Observed Total and Live Birth Prevalence of Wolf-Hirschhorn Syndrome in England 2015 -2020

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Running Head: WHS Birth Prevalence

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Abstract

Background

Birth prevalence estimates for Wolf-Hirschhorn syndrome (WHS) are frequently quoted as either 1 in 50,000, or 1 in 20,000 to 1 in 50,000. The origin of the 1 in 50,000 estimate is obscure whilst the 1 in 20,000 is based on expert opinion. A 2001 UK study of WHS cases reported a minimal live birth prevalence of 1 in 95,896.

Objective

To estimate the total birth and live birth prevalences of Wolf-Hirschhorn Syndrome (WHS) in England between 2015-2020 and compare the results with previously published reports.

Methods

Data on total births and live births were obtained from the English National Congenital Anomaly and Rare Disease Registration Service. Birth prevalence was calculated in two ways: firstly, by dividing the total number of cases of WHS by the total number of births (live births plus stillbirths, miscarriages after 20 weeks and termination of pregnancy); and secondly, by dividing the number of WHS cases resulting in live births by the total number of live births.

Results

There were 56 total births, resulting in 30 live births, identified between 2015 and 2020. Total birth prevalence was 2.16 per 100,000 (95% CI 1.63 – 2.80 per 100,00) equivalent to 1 in 46,303 (95% CI 1 in 35,656 – 1 in 61,297). The live birth prevalence was 1.16 per 100,000 (95% CI 0.78 – 1.66 per 100,00), equivalent to 1 in

86,092 (95% CI 1 in 60,307 – 1 in 127,601) consistent with the earlier UK study. Additionally, the distribution between translocations, deletions and proportion alive at 1 year (86.7%) were also consistent with the earlier UK study.

Conclusion

We believe the frequently quoted WHS birth prevalence figures are an overestimate and recommend that birth prevalence figures are based on empirical data with the nature of the numerator and denominator stated clearly.

Key words: Wolf Hirschhorn Syndrome; Birth prevalence; Trisomy 21; Trisomy 13; Trisomy 18; Congenital anomaly registration.

Introduction

Although rare, Wolf-Hirschhorn syndrome (WHS) is a well-recognised condition characterised by: pre- and post-natal growth delay, microcephaly, intellectual disability, typical facial appearance and a variety of congenital, often midline, abnormalities resulting from a contiguous gene deletion on chromosome 4p.

Recent publications have stated a birth prevalence of either 1 in 50,000, or between 1 in 20,000 and 1 in 50,000 births for, examples see references (Paprocka *et al* 2024, Popescu *et al* 2023, Tang *et al* 2023); however, the empirical data on which these estimates are based are unclear. Maas *et al* (2008) stated that the birth prevalence was 1 in 50,000 but gave no reference for this and then went on to say: "In our experience, the incidence of WHS patients is similar to Angelman syndrome patients – about 1 per 20,000 births." These figures are cited in the population genetics section of the OMIM entry for WHS 194190 (OMIM database). In a review Battagalia *et al* (2015) gave the reference for the 1 in 50,000 as Lurie *et al* (1980). Unfortunately, that study does not estimate birth prevalence, but instead reports four cases, and a review of the literature. (Lurie *et al* 1980).

Using multiple methods of ascertainment, Shannon *et al* (2001) studied 146 WHS cases from the UK: 96 were alive, 37 had died and 13 were detected prenatally with termination of pregnancy. Of that cohort, 79 children were born between 1989 and 1998, giving a minimum live birth prevalence of 1 in 95,896, considerably lower than the oft quoted figures. This figure is cited in the OMIM entry for WHS, but not in the section on population genetics (OMIM database). The 5th edition of *Gorlin's Syndromes of the Head and Neck* reports the birth prevalence as 1 in 50,000 to 1 in 100,000 (Henekam et al 2001). A Spanish paper with an English abstract reported a

birth prevalence in Spain of 1 in 172,904, well below the 1 in 50,000 typically cited; therefore, the authors used this as evidence of under-diagnosis of WHS in Spain (Blanco Lago *et al* 2022).

Given the discrepancies between the published birth prevalence figures we requested data on WHS cases from the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) in order to estimate the birth prevalence of WHS in England.

Methods

Ethical Approval

NCARDRS has legal permission to collect patient-level data on those with a confirmed or suspected congenital anomaly or rare disease for specified purposes, without consent, to use it to protect the health of the population. Data are collected under legal instructions known as Directions, from the Secretary of State for Health and Social Care, made in accordance with section 254 of the Health and Social Care Act 2012 (2012 Act). Strict technical and contractual controls are put in place to prevent unauthorised access and use of the data, with staff undergoing regular training on data protection and information governance.

Data sources

Numbers of cases of WHS were obtained from NCARDRS, part of the National Disease Registration Service in NHS England, a population congenital anomaly register that quality assures, curates and analyses individual data on pregnancies, fetuses, babies, children and adults with congenital anomalies and rare diseases across England using multiple methods of ascertainment including: antenatal screening, clinical patient management system extracts and data feeds from all 14 cytogenetic laboratories in England (Broughan *et al* 2024). Between 2015 and 2017 congenital anomaly registration was regional, covering 49% of births; from 2018 onwards, coverage was national.

A snapshot of NCARDRS data was taken on 1 August 2022 to identify babies and fetuses with a confirmed or probable diagnosis of WHS between January 1, 2015, and December 31, 2020. Possible cases were identified as records with the ICD10 code Q933 and/or those where the free-text anomaly description contained either of

the terms 'wolf' or '4p' (uppercase or lowercase). Cases initially included all babies born alive, stillbirths, miscarriages after 20 weeks and terminations of pregnancy at any stage in gestation, but in order to make a direct comparison with Shannon *et al* (2001), cases were limited to those born alive. Records were then manually reviewed by a member of NDRS, with cases categorised by causation as a complex case, a chromosome or mosaic deletion, or a translocation.

Babies and pregnancies registered on NCARDRS are followed up approximately annually using the NHS Personal Demographics Service data and a death date recorded if applicable. From this, the proportion of WHS babies born alive and who survived for one year was calculated.

The corresponding denominator number of births for the regions covered by the 14 cytogenetic laboratories was extracted from Office of National Statistics birth registration data available from the UKHSA Datalake.

Birth prevalence data on frequently occurring trisomies was obtained from published NCARDRS reports for the same period, 2015-2020 (NCARDRS Congenital Anomaly Statistics Report 2015 and 2016 and 2017, NCARDRS Congenital Anomaly Statistics Data Tables 2018 and 2019, NCARDRS Congenital Anomaly Official Statistics 2020 Data Tables).

Analysis

Following European Surveillance of Congenital Anomalies guidance (Guide 1.4 Section 4.1), birth prevalence was calculated in two ways: firstly, by dividing the total number of cases of WHS by the total number of births (live births plus stillbirths, miscarriages after 20 weeks and termination of pregnancy.); and secondly, by

dividing the number of WHS cases resulting in live births by the total number of live births. Prevalence data are presented as x per 100,000 total or live births and as the 1 in x format to facilitate comparison with previous WHS data and comparison with other conditions and future publications.

Birth prevalence confidence intervals were calculated assuming a Poisson distribution for the counts of cases (Bégaud *et al* 2005) and results compared with two previous studies with the denominator number of births back-calculated from the published number of cases and the birth prevalence (Shannon *et al* 2001 and Blanco Lago *et al* 2022). The proportions of cases classified by each aetiology (complex, chromosome or mosaic deletion, or translocation) were compared between this study and data from 141/146 cases with known chromosome breakpoints and the data on 1 year survival (82.6%) extracted from Shannon *et al* (2001) Significance was determined using the Fisher's exact test.

Results

Birth prevalence figures from this and another two observational studies are summarised in Table 1. The total number of WHS babies and fetuses registered with NCARDRS in this period was 56 but only 30 (a loss of 46.4%) were born alive, giving a minimal estimated live birth prevalence of 1.16 per 10,000 live births (95% CI 0.78 – 1.66 per 10,000 live births) representing 1 in 86,092 live births (95% CI 1 in 60,241 – 1 in 128,205) with 86.7% surviving to age 1 year. The split between the aetiological categories: complex rearrangement, chromosome or mosaic deletion and translocation is given in Table 2 and compared with corresponding data from Shannon *et al* (2001). For context, the total and live birth prevalence for the frequently occurring trisomies together with those for WHS is shown in Table 3.

Discussion

The result from this study of a minimum live birth prevalence of 1 in 86,092 (95% CI 1 in 60,307 – 1 in 127,601) is similar to that of the earlier study by Shannon *et al* (2001),1 in 95,896 (95% CI 1 in 76,945 – 1 in 121,125). The proportion surviving to 1 year and the distribution of translocations and deletions were also consistent with that earlier report. The frequently quoted figures of either 1 in 50,000 or between 1 in 20,000 and 1 in 50,000 are outside the 95% confidence intervals for the live birth prevalence from this study and Shannon *et al* (2001). Given the clinical picture, it is likely that most cases will be diagnosed antenatally or soon after birth; however, it is possible that cases will be diagnosed later but the greater availability and accessibility of chromosome micro-array technology makes this less likely. Shannon *et al* (2001) reported prior to the availability of chromosome micro-array technology but noted that 23 of 96 living patients (24%) were diagnosed after 1 year. If we apply this figure to our data (which may be an over-estimate because of the technology change) that would only give an extra 8 cases. Under-reporting is another potential source of under-ascertainment in our study but in order to achieve a live birth prevalence of 1 in 50,000 a further 21 children with WHS would have to be identified which seems unlikely. By comparison, the total birth prevalence of WHS which include live births, stillbirths, miscarriages after 20 weeks and termination of pregnancy for fetal anomaly was 1 in 46,303. Whilst this figure approximates to the more often quoted of 1 in 50,000 it does not represent a direct comparison. In addition to the origin of the 1 in 50,000 figure being unclear, it is also unclear as to whether this includes live births, stillbirths and miscarriages. It is interesting to note that the oft quoted figures are frequently given as “births” without distinguishing between live births or total births (Maas *et al* 2008, Popescu *et al* 2023, Paprocka *et*

al 2024, OMIM database) although Tang *et al* (2023) reported prevalence as not less than 1 in 50,000 live births. The WHS data can be compared with the NCARDRS registration data for the common trisomies. The live birth prevalence for trisomy 13 (1 in 36,897 95% CI 1 in 29,203 – 47,331) was in the range of the oft quoted figures for WHS which, if correct, would mean WHS live births were as common as trisomy 13 live births.

Ongoing congenital anomaly registration makes it possible to monitor the data in future years to establish whether more cases come to light from later diagnoses and to establish more detail on the outcomes for the children born with WHS. Due to the possibility of under-ascertainment, our live birth prevalence figure of 1.16 per 100,000, equivalent to 1 in 86,092 represents a minimal estimate.

In conclusion, this study confirms the results for the earlier study (Shannon *et al* 2001). The more often quoted figures of 1 in 50,000 and 1 in 20,000 may represent an over-estimate of the live birth prevalence or may be more consistent the total birth prevalence. We recommend that birth prevalence figures are based on empirical data with the nature of the numerator and denominator stated clearly.

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Table 1 Summary of WHS Birth Prevalence Data

	No of cases (years of study)	**The number of births**	**Birth Prevalence (1 in X) [95%CI]**	**Birth Prevalence (per 100,000) [95%CI]**	**Survival to 1 year (%)**
This Study: Total Births	56 (2015-20)	2,592,963	1 in 46,303 [1 in 35,656 - 1 in 61,297]	2.16 [1.63, 2.80]	N/A
This Study Live Births	30 (2015-20	2,582,757	1 in 86,092 [1 in 60,307 – 1 in 127,601]	1.16 [0.78 – 1.66]	86.7
Shannon et al 2001 Live Births	79 (1989-98)	7,575,784*	1 in 95,896 [1 in 76,945 – 1 in 121,125]	1.04 [0.83 – 1.30]	82.6
Blanco Lago et al Live Births	77 (2013-21)	13,832,320**	1 in 179,641 [1 in 143,732 – 1 in 227,628	0.56 [0.44 – 0.70]	N/A

Total Births = Live births, still births miscarriage after 20 weeks and termination of pregnancy.

* Denominator number of births back-calculated from the published number of cases and the birth prevalence.

** Denominator number of births back-calculated from the number of cases reported in the abstract (80) and the birth prevalence.

Table 2 Summary of WHS by aetiological classification for babies born in England (NCARDRS 2015-2020) and similar data taken from Shannon *et al* 2001 Table 2

	Complex	**Deletion**	**Translocation**	**TOTAL**	**P Value***
Babies with WHS born alive NCARDRS	0 (0)	24 (80)	6 (20)	**30**	0.361
Babies with WHS born alive Shannon *et al*	10 (7.7)	95 (73.1)	25 (19.2)	**130**	
Total births with WHS NCARDRS	2 (3.6)	38 (67.9)	16 (28.6)	**56**	0.292
Total births with WHS Shannon *et al*	11 (7.8)	102 (72.3)	28 (19.9)	**141**	
The % of babies born alive surviving to one year of age NCARDRS	0 (NA)	21 (87.5)	5 (83.3)	**26 (86.7)**	-

The table reports cases by aetiology (percentage of total).

1-year survival percentage is given as the percentage of live births surviving to 1-year within each aetiological classification.

*Fischer's exact test with the null hypothesis that the proportions of cases classified as complex, deletion or translocation are the same in the populations represented in the NCARDRS and Shannon studies.

Table 3 Summary data for trisomy 21, trisomy 13, and trisomy 18 and WHS from NCARDRS Congenital Anomaly Official Statistics Reports (2015 -2020)

	Total number of babies and fetuses with a common trisomy	Number of babies with a common trisomy born alive	Percentage Loss [95%CI]	Total Birth prevalence (1 in X) [95%CI]	Total Birth prevalence (per 100,000) [95%CI]	Live Birth prevalence (1 in X) [95%CI]	Live Birth prevalence (per 100,000) [95%CI]
Trisomy 21	6631	2948	55.5 [54.3 - 56.7	1 in 391 [1 in 382 – 401]	255.8 [261.8 – 249.4]	1 in 876 [1 in 845 – 909]	114.2 [118.3 – 11.0]
Trisomy 13	674	70	89.6 [87.1 - 91.8]	1 in 3,847 [1 in 3,567 – 4,155]	26.0 [28.0 – 24.1]	1 in 36,897 [1 in 29,203 - 47,331]	2.71 [3.42 – 2.11]
Trisomy 18	1862	227	[86.2 - 89.3]	1 in 1,393 [1 in 1,331 – 1,458]	71.8 [75.1 – 68.6]	1 in 11,378 [1 in 9,990 –13,016]	8.79 [10.1 – 7.7]
WHS	56	30	46.4 [33 - 60.3]	1 in46,303 [1 in 35,656 – 61,297	2.16 [1.63 – 2.80]	1 in 86,092 [1 in 60,307 – 127,601	1.16 [0.78 – 1.66