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Kleefstra Syndrome

Synonyms: 9q34.3 Microdeletion Syndrome, 9qSTDS, 9q Subtelomeric Deletion Syndrome

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Summary

Clinical characteristics

Kleefstra syndrome is characterized by intellectual disability, autistic-like features, childhood hypotonia, and distinctive facial features. The majority of individuals function in the moderate-to-severe spectrum of intellectual disability although a few individuals have mild delay and total IQ within low-normal range. While most have severe expressive speech delay with little speech development, general language development is usually at a higher level, making nonverbal communication possible. A complex pattern of other findings can also be observed; these include heart defects, renal/urologic defects, genital defects in males, severe respiratory infections, epilepsy / febrile seizures, psychiatric disorders, and extreme apathy or catatonic-like features after puberty.

Diagnosis/testing

The diagnosis of Kleefstra syndrome is established in a proband who has a heterozygous deletion at chromosome 9q34.3 that includes at least part of *EHMT1* (~50%) or a heterozygous intragenic *EHMT1* pathogenic variant (~50%).

Management

Treatment of manifestations: Ongoing routine care by a multidisciplinary team specializing in the care of children or adults with intellectual disability. Referral to age-appropriate early-childhood intervention programs, special education programs, or vocational training; speech-language therapy, physical and occupational therapy, and sensory integration therapy; specialized care for those with extreme behavior issues, movement disorders, sleep disorders, and/or epilepsy; standard treatment for vision, hearing, cardiac, renal, urologic, and other medical issues.

Surveillance: Monitoring as needed of cardiac and renal/urologic abnormalities.

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Genetic counseling

Kleefstra syndrome, caused by a deletion at 9q34.3 or pathogenic variants in *EHMT1*, is inherited in an autosomal dominant manner. Almost all cases reported to date have been *de novo*; rarely, recurrence in a family has been reported when a parent has a balanced translocation involving the 9q34.3 region or somatic mosaicism for an interstitial 9q34.3 deletion. Except for individuals with somatic mosaicism for a 9q34.3 deletion, no individuals with Kleefstra syndrome have been known to reproduce. Prenatal testing may be offered to unaffected parents of a child with a 9q34.3 deletion or an *EHMT1* pathogenic variant because of the increased risk of recurrence associated with the possibility of germline mosaicism, somatic mosaicism including the germline, or a balanced chromosome translocation.

Diagnosis

Kleefstra syndrome is characterized by intellectual disability, childhood hypotonia, and distinctive facial features. A complex pattern of other findings can also be observed [Dawson et al 2002, Cormier-Daire et al 2003, Stewart et al 2004, Kleefstra et al 2005, Yatsenko et al 2005, Kleefstra et al 2006a, Kleefstra et al 2006b, Stewart & Kleefstra 2007, Kleefstra et al 2009, Yatsenko et al 2009, Willemsen et al 2012].

Suggestive Findings

Kleefstra syndrome **should be suspected** in individuals with the following:

- Intellectual disability, usually moderate to severe and associated with severe speech delay
- Distinctive facial features (See Clinical Description.)
- Childhood hypotonia
- Visual issues (hypermetropia)
- Hearing loss (sensorineural and/or conductive)
- Motor delay
- Heart defects
- Renal/urologic defects
- Genital defects (males)
- Severe infections (respiratory)
- Epilepsy / febrile seizures
- Autism spectrum disorder
- Psychiatric disorders (mood and psychotic disorders)
- Extreme apathy or catatonic(-like) features post puberty
- Nonspecific brain abnormalities: structural defects (corpus callosum hypoplasia), cortical hypoplasia, or white matter defects

Establishing the Diagnosis

The diagnosis of Kleefstra syndrome **is established** in a proband who has one of the following on molecular genetic testing (see Table 1):

- A heterozygous deletion of 9q34.3 (~50% of affected individuals) [Author, personal experience]. In 28 unrelated individuals with a 9q34.3 deletion, three distinct categories were identified [Yatsenko et al 2009]:
  - 50% bona fide *de novo* terminal deletions
  - 25% interstitial deletions
  - 25% complex rearrangements or derivative chromosomes
- A heterozygous pathogenic (or likely pathogenic) variant involving *EHMT1* (~50% of affected individuals)

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 *EHMT1* variant of uncertain significance does not establish or rule out the diagnosis.

When the phenotypic findings suggest the diagnosis of Kleefstra syndrome, molecular genetic testing approaches can include **chromosomal microarray analysis (CMA)**, **single-gene testing**, use of a **multigene panel**, and rarely **karyotype**.

- **Chromosomal microarray analysis (CMA)** uses SNP and/or oligonucleotide arrays to detect genome-wide large deletions/duplications (including *EHMT1*) that cannot be detected by typical sequence analysis.
- **Single-gene testing.** Sequence analysis of *EHMT1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Approximately 5% of individuals with Kleefstra syndrome have an intragenic deletion detectable by an assay designed to detect single-exon deletions or duplications (e.g., multiplex ligation-dependent probe amplification [MLPA], qPCR, and gene-targeted CMA). Deletions that are not intragenic but too small to be detected by CMA (e.g., containing the last part of *C90RF37* and the first exon of *EHMT1*) require such gene-targeted methods designed for this region for detection.

  Note: (1) FISH cannot reliably detect deletions <50-100 kb and cannot routinely size the deletion. (2) The 9q34.3 deletion cannot be identified by routine chromosome analysis.
- **An intellectual disability multigene panel** that includes *EHMT1* and other genes of interest (see Differential Diagnosis) may also be considered. 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 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Karyotype.** In rare instances, Kleefstra syndrome can be caused by a balanced chromosome rearrangement that disrupts the expression of *EHMT1*. If this is suspected, karyotype and FISH analysis for the 9q34.3 region can be considered. However, the typical 9q34.3 deletion cannot be identified by routine chromosome analysis.
- **Epigenetic signature analysis / methylation array.** A distinctive epigenetic signature (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with Kleefstra syndrome [Aref-Eshghi et al 2020, Goodman et al 2020, Levy et al 2021]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with: (1) suggestive findings of Kleefstra syndrome but in whom no pathogenic variant in *EHMT1* has been identified via chromosomal microarray or sequence analysis; or (2) suggestive findings of Kleefstra syndrome and a *EHMT1* variant of uncertain

clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

The epigenetic signature results should not be interpreted in isolation, as sensitivity and specificity are not 100%; these results only provide part of the evidence used in variant interpretation [Richards et al 2015, Brnich et al 2019]. Even though no overlap between the Kleefstra syndrome epigenetic signature and those of other genetic disorders has been described to date, it is well known that pathogenic variants in molecularly related genes could have overlapping epigenetic signatures, resulting in misdiagnosis.

Table 1. Molecular Genetic Testing Used in Kleefstra Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
EHMT1	CMA [3]	~50% [4]
	Sequence analysis [5]	~50%
	Gene-targeted deletion/duplication analysis [6]	See footnote 7.
	Karyotype	Rare; see footnote 8.

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. A chromosomal microarray (CMA) that includes probe coverage of *EHMT1* can detect deletions of 9q34.3 (*de novo* terminal deletions, complex rearrangements or derivative chromosomes, interstitial deletion).
4. CMA testing is appropriate to define breakpoints of large deletions; however, intragenic deletions in *EHMT1* may not be detected by this method.
5. 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.
6. 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.
7. Gene-targeted methods will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined. Gene-targeted deletion/duplication analysis of *EHMT1* may detect an additional ~5% of affected individuals who have had a normal chromosomal microarray, but this is highly dependent on the resolution and probe coverage of the array platform that was used for analysis.
8. Routine karyotype will not detect the 9q34.3 deletion. Karyotype may be considered in those with features of Kleefstra syndrome in whom a pathogenic variant (mutation or deletion) of *EHMT1* has not been identified using other methods (e.g., CMA, sequence analysis). Karyotype can detect balanced chromosomal rearrangements that disrupt *EHMT1*.

Clinical Characteristics

Clinical Description

Kleefstra syndrome has a clinically recognizable phenotype that includes physical, developmental, and behavioral features. Males and females are affected equally [Stewart et al 2004, Yatsenko et al 2005, Kleefstra et al 2006b, Stewart & Kleefstra 2007, Kleefstra et al 2009, Willemsen et al 2012].

Birth weight is usually within the normal or above-normal range; weight increases in childhood, leading to obesity (50%) [Cormier-Daire et al 2003, Kleefstra et al 2009, Willemsen et al 2012]. The facial appearance is characterized by brachy(-micro)cephaly, broad forehead, unusual shape of eyebrows (arched or straight with synophrys), mildly upslanted palpebral fissures, midface retrusion, thickened ear helices, short nose with anteverted nares, fleshy everted vermilion of the lower lip and exaggerated Cupid's bow or "tented" appearance of the vermilion of the upper lip, and protruding tongue and relative prognathism (Figure 1, Figure 2).

With age, the facial appearance becomes coarser, with persisting midface retrusion and prognathism. An increased frequency of dental anomalies, specifically neonatal teeth and retention of primary dentition, has been observed.

Cognitive development. Individuals with Kleefstra syndrome exhibit a range of cognitive and adaptive functioning [Vermeulen et al 2017a]. Most affected individuals function in the moderate-to-severe spectrum of intellectual disability, although a few individuals with only mild delay are known. Rarely, individuals with normal total IQ levels who have a diagnosis of an autism spectrum disorder have been described [Bock et al 2016; Author, personal observation]. Most affected individuals have severe expressive speech delay with hardly any speech development, whereas general language development is usually at a higher level; thus, sign language or use of pictograms is of value to many affected individuals.

Behavior. Besides issues with social behavior, the behavioral phenotype includes sleep disturbances, stereotypies, mild self-injurious behaviors, and autism spectrum disorder usually recognized in early childhood. A few reports of adolescents and adults revealed extreme, progressive apathy and catatonic(-like) behavior [Verhoeven et al 2010, Vermeulen et al 2017a, Vermeulen et al 2017b].

- Sleep disturbance is characterized by frequent nocturnal and early-morning awakenings as well as excessive daytime wakefulness – in contrast to the sleep disturbance observed in Smith-Magenis syndrome.
- Sleep disturbance in affected adolescents and young adults may be a precursor to severe regression, as well as the later development of psychoses, for which treatment is recommended.

Motor development is impaired by childhood hypotonia, but almost all individuals achieve independent walking after age two to three years.

Hearing and vision impairment. A substantial proportion of individuals have hypermetropia at a young age. Hearing impairment (both conductive and sensorineuronal) may also be present starting at a young age.

Congenital heart defects are observed in a significant number of individuals with Kleefstra syndrome. In 50% a (conotruncal) heart defect is present. Abnormalities that have been reported include ASD/VSD, tetralogy of Fallot, aortic coarctation, bicuspid aortic valve, and pulmonic stenosis. Atrial flutter has been reported in a number of individuals.

Genitourinary anomalies. Renal defects, seen in 10%-30% of affected individuals, comprise vesicoureteral reflux, hydronephrosis, renal cysts, and chronic renal insufficiency. Genital defects such as hypospadias, cryptorchidism, and small penis are reported in 30% of males.

Seizures, reported in 30%, can include tonic-clonic seizures, absence seizures, and complex partial epilepsy.

Other. Several affected individuals have had talipes equinovarus. Other abnormalities that have been observed are epigastric hernia, tracheo-/bronchomalacia with respiratory insufficiency, and gastroesophageal reflux.

Life expectancy. Longitudinal data are insufficient to determine life expectancy; however, it should be noted that death in infancy or childhood can occur from complications such as heart defects and recurrent aspiration and pulmonary infections [Stewart & Kleefstra 2007].

Genotype-Phenotype Correlations

EHMT1 loss of function accounts for the majority of features in Kleefstra syndrome. Current data indicate that individuals with an intragenic *EHMT1* pathogenic variant (e.g., a missense, frameshift, or nonsense variant) and those with a small (<1-Mb) 9q34.3 deletion have similar clinical findings. Individuals with larger deletions (≥1 Mb), however, generally have more severe intellectual disability and more medical problems, such as congenital anomalies, feeding issues, and respiratory issues. Pulmonary infections and aspiration difficulties in particular

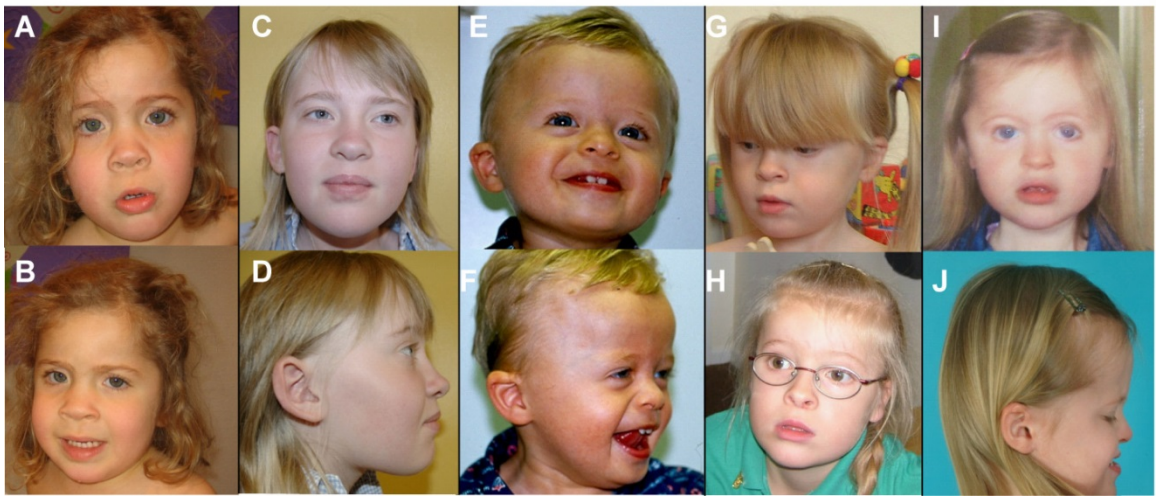

Figure 1. Photographs of affected individuals showing the characteristic facial profile comprising brachycephaly, widely spaced eyes, synophrys/arched eyebrows, midface retrusion, protruding tongue, eversion of the vermilion of the lower lip, and prognathism of chin. Five people (AB), (CD), (EF), (GH), and (IJ) with EHMT1 pathogenic variants are shown

Reproduced from Kleefstra et al [2009] with permission from BMJ Publishing Group Ltd.

appear to be more severe in individuals with larger 9q34 deletions than in those with smaller deletions or intragenic *EHMT1* pathogenic variants.

Nomenclature

The disorder was first recognized following widespread subtelomeric FISH studies [Knight et al 1999, Dawson et al 2002]. After the identification of an individual with a similar phenotype and a *de novo* balanced translocation disrupting *EHMT1*, it was hypothesized that haploinsufficiency of this gene caused the phenotype present in individuals with a 9q34 deletion [Kleefstra et al 2005]. Subsequent identification of additional individuals with intragenic *EHMT1* defects led OMIM to assign the name Kleefstra to the syndrome.

Prevalence

Based on incidence estimates of *de novo* variants in neurodevelopmental disorders together with data from other rare disorders, Kleefstra syndrome is estimated to affect 1:25,000 to 1:35,000 individuals [McRae et al 2017; López-Rivera et al 2020; Author, personal observation]. The actual prevalence of Kleefstra syndrome may be higher as many individuals are not diagnosed.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with deletion in the genes located within the 9q34.3 critical region or with pathogenic variants in *EHMT1*.

Differential Diagnosis

Kleefstra syndrome should be distinguished from other syndromes that include developmental delay, infantile hypotonia, short stature, distinctive facies, and a behavioral phenotype. The most common of these include those in Table 2, which can be distinguished using cytogenetic (FISH) and/or molecular analysis.

Figure 2. Photographs of affected individuals showing the characteristic facial profile comprising brachycephaly, widely spaced eyes, synophrys/arched eyebrows, midface retrusion, protruding tongue, eversion of the vermilion of the lower lip, and prognathism of the chin. Three different people (rows A, B, and C) with interstitial 9q34.3 microdeletions at different ages show evolution with age.

Reproduced from Kleefstra et al [2009] with permission from BMJ Publishing Group Ltd.

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

Disorder	Gene / Genetic Mechanism	MOI	Additional Overlapping Clinical Features
Down syndrome	Trisomy 21	Virtually all *de novo*	Similar facial characteristics, incl: • Brachycephaly • Protruding tongue • Hypotonia • Hypertelorism • Midface retrusion
Smith-Magenis syndrome	Deletion or mutation of *RAI1* on chromosome 17p11.2 [1]	Virtually all *de novo*	• Lethargy • Sleep disturbance • Midface retrusion
Pitt-Hopkins syndrome	Haploinsufficiency of *TCF4*	Most *de novo*	• Speech is significantly delayed & most persons are nonverbal w/ receptive language often stronger than expressive language. • Seizures • Sleep disturbance

Table 2. continued from previous page.

Disorder	Gene / Genetic Mechanism	MOI	Additional Overlapping Clinical Features
Angelman syndrome	Disruption of maternally imprinted *UBE3A*	See footnote 2.	• Receptive language better than expressive language skills • Sleep disturbances w/multiple awakenings • Midface retrusion w/ prognathism • See footnote 3 for distinguishing clinical features.
KMT2C-associated syndrome [4]	*KMT2C*	AD	• Currently under study to determine overlap • ASD & ID
MBD5 haploinsufficiency	See footnote 5.	AD; typically *de novo*	• ASD & ID • Seizures • Developmental regression

AD = autosomal dominant; ASD = autism spectrum disorder; ID = intellectual disability; MOI = mode of inheritance

1. Approximately 95% of individuals with Smith-Magenis syndrome have the disorder as a result of an interstitial 17p11.2 deletion, which may have been previously excluded by chromosomal microarray testing.

2. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of UBE3A function.

3. Facial features that differentiate Kleefstra syndrome from Angelman syndrome include synophrys and everted vermilion of the lower lip. Some mildly affected individuals with Kleefstra syndrome have a ≥100-word vocabulary & speak in sentences, which would be very unusual in an individual with Angelman syndrome.

4. Koemans et al [2017]

5. The diagnosis of *MBD5* haploinsufficiency is established in a proband with one of the following: deletion of 2q23.1 that encompasses all or part of *MBD5* (~90% of affected individuals); intragenic deletion involving one or more exons of *MBD5* (~5%); a heterozygous pathogenic sequence variant in *MBD5* (~5%); or, rarely, an apparently balanced complex chromosome rearrangement of the 2q23.1 region involving *MBD5*.

Management

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Kleefstra Syndrome

System/Concern	Evaluation	Comment
Constitutional	Weight, height, & body mass index (in those age >2 yrs)	Consider referral to nutritionist in those w/obesity.
Dental	Dental eval	To assess for dental issues, incl retention of primary dentition
Eyes	Ophthalmologic eval	To assess for refractive errors
Ears	Audiologic eval	To assess for hearing loss
Cardiovascular	Echocardiogram & EKG	To evaluate for structural heart defects & rhythm disturbance; consider referral to cardiologist.
Respiratory	Assess for history of sleep disturbance.	Consider referral to sleep disorders clinic.
Gastrointestinal/ Feeding	Assess for signs & symptoms of gastroesophageal reflux disease.	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genitourinary	Renal ultrasound	To evaluate for structural renal anomalies & hydronephrosis
Neurologic	Neurologic eval	Consider referral to neurologist.
	EEG	If seizures are suspected
	Head MRI	If seizures &/or mvmt disorder, extreme apathy / catatonia, &/or regression in psychomotor development is present
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: screen for behavior concerns incl sleep disturbances, mood issues, psychotic disorders, anxiety, &/or findings suggestive of ASD.
Miscellaneous/ Other	Developmental assessment	Evaluate motor, speech-language, general cognitive, & vocational skills.
	Consultation w/clinical geneticist &/or genetic counselor	

ASD = autism spectrum disorder

Treatment of Manifestations

Treatment is primarily supportive. Ongoing routine pediatric care by a pediatrician or neurologist, psychiatrist, and/or (for adults) specialist in the care of adults with intellectual disability is recommended.

Table 4. Treatment of Manifestations in Individuals with Kleefstra Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Refractive error	Standard treatment	
Hearing loss	Auditory amplification as appropriate	See Hereditary Hearing Loss and Deafness Overview.
Congenital heart defects & rhythm disturbance	Standard treatment per cardiologist	
Sleep disturbance	Standard treatment	No well-controlled treatment trials have been reported.
Gastroesophageal reflux disease	Standard treatment	Consider referral to gastroenterologist for those w/ severe issues.
Renal anomalies	Standard treatment	Consider referral to urologist &/or nephrologist.
Seizures	Standard treatment w/ASM by experienced neurologist [1]	Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.

ASM = anti-seizure medication

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. In the US, 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 district until age 21.
- Discussion about transition plans including financial, vocation/employment, 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 and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment 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, 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.

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 as a result of 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.

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.

Specialized neurologic and psychiatric care is advised for individuals with extreme behavior issues and/or movement disorder. Behavioral therapies include special education techniques that may help minimize behavioral outbursts in the school setting by emphasizing individualized instruction, structure, and a set daily routine.

Surveillance

Cardiac and renal/urologic abnormalities should be monitored as needed.

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

Kleefstra syndrome, caused by a deletion at 9q34.3 or an intragenic *EHMT1* pathogenic variant, is inherited in an autosomal dominant manner; almost all cases reported to date have been *de novo*.

Risk to Family Members

9q34.3 Deletion

9q34.3 deletion is usually *de novo* but may be inherited as the result of a complex chromosomal rearrangement or mosaicism in a parent.

Parents of a proband

- To date, no parent-to-child transmission of an unbalanced derivative chromosome involving the 9q34.3 region has been observed.
- Recurrence in families with a parent having a balanced translocation involving the 9q34.3 region has been described [Knight et al 1999, Dawson et al 2002].
- To date, all interstitial 9q34.3 deletions detected are *de novo*, except for three families in which one of the parents was shown to have a somatic mosaic deletion. In one family, a parent with learning difficulties had two severely affected children; in another family, a parent with learning difficulties had one affected child [Willemsen et al 2011, de Boer et al 2018].

- Recommendations for the evaluation of asymptomatic parents of a proband with a 9q34.3 deletion include routine karyotyping with additional FISH analysis to determine if a balanced chromosome rearrangement involving the 9q34.3 region is present.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the parents.
- In the (unlikely) event that a parent has either germline mosaicism for a 9q34.3 deletion, low-level somatic mosaicism that includes the germline, or a balanced structural chromosome rearrangement involving the 9q34.3 region, the risk to sibs is increased. The estimated risk depends on the specific chromosome rearrangement.

Offspring of a proband

- To date, five individuals diagnosed with a mosaic 9q34.3 deletion have been known to reproduce [Willemsen et al 2011, de Boer et al 2018].
- Individuals who have the 9q34.3 deletion would be expected to have a 50% chance of transmitting the deletion to each child.

EHMT1 Pathogenic Variant

Parents of a proband

- In the vast majority of cases, *EHMT1* pathogenic variants have occurred *de novo*. All affected individuals represent simplex cases (i.e., a single occurrence in the family).
- To date, only one parent of an individual with an *EHMT1* pathogenic variant has also had the pathogenic variant, although it was a mosaic pathogenic variant in an unaffected parent [Rump et al 2013].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *EHMT1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism [Rump et al 2013].

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the parents.
- In the (unlikely) event that a parent has germline mosaicism or low-level somatic mosaicism for an *EHMT1* pathogenic variant that also includes the germline, the risk to sibs is increased.

Offspring of a proband

- No individual with a non-mosaic *EHMT1* pathogenic variant has been known to reproduce.
- Individuals who have a non-mosaic *EHMT1* pathogenic variant would be expected to have a 50% chance of transmitting the pathogenic variant to each child.

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 may be at risk of having a child with Kleefstra syndrome.

Prenatal Testing and Preimplantation Genetic Testing

Prenatal testing for at-risk pregnancies and preimplantation genetic testing require prior identification of the 9q34.3 deletion or an *EHMT1* pathogenic variant in the proband and/or of balanced carrier status in a parent. Prenatal testing may be offered to unaffected parents who have had a child with a 9q34.3 deletion or an *EHMT1* pathogenic variant because of the recurrence risk associated with the possibility of germline mosaicism, somatic mosaicism including the germline, or a balanced chromosome translocation.

Pregnancies not known to be at increased risk for the 9q34.3 deletion. CMA performed in a pregnancy not known to be at increased risk may detect the 9q34.3 deletion [Guterman et al 2018].

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.

- **Chromosome Disorder Outreach Inc.**
  Phone: 561-395-4252
  Email: info@chromodisorder.org
  chromodisorder.org
- **Unique: Understanding Rare Chromosome and Gene Disorders**
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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. Kleefstra Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EHMT1	9q34.3	Histone-lysine N-methyltransferase EHMT1	EHMT1 database	EHMT1	EHMT1

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 Kleefstra Syndrome (View All in OMIM)

607001	EUCHROMATIC HISTONE METHYLTRANSFERASE 1; EHMT1
610253	KLEEFSTRA SYNDROME 1; KLEFS1

Gene structure. The previously defined *EHMT1* transcript (NM_024757.3) contained 26 exons, the translation start site being located in exon 2. The "updated" NM_024757.4 version varies significantly and contains an extra 5' exon. The novel open reading frame comprises 27 coding exons. The translation start site is located in the

"novel" exon 1, 97.6 kb proximal to the "old" ATG start codon. Diagnostic testing so far has been directed towards the 25 coding exons of the *EHMT1* NM_024757.3 sequence. Since three individuals with Kleefstra syndrome harbor interstitial 9q deletions encompassing only this novel *EHMT1* sequence in addition to several proximally located genes [Author, personal observation], routine diagnostic testing should be adjusted to the novel transcript. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. *EHMT1* sequence variants include nonsense, splice site, and missense variants and small deletions and duplications [Kleefstra et al 2006a, Kleefstra et al 2009, Willemsen et al 2012].

Normal gene product. The NM_024757.4 transcript encodes euchromatin histone-lysine N-methyl transferase 1, a protein of 1,298 amino acid residues involved in histone methylation. DNA is wrapped around histones, and histone tails have an important role in folding of chromatin fibers. Methylation of these histone tails is thought to regulate this folding process, thereby altering the accessibility of DNA to proteins mediating transcription [Martin & Zhang 2005]. The restricted expression of *EHMT1* in the mouse brain (olfactory bulb, the anterior/ventral ventricular wall, hippocampus, and piriform cortex) supports a role of epigenetic histone modification in normal brain development [Kleefstra et al 2005].

Abnormal gene product. Haploinsufficiency resulting from deletion or inactivation of one *EHMT1* allele is the cause of Kleefstra syndrome. The majority of pathogenic variants disrupt the open reading frame of *EHMT1* and are predicted to lead to nonsense-mediated decay. The one pathogenic missense variant described to date is predicted to have an influence on the local conformation of the pre-SET domain of the EHMT1 protein, thereby reflecting a null allele [Kleefstra et al 2009]. Besides *EHMT1*, other genes associated with intellectual disability (e.g., *MECP2*, *RSK2*, and *XNP*) appear to play a role in chromatin remodeling [Ausió et al 2003]. Loss of proper regulation of chromatin structure can result in deregulation of gene transcription and inappropriate protein expression. This can in turn contribute to complex genetic disorders including intellectual disability.

Chapter Notes

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Revision History

- 26 January 2023 (tk) Revision: prevalence updated
- 13 October 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis)
- 21 March 2019 (ma) Comprehensive update posted live
- 7 May 2015 (me) Comprehensive update posted live
- 5 October 2010 (me) Review posted live
- 28 May 2010 (tk) Original submission

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