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Asparagine Synthetase Deficiency

Synonym: ASNS Deficiency

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Summary

Clinical characteristics

Asparagine synthetase deficiency (ASD) mainly presents as a triad of congenital microcephaly, severe developmental delay, and axial hypotonia followed by spastic quadriplegia. Low cerebrospinal fluid (CSF) asparagine level can help the clinician in differentiating this disorder from others. In most cases age of onset of apnea, excessive irritability, and seizures is soon after birth. Affected individuals typically do not acquire any developmental milestones. Spastic quadriplegia can lead to severe contractures of the limbs and neurogenic scoliosis. Feeding difficulties (gastroesophageal reflux disease, frequent vomiting, swallowing dysfunction, and gastroesophageal incoordination) are a significant problem in most affected individuals. A majority have cortical blindness. MRI findings are nonspecific but may include generalized atrophy and simplified gyral pattern.

Diagnosis

The diagnosis of ASD is established in a proband by identification of biallelic pathogenic variants in *ASNS* on molecular genetic testing.

Management

Treatment of manifestations: Antispastic medication (baclofen, tizanidine, and/or Botox® injection) for spasticity; clonazepam for hyperekplexia; mechanical ventilation may be required for apnea; nasogastric or gastrostomy tube to support nutrition; standard treatment for seizures, hearing loss, gastroesophageal reflux disease, constipation, and kyphosis/scoliosis; supportive developmental therapies.

Prevention of secondary complications: Regular immunization to prevent life-threatening infections.

Surveillance

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- At each visit: evaluation of developmental progress and growth; assessment for progression of spasticity, contractures, and scoliosis/kyphosis.
- Every six months: assessment of nutritional status through serum total protein, albumin, and prealbumin levels.
- Annually: ophthalmologic evaluation.
- As needed: EEG if there are concerns for new-onset seizure activity or progression of seizures; audiologic evaluation if there are concerns for hearing loss.

Genetic counseling

Asparagine synthetase deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the *ASNS* pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Asparagine synthetase deficiency (ASD) **should be suspected** in individuals with the following clinical features, brain MRI findings, and supportive laboratory findings.

Clinical features

- Congenital and progressive microcephaly
- Severe global developmental delay
- Hypotonia followed by spastic quadriplegia, seizures, jitteriness, and hyperekplexia
- Intrauterine growth restriction with subsequent feeding difficulties, failure to thrive, and short stature
- Cortical blindness

Brain MRI findings

- Generalized brain atrophy (100%)
- Simplified gyral pattern (81%)
- Cerebellar vermis hypoplasia (41%)

Supportive laboratory findings

- **CSF asparagine level** is typically low or not detected [Alfadhel et al 2015, Yamamoto et al 2017].
- **Plasma asparagine level** is low in about half of affected individuals and is not as sensitive as CSF asparagine levels in supporting this diagnosis.
- **The following** are unremarkable:
  - Plasma acylcarnitine profile
  - Creatine kinase (CK) level
  - Total homocysteine, lactic acid, and ammonia levels
  - Urine organic acids

Establishing the Diagnosis

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

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

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *ASNS* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *ASNS* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 Asparagine Synthetase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
ASNS	Sequence analysis [3]	22/22 [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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Ruzzo et al [2013], Alfadhel et al [2015], Ben-Salem et al [2015], Palmer et al [2015], Gataullina et al [2016], Seidahmed et al [2016], Gupta et al [2017], Sun et al [2017], Yamamoto et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Gene-targeted deletion/duplication analysis has not identified any pathogenic variants to date.

Clinical Characteristics

Clinical Description

Asparagine synthetase deficiency (ASD) mainly presents as a triad of congenital microcephaly, severe developmental delay, and axial hypotonia followed by spastic quadriplegia. Low CSF asparagine level can help differentiate this disorder from others with similar clinical findings [Ruzzo et al 2013, Alfadhel et al 2015, Ben-Salem et al 2015]. Age of onset is soon after birth in the majority of reported individuals (median age of onset: 1 day; range 1 day – 9 months). Only three cases have presented after the neonatal period [Ruzzo et al 2013, Sacharow et al 2018]. Two neonates presented prenatally with microcephaly detected by antenatal ultrasound [Seidahmed et al 2016, Yamamoto et al 2017].

The common clinical manifestations summarized in Table 2 are discussed below the table.

Table 2. Clinical Manifestations of 22 Individuals with Asparagine Synthetase Deficiency

Clinical Manifestations	Frequency (%)
Neonatal onset [1]	17/18 (95%)
Severe global developmental delay	22/22 (100%)
Congenital & progressive microcephaly [2]	22/22 (100%)
Hyperreflexia	22/22 (100%)
Axial hypotonia followed by spastic quadriplegia	21/22 (95%)
Seizures	16/22 (73%)
Jitteriness	13/15 (87%)
Cortical blindness	13/22 (60%)
Hyperekplexia	7/22 (32%)

1. Congenital microcephaly, apnea, excessive irritability, and seizures
2. Head circumference is often 2 standard deviations (SD) below the mean at birth but may decline to 9 SD below the mean by early childhood.

Neurologic. All affected individuals reported have the following:

- Congenital microcephaly, ranging between 26.5 and 33.4 cm (1-4 SD below the mean)
- Severe global developmental delay with no acquisition of developmental milestones [Ruzzo et al 2013, Alfadhel et al 2015]
- Axial hypotonia followed by spastic quadriplegia [Seidahmed et al 2016] leading to severe contractures of all limbs and neurogenic scoliosis

Seizures usually start in the neonatal period and mimic pyridoxine-dependent epilepsy [Gataullina et al 2016].

- The type of seizure is not specific and can include the following [Ruzzo et al 2013, Alfadhel et al 2015, Seidahmed et al 2016, Gupta et al 2017, Sun et al 2017, Yamamoto et al 2017]:
  - Generalized tonic-clonic (64%)
  - Myoclonic (50%)
  - Tonic (50%)
  - Partial complex seizure (21%)
  - Spasms (15%) that are refractory to anti-seizure medication
- EEG abnormalities are nonspecific [Ruzzo et al 2013, Alfadhel et al 2015, Ben-Salem et al 2015, Palmer et al 2015, Gataullina et al 2016, Gupta et al 2017, Yamamoto et al 2017]:
  - Multiple independent spike foci most commonly (65%)

    - Burst suppression
    - Hypsarrhythmia
    - Discontinuous EEG pattern
- Jitteriness and hyperekplexia are present in 78% and 35% of reported individuals, respectively.

Brain MRI findings. The most common features are summarized in Suggestive Findings; other reported abnormalities (in <80%) include the following [Ruzzo et al 2013, Ben-Salem et al 2015, Gataullina et al 2016, Sun et al 2017]:

- Delayed myelination (68%)
- Small pons
- Thin corpus callosum (55%)
- Enlarged ventricular system (50%)
- Left transverse sinus thrombosis and cerebral dysgenesis
- Blake's cyst and/or arachnoid cyst
- Bilateral caudate atrophy
- Increased lactate peak on MR spectroscopy in four individuals studied [Ruzzo et al 2013, Palmer et al 2015]

Note: CSF asparagine level was normal in one reported individual [Seidahmed et al 2016].

Nonspecific dysmorphic facial features reported in approximately 50% of affected individuals include brachycephaly, pear-like head shape, sloping forehead, widely spaced eyes, big fleshy ears, prominent nasal tip, and micrognathia.

Gastrointestinal manifestations. Feeding difficulties are a major problem for most affected individuals. Contributing factors include hypotonia, gastroesophageal reflux disease, frequent vomiting, swallowing dysfunction, and gastroesophageal incoordination. Many affected individuals also have constipation.

Recurrent aspiration has been reported in eight individuals. Many require nasogastric tube feeding or gastrostomy [Ruzzo et al 2013, Sun et al 2017, Yamamoto et al 2017].

Ophthalmologic. Most individuals are unable to fix and follow with their eyes. Cortical blindness is reported in 65% of affected individuals. One affected person was reported to have left convergent squint [Gupta et al 2017].

Less frequently reported manifestations include the following [Ruzzo et al 2013, Ben-Salem et al 2015, Seidahmed et al 2016, Sun et al 2017]:

- Intrauterine growth restriction [Sun et al 2017]
- Sensorineural hearing loss [Palmer et al 2015, Yamamoto et al 2017]
- Frequent apneas necessitating mechanical ventilation, reported in nine affected individuals [Ruzzo et al 2013, Gupta et al 2017, Sun et al 2017]
- Diaphragmatic eventration [Sun et al 2017]
- Phrenic nerve palsy [Sun et al 2017]

Prognosis. ASD is associated with a high rate of morbidity and mortality, where 50% of individuals die in the first year of life [Ruzzo et al 2013, Seidahmed et al 2016, Gupta et al 2017, Sun et al 2017]. However, because only a small cohort of affected individuals have been reported, it is possible that this represents the more severe end of a clinical spectrum.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported.

Prevalence

ASD has been reported in 22 individuals from 14 families to date. Consanguinity was reported in 50% of families. Affected individuals from Saudi Arabia, United Arab Emirates, Canada, France, Japan, and India have been reported [Ruzzo et al 2013, Alfadhel et al 2015, Ben-Salem et al 2015, Palmer et al 2015, Gataullina et al 2016, Seidahmed et al 2016, Gupta et al 2017, Sun et al 2017, Yamamoto et al 2017].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The differential diagnosis of ASD is wide, and the cardinal features of spastic quadriplegia, microcephaly, and low asparagine level can aid clinicians in differentiating this disorder from the other related disorders.

Note: Many chromosomal disorders present with features that overlap with asparagine synthetase deficiency; therefore, a chromosomal microarray could be considered.

Table 3. Differential Diagnosis of Asparagine Synthetase Deficiency (ASD)

Phenotype/ Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of the Phenotype/Disorder	
			Overlapping w/ASD	Distinguishing from ASD
Primary autosomal recessive microcephalies	Multiple genes (See OMIM PS251200.)	AR	No malformations in other organ systems	• Normal CSF asparagine level • No spastic quadriplegia
Seckel syndrome	*ATR* *CENPJ* *CEP152* *CEP63* *RBBP8* *DNA2* *NIN* *NSMCE2* *TRAIP*	AR	• Intrauterine growth restriction • Sloping forehead • Short stature	• Normal CSF asparagine level • No spastic quadriplegia
Lissencephaly-pachygyria [1]	Multiple genes (See OMIM PS607432.)	AR AD XL	• Cerebellar hypoplasia • Simplified gyral pattern • Spastic quadriplegia	• Lissencephaly & generalized polymicrogyria • Normal CSF asparagine level
Miller-Dieker syndrome (See *PAFAH1B1*-Associated Lissencephaly / Subcortical Band Heterotopia.)	17p13.3 deletion *LIS1 (PAFAH1B1)* *YWHAE*	AD	• Hypotonia • Global DD • Spastic quadriplegia	• Lissencephaly • Dysmorphic features • Normal CSF asparagine level

Table 3. continued from previous page.

Phenotype/ Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of the Phenotype/Disorder	
			Overlapping w/ASD	Distinguishing from ASD
Smith-Lemli-Opitz syndrome	*DHCR7*	AR	Global DD	• Prenatal & postnatal growth restriction • Dysmorphic features • Syndactyly of 2nd & 3rd toes • Postaxial polydactyly • Congenital heart defect • Hypospadias in males • No spastic quadriplegia • Low total cholesterol w/↑ 7-dehydrocholesterol
Cornelia de Lange syndrome	*HDAC8* *NIPBL* *RAD21* *SMC1A* *SMC3*	AD XL	• Growth restriction • DD • Spastic quadriplegia	• Distinctive facial features • Hirsutism • Upper-limb reduction defects ranging from subtle phalangeal abnormalities to oligodactyly
Serine biosynthesis defects	*PHGDH* *PSAT1* *PSPH*	AR	• Neonatal seizure • Global DD • Spastic quadriplegia	• Low CSF serine & glycine level • Cataract • Nystagmus
Congenital disorders of N-linked glycosylation	Multiple genes (See OMIM PS212065.)	AR XL	• Neonatal seizure • Failure to thrive • Hypotonia • DD • Spastic quadriplegia • Cerebellar hypoplasia	• Hepatopathy • Hypoglycemia • Protein-losing enteropathy • Eye abnormalities • Immunologic findings • Skin abnormalities • Skeletal findings • Abnormal TIF
Early-infantile epileptic encephalopathy type 28	*WWOX*	AR	• Congenital microcephaly • Severe DD • Hypotonia • Spastic quadriplegia • Thin corpus callosum • Delayed myelination	Normal blood & CSF asparagine level

AD = autosomal dominant; AR = autosomal recessive; CSF = cerebrospinal fluid; DD = developmental delay; MOI = mode of inheritance; TIF = transferrin isoelectrofocusing; XL = X-linked

1. Lissencephaly-pachygyria spectrum of cortical malformation is characterized by smooth cortex with simplified gyration appearance. "Lissencephaly" refers to a brain without sulci. Pachygyria (focal or diffuse) is a mild expression of lissencephaly in which sulci are shallow and reduced in number.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with asparagine synthetase deficiency (ASD), the following evaluations are recommended if they have not already been completed.

Table 4. Recommended Evaluations Following Initial Diagnosis of Asparagine Synthetase Deficiency

System/Concern	Evaluation	Comments
Neurologic	Brain MRI to evaluate extent of disease	Consider neurologic consultation.
	EEG	If seizures are suspected
Ocular	Ophthalmologic eval	Consider visual evoked potential.
ENT	Audiologic eval	
Gastrointestinal/ Feeding	Assessment of growth parameters to identify those w/ failure to thrive	
	Assessment for feeding problems incl difficulty w/ sucking, swallowing, & GERD	Referral to feeding therapist if feeding problems identified
Musculoskeletal	Clinical eval for scoliosis &/or kyphosis	Consider radiographic scoliosis survey (x-rays of the spine) based on clinical suspicion; consider referral to orthopedist if scoliosis is present.
Other	Developmental assessment	To provide a baseline level of functioning & recommendations for services (speech, occupational, physical therapy)
	Consider referral to clinical geneticist &/or genetic counselor.	

GERD = gastroesophageal reflux

Treatment of Manifestations

The management of ASD requires a multidisciplinary team approach; treatment is primarily supportive.

Note: Asparagine supplementation has not been effective and actually exacerbated seizures in affected individuals [Alrifai & Alfadhel 2016].

Table 5. Treatment of Manifestations in Individuals with Asparagine Synthetase Deficiency

Manifestation/Concern	Treatment	Comments
Seizures	Standard treatment w/anti-seizure medication	
Spastic quadriplegia	Antispastic drugs (e.g., baclofen, tizanidine) &/or Botox® injection	
Hyperekplexia	Clonazepam appears to be the most effective treatment.	
Hearing loss	Hearing aids	See Hereditary Hearing Loss and Deafness Overview.
Apnea	Mechanical ventilation may be required.	
Inadequate nutrition / Feeding difficulties	Nasogastric tube or gastrostomy tube is frequently required.	
Gastroesophageal reflux (GERD)	Standard pharmacologic treatment	For severe GERD: consider Nissen fundoplication at the time of gastrostomy tube placement.
Constipation	Standard treatment	
Kyphosis/Scoliosis	Standard treatment as recommended by orthopedist	

Gross Motor Dysfunction

Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

For muscle tone abnormalities including hypertonia, consider involving appropriate specialists to aid in management of baclofen, Botox®, or orthopedic procedures.

Developmental Delay / Intellectual Disability Management Issues

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

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

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

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

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Prevention of Secondary Complications

Regular immunization to prevent life-threatening infections is indicated.

Surveillance

Table 6. Recommended Surveillance for Individuals with Asparagine Synthetase Deficiency

System/Concern	Evaluation	Frequency
Neurologic	Assessment of developmental progress	At each visit
	Assessment for progression of spasticity & contractures	
	EEG	If concerns for new seizure activity or progression of seizures
Ocular	Ophthalmologic eval	Annually
Hearing	Audiologic eval	If concern for hearing loss
Gastrointestinal/ Feeding	Measurement of growth parameters	At each visit
	Eval of nutritional status [1]	Every 6 mos
Musculoskeletal	Clinical assessment for scoliosis/kyphosis	At each visit

1. Serum total protein, albumin, and prealbumin levels

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Asparagine synthetase deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ASNS* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals affected with asparagine synthetase deficiency are not known to reproduce.

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

Carrier Detection

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to the parents of an affected child.

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *ASNS* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **American Epilepsy Society**
  www.aesnet.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com

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. Asparagine Synthetase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ASNS	7q21.3	Asparagine synthetase [glutamine-hydrolyzing]	ASNS	ASNS

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 Asparagine Synthetase Deficiency (View All in OMIM)

108370	ASPARAGINE SYNTHETASE; ASNS
615574	ASPARAGINE SYNTHETASE DEFICIENCY; ASNSD

Gene structure. *ASNS* spans 35 kb and contains 13 exons. See Table A, **Gene** for a detailed summary of gene and protein information. *ASNS* is expressed in most mammalian cells. The gene was transcribed into an mRNA of 2

kb that was expressed in all human, hamster, and mouse cell lines tested. It encodes a protein of about 550 amino acids [Greco et al 1987].

Pathogenic variants. Eighty-eight percent of reported pathogenic variants are missense. Others include pathogenic nonsense and frameshift variants [Ruzzo et al 2013, Alfadhel et al 2015, Ben-Salem et al 2015, Palmer et al 2015, Gataullina et al 2016, Seidahmed et al 2016, Gupta et al 2017, Sun et al 2017, Yamamoto et al 2017].

Normal gene product. *ASNS* encodes asparagine synthetase, which catalyzes the synthesis of asparagine from glutamine and aspartate [Ruzzo et al 2013].

Abnormal gene product. *ASNS* pathogenic variants result in loss of enzyme function, which in turn results in impaired synthesis of asparagine. Insufficient physiologic levels of arginine cause neurologic impairment [Ruzzo et al 2013, Alfadhel et al 2015].

Chapter Notes

Revision History

- 20 September 2018 (mpa) Review posted live
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