U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Umair M, Alfadhel M. *EMC10*-Related Neurodevelopmental Disorder. 2023 Jun 15. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

EMC10-Related Neurodevelopmental Disorder

Muhammad Umair, PhD[1] and Majid Alfadhel, MD, MHSc, SSC-Ped, ABHS(CH), FCCMG[2]

Created: June 15, 2023.

Summary

Clinical characteristics

EMC10-related neurodevelopmental disorder (*EMC10*-NDD) is characterized by moderate-to-severe developmental delay and mild-to-severe intellectual disability. Seizures, speech delay, poor weight gain, and growth deficiency are common in individuals with *EMC10*-NDD. Neurobehavioral manifestations, microcephaly, kidney and urinary tract abnormalities (nephrocalcinosis, renal cysts, and hydronephrosis), and upper limb anomalies (cubitus valgus, arachnodactyly, and bilateral fifth digit clinodactyly) have been reported in a few individuals.

Diagnosis/testing

The diagnosis of *EMC10*-NDD is established in a proband by identification of biallelic pathogenic variants in *EMC10* on molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; standard treatments for behavioral manifestations, epilepsy, and renal manifestations; nutritional support for poor weight gain; social work and family support as needed.

Surveillance: Assessment of developmental progress and educational needs, musculoskeletal manifestations, behavioral issues, new seizures or changes in seizures, growth, nutrition, and family needs at each visit. Follow-up labs and imaging for kidney function, nephrocalcinosis, and renal cysts as recommended by nephrologist.

Author Affiliations: 1 Medical Genomics Research Department, King Abdullah International Medical Research Center (KAIMRC), King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS), Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia; Email: umairmu@mngha.med.sa. 2 Genetics and Precision Medicine Department, King Abdullah Specialized Children Hospital (KASCH), King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia; Email: dralfadhelm@gmail.com; fadhelma@mngha.med.sa.

Genetic counseling

EMC10-NDD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *EMC10* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *EMC10* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

EMC10-related neurodevelopmental disorder (*EMC10*-NDD) **should be considered** in probands with the following clinical and imaging findings and family history:

Clinical findings

- Moderate-to-severe developmental delay
- Mild-to-severe intellectual disability
- Behavioral abnormalities and impaired social skills
- Seizures: multifocal, generalized tonic–clonic, and/or febrile
- Poor weight gain and growth deficiency
- Microcephaly (in some individuals)
- Upper limb anomalies: cubitus valgus, arachnodactyly, and fifth finger clinodactyly

Renal imaging findings. Medullary nephrocalcinosis, renal cysts, and hydronephrosis (in some individuals)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *EMC10*-NDD **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *EMC10* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *EMC10* variants of uncertain significance (or of one known *EMC10* pathogenic variant and one *EMC10* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *EMC10*-NDD is indistinguishable from many other neurodevelopmental disorders, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *EMC10*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability (ID) multigene panel** that includes *EMC10* and other genes of interest (see Differential Diagnosis) may 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*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID, 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.

Table 1. Molecular Genetic Testing Used in *EMC10*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
EMC10	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
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.
6. To date, no large intragenic deletions/duplications have been reported in individuals with *EMC10*-NDD.

Clinical Characteristics

Clinical Description

EMC10-related neurodevelopmental disorder (*EMC10*-NDD) is characterized by developmental delay, intellectual disability, and dysmorphic features (long face, pointed chin, nystagmus, crowded teeth). Neurobehavioral manifestations, seizures, growth deficiency, and microcephaly have been reported in some individuals. To date, 30 individuals have been identified with biallelic pathogenic variants in *EMC10* [Umair et al 2020, Shao et al 2021, Haddad-Eid et al 2022, Kaiyrzhanov et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *EMC10*-Related Neurodevelopmental Disorder: Frequency of Select Features

Feature	Proportion of Persons w/Feature	Comment
Developmental delay	29/30	Moderate to severe
Intellectual disability	29/30	Mild to severe
Seizures	13/30	
Poor weight gain / growth deficiency	9/30	

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature	Comment
Microcephaly	4/30	
Nephrocalcinosis	4/30	
Renal cysts	5/30	
Hydronephrosis/hydroureter	3/30	
Dysmorphic facial features	30/30	Long face, pointed chin, nystagmus, crowded teeth

Umair et al [2020], Shao et al [2021], Haddad-Eid et al [2022], Kaiyrzhanov et al [2022]

Developmental delay. Most individuals with *EMC10*-NDD present with developmental delay affecting motor, speech, and cognition. Developmental delays are variable, with disability ranging from moderate to severe. Most affected individuals can walk with or without support, while a few are nonambulatory (3/30). Speech delay was reported in 14 of 30 individuals. Most individuals acquire words or short sentences with speech therapy support, but a significant proportion remain nonverbal and rely on other means of communication.

Intellectual disability. Most individuals with *EMC10*-NDD present with intellectual disability ranging from mild to severe.

Neurobehavioral manifestations. Some individuals have behavioral findings including attention-deficit/hyperactivity disorder, shyness, and impaired social skills.

Epilepsy. The onset of seizures ranges from the neonatal period to childhood. Reported seizure types include subclinical tonic seizures, febrile seizures, multifocal seizures, and generalized tonic-clonic seizures. Seizures have been treated with sodium valproate and carbamazepine. EEG in one affected individual revealed bilateral frontotemporal epileptogenic dysfunction.

Growth deficiency. Most affected individuals had prenatal and postnatal growth deficiency. Although poor weight gain has been reported, feeding issues have not been reported in individuals with *EMC10*-NDD. Microcephaly was reported in four of 25 individuals; however, head circumference was not documented in all of these reports. Congenital microcephaly has been reported. In one individual head circumference was reported to be one standard deviation (SD) below the mean; in a second individual, head circumference was two SDs below the mean. Severe microcephaly has not been reported.

Craniofacial features. Variable dysmorphic facial features have been observed in all affected individuals reported to date, including a long, triangular face, tall forehead, bifrontal narrowing, thick eyebrows, narrow nasal bridge, low columella, short philtrum, and pointed chin.

Kidney and urinary tract abnormalities included nephrocalcinosis (4/30 individuals), renal cysts (5/30), and mild hydronephrosis or hydroureter (3/30). One individual had end-stage kidney disease that required kidney transplantation. To date, the outcome following kidney transplant has not been reported.

Upper limb anomalies observed in some affected individuals include cubitus valgus, arachnodactyly, and bilateral fifth digit clinodactyly.

Neuroimaging. Most affected individuals have abnormal brain MRI findings of variable severity including Chiari I malformation or ectopia, thin corpus callosum, myelination abnormalities, and white matter abnormalities.

Prognosis. It is unknown whether life span in individuals with *EMC10*-NDD is decreased. One reported individual is alive at age 27 years [Shao et al 2021], demonstrating that survival into adulthood is possible. Since

many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

The prevalence of this rare genetic disorder is unknown. To date, the clinical phenotype in 30 individuals from 15 different families has been reported [Umair et al 2020, Shao et al 2021, Haddad-Eid et al 2022, Kaiyrzhanov et al 2022]. Most affected individuals with *EMC10*-NDD are from Saudi Arabia (six affected individuals from four families) [Umair et al 2020, Shao et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *EMC10*.

Differential Diagnosis

The phenotypic features associated with *EMC10*-related neurodevelopmental disorder 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
- Syndromic X-linked intellectual developmental disorders

Management

No clinical practice guidelines for *EMC10*-related neurodevelopmental disorder (*EMC10*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *EMC10*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. *EMC10*-Related Neurodevelopmental 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)
Neurobehavioral/ Psychiatric	Neuropsychiatric eval for behavior concerns incl ADHD & impaired social skills	For persons age >12 mos

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI if not performed at time of diagnosis • EEG if seizures are suspected
Growth/Nutrition	• Measurement of growth parameters • Eval of nutritional status	
Kidneys / Urinary tract	Kidney & urinary tract ultrasound	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *EMC10*-NDD 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.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; *EMC10*-NDD = *EMC10*-related neurodevelopmental disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *EMC10*-Related Neurodevelopmental Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Behavioral manifestations	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]
Growth deficiency / Poor weight gain	Nutritional support as needed	
Renal manifestations	Standard treatments per nephrologist	
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 US; standard recommendations may vary from country to country.

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

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

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

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

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

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

Social/Behavioral Concerns

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 5 are recommended.

Table 5. *EMC10*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Assess developmental progress & educational needs.	At each visit
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Neurobehavioral/ Psychiatric	Behavioral assessment for ADHD & impaired social skills	
Neurologic	Monitor those w/seizures & asses for new seizures as clinically indicated.	
Feeding	• Measurement of growth parameters • Eval of nutritional status	
Renal	Follow-up labs & imaging	Per nephrologist
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

ADHD = attention-deficit/hyperactivity 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

EMC10-related neurodevelopmental disorder (*EMC10*-NDD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *EMC10* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *EMC10* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *EMC10* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *EMC10*-NDD are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *EMC10* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *EMC10* pathogenic variants in the family.

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 carriers or are at risk of being carriers.
- *EMC10* molecular genetic testing for the reproductive partners of known carriers should be considered, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the *EMC10* pathogenic variants have 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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page

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. EMC10-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EMC10	19q13.33	ER membrane protein complex subunit 10	EMC10 @ LOVD	EMC10	EMC10

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 EMC10-Related Neurodevelopmental Disorder (View All in OMIM)

614545	ENDOPLASMIC RETICULUM MEMBRANE PROTEIN COMPLEX, SUBUNIT 10; EMC10
619264	NEURODEVELOPMENTAL DISORDER WITH DYSMORPHIC FACIES AND VARIABLE SEIZURES; NEDDFAS

Molecular Pathogenesis

The endoplasmic reticulum membrane protein complex (EMC) protein family was first identified in yeast as a multiprotein transmembrane complex composed of ten subunits, where it was thought to be responsible for eliminating misfolded membrane proteins [Jonikas et al 2009]. The EMC may facilitate interactions between mitochondria and the endoplasmic reticulum, thus modulating the processing and folding of different proteins [Lahiri et al 2014]. It also plays a key role in the stability of different transmembrane proteins, such as rhodopsin, which has been reported to cause retinal degeneration in *Drosophila* [Xiong et al 2020].

In an in vitro study, endoplasmic reticulum membrane protein complex subunit 10 (EMC10) was suggested as a potential therapeutic target for malignant glioblastoma after being found to exert cell proliferation inhibition,

invasion, angiogenesis in endothelial cells, and cell migration in glioma cell lines [Junes-Gill et al 2014]. In schizophrenia mouse models, reduced Mirta22 (human EMC10 ortholog) levels completely rescued the dendritic deficits and spine formation at the hippocampal pyramidal neurons, thus suggesting a key role in neuronal dendrites and spine development [Xu et al 2013]. Furthermore, studies revealed that *Emc10* knockout mice ($Emc10^{-/-}$) showed abnormal behavior (hyperactivity, abnormal vocalization), abnormal gait, decreased bone mineral content, persistence of hyaloid vascular system, cardiovascular issues (decreased heart rate), deceased corpuscular volume in females, thrombocytopenia, metabolic effects, and infertility phenotypes in males (MGI: 5548589) [Zhou et al 2018].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Dr Muhammad Umair (umairmu@ngha.med.sa) and Professor Majid Alfadhel (fadhelma@mngha.med.sa) are actively involved in clinical research regarding individuals with *EMC10*-related neurodevelopmental disorder (*EMC10*-NDD). They would be happy to communicate with persons who have any questions regarding the diagnosis of *EMC10*-NDD or other considerations.

Contact Dr Muhammad Umair (umairmu@ngha.med.sa) and Professor Majid Alfadhel (fadhelma@mngha.med.sa) to inquire about review of *EMC10* variants of uncertain significance.

Dr Muhammad Umair (umairmu@ngha.med.sa) and Professor Majid Alfadhel (fadhelma@mngha.med.sa) are also interested in hearing from clinicians treating families affected by rare neurodevelopmental disorders in whom no causative variant has been identified through molecular genetic testing.

Acknowledgments

We would like to thank the patients, families, and clinicians who have participated in our previous publications delineating this condition.

We are grateful to the King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard Health Affairs (MNGHA), Kingdom of Saudi Arabia (KSA).

Revision History

- 15 June 2023 (sw) Review posted live
- 15 February 2023 (mu) Original submission

References

Literature Cited

Haddad-Eid E, Gur N, Eid S, Pilowsky-Peleg T, Straussberg R. The phenotype of homozygous EMC10 variant: a new syndrome with intellectual disability and language impairment. Eur J Paediatr Neurol. 2022;37:56–61. PubMed PMID: 35124540.

Jonikas MC, Collins SR, Denic V, Oh E, Quan EM, Schmid V, Weibezahn J, Schwappach B, Walter P, Weissman JS, Schuldiner M. Comprehensive characterization of genes required for protein folding in the endoplasmic reticulum. Science. 2009;323:1693–7. PubMed PMID: 19325107.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A,

Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Junes-Gill KS, Lawrence CE, Wheeler CJ, Cordner R, Gill TG, Mar V, Shiri L, Basile LA. Human hematopoietic signal peptide-containing secreted 1 (hHSS1) modulates genes and pathways in glioma: implications for the regulation of tumorigenicity and angiogenesis. BMC Cancer. 2014;14:920. PubMed PMID: 25481245.

Kaiyrzhanov R, Rocca C, Suri M, Gulieva S, Zaki MS, Henig NZ, Siquier K, Guliyeva U, Mounir SM, Marom D, Allahverdiyeva A, Megahed H, van Bokhoven H, Cantagrel V, Rad A, Pourkeramti A, Dehghani B, Shao DD, Markus-Bustani K, Sofrin-Drucker E, Orenstein N, Salayev K, Arrigoni F, Houlden H, Maroofian R. Biallelic loss of EMC10 leads to mild to severe intellectual disability. Ann Clin Transl Neurol. 2022;9:1080–9. PubMed PMID: 35684946.

Lahiri S, Chao JT, Tavassoli S, Wong AK, Choudhary V, Young BP, Loewen CJ, Prinz WA. A conserved endoplasmic reticulum membrane protein complex (EMC) facilitates phospholipid transfer from the ER to mitochondria. PLoS Biol. 2014;12:e1001969. PubMed PMID: 25313861.

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

Shao DD, Straussberg R, Ahmed H, Khan A, Tian S, Hill RS, Smith RS, Majmundar AJ, Ameziane N, Neil JE, Yang E, Al Tenaiji A, Jamuar SS, Schlaeger TM, Al-Saffar M, Hovel I, Al-Shamsi A, Basel-Salmon L, Amir AZ, Rento LM, Lim JY, Ganesan I, Shril S, Evrony G, Barkovich AJ, Bauer P, Hildebrandt F, Dong M, Borck G, Beetz C, Al-Gazali L, Eyaid W, Walsh CA. A recurrent, homozygous EMC10 frameshift variant is associated with a syndrome of developmental delay with variable seizures and dysmorphic features. Genet Med. 2021;23:1158–62. PubMed PMID: 33531666.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Umair M, Ballow M, Asiri A, Alyafee Y, Al Tuwaijri A, Alhamoudi KM, Aloraini T, Abdelhakim M, Althagafi AT, Kafkas S, Alsubaie L, Alrifai MT, Hoehndorf R, Alfares A, Alfadhel M. EMC10 homozygous variant identified in a family with global developmental delay, mild intellectual disability, and speech delay. Clin Genet. 2020;98:555–61. PubMed PMID: 32869858.

Xiong L, Zhang L, Yang Y, Li N, Lai W, Wang F, Zhu X, Wang T. ER complex proteins are required for rhodopsin biosynthesis and photoreceptor survival in drosophila and mice. Cell Death Differ. 2020;27:646–61. PubMed PMID: 31263175.

Xu B, Hsu PK, Stark KL, Karayiorgou M, Gogos JA. Derepression of a neuronal inhibitor due to miRNA dysregulation in a schizophrenia-related microdeletion. Cell. 2013;152:262–75. PubMed PMID: 23332760.

Zhou Y, Wu F, Zhang M, Xiong Z, Yin Q, Ru Y, Shi H, Li J, Mao S, Li Y, Cao X, Hu R, Liew CW, Ding Q, Wang X, Zhang Y. EMC10 governs male fertility via maintaining sperm ion balance. J Mol Cell Biol. 2018;10:503–14. PubMed PMID: 29659949.

License