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Wiedemann–Rautenstrauch syndrome: A phenotype analysis

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Wiedemann–Rautenstrauch syndrome (WRS) is a neonatal progeroid disorder characterized by growth retardation, lipodystrophy, a distinctive face, and dental anomalies. Patients reported to date demonstrate a remarkable variability in phenotype, which hampers diagnostics. We performed a literature search, and analyzed 51 reported patients, using the originally reported patients as "gold standard." In 15 patients sufficient information and photographic evidence was available to confirm the clinical diagnosis. In 12 patients the diagnosis was suggestive but lack of data prevented a definite diagnosis, and in 24 patients an alternative diagnosis was likely. Core manifestations of the syndrome are marked pre-natal and severe post-natal growth retardation, an unusual face (triangular shape, sparse hair, small mouth, pointed chin), dental anomalies (natal teeth; hypodontia), generalized lipodystrophy with localized fat masses, and—in some cases—progressive ataxia and tremor. It has been suggested that the syndrome might be caused by biallelic variants in *POLR3A*, identified by exome sequencing in a single patient only. Therefore, we compared the WRS phenotype with characteristics of conditions known to be caused by autosomal recessively inherited *POLR3A* mutations. There are major differences but there are also similarities in phenotype, which sustain the suggestion that the syndrome can be caused by disturbed POLR3A functioning.

KEYWORDS
4H syndrome, autosomal recessive, cerebellar hypoplasia-endosteal sclerosis, lipodystrophy, POLR3A, POLR3B, Wiedemann–Rautenstrauch syndrome

1 | INTRODUCTION

In 1977 Thomas Rautenstrauch and Friedemann Snigula, described two sisters with "the typical symptoms of progeria at birth" (Rautenstrauch & Snigula, 1977). Both children were very small at birth, lacked subcutaneous fat almost completely, except for an accumulation of fatty tissue in the caudal area, and demonstrated a triangular face, prominent scalp veins, widely open fontanelles, and natal teeth. One patient had died at 5 years of age, the other was 2 years at the time of publication, and followed till 16.5 years of age when she had lost all her teeth, and had developed spasticity, ataxia, and an aged appearance (Rautenstrauch, Snigula, & Wiedemann, 1994; Snigula & Rautenstrauch, 1981). She died aged 17, without a known cause (T. Rautenstrauch, personal communication 2016). In 1979, Hans-Rudolph Wiedemann described two unrelated patients with features that he recognized to be very similar to those of the patients reported by Rautenstrauch and Snigula (Wiedemann, 1979). Devos, Leroy, Frijns, and Van den Berghe (1981) presented a fifth patient with overlapping features and proposed the eponym "Wiedemann-Rautenstrauch syndrome" (WRS [MIM: 264090]). These authors hypothesized an autosomal recessive pattern of inheritance as the parents of their patient were consanguineous. Subsequently, 46 further patients have been published as having WRS or stated by the authors themselves or later authors resembling WRS to a great extent (Abdel-Salam & Czeizel, 1999; Akawi, Ali, & Al Gazali, 2013; Almeida, Hernández, Marti, & Hernández, 2005; Arboleda & Arboleda, 2005; Arboleda, Morales, Quintero, & Arboleda, 2011; Arboleda, Quintero, & Yunis, 1997; Barkley & O'Hagan, 2015; Becerra et al., 2014; Bitoun, Lachassine, Sellier, Sauvion, & Gaudelus, 1995; Cao & Hegele, 2003; Castiñeyra, Panal, Lopez Presas, Goldschmidt, & Sánchez, 1992; Chessa, Bastianon, Del Porto, Nardo, & Stefanini, 1992; Courtens, Nuytinck, Fricx, André, & Vamos, 1997; Delatycki et al., 1997; Dinleyici, Tekin, Dinleyici, & Aksit, 2008; Gattoo, Singh, & Aziz, 2015; Hagadorn,

TABLE 1 Main characteristics of 18 patients with Wiedemann–Rautenstrauch syndrome[a]

Reference	Present report			Rautenstrauch et al. (1977)		Wiedemann (1979)		Devos et al. (1981)	Rudin et al. (1988)	Arboleda et al. (1997)		Pivnick et al. (2000)	Arboleda et al. (2005)	Arboleda et al. (2011)			Becerra et al. (2014)	Jay et al. (2016)
Patient (code)	WRS001	WRS002	WRS003	RM	GM	TM	SvR	IV	RT	1	2	5	1	1	2	3	1	1
Sex	F	F	F	F	F	M	M	F	M	F	M	F	M	F	F	M	M	F
Duration of pregnancy (weeks)	36	40	38	42	42	40	40	40	41	30	40	30	?	41	36	?	35	32
Consanguinity	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
Weight at birth (g/centile)	1,350 (<<P3)	1,900 (P3–P10)	1,970 (<<P3)	2,380 (<P3)	2,210 (P < 3)	2,200 (<P3)	2,550 (P3–P5)	2,100 (<P3)	2,500 (P3)	1,500 (<P3)	1,700 (<P3)	960 (<P3)	1,800 (<P3)	1,410 (<P3)	1,250 (<P3)	1,200 (<P3)	1,410 (<P3)	685 (<P3)
Length at birth (cm/centile)	?	37 (P3–P10)	?	48 (P25)	47 (P15)	45 (<P3)	49 (P25–P50)	48 (P25)	49 (P25–P50)	43 (<P3)	45 (<P3)	38 (<P3)	47.6 (P5–P15)	47 (P15)	43.5 (<P3)	41 (<P3)	44 (<P3)	34.5 (<P3)
OFC at birth (cm/centile)	31.5 (<P3)	?	32.2 (P3)	32.5 (P5–P15)	32 (P5)	?	?	33 (P25)	34 (P25–P50)	29 (<P3)	30 (<P3)	25.5 (P < 3)	33.3 (P15–P25)	30 (<P3)	29.5 (<P3)	31 (<P3)	29 (<P3)	24.5 (<P3)
Age at last examination	10 y	20 y	20 y	9m	4 y	9 m	1.5 y	5 y	20 m	1 d	6 m	21 m	17 y	2 d	1 d	1 d	40 d	1 d
Weight at last exam (kg/centile)	8.3 (<<P3)	46.2 (P3–P5)	?	5.1 (<P3)	10.2 (P3)	?	?	5.4 (<P3)	<P3	?	?	<P3	40 (<P3)	?	?	?	1.9 (<P3)	?
Height at last exam (cm/centile)	85 (<P3)	140 (P3–P5)	?	70 (P50)	88 (<P3)	?	?	75 (<P3)	?	?	?	<P3	155 (<P3)	?	?	?	?	?
OFC at last exam (cm/centile)	?	56 (P50–P98)	?	?	47 (P5)	?	?	45 (<P3)	N	?	?	P3–P10	54.5 (P25–P50)	?	?	?	?	?
Sparse scalp hair	+	+	–[%]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prominent scalp veins	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Widely open sutures/fontanels	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Wide forehead	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Triangular face	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eyebrows broad (B), sparse (S)	S	B	S,B	S	S	S	S	S	S,B	S	S	S	S,B	S,B	S,B	S,B	S	S
Deeply set eyes	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Lower eyelid covering part of cornea	+	+	+	–	+	+	+	(+)	–	+	+	+	+	+	+	+	+	+
Convex nasal ridge	–	+	+	–	+	–	–	+	+	–	+	–	+	–	–	–	–	–
Small mouth	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Thin upper vermillion	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Downturned corners of mouth	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Natal teeth (number)	2	2	2	2	2	2	4	1	4	1	4	–	4	10	6	4	2	+
Teeth: absent (A), <5 teeth (O), delayed eruption (D)	A	A	O	–	A	?	?	O	A	–	–	D	O	–	–	–	–	–
Pointed chin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ears: small(S), malformed (M), small lobes (SL), low-set (L)	S,L	S,L,SL	SL,L	-	L	L	L	L	-	L,S,M	L,S	L	L	L,M	L,S	L,S,SL	L	L,M

(Continues)

TABLE 1 (Continued)

Reference	Present report			Rautenstrauch et al. (1977)		Wiedemann (1979)		Devos et al. (1981)	Rudin et al. (1988)	Arboleda et al. (1997)		Pivnick et al. (2000)	Arboleda et al. (2005)	Arboleda et al. (2011)			Becerra et al. (2014)	Jay et al. (2016)
Skin: acanthosis nigricans (AN), dry (D), hypertrichosis (H), atrophic (A), well visible veins (VW), wrinkled (W)	A	VV,H,AN	VV	D,W	A	?	?	P	D,W,VV	A,D	A	VV	A,D,W	W,A, D	D,A, W	D,A	?	T
Decreased subcutaneous fat tissue	++	+	+	+	+	+	+	++	++	+	+	+	++	+	+	+	+	+
Localized fat accumulation: armpit (Ap),caudal (C), genitalia (G), thorax (T)	C	G	C, thorax	?	C	C	C	C	C,Ap,F	C	–	C,G	C,F	–	–	–	C	–
Skeletal radiology[b]	U	np	np	np	DB	?	?	U	I,M	I,M, TD	TD,M, DB	O	TD,I,M,O	O	np	np	np	np
Tremor (age of appearance)	6 y	–	18 y	–	–	?	?	5y	–	–	–	–	–	–	–	–	–	–
Hypertonia (age of appearance)	9 y	–	–	–	16 y	?	?	–	1 d	1 d	1 d	–	–	1 d	1 d	1 d	1 d	–
Neurology: ataxia (A), seizures (S), hypotonia (H)	A	–	–	S	A	?	?	A,Hy	A,S	–	–	–	–	–	–	–	–	–
MRI brain: hypomyelination (H), polymicrogyria (P)	P	–	?	–	–	?	?	?	–	np	np	H	–	np	np	np	np	np
Intellectual disability	+	–	–	?	+	++	–	+	+	?	?	+	+	?	?	?	?	?
Eye/vision anomalies[c]	E,I,H,SO,C	E,PR	H,Ny	?	M,H	?	?	E,Ny,L	B,Ny	?	PR	?	PR,L	E,C, Ct	S	SO	–	?
Hearing anomalies	?	?	+	?	?	?	?	?	–	?	?	?	–	?	?	?	?	?
Endocrine anomalies[d]	LP	D	HH	–	–	?	?	?	–	?	HP,T, E, T4	–	–	?	?	?	?	?
Hypertriglyceridemia	+	+	?	?	?	?	?	?	–	?	?	+	–	?	?	?	?	?
Age of death	10 y	–	–	5 y	17 y	?	?	5.5 y	7 y9m	2 w	6 m	?	?	43 d	3 d	6 d	?	7 m
Cause: Cerebral hemorrhage (CH), pneumonia (P), respiratory complications (R), exhaustion €	E	–	–	CH	?	?	?	P	P	?	P	?	?	?	?	?	?	R

[a]M = male, F = female, y = year, m = month, w = week, d = day, ? = unknown, nr = not reported, np = not performed, + = present, ++ = markedly present, – = absent, N = normal, % = sparse hair in infancy and childhood.
[b]DB = delayed bone age, M = metaphyseal dysplasia, I = small iliac bones, Os = osteoporosis, TD = thin diaphyses, U = underossified cranium.
[c]B = blepharophimosis, BS = blue sclerae, C = corneal clouding, Ct = cataract, E = entropion, Ep = epicantic folds, H = hyperopia, I = inverted eyelashes, L = limited visual acuity, M = missing eyelashes, Ny = nystagmus, PR = Pigment anomaly retina, SO = Small optic discs, U = Upslanted palpebral fissures.
[d]D = diabetes mellitus, LP = low prolactin, HH = hypogonadotropic hypogonadism, HP = high prolactin, T = high testosterone, E = high estrogen, T4 = high T4.

Wilson, Hogge, Callicott, & Beale, 1990; Hermanns, Lipfert, Ladda, & Stevens, 2006; Hoppen et al., 2000; Hoppen, Naumann, Theile, & Rister, 2004; Hou, 2009; Hou & Wang, 1995; Jäger, Thorey, Westhoff, Wild, & Krauspe, 2005; Jay et al., 2016; Kárteszi, Kosztolányi, Czakó, Hadzsiev, & Morava, 2006; Kiraz et al., 2012; Korniszewski et al., 2001; Mégarbané & Loiselet, 1997; Morales et al., 2009; Narayan, Garg, Pareek, & Narayan, 2011; Nowaczyk, Hughes, Costa, & Clarke, 1998; Nowak, Sawadro-Rochowska, Siwicki, & Korniszewski, 2006; Obregon et al., 1992; Ohashi, Eguchi, & Kaji, 1987; O'Neill, Simha, Kotha, & Garg, 2007; Pandey et al., 2011; Pivnick et al., 2000; Rudin, Thommen, Fliegel, Steinmann, & Bühler, 1988; Sahay, Bhalotra, Saini, & Dhanda, 2015; Shawky, Abd-Elkhalek, Gad, & Seifeldin, 2012; Stoll, Labay, Geisert, & Alembik, 1998; Thorey, Jäger, Seller, Krauspe, & Wild, 2003; Tunc et al., 2009; Yazici, 2014; Yazici, Toka, & Çömez, 2014).

The molecular basis of WRS still remains unknown, although Jay et al. (2016) reported bi-allelic truncating variations in *POLR3A* in a single patient and hypothesized these to be causal for WRS. Autosomal recessive loss-of-function mutations in *POLR3A* (MIM: 614258), encoding the largest subunit of polymerase III, have been reported in 2011 as the major causes of various types of hypomyelinating leukodystrophies, usually grouped together as hypomyelination, hypodontia, and hypogonadotropic hypogonadism syndrome (4HS) (Bernard et al., 2011). It has been suggested that the combination of recessive mutations in *POLR3A* in patients do not cause a complete loss of POLR3A function. Subsequently, several other mutations in similarly affected patients have been reported in *POLR3A*, and other components of polymerase III, *POLR3B*, and *POLR1C* (Arai-Ichinoi et al., 2016; Azmanov et al., 2016; Cayami et al., 2015; Daoud et al., 2013; Gutierrez et al., 2015; Jurkiewicz et al., 2015; La Piana et al., 2014; La Piana et al., 2016; Potic, Brais, Choquet, Schiffmann, & Bernard, 2012; Richards et al., 2017; Saitsu et al., 2011; Shima, Fujimoto, Miyazaki, & Nonaka, 2016; Shimojima et al., 2014; Takanashi et al., 2014; Tamura et al., 2013; Terao et al., 2012; Tétreault et al., 2011; Thiffault et al., 2015; Vanderver et al., 2013; Wolf et al., 2014).

Here, we report on the clinical analysis of all individuals reported to have WRS, add three unreported patients, in order to delineate the condition more comprehensively.

2 | METHODS

We searched for potentially suitable publications in PubMed and in the web using as MeSH terms "Wiedemann Rautenstrauch" OR "Wiedemann–Rautenstrauch" OR "Wiedemann–Rautenstrauch syndrome" OR "Wiedemann–Rautenstrauch syndrome" OR "neonatal progeroid syndrome." The reference lists of all thus acquired publications were hand-searched for further potentially suitable publications. We used no initial exclusion criteria. For several patients we contacted the authors to ask for further information if these were not available in the original publications. All descriptions and clinical photographs of affected individuals were critically reviewed jointly by two authors (S.P.; R.C.H.). We used the phenotypes of the original patients reported by Rautenstrauch and Snigula (1977) and Wiedemann (1979) as basis for the diagnosis WRS. The diagnosis was made using as characteristics: pre- and post-natal growth retardation, sparse hair, triangular face, thin upper vermilion, small mouth, pointed chin, natal teeth, generalized subcutaneous lipoatrophy with supra-iliac fat accumulation. Descriptions in the text that differed clearly from the available clinical photographs were scored as visible on the photographs. If uncertainties remained, the feature was not scored for the patient involved.

3 | RESULTS

We diagnosed WRS in 15 patients reported in literature, to which we added three unreported individuals. Only the clinical history of WRS001 and WRS002 are described in detail to demonstrate the clinical history of WRS. The details of WRS003 and the other 15 patients with a reliable diagnosis reported in literature are provided in Table 1. The main findings of WRS are illustrated in Figure 1. Twenty-four of the reported patients were excluded as it was most likely that a different disorder was present (Supplemental Table S2) (Abdel-Salam & Czeizel, 1999; Akawi et al., 2013; Almeida et al., 2005; Barkley & O'Hagan, 2015; Bitoun et al., 1995; Castiñeyra et al., 1992; Courtens et al., 1997; Delatycki et al., 1997; Dinleyici et al., 2008; Hagadorn et al., 1990; Hermanns et al., 2006; Hoppen et al., 2004; Hou, 2009; Hou & Wang, 1995; Jäger et al., 2005; Kárteszi et al., 2006; Mégarbané & Loiselet, 1997; Narayan et al., 2011; Nowaczyk et al., 1998; Obregon et al., 1992; O'Neill et al., 2007; Pivnick et al., 2000; Sahay et al., 2015) and in 12 patients we remained uncertain about the diagnosis as available data were insufficient to allow for a reliable diagnosis (Supplemental Table S1) (Arboleda et al., 1997; Barkley & O'Hagan, 2015; Cao & Hegele, 2003; Chessa et al., 1992; Gattoo et al., 2015; Kiraz et al., 2012; Korniszewski et al., 2001; Morales et al., 2009; Ohashi et al., 1987; Pandey et al., 2011; Shawky et al., 2012; Stoll et al., 1998; Thorey et al., 2003; Tunc et al., 2009; Yazici, 2014; Yazici et al., 2014). We cannot exclude the possibility that there may nevertheless still be genuine patients with WRS among the latter group but decided only to include those of whom we were convinced that the diagnosis WRS was correct.

3.1 | WRS001

WRS001 (Figure 1) is the only daughter born to non-consanguineous Caucasian parents. During gestation, the fetus presented an abnormal head shape, and growth retardation by ultrasound screening. She was delivered at 36 weeks by elective caesarian section because of complete lack of intrauterine growth. Weight at birth was 1350g (−3.8 SD), length was not recorded, and occipito-frontal circumference (OFC) was 31.5 cm (−2 SD). She had a relatively large head, prominent scalp veins, deeply set eyes, bilateral superior entropion with inverted eyelashes, apparently low positioning of the eyeballs (normally positioned, lower eyelids covered half of the corneas), small mouth, thin upper vermillion, two maxillary molars, a submucous cleft palate, and a small chin. The ears were small, low-set, and posteriorly rotated.

There was no subcutaneous fat, except for fat depositions just above the buttocks. She had a thin, translucent skin, long thin fingers, hypermobile joints, and long toes. She was diagnosed as having Wiedemann–Rautenstrauch syndrome in the neonatal period.

Her milestones were significantly delayed, although her understanding was good and she used words with meaning from 2 years of age. She learned to sit but never walked independently. From the neonatal period onward, she had very marked feeding problems. She has had recurrent fever with temperature spikes to 40°C, which remained unexplained.

At 2 years of age length was 62 cm (−8 SD), and weight 3,400 g (−9 SD). She had a remarkable salty body odor, the hair was sparse, and hands and feet were very small with ridging of the second and third finger nails and of the nails on the halluces. Blood counts were normal as were liver transaminases. Plasma cholesterol levels were normal (3.6 mmol/l), triglycerides plasma concentration was extremely high (32 mmol/l; normal values [n.v.] 0.31–1.14 mmol/l). Endocrine studies yielded normal values for all axes tested, except for somewhat low prolactin levels (69 ml/l; n.v. 104–1420 mU/l). Eye examination demonstrated a hyperpigmented retina, small optic discs, and corneal clouding. A skull X-ray showed a widely patent anterior fontanelle, otherwise the full skeletal survey showed a normal bone density. Echocardiogram yielded normal results, and a brain MRI showed normal sized ventricles, polymicrogyria of the perisylvian cortex, and age-appropriate myelination. Subsequent years were characterized by continuous feeding problems leading to a very limited growth. At 6 years of age she developed a mild tremor that gradually increased, and started to go along with dystonic movements as well. From age 9 years on, she developed hypertonia in all limbs, lost the ability to sit, and reduced abilities to speak. Physical exam at age 10 years showed an extreme growth retardation: length 85 cm (−8.5 SD), weight 8,300 g (−6 SD), BMI 8.7 (n.v. 14.6–19.9). Array CGH yielded normal results. She died at age 10 years of general exhaustion. Autopsy was not performed.

3.2 | WRS002

WRS002 (Figure 1) is the first child born to consanguineous parents (fourth degree cousins), living in a remote village in Northeast of Brazil. She has a younger healthy sister. During the third month of pregnancy, the mother had a short period of high fever, myalgia, and upper respiratory symptoms. Other contacts with potential teratogens were denied. She was born at term, weighing 1,900 g (−3 SD) and with a length of 37 cm (−5 SD). She had two mandibular teeth at birth. Her motor milestones were delayed: she sat unsupported at 10 months, started to walk independently at 2 years of age, and used her first words at 22 months. Cognition was thought to be normal, but no formal testing has been performed. At 5.5 years two small maxillary teeth erupted, which were subsequently lost in the ensuing years. One additional tooth erupted when she was 18 years. Menarche was at age 11 years, and menses were irregular since then. At 12 years of age she developed symptoms of diabetes mellitus what was confirmed by further studies, and which required treatment with insulin. Since childhood she had recurrent urinary tract infections, and further studies at 12 years showed stenosis of the ureteropelvic junction and

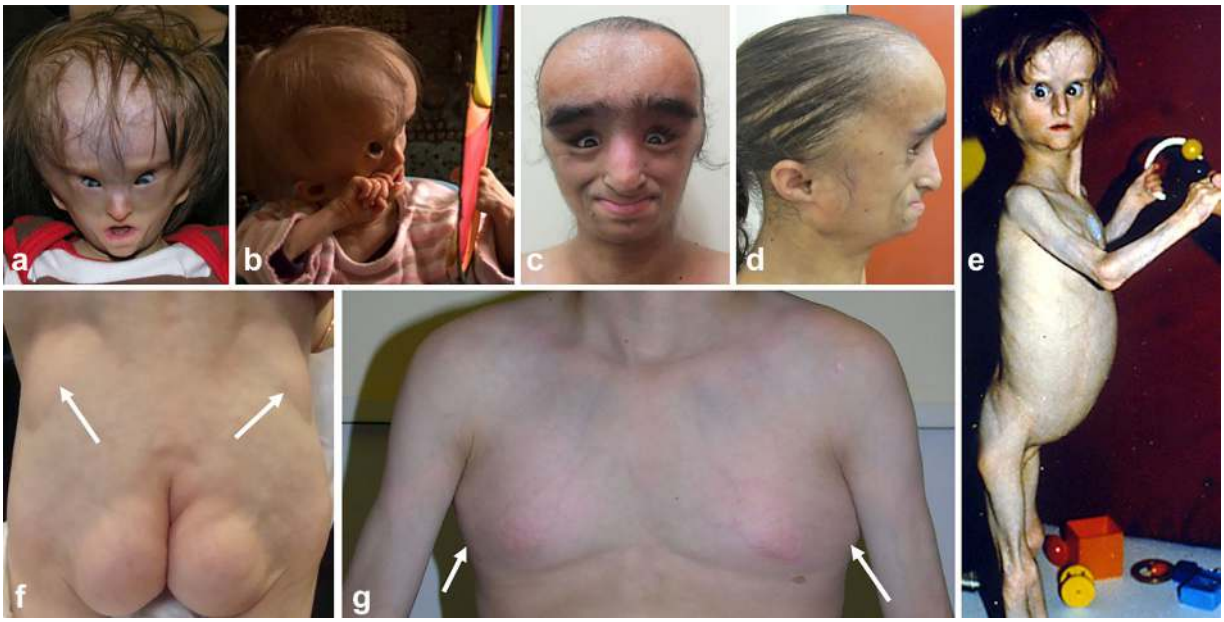

FIGURE 1 Clinical phenotype of Wiedemann–Rautenstrauch syndrome. a and b: patient WRS001 at age 15 months and 3 years. Please note the sparse hair, triangular face, prominent veins, small mouth, and small chin. In B WRS001 pulls her lower eyelid downward in order to be able to see well, as in rest the lower eyelid overs most of the cornea, likely because of the low position of the eyeball due to complete absence of fat tissue in the orbit. c and d: patient WRS002. Please note the same characteristics as in patient WRS001, but all are less marked. e: patient GM reported by Rautenstrauch and Snigula (1977) at age 4 years. Note marked generalized lipodystrophy. f and g: localized fatty tissue indicated by arrows. In g the patient was prepubertal and no mammary tissue was palpable [Color figure can be viewed at wileyonlinelibrary.com]

unilateral hydronephrosis. Surgical correction of the stenosis was successful, but complications eventually lead to unilateral nephrectomy. Evaluation at age 17 years showed her to have height of 139.5 cm (−4.8 SD), weight of 44 kg (−2 SD), and her OFC of 56 cm was at the 50th centile. Physical signs were sparse scalp hair, frontal bossing, broad and dense eyebrows, synophrys, deeply set eyes with the lower part of the cornea covered by the lower eyelid, entropion, large appearing nose with a convex and broad nasal ridge, short philtrum, thin upper vermillion, mild retrognathia, small and low-set ears, with small lobules. She had no teeth. There was a generalized lack of subcutaneous fat tissue, but she had a prominent abdomen and more marked fatty tissue around the genitalia. Nipples were enlarged but she had no mammary development, veins were prominent, and there was hypertrophy of muscles of the limbs along with mild hirsutism, and acanthosis nigricans in the neck and axilla. Additional studies showed elevated plasma triglycerides levels and liver steatosis. Ophthalmologic examinations disclosed pigmentary retinopathy. X-rays demonstrated thickening of the cranial vault but no generalized bone sclerosis. Echocardiography showed a dysplastic and stenotic pulmonary valve, and brain MRI failed to show abnormalities. Classical karyotyping and CGH microarray (180 K Agilent) yielded normal results. Because of recurrent otitis media ventilation tubes were placed at 19 years of age. Re-evaluation at 20 years showed essential the same manifestations, but hirsutism, acanthosis nigricans, and muscle hypertrophy had increased.

4 | DISCUSSION

There are at present no clinical criteria that define WRS. We have found WRS to be a very difficult diagnosis to make as patients reported to have WRS show a very variable phenotype and the phenotype that should lead to the diagnosis of WRS remained uncertain to us. Whether this can be explained by phenotypic variability or by wrongful diagnoses is unclear. The recent delineation of Marfan syndrome lipodystrophy type (also called Graul-Neumann type) as a separate entity caused by mutations in *FBN1* was very helpful in condensing the group of individuals with WRS to the core features (Garg & Xing, 2014; Goldblatt, Hyatt, Edwards, & Walpole, 2011; Graul-Neumann et al., 2010; Horn & Robinson, 2011; Jacquinet et al., 2014; O'Neill et al., 2007; Passarge, Robinson, & Graul-Neumann, 2016; Takenouchi et al., 2013) (Table 2). Even after these publications, WRS has however, been confused with Marfan syndrome lipodystrophy type (Romere et al., 2016).

We have re-evaluated all 51 individuals described in literature as having WRS, using the patients originally reported by Rautenstrauch and Snigula (Martin, Ceuterick, Leroy, Devos, & Roelens, 1984; Rautenstrauch & Snigula, 1977; Rautenstrauch et al., 1994) and by Wiedemann (1979) as "gold standard" (Table 1). This yielded 15 reliably diagnosed patients, to which we add three unpublished patients. There have been 24 patients reported in literature of whom we do not think the diagnosis WRS was right due to the lack of major characteristics of WRS or presence of unusual additional signs or symptoms, and 12 patients in whom we remained in doubt due to insufficient information and lack of photographic evidence (Supplemental Table S1). We realize that in the latter group there may still be bona fide WRS patients, but decided to include only those in whom the clinical diagnosis was beyond doubt.

The group of 18 reliably diagnosed individuals allowed us to define the core features of WRS. It confirmed that severe pre- and post-natal growth deficiency (varying for −2 to −9 SD), the face characteristics sparse scalp hair, triangular face, small mouth with thin upper vermillion, natal teeth and a pointed chin, and the generalized lipodystrophy with local fatty tissue accumulations all go along together in almost all patients. In addition we found that prominent scalp veins, wide cranial sutures, the presence of hypodontia, and the lower eyelid covering part of the cornea are also shared very often. Lastly, the progressive nature of WRS became clear in the increase with age of ataxia and tremor in some of the patients (Tables 1 and 2). Although there is still variability in the phenotype, the resemblances in the group WRS patients are very high, with the exception of life expectancy. Four patients have died within the 1st weeks of life, 2 other in the 1st year, 4 between 5 and 10 years of age, 1 at 17 years, but 2 are still alive at age 20 years. Whether this is caused by specific variants in the causative gene(s) or whether this is caused by other (epi) genetic or environmental factors remains uncertain. The similarity in age of death within the small group of affected siblings points to genetic influences. The early demise of a significant proportion of patients cause only limited information to be available on the course of WRS. Nevertheless, the three patients reported here and the original patient GM reported by Rautenstrauch and Snigula showed a clear progression in signs and symptoms with time, especially with respect of neurological signs as tremor, hypertonia, and ataxia. These symptoms arise typically in late infancy or childhood.

The progression in symptomatology would fit in with variants in *POL3RA* being the cause of WRS, as has been suggested (Jay et al., 2016). *POLR3A* encodes for the largest subunit of the DNA-dependent RNA polymerase III, forming the active center together with POLR3B. This polymerase synthesizes small RNAs, such as 5S rRNA and tRNAs. Reduction of POLR3A leads to reduction of the total pool of tRNAs and a deregulated transcription of several ncRNAs. Some of these ncRNAs, such as 7SL and 7SK RNAs, regulate the activity of DNA-dependent RNA polymerase II, hence *POLR3A* mutations can also affect levels of polymerase II-transcribed genes (Azmanov et al., 2016). The mechanism(s) through which a decrease in POLR3A leads to a clinical phenotype remains unclear. Biallelic loss-of-function mutations in *POLR3A*, and its interactor *POLR3B*, are known to cause the hypomyelination, hypodontia, and hypogonadotropic hypogonadism syndrome (4HS) (Bernard et al., 2011). Indeed it has been suggested that hypomyelination can be a feature of WRS (Martin et al., 1984; Pivnick et al., 2000; Ulrich, Rudin, Bubl, & Riederer, 1995), although it has been absent in other patients in whom neuro-imaging has been performed >10 years of age (Arboleda & Arboleda, 2005; WRS003). There are also major differences between 4HS and WRS, such as the facial manifestations, lipodystrophy, degree of growth retardation, and timing of the major manifestations, which are typically much earlier in WRS. However, there are 4HS patients with symptoms that are present at birth as well. As the clinical consequences of the diagnosis WRS and of 4HS are markedly different, WRS and 4HS remain two separate entities (Hennekam, 2007).

TABLE 2 Comparison of manifestations in Wiedemann–Rautenstrauch syndrome (WRS), to those in Hypomyelinating, Hypogonadotropic Hypogonadism, Hypodontia syndrome (4HS), Cerebellar Hypoplasia-Endosteal Sclerosis (CHES), and Marfan Syndrome Lipodystrophy Type (Marfan LT)[a]

Entity	WRS	4HS[61]	CHES	Marfan LT [74–77]
Sex	11F:7M	53F:52M	2F:4M	8F:1M
Consanguinity	2/14	7/92	1/5	0/9
Weight at birth <P3	15/18	?	0/5	+
Length at birth <P3	9/16	?	0/5	+
OFC at birth <P3	9/15	?	0/5	+
Weight at last exam <P3	7/9	?	4/6	+
Height at last exam <P3	6/7	+	4/6	–
OFC at last exam <P3	1/6	?	3/6	–
Sparse scalp hair	17/18	–	0/6	–
Prominent scalp veins	17/18	–	0/6	+
Widely open sutures/fontanels	18/18	-	0/6	+/–
Wide forehead	18/18	–	0/6	+
Triangular face	18/18	–	0/6	–
Eyebrows: broad (B), sparse (S)	7/18 (B) 17/18 (S)	–	1/6 (B) 0/6 (S)	+(S)
Deeply set eyes	16/18	–	0/6	+
Lower eyelid covering part of cornea	16/18	–	0/6	+
Convex nasal ridge	7/18	–	0/6	+
Small mouth	16/18	–	0/6	–
Thin upper vermillion	18/18	–	0/6	+
Downturned corners of mouth	16/18	–	0/6	+
Natal teeth	17/18	+/–	3/6	–
Teeth hypodontia (H), delayed eruption (D)	8/16	+ (D,H)	4/6 (H)	–
Pointed chin	18/18	–	0/6	–
Ears anomalies	16/18	–	0/6	–
Skin: atrophic (A),dry (D), well-visible veins (V), wrinkled (W)	15/15	–	0/6	+/– (A,D,V,W)
Decreased subcutaneous fat tissue	18/18	–	0/6	+
Localized fat accumulation	13/18	–	0/6	–
Skeletal radiology findings[b]	9/9	–	5/5 (ES,HD)	–
Tremor	3/16	+	2/6	–
Hypertonia	9/16	–	0/6	–
Neurology: ataxia (A), hypotonia (H), seizures (S)	5/16	+ (A,H) +/– (S)	6/6 (A)	–
Brain MRI: hypomyelination (H)	2/7	+ (H)	2/6 (H)	–
Intellectual disability	7/10	+	6/6	–
Eye anomalies[c]	11/12	+ (Ny,My) +/– (Ct)	3/5 (My) 3/5 (OA)	+/– (My,LD)
Hearing anomalies	1/3	–	1/4	–
Endocrine anomalies[d]	4/9	5/10 (GHD)	2/6 (HH)	–
Hypertriglyceridemia	3/5	?	0/5	–

[a]F = female, M = male, ? = unknown, + = present in >50% of patients, +/– = present in <50% of patients, – = absent.
[b]ES = endosteal sclerosis, HD = hip dysplasia.
[c]Ct = cataracts, LD = lens dislocation, My = myopia, Ny = nystagmus, OA = optical atrophy.
[d]GHD = growth hormone deficiency, hypogonadotropic hypogonadism.

4HS can also be caused by mutations in *POLR3B* (Saitsu et al., 2011). Mutations in *POLR3B* have been found in two individuals with cerebellar hypoplasia-endosteal sclerosis (CHES) (Charrow, Poznanski, Unger, & Robinow, 1991; Ghoumid et al., submitted; Ozgen, Overweg-Plandsoen, Blees-Pelk, Besselaar, & Hennekam, 2005; Stoll, Talon, Alembik, & Levy, 1986). CHES shows overlap with both 4HS and WRS as well, but also show differences. Patients with CHES lack the facial signs and lipodystrophy as present in WRS, and

show osteosclerosis which is absent in both WRS and 4HS (Table 2). All three entities share the unusual dentition and growth retardation, although the latter in a markedly different way.

The present study aims to facilitate future recognition of WRS by delineating the clinical characteristics of WRS and, thus, removing individuals reported in literature with other diagnoses, which will also facilitate molecular analyses. We suggest that the core features of WRS are very severe pre- and post-natal growth deficiency (−2 to −9 SD), facial signs (sparse scalp hair, prominent scalp veins, triangular face, apparently low-set eyeballs showing in lower eyelids covering part of the cornea, small mouth with thin upper vermillion, natal teeth, pointed chin), and generalized lipodystrophy with local fatty tissue accumulations. *POLR3A* seems a highly relevant candidate gene for WRS in at least some individuals with WRS. If correct, WRS will then be allelic with 4HS, which has previously been documented to be also allelic with CHES. Molecular studies in a relatively large group of WRS patients are presently under way. Such studies may also provide an explanation for the major clinical differences between the three entities, such as disease specific mutations, involvement of modulator genes or additional mutations, or polymorphisms in *POLR3A* and genes encoding its interactors.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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