**Epidemiology of Robin sequence: geographical variation in the UK/Ireland**

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**Introduction**

Pierre Robin Sequence (PRS) is a rare congenital malformation sequence characterised by micrognathia, glossoptosis and upper airway obstruction, often in association with a wide U-shaped cleft palate(1). The aetiology of non-syndromic PRS (nsPRS) remains uncertain, however non-isolated PRS can present as part of a wider syndromic diagnosis(1) (syndromic PRS (sPRS)). PRS is reported to have a prevalence of ~1/8000-1/14000 live births(1,2). A recent study by Wright et al (ADC 2023), which utilised dual-source case ascertainment and active surveillance methods, estimated a PRS prevalence of 1:5250 live births(1). This is significantly higher than previous estimates, which may have been miscalculated(1). Importantly, this study also identified a striking geographical variation in prevalence estimates, which were lowest in England and Wales (1/5789), higher in Ireland (1/4635) and highest in Scotland (1/2692)(1). These findings are broadly corroborated by an earlier study by Wright et al (2018), which identified a PRS incidence of 1/2685 in an East of Scotland patient cohort(2). This is significantly higher than previously reported estimates in the UK and globally.

**Why do PRS prevalence estimates vary?**

PRS is a complex condition that presents on a clinical spectrum and potentially as part of a wider syndrome: it is liable to misdiagnosis and requires specialist diagnostic expertise. Milder cases without respiratory distress, airway obstruction or hospital admission can be easily missed(1). The prenatal diagnosis of the condition is difficult and in cases of intrauterine death or stillbirth, access to post-mortem examination may not be ubiquitous(3). A notable source of bias stems from the variability of diagnostic criteria for PRS(1,3), which may have led to inconsistencies in identification of PRS cases, diagnostic practices and surveillance methods. Many epidemiological studies were conducted prior to the publication of consensus guidance, such as the PRS international clinical consensus report(4). Thus, it is possible that inaccurate case definition and omission of affected cases could have led to misestimation of PRS prevalence(1,3). It is possible that the lack of diagnostic consensus may also account for the lack of epidemiological studies due to a particular difficulty obtaining and interpreting PRS case data. Large-scale congenital anomaly registries, most notably EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies) and national audit databases are confounded by incomplete datasets and variable case ascertainment bias which could misestimate PRS prevalence(1,3). EUROCAT, the largest epidemiological series of PRS cases, omits data from Scotland(3), limiting its ability to provide insights into the geographical variation in the UK/Ireland. National registries that do not allow for the follow up of cases diagnosed after the neonatal period will also have omitted PRS cases(3). Epidemiological studies that only consider a subgroup population will provide limited insights into any potential geographical variation in disease prevalence. For example, analysing an isolated subgroup population with a spectrum of congenital malformations or cleft palate (not prerequisite for PRS diagnosis) will not provide insights into geographical variations in PRS prevalence(3). Furthermore, studies utilising single-source case detection may be subject to ascertainment bias(1). Multi-source case ascertainment and active surveillance methods, as utilised by Wright et al(1), allow for a more robust and consistent identification of PRS cases. The geographical variation in PRS prevalence in the UK/Ireland may also reflect different risk profiles between these populations. The cause of PRS is poorly established and is likely to be secondary to a complex multifactorial aetiology(1,2). A number of environmental factors have been postulated, including compressive intrauterine forces, maternal age*,* cigarette smoking, alcohol and methadone exposure(1-3,5). The extent to which these factors may be implicated in PRS pathogenesis and the molecular mechanisms that underpin them remain uncertain. However, elucidating the potential contribution of environmental factors may help to elucidate the cause of the condition whilst also providing insights into the geographical variation in PRS prevalence in the UK/Ireland.

**How could the factors underpinning the geographical variation be elucidated?**

A consensus definition for PRS(4) will improve the epidemiological surveillance of PRS cases by enabling a more standardised diagnostic process and study inclusion criteria. This will refine the identification and interpretation of case data, avoid the omission of affected cases and improve the accuracy of PRS prevalence estimates. There is a need for robust epidemiological studies to investigate the geographical variations in PRS prevalence in the UK/Ireland. Comparative studies will enable the identification of risk factors for PRS within and between the populations of the UK/Ireland(1). They will also allow for any differences between ethnic and sociocultural groups to be identified. Determining the geospatial patterns of PRS incidence and prevalence will enable the identification of risk factors for PRS between populations. Spatial epidemiological studies could enable a focused analysis of geographical variations in PRS prevalence, including the potential contributions of environmental, lifestyle and genetic risk factors. Prospective studies could allow for the identification of risk factors and their relation to PRS prevalence over time. Ultimately, the identification of risk factors for PRS will enable a more thorough understanding of the risk profiles between populations, whilst also aiding our understanding of the cause of the condition and the provision of treatments and healthcare services.

**The important role of genomic testing**

PRS is a heterogeneous condition. The cause of sPRS is described according to its causative gene and mutation(5). However, PRS can present in ‘PRS-plus’ forms and rare syndromes with an undefined genetic basis(5). Elucidating the genetic factors underpinning sPRS will provide vital insights into understanding the cause of the condition and informing the management of affected patients. The advent of next-generation sequencing technologies (whole genome sequencing, whole exome sequencing and targeted gene panel analysis), which are becoming increasingly commonplace in mainstream clinical care may help to accelerate our understanding of the genetic factors underpinning this condition. Whilst syndromic (for example, stickler syndrome(5)) and single gene associations have been identified (for example, *SOX9*(5)), a complex multifactorial aetiology has been hypothesised in nsPRS(1,2) and the contribution of genetic, environmental and lifestyle factors is difficult to establish and poorly understood. Association studies along with functional characterisation and experimental validation could be utilised to identify and clarify the genotype-phenotype correlations. Furthermore, there is a paucity of large-scale cohort and case-control studies and future studies could focus on the delineation of population-level genetic factors along with familial analyses. The identification of population genetic risk factors may provide vital insights into the geographical variation in PRS prevalence.

**Conclusions**

The prevalence of PRS is a vital metric to quantify the burden of the disease in a population at a given time. It is essential in planning the provision of healthcare services for PRS patients. PRS is associated with a significant morbidity and mortality: determining the prevalence of the condition is therefore of great importance in improving the recognition and management of PRS patients in the UK/Ireland. There is a need for more robust epidemiological studies, including comparative, spatial epidemiological and prospective studies to elucidate the epidemiology of the condition and thus provide insights into its cause and geographical variation. Genomic testing will be essential in helping to distinguish between syndromic and non-syndromic PRS, informing genotype-phenotype correlations and in the identification of population genetic factors that may underpin its striking geographical variation. Ultimately, this information is crucial to inform the management and delivery of healthcare services for patients with PRS in the UK/Ireland.

**References:**

1. Wright MF, Knowles RL, Cortina-Borja M, Javadpour S, Mehendale FV, Urquhart DS. Epidemiology of Robin sequence in the UK and Ireland: an active surveillance study. Arch Dis Child. 2023 Jun 27:archdischild-2023-325556. doi: 10.1136/archdischild-2023-325556.
2. Wright M, Mehendale F, Urquhart DS. Epidemiology of Robin sequence with cleft palate in the East of Scotland between 2004 and 2013. Pediatr Pulmonol. 2018 Aug;53(8):1040-1045. doi: 10.1002/ppul.24038.
3. Santoro M, Coi A, Barišić I, Pierini A, Addor MC, Baldacci S, Ballardini E, Boban L, Braz P, Cavero-Carbonell C, de Walle HEK, Draper ES, Gatt M, Haeusler M, Klungsøyr K, Kurinczuk JJ, Materna-Kiryluk A, Lanzoni M, Lelong N, Luyt K, Mokoroa O, Mullaney C, Nelen V, O'Mahony MT, Perthus I, Randrianaivo H, Rankin J, Rissmann A, Rouget F, Schaub B, Tucker D, Wellesley D, Zymak-Zakutnia N, Garne E. Epidemiology of Pierre-Robin sequence in Europe: A population-based EUROCAT study. Paediatr Perinat Epidemiol. 2021 Sep;35(5):530-539. doi: 10.1111/ppe.12776.
4. Breugem CC, Evans KN, Poets CF, Suri S, Picard A, Filip C, Paes EC, Mehendale FV, Saal HM, Basart H, Murthy J, Joosten KF, Speleman L, Collares MV, van den Boogaard MJ, Muradin M, Andersson ME, Kogo M, Farlie PG, Don Griot P, Mossey PA, Slator R, Abadie V, Hong P. Best Practices for the Diagnosis and Evaluation of Infants With Robin Sequence: A Clinical Consensus Report. JAMA Pediatr. 2016 Sep 1;170(9):894-902. doi: 10.1001/jamapediatrics.2016.0796.
5. Motch Perrine SM, Wu M, Holmes G, Bjork BC, Jabs EW, Richtsmeier JT. Phenotypes, Developmental Basis, and Genetics of Pierre Robin Complex. J Dev Biol. 2020 Dec 5;8(4):30. doi: 10.3390/jdb8040030.