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Natural history study of adults with Wolf–Hirschhorn syndrome 1: Case series of personally observed 35 individuals

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Abstract

Wolf–Hirschhorn syndrome (WHS) is a contiguous gene disorder, clinically delineated by prenatal and postnatal growth deficiency, distinctive craniofacial features, intellectual disability, and seizures. The disorder is caused by partial loss of material from the distal portion of the short arm of chromosome 4 (4p16.3). Although more than 300 persons with WHS have been reported in the literature, there is sparse, if any, long-term follow-up of these individuals and thus little knowledge about course and potential further complications and health risks during adulthood and advanced age. This study attempted to assess medical conditions and function of adult individuals with WHS. It was one component of a two-part investigation on adults with WHS. The other part of the study is the patient-reported outcomes study reported elsewhere. About 35 individuals with WHS (26 females; nine males), aged between 19 and 55 years were recruited. About 25 individuals were personally observed at the IRCCS Stella Maris Foundation by A.B. and followed up between 5 and 20 years; and 10 were recruited from the 4p-Support Group, The United States. Of note, 23/35 (66%) are close to total care. About 11 out of 35 (31%) were partly self-independent, requiring supervision on certain daily routines, and 1 out of 35 (3%) was fully independent. However, a positive perspective is given by the overall good health enjoyed by the 66% of our cohort of individuals. Overall, quality of life and level of function into adulthood appear to be less critical than anticipated from previous studies.

KEYWORDS
4p-syndrome, adults with Wolf–Hirschhorn syndrome, deletion 4p, monosomy 4p, natural history, quality of life

1 | INTRODUCTION

Wolf–Hirschhorn syndrome (WHS) is a contiguous gene disorder, clinically delineated by prenatal and postnatal growth deficiency, distinctive craniofacial features, intellectual disability, and seizures. It is generally estimated that approximately 1 in 50,000 to 1 in 20,000 individuals is diagnosed with WHS, with a female predilection of 2:1. The disorder is caused by partial loss of material from the distal portion of the short arm of chromosome 4 (4p16.3) (Battaglia et al., 2015). No single gene deletions or intragenic mutations have been shown to confer the full WHS phenotype. Since the condition was brought to the attention of geneticists, many additional individuals have been published, but only in 1999, were the first data on the natural history brought to the attention of the medical community (Battaglia et al., 1999).

Nevertheless, information on long-term survival in WHS is very limited. Only 11 adults with WHS are described in the medical

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literature, with age range between 19 and 37 years (Battaglia et al., 2018; Coppola et al., 2013; Lopes et al., 2005; Ogle et al., 1996; Opitz, 1995; Prunotto et al., 2013; Smith et al., 1995). The purpose of the present study is to help delineate in more detail and over a lifetime the natural history of WHS, in order to establish more appropriate health supervision and anticipatory guidance for all individuals with this condition.

2 | MATERIALS AND METHODS

This overall investigation comprises two methodologies divided into two parts: a patient-reported outcomes study (PROS), which is reported in a separate article (Carey et al., 2021), and a case series of 35 individuals. We recruited 35 individuals with WHS (26 females; 9 males), aged between 19 and 55 years. About 25 were personally observed at the IRCCS Stella Maris Foundation by A.B. and systematically followed up between 5 and 20 years; and 10 were recruited from the 4p-Support Group, The United States. The demographic, cytogenetic, and medical issues related to these 10 individuals were retrieved from a comprehensive questionnaire voluntarily filled out by their caretakers and/or parents. The questionnaire on the medical issues of the syndrome was developed by two of the authors (A.B. and J.C.C.) and had been used in prior work. The caretakers and/or parents were asked to attach medical records/reports whenever possible, to substantiate the included information (Figure S1) (Battaglia et al., 2015). Informed consent to participate in the study was obtained by the legal guardians/parents of all individuals.

3 | RESULTS

All of the participants had deletions involving the critical region of 4p16.3, most detected by a banded chromosome study or subtelomeric FISH due to their age of diagnosis being prior to the availability of cytogenomic microarray (Table 1).

All propositi analyzed here were described by their caregivers as being happy, friendly, affectionate, outgoing adults who enjoy being around family and friends, mostly communicating by gestures. Only three adults were using the augmentative and alternative communication. About 25%, when seen by us, showed some degree of anxiety with tendency to be frightened in new or, for them, incomprehensible situations. Less than 15% were said to show some aggressive behaviors in response to frustrations. About 23 out of 35 (66%) were close to total care with needs to be assisted in feeding, diapering/toileting, bathing, dressing/undressing, and, when walking, needing assistance on uneven ground or transitioning from carpet to tile. Of note, 4 of them required a wheelchair for locomotion. About 11 out of 35 (31%) were partly self-independent, being able to feed and dress themselves, but needing supervision and some assistance with personal hygiene, and, at times, with walking on uneven ground. About 1 out of 35 (3%) is fully independent and is volunteering at S. Vincent de Paul Food Bank (Figure 1). All had a global executive slowness and variable degrees of developmental disabilities, with a moderate to severe/profound cognitive deficit. The level of the adaptive development reached was at approximately 24 months of age. About 23 out of 35 (66%) enjoyed good health. The health and medical difficulties included the following: 2/35 (6%) had type 2 diabetes, diagnosed at age 13 and 33, associated with hypercholesterolemia, in the absence of obesity and familial risk factors; 1/35 (3%) has Raynaud's disease, diagnosed at age 18; 1/35 (3%) had esophagitis at age 19; 6/35 (17%) were diagnosed with hepatic neoplasms; and 2/35 (6%) with hepatic angioma (Figure 1). Nonfamilial hypercholesterolemia was observed in 2/35 (6%). About 13 underwent major surgery for various indications: thyroid carcinoma (1, at age 30), right mastitis (2, at age 19), acute pancreatitis secondary to calculi of the gall bladder (1, at age 25), bladder exstrophy (2, at age 9 months), intussusception (1, at age 1), cholecystectomy (1, at age 12), and unilateral/bilateral cataracts (5, between ages 22 and 28) (Tables 2 and 3). Nine individuals (26%) were still having feeding difficulties due to chewing inefficiency and needed to assume semisolid or liquid food. Most adults tended to keep the food in their mouth for a long time, eating small quantities. About 17 (49%) developed mild-to-severe thoracolumbar scoliosis between the age of 3 and 20 years. DXA scan showed low bone density in 12 individuals (34%) at different ages; only 4 of them suffered severe limited mobility. Persistence of deciduous teeth was observed in 22 (63%) (Figure 1; Table 3). One female never experienced her menarche, and another had amenorrhea from age 33. All but 1 were seizures free. Although, in 34/35 seizures stopped between ages 2 and 14 years, 10 individuals, aged between 16 and 34 years, were still receiving antiepileptic drugs (Table 1). Sleep disturbance, characterized by frequent awakenings during the night, was reported in 3/35 (9%). All were enrolled in an adult personalized rehabilitation program including physical, occupational, speech (augmentative speech program), and feeding therapies. About 3 of 35 were attending their own county workshops, 2/35 also lived in a group home, and 1/35 volunteered at S. Vincent de Paul Food Bank shredding, putting cans on shelf and packing food boxes (Figures 2 and 3).

4 | DISCUSSION

As part of our ongoing investigation of WHS, we report the health status, medical manifestations, and activities of daily life in 35 adults with the syndrome. This part of our two-part study on adults is meant to compliment the data in the PROS accompanying this article (Carey et al., 2021).

A pattern of human malformation and neurodevelopmental disabilities constitutes a chronic condition, which involves a process with a long-time extension and usually entails high costs in psychophysical and economic resources. Burnout symptoms, depression, social seclusion, and stress can occur in the primary caregivers, impacting the entire family's quality of life. In our everyday experience, the unique challenges of those rare conditions have been shown to change family structure and social roles; and because of the uncertain evolution of the condition, the different coping strategies, in family members,

TABLE 1 Summary of clinical features in 35 adult individuals with Wolf–Hirschhorn syndrome

Pat./no.	Age/sex	Cytogenetics	IUGR/PGD	Distinct cranio-face	DD/ID	Seizures/age stopped
1	40 year 5 months/F	HRB/FISH	+/+	+	Severe	+/3 year
2	37 year 7 months/F	HRB/FISH	+/+	+	Severe/profound	+/2 year
3	33 year 5 months/M	HRB/FISH	+/+	+	Severe	+/3 year 5 months
4	36 year 9 months/F	HRB/FISH	+/+	+	Severe	+/5 year
5	37 year 1 months/F	HRB/FISH	+/+	+	Severe	+/12 year
6	35 year 6 months/M	HRB/FISH	+/+	+	Severe	+/6 year
7	23 year/M	HRB/FISH	+/+	+	Severe/profound	+/15 year
8	24 year 6 months/F	FISH	+/+	+	Severe	+/13 year
9	23 year 6 months/F	HRB/FISH	+/+	+	Severe	+/3 year
10	25 year 7 months/F	HRB/FISH	+/+	+	Severe	+/3 year
11	29 year/F	FISH	+/+	+	Severe	+/6 year 5 months
12	31 year 1 months/M	HRB/FISH	+/+	+	Severe/profound	+/2 year
13	30 year/3 months/F	HRB/FISH	+/+	+	Severe	+/11 year
14	26 year 3 months/M	HRB/FISH	+/+	+	Severe	+/10 year
15	36 year 4 months/F	HRB/FISH	+/+	+	Severe/profound	+/3 year
16	26 year 6 months/M	aCGH/FISH	+/+	+	Moderate	No
17	20 year 2 months/F	HRB/FISH	+/+	+	Moderate	+/8 year
18	33 year 10 months/F	FISH	+/+	+	Severe/profound	+/6 year
19	19 year 6 months/F	HRB/FISH	+/+	+	Severe	+/4 year
20	39 year 3 months/F	HRB/FISH	+/+	+	Severe	+/13 year
21	28 year 10 months/F	HRB/FISH	+/+	+	Severe	+/14 year
22	37 year/F	FISH	+/+	+	Moderate/severe	+/7 year
23	44 year/F	FISH	+/+	+	Severe	+/14 year
24	42 year 5 months/F	HRB/FISH	+/+	+	Moderate	+/3 year
25	33 year 6 months/M	HRB/FISH	+/+	+	Moderate	+/1 year
26	40 year 5 months/F	HRB/FISH	+/+	+	Severe	+/13 year
27	55 year 9 months/F	HRB/FISH	+/+	+	Severe	No
28	31 year 6 months/F	HRB/FISH	+/+	+	Severe/profound	+/10 year
29	21 year 6 months/F	FISH	+/+	+	Severe	+/6 year
30	38 year/F	HRB/FISH	+/+	+	Profound	+/6 year
31	33 year 6 months/M	FISH	+/+	+	Moderate	+/11 year
32	22 year/F	HRB	+/+	+	Profound	+/–
33	31 year 4 months/F	HRB/FISH	+/+	+	Severe	+/10 year
34	28 year/M	HRB/FISH	+/+	+	Severe	+/11 year
35	26 year/F	FISH	+/+	+	Severe	+/10 year

could cause emotional isolation and a sense of hopelessness. In many instances, still today, the family members feel aggrieved that they are being led to believe that the long-term prognosis is universally poor. Therefore, knowledge of the natural history into adulthood ("an account of all of the consequences of that disorder over time"; Hall, 1988) is mandatory, in order to effectively plan specific health supervision in an individual with a malformation syndrome. This information would prove invaluable to the family and caregivers coping with any resultant disabilities.

Although more than 300 persons with WHS have been reported in the literature, there is limited, if any, long-term follow-up of these individuals and thus little knowledge about course and potential further complications and health risks during adulthood and advanced age.

Only 11 adults with WHS have been reported so far, with age range between 19 and 37 years (Battaglia et al., 2018; Coppola et al., 2013; Lopes et al., 2005; Ogle et al., 1996; Opitz, 1995; Prunotto et al., 2013; Smith et al., 1995). Eight of 11 were said to have health problems, such as, severe thoracic or thoracolumbar scoliosis, acute pancreatitis, hepatitis, gallstones, diabetes (developed at age 22 years in one), and chronic renal failure following bilateral renal hypoplasia. One of 11 was still having seizures by age 23.

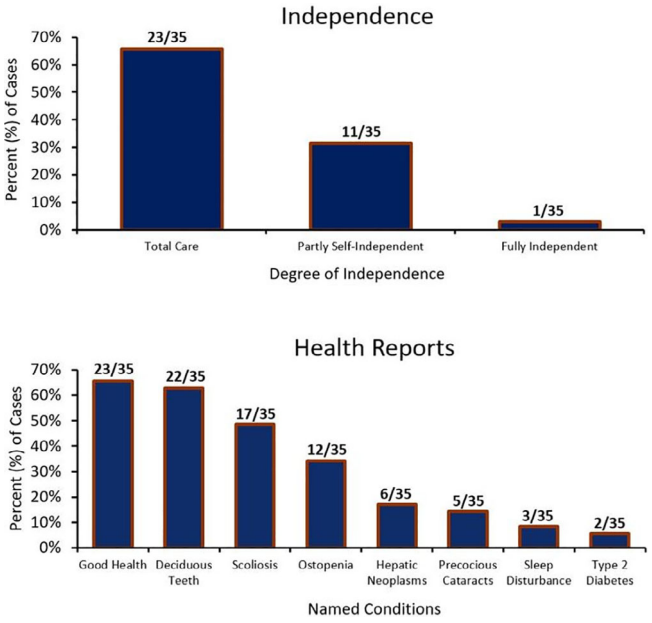

FIGURE 1 The bar graphs display the frequency distribution of the health status and daily life/independence status of the 35 adults in the case series part of the study [Color figure can be viewed at wileyonlinelibrary.com]

The results we present here are our current findings in the ongoing study of the natural history into adulthood of individuals with WHS. Of note, 23/35 (66%) are close to total care, with a consequent severe impact on the family and society. About 11 out of 35 (31%) are partly self-independent, requiring supervision on certain daily routines, and one out of 35 (3%) is fully independent. However, a positive perspective is given by the overall good health enjoyed by the 66% of our cohort of adults. Clinical problems include type 2 diabetes associated with hypercholesterolemia, Raynaud's disease, esophagitis, mild–severe thoracolumbar scoliosis, low bone density, sleep disturbance, ongoing seizures, and precocious cataracts, as shown in Figure 1 and Tables 1–3. Menses disruption seems to be rare.

Recently, Prunotto et al. (2013) reported on two adult WHS patients in whom hepatic adenomas were detected at age 20 and 11 years, respectively. More recently, Battaglia et al. (2018) documented four previously undescribed individuals with WHS who developed hepatic neoplasia between ages 15 and 32. Therefore, we are planning to study as many adults with WHS as we can recruit, in order to obtain the most accurate natural history information. We are also trying to obtain array-CGH analysis on most of them, in an attempt to accomplish a detailed phenotype–genotype correlation of these liver manifestations, as well as other complications. Several lines of research have hypothesized a potential risk for tumors in WHS (Battaglia et al., 2018). Somatic chromosomal rearrangements involving the distal short arm of four have been described in association with different malignancies (Chesi et al., 2001; Cleary et al., 1999; Herranz et al., 1999; Okumoto et al., 1999; So et al., 2000; Stec et al., 1998). Genes located within the proposed critical region for WHS, particularly *NSD2* (*WHSC1*), *LETM1*, and *FGFR3*, when overexpressed, have been associated with neoplasia and carcinogenesis on the cellular and molecular levels (Chesi et al., 2001; Kassambara et al., 2009; Li et al., 2008; Martinez-Garcia et al., 2011; Morishita & Luccio, 2011; Piao et al., 2009; Toyokawa et al., 2011). However, the impact of haploinsufficiency for these genes on neoplasia remains unclear.

All individuals were enrolled in an adult personalized rehabilitation program including physical, occupational, and feeding therapies. Unfortunately, only a small minority was also enrolled in an augmentative speech program, which we think should be introduced during the early years, in order to support the intention to communicate of children with WHS.

Most individuals were living in the parents' home, and only a minority showed some sort of difficult behavior.

Seizures are a commonly reported problem among individuals with WHS, with onset within the first 3 years of life. Previous studies reported seizures in over 90% of the patients (Battaglia et al., 2009). About 3% of our cohort of individuals receiving multiple antiepileptic drugs (carbamazepine, phenytoin, diazepam, and lamotrigine) was reported to have intractable seizures into adulthood. However, large individual cohorts have shown that, although frequent and, sometimes, hard to control during early years, seizures are brought under good control, provided they are treated as early as possible, and with the first choice drug/s (Battaglia et al., 2009; Ho et al., 2018; Worthington et al., 2008). Almost all our patients had hypotonia into adulthood. Generalized hypotonia, often associated with muscle hypotrophy of the lower legs, is usually quite severe in infancy and childhood but tends to improve over time, whenever treated, as early as possible, with the appropriate physical therapy. Feeding difficulties constitute a main challenge of infancy and childhood and may persist into adulthood, as observed in 26% of our cohort of individuals. There is little information describing the course of puberty in persons with WHS. Future research is needed to better characterize the age of onset, course, and possible complications of puberty in such individuals. Seen the variety of structural defects of the urinary tracts described in up to 50% of individuals with WHS (Battaglia et al., 2008; Battaglia & Carey, 2000; Shimizu et al., 2014), careful assessment of renal function should be pursued periodically, in order to prevent a possible renal insufficiency. We are aware of the death, caused by renal insufficiency, of three of our patients between ages 21 and 28 years. Two of the three had renal hypoplasia, whereas one had no apparent kidney malformations.

Of note, nonfamilial hypercholesterolemia (>220 mg/dl) has also been previously observed in about 35% of individuals with WHS in whom serum cholesterol levels were examined (Shimizu et al., 2014), suggesting that it could be a newly recognized rare complication.

Mild-to-severe thoracolumbar scoliosis, observed in 49% of our cohort of individuals, appears to be a common and serious complication in adults with WHS, progressing between late childhood and early adolescence.

Low bone density seems to be a further component manifestation of WHS since 8 of 12 individuals of our cohort (67%), in whom it has been detected, are ambulatory.

TABLE 2 Summary of clinical features in 35 adult individuals with WHS

Pat./no.	Heart	Genitourinary	Hearing loss	Ophthalmologic
1	–	–	Sensorineural	Strabismus
2	–	Renal hypoplasia and malrotation	–	Coloboma, glaucoma, cataract
3	–	Hypospadias	–	Strabismus
4	ASD, VSD	Renal hypoplasia and malrotation, vesicoureteric reflux	–	Glaucoma
5	ASD	–	–	Coloboma, glaucoma, cataract
6	ASD	↓ Renal function with proteinuria, hypospadias, cryptorchidism	–	Coloboma
7	PFO	Hypospadias	–	–
8	ASD	Horseshoe kidney	–	Coloboma
9	PFO	–	Sensorineural	Coloboma, strabismus
10	ASD, pulmonary stenosis	–	Sensorineural	Coloboma, cataract, glaucoma
11	ASD	–	–	Coloboma, cataract
12	–	Vesicoureteric reflux, hypospadias, left inguinal hernia and left hydrocele	–	Strabismus
13	–	Ectopia renis	–	–
14	PFO, pulmonary stenosis	Renal hypoplasia, cryptorchidism	–	Strabismus
15	ASD	–	–	Strabismus
16	–	Renal hypoplasia	–	–
17	ASD	–	Conductive	Strabismus
18	–	–	Sensorineural	Strabismus, coloboma
19	PFO, ASD	–	–	Strabismus
20	–	–	–	Strabismus
21	–	Renal hypoplasia	–	Strabismus
22	ASD	–	–	Strabismus, coloboma
23	PDA, translocation of great vessels	–	Sensorineural	–
24	–	–	Sensorineural	–
25	Pulmonary stenosis	Hypospadias	–	–
26	VSD	–	Sensorineural	–
27	ASD	–	–	Strabismus
28	PDA, aortic insufficiency	Renal hypoplasia, bladder exstrophy	Conductive	Strabismus
29	–	–	–	–
30	–	–	–	Corneal leucomas
31	–	–	–	–
32	–	Renal hypoplasia, bladder exstrophy	–	–
33	ASD	Renal hypoplasia	–	Bilateral cataracts
34	–	Cryptorchidism, horseshoe kidney	–	–
35	–	–	–	Strabismus

Current efforts are focused to clarifying in more depth the natural history of WHS into adulthood, with particular attention to the immune-hematologic status, the course of puberty, and to the age of onset, frequency, type, and severity of kidney dysfunction and hepatic neoplasias.

Based on the data from this part of the WHS adult investigation and the existing literature (Battaglia et al., 2018), we would add the following recommendations to the previously published guidelines on routine care: (a) 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; (b) annual ophthamology examination; (c) referral to neurology/epileptology if any signs of seizures; (d) DXA scan at around 20–30 years of age, or if any

TABLE 3 Summary of clinical features in 35 adult individuals with WHS

Pat./no.	Dental	Skeletal	Gastroenterology	Other complications
1	Peg-shaped, deciduous teeth	Talipes equinovarus	–	↑ Cholesterol
2	Deciduous teeth	Severe scoliosis	–	Papillary carcinoma of the thyroid, hepatic angioma, ↓bone density
3	Deciduous teeth	–	–	–
4	Deciduous teeth	Severe scoliosis	–	↓ Bone density
5	–	–	–	Pancreatitis secondary to calculi of the gall bladder
6	Deciduous teeth	Talipes varus, mild scoliosis	–	↓ Bone density
7	Agenesis of lower lateral incisors	Talipes varus	–	–
8	–	Mild scoliosis, pes planus	–	Right mastitis
9	–	Severe scoliosis, talipes equinovalgus	–	↓ Bone density
10	–	Scoliosis, talipes equinovarus	–	–
11	Deciduous teeth	–	–	–
12	Deciduous teeth	Talipes varus	Hepatic steatosis	↓Bone density
13	Deciduous teeth	Severe scoliosis	–	↓ Bone density
14	Deciduous teeth	–	–	–
15	Deciduous teeth, agenesis of upper canines	Scoliosis, small iliac wings with coxa valga subluxans, pes pronatus	Esophagitis	↓ Bone density
16	–	Mild kyphoscoliosis, talipes varus	Intussusception	–
17	Deciduous teeth	Pes valgus-pronatus	–	–
18	Agenesis of upper canines	Pes valgus-pronatus	–	↓ Bone density
19	Deciduous teeth	Pes valgus-pronatus	–	–
20	Deciduous teeth	Scoliosis	–	↓ Bone density
21	–	Scoliosis, kyphosis	–	Type 2 diabetes, ↑ cholesterol
22	Deciduous teeth	Scoliosis	–	–
23	Deciduous teeth	Club feet, scoliosis	–	Vocal cords agenesis, ↓ bone density
24	Deciduous teeth	–	–	–
25	–	–	–	–
26	Agenesis of lower lateral incisors	Accessory ribs, scoliosis	–	Hyperthyroidism, Raynaud's disease
27	–	–	–	Right mastitis
28	Deciduous teeth, agenesis of upper canines	Scoliosis, kyphosis	–	↓ Bone density, small bowel obstruction, chronic renal insufficiency
29	Deciduous teeth	Scoliosis	–	Hepatic adenomas
30	Deciduous teeth	Talipes varus, kyphosis	–	Hepatic adenomas, type 2 diabetes, ↑ cholesterol
31	Deciduous teeth	–	–	Hepatic adenomas
32	Deciduous teeth	–	Cholecystectomy	Hepatic adenomas → multifocal hepatocellular carcinoma
33	Agenesis of lower lateral incisors	–	–	Hypothyroidism, liver steatosis, hepatic angioma, ↑ cholesterol, ↓ bone density
34	–	Coxa valga	–	Hepatic adenomas
35	Deciduous teeth	Scoliosis	–	Hepatic adenomas

Abbreviations: ASD, atrial septal defect; PFO, patent foramen ovale; VSD, ventricular septal defect.

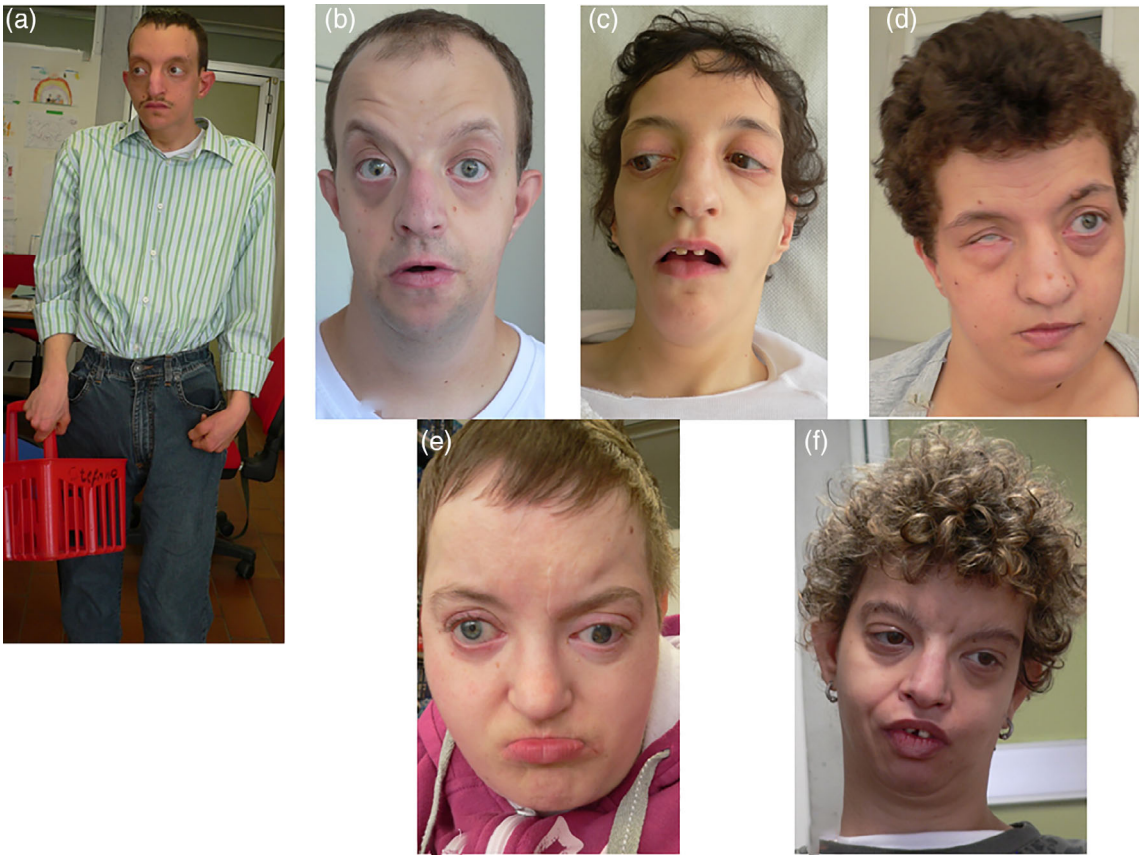

FIGURE 2 Frontal view of six Italian adult individuals with Wolf–Hirschhorn syndrome at different ages, displaying the typical craniofacial features: (a) age 28 years; (b) age 30 years and 3 months; (c) age 32 years and 3 months; (d) age 32 years and 4 months; (e) age 32 years and 7 months; and (f) age 35 years and 6 months [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Frontal view of five U.S. adult individuals with WHS at different ages, displaying the typical craniofacial features: (a) age 35 years; (b) age 21 years; (c) age 30 years; (d) age 26 years; and (e) age 23 years [Color figure can be viewed at wileyonlinelibrary.com]

occurrence of fractures; (e) routine dental evaluations; and (f) referral to an orthopedist to check on the severity of scoliosis and plan its treatment.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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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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