J Inherit Metab Dis (2016) 39:373–381
DOI 10.1007/s10545-016-9921-5

ORIGINAL ARTICLE

On the phenotypic spectrum of serine biosynthesis defects

Ayman W. El-Hattab[1] · Ranad Shaheen[2] · Jozef Hertecant[1] · Hassan I. Galadari[3] · Badi S. Albaqawi[4] · Amira Nabil[5] · Fowzan S. Alkuraya[2,6,7,8]

Received: 28 December 2015 / Revised: 3 February 2016 / Accepted: 5 February 2016 / Published online: 10 March 2016

Abstract L-serine is a non-essential amino acid that is *de novo* synthesized via the enzymes phosphoglycerate dehydrogenase (PGDH), phosphoserine aminotransferase (PSAT), and phosphoserine phosphatase (PSP). Besides its role in protein synthesis, L-serine is a precursor of a number of important compounds. Serine biosynthesis defects result from deficiencies in PGDH, PSAT, or PSP and have a broad phenotypic spectrum ranging from Neu-Laxova syndrome, a lethal multiple congenital anomaly disease at the severe end to a childhood disease with intellectual disability at the mild end, with infantile growth deficiency, and severe neurological manifestations as an intermediate phenotype. In this report, we present three subjects with serine biosynthesis effects. The first was a stillbirth with Neu-Laxova syndrome and a homozygous mutation in *PHGDH*. The second was a neonate with growth deficiency, microcephaly, ichthyotic skin lesions, seizures, contractures, hypertonia, distinctive facial features, and a homozygous mutation in *PSAT1*. The third subject was an infant with growth deficiency, microcephaly, ichthyotic skin lesions, anemia, hypertonia, distinctive facial features, low serine and glycine in plasma and CSF, and a novel homozygous mutation in *PHGDH* gene. Herein, we also review previous reports of serine biosynthesis defects and mutations in the *PHGDH, PSAT1*, and *PSPH* genes, discuss the variability in the phenotypes associated with serine biosynthesis defects, and elaborate on the vital roles of serine and the potential consequences of its deficiency.Communicated by: Ertan Mayatepek

Introduction

L-serine is a non-essential amino acid that is *de novo* synthesized from the glycolytic intermediate 3-phosphoglycerate through three steps. First, the 3-phosphoglycerate is converted to 3-phosphohydroxypyruvate by the enzyme phosphoglycerate dehydrogenase (PGDH). Then,

Communicated by: Ertan Mayatepek

Ayman W. El-Hattab and Ranad Shaheen contributed equally to this work.

✉ Fowzan S. Alkuraya
falkuraya@kfshrc.edu.sa

[1] Division of Clinical Genetics and Metabolic Disorders, Pediatrics Department, Tawam Hospital, Al-Ain, United Arab Emirates

[2] Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[3] Department of Internal Medicine, College of Medicine and Health Sciences, UAE University, Al-Ain, United Arab Emirates

[4] Women Specialized Hospital, King Fahad Medical City, Riyadh, Saudi Arabia

[5] Medical Research Institute, Alexandria University, Alexandria, Egypt

[6] Department of Anatomy and Cell Biology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

[7] College of Medicine, King Saud University, Riyadh, Saudi Arabia

[8] Developmental Genetics Unit, Department of Genetics, King Faisal Specialist Hospital and Research Center, MBC-03, P.O. Box 3354, Riyadh 11211, Saudi Arabia

phosphoserine aminotransferase (PSAT) converts 3-phosphohydroxypyruvate to 3-phosphoserine. Finally, 3-phosphoserine is converted into L-serine by phosphoserine phosphatase (PSP) (Fig. 1). Serine biosynthesis defects result from deficiency of any of the three enzymes involved in serine biosynthesis, namely PGDH, PSAT, and PSP (van der Crabben et al 2013).

PGDH deficiency, which was first descried in 1996, typically has an infantile presentation with congenital microcephaly, intrauterine growth restriction (IUGR), feeding difficulties, irritability, hypertonia evolving into spastic tetraplegia, and seizures appearing during the first weeks to months of life and has several types of epilepsy including infantile spasms, myoclonic seizures, and Lennox Gasteaux and West syndromes. Psychomotor development is extremely poor, with a developmental arrest occurring during infancy. Neuroimaging shows brain atrophy with enlarged ventricles and hypomyelination. In addition to the neurological symptoms, some patients have congenital cataracts, adducted thumbs, inguinal and umbilical hernias, hypogonadism, abnormal hair, and megaloblastic anemia (de Koning et al 1998; Häusler et al 2001; Jaeken et al 1996; Klomp et al 2000; Pineda et al 2000; Tabatabaie et al 2009; van der Crabben et al 2013). Besides this infantile presentation, milder childhood phenotypes have been reported in individuals with intellectual disability, epilepsy, behavioral problems, ataxia, and polyneuropathy (Tabatabaie et al 2011; Méneret et al 2012). The biochemical profile is consistent with decreased concentrations of serine and, to a lesser extent, glycine in cerebrospinal fluid (CSF) and plasma. The diagnosis can be confirmed by the identification of low PGHD enzyme activity in culture fibroblast (12–25 %) and/or the identification of biallelic mutations in the *PHGDH* gene which encode the PGHD (Jaeken 2012; van der Crabben et al 2013).

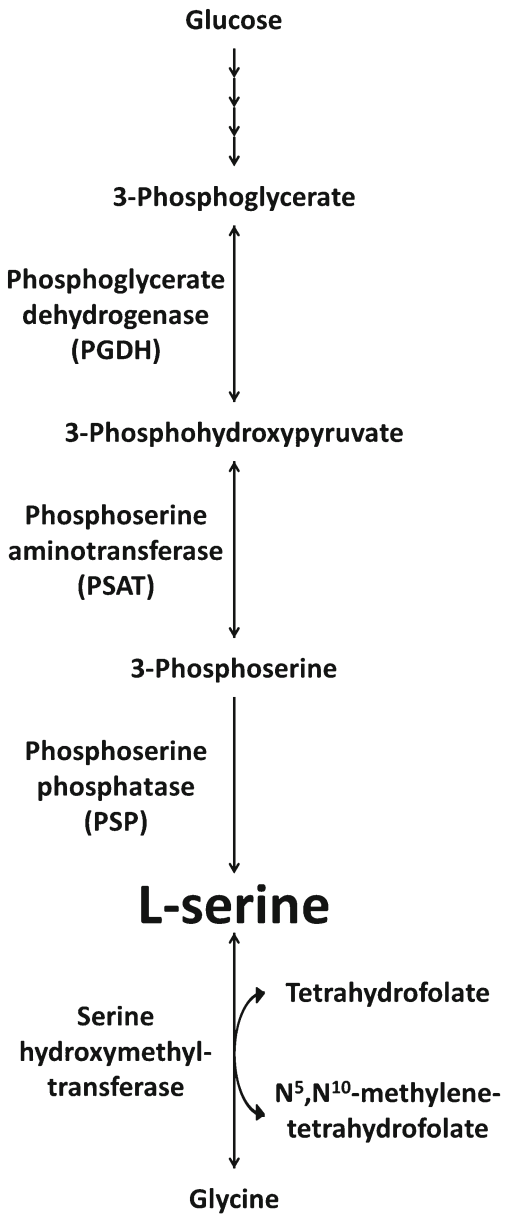

Fig. 1 L-serine biosynthesis pathway

More recently, PGDH deficiency was found to be an etiology of Neu-Laxova syndrome, a lethal multiple congenital anomaly syndrome that was initial described by Neu and colleagues and Laxova and colleagues in 1971 and 1972, respectively (Neu et al 1971; Laxova et al 1972). Neu-Laxova syndrome is characterized by prenatal marked growth deficiency with microcephaly, brain malformation (lissencephaly, corpus callosum agenesis, and hypoplastic cerebellum and pons), limb defects (short limbs, syndactyly with puffiness of hands and feet, and contractures with pterygia), thin, transparent, and edematous skin, ichthyosis, and distinctive facial features (sloping forehead, hypertelorism, proptotic eyes with absent lids or ectropion, flattened nose, thick everted lips, micrognathia, large ears, and short neck). Other features include hypoplastic genitalia, cardiovascular malformations, lung hypoplasia, cataract, spina bifida, cleft lip and palate, polyhydramnios, and short umbilical cord (Carder et al 2003; King et al 1995; Manning et al 2004; Ostrovskaya and Lazjuk 1988; Shapiro et al 1992; Shved et al 1985). It was not until 2014 that the molecular basis of this syndrome was discovered through conducting a positional-mapping study combining autozygosity mapping and whole-exome sequencing in three consanguineous families affected by Neu-Laxova syndrome. Homozygous mutations in the *PHGDH* gene were identified in these three families indicating that Neu-Laxova syndrome can be due to PGDH deficiency and represents the severe end of a broad phenotypic spectrum associated with serine biosynthesis defects (Shaheen et al 2014). That finding paved the way for the identification of additional affected subjects with Neu-Laxova syndrome and biallelic mutations in the *PHGDH* gene (Table 1) (Acuna-Hidalgo et al 2014; Mattos et al 2015).

Table 1 Mutations in serine biosynthetic pathway genes

Proband	Phenotype	Gene	Mutation		PolyPhen	SIFT	CADD
Subject 1 (this report)	Neu-Laxova syndrome	*PHGDH*	Homozygous c.418G>A (p.Gly140Arg)	Missense	Probably damaging (0.999)	Deleterious (0)	34
1 and 2 (Shaheen et al 2014)	Neu-Laxova syndrome	*PHGDH*	Homozygous c.418G>A (p.Gly140Arg)	Missense	Probably damaging (0.999)	Deleterious (0)	34
3 (Shaheen et al 2014)	Neu-Laxova syndrome	*PHGDH*	Homozygous c.488G>A (p.Arg163Gln)	Missense	Probably damaging (0.987)	Deleterious (0)	35
7 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PHGDH*	Compound heterozygous c.160C>T (p.Arg54Cys) and an intragenic deletion	Missense	Probably damaging (0.999)	Deleterious (0)	31
8 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PHGDH*	Homozygous c.793G>A (p.Glu265Lys)	Missense/ splicing	Possibly damaging (0.602)	Deleterious (0)	27.9
9 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PHGDH*	Homozygous c.856G>C (p.Ala286Pro)	Missense	Probably damaging (0.998)	Deleterious (0)	29
Patient (Mattos et al 2015)	Neu-Laxova syndrome	*PHGDH*	Homozygous c.1297C>T (p.Gln433*)	Nonsense			
1 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PSAT1*	Homozygous c.1023_1027delinsAGACCT (p.Arg342Aspfs*6)	Frameshift			
2, 4, and 5 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PSAT1*	Homozygous c.296C>T (p.Ala99Val)	Missense	Probably damaging (0.949)	Tolerated (0.08)	26.3
3 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PSAT1*	Heterozygous c.536C>T (p.Ser179Leu) in the obligate carrier parent.	Missense	Probably damaging (1)	Deleterious (0)	35
6 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PSAT1*	Compound heterozygous				
			c.296C>T (p.Ala99Val)	Missense	Probably damaging (0.949)	Tolerated (0.08)	26.3
			c.536C>T (Ser179Leu)	Missense	Probably damaging (1)	Deleterious (0)	35
10 (Acuna-Hidalgo et al 2014)	Neu-Laxova syndrome	*PSPH*	Homozygous c.267delC (p.Gly90Alafs*2)	Frameshift			
Subject 3 (this report)	Infantile PGDH deficiency/ Neu-Laxova syndrome	*PHGDH*	Homozygous c.1286G>T (p.Gly429Val)	Missense	Probably damaging (0.947)	Tolerated (0.06)	25
Subject 2 (this report)	Infantile PSAT deficiency/ Neu-Laxova syndrome	*PSAT1*	Homozygous c.296C>T (p.Ala99Val)	Missense	Probably damaging (0.949)	Tolerated (0.08)	26.3
1–5 (Klomp et al 2000)	Infantile PGDH deficiency	*PHGDH*	Homozygous c.1468G>A (p.Val490Met)	Missense	Possibly damaging (0.621)	Deleterious (0.03)	27.1
6 (Klomp et al 2000)	Infantile PGDH deficiency	*PHGDH*	Homozygous c.1273G>A (p.Val425Met)	Missense	Possibly damaging (0.685)	Deleterious (0.01)	28.7
1 (Tabatabaie et al 2009)	Infantile PGDH deficiency	*PHGDH*	Compound heterozygous				
			c.403C>T (p.Arg135Trp)	Missense	Probably damaging (0.996)	Deleterious (0)	35
			c.712delG (p.Gly238fs*)	Frameshift			
2 (Tabatabaie et al 2009)	Infantile PGDH deficiency	*PHGDH*	Homozygous c.1117G>A (p.Ala373Thr)	Missense	Probably damaging (0.943)	Deleterious (0.01)	25.3
3 (Tabatabaie et al 2009)	Infantile PGDH deficiency	*PHGDH*	Homozygous c.781G>A (p.Val261Met)	Missense	Probably damaging (0.991)	Deleterious (0.03)	34
4 and 5 (Tabatabaie et al 2009)	Infantile PGDH deficiency	*PHGDH*	Homozygous c.1129G>A (p.Gly377Ser)	Missense	Possibly damaging (0.677)	Tolerated (0.06)	24.4
Two siblings (Hart et al 2007)	Infantile PSAT deficiency	*PSAT1*	Compound heterozygous				
			c.299A>C (p.Asp100Ala)	Missense	Probably damaging (0.992)	Deleterious (0.01)	28.8
			c.107delG	Frameshift			

Table 1 (continued)

Proband	Phenotype	Gene	Mutation		PolyPhen	SIFT	CADD
Patient (Jaeken et al 1997; Veiga-da-Cunha et al 2004)	Infantile PSP deficiency	*PSPH*	Compound heterozygous				
			c.94G>A (p.Asp32Asn)	Missense	Probably damaging (0.982)	Deleterious (0.04)	25
			c.155T>C (Met52Thr)	Missense	Possibly damaging (0.568)	Deleterious (0)	25.5
Two siblings (Tabatabaie et al 2011)	Childhood PGDH deficiency	*PHGDH*	Homozygous c.1129G>A (p.Gly377Ser)	Missense	Possibly damaging (0.677)	Tolerated (0.06)	24.4
Patient (Méneret et al 2012)	Childhood PGDH deficiency	*PHGDH*	Compound heterozygous				
			c.1273G>A (p.Val425Met)	Missense	Possibly damaging (0.685)	Deleterious (0.01)	28.7
			c.1471C>T (p.Arg491Trp)	Missense	Benign (0.224)	Deleterious (0.02)	29.7
7 patients (Vincent et al 2015)	Childhood PSP deficiency	*PSPH*	Homozygous c.103G>A (p.Ala35Thr)	Missense	Probably damaging (0.999)	Deleterious (0)	28

PolyPhen classifies missense variants into benign, possibly damaging, and probably damaging, with higher scores indicating the higher possibility of having damaging mutations. SIFT classifies missense variants into deleterious (scores less than 0.05) or tolerated (score more than 0.05). The higher the combined annotation dependent depletion (CADD) score, the more likely the missense variant to be damaging

PSAT deficiency was first reported in two siblings who showed low concentrations of serine and glycine in plasma and CSF. The index patient presented with intractable seizures, acquired microcephaly, hypertonia, and psychomotor retardation and died at the age of 7 months despite supplementation with serine and glycine initiated at 11 weeks of age. The younger sibling received serine treatment from birth and showed a normal outcome at the age of 3 years. Mutational analysis revealed compound heterozygous mutations in the *PSAT1* gene that encodes PSAT (Hart et al 2007). In view of the implication of serine metabolism in the pathogenesis of Neu-Laxova syndrome, *PSAT1* was investigated as another candidate gene for the condition and this led to the identification of six individuals with Neu-Laxova syndrome and mutations in *PSAT1* (Table 1) (Acuna-Hidalgo et al 2014).

The deficiency of the last enzyme in serine biosynthesis, PSP, was initially reported in a child with Williams-Beuren syndrome who had the 7q11.23 deletion and additional features including IUGR, feeding difficulties, hypospadias, microcephaly, and low serine concentration in plasma and CSF. The diagnosis of PSP deficiency was confirmed by enzymatic assay and the identification of bilallelic mutations in the *PSPH* gene which encodes PSP (Jaeken et al 1997; Veiga-da-Cunha et al 2004). *PSPH* was investigated as a third candidate in the etiology of Neu-Laxova syndrome and one subject with biallelic mutations in this gene was indeed identified (Table 1) (Acuna-Hidalgo et al 2014). Interestingly, this defect was recently reported in seven individuals from a large consanguineous family who had a milder phenotype which includes delayed development, moderate to profound intellectual disability, hypertonia, and seizures started in childhood, all with mutated *PSPH* gene (Vincent et al 2015).

In this report we present three individuals with serine biosynthesis defects and variable phenotypes within the serine biosynthesis defect spectrum. We also discuss the variability in the phenotypes associated with serine biosynthesis defects and elaborate on the vital roles of serine and the potential consequences of its deficiency.

Clinical reports

Subject 1 was stillborn. It was the second pregnancy for a 24 year-old mother who did not have any significant medical history. Her husband and she were from the same area in Saudi Arabia, and their first child was healthy. Multiple congenital anomalies were noticed during a regular prenatal sonography, and a detailed standard 2D anatomy scan supported by 3D ultrasound at 34 weeks gestational age revealed severe IUGR, microcephaly, micrognathia, sloping forehead, protruding eyes, generalized skin edema, syndactyly with puffiness of hands, fetal akinesia, and polyhydramnios (Fig. 2a and b). Neu-Laxova syndrome was clinically diagnosed based on these prenatal findings. At 36 weeks gestational age, the mother developed spontaneous rupture of membranes and delivered a stillborn baby with a weight of 910 grams and microcephaly, IUGR, syndactyly with puffy hand and feet, thin, tight, and edematous skin, sloping forehead, proptotic eyes,

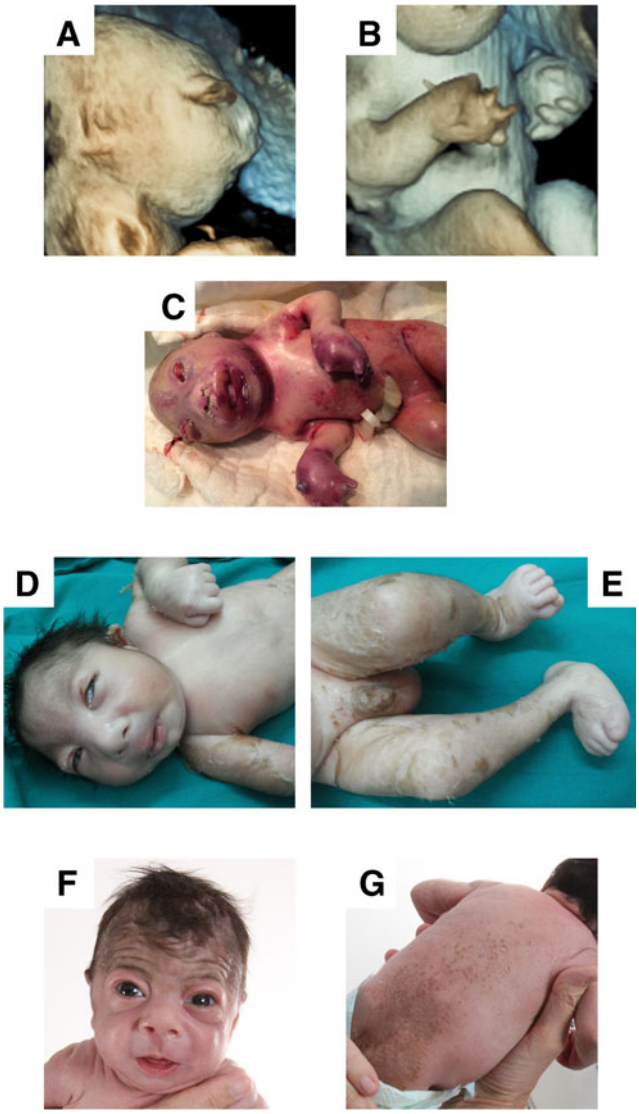

Fig. 2 Features of the three subjects with serine biosynthesis defects. **a** and **b** Prenatal ultrasound for subject 1 showing microcephaly, micrognathia, receding forehead, protruding eyes, and mitten hands. **c** Subject 1 with microcephaly, syndactyly with puffy hand and feet, thin, tight, and edematous skin, sloping forehead, proptotic eyes, hypertelorism, depressed nasal bridge, think everted lips, micrognathia, and hypoplastic genitalia. **d** and **e** Subject 2 with microcephaly, scaly skin, joint contractures, sloping forehead, hyperteloris, depressed nasal bridge, micrognathia, and short neck. **f** and **g** Subject 3 with scaly skin lesions, hypertelorism, depressed nasal bridge, and micrognathia

hypertelorism, depressed nasal bridge, think everted lips, micrognathia, and hypoplastic genitalia (Fig. 2c). Autozygome analysis highlighted *PHGDH* as a candidate and subsequent Sanger sequencing revealed the same homozygous c.418G>A (p.Gly140Arg) mutation that was previously reported in subjects with Neu-Laxova syndrome (Shaheen et al 2014).

Subject 2 was a 9 days old male Egyptian neonate who was born at term with severe microcephaly, IUGR, ichthyotic skin, joint contractures, and bilateral club feet. He developed seizures since the first day of life. In addition, his physical examination showed hypertonia and distinctive facial features including sloping forehead, hypertelorism, depressed nasal bridge, micrognathia, and short neck (Fig. 2d and e). He was lost to follow up and reported to have died at the age of 9 weeks of unknown cause. Parents were cousins and this was their only child. Autozygome analysis highlighted *PSAT1* as a candidate and subsequent Sanger sequencing revealed a homozygous c.296C>T (p.Ala99Val) mutation that was previously reported in subjects with Neu-Laxova syndrome (Acuna-Hidalgo et al 2014).

Subject 3 was a 2-month-old male infant who was born at term with birth weight of 1.9 kg. Besides IUGR, he was noticed to have generalized ichthyotic skin lesions since birth. At the age of 3 weeks he developed poor feeding and excessive crying and required hospitalization for further evaluation. He was found to have anemia (hemoglobin 6.7 mg/dl) that required blood transfusion. On examination, severe microcephalic growth deficiency was noted (head circumference -5 SD, length -6 SD, and weight -4 SD). He also had hypertonia, erythematous scaly skin lesions, and distinctive facial features including hypertelorism, depressed nasal bridge, and micrognathia (Fig. 2f and g). Plasma amino acids showed low serine (19 μmol/L, normal 127–211 μmol/L) and glycine (63 μmol/L, normal 184–356 μmol/L). CSF analysis also showed low serine (3 μmol/L, normal 56–103 μmol/L) and glycine (6 μmol/L, normal 7–15 μmol/L). Brain MRI showed volume loss with dilation of the ventricular system and subarachnoid space, as well as white matter hypomyelination. EEG did not show any epileptiform activity but diffuse attenuation of the background, suggestive of diffuse cerebral dysfunction. Skin biopsy showed hyperkeratosis in the stratum corneum and loss of granular layer with follicular plugging, features consistent with ichthyosis (Fig. 3). Parents are from the same area in United Arab Emirate and had four unaffected

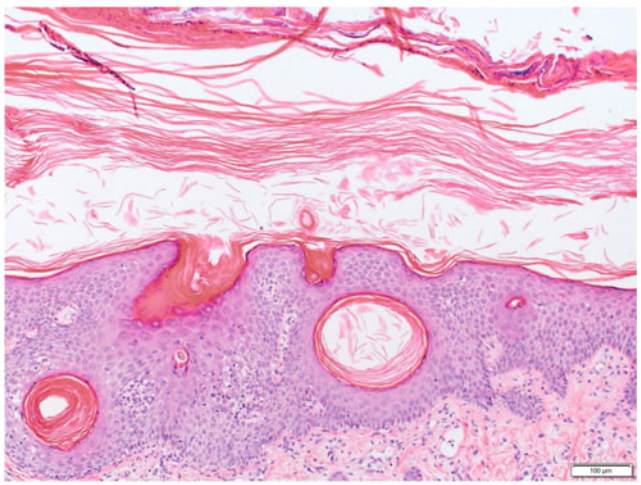

Fig. 3 The histopathology of the skin biopsy of subject 3 showing hyperkeratosis in the stratum corneum and loss of granular layer with follicular plugging which are consistent with ichthyosis

children. Genetic sequencing for *PHGDH, PSAT1*, and *PSPH* genes showed a homozygous novel mutation c.1286G>T (p.Gly429Val) in the *PHGDH* gene. This mutation affects a moderately conserved amino acid position with moderate physicochemical differences between the amino acids. In silico analysis predicts this variant to be probably damaging (Table 1). L-serine therapy was initiated for this infant at a dose of 500 mg/kg/day.

Discussion

Serine biosynthesis defects have been associated with a broad phenotypic spectrum. After more than 40 years of its initial description, Neu-Laxova syndrome, a lethal disease characterized by prenatal growth deficiency with microcephaly, brain malformation, limb defects, characteristic facial and skin features, and other congenital anomalies, was found to represent the severe end of serine biosynthesis defects with mutations in the three genes coding the three enzymes of serine biosynthesis (*PHGDH, PSAT1, PSPH*) identified in individuals with this syndrome (Acuna-Hidalgo et al 2014; Shaheen et al 2014). Milder cases of infantile serine biosynthesis defects, characterized by IUGR with microcephaly, spastic tetraplegia, seizures, psychomotor arrest, brain atrophy with hypomyelination, and anemia, have been reported (Jaeken 2012; van der Crabben et al 2013). At the mild end of this spectrum lie childhood serine biosynthesis defects, which can present with intellectual disability, epilepsy, behavioral problems, and other neurological manifestations including ataxia, hypertonia, and polyneuropathy (Méneret et al 2012; Tabatabaie et al 2011; Vincent et al 2015).

Despite this suggestive categorization of serine biosynthesis defects, a considerable overlap between these three groups exists. Such overlap suggests that the serine biosynthesis defects spectrum is a continuum of phenotypes. Indeed, examples from literature of mild Neu-Laxova syndrome with longer survival (Horn et al 1997) and severe infantile serine biosynthesis defects with early death but without typical Neu-Laxova syndrome features (Hart et al 2007) lend support to this view. Looking at the three subjects in this report, the phenotype of subject 1 fits Neu-Laxova syndrome whereas subjects 2 and 3 can be placed between Neu-Laxova and the infantile serine biosynthesis defects as they have some features of Neu-Laxova (distinctive facial feature and ichthyotic skin changes) and features of the infantile serine biosynthesis defects (seizures in subject 2 and anemia in subject 3).

The variability in the phenotypes associated with serine biosynthesis defects has been suggested to result from the degree of the residual enzyme activity (Acuna-Hidalgo et al 2014; Shaheen et al 2014). In PGDH deficiency, the enzyme activity has been reported to be reduced to 12–25 % of normal activity in both infantile and childhood phenotypes (Tabatabaie et al 2011). Although enzyme assay in subjects with Neu-Laxova has not been performed, it is expected to be lower than the range seen in the milder infantile and childhood phenotype (Acuna-Hidalgo et al 2014; Shaheen et al 2014).

Missense, nonsense, and frameshift mutations have been reported in the *PHGDH, PSAT1, PSPH* genes in individuals with variable phenotypes within the serine biosynthesis defect spectrum (Table 1). Interestingly, biallelic null mutations (nonsense or frameshift) have only been reported in subjects with Neu-Laxova syndrome; however, genotype-phenotype correlation is far from straightforward with missense mutations reported in subjects with variable phenotypes (Table 1). In general, however, a trend can be observed where missense mutations associated with Neu-Laxova syndrome are associated with higher pathogenicity scores using the *in silico* modules PolyPhen (http://genetics.bwh.harvard.edu/pph/references.html), SIFT (http://sift.bii.a-star.edu.sg/, Ng and Henikoff 2003), and Combined Annotation Dependent Depletion (CADD) (http://cadd.gs.washington.edu/, Kircher et al 2014) (Table 1). These observations further support the hypothesis that the severity of the serine biosynthesis defect phenotype depends on the residual enzyme activity. However, the effect of other modifier genes and environmental factors (e.g., maternal serine intake) may still be potential contributors to the variability of the observed phenotype of serine synthetic defects.

L-serine has important functions besides its role in protein synthesis as it is a precursor of a number of important compounds, including cysteine, phosphatidylserine (phospholipid component of cell membranes), sphingomyelin (forming the myelin of nerve fibers) and the neuromodulators D-serine and glycine. Moreover, it is a major source of N^5,N^{10}-methylene-tetrahydrofolate, a major one-carbon donor that is required for the synthesis of purines and thymidine (Jaeken 2012). Based on the variable vital functions of serine, its deficiency can explain the observed phenotypes in serine biosynthesis defects as discussed below.

First, the overall growth failure in serine biosynthesis defects can be due to both impaired protein synthesis and the depletion of the one-carbon pool required for synthesizing nucleotides and other cellular components. This suggestion is supported by studies showing that cell proliferation requires high levels of serine, and increased replication is sustained by increased expression of *PHGDH* and *PSAT1* in embryonic stem cells and cancer cells (Acuna-Hidalgo et al 2014; Labuschagne et al 2014; Possemato et al. 2011; Tedeschi et al 2013; Vié et al 2008).

Second, L-serine is also a potent neuronal trophic factor, which strongly promotes the survival, growth, differentiation, and dendritic elongation and synaptogenesis of cultured neurons (Furuya and Watanabe 2003). Therefore, serine deficiency can have detrimental effects on brain development that could explain the microcephaly, cognitive dysfunction, and

structural brain alteration observed in serine biosynthesis defects. In addition, neuromodulators dysregulation due to deficiencies of glycine and D-serine and white matter changes due to defective phophatidylserine and sphingomyelin synthesis can play roles in the neurological manifestations of serine synthesis defects. Recently, several individuals with developmental delay, microcephaly, spasticity, seizures, hypomyelination, and thin corpus callosum were reported to have biallelic mutations in the *SLC1A4* gene, which encodes the ASCT1 transporter of serine and other neutral amino acids (Heimer et al 2015; Damseh et al 2015; Srour et al 2015). PGDH is expressed in neuronal progenitor cells during embryogenesis. However, in postnatal brains, it is expressed in astroglial cells instead. Therefore, once differentiated, neurons are dependent on astroglial cells for their supply of serine (Furuya et al 2000; Yamasaki et al 2001). The *SLC1A4* mutations result in impaired L-serine transport to neuronal cells leading to clinical features reminiscent of the serine biosynthesis defects supporting the significant role that L-serine plays in normal brain development and function (Heimer et al 2015; Damseh et al 2015; Srour et al 2015).

Third, megaloblastic anemia, cleft lip and palate, and spina bifida that can be observed in individuals with serine biosynthesis defects can be due to deficient synthesis of activated tetrahydrofolate secondary to serine deficiency (Acuna-Hidalgo et al 2014; Jaeken 2012).

Finally, ichthyosis, which has been described in 50 % of individuals with Neu-Laxova syndrome, is likely a consequence of serine deficiency as well. Profilaggrin is a major protein component of the keratohyalin granules in the granular layer of epidermis. Upon terminal differentiation of granular cells, profilaggrin is proteolytically cleaved into filaggrin peptides, which aggregate the keratin filaments forming the stratum corneum. Therefore, filaggrin is a key protein in facilitating epidermal differentiation and maintaining barrier function (Holbrook et al 1982). Mutations in the *FLG* gene which encodes profilaggrin cause ichthyosis vulgaris which is the most common form of inherited ichthyosis (Smith et al 2006). Interestingly, serine proteases, a group of enzymes that carry out several physiological functions and share the histidine-aspartate-serine sequence that is necessary for their activity, play a major role in cleaving profilaggrin to filaggrin. Animal studies have demonstrated that the deficiency of certain serine proteases resulted in defective starum corneum (List et al 2003; Leyvraz et al 2005). As serine is a vital component for the enzyme active site of serine proteases, it is possible that serine deficiency can result in alterations in serine protease functions and therefore the startum corneum development. Additionally, the extracellular lipid of stratum corneum, which sphingolipid constitutes a significant part of, plays a primary role in the skin barrier function (Holleran et al 2006). As serine is a precursor of shpingolipid, it is possible that defective sphingolipid synthesis due to serine deficiency can disturb the stratum corneum. Furthermore, deficient synthesis of activated tetrahydrofolate due to serine deficiency can affect epidermal cell division and that in turn may contribute to the skin pathology.

The detrimental effect of serine deficiency is further supported by the PGDH deficient mouse (*Phgdh*-/-) that displays embryonic lethality with an extremely small size, limb defects (swollen terminal limb bud with failure to digitize), and a small brain with abnormal development (Yoshida et al 2004).

Besides *de novo* serine biosynthesis, L-serine can also be derived from diet, degradation of protein and phospholipids, and direct synthesis from glycine by serine hydroxymethyltransferase. However, these alternative sources cannot compensate for defects in the serine biosynthesis pathway, which serves as the major source of this nonessential amino acid (Acuna-Hidalgo et al 2014; Shaheen et al 2014; van der Crabben et al 2013).

As serine deficiency is the main etiological factor in serine biosynthesis defects, the use of serine has been tried in these diseases. The use of L-serine (100–150 mg/kg/day) in the childhood phenotype was reported to improve seizures, behavior, and school performance (Tabatabaie et al 2011). In the infantile phenotype, the use of L-serine (200–700 mg/kg/day) and glycine (200–300 mg/kg/day) had beneficial effects on the seizures, irritability, spasticity, and white matter volume and myelination. However, in the majority of patients there was little to no improvement of psychomotor development with these supplementations (de Koning et al 2000; de Koning et al 2002; Jaeken 2012; van der Crabben et al 2013). These disappointing results of serine supplementation are likely due to the fact that in utero serine deficiency has already resulted in neurological damage that cannot be reversed by postnatal supplementation. This notion is supported by a report of prenatal therapy when a mother pregnant with a fetus affected with PGDH deficiency received L-serine supplementation starting at week 27 of gestation, which resulted in normalization of fetal head growth. Subsequent continuation of therapy for the newborn after birth appears to have prevented the onset of neurological symptoms and the child showed normal psychomotor development (de Koning et al 2004). Although, L-serine therapy in Neu-Laxova syndrome has not been tried, it has been suggested that in utero L-serine supplementation may have potential benefit in treating or at least mitigate the severity of its associated developmental defects (Shaheen et al 2014; Acuna-Hidalgo et al 2014).

In conclusion, L-serine is a vital molecule for protein synthesis and a precursor of a number of important compounds including phosphatidylserine, sphingomyelin, D-serine, glycine, and N^5,N^{10}-methylene-tetrahydrofolate. Serine biosynthesis defects result in serine deficiency, overall growth failure, and abnormal brain structure and function. The phenotype displays a broad spectrum ranging from Neu-Laxova syndrome at the severe end to a childhood disease at the mild

end. This variability of phenotype is incompletely understood but may result from the degree of the residual enzyme activity. L-serine may be beneficial in preventing or ameliorating symptoms if started early before neurological damage happens.

Compliance with ethical standards

Conflict of interest Ayman W. El-Hattab, Ranad Shaheen, Jozef Hertecant, Hassan I. Galadari, Badi S. Albaqawi, Amira Nabil, and Fowzan S Alkuraya declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Additional informed consent was obtained from all patients for which identifying information is included in this article.

References

Acuna-Hidalgo R, Schanze D, Kariminejad A, Nordgren A, Kariminejad MH, Conner P, Grigelioniene G, Nilsson D, Nordenskjöld M, Wedell A, Freyer C, Wredenberg A, Wieczorek D, Gillessen-Kaesbach G, Kayserili H, Elcioglu N, Ghaderi-Sohi S, Goodarzi P, Setayesh H, van de Vorst M, Steehouwer M, Pfundt R, Krabichler B, Curry C, MacKenzie MG, Boycott KM, Gilissen C, Janecke AR, Hoischen A, Zenker M (2014) Neu-Laxova syndrome is a heterogeneous metabolic disorder caused by defects in enzymes of the L-serine biosynthesis pathway. Am J Hum Genet 95:285–293

Carder KR, Fitzpatrick JE, Weston WL (2003) What syndrome is this? Neu-Laxova syndrome. Pediatr Dermatol 20:78–80

Damseh N, Simonin A, Jalas C, Picoraro JA, Shaag A, Cho MT, Yaacov B, Neidich J, Al-Ashhab M, Juusola J, Bale S, Telegrafi A, Retterer K, Pappas JG, Moran E, Cappell J, Anyane Yeboa K, Abu-Libdeh B, Hediger MA, Chung WK, Elpeleg O, Edvardson S (2015) Mutations in SLC1A4, encoding the brain serine transporter, are associated with developmental delay, microcephaly and hypomyelination. J Med Genet 52:541–547

de Koning TJ, Duran M, Dorland L, Gooskens R, Van Schaftingen E, Jaeken J, Blau N, Berger R, Poll-The BT (1998) Beneficial effects of L-serine and glycine in the management of seizures in 3-phosphoglycerate dehydrogenase deficiency. Ann Neurol 44:261–265

de Koning TJ, Jaeken J, Pineda M, Van Maldergem L, Poll-The BT, van der Knaap MS (2000) Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. Neuropediatrics 31:287–292

de Koning TJ, Duran M, Van Maldergem L, Pineda M, Dorland L, Gooskens R, Jaeken J, Poll-The BT (2002) Congenital microcephaly and seizures due to 3-phosphoglycerate dehydrogenase deficiency: outcome of treatment with amino acids. J Inherit Metab Dis 25:119–125

de Koning TJ, Klomp LW, van Oppen AC, Beemer FA, Dorland L, van den Berg I, Berger R (2004) Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency. Lancet 364:2221–2222

Furuya S, Watanabe M (2003) Novel neuroglial and glioglial relationships mediated by L-serine metabolism. Arch Histol Cytol 66:109–121

Furuya S, Tabata T, Mitoma J, Yamada K, Yamasaki M, Makino A, Yamamoto T, Watanabe M, Kano M, Hirabayashi Y (2000) L-serine and glycine serve as major astroglia-derived trophic factors for cerebellar Purkinje neurons. Proc Natl Acad Sci U S A 97:11528–11533

Hart CE, Race V, Achouri Y, Wiame E, Sharrard M, Olpin SE, Watkinson J, Bonham JR, Jaeken J, Matthijs G, Van Schaftingen E (2007) Phosphoserine aminotransferase deficiency: a novel disorder of the serine biosynthesis pathway. Am J Hum Genet 80:931–937

Häusler MG, Jaeken J, Mönch E, Ramaekers VT (2001) Phenotypic heterogeneity and adverse effects of serine treatment in 3-phosphoglycerate dehydrogenase deficiency: report on two siblings. Neuropediatrics 32:191–195

Heimer G, Marek-Yagel D, Eyal E, Barel O, Oz Levi D, Hoffmann C, Ruzzo EK, Ganelin-Cohen E, Lancet D, Pras E, Rechavi G, Nissenkorn A, Anikster Y, Goldstein DB, Ben Zeev B (2015) SLC1A4 mutations cause a novel disorder of intellectual disability, progressive microcephaly, spasticity and thin corpus callosum. Clin Genet 88:327–335

Holbrook KA, Dale BA, Brown KS (1982) Abnormal epidermal keratinization in the repeated epilation mutant mouse. J Cell Biol 92:387–397

Holleran WM, Takagi Y, Uchida Y (2006) Epidermal sphingolipids: metabolism, function, and roles in skin disorders. FEBS Lett 580:5456–5466

Horn D, Müller D, Thiele H, Kunze J (1997) Extreme microcephaly, severe growth and mental retardation, flexion contractures, and ichthyotic skin in two brothers: a new syndrome or mild form of Neu-Laxova syndrome? Clin Dysmorphol 6:323–328

Jaeken J (2012) Disorders of proline and serine metabolism. In: Saudubray J-M, van den Berghe G, Walter JH (eds) Inborn metabolic diseases diagnosis and treatment, 5th edn. Springer Berlin Heidelberg, New York, pp 357–362

Jaeken J, Detheux M, Van Maldergem L, Foulon M, Carchon H, Van Schaftingen E (1996) 3-Phosphoglycerate dehydrogenase deficiency: an inborn error of serine biosynthesis. Arch Dis Child 74:542–545

Jaeken J, Detheux M, Fryns JP, Collet JF, Alliet P, Van Schaftingen E (1997) Phosphoserine phosphatase deficiency in a patient with Williams syndrome. J Med Genet 34:594–596

King JA, Gardner V, Chen H, Blackburn W (1995) Neu-Laxova syndrome: pathological evaluation of a fetus and review of the literature. Pediatr Pathol Lab Med 15:57–79

Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J (2014) A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet 46:310–315

Klomp LW, de Koning TJ, Malingré HE, van Beurden EA, Brink M, Opdam FL, Duran M, Jaeken J, Pineda M, Van Maldergem L, Poll-The BT, van den Berg IE, Berger R (2000) Molecular characterization of 3-phosphoglycerate dehydrogenase deficiency–a neurometabolic disorder associated with reduced L-serine biosynthesis. Am J Hum Genet 67:1389–1399

Labuschagne CF, van den Broek NJ, Mackay GM, Vousden KH, Maddocks OD (2014) Serine, but not glycine, supports one-carbon metabolism and proliferation of cancer cells. Cell Rep 7:1248–1258

Laxova R, Ohara PT, Timothy JA (1972) A further example of a lethal autosomal recessive condition in sibs. J Ment Defic Res 16:139–143

Leyvraz C, Charles RP, Rubera I, Guitard M, Rotman S, Breiden B, Sandhoff K, Hummler E (2005) The epidermal barrier function is dependent on the serine protease CAP1/Prss8. J Cell Biol 170:487–496

List K, Szabo R, Wertz PW, Segre J, Haudenschild CC, Kim SY, Bugge TH (2003) Loss of proteolytically processed filaggrin caused by epidermal deletion of Matriptase/MT-SP1. J Cell Biol 163:901–910

Manning MA, Cunniff CM, Colby CE, El-Sayed YY, Hoyme HE (2004) Neu-Laxova syndrome: detailed prenatal diagnostic and post-mortem findings and literature review. Am J Med Genet A 125A: 240–249

Mattos EP, Silva AA, Magalhães JA, Leite JC, Leistner-Segal S, Gus-Kessler R, Perez JA, Vedolin LM, Torreblanca-Zanca A, Lapunzina P, Ruiz-Perez VL, Sanseverino MT (2015) Identification of a premature stop codon mutation in the PHGDH gene in severe Neu-Laxova syndrome-evidence for phenotypic variability. Am J Med Genet A 167:1323–1329

Méneret A, Wiame E, Marelli C, Lenglet T, Van Schaftingen E, Sedel F (2012) A serine synthesis defect presenting with a Charcot-Marie-Tooth-like polyneuropathy. Arch Neurol 69:908–911

Neu RL, Kajii T, Gardner LI, Nagyfy SF (1971) A lethal syndrome of microcephaly with multiple congenital anomalies in three siblings. Pediatrics 47:610–612

Ng PC, Henikoff S (2003) SIFT: predicting amino acid changes that affect protein function. Nucleic Acids Res 31:3812–3814

Ostrovskaya TI, Lazjuk GI (1988) Cerebral abnormalities in the Neu-Laxova syndrome. Am J Med Genet 30:747–756

Pineda M, Vilaseca MA, Artuch R, Santos S, García González MM, Aracil A, Van Schaftingen E, Jaeken J (2000) 3-phosphoglycerate dehydrogenase deficiency in a patient with West syndrome. Dev Med Child Neurol 42:629–633

Possemato R, Marks KM, Shaul YD, Pacold ME, Kim D, Birsoy K, Sethumadhavan S, Woo HK, Jang HG, Jha AK, Chen WW, Barrett FG, Stransky N, Tsun ZY, Cowley GS, Barretina J, Kalaany NY, Hsu PP, Ottina K, Chan AM, Yuan B, Garraway LA, Root DE, Mino-Kenudson M, Brachtel EF, Driggers EM, Sabatini DM (2011) Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. Nature 476:346–350

Shaheen R, Rahbeeni Z, Alhashem A, Faqeih E, Zhao Q, Xiong Y, Almoisheer A, Al-Qattan SM, Almadani HA, Al-Onazi N, Al-Baqawi BS, Saleh MA, Alkuraya FS (2014) Neu-Laxova syndrome, an inborn error of serine metabolism, is caused by mutations in PHGDH. Am J Hum Genet 94:898–904

Shapiro I, Borochowitz Z, Degani S, Dar H, Ibschitz I, Sharf M (1992) Neu-Laxova syndrome: prenatal ultrasonographic diagnosis, clinical and pathological studies, and new manifestations. Am J Med Genet 43:602–605

Shved IA, Lazjuk GI, Cherstvoy ED (1985) Elaboration of the phenotypic changes of the upper limbs in the Neu-Laxova syndrome. Am J Med Genet 20:1–11

Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, Liao H, Evans AT, Goudie DR, Lewis-Jones S, Arseculeratne G, Munro CS, Sergeant A, O'Regan G, Bale SJ, Compton JG, DiGiovanna JJ, Presland RB, Fleckman P, McLean WH (2006) Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet 38:337–342

Srour M, Hamdan FF, Gan-Or Z, Labuda D, Nassif C, Oskoui M, Gana-Weisz M, Orr-Urtreger A, Rouleau GA, Michaud JL (2015) A homozygous mutation in SLC1A4 in siblings with severe intellectual disability and microcephaly. Clin Genet 88:e1–e4

Tabatabaie L, de Koning TJ, Geboers AJ, van den Berg IE, Berger R, Klomp LW (2009) Novel mutations in 3-phosphoglycerate dehydrogenase (PHGDH) are distributed throughout the protein and result in altered enzyme kinetics. Hum Mutat 30:749–756

Tabatabaie L, Klomp LW, Rubio-Gozalbo ME, Spaapen LJ, Haagen AA, Dorland L, de Koning TJ (2011) Expanding the clinical spectrum of 3-phosphoglycerate dehydrogenase deficiency. J Inherit Metab Dis 34:181–184

Tedeschi PM, Markert EK, Gounder M, Lin H, Dvorzhinski D, Dolfi SC, Chan LL, Qiu J, DiPaola RS, Hirshfield KM, Boros LG, Bertino JR, Oltvai ZN, Vazquez A (2013) Contribution of serine, folate and glycine metabolism to the ATP, NADPH and purine requirements of cancer cells. Cell Death Dis 4:e877

van der Crabben SN, Verhoeven-Duif NM, Brilstra EH, Van Maldergem L, Coskun T, Rubio-Gozalbo E, Berger R, de Koning TJ (2013) An update on serine deficiency disorders. J Inherit Metab Dis 36:613–619

Veiga-da-Cunha M, Collet JF, Prieur B, Jaeken J, Peeraer Y, Rabbijns A, Van Schaftingen E (2004) Mutations responsible for 3-phosphoserine phosphatase deficiency. Eur J Hum Genet 12:163–166

Vié N, Copois V, Bascoul-Mollevi C, Denis V, Bec N, Robert B, Fraslon C, Conseiller E, Molina F, Larroque C, Martineau P, Del Rio M, Gongora C (2008) Overexpression of phosphoserine aminotransferase PSAT1 stimulates cell growth and increases chemoresistance of colon cancer cells. Mol Cancer 25;7:14

Vincent JB, Jamil T, Rafiq MA, Anwar Z, Ayaz M, Hameed A, Nasr T, Naeem F, Khattak NA, Carter M, Ahmed I, John P, Wiame E, Andrade DM, Schaftingen EV, Mir A, Ayub M (2015) Phosphoserine phosphatase (PSPH) gene mutation in an intellectual disability family from Pakistan. Clin Genet 87:296–298

Yamasaki M, Yamada K, Furuya S, Mitoma J, Hirabayashi Y, Watanabe M (2001) 3-Phosphoglycerate dehydrogenase, a key enzyme for l-serine biosynthesis, is preferentially expressed in the radial glia/astrocyte lineage and olfactory ensheathing glia in the mouse brain. J Neurosci 21:7691–7704

Yoshida K, Furuya S, Osuka S, Mitoma J, Shinoda Y, Watanabe M, Azuma N, Tanaka H, Hashikawa T, Itohara S, Hirabayashi Y (2004) Targeted disruption of the mouse 3-phosphoglycerate dehydrogenase gene causes severe neurodevelopmental defects and results in embryonic lethality. J Biol Chem 279:3573–3577