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MEF2C-Related Disorder

Synonyms: MEF2C Deficiency; *MEF2C* Haploinsufficiency Syndrome (MCHS); *MEF2C*-Related Neurodevelopmental Disorder; *MEF2C*-Related Syndrome; Neurodevelopmental Disorder with Hypotonia, Stereotypic Hand Movements, and Impaired Language (NEDHSIL)

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Summary

Clinical characteristics

MEF2C-related disorder is characterized by moderate-to-profound developmental delay with subsequent intellectual disability, hypotonia, dysmorphic features, seizures, neurobehavioral manifestations (autistic features, sleep issues, stereotypic movements particularly of the hands), vision issues, and cardiac manifestations. Individuals who are able to speak typically only use a few words and are not able to communicate in sentences. Approximately half of individuals are unable to walk independently; however, many are able to walk with some assistance.

Diagnosis/testing

The diagnosis of *MEF2C*-related disorder is established in a proband by identification of a heterozygous pathogenic variant in *MEF2C* by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational services; treatment of gait abnormalities per orthopedist, physical medicine and rehabilitation specialist, and/or physical or occupational therapist; feeding support as needed; standard treatment for gastroesophageal reflux disease, constipation, and seizures; treatment of cardiac manifestations per cardiologist; treatment of refractive errors and strabismus per ophthalmologist; more complex findings or treatment per ophthalmic subspecialist; antibiotics as needed for recurrent respiratory infections and recurrent otitis media; referral to otolaryngologist for tympanostomy tubes as needed for recurrent otitis; family and social work support.

Surveillance: At each visit, assess developmental progress, educational needs, gait issues, motor abnormalities, growth parameters, nutritional status, safety of oral intake, gastroesophageal reflux disease, and constipation;

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assess new or changing seizures, tone, and movement disorders at each visit or per neurologist; annual behavioral assessment; cardiology assessment per cardiologist; ophthalmology evaluation for strabismus and refractive errors per ophthalmologist; assessment for recurrent respiratory infections and/or recurrent otitis media annually or as needed; hearing evaluation in those with recurrent otitis annually or as needed; assess family needs at each visit.

Genetic counseling

MEF2C-related disorder is an autosomal dominant disorder. Most probands reported to date with *MEF2C*-related disorder whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant. Rarely, a proband diagnosed with *MEF2C*-related disorder has the disorder as the result of a pathogenic variant inherited from an affected heterozygous parent or an unaffected mosaic parent. Each child of an individual with *MEF2C*-related disorder has a 50% chance of inheriting the pathogenic variant. Once the *MEF2C* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

MEF2C-related disorder **should be considered** in probands with the following clinical and brain MRI findings and family history.

Clinical findings

- Moderate-to-profound developmental delay (including lack of speech in 95% and inability to walk independently in 50%)
- Profound intellectual disability
- Hypotonia
- Feeding/gastrointestinal issues (constipation, gastroesophageal reflux disease, feeding difficulties)
- Dysmorphic facial features (broad forehead, prominent philtrum, tented upper lip, widely spaced teeth, large ears)
- Seizures (febrile, infantile spasms, generalized tonic-clonic, myoclonic, and focal)
- Neurobehavioral/psychiatric manifestations, including autistic features (decreased social interaction, stereotypic movements particularly of the hands, repetitive rocking and head shaking, hyperkinesis), bruxism, agitation, sleep issues, and high pain tolerance
- Cardiac manifestations (ventricular septal defect, double outlet right ventricle, patent ductus arteriosus, pulmonary stenosis, and adult-onset dilated cardiomyopathy)
- Vison issues (strabismus, refractive errors)

Brain MRI findings

- Hypoplastic corpus callosum
- Mild thinning of the cortical white matter
- Enlarged ventricles and other cerebrospinal fluid spaces (including the subarachnoid space and cortical sulcus)
- Delay in myelination and mild undermyelination

Family history. Because *MEF2C*-related disorder is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *MEF2C*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *MEF2C* 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 *MEF2C* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with exome sequencing 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 *MEF2C*, 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 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.

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

- **An intellectual disability, autism, or epilepsy/seizure multigene panel** that includes *MEF2C* and other genes of interest (see Differential Diagnosis) may also be considered 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. 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 *MEF2C*-related disorder, some panels for intellectual disability, autism, or epilepsy/seizures 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 *MEF2C*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
MEF2C	Sequence analysis [3]	65%-70% [4]
	Gene-targeted deletion/duplication analysis [5]	30%-35% [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. Sixty-four additional individuals with contiguous gene deletions including *MEF2C* and adjacent genes (not included in these calculations) have been reported (see Genetically Related Disorders).

Clinical Characteristics

Clinical Description

MEF2C-related disorder is characterized by moderate-to-profound developmental delay with subsequent intellectual disability, lack of speech or speech impairment, limited walking, hypotonia, feeding and gastrointestinal issues, dysmorphic features, seizures, neurobehavioral manifestations including autistic features, cardiac manifestations, and vision issues. Individuals who are able to speak typically only use a few words and are not able to communicate in sentences. Approximately half of individuals are unable to walk independently; however, many are able to walk with some assistance [Cooley Coleman et al 2021]. To date, 142 individuals have been identified with a pathogenic variant in *MEF2C* including large deletions of all or part of *MEF2C* [Stenson et al 2020, Cooley Coleman et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *MEF2C*-Related Disorder

Feature	% of Persons w/Feature	Comment
Developmental delay	100% (81/81)	Lack of speech (95%), inability to walk independently (50%)
Intellectual disability	98% (64/65)	
Hypotonia	95% (38/40)	
Dysmorphic features	91% (40/44)	Broad forehead, prominent philtrum, tented upper lip, widely spaced teeth, large ears
Feeding/gastrointestinal issues	87% (13/15)	Severe GERD, constipation, feeding difficulties
Seizures	86% (77/90)	Febrile, infantile spasms, generalized tonic-clonic, myoclonic, & focal
Neurobehavioral/psychiatric manifestations	86% (44/51)	Autistic features incl stereotypic movements, sleep issues
Vison issues	100% (14/14)	Strabismus, myopia

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Cardiac manifestations	92% (11/12)	PDA, PFO, PS, VSD, double outlet right ventricle, adult-onset DCM

Based on Stenson et al [2020], Cooley Coleman et al [2021]
DCM = dilated cardiomyopathy; GERD = gastroesophageal reflux disease; PDA = patent ductus arteriosus; PFO = persistent foramen ovale; PS = pulmonary stenosis; VSD = ventricular septal defect

Developmental delay and intellectual disability. Developmental delay is evident early in life with both speech and motor delays. Most affected individuals are unable to speak but may use some vocalizations or babble. Those who are able to speak typically only use a few words and are not able to form sentences. Most individuals are able to reach for objects and transfer them from hand to hand, but acquisition of fine motor skills (e.g., pincer grasp and using utensils for feeding) are less common. Hypotonia is a common feature and likely contributes to motor delay. Approximately half of individuals are able to walk, with this milestone being achieved between ages 16 months and six years [Cooley Coleman et al 2022]. For individuals able to walk, gait abnormalities are common.

Regression after acquiring milestones is not common in individuals with *MEF2C*-related disorder; however, five of 108 individuals were reported to have regression. Additionally, one individual has been reported with frontotemporal dementia in their sixth decade of life [Adrião et al 2022].

Feeding and gastrointestinal issues. Some individuals require assisted feedings. Problems with chewing and swallowing are reported. Gastroesophageal reflux disease and constipation have been common in several individuals.

Dysmorphic features. Many individuals have distinctive facial features that may include a broad forehead, thick eyebrows, deep-set eyes, large ears with prominent ear lobes, depressed nasal bridge, short and prominent philtrum, full vermilion of the upper and lower lips with tented upper lip and everted lower lip, widely spaced teeth, down-turned corners of the mouth, and micrognathia. One individual had right question mark-shaped ear and left ear dysplasia.

Epilepsy. Seizures are reported in up to 86% of affected individuals. The most reported types of seizures include febrile and myoclonic seizures. Tonic-clonic, focal, absence, afebrile, atonic, and infantile spasms are also reported. Seizure onset is within the first year of life for a majority of individuals. EEG findings include multiple epileptiform discharges, hypsarrhythmia, temporal and occipital spike-slow waves, focal or multifocal bilateral spikes, and slowing background.

Neurobehavioral/psychiatric manifestations. Many affected individuals are reported to have autistic features, some of which include lack of eye contact, lack of a social smile, lack of interest in surroundings, or limited social interactions. Several individuals display stereotypical movements, particularly of the hands, including hand clapping, hand wringing, and hand mouthing; bruxism, repetitive rocking, and head shaking are also reported. Hyperkinesis with constant movements of the hands and feet is reported in some individuals [Mikhail et al 2011, Paciorkowski et al 2013, Rocha et al 2016]. A few individuals are reported as being easily agitated and exhibiting self-mutilating behaviors including self-biting. Additional reported behavior manifestations include overstuffing the mouth when self-feeding, happy demeanor, fascination with water, and breath-holding or hyperventilation [Vrečar et al 2017, Wang et al 2018]. Some individuals have issues with sleep, including irregular sleep initiation and sleep disruption. High pain tolerance is reported in several individuals.

Cardiac manifestations. Some individuals were reported to have congenital heart defects, including ventricular septal defect, double outlet right ventricle, patent ductus arteriosus, pulmonary stenosis, and adult-onset dilated cardiomyopathy.

Growth. A few individuals were reported to have a small head circumference (2-3 standard deviations below the mean), and some (fewer than 10%) were characterized as microcephalic. Other growth parameters are typically within the normal range.

Ophthalmologic involvement. The most common reported vision issue is strabismus. One individual had bilateral esotropia, which was surgically repaired [Shim et al 2015]. Additional findings include refractive errors (e.g., myopia, hypermetropia).

Neuroimaging. Abnormalities identified on brain MRI include hypoplastic corpus callosum, mild thinning of the cortical white matter, cortical atrophy, enlarged ventricles and other cerebrospinal fluid spaces (including the subarachnoid space and cortical sulcus), Chiari I malformation, spots of nonspecific hyperintensity, delay in myelination, and mild undermyelination.

Recurrent infections, particularly upper respiratory tract infections, have been reported in several individuals. A few individuals had recurrent otitis media, some requiring tympanostomy tubes. One study, using cells from *MEF2C*-haploinsufficient individuals and mice, showed defects in natural killer cell development and effector function and an increased susceptibility to viral infection [Li et al 2024].

Other. Findings reported in one or only a few individuals include:

- Duplex left kidney [Vrečar et al 2017]
- Tremors [Nowakowska et al 2010, Paciorkowski et al 2013]

Prognosis. It is unknown whether life span in individuals with *MEF2C*-related disorder is abnormal. A number of adults with *MEF2C*-related disorder have been described. The oldest individual was reported alive at age 69 years [Adrião et al 2022]. 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

At least two individuals with a deletion encompassing only *MEF2C* exons 1-3 presented with cutaneous vascular malformations, suggesting a possible genotype-phenotype correlation [Tanteles et al 2015, Vrečar et al 2017].

Individuals with pathogenic variants affecting the proximal region of the MEF2C protein (e.g., within the MADS or MEF2 domains) may be more severely affected than individuals with more distal pathogenic variants [Wang et al 2018].

Possible genotype-phenotype correlations associated with *MEF2C* (e.g., variant type or variant position) require further study. Note: Several reported *MEF2C* genotype-phenotype correlations compare *MEF2C* single-nucleotide variants to larger contiguous deletions that encompass additional genes; these are not included in this *GeneReview*.

Penetrance

Penetrance is 100%; all individuals who have a *MEF2C* pathogenic variant have clinical manifestations of the disorder. There have been no reports of unaffected individuals with a pathogenic variant in *MEF2C*.

Nomenclature

The term "*MEF2C*-related neurodevelopmental disorder" is based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

The prevalence of *MEF2C*-related disorder is unknown. At least 142 affected individuals have been reported in the literature to date. Eight additional affected individuals are known to the authors but have not been reported in the medical literature.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *MEF2C*.

Contiguous gene deletions in the 5q14.3 region that include *MEF2C* and adjacent genes have been reported in at least 64 individuals. These individuals presented with developmental delay, intellectual disability, seizures, stereotypic movements, dysmorphic features, abnormal MRI and EEG findings, feeding difficulties, cardiac manifestations, and vision issues (OMIM 613443). Individuals with a contiguous deletion including *RASA1* are typically diagnosed with capillary malformation-arteriovenous malformation syndrome, including vascular lesions with or without telangiectatic vessels, in addition to *MEF2C*-related disorder.

Differential Diagnosis

The phenotypic features associated with *MEF2C*-related disorder are not sufficient to diagnose this condition clinically; all disorders with intellectual disability and seizures 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

Classic Rett syndrome and Angelman syndrome can be considered in individuals presenting with stereotypic hand movements, intellectual disability, and seizures (see Table 3).

Table 3. Genes of Interest in the Differential Diagnosis of *MEF2C*-Related Disorder

Gene / Genetic Mechanism	Disorder	MOI	Selected Features of Disorder	
			Overlapping w/*MEF2C*-related disorder	Distinguishing from *MEF2C*-related disorder
MECP2	Classic Rett syndrome (See *MECP2* Disorders.)	XL	ID, DD, severe speech impairment, seizures, hand stereotypes	• Normal development for 1st 6-18 mos of life followed by regression • Absence of brain structural abnormalities on MRI
UBE3A / deficient expression or function of maternally inherited *UBE3A* allele	Angelman syndrome	See footnote 1.	ID, DD, severe speech impairment, seizures, hand stereotypes, fascination w/ water	• Persons w/Angelman syndrome seek eye contact. • Cardiac abnormalities are not typically reported.

DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function (see Angelman Syndrome, Genetic Counseling).

Management

No clinical practice guidelines for *MEF2C*-related disorder 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 *MEF2C*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. *MEF2C*-Related Disorder: 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
Musculoskeletal	Orthopedics / physical medicine & rehab / 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)
Neurologic	• Neurologic eval • Cognitive assessment	• To incl brain MRI • Consider EEG if seizures are a concern.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Assess for GERD & constipation. • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk.
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for ASD, hyperkinesis, agitation, self-injury, breathing issues, sleep issues, & high pain tolerance
Cardiovascular	Cardiac eval incl EKG & echocardiogram	
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings that may require referral for subspecialty care &/or low vision services
Recurrent infections	• Assess for recurrent respiratory infections &/or recurrent otitis. • Hearing eval in those w/ recurrent otitis	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *MEF2C*-related disorder to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
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; ADL = activities of daily living; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; 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 *MEF2C*-related disorder. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in developmental behavior, neurology, ophthalmology, and cardiology (see Table 5).

Table 5. *MEF2C*-Related Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Gait abnormalities	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Feeding issues / Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Gastrointestinal	Standard treatment for gastroesophageal reflux disease	Antacids or H2 receptor blockers as needed or prescribed
	Standard treatment for constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; Keppra® (levetiracetam) has been widely prescribed in addition to other ASMs. • Education of parents/caregivers [1]
Cardiac	Treatment per cardiologist	Heart defects may require monitoring, medications (e.g., diuretics), or surgery.
Eyes	• Treatment per ophthalmologist for refractive errors, strabismus • Treatment per ophthalmic subspecialist for more complex findings	
Recurrent infections	• Antibiotics as needed for recurrent respiratory infections & recurrent otitis media • Referral to ENT for tympanostomy tubes as needed for recurrent otitis	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
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; H2 = histamine type 2; OT = occupational therapy; PT = physical therapy
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.

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 6 are recommended.

Table 6. *MEF2C*-Related Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Gait abnormalities / Motor abnormalities	Physical medicine, OT/PT assessment of mobility, self-help skills	
Growth/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Gastrointestinal	Monitor for GERD & constipation.	
Neurologic	Assess for new or changing manifestations such as seizures, changes in tone, movement disorders.	At each visit or per treating neurologist
Neurobehavioral/Psychiatric	Behavioral assessment for ASD, hyperkinesis, agitation, self-injury, breathing issues, sleep issues, & high pain tolerance	Annually
Cardiovascular	Assessment by cardiologist	Per cardiologist
Ophthalmologic	Ophthalmology eval for strabismus & refractive errors	Per ophthalmologist
Recurrent infections	• Assess for recurrent respiratory infections &/or recurrent otitis media. • Hearing eval in those w/recurrent otitis	Annually or as needed
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).	At each visit

ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; 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

MEF2C-related disorder 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 *MEF2C*-related disorder whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo MEF2C* pathogenic variant.
- Rarely, a proband diagnosed with *MEF2C*-related disorder has the disorder as the result of an *MEF2C* pathogenic variant inherited from a:
  - Heterozygous parent. Transmission of a *MEF2C* pathogenic variant from an affected parent has been reported in three families. Affected individuals in these families had intellectual disability, seizures, speech impairment, stereotypic movements, and cardiac manifestations [Qiao et al 2017, Lu et al 2018, Yuan et al 2018].
  - Parent with gonadal (or somatic and gonadal) mosaicism. Transmission of an *MEF2C* pathogenic variant from an unaffected mosaic parent to a child with *MEF2C*-related disorder has been reported in two families to date [Wan et al 2021].
- 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.

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 *MEF2C* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *MEF2C* pathogenic variant identified 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 [Wan et al 2021].

Offspring of a proband.

- Each child of an individual with *MEF2C*-related disorder has a 50% chance of inheriting the *MEF2C* pathogenic variant.
- The majority of individuals with *MEF2C*-related disorder are not known to reproduce; however, many are not yet of reproductive age.

Other family members. Given that the majority of individuals with *MEF2C*-related disorder reported to date have the disorder as the result of an *MEF2C* pathogenic variant that occurred *de novo* in the proband or 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 *MEF2C* 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.

- **Simons Searchlight**
  Phone: 855-329-5638
  Gene Guide: MEF2C-Related Syndrome
- **US MEF2C Foundation**
  Phone: 302-899-1706
  Email: info@usmef2cfoundation.org
  usmef2cfoundation.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **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. MEF2C-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MEF2C	5q14.3	Myocyte-specific enhancer factor 2C	MEF2C database	MEF2C	MEF2C

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 MEF2C-Related Disorder (View All in OMIM)

600662	MYOCYTE ENHANCER FACTOR 2C; MEF2C
613443	NEURODEVELOPMENTAL DISORDER WITH HYPOTONIA, STEREOTYPIC HAND MOVEMENTS, AND IMPAIRED LANGUAGE; NEDHSIL

Molecular Pathogenesis

MEF2C encodes myocyte-specific enhancer factor 2C (MEF2C), a member of the MADS family of transcription factors, which regulate hundreds of downstream gene targets during development and adulthood. MEF2C is particularly crucial during embryogenesis, as it plays a role in myogenesis, neural crest formation, anterior heart field development, lymphoid development, neurogenesis, and synaptic formation, among other functions. *MEF2C* haploinsufficiency occurs when *MEF2C* pathogenic variants (including loss of function and missense) produce abnormal gene products that cannot bind DNA targets properly, as shown by functional studies of some variants that cause *MEF2C*-related disorder [Harrington et al 2020]. MEF2C hypofunction in neurons is presumed to underlie most of the symptoms of *MEF2C*-related disorder.

Mechanism of disease causation. Loss of function, haploinsufficiency

***MEF2C*-specific laboratory technical considerations.** In addition to deletions and coding region variants, pathogenic deep intronic variants have been reported [Wright et al 2021, Adrião et al 2022]. Certain genetic testing methods may not be able to detect these variants.

Chapter Notes

Author Notes

Dr Jessica Cooley Coleman (jcoleman@ggc.org) became involved with *MEF2C* research during her doctoral studies by scouring the scientific literature and developing a parent survey to better characterize the disorder. She seeks to remain knowledgeable and involved in *MEF2C* research when possible. She would be happy to communicate with persons who have any questions regarding diagnosis of *MEF2C*-related disorder or other considerations.

Dr Steven A Skinner (sas@ggc.org) would be happy to communicate with persons who have any questions regarding diagnosis of *MEF2C*-related disorder or other considerations. Contact him to inquire about potential clinical evaluations or possibilities for functional evaluation of all *MEF2C* variants of uncertain significance.

Contact Dr Cooley Coleman to inquire about review of *MEF2C* variants of uncertain significance.

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