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ORIGINAL ARTICLE

Wiedemann-Steiner syndrome as a major cause of syndromic intellectual disability: A study of 33 French cases

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Wiedemann-Steiner syndrome (WSS) is a rare syndromic condition in which intellectual disability (ID) is associated with hypertrichosis cubiti, short stature, and characteristic facies. Following the identification of the causative gene (*KMT2A*) in 2012, only 31 cases of WSS have been described precisely in the literature. We report on 33 French individuals with a *KMT2A* mutation confirmed by targeted gene sequencing, high-throughput sequencing or exome sequencing. Patients' molecular and clinical features were recorded and compared with the literature data. On the molecular level, we found 29 novel mutations. We observed autosomal dominant transmission of WSS in 3 families and mosaicism in one family. Clinically, we observed a broad phenotypic spectrum with regard to ID (mild to severe), the facies (typical or not of WSS) and associated malformations (bone, cerebral, renal, cardiac and ophthalmological anomalies). Hypertrichosis cubiti that was supposed to be pathognomonic in the literature was found only in 61% of our cases. This is the largest series of WSS cases yet described to date. A majority of patients exhibited suggestive features, but others were less characteristic, only identified by molecular diagnosis. The prevalence of WSS was higher than expected in patients with ID, suggesting than *KMT2A* is a major gene in ID.

KEYWORDS
hairiness, histone methylation, hypertrichosis, intellectual disability, *KMT2A*, Wiedemann-Steiner syndrome

1 | INTRODUCTION

Intellectual disability (ID) is a neurodevelopmental disorder (NDD) reported in 1.5% to 2% of children.[1,2] Genetic etiologies account for 25% to 50% of cases of severe ID.[3] Both isolated and syndromic forms of ID can be observed. However, the molecular diagnosis of ID remains a real challenge for patient care and genetic counseling. The recent development of new genetic technologies has increased the likelihood of obtaining a molecular diagnosis. Nevertheless, the diagnostic yield in a recently described, unselected cohort of patients with ID was only 62%.[4]

Wiedemann-Steiner syndrome (WSS; MIM 605130) was described first by Wiedemann in 1989,[5] and then by Steiner in 2000.[6] WSS associates syndromic ID with short stature, developmental delay, and an unusual, supposedly pathognomonic sign referred to as hypertrichosis cubiti (hairy elbows). The main facial features include hypertelorism, narrow palpebral fissures, thick eyebrows, long philtrum, and a thin upper vermilion border.

The causative gene (*KMT2A*) for WSS was only identified in 2012.[7] *KMT2A* encodes a DNA-binding protein that methylates histone H3 lysine 4 (H3K4), modifies the chromatin architecture and upregulates the *HOX* and *WNT* genes.[8] WSS shares certain clinical features, including hirsutism, with other syndromes, which should always be considered as differential diagnosis: Coffin-Siris syndrome, Nicolaides-Baraitser syndrome,[9] atypical Kabuki syndrome,[10] Pierpont syndrome[11] Rubinstein-Taybi syndrome,[12] and Cornelia de Lange syndrome.[13] Interestingly, all of these genetic disorders result from the deregulation of chromatin-mediated transcription. The advent of high-throughput sequencing has led to a progressive but marked increase in the number of WSS case reports over the last 5 years. However, extensive clinical descriptions were given for only 31 of these cases.

Here, we provide clinical details for a French cohort of 33 WSS patients with a confirmed *KMT2A* mutation. In order to better delimit the clinical and molecular features of WSS, we compared our findings with the literature data.

2 | MATERIALS AND METHODS

2.1 | Subjects

Patients were referred by 16 clinical genetics services from across France (Amiens, Besançon, Bordeaux, Dijon, Lille, Lyon, Marseille, Montpellier, Nantes, Paris [Trousseau, Necker-Enfants Malades, La Pitié-Salpêtrière, and Robert Debré hospitals], Rennes, Rouen and Strasbourg), with valuable assistance from the Association Francophone de Génétique Clinique. Physicians with experience in clinical dysmorphology and syndromolgy examined all patients. Photographs and clinical data were reviewed by a small group of human geneticists with specific clinical experience of WSS (S.B., E.S., M.M.D., A.P., and G.M.). The karyotypes and/or array comparative genomic hybridization (CGH) results were normal for all patients. Blood samples were obtained following the provision of informed consent by the patients or their legal representatives. This and all other study procedures complied with the Declaration of Helsinki and French legislation and regulations. Consent was also obtained for the use of photographs.

2.2 | Molecular analyses

KMT2A mutations were identified using one or several different approaches. The mutations in patients #3, #5 and #13 were detected

by direct sequencing of *KMT2A* gene. Twenty patients were investigated using various high-throughput sequencing (HTS) techniques, as follows: targeted sequencing of 44 genes involved in ID for patient #16 (Rouen, France), patient #7 (Rennes, France) and patients #9, #19, #29, #30, and #32 (Lille, France); targeted sequencing of a panel of genes involved in Cornelia de Lange Syndrome and related disorders for patients #20, #26 and #33 (Necker Hospital, Paris, France); targeted sequencing of a panel of genes involved in Kabuki syndrome and related disorders for patient #8 (Montpellier, France); targeted sequencing of a small panel of genes implicated in ID for patients #6, #21 and #22 (Cochin Hospital, Paris, France); targeted sequencing of 450 genes implicated in NDDs for patients #1, #10, #11, #12, #14 and #23 (Strasbourg, France).[14] Patient #2 (Rennes, France) was screened using TruSight One technology (Illumina Inc., San Diego, California). Lastly, whole-exome sequencing (WES) was performed for 9 patients: patient #24 (Montpellier, France), patients #4, #15 and #25 (Dijon, France), patient #31 (London, UK), patient #17 (Yokohama, Japan), patients #27 and #28 (Pitié-Salpêtrière Hospital, Paris, France), and patient #18 (Necker Hospital, Paris, France). Details can be provided on request. All mutations were confirmed by Sanger sequencing.

3 | RESULTS

3.1 | *KMT2A* mutations

We identified mutations in the *KMT2A* gene in all the reported cases (Tables 1 and 2, Figure 1) of which 25 were novel ones. The sequence variants' pathogenicity was classified according to the American College of Medical Genetics and Genomics' recommendations.[15] Eight different missense mutations were found, 7 of which had not been previously described: p.Ser873Asn, p.Arg1154Trp (in 3 patients, including one brother and his sister), p.Gly1181Asp, p.His1958Arg, p.Gly2027Glu, p.Ser3147Phe, and p.Leu3617Pro (in a mother and her son). One mutation (p.Cys1155Tyr) had previously been associated with a milder phenotype.[9] Thirteen different frameshift mutations were found. Eleven were new: p.Glu219Leufs*27, p.Ala383Glyfs*6, p.Ser1299Profs*26, p.Gly1338Valfs*18, p.Val1347Trpfs*9, p.Cys1556Serfs*2, p.Pro1868Glnfs*3, p.Phe2001Trpfs*8, p.Asp2725Glyfs*31, p.Ile2758Aspfs*2, and p.Pro3239Leufs*10. One frameshift mutation was previously reported (p.Ser774Valfs*12)[16] and found in 2 patients from our cohort. Eight different nonsense mutations were found in 8 different patients. Six were new (p.Ser90*, p.Arg160*, p.Arg1101*, p.Arg2163*, p.Glu2544* and p.Arg2659*) and 2 had already been reported (p.Arg1633*)[17] and (p.Arg2480*)[10]. We also found one new splice mutation: c.4696+1G>A.

3.2 | Familial segregation

Familial segregation was studied for all patients except an adopted child (patient #31). We found three two-generation transmissions in three unrelated families. The first familial case concerns a son (patient #21) and his mother (patient #22), both bearing the p.Leu3617Pro mutation. The second familial case concerns a son (patient #23) and his mother, both carrying the c.9440C>T mutation, the mother presented with the same dysmorphia as her son, hypertrichosis of the upper limb, seizures during infancy and had a normal schooling until 16 years old. The third familial case concerns 2 sisters (patients #27 and #28), bearing the p.Arg1154Trp mutation, inherited from their healthy unaffected father, found to have the mutation in a very low proportion of blood cells (somatic mosaicism), 2 reads out of 178 in the HTS analysis. All the other mutations were de novo.

3.3 | Phenotypic analysis

The most frequent and probably the most characteristic combination was as follows: thick eyebrows (23/29; 79%), long eyelashes (24/32; 75%), small palpebral fissures (23/32; 72%), wide nasal bridge (22/31; 71%), hypertelorism (21/32; 66%), long philtrum (20/32; 63%), and thin upper vermilion border (24/32; 75%) (Tables 1 and 2).

12 and 7 patients (39% and 23%, respectively) had presented with intrauterine growth retardation (IUGR) for height and weight, respectively. Fifteen patients (15/32; 47%) had postnatal growth retardation for height. Eleven patients (11/30; 37%) had postnatal growth retardation for weight, and 9 out of 30 (9/30; 30%) had postnatal growth retardation for both height and weight. Twelve patients of the cohort were investigated for growth hormone secretion. Six of them (6/12; 50%) were found with growth hormone deficiency. The majority of patients (20/31; 65%) experienced feeding disorders: most of the patients had food aversion, 3 needed an enteral nutrition (nasogastric tube or gastrostomy), 3 had an important gastroesophageal reflux, and 4 had swallowing difficulties.

Hypertrichosis cubiti was observed in only 19 patients (19/31; 61%). Hypertrichosis of the back was noted in 21 patients (21/31; 68%), and hypertrichosis of the lower limbs was noted in 9 patients (9/24; 38%). Tapering fingers (Figure 2) were observed in only 9 patients (9/29; 31%).

Several patients exhibited skeletal anomalies. Advanced bone age was found in 7 patients (7/15; 47%), delayed bone age was observed in 5 (5/15; 33%). Early tooth eruption was noticed in 2 patients (patients #12 and #33). Four patients (4/17; 24%) had 11 pairs of ribs, and 2 of them had agenesis of the first pair of ribs. Five patients presented with congenital block vertebrae (C2-C3 in 4 cases), and 1 patient displayed hypoplasia of the C1 posterior arch. A sacral dimple was found in 8 children (8/25; 32%).

Development was delayed in most cases. Eighteen patients (18/31; 58%) had congenital hypotonia. Hypotonia persisted long after birth in twelve cases (12/30; 40%). Most of the patients had a delay in walking (19/31; 61%), and the mean age of walking was 23.9 months. Language delay was observed in 24 patients (24/30; 80%). All 33 patients presented with ID (33/33; 100%), although the severity varied markedly: the ID was mild in 18 patients (18/33; 55%), moderate in 11 (11/33; 33%), and severe in 4 (4/33; 12%). Four of 31 documented patients had epilepsy (4/31; 13%) and 10 had behavioral disorders (10/31; 32%) (auto- and hetero-aggression, attention deficit, hyperactivity, anxiety, stereotypies, low frustration tolerance).

Brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) datasets were available for 29 patients. Four of them (4/29; 14%) were seen to have corpus callosum anomalies.

TABLE 1 Molecular and clinical data of the cohort in comparison with the patients of the literature

	Cohort		Literature	
General information	Total	Percentage (%)	Total	Percentage (%)
Number of patients	33	WO	31	WO
Gender	F 11/M 22	F 33/M 67	F 15/M 16	F 52/M 48
Age at last examination (y)	3-36 (Av: 10,67)	WO	1-15 (Av: 8,7)	WO
KMT2A mutations	29 different mutations	WO	28 different mutations	WO
Nonsense mutations	8 in 8 patients	28% of mutations—24% of patients	15 in 16 patients	53% of mutations—52% of patients
Frameshift mutations	12 in 13 patients	41% of mutations—39.5% of patients	2 in 2 patients	7.2% of mutations—6.5% of patients
Missense mutations	8 in 11 patients	28% of mutations—33.5% of patients	8 in 8 patients	28% of mutations—26% of patients
Other type of mutations	1 splice in 1 patient	3% of mutations—3% of patients	2 splice +1 del exons 2-9 in 5 patients	11% of mutations—16% of patients
Growth				
Term of birth (WG)	32-40 (Av: 35,96)	WO	35-41 (Av: 38)	WO
Birth weight (W) <−2 SD	7/31	23	16/26	62
Birth height (H) <−2 SD	12/31	39	5/14	36
Postnatal H/W/H + W <−2 SD	H 15/32—W 11/30—H + W 9/30	H 47—W 37—H + W 30	30/30	100
Craniofacial features				
Microcephaly (<−2 SD)	10/30	33	15/27	56
Hypertelorism	21/32	66	27/29	93
Small palpebral fissures	23/32	72	20/27	74
Downslanted palpebral fissures	18/31	58	24/26	92
Wide nasal bridge	22/31	71	26/29	90
Long philtrum	20/32	63	14/23	61
Thin upper lip	24/32	75	23/29	79
Low-set ears	15/30	50	8/16	50
Skeletal anomalies				
Bone age (Ad—Del—Nal)	Ad 7/15—Del 5/15—Nal 3/15	Ad 47—Del 33—Nal 20	Ad 1/12—Del 2/12—Nal 9/12	Ad 8—Del 17—Nal 75
Rib anomalies	4/17	24	7/16	44
Brachydactyly	9/29	31	14/23	61
Clinodactyly	6/28	21	16/24	67
Tapering fingers	9/29	31	10/20	50
Sacral dimple	8/25	32	10/14	71
Vertebral block	5/11	45	WO	WO
Hairiness				
Thick eyebrows	23/29	79	24/30	80
Long eyelashes	24/32	75	23/24	96
Hypertrichosis cubiti	19/31	61	17/28	61
Hypertrichosis of the back	21/31	68	18/28	64
Hypertrichosis of lower limbs	9/24	38	10/28	36
Developmental and neurology				
Hypotonia (neonatal—persistent)	18/31 (18/31—12/30)	58 (58—40)	16/22	73
ID (Mild—Mod—Sev)	33/33 (Mild 18/33 + Mod 11/33 + Sev 4/33)	100 (Mild 55 + Mod 33 + Sev 12)	27/27 (Mild 12/20 + Mod 5/20 + Sev 3/20)	100 (Mild 60 + Mod 25 + Sev 15)
Seizures	4/31	13	1/24	4
Behavioral disorder	10/31	32	10/24	42
Organic problems				
Cerebral	10/29	34	6/16	38
Eye	19/32	59	ND	ND
Cardiac	8/22	36	9/28	32

TABLE 1 (Continued)

	Cohort		Literature	
Renal	7/23	30	7/26	27
Feeding difficulties	20/31	65	17/29	59
Growth hormone deficiency	6/12	50	ND	ND

Abbreviations: Ad, advance; Av, average; Del, delate; F, female; H, height; M, male; Mod, moderate; Nal, normal; ND, not determined; Sev, severe; W, weight; WG, week of gestation; WO, without object. For this comparison, we have only considered the 27 patients of the literature with molecular confirmation of WSS and detailed clinical description. Patients identified by high-throughput sequencing but without clinical description were excluded. The 7 patients of a same family reported by Saarinen et al with a *KMT2A* mutation and history of primary mediastinal large β-cell lymphoma for 4 of them, were also excluded, as none had the dysmorphic features or ID suggestive of WSS.

Eight children had cardiac anomalies (8/22; 36%): 1 inherited hypertrophic cardiomyopathy, 1 Laubry-Pezzi syndrome, 1 patent ductus arteriosus, and 5 minor cardiac anomalies.

Anomalies of the urogenital tracts were found in 7 patients (7/23; 30%).

Ophthalmologic anomalies were observed in 19 patients (19/32; 59%). Strabismus was present in 7 patients (7/32; 22%), and 2 of them required surgery. Five patients had ptosis (5/32; 16%). Lachrymal duct anomalies were seen in 3 patients (3/32; 9%) and included 2 cases of fistula and 1 case of stenosis. Retinal anomalies were noted in 1 patient and oculomotor trouble in another one. Refractive disorders were found in 15 patients (15/32; 47%), and include hyperopia (n = 9), astigmatism (n = 4) and myopia (n = 3), 2 patients having both myopia and astigmatism.

4 | DISCUSSION

The present report on 33 new cases constitutes the largest yet cohort of WSS patients to date. A number of 31 WSS patients with satisfying clinical description and *KMT2A* mutation have been reported in the literature (Tables 1 and S1, Supporting Information). More than 20 additional cases have been mentioned in exome-sequencing studies of patients with ID; however, clinical descriptions were absent or lacked detail.[16,18–28] We decided to exclude the first 5 cases described from our statistical analysis, because they didn't have a molecular diagnosis. In 2013, 7 members of a large family were identified with a mutation in *KMT2A*; 4 of them had primary mediastinal large β-cell lymphoma but none had the dysmorphic features or ID suggestive of WSS.[29] We also decided to exclude them from our statistical analysis.

The clinical characteristics of WSS patients with *KMT2A* mutations vary markedly. Only ID and dysmorphic features seem to be present in all patients. Recurrent physical traits comprise vertically narrow down-slanting palpebral fissures, hypertelorism, thick eyebrows, long eyelashes and a thin upper vermilion border. These features were fairly typical of the patients of our cohort (Figure 2), although there was a degree of clinical overlap with Kabuki syndrome[10] and Cornelia de Lange syndrome[13]—differential diagnoses that had been initially suggested for some patients.

Hypertrichosis, and particularly hypertrichosis cubiti, was initially considered to be the hallmark of WSS. In our cohort, only 61% of the patients presented with hypertrichosis of the upper limbs and 68% presented with hypertrichosis of the back, similar to the prevalence in the literature (61% for hypertrichosis cubiti and 64% for hypertrichosis of the back). This suggests that hypertrichosis cubiti is not a sine qua non-feature for WSS. Hypertrichosis appeared with age in some members of our cohort. Although many genetic syndromes are associated with hypertrichosis (eg, 122 entries in the online mendelian inheritance in man (OMIM) database), hypertrichosis is associated with ID in only 29 disorders. Interestingly, long eyelashes (75%) and thick eyebrows (79%) are more common in our cohort than hypertrichosis (61%).

Similarly, growth anomalies were not observed in all patients. In the literature, all the patients with WSS had presented with intrauterine and/or postnatal growth retardation.

IUGR for height or weight was relatively frequent in our cohort (39% and 23%, respectively) and in the literature (36% and 62%, respectively). In our cohort, thinness was observed in 11 patients (11/30; 37%). Feeding problems are observed in 65% of our patients, and in 60% of the patients in the literature. In our cohort, 15 patients (15/32; 47%) had postnatal growth retardation; explained by growth hormone deficiency for 6 of them. To the best of our knowledge, growth hormone deficiency has never previously been reported in WSS. On the basis of our present data, we recommend a systematic screening for growth hormone production in WSS patients with growth retardation. In our experience, there is a good response to treatment with growth hormone in WSS patients with growth retardation (regardless of whether or not they have growth hormone deficiency).

In our cohort, advanced bone age was noted in 7 patients (7/15; 47%) as previously reported.[30] Conversely, 5 other patients (5/15; 33%) displayed retardation of bone age—showing that bone maturation may be deregulated in different ways in WSS.

In spite of partial radiologic assessment, skeletal anomalies are frequent in WSS. Four patients (24%) had rib anomalies; this agrees with a literature report in which 7 out of 16 patients (7/16; 44%) had rib anomalies. Indeed, only 13 diseases in the OMIM database feature a combination of rib anomalies and developmental disorders. Six of the children in our cohort presented cervical spine anomalies, with block vertebra (Klippel-Feil syndrome) in 5 cases, associated with C1 posterior arch hypoplasia in one case. Some of these blocks are likely to induce spinal nerve irritation. Accordingly, MRI of the neck and spine may be of value in screening patients with WSS for spinal cord compression and spinal dysraphism. A sacral dimple was observed in 32% of the patients in our cohort, and in 71% of the patients in the literature, whereas in the general population the prevalence is between 1.5% and 12.8%, depending on the geographical area.[31] Therefore, this symptom, particularly prevalent in WSS, may be a

TABLE 2 Detailed clinical and molecular information of WSS patients in the cohort

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Gender	F	M	F	F	F	M	M	M	M	M	M	M	F	M	M	M	F
Age at last examination (y)	4.5	6	5	13	6	13.5	8	14	9.5	22	4.5	8	12	14.5	8	10	18
KMT2A mutation																	
cDNA	c.7975C>T	c.3301C>T	c.269C>A	c.4897C>T	c.6487C>T	c.7630G>T	c.7438C>T	c.478C>T	c.6002_6005del	c.9714_9735del	c.1142dup	c.4012del	c.5603del	c.654_679delinsT	c.8174_8177del	c.4032delG	c.4667_4668del
Protein	p.Arg2659*	p.Arg1101*	p.Ser90*	p.Arg1633*	p.Arg2163*	p.Glu2544*	p.Arg2480*	p.Arg160*	p.Phe2001Trpfs*8	p.Pro3239Leufs*10	p.Ala383Glyfs*6	p.Gly1338Valfs*18	p.Pro1868Glnfs*3	p.Glu219Leufs*27	p.Glu2725Valfs*22	p.Val1347Trpfs*9	p.Cys1556Serfs*2
Growth																	
Term of birth (WG)	37	39 + 5	39	ND	34 + 6	37 + 4	39	39	40	32	33	36 + 3	38	38	40 (denied)	38	ND
Birth weight (g)/SD	2690/−1.8	3130/−0.8	2900/−1	2200/ND	2260/+0.5	2610/−0.7	3760/+1.1	3100/−0.6	2600/−1.9	2700/+3.9	1500/−1.6	3150/+0.3	2255/−3.5	3295/−0.5	ND	3020/−0.3	2990/−0.9
Birth height (cm)/SD	45/−2.4	47/−1.5	45/−2.4	46/ND	43,5/−0.9	46/+1.4	50,5/+0.3	48/−1.5	45/−3.6	49/+4.3	38/−3.4	48/+1.6	40/−5	49/+0.4	41/ND	47,5/−1.2	47/−2
Postnatal weight (SD)	−3.6	+0.3	−1.7	−1	−1.3	−2.6	4.1	ND	+0.2	ND	−3	+3.2	−2.7	2	ND	−0.3	−1
Postnatal height (SD)	−3.5	−1.4	−1.1	−0.6	−2	−1.9	−0.1	0.2	+0.4	−2.1	−4.2	−0.5	−2.7	0.4	ND	−0.6	−1.9
Craniofacial features																	
Microcephaly (SD)	+ (−2.8)	− (0)	− (−1.7)	+ (−2.4)	− (−0.3)	− (−0.8)	−	−	+ (−2.1)	ND	ND	− (−0.5)	+ (−3.1)	− (−1.3)	ND	− (−0.5)	− (−1.5)
Hypertelorism	+	+	+	−	+	+	+	+	−	+	+	+	+	−	−	+	+
Small palpebral fissures	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+
Downslanted palpebral fissures	+	+	+	−	+	+	−	+	−	+	−	+	+	−	−	+	−
Thick eyebrows	+	+	+	−	+	+	+	+	−	+	ND (shaved)	+	+	+	+	−	−
Long eyelashes	−	+	+	+	+	+	+	−	+	−	−	+	+	−	+	+	−
Wide nasal bridge	+	+	+	+	+	+	+	−	−	+	+	−	+	−	+	+	+
Long philtrum	+	+	+	+	−	+	−	−	−	−	−	+	+	−	+	+	−
Thin upper lip	+	+	+	+	−	+	−	−	+	−	−	+	+	−	+	+	−
Low-set ears	−	+	−	−	+	+	−	+	−	+	+	−	+	+	−	+	−
Skeletal anomalies																	
Advance bone age (≥1 y)	− (−1 y)	ND	+ (+1 y)	ND	ND	− (+9 mo)	ND	ND	+ (+2 y)	ND	− (−1 y)	ND	+ (+1.5 y)	ND	−	+ (+1 y)	+ (+1 y 2 mo)
Rib anomalies	+ (11 pairs)	+ (11 pairs)	−	ND	ND	−	ND	ND	ND	ND	+ (11 pairs)	ND	−	−	−	−	−
Brachydactyly	−	−	ND	−	−	−	−	−	−	−	−	ND	+	−	−	−	+
Clinodactyly	+	−	ND	−	−	+	−	−	−	−	+ (Vth finger)	ND	−	−	−	−	−
Tapering fingers	+	−	ND	−	−	+	−	−	−	−	−	ND	+	−	−	−	−
Sacral dimple	+	−	+	−	+	−	−	−	ND	ND	+	ND	ND	−	−	−	−
Other skeletal anomaly	Block C2-C3 Club feet		Block C2-C3	ND	ND	Large hallux	ND	ND	ND	ND	Block C2-C3 hallux valgus kyphoscoliosis II-III syndactyly	ND	Coxa vara pes planovalgus	−	C1 posterior arch hypoplasia	Hands and feet oedema	IInd toes clinodactyly
Hairiness																	
Hypertrichosis cubiti	+	+	+	+	+	+	+	−	ND	−	−	+	+	−	+	+	+
Hypertrichosis of the back	+	−	+	+	+	+	+	−	+	−	−	−	+	−	+	+	−
Hypertrichosis of lower limbs	−	−	+	+	−	ND	ND	−	+	−	−	−	+	−	−	ND	+
Development and neurology																	
Hypotonia neonatal/ persistent	+/−	+/+	+/+	−/−	−/−	−/−	−/−	+/ND	+/+	−/−	+/−	ND/ND	+/−	−/−	−/−	+/+	−/−
Developmental delay	+	+	−	−	−	+	+	+	+	ND	+	+	+	−	+	+	−

TABLE 2 (Continued)

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Intellectual disability	Mild	Mod.	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mod.	Mod.	Mild	Mild	Mod.	Mod.	Mild
Seizures	–	–	–	–	–	–	–	ND	–	–	–	–	–	–	–	–	–
Age of walking (mo)	22	32	18	15	18	22	21	18	23	ND	24	30	ND	14	30	27	14
Behavioral disorder	–	–	–	–	Aggr.	–	Auto-aggr.	+	–	–	–	–	–	–	–	Anxiety +++	ND
Organic problems																	
Cerebral	–	–	–	Cranial asymmetry	–	–	Narrow foramen magnum	ND	–	–	Thin CC myelinisation delay	–	CC hypoplasia	–	Bulbo-medullar compression	–	ND
Eye	Hyperopia	Hyperopia lachrymal fistula	–	Hyperopia lachrymal fistula strabismus (surgery)	Myopia astigmatism	–	Bilateral ptosis	ND	–	–	Hyperopia strabismus	Hyperopia	–	–	Hyperopia strabismus	–	Divergent strabismus (surgery)
Cardiac	–	Hypertrophic cardiomyopathy	–	–	ND	–	–	ND	–	ND	Laubry-Pezzi atrial septal defect	ND	–	ND	ND	–	ND
Renal	–	–	–	–	ND	–	–	ND	–	ND	Renal hypoplasia	ND	–	ND	Horseshoe VUR	ND	ND
Feeding difficulties	+	+	+	–	ND	+ (mod.)	+	–	ND	+ (hyperphagia)	–	+	+	–	+	+	–
Others	GHD		Constipation GHD			Rhinolalia cryptorchidis Berger disease		Narrow palate	Dup Xq13.3 inherited	GHD		Nasal obstruction precocious teeth		–	GHD	Constipation thick gums included teeth	

Patient number	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	Number	Percentage
Gender	F	M	M	M	F	M	M	M	M	F	F	F	M	M	M	M	F 11/M 22	F 33%/M 67%
Age at last examination (y)	3	15	13	12	36	14	13.5	5	5	10	22	5.3	5.7	7	9	3	10.67	WO
KMT2A mutation																		
cDNA	c.2318dupC	c.8270dup	c.3895_3896del	c.10850T>C		c.9440C>T	c.3460C>T	c.3464G>A	c.3542G>A	c.3460C>T	c.3460C>T	c.2618G>T	c.6080G>A	c.5873A>G	c.4696+1G>A	c.2318dup	WO	WO
Protein	p.Ser774Valfs*12	p.Ile2758Aspfs*2	p.Ser1299Profs*26	p.Leu3617Pro		p.Ser3147Phe	p.Arg1154Trp	p.Cys1155Tyr	p.Gly1181Asp	p.Arg1154Trp	p.Arg1154Trp	p.Ser873Asn	p.Gly2027Glu	p. His1958Arg	Splice	p.Ser774Valfs*12	WO	WO
Growth																		
Term of birth (WG)	37	Full-term	39	38	40	35	39	34	39	39 + 2	40	39	38	36	36	37	35.96	WO
Birth weight (g)/SD	2710/−0.4	3120/−0.82	2745/−1.4	2320/−2	2320/−2.5	2380/−0.7	3070/−1	2240/−2	2800/−1.3	2190/−2.7	2500/−2.1	2900/−1.1	3480/+1.8	2790/−1.3	2170/−1.2	1740/−3	7/31 (≤−2 SD)	23%
Birth height (cm)/SD	48/−0.3	46/−2	46/−2.5	46.5/−1.8	46.5/−2.7	46/0.1	48/−1	41.5/+0.4	45/−1.5	41/−5.2	45/−3.6	49/−0.9	47.5/−1.2	47.5/−1.2	44/−1.9	43/−3.1	12/31 (≤−2 SD)	39%
Postnatal weight (SD)	−0.8	−3.1	−1.4	+3.9	+7.4	−0.8	+0.6	−3	−3.9	−5.5	−1.4	−2.8	−1.8	−1.1	−4.1	−4.8	11/30 (≤−2 SD)	37% (≤−2 SD)
Postnatal height (SD)	−0.9	−2.8	−2.6	−0.6	−0.7	−1.7	−2.1	−2.2	−2.1	−5.3	−2.2	−0.1	−2.8	0.7	−2,1	−3	15/32 (≤−2 SD)	47% (≤−2 SD)
Craniofacial features																		
Microcephaly (SD)	− (+0.5)	+ (−3.3)	−	−	−	−	− (−1.5)	− (−1)	+ (−4.1)	+ (−4.1)	+ (−2.7)	− (−1.2)	− (+1.3)	− (−0.7)	+ (−2.5)	+ (−3.3)	10/30	33%
Hypertelorism	+	+	−	+	−	−	−	+	−	−	+	−	+	+	ND	+	21/32	66%
Small palpebral fissures	+	+	+	+	+	−	−	+	+	−	ND	−	−	−	−	+	23/32	72%
Downslanted palpebral fissures	+	+	ND	−	−	−	+	+	−	+	ND	−	+	+	+	−	18/31	58%
Thick eyebrows	+	+	+	−	ND	+	+	+	+	+	ND	+	ND	−	+	+	23/29	79%
Long eyelashes	−	+	+	−	+	+	+	+	+	+	ND	+	+	+	+	+	24/32	75%
Wide nasal bridge	ND	+	−	+	+	−	+	+	−	+	+	−	+	−	ND	+	22/31	71%
Long philtrum	+	+	+	+	−	+	+	−	+	−	ND	+	+	+	−	+	20/32	63%
Thin upper lip	+	+	+	+	+	+	+	+	+	+	ND	+	+	−	+	+	24/32	75%
Low-set ears	+	ND	ND	+	+	−	+	−	−	−	ND	−	+	−	+	−	15/30	50%

TABLE 2 (Continued)

Patient number	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	Number	Percentage
Skeletal anomalies																		
Advance bone age (≥1 y)	ND	ND	ND	ND	ND	ND	ND	+ (+2 y)	+ (+1 y 6 mo)	ND	− (−3 y 6 mo)	ND	− (−2 y 2 mo)	ND	− (+4 mo)	− (delayed)	7/15	47%
Rib anomalies	ND	ND	−	ND	ND	ND	−	11 pairs	−	ND	−	ND	ND	ND	−	−	4/17	24%
Brachydactyly	ND	−	+	+	+	−	+ (Vth finger)	ND	+	−	+	−	+	−	−	−	9/29	31%
Clinodactyly	ND	−	ND	−	−	−	+ (Vth finger)	ND	−	−	−	+ (Vth finger)	−	−	−	+	6/28	21%
Tapering fingers	ND	ND	−	−	+	+	−	+	−	−	−	+	−	+	−	+	9/29	31%
Sacral dimple	+	ND	−	−	−	−	−	+	+	−	ND	−	ND	+	ND	−	8/25	32%
Other skeletal anomaly	ND	ND	Vertebral block	ND	ND	ND	Block C2-C3	ND	−	ND	Pectus excavatum	ND	ND	ND	ND	ND	Vertebral block 5	WO
Hairiness																		
Hypertrichosis cubiti	−	ND	+	−	−	+	−	−	+	+	−	−	+	+	+	−	19/31	61%
Hypertrichosis of the back	+	+	+	−	−	+	+	+	+	+	−	+	ND	ND	+	+	21/31	68%
Hypertrichosis of lower limbs	−	ND	ND	ND	−	ND	−	+	−	+	−	ND	+	+	−	ND	9/24	38%
Development and neurology																		
Hypotonia neonatal/ persistent	+/−	ND/ND	+/+	−/−	−/−	+/+	−/−	+/+	+/+	+/+	+/+	+/+	−/−	+/+	+/−	−/−	18/31−12/30	58%−40%
Developmental delay	+	+	+	ND	ND	+	−	+	+	+	+	+	+	+	+	+	24/30	80%
Intellectual disability	Mod.	Mild	Severe	Mod.	Mild	Mod.	Mod.	Severe	Severe	Severe	Mod.	Mod.	Mild	Mild	Mild	Mild	Mild 18/33 mod. 11/33 severe 4/33	Mild 55% mod. 33% severe 12%
Seizures	−	−	+	−	ND	−	+ (partial)	+ (absences)	−	−	+ (generalized)	−	−	−	−	−	4/31	13%
Age of walking (mo)	24	18	48	15	12	24	ND	0	48	0	36	18	42	22.5	32	15	23.9	WO
Behavioral disorder	Stereotypies	Auto-aggr. Instability	−	ND	ND	−	−	−	−	Stereotypies	−	Aggr.	ASD	ASD	−	−	10/31	32%
Organic problems																		
Cerebral	ND	−	Partial CC agenesis	−	ND	Vermis hypoplasia ventricular asymmetry	PVNH−Chiari	Dysgenesis of CC	−	−	−	−	−	−	Polymicrogyry enlarged pericerebral space	−	10/29	34%
Eye	Hyperopia, strabismus	Bilateral ptosis oculomotor trouble	−	Strabismus myopia	−	−	Astigmatism	Bilateral ptosis strabismus astigmatism lachrymal stenosis	−	Myopia astigmatism	Strabismus	−	Hyperopia ptosis retinal anomaly	−	Hyperopia	Ptosis	19/32	59%
Cardiac	Right aortic arc	Aortic insufficiency	PDA	Dilated left ventricle	ND	Bicuspid aortic valve	−	−	ND	−	−	−	−	ND	ND	Patent FO	8/22	36%
Renal	−	ND	Horseshoe	−	ND	−	−	Left pyelectasia, PUV	ND	−	−	−	−	Right pyelic hypotonia	Pyelectasis	Small kidneys	7/23	30%
Feeding difficulties	+	+	+	−	−	+	−	−	+	+ (dysphagia)	+	+	−	−	GERD	+	20/31	65%
Others	Splenomegaly		Inguinal hernia GERD			Dental malposition		Constipation frequent infections central apneas	Achilles' tendon retraction	GHD hyperpneas with cyanosis	GHD retrognathia small ears	Medial line movements	Asthma	Unilateral deafness	Bilateral cubitus valgus	Precocious teeth asthma frequent infections	GHD 6/12	WO

Abbreviations: aggr., aggressive behavior; ASD, autism spectrum disorder; CC, corpus callosum; dup, duplication; F, female; FO, foramen ovule; GERD, gastroesophageal reflux disease; GHD, growth hormone deficiency; M, male; mod., moderate; ND, not determined; PDA, patent ductus arteriosus; PVNH, periventricular nodular heterotopia; PUV, posterior urethral valve; VUR, vesicoureteral reflux; WG, week of gestation; WO, without object.

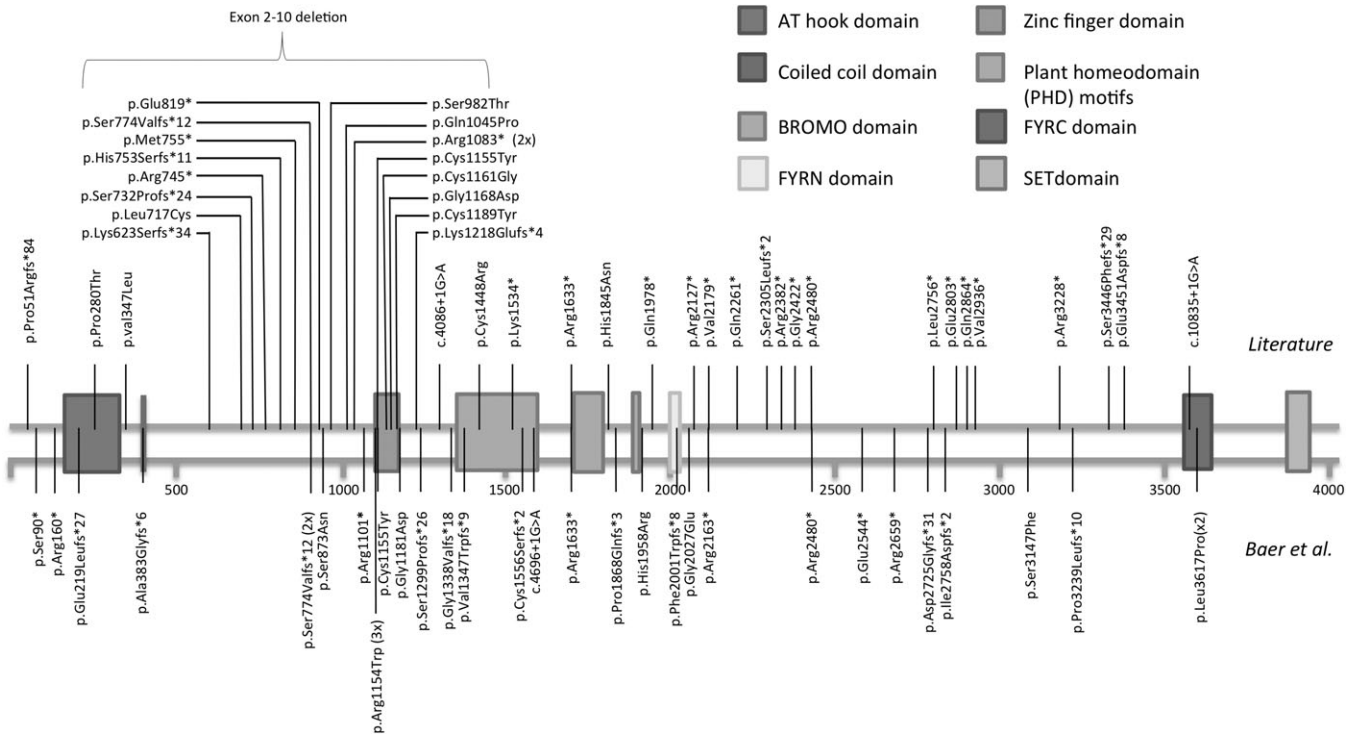

FIGURE 1 Schematic representation of the KMT2A domain structure with location of mutations causing WSS. Mutations reported in the literature were grouped in the upper part of the schema. When detailed clinical description of the patient was available, mutations were colored in green, and clinical data collected in Table S1. Mutations identified in patients of our cohort were grouped in the lower part of the schema. When a mutation was found in more than one patient, the symbol (×2) or (×3) was written behind its name

useful diagnostic sign, only 26 diseases in the OMIM database featuring a combination of sacral dimple and ID.

Although we observed a variety of hand anomalies (Figure 2C), the latter are not found in all patients with WSS. Tapering fingers are frequently observed, with a prevalence of 31% in our cohort and 50% in the literature, and may be associated with long fingers or brachydactyly.

Ophthalmological symptoms were present in 59% of the patient of our cohort. There were 7 cases of strabismus (22%), that is comparable with the prevalence of 33% observed in patients with WSS in the literature whereas in France, the prevalence of strabismus in the general population is around 3%.[32] Refractive disorders were also frequently encountered, including hyperopia (n = 9), astigmatism (n = 4) and myopia (n = 3). Ptosis was present in 5 cases. Lachrymal duct fistula was found in 2 cases (patients #2 and #4), and stenosis in 1 case (patient #25), these features were never noted in the literature. However, among the literature patients, several had unusual ophthalmologic anomalies, such as microphthalmia, optic nerve coloboma, orbital cysts, retinal detachment[18,33] and unilateral retinal atrophy in another patient.[9]

Eight of the patients in our cohort had cardiac defects. Patient #2 had inherited hypertrophic cardiomyopathy from his father (not affected by WSS) as a result of mutations in the *MYH7* and *MYBPC3* genes, not related to WSS. Patient #11 has Laubry-Pezzi syndrome, with the association of an atrial septal defect and aortic insufficiency. Like 5 patients reported in the literature, patient #20 has patent ductus arteriosus that is probably the most frequent cardiac anomaly observed in WSS. Most other cardiac defects, although episodically observed, concerned the aortic ejection pathway: right aortic arc (patient #18), aortic insufficiency (patient #19), bicuspid aortic valve (patient #23), dilated left ventricle (patient #21), and patent foramen ovale (patient #33).

ID seems to be a constant feature in WSS in our cohort and in the literature. However, the severity of ID varies from one case to another. In the literature, 12 patients had mild ID (12/20; 60%), 5 had moderate ID (5/20; 25%) and 3 had severe ID (3/20; 15%). Our cohort had much the same profile; 18 of the 33 documented patients had mild ID (18/33; 55%), 11 patients had moderate ID (11/33; 33%) and only 4 (4/33; 12%) had severe ID (including 2 with associated epilepsy and 1 with behavioral disorders). However, only few patients were evaluated with specific neuropsychological tests. We did not find any genotype-phenotype correlation in our cohort. For example, the patient #25 in our cohort with the c.3464G>A/p.Cys1155Tyr mutation presented severe ID and was unable to walk or talk at the age of 5, whereas a patient with the same mutation reported by Bramswig et al presented mild ID only.[9]

In WSS, ID is sometimes associated with seizures. One patient presented multidrug-resistant epilepsy[34] and 1 patient without molecular confirmation developed epilepsy controlled by Lamotrigine.[35] Three patients with epileptic encephalopathy were described in an exome-sequencing study.[21] In our cohort, 4 patients had experienced partial or tonic-clonic seizures. Three of these 4 patients had brain anomalies (periventricular nodular heterotopia, Arnold Chiari malformation, and corpus callosum anomalies). Overall, 4 patients in our cohort presented with corpus callosum malformations, including excessive fineness, hypoplasia, dysgenesis, and agenesis. In the literature, 1 patient had corpus callosum agenesis and 2 patients had corpus callosum hypoplasia.[10,30,36]

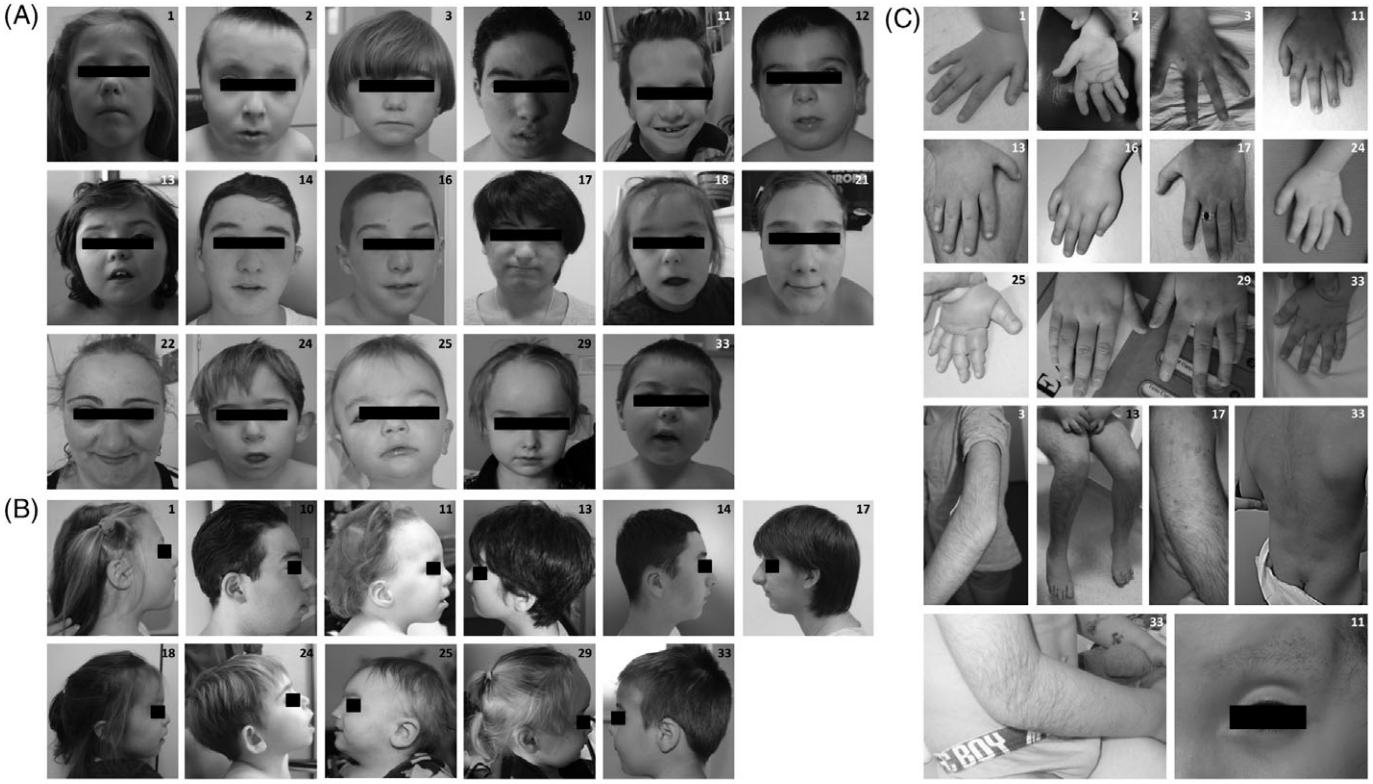

FIGURE 2 Photos of some patients of the cohort. (A) Front faces, (B) profile faces, (C) Other parts of their body especially hands, arms, legs and back. The numbers written on the pictures correspond to those used in Table 2 to designate each patient

Behavioral problems are frequent in WSS (32% in our cohort; 42% in the literature) and various including autism spectrum disorders, stereotypies, attention deficit, aggressiveness, anxiety and indiscriminately friendly behavior. The prevalence of these disorders has probably been underestimated and thus warrants further investigation.

Lastly, some symptoms were sporadically observed, coincidentally associated or not with WSS. For example, one patient was diagnosed before birth with posterior urethral valves, and also suffered from central and peripheral sleep apnoea. Narrow palate (patient #8), retrognathia (patient #28, and patient from the literature[33]), dental malposition (patient #23), rhinolalia (patient #6), early tooth eruption (patients #12 and #23) and submucosal cleft palate (twins already reported[37]) could suggest anomalies of oral development. Recurrent ear, nose and throat infections in childhood were reported for some patients (patients #12, #20, #25, #33). Interestingly in the literature, one patient died of sepsis[9] and another one exhibited immunodeficiency,[28,34] although none of the laboratory test performed in our cohort suggested the presence of this condition.

Recent research has suggested that *KMT2A* is a major gene in ID. Since 2011, the deciphering developmental disorders (DDD) study has included 14 000 children in the United Kingdom and Ireland with severe NDDs. Of these, 1133 patients underwent high-resolution exon-array CGH and trio-exome sequencing. Mutations in *KMT2A* were found in 5 patients, making this gene the 12th most likely to be involved in ID.[20] As a result, *KMT2A* was included in the HTS panel for ID at the investigating center in Strasbourg in January 2015. After large-scale HTS 450 ID-associated genes, de novo pathogenic *KMT2A* mutations were identified in 6 (patients #1, #10, #11, #12, #14 and #23) of 696 individuals with ID (0.86%). In these 6 cases, a diagnosis of WSS was not initially suspected. *KMT2A* was not sequenced in most of other large-scale HTS studies of ID.[38] A recent HTS study of 1256 genes certainly or potentially involved in ID (including *KMT2A*) revealed 2 de novo loss-of-function mutations in 92 sequenced individuals.[24] Although no mutations were identified in the first WES studies of patients with non-specific ID[39–42] the study populations were small (n < 120) and *KMT2A*'s implication in syndromic ID might not always have be known at the time. However, McRae et al recently reported at least 30 pathogenic mutations in *KMT2A* on the basis of enlargement of the DDD study to 4293 children with NDDs, and a meta-analysis of published WES results for 3287 other individuals with similar disorders (including ID, autism spectrum disorder, schizophrenia, and epilepsy).[23] This ranks *KMT2A* as the third most frequently mutated gene in autosomal forms of NDDs.

KMT2A encodes a histone methyltransferase that catalyzes the mono-, di-, and trimethylation of histone H3K4. In turn, this regulates chromatin-mediated transcription of *HOX* and *WNT* genes. The *KMT2A* protein contains 3969 amino acids and comprises a number of domains: 3 N-terminal DNA-binding AT-hooks, a cysteine-rich coiled-coil domain, 4 plant homeodomain finger motifs, a BROMO domain, a FYRN domain, a FYRC domain, and a C-terminal SET domain, which is responsible for the protein's histone-methyltransferase activity. The *KMT2A* mutations reported in this cohort and in the literature, were distributed without mutational hotspots (Figure 1).

In our cohort, we observed the vertical, 2-generation transmission of WSS in 3 unrelated families. The p.Leu3617Pro was found in

TABLE 3 Clinical guidelines for patients with Wiedemann-Steiner syndrome

Investigations to perform at the diagnosis:
- MRI and vertebral CT (looking for vertebral block and medullar consequences)
- Immunity check-up
- Growth hormone measurement if postnatal growth retardation
- Pedopsychiatric evaluation and follow-up if necessary.
- Ophthalmological examination
- ENT examination
- Echocardiography
- Abdominal echography
- EEG and cerebral MRI in case of neurological manifestation

Abbreviations: CT, computed tomography; EEG, electroencephalography; ENT, ear, nose and throat; MRI, magnetic resonance imaging.

a son (patient #21) inherited from his mother (patient #22), who also presented with a mild ID. The p.Ser3147Phe was found in patient #23 inherited from his mother. These familial observations prove that, in spite of ID, autosomal dominant transmission from one generation to the next is indeed possible in WSS. Interestingly, maternal transmission was observed in the 2 cases. This begs the question of whether there is a reduced reproductive fitness in males with ID, as it has been reported in 22q11.2 deletion, probably due to social and/or cultural pressure.[43] We also discovered the first ever case of parental mosaicism in WSS, with a non-affected father and 2 affected children, brother and sister (patients #27 and #28) bearing the p.Arg1154Trp mutation. The mutation was found in a very low proportion of the father's blood cells. This observation proves that a low frequency of mosaicism in a non-affected parent is associated with a high risk of WSS in the offspring. This observation should be considered in order to provide adequate genetic counseling.

KMT2A probably has an important role in the occurrence of hematological malignancies. In a murine model, knockout for a heterozygous mutation of the homologous *Kmt2a* gene resulted in growth retardation, and skeletal and hematopoietic abnormalities.[44,45]

Furthermore, a heterozygous missense variation in *KMT2A* (c.5533C>A/p.His1845Asn), predicted as to be "possibly damaging" by PolyPhen2, was reported in a family in which 4 members developed primary mediastinal large β-cell lymphoma. The 4 patients with lymphoma and 3 unaffected family members carried the variation.[29] If the individuals with the *KMT2A* variation were not considered to have WSS, this observation raises the question of whether hematological malignancies are likely in WSS. To date, none of the patients described here or in the literature has developed this complication. However, most patients are still young, with an average age of 10.67 years in our cohort, and 8.7 in the literature. Hence, it may be advisable to monitor patients WSS for the occurrence of malignancies (Table 3).

In conclusion, we reported on the largest yet cohort of individuals with WSS to date. We confirmed that the classical presentation of WSS associates an ID with hairy elbow, growth retardation and characteristic facial features; but we also showed that the clinical presentation varied markedly, in term of facial appearance (suggestive or not), hairiness, associated malformations, and ID severity. We described 3 cases of familial inheritance (2 maternal transmission and 1 blood mosaicism). Our cohort and the recent observations in the literature prove that *KMT2A* belongs to the major genes involved in syndromic or non-syndromic ID.

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CONFLICT OF INTEREST

The authors declare to have no conflict of interest.

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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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