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MBD5 Haploinsufficiency

Synonym: 2q23.1 Microdeletion Syndrome

Sureni V Mullegama, PhD,[1,2] Roberto Mendoza-Londono, MD,[3] and Sarah H Elsea, PhD[4]

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Summary

Clinical characteristics

MBD5 haploinsufficiency is a neurodevelopmental disorder characterized by developmental delay, intellectual disability, severe speech impairment, seizures, sleep disturbances, and abnormal behaviors. Most children lack speech entirely or have single words, short phrases, or short sentences. Seizures are present in more than 80% of children; onset is usually around age two years. Sleep disturbances, present in about 90%, can result in excessive daytime drowsiness. Abnormal behaviors can include autistic-like behaviors (80%) and self-injury and aggression (>60%).

Diagnosis/testing

The diagnosis of *MBD5* haploinsufficiency is established in a proband by identification on molecular genetic testing of a heterozygous deletion of 2q23.1 encompassing all or part of *MBD5*, or of an intragenic *MBD5* pathogenic variant.

Management

Treatment of manifestations: A multidisciplinary approach that typically includes specialists in clinical genetics, neurology, child development, behavioral therapy, nutrition/feeding, speech and language therapy, and occupational and physical therapy is recommended. Infants benefit from enrollment in an early-intervention program, and school-age children benefit from an individualized educational program. Speech therapy (including nonverbal methods of communication) should be introduced early. Seizures, behavior problems, sleep disturbances, and constipation are treated in a routine manner. Feeding therapy with gastrostomy tube feeding as needed; treatment of hip dysplasia and scoliosis per orthopedist; treatment of cardiovascular anomalies per cardiologist; family support including social work involvement and care coordination.

Author Affiliations: 1 College of Osteopathic Medicine, Sam Houston State University, Conroe, Texas; Email: svm013@shsu.edu. 2 GeneDx, Inc, Gaithersburg, Maryland; Email: svm013@shsu.edu. 3 Associate Professor of Pædiatrics and Molecular Genetics, University of Toronto; The Hospital for Sick Children, Division of Clinical and Metabolic Genetics, Toronto, Ontario, Canada; Email: roberto.mendoza@sickkids.ca. 4 Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas; Email: elsea@bcm.edu.

Surveillance: Periodic neurodevelopmental and behavioral evaluations to assist in the management of cognitive issues, behavior issues, and sleep disturbance. Assess for seizures, feeding issues, constipation, and family support needs at each visit. Clinical assessment for scoliosis annually.

Genetic counseling

MBD5 haploinsufficiency is an autosomal dominant disorder typically caused by a *de novo* genetic alteration. To date, parent-to-child transmission of a 2q23.1 deletion that encompasses all or part of *MBD5* has not been reported. Parent-to-child transmissions of *MBD5* intragenic deletions and pathogenic sequence variants have been reported. Rarely, parent-to-child transmission of an unbalanced derivative chromosome involving the 2q23.1 region occurs. Once the genetic alteration resulting in *MBD5* haploinsufficiency has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

MBD5 haploinsufficiency, a neurodevelopmental disorder, **should be suspected** in individuals with the following findings [Talkowski et al 2011, Hodge et al 2014, Mullegama & Elsea 2016].

Neurologic

- Motor delays
- Severe speech and language impairment
- Intellectual disability (ID), usually moderate to severe
- Seizures
- Sleep disturbance
- Hypotonia
- Feeding difficulties, often related to hypotonia

Behavior

- Short attention span
- Autistic-like behaviors that include gaze avoidance, inattention, and repetitive behaviors
- Self-injury and/or aggressive behaviors

Establishing the Diagnosis

The diagnosis of *MBD5* haploinsufficiency **is established** in a proband with one of the following (see Table 1):

- Deletion of 2q23.1 that encompasses all or part of *MBD5* (~80% of affected individuals)
- Intragenic deletion involving one or more exons of *MBD5* including noncoding exons 1-5 (~15%)
- A heterozygous pathogenic sequence variant in *MBD5* (~5%)
- Rarely, an apparently balanced complex chromosome rearrangement of the 2q23.1 region involving *MBD5*

Note: (1) Identification of a heterozygous *MBD5* variant of uncertain significance (e.g., intronic deletion that does not affect splicing) does not establish or rule out the diagnosis of *MBD5* haploinsufficiency (see Molecular Genetics). (2) *MBD5* intragenic deletions limited to noncoding exons 2, 4, and 5 do not result in reduced *MBD5* expression and phenotype may be milder than *MBD5* haploinsufficiency, although further study is needed [Author, unpublished data].

Molecular genetic testing approaches can include **chromosomal microarray analysis**, **multigene panel**, **exome sequencing**, **genome sequencing**, or **single-gene testing**.

Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing may not. Because many inherited disorders share the phenotypic findings of ID, seizures, and behavior problems, most children with *MBD5* haploinsufficiency are diagnosed by the following recommended testing (CMA and/or a multigene panel) or testing to be considered (exome or genome sequencing).

Recommended First-Tier Testing

Chromosomal microarray analysis (CMA) should be the first genetic test, as about 80% of *MBD5* haploinsufficiency is caused by large, nonrecurrent deletions, which cannot be detected by sequence analysis of *MBD5*.

Note: The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from *MBD5* haploinsufficiency (see Genetically Related Disorders).

Options for Second-Tier Testing

A multigene panel that includes *MBD5* 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

More comprehensive genomic testing (when available) including **exome sequencing** or **genome sequencing** may be considered if the phenotype alone is insufficient to support gene-targeted testing.

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

Note: In individuals with features that are highly suggestive of *MBD5* haploinsufficiency consider **single-gene testing** (sequence analysis of *MBD5* and gene-targeted deletion/duplication analysis including evaluation of noncoding exon 1). However, because many features of *MBD5* haploinsufficiency overlap with those of many other genetic disorders with ID, seizures, and behavior issues, a multigene panel or exome sequencing is typically used in lieu of single-gene testing.

Table 1. Molecular Genetic Testing Used in *MBD5* Haploinsufficiency

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MBD5	CMA [3]	80%
	Gene-targeted deletion/duplication analysis [4]	~15% [5, 6]
	Sequence analysis [7]	~5% [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. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *MBD5*) 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 2q23.1 region. CMA designs in current clinical use target the 2q23.1 region.
4. 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.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis should include analysis of noncoding exon 1.
7. 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.

Clinical Characteristics

Clinical Description

MBD5 haploinsufficiency is a neurodevelopmental disorder that comprises developmental delay / intellectual disability (ID), severe speech impairment, seizures, sleep disturbances, and behavior issues with autistic features [Jaillard et al 2009, van Bon et al 2010, Talkowski et al 2011, Noh & Graham 2012]. To date, 105 individuals have been identified with a pathogenic variant in *MBD5* [Mullegama & Elsea 2016]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *MBD5* Haploinsufficiency

Feature	% of Persons w/Feature
Developmental delay	100%
Seizures	>90%
Speech impairment	>80%
Sleep disturbances	~90%
Behavior issues	100%
Feeding difficulties	>90%
Hypotonia	~80%
Skeletal abnormalities	>50%
Dysmorphic features	~80%
Microcephaly	~80%
Ataxic gait	>70%
Hyperphagia	>50%
Cardiovascular abnormalities	~10%

Developmental delays, evident in all children with *MBD5* haploinsufficiency within the first year of life, include delays in gross motor and fine motor development, receptive and expressive language development, and acquisition of social skills. Children typically acquire new skills, without evidence of psychomotor regression.

Motor delays with poor coordination and broad-based/ataxic gait are seen in more than 70% of individuals. The average age of walking is two to three years [van Bon et al 2010, Talkowski et al 2011, Hodge et al 2014].

Language development is severely impaired [van Bon et al 2010]. Most reported children lack speech entirely [Talkowski et al 2011] or have single words or short (2- to 3-word) phrases [Bonnet et al 2013] or (2- to 6-word) sentences [Hodge et al 2014].

Seizures occur in more than 80% of children [Talkowski et al 2011, Hodge et al 2014]. Onset of seizures is usually around age two years [Bonnet et al 2013, Shichiji et al 2013, Hodge et al 2014, Myers et al 2021].

Although seizure types have not been well characterized, typically only one seizure type is observed in an individual. Seizure types most often include generalized tonic-clonic, focal, atypical absence, tonic, drop attacks, and myoclonic seizures. Atonic, sleep-related, and startle-induced atonic seizures have also been reported [Jaillard et al 2009, van Bon et al 2010, Williams et al 2010, Chung et al 2011, Talkowski et al 2011, Motobayashi et al 2012, Noh & Graham 2012, Bonnet et al 2013, Hodge et al 2014, Myers et al 2021].

In the few instances in which EEG studies have been performed, patterns were nonspecific; however, a few individuals were reported to have focal spikes and spike-wave complexes [van Bon et al 2010, Talkowski et al 2011, Hodge et al 2014, Myers et al 2021].

Sleep disturbances, present in about 90% of affected children, include frequent nighttime waking, short sleep duration, apparent night terrors in the early part of sleep, and waking in the early hours of the morning [Jaillard et al 2009, van Bon et al 2010, Williams et al 2010, Chung et al 2011, Talkowski et al 2011, Noh & Graham 2012, Bonnet et al 2013, Hodge et al 2014, Mullegama et al 2014, Gandhi et al 2021]. Many exhibit excessive daytime sleepiness [Mullegama et al 2015b].

Behavior issues. Short attention span and autistic-like behaviors (gaze avoidance, inattention, and repetitive behaviors) [Tan et al 2014] and stereotypic and repetitive behaviors (e.g., teeth grinding, chewing of the hands, and repetitive hand movements) are seen in more than 80% of affected individuals. Self-injury and aggression are seen in more than 60% of individuals. Other behaviors mentioned in approximately 9% of reported individuals include anxiety, hyperactivity, inappropriate happy demeanor, and social withdrawal [Talkowski et al 2011, Hodge et al 2014].

Feeding difficulties and constipation, likely related to hypotonia, are seen in more than 90% of infants.

Skeletal abnormalities (observed in 65 individuals with *MBD5* haploinsufficiency) include small hands and feet (~75%), fifth-finger clinodactyly (~70%), generalized brachydactyly (~41%), short fifth digit of the hands and feet (40%), and sandal gap (~33%) [Talkowski et al 2011].

Other musculoskeletal abnormalities mentioned in at least two affected individuals each are hip dysplasia, joint laxity, and scoliosis.

Cardiovascular abnormalities (reported in ~10%) include atrial septal defect, ventricular septal defect, and pulmonary valve stenosis [Talkowski et al 2011, Hodge et al 2014].

Dysmorphic features are seen in the majority of affected individuals. Microcephaly is common. Additional features may include broad forehead, thick / highly arched eyebrows, outer ear abnormalities (e.g., forward-facing large earlobes, protruding ears, cupped ears), short nose, depressed or wide nasal bridge, downturned corners of the mouth, everted vermilion of the lower lip, and tented and thin vermilion of the upper lip [Talkowski et al 2011, Hodge et al 2014, Mullegama & Elsea 2016].

Genotype-Phenotype Correlations

No genotype-phenotype correlations distinguish individuals with pathogenic sequence variants from those with *MBD5* deletions. Individuals with larger deletions involving multiple genes may exhibit a more severe phenotype.

Penetrance

Penetrance is predicted to be complete.

Nomenclature

MBD5 haploinsufficiency was initially referred to as 2q23.1 deletion syndrome; however, delineation of the smallest region of overlap among individuals with a 2q23.1 deletion confirmed that haploinsufficiency of *MBD5* is responsible for the disorder. In addition, subsequent identification of heterozygous pathogenic sequence variants in *MBD5* further supports the use of the term "*MBD5* haploinsufficiency."

The commonly used term, "*MBD5*-associated neurodevelopmental disorder," encompasses *MBD5* haploinsufficiency and the neurodevelopmental phenotype associated with nonrecurrent duplications involving *MBD5* [Mullegama & Elsea 2016] (see also Genetically Related Disorders). OMIM refers to this disorder as intellectual developmental disorder, autosomal dominant 1 (OMIM 156200). Both *MBD5* deletions and duplications are encompassed in the OMIM entry.

Prevalence

The prevalence of *MBD5* haploinsufficiency is not known. Because many individuals with *MBD5* haploinsufficiency may go undiagnosed, the prevalence may be greater than observed to date.

Approximately 1% of 4,808 individuals (from 3 cohorts) ascertained for autism spectrum disorder were found to have *MBD5* haploinsufficiency when assessed for copy number variants involving *MBD5* and for *MBD5* sequence variants not present in controls [Talkowski et al 2011].

MBD5 haploinsufficiency has been identified worldwide and in all populations.

Genetically Related Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with either deletion of the 2q23.1 region involving *MBD5* or germline pathogenic variants in *MBD5*.

Nonrecurrent duplications involving *MBD5* have been described in 35 individuals to date [Mullegama et al 2014, Stenson et al 2020, Myers et al 2021, Saleh et al 2021]. The clinical phenotype is similar to but perhaps less severe than that of *MBD5* haploinsufficiency and includes mild dysmorphic features, intellectual disability, developmental delay, motor delay, severe language impairment, infantile hypotonia, sleep disturbances, behavioral issues, and autistic-like features.

Differential Diagnosis

Because the phenotypic features associated with *MBD5* haploinsufficiency 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 Autosomal Dominant, Autosomal Recessive, and Nonsyndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MBD5* haploinsufficiency, 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 *MBD5* Haploinsufficiency

System/Concern	Evaluation	Comment
Development	Developmental assessment	Eval for early intervention / special education
	PT/OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Speech eval	Incl feeding eval & nutrition consultation as needed
Neurologic	Neurologic eval	Consider EEG if seizures are a concern.
	Sleep assessment	To incl consideration of sleep onset delay, early waking, & daytime sleepiness, as well as parental sleep
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	Persons age >12 mos: screening for concerns incl assoc sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Assess for feeding problems &/or constipation.
Musculoskeletal	Clinical assessment for hip dysplasia, joint laxity, &/or scoliosis	
Cardiovascular	Cardiac eval	
Audiology	Hearing assessment	As part of routine eval of children w/speech delay
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *MBD5* haploinsufficiency in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	• Ensure that IEP is in place. • Counsel parents re guardianship & adult services.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; IEP = individualized education plan; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

A multidisciplinary approach to manage the features and specific issues identified is recommended. Specialists in the following fields are often involved: clinical genetics, neurology, child development, behavioral therapy, nutrition/feeding, speech and language therapy, and occupational and physical therapy.

Table 4. Treatment of Manifestations in Individuals with *MBD5* Haploinsufficiency

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	Speech therapy w/early intro of nonverbal communication methods (e.g., sign language & computer-assisted technologies) is appropriate given high risk for poor or absent speech.
Epilepsy	• ASM such as valproate, clonazepam, zonisamide, & clobazam appear to be effective in reducing incidence of seizures. [1] • Education of parents/caregivers [2]	Many different ASMs may be effective. [1]
Sleep disturbance	Consider combined approach of targeted sleep hygiene (to develop firm daily schedules) & daily medications (e.g., melatonin, clonidine, trazodone).	Mullegama et al [2015b]
Feeding Issues	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs/ symptoms of dysphagia
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	Constipation can affect behavior.
Musculoskeletal features	Treatment of hip dysplasia & scoliosis per orthopedist	
Cardiovascular anomalies	Treatment per cardiologist	
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. Jaillard et al [2009], van Bon et al [2010], Williams et al [2010], Chung et al [2011], Talkowski et al [2011], Motobayashi et al [2012], Noh & Graham [2012], Bonnet et al [2013], Hodge et al [2014], Gandhi et al [2021]
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.
  - 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.

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.

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 (ADHD), sleep disturbance, and behavior issues when necessary.

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

Surveillance

Table 5. Recommended Surveillance for Individuals with *MBD5* Haploinsufficiency

System/Concern	Evaluation	Frequency
Development	• Monitor developmental progress & educational needs. • Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit &/or as needed
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new seizures.	At each visit
Neurobehavioral/ Psychiatric	• Assessment for sleep disturbance • Assessment for anxiety, attention, & aggressive or self-injurious behavior	
Feeding/ Gastrointestinal	• Eval of nutritional status • Monitor for constipation.	
Musculoskeletal	Clinical assessment for scoliosis	Annually throughout childhood
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

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

MBD5 haploinsufficiency is an autosomal dominant disorder typically caused by a *de novo* genetic alteration.

Risk to Family Members

Parents of a proband

- Most probands with *MBD5* haploinsufficiency have the disorder as the result of a *de novo* genetic alteration.
- Rarely, a proband with *MBD5* haploinsufficiency has the disorder as the result of a genetic alteration inherited from a parent [Talkowski et al 2011, Hodge et al 2014, Han et al 2017, Myers et al 2021]. (Note: Parent-to-child transmission of a 2q23.1 deletion that encompasses all or part of *MBD5* has not been reported to date.)
- For accurate assessment of recurrence risk, evaluation of the parents by molecular genetic or genomic testing that will detect the genetic alteration identified in the proband is recommended. Parental testing for a balanced chromosome rearrangement involving the 2q23.1 region is also recommended.
- If the genetic alteration identified in the proband is not identified in a parent, neither parent has a chromosome rearrangement, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* genetic alteration.
  - The proband inherited a genetic alteration from a parent with germline (or somatic and germline) mosaicism. Parental mosaicism has been reported in several families [Myers et al 2021]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a genetic alteration that is present in the germ cells only.
- The family history of some individuals diagnosed with *MBD5* haploinsufficiency may appear to be negative because of failure to recognize the disorder in affected family members with a milder phenotype (i.e., variable expressivity) or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless genetic testing has demonstrated that neither parent has the genetic alteration identified in the proband.

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 has the genetic alteration identified in the proband, the risk to each sib of inheriting the genetic alteration is 50%. Several families with *MBD5* haploinsufficiency recurrence have been reported [Talkowski et al 2011, Hodge et al 2014, Han et al 2017].
- If a parent has a balanced structural chromosome rearrangement involving the 2q23.1 region, the risk to sibs is increased. The estimated risk depends on the specific chromosome rearrangement.
- If the causative genetic alteration identified in the proband is not identified in the parents and neither parent has a chromosome rearrangement, the risk to sibs is presumed to be slightly greater than that of the general population because of the possibility of parental germline mosaicism [Myers et al 2021].

Offspring of a proband. Each child of an individual with *MBD5* haploinsufficiency is at a 50% risk of inheriting the causative genetic alteration.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has an *MBD5* haploinsufficiency-related genetic alteration, other members of the parent's family 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 young adults who are at risk of having a child with *MBD5* haploinsufficiency.

Prenatal Testing and Preimplantation Genetic Testing

Once the genetic alteration resulting in *MBD5* haploinsufficiency 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.

- **2q23.1 Microdeletion Syndrome**
  Unique 2q23.1 microdeletion brochure
- **Chromosome Disorder Outreach Inc.**
  Phone: 561-395-4252
  Email: info@chromodisorder.org
  chromodisorder.org
- **MedlinePlus**
  Intellectual Disability
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org

Molecular Genetics

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

Table A. MBD5 Haploinsufficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MBD5	2q23.1	Methyl-CpG-binding domain protein 5	MBD5 database	MBD5	MBD5

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 MBD5 Haploinsufficiency (View All in OMIM)

156200	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 1; MRD1
611472	METHYL-CpG-BINDING DOMAIN PROTEIN 5; MBD5

Molecular Pathogenesis

MBD5 belongs to MBD family of proteins, which includes MBD1-6 and MeCp2 (encoded by *MECP2*, the gene involved in Rett syndrome). The MBD proteins play key roles in regulating gene transcription. Most MBD proteins participate in chromatin remodeling and mediate gene silencing through their MBD motifs [Tao et al 2014]. Using immunocytochemistry, Camarena et al [2014] showed that MBD5 localizes to non-heterochromatin regions of the nucleus, suggesting that MBD5 acts as a transcriptional activator. At the transcriptome level, deletions of *MBD5* lead to significant dysregulation of mRNA expression levels of several neurodevelopmental genes such as *FOXG1* [Mullegama et al 2021]. MBD5 was shown to be recruited to chromatin by recognition of CG methylation and redundantly represses a subset of genes and transposons without affecting DNA methylation levels [Ichino et al 2021]. Haploinsufficiency of *MBD5* results in dysregulation of other autism-associated genes including *UBE3A* (Angelman syndrome), *RAI1* (Smith-Magenis syndrome), *TCF4* (Pitt-Hopkins syndrome), *MEF2C* (5q14.3 deletion syndrome), and *FMR1* (*FMR1*-related disorders) [Mullegama et al 2015a]. In haploinsufficient *RAI1* cells, *MBD5* is also dysregulated [Mullegama et al 2015b]. Whether MBD5 directly or indirectly regulates some of these genes remains to be determined.

Mechanism of disease causation. Loss of function

***MBD5*-specific laboratory technical considerations.** Intronic *MBD5* deletions that do not affect splicing and deletions and duplications involving the 5'UTR have been reported. Further study is needed to classify many of these variants [Author, personal communication].

Chapter Notes

Author Notes

The parent Facebook group 2q23.1 Syndromes/MBD5 Disorders/MAND Caregiver Support Network is a support group for families with children who have a molecular diagnosis of *MBD5*-associated neurodevelopmental disorder (MAND).

Sureni V Mullegama, PhD, FACMG, is a board-certified clinical molecular geneticist. Her clinical and scholarly work is rooted in providing answers to patients and their families regarding the genetic conditions they have. The answers may come through clinical genetic testing, molecular genetic research, or genetics education. Her

interests include autism spectrum disorders, cohesinopathies, epigenetic disorders, epilepsy disorders and other neurogenetic conditions. She studies the following disorders: Smith-Magenis syndrome, MAND – 2q23.1 deletion syndrome and 2q23.1 duplication syndrome, and Mullegama-Klein-Martinez syndrome.
SHSU College of Osteopathic Medicine website

Roberto Mendoza-Londono, MD, MSc, FACMG, is a licensed clinical geneticist. His interests include genetics of skeletal dysplasias and connective tissue disorders. His research interests include the identification of the genetic basis and molecular pathophysiologic mechanisms underlying common and novel genetic disorders, and the delineation of the natural history and best management strategies for patients with connective tissue disorders.
LinkedIn page

Sarah H Elsea, PhD, FACMG, is a board-certified clinical biochemical geneticist. Her research is targeted toward defining the biochemical mechanisms and molecular pathways affected in human genetic disease. Investigations of neurodevelopmental disorders complicated by obesity and circadian rhythm defects, including autism, intellectual disability, seizures, and behavioral phenotypes, are a primary focus. Studies include the clinical and molecular analysis of genomic conditions, wherein deletion or duplication of a portion of the genome is the primary underlying etiology, leading to altered gene dosage. Disorders include MAND – 2q23.1 deletion syndrome and 2q23.1 duplication syndrome, as well as 2q37.3 deletion syndrome, Smith-Magenis syndrome, Potocki-Lupski syndrome, Pitt-Hopkins syndrome, and others.
Web page

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- 28 April 2022 (sw) Comprehensive update posted live
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