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SERAC1 Deficiency

Saskia B Wortmann, MD, PhD,[1] Arjan PM de Brouwer, PhD,[2] Ron A Wevers, PhD,[3] and Eva Morava, MD, PhD[4]

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Summary

Clinical characteristics

The phenotypic spectrum of SERAC1 deficiency comprises MEGD(H)EL syndrome (3-*me*thylglutaconic aciduria with *d*eafness-dystonia, [*h*epatopathy], *e*ncephalopathy, and *L*eigh-like syndrome), juvenile-onset complicated hereditary spastic paraplegia (in 1 consanguineous family), and adult-onset generalized dystonia (in 1 adult male). MEGD(H)EL syndrome is characterized in neonates by hypoglycemia and a sepsis-like clinical picture for which no infectious agent can be found. During the first year of life feeding problems, failure to thrive, and/or truncal hypotonia become evident; many infants experience (transient) liver involvement ranging from undulating transaminases to prolonged hyperbilirubinemia and near-fatal liver failure. By age two years progressive deafness, dystonia, and spasticity prevent further psychomotor development and/or result in loss of acquired skills. Affected children are completely dependent on care for all activities of daily living; speech is absent.

Diagnosis/testing

The diagnosis of SERAC1 deficiency is established in a proband with suggestive clinical and metabolic (3-methylglutaconic aciduria) findings and biallelic pathogenic variants in *SERAC1* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment of MEGD(H)EL syndrome is supportive. Care is best provided by a multidisciplinary team including a metabolic pediatrician, pediatric neurologist, dietician, and physical therapist when possible. Some individuals have experienced (temporary) improvement of spasticity with oral or intrathecal baclofen treatment. Respiratory problems resulting from excessive drooling improve with botulinum

Author Affiliations: 1 Pediatric Metabolic Disorders, Department of Pediatrics, Salzburger Landeskliniken and Paracelsus Medical University, Salzburg, Austria; Email: s.wortmann@salk.at. 2 Department of Human Genetics, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; Email: arjan.debrouwer@radboudumc.nl. 3 Department of Laboratory Medicine, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; Email: ron.wevers@radboudumc.nl. 4 Department of Clinical Genomics and Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota; Email: morava-kozicz.eva@mayo.edu.

toxin injection in the salivary glands, extirpation of salivary glands, and/or rerouting of glandular ducts. An age-appropriate diet given via nasogastric tube or gastrostomy can greatly improve overall clinical condition.

Surveillance: Neurologic and orthopedic evaluations as needed based on individual findings are appropriate.

Genetic counseling

SERAC1 deficiency is inherited in an autosomal recessive manner. 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. Once the *SERAC1* 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.

GeneReview Scope

SERAC1 Deficiency: Phenotypic Spectrum [1]
• MEGD(H)EL syndrome (3-*me*thylglutaconic aciduria with *d*eafness-dystonia, [*h*epatopathy], *e*ncephalopathy, and *L*eigh-like syndrome) • Juvenile-onset complicated hereditary spastic paraplegia (cHSP) with mild nonprogressive intellectual disability • Adult-onset generalized dystonia

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

Suggestive Findings

SERAC1 deficiency **should be suspected** in an individual with: one of the three main clinical phenotypes defined within the SERAC1 deficiency spectrum; characteristic imaging findings; and autosomal recessive family history.

Three Main Clinical Phenotypes

1. Infantile, severe MEGD(H)EL syndrome (3-*me*thylglutaconic aciduria with *d*eafness-dystonia, [*h*epatopathy], *e*ncephalopathy, and *L*eigh-like syndrome):

- Transient hypoglycemia
- Sepsis-like episodes without infection
- Transient liver involvement ranging from undulating elevation of transaminases to prolonged hyperbilirubinemia and hyperammonemia and near-fatal liver failure
- Feeding problems
- Failure to thrive
- Optic atrophy
- Developmental delay followed by motor and cognitive regression
- Progressive sensorineural hearing loss
- Progressive dystonia
- Progressive spasticity
- Laboratory findings:
  - Elevated urinary concentration of 3-methylglutaconic acid (3-MGA) and 3-methylglutaric acid (3-MGC) on routine analysis of urine organic acids (see Table 1).
  - Serum lactate concentration and serum alanine concentration can be elevated; serum cholesterol concentration may be decreased [Wortmann et al 2006, Wortmann et al 2012b, Sarig et al 2013, Tort et al 2013].

Table 1. Urinary Concentration of 3-MGA in MEGD(H)EL Syndrome

Phenotype	Urinary Concentration of 3-MGA (mmol/mol creatinine)
MEGD(H)EL syndrome	16-196
Normal controls	<10 [1]

Wortmann et al [2012b]
1. Reference range as used at the Laboratory for Genetic Endocrine and Metabolic Diseases (LGEM), Department of Laboratory Medicine, Radboud UMC Nijmegen, Nijmegen, the Netherlands

2. Juvenile-onset complicated hereditary spastic paraplegia (described in a single consanguineous family) [Roeben et al 2018]:

- Cognitive delay
- Spasticity manifesting as slowly progressive lower limb spasticity beginning in adolescence
- Laboratory findings: 3-MGA excretion

3. Adult-onset generalized dystonia (single case) [Giron et al 2018]:

- Cognitive delay
- Progressive generalized hyperkinetic movement disorder beginning in early adulthood (3rd decade)
- Laboratory findings: variable degree of 3-MGA excretion

Brain MRI

Bilateral basal ganglia involvement is seen on brain MRI (comparable to Leigh syndrome) [Wortmann et al 2015]. All affected individuals with MEGD(H)EL syndrome had a distinctive brain MRI pattern with five characteristic disease stages affecting the basal ganglia, especially the putamen.

- Stage 0. Normal MRI
- Stage 1. T_2-weighted signal changes present in the pallidum
- Stage 2. Swelling of the putamen and caudate nucleus. The dorsal putamen contains an "eye" that shows no signal alteration and (thus) seems to be spared during this stage of the disease.
- Stage 3. The putaminal eye increases, reflecting progressive putaminal involvement. This "eye" was found in all individuals with MEGD(H)EL syndrome during a specific age range (>1-4 years), and has not been reported in other disorders, making it pathognomonic for MEGD(H)EL syndrome and allowing diagnosis based on MRI findings.
- Stage 4. Basal ganglia degeneration until near loss; cortical and cerebellar atrophy

Family History

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 SERAC1 deficiency **is established** in a proband with suggestive clinical and metabolic (3-methylglutaconic aciduria [3-MGA-uria]) findings and biallelic pathogenic (or likely pathogenic) variants in *SERAC1* identified by molecular genetic testing (see Table 2).

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 *SERAC1* variants of

uncertain significance (or identification of one known *SERAC1* pathogenic variant and one *SERAC1* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive laboratory findings described in Suggestive Findings (see Table 1) are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of SERAC1 deficiency has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SERAC1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A spasticity, dystonia, deafness, nuclear mitochondrial, or intellectual disability multigene panel that includes *SERAC1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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 SERAC1 deficiency, some panels for spasticity, dystonia, deafness, nuclear mitochondrial, or intellectual disability may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **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 2. Molecular Genetic Testing Used in SERAC1 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SERAC1	Sequence analysis [3]	~99% [4]
	Deletion/duplication analysis [5]	~1% [6]

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. Wortmann et al [2012b], Sarig et al [2013], Tort et al [2013], Maas 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.
6. A deletion of exons 5-8 has been reported [Maas et al 2017].

Clinical Characteristics

Clinical Description

To date, SERAC1 deficiency has been identified in more than 67 individuals with MEGD(H)EL syndrome (3-*me*thylglutaconic aciduria with *d*eafness-dystonia, [*h*epatopathy], *e*ncephalopathy, and *L*eigh-like syndrome) [Maas et al 2017, Giron et al 2018, Roeben et al 2018], one consanguineous family with juvenile-onset **complicated** hereditary spastic paraplegia [Roeben et al 2018], and one man with adult-onset generalized dystonia [Giron et al 2018]. The following descriptions of the phenotypic features associated with SERAC1 deficiency are based on these reports.

Table 3. Select Features of SERAC1 Deficiency

Feature	% of Persons w/Feature	Comment
Muscular hypotonia	91%	
Moderate-to-severe intellectual disability	88%	• 68% of affected persons never learn to walk. • 58% never learn to speak.
Progressive spasticity	81%	
Dystonia	81%	
Sensorineural hearing loss	80%	
Loss of skills	75%	
Neonatal liver dysfunction	52%	
Neonatal hypoglycemia	49%	
Seizures	38%	Febrile seizures, myoclonic epilepsy
Neonatal liver failure	30%	
Optic atrophy	25%	

Based on Maas et al [2017]

The following clinical findings of SERAC1 deficiency are based on the combined personal experience of the authors as well as published data [Maas et al 2017, Giron et al 2018, Roeben et al 2018].

Infantile, Severe MEGD(H)EL Syndrome

Most children with MEGD(H)EL syndrome present in the **neonatal period** with hypoglycemia and a sepsis-like clinical picture for which no infectious agent can be found. Several neonates with prolonged jaundice were reported.

During the **first year of life** affected infants often come to the attention of a physician because of feeding problems, failure to thrive, and/or truncal hypotonia. Liver involvement (ranging from cholestasis to hepatitis of unknown origin to fulminant liver failure) is also frequently seen but mostly transient.

By **age two years** the neurologic findings become more apparent. Progressive spasticity (as defined by increasing resistance to speed or angle with passive flexion as well as hypertonia and hyperreflexia) and dystonia either prevent further development or lead to loss of acquired skills. Speech is often completely absent, leading to investigation and detection of progressive deafness.

The **further clinical course** is slowly progressive. Affected children are completely dependent on care for all activities of daily living: they are unable to sit independently and are wheelchair bound and nonambulatory. Scoliosis and/or contractures may require bracing.

Communication is limited to the expression of comfort and discomfort; speech is absent.

Feeding is complicated by the movement disorder and often also by excessive drooling, often requiring tube feeding.

Some affected individuals have epilepsy which occurs either in the neonatal period or later in the disease course.

The length of survival varies. Some do not survive the neonatal period due to multiorgan failure, some succumb to liver failure in infancy, and others to (pulmonary) infections later in life. The oldest living affected individual is older than age 24 years.

Milder Juvenile-Onset Complicated Hereditary Spastic Paraplegia (cHSP)

Juvenile-onset paraspasticity, complicated by nonprogressive mild cognitive deficits, was observed in one family in which five of six affected sibs were homozygous for the splice site variant c.91+6T>C [Roeben et al 2018].

- Three had a relatively benign cHSP disease course. Cognitive delay was detected at school age. None had a history of infantile feeding problems, liver failure, hearing loss, or truncal hypotonia. All were still able to walk several miles without assistance at age ten to 20 years, and the youngest sib did not show any motor problems at age ten years.
- Only one of six, who was the most severely affected, showed signs of dystonia.

Adult-Onset Generalized Dystonia

A man age 31 years (compound heterozygous for c.1347-1350dupATCT [p.Val451fs] and c.1598C.T [p.Pro533Leu]) is the only person with SERAC1 deficiency with this phenotype described to date [Giron et al 2018]. He had a history of mild psychomotor delay, and was referred for evaluation of generalized dystonia with chorea-like movements at age 31 years. At age 24 years, he had had a few episodes of subacute encephalopathy triggered by fever; he subsequently developed cervical dystonia that gradually worsened, becoming generalized. He also developed progressive lower-limb spasticity and hyperkinetic dysarthria. These findings began with and worsened after episodes of fever. Brain MRI showed bilateral shrunken striata, suggestive of Leigh syndrome. Electromyography showed severe axonal neuropathy. Visual evoked potentials revealed bilateral optic neuropathy. Audiograms were normal.

Genotype-Phenotype Correlations

Currently, no clear relationship exists between the type and position of the *SERAC1* pathogenic variants and phenotype.

The level of 3-methylglutaconic aciduria does not correlate with the clinical course.

Prevalence

The prevalence of MEGD(H)EL syndrome is estimated at 0.09:100,000 [Tan et al 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SERAC1*.

Differential Diagnosis

Differential diagnosis of 3-methylglutaconic aciduria (3-MGA-uria). Increased urinary excretion of the branched-chain organic acid 3-MGA (3-MGA-uria) is a relatively common finding in children investigated for suspected inborn errors of metabolism [Wortmann et al 2013b]. Inborn errors of metabolism with 3-MGA-uria as a discriminative feature (see Table 4) show a characteristic "syndromal" pattern of signs and symptoms [Wortmann et al 2013a, Wortmann et al 2013b, Kovacs-Nagy et al 2018]. The exact source of 3-MGA-uria is known only in AUH defect, the rarest type, caused by primary deficiency of the mitochondrial enzyme 3-methylglutaconyl-CoA hydratase resulting in blockage of leucine catabolism. The origin of the increased 3-MGA excretion in all other types is unknown, but mitochondrial dysfunction is thought to be the common denominator [Wortmann et al 2009].

Table 4. Genes of Interest in the Differential Diagnosis of SERAC1 Deficiency

Gene	Disorder	MOI	Features of Differential Diagnosis Disorder	
			3-MGA-uria	Key clinical characteristics
ACTB	*ACTB* Baraitser-Winter cerebrofrontofacial syndrome w/ juvenile-onset dystonia	AD	Absent	Deafness, dystonia, ID, DD
AGK	Sengers syndrome (See Mitochondrial DNA Maintenance Defects Overview.)	AR	Present *	Cataracts, cardiomyopathy, (DD [1])
ATAD3A	Harel-Yoon syndrome (OMIM 617183)	AD AR	Present *	Global DD, hypotonia, optic atrophy, axonal neuropathy, hypertrophic cardiomyopathy [2]
AUH	AUH defect (OMIM 250950)	AR	Present *	Adult-onset progressive spasticity & dementia w/ characteristic slowly developing radiologic picture of extensive leukoencephalopathy [3, 4]
BCAP31	Deafness, dystonia, & cerebral hypomyelination (OMIM 300475)	XL	Absent	Deafness, dystonia, ID, DD, cerebral hypomyelination
CLPB	CLPB deficiency	AR	Present *	Cataracts, central hypopnea, DD, ID, movement disorder, neutropenia, (epilepsy [1])
DNAJC19	DNAJC19 defect (DCMA syndrome) (OMIM 610198)	AR	Present *	Characteristic combination of childhood-onset dilated cardiomyopathy, nonprogressive cerebellar ataxia, testicular dysgenesis, & growth failure
FITM2	Siddiqi syndrome (OMIM 618635)	AR	Absent	Deafness, dystonia, ID, DD

Table 4. continued from previous page.

Gene	Disorder	MOI	Features of Differential Diagnosis Disorder	
			3-MGA-uria	Key clinical characteristics
HTRA2	MGCA8 (OMIM 617248)	AR	Present *	Cataracts, central hypopnea, DD, ID, epilepsy, movement disorder, neutropenia
MICOS13 (*C19orf70*, *QIL1*)	Combined oxidative phosphorylation deficiency 37 (OMIM 618329)	AR	Present *	Hypotonia, failure to thrive, neurodegeneration w/ loss of developmental milestones, liver dysfunction
OPA3	Costeff syndrome	AR	Present *	Optic atrophy, movement disorder (ataxia or extrapyramidal disorder)
SUCLA2	*SUCLA2* mtDNA depletion syndrome, encephalomyopathic form w/methylmalonic aciduria	AR	May be present	• Early-onset dystonia, deafness, severe failure to thrive • Basal ganglia involvement visible on brain MRI in some • Movement disorder, epilepsy, 3-MGA-uria, & ↑ serum lactate common. • Characteristic metabolite profile: mild ↑ in urinary methylmalonic acid & serum acyl-carnitine ester abnormalities [5] (metabolite profile not found in MEGD[H]EL syndrome)
TAFAZZIN (*TAZ*)	Barth syndrome	XL	Present *	In males, cardiomyopathy (left ventricular noncompaction), neutropenia, myopathy, typical facial features, hypocholesterolemia, & cognitive phenotype
TIMM50	MGCA9 (OMIM 617698)	AR	Present *	DD, ID, epilepsy
TIMM8A	Deafness-dystonia-optic neuronopathy syndrome	XL	Absent [6]	• Progressive deafness in infancy • Dystonia develops later in life; may develop in adulthood. • Basal ganglia lesions can be found on brain MRI.
TMEM70	TMEM70 defect (OMIM 614052)	AR	Present *	• Typically neonatal onset w/muscular hypotonia, hypertrophic cardiomyopathy, psychomotor disability, hyperammonemia, & lactic acidosis • Children surviving neonatal period later show DD. • Phenotypic spectrum is variable. [7]

3-MGA-uria = 3-methylglutaconic aciduria; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

See also Kovacs-Nagy et al [2018], Table 1.

* 3-MGA-uria is a discriminative feature of this disorder.

1. Seen in some affected persons

2. Harel et al [2016]

3. Wortmann et al [2010]

4. AUH defect is the only one of the five inborn errors of metabolism with 3-MGA-uria with a distinct biochemical finding: elevated urinary excretion of 3-hydroxyisovaleric acid (3-HIVA).

5. Increased C3- & C4-dicarboxyli-carnitine esters.

6. Wortmann et al [2012a]

7. The phenotypic spectrum of TMEM70 defect is variable and becoming broader as more affected individuals are reported. At this time no specific syndromic presentation is evident.

Mitochondrial disorders should also be considered in the differential diagnosis of SERAC1 deficiency. Mitochondrial disorders are caused by pathogenic variants in mitochondrial DNA or nuclear DNA and can present with any sign or symptom. Over 320 mitochondrial disorders have been identified [Wortmann et al 2017]. Tissues with higher requirements for oxidative metabolism, such as the central nervous system and cardiac and skeletal muscle, are predominantly affected.

3-MGA-uria is common in mitochondrial disorders [Wortmann et al 2012a], although 3-MGA excretion is lower than in MEGD(H)EL syndrome, and clinical features observed in MEGD(H)EL syndrome are frequently found in mitochondrial disorders. For example: progressive deafness is often reported with the mitochondrial DNA pathogenic variant m.3243A>G; and Leigh syndrome and dystonia are a typical neuro(radio)logic finding in mitochondrial disorders in relation to deficiency of complex I or IV of the respiratory chain. SERAC1 deficiency can be distinguished from mitochondrial disorders by the distinctive combination of deafness, spasticity, dystonia, and Leigh syndrome associated with MEGD(H)EL syndrome.

Other SERAC1 deficiency phenotypes. The phenotypic features associated with *SERAC1* juvenile-onset complicated hereditary spastic paraplegia (cHSP) and *SERAC1* adult-onset generalized dystonia are not sufficient to diagnose these conditions. All cHSP types with juvenile onset (see Hereditary Spastic Paraplegia Overview) and all types of adult-onset generalized dystonia (see Hereditary Dystonia Overview) should be considered in the differential diagnoses for these conditions.

Cerebral palsy. Slowly progressive spasticity and dystonia as seen in MEGD(H)EL syndrome may be misdiagnosed as cerebral palsy when deafness or abnormalities on brain MRI are not recognized. Therefore, the authors recommend that urinary organic acid analysis be performed on individuals with atypical cerebral palsy.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SERAC1 deficiency, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with SERAC1 Deficiency

System/Concern	Evaluation	Comment
Liver dysfunction	Assess liver function	Incl ASAT, ALAT, gamma-GT, serum concentration of bilirubin (total & direct), serum concentration of ammonia, clotting tests.
Neonatal hypoglycemia	Assess blood sugar	
Neurologic	Neurologic eval	To assess: • Spasticity • Dystonia • Possible seizures, incl EEG • MRI if not performed previously
DD/ID (static)	Developmental assessment	To evaluate: • Motor, adaptive, cognitive, & speech/language • Need for early intervention / special education

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	Incl assessment of: • Gross motor & fine motor skills; • Contractures, scoliosis; • Mobility, ADLs, & need for adaptive devices; • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills).
Excessive drooling		Assess for evidence of aspiration &/or dehydration &/or need for definitive treatment.
Feeding difficulties / Dysphagia	Gastroenterology / nutrition / feeding team eval	• Incl eval of aspiration risk & nutritional status. • Consider eval for gastric tube placement in patients w/ dysphagia &/or aspiration risk.
Sensorineural hearing loss	Complete audiologic exam incl hearing test, BAEP	Perform even if newborn hearing screening was NL.
Optic atrophy	Ophthalmologic exam by pediatric ophthalmologist	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SERAC1 deficiency to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community resources & support/advocacy organizations (e.g., Parent to Parent); • Social work involvement for parental support; • Home nursing referral.

ADLs = activities of daily living; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; BAEP = brain stem auditory evoked potentials; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

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

Treatment of Manifestations

Treatment is supportive. Care is best provided by a multidisciplinary team including a metabolic pediatrician, pediatric neurologist, dietician, and physical therapist when possible.

Table 6. Treatment of Manifestations in Individuals with SERAC1 Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	Can be static or progressive cognitive decline
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
	Pharmacologic treatment	Temporary improvement may occur w/oral or intrathecal baclofen
Seizures	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]

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Dysphagia	• 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
Drooling	Botulinum toxin injection in salivary glands, extirpation of salivary glands, &/or rerouting of glandular ducts	These measures can improve secondary respiratory problems.
Hearing loss	Consider hearing aids or cochlear implant in patient w/ mild cognitive impairment.	
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; DD = developmental delay; ID = intellectual disability; 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.

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.

Surveillance

Table 7. Recommended Surveillance for Individuals with SERAC1 Deficiency

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Respiratory	Monitor for evidence of aspiration & respiratory insufficiency.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Development	• Monitor developmental progress incl possibility of cognitive decline. • Monitor educational needs.	
Musculoskeletal	Physical medicine, OT/PT assessment of scoliosis, contractures, mobility, self-help skills	
Hearing loss	Monitor effectiveness of hearing aids & possible need for alternative means of communication.	
Optic atrophy	Monitor vision.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

Agents/Circumstances to Avoid

Medications known to impair mitochondrial function (e.g., valproic acid) should be avoided.

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

SERAC1 deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *SERAC1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *SERAC1* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- 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 a *SERAC1* 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 MEGD(H)EL syndrome are not known to reproduce.
- Unless an affected individual's reproductive partner also has *SERAC1* juvenile-onset complicated hereditary spastic paraplegia or adult-onset generalized dystonia or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SERAC1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SERAC1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SERAC1* 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 young adults who are carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SERAC1* 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.

- **National Library of Medicine Genetics Home Reference**
  MEGDEL syndrome
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org

Molecular Genetics

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

Table A. SERAC1 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SERAC1	6q25.3	Protein SERAC1	SERAC1	SERAC1

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 SERAC1 Deficiency (View All in OMIM)

614725	SERINE ACTIVE SITE-CONTAINING PROTEIN 1; SERAC1
614739	3-METHYLGLUTACONIC ACIDURIA WITH DEAFNESS, ENCEPHALOPATHY, AND LEIGH-LIKE SYNDROME; MEGDEL

Molecular Pathogenesis

SERAC1 encodes SERAC1, which contains a conserved serine-lipase domain (consensus lipase motif GxSxG) and is a member of the PGAP-like protein domain family (PFAM PF07819).

Loss of SERAC1 in phospholipid remodeling has consequences for mitochondrial function and intracellular cholesterol trafficking. SERAC1 is involved in remodeling phosphatidylglycerol-34:1 (PG-34:1) to phosphatidylglycerol-36:1 (PG-36:1). PG-36:1 is the precursor for bis(monoacylglycerol)phosphate (BMP) and a precursor to cardiolipin-68:5. Loss of SERAC1 reduces PG-36:1 and lowers concentrations of BMP, leading to the accumulation of intracellular free cholesterol. In addition, the altered cardiolipin species distribution in the mitochondrial membranes likely causes the mitochondrial dysfunction.

Mechanism of disease causation. Loss of function

Table 8. Notable *SERAC1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_032861.4	c.1822_1828+10delinsACCAACAGG		Found in multiple families of European descent [Maas et al 2017]

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.

Chapter Notes

Author Notes

Radboud UMC

Dr SB Wortmann and Prof RA Wevers are interested in patients with elevated urinary excretion of 3-methylglutaconic acid. Combining the clinical, biochemical, and neuroradiologic findings of these patients, they are able to define homogeneous subgroups on which they perform next-generation sequencing to unravel the underlying genetic disorders. This is followed by biochemical investigations to characterize the function of the affected protein.

Revision History

- 23 July 2020 (bp) Comprehensive update posted live
- 17 April 2014 (me) Review posted live
- 17 January 2014 (adb) Original submission

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