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GLYT1 Encephalopathy

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Summary

Clinical characteristics

GLYT1 encephalopathy is characterized in neonates by severe hypotonia, respiratory failure requiring mechanical ventilation, and absent neonatal reflexes; encephalopathy, including impaired consciousness and unresponsiveness, may be present. Arthrogryposis or joint laxity can be observed. Generalized hypotonia develops later into axial hypotonia with limb hypertonicity and a startle-like response to vocal and visual stimuli which should not be confused with seizures. To date, three of the six affected children reported from three families died between ages two days and seven months; the oldest reported living child is severely globally impaired at age three years. Because of the limited number of affected individuals reported to date, the phenotype has not yet been completely described.

Diagnosis/testing

The diagnosis of GLYT1 encephalopathy is established in a proband with mildly elevated cerebrospinal fluid glycine levels, normal or slightly elevated serum or plasma glycine levels, and biallelic pathogenic variants in *SLC6A9* on molecular genetic testing.

Management

Treatment of manifestations: To date, no treatment has been effective in mitigating the manifestations of GLYT1 encephalopathy. A multidisciplinary team is recommended to manage global developmental delay, respiratory failure, and feeding difficulties and to maintain range of motion and prevent contractures.

Surveillance: The following should be routinely monitored:

- Developmental status
- Respiratory function
- Neurologic status
- Musculoskeletal involvement

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- Nutritional status and feeding

Monitor as needed: blood pressure, renal function, vision, hearing.

Agents/circumstances to avoid: None known; however, valproate – which is contraindicated in glycine encephalopathy – should be avoided as it increases the concentration of blood and CSF glycine.

Genetic counseling

GLYT1 encephalopathy is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *SLC6A9* 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

GLYT1 encephalopathy **should be suspected** in individuals with the following clinical and laboratory findings [Alfadhel et al 2016, Kurolap et al 2016].

Clinical findings

- Early respiratory insufficiency
- Hypotonia later transitioning to hypertonicity of the extremities
- Startle response provoked by sudden loud sounds and tactile stimulation (which may be confused with myoclonic seizures)
- Encephalopathy (present in some)
- Arthrogryposis multiplex congenita or joint laxity
- Dysmorphic features that may include trigonocephaly or dolichocephaly, low-set ears, long myopathic face, broad forehead, broad or sparse eyebrows, long eyelashes, esotropia, ptosis, depressed nasal bridge, short nose, upturned nasal tip, prominent philtrum, tented vermilion of the upper lip, and retrognathia (Figure 1)
- Microcephaly and failure to thrive

Laboratory findings

- Cerebrospinal fluid (CSF) glycine levels*: mildly elevated (21-33 µmol/L) (normal 3.8-8 µmol/L) [Kurolap et al 2016]. Note: Normal values vary by laboratory.
- Blood (serum or plasma) glycine levels*: normal. Note: Normal values vary by age.
- Glycine CSF-to-plasma ratio: abnormal (>0.04)

* Amino acid concentrations should be measured simultaneously in CSF and blood.

Establishing the Diagnosis

The diagnosis of GLYT1 encephalopathy **is established** in a proband by identification of biallelic pathogenic variants in *SLC6A9* by molecular genetic testing [Alfadhel et al 2016, Kurolap et al 2016] (see Table 1).

Molecular genetic testing approaches to be considered include **single-gene testing** and use of a **multigene panel**:

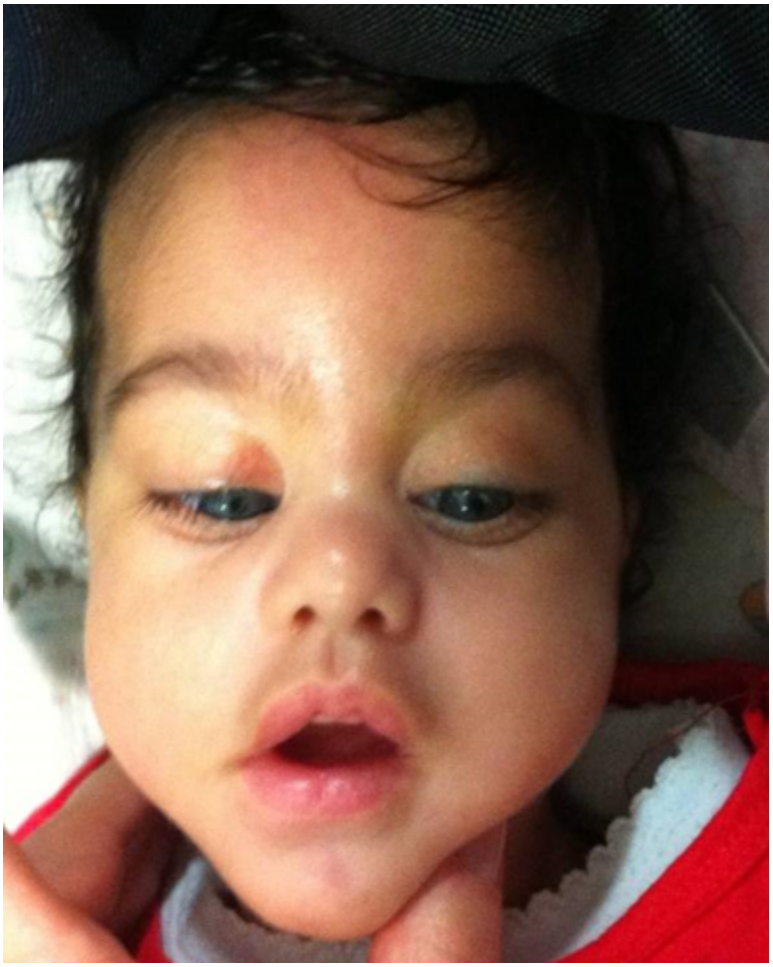

Figure 1. A girl age six months with GLYT1 encephalopathy. Note facial dysmorphism including trigonocephaly, long myopathic facies, broad forehead, broad eyebrows, long eyelashes, esotropia, ptosis, depressed nasal bridge, short nose, upturned nasal tip, prominent philtrum, tented vermilion of the upper lip, and retrognathia.

- **Single-gene testing.** Sequence analysis of *SLC6A9* is performed first. Gene-targeted deletion/duplication analysis may be performed if only one or no pathogenic variant is found; however, to date no deletions/duplications have been described.
- **A multigene panel** that includes *SLC6A9* and the two genes causing classic nonketotic hyperglycinemia (*GLDC* and *AMT*) (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 at the most reasonable cost 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.

Table 1. Molecular Genetic Testing Used in GLYT1 Encephalopathy

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
SLC6A9	Sequence analysis [3]	All variants reported to date (3/3) [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Three families with GLYT1 encephalopathy have been described to date, all harboring pathogenic homozygous variants in *SLC6A9* [Alfadhel et al 2016, Kurolap et al 2016].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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

GLYT1 encephalopathy is characterized in neonates by severe hypotonia, respiratory failure requiring mechanical ventilation, and absent neonatal reflexes; encephalopathy, including impaired consciousness and unresponsiveness, may be present. Arthrogryposis or joint laxity may be observed. Generalized hypotonia later develops into axial hypotonia with limb hypertonicity and a startle-like response provoked by vocal and visual stimuli as well as sudden loud sounds and tactile stimulation and not to be confused with seizures. To date, six affected individuals from three families have been reported [Alfadhel et al 2016, Kurolap et al 2016]. Because of the limited number of affected individuals reported to date, the phenotype has not yet been completely described.

Prenatal. Findings on prenatal ultrasound examination can include increased nuchal translucency, hydrops fetalis, polyhydramnios, arthrogryposis, and\or absent or limited fetal movements.

Respiratory. Shortly after birth infants develop respiratory failure requiring mechanical ventilation. Although with time they may be weaned off ventilatory support, they remain dependent on supplemental oxygen.

Musculoskeletal. Severe hypotonia present at birth may progress to limb hypertonicity.

Arthrogryposis multiplex congenita with club feet, hyperextension of knees, bilateral hip dislocation, contractures of the elbows, wrists, and hips, and overriding toes and fingers was described in children from two of the three families reported.

Absent patellae were observed in one child.

Joint laxity with bilateral club feet was documented in the third family.

Neurologic. Encephalopathy, including impaired consciousness and unresponsiveness, was observed in two of the three families.

All affected children showed startle-like clonus with a normal electroencephalogram (EEG). The startle-like response may resolve over time.

All had severe global developmental delay. Developmental information, available for one child at age three years, revealed that the child had not reached any motor or speech milestones.

Disease complications include feeding difficulties requiring insertion of a gastrostomy tube.

Brain imaging (CT or MRI) findings may include ventriculomegaly, optic nerve atrophy, thin or normal corpus callosum, atrophy in the caudate nucleus, and white matter abnormalities. In addition, MRI in a child age two years (proband of Family 1 [Kurolap et al 2016]) showed a focal area of diffusion restriction in one cerebellar hemisphere.

Abnormal visual evoked potentials and brain stem evoked response audiometry as well as motor and sensory polyneuropathy were reported in one child [Kurolap et al 2016].

Additional features

- Hypertension with elevated urinary catecholamines was described in one child.
- Children from two families had hydronephrosis.
- One child had atrial septal defect, cryptorchidism, and inguinal hernia.

Life expectancy. Three affected sibs died from respiratory complications between ages two days and seven months. One child from a different family is currently three years old; long-term follow up is required to determine life expectancy.

Genotype-Phenotype Correlations

Given the small number of individuals reported to date, no genotype-phenotype correlations can be drawn.

Nomenclature

Collectively, neurologic disorders caused by disturbance of glycine metabolism and transport are termed glycine encephalopathy.

- Disorders of glycine metabolism that are caused by deficient activity of the glycine cleavage enzyme system (GCS) are called nonketotic hyperglycinemia (NKH).
  - Classic NKH is caused by biallelic pathogenic variants in one of the two genes encoding components of the GCS (*GLDC* and *AMT*).
  - Variant nonketotic hyperglycinemia (NKH) refers to a glycine encephalopathy phenotype with elevated glycine levels and deficient GCS enzyme activity, but no pathogenic variants observed in *GLDC* or *AMT*. Some individuals with variant NKH have impaired lipoylation or deficient lipoate, a cofactor of the GCS enzymes, caused by biallelic pathogenic variants in *BOLA3, GLRX5, IBA57, LIAS*, or *NFU1* [Baker et al 2014].
- Disorders of glycine transport include GLYT1 encephalopathy, the subject of this *GeneReview*.

Prevalence

GLYT1 encephalopathy is rare; to date, only three families have been described, all of Muslim Arab origin. Two families reside in Israel; one family resides in Saudi Arabia [Alfadhel et al 2016, Kurolap et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *SLC6A9*.

Differential Diagnosis

The following disorders with features overlapping with GLYT1 encephalopathy should be considered in the differential diagnosis.

Classic nonketotic hyperglycinemia (NKH) (see Glycine Encephalopathy) is a disorder of glycine metabolism caused by biallelic pathogenic variants in one of the two genes encoding the components of the glycine cleavage system (GCS) enzymes: *GLDC* (P-protein) and *AMT* (T-protein). Clinical manifestations are similar to those of GLYT1 encephalopathy: affected infants have encephalopathy, hypotonia, respiratory insufficiency, and intractable seizures. Those who survive infancy have global developmental delay. Classic NKH is inherited in an autosomal recessive manner.

The major differences between classic NKH and GLYT1 encephalopathy are:

- In classic NKH, glycine concentration is usually high in both CSF and serum. Nevertheless, classic NKH can present with normal serum glycine. (Note that the glycine CSF-to-plasma ratio is abnormal [>0.04] in both disorders.)
- Children with GLYT1 encephalopathy show a startle-like response with a normal EEG whereas those with classic NKH have seizures (with an abnormal EEG) requiring treatment with antiepileptic drugs.
- Brain MRI in neonates and infants with classic NKH shows a pattern of diffusion restriction involving the corticospinal tracts in the posterior part of the internal capsule (PLIC), the brain stem and central tegmental tracts in the brain stem, and the white matter of the cerebellum. After age three months, this recedes in the brain stem and becomes more prominent between the subperirolandic cortex and the PLIC. Data are limited in GLYT1 encephalopathy: diffusion restriction brain MRI in one child showed a focal area of restriction diffusion in one cerebellar hemisphere (proband of Family 1 [Kurolap et al 2016]).
- Although no effective treatment is available for either disorder, children with classic NKH may respond to sodium benzoate (which reduces serum glycine concentrations) and an NMDA receptor blocker (e.g., ketamine or dextromethorphan), whereas those with GLYT1 encephalopathy do not.

Variant nonketotic hyperglycinemia (variant NKH) refers to children with a glycine encephalopathy-like phenotype including elevated glycine levels and deficient GCS enzyme activity, but no pathogenic variants observed in *GLDC* or *AMT*. Some individuals with variant NKH have impaired lipoylation or deficient lipoate, a cofactor of the GCS enzymes, caused by biallelic pathogenic variants in one of the following genes: *BOLA3* (OMIM 613183, 614299), *GLRX5* (OMIM 609588, 616859), *IBA57* (OMIM 615316, 615330), *LIAS* (OMIM 607031, 614462), or *NFU1* (OMIM 608100, 605711) [Baker et al 2014].

X-linked cobalamin disorder (cblX) is a disorder of intracellular cobalamin metabolism caused by hemizygous pathogenic variants in *HCFC1* (OMIM 300019, 309541). cblX is characterized by neonatal epileptic encephalopathy, hypotonia, severe developmental delay, and cerebral atrophy on brain MRI. CSF glycine is mildly elevated, similar to that observed in GLYT1 encephalopathy; the presence of methylmalonic aciduria and homocystinuria distinguishes cblX from the glycine encephalopathies [Scalais et al 2017].

Hyperekplexia (HPX) is characterized by generalized stiffness and excessive startle reflex to different stimuli. It is attributed to impaired glycinergic neurotransmission as a result of disruption of the glycine receptor (GlyR) caused by biallelic pathogenic variants in *ARHGEF9*, *GLRA1*, *GLRB*, *GPHN*, or *SLC6A5* – the latter encoding glycine transporter 2 (GLYT2). The startle-like response is the main phenotypic overlap between HPX and GLYT1 encephalopathy. HPX is inherited in an autosomal dominant, autosomal recessive, or, rarely, X-linked manner.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with GLYT1 encephalopathy, the following evaluations are recommended if they have not already been completed:

- Metabolic evaluation including blood and CSF amino acid profile
- Neurologic assessment including EEG to distinguish seizures from a startle response. Brain imaging and physiologic tests, such as visual evoked potentials, brain stem evoked response audiometry, and evaluation of motor and sensory nerves, may be performed to better understand the extent of the clinical involvement.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

To date, no treatment has been effective in mitigating the manifestations of GLYT1 encephalopathy.

The core management of GLYT1 encephalopathy is supportive care provided by a multidisciplinary team including specialists from clinical genetics, pediatric neurology and child development, pulmonology, orthopedics, physiotherapy, nutrition, and others depending on clinical findings (e.g., pediatric nephrology if hypertension is observed).

The management of GLYT1 encephalopathy includes the following:

- Address global developmental delay.
- While benzodiazepines or antiepileptic drugs are used to control the startle response in hyperekplexia [Bakker et al 2006], it is unknown whether these could also be helpful in GLYT1 encephalopathy.
- Mechanical ventilation is indicated when first signs of respiratory failure appear. If successful weaning off ventilation is achieved, supplemental oxygen may be required.
- Gastrostomy should be considered to assure adequate nutrition and to prevent microaspiration.
- Physiotherapy should be considered to preserve range of motion and prevent contractures.
- If hypertension is present, refer to pediatric nephrologist for appropriate treatment.

Note: Treatment with sodium benzoate and an NMDA receptor antagonist (e.g., ketamine or dextromethorphan), as customary in classic NKH, was unsuccessful in one child with GLYT1 encephalopathy [Kurolap et al 2016].

Surveillance

The following should be routinely monitored:

- Developmental status
- Neurologic status
- Respiratory function
- Nutritional status and feeding
- Musculoskeletal involvement
- Sensory organ involvement (vision, hearing)

Monitor as needed:

- Blood pressure
- Renal function

Agents/Circumstances to Avoid

Although no specific agents/circumstances are known to exacerbate disease manifestations, valproate – which is contraindicated in classic NKH – should be avoided as it increases the concentration of blood and CSF glycine [Hall & Ringel 2004].

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

GLYT1 encephalopathy is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SLC6A9* 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. Individuals with GLYT1 encephalopathy 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 a *SLC6A9* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC6A9* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC6A9* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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.

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org

Molecular Genetics

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

Table A. GLYT1 Encephalopathy: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SLC6A9	1p34.1	Sodium- and chloride-dependent glycine transporter 1	SLC6A9	SLC6A9

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 GLYT1 Encephalopathy (View All in OMIM)

601019	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, GLYCINE), MEMBER 9; SLC6A9
617301	GLYCINE ENCEPHALOPATHY WITH NORMAL SERUM GLYCINE

Molecular Pathogenesis

GLYT1 encephalopathy is a glycinopathy caused by dysfunction of the sodium- and chloride-dependent glycine transporter 1 (also known as glial glycine transporter 1) (GLYT1) [Alfadhel et al 2016, Kurolap et al 2016]. GLYT1 is responsible for termination of glycinergic neurotransmission by removing glycine from the synapse;

therefore, the clinical manifestations of the disorder are mostly attributed to excess glycinergic inhibitory neurotransmission [Eulenburg et al 2005, Harvey et al 2008].

Gene structure. The transcript variant NM_201649.3 (ENST00000360584) comprises 14 protein-coding exons. It represents the longest transcript and encodes the longest isoform NP_964012.2. *SLC6A9* has multiple transcripts; for a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants

Table 2. *SLC6A9* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.928_932delAAGTC	p.Lys310PhefsTer31	NM_201649.3 NP_964012.2
c.1717C>T	p.Gln573Ter	
c.1219A>G	p.Ser407Gly	

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.

Normal gene product. GLYT1 (NP_964012.2) comprises 706 amino acids that form 12 transmembrane domains and intracellular N- and C-termini. The isoforms vary by splicing in the N- and C-termini [Eulenburg et al 2005]. GLYT1 is a transporter belonging to the Na+/Cl- dependent superfamily, similar to other monoamine transporters; it requires 2Na+/Cl-/glycine binding for activation and subsequent glycine uptake from the synapse [Eulenburg et al 2005].

Abnormal gene product. Both truncating variants known to date (Table 2) are predicted to cause premature termination and loss of protein expression [Kurolap et al 2016]. The missense variant p.Ser407Gly, which was observed in one affected individual, is predicted to affect the ion-binding site of the protein, thus disrupting the normal function of the transporter [Alfadhel et al 2016]. Abolished or decreased GLYT1 activity may result in glycine accumulation in the glycinergic synapses, causing over-inhibition, which leads to the clinical findings of hypotonia and respiratory failure.

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Chapter Notes

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