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Natural history study of adults with Wolf–Hirschhorn syndrome 2: Patient-reported outcomes study

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Abstract

Wolf–Hirschhorn syndrome (WHS) is a contiguous gene disorder consisting of prenatal and postnatal growth deficiency, distinctive craniofacial features, intellectual disability, and seizures. The condition is caused by a partial loss of material from the distal portion of the short arm of chromosome 4 (4p16.3). While there are many reports of individuals with WHS, useful data on long-term survival and life status of adults with the syndrome are very limited. There are only 11 reports of individuals over the age of 18 years in the literature. Establishing the medical manifestations of adults with WHS would be helpful in establishing appropriate health supervision guidelines. This study was one component of a two-part investigation on adults with WHS. This patient-reported outcomes study (PROS) was accomplished by using the registry of rare diseases at Sanford Research, Coordination of Rare Diseases (CoRDS) at Sanford. Thirty family members or caretakers of 30 adults with WHS/4p- entered into the CoRDS registry and completed some or all of the survey data. Twelve caretakers completed the recently-added survey on activities of daily living. Two of the individuals with WHS were partly independent while 10 required total care. The results provide novel information on daily life and independence in adults with WHS. Importantly, the majority of caretakers reported that the adults were in good health. The data from both parts of the study will contribute to our knowledge of the natural history of the syndrome and guide in establishing appropriate health supervision guidelines for adults with WHS.

KEYWORDS
4p minus, adults with Wolf–Hirschhorn syndrome, natural history, quality of life, seizures

1 | INTRODUCTION

The Wolf–Hirschhorn syndrome (WHS) is a contiguous gene disorder consisting of the four defining core manifestations of growth deficiency (both prenatal and postnatal), recognizable craniofacial features, varying degrees of intellectual disability, and seizures (Battaglia et al, 2015). The syndrome is caused by a partial loss of material from the distal portion of the short arm of chromosome 4, band 4p16.3 (Battaglia et al., 2015). There are many reports and case series of individuals with WHS documented since the original two papers in 1966 by Wolf and Hirschhorn (Battaglia et al., 2015; Hirschhorn, 2008). Information, however, on long-term survival and status of older persons is very limited with only 11 well-characterized adults recorded in the medical scientific literature (Battaglia et al., 2018, 2021; Opitz, 1995). Knowledge of natural history and manifestations in adulthood of the syndrome would inform clinicians in the establishment of appropriate health supervision guidelines throughout life, not just for childhood.

Documentation of clinical and phenotypic data derived from patient registries has become an important method in the investigation of the natural history of rare syndromes (Glassford et al., 2016). In recent years, patient-reported outcome studies have been

recognized as a valuable source of data (Deshpande et al., 2011). The purpose of this study is to delineate the natural history of adults with WHS using patient-reported data from an international rare disease registry.

2 | METHODS

This overall investigation comprises two methodologies divided into two parts: A case series of 28 individuals, which is reported in a separate paper (Battaglia et al., 2021), and this patient-reported outcomes study (PROS). Thirty caretakers and parents of individuals over 18 years of age voluntarily answered a survey instrument consisting of demographic, cytogenetic, and medical issues. These data were entered into the online Coordination of Rare Diseases at Sanford (CoRDS) database (https://research.sanfordhealth.org/rare-disease-registry). CoRDS is based at Sanford Research in Sioux Falls, South Dakota, and is a nonprofit research institution that hosts a centralized international patient registry for rare diseases. CoRDS works with patient advocacy groups, individuals, and researchers to capture medical information of a rare diagnosis. Currently, CoRDS has 77 "partners" and over 50 have developed registries. The CoRDS 4p minus Support Group Registry was created in 2014 and is one of the longest standing registries within the system. Currently, 103 caretakers of persons of all ages with 4p- have registered with CoRDS and entered data into the online survey.

The survey was developed by the authors using a framework created by CoRDS for the registries. The questions for the survey were adapted from the comprehensive questionnaire on the medical issues of the syndrome used by two of the authors in prior work (AB, JCC) (Battaglia et al., 2015). Three parents recruited by one of the authors (AL) completed the survey providing input about the clarity of questions and the time for completion; their input led to some revisions. A number of scientific publications have been published on survey data developed by CoRDS in collaboration with their partner groups, and an example was recently published in this journal (Giangiobbe et al., 2020).

Thirty parents or caretakers of 30 individuals with 4p- over 18 years of age entered online, gave consent, and answered the questions. (The survey instrument is available in the Supplemental Files online.) The submitted information is curated by the team at CoRDS. The University of Utah team sought and received Institutional Review Board (IRB) approval from both the University of Utah Health IRB and the IRB at Sanford Research. The patient data were anonymized by the CoRDS staff (AM) and sent to one of the authors (JCC) digitally. The data were analyzed and tabulated by the authors and represent the results of this study, which focuses on the adult-onset medical problems and activities of daily living in individuals with WHS.

3 | RESULTS

Caretakers of 30 adults over the age of 18 years completed some or all of the survey by September 30, 2019. Families of individuals with WHS/4p- were recruited by the 4p- Family Support Group to enroll into the CoRDS registry in July of 2014; enrollment gradually increased from 2014 to 2019, and in the summer of 2019 the families were informed by a coauthor (AL) that additional survey questions had been added regarding older individuals with the condition (complete survey in Supplemental Information online). Denominators mentioned below varied according to the number that responded to the survey question. Twelve caretakers of adults enrolled on the website in September of 2019 and represent the bulk of the data presented below. Table 1 displays the number of parents/caretakers who completed the sections of the survey.

Four of the 30 adults had their 4p deletion due to an unbalanced translocation, the remainder having a presumed simple deletion of 4p. All of the participants had deletions involving the critical region of 4p16.3, most detected by a banded chromosome study due to their age of diagnosis being prior to the availability of cytogenomic microarray. Twenty-six of the 30 were from the United States and four individuals were from Europe, Canada, and Australia. Two of the 30 individuals were deceased. Twenty-one of 28 individuals were female (two of the 30 registered did not answer this question), confirming the female predominance of WHS documented previously in the literature (Battaglia et al., 2015). The average age of the 30 individuals with WHS was 30 years (rounded to the nearest year, range 22–64 years), similar to the average of the 12 individuals (29 years) whose parents or caretakers enrolled in September 2019.

Notable results regarding medical issues are documented in the bar graphs (see Figure 1). Five of the 12 caretakers indicated that their family member was having seizures. Ten of the 12 had delayed eruption of adult teeth with retention of deciduous teeth. Two of the 12 were being followed for scoliosis, one of the 12 had osteoporosis, one had a previous history of leukemia, and one of the 12 had diabetes of unknown type. Further medical details on these medical

TABLE 1 Summary of major sections of the CoRDS registry survey instrument and Number of caretakers completing the section

Major sections[a]	# of parents/caretakers completing section
Instructions	30
Permissions and data sharing[b]	30
Demographic information[b]	30
Diagnosis	30
Primary diagnosis	
Rare disease symptoms	
Anomalies	
Genetic diagnosis	30
Gestation/Birth	30
Medical history	30
Seizures/Epilepsy	30
Daily living	12

[a]The entire survey is available in Supplemental Information online.
[b]Not available to the authors.

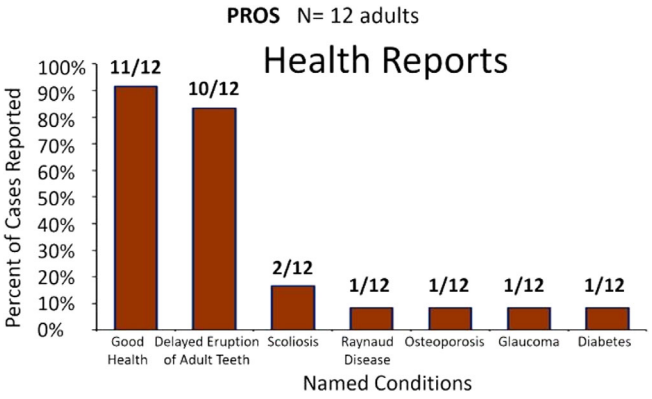

FIGURE 1 The bar graph displays the frequency distribution of the health status of the 12 adults in the PROS part of the overall study. No further information is available on the medical details of the osteoporosis, glaucoma, and diabetes. The person with osteoporosis could have been in the 6 of 12 requiring a wheelchair for locomotion (see Results) [Color figure can be viewed at wileyonlinelibrary.com]

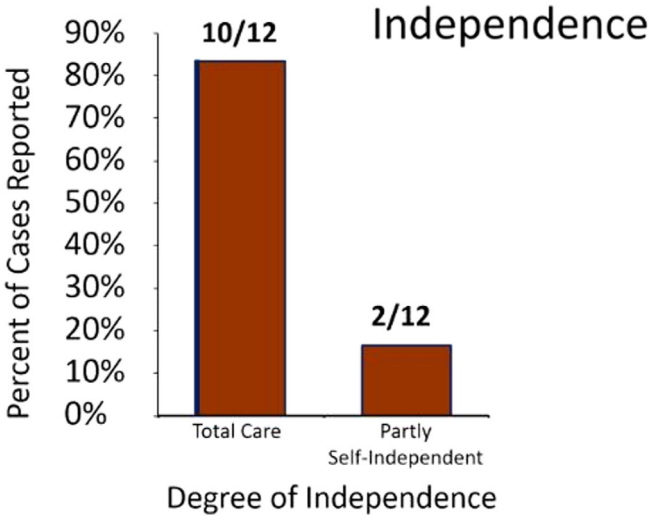

FIGURE 2 The bar graph displays the frequency distribution of the Independence status of the 12 adults. Ten of the 12 individuals required total care, that is, needing assistance in feeding, diapering, bathing, and dressing; 4 of 10 were able to walk independently, and six required a wheelchair. Two of 12 were partially independent and able to feed and dress themselves to some degree, but needed supervision and assistance with personal hygiene and had variable bowel and bladder control [Color figure can be viewed at wileyonlinelibrary.com]

problems are not available in the survey but are worthy of further investigation. Notably, 11 of the 12 reported the individual to be in good health. None in this sample had hepatic adenomas as reported in the accompanying paper, the other part of this study (Battaglia et al., 2021). Two indicated that their family member had moderate and 10 indicated severe/profound developmental disability.

Regarding activities of daily living, 10 of the 12 individuals with WHS required total care, meaning that they needed assistance in feeding, diapering, bathing, and dressing; four of these 10 were able to walk independently, and the other six required a wheelchair for locomotion (see Figure 2). Two of the 12 indicated that they were partially independent and able to feed and dress themselves to some degree, but needing supervision and assistance with personal hygiene. Those two were able to walk unassisted and had variable bowel and bladder control. These figures varied somewhat from the 28 individuals in the case series reported in the accompanying paper (Battaglia et al., 2021) where nine of 28 individuals were partly independent and one was fully independent.

Five of the 12 individuals with WHS lived in their parents' home, five lived in a group home, and the remaining two resided in a care facility.

4 | DISCUSSION

The survey study herein provides information on health issues, activities of daily life, and degree of independence of adults with WHS. Prior knowledge of this came entirely from single case reports, which were often very limited in how much was provided about the living situation and independence of the adult.

Of note, most of the caretakers in the study reported that the adult was generally in good health. This is important since younger children with WHS, especially those having significant seizures and developmental disability, are recognized as having major challenges in health and living with the serious impact of chronic disease. Thus, as underscored by Battaglia and coauthors (2020), this observation varies from the general perception of poor prognosis for health and outcome portrayed for patients with WHS/4p- in early years of life.

The sample of adults in the PROS may have a selection bias that affects the outcomes. Most of the individuals in this study were born in the 1990s or earlier. The different seizure management capabilities two decades ago or earlier may have resulted in now-adult patients suffering neurological insult as a result of poor seizure control, which may have in turn resulted in sampling bias with more severely developmentally disabled patients. These individuals, however, may have had milder seizure courses leading to better survival to adulthood, i.e., a survival bias. Additionally, the detection of the deletion was by a G-banded karyotype and/or FISH, selecting against patients with the smallest of microdeletions being included in this sample.

The occurrence of seizures in children with WHS/4p- is a widely discussed topic (Battaglia et al., 2009; Battaglia & Carey, 2005). Worthington et al. (2008) investigated the course of seizures in a cross-sectional study of older persons with WHS. These authors suggested that seizures in the syndrome decreased in complexity and frequency over time. Five of the 12 individuals in our PROS investigation were experiencing seizures into the adult years. In this survey, we were unable to distinguish whether the seizures had stopped in childhood and resumed in adulthood or were continuously a problem. From the experience of the authors, the latter seems more likely; this question deserves study and we intend to add text questions to the CoRDS registry to distinguish this and obtain more information on

the nature and complexity of the seizures in the adults. This theme is also discussed in the accompanying paper (Battaglia et al., 2021).

One of the challenges of caring for adults with syndromes and rare diseases like WHS is the transition of care from the pediatric to adult providers. This issue is of high importance to older individuals with WHS who have a medically complex condition involving management of multiple systems. The American Academy of Pediatrics has provided guidelines for this important milestone (White et al., 2018). Because of their unique training experience, the physicians who have completed the combined accredited medicine-pediatrics residencies in the United States represent an appropriate potential specialist to assume this complex care in the primary care setting.

Investigations of patient (or parent) reported outcomes represent an important methodology for the study of the natural history of rare conditions (Deshpande et al., 2011). Historically, Unique-the Rare Chromosome Disorder Support Group (http://www.rarechromo.org/html/home.asp) based in the United Kingdom, has provided parent-reported data on persons with chromosome disorders for over three decades; this invaluable resource has the potential for the study of the natural history of many rare syndromes. Glassford et al. (2016) capitalized on this opportunity and analyzed the extant data on individuals with the 3q29 deletion syndrome, providing a prototypic work on this model. Recently, Murali et al. (2020) demonstrated the value of patient-reported outcome measures in physical functioning in children with various forms of osteogenesis imperfecta.

4.1 | Strengths and limitations

The main strength of the PROS part of the WHS adult investigation is that the participants consist of caretakers in the 4p- Family Support group who chose to enter their family member into the CoRDS Registry without any selection by the authors. While the number with complete information about adult issues (12) is relatively small, the figure still exceeds the number of individual case reports of adults in the medical literature and will likely increase over time. Despite these numbers, we think that this information is generalizable to adults with WHS because it fits our joint experience (AB, JCC) with participation at support group conferences for WHS in several countries in the world.

The main limitations of our study are mentioned above: the potential selection bias toward those individuals who survived complex medical issues of more than two decades ago (survival bias) and the exclusion of patients with 4p- who have microdeletions that would not have been detected until the last 15 years.

Based on the data from this part of the WHS adult investigation, we would add the following recommendations to the previously published guidelines on routine care: annual ophthalmology examination; annual HbA1C; referral to neurology if any signs of seizures; DEXA scan if any occurrence of fractures. Based on the other part of the study (Battaglia et al., 2021) and the existing literature (Battaglia et al., 2018), we would recommend annual abdominal sonograms of the liver looking for hepatic adenomas and referral to a gastroenterologist and/or oncologist if detected. The age at which this screening would stop is not known and deserves further investigation.

In conclusion, we have documented the overall health issues, independence, and life situation of a series of adults with WHS whose caretakers have anonymously participated in a voluntary registry database. Coupled with the more detailed clinical observations in the accompanying case series part of the study, the PROS adds to our sparse knowledge of the natural history and the outcome of adults with WHS and informs on daily care issues of adults. This information provides the framework for development of health supervision guidelines for older individuals with WHS and related rare conditions.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The survey data are available on request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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