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# Associated anomalies in Pierre Robin sequence

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## Abstract

Pierre Robin sequence (PRS) is frequently co-occurring with other non-PRS congenital anomalies. The types and the prevalence of anomalies co-occurring with PRS vary in the reported studies. The aims of this report was to study the types and the prevalence of the anomalies co-occurring with PRS in a well-studied population northeastern France. The types and the prevalence of anomalies co-occurring in cases with PRS were ascertained in all terminations of pregnancy, stillbirths and live births in 387,067 births occurring consecutively during the period 1979–2007 in the area covered by our registry of congenital anomalies which is population-based, 89 cases of PRS were registered during the study period with a prevalence of 2.29 per 10,000 births, 69.7% of the cases had associated non-PRS anomalies. Chromosomal abnormalities were present in 10 (11.2%) cases including three 22 q11.2 deletion. Non-chromosomal recognizable conditions were diagnosed in 27 cases (30.3%) including 10 Stickler syndrome, 8 Treacher Collins syndrome, 3 cases with short stature and 6 other syndromes. Multiple congenital anomalies (MCA) were present in 25 cases (28.1%). The most frequent MCA were in the ear, face and neck (35 out of 98 anomalies, 35.7%), cardiovascular (18 anomalies, 18.4%), musculoskeletal (11 anomalies, 11.2%), central nervous (7 anomalies, 7.1%), urinary (6 anomalies, 6.1%), and eye (6 anomalies, 6.1%) system. The high prevalence of associated anomalies justifies a thorough screening for other congenital anomalies in cases with PRS.

## KEYWORDS

airway obstruction, associated anomalies, cleft palate, glossoptosis, micrognathia, retrognathia

## 1 | INTRODUCTION

The triad of micrognathia, glossoptosis and concomitant airway obstruction defines the Pierre Robin sequence (PRS) (Breugem & Courtemanche, 2010). This sequence of abnormal embryonic development also results in an anatomical configuration that might predispose the fetus to a cleft palate (Logjes et al., 2018). In PRS, the primary developmental disturbance is the micrognathia leading to a retropositioning of the tongue, obstructing the fetal closure of the secondary palatal shelves, and eventually causing neonatal respiratory problems

by mechanical obstruction of the oropharynx (Cohen, 1999; Hanson & Smith, 1975). Historically, cleft palate has not been regarded pathognomonic of the PRS population, and even today some authors regard this feature as optional (Printzlau & Andersen, 2004). At the other end of the spectrum, some authors consider only children with a typical long, U-shaped cleft palate as being truly Pierre Robin (Shprintzen, 1988).

PRS is a relatively common congenital anomaly with a prevalence ranging from 1:8500 to 1: 20,000 live births (Junaid et al., 2022; Paes et al., 2015; Printzlau & Andersen, 2004; Santoro et al., 2021; Scott &

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Mader, 2014; Vatlach et al., 2014; Wright et al., 2018). PRS may occur in isolation or in the context of other, associated anomalies. Among the various reported studies the proportion of isolated versus non-isolated PRS is highly variable as shown in Table 1. Mortality associated with Robin sequence is reported to be between 1.7% and 65% (Costa et al., 2014). Surgical intervention has been reserved for patients with severe airway obstruction in which conservative treatment has been unsuccessful. The prognosis of patients with idiopathic PRS without associated anomalies is usually good or with slight handicap but outcome may be bad in patients with associated anomalies (Scott & Mader, 2014).

The aim of this study was to determine the prevalence, the frequency and the type of congenital anomalies co-occurring in cases with PRS in a well-studied population.

## 2 | CASES AND METHODS

Our study included all cases of PRS collected from 387,067 consecutive pregnancies of known outcome recorded through our registry of congenital malformations (RMCBR), previously described (Stoll, 1985). The newborns of 11 maternity hospitals were examined from January 1, 1979, to December 31, 2007. The region of investigation was the area defined by the “Departement du Bas-Rhin” which includes the urban area of Strasbourg and surrounding rural areas. This research project was reviewed and approved by the Ethics Committee of the Medical Faculty of Strasbourg following the World Medical Association Declaration of Helsinki. Parental informed consent is

mandatory for RMCBR. All newborns including live births and stillbirths of at least 22 weeks of gestation were registered within the first 8 days postpartum, as well as all TOPFA (Terminations Of Pregnancy for Fetal Anomaly), regardless of gestational ages. In this area all deliveries take place in maternity hospitals resulting in a complete ascertainment. A clinical geneticist examined every case and interviewed pediatricians/neonatologists. Surveillance for anomalies was carried out until 2 years of age. Every case was reported to RMCBR. Analysis of the data was done retrospectively. In the region under study, in the mid-trimester of pregnancy, a prenatal ultrasound examination for congenital anomalies was proposed to every pregnant woman. When a suspected or confirmed case was reported, information was obtained from all available records. PRS was defined by the triad of micrognathia, glossoptosis and concomitant airway obstruction with or without cleft palate. Cases with anomalies were subdivided into “isolated,” when only PRS was present, and “associated,” when one or more additional non-PRS major anomalies were recognized. The cases with non-chromosomal syndromic associated anomalies were classified as having either a syndrome, a sequence, an association, or a spectrum (Hennekam et al., 2013). The non-syndromic multiple congenital anomalies (MCA), were sub-classified according to the main organ system affected. For each case with associated anomalies, a complete description was obtained, including photographs, radiographs, karyotype, and autopsy. However, at the period of the study, chromosomal microarray (aCGH) was not available in our region as well as molecular testing, WGS and whole exome sequencing. A major anomaly was defined as a structural defect of the body and/or organs that impair viability and require intervention,

**TABLE 1** Isolated, syndromic, associated and non-isolated congenital anomalies in the studies with Pierre Robin sequence recently reported.

Authors	Isolated	Syndromic	Associated non-isolated
Hanson and Smith (1975)	39	25	36
Williams et al. (1981)	36	38	26
Sheffield et al. (1987)	19	71	11
Caouette-Laberge et al. (1994)	54		46
Van den Elzen et al. (2001)	63		37
Holder-Espinasse et al. (2001)	48	35	17
Printzlau and Andersen (2004)	62		38
Evans et al. (2006)	63		37
Butow et al. (2009)	66	18	16
Glynn et al. (2011)	91		9
Izumi et al. (2012)	42	38	20
Thouvenin et al. (2013)	51		49
Scott and Mader (2014)	57		43
Vatlach et al. (2014)	66		34
Flores et al. (2015)	21		79
Paes et al. (2015)	36		64
Gomez-Ospina and Bernstein (2016)	35		65
Wright et al. (2018)	75		25
Santoro et al. (2021)	69		31
Weaver et al. (2022)	27		73

need to be treated (Queißer-Luft & Spranger, 2006). Major non-PRS anomalies within a system were counted as one defect. For example, a case with hydronephrosis and kidney agenesis was counted once as kidney agenesis and a case with omphalocele, intestinal atresia, and malrotation was counted once as omphalocele (Lowry et al., 2013). A case with a Mendelian disorder that includes multiple anomalies e.g. Stickler syndrome (MIM#609508) was classified as having a recognizable non-chromosomal condition. Minor congenital anomalies such as cryptorchidism were excluded. Intellectual disability was not included because it is difficult to assess in infancy.

The prevalence of the anomalies most frequently associated with cases of PRS with MCA as for example ventricular septal defect, was compared with the prevalence of these anomalies (here ventricular septal defect) in the population under study.

For the calculation of prevalence rates the total number of births including livebirths, stillborn and termination of pregnancy for fetal anomalies from 1979 to 2007 was used: 387,067.

SAS Version 8 (SAS Institute, Inc, Cary, NC) was used for statistical analysis. The chi-squared test was used for comparisons.

### 3 | RESULTS

Eighty-nine cases of PRS were registered resulting in a prevalence at birth of 2.29 per 10,000 including 27 (30.3%) isolated, idiopathic cases of PRS (Table 2) and 62 cases (69.7%) with associated anomalies (Table 3) including chromosomal anomalies, syndromes, and MCA, 74 cases were live births (83.1%), 2 stillbirths (2.2%), and 13 TOPFA (14.6%), 72 cases had cleft palate (80.9%), 4 children died in the first year of life.

There were no changes in prevalence over time.

Fifty-three (59.6%) cases were males, 36 (40.4%) were females resulting in a sex ratio of 1.47.

Out of the 62 cases with associated anomalies 10 (11.2%) had a chromosomal anomaly, including 3 microdeletion 22q11.2 and 7 other anomalies: one Turner syndrome and 6 autosomal anomalies, 4 deletions and 2 unbalanced translocations (Tables 2 and 3), 27 (30.3%) had a recognizable non-chromosomal condition including 10 Stickler syndrome, 8 Treacher Collins syndrome, 3 short stature including one

**TABLE 2** Isolated and co-occurring congenital anomalies in 89 cases with Pierre Robin sequence in Northeastern France from 1979 to 2007.

	n	%	Prevalence <sup>a</sup>
Associated anomalies	62	69.7	1.60
Genetic syndromes <sup>b</sup>	27	30.3	0.69
Multiple congenital anomalies	25	28.1	0.64
Chromosomal abnormalities	10	11.2	0.25
Isolated anomalies	27	30.3	0.69
Total	89	100	2.29

<sup>a</sup>Prevalence per 10,000 births.

<sup>b</sup>Include syndromes, associations, sequences and spectrums.

achondroplasia, and one each: de Lange, fetal alcoholic, Marshall, oculo-auriculo-vertebral, Smith-Lemli-Opitz, and van der Woude syndrome. The diagnoses of the syndromes were obtained clinically. Twenty-five cases (28.1%) were MCA. These 25 cases had 98 anomalies as one patient can have several co-occurring anomalies. One associated anomaly was present in 36 cases, two anomalies in 16 cases, and three or more anomalies in 10 cases. In the patients with MCA the most common other anomalies were ear, face and neck (35 anomalies, 35.7%), cardiovascular (18 anomalies, 18.4%), musculoskeletal (11 anomalies, 11.2%), central nervous (7 anomalies, 7.1%), urinary (6 anomalies, 6.1%), and eye (6 anomalies, 6.1%). These organ system anomalies appear in Table 3.

In 37 (59.7%) out of the 62 cases with associated anomalies, the anomalies could be included into a recognizable pattern or syndrome.

Table 4 shows the observed prevalence of the anomalies more commonly associated with PRS compared with the expected prevalence of these anomalies in the population under study.

### 4 | DISCUSSION

The congenital anomalies included in the triad defining the PRS are often associated with other congenital anomalies. These associated anomalies are responsible for most of the morbidity and mortality associated with PRS (Costa et al., 2014). In the population studied, the prevalence of PRS was 22.9 per 100,000 births and 69.7% of the cases had associated anomalies. However, the data used for estimating prevalence were old. The prevalence of PRS as well as the proportion and the type of anomalies associated with PRS varied considerably among the various reported studies. The 16 studies on PRS reported from 1988 to 2015 were reviewed by Gomez-Ospina and Bernstein (2016) and the 42 studies on PRS reported from 1962 to 2014 were analyzed by Paes et al. (2015). No duplications appear in these two reviews. We added 7 studies published in and after 2014 to the reviews of Gomez-Ospina and Bernstein (2016) and of Paes et al. (2015) and the study of Thouvenin et al. (2013) which was not included in the reviews of Gomez-Ospina and Bernstein (2016) and of Paes et al. (2015). The 16 studies on PRS reported from 1988 to 2015 by Gomez-Ospina and Bernstein (2016) were all based on hospital records, 21 of the studies reviewed by Paes et al. (2015) were based on hospital records, 21 on congenital malformations registries, 4 on social services, 3 on birth certificates, one on the National Healthcare System, one on an institute for speech disorders, and one on records of insurance companies (some authors used several data sources). Six studies only, based on well-studied population, on all types of PRS, isolated or associated, were reported (Bush & Williams, 1983; Kallen et al., 1996; Lary & Paulozzi, 2001; Paes et al., 2015; Scott & Mader, 2014; Vatlach et al., 2014). The prevalence per 100,000 births of PRS calculated by dividing the total number of cases of PRS by the total number of births ranged from 11.6 in The Netherlands (Paes et al., 2015) to 37.2 in East Scotland (Wright et al., 2018) (Table 5). However, if the definition most commonly used for the diagnosis of PRS is cleft palate, glossoptosis and micro- or retrognathia (Wright

**TABLE 3** Syndromes, chromosomal abnormalities and multiple congenital anomalies (MCA) in 62 cases with Pierre Robin sequence and associated anomalies.

	Number of cases (%) <sup>a</sup>
<b>Recognizable conditions</b>	
<i>Chromosomal</i>	
Trisomy 21	
22q11.2 deletion	3 (30.0)
Trisomy 18	
Other <sup>b</sup>	7 (70.0)
Total	10 (11.2)
<i>Non chromosomal</i>	
Stickler syndrome	10 (37.0)
Treacher Collins syndrome	8 (29.6)
Other <sup>c</sup>	9 (33.3)
Total	27 (30.2)
<b>Non-recognizable conditions<sup>d</sup></b>	
<i>Musculoskeletal</i>	
Syndactyly	3 (27.3)
Polydactyly	1 (9.1)
Spine, rib and sternum	2 (18.2)
Limb deficiency	3 (27.3)
Other	2 (18.2)
Total	11 (11.2)
<i>Congenital heart defects</i>	
VSD	9 (50.0)
ASD	5 (27.8)
CoA	1 (5.5)
Other	3 (16.6)
Total	18 (18.4)
<i>Urinary system</i>	
Renal agenesis	
Congenital anomaly of ureter	3 (50.0)
Hydronephrosis	
Other	3 (50.0)
Total	6 (6.1)
<i>Genital anomalies</i>	
Hypospadias	2 (66.6)
Other	1 (33.3)
Total	3 (3.1)
<i>Gastrointestinal anomalies</i>	
Esophageal atresia	1 (33.3)
Other	2 (66.6)
Total	3 (3.1)
<i>Central Nervous System</i>	
Arnold-Chiari anomaly	
Hydrocephaly	2 (28.6)
Pachygyria	

(Continues)

**TABLE 3** (Continued)

	Number of cases (%) <sup>a</sup>
<i>Agenesis corpus callosum</i>	
Other	5 (71.4)
Total	7 (7.1)
<i>Eye</i>	
Cataract	3 (50.0)
Microphthalmia	1 (16.7)
Other	2 (33.3)
Total	6 (6.1)
<i>Ear, face and neck</i>	35 (35.7)
<i>Abdominal wall</i>	
Omphalocele	1 (100.0)
Total	1 (1.0)
<i>Skin</i>	
Hemangioma	
Total	
Other	8 (8.2)
Total	98 <sup>a</sup>

Abbreviations: ASD, atrial septal defect; CoA: coarctation of aorta; VSD, ventricular septal defect.

<sup>a</sup>Number of cases (N) and percentage (%). The percentages for recognizable conditions are the percentages of the total number of cases, the percentages for non-recognizable conditions are the percentages of the 98 anomalies occurring in 25 cases with multiple congenital anomalies.

<sup>b</sup>Other chromosomal abnormalities including one each: Turner syndrome, 2q13 del, 4q31 del, 16q11.2 del, 18 q 22.3 del, and 2 unbalanced translocations: t (4;17) (q31; q24), t(6;17) (q25;q24).

<sup>c</sup>Other syndromes including one each: de Lange, fetal alcoholic, Marshall, oculo-auriculo-vertebral, Smith-Lemli-Opitz, and van der Woude.

<sup>d</sup>Congenital anomalies by organ system (recognizable conditions excluded).

et al., 2018), the definition used in several studies as for example that of Printzlau and Andersen (2004) and of Paes et al. (2015) is micrognathia, cleft palate and respiratory distress. Vatlach et al. (2014) use micrognathia or retrognathia plus cleft palate or signs of upper airway obstruction, feeding difficulties and underweight. For Gomez-Ospina and Bernstein (2016) the diagnosis of PRS is based on the triad of micrognathia, airway obstruction and cleft palate. Thouvenin et al. (2013) consider the triad of retrognathia, glossoptosis and posterior U-shaped cleft palate. Some authors are using codes to identify patients with PRS as Scott and Mader (2014) who used ICD-9 codes for micrognathia and cleft palate and Santoro et al. (2021) who extracted PRS cases from the EUROCAT Central Database using the ICD10-BPA code Q8708 and the ICD9-BPA code 75603. We used the triad of micrognathia, glossoptosis and concomitant airway obstruction with or without cleft palate for ascertaining our cases with PRS. Despite the use by some authors of the same definition for ascertaining cases with PRS there are large variations in the prevalence of PRS between their series. For example Printzlau and Andersen (2004) find a prevalence of 7.5 whereas for Paes et al. (2015) this

**TABLE 4** Comparison of the prevalence of the most frequently co-occurring congenital anomalies in the cases with Pierre Robin sequence with the prevalence of these anomalies in the general population.

	Present study prevalence per 10,000			Population prevalence per 10,000						
	N	Rate	95% CI	N	Rate	95% CI	O/E	OR	CI	p
Ventricular septal defect	9	1011.2	[472.9; 1833.0]	1935	50.0	[47.8; 52.3]	20.2	22.4	[9.9; 44.7]	8.8e-10
Limb deficiency	3	337.1	[70.1; 953.6]	310	8.0	[7.1; 9.0]	42.1	43.5	[8.6; 132.2]	5.6e-05
Hydrocephaly	2	224.7	[27.3; 788.3]	318	8.2	[7.3; 9.2]	27.4	28.0	[3.3; 104.8]	0.002543
Hypospadias	2	224.7	[27.3; 788.3]	681	17.6	[16.3; 19.0]	12.8	13.0	[1.6; 48.8]	0.011
Intestinal malrotation	2	224.7	[27.3; 788.3]	202	5.2	[4.5; 6.0]	43.2	44.0	[3.2; 166.4]	0.00105

Abbreviations: CI, confidence interval; N, number of cases; O/E, observed/expected; OR, odds ratios; p, p-values.

prevalence was 11.6 and for Scott and Mader (2014) the prevalence was 32.0 but it was only 12.0 for Santoro et al. (2021). ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research), an international network of registries of congenital anomalies does not ascertain PRS. In EUROCAT, a European network of registries of congenital anomalies (<http://www.eurocat-network.eu/>) the prevalence per 100,000 births of PRS ranged from 2.3 in Tuscany, Italy to 16.9 in Vaud, Switzerland. In our population-based study the prevalence of PRS was high, 22.9. This may be the result of the inclusion of all types of PRS in our series including TOPFA. In our series 69.7% of the cases had associated anomalies. The percentage of anomalies associated with PRS reported in the literature is shown on Table 5, it ranged from 25.0 in East Scotland (Wright et al., 2018) to 79.0 in Indianapolis (Flores et al., 2014). However, only 17% of the cases with PRS examined by Shprintzen (1992) in New York had associated anomalies. Comparing our results with previously published studies is difficult because of methodological variations. For instance, in population-based registries the results vary in whether ascertainment is passive or active. Other causes that may explain the variable frequencies of co-occurring anomalies could be the length of time after birth that the cases were studied, the selection of cases, the difference of clinical expression of associated anomalies, the sources of ascertainment, the time of continuation of the surveillance after birth, the differences in inclusion/exclusion criteria and in clinical definitions, the hardness to know the percentage of cases diagnosed by objective techniques, the size of the sample, if all patients were ascertained, including stillbirths and terminations of pregnancy, if autopsies were performed or not, if there was follow-up or not, some authors reported cases referred to a health care facility instead of all cases born in a certain geographical area. In addition, many authors group together the cases with isolated PRS and the cases with associated anomalies. Moreover, there are true population variations and differences in frequency over time (Stoll et al., 2010).

In PRS a higher male–female ratio has been reported by Gomez-Ospina and Bernstein (2016), 39 males v. 27 females, with a male–female ratio of 1.44. The male female ratio was 1.47 in this study. However, in 16 out of the 42 studies reviewed by Paes et al. (2015) providing the number of males and females, there were no proportion difference between males and females.

In this series, chromosomal abnormalities were observed in 10 cases, 11.2%. The reported percentages of chromosomal

abnormalities in cases with PRS varied ranging from 0.9 in Oslo (Filip et al., 2015) to 16.6 in Indianapolis (Costa et al., 2014). In this series the most common chromosomal abnormality was 22q11.2 deletion. In the previously reported series the most common chromosomal abnormalities were also 22q11.2 deletion, 30 out of 170 cases (17.6%) of PRS with chromosomal anomalies reported in the literature were 22q11.2 deletion, with a percentage ranging from 10.0 in Indianapolis (Costa et al., 2014) to 100.0 in Denmark (Printzlau & Andersen, 2004) and in Oslo (Filip et al., 2015). Trisomy 21 and trisomy 18 were less frequent with a percentage ranging for trisomy 21 from 3.4 in Cincinnati (Weaver et al., 2022) to 10 in Indianapolis (Costa et al., 2014) and for trisomy 18 from 3.4 in Cincinnati (Weaver et al., 2022) to 50.0 in Taiwan (Hsieh et al., 1999). Gomez-Ospina and Bernstein (2016) studied the cytogenetic and molecular outcomes in a series of 66 patients with PRS ascertained in Stanford, California and performed a literature review. They observed that chromosome arrays, performed for 72% of idiopathic PRS with associated anomalies, revealed two cases of 18q22-qter deletion, a region not previously reported in association with PRS. A review of the cytogenetic anomalies identified in the population supports an association between the 4q33- qter, 17q24.3, 2q33.1, and 11q23 chromosomal loci and PRS. They found a low frequency of 22q11.2 deletion in PRS, suggesting it is less commonly implicated in this malformation. Their data also indicate a higher frequency of cytogenetic anomalies in PRS cases with associated anomalies. Therefore, on individuals with PRS and any associated malformations the recommendations of Miller et al. (2010) are advisable, involving more detailed genetic tests beyond karyotype: chromosomal microarray as first-tier clinical diagnosis test and for some cases further testing: FISH, qPCR, MLPA, and single gene tests.

Many non-chromosomal syndromes were reported to be associated with PRS including syndromes with identified genes (Basart et al., 2015; Costa et al., 2014; Gomez-Ospina & Bernstein, 2016; Logies et al., 2018; Weaver et al., 2022). The vast majority of reported cases were single cases reports with a few cases series. In the current series 27 (30.3%) out of 89 cases with PRS had non-chromosomal recognizable conditions. In the previously reported series the percentage of non-chromosomal recognizable conditions in cases with PRS varied considerably ranging from 5.0 in Taiwan (Hsieh et al., 1999) to 45.1 in Cincinnati (Weaver et al., 2022). Among them the most common were Stickler syndrome 96 (32.1%) out of 299 reported cases (Table 6) with a percentage ranging from 16.6 (Gomez-Ospina & Bernstein, 2016) to

**TABLE 5** Prevalence and percentage of associated congenital anomalies in recently published studies with Pierre Robin sequence.<sup>a</sup>

	Thouvenin et al. (2013) (Paris)	Scott and Mader (2014) (USA) <sup>c</sup>	Vatlach et al. (2014) (Germany)	Flores et al. (2015) (Indianapolis, USA)	Paes et al. (2015) (Netherlands)	Gomez-Ospina and Bernstein (2016) (Stanford California)	Wright et al. (2018) (East Scotland)
Study years		2006 and 2009	2011–2012	2003–2012	2000–2010	2001–2014	2004–2013
Number of births	Case series	1,654,805	662,712	Case series	2,113,858	Case series	281,885
Study population	LB	LB	LB	LB	LB	LB	LB
Total number	141	529	82	81	246 (118)	66	105
Prevalence <sup>b</sup>	?	32.0	12.4	?	11.6 (17.7)	?	37.2
Associated number (%)	68(49)	227 (43.1)	28 (34.1)	64 (79.0)	75/118 (63.6) <sup>d</sup>	43 (65.1)	25/100 (25.0)
	Santoro et al. (2021) (Europe)	Junaid et al. (2022) (Western Australia)		Weaver et al. (2022) (Cincinnati)	This study		
Study years	1998–2017	1980–2010		2002–2016	1979–2007		
Number of births	11,669,155	792,373		Case series	387,067		
Study population	LB, SB, TOP	LB, SB, TOP		LB	LB, SB, TOP		
Total number	1224	146		175	89		
Prevalence	12.0	18.5		?	22.9		
Associated number (%)	404/1286 (31.4)	/?		128 (73.1)	62 (69.7)		

Abbreviations: LB, live births; SB, stillbirths; TOP, termination of pregnancy for fetal anomaly.

<sup>a</sup>The studies reported before 2015 except Thouvenin et al. (2013) were reviewed by Paes et al. (2015) and by Gomez-Ospina and Bernstein (2016).

<sup>b</sup>Per 100,000 births.

<sup>c</sup>The Dartmouth Atlas of Health Care in the United States, 1996, the Healthcare Cost and Utilization Project (HCUP) including the Kids' Inpatient Database (KID).

<sup>d</sup>Including 246 cases from the Dutch Cleft Registry and 118 cases from 3 academic hospitals. These 118 cases were included in the study of Basart et al. (2015).

85.7 (Printzlau & Andersen, 2004) and Treacher Collins syndrome, 30 (10.0%) out of 299 cases with a percentage ranging from 6.3 (Weaver et al., 2022) to 29.6 (this study). The Online Mendelian Inheritance in Man (OMIM: <http://omim.org>) lists 34 conditions associated with PRS, 18 of which have a known molecular basis.

The organ system that was the more commonly affected by associated anomalies in the cases of PRS reported in the literature was the cardiovascular system (276, 30.3% out of 911 anomalies in cases with MCA), the ear, face and neck system (107 anomalies, 11.7%), the central nervous system (112 anomalies, 12.3%), the musculoskeletal system (152 anomalies, 16.7%), the urogenital system (74 anomalies, 8.1%), the eye (46 anomalies, 5.0%), and the gastrointestinal system (43 anomalies, 4.7%). In this study, anomalies of the cardiovascular system were observed in 18.4% of the cases of PRS with MCA. Similar figures were reported in other studies with a percentage of anomalies of the cardiovascular system varying from 12.1 (Weaver et al., 2022) to 75.0 (Hsieh et al., 1999) with variations for the ventricular septum defects from 24.3 in Indianapolis (Costa et al., 2014) to 50.0 in Strasbourg (this study) and for atrial septum defect from 16.4 in Europe (Santoro et al., 2021) to 40.0 in

Denmark (Printzlau & Andersen, 2004). For the anomalies of the central nervous system, the percentages of reported anomalies varied from 6.2 in Denmark (Printzlau & Andersen, 2004) to 19.6 in Indianapolis (Costa et al., 2014) with variation for Arnold Chiari anomaly from 12.1 in Indianapolis (Costa et al., 2014) to 20.0 in Cincinnati (Weaver et al., 2022). For the musculoskeletal system, the percentages of anomalies reported varied from 11.2 in this series to 34.4 in Europe (Santoro et al., 2021) with variation for syndactyly from 6.8 in Europe (Santoro et al., 2021) to 27.3 in this series, for polydactyly from 2.8 in Europe (Santoro et al., 2021) to 9.1 in Strasbourg (This study) and for limb deficiency from 16.6 in Denmark (Printzlau & Andersen, 2004) to 27.3 in this series, for hypospadias from 5.2 in Europe (Santoro et al., 2021) to 100.0 in Denmark (Printzlau & Andersen, 2004) and in Stanford (Gomez-Ospina & Bernstein, 2016).

Children with PRS have higher incidences of other congenital anomalies than in the general population. In our series, the presence of PRS increased the risk of ventricular septal defect, limb deficiency, hypospadias, hydrocephaly, and intestinal malrotation with odds ratios of 22.4, 43.5, 13.0, 28.0 and 44.0, respectively.

**TABLE 6** Chromosomal abnormalities, syndromes and multiple congenital anomalies in the series with Pierre Robin sequence recently reported.<sup>a</sup>

	Hsieh et al. (1999) (Taiwan)	Printzlau and Andersen (2004) (Denmark)	Costa et al. (2014) (Indianapolis, USA)	Filip et al. (2015) Oslo (Norway)	Gomez-Ospina and Bernstein (2016) (Stanford, CA)	Basart et al. (2015) (Netherlands)
Number of cases	20 <sup>b</sup>	50	181	104	66	191
<b>Recognizable conditions</b>						
<i>Chromosomal</i>						
Trisomy 21	1 (50.0)		3 (10.0)			
22q11.2 deletion		1(100.0)	3 (10.0)	1 (100.0)	1 (33.3)	2 (11.7)
Trisomy 18	1 (50.0)		2 (6.6)			
Other			22 (73.3)		2 (66.6)	15 (88.2)
Total	2 (10.0)	1 (2.0)	30 (16.6)	1 (0.9)	3 (4.5)	17 (8.9)
<i>Non chromosomal conditions</i>						
Stickler syndrome		6 (85.7)	5 (18.5)	5 (50.0)	2 (16.6)	27 (48.1)
Treacher Collins syndrome			2 (7.4)		3 (25.0)	4 (7.1)
Other	1 (100.0)	1 (14.3)	20 (74.1)	5 (50.0)	7 (58.3)	25 (44.6)
Total	1 (5.0)	7 (14.0)	27 (14.9)	10 (9.6)	12 (18.2)	56 (29.3)
<b>Non recognizable conditions</b>						
<i>Musculoskeletal</i>						
Syndactyly		1 (16.6)			1(12.5)	
Polydactyly		1 (16.6)			1 (12.5)	
Spine, rib and sternum		2 (33.3)				
Limb deficiency		1 (16.6)			2 (25.0)	
Other	1 (100.0)	1 (16.6)			4 (50.0)	
Total	1 (25.0)	6 (37.5)			8 (16.3)	
<i>Congenital heart defects</i>						
VSD	1 (33.3)	2 (40.0)	19 (24.3)		6 <sup>c</sup> (46.1)	
ASD	1 (33.3)	2 (40.0)	22 (28.2)			
CoA			7 (8.9)			
Other	1 (33.3)	1 (20.0)	30 (38.5)		7 (53.8)	
Total	3 (75.0)	5 (31.2)	78 (46.4)		13 (26.5)	
<i>Urinary system</i>						
Renal agenesis						
Congenital anomaly of ureter						
Hydronephrosis						
Other					1(100.0)	
Total					1(2.0)	
<i>Genital anomalies</i>						
Hypospadias		2 (100.0)			2 (100.0)	
Other						
Total		2 (12.5)			2 (4.1)	

TABLE 6 (Continued)

	Hsieh et al. (1999) (Taiwan)	Printzlau and Andersen (2004) (Denmark)	Costa et al. (2014) (Indianapolis, USA)	Filip et al. (2015) Oslo (Norway)	Gomez-Ospina and Bernstein (2016) (Stanford, CA)	Basart et al. (2015) (Netherlands)
<i>Gastrointestinal anomalies</i>						
Esophageal atresia		1(100.0)				
Other					2 (100.0)	
Total		1 (6.2)			2 (4.1)	
<i>Central nervous system</i>						
Arnold-Chiari anomaly			4 (12.1)		1 (20.0)	
Hydrocephaly			5 (15.1)		1 (20.0)	
Pachygyria						
Agenesis corpus callosum			4 (12.1)			
Other		1(100.0)	20 (60.6)		3 (60.0)	
Total		1(6.2)	33 (19.6)		5 (10.2)	
<i>Eye</i>						
Cataract					1 (7.70)	
Microphthalmia						
Other					3 (23.1)	
Total					4 (30.7)	
<i>Ear, face, and neck</i>		1(6.2)			13 (26.5)	
<i>Orofacial</i>						
Cleft lip and/or palate					1 (100.0)	
Cleft palate						
Total					1 (2.0)	
<i>Abdominal wall</i>						
Omphalocele						
Total						
<i>Skin</i>						
Hemangioma						
Total						
Other			57			
Total	4	16	168		49	
		Santoro et al. (2021) (Europe)		Weaver et al. (2022) (Cincinnati, OH)		This study
Number of cases		1294		175		89
<i>Recognizable conditions</i>						
<i>Chromosomal</i>						
Trisomy 21		2 (2.6)		1 (3.4)		
22q11.2 deletion		16 (20.8)		3 (10.3)		3 (30.0)
Trisomy 18		11 (14.3)		1 (3.4)		
Other		48 (62.3)		24 (82.7)		7 (70.0)
Total		77 (5.9)		29 (16.0)		10 (11.2)
<i>Non chromosomal conditions</i>						
Stickler syndrome		24 (31.2)		17 (21.5)		10 (37.0)

(Continues)

TABLE 6 (Continued)

Treacher Collins syndrome	8 (10.4)	5 (6.3)	8 (29.6)
Other	45 (58.4)	57 (72.1)	9 (33.3)
Total	77 (5.9)	79 (45.1)	27 (30.2)
Non recognizable conditions			
<i>Musculoskeletal</i>			
Syndactyly	17 (6.8)		3 (27.3)
Polydactyly	7 (2.8)		1 (9.1)
Spine, rib and sternum	5 (2.0)		2 (18.2)
Limb deficiency			3 (27.3)
Other	54 (70.1)		2 (18.2)
Total	86 (34.4)	40 (19.4)	11 (11.2)
<i>Congenital heart defects</i>			
VSD	63 (25.2)		9 (50.0)
ASD	41 (16.4)		5 (27.8)
CoA	8 (3.2)		1 (5.5)
Other	43 (17.3)		3 (16.6)
Total	134 (53.6)	25 (12.1)	18 (18.4)
<i>Urinary system</i>			
Renal agenesis	8 (3.2)		
Congenital anomaly of ureter			3 (50.0)
Hydronephrosis	14 (5.6)		
Other	4 (1.6)		3 (50.0)
Total	39 (15.6)	29 <sup>d</sup> (14.1)	6 (6.1)
<i>Genital anomalies</i>			
Hypospadias	13 (5.2)		2 (66.6)
Other	8 (3.2)		1 (33.3)
Total	21 (8.4)		3 (3.1)
<i>Gastrointestinal anomalies</i>			
Esophageal atresia			1 (33.3)
Other	25 (10.0)		2 (66.6)
Total	25 (10.0)	12 (5.8)	3 (3.1)
<i>Central nervous system</i>			
Arnold-Chiari anomaly			
Hydrocephaly	6 (2.4)		2 (28.6)
Pachygyria			
Agenesis corpus callosum	13 (5.2)		
Other	11 (4.4)		5 (71.4)
Total	40 (16.0)	26 (12.6)	7 (7.1)
<i>Eye</i>			
Cataract			3 (50.0)
Microphthalmia			1 (16.7)
Other			2 (33.3)
Total		25 (12.1)	6 (6.1)
<i>Ear, face and neck</i>	14 (5.6)	44 (21.4)	35 (35.7)
<i>Orofacial</i>			
Cleft lip and /or palate			
Cleft palate			

**TABLE 6** (Continued)

Total			
<i>Abdominal wall</i>			
Omphalocele			1 (100.0)
Total			1 (1.0)
<i>Skin</i>			
Hemangioma			
Total			
Other	5 (2.4)		8 (8.2)
Total	370	206	98

Abbreviations: ASD, atrial septal defect; CoA, coarctation of aorta; VSD, ventricular septal defect.

<sup>a</sup>The studies reported before 2014 were reviewed by Gomez-Ospina and Bernstein (2016) and by Paes et al. (2015).

<sup>b</sup>The number of cases is under the authors names. For recognizable conditions the percentage after total is the percentage of the total number of cases.

For non-recognizable patterns the percentage is the percentage of the total number of anomalies.

<sup>c</sup>Septal defects.

<sup>d</sup>Genitourinary.

However, it is difficult to compare our results with those of other authors as some of them, for example Weaver et al. (2022) took as denominator for the calculation of the percentages of symptom categories the total number of cases, including the cases with isolated PRS.

The higher frequency of additional malformations in this series may be related to the fact that our study was population based, that the ascertainment of cases was complete, that all patients were taken into consideration, including stillborn and terminations of pregnancy, and the surveillance for anomalies was continued until 2 years of age.

In order to evaluate patients and to compare studies, it is necessary to standardize the methods of case classification. Congenital anomalies and associated anomalies must be grouped into meaningful syndromes and conditions. Methods for case classification into isolated, multiple and syndrome categories were described (Rasmussen et al., 2003). Consideration of these guidelines will lead to more comparable case groups, an important element of careful studies aimed at identifying etiology of congenital anomalies.

The causes of PRS include single mutant genes, familial occurrence, known syndromes, chromosome abnormalities, vascular disruption, teratogens, and unknown causes. Several theories on the causes of PRS have been proposed, although the exact etiology has not been established (Gomez-Ospina & Bernstein, 2016).

Some studies have shown an association between maternal use of methadone and increased risk of PRS (Cleary et al., 2020). A number of other environmental risk factors and medical conditions have been related to the risk of PRS in some studies, but not in others. Maternal smoking has been associated with cleft palate with PRS (Honein et al., 2007). Fetal alcohol syndrome was reported in 10% of a US sample of 100 children consecutively diagnosed with PRS (Shprintzen, 1992) and in 3 out of 110 cases of PRS of a French case series (Holder-Espinasse et al., 2001).

A discussion on the molecular basis of PRS is beyond the scope of this paper. As mentioned above many syndromes with identified

genes were reported to be associated with PRS. Our study comprised many strengths: the registration of cases was active, a clinical geneticist examined every case, a geographically well-characterized population was studied, all cases were ascertained by the Registry of Congenital Malformations including termination of pregnancies for fetal anomalies, stillbirths, and live births, and the surveillance for anomalies was extended until 2 years of age. This study had potential limitations as a small number of patients were included. However, complete ascertainment was achieved and a homogeneous population was studied.

## 5 | CONCLUSION

In conclusion, the prevalence of PRS at birth was 2.29 per 10,000 in the population studied and the percentage of cases of PRS with associated anomalies was 69.7%, 7 in 10 cases. These figures were obtained from the study of a well-defined population of close to 400,000 births. The anomalies associated with PRS represent a large number of different conditions. An anomaly syndrome or pattern was recognizable in 59.7% of the cases of PRS with associated anomalies. Therefore, cases with PRS should have a careful multidisciplinary checkup. A search for associated congenital anomalies, particularly of the ear, face and neck, the cardiovascular, the musculoskeletal, the urogenital, and the central nervous systems is recommended for the cases with PRS. Genetic counseling may be indicated in many of the cases of PRS with associated anomalies.

## AUTHOR CONTRIBUTIONS

The authors contributed equally to data gathering, study design and analysis, revisions to the manuscript.

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**CONFLICT OF INTEREST STATEMENT**

The authors declare no conflict of interest.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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