

Wolf–Hirschhorn syndrome in a Brazilian family-association group: Clinical profile and factors associated with time to genetic diagnosis

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Research Article

Keywords: Wolf–Hirschhorn syndrome, 4p deletion, Rare genetic disorders, Diagnostic delay, Health services accessibility

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10933205/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Wolf–Hirschhorn syndrome (WHS) is a rare chromosomal disorder resulting from the partial deletion of the short arm of chromosome 4 (4p16.3), characterized by a broad spectrum of developmental disabilities and marked phenotypic variability. Despite its clinical and genetic complexity, the epidemiological profile and developmental impact of WHS remain poorly characterized in low- and middle-income countries (LMICs). In Brazil, no studies have specifically addressed this condition, representing a critical gap in understanding its burden and management within the Brazilian healthcare and educational contexts. We conducted an epidemiological study in two stages, combining a descriptive analysis of 68 individuals with genetically confirmed WHS recruited through the Brazilian WHS Family Movement and a retrospective cohort with survival analysis. Sociodemographic, gestational, clinical, genetic, and healthcare data were obtained from records and semistructured caregiver interviews. The time to diagnosis was analyzed via Kaplan–Meier curves and Cox proportional hazards models.

Results

Most participants lived in the Southeast and South region of Brazil, were female and White, and had access to private health insurance in addition to the public system. The median time to genetic diagnosis was 334 days. In the multivariate analysis, intrauterine growth restriction, maternal age > 32 years at delivery, and the use of molecular genetic testing were significantly associated with an earlier diagnosis.

Conclusions

This study reveals substantial regional and structural inequities in access to genetic diagnosis for WHS and highlights clinical and care determinants that can guide earlier identification and intervention for children with developmental disabilities in Brazil.

1. Background

Wolf–Hirschhorn syndrome (WHS; OMIM#194190; ICD-10:Q93.3; ICD-11:LD44.41) is a rare genetic disease characterized by alterations in multiple aspects of the pre- and postnatal development of affected individuals. This syndrome results from a partial deletion of the short arm of chromosome 4 (4p16.3), causing a wide spectrum of congenital and multisystem malformations, which mainly include craniofacial dysmorphisms, delayed neuropsychomotor development, epileptic seizures, hypotonia, and growth restriction [1–7]. The estimated birth incidence ranges from 1:20,000 to 1:50,000 live births, with a higher incidence in females [2:1]. However, there are indications that this rate may be underestimated, mainly due to limitations in access to diagnosis in several countries [2,7–10].

Previous studies have indicated that the geographic distribution of this syndrome is not homogeneous. In Spain, the data showed that the prevalence of the syndrome in that country is lower than that estimated globally, with 1:172,904 live births in the Spanish population; in the United Kingdom, it is approximately 1:96,000; and in Italy, it is 1:500,000, suggesting underdiagnosis in these and other countries [1,7,8].

Since the first cases described in the literature in the 1960s by Wolf and Hirschhorn [11–13], the phenotypic characteristics of WHS have been described as highly variable [1,2,14–16]. Among the main clinical manifestations of the syndrome, hypertelorism, microcephaly, and a broad nasal dorsum stand out, which give the individual's face a characteristic shape, often referred to as the "Greek warrior helmet." The severity of the clinical manifestations depends largely on the size of the deletion and the genes affected [1,2,4,5,17–20].

The diagnosis of WHS requires clinical evaluation and genetic analysis of suspected cases. The objective of cytogenetic and molecular analyses is to establish the presence of a Wolf–Hirschhorn syndrome critical region (*WHSCR*) deletion on chromosome 4, located approximately 2 Mb from the telomere 4p in band 4p16.3. Currently, this region includes the *WHSC1*, *LETM1*, *NSD2*, *CPLX1*, and *PIGG* genes. Two critical regions related to the syndrome are described: critical region 1 (*WHSCR1*), which partially includes candidate gene 1 (*WHSC1* or *NSD2*) and candidate gene 2 (*WHSC2* or *NELF-A*), and critical region 2 (*WHSCR2*), where the *LETM1*, *MSX1* and *CRIP1* genes are located [1,5,21,22].

Early identification of the syndrome is still a challenge, mainly due to phenotypic variability and the restricted availability of genetic tests in some regions of countries where studies have already been carried out [5,7]. Among the methods of genetic analysis used in diagnosis, conventional karyotyping is still widely used, but it has limitations in the detection of deletions smaller than 5 Mb, as approximately 50–60% of individuals can be identified via this method [4,2]. Fluorescence in situ hybridization (FISH) can identify 95% of mutations, and

microarray-based comparative genomic hybridization (CGH array) can detect microdeletions and changes in specific regions but cannot detect balanced translocations or inversions [4,5,24].

The prognosis of individuals diagnosed with WHS varies according to the complexity of the clinical manifestations and control of complications [5,6]. Studies conducted with adults living with this syndrome have shown that despite motor and cognitive difficulties, many individuals have a good quality of life when they receive adequate multidisciplinary support [1,5–7]. However, survival may be reduced in the first years of life due to complications associated with congenital malformations and difficulties in feeding and controlling epileptic seizures [2–5,24,25].

In Brazil, WHS data are scarce and limited to case reports or regional studies. Children and adults with WHS typically present with complex developmental disabilities, including intellectual disability, epilepsy, growth restriction, and multiple congenital anomalies, requiring long-term multidisciplinary care and educational support. In this context, understanding the patterns of access to genetic diagnosis and the clinical and care determinants of diagnostic timing is critical for planning early intervention, family support, and equitable services for individuals with developmental disabilities in low- and middle-income settings such as Brazil. Importantly, comprehensive knowledge of the epidemiological, sociodemographic, and clinical characteristics of WHS is essential to support improvements in early diagnosis, management, and intervention strategies. Consequently, this study provides a pioneering characterization of the profile of individuals diagnosed with WHS, encompassing aspects of care and assistance in the country, thereby contributing new scientific evidence.

2. Methods

2.1 Study design

This epidemiological study was conducted in two stages. The first consisted of a descriptive analysis of the sociodemographic, clinical, and healthcare characteristics of patients with WHS in Brazil. The second stage was a retrospective cohort study with survival analysis to investigate the factors associated with the time to diagnosis of WHS in the country.

2.2 Study participants

Given the lack of specific surveillance systems for this syndrome and its low incidence, the study population was recruited on the basis of records of individuals registered in the "Wolf–Hirschhorn Syndrome Movement Brazil". This virtual group, established in 2014, brings together Brazilian families impacted by this genetic condition to promote and improve their quality of life. Currently, the movement has 230 registered members, primarily residing in the Southeast, Northeast, and South regions of Brazil (Fig. 1), with four individuals living in other countries (Argentina, Canada, Colombia, and Paraguay). Members were included if they had a definitive etiological diagnosis confirmed by cytogenetic and/or molecular tests and if their legal guardians provided a written informed consent form (ICF). Individuals with an exclusively clinical diagnosis and those who did not undergo confirmatory genetic or other complementary tests were excluded (Fig. 2).

2.3 Data collection

Data collection occurred between March 2024 and January 2025 in two phases. The first involved obtaining sociodemographic information through the registration form and clinical data through documentary analysis of cytogenetic tests, clinical examinations, reports of health conditions, and hospital admissions. The second phase was conducted through semistructured interviews with parents/guardians. The interview instrument consisted of open and closed questions addressing the sociodemographic profile, as well as clinical data encompassing obstetric and neonatal history, physical characteristics, diagnostic characterization, therapeutic management and follow-up. The instrument was validated via a pilot test ($n = 10$) between November 2023 and February 2024.

2.4 Data analysis

The data were processed via double entry into Epi Info software (version 7.2.5, CDC). Initially, the sociodemographic, clinical, and diagnostic profiles of patients with WHS were described by determining the absolute and relative frequencies. Continuous variables (age and family income) are presented as the means and standard deviations. The diagnosis of this genetic syndrome is usually challenging [1,2,4]. This study tested the hypothesis that sociodemographic, clinical, and care characteristics are associated with the time to diagnosis. In this sense, the median time (in days) until diagnosis among individuals diagnosed after birth was used as a cutoff point to categorize cases with timely diagnosis ($<$ median) or late diagnosis ($>$ median). In a preliminary exploratory analysis, the frequencies of sociodemographic, clinical, and care variables were described according to the timeliness of diagnosis, with continuous variables categorized on the basis of the median. Survival analysis was subsequently conducted via the Kaplan–Meier method to estimate the time to diagnosis, and the log-rank test was subsequently used to compare survival curves between categories of explanatory variables. For the multiple analysis, variables with a p value < 0.20 in the univariate analysis were selected to construct a Cox proportional hazards model. The selection of

predictors was performed via the *stepwise forward* method, and Akaike's information criterion was used to analyze the impact of the inclusion of variables on the fit of the model. Variables with a p value < 0.05 in the final model were considered statistically associated with the time until the diagnosis of WHS. The assumption of proportionality of the risks was verified via the Grambsch and Therneau test, which is based on Schoenfeld residuals. Additionally, the deviance and dfbeta residuals were graphically analyzed to identify possible *outliers* and observe the individual influence of the observations on the model coefficients. In both the univariate and multiple analyses, the strength of the associations was estimated by calculating the hazard ratio (HR) with the respective 95% confidence intervals (95% CI). The analyses were performed via STATA version 16.1 (StataCorp LP, College Station, United States) and RStudio version 2024.04.2 (Posit Software, PBC, Boston, United States) with the survival package.

2.5 Ethical considerations

The study has the consent and formal authorization of the Wolf–Hirschhorn Syndrome Movement Brazil. The study was approved by the Research Ethics Committee of the Federal University of Rondonópolis (opinion No. 6.477.794 of October 2023 (CAAE: 74207223.4.0000.0126)). The research guaranteed the anonymity of the participants and did not involve exposing the participants to situations that would pose risks to life and physical integrity; however, the possibility of discomfort related to the emotional aspects of the guardians was not excluded, and this was minimized by the interviewer in charge of clarifying any doubts that may arise, emphasizing the confidentiality of the information provided, and the guarantee of freedom to give up at any stage. Data collection began after the participants or their legal guardians signed the ICF. The investigation followed the ethical principles described in the Declaration of Helsinki, the Belmont Report, and required by Resolution 466, of December 12, 2012, of the National Health Council of the Brazilian Ministry of Health.

3. Results

3.1 Sociodemographic and epidemiological characteristics

Among the 95 individuals initially included in the study, 6 records were excluded because of incorrect completion of the informed consent form, etiological diagnosis compatible with another genetic condition, withdrawal by the parents, and lack of response to contacts made by the research team. In addition, 21 registered candidates did not proceed to the interview stage because of the failure to send cytogenetic test results. Thus, 68 individuals with a confirmed etiological diagnosis of the syndrome were included in the analyses (Fig. 2).

The geographic distribution of the participants revealed that most lived in the Southeast Region (52.94%), with the state of São Paulo accounting for the highest percentage of respondents (n = 18; 26.47%), followed by Rio de Janeiro and Minas Gerais (n = 8; 11.76%). The sociodemographic characterization revealed that 55.88% of the individuals were female and that 72.06% declared themselves white. The mean age was 8.47 years (SD ± 8.10 years; range, 0.20–43.81 years), with a predominance of the age group of 4–9 years (39.71%) (Table 1).

Table 1

Distribution of participants diagnosed with Wolf–Hirschhorn syndrome according to sociodemographic variables. Brazil, 2025 (n = 68).

Variable	N	%
Region of origin		
Southeast	36	52,94
On	15	22,06
Northeast	12	17,65
Midwest	4	5,88
North	1	1,47
Sex		
Female	38	55,88
Male	30	44,12
Race/Color		
White	49	72,06
Curtain	18	26,47
Black	1	1,47
Age group (years)		
< 1	5	7,35
1 - 4	14	20,59
4 - 9	27	39,71
9 - 14	12	17,65
14 - 17	3	4,41
17 - 25	3	4,41
> 25	4	5,88
Death		
No	65	95,59
Yes	3	4,41
Care network used in treatment and follow-up		
Health insurance and SUS	21	30,88
Health insurance	17	25,00
SUS only	12	17,65
Private and health insurance	9	13,24
Private	2	2,94
Private and SUS	4	5,88
Other	3	4,41
Others: Judicialization; SUS, health plan and private; SUS, health insurance and Association of Parents and Friends of the Exceptional (APAE).		

With respect to socioeconomic conditions, 39.71% of the families reported income above 5 minimum wages, with an average income of 8,219.08 Brazilian reais (R\$) (equivalent to 1,486.27 USD) (SD $\pm$ R\$ 6,673.38, equivalent to US\$ 1,206.75; range R\$ 1,412.00–28,240.00, US\$ 255.33–5,106.69). Approximately 35.29% received some type of social assistance, especially continuous cash benefits (*Benefício de*

Prestação Continuada – BPC), which were granted in 79.17% of these cases. Access to treatment networks and monitoring of health conditions occurred mostly through health insurance and the Brazilian Unified Health System (*Sistema Único de Saúde* – SUS) combined (30.88%), followed by exclusive use of health insurance (25.00%) and only the SUS (17.65%) (Table 1).

The analysis of housing conditions indicated that most families lived in households with four to five residents (52.95%), that most of the properties were houses (72.06%), owned (63.24%), with access to the public water network (85.29%), sanitary sewage drained through a collection network (80.88%), and garbage collection by public service (89.71%).

The profile of the caregivers was predominantly composed of mothers (92.65%), and the age range of the caregivers was 34–44 years (47.76%), with a mean age of 38.98 years and a range of 22.52–70.54 years ($SD \pm 8.91$ years). Stable union or marriage represented the marital status of 79.41% of the parents. With respect to education, 32.35% had a postgraduate degree, and 23.53% had completed higher education, with 61.76% employed and 44.12% being the main income earners of their families.

3.2 Gestational and neonatal characteristics

Most mothers at the time of delivery were in the age group of 24–34 years (47.06%), and the mean maternal age was 31.05 years ($SD \pm 6.34$ years; range, 17–44 years). Most of the fathers were also in the 24–34 years age group (41.18%), and the mean paternal age was 34.55 years ($SD \pm 8.29$ years; range 21–55 years) (Table 2).

Table 2
Gestational and neonatal characteristics of participants diagnosed with Wolf–Hirschhorn syndrome. Brazil, 2025 (n = 68).

Variable	N	%
Maternal age group at birth (years)		
< 24	11	16,18
24 - 34	32	47,06
34 - 44	24	35,29
44 - 54	1	1,67
Paternal age range at birth (years)		
< 24	6	8,82
24 - 34	28	41,18
34 - 44	23	33,82
44 - 54	6	8,82
≥ 55	5	7,35
Number of pregnancies		
1–2	46	67,65
≥ 3	21	30,88
Ignored	1	1,47
Abortions		
No	54	79,41
Yes	13	19,11
Ignored	1	1,67
Gestational age at birth		
Preterm ^{to}	18	26,47
Term ^B	50	73,53
Intrauterine growth restriction		
Yes	55	80,88
No	11	16,18
Ignored	3	2,94
Amniotic fluid change		
No changes	50	73,53
Decreased	14	20,59
Increased	2	2,94
Ignored	2	2,94
Decreased fetal movement		

^a Preterm: Gestational age < 37 weeks. ^b Full-term: Gestational age from 37 weeks to 41 weeks. ^c Clinical hospitalization unit and/or clinical ward. ^d NICU: Neonatal intensive care unit. ^{and} NICU: Neonatal Intermediate Care Unit of the type UCINCo (conventional intermediate care unit) or UCINCa (Kangaroo Intermediate Care Unit). ^f Low at birth: weight < 2,500 g. ^g Gestational age < 37 weeks and weight < 2,500 g. ^h Prematurity: gestational age < 37 weeks. ⁱ Other reasons: Monitoring, neonatal infection, hypoglycemia and hydronephrosis. ^j Not applicable: Not hospitalized after birth (n = 14).

Variable	N	%
Maternal age group at birth (years)		
No	42	61,76
Yes	24	35,29
Ignored	2	2,94
Complications in childbirth		
No	54	79,41
Yes	13	19,12
Ignored	1	1,47
Hospitalization after birth		
Yes	54	79,41
No	14	20,59
Inpatient unit		
Clinical Hospitalization ^c	6	8,82
UTIN ^d	41	60,30
UCIN ^e	4	5,88
Ignored	17	25,00
Reasons for hospitalization		
Low weight ^f	28	51,85
Diagnosis	8	14,81
Prematurity and low birth weight ^g	6	11,11
Respiratory distress	4	7,40
Prematurity ^h	1	1,85
Other ⁱ	7	12,96
Not applicable ^j	14	20,58
Length of hospital stay after birth (days)		
≤ 15	17	25,00
15 - 30	18	26,47
30 - 60	10	14,70
≥ 60	9	13,23
Not applicable ^j	14	20,60
^a Preterm: Gestational age < 37 weeks. ^b Full-term: Gestational age from 37 weeks to 41 weeks. ^c Clinical hospitalization unit and/or clinical ward. ^d NICU: Neonatal intensive care unit. ^{and} NICU: Neonatal Intermediate Care Unit of the type UCINCo (conventional intermediate care unit) or UCINCa (Kangaroo Intermediate Care Unit). ^f Low at birth: weight < 2,500 g. ^g Gestational age < 37 weeks and weight < 2,500 g. ^h Prematurity: gestational age < 37 weeks. ⁱ Other reasons: Monitoring, neonatal infection, hypoglycemia and hydronephrosis. ^j Not applicable: Not hospitalized after birth (n = 14).		

The maternal obstetric history indicated that most women had between one and two pregnancies (67.65%), and approximately 19.11% had confirmed previous abortions. With respect to the gestational alterations frequently associated with the syndrome, intrauterine growth restriction (IUGR) was observed in 80.88% of cases, decreased fetal movements in 35.29%, and reduced amniotic fluid in 20.59% of

pregnancies (Table 2). The mean gestational age (GA) at birth was 37.20 weeks, ranging from 30 to 42 weeks (SD $\pm$ 2.54 weeks). Most births occurred at term (73.53%), with a mean weight of 2.012 kg (n = 67; SD $\pm$ 0.512 kg; range, 0.840–3.385 kg).

In the neonatal period, approximately 79.41% of newborns required hospitalization in the neonatal intensive care unit (NICU) soon after delivery (60.29%). The main reason for hospitalization was low birth weight (51.85%), with a mean length of stay of 31.25 days, ranging from 1-150 days (SD $\pm$ 31.05 days).

3.3 Clinical and diagnostic characteristics

The diagnostic and clinical characterization results presented in Table 3 revealed that most patients had access to genetic diagnosis through the health plan (41.18%), especially in the postnatal period (95.59%). A mean duration of 896.07 days (SD $\pm$ 2194.36 days) was required to determine the etiology of the syndrome, or approximately 2.46 years (SD $\pm$ 6.01 y). When stratifying the time until diagnosis, most families (32.31%) took between 365 and 1825 days to obtain a diagnosis.

Table 3
Distribution of research participants according to diagnostic and clinical variables. Brazil, 2025 (n = 68).

Variable	N	%
Genetic counseling		
Yes	34	50,00
No	29	42,65
Ignored	5	7,35
Access to diagnostics		
Health insurance	28	41,18
SUS only	16	23,53
Private	16	23,53
Health insurance and SUS	5	7,35
Other	3	4,41
Diagnostic period		
Postnatal ^b	65	95,59
Prenatal ^{care c}	3	4,41
Time to diagnosis (days)		
< 30	9	13,85
30 - 90	9	13,85
90 - 365	18	27,69
365 - 1825	21	32,31
≥ 1825	8	12,31
Examination(s) employed in diagnosis		
Karyotype and CGH-Array	24	35,29
Karyotype	19	27,94
CGH-Array	11	16,18
Karyotype, FISH, and CGH-Array	3	4,41
Karyotype and FISH	2	2,94
CGH-Array and FISH	1	1,47
NGS Panel	1	1,47
FISH	1	1,47
Other ^d	6	8,82
Genetic alterations according to tests		
Deletion	53	77,94
Deletion and duplication	11	16,18
Others ^{and}	4	5,88
Other. [.] Judicial; Support network; and Clinical Research. ^b Prenatal care: During the gestational period.		
^c Postnatal: After birth. ^d Other exams: CGH array and SNP; karyotype and CMA; karyotype and NGS; karyotype, FISH and MLPA; karyotype, CGH array, NGS; and exome. ^{and} other genetic alterations: Xq duplication; loss at Xq25; and LOH (<i>loss of heterozygosity</i>).		

Variable	N	%
Genetic counseling		
Associated genetic syndrome		
No	61	89,71
Yes	7	10,29
Recurrence of the syndrome in the family		
No	61	89,71
Yes	6	8,82
Ignored	1	1,47
Consanguinity		
No	67	98,53
Ignored	1	1,47
Balanced translocation present in parents		
Yes	6	8,82
No	36	52,94
Ignored	26	38,24
Other: Judicial; Support network; and Clinical Research. ^b Prenatal care: During the gestational period.		
^c Postnatal: After birth. ^d Other exams: CGH array and SNP; karyotype and CMA; karyotype and NGS; karyotype, FISH and MLPA; karyotype, CGH array, NGS; and exome. ^{and} other genetic alterations: Xq duplication; loss at Xq25; and LOH (<i>loss of heterozygosity</i>).		

The tests frequently used in the diagnosis were karyotype and CGH array (35.29%) and isolated karyotype (27.94%). The main genetic alteration detected was chromosomal deletion (77.94%). In 16.18% of the cases investigated, deletions were associated with duplications. The mean size of the deletions was 7.99 Mb (SD $\pm$ 6.13 Mb; range, 0.624–25.7 Mb), and the mean size of the duplications was 7.7 Mb (SD $\pm$ 10.84 Mb; range, 0.190–40.11 Mb). Most participants (89.71%) did not have genetic syndromes associated with WHS. In 8.82% of the cases, the parents confirmed the family history of the syndrome and the presence of a balanced translocation in one of the parents. However, approximately 38.24% of parents did not undergo genetic evaluation, and only 50% of families had access to genetic counseling (Table 3).

The median time to diagnosis was 334 days (range, 5–15,330 days). Among the individuals with timely genetic diagnosis (< 334 days), there was a predominance of males (52.78%) and white individuals (66.67%). Most parents or guardians had higher education (58.33%), a monthly family income of more than R\$ 1,765.00 (equivalent to US\$ 319.16) (52.78%), and extensive health insurance coverage (86.11%). Most mothers were over 32 years of age (58.33%), and fathers were > 33 years of age (51.43%) at the time of their child's birth. Notably, prenatal consultations were initiated in the 1st trimester of pregnancy for all patients, with 91.67% exceeding six consultations during pregnancy (Table 4).

Table 4

Distribution of participants according to time to genetic diagnosis of Wolf–Hirschhorn syndrome and sociodemographic, gestational, and clinical variables. Brazil, 2025 (n = 65).

Variable	Time to diagnosis (days) ^{to}		p	HR** (IC 95%)
	≤ 334	> 334		
	n (%)	n (%)		
Sex				
Female	17 (47,22)	18 (62,07)	0,643	0,89 (0,53 – 1,48)
Male	19 (52,78)	11 (37,93)		Ref.
Race/Color				
White	24 (66,67)	22 (75,86)	0,738	1,09 (0,63 – 1,87)
Black or brown	12 (33,33)	7 (24,14)		Ref.
Responsible for higher education				
Yes	21 (58,33)	15 (51,72)	0,953	1,01 (0,61 – 1,68)
No	15 (41,67)	14 (48,28)		Ref.
Family income (R\$) ^a				
≤ 1765.00*	17 (47,22)	17 (58,62)	0,455	Ref.
> 1765,00	19 (52,78)	12 (41,38)		1,20 (0,73 – 1,98)
Water supply at home				
Public network	31 (86,11)	24 (82,76)	0,990	1,00 (0,50 – 1,98)
Well or spring	5 (13,89)	5 (17,24)		Ref.
Household sewer network				
Yes	30 (83,33)	22 (75,86)	0,919	1,03 (0,55 – 1,90)
No	6 (16,67)	7 (24,14)		Ref.
Garbage collection by public service				
Yes	34 (94,44)	24 (82,76)	0,650	1,19 (0,54 – 2,63)
No	2 (5,56)	5 (17,24)		Ref.
Possession of health insurance				
Yes	31 (86,11)	22 (75,86)	0,891	1,04 (0,55 – 1,97)
No	5 (13,89)	7 (24,14)		Ref.
Maternal age at birth (years) ^{to}				
≤ 32	15 (41,67)	19 (65,62)	0,061	Ref.
> 32	21 (58,33)	10 (34,48)		1,59 (0,96 – 2,66)

^a Values defined according to the median calculation. ^b Multiple analysis: Cox proportional hazards regression model, $p < 0.05$. ^c Methods used in the diagnosis: Molecular–next-generation sequencing (NGS), multiplex ligation-dependent probe amplification (MLPA), comparative genomic hybridization (CGH)-array, single-nucleotide polymorphism (SNP-array), whole-genome sequencing (WES) and whole-genome sequencing (WGS); and cytogenetic–karyotyping (G and GTG Bandamento), fluorescence in situ hybridization (FISH) and chromosomal microarray analysis (CMA). ^c Craniofacial phenotype: According to the minimum criterion > three characteristics (microcephaly, hypertelorism, epicanthus, prominent glabella, enlarged dorsum of the nose, short philtrum, downwardly inclined lip commissures, micrognathia, ear deformity and/or low implantation). * The median family income of R\$ 1,765.00 corresponds to US\$ 319.00. The conversion value uses the average exchange rate (Ptax sale) from R\$5.53 to US\$1.00, referring to the period from March 2024 to January 2025. ** HR: hazard ratio; 95% CI: 95% confidence interval.

Variable	Time to diagnosis (days) ^{to}			
	≤ 334	> 334	p	HR** (IC 95%)
Paternal age at birth (years) ^{to}				
≤ 33	17 (48,57)	15 (55,56)	0,433	Ref.
> 33	18 (51,43)	12 (44,44)		1,21 (0,73 – 2,02)
Children prior to the syndrome case				
Yes	22 (61,11)	14 (50,00)	0,554	1,15 (0,70 – 1,92)
No	14 (38,89)	14 (50,00)		Ref.
Start of prenatal care in the 1st trimester				
Yes	36 (100,00)	25 (89,29)	0,176	2,14 (0,66 – 6,90)
No	0 (0,00)	3 (10,71)		Ref.
Number of prenatal consultations performed				
≤ 6	3 (8,33)	4 (14,29)	0,340	Ref.
> 6	33 (91,67)	24 (85,71)		1,45 (0,65 – 3,23)
Gestational age at birth				
Preterm	9 (25,00)	8 (27,59)	0,353	Ref.
Forward	27 (75,00)	21 (72,41)		1,29 (0,74 – 2,27)
Intrauterine growth retardation				
Yes	33 (91,67)	19 (70,37)	0,008b	2,41 (1,21 – 4,83)
No	3 (8,33)	8 (29,63)		Ref.
Decreased fetal movement				
Yes	11 (30,56)	11 (40,74)	0,348	0,78 (0,46 – 1,32)
No	25 (69,44)	16 (59,26)		Ref.
Amniotic fluid change				
Yes	10 (27,78)	6 (22,22)	0,798	1,07 (0,60 – 1,92)
No	26 (72,22)	21 (77,78)		Ref.
Hospitalization after birth				
Yes	32 (88,89)	18 (62,07)	0,047b	1,78 (0,98 – 3,24)
No	4 (11,11)	11 (37,93)		Ref.
Genetic counseling consultation				
Yes	19 (55,88)	13 (50,00)	0,715	1,10 (0,65 – 1,84)
No	15 (44,12)	13 (50,00)		Ref.

^a Values defined according to the median calculation. ^b Multiple analysis: Cox proportional hazards regression model, $p < 0.05$. ^c Methods used in the diagnosis: Molecular–next-generation sequencing (NGS), multiplex ligation-dependent probe amplification (MLPA), comparative genomic hybridization (CGH)-array, single-nucleotide polymorphism (SNP-array), whole-genome sequencing (WES) and whole-genome sequencing (WGS); and cytogenetic–karyotyping (G and GTG Bandeamento), fluorescence in situ hybridization (FISH) and chromosomal microarray analysis (CMA). ^c Craniofacial phenotype: According to the minimum criterion > three characteristics (microcephaly, hypertelorism, epicanthus, prominent glabella, enlarged dorsum of the nose, short philtrum, downwardly inclined lip commissures, micrognathia, ear deformity and/or low implantation). * The median family income of R\$ 1,765.00 corresponds to US\$ 319.00. The conversion value uses the average exchange rate (Ptax sale) from R\$5.53 to US\$1.00, referring to the period from March 2024 to January 2025. ** HR: hazard ratio; 95% CI: 95% confidence interval.

Variable	Time to diagnosis (days) ^{to}			
	≤ 334	> 334	p	HR** (IC 95%)
Assistance network of access to diagnosis exclusively public				
No	28 (77,78)	18 (62,07)	0,263	1,34 (0,78 – 2,32)
Yes	8 (22,22)	11 (37,93)		Ref.
Molecular diagnostic method				
No	21 (58,33)	23 (73,31)	0,004b	Ref.
Yes	15 (41,67)	6 (20,69)		2,11 (1,23 – 3,62)
Identification of genetic deletion				
Yes	30 (83,33)	24 (82,76)	0,612	0,85 (0,44 – 1,63)
No	6 (16,67)	5 (17,24)		Ref.
Craniofacial phenotype				
Yes	32 (91,43)	19 (73,08)	0,828	Ref.
No	3 (8,00)	7 (26,92)		1,08 (0,53 – 2,17)
Epilepsy				
Yes	29 (80,56)	24 (82,76)	0,748	1,11 (0,57 – 2,14)
No	7 (19,44)	5 (17,24)		Ref.
^a Values defined according to the median calculation. ^b Multiple analysis: Cox proportional hazards regression model, p < 0.05. ^c Methods used in the diagnosis: Molecular–next-generation sequencing (NGS), multiplex ligation-dependent probe amplification (MLPA), comparative genomic hybridization (CGH)-array, single-nucleotide polymorphism (SNP-array), whole-genome sequencing (WES) and whole-genome sequencing (WGS); and cytogenetic–karyotyping (G and GTG Bandamento), fluorecence in situ hybridization (FISH) and chromosomal microarray analysis (CMA). ^c Craniofacial phenotype: According to the minimum criterion > three characteristics (microcephaly, hypertelorism, epicanthus, prominent glabella, enlarged dorsum of the nose, short philtrum, downwardly inclined lip commissures, micrognathia, ear deformity and/or low implantation). * The median family income of R\$ 1,765.00 corresponds to US\$ 319.00. The conversion value uses the average exchange rate (Ptax sale) from R\$5.53 to US\$1.00, referring to the period from March 2024 to January 2025. ** HR: hazard ratio; 95% CI: 95% confidence interval.				

In addition, the results revealed that among those diagnosed in a timely manner, 91.67% presented with gestational alterations of intrauterine growth restriction (IUGR) (91.67%), resulting in hospitalization after birth (88.89%). Survival analysis via the log-rank test revealed significant differences in the following variables: intrauterine growth restriction (p = 0.008), hospitalization after birth (p = 0.047), and the use of a molecular diagnostic method (p = 0.004). The Kaplan–Meier curves illustrating the overall survival of the cohort and survival according to the categories of variables with p < 0.20 in the univariate analysis are shown in Fig. 3.

Considering the factors associated with timely diagnosis identified in Cox's multiple proportional hazards model, the time to genetic diagnosis was significantly shorter among individuals with IUGR (HR = 2.18; CI = 1.06–4.50), whose mothers were over 32 years of age at the time of delivery (HR = 1.81; CI = 1.01–3.25), and among those who underwent molecular genetic testing in the diagnostic investigation (HR = 2.51; CI = 1.39–4.55), as shown in Table 5.

Table 5

Factors associated with the time to define the genetic diagnosis of Wolf–Hirschhorn syndrome on the basis of a Cox proportional hazards regression model. Brazil, 2025 (n = 65).

Variable	p	HR brainstorn (IC 95%)
Molecular testing in diagnostic investigation	0,002	2,51 (1,39 – 4,55)
Intrauterine growth retardation	0,034	2,18 (1,06 – 4,50)
Maternal age at birth > 32 years ^{to}	0,048	1,81 (1,01–3,25)
^a Defined according to the median.		
* Cytogenetic and/or molecular tests not forwarded to the researchers. ** Definitive exclusion due to incorrect completion of registration documentation (n = 2), etiological diagnosis compatible with another genetic condition (n = 1), withdrawal by parents (n = 2) and absence of response to scheduling the interview (n = 1).		

4. Discussion

This study provides unprecedented data on the sociodemographic, gestational, diagnostic, and clinical aspects of a population with this rare genetic syndrome, as well as relevant evidence on the factors that impact access to genetic diagnoses. The results reinforce the current knowledge of Wolf–Hirschhorn syndrome, contributing significantly to the expansion of the literature in Brazil.

The analysis of the geographic distribution of the individuals investigated reaffirmed the existence of regional inequalities in access to genetic diagnosis in the country. There is a concentration of cases in Southeast and South regions, where there is a greater presence of specialized services and resources for highly complex exams. This pattern is in line with the findings of previous studies on rare diseases (RDs) in Brazil and internationally, which point to geographic location and degree of urbanization as important determinants for access to diagnosis [26–32]. Furthermore, this regional distribution is compatible with international data, as demonstrated in a Spanish study that revealed a concentration of cases in regions with greater access to medical genetics centers [28].

The median duration of 334 days and the average duration of 896.07 days (equivalent to 2.46 years) until genetic diagnosis, ranging from 5–15,330 days, evidenced the long journey of seeking a diagnosis faced by many Brazilian families. Data from other countries on the time of diagnosis of this condition are scarce. However, a study in Spain established a median of approximately 4 years and a mean time of 6.67 years for diagnosis, surpassing the value identified in Brazil [28]. In this context, although the interval for the syndrome is lower than the mean of 5.4 years reported for RDs in Brazil and 4.7 years reported in the European population, diagnosis still represents a significant challenge (33–35). This delay can be attributed to the low availability of genetic tests in the SUS and the lack of trained professionals for suspicion and appropriate referral, as evidenced by studies on the Brazilian health network [29]. The main determinants of a delayed diagnosis of RD, according to data from the EURORDIS rare barometer, include the onset of symptoms in childhood (OR = 3.11) or adolescence (OR = 4.79) and the genetic etiology of the disease (OR = 1.33), which corresponds to 80% of RD cases (35).

The predominance of diagnoses in the postnatal period (95.59%) emphasizes that the phenotypic alterations observed at birth and in the first year of life are the main indicators for diagnostic investigation [4]. International findings corroborate these data, highlighting facial dysmorphisms and developmental delay as key signs for the suspicion of WHS [2,4,5,36].

In the Brazilian group, phenotypic manifestations of high occurrence of the syndrome were also identified, the most frequent being typical craniofacial dysmorphisms (83.61%), intrauterine growth restriction (IUGR) (82.54%), and epilepsy (81.54%). The classic phenotype of this genetic condition includes the "Greek warrior helmet" appearance (wide nasal bridge and prominent glabella), delayed cognitive development, pre- and postnatal growth delay, and seizures [1,2,37].

The international literature corroborates these clinical findings, with emphasis on the high frequency of the craniofacial phenotype, the presence of epilepsy, and IUGR in more than 80% of cases [2,4,7]. The characteristic facial phenotype has been consistently reported in genotype–phenotype correlation studies conducted in Italy, Europe, and the USA and in case series with adults (USA), which revealed its presence in 80.95–100% of individuals [1,2,4,16]. Epilepsy is another high-frequency manifestation, occurring in 71.42–100% of cases, and the presence of IUGR has been reported in 75–100% of published studies and literature reviews [1,2,4,6,16]. The findings of this study are consistent with global observational data, reinforcing the role of these manifestations as crucial clinical markers for early diagnosis.

Multivariate Cox regression analysis, one of the most robust findings of this study, revealed that the presence of IUGR, maternal age greater than 32 years at the time of delivery, and the performance of molecular genetic testing in the investigation were factors significantly

associated with timely diagnosis. IUGR, as a detectable indicator in prenatal care, can serve as a warning sign for in-depth investigation, as observed in previous studies.

Adequate gestational monitoring, evaluation of fetal development, and recognition of warning signs in the neonatal period can anticipate etiological investigation of the syndrome. However, prenatal diagnosis is challenging because craniofacial dysmorphism may not manifest or appear normal on fetal ultrasound examinations owing to subtle and nonspecific morphological alterations. In addition, the accuracy of prenatal ultrasound is influenced by the operator's technique, equipment, and maternal and fetal factors [36,38]. Among the gestational alterations reported in investigations on this syndrome, the most recurrent are decreased fetal movements [4], IUGR (75% to 97.7%), which is observed in fetuses over 20 weeks, a distinct craniofacial appearance (82.9 to 94.4%) [36,39] and microcephaly (72.2%) [4,36]. The identification of these findings can contribute to the suspicion of WHS and guide the performance of confirmatory genetic tests [36]. Cox regression revealed that mothers older than 32 years at delivery may have more rigorous prenatal care or greater access to information and resources, leading to more proactive diagnosis-seeking behavior. This finding should be explored in future studies, as it has not been reported as a direct predictor of time to diagnosis in other WHS cohorts.

The importance of molecular genetic testing (such as CGH array, the most widely used) for rapid diagnosis is crucial. These high-resolution methods are essential for identifying microdeletions that cannot be detected by conventional karyotyping, and their availability and use are imperative for reducing the time to diagnosis, although they have a greater financial impact [4,5].

The analysis of the genetic results of the investigated group revealed wide variability in the extent of deletions, ranging from 0.624 to 25.7 Mb, which is in line with previous reports describing deletion intervals between < 2 Mb and 30 Mb. This heterogeneity reflects the nature of the syndrome as a broad-spectrum condition whose phenotype is determined not only by the size of the deletion but also by the involvement of critical genes within the WHSCR region [1,4,5].

Among the alterations that can cause this condition, *de novo* deletions are the most common, present in 55–75% of cases, whereas unbalanced translocations appear in 40–45% of cases [1,4,5,15,40]. These rearrangements may occur spontaneously in 85–90% of cases or are inherited due to balanced parental translocation in 10–15% of cases [1,4]. In the present study, both cases of isolated deletion (77.94%) and deletions associated with duplication (16.18%) were identified. These data agree with those of international studies, which revealed a greater predominance of isolated deletions (70% of cases), followed by unbalanced translocations (22%), and inverted duplications associated with terminal deletions (6%) [1].

The correlation between the size of the deletion and the severity of the clinical phenotype, analyzed in a previous study, revealed three phenotypic categories defined as mild (≤ 3.5 Mb), moderate (5–18 Mb) and severe (> 22 –25 Mb), impacting the prognosis and clinical management of the syndrome [1]. The data obtained in our group of participants were distributed among these three categories, corroborating the hypothesis that individuals with more extensive deletions present more complex clinical conditions with multiple associated malformations. This finding reinforces the idea that the extent of deletion is an important determinant of clinical prognosis and multiprofessional management needs.

In this study, the most commonly used test was the karyotype associated with the CGH array (35.29%), followed by isolated karyotyping (27.94%). Despite the diagnostic utility of these methods, their scope is limited in the face of microdeletions, making it necessary to expand the use of molecular testing. The detection rate of karyotyping varies from 50 to 60% because of its limited resolution for identifying rearrangements of up to 5 Mb. Although the FISH method provides a sensitivity of 95%, it does not allow the extent of the critical region 4p16.3 to be determined. Recently, microarray chromosomal analysis (CMA) has been used as a noninvasive prenatal test and for screening for microdeletions and duplications. The CGH array and SNP array allow the tracking of specific regions or all genomic DNA; however, the CGH array does not detect balanced translocations or inversions; however, it allows the determination of the extent of the deletion [2,4,7,16,38].

The finding that most participants obtained the diagnosis through health plans (41.18%) shows that the private sector is still the main provider of highly complex genetic tests, owing to the fragility of the public network in meeting this demand. This scenario is corroborated by data from a study by the Brazilian Network of Rare Diseases (RARAS), which revealed that only 62.16% of reference services offered cytogenetic tests and that 54.05% offered molecular tests. In the North and Central-Western regions of Brazil, at least 40% of the evaluated institutions did not use these methods. Although molecular diagnostic tests are available in just over half of the participating centers, cytogenetic testing is the most accessible diagnostic method [29,32].

The low rate of genetic evaluation in parents (61.76%) and the number of families that received genetic counseling (50%) reveal important gaps in comprehensive care. Genetic counseling is essential for understanding the prognosis and for reproductive planning, since the risk to family members depends on the mechanism of origin of WHS deletion [1,4,41].

Finally, most parents or guardians had a high level of education and employment. However, even in this group, structural barriers to diagnosis persisted. This suggests that access to precision genetic diagnosis does not depend only on a favorable social structure but is intrinsically linked to the existence of a comprehensive, qualified, and equitable care network.

Recent evidence from Spanish families of children and adolescents with Wolf–Hirschhorn syndrome reinforces that the impact of this condition extends well beyond the clinical phenotype of the affected child and substantially influences family well-being, emotional health, and daily support requirements. This study revealed that the quality of life of families was driven mainly by emotional well-being, family interaction, and the availability of external support, whereas clinical and sociodemographic factors were not clearly associated with family outcomes [42]. These findings are highly relevant to the present Brazilian cohort because they suggest that reducing the time to genetic diagnosis may have implications that go beyond etiologic confirmation, as an earlier diagnosis can support counseling, anticipatory guidance, and timely referral to psychosocial and developmental resources. This perspective is particularly important because it may connect genetic diagnosis with family adaptation, service access, and the lived experience of disability across childhood and adolescence.

This study has limitations inherent to the investigation of rare diseases. Although the WHS Brazil Movement includes 230 registered individuals, only 68 (29.56%) participated in this study, which limits the generalizability of the findings. The data reflect the challenges of access to families and compliance with the inclusion criteria, since the exclusive clinical diagnosis, due to the lack of confirmatory genetic tests, restricted the number of participants in the study. Despite these limitations, the findings remain relevant in describing, in an unprecedented way in the Brazilian context, the factors associated with the time until diagnosis of the syndrome. In addition, it provides important support for the improvement of public policies aimed at timely access to family genetic diagnosis, management, and counseling.

5. Conclusion

The results of this study demonstrate that the diagnostic journey of WHS was markedly prolonged, with most individuals receiving a definitive diagnosis only in the postnatal period and a median interval of 334 days between birth and genetic confirmation. These findings reflect substantial regional and structural inequalities in access to genomic testing across Brazil. Survival analysis further revealed that intrauterine growth restriction, maternal age greater than 32 years at delivery, and the use of molecular genetic testing were independently associated with a shorter time to diagnosis. These determinants carry direct relevance to the field of developmental disabilities, representing concrete clinical and care opportunities for earlier diagnosis and enabling timely initiation of comprehensive developmental assessment, early intervention, and genetic counseling.

Abbreviations

CGH- Array	Comparative Genomic Hybridization
CRIPIT	Cysteine-Rich PDZ-Binding
CPLX1	Complexin
EURORDIS	Rare Diseases Europe
FISH	Fluorescence in situ hybridization
LETM1	Leucine zipper and EF-hand containing transmembrane
LMIC	Low and middle income countries
NGS	Next Generation Sequency
OMIM	Online Mendelian Inheritance
PIGG	Phosphatidylinositol glycan anchor biosynthesis class G
SUS	Sistema Único de Saúde (Unified Health System)

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Federal University of Rondonópolis - MT.

Conflict of interest:

The authors have no conflicts of interest to disclose.

Author Contributions

KCS, CA and JHCP contributed to the conception and discussion of the manuscript, data analysis, drafting of the first version. KCS, AAM and JGGL, contributed to data analysis and manuscript writing. KCS, GC, RSFJ, BPB and SGS conducted data collection and documentary analysis. KCS, BPB and SGS contributed to data collection and entry of the research database. All authors approved the final version of the manuscript.

Funding:

This work was supported by a grant from the National Council for Scientific and Technological Development and the Research Support Foundation of the State of Mato Grosso.

Author Contribution

KCS, CA and JHCP contributed to the conception and discussion of the manuscript, data analysis, drafting of the first version. KCS, AAM and JGGL, contributed to data analysis and manuscript writing. KCS, GC, RSFJ, BPB and SGS conducted data collection and documentary analysis. KCS, BPB and SGS contributed to data collection and entry of the research database. All authors approved the final version of the manuscript.

Acknowledgement

We are grateful for the collaboration of the families that are members of the Wolf–Hirschhorn Syndrome Movement Brazil.

Data Availability

The datasets generated and/or analyzed during the current study are included in the published article and its Supplementary Information. Additional data supporting the findings are available from the corresponding author upon reasonable request, subject to applicable ethical, privacy, and confidentiality restrictions.

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Figures

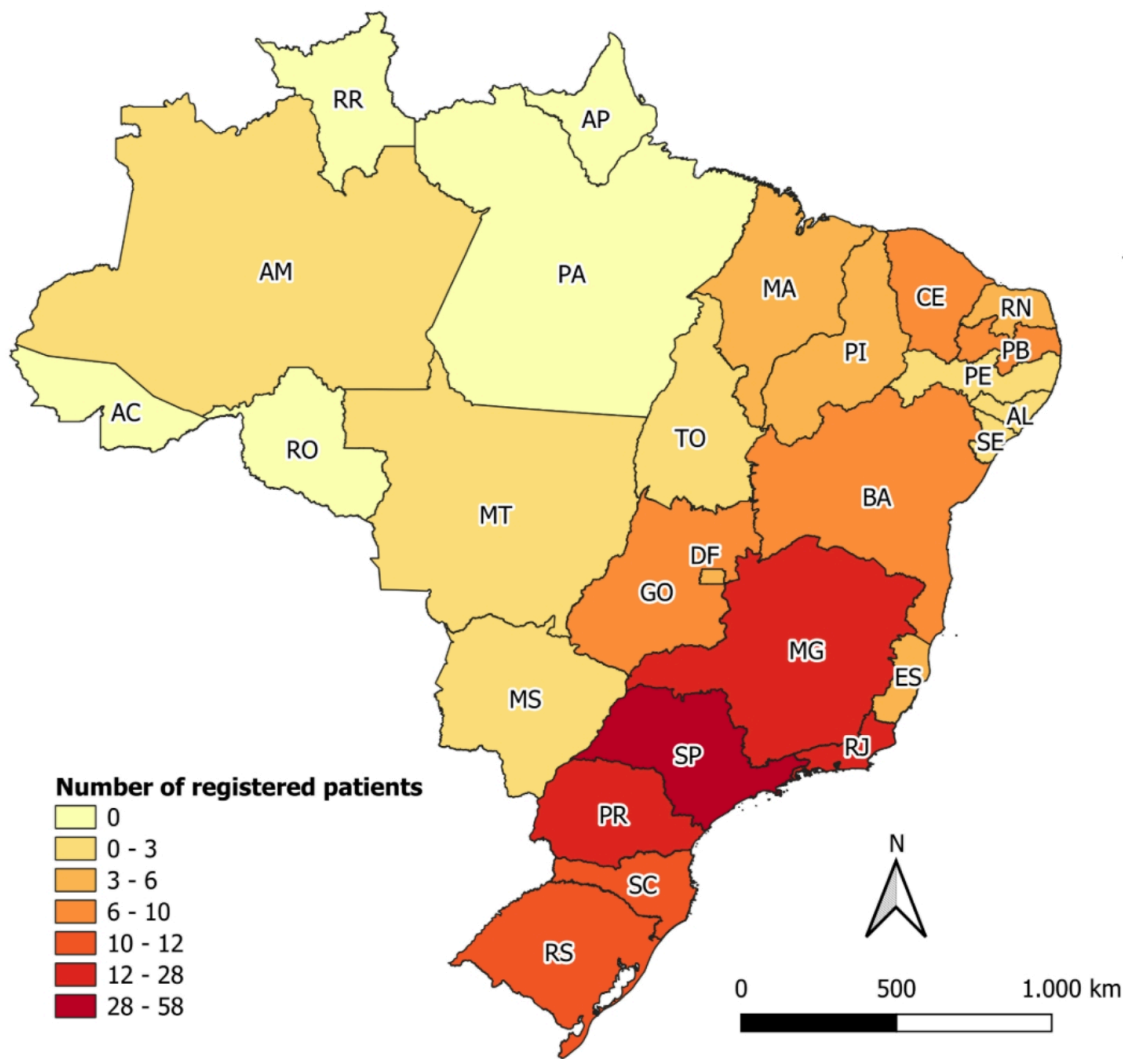


Figure 1
Distribution of individuals registered in the Wolf–Hirschhorn syndrome movement in Brazil according to the federative units of Brazil (2014-2025).

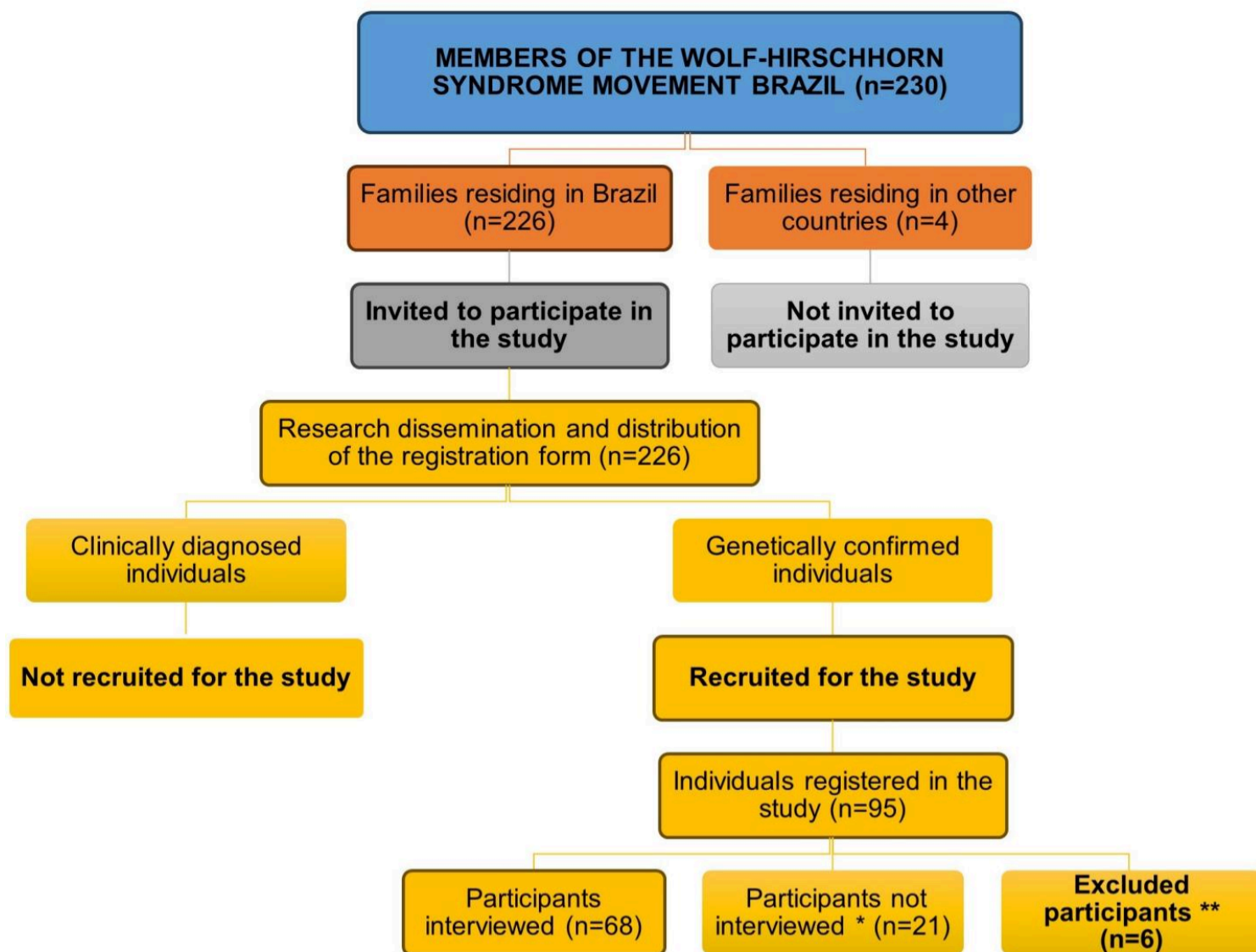


Figure 2

Flowchart of the process of recruiting participants for the study according to the diagnosis of Wolf-Hirschhorn syndrome.

* Cytogenetic and/or molecular tests not forwarded to the researchers. ** Definitive exclusion due to incorrect completion of registration documentation (n=2), etiological diagnosis compatible with another genetic condition (n=1), withdrawal by parents (n=2) and absence of response to scheduling the interview (n=1).

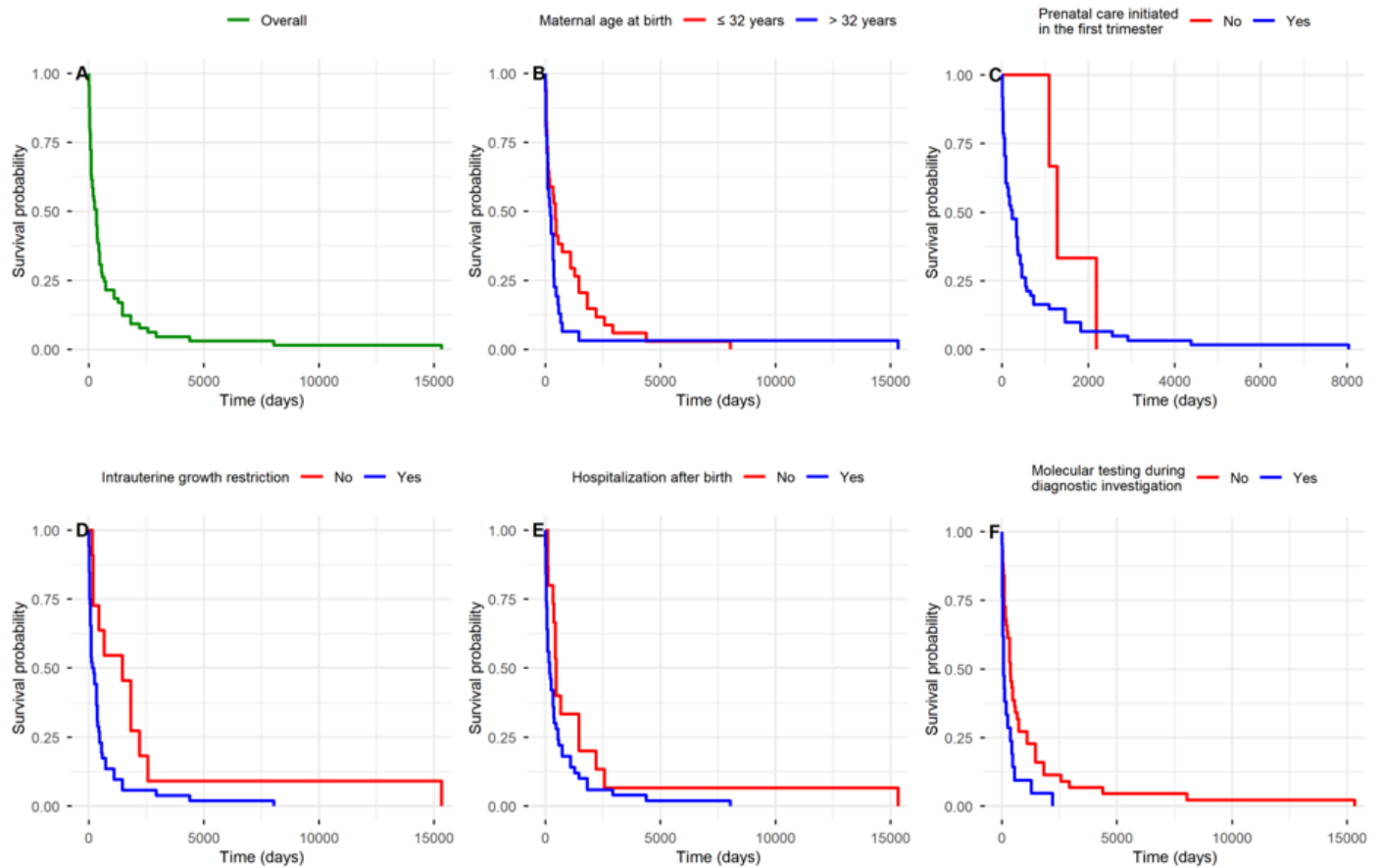


Figure 3

Kaplan-Meier survival curves of factors associated with time to genetic diagnosis of Wolf-Hirschhorn syndrome. Brazil, 2025 (n=65).

(A) Overall survival curve of the subjects under study. **(B)** Survival according to maternal age at birth. **(C)** Survival according to the start of prenatal care in the 1st trimester. **(D)** Survival according to intrauterine growth retardation ($p<0.05$). **(E)** Survival according to hospitalization after birth ($p<0.05$). **(F)** Survival according to molecular testing in the diagnostic investigation ($p<0.05$).