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SCARB2-Related Action Myoclonus – Renal Failure Syndrome

Changrui Xiao, MD,[1,2] Haejun Ahn, MD,[3] Sara Kibrom, MD,[3] and Camilo Toro, MD[1]

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Summary

Clinical characteristics

SCARB2-related action myoclonus – renal failure syndrome (*SCARB2*-AMRF) comprises a continuum of two major (and ultimately fatal) manifestations: progressive myoclonic epilepsy (PME) and renal involvement that is apparently due to steroid-resistant nephrotic syndrome (SRNS). The neurologic and renal manifestations progress independently. In some instances, renal involvement is not observed; thus, PME without renal manifestations caused by biallelic *SCARB2* pathogenic variants is considered to be one end of the spectrum of *SCARB2*-AMRF. All individuals reported to date developed neurologic findings; in some instances renal manifestations predated neurologic involvement by decades. The disease progresses relentlessly, with neurologic deterioration (especially increasing severity of myoclonus) and/or end-stage kidney disease (ESKD) leading to death within seven to 15 years after onset.

Diagnosis/testing

The diagnosis of *SCARB2*-AMRF is established in a proband with suggestive findings and biallelic loss-of-function pathogenic variants in *SCARB2* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *SCARB2*-AMRF.

The supportive care for neurologic manifestations that is recommended to improve quality of life, maximize function, and reduce complications includes pharmacotherapy to reduce myoclonus; anti-seizure medication (ASM) and vagus nerve stimulation to reduce seizures; physical and occupational therapy to help maintain mobility and optimize activities of daily living; adaptive devices to help maintain/improve independence in mobility; educational support for those with cognitive decline; speech-language therapy to explore use of

Author Affiliations: 1 National Human Genome Research Institute, Bethesda, Maryland; Email: changrx@hs.uci.edu; Email: toroc@mail.nih.gov. 2 Department of Neurology, University of California Irvine, Orange, California; Email: changrx@hs.uci.edu. 3 Stanford University School of Medicine, Palo Alto, California; Email: hcahn@stanford.edu; Email: skibrom@stanford.edu.

alternative communication methods; feeding therapy programs for those with dysphagia to improve nutrition and reduce aspiration risk.

Treatment for renal involvement, under the care of a nephrologist, is typically focused on remission of proteinuria and often includes a combination of renin-angiotensin-aldosterone inhibition and immunosuppressive medications. Treatment of ESKD is supportive; while renal replacement therapy can prolong survival, it does not improve neurologic features.

Surveillance: Regular follow up with multidisciplinary care providers to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations.

Agents/circumstances to avoid: Phenytoin may aggravate neurologic manifestations or even accelerate cerebellar degeneration; sodium channel blockers (carbamazepine, oxcarbazepine), GABAergic drugs (tiagabine, vigabatrin), and gabapentin and pregabalin may aggravate myoclonus and myoclonic seizures.

Pregnancy management: Some ASMs can increase the risk of malformations, growth restriction, and/or neurodevelopmental disabilities in exposed fetuses. However, when pregnant women experience prolonged seizures during pregnancy, the risk of adverse fetal outcomes is increased. Therefore, it is recommended that pregnant women with a known seizure disorder continue to take ASMs and that the prescribing physician follow standard measures to prevent fetopathy, including possible changes of medication prior to pregnancy; spacing of ASMs during pregnancy into four doses a day or taking extended-release medications, so that ASM levels do not have significant peaks or troughs; monitoring ASM dosages and levels during pregnancy.

In addition, all women of childbearing age should be advised to take 1 mg/day of folic acid and to increase it to 4 mg/day when planning a pregnancy (ideally three months prior to conception) and during the pregnancy, in order to reduce the risk of congenital malformations that can be associated with fetal exposure to ASMs.

Genetic counseling

SCARB2-AMRF is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *SCARB2* 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 *SCARB2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *SCARB2*-related action myoclonus – renal failure syndrome (*SCARB2*-AMRF) have been published.

Suggestive Findings

SCARB2-AMRF **should be suspected** in a previously healthy teenager or young adult with the following neurologic and renal manifestations, especially if family history is suggestive of an autosomal recessive disorder [Andermann 2011, Tian et al 2018, Atasu et al 2022].

Neurologic manifestations

- **Tremor,** which is commonly the first finding, initially manifests in the fingers and hands during actions such as the fine motor activities involved in handwriting. The tremor, which is cortical in nature, is usually absent at rest and is relieved by alcohol.

  The tremor can later involve the head, trunk, lower extremities, and sometimes tongue and voice. In the later stages of the disease, it may become masked by striking myoclonic jerks.

- **Involuntary, action-induced myoclonic jerks** including orolingual myoclonic jerks induced by attempts to speak or swallow. Myoclonus could be multifocal or generalized. There is a sensory-reflex myoclonic response to sensory stimulation, particularly to tendon stretch; the reflex response may spread beyond the stimulated body segment.
- **Involuntary spontaneous myoclonic jerks** of the face (particularly perioral) as well as synchronous and asynchronous jerks of the trunk and limbs at rest could be present but are certainly less prevalent than those induced by action.
- **Generalized tonic-clonic, myoclonic, and mixed seizure types** might occur during wakefulness or sleep. A crescendo of myoclonic jerks might herald seizures.
- **Other findings** can include:
  - Sensorimotor peripheral neuropathy (most often predominantly demyelinating or more rarely axonal);
  - Sensorineural hearing loss.
- **Cerebellar ataxia and cerebellar degeneration** are common later in the disease course. Note that myoclonus, which occurs during the kinetic phase of movements, leads to dysmetria (myoclonic dysmetria) and is often confused for limb ataxia. At least one individual with *SCARB2*-AMRF was identified in a spinocerebellar ataxia cohort despite the fact that myoclonic seizures and dementia were also present [Guan et al 2020].

Renal manifestations

- Proteinuria, the first manifestation of kidney disease, is initially mild and asymptomatic.
- Kidney disease can progress to nephrotic syndrome and end-stage kidney disease.
- Common histologic findings on kidney biopsy include tubular abnormalities and focal segmental glomerulosclerosis.
- In some families, renal manifestations appear first in late childhood or the early teenage years and neurologic manifestations in the late third or early fourth decade [Badhwar et al 2004].

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 *SCARB2*-AMRF **is established** in a proband with suggestive findings and biallelic loss-of-function pathogenic (or likely pathogenic) variants in *SCARB2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *SCARB2* variants of uncertain significance (or of one known *SCARB2* pathogenic variant and one *SCARB2* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas genomic testing does not (see Option 2).

Option 1

A multigene panel for lysosomal storage diseases, nephrotic syndrome, focal segmental glomerulosclerosis, movement disorders, ataxia, or epilepsy (based on the individual's presenting features) that includes *SCARB2* 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*. (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.

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 *SCARB2*-Related Action Myoclonus – Renal Failure Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SCARB2	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions and 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

SCARB2-related action myoclonus – renal failure syndrome (*SCARB2*-AMRF) comprises a continuum of two major (and ultimately fatal) manifestations: progressive myoclonic epilepsy (PME) and renal involvement that can range from mild proteinuria to steroid-resistant nephrotic syndrome (SRNS) and end-stage kidney disease (ESKD) (see Table 2). In some instances, renal involvement is not observed; thus, PME without proteinuria caused by biallelic *SCARB2* pathogenic variants is considered to be one end of the spectrum of *SCARB2*-AMRF [Tian et al 2018, Atasu et al 2022]. Of note, while all reported individuals developed neurologic findings, renal

manifestations were reported to predate neurologic involvement by decades in some instances. Thus, the absence of neurologic involvement should not preclude consideration of *SCARB2*-AMRF in individuals with kidney disease [Badhwar et al 2004].

The age of onset varies, even within the same family.

- Neurologic manifestations can appear before (in one third of affected individuals), simultaneously, or after renal manifestations. In juvenile *SCARB2*-AMRF, onset is usually in the late teenage years or early in the third decade [Badhwar et al 2004].
- In some persons renal manifestations occur early (late childhood or early teenage years) and neurologic involvement much later (late in the third decade or early in the fourth decade) [Badhwar et al 2004, Hopfner et al 2011].
- In three persons of Japanese descent who did not develop SRNS, neurologic manifestations appeared in the fifth or sixth decade [Higashiyama et al 2013, Fu et al 2014]. See Late-Onset *SCARB2*-AMRF.

The neurologic and renal manifestations progress independently. Of note, the neurologic manifestations are not the result of a metabolic encephalopathy due to renal involvement (chronic kidney disease [CKD] or ESKD) and are not improved by treatment of the renal disease by either dialysis or by kidney transplantation [Andermann et al 1986, Badhwar et al 2004]. The use of anti-rejection medications such as cyclosporine known to induce tremor can mistakenly be blamed for the emergence of myoclonus before a molecular diagnosis of *SCARB2*-AMRF is established.

Even in the same family, the number and range of clinical manifestations and the order of their appearance can vary. Neurologic manifestations may occur first or in isolation in some family members, and renal manifestations may occur first or in isolation in other family members [Badhwar et al 2004].

Renal manifestations can be variable even within the same family, including proteinuria, reduced creatinine clearance, CKD, or ESKD. Some individuals do not develop kidney disease [Atasu et al 2022].

The disease progresses relentlessly, with neurologic deterioration (especially increasing severity of myoclonus) and/or ESKD leading to death within seven to 15 years after onset.

Table 2. SCARB2-Related Action Myoclonus – Renal Failure Syndrome: Frequency of Select Neurologic Features

Feature	Frequency			Comment
	Nearly all	Common	Infrequent	
Progressive action & reflex myoclonus	●			
Ataxia	●			Usually late in disease course
Tremor		●		Action & posture induced, irregular amplitude (cortical tremor)
Myoclonus at rest		●		
Dysarthria		●		Usually late in disease course
Severe epileptic photosensitivity		●		
Generalized tonic-clonic seizures		●		
Dysphagia			●	Not discussed in most reports, may be late finding
Cognitive decline			●	
Sensorineural hearing loss			●	

Neurologic Disease

Fine tremor. Usually noted in the second or third decade of life beginning with bilateral fine rhythmic tremor of the fingers noted during delicate movement such as isometric contractions or posture, writing, or by intention of movement [Tian et al 2018, Atasu et al 2022]. The tremor can be relieved by alcohol [Andermann et al 1986, Andermann 2011, Guerrero-López et al 2012]. It becomes progressively worse until it is masked by myoclonic jerks.

Action myoclonus usually appears within ten years of tremor onset (third decade of life) as jerking movements first of the upper extremities and then of the lower extremities. Action myoclonus is typically triggered by movements or intended movements. Action myoclonus can be asynchronous, multifocal, and of variable severity. Action myoclonus can also be reflex sensitive to touch over the distal extremities and can be exacerbated by anxiety, excitement, stress, fatigue, auditory stimuli, or startle [Badhwar et al 2004, Perandones et al 2012, Zeigler et al 2014].

With time, myoclonic jerks involve the proximal limbs. Their amplitude and frequency increase by movements of the limbs, typically by walking down stairs. Action myoclonus can also involve the trunk. Attempts at speaking and executed speech can induce myoclonus of the bulbar musculature, contributing to the dysarthria.

Myoclonus can also be "negative" and characterized by a sudden cessation of postural tone that leads to postural lapses. This is particularly prominent in the standing position, where postural lapses of the antigravity muscles create a "bouncing" stance [Toro et al 1995].

Action myoclonus is often the most disabling neurologic manifestation and may prevent affected individuals from performing activities of daily living such as speaking, swallowing food, or walking [Andermann et al 1986, Badhwar et al 2004, Vadlamudi et al 2006].

Myoclonus at rest. Subtle myoclonic movements of the eyelids, jaws, and perioral musculature appear at rest and while speaking. They represent the absence of complete relaxation. Ocular dysmetria can occur later in the disease course.

Seizures, a common feature of *SCARB2*-AMRF, usually present within a few years of myoclonus (second or third decade of life). Both myoclonic seizures and generalized tonic-clonic seizures (in some instances progressing to status epilepticus) have been described. Seizures can be diurnal or nocturnal. Light stimulation, eye closure, and TV viewing have all been reported triggers [Rubboli et al 2011].

EEG findings. Although background activity may be normal in some individuals, over time it slowly progresses to include diffuse slowing at 6.5-7.5 Hz. Low-voltage spike and spike/polyspike-wave discharges may be present [Badhwar et al 2004]. As in most PME syndromes, myoclonic jerks are often preceded by a contralateral and somatotopically organized cortical discharge originating in the motor cortex (cortical or epileptic myoclonus).

Intermittent photic stimulation may produce whole-body myoclonus with multiple spikes in the EEG record associated with slow waves. These generalized spike/polyspike-wave bursts can outlast the duration of light stimulation [Rubboli et al 2011].

Follow up over the course of the disease shows a preserved alpha background activity at disease onset, with rare generalized or focal epileptiform discharges. Over the years, irregular slower theta and delta waves progressively intermix with the alpha waves, and the epileptic activity becomes more frequent [Rubboli et al 2011].

Ataxia and dysarthria. Both are commonly seen later in the disease course (i.e., a few years after onset of myoclonus). Some individuals who develop significant progressive ataxia before or around the appearance of myoclonus and/or myoclonic dysmetria that is interpreted as cerebellar in origin have been reported to have "progressive myoclonus ataxia" or recessive spinocerebellar ataxia [Guan et al 2020, Atasu et al 2022].

Peripheral neuropathy. In some families, a sensorimotor peripheral neuropathy (both demyelinating and axonal neuropathy) may be present [Atasu et al 2022].

Some affected individuals may be diagnosed with a predominantly demyelinating peripheral neuropathy before the onset of renal involvement [Badhwar et al 2004, Costello et al 2009, Dibbens et al 2011, Hopfner et al 2011].

Sensorineural hearing loss / deafness can be clinically evident or subclinical even within the same family. Three individuals from a German family and another individual from Australia developed hearing loss in adulthood. Family members with subclinical hearing changes have also been reported [Rubboli et al 2011, Perandones et al 2014].

Cognitive function. While the majority of individuals with *SCARB2*-AMRF have not been reported to have cognitive impairment, four different families were reported to have dementia, cognitive impairment, and executive dysfunction [Fu et al 2014, Atasu et al 2022].

Brain MRI may show cerebral, cerebellar, brain stem, or cortical atrophy. Normal MRIs have also been reported [Tian et al 2018].

Renal Disease

The initial manifestation of renal disease is mild proteinuria that may progress to nephrotic syndrome and ultimately to end-stage kidney disease (ESKD). In 15 individuals with AMRF, proteinuria, which occurred in all individuals, was detected between ages nine and 30 years (mean: 20.1 years, median: 19 years); in 12 individuals progression to ESKD requiring dialysis or kidney transplant occurred within zero to eight years of diagnosis (mean: 3.8 years, median: 4.5 years) [Badhwar et al 2004].

The renal manifestations may precede or follow the onset of neurologic findings and can be variable, even within the same family. In two sibs with molecularly confirmed *SCARB2*-AMRF, the sister presented initially with progressive gait difficulty and loss of fine motor skills, and subsequently was found to have proteinuria. In contrast, her brother presented with ESKD secondary to focal segmental glomerulosclerosis (FSGS) and underwent kidney transplantation one year prior to the onset of neurologic manifestations. Of note, another brother had died at age 12 years of ESKD secondary to FSGS [Tanriverdi et al 2022].

In another family, proteinuria was detected in two sisters three to four years following the onset of neurologic manifestations. Both subsequently developed nephrotic syndrome (proteinuria, anasarca, and pleural effusions). One died of *Staph aureus* and *Candida albicans* septicemia; the other died of fulminant pneumonia from an unidentified organism [Balreira et al 2008]. Although the treatments they received for the nephrotic syndrome and the details of their infections are not available for review, it is important to note that individuals with proteinuria in the range observed in nephrotic syndrome are at increased risk for infections and hypogammaglobulinemia [Trautmann et al 2020].

Renal histology. FSGS, a histologic pattern of kidney injury affecting the podocytes, is a leading cause of kidney disease worldwide and is a common cause of steroid-resistant nephrotic syndrome (SRNS), defined as a lack of remission after four to six weeks of standard prednisone treatment. FSGS and SRNS are often used interchangeably, but not all FSGS presents with nephrotic syndrome nor are all instances of FSGS steroid resistant.

FSGS can be classified as primary (idiopathic), secondary (infection/inflammation, malignancy, drug related), and genetic. Individuals with genetic forms of FSGS or SRNS are unlikely to benefit from prolonged immunosuppression [Rood et al 2012, Rosenberg & Kopp 2017, Trautmann et al 2020]. In most published case reports of *SCARB2*-AMRF, the immunosuppression regimens used to treat the renal manifestations are not available for review; hence, the label "SRNS" cannot be accurately applied in those individuals. However, SRNS is presumed based on the progressive and hereditary nature of the renal disease.

Other Findings

Cardiac disease. In a German family, echocardiography revealed dilated cardiomyopathy at ages 14 and 21 years in two of three affected sibs [Hopfner et al 2011].

Mild generalized muscle atrophy was reported in two individuals who exhibited mild generalized reduced tone and no fasciculations [Zeigler et al 2014, He et al 2018]. Although electromyography in one individual showed signs consistent with chronic motor neuron involvement, this has not been reported in any other individuals with *SCARB2*-AMRF [Zeigler et al 2014].

Late-Onset *SCARB2*-AMRF

Disease onset in the fifth or sixth decade has been reported in two Japanese families to date.

Higashiyama et al [2013] reported two sibs with *SCARB2*-AMRF without kidney failure. The sister presented with myoclonic jerks at age 43 years; her older brother presented with gait difficulties at age 52 years. Both were homozygous for the *SCARB2* pathogenic variant c.1385_1390delGATCCAinsATGCATGCACC.

Fu et al [2014] reported a single affected individual from two other Japanese families, one of whom had late-onset disease. This individual presented with gait changes at age 45 years. Of note, he was homozygous for the same pathogenic variant as the two sibs reported by Higashiyama et al [2013]. The two families with reported late-onset *SCARB2*-AMRF originate from the same geographic area; however, it is unknown if these variants are identical by descent.

Prognosis

No data on long-term survival exists for *SCARB2*-AMRF. Sudden death may occur during or after a generalized seizure due to aspiration or sudden unexpected death in epilepsy (SUDEP). Death can also occur due to aspiration pneumonia, ESKD, or rejection of a kidney transplant [Andermann et al 1986, Badhwar et al 2004, Vadlamudi et al 2006, Rubboli et al 2011].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed.

Of note, three individuals known to have late-onset disease were homozygous for the *SCARB2* pathogenic variant c.1385_1390delGATCCAinsATGCATGCACC. See Clinical Description, Late-Onset *SCARB2*-AMRF. Two were sibs and the other individual was unrelated; however, all three came from the same geographic area in Japan.

Nomenclature

The title of this *GeneReview*, *SCARB2*-related action myoclonus – renal failure syndrome, is based on the dyadic naming approach proposed by Biesecker et al [2021], in which mendelian disorders are designated by combining the mutated gene and resulting phenotype. Because the number and range of clinical manifestations and the order of their appearance can vary among affected individuals, a dyadic naming approach tailored to the specific phenotype seen in a given individual (e.g., *SCARB2*-related myoclonic ataxia and renal failure or *SCARB2*-related action myoclonus) may be appropriate in clinical practice [Author, personal observation].

SCARB2-AMRF has also been referred to as the following:

- Familial myoclonus with renal failure
- Progressive myoclonus epilepsy with renal failure

- Epilepsy, progressive myoclonic 4 (EPM4), with or without renal failure. However, the presence or absence of renal failure represents only part of the clinical spectrum of AMRF.

The term "progressive myoclonus epilepsy (PME)" covers a large group of diseases characterized by myoclonus, epilepsy, and progressive neurologic deterioration.

Prevalence

Exact prevalence figures are not available.

SCARB2-AMRF was first reported in several French Canadian families [Andermann et al 1986]; it occurs worldwide and appears to be a pan ethnic disease.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SCARB2*.

Differential Diagnosis

Neurologic Manifestations

At the onset of neurologic manifestations, the differential diagnosis includes other causes of myoclonus such as:

- Acquired causes including toxic exposure (e.g., medication effects) and Lance-Adams syndrome;
- Metabolic encephalopathies;
- Hereditary, non-progressive neurologic conditions (see Table 3).

Table 3. Hereditary Non-Progressive Myoclonic Disorders in the Differential Diagnosis of *SCARB2*-Related Action Myoclonus – Renal Failure Syndrome

Gene	Disorder	MOI	Clinical Characteristics	Comment
CACNB4 *CILK1 (ICK)* *CLCN2* *EFHC1* *GABRA1* *GABRD*	Juvenile myoclonic epilepsy (JME) (OMIM PS254770)	AD	Normal neurologic exam; EEG background activity is undisturbed; myoclonus is not progressive. [1]	JME, which has a favorable outcome, should be considered at onset of myoclonus.
CNTN2 *MARCHF6* *RAPGEF2* *SAMD12* *STARD7* *TNRC6A* *YEATS2*	Cortical tremor syndrome [2] (OMIM PS601068)	AD AR	Adult-onset cortical myoclonus of extremities & seizures (mainly generalized tonic-clonic, less frequently myoclonic seizures or complex partial seizures) in 40% of affected persons	Cortical tremor syndrome, which usually has a favorable outcome, should be considered at onset of fine tremor.

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics	Comment
SGCE	*SGCE* myoclonus-dystonia (DYT11)	AD [3]	Onset of myoclonus is usually in 1st or 2nd decade of life; myoclonus is subcortical in origin; ~50% of affected persons have segmental dystonia.	The assoc of myoclonus & dystonia suggests DYT11. No other neurologic features (in particular ataxia & cognitive deficits) are assoc w/DYT11.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Zifkin et al [2005], Genton et al [2013]
2. Also referred to as familial adult myoclonic epilepsy (FAME) & familial cortical myoclonic tremor associated with epilepsy (FCMTE)
3. SGCE myoclonus-dystonia is inherited in an autosomal dominant manner with penetrance determined by the parental origin of the altered *SGCE* allele: an *SGCE* pathogenic variant on the paternally derived (expressed) *SGCE* allele generally results in disease; a pathogenic variant on the maternally derived (silenced) *SGCE* allele typically does not result in disease.

In individuals with a progressive myoclonic epilepsy (PME) phenotype who do not have biallelic *SCARB2* pathogenic variants, the disorders included in Table 4 should be considered.

Table 4. Disorders with a Progressive Myoclonic Epilepsy Phenotype in the Differential Diagnosis of *SCARB2*-Related Action Myoclonus – Renal Failure Syndrome

Gene	Disorder	MOI	Clinical Characteristics	Comment
ATN1	DRPLA	AD	Persons w/juvenile onset (age <20 yrs) present w/PME & assoc progressive cognitive deterioration & behavioral changes; those w/adult onset (age >20 yrs) present w/ataxia, choreoathetosis, & dementia.	DRPLA is relatively more common in the Japanese population than in other ethnic populations.
ATP13A2	Kufor-Rakeb syndrome (See Neurodegeneration with Brain Iron Accumulation Disorders Overview.)	AR	Juvenile-onset w/(typically) gait abnormalities & neuropsychiatric changes.	
Multiple genes incl: *CLN3* *PPT1* *TPP*	Neuronal ceroid-lipofuscinoses (NCL) (OMIM PS256730)	AR	Persons w/juvenile-onset NCL (most commonly *CLN3* related) typically present before age 10 yrs w/epilepsy, progressive cognitive impairment, & visual impairment.	There are many types of NCLs that can present at any age ranging from congenital to adulthood; juvenile & adult-onset NCLs can overlap w/*SCARB2*-AMRF in age at presentation, cognitive decline, & seizure types; persons w/ juvenile-onset NCL typically have ↓ visual acuity.
CSTB	PME type 1 (EPM1)	AR	Progressive myoclonus, epilepsy, & ataxia typically presenting between age 6-15 yrs.	Cognition is typically spared & disease may stabilize in adulthood.
CTSA	Galactosialidosis (OMIM 256540)	AR	PME w/cognitive decline	Cathepsin A contributes to stability of neuraminidase & beta-galactosidase. Affected persons can present as a phenocopy for sialidosis type 1, GM1 gangliosidosis (see *GLB1*-Related Disorders), or w/mixed features.
EPM2A *NHLRC1*	PME, Lafora type	AR	Visual hallucinations (occipital epilepsy) & cognitive decline; skin biopsy shows pathognomonic Lafora bodies.	

Table 4. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics	Comment
GBA1 (*GBA*)	Gaucher disease (GD) type 3	AR	Primary neurologic disease; may have onset age <2 yrs but often has more slowly progressive course w/survival into 3rd or 4th decade.	
GOSR2	EPM6 (OMIM 614018)	AR	Ataxia in 1st 2 yrs of life followed by action myoclonus & seizures typically present in late childhood.	Cognition is usually preserved though memory difficulties can occur later in adulthood.
KCNC1 [1]	EPM7 (OMIM 616187)	AD	Clinically similar to EPM1.	
KCTD7	EPM3 (neuronal ceroid-lipofuscinoses type 14) (OMIM 611726)	AR	PME, ataxia, developmental regression	Tends to present in early childhood
MT-TF *MT-TH* *MT-TI* *MT-TK* *MT-TL1* *MT-TP* *MT-TS1* *MT-TS2*	MERRF	Mat	Multisystem disorder characterized by myoclonus (often 1st symptom) followed by generalized epilepsy, ataxia, weakness, & dementia	Blood & CSF concentrations of lactate & pyruvate are commonly ↑ at rest & ↑ excessively after moderate activity.
NEU1	Sialidosis type 1 (OMIM 256550)	AR	PME w/cognitive decline	Can be assessed w/neuro-ophthalmologic exam, incl electroretinography
POLG	POLG-related ataxia neuropathy spectrum (See *POLG*-Related Disorders.)	AR	Ataxia, neuropathy, & (in most but not all affected persons) encephalopathy w/seizures	
PRICKLE1	*PRICKLE1*-related PME w/ ataxia (EPM1B) (See *PRICKLE1*-Related Disorders.)	AR	Ataxia begins at age 4-5 yrs & evolves to PME w/ataxia & mild or no cognitive decline; impaired upward gaze observed in several affected persons.	
SERPINI1	Familial encephalopathy w/ neuroserpin inclusion bodies (OMIM 604218)	AD	Age of onset & clinical manifestations vary considerably; clinical phenotypes range from cognitive decline/dementia, dysarthria, & tremors to various forms of refractory epilepsy incl PME & focal or generalized seizures.	

AD = autosomal dominant; AR = autosomal recessive; CSF = cerebrospinal fluid; DRPLA = dentatorubral-pallidoluysian atrophy; Mat = maternal; MERRF = myoclonic epilepsy with ragged red fibers; MOI = mode of inheritance; PME = progressive myoclonic epilepsy

1. A recurrent *de novo KCNC1* pathogenic variant, c.959G>A (p.Arg320His), which causes loss of function of KV3.1, a subunit of the KV3 voltage-gated potassium ion channels, is causative [Muona et al 2015].

Renal Manifestations

See Genetic Steroid-Resistant Nephrotic Syndrome Overview for genes known to be associated with genetic SRNS.

Primary coenzyme Q_{10} (CoQ_{10}) deficiency can present with intellectual disability, seizures, or progressive ataxia and SRNS. CoQ_{10} deficiency is important to consider, as treatment with CoQ_{10} supplementation can limit disease progress.

***INF2*-related hereditary neuropathy with focal segmental glomerulonephritis** (OMIM 614455) should also be considered in persons with peripheral neuropathy and glomerulonephritis. Inheritance is autosomal dominant. (See also Charcot-Marie-Tooth Hereditary Neuropathy Overview.)

Management

No clinical practice guidelines for the neurologic manifestations of *SCARB2*-related action myoclonus – renal failure syndrome (*SCARB2*-AMRF) have been published.

Generally, myoclonus and seizure management follow the same guidelines as other PME syndromes [Holmes 2020].

Clinical practice recommendations have been published for the diagnosis and management of steroid-resistant nephrotic syndrome, the likely renal disease of *SCARB2*-AMRF [Trautmann et al 2020] (full text). See also Genetic Steroid-Resistant Nephrotic Syndrome Overview, Management.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SCARB2*-AMRF, 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 *SCARB2*-Related Action Myoclonus – Renal Failure Syndrome

System/Concern	Evaluation	Comment
Neurologic	**Neurologist assess:** myoclonus incl myoclonus w/action, in response to stimuli, & at rest	Use standardized UMRS.
	Seizure type & frequency	Obtain baseline EEG.
	Cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit)	Use standardized scale to establish baseline for ataxia (BARS, ICARS, or SARA).
	Sensorimotor involvement	NCV, EMG as needed
Musculoskeletal/ADL	By physical medicine & rehab / OT & PT	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices, need for ongoing PT/OT
Hearing	Audiogram & BAEP	Assess for clinical or subclinical SNHL.
Dysarthria	Speech-language eval	Consider referral to speech-language pathologist.
Ophthalmologic involvement	Complete eye exam	Incl extraocular movement
Cognitive	Neuropsychologist	Cognitive eval to establish baseline
Psychiatric/Emotional	Psychiatrist	Evaluate as needed for depression & supportive therapy.
Development / School performance	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for special education
SRNS	Referral to nephrologist	• Serum creatinine/BUN; urine protein/creatinine; renal ultrasound exam • May require kidney biopsy.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Poor weight gain	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SCARB2*-AMRF to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent and patient organizations; • Social work involvement for parental/ care-giver support; • Home nursing referral.	To facilitate peer support for affected persons & their families
Ethics consultation	Clinical ethics services	Assess health care decisions in the context of the best interest of the child & the values & preferences of the family.

ADL = activities of daily living; BAEP = brain stem auditory evoked potentials; BARS = Brief Ataxia Rating Scale; BUN = blood urea nitrogen; ICARS = International Cooperative Ataxia Rating Scale; EMG = electromyogram; MOI = mode of inheritance; NCV = nerve conduction velocities; OT = occupational therapist/therapy; PT = physical therapist/therapy; SARA = Scale for the Assessment and Rating of Ataxia; *SCARB2*-AMRF = *SCARB2*-related action myoclonus – renal failure syndrome; SNHL = sensorineural hearing loss; SRNS = steroid-resistant nephrotic syndrome; UMRS = Unified Myoclonus Rating Scale
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *SCARB2*-AMRF.

Neurologic Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications of neurologic manifestations is recommended. This can include multidisciplinary care by specialists (see Table 6).

Table 6. Supportive Treatment of Neurologic Manifestations in Individuals with *SCARB2*-Related Action Myoclonus – Renal Failure Syndrome

Manifestation/Concern		Treatment	Considerations/Other
Myoclonus	**Pharmacologic**	Valproic acid	1st drug of choice; diminishes myoclonus & frequency of generalized seizures
		Clonazepam	FDA approved for treatment of myoclonic seizures; used as add-on therapy [1]
		Other medications	See Agents/Circumstances to Avoid; refer to epileptologist for personalized mgmt.
		High-dose piracetam	Useful in treatment of myoclonus [2]
		N-acetylcysteine	Variable results [3]
		Vagus nerve stimulation	Reduces seizures & significantly improves cerebellar function on neurologic exam [4]
	Other	Avoiding extreme stimuli (lights, noises, stress)	
Seizures		Anti-seizure medication	Follow standard measures for prevention of aspiration pneumonia & SUDEP
ADL		PT/OT	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL (incl use of adaptive devices, e.g., weighted eating utensils & dressing hooks) • Adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs) • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) & improve mobility (e.g., ramps to accommodate motorized chairs)
Developmental plateau / Cognitive decline		See Developmental Delay / Intellectual Disability / Educational Issues.	Persons w/cognitive decline may benefit from the same resources available to those w/intellectual disability.
Dysarthria		Speech-language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia		Feeding therapy programs to improve nutrition & reduce aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration • PEG tube in advanced cases
Hearing loss		Per audiologist	Hearing aids may be of benefit.
SRNS		Medical mgmt per treating nephrologist	Renal replacement therapy (dialysis, kidney transplantation) if refractory to medical mgmt
Psychiatric comorbidity		Per psychiatrist & psychotherapist	Treatment needs to be individualized.
Weight		Nutrition assessment	• Consider nutritional & vitamin supplementation to meet dietary needs. • Avoid obesity, which can exacerbate difficulties w/ ambulation & mobility.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family support & resources	• Social work involvement for parental/caregiver support • Home nursing referral	As needed

ADL = activities of daily living; OT = occupational therapy; PEG = percutaneous endoscopic gastrostomy; PT = physical therapy; SRNS = steroid-resistant nephrotic syndrome; SUDEP = sudden unexpected death in epilepsy

1. Shahwan et al [2005]
2. Koskiniemi et al [1998]
3. Edwards et al [2002]
4. Smith et al [2000]

Renal Disease

The goal of treatment in FSGS is remission of proteinuria. Treatment often includes a combination of renin-angiotensin-aldosterone system inhibition and immunosuppressive medications such as glucocorticoids, calcineurin inhibitors, mycophenolate mofetil, and rituximab. Therapy should be guided by a nephrologist. Treatment of end-stage kidney disease in *SCARB2*-AMRF is supportive. Dialysis and kidney transplantation can prolong survival but do not improve the neurologic features.

Developmental Delay / Intellectual Disability / Educational Issues

The following information represents typical management recommendations for school-age individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

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:

- Individualized education plan (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.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Recommended Surveillance for Individuals with *SCARB2*-Related Action Myoclonus – Renal Failure Syndrome

System/Concern	Evaluation	Frequency
Myoclonus	Severity of myoclonus using UMRS	At least annually
Seizures	Seizure type & frequency	
Cerebellar involvement	Clinical eval	Per symptom progression
Sensorimotor nerve involvement	EMG, neurologic exam	As needed based on clinical findings
Hearing	Audiogram & BAEP	Annually
Dysarthria	Assess need for alternative communication method or speech therapy.	Per symptom progression
Dysphagia	Assess aspiration risk & feeding methods.	
Weight / Nutritional status	• Monitor BMI. • Consult a nutritionist. • High-calorie supplementation	
ADL	Clinical assessment to evaluate rehab plan	At least annually
School performance	Interview	
Cognitive/ Psychiatric	Evaluate mood, signs of psychosis, & cognitive complaints to identify need for pharmacologic & psychotherapeutic interventions.	Per symptom progression & development of psychiatric symptoms
Renal involvement	For those w/known renal disease: • Urine protein/creatinine • Nephrology follow up	Per treating nephrologist
	For those w/o known renal disease: • Measurement of blood pressure • Urine protein/creatinine • Serum creatinine concentration	Annually
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

ADL = activities of daily living; BAEP = brain stem auditory evoked potentials; EMG = electromyogram; UMRS = Unified Myoclonus Rating Scale

Agents/Circumstances to Avoid

Phenytoin may aggravate neurologic symptoms or even accelerate cerebellar degeneration.

Sodium channel blockers (carbamazepine, oxcarbazepine), GABAergic drugs (tiagabine, vigabatrin), and gabapentin and pregabalin may aggravate myoclonus and myoclonic seizures [Mantoan & Walker 2011].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Some anti-seizure medications (ASMs) can increase the risk of malformations, growth restriction, or neurodevelopmental disabilities in exposed fetuses. However, when pregnant women experience prolonged seizures, the risk of adverse fetal outcomes is increased. Therefore, it is recommended that pregnant women with a known seizure disorder continue to take ASMs and the prescribing physician follows standard measures to prevent fetopathy, including:

- Possible changes of medication prior to pregnancy;
- During pregnancy, spacing of ASMs into four doses a day or taking extended-release medications, so that the drug levels do not have significant peaks or troughs;
- Monitoring ASM dosages and levels during pregnancy and after delivery.

In addition, all women of childbearing age should be advised to take 1 mg/day of folic acid and increase it to 4 mg/day when planning a pregnancy (ideally three months prior to conception) and during the pregnancy, in order to reduce the risk of neural tube defects and other congenital malformations that can be associated with fetal exposure to ASMs.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Substrate reduction therapy (SRT) with miglustat (600 mg daily) has been reported to improve myoclonus, epilepsy, and dysphagia [Chaves et al 2011, Quraishi et al 2021].

While venglustat theoretically has a similar mechanism of action with better central nervous system penetration than miglustat, no reports of its use in *SCARB2*-AMRF have been published to date.

Search Clinical Trials.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.

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

SCARB2-related action myoclonus – renal failure syndrome (*SCARB2*-AMRF) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *SCARB2* pathogenic variant.

- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *SCARB2* 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 a *SCARB2* 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.
- The number and range of clinical manifestations and the order of their appearance can vary between affected sibs. Neurologic manifestations may occur first or in isolation in some family members, and renal manifestations may occur first or in isolation in other family members [Badhwar et al 2004].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has *SCARB2*-AMRF or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SCARB2*.

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of a *SCARB2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SCARB2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- For women who are affected with *SCARB2*-AMRF and considering pregnancy, standard measures for prevention of fetopathy should be followed (see Pregnancy Management).
- 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 affected, are carriers, or at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SCARB2* 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**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **Citizens United for Research in Epilepsy (CURE)**
  www.cureepilepsy.org
- **EpiCARE: a European Reference Network for rare and complex epilepsies**
  www.epi-care.eu
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **American Kidney Fund**
  Phone: 800-638-8299
  www.kidneyfund.org
- **European Rare Kidney Disease Reference Network (ERKNet)**
  Phone: 49 0 6221 56-34191
  Email: contact@erknet.org
  www.erknet.org
- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806; 800-361-7494
  Email: info@kidney.ca
  www.kidney.ca
- **NephCure Kidney International**
  Phone: 866-NephCure; 866-637-4287
  Email: info@nephcure.org
  nephcure.org
- **Nephrotic Syndrome Study Network (NEPTUNE)**

As a research consortium of physician scientists at 26 sites in the United States and Canada, along with patient advocacy groups NephCure Kidney International and the Halpin Foundation, NEPTUNE strives to bring the latest advances in research to patients diagnosed with Focal Segmental Glomerulosclerosis (FSGS), Minimal Changes Disease (MCD), and Membranous Nephropathy (MN) with an overarching goal of utilizing precision medicine for rare diseases.

Phone: 734-615-5020

Email: NEPTUNE-STUDY@umich.edu

www.neptune-study.org

- **PodoNet Registry**

  The PodoNet Registry explores the demographics, causes and prognosis of patients with congenital and steroid resistant nephrotic syndrome.

  Clinical, Genetic and Experimental Research into Hereditary Disease of the Podocyte

  PodoNet

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. SCARB2-Related Action Myoclonus – Renal Failure Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SCARB2	4q21.1	Lysosome membrane protein 2	SCARB2 database	SCARB2	SCARB2

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 SCARB2-Related Action Myoclonus – Renal Failure Syndrome (View All in OMIM)

254900	EPILEPSY, PROGRESSIVE MYOCLONIC, 4, WITH OR WITHOUT RENAL FAILURE; EPM4
602257	SCAVENGER RECEPTOR CLASS B, MEMBER 2; SCARB2

Molecular Pathogenesis

SCARB2 encodes lysosome membrane protein 2 (LMP2), a lysosomal membrane protein necessary for proper sorting, retention, and targeting of the enzyme beta-glucocerebrosidase (GC). GC binds to LIMP2 early in the endoplasmic reticulum secretory pathway and is targeted into the lysosome in a manner independent from the mannose-6-phosphate receptor pathway [Reczek et al 2007]. GC is required for lysosomal hydrolysis of glucosylceramide and is implicated in Gaucher disease. Pathogenic variants in *SCARB2* result in missorting and depletion of GC in lysosomes. As neurologic phenotypes are associated with pathogenic *GBA* (which encodes GC) variants in both the homozygous and heterozygous states, this is thought to be one of the drivers of *SCARB2*-related action myoclonus – renal failure syndrome (*SCARB2*-AMRF) pathogenesis.

LMP2 likely also has other less well-characterized functions possibly related to cholesterol transport that may also contribute to disease pathogenesis [Heybrock et al 2019].

Mechanism of disease causation. Loss-of-function variants or variants that lead to abnormal localization of LMP2 lead to *SCARB2*-AMRF.

Table 8. Notable *SCARB2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005506.4 NP_005497.1	c.862C>T	p.Gln288Ter	In the French Canadian population, the vast majority of probands are homozygous for this variant [Dibbens et al 2011].
NM_005506.4	c.1187+2dupT	--	In the French Canadian population, a small proportion of probands are compound heterozygotes for this variant & c.862C>T [Dibbens et al 2011].
NM_005506.4 NP_005497.1	c.1385_1390delGATCCAinsATGCATGCACC	p.Gly462AspfsTer34	Homozygosity for this variant was reported in 2 Japanese families w/ late-onset disease [Higashiyama et al 2013, Fu et al 2014].

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

Dr Changrui Xiao (changrx@hs.uci.edu), Dr Camilo Toro (toroc@mail.nih.gov), and Dr Sara Kibrom (skibrom@stanford.edu) would be happy to communicate with persons who have any questions regarding the diagnosis of *SCARB2*-related action myoclonus – renal failure syndrome or other considerations.

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Author History

Dina Amrom, MD; McGill University (2015-2023)
Eva Andermann, MDCM, PhD, FCCMG; McGill University (2015-2023)
Frederick Andermann, MD, FRCP(C); McGill University (2015-2023)
Haejun Ahn, MD (2023-present)
Sara Kibrom, MD (2023-present)
Camilo Toro, MD (2023-present)
Changrui Xiao, MD (2023-present)

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