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NLM Citation: Weaver KN, Sullivan B, Hildebrandt F, et al. Sphingosine Phosphate Lyase Insufficiency Syndrome. 2020 Oct 15. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Sphingosine Phosphate Lyase Insufficiency Syndrome

Synonyms: SGPL1 Deficiency, Steroid-Resistant Nephrotic Syndrome Type 14

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Created: October 15, 2020.

Summary

Clinical characteristics

Sphingosine phosphate lyase insufficiency syndrome (SPLIS) is characterized by varying combinations of steroid-resistant nephrotic syndrome (ranging from nonimmune fetal hydrops to adolescent onset), primary adrenal insufficiency (with or without mineralocorticoid deficiency), testicular insufficiency, hypothyroidism, ichthyosis, lymphopenia/immunodeficiency, and neurologic abnormalities that can include developmental delay, regression / progressive neurologic involvement, cranial nerve deficits, and peripheral motor and sensory neuropathy.

Diagnosis/testing

The diagnosis of SPLIS is established in a proband with at least one suggestive finding and biallelic pathogenic variants in *SGPL1* identified by molecular genetic testing.

Management

Treatment of manifestations: Multidisciplinary management of steroid-resistant nephrotic syndrome, endocrine involvement, immunodeficiency, poor weight gain / feeding issues, developmental delay / intellectual disability, neurologic involvement, hearing loss, ichthyosis.

Surveillance: Routine follow up as requested by specialty care providers and routine monitoring of development progress and educational needs.

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Agents/circumstances to avoid: Nephrotoxic medications; medications that require renal excretion (individuals with renal insufficiency); live vaccines, exposure to infectious agents, and transfusion products that have not been irradiated.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and awareness of agents and circumstances to avoid.

Genetic counseling

SPLIS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SGPL1* 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 *SGPL1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Sphingosine phosphate lyase insufficiency syndrome (SPLIS) **should be suspected** in individuals with any combination of the following clinical, laboratory, and imaging findings and family history.

Clinical findings

- **Steroid-resistant nephrotic syndrome.** Typically congenital or infantile-onset, often associated with focal segmental glomerulosclerosis
- **Endocrine**
  - Primary adrenal insufficiency (low cortisol with normal or high ACTH). Typically, glucocorticoid deficiency; some individuals also have mineralocorticoid deficiency.
  - Testicular insufficiency (increased gonadotropins, poor response to LH stimulation); typically manifest in newborns as micropenis and cryptorchidism or microorchidism
  - Primary hypothyroidism (low-to-normal free thyroxine levels with increased thyroid stimulating hormone)
- **Immunodeficiency**
  - T-cell lymphopenia or pan lymphopenia. Low absolute lymphocyte counts; low CD3, CD4, CD8 T-cell subsets with or without low absolute B- and NK-cell counts
  - Low-to-normal immunoglobulins
  - Abnormal TREC (T-cell receptor excision circle) newborn screening test (on occasion)
  - Normal or impaired T-cell functional assays, proliferation, and response to vaccinations
- **Neurologic abnormalities** including:
  - Cranial nerve deficits
  - Sensorineural hearing loss
  - Developmental delay
  - Regression / progressive neurologic involvement
  - Upper motor neuron involvement presenting as weakness and/or spasticity
  - Lower motor neuron involvement including motor and sensory neuropathy
  - Seizures (generalized or complex partial)
- **Skin.** Ichthyosis, often generalized and present at birth. Acanthosis/hyperpigmentation including conjunctival hyperpigmentation can also be seen.

Laboratory findings. Increased sphingosine-1-phosphate and/or other sphingolipids on plasma metabolic analysis. In most individuals, specialized tests were obtained by tandem mass spectrometry-based analysis under research protocols. However, accumulation of sphingolipid intermediates may be detected on a comprehensive plasma/serum metabolomics profiling test designed to capture a broad range of small molecules [Guerrero et al 2018]. Increased plasma sphingosine/dihydrosphingosine ratio may be observed.

Imaging findings

- **Brain MRI.** Nonspecific abnormalities can include structural brain anomalies (most commonly agenesis or dysgenesis of the corpus callosum) abnormal deep gray nuclei, involvement of dopaminergic neurons, microcephaly, prominent involvement of basal ganglia, cortical atrophy, and/or progressive worsening and expansion of brain lesions observed on T_2-weighted or FLAIR images [Martin et al 2020]. One individual had generalized cortical atrophy, simplified gyral pattern, hypoplastic temporal lobe, and cerebellar hypoplasia [Bamborschke et al 2018].
- **Abdominal ultrasound.** Enlarged kidneys or adrenal glands, calcifications of adrenal gland

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). There may be family history of unexplained fetal loss or nonimmune fetal hydrops. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of sphingosine phosphate lyase insufficiency syndrome (SPLIS) **is established** in a proband with at least one suggestive finding and biallelic pathogenic (or likely pathogenic) variants in *SGPL1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SGPL1* variants of uncertain significance (or of one known *SGPL1* pathogenic variant and one *SGPL1* 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, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of SPLIS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SGPL1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. 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 typically is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; to date, however, such variants have not been identified as a cause of this disorder.

A steroid-resistant nephrotic syndrome, **hereditary neuropathy**, or **primary adrenal insufficiency multigene panel** that includes *SGPL1* 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 sphingosine phosphate lyase insufficiency syndrome, some panels for steroid-resistant nephrotic syndrome, hereditary neuropathy, and/or primary adrenal insufficiency 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. Note: To date such variants have not been identified as a cause of this disorder.

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 Sphingosine Phosphate Lyase Insufficiency Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SGPL1	Sequence analysis [3]	All reported [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Atkinson et al [2017], Janecke et al [2017], Lovric et al [2017], Prasad et al [2017], Bamborschke et al [2018], Linhares et al [2018], Saygili et al [2019a], Saygili et al [2019b], Settas et al [2019], Zhao et al [2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Sphingosine phosphate lyase insufficiency syndrome (SPLIS) is characterized by varying combinations of steroid-resistant nephrotic syndrome, primary adrenal insufficiency (with or without mineralocorticoid deficiency), testicular insufficiency, immunodeficiency, and neurologic abnormalities, and may also include primary hypothyroidism and ichthyosis (Table 2).

To date, 46 individuals with sphingosine phosphate lyase insufficiency syndrome (SPLIS) have been reported [Atkinson et al 2017, Janecke et al 2017, Lovric et al 2017, Prasad et al 2017, Bamborschke et al 2018, Linhares et al 2018, Saygili et al 2019a, Settas et al 2019, Taylor et al 2019, Maharaj et al 2020, Zhao et al 2020]. Of note, the individual reported by Taylor et al [2019] is also included in the report by Zhao et al [2020]. The following description of the phenotypic features of SPLIS is based on these reports.

Table 2. Features of Sphingosine Phosphate Lyase Insufficiency Syndrome

Feature		# of Persons	Comment
Steroid-resistant nephrotic syndrome		37/46	
Endocrine	Primary adrenal insufficiency	31/46	5 who also had mineralocorticoid deficiency [1]
	Testicular insufficiency		8/26 w/cryptorchidism &/or micropenis
	Hypothyroidism	6/46	
Immunodeficiency		31/46	
Neurologic abnormalities		22/46	• Cranial nerve deficits (11/46) • Strabismus (6/46) • Ptosis (2/46) • Developmental delay (9/46) • Regression/progressive neurologic involvement (6/46) • Peripheral motor & sensory neuropathy (5/46) • Spasticity
Sensorineural hearing loss		8/45	
Ichthyosis/acanthosis		13/46	

1. Prasad et al [2017], Linhares et al [2018], Maharaj et al [2020]

Nephrotic Syndrome

The range of renal involvement extends from nonimmune fetal hydrops at the severe end to delayed evidence of nephrosis for many years after diagnosis or no renal involvement after years of follow up, as observed in two sibs in their twenties and thirties [Atkinson et al 2017]. Typically, the nephrotic syndrome is congenital or occurs during infancy, is unresponsive to steroids, and progresses rapidly to end-stage kidney disease within one year. The oldest age of diagnosis of nephrotic syndrome among the 46 reported individuals is 18 years [Lovric et al 2017].

Six affected individuals underwent kidney transplantation: two at age five years; one at age five years and again at age 12 years; and one at age eight years. Age at transplant of the other two individuals was not provided; however, at time of last update one was age 8.4 years and the other 17.5 years.

Pathology of renal biopsies is usually consistent with glomerulosclerosis, especially with focal segmental glomerulosclerosis (FSGS) and ultrastructural finding of podocyte foot-process effacement. Three affected individuals had collapsing variant FSGS, a subclassification associated with rapid disease progression [Zhao et al 2020]. Some individuals had a pathologic diagnosis of diffuse mesangial sclerosis. Focal tubular dilatation, diffuse IgM staining, foci of calcification, lipid or hyaline droplets, perivascular sclerosis, and hypertrophic blood vessel walls have been reported in some renal biopsies.

Endocrine Involvement

Primary adrenal insufficiency may occur with or without adrenal calcifications, and may present as an Addisonian crisis requiring emergent treatment with corticosteroid and electrolyte replacement therapy. All individuals with primary adrenal insufficiency have glucocorticoid deficiency; some also have mineralocorticoid deficiency.

Most individuals with adrenal insufficiency have become symptomatic in the first decade of life. The oldest reported age of onset was 11 years [Lovric et al 2017].

Adrenal calcifications or enlargement, which may be seen prenatally, are likely a risk factor for adrenal insufficiency [Janecke et al 2017, Zhao et al 2020].

Testicular insufficiency is suspected in newborns with micropenis, cryptorchidism, or microorchidism. Hormone studies show low baseline levels of testosterone, no increase in testosterone levels in response to human chorionic gonadotropin (HCG), exaggerated gonadotropin response to luteinizing hormone-releasing hormone test in early infancy, low müllerian inhibitory factor, and low serum levels of inhibin B.

Hypothyroidism. The age of onset is unknown. Endocrine studies show low or normal T4, high TSH. Thyroxine replacement is necessary

Lymphopenia. Among individuals with SPLIS, the lower incidence of lymphopenia compared to nephrotic syndrome, adrenal insufficiency, and neurologic defects may be due to failure to recognize and report the presence of asymptomatic lymphopenia in the earliest descriptions of this disorder.

Multiple individuals with SPLIS have experienced frequent infections including several whose cause of death was related to infection [Lovric et al 2017, Bamborschke et al 2018, Saygili et al 2019b, Zhao et al 2020]. Most individuals who died of sepsis had experienced prolonged hospitalizations, complex courses, and other risk factors for infection.

To date, two individuals with SPLIS have had abnormal TREC (T-cell receptor excision circle) on newborn screening. In one, absolute lymphocyte count was low with distorted distribution of naive to memory cells and low B and NK cell counts; IgG levels were not determined; immune response to vaccinations was protective. In the other, absolute lymphocyte count was low with low absolute CD3 T cells and normal B and NK cell counts; IgG levels were low; immune response to vaccinations was not determined [Zhao et al 2020].

Neurologic Abnormalities

Cranial nerve deficits can affect cranial nerves III, IV, VI manifesting as ptosis, strabismus, esotropia, and/or amblyopia.

Cranial nerve VIII involvement manifests as sensorineural hearing loss. The loss may be congenital or diagnosed later in the first decade; it can be progressive and severe, and unilateral or bilateral (e.g., bilateral, upward sloping with air-bone gap at 500 Hz).

Developmental delay. Some children demonstrate normal development for a period of time and achieve expected milestones as indicated by Denver Developmental Screening Test, followed by impaired acquisition of new skills. For the majority of reported individuals, detailed information about developmental progression is not available.

Regression / progressive neurologic changes. Some individuals demonstrate normal development for a period of time without signs of neurologic impairment, followed by delay in gross motor, language, and social skill development, and subsequently by a loss of skills and function (gait, language, and social interaction). This regression is often associated with progressive MRI changes and can progress to generalized hypotonia, seizures, and death.

Age of onset of deterioration and type of first manifestation are variable, in some cases as young as 12 months (case 4 in Zhao et al [2020]) and as old as 25 years (ptosis [Lovric et al 2017]). Some individuals have no reported neurologic impairment.

Peripheral neuropathy manifestations can be any of the following:

- Acute or subacute onset
- Mononeuropathy or polyneuropathy involving upper or lower limbs, often distal
- Median or ulnar paralysis
- Absent reflexes
- Sensory neuropathy, transient pain, loss of vibration sense
- Spontaneous resolution that is complete or with residual deficits
- Progression leading to muscle wasting, contractures, scoliosis, hemiparesis

In two sisters who had no other manifestations of SPLIS, the following were observed [Atkinson et al 2017]:

- Nerve conduction studies showed undetectable compound muscle and sensory nerve action potentials;
- EMG showed spontaneous activity and a neuropathy pattern;
- Axonal neuropathy was demonstrated by axonal disintegration on sural nerve biopsy in one sib.

Seizures. Generalized and complex partial seizures may be associated with adrenal insufficiency, hypoglycemia, or progressive neurologic disease.

Microcephaly (n=4). Usually reported without details or neuroradiologic measurements of brain size. In one individual with additional brain developmental defects, occipitofrontal head circumference was recorded at 31.5 cm at age two weeks (i.e., <3rd centile) [Bamborschke et al 2018].

Other

- One individual was hospitalized on numerous occasions due to gastrointestinal symptoms with no identified infectious etiology.
- In some instances, affected infants were below normal weight, often in association with severe illness requiring hospitalization. Failure to thrive may be the presenting complaint, and may be associated with adrenal insufficiency, nephrotic syndrome, or poor feeding.
- Rare skeletal abnormalities have been observed (craniotabes, short stature, rachitic rosary sign, scoliosis, asymmetric skull). Scoliosis may be secondary to neurologic defects.
- Rarely: intestinal malrotation; pericardial effusion, dilated cardiomyopathy, dysmorphic features (hypertelorism, down-slanting palpebral fissures).

Ichthyosis/acanthosis. Ichthyosis may present at birth or later. Hyperpigmentation has been a presenting manifestation in numerous individuals usually as a consequence of primary adrenal insufficiency. Skin biopsies have shown thinned epidermis with hyperkeratosis and decreased granular layer of skin.

Abnormalities noted prenatally in 14/15 pregnancies included nonimmune hydrops, adrenal calcifications, and increased nuchal translucency. There have been several instances of intrauterine fetal demise.

Genotype-Phenotype Correlations

Genotype-phenotype correlations are not fully defined for SPLIS.

Intrafamilial variability is observed as the clinical manifestations and age of onset can vary within the same family in which affected individuals have the same *SGPL1* pathogenic variants. For example, some can be a fetal loss, whereas others develop manifestations in infancy or later in childhood.

Prevalence

The prevalence of SPLIS is unknown. To date, approximately 46 individuals with SPLIS have been reported. The total number of reported individuals depends on whether or not sibs of index cases whose presentations are consistent with the diagnosis of SPLIS (but without molecular genetic confirmation) were counted.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic germline pathogenic variants in *SGPL1*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Sphingosine Phosphate Lyase Insufficiency Syndrome

Gene(s)	DiffDx Disorder(s)	MOI	Features of the DiffDx Disorder	
			Overlapping w/SPLIS	Distinguishing from SPLIS
ALDH3A2	Sjögren-Larsson syndrome [1]	AR	Ichthyosis; intellectual disability; abnormal brain MRI	Spasticity; lack of kidney involvement
GBA1 (*GBA*)	Gaucher disease type 2	AR	Ichthyosis; nonimmune hydrops; abnormal brain MRI	Hepatosplenomegaly; pancytopenia
LAMB2	Pierson syndrome (OMIM 609049)	AR	Steroid-resistant nephrotic syndrome; developmental delay	Microcoria
LIPA	Lysosomal acid lipase deficiency	AR	Adrenal calcifications	Hepatic fibrosis & cirrhosis; intestinal malabsorption
LMX1B	Nail-patella syndrome	AD	Steroid-resistant nephrotic syndrome; sensorineural hearing loss	Nail dysplasia; hypoplastic or absent patellae; eye anomalies
NPHS1 *NPHS2* *PLCE1*	Congenital nephrotic syndrome types 1, 2, & 3 (OMIM 256300, 600995, 610725)	AR	Steroid-resistant nephrotic syndrome	Absence of additional syndromic findings
SMARCAL1	Schimke immunoosseous dysplasia	AR	Steroid-resistant nephrotic syndrome; T-cell lymphopenia	Spondyloepiphyseal dysplasia; numerous lentigines

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; SPLIS = sphingosine phosphate lyase insufficiency syndrome

1. Cho et al [2018]

Table 4. Differential Diagnosis of Clinical Findings Associated with Sphingosine Phosphate Lyase Insufficiency Syndrome

Clinical Finding	Distinguishing Features	Comment
Motor/sensory neuropathy	Often autosomal dominant	See Charcot-Marie-Tooth Hereditary Neuropathy Overview.
Congenital ichthyosis	Acanthosis may be observed in SPLIS.	• Congenital ichthyosis is a feature of several genetic syndromes. • Nonsyndromic ichthyosis (e.g., autosomal recessive congenital ichthyosis) can be considered if ichthyosis is the presenting finding; syndromic ichthyosis can be assoc w/Netherton syndrome, Sjögren-Larsson syndrome, & trichothiodystrophy
Nonimmune hydrops	Enlarged/hemorrhagic adrenals	Many genetic conditions are assoc w/fetal hydrops (e.g., chromosome anomalies, RASopathies, & lysosomal storage disorders). [1]

Table 4. continued from previous page.

Clinical Finding	Distinguishing Features	Comment
Primary adrenal insufficiency	Adrenal calcifications, hypothyroidism, cryptorchidism, & micropenis may be assoc w/ primary adrenal insufficiency.	• Many disorders affect the adrenal cortex → inadequate production of adrenal steroids & features incl vomiting, hypoglycemia, poor weight gain, & fatigue. • Causes can include: disorders that affect steroid biosynthesis, cholesterol metabolism, mitochondrial function (see Mitochondrial Disorders Overview); those assoc w/various metabolic defects (e.g., peroxisomal disorders); adrenal dysgenesis; & resistance to adrenocorticotropic hormone. [2]
Primary immunodeficiency / T-cell lymphopenia (CD4 & CD8) w/or w/o low B & NK cells	Persons w/SPLIS have lymphopenia w/↓ T cells & frequently low B & NK cells; however, T-cell function & vaccine responsiveness is generally retained in SPLIS (vs in persons w/SCID).	• Isolated T-cell deficiency may be found in many primary immune deficiencies (e.g., SCID, 22q11.2 deletion syndrome, CHARGE syndrome, *FOXN1* haploinsufficiency, CD3 deficiency, & IL7R deficiency). [3] • Combined T-, B-, & NK-cell deficiency can be seen in primary immune deficiencies incl adenosine deaminase deficiency & PNP deficiency.
Steroid-resistant nephrotic syndrome (SRNS)	High incidence of collapsing variant FSGS in SRNS [4]	>50 monogenic causes of SRNS have been identified [5]; disease is largely limited to kidneys in many affected persons.

FSGS = focal segmental glomerulosclerosis; PNP = purine nucleoside phosphorylase; SCID = severe combined immunodeficiency; SPLIS = sphingosine phosphate lyase insufficiency syndrome

1. Mardy et al [2019]

2. Flück [2017], Buonocore & Achermann [2020]

3. Tangye et al [2020]

4. Collapsing variant FSGS is a pathologic diagnosis given when one or more glomeruli show segmental or global obliteration of the glomerular capillary lumen due to collapse of the glomerular basement membrane associated with podocyte hypertrophy and hyperplasia. It is most often seen in association with severe nephrotic syndrome and rapid progression to end-stage kidney disease.

5. Preston et al [2019]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with sphingosine phosphate lyase insufficiency syndrome (SPLIS), 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 Sphingosine Phosphate Lyase Insufficiency Syndrome

System/Concern	Evaluation	Comment
Steroid-resistant nephrotic syndrome	Referral to nephrologist	• Serum creatinine/BUN; urine protein/creatinine; renal ultrasound • May require kidney biopsy

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Primary adrenal insufficiency	Endocrinology referral	• Early morning ACTH & cortisol • Serum electrolytes • Plasma renin activity • Adrenal ultrasound; ACTH stimulation test if baseline results borderline
Hypothyroidism		Serum TSH & free T4
Testicular insufficiency		Age-related lab investigations: luteinizing hormone, follicle-stimulating hormone, testosterone, serum inhibin B, anti-müllerian hormone
Immunodeficiency	Consider referral to immunologist.	• T-, B-, & NK-cell subset analysis • Serum immunoglobulins • T-cell proliferation assays • Antibody titers to vaccinations
Poor weight gain / Failure to thrive	Eval by gastroenterology, nutrition, feeding team	Initiation of tube feeding if needed
Neurologic involvement	Neurologic exam	• Assess for UMN involvement (spasticity, ↑ DTRs) & LMN involvement (strength, sensation, DTRs); if abnormal consider EMG & NCV. • Consider EEG if seizures are a concern. • Brain MRI if not previously performed
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiologic eval	For sensorineural hearing loss
Speech	Speech & language pathology assessment	For those w/DD &/or hearing loss
Development	Developmental assessment	To incl: • Motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Ichthyosis/ Acanthosis	Dermatology referral if skin abnormalities	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SPLIS to facilitate medical & personal decision making

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ACTH = adrenocorticotropic hormone; ADL = activities of daily living; DD = developmental delay; DTRs = deep tendon reflexes; EEG = electroencephalogram; EMG = electromyogram; LMN = lower motor neuron; MOI = mode of inheritance; NCV = nerve conduction velocity; OT = occupational therapy; PT = physical therapy; TSH = thyroid stimulating hormone; UMN = upper motor neuron
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Sphingosine Phosphate Lyase Insufficiency Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Steroid-resistant nephrotic syndrome	• Medical mgmt of kidney failure per nephrologist • Kidney replacement therapy if refractory to medical mgmt	Outcomes of kidney transplant are largely unknown.
Primary adrenal insufficiency	By pediatric endocrinologist	• Glucocorticoid replacement • Mineralocorticoid replacement as required ± sodium supplementation • Appropriate counseling for sick days; emergency & perioperative mgmt
Hypothyroidism		Thyroxine replacement as required
Testicular insufficiency		• Infants w/micropenis: consider testosterone Rx to ↑ penile length & allow for urination standing up. • At puberty: consider need for testosterone Rx. • Consider counseling re potential ↓ spermatogenesis & possible sperm banking.
Immunodeficiency	Care by immunologist	Monitor absolute lymphocyte count over time. If proliferation is abnormal, consider avoiding live vaccines. Most affected persons have normal or near-normal T-cell function despite ↓ absolute levels. To consider: supportive therapy (e.g., IVIG) to prevent infection based on history & lab testing.
Poor weight gain / Failure to thrive	Search for underlying etiology, e.g., renal or endocrine problem.	Consider input from nutritionist, parenteral feeding.
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Neurologic involvement	Seizure management	• Rule out electrolyte disturbances & hypoglycemia. • Information is insufficient re specific antiseizure mgmt. Consider pyridoxine trial.
Mobility/ADL	Orthopedics / physical medicine & rehab / PT & OT	Consider need for positioning & mobility devices, disability parking placard.

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Hearing	Hearing aids may be helpful; per audiologist.	Community hearing services through early intervention or school district
Speech	Speech therapy	
Ichthyosis	Topical emollients	
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

ADL = activities of daily living; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

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.
  - 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, and modified assignments.
- 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

There are no published surveillance guidelines. Based on the known potential medical conditions associated with SPLIS, we propose consideration of the following (see Table 7).

Table 7. Recommended Surveillance for Individuals with Sphingosine Phosphate Lyase Insufficiency Syndrome

System/Concern	Evaluation	Frequency
Steroid-resistant nephrotic syndrome	For those w/known kidney disease: • Urine protein/creatinine • Nephrology follow up	Per treating nephrologist
	For those w/o known kidney disease	• Annual urine protein/creatinine if w/o known disease • Annual blood pressure
Primary adrenal insufficiency	Early morning ACTH, serum cortisol (thereafter ACTH stimulation test if baseline results borderline/abnormal), electrolytes, & plasma renin activity	Clinical review & analysis every 6-12 mos; in addition, consider before any major procedure.
Hypothyroidism	Free T4, TSH	Annually
Testicular insufficiency	Clinical review w/close assessment of pubertal progression, further investigation if delayed onset or poor progression	Annually
Immunodeficiency	Ongoing eval of lymphocyte count & immune function	Every 6-12 mos or more frequent if ongoing infections or other concerns
Feeding/Nutrition	Monitor growth on age- & sex-appropriate curve.	Standard intervals for well-child check-ups; more frequent weight checks if growth rate ↓
Neurologic involvement	Neurologic exam for new manifestations &/or progression	At least annually
Musculoskeletal/ Mobility/ADL	OT/PT assessment	
Hearing	Audiogram	At least annually
Speech	Speech & language pathologist	
Development / Educational needs	Monitor developmental progress & educational needs.	
Ichthyosis	Photograph lesion & measure for monitoring; optional skin biopsy	As needed
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Any nephrotoxic drug should be avoided.

If renal insufficiency is present, avoid medications that require renal excretion.

Live vaccines or exposure to infectious agents may be particularly dangerous due to immunodeficiency.

Transfusion products should be irradiated.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and awareness of agents and circumstances to avoid.

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

Therapies Under Investigation

Responsiveness to cofactor supplementation (pyridoxine HCl) has been reported in two individuals with sphingosine phosphate lyase insufficiency syndrome [Zhao et al 2020].

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

Sphingosine phosphate lyase insufficiency syndrome (SPLIS) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *SGPL1* 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 an *SGPL1* 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 an *SGPL1* 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.

- Intrafamilial variability is observed in SPLIS; age of onset and clinical manifestations of SPLIS may vary in sibs with biallelic *SGPL1* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Fertility may be reduced in some individuals with SPLIS.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SGPL1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SGPL1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SGPL1* 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 Kidney Fund**
  Phone: 800-638-8299
  www.kidneyfund.org
- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806
  Email: info@kidney.ca
  kidney.ca
- **NephCure Kidney International**
  Phone: 866-NephCure; 866-637-4287
  Email: info@nephcure.org
  nephcure.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. Sphingosine Phosphate Lyase Insufficiency Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SGPL1	10q22.1	Sphingosine-1-phosphate lyase 1	SGPL1	SGPL1

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 Sphingosine Phosphate Lyase Insufficiency Syndrome (View All in OMIM)

603729	SPHINGOSINE-1-PHOSPHATE LYASE 1; SGPL1
617575	RENI SYNDROME; RENI

Molecular Pathogenesis

SGPL1 encodes sphingosine phosphate lyase (SPL), which resides in the outer membrane of the endoplasmic reticulum and functions as a homodimer. SPL, the final enzyme in the pathway of sphingolipid degradation, is a vitamin B_6-dependent intracellular enzyme required for irreversible degradation of a sphingolipid metabolite called sphingosine-1-phosphate (S1P) [Choi & Saba 2019, Saba 2019]. S1P circulates in the bloodstream bound to albumin and HDL and activates signals through its G protein-coupled receptors, which are expressed on most cell types. S1P signaling regulates T-cell egress from the thymus and peripheral lymphoid organs. S1P signaling is also important for vascular integrity.

Loss of SPL activity results in the following:

- Accumulation of S1P as well as other sphingolipids that can be cytotoxic and may contribute to the neurologic features of SPLIS
- Failure of lymphocytes to egress from the thymus and peripheral lymphoid organs resulting in lymphopenia
- Altered morphology of glomerular cells called podocytes that support the filtration function of the kidney, suggesting that disruption of sphingolipid metabolism causes glomerular damage leading to nephrosis
- Reduction of specialized ceramides and long-chain aldehydes formed by the degradation of S1P that are important in the skin barrier function – which may explain the occurrence of ichthyosis in SPLIS

SPL may play a role in adrenal gland development, which may explain the primary adrenal insufficiency observed in SPLIS. Furthermore, accumulation of upstream sphingolipid intermediates may impair acute steroidogenesis [Lucki & Sewer 2010, Prasad et al 2017].

Note: While SPLIS is considered a sphingolipidosis, it is not a lysosomal storage disease.

Mechanism of disease causation. Loss of function

***SGPL1*-specific laboratory technical considerations.** Biochemical analysis of skin fibroblasts derived from affected individuals (i.e., enzyme assays, protein expression, and sphingolipid profiling) and plasma sphingolipid profiling may be useful in evaluating variants of uncertain significance.

Table 8. Notable *SGPL1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003901.4 NP_003892.2	c.665G>A	p.Arg222Gln	Pathogenic variant present in 10/46 persons reported w/SPLIS [Lovric et al 2017, Prasad et al 2017, Zhao et al 2020]

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

NIH GARD – Sphingosine phosphate lyase insufficiency syndrome

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Acknowledgments

We are grateful to all those who have reported cases and cohorts of individuals with SPLIS/NPHS14, helping to reveal the range of presentations, pathogenic variants associated with the condition, and initial insights into its pathogenesis. We are also grateful to the families who have shared medical information in the interest of advancing care and treatment for individuals suffering from SPLIS.

Revision History

- 15 October 2020 (bp) Review posted live
- 31 March 2020 (knw) Original submission

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