Genetic Mutations Associated with Pierre Robin Syndrome/Sequence: A Systematic Review

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Keywords

Gene · Mutation · Pierre Robin sequence · Pierre Robin syndrome · Systematic review

Abstract

Pierre Robin syndrome/sequence (PRS) is associated with a triad of symptoms that includes micrognathia, cleft palate, and glossoptosis that may lead to respiratory obstruction. The syndrome occurs in 2 forms: nonsyndromic PRS (nsPRS), and PRS associated with other syndromes (sPRS). Studies have shown varying genetic mutations associated with both nsPRS and sPRS. The present systematic review aims to provide a comprehensive collection of published literature reporting genetic mutations in PRS. Web of Science, PubMed, and Scopus were searched using the keywords: “Pierre Rob-

in syndrome/sequence AND gene mutation.” The search resulted in 208 articles, of which 93 were excluded as they were duplicates/irrelevant. The full-text assessment led to the further exclusion of 76 articles. From the remaining 39 articles included in the review, details of 324 cases were extracted. 56% of the cases were sPRS, and 22% of the cases were associated with other malformations and the remaining were nsPRS. Genetic mutations were noted in 30.9% of the 300 cases. Based on the review, *SOX9* was found to be the most common gene associated with both nsPRS and sPRS. The gene mutation in sPRS was specific to the associated syndrome. Due to the lack of original studies, a quantitative analysis was not possible. Thus, future studies must focus on

This study was conducted at the College of Dentistry, Jazan University.

conducting large-scale cohort studies. Along with generating data on genetic mutation, future studies must also conduct pedigree analysis to assess potential familial inheritance, which in turn could provide valuable insights into the etiopathogenesis of PRS.

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Introduction

A triad of micrognathia, glossoptosis, and obstruction of the upper airways was first reported by the Parisian stomatologist Pierre Robin in 1923. The frequent association of cleft palate with the abovementioned triad was reported in 1934 [Robin, 1923, 1934]. Carey et al. [1982] coined the term Pierre Robin syndrome or sequence (PRS). This heterogenic entity can occur isolated as nonsyndromic PRS (nsPRS) or in association with other syndromes (sPRS). In some cases, nonsyndromic PRS is associated with other malformations and they have been termed as PRS Plus [Xu et al., 2016]. The disease is rare in occurrence with an incidence rate from 1/8,500 to 1/30,000 newborns [Bush and Williams, 1983; Tolarova and Harris, 1995; Printzlau and Andersen, 2004]. The highest incidence rate reported is 1 per 3,120 live births in the USA [Côté et al., 2015]. Studies have reported that around 50% of all PRS cases are sPRS [Caouette-Laberge et al., 1994; Evans et al., 2006; Izumi et al., 2012b]. About 34 syndromes have been reported to be associated with PRS [Levaillant et al., 2017]. Several studies have assessed the genetic mutations that have been associated with nsPRS and sPRS. Considering the pathogenesis of the disease, 3 major theories have been proposed: mechanical theory, neurological maturation theory, and mandible compression theory. It is important to distinguish between nsPRS and sPRS as the treatment strategy in the latter would have to account for PRS and the associated syndrome. A complete clinical evaluation is required to assess the severity of the disease and to formulate the ideal treatment plan (conservative or surgical management). The priority of the treatment protocol is to maintain the viability of the upper respiratory tract [Giudice et al., 2018]. The mortality rates of children diagnosed with PRS range between 1.7 and 65%. The mortality rates are higher in children with other associated syndromes, cardiac, and central nervous system-related comorbidities [Marcus et al., 1994; Lee et al., 2015; Blechner and Williamson, 2016]. The advent of molecular biology has provided a platform to decode the genetic profile of PRS. Although several studies and case reports have reported a wide range of genetic mutations in both sPRS and nsPRS,

there is no available comprehensive literature on the genetic mutations associated with the reported cases of PRS to date. Thorough knowledge of the genetic mutations associated with the syndrome could aid in the early confirmatory diagnosis of the disease and formulate an appropriate treatment plan. It is an interesting fact that PRS and genetic mutations associated with PRS could be detected during the prenatal period as early as the first trimester of pregnancy [Capkova et al., 2017]. This would help the parents to decide upon medical termination of pregnancy based on the severity of the syndrome. To the best of our knowledge, this is the first study making a qualitative attempt to summarize the various genetic mutations associated with nsPRS and sPRS based on the published literature.

Materials and Methods

Protocol and Registration: The International Prospective Register of Systematic Reviews (PROSPERO) database was screened for similar systematic reviews. No registered protocol was found reviewing the genetic mutations in PRS. The report of the present systematic review was formulated according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [Moher et al., 2009; Hutton et al., 2015].

Inclusion Criteria: Original research, case reports/series in the English language assessing the genetic mutations in PRS.

Exclusion Criteria: Reviews, letters, conference abstracts, articles in a language other than English, articles based on animal models, articles wherein sufficient details on the genetic mutation of PRS was not provided.

Focus Question: “What are the genetic mutations associated with PRS?”

Search Strategy: The key-word combination: “Pierre Robin syndrome/sequence AND gene mutation” was searched on May 18, 2020, in the Web of Science, PubMed, and Scopus. The identified articles were manually cross-referenced for potential articles.

Study Selection and Data Extraction

1. The identified articles were screened using their titles and abstracts for potential duplicates and relevance to the topic of interest. Articles not related to the topic were excluded along with duplicates.
2. The full text of the screened articles was assessed using the abovementioned selection criteria. Only articles meeting the inclusion criteria were part of the qualitative analysis.

Steps 1 and 2 were performed independently by 2 reviewers (S.V. and T.M.B.). The kappa coefficient (κ) was calculated to assess the reliability between the 2 reviewers. Vital data including the study characteristics (first author's name, year of publication, country of origin), study design, sample population, diagnostic criteria employed, the affected genes, and their corresponding mutations were extracted from the studies included in the qualitative review.

Fig. 1. Summary of the search strategy employed in the systematic review.

Risk of bias evaluation: The quality of the case series and case reports were evaluated using The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (last amended in 2017) for the case series and case reports [Joanna Briggs Institute, 2020].

Results

Study Selection

208 articles (PubMed = 69; Scopus = 104; Web of Science = 34; Cross Reference = 1) were identified in the search. Title and abstract screening led to the exclusion of 93 articles as they were either duplicate or lacked relevance to the topic of interest. Of the 115 articles subjected to full-text review, only 39 articles met the eligibility criteria and were included in this review. The κ value for the first and second step of the review was 0.98 and 0.96, respectively. Figure 1 summarizes the selection strategy employed in the qualitative analysis. Table 1 summarizes the data extracted from the studies included in the systematic review [Aboura et al., 2002; Ferreira de Lima et al., 2003; Melkonien et al., 2003; Ounap et al., 2005; Velagaleti et al., 2005; Jakobsen et al., 2007; Manzke et al., 2008; Johnston et al., 2010; Tanpaiboon et al., 2010; Gerth-Kahlert et al., 2011; Gripp et al., 2011; Nelson et al., 2011; Said et al., 2011; Sahoo et al., 2011; Davidson et al., 2012; Fukami et al., 2012; Izumi et al., 2012a, 2015; Amarillo et al., 2013; Zechi-Ceide et al., 2013; Ehmke et al., 2014; Suemori et al., 2014; Takenouchi et al., 2014; Utami et al., 2014; Bacrot et

al., 2015; Basart et al., 2015; Smyk et al., 2015; Braddock et al., 2016; Castori et al., 2016; Kohmoto et al., 2016; Xu et al., 2016; Capkova et al., 2017; Powis et al., 2017; Schoner et al., 2017; Sleiman et al., 2017; Yang et al., 2017; Højland et al., 2018; Roberti et al., 2018; Knapp et al., 2019].

Study Characteristics

Of the 39 included articles, 11 were from the United States of America [Velagaleti et al., 2005; Gripp et al., 2011; Nelson et al., 2011; Sahoo et al., 2011; Davidson et al., 2012; Izumi et al., 2012a; Amarillo et al., 2013; Smyk et al., 2015; Braddock et al., 2016; Powis et al., 2017; Sleiman et al., 2017], 5 from Japan [Fukami et al., 2012; Suemori et al., 2014; Takenouchi et al., 2014; Izumi et al., 2015; Kohmoto et al., 2016], 5 from Germany [Ounap et al., 2005; Manzke et al., 2008; Gerth-Kahlert et al., 2011; Ehmke et al., 2014; Schoner et al., 2017], 2 from France [Aboura et al., 2002; Bacrot et al., 2015], 2 from Brazil [Ferreira de Lima et al., 2003; Zechi-Ceide et al., 2013], 2 from Italy [Castori et al., 2016; Roberti et al., 2018], 2 from Denmark [Jakobsen et al., 2007; Højland et al., 2018], 1 each from Belgium [Said et al., 2011], Singapore [Utami et al., 2014], Netherlands [Basart et al., 2015], China [Yang et al., 2017], Finland [Melkonien et al., 2003], Thailand [Tanpaiboon et al., 2010], Czech Republic [Capkova et al., 2017], New Zealand [Knapp et al., 2019], Canada [Johnston et al., 2010], and Australia [Xu et al., 2016]. Concerning the study design of the included articles, 5 were cohort studies [Ferreira de Lima et al., 2003; Melkonien et al., 2003; Ja-

Table 1. Characteristics of the included studies

S. No	First authors name/ Country of origin/ Year of publication	Study design	Sample size	Patients with genetic mutation, <i>n</i>	Additional information	Associated syndrome
1	Basart/Netherland/2015	Cohort	191	24	Classical cytogenetic analysis with FISH for a 22q11.2 deletion in the first years of the study period. Array-CGH is routinely performed, and next-generation sequencing is used in a small number of patients. Additional molecular studies were detected by clinical findings Of 24 cases with mutations, 7 were of unknown etiology and 17 were sPRS.	Results: The non-isolated patient reported carrying a mutation in <i>NGFR72</i> 46 – no etiologic diagnosis Etiology: 72 – isolated form of RS (2 were familial) Of 119 non-isolated forms, 17 had proven chromosomal abnormality Mendelian disorder in 56 and Stickler syndrome in 27 Cognition: 184 – no intellectual disability Pathologic mechanism 43.8% of non-isolated patients had connective tissue dysplasia 5.5% presented with a neuromuscular disorder 47.9% presented with a multi-system disorder 2.7% – pathologic mechanism remained unknown
2	Yang/China/2017	Case series	5	5	First family 3 members Second family 2 members	nsPRS
3	Jakobsen/Denmark/2007	Cohort	10	6	For expression analysis, case group had 5 patients with nsPRS and 1 patient with nsPRS with a balanced translocation. The control group comprised 11 healthy controls. A significantly reduced <i>SOX9</i> ($p = 0.04$), <i>KCNJ2A</i> ($p = 0.07$), and <i>KCNJ2B</i> ($p = 0.05$) mRNA expression was observed in patients with PRS. Although SNP was detected in all the 10 patients, they were not pathogenic. One of the 10 patients reported with translocation. Her father was detected with PRS but did not participate in the genetic analysis. No other parent/family history of other participants reported with congenital anomalies.	nsPRS 1/10 patients with a balanced translocation had mild facial dysmorphism Micrognathia, flat face, broad nasal bridge, low-set ears, and low-set hairline She received speech therapy, and a pharyngeal flap operation was performed to decrease hypernasal speech. No visual or hearing deficits were reported. Growth and sexual maturation were normal
4	Melkonien/Finland/2003	Cohort	25	8+1	150 control patients were included in the study Severe breathing difficulties immediately after birth had been confirmed in 7 of the 23 unrelated Robin patients. 7 patients with nsPRS reported that one of their first-degree relatives had a cleft palate. Parents of 6 patients with nsPRS were assessed for mutation analysis. Among 8 patients with mutation, 1 patient's father had partial phenotype, 1 patient died of diabetic complication and proband's aunt's son had cleft lip and palate, 2 patients inherited mutation from parents, 1 patient's father was heterozygous for the mutation and 1 patient's mother was homozygous for the mutation. 1 patient with a Marshall syndrome father had the same mutation, and the grandmother had flexible joints. Genomic DNA was used for mutation screening by conformation-sensitive gel electrophoresis. RT-PCR analysis failed to indicate a splicing defect.	1 patient had Marshall syndrome 24 patients had nsPRS
5	Zeichi-Ceide/Brazil/2013	Case series	2	2	Two Brazilian sisters, born to healthy and nonconsanguineous parents	Mild shortening of upper and lower limbs, brachymetacarpalia/tarsalia, additional and accelerated carpal ossification, marked genu valgum, and multiple epiphyseal dysplasias Autosomal recessive chondrodysplasias that range from the mildest recessive form of multiple epiphyseal dysplasias through the most common diastrophic dysplasia to lethal atelosteogenesis type II and achondrogenesis type IB
6	Nelson/USA/2011	Case series	2	1	Not reported Karyotype (46,XX and 46,XY) and chromosomal microarray analyses (EmArray, 44K), which included 8 <i>SOX9</i> intragenic probes, gave a normal result in both patients; <i>SOX9</i> gene sequencing gave a normal result in patient 1, whereas sequencing in patient 2 revealed a heterozygous mutation (c.1312_1318del7ins5) resulting in a premature stop codon	Campomelic dysplasia
7	Bacrot/France/2015	Case series	5	5	Four cases were isolated and 1 was a familial form (patient 5 has an affected daughter), supporting autosomal dominant inheritance RT-qPCR analyses: Significantly higher levels of PTC-containing transcript in patients ($p = 0.035$) Transcript 3 is 4–7.2 times more abundant in patients than controls No differences in transcripts 1 and 2 levels and no significant differences in NABP1 and NABP2 transcript levels between patients and controls were noted	Cerebro-costo-mandibular syndrome CCMS acts as a novel developmental disease caused by defects in the core splicing machinery. Heterozygous mutations in <i>SNRNPB</i> PTC-introducing alternative exon are responsible for this unique chondro-osseous phenotype, supporting a specific role of <i>SNRNPB</i> in the ossification process
8	Ehmke/Germany/2014	Case series	7	7	(1 Camerion, 3 German, 1 Dutch, 1 French 1 British/S American) Sanger sequencing demonstrated a biparental mode of inheritance of the compound heterozygous mutations in the parents except individual 7 whose parents were not available	Catel-Manzke syndrome All 7 individuals with Catel-Manzke syndrome carried homozygous or compound heterozygous mutations in <i>TGDS</i> Because of the clinical overlap of Catel-Manzke syndrome with a spectrum of disorders caused by defects in proteoglycan synthesis or sulfation, it was supposed that <i>TGDS</i> could also be involved in nucleotide sugar metabolism
9	Velagaleti/USA/2005	Case series	2	2	Not reported Repeated chromosome studies, FISH and G-banding from phytohemagglutinin-stimulated peripheral blood lymphocytes were conducted	Campomelic dysplasia The study reported that in some individuals with isolated Robin sequence, their phenotype may result from dysregulation of <i>SOX9</i> by mutations or genomic rearrangements that affect the <i>cis</i> -acting regulatory elements of this gene

Table 1 (continued)

S. No	First authors name/ Country of origin/ Year of publication	Study design	Sample size	Patients with genetic mutation, <i>n</i>	Additional information	Associated syndrome
10	Castori/Italy/2016	Case series in a family	5	5	Three generation inheritance. 3 control samples were analyzed Genomic DNA from all affected individuals was analyzed by the commercially available Human Genome aCGH Kit 8 × 60K (Agilent Technologies, Santa Clara, CA). Visualization of data was performed with Agilent genomic workbench version 6.5	Acampomelic campomelic dysplasia
11	Ferreira de Lima/ Brazil/2003	Cohort study	15	0	14 from Brazilian origin Parental consanguinity in 7 families 35 unaffected relative samples were taken in the study	Richieri-Costa-Pereira syndrome
12	Braddock/USA/2016	Case series	2	2	Not reported	Braddock-Carey syndrome
13	Davidson/USA/2012	Case report	1	1	Not reported	Neurofibroma
14	Smyk Poland/USA/2015	Case report	1	1	No family history of developmental anomalies, consanguineous marriage, recurrent fractures	Osteopenia, multiple fractures along with other clinical findings such as prominent head, sparse anterior hair, light blue sclerae, mildly depressed nasal bridge, repaired cleft palate, retrognathia, etc.
15	Izumi/Japan/2015	Case report	1	1	Probable cause maternal uniparental disomy of chromosome 20 and 4 meiosis II non-disjunction event during oogenesis	SMC syndromes?
16	Fukami/Japan/2012	Case report	1	1	Parental samples were not available for analysis	Craniofacial anomalies, mild hypoplasia of the left scapula
17	Tanpaiboon/Thailand/ 2010	Case report	1	1	First case PRS and Lymphedema–distichiasis syndrome, first child of nonconsanguineous marriage	Lymphedema–distichiasis syndrome with PRS
18	Sleiman/USA/2017	Case report	1	1	Consanguineous marriage in Saudi Arabian family Exome sequencing was carried out on 5 out of 6 family members, proband's parents, and 3 siblings were unaffected with the disease. Recessive inheritance model The first case of <i>KIF15</i> to be associated with thrombocytopenia	Braddock-Carey syndrome
19	Johnston/Canada/2010	Case series	3	3	The rest of the family members did not show PRS All 3 children are not alive	TARP syndrome
20	Ounap Estonia/ Germany/2005	Case report	1	1	Nonconsanguineous parents, normal parental karyotype	Celiac disease, failure to thrive, developmental delay, and cardiac anomalies
21	Amarillo/USA/2013	Case report	1	1	African-American mother had a cleft palate and had the same mutation	nsPRS
22	Aboura/France/2002	Case report	1	1	First case of prenatal diagnosis was reported; the parents were healthy	Campodactyly
23	Sahoo/USA/2011	Case series	2	2	Patient 1: patient's mother, maternal grandmother, and maternal great grandmother had reported developmental defects. Of the 3 patients described in the case series, only 2 had PRS.	Patient 1: communicating fontanelles, a long well-formed philtrum, pectus excavatum, diastasis recti, a gap between her halluces and second toes with vertical creases, deep palmar flexion creases, and short fifth fingers Patient 2: other dysmorphic facial features (including flat facial profile, downsloping palpebral fissures, depressed nasal bridge, small, upturned nose with anteverted nares, pinpoint hemangioma on the tip of the nose, long philtrum, transverse crease across the chin)
24	Utami/Singapore/2014	Case report	1	1	Parents had a nonconsanguineous marriage Gene ontology and pathway enrichment analysis revealed that knockdown of <i>MED13L</i> orthologue in zebrafish, <i>med13b</i> , demonstrated an early defective migration of cranial neural crest cells. This in turn leads to a defect in cartilage structure causing deformities. Thus the authors concluded that the defective <i>MED13L</i> gene could be the cause for recapitulating craniofacial anomalies reported in humans	Moderate intellectual disability, craniofacial anomalies, and muscular defects
25	Højland/Denmark/2018	Case report	1	1	The parents were unrelated. The family members did not report developmental anomalies. A pedigree analysis was done, and it was found that one of the sisters was heterozygous for the mutation. The authors recommend that sisters of patients with TARP syndrome should be assessed for carrier status before family planning, although the mother is negative for the mutation. The patient was the first adult to be diagnosed with TARP syndrome with a milder phenotype that leads to survival to adulthood.	TARP syndrome
26	Gripp/USA/2011	Case report	1	1	Inherited from the mother who was heterozygous for the variant The younger brother was normal	TARP syndrome
27	Manzke/Germany/2008	Case report	3	0	Patient 1 was born to nonconsanguineous parents (first child of a father and third child of a mother) and has 2 healthy step-sisters. Patient 2 is the fourth child of nonconsanguineous parents and the siblings are healthy. Patient 3 was a follow-up of a patient described in 1966.	Catel-Manzke syndrome
28	Izumi/USA/2012	Case report	1	1	Parents assessed for the mutation but none detected. Pregnancy had several complications	Braddock-Carey syndrome

Table 1 (continued)

S. No	First authors name/ Country of origin/ Year of publication	Study design	Sample size	Patients with genetic mutation, <i>n</i>	Additional information	Associated syndrome
29	Gerth-Kahlert/ Germany/2011	Case report	1	1	A similar mutation is seen in the mother. Mother had myopia, midface hypoplasia without cleft palate. No family history of bleeding disorder. Family members not assessed	Stickler syndrome
30	Suemori/Japan/2014	Case report	1	1	Mother and one sibling had the same mutation and Stickler syndrome without PRS	Stickler syndrome
31	Said/Belgium/2011	Case report	1	1	Parents had nonconsanguineous marriage, uneventful pregnancy	Toriello-Carey syndrome
32	Takenouchi/Japan/2014	Case report	1	1	No family history of genetic disorders, complicated pregnancy	Type 2 collagen disorder-like phenotype
33	Knapp/New Zealand/ 2019	Case report	1	1	The patient and parents were assessed for mutation. Parents had a nonconsanguineous marriage	Coffin-Siris syndrome
34	Powis/USA/2017	Case report	1	1	Nonconsanguineous parents of Mexican origin. Prenatal chromosome analysis did not identify the mutations. Proband, mother, and father were tested, maternally inherited	TARP syndrome
35	Schoner/Germany/2017	Case report	1	1	Medical termination of pregnancy, autopsy of fetus Biparental inheritance	Atypical Catel-Manzke syndrome
36	Kohmoto/Japan/2016	Case report	1	1	Sibling with cleft palate and hearing loss was also detected with the same mutation.	Non-ocular Stickler syndrome
37	Roberti/Italy/2018	Case report	1	1	Two siblings are normal without congenital abnormalities.	Diamond-Blackfan anemia, Klippel-Feil syndrome
38	Capkova/Czech Republic/2017	Case report	1	1	Parents assessed for mutation and had a normal karyotype. Medical termination of pregnancy was done. During the second trimester of pregnancy, if any of the features including micro-/retrognathia or PRS are observed during ultrasonography, the presence of micro- or anophthalmia should be assessed as a possible marker of microdeletion 14q22q23	Microphthalmia/anophthalmia, pituitary anomalies, polydactyly/syndactyly of hands and feet, micrognathia/retrognathia were associated features
39	Xu/Australia/2016	Cohort	22	4	A total of 141 patients with nsPRS were screened of which 83 were nsPRS and 58 had PRS plus. Family history data were available in 136 patients. Among the 141 patients, 39 patients were selected for clinical assessment based on family history and a musculoskeletal anomaly of which 17 participants declined to participate in the study. Hence, 22 participants were selected for genetic analysis of which 8 patients gave a family history PRS or cleft palate, 12 patients had PRS with a musculoskeletal anomaly, and 2 patients had both features. Out of the 22 patients, only 4 were positive for the mutation. 3 patients with the mutation had PRS plus and 1 patient with the mutation had nsPRS. Parental analysis of patients with nsPRS confirmed that the variant was inherited from a phenotypically unaffected mother.	8 PRS 14 PRS plus (musculoskeletal anomaly) The most common associated anomalies were facial dysmorphic features such as hypertelorism, low-set ears, and preauricular skin tags; musculoskeletal anomalies such as congenital talipes equinovarus, congenital dislocated hips metatarsus varus, pectus excavatum, and scoliosis; ocular anomalies were strabismus.
Total	11 USA 5 Japan 5 Germany 2 France 2 Brazil 2 Italy 2 Denmark 1 Belgium 1 Singapore 1 Netherlands 1 China 1 Finland 1 Thailand 1 Canada 1 Czech Republic 1 Australia 1 New Zealand	Cohort 5 Case series 10 Case report 24	324	100/324	21 studies assessed family members for the presence of the mutation	nsPRS: 120 PRS plus: 22 sPRS: 182

kobsen et al., 2007; Basart et al., 2015; Xu et al., 2016], 10 were case series [Velagaleti et al., 2005; Johnston et al., 2010; Nelson et al., 2011; Sahoo et al., 2011; Zechi-Ceide et al., 2013; Ehmke et al., 2014; Bacrot et al., 2015; Brad-dock et al., 2016; Castori et al., 2016; Yang et al., 2017], and 24 were case reports [Aboura et al., 2002; Ounap et al., 2005; Manzke et al., 2008; Tanpaiboon et al., 2010; Gerth-

Kahlert et al., 2011; Gripp et al., 2011; Said et al., 2011; Davidson et al., 2012; Fukami et al., 2012; Izumi et al., 2012a; Amarillo et al., 2013; Suemori et al., 2014; Take-nouchi et al., 2014; Utami et al., 2014; Smyk et al., 2015; Kohmoto et al., 2016; Capkova et al., 2017; Powis et al., 2017; Schoner et al., 2017; Sleiman et al., 2017; Højland et al., 2018; Roberti et al., 2018; Knapp et al., 2019].

Table 2. Risk of bias evaluation of the included studies

S.no	1. Were the patient's demographic characteristics clearly described?	2. Was the patient's history clearly described and presented as a timeline?	3. Was the current clinical condition of the patient on presentation clearly described?	4. Were diagnostic tests or assessment methods and the results clearly described?	5. Was the intervention(s) or treatment procedure(s) clearly described?	6. Was the post-intervention clinical condition clearly described?	7. Were adverse events (harm) or unanticipated events identified and described?	8. Does the case report provide takeaway lessons?	9. Risk of bias
1	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
2	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
3	No	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
4	Unclear	Unclear	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Moderate
5	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
6	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
7	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
8	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
9	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
10	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
11	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
12	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
13	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
14	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
15	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
16	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
17	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
18	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
19	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
20	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
21	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
22	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
23	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
24	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
25	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
26	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
27	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
28	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
29	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
30	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
31	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
32	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
33	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low
34	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Yes	Low

According to The Joanna Briggs Institute (JBI), Critical Appraisal Checklist for Case Reports and Case Series.

Risk of Bias

Of the 34 case series and case reports included in the present review, 34 studies have met 80–100% of the criteria and were classified as low risk of bias, whereas 1 study met 60% of the quality criteria and was classified as moderate risk of bias [Bacrot et al., 2015], reported in Joanna Briggs Institute Critical Appraisal tools for case reports. The results are depicted in Table 2.

sPRS, nsPRS, and PRS Plus

A total of 324 cases were reported in the 39 selected articles. 182 (56%) of the PRS cases were sPRS, and 22 (6.8%) were PRS Plus. The remaining 120 (37%) cases were nsPRS.

Syndromes associated with PRS

The most common syndrome associated with PRS was Stickler syndrome (30 cases, 16%), followed by chromosomal abnormalities (17 cases, 9%), Richieri-Costa-Pereira syndrome (15 cases, 8%), Catel-Manzke Syndrome (10 cases, 5.5%), TARP Syndrome (6 cases, 3%), acampomelic dysplasia (5 cases, 2.7%), cerebro-costomandibular syndrome (5 cases, 2.7%), campomelic dysplasia (4 cases, 2%), Braddock-Carey syndrome (4 cases, 2%), autosomal recessive chondrodysplasias (2 cases, 1%), Marshall syndrome (1 case, 0.5%), lymphedema-distichiasis syndrome (1 case, 0.5%), SMC syndromes (1 case, 0.5%), Toriello-Carey syndrome (1 case, 0.5%), type 2 collagen disorder-like phenotype (1 case, 0.5%), Coffin-Siris syndrome (1 case, 0.5%), Diamond-Blackfan anemia, and Klippel Feil syndrome (1 case, 0.5%). In 46 cases (25%) the diagnosis of the syndrome associated with sPRS was not mentioned or not evaluated.

Diagnostic Modalities Employed

Genetic mutations were assessed most commonly by FISH and G-banding. Other diagnostic techniques used were exome sequencing, polymerase chain reaction, microarray, and Sanger sequencing. Very few studies had used array-CGH studies, next-generation sequencing, conformation-sensitive gel electrophoresis or expression profiling.

Genetic Mutations

100 out of 324 (37%) cases had genetic mutations (Tables 3, 4). Forty-seven cases (47%) had deletion, 20 cases (20%) had translocation, 12 cases (12%) had duplication, 9 cases (9%) had single nucleotide polymorphism, 6 cases (6%) had missense mutation, breakpoint mutation was seen in 5 cases (5%), splicing defect mutation in 4 cases

(4%), insertion was seen in 2 cases (2%), and an inversion was seen in 1 case (1%). 34 cases had an abnormal karyotype. 22 cases had SOX9 gene mutation (8 isolated PRS and 9 associated with syndromes acampomelic dysplasia, campomelic dysplasia, type 2 collagen-like disorder, and craniofacial malformations 5 cases with PRS Plus). 12 cases had KCJN2 gene mutation (6 isolated PRS, 1 with PRS Plus osteopenia, 5 with acampomelic dysplasia). *BM-PR1B* was seen in 5 cases with isolated PRS. 6 cases had *COL11A1* mutation (6 with isolated PRS, 1 each with Stickler and Marshall syndrome). 1 case had *COL11A2* mutation (isolated PRS). *COL2A1* was seen in 4 cases (2 with isolated PRS and 2 with Stickler syndrome). 2 cases had chromosome 2 mutation (1 with PRS Plus and 1 with Toriello-Carey syndrome). *KIF15* mutation was seen in 1 patient with Braddock-Carey syndrome. *BMP2* mutation was seen in 1 case (PRS Plus craniofacial malformation). *BMP4* and *OTX2* mutation was seen in 1 case (PRS Plus craniofacial malformation). *DPF2* mutation was seen in 1 case (with Coffin-Siris syndrome). *NF2* and *MN1* mutation was seen in 1 patient (PRS Plus neurofibroma). *MAP2K6* mutation was seen in 1 case (PRS Plus craniofacial malformation). *FOXC2* mutation was seen in 1 case (lymphedema-distichiasis syndrome), *SLC26A2* mutation was seen in 2 cases (with autosomal recessive chondrodysplasia). *RUNX* mutation was seen in 2 cases (Braddock-Carey syndrome), *TGDS* mutation was seen in 7 cases (with Catel-Manzke syndrome), *RMB10* mutation was seen in 6 cases (with TARP syndrome). Mutations in chromosome 20 were seen in 1 case (1 with SMC syndrome and deletion in chromosome 20p13p12.2 was seen in 1 case (PRS Plus craniofacial malformation). Chromosome 21 q22.11 mutation was noted in 1 case (with Braddock-Carey syndrome). Chromosome 1 had a mutation in 1 case (PRS Plus craniofacial abnormalities) and chromosome 12 q involving 26 genes in 1 case (with Diamond-Blackfan anemia, Klippel Feil syndrome). *SNRPB* gene mutation was seen in 5 cases with cerebro-costomandibular syndrome. A total of 21 studies [Melkonien et al., 2003; Ounap et al., 2005; Johnston et al., 2010; Gerth-Kahlert et al., 2011; Gripp et al., 2011; Izumi et al., 2012a, 2015; Amarillo et al., 2013; Ehmke et al., 2014; Suemori et al., 2014; Bacrot et al., 2015; Castori et al., 2016; Kohmoto et al., 2016; Xu et al., 2016; Capkova et al., 2017; Powis et al., 2017; Schoner et al., 2017; Sleiman et al., 2017; Yang et al., 2017; Højland et al., 2018; Knapp et al., 2019] had assessed the family members for the presence of the mutation and inheritance patterns.

Table 3. Detailed description of the genetic mutations associated with PRS

SNo	Author's name	No of cases	Gene	Mutation	Karyotype	Diagnostic criteria	Associated syndrome
1	Basart	1	46,XX,der(6)(t(6;9)(p21.3;q22.2))ins(6;13)(p21.3;q22.2)q13.1, der(9)(t(6;9)(p21.3;q22.2))dnarr cgn 1q21.1, deletion 13q21.33q22.2 deletion 13q22.3	Unbalanced translocation Deletion (6.1 Mb) Deletion (800 kb)	46,XX,der(6)(t(6;9)(p21.3;q22.2))ins(6;13)(p21.3;q22.2)q13.1, der(9)(t(6;9)(p21.3;q22.2))dnarr cgn 1q21.1, deletion 13q21.33q22.2 deletion 13q22.3	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	4p16.3	Deletion (1.5 Mb)	46,XX,ish,del(4)(p16.3) dn	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	46,XY,t(8;17)	Balanced translocation	46,XY,t(8;17)(q24.1;q24.2)	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	45,XO	Deletion X	45,XO	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	9q24.1	Deletion (1.1 Mb)	46,XY, arr[hgl 9] 9p24.1 deletion arrp24.1	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	46,XY,ish der(14)(t(14;16)(p11;p12.3))14p11 16pterp12.3	Unbalanced translocation Deletion dup (19.3 Mb)	46,XY,ish der(14)(t(14;16)(p11;p12.3))14p11 16pterp12.3	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	5p15.33p14.3	Deletion (20.1 Mb)	46,XY,del(5)(p14)arr 5p15.33p14.3	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	Yq11.223q11.23	Deletion (2.4 Mb)	46,XY, arr Yq11.223q11.23(23283651_2573772222)x0.22q11.2 1q11.23(20043011_22973937)x1 dn	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	6p21.2	Deletion (31 kb)	46,XX,del(6)(p21.2)	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	1q21.1	Dup (2.8 Mb)	46,XY,dup(1)(q21.1)	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	46,XX,der(13)(t(13;21)13pterq12 21pterq22	Unbalanced translocation, dup (20 Mb) Deletion (25–45 Mb)	46,XX,der(13)(t(13;21)(q12;q22))13pterq12 21pterq22	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	46,XY,der(18)(t(13;18)13q32.3qter 18q21.33qter	Unbalanced translocation dup (15 Mb) Deletion (18 Mb)	46,XY,der(18)(t(13;18)(q32.3;q21.33)mat)13q32.3qter 18q21.33qter	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	46,XX,t(17;18)	Apparently balanced translocation	46,XX,t(17;18)(p11.2;q21.1)mat	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	22q11.2	Deletion (1.5–3.0 Mb)	46,XX,del(22)(q11.2)dn	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	2q33.1 10q21.3	Deletion (675 kb) dup (730 kb)	46,XX, deletion(2)(q33.1;q33.1) duplication 10q21.3 dn	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	46,XX,der(1)(t(1;15)1q42 15q15	Unbalanced translocation deletion (25 Mb) dup(62 Mb)	46,XX,der(1)(t(1;15)(q42;q15)dn)1q42 15q15	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	1p36 19q13.4qter	Unbalanced translocation Deletion pter (5.9 Mb) dup (3.2 Mb)	46,XX, 1pter-p36.31; 19q13.42–19qter 19q13.4qter	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	11q23.3qter 12q24.3qter	Unbalanced translocation, deletion (15 Mb) dup (12 Mb)	46,XY,der(12)(t(1;12)(q23.3;q24.3)mat)11q23.3qter 12q24.3qter	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown

Table 3 (continued)

S No	Author's name	No of cases	Gene	Mutation	Karyotype	Diagnostic criteria	Associated syndrome
1	Basart	1	5q23.1 Xp22.31	dup (2.1 Mb) dup (1.6 Mb)	46,XY, duplication 5q23.1 duplication Xp22.31	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	4q31.3q35	Deletion (50 Mb)	46,XX, deletion 4q31.3–q35	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	9p22.2p22.3	dup (142b)	46,XX,dup(9)(p22.2p22.3)dn	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	(15)(q13)	ish idic (10 Mb)	47,XX,+idic(15)(q13).ish idic(15)(q13) dn	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	Xp21.1 3p14.1	dup (311 kb) dup (234 Kb)	46,XX, duplication Xp21.1, duplication 3p14.1	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
1		1	3q22.2q22.3	Deletion (2.19 Mb)	46,XY, Arr sup 3q22.2q22.3	Cytogenetic analysis, FISH (1995–2008) Array-CGH (2008–2012) Next generation sequencing (2012–2013)	17 sPRS 7 unknown
2	Yang	3	t(4;6)(q22;p21) BMP receptor type 1B (<i>BMPRI</i>) <i>BMPRI</i> - <i>GRM4</i>	Reciprocal translocation Fusion transcript	Not reported	GTG-banding, comparative genomic hybridization, whole-genome sequencing, and Sanger sequencing in blood samples Blood cDNA analysis	None
2		2	<i>BMPRI</i>	Splicing mutation (IVS2+2T>G)	Not reported	Sanger sequencing on the coding regions, namely, exon-intron boundaries of <i>BMPRI</i> and <i>GRM4</i> A negative result with GTG-banding, comparative genomic hybridization Altered transcript	None
3	Jakobsen	1	t(2;17)(q23.3;q24.3)	Balanced translocation in 1/10 patients	Not reported	Chromosome analyses were done in all 10 patients and only in 1 patient translocation was observed	None
1		1	7q21.13 coding <i>SOX9</i> gene and <i>KCNJ2</i>	0.4-Mb microdeletion (1/7 patients)	Not reported	Array CGH confirmed by FISH	None
5		5	<i>SOX9</i> expression in lymphoblast	Decreased expression 5 non-translocation patients $p < 0.05$	Not reported	Quantitative real-time PCR 6 (5 non-translocation 1 translocation) out of 10 patients	None
5		5	<i>KCNJ2</i> expression in lymphoblasts	Decreased expression in 5 non-translocation patients	Not reported	Quantitative real-time PCR 6 (5 non-translocation 1 translocation) out of 10 patients	None
4	Melkonimi	1	<i>COL11A2</i>	Single-nucleotide mutation	Not reported	Conformation-sensitive gel electrophoresis	nsPRS
1		1	<i>COL11A1</i>	Insertion of a T at the donor splice site of intron 50	Not reported	Conformation-sensitive gel electrophoresis, similar to Marshall syndrome	nsPRS
1		1	<i>COL11A1</i>	Sequence variation, IVS45+3 G4A	Not reported	Conformation-sensitive gel electrophoresis	nsPRS
2		2	<i>COL11A1</i>	One nucleotide substitution, IVS31+92 T4A (3)	Not reported	Conformation-sensitive gel electrophoresis	nsPRS
2		2	<i>COL11A1</i>	IVS50+3insT, splicing defect	Not reported	Conformation-sensitive gel electrophoresis	1 nsPRS 1 Marshall syndrome
2		2	<i>COL2A1</i>	Unique nucleotide change, E17+99C>T	Not reported	Conformation-sensitive gel electrophoresis	nsPRS
5	Zechi-Ceide	2	<i>SLC26A2</i>	"Founder Finnish mutation" c.26 p 2T>C, c.862C>T (R279W)	No data available	Screening of mutation in the <i>SLC26A2</i> gene was performed. Direct sequencing of all 3 exons of the <i>SLC26A2</i> gene and the corresponding exon/intron boundaries showed mutations in 2 copies of the <i>SLC26A2</i> gene in both patients	Autosomal recessive chondrodysplasia, mild shortening of upper and lower limbs, brachymetacarpalia/tarsalia, ossification, marked genu valgum, and multiple epiphyseal dysplasias

Table 3 (continued)

S No	Author's name	No of cases	Gene	Mutation	Karyotype	Diagnostic criteria	Associated syndrome
6	Nelson	1	SOX9	Heterozygous mutation (c.1312_1318del7ins5)	46,XY	Karyotype (46,XX in patient 1 and 46,XY in patient 2) and chromosomal microarray analyses (InArray, 44K), which included 8 <i>SOX9</i> intragenic probes gave a normal result in both patients <i>SOX9</i> gene sequencing gave a normal result in patient 1, whereas sequencing in patient 2 revealed a heterozygous mutation (c.1312_1318del7ins5) resulting in a premature stop codon	Campomelic dysplasia
7	Bacrot	5	Small nuclear ribonucleoprotein polypeptides B and B1 (SNRPB) gene, (GRCh37) (ENST0000047384)	Case 1: g.2447951C>G, c.166G>C; p. Gly56Arg Case 2: g.2447952C>G, c.165G>C; p. Arg55Ser Case 3: g.2447953C>A, c.164G>T; p. Arg55Met Case 4: g.2447847G>T, c.213+57C>A Case 5: g.2447953C>G, c.164G>C; p. Arg55Thr	Not reported	Exome sequencing and Sanger sequencing	Cerebro-costo-mandibular syndrome
8	Ehmke	7	TGDS (TDP-glucose 4,6-dehydratase	Compound heterozygous in 4/7 heterozygous in 2/7 patients c.892A>G; p.Asn298Asp, c.270_271del; p. Lys91Asnfs*22, c.298 G>T; p. Ala100Ser, c.294T>G; p.Phe98Leu, c.289A>G; p.Glu90Gly, and c.700T>C; p.Tyr234His founder mutation c.298G>T	Not reported	Exome sequencing	Catel-Manzke syndrome
9	Velagaleti	1	Upstream <i>SOX9</i> chromosome 17q24.3	Translocation and breakpoint	46,XX,(4;17)(q28.3;q24.3)	G-banded chromosome analysis, FISH	Campomelic dysplasia
		1	Downstream of <i>SOX9</i> 917q25.1	Breakpoint	46,XX,(4;7;8;17)(4qter;4p15.1::17q25.1r17qter;7qter7p15.3::4p15.1r4pter;8pter8q12.1::7p15.3r7pter;17pter17q25.1::8q12.1r8qter) <i>PCDH7</i> gene in chromosome 4 <i>RAPGEF5</i> in chromosome 7	G-banded chromosome analysis, FISH	Campomelic dysplasia
10	Castor	5	17q24.3 upstream of <i>SOX9</i>	Heterozygous deletion in the coding region of <i>KCNJ16</i> , <i>KCNJ2</i> , <i>HGNE-F2</i> , <i>9CE4Z</i> , and <i>SOX9</i> 9c1	Not reported	Human Genome array CGH and confirmed by SYBR Green-based experiment on an ABI7900 HT Fast Real-Time PCR system	Acampomelic campomelic dysplasia
11	Ferreira de Lima	15	497 polymorphic markers and <i>PAX9</i> , <i>MSX1</i> , <i>PITX1</i> , <i>DLX5</i> , <i>DLX6</i> , <i>PITX2</i> , <i>TBX4</i> , <i>TBX5</i> , <i>CLIMB2</i> , and <i>FGF8</i>	No mutation	Not reported	Affected patients were genotyped using the Cooperative Human Linkage center markers 497 polymorphic markers and <i>PAX9</i> , <i>MSX1</i> , <i>PITX1</i> , <i>DLX5</i> , <i>DLX6</i> , <i>PITX2</i> , <i>TBX4</i> , <i>TBX5</i> , <i>CLIMB2</i> , and <i>FGF8</i>	Richieri-Costa-Pereira syndrome
12	Braddock	1	<i>RUNX1</i> at chromosome 21q21.3;q22.13	Deletion	Not reported	Alleymatrix SNP 6.0 microarray platform from peripheral blood	Braddock-Carey syndrome
		1	<i>RUNX1</i> at 21q21.3;q22.12	Deletion	Not reported	Genomic microarray hybridization using OncoScan array from the archival FFPE liver tissue block	Braddock-Carey syndrome Patient deceased
13	Davidson	1	22q12.2 <i>NF2</i> and <i>MNI</i>	Interstitial deletion 3,693-kb deletion	46,XX,del(22)(q12.2)	G-banding high-resolution karyotype, FISH Chromosomal microarray analysis	Neurofibroma
14	Smyk	1	17q24.3 (1.28 Mb) upstream of <i>SOX9</i> , <i>ABCA5</i> , <i>MAP2K6</i> , <i>KCNJ16</i> , and <i>KCNJ2</i> protein genes, <i>LINC01483</i> , <i>LINC01497</i> , and <i>LINC01028</i> long non-coding RNA genes, and the putative long-range cis-regulatory element(s) of <i>SOX9</i> arr 17q24.3(67,260,696–68,838,864) -1 (GRCh37/hg19) Negative for the mutation in Sanger sequence)	1.6-Mb deletion upstream of <i>SOX9</i> encompassing <i>MAP2K6</i>	Not reported	G-banded karyotype FISH analysis Sanger Sequencing of 23 genes Array CGH, PCR, and DNA sequence analyses	Osteopenia

Table 3 (continued)

SNo	Author's name	No of cases	Gene	Mutation	Karyotype	Diagnostic criteria	Associated syndrome
15	Izumi	1	Chromosome 20	19-Mb gain loss of heterozygosity	47,XY,-mar[13]/46,XY[7]	G-banded karyotype SNP array analysis	SMC syndromes?
16	Fukami	1	Chromosome 17 17q21.31 and 17q24.3 5' region of <i>SOX9</i>	Paracentric inversion Breakpoint microdeletion Spanning from 4.15 to 1.16 Mb relative heterozygous genomic rearrangement	46,XY,der(17)inv(17)(q21.31;q24.3)del(17)(q24.3q23?)	High-resolution chromosomal banding FISH analysis using RP11-84E24-BAC containing <i>SOX9</i> and RP11-20N01-BAC on 17q21.31 Comparative genomic hybridization analysis, silica analysis using UCSC genome browser	Craniofacial anomalies, mild hypoplasia of the left scapula
17	Tanpaiboon	1	<i>FOXC2</i> 595-596 insC	de novo heterozygous insertion causing frameshift mutation	Not reported	Mutation analysis	Lymphedema-distichiasis syndrome with PRS
18	Sleiman	1	<i>KIF15</i>	Loss-of-function mutation, homozygous nonsense mutation recessive inheritance	Not reported	Exome sequencing, Homozygosity Mapper	Braddock-Carey syndrome
19	Johnston	3	<i>RBM10</i>	Nonsense mutation, missense mutation	Not reported	PCR amplification, Sanger sequencing, and in situ analysis	TARP syndrome
20	Ounap	1	Chromosome 2q13q2 Chromosome 2q14.2q14.3	Duplication, cytogenetic breakpoint	q22.2-q13;q13-qter)ish dup(2)(wcp2+;D2S2209+;D2S2264/ D2S373+;D2S1879+;D2S2023/ D2S2498+;D2S110+)+-dn	G-banding, karyotype analysis, FISH	PRS plus celiac disease, failure to thrive, and developmental delay, cardiac anomalies
21	Amarillo	1	Chromosome locus 17q24.3725 kb upstream of <i>SOX9</i>	Microdeletion	Not reported	Microarray was performed independently using 2 Affymetrix SNP array platforms and confirmed with CytoScan HD	nsPRS
22	Aboura	1	1q23.1q31.1	Duplication leading to trisomy	46,XX,1q+	Comparative genomic hybridization and FISH	Campodactyly
23	Sahoo	1	The short arm of chromosome 20 at 20p12.3 <i>BMP2</i>	Deletion 592.7 kb	-	Microarray FISH	Patient 1: communicating fontanelles, a long well-formed philtrum, pectus excavatum, diastasis recti, a gap between her halluces and second toes with vertical creases, deep palmar flexion creases and short fifth fingers
24	Utami	1	t(12;19)(q24;q1) Chromosome 12 (chr12:114,971,734-114,971,744, hg18), <i>MED13L</i> chromosome 19 breakpoint (chr19:35,769,937- 35,769,968, hg18) no coding gene	Balanced translocation, breakpoint	Not reported	Chromosome analysis Array-CGH DNA-PET sequencing, Sanger sequencing validation, quantitative RT-PCR, western blot, in situ hybridization, Morpholino microinjection, MED13L mRNA synthesis, Alcian Blue Staining, neural progenitor cells maintenance, shRNA transfection, neuronal differentiation, and immunocytochemistry microarray Gene ontology and pathway enrichment analysis was performed	Moderate intellectual disability, craniofacial anomalies, and muscular defects
25	Højland	1	exon 4 of <i>RBM10</i>	Hemizygous c.273_283delinsA mutation	Not reported	Exome sequencing	TARP syndrome
26	Gripp	1	<i>RBM10</i>	Hemizygous for c.del159C	Not reported	Exon sequencing in the affected child and mother	TARP syndrome
27	Manzke	3	22q11.2, <i>BMPT1B</i> , <i>GDF5</i> , and <i>NOG</i>	No mutations	Not mentioned	Chromosome analysis, array CGH, FISH, PCR	Catel-Manzke syndrome
28	Izumi	1	21q22.11	1.9-Mb deletion	46,XX,arr snp 21q22.11(32,273,189-34,168,705) x1 dn (hg18)	SNP array	Braddock-Carey syndrome

Table 3 (continued)

S No	Author's name	No of cases	Gene	Mutation	Karyotype	Diagnostic criteria	Associated syndrome
29	Gerth-Kahlert	1	COL2A1 exon 38	Heterozygous novel deletion of 2 nucleotides	Not reported	Polymerase chain reaction, bidirectional sequencing, sequencing of the coding area of the COL2A1 was done	Stickler syndrome
30	Suomori	1	COL2A1 exon 28	Heterozygous sequence variation, C to T substitution Autosomal dominant mutation	Not reported	Sequencing analyses	Stickler syndrome
31	Said	1	Chromosome 2q12.1122q12.2	De novo interstitial deletion approximately 6 Mb	46,XX arr cgh 22q12.1q12.2(CTA-992D9>RP3-515N1)	Karyotyping, FISH, array CGH	Toriello-Carey syndrome
32	Takenouchi	1	SOX9	de novo heterozygous missense mutation, i.e., c.239T>G; p. Val80Gly, in exon 1	Not reported	Custom-designed mutation analysis panel for genes COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, and SOX9 Target resequencing using a custom-designed mutation analysis panel (expanded next-generation sequencing), confirmation with Sanger sequencing	Type 2 collagen disorder-like phenotype
33	Knapp	1	DPF2	de novo missense mutation c.1066T>G; p.Cys356Gly	Not reported	Array CGH trio exome sequencing and bioinformatic analysis	Coffin-Siris syndrome
34	Powis	1	RBM10, c.1352_1353delAG; p. E451Vfs 66 (Chr X:47040717-47040718)	Hemizygous alteration	Not reported	Exome library preparation, sequencing, bioinformatics	TARP syndrome
35	Schoner	1	TGDS	2 sequence alterations 1 known variant c.298 G>T; p. Ala100Ser; chr13: g.95243122C>A 2. novel variant c.895 G>A; p. Asp299Asn; chr13:g.9528655C>T	Normal 46,XX karyotype	Chorionic villus sampling Sanger sequencing	Atypical Catel-Manzke syndrome
36	Kohmoto	1	COL11A1	Novel heterozygous missense mutation NM_001854.3:n.4838 G4A [NM_001854.3 (COL11A1_v001):c.4520 G4A], in exon 61	Not reported	Targeted exome sequencing	Non-ocular Stickler syndrome
37	Roberti	1	Chromosome 12q13.2q13.3, RPS26 and 25 genes (SARNP, DNAJC14, ORAMD12, MMP19, PYML, DGKA, PAMEL, CDK2, RAB5B, SUOX, IKZF4, ERBB3, PA2G4, RPL41, ZC3H10, ESYT1, MYL6B, MYL6, SMARCC2, RNFI41, NABP2, SLC39A5, ANKRD52, COQ10A, CS)	de novo deletion 500 kb	Not reported	MLPA, array-CGH, expression profiling by Taqman assay	Diamond-Blackfan anemia, Klippel feil syndrome
38	Capkova	1	Chromosome 14q22.1q23.1, BMP4 and OTX2, other genes involved in the deleted region were PTGDR, PTGER2, DDHD1, GCHI, TMEM260, KIAA0586, DACT1	Microdeletion of 7.7 Mb	46,XY (500 bphs)	G-banding, MLPA, microarray in the fetus	Microphthalmia/anophthalmia, pituitary anomalies, polydactyly/syndactyly of hands and feet, micrognathia/retrognathia were associated features
39	Xu	4	SOX9 CNE	SOX9 CNE variant observed in dbSNP141 In 3 PRS plus patients, heterozygous variants were identified within CNEs 1, 3, and 4. Single heterozygous nucleotide substitution (T to C) in CNE 1 in putative GATA1 binding site was in the patient with PRS	Not reported	Sanger sequencing of 14 CNEs in the upstream region of SOX9	3 patients with PRS plus and 1 patient with PRS Parental analysis of a patient with PRS confirmed that the variant was inherited from a phenotypically unaffected mother

Table 4. Summary of genetic mutations in PRS

Parameter	Number of cases/total	Gene (<i>n</i> cases with mutation)
Total: 324		
Type of PRS		
nsPRS	120/324 (37%)	
sPRS associated with the syndrome	182/324 (56%)	
PRS plus	22/324 (6.8%)	
Presence of genetic mutations	100/324 (30.9%)	
Genes and syndromes associated with nsPRS		
Isolated PRS <i>n</i> -120		SOX9 (8) Translocation (1) KCNJ2 (6) BMPR1B (5) COL11A1 (6) COL11A2(1) COL2A1(2)
Syndromes associated with sPRS, <i>n</i> = 182		
Sticklers syndrome	30/182 (16.5%)	COL2A1 (2), COL11A1 (1)
Chromosomal abnormalities	17/182(9%)	Abnormal karyotype 17
Richieri-Costa-Pereira syndrome	15/182 (8%)	No mutations detected
Catel-Manzke syndrome	10/182 (5.5%)	TGDS (7)
TARP syndrome	6/182 (3%)	RMB10 (6)
Acampomelic dysplasia	5/182 (2.7%)	SOX9 (5) KCNJ2 (5) SNRPB (5)
Cerebro-costo-mandibular syndrome	5/182 (2.7%)	SOX9 (3)
Campomelic dysplasia	4/182 (2%)	RUNX (2)
Braddock-Carey syndrome	4/182 (2%)	Chromosome 21q22.11 (1) KIF15 (1) COL11A1 (1) FOXC2 (1)
Marshall syndrome	1/182 (0.5%)	Chromosome 20 (1)
Lymphedema–distichiasis syndrome	1/182 (0.5%)	Chromosome 2q12.1, 22q12.2. (1)
SMC syndromes	1/182 (0.5%)	SOX9 (1)
Toriello-Carey syndrome	1/182 (0.5%)	DPF2 (1)
Type 2 collagen disorder-like phenotype	1/182 (0.5%)	Chromosome 12q13.2q13.3 (26 genes) (1)
Coffin-Siris syndrome	1/182 (0.5%)	SL26A2 (2)
Diamond-Blackfan anemia, Klippel-Feil syndrome	1/182 (0.5%)	
Autosomal recessive chondrodysplasias	2/182 (1%)	
Syndrome associated with sPRS was not mentioned or not evaluated	46/182 (25%)	
PRS plus, <i>n</i> = 22		
PRS cases with additional malformations	11/22 (50%) Craniofacial and musculoskeletal malformations in 20, osteopenia in 1, and neurofibroma in 1 patient	SOX9 (1), SOX9 and MAP2K6 (1) Chromosome 2 (1) BMP2 (1) Chromosome 12 translocation (1) SOX9 CNE (3) NF2, MN1 (1) Chromosome 1, chromosome 4 BMP4 and OTX2, KCNJ2 (1) Chromosome 20 (2)
Type of mutation		
Deletion	47/100 (47%)	
Translocation	20/100 (20%)	
Missense mutation	6/100 (6%)	
Duplication	12/100 (12%)	
Inversion	1/100 (1%)	
Splicing defect mutation	4/100 (4%)	
Breakpoint mutation	5/100(5%)	
Single nucleotide mutation	9/100(9%)	
Insertion	2/100 (2%)	

Discussion

It is a well-known fact that accurate diagnosis aids in treatment planning and determination of prognosis. PRS is a rare congenital disorder associated with or without syndromes and craniofacial malformations. A comprehensive data on the exact etiopathogenesis and associated genetic mutations are not available till date. Hence, we reviewed the currently available scientific data on the genetic mutations in PRS. Given the scarcity of cohort studies, the present review also included case reports and series reporting genetic mutations in PRS. The number of cases of sPRS or associated anomalies was higher (56%) than isolated PRS (37%) and PRS Plus (6.8%). In the 39 included studies, a total of 324 cases were reported (Table 1). The most common syndrome associated with PRS was Stickler syndrome which is concurrent with Giudice et al. [2018]. All of the included studies assessed the genetic mutations using standard protocols and techniques that included FISH, array CGH studies, next-generation sequencing, Sanger sequencing, exome sequencing, G-banded chromosome analysis, microarray, polymerase chain reaction, conformation-sensitive gel electrophoresis, and expression profiling. However, there was heterogeneity in the techniques used for the assessment of genetic mutations.

Considering the risk of bias of the included case reports all the studies reported low risk and hence were included in the present review. The most common gene associated with PRS was found to be *SOX9* which is important for cartilage development. This gene was found to be mutated in isolated PRS as well as campomelic dysplasia and acampomelic dysplasia. Loss of function or haploinsufficiency of the gene causes lethal skeletal malformations and syndromes associated with PRS, whereas disruptions that are upstream or downstream of *SOX9* cause milder abnormalities and nsPRS. These regions contain the highly conserved noncoding *cis*-regulatory elements that play a vital role in the development of the jaw, tongue, and palate [Benko et al., 2009]. The other genes found to be associated with isolated PRS were *KCNJ2*, *BMPR1B*, *COL11A1*, *COL11A2*, *COL2A1*. Mutations in chromosome 2 were also found to be associated with isolated PRS. The genetic mutations associated with syndromic PRS were specific for the associated syndromes (The results have been depicted in Table 2).

Considering the etiopathogenesis of PRS Plus additional malformations, the mutations were not specific although *SOX9* mutation was observed in the majority of the cases (5/22). However, the number of cases reported

was found to be lower. Also, studies have reported a change in diagnosis of syndromes during the later stage of development which could be attributed to the difficulty in diagnosis and etiopathogenesis [Basart et al., 2015].

Also, abnormal karyotypes were seen in 34 cases with the reported genetic mutations [Aboura et al., 2002; Ounap et al., 2005; Velagaleti et al., 2005; Gerth-Kahlert et al., 2011; Davidson et al., 2012; Fukami et al., 2012; Izumi et al., 2012a, 2015; Basart et al., 2015; Capkova et al., 2017; Schoner et al., 2017]. Although all the 39 studies had assessed the genetic mutations associated with PRS, a few critical limitations were observed: All the studies were heterogeneous, and only 5 cohort studies that met the inclusion criteria were available for data analysis. Most of the studies had a very small sample or reported only 1 case. The small sample size in most of the cohort studies could be attributed to the rarity of the syndrome and other factors such as willingness to participate, case selection based on inclusion criteria, and availability of family history.

Although genetic mutations were reported in most of the studies, only 21 studies had assessed genetic mutations in the proband's family members to demonstrate familial inheritance [Melkonien et al., 2003; Ounap et al., 2005; Johnston et al., 2010; Gerth-Kahlert et al., 2011; Gripp et al., 2011; Izumi et al., 2012a, 2015; Amarillo et al., 2013; Ehmke et al., 2014; Suemori et al., 2014; Bacrot et al., 2015; Castori et al., 2016; Kohmoto et al., 2016; Xu et al., 2016; Capkova et al., 2017; Powis et al., 2017; Schoner et al., 2017; Sleiman et al., 2017; Yang et al., 2017; Højland et al., 2018; Knapp et al., 2019]. Yang et al. [2017] reported genetic mutations in 3 members from a family with manifestations of nsPRS, while the family members without any clinical signs of nsPRS did not exhibit genetic mutations. Similarly, 2 members from another family showing manifestation had genetic mutations, while their unaffected family members did not report any mutations. Amarillo et al. [2013] reported maternal inheritance of genetic mutations in a proband diagnosed with nsPRS. In this case, the mother had a cleft palate. Xu et al. [2016] reported that parental analysis of 1 patient with nsPRS confirmed that the variant was inherited from a phenotypically unaffected mother. Melkonien et al. [2003] reported 7 Patients with nsPRS: one of their first-degree relatives had cleft palate, and parents of 6 patients with nsPRS were assessed and reported similar mutations. On the contrary, Ounap et al. [2005] reported normal parental karyotype in the patient with PRS Plus.

Castori et al. [2016] reported a 3-generation familial inheritance of acampomelic/campomelic dysplasia char-

acterized by PRS, bell-shaped thorax with 11 pairs of ribs, hypoplastic pedicles of the thoracic vertebrae and scapulae, narrow iliac bones, ossification delay of the pubis and cervical vertebrae, clubfeet, and bent long bones (i.e., campomelia). Izumi et al. [2015] reported a nondisjunction event during oogenesis to have caused SMC syndrome due to gene dosage effects on the genes located in the supernumerary marker chromosome. The recessive inheritance model was reported by Slieman et al. [2017] in Braddock-Carey syndrome which is characterized by microcephaly, congenital thrombocytopenia the Pierre-Robin sequence (PRS), and agenesis of the corpus callosum. On the contrary, Izumi et al. [2012a] reported a patient with Braddock-Carey syndrome, wherein no genetic mutations were detected in the parents. Johnston et al. [2010] reported familial inheritance of TARP syndrome (talipes equinovarus, atrial septal defect, Robin sequence, and persistent left superior vena cava) caused by mutations in the *RBM10* gene. Gripp et al. [2011] reported maternal inheritance of genetic mutations in a proband affected with TARP syndrome; however, other family members were not assessed for mutations. Powis et al. [2017] assessed the proband's parents and reported maternal inheritance of genetic mutations associated with TARP syndrome. Similarly, Højland et al. [2018] reported that one of the sisters of a patient with TARP syndrome was heterozygous for the mutation. The authors recommended that the sisters of the patients with TARP syndrome should be assessed for carrier status prior to family planning, although the mother is negative for mutation.

Gerth-Kahlert et al. [2011] reported maternal inheritance of genetic mutations in the proband affected with Stickler syndrome characterized by ocular malformations, orofacial malformations, and auditory and skeletal malformations; however, the other family members were not assessed. Similarly, Suemori et al. [2014] reported maternal inheritance of genetic mutations in Stickler syndrome, and the proband's sibling was affected with Stickler syndrome without PRS. Kohmoto et al. [2016] reported genetic mutations in a proband's sibling with non-ocular Stickler syndrome. Melkonniemi et al. [2003] reported familial cerebro-costo-mandibular syndrome in 1 patient demonstrating autosomal dominant inheritance. Ehmke et al. [2014] reported a biparental mode of inheritance in 6 out of 7 patients with Catel-Manzke syndrome as 1 patient's parent was not available for genetic analysis.

However, in a few studies, genetic mutations in all the family members were not assessed. In a cohort study by Basart et al. [2015], although 2 patients with nsPRS were

familial, only the probands were included in the study. Similarly in a study by Jakobsen et al. [2007], although 1 of the 10 patients' father was detected with PRS, he did not consent for genetic analysis. This could be attributed to the non-willingness to participate in the study, which is a major limitation of studies assessing the etiopathogenesis of congenital anomalies.

Aboura et al. [2002], Schoner et al. [2017], and Capkova et al. [2017] reported prenatal diagnosis of the congenital anomalies. Aboura et al. [2002] reported a confirmatory diagnosis of PRS with campodactyly (autopsy of the fetus). Schoner et al. [2017] reported atypical Catel-Manzke in an autopsy of the fetus, and Capkova et al. [2017] reported PRS Plus with craniofacial anomalies, wherein medical termination of pregnancy was done in both the cases. Thus, a complete pedigree analysis with a larger sample population would shed light on the inheritance pattern. Also, it would aid in prenatal diagnosis when family history is elucidated.

It is also vital to acknowledge, that given the varying pattern of genetic mutations observed, it is unclear if the genetic mutations are the sole cause of PRS, or is it just an associated finding. Gene ontology and pathway enrichment analysis is warranted to understand the exact etiopathogenesis, severity of the mutation, and clinical condition that would aid in accurate treatment planning to improve the quality of life of the affected individual. Only 1 study by Utami et al. [2014] performed pathway enrichment analysis to confirm the genetic mutation.

Conclusion

Several genetic mutations associated with PRS have been identified from the qualitative analysis of the 39 articles. Despite abundant literature in the form of case reports/series, the major limitation noted in the present qualitative review was the lack of cohort studies. Without large-scale cohort studies, it is not possible to statistically evaluate vital factors including disease progression and response to the treatment protocol. Thus, researchers must focus on conducting multicenter cohort studies with large sample sizes. A standardized protocol must be followed for assessing genetic mutations in all cases to avoid bias due to the varying sensitivity and specificity of the diagnostic modality. In addition to evaluating the genetic mutations, pedigree analysis is required to assess potential familial inheritance.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Thodur Madapusi Balaji, Saranya Varadarajan, Archana Gupta, and A. Thirumal Raj contributed to conception and design of the study, analysis, and interpretation of data. Shankargouda Patil, Tariq Hassan Alhazmi, Halah Athman Ali Alaqi, Neda Essa M Al Omar, Somayh Abu Baker A Almutaher, Alhassen Abdurabu Jafer, Ismaeel Abker Hedad contributed to the data acquisition, analysis, and interpretation of data. All the authors participated in drafting and revising the manuscript. All authors confirm that the manuscript was read and approved for publication.

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