutations is high. In the Neumann

*et al.* study, 59% of patients aged  $\leq 18$  years with apparently sporadic presentation had underlying germline mutations with a higher frequency of germline mutations in 70% of children younger than 10 years.<sup>[2]</sup> In Babic *et al.* study, 66.67% (22/33) of children without family history had underlying germline mutations.<sup>[3]</sup> Prevalence of germline mutations in solitary nonmetastatic PCC with no family history was 62% (8/13) in the Babic *et al.* study, whereas in Currás-Freixes *et al.* study from Spain where *SDHB* founder mutations are present, 53.3% of children with apparently sporadic PCC/PGL had germline mutations, the most common being *SDHB* mutations.<sup>[3,31]</sup> In addition, three out of the five mutation negative children also had somatic mutations in *VHL* gene increasing the presence of genetic drivers in 73.3% of children with solitary PCC/PGL.<sup>[30]</sup> With rapidly evolving advances in the genetic understating of PCC/PGL, we are not too far from identifying the genetic drivers (germline and/or somatic) in 100% of pediatric PCC/PGL patients.

To summarize, pediatric PCC/PGLs appear to follow a pattern, which we call “10%–90% rule” and is as mentioned below:

- 10%: Malignant
- 20%: Synchronous bilateral
- 30%: Extra-adrenal
- 40%: Familial
- 50%: Recur (second PCC/PGL) by 30 years
- 60%: Boys
- 70%: Sustained hypertension
- 80%: Germline mutations
- 90%: Secretory
- 100%: Germline + somatic?!

This new rule will help to understand and easily remember the characteristics of pediatric PCC/PGLs. However, this new rule needs evaluation in larger cohorts from different parts of the world.

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### Conflicts of interest

There are no conflicts of interest.

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