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NLM Citation: Tatton-Brown K, Rahman N. *EZH2*-Related Overgrowth. 2013 Jul 18 [Updated 2018 Aug 2]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

EZH2-Related Overgrowth

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Created: July 18, 2013; Updated: August 2, 2018.

Summary

Clinical characteristics

EZH2-related overgrowth includes *EZH2*-related Weaver syndrome at one end of the spectrum and tall stature at the other. Although most individuals diagnosed with a heterozygous *EZH2* pathogenic variant have been identified because of a clinical suspicion of Weaver syndrome, a minority have been identified through molecular genetic testing of family members of probands or individuals with overgrowth who did not have a clinical diagnosis of Weaver syndrome. Thus, the extent of the phenotypic spectrum associated with a heterozygous *EZH2* pathogenic variant is not yet known.

Weaver syndrome is characterized by tall stature, variable intellect (ranging from normal intellect to severe intellectual disability), characteristic facial appearance, and a range of associated clinical features including advanced bone age, poor coordination, soft doughy skin, camptodactyly of the fingers and/or toes, umbilical hernia, abnormal tone, and hoarse low cry in infancy. Brain MRI has identified abnormalities in a few individuals with *EZH2*-related overgrowth. Neuroblastoma occurs at a slightly increased frequency in individuals with a heterozygous *EZH2* pathogenic variant but data are insufficient to determine absolute risk. There is currently no evidence that additional malignancies (including hematologic malignancies) occur with increased frequency.

Diagnosis/testing

The diagnosis of *EZH2*-related overgrowth is based on detection of a heterozygous germline *EZH2* pathogenic variant on molecular genetic testing.

Management

Treatment of manifestations: For individuals with developmental delay and/or learning disability, referral for learning/behavior/speech assessment and support may be indicated. Occasionally, toe camptodactyly may require surgical release. Physiotherapy may be of benefit to those experiencing joint pain secondary to

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ligamentous laxity or joint contractures. Treatment of scoliosis is routine. The appropriate specialist referral(s) should be made for other clinical issues.

Surveillance: Regular medical follow up of young children with *EZH2*-related Weaver syndrome to monitor developmental progress, camptodactyly (for resolution/improvement), and/or hypotonia; medical follow up of older children/teenagers who do not have medical complications may be less frequent. If scoliosis is present, monitoring as per the recommendations of an orthopedist. Although current data do not support specific tumor surveillance programs, clinicians should have a low threshold for investigating any findings that may be tumor (particularly neuroblastoma) related.

Pregnancy management: Families and their health care providers should be aware that an affected baby may be large so that appropriate delivery plans can be made.

Genetic counseling

EZH2-related overgrowth is inherited in an autosomal dominant manner; however, many germline pathogenic *EZH2* variants arise *de novo*. Each child of an individual with an *EZH2* pathogenic variant has a 50% chance of inheriting the pathogenic variant; the severity of the phenotype in an individual inheriting the *EZH2* pathogenic variant cannot be predicted. If the pathogenic variant has been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

GeneReview Scope

EZH2-Related Overgrowth: Included Phenotypes
• *EZH2*-related Weaver syndrome [1]

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of this phenotype see Differential Diagnosis.

Diagnosis

Suggestive Findings

EZH2-related overgrowth **should be suspected** in an individual with combinations of the following clinical and imaging findings [Tatton-Brown et al 2013]:

Clinical findings

- Tall stature (height ≥+2 SD)
- Macrocephaly (head circumference ≥+2 SD)
- Intellectual disability
- Characteristic facial appearance
  - In children younger than age three years: retrognathia, large and fleshy ears, and a "stuck on" appearance to the chin associated with a horizontal skin crease and sometimes a central dimple
  - In affected individuals of all ages, additional features including (Figure 1):
    - Broad forehead
    - Widely spaced eyes
    - Almond-shaped palpebral fissures

Note: The characteristic facial appearance (which is most distinctive at a younger age) evolves over time; therefore, review of younger-childhood photographs may help the clinician reach a clinical diagnosis.

- Poor coordination
- Soft and doughy skin
- Camptodactyly of the fingers and/or toes (see **Note**)
- Umbilical hernia that is occasionally significant enough to require surgical reduction
- Abnormal tone (central hypotonia and/or peripheral hypertonia) (see **Note**)
- Hoarse, low-pitched cry (sometimes described as a quiet cry)

Note: A detailed medical history may be necessary to determine if these findings were present in the newborn period / infancy given that they can resolve/improve throughout childhood.

Imaging findings. Advanced bone age on plain radiographs

Brain MRI. In many individuals a brain MRI has not been undertaken and thus imaging data are not available. One or more abnormalities identified in ten individuals included: isolated ventriculomegaly (in 5); ventriculomegaly and periventricular leukomalacia (1); periventricular leukomalacia (1); cerebellar infarct (1); and cerebellar hypoplasia and neuronal migration defects (polymicrogyria) with and without pachygyria (2) [Al-Salem et al 2013, Tatton-Brown et al 2013].

Establishing the Diagnosis

The diagnosis of *EZH2*-related overgrowth **is established** in a proband by identification of a heterozygous germline *EZH2* pathogenic variant on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **single-gene testing**, **multigene panel testing**, and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing):

- **Single-gene testing.** Single-gene testing requires that the clinician recognize the Weaver syndrome / *EZH2*-related overgrowth phenotype and request *EZH2* molecular genetic testing. However, given that the phenotype is broad and the facial gestalt subtle, this can be challenging even for the experienced dysmorphologist.

  Sequence analysis of *EZH2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. If sequence analysis does not identify a pathogenic variant, targeted deletion/duplication analysis to detect intragenic deletions or duplications can be considered. Note: Whole- or partial-gene deletions have been reported in several individuals with increased growth possibly due to Weaver syndrome [Imagawa et al 2017, Suri & Dixit 2017].

- **Multigene panel testing.** More frequently, an individual with *EZH2*-related overgrowth is diagnosed following testing with a multigene panel for conditions characterized by increased growth (height and/or head circumference) in association with intellectual disability (see Differential Diagnosis). *EZH2* is frequently included in such multigene panels. Such a panel is most likely to identify the genetic cause of the condition at the most reasonable cost 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 laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that

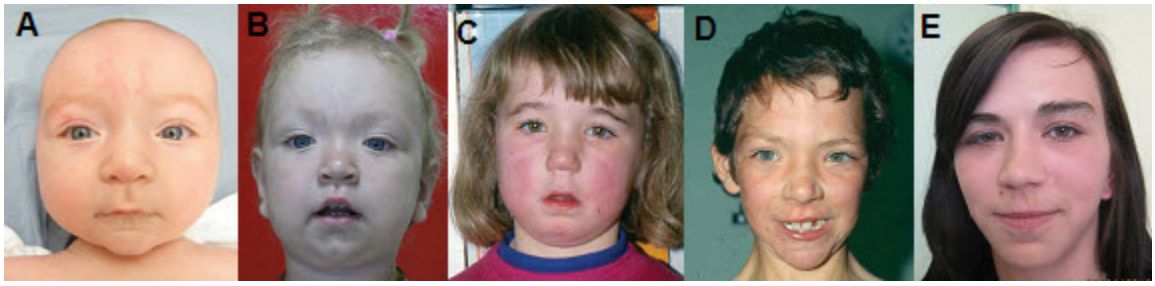

Figure 1. Retrognathia present in younger children with *EZH2*-related Weaver syndrome usually resolves with age. In individuals of all ages the palpebral fissures are frequently almond-shaped and the eyes are widely spaced.

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.

- **Comprehensive genomic testing.** Comprehensive genomic testing allows the sequencing of many genes, often with unrelated phenotypes, in a single experiment. This has particular clinical utility when the clinician does not recognize a particular phenotype and/or genes involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. **Exome array** (when clinically available) may be considered if exome sequencing is not diagnostic.

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

Table 1. Molecular Genetic Testing Used in *EZH2*-Related Overgrowth

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
EZH2	Sequence analysis [3]	Majority of variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 6

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. 54 individuals with an *EZH2* germline pathogenic variant have been reported [Tatton-Brown et al 2011, Gibson et al 2012, Al-Salem et al 2013, Tatton-Brown et al 2013, Usemann et al 2016, Lui et al 2018].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Two individuals have had deletions wholly or partially encompassing *EZH2* [Imagawa et al 2017, Suri & Dixit 2017].

Clinical Characteristics

Clinical Description

The phenotypic spectrum associated with germline *EZH2* pathogenic variants is broad, with classic Weaver syndrome at one end of the spectrum and tall stature at the other. Although most individuals diagnosed with a heterozygous germline *EZH2* pathogenic variant have been identified because of a clinical suspicion of Weaver

syndrome, a minority have been identified through molecular genetic testing of family members of probands or individuals with overgrowth who did not have a clinical diagnosis of Weaver syndrome [Tatton-Brown et al 2011, Gibson et al 2012]. Thus, the extent of the phenotypic spectrum of heterozygous *EZH2* pathogenic variants is not yet known. While data are still limited, clinical associations reported to date in 54 individuals with Weaver syndrome are summarized below [Tatton-Brown et al 2011, Gibson et al 2012, Al-Salem et al 2013, Tatton-Brown et al 2013, Usemann et al 2016, Suri & Dixit 2017, Lui et al 2018]. The denominators reflect the numbers of individuals for whom data are available.

Growth. From data available on 23 newborns, the mean birth length was 2.2 standard deviations above the mean (+2.2 SD) with a range of -0.5 SD to +4.9 SD; the mean birth weight of 45 newborns was +1.7 SD with a range of -1.6 SD to +4.6 SD [Tatton-Brown et al 2013].

Tall stature is a near-consistent finding: height in 47/52 individuals was at least two standard deviations above the mean (ages 1-70 years). Of note, three of the four individuals with a height less than +2 SD had been tall as young children. The mean postnatal height was +3.5 SD.

Of 45 individuals on whom information was available, 24 had a head circumference less than +2 SD and 21 had macrocephaly with a head circumference ranging up to +5.5 SD.

Cognitive features. Information on cognitive function was available for 50 individuals. Eight had normal intellect; 42 individuals had variable intellectual disability (ID) including the following:

- **Mild ID** (24/50). Children attend mainstream school and need some extra help – e.g., a statement of educational needs – but would be expected to live independently as adults and would be likely to have their own family.
- **Moderate ID** (14/50). Children develop speech and need a high level of support in mainstream education but more likely will attend a school for individuals with special educational needs. While unlikely to live independently as adults, they may live in sheltered accommodation or with some additional support.
- **Severe ID** (2/50). Individuals require special education during schooling and are likely to require considerable support in adulthood.
- **Unclassified ID** (2/50). Information provided is insufficient to make a determination.

Behavioral issues including autistic spectrum disorder, phobias, and anxiety have been anecdotally reported.

Neurologic. Ventriculomegaly, reported in six individuals, was generally associated with normal CSF pressure and did not require shunting [Tatton-Brown et al 2013]. Other brain MRI findings included neuronal migration defects (pachy/polymicrogyria; in 2 individuals), periventricular leukomalacia (2 individuals), and cerebellar abnormalities (2 individuals).

Intellectual disability in those with a brain MRI abnormality was:

- Mild in six (ventriculomegaly [4], periventricular leukomalacia [1], and cerebellar hypoplasia [1]);
- Moderate in three (periventricular leukomalacia with ventriculomegaly [1] and isolated ventriculomegaly [2]);
- Severe in an individual with polymicrogyria and pachygyria; in contrast, the individual with polymicrogyria reported by Al-Salem et al [2013] had normal developmental milestones and body asymmetry (left side smaller than the right) with brisk reflexes and increased tone on the left.
- Note: The degree of intellectual disability was not reported for one individual with ventriculomegaly.

Four individuals had afebrile seizures.

Skeletal features

- **Advanced bone age.** Of 29 individuals evaluated, all had advanced bone age.

- **Scoliosis** was reported in nine individuals and pectus abnormalities (excavatum or carinatum) in three. Scoliosis ranged from severe (early-childhood onset requiring surgical intervention) to mild (requiring monitoring but no therapeutic intervention).
- **Camptodactyly.** Some affected individuals had camptodactyly of the fingers, some had camptodactyly of the toes, and some had camptodactyly of fingers and toes. On occasion the toe camptodactyly required surgical correction.
- **Adult boutonniere deformity.** Several adults developed hyperextension of the distal interphalangeal joints and flexion of the proximal interphalangeal joints of the hands analogous to a mild boutonniere deformity (Figure 2).
- **Talipes equinovarus.** Six individuals had talipes equinovarus ranging from fixed and bilateral (requiring surgery) in two individuals to mild (unilateral that resolved with physiotherapy) in three.

Connective tissue

- **Ligamentous laxity.** While ligamentous laxity with associated joint hypermobility and *pes planus* is common, it is not usually reported unless complicated by joint pain. Individuals with *EZH2*-related overgrowth are frequently reported to have poor coordination that may be (at least partially) attributable to lax ligaments.
- **Skin** that was soft and doughy to the touch was seen in 19/37 affected children.
- **Umbilical hernia,** seen in 21/44 children, was sufficiently large to require surgery in the neonatal period in eight.

Abnormal tone. In general, if present, abnormal tone (hypotonia, hypertonia, or mixed central hypotonia and peripheral hypertonia) resolved during childhood.

- Hypotonia (predominantly central) was reported in 22/45 individuals.
- Hypertonia (predominantly peripheral manifesting as stiffness in the limbs with brisk reflexes) was reported in 13/41.

  Note: Five of the individuals presenting with peripheral hypertonia were also reported to have central hypotonia.

Poor feeding was reported in 10/28 neonates including one who required nasogastric tube feeding for two weeks. Although poor feeding may be attributable to neonatal hypotonia, this was only reported in three of the infants with poor feeding.

Hoarse, low-pitched cry was reported in 10/27 affected infants.

Tumors have been reported in four of 54 affected individuals [Tatton-Brown et al 2013, Usemann et al 2016].

- One boy with a c.2233G>A pathogenic variant developed a pre-T cell non-Hodgkins lymphoma at age 13 years. At age 25 years he remains well with no relapses or additional tumors.
- One boy with a c.2044G>A pathogenic variant was diagnosed at age 13 months with acute lymphoblastic leukemia and neuroblastoma, both of which responded to therapy; he is well at age seven years.
- One girl with a c.458A>G pathogenic variant was diagnosed with a neuroblastoma at age four years.
- One girl with a c.395C>T pathogenic variant was diagnosed with acute myeloid leukemia and secondary hemophagocytic lymphohistiocytosis at age 16 years.

Additional clinical features reported in a small number of individuals (and therefore, possibly not associated with the *EZH2* pathogenic variant) are included for completeness:

- Café au lait macules (in 2 individuals), hemangioma (in 4)
- Hypermetropia (hyperopia) (3), myopia (1), strabismus (3)

- Cryptorchidism (1), hydrocele (2), hypospadias (1)
- Cleft palate (3)
- Hearing loss (3) – conductive and sensorineural
- Cardiac anomalies (4) including mitral valve prolapse (1), ventricular septal defect (2), and patent ductus arteriosus (1)
- Gastroesophageal reflux (1), hiatal hernia (1)
- Neonatal hypoglycemia (2)
- Neonatal hypocalcemia (1)

Genotype-Phenotype Correlations

Because findings along the entire phenotypic spectrum have been observed in individuals with heterozygous truncating pathogenic variants or heterozygous missense pathogenic variants, within or outside the conserved SET domain (see Molecular Genetics, **Normal gene product**), no genotype-phenotype correlations are evident among the small number of individuals reported with *EZH2*-related overgrowth.

Penetrance

Data are currently insufficient to determine penetrance of *EZH2* germline pathogenic variants. However, given the subtlety of the phenotype in some persons with a pathogenic *EZH2* variant, the penetrance for some *EZH2* pathogenic variants may be reduced [Tatton-Brown et al 2013].

Nomenclature

Weaver syndrome is named after David Weaver, who reported two boys with accelerated osseous maturation, unusual facies, and camptodactyly [Weaver et al 1974].

Although pathogenic variants in *NSD1* (the cause of Sotos syndrome) were once reported to cause Weaver syndrome [Douglas et al 2003], this association has been refuted [Tatton-Brown et al 2005].

Prevalence

Because *EZH2* pathogenic variants have only recently been shown to cause Weaver syndrome, and individuals with a mild phenotype may escape clinical diagnosis, it is currently difficult to estimate the prevalence of Weaver syndrome.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *EZH2*.

Sporadic tumors (including hematopoietic malignancies) occurring in the absence of any other findings of Weaver syndrome frequently harbor somatic variants in *EZH2* that are **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

Conditions to be considered in the differential diagnosis of Weaver syndrome are summarized in Table 2.

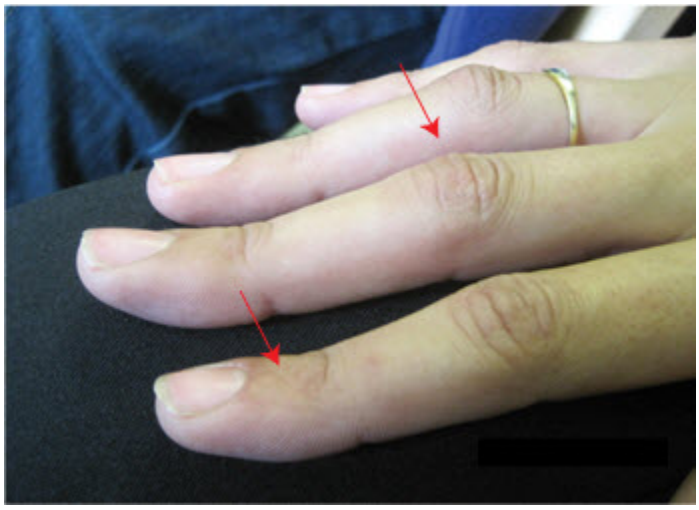

Figure 2. Mild hyperextension of the distal interphalangeal joints and flexion of the proximal interphalangeal joints in a woman age 22 years with a heterozygous *EZH2* pathogenic variant

Table 2. Disorders to Consider in the Differential Diagnosis of Weaver Syndrome

Disorder	Gene / Genetic Mechanism	MOI	Clinical Features	
			Overlapping	Distinguishing
Sotos syndrome	*NSD1* [1]	AD [2]	• Pre- & postnatal overgrowth • Variable ID • Similar (but distinctive; see **Distinguishing** →) facial appearance • Advanced bone age • Scoliosis • Joint hypermobility	Facial features in Sotos syndrome: • Downslanted palpebral fissures, prominent chin, malar flushing in children • Most easily distinguishable from Weaver syndrome at ages 1-3
Malan syndrome (OMIM 614753)	*NFIX*	AD	• Sotos syndrome-like condition • Tall stature • Variable ID [3]	In Malan syndrome: • Ophthalmologic abnormalities common • Growth frequently normalizes in teenagers & young adults
DNMT3A overgrowth (Tatton-Brown-Rahman) syndrome (OMIM 615879)	*DNMT3A* [4]	AD	• Tall stature • Variable ID • ASD • Scoliosis • Joint hypermobility	In DNMT3A overgrowth syndrome: • Facial appearance (round, heavy; w/horizontal eyebrows & narrow palpebral fissures) most recognizable in early teen/adult yrs • ↑ weight • Neuropsychiatric issues

Table 2. continued from previous page.

Disorder	Gene / Genetic Mechanism	MOI	Clinical Features	
			Overlapping	Distinguishing
Beckwith-Wiedeman syndrome (BWS)	Abnormal regulation of gene transcription in two imprinted domains at 11p15.5 [5]	Footnote 6	• ↑ birth weight • Tall stature (not as frequent in BWS as the other conditions in the differential diagnosis) • Umbilical hernia	In BWS: • Macroglossia • Earlobe creases/pits • Omphalocele • Visceromegaly • Usually normal intellect • Neonatal hypoglycemia • Polyhydramnios • Predisposition to embryonal tumors, esp Wilms tumor
Simpson-Golabi-Behmel syndrome type 1 (SGBS1)	*GPC3* (possibly *GPC4*)	XL	• ↑ birth weight • Tall stature • Variable ID	In SGBS1: • Characteristic facial appearance • Supernumerary nipples • Polydactyly • Diastasis recti [7]
Marfan syndrome	*FBN1*	AD	• Tall stature • Scoliosis • Joint hypermobility	In Marfan syndrome: • Cognitive abilities usually normal • Ocular findings (myopia & lens dislocation) • Cardiovascular findings (dilatation of the aorta; mitral & tricuspid valve prolapse) • Pectus abnormalities common

Table 2. continued from previous page.

Disorder	Gene / Genetic Mechanism	MOI	Clinical Features	
			Overlapping	Distinguishing
Congenital contractural arachnodactyly (CCA; Beals syndrome)	*FBN2*	AD	• Tall stature • Scoliosis • Camptodactyly	In CCA: • Cognitive abilities usually normal • Cardiovascular findings (dilatation of the aorta; mitral & tricuspid valve prolapse) • Crumpled appearance to the top of the ear • Pectus abnormalities common

AD = autosomal dominant; ASD = autism spectrum disorder; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked
1. Pathogenic variants in *NSD1* (the cause of Sotos syndrome) were once reported to cause Weaver syndrome [Douglas et al 2003]. However, this association has been refuted [Tatton-Brown et al 2005].
2. More than 95% of individuals have a *de novo* pathogenic variant.
3. Malan et al [2010], Schanze et al [2014], Klaassens et al [2015], Priolo et al [2018]
4. Tatton-Brown et al [2014], Tatton-Brown et al [2018]
5. A clinical suspicion of BWS can be confirmed through testing that reveals dysregulation of the normal imprint at the 11p15 growth regulatory region [Choufani et al 2010]: loss of methylation at imprinting center 2 (IC2; see Beckwith-Wiedeman Syndrome, Figure 1 for detailed molecular mechanism) on the maternal allele (in ~50% of affected individuals); uniparental disomy for 11p15 (in ~20% of affected individuals); gain of methylation at imprinting center 1 (IC12; see Beckwith-Wiedeman Syndrome, Figure 1 for detailed molecular mechanism) of the maternal allele (in ~5% of affected individuals); or pathogenic variants within the maternal copy of *CDKN1C* (in 5%-10% of sporadic cases of BWS; ≤40% of familial cases). In approximately 20% of individuals with a clinical diagnosis of BWS the underlying molecular abnormality is not elucidated.
6. Approximately 85% of individuals with BWS have no family history of BWS; approximately 15% have a family history consistent with parent-of-origin autosomal dominant transmission.
7. Golabi & Rosen [1984], Cottereau et al [2013]

Management

The following information represents typical evaluation and management recommendations for individuals in the United States; standard recommendations may vary from country to country [Author, personal observation].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a heterozygous *EZH2* pathogenic variant, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *EZH2*-Related Overgrowth

System/ Concern	Evaluation	Comment
Neurologic	Developmental assessment	To incl motor, speech/language evaluation, general cognitive, & vocational skills
	Muscle tone	Hypotonia & mixed hypo/hypertonia common
	Seizures	If seizure activity is suspected: • Brain MRI • EEG
Psychiatric/ Behavioral	Assessment for ASD & other behavioral issues	
Constitutional	Measurement of height, weight, head circumference	
Musculoskeletal	Assessment for scoliosis, camptodactyly, ligamentous laxity	
Genitourinary	Assessment for cryptorchidism, hydrocele, hypospadias	
Cardiovascular	Cardiac auscultation	Baseline echocardiogram for evidence of structural cardiac anomalies
Malignancy	Assessment for potential malignancy, esp neuroblastoma & hematologic malignancies	While no specific surveillance is recommended, a low threshold for investigation of any possible tumor-related symptoms is advised.

ASD = autism spectrum disorder

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *EZH2*-Related Overgrowth

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay &/or learning disability	Educational support	Referral for learning/behavior/speech assessment & support may be indicated.
Camptodactyly	Surgical intervention	Occasionally toe camptodactyly may require surgical intervention.
	Physiotherapy	May be beneficial
Abnormal muscle tone	Physiotherapy	May be beneficial
Ligamentous laxity	Physiotherapy	May reduce joint pain secondary to ligamentous laxity
Scoliosis	Further evaluation & monitoring	Referral to orthopedist

If additional clinical issues are detected through the history and/or examination, the appropriate specialist referral(s) should be made.

Global Developmental Disability / Intellectual Disability Management Issues

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the United States, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school system until age 21.
- Discussion about transition plans including financial, vocation/employment if feasible, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a 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.
- Consider use of durable medical equipment 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. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., Augmentative and Alternative Communication [AAC]) for individuals who have expressive language difficulties.

Surveillance

Table 5. Recommended Surveillance for Individuals with *EZH2*-Related Overgrowth

System/Concern	Evaluation	Frequency [1]
Musculoskeletal	Monitoring by pediatrician for resolution/improvement of camptodactyly &/or hypotonia	Regular follow up w/frequency dependent on severity
	If scoliosis is present, monitoring per orthopedic recommendations	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency [1]
Malignancy	Neuroblastoma surveillance: current recommendations include clinical vigilance & thorough investigation of any symptoms that may be tumor related. [2] Note: Neuroblastoma surveillance has been inconsistent, w/no data supporting modality of surveillance, screening interval, or duration.	
Miscellaneous/ Other	Monitoring of developmental progress & educational needs	Regular follow up w/frequency dependent on severity
	Clinical genetics evaluation	At diagnosis, soon after to answer further questions, & when appropriate to support reproductive decisions (i.e., for parents to discuss recurrence risk or for affected individuals to discuss offspring risk)

1. In older children/teenagers who do not have medical complications, the clinician may wish to review less frequently than in yonger children.
2. Current data suggest a slightly increased relative risk for the development of neuroblastoma in individuals with heterozygous germline *EZH2* pathogenic variants. Although the numbers are too small to quantify the absolute tumor risk, it appears to be low (see Clinical Description, **Tumors**).

Evaluation of Relatives at Risk

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

Pregnancy Management

In general, pregnancies in which the mother and/or fetus has a heterozygous *EZH2* pathogenic variant are uncomplicated. Families and their health care providers should be aware that an affected baby may be large so that appropriate delivery plans can be made; in addition, information about the *EZH2*-related overgrowth phenotype should be provided.

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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

EZH2-related overgrowth is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with *EZH2*-related overgrowth have an affected parent.
- Some individuals diagnosed with *EZH2*-related overgrowth have the disorder as the result of a *de novo* *EZH2* pathogenic variant. The proportion of *EZH2*-related overgrowth caused by a *de novo* pathogenic variant is unknown. In the series of 48 individuals identified with an *EZH2* pathogenic variant [Tatton-Brown et al 2013]:
  - 23 were simplex cases with a *de novo* pathogenic variant.
  - 14 were familial cases.
  - 11 could not be confirmed as having a *de novo* or a familial pathogenic variant as parental testing was not performed or clinical information was not available from a parent.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* germline *EZH2* pathogenic variant in the proband or germline mosaicism in a parent (although no instances of germline mosaicism have been reported it remains a possibility).
- Evaluation of parents may determine that one has a heterozygous germline *EZH2* pathogenic variant but has escaped previous diagnosis because of a milder phenotype. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be mildly/minimally affected.

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

- If testing reveals that a parent of the proband has the *EZH2* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. The phenotype of an individual inheriting the *EZH2* pathogenic variant cannot be predicted.
- If the *EZH2* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

If the parents have not been tested for the *EZH2* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband is unclear because of the possibility of reduced penetrance (or germline mosaicism) in a parent.

Offspring of a proband. Each child of an individual with *EZH2*-related overgrowth has a 50% chance of inheriting the *EZH2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has an *EZH2* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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 or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *EZH2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

- **National Library of Medicine Genetics Home Reference**
  Weaver syndrome
- **Child Growth Foundation**
  21 Malvern Drive
  West Midlands B76 1PZ
  United Kingdom
  Phone: 020 8995 0257
  Email: nfo@childgrowthfoundation.org
  www.childgrowthfoundation.org
- **MAGIC Foundation**
  4200 Cantera Drive #106
  Warrenville IL 60555
  Phone: 800-362-4423 (Toll-free Parent Help Line); 630-836-8200
  Fax: 630-836-8181
  Email: contactus@magicfoundation.org
  www.magicfoundation.org

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. EZH2-Related Overgrowth: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

EZH2	7q36.1	Histone-lysine N-methyltransferase EZH2	EZH2 database	EZH2	EZH2

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 EZH2-Related Overgrowth (View All in OMIM)

277590	WEAVER SYNDROME; WVS
601573	ENHANCER OF ZESTE 2 POLYCOMB REPRESSIVE COMPLEX 2 SUBUNIT; EZH2

Gene structure. There are multiple alternative transcripts. The longest, NM_004456.4, comprises 20 exons; the first exon is noncoding. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Factors to consider in the interpretation of sequence variants:

- All *de novo* germline missense and truncating variants in a simplex case (i.e., a single occurrence in a family) of Weaver syndrome are likely to be pathogenic.
- Inherited missense and truncating variants that segregate with the overgrowth phenotype are likely to be pathogenic.
- If parental samples are not available, missense and truncating variants should be interpreted with caution. Based on a small number of cases, current data (in which distribution of *EZH2* variants in cases vs controls, conservation of the SET domain [see **Normal gene product**] residues, and critical function of the SET domain in mediating histone methyltransferase activity were analyzed) suggest that SET domain missense variants are likely pathogenic. In addition, the few truncating variants that have been identified are all located in the final exon after the SET domain, although further studies are required to clarify the mechanism by which these variants cause overgrowth.

Table 6. *EZH2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.395C>T	p.Pro132Leu	NM_004456.4 NP_004447.2
c.458A>G	p.Tyr153Cys	
c.2044G>A	p.Ala682Thr	
c.2233G>A	p.Glu745Lys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. EZH2 (NP_004447.2), encoded by the longest transcript, is a 751-amino acid histone methyltransferase with a critical SET (su(var)3-9, enhancer of zeste, trithorax) domain, a pre-SET CXC domain, and two additional SANT (Sw13, Ada2, N-cor TFIIIB) domains [Wu et al 2013]. In combination with SUZ12 and EED (to form the polycomb repressor complex 2 [PCR2]), EZH2 acts to repress transcription through the methylation of lysine residue 27 of histone 3, a function catalyzed by the SET domain [Cao et al 2002].

Abnormal gene product. The protein alterations and the mechanism by which *EZH2* missense and truncating variants cause Weaver syndrome are currently unknown. It is, however, noteworthy that pathogenic missense variants are the primary mutational mechanism; the few pathogenic truncating variants identified to date target the final exon and thus are likely to escape nonsense-mediated RNA decay. Current evidence suggests that

Weaver syndrome may be caused by impaired histone methyltransferase function [Cohen et al 2016, Lui et al 2018].

Cancer and Benign Tumors

Somatic activating and inactivating mono- and biallelic *EZH2* pathogenic variants have been identified in various hematopoietic malignancies. Of particular note, a recurrent activating pathogenic variant targeting the Tyr646 residue has been identified in lymphomas, particularly large B-cell lymphomas and follicular lymphomas; inactivating pathogenic variants throughout the gene are identified in myelodysplastic and myeloproliferative neoplasms with a poor prognosis [Morin et al 2010, Sneeringer et al 2010, Chase & Cross 2011].

Despite the association between somatic inactivating *EZH2* pathogenic variants and older-onset, chronic myeloproliferative/dysplastic syndromes, these malignancies do not appear to occur at increased frequencies in individuals with *EZH2*-related overgrowth. Possible explanations for this finding:

- Myeloproliferative/dysplastic syndromes usually occur at ages older than the age of most individuals currently identified with a germline (constitutional) *EZH2* pathogenic variant.
- The mechanisms by which *EZH2* somatic pathogenic variants cause malignancy and *EZH2* germline pathogenic variants cause overgrowth differ.
- Relatively few individuals with *EZH2* germline pathogenic variants have been identified to date.

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Chapter Notes

Revision History

- 2 August 2018 (bp) Comprehensive update posted live

- 6 August 2015 (me) Comprehensive update posted live
- 18 July 2013 (me) Review posted live
- 23 January 2013 (ktb) Original submission

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