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KMT2E-Related Neurodevelopmental Disorder

Synonym: O'Donnell-Luria-Rodan Syndrome (ODLURO)

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Summary

Clinical characteristics

KMT2E-related neurodevelopmental disorder (*KMT2E*-NDD) is a condition characterized by global developmental delay, variable intellectual disability (typically in the mild-to-moderate range), and hypotonia. The majority of affected individuals are verbal but experience speech delays with or without articulation problems. All reported individuals who are older than infants have been able to obtain independent ambulation. About one third of affected individuals develop seizures, with no consistent seizure semiology or epilepsy syndrome. However, females may be more likely to develop seizures compared to males. Similarly, about one third of affected individuals have an autism spectrum disorder diagnosis, of which most to date are male. Growth parameters are typically in the normal range for length/height and weight, although about half of affected individuals have macrocephaly or relative macrocephaly. Constipation is the most frequent gastrointestinal issue, although gastroesophageal reflux, vomiting, and/or reduced bowel motility have been reported in almost half of affected individuals. About half of affected individuals experience some type of sleep disturbance, including frequent awakening and difficulties falling asleep.

Diagnosis/testing

The diagnosis of *KMT2E*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *KMT2E* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for developmental delay / intellectual disability, neuropsychiatric issues, seizures, constipation, gastroesophageal reflux/dysmotility, vomiting, and sleep disturbance.

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Surveillance: At each visit, measure growth parameters (including head circumference); assess for new neurologic manifestations and monitor those with seizures as clinically indicated; monitor developmental progress and educational need; assess for behavioral issues, including anxiety, ADHD, aggression, and self-injury; and assess for chronic vomiting, constipation, and signs/symptoms of sleep disturbance.

Genetic counseling

KMT2E-NDD is an autosomal dominant disorder. Most probands reported to date with *KMT2E*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant. Rarely, individuals diagnosed with *KMT2E*-NDD inherited a pathogenic variant from an affected parent who typically has mild intellectual disability. Each child of an individual with *KMT2E*-NDD has a 50% chance of inheriting the pathogenic variant. Once the *KMT2E* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *KMT2E*-related neurodevelopmental disorder (*KMT2E*-NDD) have been published.

Suggestive Findings

KMT2E-NDD **should be considered** in individuals with the following clinical and brain MRI findings.

Clinical findings

- Mild-to-profound developmental delay (DD) or intellectual disability (ID), although most individuals fall within the mild-to-moderate range

AND

- Any of the following features presenting in infancy or childhood:
  - Generalized hypotonia of infancy
  - Gastrointestinal symptoms, including vomiting and reduced bowel motility
  - Seizures, including febrile seizures
  - Autism spectrum disorder
  - Behavioral issues
  - Macrocephaly (often relative to length/height)
  - Microcephaly (in some individuals with missense pathogenic variants) (See Genotype-Phenotype Correlations.)
  - Sleep disturbance, including frequent awakenings and difficulty falling asleep
  - Minor dysmorphic features (See Clinical Description and Figure 1.)
  - Nonspecific brain abnormalities, including hypoplasia of the corpus callosum, ventriculomegaly, cerebral cysts, and/or delayed myelination

Family history. Because *KMT2E*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family).

Establishing the Diagnosis

The diagnosis of *KMT2E*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathoge variant in *KMT2E* identified by molecular genetic testing (see Table 1).

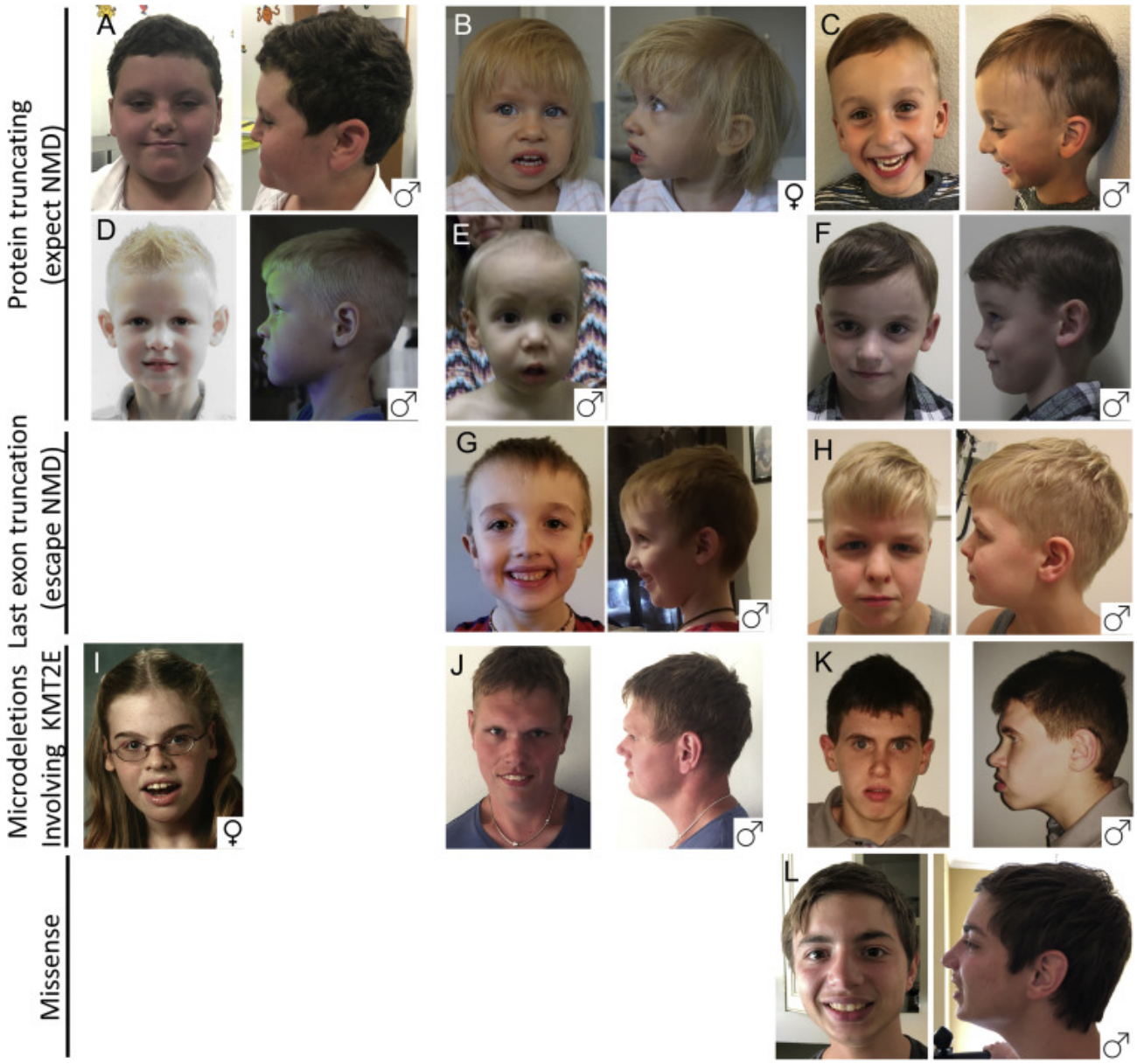

Figure 1. Consistent facial features of individuals with *KMT2E*-related neurodevelopmental disorder include dolichocephaly, tall forehead, and deep-set eyes, often with downslanting palpebral fissures, periorbital fullness, prominent cheeks, and prominent nasolabial folds.

(A) Individual 9 – age 11 years; (B) Individual 11 – age 1 year, 10 months; (C) Individual 12 – age 4.5 years; (D) Individual 13 – age 6 years; (E) Individual 15 – age 1 year, 7 months; (F) Individual 20 – age 6 years; (G) Individual 24 – age 5 years; (H) Individual 25 – age 12 years; (I) Individual 30 – age 18 years; (J) Individual 31 – age 22 years; (K) Individual 32 – age 7 years; (L) Individual 33 – age 16 years. Included on the bottom right of each cluster is the individual's sex.

NMD = nonsense mediated decay

Reprinted with permission from O'Donnell-Luria et al [2019]

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this chapter is understood to include likely pathogenic variants. (2) Identification of a heterozygous *KMT2E* variant of uncertain significance (*KMT2E* missense variants of uncertain significance are a common finding [Author, personal observation]) does not establish or rule out the diagnosis. Segregation in parents should be considered

in these situations to determine if the variant is *de novo* or inherited from an affected parent (supporting pathogenicity) or inherited from an unaffected parent (suggesting it may be benign).

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with chromosomal microarray analysis (CMA). Other options include use of a multigene panel or exome/genome sequencing. Note: Single-gene testing (sequence analysis of *KMT2E*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability multigene panel** that includes *KMT2E* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of *KMT2E*-NDD, some panels for intellectual disability may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability, whereas some multigene panels may not.

  Genome sequencing is also possible; this method has been proposed to be able to improve variant detection in coding regions, expand the assessment of noncoding regions (i.e., identifying variants that may alter splicing of *KMT2E*), and detect copy-neutral (e.g., inversions, translocations) or noncoding structural variants.

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

Table 1. Molecular Genetic Testing Used in *KMT2E*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2, 3] Identified by Method
KMT2E	Sequence analysis [4]	~95% [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown; at least 2% [7]
	CMA [8]	~2% [5]

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. Six individuals with contiguous gene deletions have been reported and are also included in this calculation (see Genetically Related Disorders) [O'Donnell-Luria et al 2019, Kosma et al 2021, Velmans et al 2022].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. O'Donnell-Luria et al [2019], Conforti et al [2021], Kosma et al [2021], Li et al [2021], Sharawat et al [2021], Abreu et al [2022], Cao et al [2022], Lee et al [2022], Velmans et al [2022]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by O'Donnell-Luria et al [2019] and Kosma et al [2021]) may not be detected by these methods.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available, but this methodology should detect at least all of those deletions/duplications involving *KMT2E* detected through chromosomal microarray (CMA) analysis.
8. CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *KMT2E*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 7q22.3 region. CMA designs in current clinical use target the 7q22.3 region.

Clinical Characteristics

Clinical Description

KMT2E-related neurodevelopmental disorder (*KMT2E*-NDD) is a condition characterized by global developmental delay, variable intellectual disability (typically mild to moderate), and hypotonia [O'Donnell-Luria et al 2019, Velmans et al 2022]. To date, 61 individuals have been reported in the medical literature with a pathogenic variant in *KMT2E* [O'Donnell-Luria et al 2019, Conforti et al 2021, Li et al 2021, Sharawat et al 2021, Abreu et al 2022, Cao et al 2022, Lee et al 2022, Velmans et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *KMT2E*-Related Neurodevelopmental Disorder: Select Features

Feature	% of Persons w/Feature	Comment
Developmental delay	56/58 (97%)	
Intellectual disability	31/37 (84%)	Typically in the mild-to-moderate range
Brain abnormalities	27/43 (63%)	
Macrocephaly	29/52 (56%)	Incl relative macrocephaly compared to length/height
Gastrointestinal issues	20/45 (44%)	Most frequently constipation; gastroesophageal reflux & vomiting has also been reported
Sleep disturbance	8/17 (47%)	
Hypotonia	23/50 (46%)	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Autism spectrum disorder	18/47 (38%)	
Seizures	16/56 (29%)	
Microcephaly	3/5 (60%)	In persons w/missense pathogenic variants only (See Genotype-Phenotype Correlations.)

Developmental delay (DD) and intellectual disability (ID). Almost all individuals with *KMT2E*-NDD present with global developmental delay. The majority are verbal but experience speech delays with or without articulation problems. A few individuals were reported to have speech regression. Four individuals with pathogenic missense variants were not verbal [O'Donnell-Luria et al 2019]. All reported individuals older than infants have been able to obtain independent ambulation, though many were delayed in achieving this milestone, and most presented with additional motor delays [O'Donnell-Luria et al 2019, Velmans et al 2022]. Intellectual disability, usually in the mild-to-moderate range, has been reported in a majority of affected individuals [O'Donnell-Luria et al 2019, Velmans et al 2022].

Seizures. Almost one third of reported individuals have developed seizures. There is no consistent seizure semiology or epilepsy syndrome described in individuals with *KMT2E*-NDD.

- About 14% of individuals with protein-truncating pathogenic variants have been reported to have seizures (two with unprovoked seizures, one with a single seizure, and two with treatment-resistant epilepsy).
- All five individuals with pathogenic missense variants had epilepsy, four of whom had treatment-resistant infantile epilepsy [O'Donnell-Luria et al 2019, Li et al 2021].
- Three affected individuals were noted to have febrile seizures [Li et al 2021, Velmans et al 2022].
- Sex-related differences have also been noted, with epilepsy reported in 43% of females (3/7) but in only 5% of males (1/21) in one study [O'Donnell-Luria et al 2019]. This suggests the possibility of decreased penetrance or variable expressivity of the seizure phenotype in females with *de novo* protein-truncating pathogenic variants.

Two individuals (one with a missense pathogenic variant and the other with a frameshift pathogenic variant) are known to have experienced developmental regression with some improvement in epilepsy when started on a ketogenic diet, so careful monitoring should be in place if this therapy is considered (see Management) [O'Donnell-Luria et al 2019; A O'Donnell-Luria, personal observation]. More evidence is needed to determine if ketogenic diet is contraindicated in individuals with this condition.

Neurobehavioral/psychiatric problems

- Autism spectrum disorder (ASD) is seen more frequently in males with *KMT2E*-NDD than in affected females [O'Donnell-Luria et al 2019, Conforti et al 2021, Li et al 2021, Sharawat et al 2021, Velmans et al 2022].
- Some affected individuals have behavioral concerns other than ASD; stereotypies, skin-picking behavior, self-injurious behavior, aggression, anxiety, and sensory integration disorder has been reported in 17% of individuals. At least two affected individuals have been diagnosed with attention-deficit/hyperactivity disorder (ADHD) [O'Donnell-Luria et al 2019, Velmans et al 2022].

Musculoskeletal features / tone abnormalities

- Hypotonia is reported in about 46% of individuals with *KMT2E*-NDD. In two individuals, this presented as feeding difficulties in the newborn period. There is not enough data to determine if hypotonia resolves with time, although it tends to improve with age.

- General joint laxity is reported in some affected individuals [O'Donnell-Luria et al 2019, Abreu et al 2022, Velmans et al 2022, Cao et al 2022]. No joint dislocations have been reported.

Growth. Growth parameters can be variable, but most are in the normal range for length/height and weight, both at birth and later in life. About half of individuals have macrocephaly (>2 standard deviations above the mean, i.e., z score for age >2) or relative macrocephaly (defined as head circumference z score for age 1 or more points higher than the length z score). Several individuals with pathogenic missense variants had microcephaly (see Genotype-Phenotype Correlations) [O'Donnell-Luria et al 2019, Velmans et al 2022].

Gastrointestinal issues, including gastroesophageal reflux, vomiting, and/or reduced bowel motility has been reported in almost 50% of affected individuals [O'Donnell-Luria et al 2019, Velmans et al 2022]. Constipation was the most frequently reported gastrointestinal issue and is likely related to low muscle tone.

Sleep disturbance. About half of affected individuals have some type of sleep disturbance, including frequent awakening and difficulties falling asleep [Velmans et al 2022]. While data on sleep issues are limited, mild sleep apnea has only been reported in one affected individual [A O'Donnell-Luria, personal observation].

Facial features. If present, dysmorphic features are usually subtle and nonspecific. Facial features including dolichocephaly, tall forehead, deep-set eyes, periorbital fullness, malar prominence, and prominent nasolabial folds are seen in a subset of affected individuals (see Figure 1) [O'Donnell-Luria et al 2019, Li et al 2021, Velmans et al 2022]. A composite facial phenotype is provided in Figure 2. However, no recognizable dysmorphic pattern has been observed in individuals with this condition.

Neuroimaging. Brain imaging was reported as normal in most affected individuals who underwent imaging. About 20% showed nonspecific findings, such as abnormal corpus callosum, signal abnormalities in the white matter, decreased volume, ventriculomegaly, pachygyria, delayed myelination, small areas of heterotopia, or small localized cysts [O'Donnell-Luria et al 2019, Velmans et al 2022]. Hydrocephalus has not been reported.

Prognosis. It is unknown whether life span in *KMT2E*-NDD is abnormal. One reported individual is alive at age 54 years [Conforti et al 2021], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Only five individuals have been reported with pathogenic missense variants.

Individuals with pathogenic missense variants in *KMT2E* have been reported to have microcephaly (as opposed to macrocephaly) and more severe seizures compared to those who have pathogenic protein-truncating variants [O'Donnell-Luria et al 2019, Conforti et al 2021, Li et al 2021, Sharawat et al 2021, Velmans et al 2022].

Prevalence

To date, 61 individuals have been identified with a pathogenic variant in *KMT2E* [O'Donnell-Luria et al 2019, Conforti et al 2021, Li et al 2021, Sharawat et al 2021, Abreu et al 2022, Cao et al 2022, Velmans et al 2022]. There is no evidence to indicate a higher prevalence in any particular population.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline intragenic pathogenic variants in *KMT2E*.

Contiguous gene deletions that include *KMT2E*

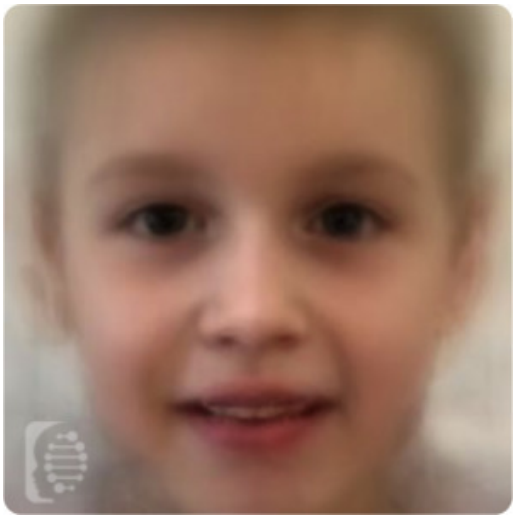

Figure 2. Composite figure analysis of the facial phenotype of individuals with *KMT2E*-related neurodevelopmental disorder in Figure 1, excluding Individual 30, who is wearing glasses

Reprinted with permission from O'Donnell-Luria et al [2019]

- Kosma et al [2021] described a male individual with a 239-kilobase (kb) deletion of 7q22.3 that included *KMT2E* and *LHFPL3*. This is one of the smallest deletions of this region reported to date and helped to confirm the core features of *KMT2E*-NDD, including the dysmorphic facial features, developmental delay, hypotonia, and gastrointestinal symptoms. Abnormalities of the urinary tract were also noted in this individual, but it cannot be definitively attributed to the disruption of *KMT2E* alone.
- O'Donnell-Luria et al [2019] and Velmans et al [2022] reported a total of five other individuals with 7q22.2-22.3 deletions involving *KMT2E* and adjacent gene(s). These individuals presented similarly to those with truncating *KMT2E* pathogenic variants but with more severe developmental delays, which is likely explained by the influence of additional genes included in their deletions.

Differential Diagnosis

Because the phenotypic features associated with *KMT2E*-related neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series for genes associated with:

- Autosomal dominant intellectual developmental disorder
- Autosomal recessive intellectual developmental disorder
- Nonsyndromic X-linked intellectual developmental disorder
- Syndromic X-linked intellectual developmental disorder

Management

No clinical practice guidelines for *KMT2E*-related neurodevelopmental disorder (*KMT2E*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *KMT2E*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. *KMT2E*-Related Neurodevelopmental Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Growth	Measurement of head circumference	To assess for (relative) macrocephaly or microcephaly
Neurologic	Neurologic eval	• Consider referral to a neurologist. • Consider brain MRI as clinically indicated for seizures or focal neurologic concerns. • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl ADHD, anxiety, &/or findings suggestive of ASD
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of nutritional status • Consider eval for gastrostomy tube placement in persons who have inadequate nutrition or concern for dysphagia.
	Clinical assessment for signs & symptoms of GERD, chronic vomiting, & bowel dysmotility	Consider referral to gastroenterologist.
Respiratory/ Sleep	Assessment for sleep disturbance	Consider referral to sleep disorders clinic.
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *KMT2E*-NDD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; *KMT2E*-NDD = *KMT2E*-related neurodevelopmental disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *KMT2E-NDD*. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *KMT2E*-Related Neurodevelopmental Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • 1 affected person experienced developmental regression while being treated w/ketogenic diet; more data is required to determine if ketogenic diet is contraindicated in this condition. [1] • Education of parents/caregivers [2]
Gastroesophageal reflux / Vomiting	Standard therapy per gastroenterologist	
Bowel dysmotility / Constipation		
Sleep disturbance	Standard treatment per sleep medicine specialist	At least 1 affected person has been treated w/ melatonin.
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy

1. O'Donnell-Luria et al [2019]

2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

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

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

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

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility.

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

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

Social/Behavioral Concerns

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

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

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. *KMT2E*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth	Measurement of growth parameters, incl head circumference [1]	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. [2] • Assess for new manifestations such as seizures or changes in tone.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assess for anxiety, ADHD, ASD, aggression, & self-injury.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Gastrointestinal	Monitor for chronic vomiting & constipation.	
Respiratory/Sleep	Assess for signs/symptoms of sleep disturbance.	
Family/Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy
1. To assess for macrocephaly, relative macrocephaly, and microcephaly (see Clinical Characteristics)
2. Careful monitoring is required if an affected individual is placed on a ketogenic diet, given that one affected individual placed on this therapy experienced developmental regression (without improvement in seizure control) [O'Donnell-Luria et al 2019].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

KMT2E-related neurodevelopmental disorder (*KMT2E*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *KMT2E*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo KMT2E* pathogenic variant.
- Rarely, individuals diagnosed with *KMT2E*-NDD inherited a *KMT2E* pathogenic protein-truncating variant from an affected parent with (typically) mild intellectual disability. Confirmed parental transmission of a *KMT2E* pathogenic protein-truncating variant has been reported in two families with one affected child (one maternally and one paternally inherited) and one family with two affected children (paternally inherited); presumed parental transmission has been reported in one family with three affected children (the pathogenic variant was not maternally inherited and the father was not available for testing) [O'Donnell-Luria et al 2019, Velmans et al 2022].
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * Theoretically, a parent with somatic and germline mosaicism for a *KMT2E* pathogenic variant may be mildly/minimally affected.

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

- If a parent of the proband is known to have the *KMT2E* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *KMT2E* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *KMT2E*-NDD has a 50% chance of inheriting the *KMT2E* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *KMT2E* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *KMT2E* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Simons Searchlight**
  Phone: 855-329-5638
  Email: coordinator@simonssearchlight.org
  KMT2E
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**
  Intellectual Disability

Molecular Genetics

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

Table A. KMT2E-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
KMT2E	7q22.3	Inactive histone-lysine N-methyltransferase 2E	KMT2E	KMT2E

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 KMT2E-Related Neurodevelopmental Disorder (View All in OMIM)

608444	LYSINE-SPECIFIC METHYLTRANSFERASE 2E; KMT2E
618512	O""DONNELL-LURIA-RODAN SYNDROME; ODLURO

Molecular Pathogenesis

KMT2E encodes a histone methyltransferase protein, inactive histone-lysine N-methyltransferase 2E (KMT2E), but studies suggest lack of an intrinsic methyltransferase activity. The gene product functions as a transcriptional regulator in diverse biological processes, including cell cycle progression, maintenance of genomic stability, adult hematopoiesis, and spermatogenesis. KMT2E is ubiquitously expressed in most tissues including the developing fetal brain [Fagerberg et al 2014]. However, how disruption of KMT2E results in a neurodevelopmental condition is currently not understood.

Mechanism of disease causation. Likely loss of function. The majority of individuals with *KMT2E*-related neurodevelopmental disorder have protein-truncating pathogenic variants, including nonsense, frameshift, and splice-disrupting pathogenic variants, suggesting that haploinsufficiency is the likely disease mechanism, but this has not been confirmed. Some individuals with *de novo* pathogenic missense variants presented with a more severe phenotype, leading authors to hypothesize an alternate mechanism such as gain of function and dominant-negative, though additional research is needed [O'Donnell-Luria et al 2019].

Chapter Notes

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