European Journal of Musculoskeletal Diseases
ISSN 2038-4106/2023

Review

GENETIC BASIS OF PIERRE ROBIN SYNDROME

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ABSTRACT

The clinical characteristic of Pierre Robin syndrome(/sequence) or PRS include glossoptosis, micrognathia, and blockage of the upper airways, commonly linked with a palatal cleft. It is a heterogenic pathogenic entity that can exist as an isolated disease or not syndromic nsPRS or in connection with some other syndromes or sPRS, with more prominent manifestations. Key phrases such as "Pierre Robin syndrome(/sequence)", OR "PRS", "genetic factor", "genetics", "mutations", "mutations in PRS", and "genetic relation" were used to search MEDLINE, PUBMED, and Google Scholar databases. The included methodological dataset was assessed using the EPPI (Evidence for Policy and Practice Information) Tool. The graphical depiction was produced using PRISMA flowchart generation. The data acquired from the systematic investigation showed that the deletion of chromosome 10q at the 4.34 Mb terminal and the microdeletion of gene 2q33 cause PRS. SOX9 is important in the development of illness. Comparing the amount and breakpoints of microdeletions as well as genotype-based associations led researchers to hypothesise that modulator genes near MN1 and NF2 may have an impact on the severity of cleft palate. It is yet unknown how SOX9 mutant protein causes the symptoms of PRS. This study emphasises the requirement for early genetic counselling and testing in this community of patients, in addition to research efforts to create genetic classifications to guide clinical therapy.

KEYWORDS: *genetic, syndromes, SOX9, Pierre Robin, palate, cleft*

INTRODUCTION

In a group of infants, Pierre Robin discovered a trio of clinical signs in 1923 (1). Glossoptosis, micrognathia, and obstruction of the upper airways were these markers. He originally discussed the connection between palatal cleft and common signs in 1934 (2). The Pierre-Robin syndrome/sequence, or PRS, is the official name for this condition in medicine. The first time the idea of the Pierre Robin sequence was proposed was by Carey et al. in 1982 (3). That

Received: 13 March 2023
Accepted: 20 April 2023

ISSN: 2038-4106

the Pierre Robin trio is clinically demonstrated as an effective succession of pathogenic events (4). The Pierre Robin sequence exemplifies a heterogenic disease category. It can appear alone (i.e., not syndromic nsPRS) or in combination with other syndromes (sPRS), the former characterised by more intense symptoms and greater systemic involvement.

Epidemiological studies have shown that the Pierre Robin sequence is a very rare disease, occurring between 1 in 8,500 and 1 in 30,000 newborns (5). This wide range, in particular, is the consequence of studies conducted using very different individuals and nations at quite different times and with entirely different diagnostic techniques. With one instance for every 3120 live births, the United States of America has the high prevalence rate. Other nations have lower rates, with Germany having one case for every 8060 live births. One case per 8850 live births in Australia, 1 per 8,500 live births in the UK, 1 per 14,000 live births in Denmark, and 1 per 16,000 live births in Italy.

The Robin sequence is a remarkable organism in respect of its pathogenetic pathways and its phenotypic expressions (1). The aetiology of the condition is still poorly known, despite the significant advancements achieved in the subject over the previous few decades. It is important to distinguish between isolated cases of Pierre Robin syndrome and syndrome PRS cases where the etiopathogenesis has already been identified. According to a recent study (6), the Robin sequence can be linked to various factors. A genetic background with altered signalling pathways, airway disorders during the first three months of birth, brainstem malfunction, and/or neuromotor impairments can have an impact on mandibular growth and respiratory distress. An autosomal dominant and fully penetrant PRS locus was located on chromosome 17q24.3-25.1 in 2009 by Benko et al. (7) using genetic linkage analysis in 12 affected people from a four-generation PRS-affected family (the PRS locus).

Numerous studies suggested that the existence of mutated genes could explain Robin anomalies. It is probable that alterations in any of the mandibular development's four key genes—SOX9, KCNJ2, KCNJ16, and MAP2K6—could have contributed to the formation of isolated PRS (7-9). In reality, numerous studies on animals have shown that the in-issue mutations have a changed effect on the craniofacial phenotype. The SOX9 gene is a crucial part of the chondrogenic regulatory network; it performs a number of crucial functions throughout embryogenesis and is required for cartilage formation (4, 10-12). In humans, haploinsufficiency or loss of function of the SOX9 gene can result in campomelic dysplasia, a skeletal deformity condition. This condition and PRS are frequently linked. Deletions in the SOX9 enhancer and upstream of SOX9 can alter the gene's expression (17q24.3-q25.1). During the development of the craniofacial structure, several regulatory factors may be at play that helps SOX9 express correctly. Researchers hypothesised that the lack of these genes influenced the PRS phenotype. Milder phenotypes are brought on by disruptions that occur upstream or downstream of an intact SOX9 coding region, such as the non-syndromic version of PRS (7). Despite the absence of genes, these regions are abundant with HCNEF2 (highly conserved non-coding cis-regulatory elements) that operate as mandibular enhancers and are crucial for the proper development of the jaw, tongue, and palate.

The interaction bonding with MSX1, a chondrocyte-specific protein necessary for the development of the orofacial region, is altered specifically by the mutation of HCNE-F2. The OMIM database acknowledges a link between syndromic-PRS and distinct illnesses (13). A review of the literature on related Robin syndrome indicated the illness's well-established etiopathogenesis and the connection between PRS and these conditions. Mutations specifically characterise Stickler syndrome in type 2 and occasionally type 1 collagen genes such as COL2A1, COL11A1, COL9A1, or COL11A2 (14). While molecular research is useful, clinical outcomes usually offer the clearest proof of a diagnosis. Along with PRS, there is another syndrome called a velocardiofacial syndrome. An area of the 22q11.2 chromosome with a 3 million base pair deletion has been related to the aetiology of this disease (1). Therefore, this study has been designed to find the genetics roles in PRS.

MATERIALS AND METHODS

Data collection

In order to find relevant studies, we employed a variety of search techniques. Websites were utilised as data collection tools to gather studies and to find information. This approach involved using search engines like Medline, Google Scholar and Pubmed. Key phrases that were used are: "Pierre Robin syndrome(/sequence)", OR "PRS", "transcriptional factor", "genetics", "mutations", "mutations in PRS", and "genetic relation". About 20 articles were gathered using the following as the baseline statement: "Genetics of Pierre Robin syndrome."

Data cleaning and processing

Since the data was acquired from numerous websites, duplicates from the articles were removed. The automation software EPPI (Evidence for Policy and Practice Information) was selected for additional processing (15). The tool determined the articles that were incompatible with the platform or were outside of the domain it rejected them. Publications in English, journal articles of research documented within the past four years (2019-2022), authentic and adequate describing PRS, in particular, research papers addressing Pierre Robin Syndrome and genetics of PRS are the records inclusion criteria that are considered to be acceptable for conducting a systematic review. For this systematic review to be regarded appropriately, each and every one of these criteria must be satisfied by the records in question. Studies that are difficult to track down and do not contain references that may be relied upon or have an unjustified price tag are omitted from the review.

Systematic analysis

The results of collected studies are evaluated using PRISMA tools (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (16, 17), and a flowchart concentrated on the 2020 PRISMA checklist. Articles that do not fulfil the standards for identification, screening, authenticity, and, finally, accessing the necessary information are discarded; this guarantees that only the articles most pertinent to the discussion are accessed. On the body of work that has been chosen, a comprehensive study was undertaken (Fig. 1).

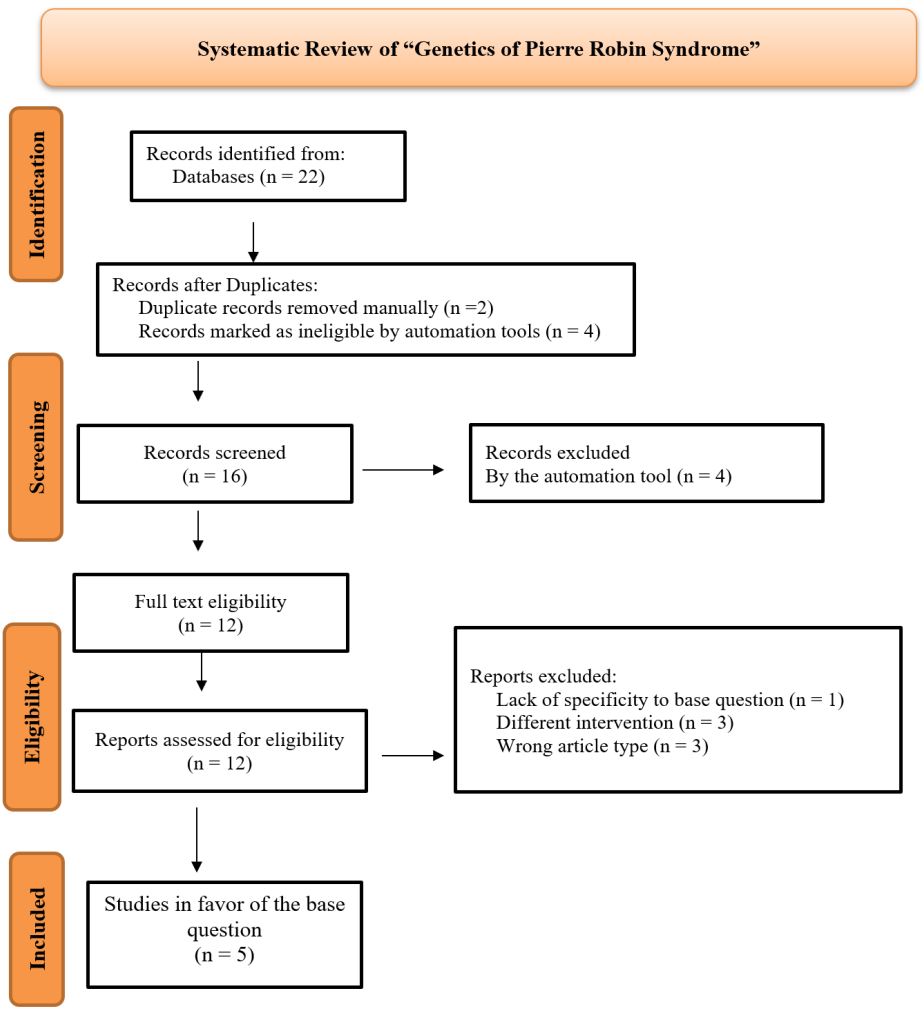

Fig. 1. *Graphical representation of systematic review process retrieved from PRISMA.*

RESULTS AND DISCUSSION

A study published by Resende et al. (18) describes research on a boy, age 29, with a history of right eye hypertropia from birth. In the English literature, more than 50 different cranial syndromes and deformities, many of which involve facial and ocular defects, have been linked to Pierre Robin syndrome (Table I). The hypothesis is that PRS-caused microdeletion of the gene 2q33 on the long arm of chromosome 2 is the root cause of such an occurrence (18). In another case study by Yekula et al. (19), a six-year-old with a history of premature 31st-week birth with observed diffuse hypotonia and developmental delay was observed. The findings declare that deletion of chromosome 10q at the terminal 14.34 Mb leads to PRS.

Murtaza et al. (20) reported the case of a male neonate who was four days old and had no family background of congenital abnormalities. Micrognathia and glossoptosis were symptoms the proband was experiencing, and eating and breathing were concerns. The study's findings revealed a strong correlation, indicating that the SOX9 gene may be involved. The SOX9 protein regulates how the facial structure should develop. The author, therefore, proposed that the haploinsufficiency of the SOX9 gene was the primary reason for PRS in this proband.

Another investigation by Al-Qattan et al. (21) claimed that SOX9 protein's positive regulator, SOX9, can specify the pathogenesis of PRS. SOX9 mutations are the primary cause of this autosomal dominant disease; a chromosome 22q12-based microdeletion that includes NF2 results in a condition that overlaps PRS and NF2. Saito et al. (22) present a patient with glossoptosis, micrognathia, a modest cleft palate form and severe early-onset NF2 that overlapped with PRS. In the patient, the author discovered a de novo chromosome 22q12 microdeletion in MN1 and NF2. The severity of the NF2 phenotypes in this example overlapping PRS and NF2 varied according to the severity of the cleft palate, as well as the size of the microdeletions. The size and termination of microdeletions have been compared, and connections between genotype and phenotype imply that several modifier genes proximal to MN1 and NF2 may be connected to the severity of cleft lip and palate.

Table I. *Average values obtained from the analysis.*

Author (REF)	Study characteristics	Findings
Resende et al. 2019 (18)	Case Report Gender= male Age=29 years old History=right eye hypertropia since birth	Microdeletion of gene 2q33 due to PRS
Yekula et al. 2020 (19)	Gender= Female Age=Six years old. History=diffuse hypotonia and delay development	Deletion of chromosome 10q. at 4.34 Mb terminal
Murtaza et al. 2021 (20)	Gender= male neonate Age= four-days old History= without congenital anomalies	SOX9 plays a role in PRS.
Al-Qattan et al. 2022 (21)	Pathogenic based systematic study	SOX9 is the positive regulator of PRS.
Saito et al. 2022 (22)	Patient with severe early-onset NF2. Patient exhibited showed micrognathia, glossoptosis, and cleft palate.	Genotype-phenotype based correlations and microdeletion size and breakpoint comparisons imply that modulator genes proximal to MN1 and NF2 may affect cleft palate severity.

CONCLUSION

The data gathered from the systematic analysis revealed that PRS is caused by a microdeletion of gene 2q33 and deletion of chromosome 10q. at 4.34 Mb terminal. Moreover, SOX9 plays a crucial role in the occurrence of the disease. Microdeletion, breakpoint comparisons and genotype-based correlations suggest that modulator genes close to MN1 and NF2 may influence the severity of cleft palate. In addition to research attempts to develop genetic classifications to inform clinical therapy, this study stresses the necessity for early genetic counselling and testing in this population of patients.

REFERENCES

1. Giudice A, Barone S, Belhous K, et al. Pierre Robin sequence: A comprehensive narrative review of the literature over time. *Journal of stomatology, oral and maxillofacial surgery*. 2018;119(5):419-428. doi:10.1016/j.jormas.2018.05.002
2. Robin P. Glossoptosis due to atresia and hypotrophy of the mandible. *American Journal of Diseases of Children*. 1934;48(3):541. doi:10.1001/archpedi.1934.01960160063005
3. Carey JC, Fineman RM, Ziter FA. The Robin sequence as a consequence of malformation, dysplasia, and neuromuscular syndromes. *The Journal of Pediatrics*. 1982;101(5):858-864. doi:10.1016/s0022-3476(82)80348-x
4. Xu JX, Kilpatrick N, Baker NL, Penington A, Farlie PG, Tan TY. Clinical and molecular characterisation of children with Pierre Robin sequence and additional anomalies. *Molecular Syndromology*. 2016;7(6):322-328. doi:10.1159/000449115
5. J-M Levaillant, J-P Bault, Benoit B, G Couly. *Normal and Abnormal Fetal Face Atlas: Ultrasonographic Features*. Springer International Publishing; 2017.
6. Basart H, Paes EC, Maas SM, et al. Etiology and pathogenesis of robin sequence in a large Dutch cohort. *American Journal of Medical Genetics Part A*. 2015;167A(9):1983-1992. doi:10.1002/ajmg.a.37154
7. Benko S, Fantes JA, Amiel J, et al. Highly conserved non-coding elements on either side of SOX9 associated with Pierre Robin sequence. *Nature Genetics*. 2009;41(3):359-364. doi:10.1038/ng.329
8. Velagaleti GVN, Bien-Willner GA, Northup JK, et al. Position effects due to chromosome breakpoints that map approximately 900 Kb upstream and approximately 1.3 Mb downstream of SOX9 in two patients with campomelic dysplasia. *American Journal of Human Genetics*. 2005;76(4):652-662. doi:10.1086/429252
9. Jakobsen LP, Ullmann R, Christensen SB, et al. Pierre Robin sequence may be caused by dysregulation of SOX9 and KCNJ2. *Journal of Medical Genetics*. 2007;44(6):381-386. doi:10.1136/jmg.2006.046177
10. Sperber GH, Sperber SM. Embryogenetics of cleft lip and palate. In: *Cleft Lip and Palate Diagnosis and Management*. Springer; 2013:3-33.
11. Abu-Hussein M, Watted N, Hegedűs V, Borbély P, Azzaldeen A. Human genetic factors in non-syndromic cleft lip and palate: an update. *International Journal of Maxillofacial Research*. 2015;1(3):1-17.
12. Yuan Q, Blanton SH, Hecht JT. Genetic causes of non-syndromic cleft lip with or without cleft palate. *Advances in Oto-Rhino-Laryngology*. 2011;70:107-113. doi:10.1159/000322486
13. Ferreira de Lima RLL, Moretti-Ferreira D, Richieri-Costa A, Murray JC. Identity by descent and candidate gene mapping of Richieri-Costa and Pereira syndrome. *American Journal of Medical Genetics Part A*. 2003;122A(1):56-58. doi:10.1002/ajmg.a.20270
14. Kohmoto T, Tsuji A, Morita K, et al. A novel COL11A1 missense mutation in siblings with non-ocular Stickler syndrome. *Human Genome Variation*. 2016;3(1). doi:10.1038/hgv.2016.3
15. Bennett J, Lubben F, Hogarth S, Campbell B. Systematic reviews of research in science education: rigour or rigidity? *International Journal of Science Education*. 2005;27(4):387-406. doi:10.1080/0950069042000323719
16. Moher D, Shamseer L, Clarke M, et al. Preferred Reporting Items for Systematic Review and meta-analysis Protocols (PRISMA-P) 2015 Statement. *Systematic Reviews*. 2015;4(1):1-9. doi:10.1186/2046-4053-4-1
17. Lakhanpal M, Gupta N, Vashisth S. Genetics of Cleft Lip and Palate - Is it still patchy? *JSM Dent*. 2014;2(3):1030. doi:10.47739/2333-7133/1030

18. Resende DG, Nespolo DF, Assis LLA, Cunha BRR. Pierre Robin Syndrome associated with type III familial Duane Retraction Syndrome. *Revista Brasileira de Oftalmologia*. 2019;78(1):46-48. doi:10.5935/0034-7280.20190010
19. Yekula A, Grant C, Gupta M, et al. Clinical and genetic characterisation of patients with Pierre Robin sequence and spinal disease: review of the literature and novel terminal 10q deletion. *Child's Nervous System*. 2020;36(7):1367-1377. doi:10.1007/s00381-020-04642-2
20. Murtaza M, Ali MN, Zargar MH. Pierre Robin sequence with a novel mutation in SOX9 gene: Case study. *Human Pathology: Case Reports*. 2021;24:200523.
21. Al-Qattan MM, Almohrij SA. The Pathogenesis of Pierre Robin Sequence through a Review of SOX9 and Its Interactions. *Plastic and Reconstructive Surgery - Global Open*. 2022;10(4):e4241. doi:10.1097/gox.0000000000004241
22. Saito S, Ono N, Sasaki T, et al. Neurofibromatosis type 2 with mild Pierre-Robin sequence showing a heterozygous chromosome 22q12 microdeletion encompassing NF2 and MN1. *Journal of Human Genetics*. 2022;67(11):675-678. doi:10.1038/s10038-022-01068-3