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Case Report

A novel mutation in *sphingosine-1-phosphate lyase* causing congenital brain malformation

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Abstract

Introduction: Recently recessive mutations in *sphingosine-1-phosphate lyase* (*SGPL1*) have been published as a cause of syndromic congenital nephrotic syndrome with adrenal insufficiency. We have identified a case with fetal hydrops and brain malformations due to a mutation in *SGPL1*.

Case report: We report a patient presenting with severe fetal hydrops, congenital nephrotic syndrome and adrenal calcifications. MRI imaging showed generalized cortical atrophy with simplified gyral pattern and hypoplastic temporal lobes as well as cerebellar hypoplasia and hyperintensity in the pons. The boy deceased at 6 weeks of age. Via whole exome sequencing, we identified a novel homozygous frameshift mutation c.1233delC (p.Phe411Leufs*56) in *SGPL1*.

Conclusion: In our patient, we describe a novel mutation in *sphingosine-1-phosphate lyase* (*SGPL1*) leading to severe brain malformation. Neurodevelopmental phenotypes have been reported earlier, but not described in detail. To this end, we present a review on all published *SGPL1*-mutations and genotype-phenotype correlations focusing on neurodevelopmental outcomes. We hypothesized on the severe neurological phenotypes, which might be due to disruption of neuronal autophagy. Mutations in *SGPL1* shall be considered in the differential diagnosis of fetal hydrops as well as congenital brain malformations and neuropathies.

Keywords: Congenital brain malformation; Cerebellar hypoplasia; Sphingosine-1-phosphate lyase; Next generation sequencing

1. Introduction

Sphingosine-1-phosphate lyase (SGPL1) is a ubiquitously expressed enzyme involved in the degradation of the regulatory sphingolipid sphingosine-1-phosphate (S1P). Recently *SGPL1* mutations have been published to cause a syndromic form of a congenital nephrotic syndrome associated with adrenal insufficiency and/or calcification, ichthyosis, immunodeficiency and a wide range of pathological neurological features (Fig. 1, Supplementary Tables 1, 2) [1–3]. Here we present a novel mutation in *SGPL1* causing microcephaly, neuronal migration defects, and cerebellar hypoplasia additionally to the classical features of fetal hydrops. We have elaborated on the neurological spectrum and provide a review of *SGPL1* related phenotypes.

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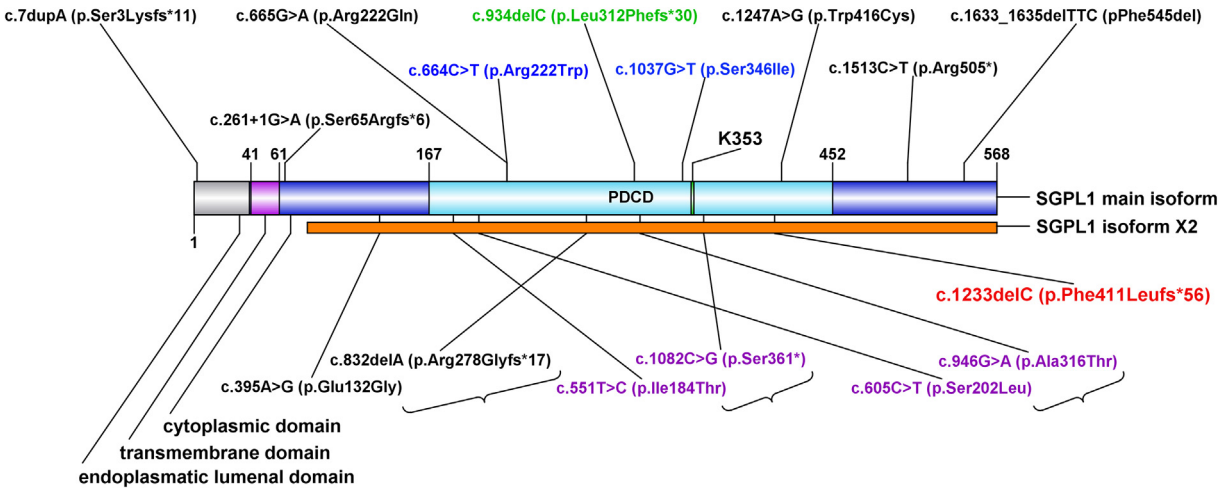

Fig. 1. SGPL1 is a pyridoxal phosphate (PLP) dependent enzyme. Its functional pyridoxal-dependent decarboxylase conserved domain (PDCD) contains a Lysine residue (K353) as an active site forming an internal Schiff base with PLP. All published mutations are shown. Patients with a severe phenotype are marked blue (fetal hydrops and microcephaly) or green (fetal hydrops). Heterozygous mutations causing peripheral neuropathy are marked violet. Our patient (red) had a novel frameshift mutation presenting with fetal hydrops and microcephaly. Interestingly in two families the truncating frameshift mutation (c.7dupA (p.Ser3Lysfs*11) in the endoplasmatic luminal domain close to the N-terminus leads to a mild phenotype with late onset steroid resistant nephrotic syndrome and a mild or normal neurologic phenotype.[2,3] This might be explained by an alternative start codon after the mutation leading to the expression of a shorter transcript still containing the functional domain, as the *SGPL1* isoform X2 (XP_006718116.1, shown in orange), predicted in silico by comparison with mRNA clones. No mutations in the transmembrane domain have been identified.

2. Case report

Our patient was the second child of consanguineous first cousin parents from Afghanistan (Supplementary Fig. 1). During the pregnancy, a fetal hydrops was noted on ultrasound at gestational week 30. The patient was delivered by C-section at 36 1/7 weeks of gestation (birth weight 2500 g) due to signs of fetal stress. He presented with perinatal asphyxia (Apgar 1/1/2; umbilical artery pH: 6.85) and needed resuscitation including invasive ventilation and catecholamine administration. For neuroprotection, the patient received magnesium, erythropoietin and caffeine. Severe congenital nephrotic syndrome leading to generalized edema, massive pleural effusions and ascites as well as end-stage renal failure in the first days of life required intensive albumin substitution and peritoneal dialysis. Laboratory diagnostics (Supplementary Tables 3 and 4) showed persisting thrombocytopenia, severe immunodeficiency with hypogammaglobinaemia and permanent lymphopenia (low CD3, CD4 and CD8 cell counts) hypothyroidism and secondary hyperparathyroidism. Initially, the patient showed hypoglycemia despite the treatment with hydrocortisone. Later at the age of 4 weeks, he developed glucose intolerance requiring insulin substitution (blood cortisone level at 4 weeks: 116 nmol/l). X-rays and ultrasound examinations showed adrenal calcification (Fig. 2B and C). Dysmorphic facial features were hypertelorism and down-slanting palpebral fissures (Fig. 2A). No testes could be palpated in the scrotum.

Neurological examination revealed microcephaly (occipitofrontal circumference 31.5 cm at 2 weeks (below the 3 percentile) (Fig. 2A). Cranial magnetic resonance imaging (MRI) showed generalized cortical atrophy with simplified gyral pattern and hypoplastic temporal lobes as well as cerebellar hypoplasia (Fig. 2E and F). In the thalamus and hippocampus hyperintensity (T2 FLAIR) extending through the mesencephalon to the pons was noted (Fig. 2D). No diffusion restriction was noted as a sign of recent ischemia. Electroencephalograms were performed at 3 days and 1 month of life under deep sedation with opioids and showed long phases of almost flat suppression interrupted by short phases of irregular activity composed of slow waves mixed with spikes or sharp waves (amplitude 40–80 μV) (Supplementary Figs. 2 and 3).

Several attempts to extubate failed. The patient died after a septic shock as a complication of coagulase negative staphylococci peritonitis at the age of 6 weeks.

Metabolic and infectious diseases were excluded and initial conventional genetic workup unremarkable (Supplementary material). Subsequently, we performed whole exome sequencing (Supplementary material) and identified the novel homozygous frameshift mutation c.1233delC (p.Phe411Leufs*56) in Exon 12 of *SGPL1* (NM_003901.3).

3. Discussion

Neurological pathologies are an important feature of *SGPL1*-associated phenotypes since half of the reported