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Glycine Encephalopathy

[*NKH, Non-Ketotic Hyperglycinemia. Includes: AMT-Related Glycine Encephalopathy, GCSH-Related Glycine Encephalopathy, GLDC-Related Glycine Encephalopathy*]

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Summary

Disease characteristics. Glycine encephalopathy (also known as nonketotic hyperglycinemia, NKH) is an inborn error of glycine metabolism in which large quantities of glycine accumulate in all body tissues, including the brain. A neonatal (classic) form and several atypical forms exist. The vast majority of individuals with NKH have the neonatal (classic) form; a minority of individuals with NKH have atypical forms. The neonatal form manifests in the first hours to days of life with progressive lethargy, hypotonia, and myoclonic jerks leading to apnea and often death. Surviving infants develop profound mental retardation and intractable seizures. The atypical forms range from infantile- to late-onset milder disease to late-onset disease with a rapid and severe course. The infantile form is characterized by onset of seizures beyond the neonatal period. The developmental outcome may be better than in the neonatal form, but does not exceed moderate mental retardation. The mild-episodic form of glycine encephalopathy is associated with mild mental retardation and episodes of chorea, agitated delirium, and vertical gaze palsy. The late-onset form has variable mild spastic paraparesis, optic atrophy, mild mental retardation, and choreoathetosis.

Diagnosis/testing. Glycine encephalopathy is suspected in individuals with elevated glycine concentration in urine. An increased CSF-to-plasma glycine ratio suggests the diagnosis. Reliable enzymatic confirmation of the diagnosis requires measurement of glycine cleavage enzyme (GCS) activity of liver obtained by biopsy or autopsy. The vast majority of affected individuals have no detectable activity; such testing is available on a research basis only. Molecular genetic testing of the *GLDC* gene, encoding the P-protein component of the GCS complex and accounting for disease in 80% of individuals with NKH, and the *AMT* gene, encoding the T-protein component of the GCS complex and accounting for disease in 10-15% of individuals with NKH, is available on a clinical basis. Molecular genetic testing of the *GCSH* gene (encoding the H-protein component of the GCS complex) is available on a clinical basis.

Genetic counseling. Glycine 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 an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3. Individuals with glycine encephalopathy do not reproduce. Prenatal testing is available.

Diagnosis

Clinical Diagnosis

Neonates presenting with unexplained coma and/or seizures should be suspected of having glycine encephalopathy (nonketotic hyperglycinemia, NKH). Older infants and children with intractable seizures should also be suspected of having glycine encephalopathy.

Testing

For laboratories offering biochemical testing, see Testing.

Quantitative Amino Acid Analysis—Affected individuals

- Glycine encephalopathy is suspected in individuals with elevated glycine concentration in urine, plasma, and CSF.
- Simultaneous CSF and plasma samples are required to establish the diagnosis of glycine encephalopathy. An abnormal CSF-to-plasma glycine ratio suggests the diagnosis of glycine encephalopathy (see Table 1). The presence of any blood in the CSF invalidates the results.

Table 1. CSF and Plasma Glycine Concentration (µmol/L) in Glycine Encephalopathy

	Glycine Encephalopathy Phenotype		Normal Control
	Neonatal Form	Atypical Form	
CSF glycine concentration	>80 µm/L	30-70 µm/L	<10 µm/L
Plasma glycine concentration	Varies [1]	Varies [1]	125-318 [Applegarth et al 1979]
CSF/plasma glycine ratio [2]	>0.08	0.04-0.1	<0.02

From Applegarth et al 1979, Toone & Appplegarth 1989, Steiner et al 1996, Applegarth & Toone 2001

1. Can be normal [Toone & Applegarth 1989, Steiner et al 1996]
2. Samples must be obtained simultaneously.

Carriers. Carrier testing using biochemical methodologies is not reliable. However, a series of Finnish obligate heterozygotes for glycine encephalopathy have been reported with slightly higher plasma glycine concentrations compared to controls [von Wendt et al 1979]. Others observed somewhat increased plasma glycine concentrations in at-risk siblings monitored soon after birth [Toone & Applegarth 1989].

Urine Organic Acid Analysis—Urine organic acid profile obtained simultaneously with the plasma and CSF glycine concentration is expected to be normal.

Enzyme Testing: Glycine Cleavage Enzyme (GCS) Activity—The diagnosis of glycine encephalopathy may be confirmed on a research basis only by measurement of glycine cleavage enzyme (GCS) activity in liver. In its major degradative pathway, glycine is metabolized by GCS (see Figure 1). A defect of P-, H- or T-proteins of this complex causes glycine encephalopathy.

Affected individuals. Reliable enzymatic confirmation of the diagnosis of glycine encepthalopathy requires 80 mg of liver obtained by biopsy or autopsy to measure the activity of GCS. The vast majority of affected individuals have no detectable activity. The highest residual activity of an individual tested in one series is 0.4 units (normal 2.1 - 11.9) [Steiner et al 1996]. [Note: Although enzymatic confirmation of glycine encephalopathy using Epstein-Barr virus cultured lymphoblasts from peripheral blood samples was reported in six individuals with P-protein defects [Kure, Narisawa et al 1992], others have obtained overlapping GCS

activity in both controls and individuals with glycine encephalopathy making this method less reliable than the testing of enzyme activity in liver [Applegarth, Toone, Rolland et al 2000].

Carriers. The initial report of measurement of GCS activity in lymphoblasts [Kure, Narisawa et al 1992] included ten obligate heterozygotes for P-protein deficiency. A subsequent report showed overlap of GCS activity in lymphoblasts in normals and carriers [Kure, Takayanagi et al 1999]. No attempts have been made to measure GCS activity in liver biopsies from obligate heterozygotes.

Identification of specific protein deficiency. More than 80% of individuals with glycine encephalopathy have a defect in P-protein; up to 15% have a T-protein defect [Tada & Kure 1993, Toone et al 2000a]. H-protein deficiency is rare and has been documented in only one individual in whom H-protein was found to be devoid of lipoic acid [Hiraga et al 1981, Trauner et al 1981]. To delineate which of the four proteins is defective requires an additional 150 mg of liver for the glycine exchange assay, which is often not performed because of the difficulty in obtaining a liver sample of this size.

Glycine exchange reaction. The glycine exchange reaction measures the combined activity of P- and H-proteins (see Figure 1) [Hayasaka et al 1983,Toone et al 2000a]. This test is available on a research basis for the diagnosis of affected individuals; it is not used in carrier detection.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. The *GLDC* gene (encoding the P-protein component of the glycine cleavage system [GCS] complex), *AMT* gene (encoding the T-protein component of the GCS complex), and *GCSH* gene (encoding the H-protein component of the GCS complex) are the only genes known to be associated with glycine encephalopathy.

- ***GLDC*.** More than 80% of individuals with glycine encephalopathy have defects in the P-protein component of the GCS complex (encoded by the *GLDC* gene) [Tada & Kure 1993, Toone et al 2000a]. The experience so far suggests that in nonconsanguineous families, the affected individual is likely to be a compound heterozygote.
- ***AMT***
  - Approximately 10-15% of all individuals with glycine encephalopathy have defects in the T-protein component of the GCS complex (encoded by the *AMT* gene).
  - Fifty percent of individuals with residual enzyme activity in liver or lymphoblasts on postnatal studies and/or increased amniotic fluid glycine/serine ratio with a normal glycine amniotic fluid concentration on prenatal studies have *AMT* mutations [Toone et al 2003].

Molecular genetic testing: Clinical method

- **Sequence analysis.** Mutations are identified in one of the three genes associated with glycine encephalopathy in 60-90% of individuals with this clinical diagnosis.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Glycine Encephalopathy

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*GLDC* sequence variations	60-90% [1]	Clinical Testing
	AMT sequence variations		
	GCSH sequence variations		

1. For at least one mutation

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

No other phenotypes are known to be associated with mutations in the the *GLDC*, *AMT*, or *GCSH* genes.

L-protein deficiency. Individuals with L-protein deficiency present with a variant form of branched chain amino acidemia (maple syrup urine disease, MSUD) [Yoshino et al 1986, Liu et al 1993] rather than glycine encephalopathy.

Clinical Description

Natural History

Glycine encephalopathy (also known as nonketotic hyperglycinemia, NKH) is an inborn error of glycine metabolism in which large quantities of glycine accumulate in all body tissues, including the brain. A neonatal (classic) form and several atypical forms exist. The vast majority of individuals with NKH have the neonatal (classic) form; a minority of individuals with NKH have atypical forms of the disorder.

Neonatal (classic) form. The neonatal form of glycine encephalopathy manifests in the first hours to days of life with progressive lethargy, hypotonia, and myoclonic jerks leading to apnea and often death. Those infants regaining spontaneous respiration develop profound mental retardation and intractable seizures. Even individuals who become seizure free have moderate to profound mental retardation. In a recent retrospective study of 65 individuals with NKH, up to 20% of surviving children learned to walk and say or sign words [Hoover-Fong et al 2004].

Initial EEG shows a burst-suppression pattern that evolves into multifocal spikes and ultimately into hypsarrhythmia by about three months of age.

The MRI may be normal or may show agenesis or thinning of the corpus callosum. Delayed myelination, and atrophy are later findings. In several reported cases, diffusion-weighted MR showed high-signal lesions in symmetric weight matter consistent with vacuolating myelin [Khong et al 2003, Seo et al 2003, Sener 2003]. No other physical anomalies are present.

Atypical forms. The atypical forms range from milder disease, with onset from infancy to adulthood, to rapidly progressing and severe disease with late onset. The infantile form is characterized by onset of seizures beyond the neonatal period. Affected children may have a symptom-free interval and apparently normal development for the first six months. The developmental outcome may be better than in the neonatal form, but does not exceed moderate mental retardation.

The mild-episodic form of glycine encephalopathy was reported in four children with mild mental retardation and episodes of chorea, agitated delirium, and vertical gaze palsy associated with febrile illness [Frazier et al 1978, Nightingale & Barton 1991, Steiner et al 1996]. One individual had confirmed GCS deficiency [Steiner et al 1996]. An adult with the mild-episodic form experienced acute decompensation following a protein load while on valproate (which is contraindicated in this disorder because it raises serum glycine concentration) [Hall & Ringel 2004].

The late-onset form of glycine encephalopathy has been described in seven individuals: four had spastic paraparesis and optic atrophy without seizures or cognitive impairment, two had mild mental retardation with choreoathetosis, and one had severe mental retardation and rare seizures [Bank & Morrow 1972, Steinmann et al 1979, Singer et al 1989].

Intrafamilial variability. Discordance between affected children in the same family has been reported for age at presentation, the clinical severity of disease, and/or glycine concentration [Borrone et al 1986; Haan et al 1986 (and references therein); Applegarth, Toone, Rolland et al 2000]. More recently a retrospective study showed a consistent phenotype within seven families with two or more affected children [Hoover-Fong et al 2004].

Genotype-Phenotype Correlations

With the exception of the S564I mutation in the *GLDC* gene encoding the P-protein observed in Finnish individuals with severe neonatal onset, most reported mutations seem to be rare or private; thus, it is not presently possible to predict phenotype from genotype.

Prevalence

The birth incidence of glycine encephalopathy is one in 55,000 newborns in Finland (one in 12,000 in an area of Northern Finland) [von Wendt & Simila 1982] and one in 63,000 in British Columbia, Canada [Applegarth, Toone, Lowry 2000]. Because it is often the finding of an increased plasma glycine concentration that triggers the request for measurement of CSF glycine concentration, glycine encephalopathy may be underdiagnosed.

The calculated carrier frequency is approximately one in 125 of the British Columbia, Canada population (a predominantly Caucasian population at the time of data collection for disease incidence).

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Transient glycine encephalopathy was the term used initially to describe the findings in seven neonates [Schiffman et al 1989, Eyskens et al 1992, Zammarchi et al 1995, Boneh et al 1996] who presented with seizures and/or a burst suppression pattern on EEG. All had the biochemical features of glycine encephalopathy, which then resolved. Five developed normally; two had neurologic impairment. GCS activity was not measured in these children.

Currently the diagnosis of transient glycine encephalopathy requires that subsequent CSF and plasma glycine concentrations be normal when the affected individual is not on medication. It remains a rare and controversial diagnosis.

Alienfendioglu et al (2003) reported two additional unrelated children who were born to consanguineous parents; one had a positive family history. At follow up plasma glycine concentrations were normal, but CSF glycine concentrations were not determined in either

child. The child with the positive family history was severely retarded at eight months of age; the other died of pneumonia at three months of age.

Three infants with transient glycine encephalopathy and heterozygosity for either *GLDC* or *GCSH* mutations were reported by Kure et al (2002). One was subsequently shown to have persistent glycine encephalopathy with severe seizures and mental retardation [Hamosh & Van Hove 2003].

Four individuals homozygous for the A802V mutation in *GLDC*, treated with assisted ventilation and/or sodium benzoate with or without ketamine, had transient or absent neonatal symptoms and normal developmental outcome despite persistence of biochemical findings consistent with glycine encephalopathy [Korman et al 2004]. Of note, the P-protein encoded by the allele with A802V mutation retains 32% of wild-type activity.

Hyperglycinemia. The differential diagnosis for hyperglycinemia includes D-glyceric acidemia and valproate treatment, both of which cause a secondary decrease in liver GCS enzyme activity and can mimic the laboratory findings of glycine encephalopathy. Ketotic hyperglycinemia can be seen in propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and ß-ketothiolase deficiency (see Organic Acidemias Overview). All of the foregoing can be distinguished from glycine encephalopathy by determination of urine organic acids by gas chromatography/mass spectrometry. The diagnosis of glycine encephalopathy cannot be established by amino acid analysis of plasma or CSF alone in an individual receiving valproate.

Hyperglycinuria. Hyperglycinuria can be seen in type I or type II hyperprolinemia, familial iminoglycinuria, and benign hyperglycinuria, which is a common transient finding due to immaturity of renal glycine reabsorption.

Neonatal seizures. The differential diagnosis for neonatal seizures includes peroxisome biogenesis disorders, Zellweger syndrome spectrum, neonatal adrenoleukodystrophy, and infantile Refsum syndrome, all of which cause an increase in plasma concentration of very long chain fatty acids; sulfite oxidase and molybdenum cofactor deficiency, which are suggested by very low concentration of cysteine on quantitative plasma amino acid determination and low concentration of serum uric acid; pyridoxine-dependent seizures; folinic acid-responsive seizures; and phosphoglycerate dehydrogenase deficiency, a disorder of glycine and serine metabolism. It should be noted that the cause of many neonatal seizures is unknown.

Management

Treatment of Manifestations

No effective treatment exists for glycine encephalopathy.

- Oral administration of sodium benzoate at doses of 250-750 mg/kg/day can reduce the plasma glycine concentration into the normal range (see Table 1); this dose substantially reduces but does not normalize CSF glycine concentration [Hamosh et al 1992]. Benzoate is a useful anticonvulsant agent in this disorder. In more mildly affected individuals, it may also improve behavior. The higher dose of this range (500-750 mg/kg/day) is frequently associated with gastritis, which may require oral administration of antacids, H2 antagonists, or proton pump inhibitors. Cimetidine slows the metabolism of dextromethorphan (see below) and should not be used in slow metabolizers (a separate pharmacogenetic phenotype) of dextromethorphan, as it may cause toxicity.

- Individuals with intractable seizures may benefit from benzodiazepines. Standard anticonvulsants such as phenobarbital or phenytoin have limited efficacy for control of the seizures of glycine encephalopathy.
- Antagonism of a presumably overstimulated N-methyl D-aspartate (NMDA) receptor channel complex with use of dextromethorphan, ketamine, felbamate, and lamictal has had limited success [Hamosh et al 1998, Hamosh & Johnston 2001].

Agents/Circumstances to Avoid

- Valproate is contraindicated as an antiepileptic drug (AED) in glycine encephalopathy. It raises blood and CSF glycine concentrations and may increase seizure frequency.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Glycine encephalopathy is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Individuals with glycine encephalopathy do not reproduce.

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

Carrier Detection

- Carrier testing using molecular genetic techniques is available on a clinical basis once the mutations have been identified in the proband.
- Reliable carrier testing using biochemical methodology is not available.

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 testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Biochemical testing. Earlier prenatal testing using measurement of amniotic fluid glycine concentration and the glycine/serine ratio was unreliable because normal and affected values overlapped [Mesavage et al 1983, Garcia-Munoz et al 1989].

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Glycine Encephalopathy

Gene Symbol	Chromosomal Locus	Protein Name
AMT	3p21.2-p21.1	Aminomethyltransferase
GCSH	16q24	Glycine cleavage system H protein
GLDC	9p22	Glycine dehydrogenase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Glycine Encephalopathy

238300	GLYCINE DECARBOXYLASE; GLDC
238310	AMINOMETHYLTRANSFERASE; AMT
238330	GLYCINE CLEAVAGE SYSTEM H PROTEIN; GCSH
605899	GLYCINE ENCEPHALOPATHY; GCE

Table C. Genomic Databases for Glycine Encephalopathy

Gene Symbol	Entrez Gene	HGMD
AMT	275 (MIM No. 238310)	AMT
GCSH	2653 (MIM No. 238330)	GCSH
GLDC	2731 (MIM No. 238300)	GLDC

For a description of the genomic databases listed, click here.

GLDC

Normal allelic variants: The gene has 25 exons and intron/exon boundaries [Takayanagi et al 2000]. Its molecular analysis has been hampered by the presence of a processed full-length pseudogene with 97.5% homology to the true gene, differing in point mutations along its length [Takayanagi et al 2000]. Primers based on intronic sequence are required to avoid amplification of the pseudogene. Genomic structure for exons 6-14 with intervening sequence has been deposited with Genbank (AF288639 S1-S6).

Pathologic allelic variants:

- The S564I and G761R mutations have been identified in 70% of alleles and 8% of alleles, respectively, in individuals from a particular area of Finland [Kure, Takayanagi et al 1992; Kure, Takayanagi et al 1999].
- The R515S mutation was identified in nine unrelated individuals and in 5% of glycine encephalopathy alleles in a series of 50 non-Finnish individuals [Toone et al 2001].
- Other mutations have been described in single individuals [Kure et al 1991, Takayanagi et al 2000, Applegarth & Toone 2001, Toone et al 2002] and rare mutations have been found in Japanese individuals [Kure, Takayanagi et al 1999].

AMT

Normal allelic variants: The gene is small and the coding region can be sequenced in three PCR products [Nanao et al 1994]. Genomic sequence for T-protein is found under Genbank accession numbers D14681-86.

Pathologic allelic variants: Three recurrent mutations have been found:

- H42R was identified in an extended Israeli-Arab kindred [Kure, Mandel et al 1998].
- Combined screening for the R320H mutation [Nanao et al 1994, Toone et al 2000a] and the IVS7-1G↓A splice site mutation [Toone et al 2000b] identified 12 individuals in a series of 50 individuals of predominantly European descent [Toone et al 2001]. Since T-protein defects represent only 10-15% of glycine encephalopathy, screening for these two point mutations would presumably have detected most individuals with T-protein deficiency in this population.

Other mutations have been identified in single cases [Nanao et al 1994; Kure, Shinka et al 1998; Toone et al 2000a; Toone et al 2001, Toone et al 2003].

GCSH

Normal allelic variants: The gene has five exons and spans 13.5 kb. The lipoic acid-binding site is in exon 4. Three highly homologous pseudogenes have been found [Kure et al 2001].

Resources

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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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Revision History

- 26 July 2005 (ah) Revision: molecular genetic testing clinically available
- 14 December 2004 (me) Comprehensive update posted to live Web site
- 16 May 2003 (cd) Revision: enzymatic prenatal testing no longer available
- 14 November 2002 (me) Review posted to live Web site
- 7 March 2002 (da) Original submission

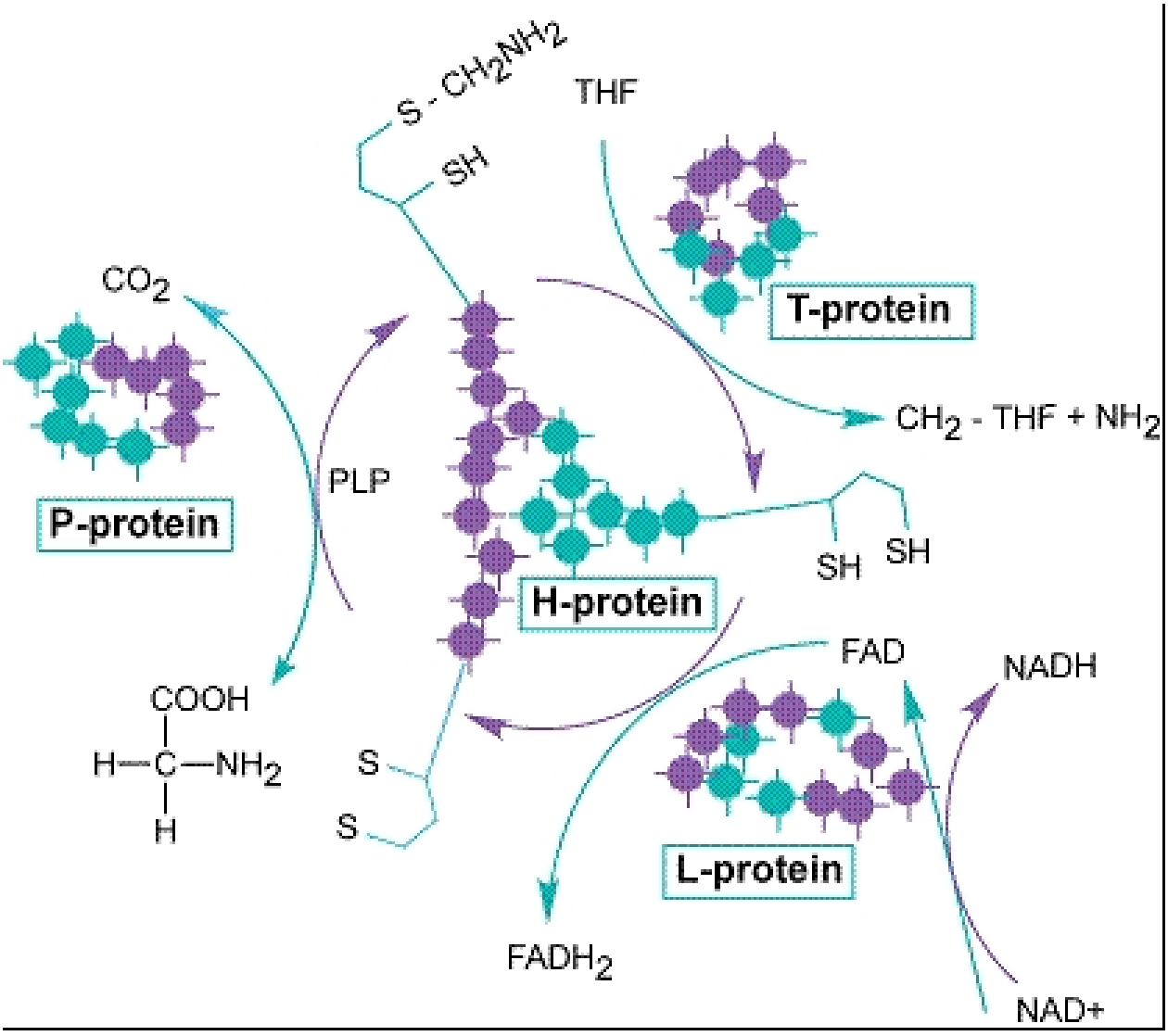

Figure 1. Metabolism of Glycine by glycine cleavage enzyme (GCS).