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NLM Citation: Sheppard SE, Quintero-Rivera F. Wiedemann-Steiner Syndrome. 2022 May 26. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Wiedemann-Steiner Syndrome

Synonym: *KMT2A*-Related Neurodevelopmental Disorder

Sarah E Sheppard, MD, PhD[1] and Fabiola Quintero-Rivera, MD[2]

Created: May 26, 2022.

Summary

Clinical characteristics

Wiedemann-Steiner syndrome (WSS) is characterized by developmental delay, intellectual disability, and characteristic facial features, with or without additional congenital anomalies. The facial features include thick eyebrows with lateral flare, vertically narrow and downslanted palpebral fissures, widely spaced eyes, long eyelashes, wide nasal bridge, broad nasal tip, thin vermilion of the upper lip, and thick scalp hair. About 60% of affected individuals have hypertrichosis cubiti ("hairy elbows"), which was once thought to be pathognomic for the syndrome, with a majority having hypertrichosis of other body parts. Other clinical features include feeding difficulties, prenatal and postnatal growth restriction, epilepsy, ophthalmologic anomalies, congenital heart defects, hand anomalies (such as brachydactyly and clinodactyly), hypotonia, vertebral anomalies (especially fusion anomalies of the cervical spine), renal and uterine anomalies, immune dysfunction, brain malformations, and dental anomalies.

Diagnosis/testing

The diagnosis of WSS is established in a proband with suggestive findings and a heterozygous pathogenic variant in *KMT2A* identified by molecular genetic testing.

Management

Treatment of manifestations: Feeding therapy with possible supplemental tube feeding for those with poor weight gain / failure to thrive; growth hormone therapy for those with growth hormone deficiency; thyroid replacement therapy for hypothyroidism; consideration of IVIG therapy in those with low antibody levels; consideration of prophylactic antibiotics in those with frequent infections; stool softeners or osmotic agents for bowel dysfunction; oculoplasty for blepharoptosis; CPAP, BiPAP, or surgical removal of the tonsils and adenoids for those with obstructive sleep apnea; behavioral therapy; standard treatment for epilepsy, developmental delay / intellectual disability, congenital hip dysplasia, cervical vertebral fusion, eye anomalies, congenital heart defects,

Author Affiliations: 1 Unit on Vascular Malformations, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland; Email: sarah.sheppard@nih.gov. 2 Division of Genetic and Genomic Medicine, Departments of Pathology, Laboratory Medicine, and Pediatrics, School of Medicine, University of California, Irvine; UC Irvine Health, Orange, California; Email: fabiolaq@hs.uci.edu.

renal anomalies, uterine anomalies, and metabolic bone disease (which may include vitamin D supplementation).

Surveillance: At each visit: measurement of growth parameters; evaluation of nutritional status; assessment for constipation; evaluation for new neurologic features and seizure activity with EEG follow up as indicated; assessment of clinical signs of medullar compression; monitoring for signs/symptoms of arrhythmia; assessment of developmental progress, behavior, and physical skills; monitoring for frequent infections. Dental evaluation every six months after the eruption of primary teeth. Assessment for premature thelarche or primary amenorrhea in childhood until growth/menarche is complete. Ophthalmologic evaluation annually, or as clinically indicated.

Agents/circumstances to avoid: The authors are aware of one individual with WSS who developed hyperammonemia with the use of the anti-seizure medication valproate. While this is not specific to individuals with WSS, valproate should be used with caution.

Pregnancy management: In affected pregnant women who have a seizure disorder, discussion of the most appropriate anti-seizure medication regimen during pregnancy is recommended. Cervical spine anomalies may lead to immobility or instability, which may complicate airway management. Vertebral anomalies or scoliosis in the thoracic or lumbar spine may complicate spinal or epidural anesthesia.

Genetic counseling

Most individuals diagnosed with WSS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant. Rarely, individuals diagnosed with WSS have an affected parent. In this situation, WSS can be inherited in an autosomal dominant fashion. Each offspring of an individual with WSS is at a 50% risk of being affected. Once the *KMT2A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Wiedemann-Steiner syndrome (WSS) have been published.

Suggestive Findings

Wiedemann-Steiner syndrome **should be suspected** in individuals with the following clinical, imaging, and family history findings.

Clinical findings

- Distinctive facial features (Figures 1, 2, 3)
- Hypertrichosis cubiti ("hairy elbows"), hypertrichosis of the back, and/or hypertrichosis of the lower limbs
- Sacral dimple
- Developmental delay / intellectual disability
- Hypotonia
- Feeding difficulties
- Failure to thrive
- Short stature
- Constipation

Imaging findings

- Abnormal brain MRI, most commonly demonstrating abnormalities of the corpus callosum or abnormal myelination

- Congenital heart disease
- Genitourinary anomalies, most commonly vesiculouretal reflux with hydronephrosis, cryptorchidism in males, or absent uterus in females
- Vertebral anomalies, especially fusion anomalies in the cervical spine

Family history. Because WSS is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of WSS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *KMT2A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *KMT2A* variant of uncertain significance does not establish or rule out a diagnosis. (3) Because KMT2A is a histone methyltransferase that regulates chromatin-mediated transcription (see Molecular Genetics), it has the ability to alter the epigenetic state of the genome; as such, assessment of the epigenetic signature may be considered to aid in the interpretation of the pathogenicity of a variant of uncertain clinical significance.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype. Methylation studies, such as an epigenetic signature, can be considered in those individuals who have suggestive findings but in whom no pathogenic variant in *KMT2A* has been identified via sequence analysis or genomic testing.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas comprehensive genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with intellectual disability are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of WSS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *KMT2A* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **An autism / intellectual disability multigene panel** that includes *KMT2A* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some

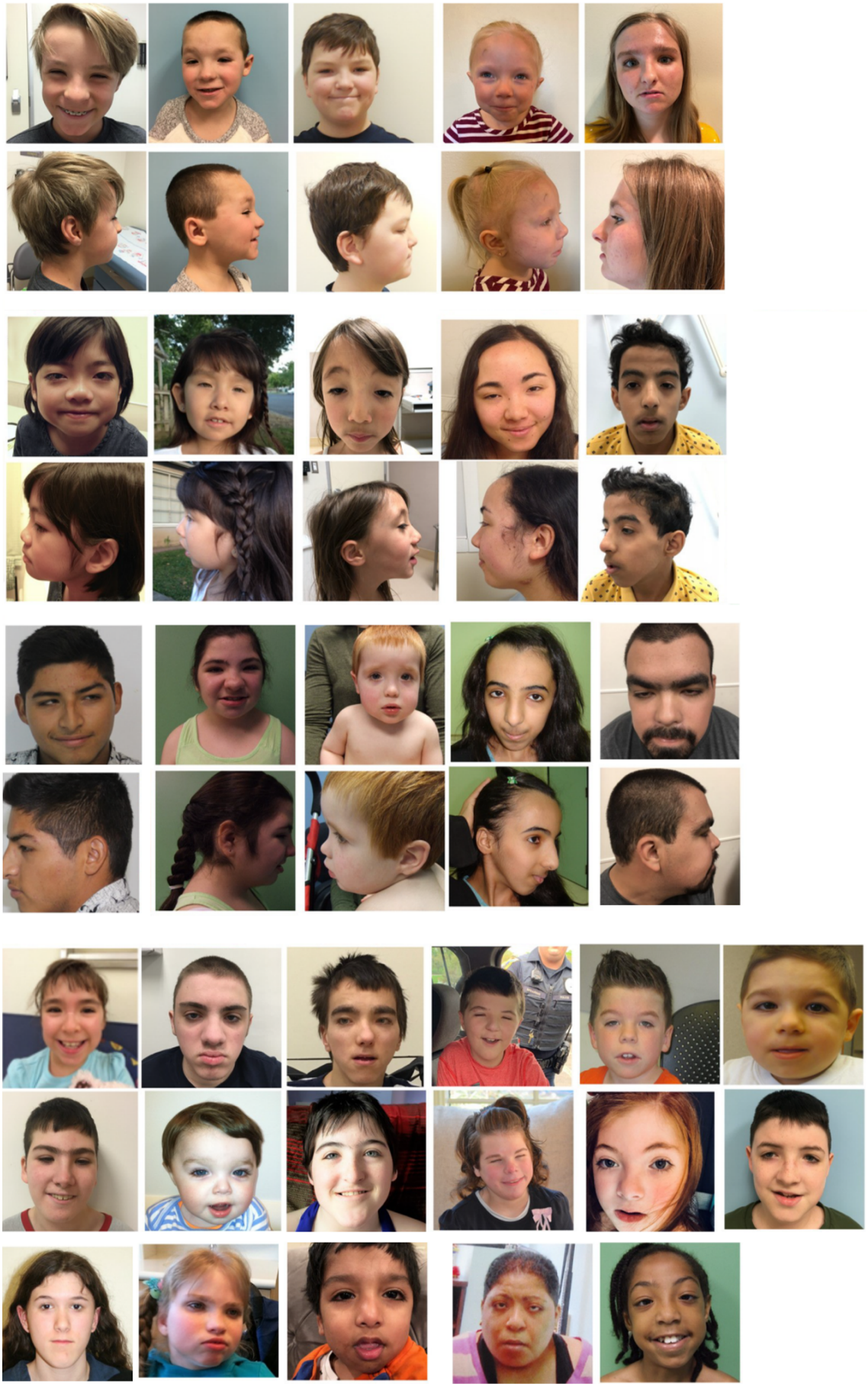

Figure 1. Individuals with characteristic facial features of Wiedemann-Steiner syndrome; first 15 are shown in front and side views.

Modified from Sheppard et al [2021]

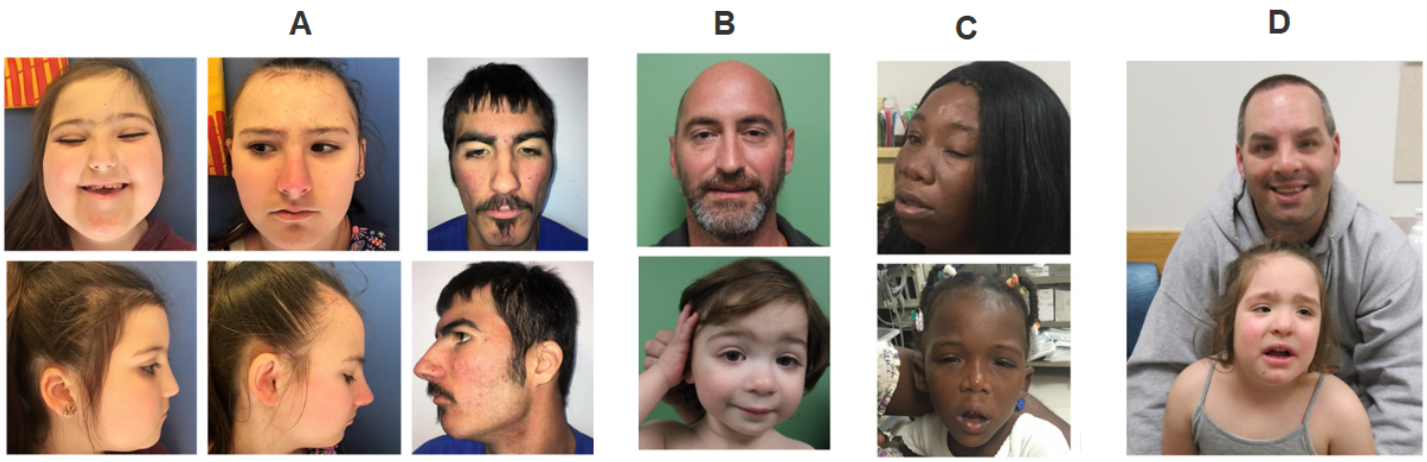

Figure 2. Individuals with characteristic facial features of Wiedemann-Steiner syndrome: family groups

A. 3 sibs shown in front and side views

B. Father and son

C. Mother and daughter

D. Father and daughter

Modified from Sheppard et al [2021]

laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by intellectual disability, comprehensive genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If testing for single-nucleotide pathogenic variants is normal but the suspicion for WSS remains high, methylation testing, including epigenetic signature, can be considered.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Figure 3. Eight individuals with Wiedemann-Steiner syndrome shown as they age

Modified from Sheppard et al [2021]

Table 1. Molecular Genetic Testing Used in Wiedemann-Steiner Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KMT2A	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Chan et al [2019], Sheppard et al [2021]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.

Clinical Characteristics

Clinical Description

Wiedemann-Steiner syndrome (WSS) is characterized by developmental delay, intellectual disability, and characteristic facial features, with or without additional congenital anomalies. To date, more than 200 individuals have been reported in the medical literature with a pathogenic variant in *KMT2A* [Jones et al 2012, Mendelsohn et al 2014, Strom et al 2014, Bramswig et al 2015, Calvel et al 2015, Steel et al 2015, Yuan et al 2015, Miyake et al 2016, Stellacci et al 2016, Aggarwal et al 2017, Bogaert et al 2017, Enokizono et al 2017, Min Ko et al 2017, Sun et al 2017, Baer et al 2018, Lebrun et al 2018, Li et al 2018, Stoyle et al 2018, Chan et al 2019, Chen et al 2019, Feldman et al 2019, Negri et al 2019, Giangiobbe et al 2020, Matis et al 2020, Mendoza 2020, Demir et al 2021, Di Fede et al 2021, Nardello et al 2021, Sheppard et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Wiedemann-Steiner Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Developmental delay / Intellectual disability	97%	
Characteristic dysmorphic features	~75%	Most typically thick eyebrows, long eyelashes, widely spaced eyes, narrow & downslanted palpebral fissures
Hypotonia	~63%	
Constipation	50%	
Failure to thrive	64%	
Feeding difficulties	62%	Generally only in infancy & childhood
ENT issues	63%	About 60% of the cohort in Sheppard et al [2021] had an ENT issue; issues also reported in other cohorts incl obstructive sleep apnea (18%), hearing loss (3%), & submucous cleft palate (3%).
Hypertrichosis	44%-75%	Most frequently of the face (thick eyebrows [73%] & long eyelashes [75%]), followed by the back (69%), elbows (58%), & lower limbs (44%)

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Short stature [1]	~57%	
Abnormal brain imaging	~49%	Most commonly abnormal corpus callosum or abnormal myelination
Dental anomalies [2]	57%	Incl advanced dental age w/premature loss of deciduous teeth & emergence of secondary teeth at atypical earlier age
Sacral anomaly	~45%	Most commonly sacral dimple, followed by tethered cord & spina bifida occulta
Vertebral anomalies	46%	Most commonly fusion anomaly in cervical spine
Abnormalities in genitourinary system	~46.8%	Renal anomalies (29%); also uterine, testicular, & external genitalia anomalies
Neuropsychiatric differences	17%-38%	Hyperactivity (38%), aggressive behavior (28%), & ASD (17%)
Ophthalmologic abnormalities	18%-32%	Most commonly strabismus, followed by astigmatism & blepharoptosis
Cardiac abnormalities	29%	Most commonly patent ductus arteriosus & ventriculoseptal defects
Endocrinologic issues	30%-64%	Incl growth hormone deficiency (30%), premature adrenarche (27%), pituitary abnormality seen on brain MRI (64%), & abnormal bone age (63%)
Seizures	18%	Incl focal, absence, & generalized
Immunologic issues	21%-54%	Abnormal immunoglobulin levels, insufficient response to pneumococcal vaccinations, recurrent infections (21%)

ASD = autism spectrum disorder; ENT = ears, nose, throat
1. Defined as length/height that is more than two standard deviations below the mean for age and sex or less than the fifth centile, or postnatal growth failure
2. Aggarwal et al [2017], Sheppard et al [2021]

Characteristic dysmorphic features. Hypertrichosis cubiti, initially thought to be pathognomonic, is present in the majority of affected individuals [Strom et al 2014, Aggarwal et al 2017, Baer et al 2018, Sheppard et al 2021]. Characteristic facial features:

- Thick eyebrows
- Long eyelashes
- Vertically narrow palpebral fissures
- Widely spaced eyes
- Wide nasal bridge with broad or bulbous tip
- Lateral (or other) flare to the eyebrow
- Downslanted palpebral fissures
- Blepharoptosis
- Exaggerated Cupid's bow
- Thin vermilion border to the upper lip
- Posteriorly rotated ears

Developmental delay. Most affected individuals have delayed developmental milestones, and some remain nonverbal and nonambulatory [Baer et al 2018, Li et al 2018, Chan et al 2019, Sheppard et al 2021]. The median ages for developmental milestones:

- **Sitting.** Ten months (range 6-36 months)

- **Standing.** 17 months (range 8-60 months)
- **Walking.** 20 months (range 11-60 months)
- **First words.** 18 months (range 8-60 months)

Intellectual disability and educational achievement. Most affected individuals require some degree of special education, but the majority of adults in one study completed high school.

- Some affected individuals are able to maintain jobs as adults.
- IQ in those tested ranges from 40 to 85 (median 65).
- For more detailed information on developmental and learning issues, see Feldman et al [2019] and Sheppard et al [2021].

Behavioral problems. About 30% of affected individuals have aggressive behavior such as self-harm, though some also have physical aggression and tantrums. About 20% of affected individuals have autistic features suggestive of an autism spectrum diagnosis. Many children with WSS are described by their families as sweet and having a happy demeanor [Sheppard et al 2021].

Growth. Most individuals have birth weights below the 25th centile.

- Weight remains below the fifth centile for age in about one third of affected individuals.
- Almost 60% of affected individuals have short stature (defined as height <5th centile for age and sex OR 2 SD below the mean for age and sex OR "postnatal growth failure").

  Bone age radiographs were abnormal (delayed, advanced, or disharmonic – i.e., different levels of maturation) in almost 65%.
- About one third of affected individuals have microcephaly (head circumference >5th centile for age OR 2 SD below the mean for age).

Gastrointestinal. About two thirds of affected individuals have a history of failure to thrive (FTT) and feeding difficulties, but fewer than one quarter require tube feeding. FTT can be transitory and nasogastric tube feedings can be temporarily useful. Constipation is present in about half of affected individuals and is more common in those with associated FTT.

Neurologic

- Sacral anomaly, most commonly a sacral dimple, was seen in about 45% of affected individuals. Other sacral anomalies include spina bifida occulta and tethered cord requiring surgery.
- Hypotonia is present in about two thirds of affected individuals.
  - Hypotonia can be present at birth and may lead to recommendation for a gastrostomy tube or nasogastric tube.
  - Some individuals continue to require supplemental nutrition through their gastrostomy tube.
  - Hypotonia appears to improve over time in some.
- Seizures are present in almost one fifth of affected individuals.
  - Seizure types include absence, partial complex epilepsy, eyelid myoclonia, tonic-clonic, febrile seizures, and infantile spasms [Helbig et al 2016].
  - Epileptic encephalopathy has also been reported.
  - Limited treatment information is available; however, multidrug resistance has been reported, and treatment with lamotrigine has been reported to be successful, although some affected individuals have not required treatment [Koenig et al 2010, Stellacci et al 2016, Baer et al 2018, Sheppard et al 2021].
- Central apnea has also been reported.

Brain MRI findings. A structural brain abnormality is present in about half of affected individuals who have undergone brain imaging. Examples of findings [Baer et al 2018, Sheppard et al 2021]:

- Abnormalities of the corpus callosum
- Abnormal myelination
- White matter changes, such as punctate foci of hyperintensity within the white matter, evidence of white matter volume loss, and paucity of white matter
- Chiari 1 malformation spectrum, which may include relatively narrow foramen magnum and platybasia
- Periventricular nodular heterotopia
- Choroid plexus cysts
- Abnormalities involving the pituitary gland, such as absent pituitary neurohypophysis, abnormal shape of the sella turcica, ectopic posterior bright spot with hypoplasia of hypothalamic pituitary axis, and pituitary hypoplasia (see **Endocrinologic** in this section)
- Cortical malformations, including bilateral frontal polymicrogyria [Grangeia et al 2020, Nardello et al 2021]
- Hypoplastic optic nerves [Chen et al 2019]
- Cerebrospinal fluid anomalies including aqueductal stenosis and third ventricle dilatation [Arora et al 2020]
- Cerebral atrophy
- Vermis hypoplasia [Di Fede et al 2021]
- Cerebellar atrophy [Giangiobbe et al 2020]

Integument/hair. Hypertrichosis is common, occurring in approximately 50%-75% of affected individuals, and includes:

- Eyebrows
- Long eyelashes
- Thick hair on the scalp
- Hypertrichosis of the back
- Hypertrichosis cubiti
- Hypertrichosis of the lower limbs

Skeletal/limb. Vertebral anomalies are the most common musculoskeletal finding, occurring in about half of affected individuals. Most of those who have vertebral anomalies have fusion in the cervical spine, most commonly at C2-C3, though some have abnormalities in the thoracic, lumbar, or sacral spine. Other skeletal anomalies include the following:

- Rib anomalies (e.g., reduced number of rib pairs, hypoplastic appearance of ribs, cervical ribs) are found in about one third of affected individuals.
- Broad first digits and/or tapering fingers are present in about one quarter of affected individuals, with some individuals having persistent fetal fingertip pads [Miyake et al 2016, Enokizono et al 2017, Wang et al 2021].
- Fewer than one fifth of affected individuals have scoliosis, which in rare cases can be severe enough to require surgery.
- Pectus excavatum has been described in a small number of affected individuals.
- Hip dysplasia has also been seen in a small number of affected individuals, although none of those with hip dysplasia were breech at birth.

  Several individuals required surgery and one required a Pavlik harness.

- One individual had scaphocephaly and another had metopic craniosynostosis [Nardello et al 2021]. The authors are also aware of a second individual with metopic craniosynostosis.

Cardiac. Cardiac abnormalities were present in about one third of those who underwent cardiac evaluation. Cardiac issues can include:

- Structural cardiac anomalies (patent ductus arteriosus, patent foramen ovale, right aortic arch, aortic insufficiency, bicuspid aortic valve, atrial septal defect, ventricular septal defect, tetralogy of Fallot, aberrant right subclavian artery, mitral valve prolapse, dextrocardia, mitral regurgitation, tricuspid regurgitation, overriding aorta, and thickened aortic valve)
- Arrhythmia (one affected individual required a pacemaker), including third-degree AV block [Bogaert et al 2017, Li et al 2018]
- Pulmonary hypertension
- Syncopal episodes

Genitourinary. Abnormalities in the genitourinary system are present in almost half of affected individuals.

- Renal anomaly was seen in about one quarter and included vesiculouretal reflux with hydronephrosis.
- Uterine or testicular anomalies were seen in almost 20%, including absent uterus in females and cryptorchidism in males.
- About 10% have an external genital anomaly, including prominent clitoris, underdeveloped scrotum, and hypospadias.

Eyes. A wide variety of ophthalmologic abnormalities are seen, including:

- Strabismus
- Astigmatism
- Hyperopia
- Myopia
- Amblyopia
- Lacrimal duct abnormalities
- Ptosis
- Rarely, cataract, coloboma, or glaucoma

ENT. Obstructive sleep apnea is the most common finding, occurring in about one quarter of affected individuals and necessitating tonsillectomy and adenoidectomy in close to 20% of those who have obstructive sleep apnea.

Dental/oral. More than half of affected individuals have a dental issue, the most common of which is advanced dental age characterized by premature loss of deciduous teeth and emergence of secondary teeth at an atypical earlier age. Other features include malocclusion, dysmorphic teeth, hypodontia, supernumerary teeth, poor enamel, caries, high-arched palate needing a palate expander, and gum issues.

Endocrinologic. Endocrine abnormalities include:

- Short stature (see **Growth** in this section)
- Premature adrenarche
- Menorrhagia, polycystic ovary syndrome, and/or irregular menses
- Abnormality of the pituitary gland seen on brain MRI (see **Brain MRI findings** in this section)
- Growth hormone (GH) deficiency, defined by low serum GH, IGF-1 or GH stimulation test
- Osteopenia
- Hypothyroidism (including congenital hypothyroidism and Hashimoto thyroiditis)
- Hypoparathyroidism

Immunologic issues have also been reported, including [Jones et al 2012, Stellacci et al 2016, Bogaert et al 2017, Baer et al 2018, Sheppard et al 2021]:

- Immunodeficiency, including common variable immunodeficiency
- Insufficient response to vaccinations
- History of recurrent infections
- Recurrent fevers of unknown origin
- Eosinophilia [Zhang et al 2019]

One boy had recurrent pulmonary infections and died of sepsis [Bramswig et al 2015].

Prognosis. It is unknown whether life span in WSS is abnormal. Multiple adults have been reported in the literature [Li et al 2018, Feldman et al 2019, Sheppard et al 2021]. While some adults do not work, one attended a daytime rehabilitation program, another owned a construction business, and another was currently in college managing without academic assistance. Adults with WSS could have affected children. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Some genotype-phenotype correlations have been established.

- Individuals with loss-of-function variants in *KMT2A* are more likely to have hypotonia than those with non-loss-of-function variants [Sheppard et al 2021].
- In contrast, participants with non-loss-of-function variants are more likely to have seizures [Sheppard et al 2021].
- Missense variants in the CXXC DNA-binding domain (amino acids 1147-1195) may be associated with more significant neurodevelopmental issues [Min Ko et al 2017, Li et al 2018, Lebrun et al 2018].

Nomenclature

In 1970, Dr P Beighton described a father and two of his children with familial hypertrichosis cubiti or "hairy elbows" syndrome [Beighton 1970]. Subsequently, Dr HR Wiedemann and colleagues described a male with growth deficiency, developmental delay, strabismus, renal calyceal dilatation, and characteristic facial features [Wiedemann et al 1989]. In 2000, Dr CE Steiner and Dr AP Marques reported a female with features similar to those reported by Beighton and Wiedemann and suggested a common diagnosis [Steiner & Marques 2000]. Although "hairy elbows syndrome" has been used to describe WSS in some articles, "Wiedemann-Steiner syndrome" is now commonly used. Alternatively, *KMT2A*-related neurodevelopmental disorder can be used, following the naming system proposed by Biesecker et al [2021].

Prevalence

The prevalence of WSS is not known. Almost 250 individuals have been reported in the literature. Multiple adults were diagnosed as part of their child's evaluation, so it is possible that WSS could be underdiagnosed [Sheppard et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *KMT2A*.

Sporadic tumors (including acute leukemia, thymomas, and breast cancer) occurring as single tumors in the absence of any other findings of Wiedemann-Steiner syndrome frequently harbor a somatic pathogenic variant

in (or a genomic rearrangement that includes) *KMT2A* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

The features associated with Wiedemann-Steiner syndrome (WSS) overlap those of a wide range of disorders. Table 3 summarizes those disorders most commonly considered in individuals with clinical findings consistent with WSS. For less commonly considered disorders in the differential diagnosis, refer to Sheppard et al [2021].

Table 3. Key Disorders in the Differential Diagnosis of Wiedemann-Steiner Syndrome

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/WSS	Distinguishing from WSS
ARID1A *ARID1B* *ARID2* *DPF2* *SMARCA4* *SMARCB1* *SMARCC2* *SMARCE1* *SOX4* *SOX11*	Coffin-Siris syndrome	AD	Syndromic short stature, hypertrichosis w/long eyelashes & prominent eyebrows	Distal digit hypoplasia (usually 5th digit)
BRAF *KRAS* *LZTR1* *MAP2K1* *NRAS* *PTPN11* *RAF1* *RIT1* *SOS1*	Noonan syndrome	AD AR [1]	Short stature, structural heart abnormalities, pulmonary hypertension, ocular abnormalities, & hypotonia	Higher frequency of congenital heart defects (50%-80%), pulmonary valve stenosis, & absence of hypertrichosis
BRD4 *HDAC8* *NIPBL* *RAD21* *SMC1A* *SMC3*	Cornelia de Lange syndrome	AD XL [2]	Hypertrichosis, short stature, growth failure, DD/ID, ophthalmologic abnormalities, & recurrent infections	Limb involvement, upper-extremity deficiencies ranging from severe reduction defects w/complete absence of forearms to various forms of oligodactyly
CREBBP *EP300*	Rubinstein-Taybi Syndrome	AD	Short stature, DD/ID, hypertrichosis, congenital heart disease	Hyperinsulinism, grimacing/typical smile
KDM6A *KMT2D*	Kabuki syndrome	AD XL [3]	Hypertrichosis, short stature, growth deficiency, DD/ID, multiple congenital anomalies	Hyperinsulinism

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/WSS	Distinguishing from WSS
TASP1	Suleiman-El-Hattab syndrome (OMIM 618950)	AR	DD, hypotonia, microcephaly, feeding difficulties w/FTT, recurrent respiratory infections, cardiovascular malformations, happy demeanor, & distinctive facial features [4]	Prominent glabella

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; FTT = failure to thrive; ID = intellectual disability, MOI = mode of inheritance; WSS = Wiedemann-Steiner syndrome; XL = X-linked

1. Noonan syndrome (NS) is most often inherited in an autosomal dominant manner. *LZTR1*-related NS can be inherited in either an autosomal dominant or an autosomal recessive manner.

2. NIPBL-related Cornelia de Lange syndrome (CdLS), *RAD21*-related CdLS, *SMC3*-related CdLS, and *BRD4*-related CdLS are inherited in an autosomal dominant manner; *HDAC8*-related CdLS and *SMC1A*-related CdLS are inherited in an X-linked manner.

3. KMT2D-related Kabuki syndrome (KS) is inherited in an autosomal dominant manner; *KDM6A*-related KS is inherited in an X-linked manner.

4. TASP1 cleaves *KMT2A*, which may account for the similarity between WSS and Suleiman-El-Hattab syndrome [Sheppard et al 2021].

Management

Suggested clinical practice guidelines for Wiedemann-Steiner syndrome (WSS) have been published. See Baer et al [2018] (full text), Sheppard et al [2021] (full text). Note: Institutional access or purchase required.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with WSS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Wiedemann-Steiner Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To identify those w/poor growth, incl those who have FTT & those who may have growth hormone deficiency
Neurologic	Neurologic eval	• To incl brain MRI, as clinically indicated • Consider EEG if seizures are a concern & in those who have a loss-of-function pathogenic *KMT2A* variant.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: screen for behavior concerns incl sleep disturbances, aggressive behaviors, &/or traits suggestive of ASD.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Consider spinal radiographs, vertebral computed tomography or tonodensometry.	To inform mgmt
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Signs/symptoms suggestive of vertebral anomalies & hip dysplasia • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of nutritional status • Consider eval for gastrostomy tube placement in those w/FTT.
	Evaluate for signs/symptoms of constipation.	
Eyes	Ophthalmologic eval	For diagnosis & treatment of strabismus, blepharoptosis, refractive disorders, & other rare eye complications
ENT/Mouth	Consider sleep study.	Assess for sleep apnea
	Pediatric dentistry eval in those age >1 yr	To evaluate early loss of deciduous teeth & emergence of secondary dentition
Cardiovascular	Echocardiogram & EKG	To evaluate for congenital heart defects & to screen for arrhythmia
Genitourinary	Abdominal ultrasound	To assess for renal & bladder abnormalities
	Consider external pelvic ultrasound in female neonates or in females of pubertal age or older. [1]	To screen for uterine anomalies
Integument	Dermatologic eval	If desired by family to assist in mgmt of hypertrichosis
Endocrine	Endocrinology eval	• To assess for short stature, growth hormone deficiency, hypothyroidism, & metabolic bone disease • May consist of blood tests as well as radiographs (e.g., bone age x-rays) depending on clinical context
Immunologic	Immunologic eval	• To assess for immunodeficiency & vaccine response • May incl quantitative immunoglobulins, vaccine titers, lymphocyte profile
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of WSS to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; [3] • Social work involvement for parental support; • Home nursing referral.

ADL = activities of daily living; ASD = autism spectrum disorder; EEG = electroencephalogram; EKG = electrocardiogram; FTT = failure to thrive; MOI = mode of inheritance; MRI = magnetic resonance imaging; OT = occupational therapy; PT = physical therapy
1. Pelvic ultrasound and even pelvic MRI in females who have not experienced recent estrogen may not be able to identify a uterus. Neither of these imaging modalities is sufficient in this scenario to confirm absence of a uterus. Referral to a gynecologist for evaluation could be considered.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse
3. WSS parent-specific resources may include the WSS Foundation (see Resources) or the WSS Facebook group.

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Wiedemann-Steiner Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist or epileptologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Developmental delay / Intellectual disability / Behavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Congenital hip dysplasia	Standard treatment per orthopedist	May incl use of Pavlik harness, & in extreme cases may require surgical intervention
Fusion of cervical vertebrae	Individual assessment per orthopedist	Rarely, affected persons have required laminectomy.
Poor weight gain / Failure to thrive	• Feeding therapy • Nasogastric or gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval
Bowel dysfunction	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Strabismus, astigmatism, & other refractive errors	Standard treatment by ophthalmologist	
Blepharoptosis	Consideration of oculoplastic surgery	
Obstructive sleep apnea	Treatment may incl CPAP, BiPAP, or surgical removal of tonsils & adenoids.	
Congenital heart defects & arrhythmias	Standard treatment per cardiologist	May incl medical mgmt w/antiarrhythmic or surgical mgmt
Renal anomalies	Standard treatment per nephrologist	
Uterine anomalies	Standard treatment per gynecologist	
Growth hormone deficiency	Growth hormone therapy	This treatment is typically undertaken by an endocrinologist.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Thyroid dysfunction	Thyroid hormone replacement therapy	
Metabolic bone disease	Standard treatment per endocrinologist	May incl vitamin D supplementation
Frequent infections / Immune dysfunction	Consider IVIG in those w/low antibody levels &/or prophylactic antibiotic in those w/frequent infections.	Mgmt by immunologist is recommended.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; IVIG = intravenous immunoglobulin; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., scoliosis, hip dislocation) [Mendoza 2020].
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 6. Recommended Surveillance for Individuals with Wiedemann-Steiner Syndrome

System/Concern	Evaluation	Frequency
Growth/Feeding	• Measure growth parameters & evaluate growth velocity. • Evaluate nutritional status.	At each visit [2]
Gastrointestinal	Monitor for constipation.	
Neurologic	• Monitor those w/seizures as clinically indicated. [1] • Assess for new manifestations such as seizures. • Assess for clinical signs of medullar compression, esp in those w/ vertebral anomalies.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavior assessment for attention & aggressive behaviors	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Cardiovascular	Monitor for any signs/symptoms of arrhythmia.	
Immunologic	Monitor for any signs of frequent infection.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	
ENT/Mouth	Monitor for signs/symptoms of sleep disturbance.	
	Dental eval	After eruption of primary teeth, every 6 mos
Endocrine	Assessment for premature thelarche or pubertal abnormalities (primary amenorrhea)	Starting in childhood until growth/ menarche is complete
Eyes	Ophthalmology eval	Annually or as clinically indicated

1. May include EEG follow up, as indicated
2. Visit frequency may vary based on individual needs, but generally visits may be every six months in early childhood and transition to annual visits around school age.

Agents/Circumstances to Avoid

The authors are aware of one individual with WSS who developed hyperammonemia with the use of the anti-seizure medication valproate. While this is not specific to individuals with WSS, valproate should be used with caution.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Some women with WSS have a seizure disorder that is treated with an anti-seizure medication. In general, women with epilepsy or a seizure disorder of any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication during pregnancy reduces this risk. However, exposure to anti-seizure medication may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which the medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from anti-seizure medication exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of anti-seizure medication to treat a maternal

seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given anti-seizure medication during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

Cervical spine anomalies may lead to immobility or instability, which may complicate airway management. Vertebral anomalies or scoliosis in the thoracic or lumbar spine may complicate spinal or epidural anesthesia.

Affected fetuses may be at risk for late prematurity, with average gestation ranging from 36 to 38 weeks [Baer et al 2018].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Wiedemann-Steiner syndrome (WSS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with WSS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant.
- Rarely, individuals diagnosed with WSS have an affected parent [Baer et al 2018, Sheppard et al 2021].
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either apparently asymptomatic parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

  * A parent with somatic and germline mosaicism for a *KMT2A* pathogenic variant may be mildly/minimally affected [Baer et al 2018].

- The family history of some individuals diagnosed with WSS may appear to be negative because of failure to recognize the disorder in mildly affected family members. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- Clinical variability among affected sibs with the same pathogenic variant has been observed. In a family with six sibs with WSS, all had failure to thrive and feeding difficulties, there was a range of developmental delay, and some had structural malformations whereas others did not [Sheppard et al 2021].
- If the proband has a known *KMT2A* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of germline mosaicism in a clinically unaffected parent. Mosaicism for a *KMT2A* pathogenic variant in a clinically unaffected parent has been described in one family [Baer et al 2018].
- If the parents are clinically unaffected after a thorough evaluation for subtle findings but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with WSS has a 50% chance of inheriting the *KMT2A* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, members of the parent's family may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *KMT2A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Wiedemann-Steiner Syndrome Foundation**

1314 44th Street
Sacramento 95819
Phone: 916-502-2120
Email: info@wssfoundation.org
www.wssfoundation.org

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **MedlinePlus**
  Intellectual Disability
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Wiedemann-Steiner Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KMT2A	11q23.3	Histone-lysine N-methyltransferase 2A	KMT2A database	KMT2A	KMT2A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Wiedemann-Steiner Syndrome (View All in OMIM)

159555	LYSINE-SPECIFIC METHYLTRANSFERASE 2A; KMT2A
605130	WIEDEMANN-STEINER SYNDROME; WDSTS

Molecular Pathogenesis

The *KMT2A* gene product is a DNA-binding protein that methylates histone H3 and thereby regulates expression of numerous target genes.

KMT2A is the mammalian homolog of *Drosophila* Trithorax, which regulates *Hox* expression. KMT2A is important in hematopoiesis and axial skeletal patterning [Hess et al 1997].

Mechanism of disease causation. *KMT2A* pathogenic nonsense variants lead to nonsense-mediated decay, suggesting haploinsufficiency as the mechanism [Jones et al 2012]. The pathogenesis of missense variants may vary by the location, though preliminary studies suggest decreased expression of target genes. The CXXC domain is thought to be important for binding to target genes and the TAD domain is important for

transcriptional activation. A missense variant in the CXXC domain (c.3460C>T; p.Arg1154Trp) resulted in overexpression of the *KMT2A* transcript and reduction of downstream target genes *SIX2* and *MEIS1*, suggestive of impaired DNA binding. Conversely, a missense variant in the TAD domain (c.8558T>G; p.Met2853Trp) did not lead to significant changes in transcript level, but also resulted in a significant reduction in *SIX2* and *MEIS1* transcript, suggesting an issue with transcriptional activation [Lebrun et al 2018].

Cancer and Benign Tumors

About 10% of all pediatric and adult leukemias are caused by more than 90 different fusions involving *KMT2A*, which are thought to lead to disordered epigenetic regulation and thus abnormal gene transcription [Winters & Bernt 2017, Meyer et al 2018].

There is a single report of a family including three sibs with primary mediastinal large B-cell lymphoma and their cousin with diffuse large B-cell lymphoma, both subtypes of non-Hodgkin lymphoma, with a variant in *KMT2A* (referred to as *MLL* 5533C>A [His1845Asn] in the article) discovered via exome sequencing. This variant was also found in three healthy family members. The variant was not found in 86 healthy Finnish controls, 92 sporadic non-Hodgkin lymphoma cases, or 14 familial non-Hodgkin lymphoma cases that were screened [Saarinen et al 2013].

Chapter Notes

Acknowledgments

We thank the participants and their families and our co-authors [Sheppard et al 2021]. This work was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number TL1TR001880 (S.E.S.). Figures included in this chapter are adapted from Sheppard et al [2021].

Revision History

- 26 May 2022 (ma) Review posted live
- 3 August 2021 (fqr) Original submission

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