Received: 29 June 2018 | Revised: 28 September 2018 | Accepted: 29 October 2018

DOI: 10.1002/ajmg.a.60698

WILEY AMERICAN JOURNAL OF medical genetics PART A

CLINICAL REPORT

The progression of Wiedemann–Steiner syndrome in adulthood and two novel variants in the *KMT2A* gene

Hailey R. Feldman[1] | Stephen R. Dlouhy[1] | Melissa D. Lah[1] | Katelyn K. Payne[2] | David D. Weaver[1]

[1]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana

[2]Section of Child Neurology, Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana

Correspondence
Hailey R. Feldman, MS, CGC, Maternal Fetal Medicine, Carilion Clinic, 101 Elm Ave Suite 400, Roanoke, VA 24013.
Email: hrfeldman@carilionclinic.org

Wiedemann–Steiner syndrome is a genetic condition associated with dysmorphic facies, hypertrichosis, short stature, developmental delay, and intellectual disability. Congenital malformations of the cerebral, cardiac, renal, and optic structures have also been reported. Because the majority of reported individuals with this condition have been under age 20, the long-term prognosis is not well defined. Here we report on two further unrelated individuals diagnosed with Wiedemann–Steiner syndrome, one of whom is in her third decade of life. In addition, both individuals have novel *KMT2A* mutations. The information provided below about the outcome in Wiedemann–Steiner syndrome is important for families of affected individuals.

KEYWORDS

hypertrichosis, hypertrichosis cubiti, *KMT2A*, lysine methyltransferase, Wiedemann–Steiner syndrome

1 | INTRODUCTION

In 1989, Wiedemann et al. reported on a boy with unusual facial features, hypertrichosis, short stature, and intellectual disability. The dysmorphic facial features included long eyelashes, thick and arching eyebrows and downslanting palpebral fissures. In 2000, Steiner & Marques, 2000 reported on an 8-year-old girl who had findings similar to those described by Wiedemann, Kunze, Gross, and Dibbern (1989). The patient had synophyrs, downslanting palpebral fissures, a high arched palate, fifth finger clinodactyly, hypertrichosis, short stature, hypotonia and intellectual disability. Her hypertrichosis increased with age. At least 62 additional reported cases have further delineated the condition, with dysmorphic facial features, hypertrichosis cubiti, short stature and intellectual disability being the key features (Aggarwal, Rodriguez-Buritica, & Northrup, 2017; Baer et al., 2018; Miyake et al., 2015; Sun et al., 2017).

In 2012, Jones et al. published that the gene causing Wiedemann–Steiner syndrome (WSS) was *KMT2A*. The gene is responsible for creating histone methyltransferase, an enzyme involved in post-translational modification of chromatin associated with the epigenetic process of methylation (Bogaert et al., 2017; Jones et al., 2012). Based on our knowledge of the *KMT2A* gene, the exact mechanism responsible for the features of WSS is still unexplained.

To our knowledge, there are only six adults described with WSS (Baer et al., 2018; Bogaert et al., 2017; Jones et al., 2012). Here we report on two further unrelated patients diagnosed with WSS. One of these patients is in her third decade of life and provides additional information on the features of WSS in adults. Both individuals also have novel mutations in the *KMT2A* gene.

2 | CLINICAL REPORT

2.1 | Patient 1

Our first patient initially presented for genetics evaluation at age 26 months with a history of mild dysmorphic features, pervasive developmental disorder, intellectual disability, and significant behavioral issues. The patient was born at 37 weeks gestation by cesarean section because of fetal distress. She had a birth weight of 2.75 kg (10th %tile) and a length of 47.0 cm (14th %tile). Her occipitofrontal circumference (OFC) at birth is not available. At her first evaluation, her height was 80.1 cm (5th %tile), her weight was 5.8 kg (5th %tile) and OFC was 49.1 cm (50th %tile). She also had synophrys, a small auricular left ear tag, left low-set and posteriorly rotated ear, a short philtrum, a narrow jaw and palate, brachydactyly with bilateral fifth

finger clinodactyly, a left single transverse palmar crease, mildly restricted flexion of the elbows, generalized hypertrichosis, edema of the hands and feet, and developmental delay. On her most recent evaluation at age 23 years, her height was 150.6 cm (4th %tile), her weight was 76.1 kg (86th %tile) and her OFC was 56.7 cm (75th % tile). She also had coarse facial features, a marked posteriorly sloping forehead, long eyelashes, thick eyebrows, downward slanting palpebral fissures, mild ptosis, telecanthus, slight micrognathia leading to dental malocclusion, an auricular left ear tag and general hypertrichosis that involved her eyebrows, shoulders, abdomen, lower back, elbows, arms and legs (Figure 1).

The family history is significant for a maternal cousin with cystic fibrosis and the paternal grandfather who died from complications of both Parkinson and Alzheimer diseases. Both sides of the family are of western European ethnicity. Parental consanguinity was denied.

Because of concerns for her delayed growth, she received growth hormone therapy for approximately 15 months when she was about 5 years old. Bone age studies performed when the patient was 3 years, 6 months and again when she was 4 years, 10 months showed the patient's skeletal maturity to be appropriate for her chronologic ages. A renal ultrasound at 3 years was normal with no structural abnormalities or cystic masses noted. Pelvic ultrasound at both 3 years and 19 years were normal. The patient was evaluated for a heart murmur as an infant, the evaluation was reported to be unremarkable and the murmur subsequently resolved spontaneously. A brain MRI at 8 years was also insignificant, with no brain malformations noted. Although she weighed 5.8 kg (5th %tile) at 26 months old, she now is overweight with a BMI of 33.9. Immunological function has not been studied in this patient but she does not have a history of recurrent infections.

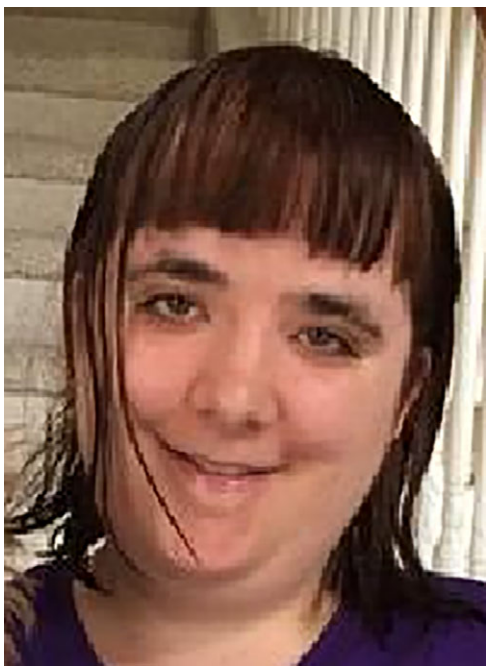

FIGURE 1 The patient at age 24 years. Note the patient's thick and arching eyebrows, broad nasal tip, and downslanting palpebral fissures [Color figure can be viewed at wileyonlinelibrary.com]

The patient had developmental delay when she was first seen in our clinic at 26 months. At that time, she had been diagnosed with pervasive developmental disorder, a diagnosis which now has been revised to autism spectrum disorder. At approximately age 16 years, she had a full-scale IQ score of 71 with a verbal IQ of 82 via the Wechsler Adult Intelligence scale. She was able to obtain a general equivalency diploma (GED) from her high school where she took life skills classes that were focused on independent living skills. After she received her GED, her parents removed her from school at 18 years old, because of behavioral concerns. Previously, at the age of 16, anger issues developed, which at times have, escalated to hitting and yelling at others. These behaviors worsened significantly between the ages of 17 and 19 years. At this time, she became more paranoid, violent, argumentative and noncompliant. She also became more anxious and began lying more frequently. Because of her behaviors, she now meets regularly with a psychiatrist. Medications to treat her behavioral issues and anxiety have included venlafaxine, iloperidone, and gabapentin. These medications have been of minimal help in the past.

Genetic testing performed over the last 23 years has included oligo comparative genomic hybridization, Sanfilippo disease panel, transferrin isoelectric for congenital disorders of glycosylation, atypical Rett syndrome panel, Prader–Willi syndrome chromosome deletion testing, DiGeorge syndrome testing via subtelomeric FISH, 21-alpha-hydroxylase mutation analysis, telomere rearrangement, fragile X analysis and karyotype, all of which were normal. Whole blood and skin fibroblast chromosomal analysis did not find mosaic Turner syndrome. She additionally had normal lactate, pyruvate, serum amino acids, carnitine level, acylcarnitine profile and urine genetics screen. At the age of 21 years, she had whole exome sequencing (WES) through GeneDx that revealed she is heterozygous for a pathogenic de novo mutation in the *KMT2A* gene (c.6079+1G>C, p.IVS23+1G>C), a mutation consistent with the diagnosis of WSS.

Additional history includes that when the patient was 8 years old; she was diagnosed with late onset adrenal hyperplasia and at 16 years with hyperlipidemia. She had a serum triglyceride level of 167 mg/dL (reference range < 150 mg/dL), cholesterol 222 mg/dL (reference range < 200 mg/dL), and low-denisty lipoprotein of 104 mg/dL (reference range < 100 mg/dL). She now takes 10 mg atorvastatin daily. Further, at 23 years old, she was diagnosed with irritable bowel syndrome and later with narcolepsy complicated by obstructive sleep apnea. For her narcolepsy, she has been treated with modafinil and for her sleep apnea continuous positive airway pressure at night. Currently, our patient lives in an apartment with one other roommate who also has special needs. Both are supervised by visiting support staff. At present, she works part time (~15 hr per week) at two different jobs, one of which she has held for the last 2.5 years. She also volunteers at her local church.

2.2 | Patient 2

The second subject is a 2-year-old male who we first evaluated at 17 months for developmental delay and microcephaly. The patient was born at 37 weeks gestation by spontaneous vaginal delivery following a pregnancy complicated by intrauterine growth restriction and oligohydramnios. He had a birth weight of 2.49 kg (4th %tile). His

birth length and OFC are not available. Head and cervical CT scans and MRIs at 16 months for evaluation of his microcephaly showed normal brain structure with no appearance of intracranial calcifications and a normal skull with symmetrical sutures, but also revealed narrowing at the craniocervical junction with mild posterior indentation at the upper cervical cord and possible C1 compression. At that time his OFC was 44.5 cm (−2.34 *SD*). At 24 months, his OFC had not increased much and was 45.0 cm (−2.58 *SD*). In addition to the above findings, the patient also has had developmental delay. He first sat unassisted at 10 months, crawled at 11 months and started walking at 17 months. Immunological, renal, and cardiac evaluations have not been performed.

On physical exam, at 17 months, the patient had mild microcephaly (44.5 cm, −2.43 *SD*), plagiocephaly without cranial suture ridging, slightly upturned nose, neck pterygia, and normal extremities with average muscle tone and strength. He did not have hypertrichosis at that time and is not known to have developed it. There is no family history of WSS or other genetic conditions. The patient's ethnicity is unknown, but both sides of the family are of Caucasian race. Consanguinity was denied.

Chromosomal microarray analysis was normal, however, a GeneDx Microcephaly Xpanded Panel revealed a single de novo pathogenic mutation in the *KMT2A* gene, consistent with WSS. The patient's mutation is c.173dupC (p.A59GfsX88), a mutation that has not previously been reported in this gene.

3 | DISCUSSION

Our first patient was diagnosed with WSS at the age of 23 years by WES with a pathogenic and novel mutation in the *KMT2A* gene. She has mild intellectual impairment with an IQ score of 71, mild dysmorphic facial features, hypertrichosis, major behavioral problems, and obesity as an adult. Our second patient is a 2-year-old male with microcephaly, mild dysmorphic features, and significant developmental delay. He also has a novel mutation in the *KMT2A* gene.

There have been more than 62 mutation-confirmed patients with WSS. In 2017, Sun et al. reviewed 21 patients with WSS and found that all of these individuals had generalized hypertrichosis, postnatal growth restriction, development delay, and intellectual disability. Additional common findings reported by these authors included hypotonia (77%), narrow and downslanting palpebral fissures (80%, 94%), long eyelashes (94%), and a wide nasal bridge (94%). Hypertrichosis cubiti was reported in 63% of individuals from the study by Sun et al. (2017). In a recent publication, Aggarwal et al. (2017) cited that out of 26 individuals with WSS, 88% had developmental delay and 85% had postnatal growth restriction. Facial features such as thick eyebrows, long eyelashes, a wide nasal bridge, broad nasal tip, and downslanting palpebral fissures were also present in 46–62% of individuals. In addition, fifth finger clinodactyly was present in 35% of individuals.

A more recent review by Baer et al. (2018) reported on 33 individuals with WSS. Out of these 33 individuals, all were reported to have intellectual disability and up to 75% of individuals were reported to have at least one dysmorphic facial feature. Dysmorphic facial features in this group most commonly included small palpebral fissures (72%), a wide nasal bridge (71%), and a thin upper lip (75%). Thirty percent of individuals in this cohort had generalized postnatal growth restriction, whereas 47% had postnatal height restriction. Additional common findings reported by these authors included congenital birth defects of the heart (36%), eye (59%), and kidneys (30%).

Other features in WSS have been reported. Enokizono et al. (2017) found preaxial polydactyly, a finding previously not associated with WSS. Small hands and feet, prominent digit pads, and advanced bone age have also been published (Baer et al., 2018; Enokizono et al., 2017; Koenig, Meinecke, Kuechler, Schafer, & Muller, 2010; Mendelsohn, Pronold, Long, Smaoui, & Slavotinek, 2014). In 2015, Calvel et al. (2015) reported on a female with WSS who also had gonadal dysgenesis, a finding previously not described. Additionally, 63% individuals with WSS in one study by Sun et al. (2017) and 61% of individuals with WSS from another study by Baer et al. (2018) had hypertrichosis cubiti, which is an uncommon dysmorphic feature. There latter observations are interesting given that hypertrichosis cubiti was once considered a defining feature of WSS, affecting almost all individuals reported with the condition. When present, however, this finding likely raises the chance that the diagnosis is WSS.

While it is thought that haploinsufficiency of *KMT2A* is responsible for the features of WSS, the exact mechanism by which individual features develop is still unexplained by our understanding of *KMT2A* (Jakovcevski et al., 2015; Lebrun et al., 2017; Sun et al., 2017). However, what we do know of the mechanism suggests an autosomal dominant pattern of inheritance (Jakovcevski et al., 2015; Lebrun et al., 2017). The gene causing WSS, *KMT2A*, was first reported by Jones et al. (2012). These investigators performed WES on six patients with the clinical diagnosis of WSS. They found five had truncating mutations in the *KMT2A* gene whereas the other individual had no identifiable genomic alterations. Since then, an additional 28 individuals have been found to have *KMT2A* mutations (Aggarwal et al., 2017; Miyake et al., 2015; Sun et al., 2017), supporting that pathogenic mutations in this gene cause WSS.

The majority of mutations associated with WSS have been frameshift mutations, exonic deletion, nonsense mutations and splice site variants (Jones et al., 2012; Min Ko et al., 2017). Missense mutations have been cited as the underlying etiology less frequently (Baer et al., 2018; Strom et al., 2014). Our first patient's mutation, c.6079+1G>C (p.IVS23+1G>C), has not been previously reported in the literature or in the Leiden Open Variation Database (LOVD) for *KMT2A*. Her mutation is a splice site mutation that is predicted to lead to abnormal gene splicing and ultimately an abnormal protein product. As yet, no genotype–phenotype correlations have been associated with splice site variants in the *KMT2A* gene.

Our second patient's mutation, c.173dupC (p.A59GfsX88), is also a novel variant, and has not been identified in the literature or in the LOVD for *KMT2A*. The cytosine duplication results in a frame-shift at codon 59, changing an alanine to a glycine. This change creates a premature stop codon, which is predicted to lead to protein dysfunction. Other frame-shift mutations in the *KMT2A* gene have been reported, but at this point do not appear to offer any specific genotype–phenotype correlation (Jones et al., 2012; Miyake et al., 2015).

Additionally, review of the literature does not suggest any genotype–phenotype correlations with exonic deletion, nonsense or missense mutations.

The average age of diagnosis of WSS appears to be 9.8 years with a range from 1 to 46 years in the 62 molecularly confirmed cases we cited in the literature (cases that did not provide age of individuals were excluded). Jones et al.'s (2012) cohort were ages 6, 8, 8, 12, and 24 years. Miyake et al. (2015) described six others with ages 3, 3, 4, 4, 8, and 9 years. Other reported individuals have been 1 and 10 years (Strom et al., 2014), 4 years (Mendelsohn et al., 2014), 10 and 10 years (Dunkerton et al., 2015), 1.83 years (Bramswig et al., 2015) 1.75 years (Steel et al., 2015), 1.75 years (Yuan et al., 2015) 14 years (Stellacci et al., 2016), 4 and 6 years (Sun et al., 2017), 11 and 46 years (Bogaert et al., 2017), 12 years (Enokizono et al., 2017), 4.2 and 8 years (Min Ko et al., 2017). Baer et al. (2018) reported 33 individuals with WSS who had ages ranging from 3 to 36 years. Because of the limited number of teenagers and adults reported, our understanding of older patients is limited. This lack of information leaves parents and clinicians alike with little knowledge as to the capabilities of individuals with this syndrome in adulthood.

There have been only six adults published with WSS. The first one, reported by Jones et al. (2012), was a 24-year-old female. The patient's description included her having thick eyebrows, long eyelashes, down-slanting palpebral fissures, a wide nasal bridge with a broad tip, a thin upper vermillion, and general hypertrichosis including the elbows, patent ductus arteriosus and mild developmental delay. The second adult patient was reported by Bogaert et al. (2017). These authors were performing WES on individuals with syndromic early-onset primary antibody deficiency. In one family, WES revealed that a set of 11-year-old monozygotic male twins had pathogenic mutations in *KMT2A* (c.10835+1G>A) indicating the twins had WSS. Subsequent testing of their parents revealed that the mother possessed the same *KMT2A* mutation. She reportedly had mild intellectual disability and dysmorphic facial features consisting of hypertelorism, downslanting palpebral fissures, a wide nasal bridge with a broad nasal tip, a thin upper lip, micrognathia and thick eyebrows and undetectable serum IgM. The authors did not state if she had hypertrichosis. At the time of their report, she was 46 years old.

Most recently, in 2018, Baer et al. (2018) reported four adults with WSS. These authors reported on one adult male, age 22 years, and three adult females, ages 18, 22, and 36 years (Baer et al., 2018). Description of the male patient included thick eyebrows, hypertelorism, small and downslanting palpebral fissures, a wide nasal bridge, low set ears, hyperphagia and mild intellectual disability. It was noted that he did not have hypertrichosis. The youngest adult female (18 years) reported in this cohort, was described as having hypertelorism, small palpebral fissures, strabismus, a wide nasal bridge, hypertrichosis cubiti, hypertrichosis of the lower limbs, and mild intellectual disability. The 22-year-old adult female had hypertelorism, strabismus, a wide nasal bridge, small ears, retrognathia, and moderate intellectual disability. She did not have hypertrichosis. The final adult, a female of 36 years, was reported to have long eyelashes, small palpebral fissures, a wide nasal bridge, thin upper lip, low-set ears, and mild intellectual disability. She did not have hypertrichosis. None of these

TABLE 1 A comparison of features between our adult, Patient 1 and other adults with WSS reported in the literature

	Patient 1	Adult 1 Jones et al. (2012)	Adult 2 Bogaert et al. (2017)	Adult 3 Baer et al. (2018)	Adult 4 Baer et al. (2018)	Adult 5 Baer et al. (2018)	Adult 6 Baer et al. (2018)
Age (at last examination)	23 y	24 y	46 y	22 y	18 y	36 y	22 y
Dysmorphic facial features	+	+	+	+	+	+	+
Congenital anomalies	–	Patent ductus arteriosus	NS	Strabismus	–	–	–
General hypertrichosis	+	+	NS	–	+	–	–
Hypertrichosis cubiti	+	+	NS	–	+	–	–
Postnatal weight	+1.14 *SD*	–0.7 *SD*	NS	NS	–1 *SD*	+7.4 *SD*	–1.4 *SD*
Postnatal height	–1.95 *SD*	–2.19 *SD*	NS	–2.1 *SD*	–1.9 *SD*	–0.7 *SD*	–2.2 *SD*
Level of intellectual disability	Borderline	Mild	Mild	Mild	Mild	Mild	Moderate
Behavioral concerns	Aggression, anxiety, and autism spectrum disorder	–	NS	–	NS	NS	–
Sleep apnea/ sleep disturbances	+	–	NS	–	–	–	–
Other	Micrognathia	Sacral dimple	Undetectable serum IgM and micrognathia	Micrognathia	Brachydactyly	Brachydactyly	Retrognathia, small ears, pectus excavatum, and brachydactyly

Abbreviations: NS = not stated; *SD* = standard deviation; y = years old.

adults were reported as having congenital cerebral, cardiac, or renal anomalies.

Similar to our Patient 1, the above six adults had dysmorphic facial features, however the features varied between individuals and included, but were not limited to, thick brows (4/7), long eyelashes (4/7), downslanting palpebral fissures (4/7), and a wide nasal bridge (6/7). Bogaert et al.'s (2017) adult patient and Baer et al.'s (2018) 22-year-old male patient also had micrognathia, as did our Patient 1. Baer et al. (2018) reported an additional adult with mandibular malformation; the 22-year-old female in their study had retrognathia. General hypertrichosis including the elbow is present in our Patient 1 and Jones et al. (2012) adult patient. However, three out of four of Baer et al.'s (2018) adult patients did not have hypertrichosis. Only one had hypertrichosis, which included the elbow (Baer et al., 2018). While our adult Patient 1 has a history of psychiatric disturbance, anxiety and obstructive sleep apnea, none of the other reported adult patients have had these features. Steel et al. (2015) did report on a 21-month-old female who had obstructive sleep apnea, however her apnea resolved by the time she was 15-month-old. Although six out of seven adults compared here did not have behavioral issues, Baer et al. (2018) did report that 32% of individuals in their study had a behavioral disorder. These authors also reported that 100% of individuals in their cohort had some level of intellectual disability, a finding equally demonstrated within the adult population detailed here (Baer et al., 2018). Lastly, similar to our Patient 1, Baer et al. (2018) reported one of their adult patients as having obesity, a less common finding in individuals with WSS (Table 1).

While it appears that many of the features seen in children with WSS are also present in adults with this condition, the adult patient we present here has other features not reported in either age group. This likely expands the clinical phenotype of WSS. Based on past history, the diagnosis of WSS is infrequently made clinically in adults. However, because of the wider use of WES, there likely will be more adult individuals diagnosed with this condition in the future. If this is the case, it will be interesting to see if these adults have other unique features not previously seen in affected children.

ACKNOWLEDGEMENT

The authors would like to thank our patients, their families, the clinicians who continue to care for them and the WSS Facebook group for providing support for individuals and families of individuals with WSS.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Hailey R. Feldman https://orcid.org/0000-0003-4813-377X
David D. Weaver https://orcid.org/0000-0002-8312-8995

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How to cite this article: Feldman HR, Dlouhy SR, Lah MD, Payne KK, Weaver DD. The progression of Wiedemann–Steiner syndrome in adulthood and two novel variants in the *KMT2A* gene. *Am J Med Genet Part A*. 2019;179A:300–305. https://doi.org/10.1002/ajmg.a.60698