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SLC12A5-Related Epilepsy of Infancy with Migrating Focal Seizures

Synonyms: Early-Infantile Epileptic Encephalopathy 34 (EIEE34), *SLC12A5*-EIMFS

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Summary

Clinical characteristics

SLC12A5-related epilepsy of infancy with migrating focal seizures (*SLC12A5*-EIMFS), reported to date in nine children, is characterized by onset of seizures before age six months and either developmental delay or developmental regression with seizure onset. Of these nine children, six had severe developmental delay with no progress of abilities and three made notable neurodevelopmental progress. Eight had postnatal microcephaly and hypotonia. In most children epilepsy begins as focal motor seizures (typically involving head and eye deviation) that become multifocal and intractable to conventional anti-seizure medication (ASM).

Diagnosis/testing

The diagnosis of *SLC12A5*-EIMFS is established by identification of biallelic *SLC12A5* pathogenic variants on molecular genetic testing.

Management

Treatment of manifestations: There are no specific treatments for seizures in *SLC12A5*-EIMFS. In general, seizures in EIMFS are resistant to most ASM. A ketogenic diet and potassium bromide showed attenuation of seizures in three patients each. A multidisciplinary approach to management of hypotonia, feeding difficulties, respiratory problems, and developmental delay is recommended.

Surveillance: Routine monitoring of: feeding, nutritional status, swallowing, gastroesophageal reflux, aspiration, and respiratory problems; back for scoliosis and hips for dislocation with spine and hip x-rays; effectiveness of seizure control; development including motor skills, speech/language, and general cognitive and vocational skills.

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Genetic counseling

SLC12A5-EIMFS is inherited in an autosomal recessive manner. The parents of a child with *SLC12A5*-EIMFS are typically heterozygotes (i.e., carriers of one *SLC12A5* pathogenic variant). Heterozygous parents of a child with *SLC12A5*-EIMFS are not at risk of developing EIMFS. When both parents are heterozygotes (carriers) each sib of an affected individual has 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 *SLC12A5* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Since 2010 a description of the characteristic symptoms and findings of epilepsy of infancy with migrating focal seizures (EIMFS) has been included in the classification of epilepsy syndromes by the International League Against Epilepsy. The diagnosis of *SLC12A5*-EIMFS is established by molecular genetic testing.

Suggestive Findings

SLC12A5-related epilepsy of infancy with migrating focal seizures (*SLC12A5*-EIMFS) **should be considered** in children with the following epilepsy and electroencephalogram (EEG) findings and family history.

Epilepsy features

- Seizure onset before age six months
- Developmental delay or developmental regression with seizure onset

Seizure type

- At onset in most children: focal motor seizures that also frequently involve head and eye deviation
- Multifocal seizures proving intractable to conventional anti-seizure medication

Epilepsy syndromes. Epilepsy of infancy with migrating focal seizures

EEG findings

- Interictal multifocal spikes
- In a single seizure, ictal-independent, unilateral, and migrating involvement of varying cortical areas with clinical-EEG correlation
- Initial EEG may be normal shortly after seizure onset, but epileptiform abnormalities are usually present within one month after first presentation.
- Migrating ictal foci may not be seen for several months after presentation.

Family history. Consistent with autosomal recessive inheritance, including parental consanguinity or more than one affected child

Establishing the Diagnosis

The diagnosis of *SLC12A5*-EIMFS **is established** in a proband with biallelic *SLC12A5* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1).

Note: 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.

Due to the genetic heterogeneity of early-onset epilepsy, use of either a multigene epilepsy panel or comprehensive genomic testing (exome or genome sequencing) is the preferred initial approach [McTague et al 2016]. Note: Single-gene testing (sequence analysis of *SLC12A5*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Testing Options to Consider

An epilepsy multigene panel that includes *SLC12A5* and other genes of interest (see Differential Diagnosis) typically provides the best opportunity to identify the genetic cause of the condition while limiting identification of 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 *SLC12A5*-related epilepsy, some epilepsy panels may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 *SLC12A5*-EIMFS

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC12A5	Sequence analysis [3]	9/9 (100%) [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown (no data available)

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Stödberg et al [2015], Saitsu et al [2016], Saito et al [2017]
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.

Clinical Characteristics

Clinical Description

SLC12A5-related epilepsy of infancy with migrating focal seizures (*SLC12A5*-EIMFS) is characterized by severe early-onset epileptic encephalopathy, with a distinct electroclinical phenotype that is common to all EIMFS

regardless of cause. To date nine children have been reported with *SLC12A5*-EIMFS [Stödberg et al 2015, Saitsu et al 2016, Saito et al 2017].

Seizures. In the nine children reported, three clinical stages were evident:

- An **early stage** with emerging focal seizures. Median age of seizure onset was 1.5 months; mean age 1.8 months (range: 1 day - 4 months).
  - Seizures are characterized by apnea and focal clonic and tonic seizures with prominent head and eye deviation.
  - Subtle seizures with behavioral arrest, apnea, and cyanosis or generalized tonic or tonic-clonic seizures are also seen at onset. All children eventually develop focal motor seizures.
  - Clinically migrating seizures (which affect differing or alternating body parts) are seen in approximately 50% of children.
  - Autonomic features such as facial flushing, salivation, apnea, and cyanosis are common.
- A **second stage** with up to 200 seizures per day at the peak of the seizures, usually at a median age of 16 weeks (range: 1-40 weeks). Either focal status epilepticus or frequent clusters of focal seizures are seen.
- A **late stage** (age >1-2 years) with a reduction of seizure frequency. Of the four children who had seizure-free periods, two relapsed to frequent recurrent seizures.

Developmental delay was seen in all nine children. Five children experienced developmental regression (i.e., loss of previously acquired skills) at seizure onset.

Severe developmental delay with no progression of skills was seen in six of the nine. In contrast, three of the nine had notable neurodevelopmental progress, either regaining lost skills or acquiring new skills during periods of good seizure control. Two achieved independent ambulation (at ages 2.9 and 4 years) and one spoke single words at age six years.

Other

- Postnatal (i.e., acquired) microcephaly and hypotonia was noted in eight of the nine children.
- Of the four for whom feeding information was available, two had feeding difficulties; none had growth failure.
- One had unilateral pyramidal signs.
- Hyperkinetic movement disorders, seen in other causes of EIMFS including *KCNT1* and *SCN2A*, have not been reported in *SLC12A5*-EIMFS [Howell et al 2015, McTague et al 2018].

Outcome. One child with frequent seizures died at age 2.5 years from respiratory infection and cardiac arrest [Stödberg et al 2015]; the others with *SLC12A5*-EIMFS (ages 3-22 years) are living as of this writing.

Electroencephalogram (EEG). Eight children had ictal EEGs consistent with a diagnosis of EIMFS. Early EEGs were not available for one child; thus, a formal diagnosis could not be made despite a clinical history consistent with EIMFS.

Interictal EEG features included background slowing and multifocal abnormalities.

MRI findings. The following nonspecific MRI features of EIMFS have been observed in *SLC12A5*-EIMFS:

- Delayed myelination
- Thin corpus callosum
- Cerebral atrophy, either predominantly frontal or global
- Increased signal in white matter on diffusion-weighted imaging

The following focal abnormalities have been reported in *SLC12A5*-EIMFS:

- Unilateral hippocampal sclerosis noted at age four years (n=1) [Saito et al 2017]
- Cerebellar atrophy and bilateral hippocampal atrophy with increased signal on FLAIR imaging at ages ten and 20 years in the oldest individual imaged to date [Saitsu et al 2016]. It is unclear if these findings represent the typical progression of imaging findings in *SLC12A5*-EIMFS as all other individuals imaged were age four years or younger.

Magnetic resonance spectroscopy (MRS) in a child age eight months demonstrated reduction in the relative N-acetyl aspartate peak, consistent with delayed maturation of myelin [Stödberg et al 2015].

Genotype-Phenotype Correlations

No clear correlation exists between biallelic *SLC12A5* variants and phenotype, which may reflect the limited number of affected individuals reported to date.

Nomenclature

EIMFS is a type of early-infantile epileptic encephalopathy (EIEE); OMIM classifies *SLC12A5*-related epilepsy as EIEE34.

Terms previously used for EIMFS include the following:

- Migrating partial seizures of infancy (MPSI)
- Malignant migrating partial seizures of infancy (MMPSI)
- Migrating focal seizures of infancy (MFSI)

SLC12A5-related epilepsy includes EIMFS and EIMFS-like severe early-onset epileptic encephalopathy (EIEE with some features of EIMFS but not fulfilling all criteria; e.g., when EEG is not available).

Prevalence

To date, nine probands with *SLC12A5*-related epilepsy have been reported.

The clinical syndrome epilepsy of infancy with migrating focal seizures (EIMFS) of all causes is itself rare. Prevalence of EIMFS was estimated at 0.11 per 100,000 children in the UK (using data that were not from a population-based epidemiologic study) [McTague et al 2013].

Genetically Related (Allelic) Disorders

Heterozygous (carrier) parents of a child with *SLC12A5*-related epilepsy – when tested – were unaffected. Although *SLC12A5* pathogenic variants associated with EIMFS in general have not been associated with epilepsy in the heterozygous state, two possible exceptions are the following:

- **Possible association with febrile seizures.** The *SLC12A5* p.Arg952His variant was identified in an extended kindred with infrequent febrile seizures (1–3 episodes on average) occurring between ages 12 months and 2.5 years. Only three of four affected family members could be tested for the variant [Puskarjov et al 2014]. Although the mean allele frequency in gnomAD in all populations is 0.003090, in South Asian populations the mean allele frequency is 0.01934. In addition, in gnomAD 13 unaffected individuals are identified as homozygous for this variant. Therefore, additional studies are needed to determine if heterozygous variants in *SLC12A5* are associated with febrile seizures.
- **Possible association with idiopathic generalized epilepsy.** While the rare *SLC12A5* variants p.Arg952His and p.Arg1049Cys were observed in controls, they were also enriched in a cohort of individuals with idiopathic generalized epilepsy (IGE) characterized by generalized tonic-clonic, myoclonic, and absence seizures [Kahle et al 2014]. Seizure onset was between 14 and 21 years. However, data are limited;

additional studies are needed to determine if heterozygous variants in *SLC12A5* are associated with idiopathic generalized epilepsy.

Differential Diagnosis

Since first described by Coppola et al [1995], epilepsy of infancy with migrating focal seizures (EIMFS) has been reported in over 170 individuals. EIMFS is genetically heterogeneous (Table 2). EIMFS can be isolated or have multisystem involvement; both autosomal dominant and recessive inheritance are observed.

Table 2. Other Disorders to Consider in the Differential Diagnosis of *SLC12A5*-EIMFS

Disorder	Gene [1]	MOI	Comments
Isolated EIMFS			
EIEE43 (OMIM 617113)	*GABRB3* [2]	AD	1 set of monozygotic twins
EIEE14 (OMIM 614959)	*KCNT1*	AD [3]	Causes 30%-50% of EIMFS [4, 5, 6]
EIEE12 (OMIM 613722)	*PLCB1* [7]	AR [8]	1 individual [7]
Progressive microcephaly w/seizures & cerebral & cerebellar atrophy (OMIM 615760)	*QARS*	AR [8]	2 individuals [9]
SMC1A-related EIMFS	*SMC1A* [10]	XL	1 female infant
EIEE6	*SCN1A* [11, 12, 13, 14]	AD [3]	3 individuals [11, 12, 13, 14]
EIEE11 (OMIM 613721)	*SCN2A* [15, 16]	AD [3]	Severe movement disorder [4]; otherwise indistinguishable from other causes of EIMFS
EIEE13	*SCN8A* [17]	AD [3]	1 individual [17]
EIEE3 (OMIM 609304)	*SLC25A22* [18]	AR [8]	2 individuals [18]
EIEE16	*TBC1D24* [19, 20]	AR [8]	3 families [19, 20]
EIMFS with multisystem abnormalities			

Table 2. continued from previous page.

Disorder	Gene [1]	MOI	Comments
ALG3-CDG (*CDG-Id*) [21]	*ALG* [22]	AR	• Abnormalities: gastrointestinal problems, coagulopathy, dysmorphic facial features, spastic quadriparesis • Transferrin isoelectric focusing testing consistent w/CDG type I • On brain MRI: cerebellar atrophy in all; brain stem atrophy in 3/4 • Note: Extensive metabolic investigation in EIMFS is usually unrevealing.
ALG1-CDG (*CDG-Ik*) [21]	*ALG1* [22]		
RFT1-CDG (*CDG-In*) [21]	*RFT1* [22]		

Adapted from "Supplementary Table 1: Genes Reported in Migrating Partial Seizures of Infancy (MPSI)" [Stödberg et al 2015]
AD = autosomal dominant; AR = autosomal recessive; CDG = congenital disorder of glycosylation; EIEE = early-infantile epileptic encephalopathy; EIMFS = epilepsy of infancy with migrating focal seizures; MOI = mode of inheritance; XL = X-linked
1. Genes are in alphabetic order.
2. Štěrbová et al [2018]
3. Typically *de novo*
4. Barcia et al [2012]
5. Møller et al [2015]
6. Lim et al [2016]
7. Poduri et al [2012], Poduri et al [2013]
8. Autosomal recessive inheritance of EIMFS is often described in consanguineous families or families with more than one affected individual.
9. Zhang et al [2014]
10. Gorman et al [2017]
11. Carranza Rojo et al [2011]
12. Howell et al [2015]
13. Larsen et al [2015]
14. Freilich et al [2011]
15. Howell et al [2015]
16. Wolff et al [2017]
17. Ohba et al [2014]
18. Poduri et al [2013]
19. Milh et al [2013]
20. See *TBC1D24*-Related Disorders.
21. See Congential Disorders of N-Linked Glycosylation and Multiple Pathway Overview.
22. Barba et al [2016]

Other early-infantile epileptic encephalopathies. A large number of genes have been implicated in the broader phenotype of early-onset epilepsy with developmental delay. See Early Infantile Epileptic Encephalopathy, OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SLC12A5*-related epilepsy of infancy with migrating focal seizures (*SLC12A5*-EIMFS), 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 *SLC12A5*-EIMFS

System/Concern	Evaluation	Comment
Constitutional	Assess for evidence of failure to thrive.	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval incl assessment of vision	
ENT/Mouth	Assess hearing.	
Gastrointestinal/ Feeding	Assess swallowing, gastroesophageal reflux, feeding, & nutritional status.	Incl assessment by speech & language therapist.
Respiratory	Assess respiratory status for evidence of ↑ risk of respiratory infections & aspiration.	Preventive measures may be needed (e.g., flu vaccination & prophylactic antibiotics in winter).
Neurologic	Neurologic eval	Incl EEG & brain MRI.
Musculoskeletal	Assessment of tone by pediatric rehab specialist &/or PT	
Development	Developmental assessment	Incl eval of motor skills, speech/ language, general cognitive, & vocational skills.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

PT = physical therapist

Treatment of Manifestations

Seizures. There are no specific treatments for seizures in *SLC12A5*-EIMFS. Seizures in EIMFS are generally resistant to most anti-seizure medication.

Periods free of seizures or with reduced seizure frequency have been achieved with a ketogenic diet or potassium bromides [Fasulo et al 2012, Ünver et al 2013, Caraballo et al 2014, Caraballo et al 2015] including in children with *SLC12A5*-EIMFS [Stödberg et al 2015, Saitsu et al 2016, Saito et al 2017].

Seizure reduction has also been reported with:

- Levetiracetam, rufinamide, stiripentol, and clonazepam [Coppola et al 1995, Cilio et al 2009, Djuric et al 2011, Vendrame et al 2011, Merdariu et al 2013];
- Cannabinoids [Saade & Joshi 2015].

Epileptic apneas are reported to respond to acetazolamide [Irahara et al 2011].

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

Hypotonia. Manage postural problems with appropriate seating support.

Feeding. Consider gastrostomy insertion and feeding if swallowing is impaired.

Respiratory. Children may be susceptible to respiratory infections and aspiration pneumonia if swallowing is impaired. Consider influenza vaccine, prophylactic antibiotics, and chest physiotherapy as appropriate.

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. In the US, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion of transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a 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 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.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy, typically from an occupational or speech therapist is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

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 is 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

Routine monitoring of:

- Feeding, nutritional status, swallowing abilities, gastroesophageal reflux, risk of aspiration pneumonia / respiratory infection
- Postural problems (resulting from such complications as scoliosis and hip abnormalities) with regular spine and hip x-rays
- Effectiveness of seizure control
- Development including motor skills, speech/language, and general cognitive and vocational skills

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

SLC12A5-related epilepsy of infancy with migrating focal seizures (*SLC12A5*-EIMFS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a child with *SLC12A5*-EIMFS are typically heterozygotes (i.e., carriers of one *SLC12A5* pathogenic variant). In a one family reported to date, a compound heterozygous proband was found to have one maternally inherited *SLC12A5* pathogenic variant and one *de novo* variant (the father was not a carrier of an *SLC12A5* pathogenic variant) [Saito et al 2017].
- Heterozygous parents of a child with *SLC12A5*-EIMFS are not at risk of developing EIMFS. (*SLC12A5* pathogenic variants associated with EIMFS have not been associated with epilepsy in the heterozygous state; see Genetically Related Disorders).

Sibs of a proband

- At conception, each sib of an affected individual has 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) of an EIMFS-related *SLC12A5* pathogenic variant are not at risk of developing EIMFS.

Offspring of a proband

- Each child of an individual with *SLC12A5*-EIMFS has a 50% chance of inheriting the *SLC12A5* pathogenic variant.
- To date, individuals with biallelic *SLC12A5*-EIMFS 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 *SLC12A5* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC12A5* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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 and young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC12A5* 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 Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Contact - For Families with Disabled Children**
  United Kingdom
  Phone: 0808 808 3555 (toll free); 020 7608 8700
  Email: helpline@cafamily.org.uk
  www.contact.org.uk
- **Epilepsy Action**
  New Anstey House
  Gate Way Drive

Yeadon Leeds LS19 7XY
United Kingdom
Phone: 0808 800 5050
Email: epilepsy@epilepsy.org.uk
www.epilepsy.org.uk

- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  epilepsy.ca
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Epilepsy and Seizures

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. SLC12A5-Related Epilepsy of Infancy with Migrating Focal Seizures: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SLC12A5	20q13.12	Solute carrier family 12 member 5	SLC12A5	SLC12A5

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 SLC12A5-Related Epilepsy of Infancy with Migrating Focal Seizures (View All in OMIM)

606726	SOLUTE CARRIER FAMILY 12 (POTASSIUM/CHLORIDE TRANSPORTER), MEMBER 5; SLC12A5
616645	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 34; DEE34

Molecular Pathogenesis

SLC12A5 encodes KCC2, the neuronal-specific potassium chloride cotransporter which is a member of the family of cation chloride cotransporters [Payne et al 1996]. KCC2 is mainly expressed in the central nervous system [Chamma et al 2012].

KCC2 is the major extruder of chloride in neurons and is responsible for generating neuronal chloride gradients, which determine the magnitude and polarity of GABA-mediated currents. Thus, when GABA, which has an important role in neuronal inhibition, binds to the GABA-A receptor, the low intraneuronal chloride allows influx of chloride and subsequent hyperpolarization, contributing to neuronal inhibition. KCC2 has been implicated as the major factor in the developmental $GABA_A$ shift from excitation to inhibition seen in early postnatal life in animal models and is vital to normal brain development [Chamma et al 2012].

Gene structure. *SLC12A5* has two major neuron-specific isoforms, KCC2a (corresponding to transcript variant 1, NM_001134771) and the shorter KCC2b (transcript variant 2, NM_020708) [Uvarov et al 2007, 2009], both

containing 26 exons. KCC2a differs from KCC2b by 40 unique amino acids in the N terminus encoded by alternate exon 1a.

Pathogenic variants. Pathogenic variants identified to date are mostly missense variants; however, a few splice site and in-frame variants have been reported.

Table 4. Selected *SLC12A5* Pathogenic Variants

DNA Nucleotide Change (See footnote 1.)	Predicted Protein Change (See footnote 1.)	Reference Sequences
c.279+1G>C	p.Glu50_Gln93del	NM_020708.4 NP_065759
c.572C>T	p.Arg191Val	
c.863T>A (c.932T>A)	p.Leu288His (p.Leu311His)	
c.953G>C	p.Trp318Ser	
c.967T>C	p.Ser323Pro	
c.1127C>T (c.1196C>T)	p.Ser376Leu (p.Ser399Leu)	
c.1208T>C (c.1277T>C)	p.Leu403Pro (p.Leu426Pro)	
c.1243A>G	p.Met415Val	
c.1583G>A (c.1652G>A)	p.Gly528Asp (p.Gly551Asp)	
c.2242_2244del	p.Ser748del	
c.2570G>T (c.2639G>T)	p.Arg857Leu (p.Arg880Leu)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Shown in ( )s: variant designations as published on reference sequence position NM_001134771.1, NP_001128243.1

Normal gene product. *SLC12A5* encodes KCC2, the neuronal-specific potassium chloride cotransporter, a member of the family of cation chloride cotransporters [Payne et al 1996]. KCC2 is mainly expressed in the central nervous system [Chamma et al 2012]. The two major *SLC12A5* transcripts KCC2a (corresponding to NM_001134771) and KCC2b (NM_020708) comprise 26 exons and are translated into 1,139 and 1,116 amino acids, respectively.

KCC2 also plays a role at excitatory synapses and in dendritic spine formation [Chamma et al 2012, Puskarjov et al 2014]. Further evidence for the role of KCC2 in epileptogenesis comes from animal models of acquired epilepsy in which reduced KCC2 expression is seen following status epilepticus, and from human studies in which tumor-associated epilepsy is associated with alterations in KCC2 expression [Pallud et al 2014, Moore et al 2017].

Abnormal gene product. *SLC12A5* pathogenic variants have been shown in several studies to be associated with a loss of transporter function in cellular models [Stödberg et al 2015, Saitsu et al 2016].

The variants p.Arg952His and p.Arg1049Cys have also been studied for pathogenic effects. (See Genetically Related Disorders.)

The p.Arg952His variant was shown to have reduced cell surface expression and reduced chloride extrusion capacity compared to wild type KCC2 [Kahle et al 2014, Puskarjov et al 2014]. In addition, p.Arg952His led to reduced dendritic spine formation in vitro, which could be rescued by overexpression of wild type KCC2.

The p.Arg1049Cys variant was shown to have decreased chloride extrusion ability [Kahle et al 2014].

Both p.Arg952His and p.Arg1049Cys were also shown to have decreased phosphorylation at serine 940, a key site for the regulation of KCC2 function [Kahle et al 2014].

Complete knockout of *SLC12A5* in animal models leads to neonatal death due to respiratory failure, and knockout of the KCC2b isoform only leads to spontaneous seizures and early postnatal mortality [Hübner et al 2001, Woo et al 2002, Tornberg et al 2005].

Chapter Notes

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References

Literature Cited

Barba C, Darra F, Cusmai R, Procopio E, Dionisi Vici C, Keldermans L, Vuillaumier-Barrot S, Lefeber DJ, Guerrini R, Parrini E, Ashikov A, Bordugo A, Cantalupo G, Casara G, Bernardina BD, Falchi M, Ferri L, Martinelli D, Morrone A, Race V, Rosati A, Souche E. Congenital disorders of glycosylation presenting as epileptic encephalopathy with migrating partial seizures in infancy. Dev Med Child Neurol. 2016;58:1085–91. PubMed PMID: 27172925.

Barcia G, Fleming M. R, Deligniere A, Gazula VR, Brown MR, Langouet M, Chen H, Kronengold J, Abhyankar A, Cilio R, Nitschke P, Kaminska A, Boddaert N, Casanova JL, Desguerre I, Munnich A, Dulac O, Kaczmarek LK, Colleaux L, Nabbout R. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet. 2012;44:1255–9. PubMed PMID: 23086397.

Caraballo R, Noli D, Cachia P. Epilepsy of infancy with migrating focal seizures: three patients treated with the ketogenic diet. Epileptic Disord. 2015;17:194–7. PubMed PMID: 25895661.

Caraballo R, Pasteris MC, Fortini PS, Portuondo E. Epilepsy of infancy with migrating focal seizures: six patients treated with bromide. Seizure. 2014;23:899–902. PubMed PMID: 25044045.

Carranza Rojo D, Hamiwka L, McMahon JM, Dibbens LM, Arsov T, Suls A, Stödberg T, Kelley K, Wirrell E, Appleton B, MacKay M, Freeman JL, Yendle SC, Berkovic SF, Bienvenu T, De Jonghe P, Thorburn DR, Mulley JC, Mefford HC, Scheffer IE. De novo SCN1A mutations in migrating partial seizures of infancy. Neurology. 2011;77:380–3. PubMed PMID: 21753172.

Chamma I, Chevy Q, Poncer JC, Lévi S. Role of the neuronal K-Cl co-transporter KCC2 in inhibitory and excitatory neurotransmission. Front Cell Neurosci. 2012;6:5. PubMed PMID: 22363264.

Cilio MR, Bianchi R, Balestri M, Onofri A, Giovannini S, Di Capua M, Vigevano F. Intravenous levetiracetam terminates refractory status epilepticus in two patients with migrating partial seizures in infancy. Epilepsy Res. 2009;86:66–71. PubMed PMID: 19520548.

Coppola G, Plouin P, Chiron C, Robain O, Dulac O. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. Epilepsia. 1995;36:1017–24. PubMed PMID: 7555952.

Djuric M, Kravljanac R, Kovacevic G, Martic J. The efficacy of bromides, stiripentol and levetiracetam in two patients with malignant migrating partial seizures in infancy. Epileptic Disord. 2011;13:22–6. PubMed PMID: 21393091.

Fasulo L, Saucedo S, Cáceres L, Solis S, Caraballo R. Migrating focal seizures during infancy: a case report and pathologic study. Pediatr Neurol. 2012;46:182–4. PubMed PMID: 22353295.

Freilich ER, Jones JM, Gaillard WD, Conry JA, Tsuchida TN, Reyes C, Dib-Hajj S, Waxman SG, Meisler MH, Pearl PL. Novel SCN1A mutation in a proband with malignant migrating partial seizures of infancy. Arch Neurol. 2011;68:665–71. PubMed PMID: 21555645.

Gorman KM, Forman E, Conroy J, Allen NM, Shahwan A, Lynch SA, Ennis S, King MD. Novel SMC1A variant and epilepsy of infancy with migrating focal seizures: expansion of the phenotype. Epilepsia. 2017;58:1301–2. PubMed PMID: 28677859.

Howell KB, McMahon JM, Carvill GL, Tambunan D, Mackay MT, Rodriguez-Casero V, Webster R, Clark D, Freeman JL, Calvert S, Olson HE, Mandelstam S, Poduri A, Mefford HC, Harvey AS, Scheffer IE. SCN2A encephalopathy: a major cause of epilepsy of infancy with migrating focal seizures. Neurology. 2015;85:958–66. PubMed PMID: 26291284.

Hübner CA, Stein V, Hermans-Borgmeyer I, Meyer T, Ballanyi K, Jentsch TJ. Disruption of KCC2 reveals an essential role of K-Cl cotransport already in early synaptic inhibition. Neuron. 2001;30:515–24. PubMed PMID: 11395011.

Irahara K, Saito Y, Sugai K, Nakagawa E, Saito T, Komaki H, Nabatame S, Kaneko Y, Hotate M, Sasaki M. Effects of acetazolamide on epileptic apnea in migrating partial seizures in infancy. Epilepsy Res. 2011;96:185–9. PubMed PMID: 21636251.

Kahle KT, Merner ND, Friedel P, Silayeva L, Liang B, Khanna A, Shang Y, Lachance-Touchette P, Bourassa C, Levert A, Dion P, Walcott B, Spiegelman D, Dionne-Laporte A, Hodgkinson A, Awadalla P, Nikbakht H, Majewski J, Cossette P, Deeb TZ, Moss SJ, Medina I, Rouleau G. Genetically encoded impairment of neuronal KCC2 cotransporter function in human idiopathic generalized epilepsy. EMBO Rep. 2014;15:766–74. PubMed PMID: 24928908.

Larsen J, Carvill GL, Depienne C, Brilstra E, Erik J, Nielsen K, Goldman R, Jepsen B, McMahon JM, Koeleman B, Harris M. The phenotypic spectrum of SCN8A encephalopathy. Neurology. 2015;84:480–9. PubMed PMID: 25568300.

Lim CX, Ricos MG, Dibbens LM, Heron SE. KCNT1 mutations in seizure disorders: the phenotypic spectrum and functional effects. J Med Genet. 2016;53:217–25. PubMed PMID: 26740507.

McTague A, Appleton R, Avula S, Cross JH, King MD, Jacques TS, Bhate S, Cronin A, Curran A, Desurkar A, Farrell MA, Hughes E, Jefferson R, Lascelles K, Livingston J, Meyer E, McLellan A, Poduri A, Scheffer IE, Spinty S, Kurian MA, Kneen R. Migrating partial seizures of infancy: expansion of the electroclinical, radiological and pathological disease spectrum. Brain. 2013;136:1578–91. PubMed PMID: 23599387.

McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol. 2016;15:304–16. PubMed PMID: 26597089.

McTague A, Nair U, Malhotra S, Meyer E, Trump N, Gazina EV, Papandreou A, Ngoh A, Ackermann S, Ambegaonkar G, Appleton R, Desurkar A, Eltze C, Kneen R, Kumar AV, Lascelles K, Montgomery T, Ramesh V, Samanta R, Scott RH, Tan J, Whitehouse W, Poduri A, Scheffer IE, Chong WK, Cross JH, Topf M, Petrou S, Kurian MA. Clinical and molecular characterisation of KCNT1-related severe early onset epilepsy. Neurology. 2018;90:e55–e66. PubMed PMID: 29196579.

Merdariu D, Delanoë C, Mahfoufi N, Bellavoine V, Auvin S. Malignant migrating partial seizures of infancy controlled by stiripentol and clonazepam. Brain Dev. 2013;35:177–80. PubMed PMID: 22521903.

Milh M, Falace A, Villeneuve N, Vanni N, Cacciagli P, Assereto S, Nabbout R, Benfenati F, Zara F, Chabrol B, Villard L, Fassio A. Novel compound heterozygous mutations in TBC1D24 cause familial malignant migrating partial seizures of infancy. Hum Mut. 2013;34:869–72. PubMed PMID: 23526554.

Møller RS, Heron SE, Larsen LHG, Lim CX, Ricos MG, Bayly MA, van Kempen MJA, Klinkenberg S, Andrews I, Kelley K, Ronen GM, Callen D, McMahon JM, Yendle SC, Carvill GL, Mefford HC, Nabbout R, Poduri A, Striano P, Baglietto MG, Zara F, Smith NJ, Pridmore C, Gardella E, Nikanorova M, Dahl HA, Gellert P, Scheffer IE, Gunning B, Kragh-Olsen B, Dibbens LM. Mutations in KCNT1 cause a spectrum of focal epilepsies. Epilepsia. 2015;56:e114–20. PubMed PMID: 26122718.

Moore YE, Kelley MR, Brandon NJ, Deeb TZ, Moss SJ. Seizing control of KCC2: a new therapeutic target for epilepsy. Trends Neurosci. 2017;40:555–71. PubMed PMID: 28803659.

Ohba C, Kato M, Takahashi S, Lerman-Sagie T, Lev D, Terashima H, Kubota M, Kawawaki H, Matsufuji M, Kojima Y, Tateno A, Goldberg-Stern H, Straussberg R, Marom D, Leshinsky-Silver E, Nakashima M, Nishiyama K, Tsurusaki Y, Miyake N, Tanaka F, Matsumoto N, Saitsu H. Early onset epileptic encephalopathy caused by de novo SCN8A mutations. Epilepsia. 2014;55:994–1000. PubMed PMID: 24888894.

Pallud J, Le Van Quyen M, Bielle F, Pellegrino C, Varlet P, Labussiere M, Cresto N, Dieme MJ, Baulac M, Duyckaerts C, Kourdougli N, Chazal G, Devaux B, Rivera C, Miles R, Capelle L, Huberfeld G. Cortical GABAergic excitation contributes to epileptic activities around human glioma. Sci Transl Med. 2014;6:244ra89.

Payne JA, Stevenson TJ, Donaldson LF. Molecular characterization of a putative K-Cl cotransporter in rat brain: a neuronal-specific isoform. J Biol Chem. 1996;271:16245–52. PubMed PMID: 8663311.

Poduri A, Chopra SS, Neilan EG, Christina Elhosary P, Kurian MA, Meyer E, Barry BJ, Khwaja OS, Salih MA, Stödberg T, Scheffer IE, Maher ER, Sahin M, Wu BL, Berry GT, Walsh CA, Picker J, Kothare SV. Homozygous PLCB1 deletion associated with malignant migrating partial seizures in infancy. Epilepsia. 2012;53:e146–150. PubMed PMID: 22690784.

Poduri A, Heinzen EL, Chitsazzadeh V, Lasorsa FM, Elhosary PC, Lacoursiere CM, Martin E, Yuskaitis CJ, Hill RS, Atabay KD, Barry B, Partlow JN, Bashiri FA, Zeidan RM, Elmalik SA, Kabiraj MMU, Kothare S, Stödberg T, McTague A, Kurian MA, Scheffer IE, Barkovich AJ, Palmieri F, Salih MA, Walsh CA. SLC25A22 is a novel gene for migrating partial seizures in infancy. Ann Neurol. 2013;74:873–82. PubMed PMID: 24596948.

Puskarjov M, Seja P, Heron SE, Williams TC, Ahmad F, Iona X, Oliver KL, Grinton BE, Vutskits L, Scheffer IE, Petrou S, Blaesse P, Dibbens LM, Berkovic SF, Kaila K. A variant of KCC2 from patients with febrile seizures impairs neuronal Cl- extrusion and dendritic spine formation. EMBO Rep. 2014;15:723–9. PubMed PMID: 24668262.

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.

Saade D, Joshi C. Pure cannabidiol in the treatment of malignant migrating partial seizures in infancy: a case report. Pediatr Neurol. 2015;52:544–7. PubMed PMID: 25882081.

Saito T, Ishii A, Sugai K, Sasaki M, Hirose S. A de novo missense mutation in SLC12A5 found in a compound heterozygote patient with epilepsy of infancy with migrating focal seizures. Clin Genet. 2017;92:654–8. PubMed PMID: 28477354.

Saitsu H, Watanabe M, Akita T, Ohba C, Sugai K, Ong WP, Shiraishi H, Yuasa S, Matsumoto H, Beng KT, Saitoh S, Miyatake S, Nakashima M, Miyake N, Kato M, Fukuda A, Matsumoto N. Impaired neuronal KCC2 function by biallelic SLC12A5 mutations in migrating focal seizures and severe developmental delay. Sci Rep. 2016;6:30072. PubMed PMID: 27436767.

Štěrbová K, Vlčková M, Klement P, Neupauerová J, Staněk D, Zůnová H, Seeman P, Laššuthová P. Neonatal onset of epilepsy of infancy with migrating focal seizures associated with a novel GABRB3 variant in monozygotic twins. Neuropediatrics. 2018;49:204–8. PubMed PMID: 29444535.

Stödberg T, McTague A, Ruiz AJ, Hirata H, Zhen J, Long P, Farabella I, Meyer E, Kawahara A, Vassallo G, Stivaros SM, Bjursell MK, Stranneheim H, Tigerschiöld S, Persson B, Bangash I, Das K, Hughes D, Lesko N, Lundeberg J, Scott RC, Poduri A, Scheffer IE, Smith H, Gissen P, Schorge S, Reith MEA, Topf M, Kullmann DM, Harvey RJ, Wedell A, Kurian MA. Mutations in SLC12A5 in epilepsy of infancy with migrating focal seizures. Nat Commun. 2015;6:8038. PubMed PMID: 26333769.

Tornberg J, Voikar V, Savilahti H, Rauvala H, Airaksinen MS. Behavioural phenotypes of hypomorphic KCC2-deficient mice. Eur J Neurosci. 2005;21:1327–37. PubMed PMID: 15813942.

Ünver O, Incecik F, Dündar H, Kömür M, Ünver A, Okuyaz Ç. Potassium bromide for treatment of malignant migrating partial seizures in infancy. Pediatr Neurol. 2013;49:355–7. PubMed PMID: 23968569.

Uvarov P, Ludwig A, Markkanen M, Pruunsild P, Kaila K, Delpire E, Timmusk T, Rivera C, Airaksinen MS. A novel N-terminal isoform of the neuron-specific K-Cl cotransporter KCC2. J Biol Chem. 2007;282:30570–6. PubMed PMID: 17715129.

Uvarov P, Ludwig A, Markkanen M, Soni S, Hübner CA, Rivera C, Airaksinen MS. Coexpression and heteromerization of two neuronal K-Cl cotransporter isoforms in neonatal brain. J Biol Chem. 2009;284:13696–704. PubMed PMID: 19307176.

Vendrame M, Poduri A, Loddenkemper T, Kluger G, Coppola G, Kothare SV. Treatment of malignant migrating partial epilepsy of infancy with rufinamide: report of five cases. Epileptic Disord. 2011;13:18–21. PubMed PMID: 21393094.

Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, Lesca G, Ville D, Milh M, Villard L, Afenjar A, Chantot-Bastaraud S, Mignot C, Lardennois C, Nava C, Schwarz N, Gérard M, Perrin L, Doummar D, Auvin S, Miranda MJ, Hempel M, Brilstra E, Knoers N, Verbeek N, van Kempen M, Braun KP, Mancini G, Biskup S, Hörtnagel K, Döcker M, Bast T, Loddenkemper T, Wong-Kisiel L, Baumeister FM, Fazeli W, Striano P, Dilena R, Fontana E, Zara F, Kurlemann G, Klepper J, Thoene JG, Arndt DH, Deconinck N, Schmitt-Mechelke T, Maier O, Muhle H, Wical B, Finetti C, Brückner R, Pietz J, Golla G, Jillella D, Linnet KM, Charles P, Moog U, Õiglane-Shlik E, Mantovani JF, Park K, Deprez M, Lederer D, Mary S, Scalais E, Selim L, Van Coster R, Lagae L, Nikanorova M, Hjalgrim H, Korenke GC, Trivisano M, Specchio N, Ceulemans B, Dorn T, Helbig KL, Hardies K, Stamberger H, de Jonghe P, Weckhuysen S, Lemke JR, Krägeloh-Mann I, Helbig I, Kluger G, Lerche H, Møller RS. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain. 2017;140:1316–36. PubMed PMID: 28379373.

Woo NS, Lu J, England R, McClellan R, Dufour S, Mount DB, Deutch AY, Lovinger DM, Delpire E. Hyperexcitability and epilepsy associated with disruption of the mouse neuronal-specific K-Cl cotransporter gene. Hippocampus. 2002;12:258–68. PubMed PMID: 12000122.

Zhang X, Ling J, Barcia G, Jing L, Wu J, Barry BJ, Mochida GH, Hill RS, Weimer JM, Stein Q, Poduri A, Partlow JN, Ville D, Dulac O, Yu TW, Lam AT, Servattalab S, Rodriguez J, Boddaert N, Munnich A, Colleaux L, Zon LI, Söll D, Walsh CA, Nabbout R. Mutations in QARS, encoding glutaminyl-tRNA synthetase, cause

progressive microcephaly, cerebral-cerebellar atrophy, and intractable seizures. Am J Hum Genet. 2014;94:547–58. PubMed PMID: 24656866.

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