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NLM Citation: Campbell AN, Bain J, Doyle SJ. *MED13L* Syndrome. 2025 Apr 10. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

MED13L Syndrome

Synonyms: *MED13L* Haploinsufficiency Syndrome, *MED13L*-Related Intellectual Disability

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Created: April 10, 2025.

Summary

Clinical characteristics

MED13L syndrome is characterized by mild-to-profound developmental delay, intellectual disability, and hypotonia. Neurobehavioral manifestations (autistic features, agitation/aggression, restlessness, self-harm, tantrums, frustration, overfriendliness, and/or hyperactivity) are also reported. Some individuals have abnormal findings on brain imaging (ventriculomegaly, delayed or lack of myelination, thin or absent corpus callosum, periventricular foci, and/or subcortical white matter abnormalities). Dysmorphic facial features, including depressed nasal bridge, bulbous nose, and hypotonic open mouth, are present in most individuals. Distal limb and/or digit anomalies, ocular manifestations and vision issues, and congenital heart defects have been reported. Other reported features include seizures and/or hearing impairment.

Diagnosis/testing

The diagnosis of *MED13L* syndrome is established in a proband with a heterozygous pathogenic variant in *MED13L* identified by molecular genetic testing.

Management

Treatment of manifestations: Standardized treatment for developmental, intellectual, and behavioral issues and seizures; treatment of orthopedic manifestations, congenital heart disease, and ocular manifestations per relevant specialist; hearing aids may be helpful per otolaryngologist; community hearing services through early intervention or the school district; treatment of neonatal respiratory issues per intensivist and/or pulmonologist; feeding therapy; gastrostomy tube placement as needed; social work and family support.

Surveillance: Monitor developmental progress, educational needs, behavior issues, and development of or changes in seizures at each visit; assessment of mobility and self-help skills at each visit; clinical assessment for scoliosis at each visit with radiographs as needed; assess for changes in visual acuity and strabismus per treating

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ophthalmologist; audiology evaluation annually or as needed; monitor for evidence of aspiration and/or respiratory insufficiency, nutritional status, safety of oral intake, and family needs at each visit.

Genetic counseling

MED13L syndrome is an autosomal dominant disorder. The majority of probands reported to date whose parents have undergone molecular genetic testing have the disorder as the result of a pathogenic variant that occurred as a *de novo* event in the proband. Rarely, individuals diagnosed with *MED13L* syndrome have the disorder as the result of a pathogenic variant inherited from a mosaic, apparently unaffected parent. Once the *MED13L* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

MED13L syndrome **should be considered** in probands with the following clinical and brain MRI findings and family history.

Clinical findings

- Mild-to-profound developmental delay
- Intellectual disability of variable degree
- Hypotonia
- Neurobehavioral manifestations
- Facial dysmorphisms. Depressed nasal bridge and bulbous nose, broad forehead, frontal bossing, up- or down-slanted palpebral fissures, large, low-set ears with prominent antihelix stem, short and deep philtrum, exaggerated Cupid's bow, macroglossia with hypotonic open mouth and/or tongue protrusion, and cleft or highly arched palate (See Figure 1.)
- Musculoskeletal features, ophthalmologic involvement, congenital heart defects, and seizures in some individuals

Brain MRI findings

- Ventriculomegaly (9/62 individuals)
- Delayed or lack of myelination (6/62)
- Thin or absent corpus callosum (5/62)
- Periventricular foci and subcortical white matter abnormalities (7/62)

Family history. Because *MED13L* syndrome 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 *MED13L* syndrome **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *MED13L* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *MED13L* variant of uncertain significance does not establish or rule out the diagnosis.

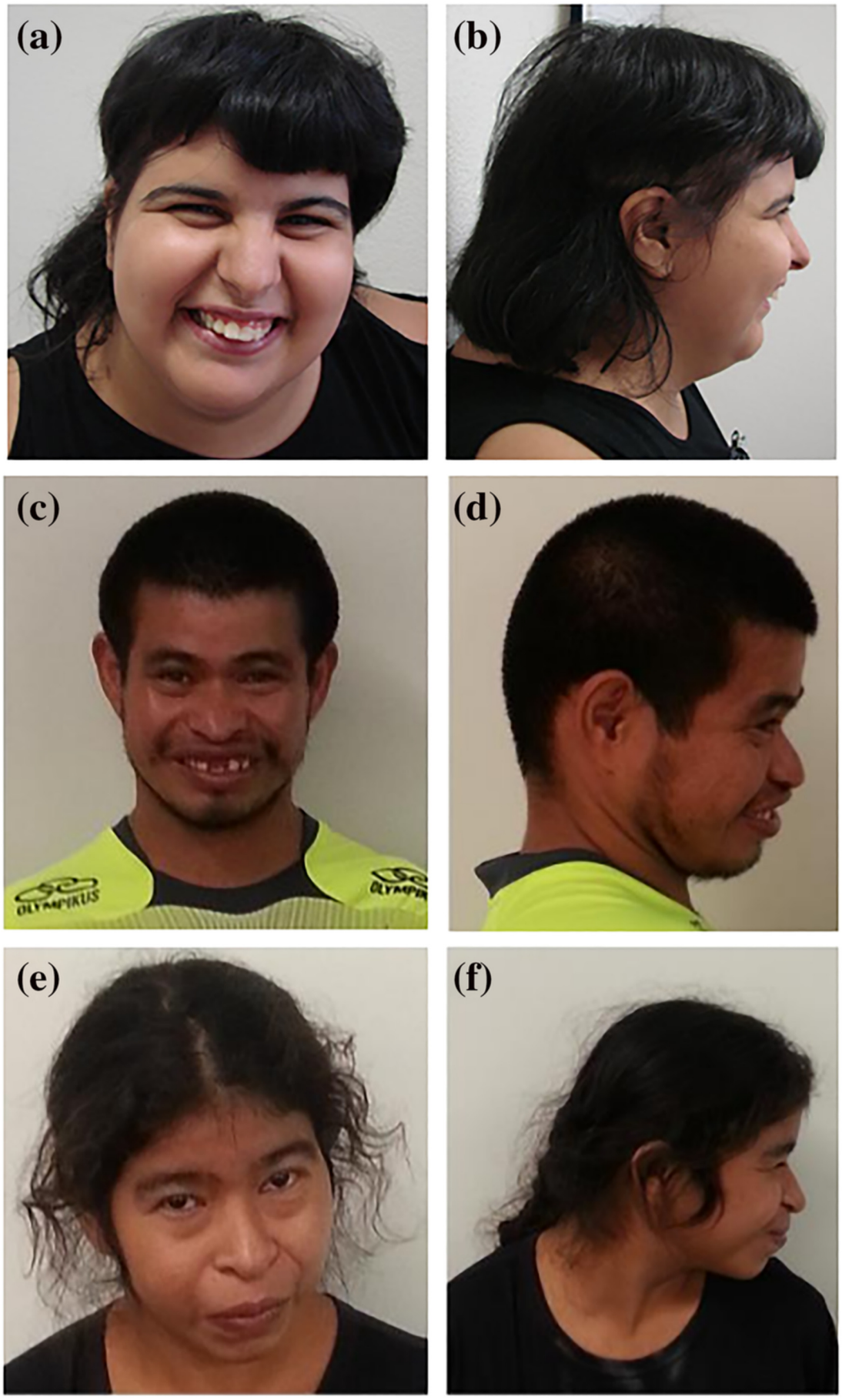

Figure 1. Characteristic facial features of individuals with *MED13L* syndrome

(a, b) Female age 22 years with low columella, short philtrum, retrognathia, and prominent antihelix stem

(c–d) Male age 33 years with mild bitemporal narrowing, everted palpebral fissures, midface retrusion, depressed nasal bridge, long

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with exome or genome sequencing [Manickam et al 2021, van der Sanden et al 2023]. Other options include use of a multigene panel. Note: Single-gene testing (sequence analysis of *MED13L*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome and genome sequencing** is widely used and yields results similar to an intellectual disability multigene panel, with the additional advantage that exome and genome sequencing includes genes recently identified as causing intellectual disability, whereas some multigene panels may not. To date, the majority of *MED13L* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome or genome sequencing.

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

- **An intellectual disability multigene panel** that includes *MED13L* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of pathogenic variants and variants of uncertain significance 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 *MED13L* syndrome, 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.

Table 1. Molecular Genetic Testing Used in *MED13L* Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
MED13L	Sequence analysis [3]	~90%-95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5%-10% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. A few additional individuals with contiguous gene deletions and whole-gene duplications (not included in these calculations) have been reported (see Genetically Related Disorders).

Clinical Characteristics

Clinical Description

MED13L syndrome is characterized by developmental delay, intellectual disability, hypotonia, and often behavioral abnormalities. Characteristic facial features have been described. Some individuals have distal limb and/or digit anomalies, ocular manifestations and/or vision defects, and/or congenital heart defects. To date, more than 100 published individuals have been identified with a pathogenic variant in *MED13L*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *MED13L* Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Developmental delay	>99%	Mild to profound; minimal or absent speech (99%); impaired motor capabilities
Intellectual disability	100%	Includes learning disabilities; ranging from mild (<10%) to severe (15%); most commonly moderate disability (71%)
Hypotonia	63%	Generalized hypotonia; can include open mouth w/ tongue protrusion
Neurobehavioral manifestations	~60%	Autistic features, agitation/aggression, restlessness, self-harm, tantrums, frustration, overfriendliness, & hyperactivity
Characteristic facial features	>99%	Most commonly depressed nasal bridge & bulbous nose
Musculoskeletal features	51%	Typically affecting feet &/or hands
Ocular manifestations / vision defects	31%	Most commonly strabismus
Congenital heart defects	23%	Most commonly PFO, dTGA, CoA (mild), & pVSD

Based on Muncke et al [2003], Asadollahi et al [2013], Utami et al [2014], Adegbola et al [2015], Cafiero et al [2015], van Haelst et al [2015], Caro-Llopis et al [2016], Asadollahi et al [2017], Yamamoto et al [2017], Gordon et al [2018], Jiménez-Romero et al [2018], Smol et al [2018], Tørring et al [2019], Yi et al [2020], Carvalho et al [2021], Bessenyei et al [2022], Siavrienė et al [2023], Heilmann et al [2024]

PFO = patent foramen ovale; dTGA = dextro-loop transposition of the great arteries; CoA = coarctation of the aorta; pVSD = perimembranous ventricular septal defect

Developmental delay. Developmental delay is reported in all individuals. This can range from mild to profound and can affect various developmental domains.

Hypotonia is common. Some individuals have facial hypotonia, including an open mouth and protruding tongue [Adegbola et al 2015, van Haelst et al 2015, Asadollahi et al 2017]. Delayed head control is reported during infancy [Caro-Llopis et al 2016]. The range of age for sitting without assistance is 8 months to 17 months. Most individuals become ambulatory. The range in age in those that achieve walking without assistance is 20 months to 3.5 years. Some individuals walk only with assistance, and some do not become ambulatory.

Speech and language development is delayed or completely lacking in most individuals (99%). Several individuals are able to follow short commands but lack expressive language [Asadollahi et al 2013].

Intellectual disability. Intellectual disability is reported in all individuals; this includes specific learning disabilities. This ranges from mild (fewer than 10%) to severe (15%), with the majority of individuals reported as having moderate disability. Most require specialized education programs. Some individuals progress to relative

independence with educational support [Muncke et al 2003, Utami et al 2014, Adegbola et al 2015, Caro-Llopis et al 2016, Asadollahi et al 2017, Smol et al 2018, Carvalho et al 2021, Bessenyei et al 2022].

Neurobehavioral manifestations. Roughly 60% of individuals have behavioral issues. Autistic features are the most common. Agitation/aggression, restlessness, self-harm, tantrums, frustration, overfriendliness, and hyperactivity have also been reported. Individuals may have bursts of energy and then tire easily.

Seizures are reported in 22% of individuals. The types of seizures reported include absence seizures and febrile seizures; however, due to low numbers reported, no seizure subtype patterns can be discerned. Some individuals had epileptiform discharges on EEG; however, this is not a common feature. Of those individuals reported with seizures, the seizures are managed with anti-seizure medications.

Other neurologic manifestations. Ataxia was reported in 9/25 individuals and mainly consisted of dynamic ataxia. The average age of individuals with ataxia was 12 years, but no age of onset has been reported. Dysarthria was reported in 4/9 individuals, who all presented with this manifestation.

Brain MRI findings have been reported for 33 individuals. These findings included ventriculomegaly (n=9), white matter abnormalities (n=7), myelination defects (n=6), and corpus callosum thinning or agenesis (n=5).

Characteristic facial features (see Figure 1). Many individuals have a distinct depressed nasal bridge and bulbous nose (>75%). Additional common features include broad forehead, frontal bossing, up- or down-slanted palpebral fissures, large, low-set ears with prominent antihelix stem, short and deep philtrum, exaggerated Cupid's bow, cleft or high-arched palate, and macroglossia. Less common features include brachycephaly (7%), flat occiput (<1%), and plagiocephaly (3%) [Adegbola et al 2015, Asadollahi et al 2017].

Musculoskeletal features. Manifestations in the lower extremities can include clubfoot (10%), metatarsus varus (6%), and abnormalities of the toes including clinodactyly (10%), syndactyly (7%), and camptodactyly (3%). Abnormalities of the hands can include decreased palmar creases, extra phalangeal creases (5%), and/or radial clubhand (<1%). The most common spine abnormality is scoliosis (5%).

Ophthalmologic involvement. The most common ocular abnormality is strabismus (31 individuals). Other ocular manifestations include Duane anomaly and nystagmus. Myopia, hyperopia, and astigmatism have also been reported [Adegbola et al 2015, Caro-Llopis et al 2016].

Congenital heart disease. Approximately 20% (22/94) of individuals reported have congenital heart defects, including patent foramen ovale (10%), perimembranous ventricular septal defect (6%), dextro-looped transposition of the great arteries (5%), and mild coarctation of the aorta (5%).

Hearing impairment. Sensorineural and conductive hearing loss have been reported in 6% of persons with *MED13L* syndrome [Adegbola et al 2015, Cafiero et al 2015, Caro-Llopis et al 2016, Smol et al 2018]. The age of onset of hearing loss has not been reported.

Respiratory abnormalities. One infant had asphyxia at birth [Yi et al 2020]. Respiratory distress has been reported in some neonates. One infant required oxygen therapy, while another was intubated for six days. In most individuals, respiratory issues did not persist beyond infancy [Cafiero et al 2015, Caro-Llopis et al 2016]. One infant had persistent respiratory infections including pneumonia, but respiratory function significantly improved by age six years.

Gastrointestinal manifestations. Gastrointestinal reflux during infancy, leading to feeding problems, has been reported in 2% of infants. Frequent vomiting is uncommon but has been reported [Asadollahi et al 2013, van Haelst et al 2015, Asadollahi et al 2017]. Abnormal positioning of the anus has been reported in three individuals (either posteriorly or anteriorly) [Asadollahi et al 2013, Adegbola et al 2015]. Both inguinal and umbilical hernias have been reported (10%) [Adegbola et al 2015, Gordon et al 2018, Smol et al 2018, Tørring et al 2019].

Genitourinary abnormalities. Cryptorchidism (8%) [Adegbola et al 2015, Caro-Llopis et al 2016] and micropenis (2%) have both been reported [Gordon et al 2018, Smol et al 2018]. Congenital ureteropelvic junction obstruction (<1%) [Yi et al 2020], hydroureter (<1%) [Tørring et al 2019], kidney cysts (<1%) [Smol et al 2018], and renal agenesis (<1%) have all been rarely reported [Caro-Llopis et al 2016]. In addition, some individuals had delayed bladder control or persistent urinary incontinence [Asadollahi et al 2013].

Growth. Most individuals have normal growth parameters at birth including head circumference, weight, and length. Microcephaly (2%) and macrocephaly (<1%) are rarely reported.

Prognosis. Based on current data, life span is not limited by this condition, as several adults have been reported. Data on possible progression of behavior abnormalities or neurologic findings are still limited.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified; however, pathogenic missense variants appear to be associated with more severe manifestations, including severe motor delay, seizures, and autism / behavioral issues. A higher likelihood of absent speech (5/9), absent ambulation (4/9), seizures (5/9), and autistic features (5/8) were reported in individuals with *MED13L* pathogenic missense variants compared to other variant types [Smol et al 2018]. These missense variants have been located in exons 15 through 17 and exons 25 through 31. These correlations are still not completely understood and require further testing.

Penetrance

There are no reported individuals with a *MED13L* pathogenic variant that do not have manifestations of the disorder; therefore, penetrance is complete.

Prevalence

To date, more than 100 published individuals have been identified with a pathogenic variant in *MED13L*. The authors are aware of many additional affected individuals, and prevalence is likely higher than suggested by the number of individuals reported in the literature.

Genetically Related (Allelic) Disorders

Contiguous gene deletions in the 12q24.21 region involving *MED13L* have been reported in individuals with other phenotypic features in addition to those observed in individuals with *MED13L* syndrome [Adegbola et al 2015]. Additional features in individuals with larger deletions are likely caused by haploinsufficiency of other genes.

Whole-gene duplication of *MED13L*. Although rarely reported, there are individuals with whole-gene duplications who are reported to have a milder phenotype that includes developmental delay, intellectual difficulties, hypotonia, cardiac malformations, and facial dysmorphisms [Asadollahi et al 2013, Adegbola et al 2015, Meng et al 2017].

Differential Diagnosis

The phenotypic features associated with *MED13L* syndrome are not sufficient to diagnose this condition clinically; thus, 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 disorders;
- Autosomal recessive intellectual developmental disorders;
- Nonsyndromic X-linked intellectual developmental disorders;

- Syndromic X-linked intellectual developmental disorders.

Overlap in clinical features has been noted between *MED13L* syndrome and the disorders listed in Table 3 [Asadollahi et al 2017].

Table 3. Selected Disorders in the Differential Diagnosis of *MED13L* Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Key Features of Disorder	
			Overlapping w/*MED13L* syndrome	Distinguishing from *MED13L* syndrome
1p36 deletion	1p36 deletion syndrome (OMIM 607872)	AD	• Bulbous nose w/depressed nasal bridge & deep philtrum • ID, speech delay • Hypotonia • ASD • Seizures • Structural abnormalities of brain	Dysphagia
9q34.3 deletion or *EHMT1* pathogenic variant	Kleefstra syndrome	AD	• Macroglossia • ID, speech delay • Hypotonia • Congenital heart defects • Autistic features • Seizures	
22q11.2 deletion	22q11.2 deletion syndrome	AD	• DD • Congenital heart defects	Immunologic deficiency

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

Management

No clinical practice guidelines for *MED13L* syndrome have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MED13L* syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. *MED13L* Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
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 findings suggestive of ASD, agitation/aggression, restlessness, self-harm, tantrums, frustration, &/or hyperactivity
Neurologic	Neurologic eval	• Consider brain MRI. • Consider EEG if seizures are a concern.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Radial clubhand, clubfoot, metatarsus varus, & scoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, & strabismus
Cardiovascular	Cardiology eval	• For congenital heart defects • To incl echocardiogram
Hearing	Audiologic eval	To assess for sensorineural &/or conductive hearing loss
Respiratory	Pulmonary eval	As needed for those w/respiratory compromise
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Assess impact of facial hypotonia, macroglossia, &/or protruding tongue on feeding. • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk. • Assess for hernia.
ENT	ENT eval	In those w/cleft palate &/or macroglossia
Genitourinary	• Assess for cryptorchidism &/or micropenis. • Referral to urologist &/or endocrinologist as needed	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *MED13L* syndrome 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

ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Clinical geneticist, certified genetic counselor, certified genetic nurse, genetics advanced practice provider (nurse practitioner or physician assistant)

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in pediatric/adult neurology, occupational therapy, audiology, speech-language pathology, clinical genetics, orthopedics, physical therapy, and mental health (see Table 5).

Table 5. *MED13L* Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Orthopedic manifestations	Treatment of radial clubhand, clubfoot, metatarsus varus, &/or scoliosis per orthopedist	
Eyes	Treatment per ophthalmologist for refractive errors, strabismus	
Congenital heart disease	Treatment per cardiologist	
Hearing	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Respiratory	Treatment of neonatal respiratory issues per intensivist &/or pulmonologist	
Feeding/Nutrition	• Feeding therapy • Gastronomy tube placement may be required for persistent feeding issues.	
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

1. 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.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters 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 and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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.

Neurobehavioral/Psychiatric 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.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *MED13L* Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurobehavioral/ Psychiatric	Assess for agitation, ASD, & hyperactivity,	
Neurologic	Monitor those w/seizures & assess for new seizures.	
Musculoskeletal	• Physical medicine, OT/PT assessment of mobility, self-help skills • Clinical assessment for scoliosis w/radiographs as needed	
Ophthalmologic involvement	Assess for changes in visual acuity & strabismus.	Per treating ophthalmologist(s)
Hearing	Audiologic eval	Annually or as needed
Respiratory	Monitor for evidence of aspiration &/or respiratory insufficiency.	At each visit
Feeding	Eval of nutritional status & safety of oral intake	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

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

MED13L syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- The majority of probands reported to date with *MED13L* syndrome whose parents have undergone molecular genetic testing have the disorder as the result of a *MED13L* pathogenic variant that occurred as a *de novo* event in the proband.
- Rarely, individuals diagnosed with *MED13L* syndrome have the disorder as the result of a *MED13L* pathogenic variant inherited from a mosaic, apparently unaffected parent [Yamamoto et al 2017, Smol et al 2018, Bessenyei 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 gonadal (or somatic and gonadal) 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 (gonadal) cells only.

      * A parent with somatic and gonadal mosaicism for an *MED13L* 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 *MED13L* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Transmission of a *MED13L* pathogenic variant from a heterozygous parent to an affected child has not been reported to date.
- If the *MED13L* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental gonadal mosaicism. Transmission of a *MED13L* pathogenic variant from a mosaic parent to affected sibs has been reported in several families [Yamamoto et al 2017, Smol et al 2018, Bessenyei et al 2022].

Offspring of a proband. Each child of an individual with *MED13L* syndrome has a 50% chance of inheriting the *MED13L* pathogenic variant; to date, individuals with *MED13L* syndrome are not known to reproduce.

Other family members. Given that all probands with *MED13L* syndrome reported to date have the disorder as a result of an *MED13L* pathogenic variant that occurred *de novo* in the proband or in a mosaic parent, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *MED13L* 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **Global Genes**
  Developmental delay-facial dysmorphism syndrome due to MED13L deficiency
- **MED13L Foundation**
  med13l.org
- **Simons Searchlight**
  MED13L
- **RARE X Registry (Research Program of Global Genes)**
  MED13L - Data Collection Program

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. MED13L Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

MED13L	12q24.21	Mediator of RNA polymerase II transcription subunit 13-like	MED13L database	MED13L	MED13L

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 MED13L Syndrome (View All in OMIM)

608771	MEDIATOR COMPLEX SUBUNIT 13-LIKE; MED13L
616789	IMPAIRED INTELLECTUAL DEVELOPMENT AND DISTINCTIVE FACIAL FEATURES WITH OR WITHOUT CARDIAC DEFECTS; MRFACD

Molecular Pathogenesis

MED13L encodes mediator of RNA polymerase II transcription subunit 13-like (MED13L), which along with its paralog MED13 are interchangeable subunits of the CDK8-kinase module (CKM) [Knuesel et al 2009]. The CKM, composed of either protein paralog, is associated with the larger mediator complex that is responsible for controlling RNA polymerase II-dependent transcription [Chang et al 2022]. MED13L and MED13 serve as a protein tether for the CKM to the mediator. Additional members of the CKM include cyclin C, CDK8, CDK19, MED12, and MED12L [Knuesel et al 2009, Ježek et al 2019]. As MED13L and MED13 play a major role in the mediator complex, necessary for transcription of almost all RNA polymerase II-dependent genes, *MED13L* pathogenic variants cause known transcriptional defects [Chang et al 2022].

Studies have also shown that *MED13L* pathogenic variants lead to mislocalization of cyclin C [Chang et al 2022]. Cyclin C has been extensively characterized for its role in mitochondrial fragmentation within the cell [Chang et al 2022].

Mechanism of disease causation. Reports suggest that *MED13L* syndrome is the result of *MED13L* haploinsufficiency. A dominant-negative effect cannot be ruled out, and further studies are necessary to confirm disease causation. It is also possible that some variants have a gain-of-function effect. This could potentially provide an explanation for the more severe phenotype associated with *MED13L* missense pathogenic variants.

Chapter Notes

Author Notes

Alicia Campbell is a PhD candidate who is actively involved in clinical and molecular biology research regarding individuals with *MED13L* syndrome. For those with questions regarding molecular and genetic work for *MED13L* syndrome, contact her (campbe26@rowan.edu) or her mentor, Dr Randy Strich (strichra@rowan.edu) at the Rowan-Virtua School of Translational Biomedical Engineering and Sciences.

If there are questions related to diagnosis/management of *MED13L* syndrome, contact Dr Jennifer Bain (jb3634@cumc.columbia.edu), who sees patients with *MED13L* syndrome.

Additionally, contact Dr Reza Asadollahi (r.asadollahi@greenwich.ac.uk), who actively sees patients with *MED13L* syndrome, and whose research has laid much of the foundation for clinicians caring for those with *MED13L* syndrome today.

Contact any of those listed above to inquire about review of *MED13L* variants of uncertain significance.

Acknowledgments

The authors would like to acknowledge the *MED13L* Foundation for all initiatives regarding clinical accessibility and increasing awareness of *MED13L* syndrome. Additionally, the authors would like to thank members of the Strich/Cooper lab, specifically Dr Steven Doyle, for his insight into diagnosis and management.

Revision History

- 10 April 2025 (sw) Review posted live
- 2 May 2024 (ac) Original submission

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