Kleefstra Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK47079/

SummaryClinical 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.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.

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.

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.

DiagnosisKleefstra 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 FindingsKleefstra syndrome should be suspected in individuals with the following:Intellectual disability, usually moderate to severe and associated with severe speech delayDistinctive facial features (See Clinical Description.)Childhood hypotoniaVisual issues (hypermetropia)Hearing loss (sensorineural and/or conductive)Motor delayHeart defectsRenal/urologic defectsGenital defects (males)Severe infections (respiratory)Epilepsy / febrile seizuresAutism spectrum disorderPsychiatric disorders (mood and psychotic disorders)Extreme apathy or catatonic(-like) features post pubertyNonspecific brain abnormalities: structural defects (corpus callosum hypoplasia), cortical hypoplasia, or white matter defectsEstablishing the DiagnosisThe 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 deletions25% interstitial deletions25% complex rearrangements or derivative chromosomesA 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 SyndromeView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

EHMT1

CMA 3~50% 4Sequence analysis 5~50%Gene-targeted deletion/duplication analysis 6See footnote 7.KaryotypeRare; 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.

Suggestive FindingsKleefstra syndrome should be suspected in individuals with the following:Intellectual disability, usually moderate to severe and associated with severe speech delayDistinctive facial features (See Clinical Description.)Childhood hypotoniaVisual issues (hypermetropia)Hearing loss (sensorineural and/or conductive)Motor delayHeart defectsRenal/urologic defectsGenital defects (males)Severe infections (respiratory)Epilepsy /

febrile seizuresAutism spectrum disorderPsychiatric disorders (mood and psychotic disorders)Extreme apathy or catatonic(-like) features post pubertyNonspecific brain abnormalities: structural defects (corpus callosum hypoplasia), cortical hypoplasia, or white matter defects

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 DiagnosisThe 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 deletions25% interstitial deletions25% complex rearrangements or derivative chromosomesA 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 SyndromeView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

EHMT1

CMA 3~50% 4Sequence analysis 5~50%Gene-targeted deletion/duplication analysis 6See footnote 7.KaryotypeRare; 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.

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)

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 SyndromeView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

EHMT1

CMA 3~50% 4Sequence analysis 5~50%Gene-targeted deletion/duplication analysis 6See footnote 7.KaryotypeRare; 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.

Molecular Genetic Testing Used in Kleefstra Syndrome

Gene 1Method Proportion of Probands with a Pathogenic Variant 2 Detectable by Method

EHMT1

CMA 3~50% 4Sequence analysis 5~50%Gene-targeted deletion/duplication analysis 6See footnote 7.KaryotypeRare; 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.

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.

See Table A. Genes and Databases for chromosome locus and protein.

See Molecular Genetics for information on variants detected in this gene.

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).

CMA testing is appropriate to define breakpoints of large deletions; however, intragenic deletions in EHMT1 may not be detected by this method.

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.

Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Gene-targeted 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.

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 CharacteristicsClinical DescriptionKleefstra 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).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 (more...)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 (more...)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 CorrelationsEHMT1 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 appear to be more severe in individuals with larger 9q34 deletions than in those with smaller deletions or intragenic EHMT1 pathogenic variants.NomenclatureThe 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.PrevalenceBased 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.

Clinical DescriptionKleefstra 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).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 (more...)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 (more...)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].

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 (more...)

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 (more...)

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 (more...)

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 (more...)

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.

Genotype-Phenotype CorrelationsEHMT1 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 appear to be more severe in individuals with larger 9q34 deletions than in those with smaller deletions or intragenic EHMT1 pathogenic variants.

NomenclatureThe 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.

PrevalenceBased 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) DisordersNo 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 DiagnosisKleefstra 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.Table 2. Disorders to Consider in the Differential Diagnosis of Kleefstra SyndromeView in own windowDisorderGene / GeneticMechanismMOIAdditional Overlapping Clinical FeaturesDown syndromeTrisomy 21Virtually all de novoSimilar facial characteristics, incl: BrachycephalyProtruding tongueHypotoniaHypertelorismMidface retrusion

Smith-Magenis syndrome
Deletion or mutation of RAI1 on chromosome 17p11.2 1Virtually all de novoLethargySleep disturbanceMidface retrusion

Pitt-Hopkins syndrome
Haploinsufficiency of TCF4Most de novoSpeech is significantly delayed & most persons are nonverbal w/receptive language often stronger than expressive language.SeizuresSleep disturbance

Angelman syndrome
Disruption of maternally imprinted UBE3ASee footnote 2.Receptive language better than expressive language skillsSleep disturbances w/multiple awakeningsMidface retrusion w/prognathismSee

footnote 3 for distinguishing clinical features.

KMT2C-associated syndrome 4

KMT2C

ADCurrently under study to determine overlapASD & ID

MBD5 haploinsufficiency

See footnote 5.AD; typically de novoASD & IDSeizuresDevelopmental regression

AD = autosomal dominant; ASD = autism spectrum disorder; ID = intellectual disability; MOI = mode of inheritance1. 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.

Table 2. Disorders to Consider in the Differential Diagnosis of Kleefstra SyndromeView in own windowDisorderGene / GeneticMechanismMOIAdditional Overlapping Clinical FeaturesDown syndromeTrisomy 21Virtually all de novoSimilar facial characteristics, incl: BrachycephalyProtruding tongueHypotoniaHypertelorismMidface retrusion

Smith-Magenis syndrome

Deletion or mutation of RAI1 on chromosome 17p11.2 1Virtually all de novoLethargySleep disturbanceMidface retrusion

Pitt-Hopkins syndrome

Haploinsufficiency of TCF4Most de novoSpeech is significantly delayed & most persons are nonverbal w/receptive language often stronger than expressive language.SeizuresSleep disturbance

Angelman syndrome

Disruption of maternally imprinted UBE3ASee footnote 2.Receptive language better than expressive language skillsSleep disturbances w/multiple awakeningsMidface retrusion w/prognathismSee footnote 3 for distinguishing clinical features.

KMT2C-associated syndrome 4

KMT2C

ADCurrently under study to determine overlapASD & ID

MBD5 haploinsufficiency

See footnote 5.AD; typically de novoASD & IDSeizuresDevelopmental regression

AD = autosomal dominant; ASD = autism spectrum disorder; ID = intellectual disability; MOI = mode of inheritance1. 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.

Disorders to Consider in the Differential Diagnosis of Kleefstra Syndrome

DisorderGene / GeneticMechanismMOIAdditional Overlapping Clinical FeaturesDown syndromeTrisomy 21Virtually all de novoSimilar facial characteristics, incl: BrachycephalyProtruding tongueHypotoniaHypertelorismMidface retrusion

Smith-Magenis syndrome

Deletion or mutation of RAI1 on chromosome 17p11.2 1Virtually all de novoLethargySleep disturbanceMidface retrusion

Pitt-Hopkins syndrome

Haploinsufficiency of TCF4Most de novoSpeech is significantly delayed & most persons are nonverbal w/receptive language often stronger than expressive language.SeizuresSleep disturbance

Angelman syndrome

Disruption of maternally imprinted UBE3ASee footnote 2.Receptive language better than expressive language skillsSleep disturbances w/multiple awakeningsMidface retrusion w/prognathismSee footnote 3 for distinguishing clinical features.

KMT2C-associated syndrome 4

KMT2C

ADCurrently under study to determine overlapASD & ID

MBD5 haploinsufficiency

See footnote 5.AD; typically de novoASD & IDSeizuresDevelopmental regression

Brachycephaly

Protruding tongue

Hypotonia

Hypertelorism

Midface retrusion

Lethargy

Sleep disturbance

Midface retrusion

Speech is significantly delayed & most persons are nonverbal w/receptive language often stronger than expressive language.

Seizures

Sleep disturbance

Receptive language better than expressive language skills

Sleep disturbances w/multiple awakenings

Midface retrusion w/prognathism

See footnote 3 for distinguishing clinical features.

Currently under study to determine overlap

ASD & ID

ASD & ID

Seizures

Developmental regression

AD = autosomal dominant; ASD = autism spectrum disorder; ID = intellectual disability; MOI = mode of inheritance1. 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.

AD = autosomal dominant; ASD = autism spectrum disorder; ID = intellectual disability; MOI = mode of inheritance1. 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.

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

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.

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

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.

Koemans et al [2017]

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.

ManagementEvaluations Following Initial DiagnosisTo 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 SyndromeView in own windowSystem/ConcernEvaluationComment

Constitutional

Weight, height, & body mass index (in those age >2 yrs)Consider referral to nutritionist in those w/obesity.

Dental

Dental evalTo assess for dental issues, incl retention of primary dentition

Eyes

Ophthalmologic evalTo assess for refractive errors

Ears

Audiologic evalTo assess for hearing loss

Cardiovascular

Echocardiogram & EKGTo 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.

Genitourinary

Renal ultrasoundTo evaluate for structural renal anomalies & hydronephrosis

Neurologic

Neurologic evalConsider referral to neurologist.EEGIf seizures are suspectedHead MRIIf seizures &/or mvmt disorder, extreme apathy / catatonia, &/or regression in psychomotor development is present

Psychiatric/

Behavioral

Neuropsychiatric evalPersons age >12 mos: screen for behavior concerns incl sleep disturbances, mood issues, psychotic disorders, anxiety, &/or findings suggestive of ASD.

Miscellaneous/

Other

Developmental assessmentEvaluate motor, speech-language, general cognitive, & vocational skills.Consultation w/clinical geneticist &/or genetic counselorASD = autism spectrum disorderTreatment of ManifestationsTreatment 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 SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Refractive error

Standard treatment

Hearing loss

Auditory amplification as appropriateSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

& rhythm disturbance

Standard treatment per cardiologist

Sleep disturbance

Standard treatmentNo well-controlled treatment trials have been reported.

Gastroesophageal reflux

disease

Standard treatmentConsider referral to gastroenterologist for those w/severe issues.

Renal anomalies

Standard treatmentConsider referral to urologist &/or nephrologist.

Seizures

Standard treatment w/ASM by experienced neurologist 1Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.ASM = anti-seizure medication1.

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 IssuesThe 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 ConcernsChildren 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.SurveillanceCardiac and renal/urologic abnormalities should be monitored as needed.Evaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo 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 SyndromeView in own windowSystem/ConcernEvaluationComment

Constitutional

Weight, height, & body mass index (in those age >2 yrs)Consider referral to nutritionist in those w/obesity.

Dental

Dental evalTo assess for dental issues, incl retention of primary dentition

Eyes

Ophthalmologic evalTo assess for refractive errors

Ears

Audiologic evalTo assess for hearing loss

Cardiovascular

Echocardiogram & EKGTo 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.

Genitourinary

Renal ultrasoundTo evaluate for structural renal anomalies & hydronephrosis

Neurologic

Neurologic evalConsider referral to neurologist.EEGIf seizures are suspectedHead MRIIf seizures

&/or mvmt disorder, extreme apathy / catatonia, &/or regression in psychomotor development is present

Psychiatric/

Behavioral

Neuropsychiatric evalPersons age >12 mos: screen for behavior concerns incl sleep disturbances, mood issues, psychotic disorders, anxiety, &/or findings suggestive of ASD.

Miscellaneous/

Other

Developmental assessmentEvaluate motor, speech-language, general cognitive, & vocational skills.Consultation w/clinical geneticist &/or genetic counselorASD = autism spectrum disorder

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Kleefstra SyndromeView in own windowSystem/ConcernEvaluationComment

Constitutional

Weight, height, & body mass index (in those age >2 yrs)Consider referral to nutritionist in those w/obesity.

Dental

Dental evalTo assess for dental issues, incl retention of primary dentition

Eyes

Ophthalmologic evalTo assess for refractive errors

Ears

Audiologic evalTo assess for hearing loss

Cardiovascular

Echocardiogram & EKGTo 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.

Genitourinary

Renal ultrasoundTo evaluate for structural renal anomalies & hydronephrosis

Neurologic

Neurologic evalConsider referral to neurologist.EEGIf seizures are suspectedHead MRIIf seizures &/or mvmt disorder, extreme apathy / catatonia, &/or regression in psychomotor development is present

Psychiatric/

Behavioral

Neuropsychiatric evalPersons age >12 mos: screen for behavior concerns incl sleep disturbances, mood issues, psychotic disorders, anxiety, &/or findings suggestive of ASD.

Miscellaneous/

Other

Developmental assessmentEvaluate motor, speech-language, general cognitive, & vocational skills.Consultation w/clinical geneticist &/or genetic counselorASD = autism spectrum disorder

Recommended Evaluations Following Initial Diagnosis in Individuals with Kleefstra Syndrome

System/ConcernEvaluationComment

Constitutional

Weight, height, & body mass index (in those age >2 yrs)Consider referral to nutritionist in those w/obesity.

Dental

Dental evalTo assess for dental issues, incl retention of primary dentition

Eyes

Ophthalmologic evalTo assess for refractive errors

Ears

Audiologic evalTo assess for hearing loss

Cardiovascular

Echocardiogram & EKGTo 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.

Genitourinary

Renal ultrasoundTo evaluate for structural renal anomalies & hydronephrosis

Neurologic

Neurologic evalConsider referral to neurologist.EEGIf seizures are suspectedHead MRIIf seizures &/or mvmt disorder, extreme apathy / catatonia, &/or regression in psychomotor development is present

Psychiatric/

Behavioral

Neuropsychiatric evalPersons age >12 mos: screen for behavior concerns incl sleep disturbances,

mood issues, psychotic disorders, anxiety, &/or findings suggestive of ASD.

Miscellaneous/

Other

Developmental assessmentEvaluate motor, speech-language, general cognitive, & vocational skills.Consultation w/clinical geneticist &/or genetic counselor

ASD = autism spectrum disorder

ASD = autism spectrum disorder

ASD = autism spectrum disorder

Treatment of ManifestationsTreatment 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 SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Refractive error

Standard treatment

Hearing loss

Auditory amplification as appropriateSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

& rhythm disturbance

Standard treatment per cardiologist

Sleep disturbance

Standard treatmentNo well-controlled treatment trials have been reported.

Gastroesophageal reflux

disease

Standard treatmentConsider referral to gastroenterologist for those w/severe issues.

Renal anomalies

Standard treatmentConsider referral to urologist &/or nephrologist.

Seizures

Standard treatment w/ASM by experienced neurologist 1Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.ASM = anti-seizure medication1. 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 IssuesThe 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 ConcernsChildren 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.

Table 4. Treatment of Manifestations in Individuals with Kleefstra SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Refractive error

Standard treatment

Hearing loss

Auditory amplification as appropriateSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

& rhythm disturbance

Standard treatment per cardiologist

Sleep disturbance

Standard treatmentNo well-controlled treatment trials have been reported.

Gastroesophageal reflux

disease

Standard treatmentConsider referral to gastroenterologist for those w/severe issues.

Renal anomalies

Standard treatmentConsider referral to urologist &/or nephrologist.

Seizures

Standard treatment w/ASM by experienced neurologist 1Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.ASM = anti-seizure medication1. 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.

Treatment of Manifestations in Individuals with Kleefstra Syndrome

Manifestation/ConcernTreatmentConsiderations/Other

Refractive error

Standard treatment

Hearing loss

Auditory amplification as appropriateSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

& rhythm disturbance

Standard treatment per cardiologist

Sleep disturbance

Standard treatmentNo well-controlled treatment trials have been reported.

Gastroesophageal reflux

disease

Standard treatmentConsider referral to gastroenterologist for those w/severe issues.

Renal anomalies

Standard treatmentConsider referral to urologist &/or nephrologist.

Seizures

Standard treatment w/ASM by experienced neurologist 1Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.

ASM = anti-seizure medication1. 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.

ASM = anti-seizure medication1. 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.

ASM = anti-seizure medication

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 IssuesThe 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.

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.

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.

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.

Social/Behavioral ConcernsChildren 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.

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

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

Therapies Under InvestigationSearch 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 InheritanceKleefstra 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 Members9q34.3 Deletion9q34.3 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 TestingPrenatal 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].

Mode of InheritanceKleefstra 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 Members9q34.3 Deletion9q34.3 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.

9q34.3 Deletion9q34.3 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.

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.

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.

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.

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].

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.

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.

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 TestingPrenatal 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: 561-395-4252Email: info@chromodisorder.org

www.chromodisorder.org

Unique: Understanding Rare Chromosome and Gene Disorders

United KingdomPhone: +44 (0) 1883 723356Email: info@rarechromo.org

www.rarechromo.org

Chromosome Disorder Outreach Inc.

Phone: 561-395-4252

Email: info@chromodisorder.org

www.chromodisorder.org

Unique: Understanding Rare Chromosome and Gene Disorders

United Kingdom

Phone: +44 (0) 1883 723356

Email: info@rarechromo.org

www.rarechromo.org

Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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) View in own window

607001EUCHROMATIC HISTONE METHYLTRANSFERASE 1; EHMT1

610253KLEEFSTRA SYNDROME 1; KLEFS1Gene 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.

Table A.Kleefstra Syndrome: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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.

Kleefstra Syndrome: Genes and Databases

GeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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.

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.

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) View in own window

607001EUCHROMATIC HISTONE METHYLTRANSFERASE 1; EHMT1

610253KLEEFSTRA SYNDROME 1; KLEFS1

OMIM Entries for Kleefstra Syndrome (View All in OMIM)

607001EUCHROMATIC HISTONE METHYLTRANSFERASE 1; EHMT1

610253KLEEFSTRA SYNDROME 1; KLEFS1

Chapter NotesAuthor HistoryNicole de Leeuw, PhD (2019-present)Tjitske Kleefstra, MD, PhD (2010-present)Willy M Nillesen, BSc; Radboud University Medical Center (2010-2019)Helger G Yntema, PhD; Radboud University Medical Center (2010-2019)Revision History26 January 2023 (tk) Revision: prevalence updated13 October 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis)21 March 2019 (ma) Comprehensive update posted live7 May 2015 (me) Comprehensive update posted live5 October 2010 (me) Review posted live28 May 2010 (tk) Original submission

Author HistoryNicole de Leeuw, PhD (2019-present)Tjitske Kleefstra, MD, PhD (2010-present)Willy M Nillesen, BSc; Radboud University Medical Center (2010-2019)Helger G Yntema, PhD; Radboud University Medical Center (2010-2019)

Revision History26 January 2023 (tk) Revision: prevalence updated13 October 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis)21 March 2019 (ma) Comprehensive update posted live7 May 2015 (me) Comprehensive update posted live5 October 2010 (me) Review posted live28 May 2010 (tk) Original submission

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

ReferencesLiterature CitedAref-Eshghi E, Kerkhof J, Pedro VP, Groupe DI. France, Barat-Houari M, Ruiz-Pallares N, Andrau JC, Lacombe D, Van-Gils J, Fergelot P, Dubourg C, Cormier-Daire V, Rondeau S, Lecoquierre F, Saugier-Veber P, Nicolas G, Lesca G, Chatron N, Sanlaville D, Vitobello A, Faivre L, Thauvin-Robinet C, Laumonnier F, Raynaud M, Alders M, Mannens M, Henneman P, Hennekam RC, Velasco G, Francastel C, Ulveling D, Ciolfi A, Pizzi S, Tartaglia M, Heide S, Héron D, Mignot C, Keren B, Whalen S, Afenjar A, Bienvenu T, Campeau PM, Rousseau J, Levy MA, Brick L, Kozenko M, Balci TB, Siu VM, Stuart A, Kadour M, Masters J, Takano K, Kleefstra T, de Leeuw N, Field M, Shaw M, Gecz J, Ainsworth PJ, Lin H, Rodenhiser DI, Friez MJ, Tedder M, Lee JA, DuPont BR, Stevenson RE, Skinner SA, Schwartz CE, Genevieve D, Sadikovic B. Evaluation of dna methylation episignatures for diagnosis and phenotype correlations in 42 mendelian neurodevelopmental disorders. Am J Hum Genet. 2020;106:356–70.Ausió J, Levin DB, de Amorim GV, Bakker S, MacLeod PM. Syndromes of disordered chromatin remodeling. Clin Genet. 2003;64:83–95. [PubMed: 12859401]Bock I, Németh K, Pentelényi K, Balicza P, Balázs A, Molnár MJ, Román V, Nagy J, Lévay G, Kobolák J, Dinnyés A. Targeted next generation sequencing of a panel of autism-related genes identifies an EHMT1 mutation in a Kleefstra syndrome patient with autism and normal intellectual performance. Gene. 2016;595:131–41. [PubMed: 27651234]Brnich SE, Abou Tayoun AN, Couch FJ, Cutting GR, Greenblatt MS, Heinen CD, Kanavy DM, Luo X, McNulty SM, Starita LM, Tavtigian SV, Wright MW, Harrison SM, Biesecker LG, Berg JS, et al. Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework. Genome Med. 2019;12:3. [PMC free article: PMC6938631] [PubMed: 31892348]Cormier-Daire V, Molinari F, Rio M, Raoul O, de Blois MC, Romana S, Vekemans M, Munnich A, Colleaux L. Cryptic terminal deletion of chromosome 9q34: a

novel cause of syndromic obesity in childhood? J Med Genet. 2003;40:300–3. [PMC free article: PMC1735435] [PubMed: 12676904]Dawson AJ, Putnam S, Schultz J, Riordan D, Prasad C, Greenberg CR, Chodirker BN, Mhanni AA, Chudley AE. Cryptic chromosome rearrangements detected by subtelomere assay in patients with mental retardation and dysmorphic features. Clin Genet. 2002;62:488–94. [PubMed: 12515261]de Boer A, Vermeulen K, Egger JIM, Janzing JGE, de Leeuw N, Veenstra-Knol HE, den Hollander NS, van Bokhoven H, Staal W, Kleefstra T. EHMT1 mosaicism in apparently unaffected parents is associated with autism spectrum disorder and neurocognitive dysfunction. Mol Autism. 2018;9:5. [PMC free article: PMC5784506] [PubMed: 29416845]Goodman SJ, Burton CL, Butcher DT, Siu MT, Lemire M, Chater-Diehl E, Turinsky AL, Brudno M, Soreni N, Rosenberg D, Fitzgerald KD, Hanna GL, Anagnostou E, Arnold PD, Crosbie J, Schachar R, Weksberg R. Obsessive-compulsive disorder and attention-deficit/hyperactivity disorder: distinct associations with DNA methylation and genetic variation. J Neurodev Disord. 2020;12:23. [PMC free article: PMC7429807] [PubMed: 32799817]Guterman S, Hervé B, Rivière J, Fauvert D, Clement P, Vialard F. First prenatal diagnosis of a 'pure' 9q34.3 deletion (Kleefstra syndrome): a case report and literature review. J Obstet Gynaecol Res. 2018;44:570–5. [PubMed: 29160022]Kleefstra T, Brunner HG, Amiel J, Oudakker AR, Nillesen WM, Magee A, Geneviève D, Cormier-Daire V, van Esch H, Fryns JP, Hamel BC, Sistermans EA, de Vries BB, van Bokhoven H. Loss-of-function mutations in euchromatin histone methyl transferase 1 (EHMT1) cause the 9q34 subtelomeric deletion syndrome. Am J Hum Genet. 2006a;79:370–7. [PMC free article: PMC1559478] [PubMed: 16826528]Kleefstra T, Koolen DA, Nillesen WM, de Leeuw N, Hamel BC, Veltman JA, Sistermans EA, van Bokhoven H, van Ravenswaay C, de Vries BB. Interstitial 2.2 Mb deletion at 9q34 in a patient with mental retardation but without classical features of the 9q subtelomeric deletion syndrome. Am J Med Genet A. 2006b;140:618–23. [PubMed: 16470689]Kleefstra T, Smidt M, Banning MJ, Oudakker AR, Van Esch H, de Brouwer AP, Nillesen W, Sistermans EA, Hamel BC, de Bruijn D, et al. Disruption of the gene euchromatin histone methyl transferase1 (Eu-HMTase1) is associated with the 9q34 subtelomeric deletion syndrome. J Med Genet. 2005;42:299–306. [PMC free article:

PMC1736026] [PubMed: 15805155]Kleefstra T, van Zelst-Stams WA, Nillesen WM, Cormier-Daire V, Houge G, Foulds N, van Dooren M, Willemsen MH, Pfundt R, Turner A, Wilson M, McGaughran J, Rauch A, Zenker M, Adam MP, Innes M, Davies C, López AG, Casalone R, Weber A, Brueton LA, Navarro AD, Bralo MP, Venselaar H, Stegmann SP, Yntema HG, van Bokhoven H, Brunner HG. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. J Med Genet. 2009;46:598–606. [PubMed: 19264732]Knight SJ, Regan R, Nicod A, Horsley SW, Kearney L, Homfray T, Winter RM, Bolton P, Flint J. Subtle chromosomal rearrangements in children with unexplained mental retardation. Lancet. 1999;354:1676–81. [PubMed: 10568569]Koemans TS, Kleefstra T, Chubak MC, Stone MH, Reijnders MRF, de Munnik S, Willemsen MH, Fenckova M, Stumpel CTRM, Bok LA, Sifuentes Saenz M, Byerly KA, Baughn LB, Stegmann APA, Pfundt R, Zhou H, van Bokhoven H, Schenck A, Kramer JM. Functional convergence of histone methyltransferases EHMT1 and KMT2C involved in intellectual disability and autism spectrum disorder. PLoS Genet. 2017;13:e1006864. [PMC free article: PMC5656305] [PubMed: 29069077]Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dyment D, Esber N, Fahrner JA, Fleming MD, Genevieve D, Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of mendelian disorders. HGG Adv. 2021;3:100075. [PMC free article: PMC8756545] [PubMed:

35047860]López-Rivera JA, Pérez-Palma E, Symonds J, Lindy AS, McKnight DA, Leu C, Zuberi S, Brunklaus A, Møller RS, Lal D. A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants. Brain. 2020;143:1099–105. [PMC free article: PMC7174049] [PubMed: 32168371]Martin C, Zhang Y. The diverse functions of histone lysine methylation. Nat Rev Mol Cell Biol. 2005;6:838–49. [PubMed: 16261189]McRae JF, Clayton S, Fitzgerald TW, Kaplanis J, Prigmore E, Rajan D, Sifrim A, Aitken S, Akawi N, Alvi M, et al. Prevalence and architecture of de novo mutations in developmental disorders. Nature. 2017;542:433–8. [PMC free article: PMC6016744] [PubMed: 28135719]Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. [PMC free article: PMC4544753] [PubMed: 25741868]Rump A, Hildebrand L, Tzschach A, Ullmann R, Schrock E, Mitter D. A mosaic maternal splice donor mutation in the EHMT1 gene leads to aberrant transcripts and to Kleefstra syndrome in the offspring. Eur J Hum Genet. 2013;21:887–90. [PMC free article: PMC3722677] [PubMed: 23232695]Stewart DR, Huang A, Faravelli F, Anderlid BM, Medne L, Ciprero K, Kaur M, Rossi E, Tenconi R, Nordenskjöld M, Gripp KW, Nicholson L, Meschino WS, Capua E, Quarrell OW, Flint J, Irons M, Giampietro PF, Schowalter DB, Zaleski CA, Malacarne M, Zackai EH, Spinner NB, Krantz ID. Subtelomeric deletions of chromosome 9q: a novel microdeletion syndrome. Am J Med Genet A. 2004;128A:340–51. [PubMed: 15264279]Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet. 2007;145C:383–92. [PubMed: 17910072]Verhoeven WM, Kleefstra T, Egger JI. Behavioral phenotype in the 9q subtelomeric deletion syndrome: a report about two adult patients. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:536–41. [PubMed: 19642112]Vermeulen K, de Boer A, Janzing JGE, Koolen DA, Ockeloen CW, Willemsen MH, Verhoef FM, van Deurzen PAM, van Dongen L, van Bokhoven H, Egger JIM, Staal WG, Kleefstra T. Adaptive and maladaptive

functioning in Kleefstra syndrome compared to other rare genetic disorders with intellectual disabilities. Am J Med Genet A. 2017a;173:1821–30. [PubMed: 28498556]Vermeulen K, Staal WG, Janzing JG, van Bokhoven H, Egger JIM, Kleefstra T. Sleep disturbance as a precursor of severe regression in Kleefstra syndrome suggests a need for firm and rapid pharmacological treatment. Clin Neuropharmacol. 2017b;40:185–8. [PubMed: 28622207]Willemsen MH, Beunders G, Callaghan M, de Leeuw N, Nillesen WM, Yntema HG, van Hagen JM, Nieuwint AW, Morrison N, Keijzers-Vloet ST, Hoischen A, Brunner HG, Tolmie J, Kleefstra T. Familial Kleefstra syndrome due to maternal somatic mosaicism for interstitial 9q34.3 microdeletions. Clin Genet. 2011;80:31–8. [PubMed: 21204793]Willemsen MH, Vulto-van Silfhout AT, Nillesen WM, Wissink-Lindhout WM, van Bokhoven H, Philip N, Berry-Kravis EM, Kini U, van Ravenswaaij-Arts CM, Delle Chiaie B, Innes AM, Houge G, Kosonen T, Cremer K, Fannemel M, Stray-Pedersen A, Reardon W, Ignatius J, Lachlan K, Mircher C, Helderman van den Enden PT, Mastebroek M, Cohn-Hokke PE, Yntema HG, Drunat S, Kleefstra T. Update on Kleefstra syndrome. Mol Syndromol. 2012;2:202–12. [PMC free article: PMC3366700] [PubMed: 22670141]Yatsenko SA, Brundage EK, Roney EK, Cheung SW, Chinault AC, Lupski JR. Molecular mechanisms for subtelomeric rearrangements associated with the 9q34.3 microdeletion syndrome. Hum Mol Genet. 2009;18:1924–36. [PMC free article: PMC2678925] [PubMed: 19293338]Yatsenko SA, Cheung SW, Scott DA, Nowaczyk MJ, Tarnopolsky M, Naidu S, Bibat G, Patel A, Leroy JG, Scaglia F, et al. Deletion 9q34.3 syndrome: genotype-phenotype correlations and an extended deletion in a patient with features of Opitz C trigonocephaly. J Med Genet. 2005;42:328–35. [PMC free article: PMC1736036] [PubMed: 15805160]

Literature CitedAref-Eshghi E, Kerkhof J, Pedro VP, Groupe DI. France, Barat-Houari M, Ruiz-Pallares N, Andrau JC, Lacombe D, Van-Gils J, Fergelot P, Dubourg C, Cormier-Daire V, Rondeau S, Lecoquierre F, Saugier-Veber P, Nicolas G, Lesca G, Chatron N, Sanlaville D, Vitobello A, Faivre L, Thauvin-Robinet C, Laumonnier F, Raynaud M, Alders M, Mannens M, Henneman P, Hennekam RC, Velasco G, Francastel C, Ulveling D, Ciolfi A, Pizzi S, Tartaglia M, Heide S,

Héron D, Mignot C, Keren B, Whalen S, Afenjar A, Bienvenu T, Campeau PM, Rousseau J, Levy MA, Brick L, Kozenko M, Balci TB, Siu VM, Stuart A, Kadour M, Masters J, Takano K, Kleefstra T, de Leeuw N, Field M, Shaw M, Gecz J, Ainsworth PJ, Lin H, Rodenhiser DI, Friez MJ, Tedder M, Lee JA, DuPont BR, Stevenson RE, Skinner SA, Schwartz CE, Genevieve D, Sadikovic B. Evaluation of dna methylation episignatures for diagnosis and phenotype correlations in 42 mendelian neurodevelopmental disorders. Am J Hum Genet. 2020;106:356–70.Ausió J, Levin DB, de Amorim GV, Bakker S, MacLeod PM. Syndromes of disordered chromatin remodeling. Clin Genet. 2003;64:83–95. [PubMed: 12859401]Bock I, Németh K, Pentelényi K, Balicza P, Balázs A, Molnár MJ, Román V, Nagy J, Lévay G, Kobolák J, Dinnyés A. Targeted next generation sequencing of a panel of autism-related genes identifies an EHMT1 mutation in a Kleefstra syndrome patient with autism and normal intellectual performance. Gene. 2016;595:131–41. [PubMed: 27651234]Brnich SE, Abou Tayoun AN, Couch FJ, Cutting GR, Greenblatt MS, Heinen CD, Kanavy DM, Luo X, McNulty SM, Starita LM, Tavtigian SV, Wright MW, Harrison SM, Biesecker LG, Berg JS, et al. Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework. Genome Med. 2019;12:3. [PMC free article: PMC6938631] [PubMed: 31892348]Cormier-Daire V, Molinari F, Rio M, Raoul O, de Blois MC, Romana S, Vekemans M, Munnich A, Colleaux L. Cryptic terminal deletion of chromosome 9q34: a novel cause of syndromic obesity in childhood? J Med Genet. 2003;40:300–3. [PMC free article: PMC1735435] [PubMed: 12676904]Dawson AJ, Putnam S, Schultz J, Riordan D, Prasad C, Greenberg CR, Chodirker BN, Mhanni AA, Chudley AE. Cryptic chromosome rearrangements detected by subtelomere assay in patients with mental retardation and dysmorphic features. Clin Genet. 2002;62:488–94. [PubMed: 12515261]de Boer A, Vermeulen K, Egger JIM, Janzing JGE, de Leeuw N, Veenstra-Knol HE, den Hollander NS, van Bokhoven H, Staal W, Kleefstra T. EHMT1 mosaicism in apparently unaffected parents is associated with autism spectrum disorder and neurocognitive dysfunction. Mol Autism. 2018;9:5. [PMC free article: PMC5784506] [PubMed: 29416845]Goodman SJ, Burton CL, Butcher DT, Siu MT, Lemire M, Chater-Diehl E, Turinsky AL,

Brudno M, Soreni N, Rosenberg D, Fitzgerald KD, Hanna GL, Anagnostou E, Arnold PD, Crosbie J, Schachar R, Weksberg R. Obsessive-compulsive disorder and attention-deficit/hyperactivity disorder: distinct associations with DNA methylation and genetic variation. J Neurodev Disord. 2020;12:23. [PMC free article: PMC7429807] [PubMed: 32799817]Guterman S, Hervé B, Rivière J, Fauvert D, Clement P, Vialard F. First prenatal diagnosis of a 'pure' 9q34.3 deletion (Kleefstra syndrome): a case report and literature review. J Obstet Gynaecol Res. 2018;44:570–5. [PubMed: 29160022]Kleefstra T, Brunner HG, Amiel J, Oudakker AR, Nillesen WM, Magee A, Geneviève D, Cormier-Daire V, van Esch H, Fryns JP, Hamel BC, Sistermans EA, de Vries BB, van Bokhoven H. Loss-of-function mutations in euchromatin histone methyl transferase 1 (EHMT1) cause the 9q34 subtelomeric deletion syndrome. Am J Hum Genet. 2006a;79:370–7. [PMC free article: PMC1559478] [PubMed: 16826528]Kleefstra T, Koolen DA, Nillesen WM, de Leeuw N, Hamel BC, Veltman JA, Sistermans EA, van Bokhoven H, van Ravenswaay C, de Vries BB. Interstitial 2.2 Mb deletion at 9q34 in a patient with mental retardation but without classical features of the 9q subtelomeric deletion syndrome. Am J Med Genet A. 2006b;140:618–23. [PubMed: 16470689]Kleefstra T, Smidt M, Banning MJ, Oudakker AR, Van Esch H, de Brouwer AP, Nillesen W, Sistermans EA, Hamel BC, de Bruijn D, et al. Disruption of the gene euchromatin histone methyl transferase1 (Eu-HMTase1) is associated with the 9q34 subtelomeric deletion syndrome. J Med Genet. 2005;42:299–306. [PMC free article: PMC1736026] [PubMed: 15805155]Kleefstra T, van Zelst-Stams WA, Nillesen WM, Cormier-Daire V, Houge G, Foulds N, van Dooren M, Willemsen MH, Pfundt R, Turner A, Wilson M, McGaughran J, Rauch A, Zenker M, Adam MP, Innes M, Davies C, López AG, Casalone R, Weber A, Brueton LA, Navarro AD, Bralo MP, Venselaar H, Stegmann SP, Yntema HG, van Bokhoven H, Brunner HG. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. J Med Genet. 2009;46:598–606. [PubMed: 19264732]Knight SJ, Regan R, Nicod A, Horsley SW, Kearney L, Homfray T, Winter RM, Bolton P, Flint J. Subtle chromosomal rearrangements in children with unexplained mental retardation. Lancet. 1999;354:1676–81. [PubMed: 10568569]Koemans

TS, Kleefstra T, Chubak MC, Stone MH, Reijnders MRF, de Munnik S, Willemsen MH, Fenckova M, Stumpel CTRM, Bok LA, Sifuentes Saenz M, Byerly KA, Baughn LB, Stegmann APA, Pfundt R, Zhou H, van Bokhoven H, Schenck A, Kramer JM. Functional convergence of histone methyltransferases EHMT1 and KMT2C involved in intellectual disability and autism spectrum disorder. PLoS Genet. 2017;13:e1006864. [PMC free article: PMC5656305] [PubMed: 29069077]Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dyment D, Esber N, Fahrner JA, Fleming MD, Genevieve D, Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of mendelian disorders. HGG Adv. 2021;3:100075. [PMC free article: PMC8756545] [PubMed: 35047860]López-Rivera JA, Pérez-Palma E, Symonds J, Lindy AS, McKnight DA, Leu C, Zuberi S, Brunklaus A, Møller RS, Lal D. A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants. Brain. 2020;143:1099–105. [PMC free article: PMC7174049] [PubMed: 32168371]Martin C, Zhang Y. The diverse functions of histone lysine methylation. Nat Rev Mol Cell Biol. 2005;6:838–49. [PubMed: 16261189]McRae JF, Clayton S, Fitzgerald TW, Kaplanis J, Prigmore E, Rajan D, Sifrim A, Aitken S, Akawi N, Alvi M, et al. Prevalence and architecture of de novo mutations in developmental disorders. Nature. 2017;542:433–8. [PMC free article: PMC6016744] [PubMed: 28135719]Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW,

Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. [PMC free article: PMC4544753] [PubMed: 25741868]Rump A, Hildebrand L, Tzschach A, Ullmann R, Schrock E, Mitter D. A mosaic maternal splice donor mutation in the EHMT1 gene leads to aberrant transcripts and to Kleefstra syndrome in the offspring. Eur J Hum Genet. 2013;21:887–90. [PMC free article: PMC3722677] [PubMed: 23232695]Stewart DR, Huang A, Faravelli F, Anderlid BM, Medne L, Ciprero K, Kaur M, Rossi E, Tenconi R, Nordenskjöld M, Gripp KW, Nicholson L, Meschino WS, Capua E, Quarrell OW, Flint J, Irons M, Giampietro PF, Schowalter DB, Zaleski CA, Malacarne M, Zackai EH, Spinner NB, Krantz ID. Subtelomeric deletions of chromosome 9q: a novel microdeletion syndrome. Am J Med Genet A. 2004;128A:340–51. [PubMed: 15264279]Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet. 2007;145C:383–92. [PubMed: 17910072]Verhoeven WM, Kleefstra T, Egger JI. Behavioral phenotype in the 9q subtelomeric deletion syndrome: a report about two adult patients. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:536–41. [PubMed: 19642112]Vermeulen K, de Boer A, Janzing JGE, Koolen DA, Ockeloen CW, Willemsen MH, Verhoef FM, van Deurzen PAM, van Dongen L, van Bokhoven H, Egger JIM, Staal WG, Kleefstra T. Adaptive and maladaptive functioning in Kleefstra syndrome compared to other rare genetic disorders with intellectual disabilities. Am J Med Genet A. 2017a;173:1821–30. [PubMed: 28498556]Vermeulen K, Staal WG, Janzing JG, van Bokhoven H, Egger JIM, Kleefstra T. Sleep disturbance as a precursor of severe regression in Kleefstra syndrome suggests a need for firm and rapid pharmacological treatment. Clin Neuropharmacol. 2017b;40:185–8. [PubMed: 28622207]Willemsen MH, Beunders G, Callaghan M, de Leeuw N, Nillesen WM, Yntema HG, van Hagen JM, Nieuwint AW, Morrison N, Keijzers-Vloet ST, Hoischen A, Brunner HG, Tolmie J, Kleefstra T. Familial Kleefstra syndrome due to maternal somatic mosaicism for interstitial 9q34.3 microdeletions. Clin Genet. 2011;80:31–8. [PubMed: 21204793]Willemsen MH, Vulto-van Silfhout AT, Nillesen WM,

Wissink-Lindhout WM, van Bokhoven H, Philip N, Berry-Kravis EM, Kini U, van Ravenswaaij-Arts CM, Delle Chiaie B, Innes AM, Houge G, Kosonen T, Cremer K, Fannemel M, Stray-Pedersen A, Reardon W, Ignatius J, Lachlan K, Mircher C, Helderman van den Enden PT, Mastebroek M, Cohn-Hokke PE, Yntema HG, Drunat S, Kleefstra T. Update on Kleefstra syndrome. Mol Syndromol. 2012;2:202–12. [PMC free article: PMC3366700] [PubMed: 22670141]Yatsenko SA, Brundage EK, Roney EK, Cheung SW, Chinault AC, Lupski JR. Molecular mechanisms for subtelomeric rearrangements associated with the 9q34.3 microdeletion syndrome. Hum Mol Genet. 2009;18:1924–36. [PMC free article: PMC2678925] [PubMed: 19293338]Yatsenko SA, Cheung SW, Scott DA, Nowaczyk MJ, Tarnopolsky M, Naidu S, Bibat G, Patel A, Leroy JG, Scaglia F, et al. Deletion 9q34.3 syndrome: genotype-phenotype correlations and an extended deletion in a patient with features of Opitz C trigonocephaly. J Med Genet. 2005;42:328–35. [PMC free article: PMC1736036] [PubMed: 15805160]

Aref-Eshghi E, Kerkhof J, Pedro VP, Groupe DI. France, Barat-Houari M, Ruiz-Pallares N, Andrau JC, Lacombe D, Van-Gils J, Fergelot P, Dubourg C, Cormier-Daire V, Rondeau S, Lecoquierre F, Saugier-Veber P, Nicolas G, Lesca G, Chatron N, Sanlaville D, Vitobello A, Faivre L, Thauvin-Robinet C, Laumonnier F, Raynaud M, Alders M, Mannens M, Henneman P, Hennekam RC, Velasco G, Francastel C, Ulveling D, Ciolfi A, Pizzi S, Tartaglia M, Heide S, Héron D, Mignot C, Keren B, Whalen S, Afenjar A, Bienvenu T, Campeau PM, Rousseau J, Levy MA, Brick L, Kozenko M, Balci TB, Siu VM, Stuart A, Kadour M, Masters J, Takano K, Kleefstra T, de Leeuw N, Field M, Shaw M, Gecz J, Ainsworth PJ, Lin H, Rodenhiser DI, Friez MJ, Tedder M, Lee JA, DuPont BR, Stevenson RE, Skinner SA, Schwartz CE, Genevieve D, Sadikovic B. Evaluation of dna methylation episignatures for diagnosis and phenotype correlations in 42 mendelian neurodevelopmental disorders. Am J Hum Genet. 2020;106:356–70.

Ausió J, Levin DB, de Amorim GV, Bakker S, MacLeod PM. Syndromes of disordered chromatin remodeling. Clin Genet. 2003;64:83–95. [PubMed: 12859401]

Bock I, Németh K, Pentelényi K, Balicza P, Balázs A, Molnár MJ, Román V, Nagy J, Lévay G, Kobolák J, Dinnyés A. Targeted next generation sequencing of a panel of autism-related genes identifies an EHMT1 mutation in a Kleefstra syndrome patient with autism and normal intellectual performance. Gene. 2016;595:131–41. [PubMed: 27651234]

Brnich SE, Abou Tayoun AN, Couch FJ, Cutting GR, Greenblatt MS, Heinen CD, Kanavy DM, Luo X, McNulty SM, Starita LM, Tavtigian SV, Wright MW, Harrison SM, Biesecker LG, Berg JS, et al. Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework. Genome Med. 2019;12:3. [PMC free article: PMC6938631] [PubMed: 31892348]

Cormier-Daire V, Molinari F, Rio M, Raoul O, de Blois MC, Romana S, Vekemans M, Munnich A, Colleaux L. Cryptic terminal deletion of chromosome 9q34: a novel cause of syndromic obesity in childhood? J Med Genet. 2003;40:300–3. [PMC free article: PMC1735435] [PubMed: 12676904]

Dawson AJ, Putnam S, Schultz J, Riordan D, Prasad C, Greenberg CR, Chodirker BN, Mhanni AA, Chudley AE. Cryptic chromosome rearrangements detected by subtelomere assay in patients with mental retardation and dysmorphic features. Clin Genet. 2002;62:488–94. [PubMed: 12515261]

de Boer A, Vermeulen K, Egger JIM, Janzing JGE, de Leeuw N, Veenstra-Knol HE, den Hollander NS, van Bokhoven H, Staal W, Kleefstra T. EHMT1 mosaicism in apparently unaffected parents is associated with autism spectrum disorder and neurocognitive dysfunction. Mol Autism. 2018;9:5. [PMC free article: PMC5784506] [PubMed: 29416845]

Goodman SJ, Burton CL, Butcher DT, Siu MT, Lemire M, Chater-Diehl E, Turinsky AL, Brudno M, Soreni N, Rosenberg D, Fitzgerald KD, Hanna GL, Anagnostou E, Arnold PD, Crosbie J, Schachar R, Weksberg R. Obsessive-compulsive disorder and attention-deficit/hyperactivity disorder: distinct associations with DNA methylation and genetic variation. J Neurodev Disord. 2020;12:23. [PMC free article: PMC7429807] [PubMed: 32799817]

Guterman S, Hervé B, Rivière J, Fauvert D, Clement P, Vialard F. First prenatal diagnosis of a 'pure' 9q34.3 deletion (Kleefstra syndrome): a case report and literature review. J Obstet Gynaecol Res. 2018;44:570–5. [PubMed: 29160022]

Kleefstra T, Brunner HG, Amiel J, Oudakker AR, Nillesen WM, Magee A, Geneviève D, Cormier-Daire V, van Esch H, Fryns JP, Hamel BC, Sistermans EA, de Vries BB, van Bokhoven H. Loss-of-function mutations in euchromatin histone methyl transferase 1 (EHMT1) cause the 9q34 subtelomeric deletion syndrome. Am J Hum Genet. 2006a;79:370–7. [PMC free article: PMC1559478] [PubMed: 16826528]

Kleefstra T, Koolen DA, Nillesen WM, de Leeuw N, Hamel BC, Veltman JA, Sistermans EA, van Bokhoven H, van Ravenswaay C, de Vries BB. Interstitial 2.2 Mb deletion at 9q34 in a patient with mental retardation but without classical features of the 9q subtelomeric deletion syndrome. Am J Med Genet A. 2006b;140:618–23. [PubMed: 16470689]

Kleefstra T, Smidt M, Banning MJ, Oudakker AR, Van Esch H, de Brouwer AP, Nillesen W, Sistermans EA, Hamel BC, de Bruijn D, et al. Disruption of the gene euchromatin histone methyl transferase1 (Eu-HMTase1) is associated with the 9q34 subtelomeric deletion syndrome. J Med Genet. 2005;42:299–306. [PMC free article: PMC1736026] [PubMed: 15805155]

Kleefstra T, van Zelst-Stams WA, Nillesen WM, Cormier-Daire V, Houge G, Foulds N, van Dooren M, Willemsen MH, Pfundt R, Turner A, Wilson M, McGaughran J, Rauch A, Zenker M, Adam MP, Innes M, Davies C, López AG, Casalone R, Weber A, Brueton LA, Navarro AD, Bralo MP, Venselaar H, Stegmann SP, Yntema HG, van Bokhoven H, Brunner HG. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. J Med Genet. 2009;46:598–606. [PubMed: 19264732]

Knight SJ, Regan R, Nicod A, Horsley SW, Kearney L, Homfray T, Winter RM, Bolton P, Flint J. Subtle chromosomal rearrangements in children with unexplained mental retardation. Lancet. 1999;354:1676–81. [PubMed: 10568569]

Koemans TS, Kleefstra T, Chubak MC, Stone MH, Reijnders MRF, de Munnik S, Willemsen MH, Fenckova M, Stumpel CTRM, Bok LA, Sifuentes Saenz M, Byerly KA, Baughn LB, Stegmann APA, Pfundt R, Zhou H, van Bokhoven H, Schenck A, Kramer JM. Functional convergence of histone methyltransferases EHMT1 and KMT2C involved in intellectual disability and autism spectrum disorder. PLoS Genet. 2017;13:e1006864. [PMC free article: PMC5656305] [PubMed: 29069077]

Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dyment D, Esber N, Fahrner JA, Fleming MD, Genevieve D,

Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of mendelian disorders. HGG Adv. 2021;3:100075. [PMC free article: PMC8756545] [PubMed: 35047860]

López-Rivera JA, Pérez-Palma E, Symonds J, Lindy AS, McKnight DA, Leu C, Zuberi S, Brunklaus A, Møller RS, Lal D. A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants. Brain. 2020;143:1099–105. [PMC free article: PMC7174049] [PubMed: 32168371]

Martin C, Zhang Y. The diverse functions of histone lysine methylation. Nat Rev Mol Cell Biol. 2005;6:838–49. [PubMed: 16261189]

McRae JF, Clayton S, Fitzgerald TW, Kaplanis J, Prigmore E, Rajan D, Sifrim A, Aitken S, Akawi N, Alvi M, et al. Prevalence and architecture of de novo mutations in developmental disorders. Nature. 2017;542:433–8. [PMC free article: PMC6016744] [PubMed: 28135719]

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. [PMC free article: PMC4544753] [PubMed: 25741868]

Rump A, Hildebrand L, Tzschach A, Ullmann R, Schrock E, Mitter D. A mosaic maternal splice donor mutation in the EHMT1 gene leads to aberrant transcripts and to Kleefstra syndrome in the offspring. Eur J Hum Genet. 2013;21:887–90. [PMC free article: PMC3722677] [PubMed:

23232695]

Stewart DR, Huang A, Faravelli F, Anderlid BM, Medne L, Ciprero K, Kaur M, Rossi E, Tenconi R, Nordenskjöld M, Gripp KW, Nicholson L, Meschino WS, Capua E, Quarrell OW, Flint J, Irons M, Giampietro PF, Schowalter DB, Zaleski CA, Malacarne M, Zackai EH, Spinner NB, Krantz ID. Subtelomeric deletions of chromosome 9q: a novel microdeletion syndrome. Am J Med Genet A. 2004;128A:340–51. [PubMed: 15264279]

Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet. 2007;145C:383–92. [PubMed: 17910072]

Verhoeven WM, Kleefstra T, Egger JI. Behavioral phenotype in the 9q subtelomeric deletion syndrome: a report about two adult patients. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:536–41. [PubMed: 19642112]

Vermeulen K, de Boer A, Janzing JGE, Koolen DA, Ockeloen CW, Willemsen MH, Verhoef FM, van Deurzen PAM, van Dongen L, van Bokhoven H, Egger JIM, Staal WG, Kleefstra T. Adaptive and maladaptive functioning in Kleefstra syndrome compared to other rare genetic disorders with intellectual disabilities. Am J Med Genet A. 2017a;173:1821–30. [PubMed: 28498556]

Vermeulen K, Staal WG, Janzing JG, van Bokhoven H, Egger JIM, Kleefstra T. Sleep disturbance as a precursor of severe regression in Kleefstra syndrome suggests a need for firm and rapid pharmacological treatment. Clin Neuropharmacol. 2017b;40:185–8. [PubMed: 28622207]

Willemsen MH, Beunders G, Callaghan M, de Leeuw N, Nillesen WM, Yntema HG, van Hagen JM, Nieuwint AW, Morrison N, Keijzers-Vloet ST, Hoischen A, Brunner HG, Tolmie J, Kleefstra T. Familial Kleefstra syndrome due to maternal somatic mosaicism for interstitial 9q34.3

microdeletions. Clin Genet. 2011;80:31–8. [PubMed: 21204793]

Willemsen MH, Vulto-van Silfhout AT, Nillesen WM, Wissink-Lindhout WM, van Bokhoven H, Philip N, Berry-Kravis EM, Kini U, van Ravenswaaij-Arts CM, Delle Chiaie B, Innes AM, Houge G, Kosonen T, Cremer K, Fannemel M, Stray-Pedersen A, Reardon W, Ignatius J, Lachlan K, Mircher C, Helderman van den Enden PT, Mastebroek M, Cohn-Hokke PE, Yntema HG, Drunat S, Kleefstra T. Update on Kleefstra syndrome. Mol Syndromol. 2012;2:202–12. [PMC free article: PMC3366700] [PubMed: 22670141]

Yatsenko SA, Brundage EK, Roney EK, Cheung SW, Chinault AC, Lupski JR. Molecular mechanisms for subtelomeric rearrangements associated with the 9q34.3 microdeletion syndrome. Hum Mol Genet. 2009;18:1924–36. [PMC free article: PMC2678925] [PubMed: 19293338]

Yatsenko SA, Cheung SW, Scott DA, Nowaczyk MJ, Tarnopolsky M, Naidu S, Bibat G, Patel A, Leroy JG, Scaglia F, et al. Deletion 9q34.3 syndrome: genotype-phenotype correlations and an extended deletion in a patient with features of Opitz C trigonocephaly. J Med Genet. 2005;42:328–35. [PMC free article: PMC1736036] [PubMed: 15805160]