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EED-Related Overgrowth

Ana Sequerra Amram Cohen, PhD[1] and William Thomas Gibson, MD, PhD, FRCPC, FCCMG[2]

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Summary

Clinical characteristics

EED-related overgrowth is characterized by fetal or early childhood overgrowth (tall stature, macrocephaly, large hands and feet, and advanced bone age) and intellectual disability that ranges from mild to severe. To date, *EED*-related overgrowth has been reported in eight individuals.

Diagnosis/testing

The diagnosis of *EED*-related overgrowth is established in a proband with suggestive findings and a heterozygous germline *EED* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental delay / intellectual disability requires early referral for developmental support and educational interventions tailored to the child's needs. Seizures, cervical spine instability, palatal abnormalities, kyphoscoliosis, congenital heart defects, cryptorchidism, and ophthalmologic findings are treated per standard practice.

Surveillance: Routine assessment of the following: development; spine for scoliosis or deformities; joint range of motion for joint contractures; and eyes for refractive errors, myopia, and strabismus.

Agents/circumstances to avoid: Activities that involve rapid neck motion and/or possible trauma to the head and neck region (e.g., contact sports or thrill rides at amusement parks) because of the possible increased risk for cervical spine instability.

Genetic counseling

EED-related overgrowth is inherited in an autosomal dominant manner. To date all probands whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo EED* pathogenic variant. The

Author Affiliations: 1 Icahn School of Medicine at Mount Sinai, New York, New York; Email: ana.cohen@mssm.edu. 2 Associate Professor, Department of Medical Genetics and Genomics, UBC Senior Clinician Scientist, BC Children's Hospital, Vancouver, British Columbia, Canada; Email: wtgibson@bcchr.ca.

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risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *EED* pathogenic variant found in the proband 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. Once a family member has a confirmed molecular diagnosis of *EED*-related overgrowth, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

EED-related overgrowth **should be suspected** in individuals with the following major findings.

Clinical findings

Overgrowth manifesting as:

- Tall stature (z score ≥2 for age, equivalent to SD ≥2)

  Note: An adult of normal stature who had relatively tall stature and/or advanced bone age in childhood or adolescence could meet criteria for overgrowth.

- Macrocephaly (z score ≥2 for age)
- Large hands and feet (length z score ≥2 for age)

Intellectual disability, developmental delay

- Delay of gross motor skills
- Delay of fine motor skills
- Delay of speech acquisition
- Delay of social development
- Intellectual disability (by clinical assessment and/or formal testing)

Skeletal radiographs

- Advanced bone age (bone age ≥2 chronologic age)
- Metaphyses may be widened, flared, and/or abnormally lucent.
- Skeletal surveys have variously revealed flattened glenoid fossae, humeral heads, femoral heads, and flattened acetabulum. Other findings include small iliac wings and coxa valga as well as asymmetric limb lengths (1 individual) and flaring of the distal clavicles and distal ribs (1 individual).
- Osteopenia has been documented on skeletal survey; however, to date no increased risk of fractures has been documented.

Supportive findings include **characteristic craniofacial features** that are more evident in infancy and childhood and tend to become less evident with age: a round face; prominent (tall, wide, or broad) forehead; hypertelorism; low, wide, and/or depressed nasal bridge; large ears (with or without posterior helical pits and earlobe creases), which may appear low-set; prominent and/or long philtrum; horizontal chin crease; and retrognathia. Facial hypotonia may contribute to an open-mouthed appearance (see Figure 1). Published photographs showing the characteristic craniofacial features of *EED*-related overgrowth are accessible (with registration or institutional access) in Cohen et al [2015] (full text; see Figure 1), Cohen & Gibson [2016] (full text; see Figure 2), Cooney et al [2017] (full text; see Figure 1), Imagawa et al [2017] (full text; see Figure 2), Smigiel et al [2018] (full text; see Figure 1), and Griffiths et al [2019] (full text; see Figure 1).

Figure 1. Photographs of an affected male at age one day (A), 3.5 weeks (B), three months (C), six months (D), one year (E), two years (F), seven years (G), 11 years (H), 12 years (I), and 33 years (J, K, L, M, N, O, P)

Note round face with prominent forehead, hypertelorism, and depressed nasal bridge (A-F); large ears (C, G, H, I, K); prominent philtrum (A, B, C, J); prominent crease between the lower lip and chin (A, C, E, H, I, J); retrognathia (A, B, C, K); multiple pigmented nevi (J, K, L, M); overall body habitus (L, M); and large hands and feet (N, O, P).

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Establishing the Diagnosis

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

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *EED* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the scenario.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of disorders of overgrowth with intellectual disability (OGID) can be indistinguishable, children with the distinctive findings described in Suggestive Findings who have not undergone previous genetic testing are likely to be diagnosed using a multigene panel or genomic testing (see Scenario 1) – whereas children with OGID who have previously undergone genetic testing that did not include sequence analysis of *EED* may be diagnosed using single-gene testing (see Scenario 2).

Scenario 1

When the phenotype of a child with a disorder of overgrowth with intellectual disability (OGID) does not strongly suggest a specific diagnosis, molecular genetic testing approaches can include use of a **multigene panel for OGID disorders or comprehensive genomic testing**:

- **A multigene panel** that includes *EED* 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*. Of note, given the rarity of *EED* overgrowth, some panels for overgrowth and intellectual disability disorders may not include this gene. (3) In some 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.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) could be the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Scenario 2

When the phenotypic findings suggest the diagnosis of *EED*-related overgrowth in an individual who has already had molecular genetic testing for the other common overgrowth and intellectual disability disorders (see Differential Diagnosis), **single-gene testing** of *EED* is an option:

- Sequence analysis of *EED* is performed first.
- If a pathogenic variant is not found, gene-targeted deletion/duplication analysis could be considered; however, to date no exon or whole-gene deletions have been reported in the literature.

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

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
EED	Sequence analysis [3]	7/7 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. *EED* coding region sequence analysis has detected 8/8 individuals reported to date [Cohen et al 2015, Cohen & Gibson 2016, Cooney et al 2017, Imagawa et al 2017, Tatton-Brown et al 2017, Smigiel et al 2018]. However, causative noncoding variants may exist; in the case of an individual with a phenotype strongly evocative of *EED*-related overgrowth, the predictive value of a negative test is unknown.
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.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

EED-related overgrowth is characterized by fetal or early childhood overgrowth (tall stature, macrocephaly, large hands and feet, and advanced osseous maturation) and intellectual disability that ranges from mild to severe. See Figure 1 for photographs of one individual from age one day to 33 years.

To date, *EED*-related overgrowth has been reported in eight individuals [Cohen et al 2015, Cohen & Gibson 2016, Cooney et al 2017, Imagawa et al 2017, Tatton-Brown et al 2017, Smigiel et al 2018, Griffiths et al 2019].

Prenatal growth. Gestational age at delivery has ranged from 36 to 42 weeks.

Birth weight ranges from appropriate to large for gestational age, with weights ranging from 3,550 g (male, 38 weeks' gestation [Smigiel et al 2018]) to 4,800 g (female, 36 weeks' gestation [Cooney et al 2017]) with z scores from +0 to +4.2. To date, birth weights below the mean for gestational age have not been reported.

Birth length typically ranges from 52 cm (z score +0.5) to 57 cm (z score +3.0).

Birth head circumference ranges from 34 cm (z score -0.78) to 37.2 cm (z score +2.0).

Postnatal growth. During childhood and adolescence, increased height, weight, and head circumference manifest as increased z scores in height (+2.8 to +5.1), weight (+1.4 to +3.8), and head circumference (+2.0 to

+2.6). Z scores for body-mass index vary from approximately +1.4 to +1.8; thus, based on data available to date, obesity does not appear to be a major feature of *EED*-related overgrowth.

Growth parameter z scores in adults using World Health Organization curves vary from +1.85 to +3.1 in height and +1.46 to +3.9 in head circumference. The two adults reported by Griffiths et al [2019] had body-mass indices of 32.6 kg/m^2 and 38.2 kg/m^2 (in the obese range) in their mid-20s. Registry-based longitudinal growth curves are not yet available.

Psychomotor development. Delay of gross motor, fine motor, and speech milestones is common.

Intellectual disability, present in all individuals reported to date, may be mild [Cohen et al 2015], moderate [Cooney et al 2017], or severe [Tatton-Brown et al 2017]. Difficulties with coordination and balance may persist into adulthood.

Two affected individuals had relatively sociable, friendly personalities; a third was somewhat hyperactive and lacking inhibition, with occasional aggression toward peers at school. In one individual who had had more detailed testing, specific weaknesses were noted in problem-solving and memory, whereas visual memory was a relative strength.

Craniofacial. The voice may be hypernasal, low, or hoarse.

Bilateral cleft palate has been reported in one individual, and bifid uvula has been reported in another.

Skeletal. Large hands and feet are notable in childhood and into adulthood. Fingers may be long and slender. Broad thumbs and small nails were seen in two individuals.

Camptodactyly, joint contractures, flat feet (*pes planovalgus*), and/or clubfoot may be seen.

Hypermobility of the small joints of the hands, recurrent patellar subluxation and dislocation, and skin fragility (poor wound healing, fragile nails) have also been described and suggest more generalized laxity of connective tissue.

Scoliosis and/or kyphoscoliosis of the thoracic spine have been reported frequently.

Stenosis of the cervical spine has been reported in two individuals, one of whom required laminectomy and arthrodesis; the other had associated myelopathy at the level of the third cervical vertebra.

Osteopenia, reported in two individuals, was a secondary finding on bone age radiographs or skeletal survey.

Skeletal findings reported in one individual each:

- Atlantoaxial instability requiring surgical intervention after neurologic compromise
- Above-knee amputation as a result of vascular circulatory failure following patellar surgery

Neurologic. Low muscle tone with delayed gross motor milestones is common. Gait may appear clumsy; coordination is often poor.

Epilepsy has been reported in one individual; a second had seizures associated with hyperinsulinemic hypoglycemia (see **Endocrine** in this section).

Cerebral imaging has shown nonspecific enlargement of the ventricles in one individual and moderate-to-severe thinning of the corpus callosum and loss of white matter (disproportionately affecting the frontal lobe) in another; both had moderate intellectual disability. Cerebral imaging has also been normal in several individuals.

Skin findings have included the following:

- Multiple pigmented nevi (2 individuals)

- Soft, doughy skin with increased elasticity (1 individual)
- Fragile fingernails and toenails (1 individual)
- Poor wound healing with hyperpigmentation and keloid overgrowth of a surgical scar (1 individual)

Hernias. Inguinal and femoral hernias may be seen. Umbilical hernias may be large enough to require surgical management.

Cardiovascular. Structural cardiac anomalies (patent ductus arteriosus, septal defects, and mild or moderate mitral valve prolapse) have been reported.

Genitourinary. Bilateral cryptorchidism has been reported in males and may require surgical correction.

One female had nephromegaly and a duplicated collecting system.

Ophthalmologic. Ocular findings have included hypertelorism, telecanthus, hyperopia, myopia, exotropia, astigmatism, and strabismus. Narrow and/or short palpebral fissures with a downslant to the lateral aspect of the upper eyelid have also been reported. Eversion of the lateral lower eyelid has also been suggested, based on panel review of published photographs.

The following were reported in one individual each:

- Ptosis requiring surgical correction
- Early-onset cataracts (age 30 years)

Hearing loss

- Bilateral hypoacusis of 50 dB (frequencies not specified) (1 individual)
- Mild-moderate conductive hearing loss (1 individual)

Respiratory. Neonatal respiratory distress may be seen. One individual had significant tracheomalacia requiring surgical intervention, as well as frequent respiratory infections.

Feeding/gastrointestinal findings include:

- Gastrostomy tube feeds in infancy, later requiring partial bowel resection for obstruction (the latter possibly associated with anticholinergic medications) (1 individual)
- Chronic constipation (1 individual)

Endocrine

- Neonatal hyperinsulinemic hypoglycemia was treated by glucose infusion and resolved at 21 days (1 individual).
- Childhood-onset hyperinsulinemic hypoglycemia was treated with octreotide (1 individual).

Cancer predisposition. No instances of benign or malignant tumors in individuals with germline *EED* pathogenic variants have been reported to date. The risk for certain cancers, such as hematologic cancers and malignant peripheral nerve sheath tumors, could theoretically be increased (see Molecular Genetics).

Genotype-Phenotype Correlations

With only eight probands reported to date, data are insufficient to consider genotype-phenotype correlations.

Penetrance

Because most germline *EED* coding variants associated with overgrowth are *de novo*, penetrance is expected to be high. Estimates of penetrance for inherited *EED* coding variants are not yet available.

Prevalence

To date eight individuals have been reported with *EED*-related overgrowth.

Ancestry has included Turkish [Cohen et al 2015], European American [Cohen & Gibson 2016], Hispanic American [Cooney et al 2017], Japanese [Imagawa et al 2017], and Polish [Smigiel et al 2018]. Three individuals were identified in a UK international consortium [Tatton-Brown et al 2017, Griffiths et al 2019].

Genetically Related (Allelic) Disorders

To date, no phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *EED*.

Differential Diagnosis

Table 2. Autosomal Dominant Disorders with Macrocephaly and Intellectual Disability to Consider in the Differential Diagnosis of *EED*-Related Overgrowth

DiffDx Disorder	Gene	Clinical Features of Disorder	
		Overlapping w/*EED*-related overgrowth	Distinguishing from *EED*-related overgrowth
EZH2-related overgrowth (includes Weaver syndrome)	*EZH2*	• Macrosomia • Craniofacial dysmorphism • Advanced bone age	• Cancer predisposition • Less frequent cervical spine anomalies
SUZ12-related overgrowth [1]	*SUZ12*	• Postnatal overgrowth • Craniofacial dysmorphism • Advanced bone age	• Prenatal overgrowth apparently less severe • Postnatal overgrowth apparently more severe
Sotos syndrome	*NSD1*	• Macrosomia • Craniofacial dysmorphism • Advanced bone age	Cancer predisposition
NFIX-related Malan syndrome	*NFIX*	• Macrosomia • Craniofacial dysmorphism • Advanced bone age	• Cancer predisposition • Less frequent cervical spine anomalies
HIST1H1E syndrome	*HIST1H1E*	• Neonatal hypoglycemia • Camptodactyly • Kyphoscoliosis	Neonatal hypertonia
Beckwith-Wiedemann syndrome	*CDKN1C*	• Macrosomia • Neonatal hypoglycemia • Umbilical hernia	• Cancer predisposition • Organomegaly • Macroglossia
PTEN hamartoma tumor syndrome	*PTEN*	• Macrocephaly • Intellectual disability	• Cancer predisposition • Mucocutaneous lesions

1. Imagawa et al [2017]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *EED*-related overgrowth, 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 and Referrals Following Initial Diagnosis of *EED*-Related Overgrowth

System/ Concern	Evaluation	Comment
Growth	Plot prenatal ultrasound &/or birth parameters according to gestational age at assessment or delivery.	Z scores may be unusually high relative to norms for gestational age (e.g., birth head circumference of +2.4 SD above the mean at 36 wks).
Neurologic	Developmental	Consider eval by speech therapist, occupational therapist, & physiotherapist.
	Neuropsychological assessment	For behavioral issues
	EEG if seizures are suspected	Refer to neurologist for seizure disorder management. Rule out hyperinsulinism.
	CT of cervical spine to assess for spinal cord impingement & spinal stenosis	Only if signs or symptoms warrant – refer to neurosurgeon as needed.
	MRI	May be done electively to look for structural brain abnormalities; because infants & very young children may require sedation or anesthesia for MRI, additional clinical indications (e.g., seizures) may inform timing of imaging.
Oropharynx	Exam for palatal anomalies	Refer to craniofacial team or otolaryngologist as needed.
Skeletal	Assessment for skeletal anomalies (e.g., scoliosis, kyphosis, limited joint mobility, recurrent dislocations)	Refer to orthopedist as neeeded.
	Assessment for osteopenia	If a fracture has occurred, consider bone mineral density scan to quantify risk of future fractures.
Skin	Exam for pigmented nevi	Monitor clinically for potential malignancy.
Cardiac	Echocardiogram	To assess for structural heart defects
Genitourinary	Males: Examine for undescended testes. All patients: Examine for umbilical hernia.	
	Renal ultrasound exam	Assess for structural renal abnormalities.
Eyes	Ophthalmologic eval	Assess for strabismus, myopia, & refractive error.
Hearing	Audiologic eval	Newborn audiology screening may be insufficient – consider additional audiology screening if speech is delayed & possibly also at school entry.
Endocrine	Glucose level in neonatal period	If lethargy &/or poor feeding If seizures occur, measure glucose & insulin simultaneously.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Treatment is symptomatic; no therapy specific to the disorder is available. The appropriate interventions are summarized in Table 4.

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

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / intellectual disability	Early referral for developmental support / special education	See text following this table.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Seizure disorder	Standard treatment per neurologist	See footnote 1.
Cervical spine instability	Surgical intervention if instability is severe & neurologic compromise is present or likely	Expert neurosurgical advice recommended, particularly for prophylactic intervention
Cleft palate	Mgmt by cleft/craniofacial team; surgical correction of cleft palate; orthodontic interventions to correct retrognathia (overbite) as needed	
Scoliosis/kyphosis	Standard treatment per orthopedist	
Congenital heart defects	Standard therapy per cardiologist	
Undescended testes, inguinal hernia	Standard treatment per urologist	
Strabismus, refractive error, cataracts	Standard treatment per ophthalmologist	
Hyperinsulinemic hypoglycemia	Glucose; consider octreotide.	Endocrine eval recommended if hypoglycemia persists &/or insulin levels ↑
Joint contractures &/or hypertonia	Physiotherapy/surgery as needed	

1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of 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 and 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; however, 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 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 if 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 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.
- 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 and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

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 is 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 when necessary.

Autism or other major behavior problems have not been reported to date in *EED*-related overgrowth. The presence of autistic spectrum disorders, major behavioral difficulties, and/or another significant

neuropsychiatric phenotype in an individual with *EED*-related overgrowth may prompt a search for an additional underlying cause for these features.

Surveillance

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

System/Concern	Evaluation	Frequency/Comment
Neurologic	Developmental assessments	At routine intervals, to adjust therapies & adapt educational needs
	Assessment by a neurologist	Per routine for persons w/epilepsy
	Screening for cervical spine instability [1] / spinal stenosis	As dictated by signs & symptoms; see also footnote 1.
Musculoskeletal	Evaluate for scoliosis & spine deformities.	At each visit
	Joint contractures	Physiotherapy, surgery as necessary
Eyes	Ophthalmologist to screen for refractive errors, myopia, & strabismus	At routine intervals
Endocrine	Glucose/insulin levels	Hyperinsulinemic hypoglycemia confirmed in 2 patients (1 as a neonate); evidence of poor neonatal adaptation suggests glucose should be checked.

1. Though to date data are insufficient to recommend routine imaging of the cervical spine to screen for atlantoaxial instability, practitioners should have a low threshold for imaging when signs and symptoms are consistent with cord impingement (particularly when of rapid onset). Elective cervical spine imaging should be considered when activities involve possible sudden movement of the neck and/or head and neck (e.g., contact sports, amusement park thrill rides).

Although malignant peripheral nerve-sheath tumors (MPNSTs) have not been reported to date in individuals with *EED*-related overgrowth caused by germline *EED* pathogenic variants, the observation of somatic *EED* pathogenic variants in malignant MPNSTs [Lee et al 2014] (see Molecular Genetics, Cancer and Benign Tumors) suggests that lesions with features suspicious for MPNSTs should be followed with clinical examination and/or imaging as per guidelines for such lesions in individuals with neurofibromatosis type 1.

Agents/Circumstances to Avoid

In one individual, neurologic compromise resulting from neck motion during gymnastics required surgical intervention. Caution is advised for activities that involve rapid neck motion and/or possible trauma to the head and neck region (e.g., contact sports or thrill rides at amusement parks).

Side effects of pharmacologic agents that inhibit the activity of the PRC2 complex (which includes the protein EED) may be increased; also the efficacy in individuals with *EED*-related overgrowth may differ from that in other individuals.

Evaluation of Relatives at Risk

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

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

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

Risk to Family Members

Parents of a proband

- All probands reported to date with *EED*-related overgrowth whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo EED* pathogenic variant.
- If a parent of an individual with an identified *EED* pathogenic variant does not have any clinical features of *EED*-related overgrowth, that parent is unlikely to have a pathogenic variant in *EED*. However, molecular genetic testing of both parents for the *EED* pathogenic variant identified in the proband is generally advisable.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected. Subtle features such as tall stature, larger-than-normal head circumference, mild facial dysmorphisms, and a history of mild developmental delay may not be obvious unless sought specifically during the parental assessment.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *EED* pathogenic variant found in the proband 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].

Offspring of a proband. To date, individuals with *EED*-related overgrowth are not known to reproduce.

Other family members. Given that all probands with *EED*-related overgrowth (in whom parental samples have been analyzed) have the disorder as a result of a *de novo EED* pathogenic variant, the risk to other family members is presumed to be low.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once a family member has a confirmed molecular diagnosis of *EED*-related overgrowth, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: nfo@childgrowthfoundation.org
  childgrowthfoundation.org
- **Human Growth Foundation**
  www.hgfound.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs
- **Canadian Organization for Rare Disorders (CORD)**
  Canada
  www.raredisorders.ca
- **Rare Disease Foundation**
  Canada
  Email: families@rarediseasefoundation.org; info@rarediseasefoundation.org
  rarediseasefoundation.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. EED-Related Overgrowth: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
EED	11q14.2	Polycomb protein EED	EED	EED

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 EED-Related Overgrowth (View All in OMIM)

605984	EMBRYONIC ECTODERM DEVELOPMENT; EED
617561	COHEN-GIBSON SYNDROME; COGIS

Gene structure. *EED* (NM_003797.4) comprises 12 coding exons distributed along 2,476 bp. The initiation codon is located in exon 1, and there are 441 coding residues (NP_003788.2). Two additional RefSeq transcripts are listed in NCBI: NM_001308007.1 (encoding one additional exon located between exons 9 and 10, totaling 2,551 bp) and NM_001330334.1 (skipping exons 8 and 9, totaling 2,236 bp). Transcript NM_003797.4 is typically used as the primary transcript; relevance of the alternative transcripts is currently unknown.

See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Seven of the eight pathogenic variants reported to date have been missense variants across exons 6-9, whereas the eighth is an indel affecting two amino acids. Where complete familial analysis has been possible, all pathogenic variants have been proven to be *de novo*.

The population prevalence of pathogenic variants in *EED* is unknown. However, multiple *EED* variants predicted to have missense or loss-of-function effects have been reported in the ExAC and gnomAD population samples (217/60,706 and 538/138,632, respectively). These data suggest a crude estimation of population prevalence of approximately 0.4% for rare variants of uncertain significance.

Table 6. Selected *EED* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.581A>G	p.Asn194Ser	NM_003797.4 NP_003788.2
c.706A>G	p.Arg236Gly	
c.707G>C	p.Arg236Thr	
c.710A>G	p.Asp237Gly	
c.772C>T	p.His258Tyr	
c.904A>G	p.Arg302Gly	
c.906A>C (originally reported as 1372A>C)	p.Arg302Ser	
c.917_919delinsCGG	p.Arg306_Asn307delinsThrAsp	

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. The primary transcript of the human *e*mbryonic *e*ctoderm *d*evelopment (EED) gene encodes a protein of 441 amino acid residues (NP_003788.2). EED is highly conserved among distantly related phyla and is expressed ubiquitously. EED is a core member of the polycomb repressive complex type 2 (PRC2). Other PRC2 members include EZH2, SUZ12, RBBP7, and RBBP4; their complex with EED is thought to be necessary for the lysine methyltransferase activity of PRC2.

There are seven WD40 domains, though whether these domains have redundant or distinct functions is not yet known. The C-terminal domain of EED binds specifically to trimethylated H3K27 (i.e., H3K27me3) histone tails, and this function is thought to be necessary for the propagation of H3K27me3 marks to daughter cells that initially lack sufficient H3K27 marks after mitosis.

In general, PRC2 is a key chromatin modifier involved in the maintenance of transcriptional silencing. PRC2-mediated trimethylation of H3K27 is thought to correlate with transcriptional repression of local DNA. Correct propagation of H3K27me3 marks is in turn thought necessary in order for repressive domains to persist in the newly synthesized chromatin [Margueron et al 2009].

Abnormal gene product. In an *ex vivo* assay, a lymphoblastoid cell line derived from a Japanese individual with the p.(Arg236Thr) pathogenic variant showed reduced levels of H3K27 trimethylation by Western blotting, consistent with reduced methyltransferase activity of the mutated PRC2 complex toward this substrate [Imagawa et al 2017]. These data suggest that *EED*-related overgrowth is caused by partial loss of function of EED protein.

Cancer and Benign Tumors

Though to date malignant peripheral nerve-sheath tumors (MPNSTs) have not been reported in individuals with *EED*-related overgrowth caused by germline *EED* pathogenic variants, the presence of somatic variants in *EED* in individuals with MPNSTs [Lee et al 2014] suggests that persons with *EED*-related overgrowth may also be at increased risk for these tumors.

Wassef & Margueron [2017] reviewed the role of PCR2 alterations in MPNSTs and other cancers that included somatic variants in *EED*.

Chapter Notes

Author Notes

Dr Gibson's clinical and laboratory research focuses on Cohen-Gibson syndrome, Weaver syndrome, and similar rare disorders, including rare genetic versions of common, complex diseases.

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