Report of a New Pediatric Patient with the *SLC1A4* Variant and a Brief Review of the Literature

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Abstract

Spastic tetraplegia, thin corpus callosum, and progressive microcephaly (SPATCCM) is an autosomal recessive disorder characterized by the onset of those features and severely impaired global development in early infancy, and caused by biallelic deleterious *SLC1A4* variants. *SLC1A4* encodes for the neutral amino acid transporter, ASCT1, which is necessary for L-serine and D-serine cellular transport to neurons. The objective of this study was to contribute to the genotype–phenotype correlation of *SLC1A4* variants. We evaluated a Turkish patient presenting with SPATCCM without seizures and reviewed all previously reported cases of the *SLC1A4* mutation. Whole exome sequencing revealed a missense biallelic p.R457W variant in *SLC1A4* in a child of Palestinian origin. We suggest that the *SLC1A4* should be considered in the diagnosis of unexplained severe early-onset neurodevelopmental impairment, progressive microcephaly, and spastic tetraparesis with or without epilepsy, regardless of ethnicity and encourage the analysis of *SLC1A4* variants via molecular genetic testing. The presence or absence of epilepsy should not distract from the diagnosis.

Keywords
- *SLC1A4*
- microcephaly
- spasticity
- thin corpus callosum
- epilepsy

Introduction

Spastic tetraplegia, thin corpus callosum, and progressive microcephaly (SPATCCM) is a rare autosomal recessive neurodevelopmental disorder (MIM: 616657). The phenotype was first described by Damseh et al in 2015[1] in 11 patients from unrelated families descending from the Ashkenazi-Jewish population. The prevalence of the disease is estimated at <1/1,000,000 worldwide. It is caused by biallelic loss-of-function mutations in *SLC1A4*, which encodes ASCT1, a Na (+)-dependent neutral amino acid transporter protein for serine, alanine, cysteine, and threonine.[2] ASCT1 transports L-serine from astrocytes to neurons in exchange for D-serine and other amino acid substrates for their survival, growth, and differentation.[3–6] D-serine is a physiologic coagonist of N-methyl-D-aspartate (NMDA) receptors which play key roles in neurodevelopment, synaptic plasticity, learning, and memory.[5,6] Thus, pathogenic variants in *SLC1A4* result in severe global developmental delay without specific symptom patterns.[7]

Herein, we present a new case of SPATCCM. The present study aimed to broaden the spectrum of *SLC1A4* variants in patients with SPATCCM.

Patient and Methods

Case Study

The patient was a 5-year-old boy born at 39 weeks of gestation from an uneventful pregnancy and delivery. He

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Fig. 1 Pictures of the patient: Note the dysmorphic features (brachycephaly, square face, plump cheeks, midface retrusion, deep-set eyes, flat nose root, and short neck).

was born as the second child of a consanguineous family. He was referred to us from the pediatric neurology clinic due to hypotonia, growth retardation, and microcephaly. On physical examination his weight was 17 kg (25th percentile), his height was 99 cm (<3rd percentile), and his head circumference was 46 cm (<1st percentile). He had microcephaly, a square face, plump cheeks, deep-set eyes, midface retrusion, flat nose root, high palate, short neck, and pectus carinatum (►**Fig. 1**). His acquired microcephaly and global developmental delay became evident at 5 months. Spasticity developed at the age of 1 years. At the age of 5 years, his developmental stages were limited to head control and supported sitting only.

He had central hypotonia and peripheral/appendicular hypertonia. He presented with spastic quadriparesis in all extremities. He had contractures in the knees and elbows. Deep tendon reflexes were brisk, especially in the lower extremities, were not accompanied by clonus, and appeared to worsen with age. He had extensor plantar reflexes. He presented with hypersensitivity and irritability to loud noise, and he had a sleep disorder. On repeated examinations, a severe progressive microcephaly was noted (occipito-frontal circumference: 33 cm [3–10th percentile at birth], 44 cm [−2.22 standard deviation score (SDS), 1st percentile at the age of 1 year], 45 cm [−2.50 SDS, <1st percentile at the age of 2 years 5 months], 45.5 cm [−3.00 SDS, <1st percentile at the age of 3 years 7 months], and 46 cm [−3.00 SDS, <1st percentile at the age of 4 years 5 months]). He had no history of epilepsy and his electroencephalogram was normal. No hearing or vision impairments were identified. Brain magnetic resonance imaging (MRI) performed at 2 years of age revealed a thin corpus callosum, cerebral atrophy, and dilatation of the lateral ventricles (►**Fig. 2**). The echocardiogram and abdominal ultrasound were normal.

Methods

Whole Exome Sequencing

Whole exome sequencing (WES) was performed by the GENOKS laboratory in Türkiye. WES was performed on the MGISEQ-2000 Sequencing System (BGI, Shenzhen, Guangdong, China) using the Twist Comprehensive Exome (Twist Bioscience) kit according to the manufacturer's instructions. Sequencing reads were mapped to the Genome Reference Consortium Human Genome Build 37 (GRCh37/hg19) which was used as the reference genome in the analysis.

In addition, molecular testing was performed on the parents and siblings using Sanger DNA sequencing (►**Fig. 3**).

Results

In the reported patient, a biallelic loss-of-function missense p.R457W variant was identified in *SLC1A4* through WES. This variant was subsequently confirmed using Sanger sequencing. The patient was homozygous for this variant; the parents and one sibling were heterozygous. Function studies have shown that this variant does not affect the protein level at the plasma membrane but abolishes the uptake of L-serine and L-alanine[1]

Discussion

SLC1A4 encodes ASCT1, a Na (+)-dependent neutral amino acid transporter for serine, alanine, cysteine, and threonine, which transports L-serine via heteroexchange, supplying

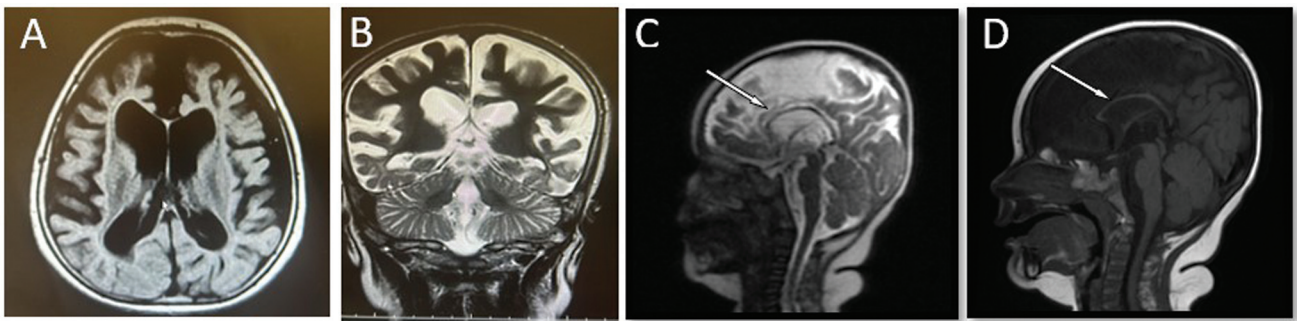

Fig. 2 Neuroimaging findings of the patient. (**A–D**) Axial T2, coronal T2, midsagittal T2, and T1 MR images show cerebral atrophy most prominent in frontal and temporal lobes. (**A, B**) Axial and coronal T2 MR images showing enlargement of lateral ventricles. (**C, D**) Midsagittal T2 and T1 images also show thin corpus callosum indicated by white arrows. MR, magnetic resonance.

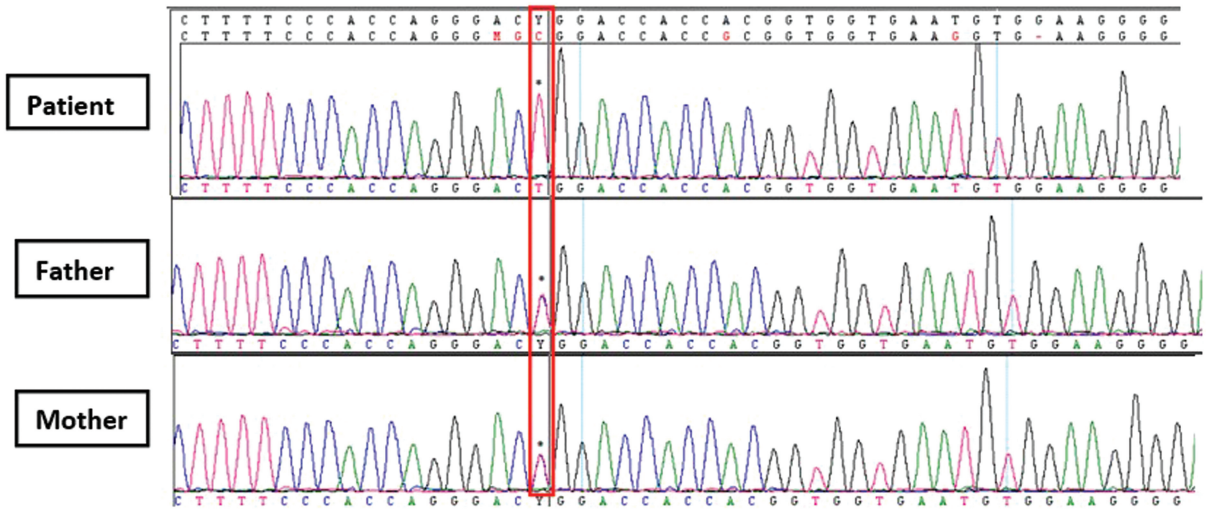

Fig. 3 Sequence images of the patient and their parents.

neurons with the substrate for D-serine synthesis.[1,3–6] L-serine is a nonessential amino acid and a potent neurotrophic factor. It plays an essential role in neuronal development and function by remaining survival, differentiation, and growth of neurons.[2,3,5] Its metabolism is highly dependent on the Na (+)-dependent transporter system ASC (ASCT1).[4–6] D-serine is synthesized from L-serine by the enzyme serine racemase in the brain. Release of D-serine from neurons via the Na-independent ASCT1 has been suggested to regulate synaptic NMDA receptor activity.[6] Deleterious variants of *SLC1A4* are extremely rare and have been found to cause defective ASCT1 function and result in severe neurodevelopmental disorders without specific symptom patterns.[7]

The phenotype was first described by Damseh et al in 2015[1] in 11 patients who were descendants of the Ashkenazi-Jewish population. All patients shared similar phenotypes: spastic paraplegia, microcephaly, and global developmental delay. They detected a founder variant p.E256K in *SLC1A4* in 10 of the 11 patients using WES, the 10th one in a compound heterozygous state with p.L314Hfs*42 variant, and p.R457W in the 11th patient of Palestinian origin.[1] The patient we described here had the same biallelic missense p.R457W variant in *SLC1A4*. In comparison to our patient, she was hypotonic and had no spasticity, whereas our patient had central hypotonia, peripheral hypertonia, and spastic tetraparesis. Neither had stereotypies, abnormal movements, nor clonus. Unlike our patient, she had neither irritability nor sleep disturbance. Both of two had brisk deep tendon reflexes. She could not speak words clearly, only babbling. There was no history of epilepsy and severe early global developmental delay with acquired microcephaly was seen in both cases. Like our patient, her MRI revealed cerebral atrophy.

The disease has been reported in 23 patients to date. Twelve of 23 presented with seizures, 10 of 12 were diagnosed as having epilepsy.[1,7–12] Eleven of 23 presented without seizures.[1,7,13,14]

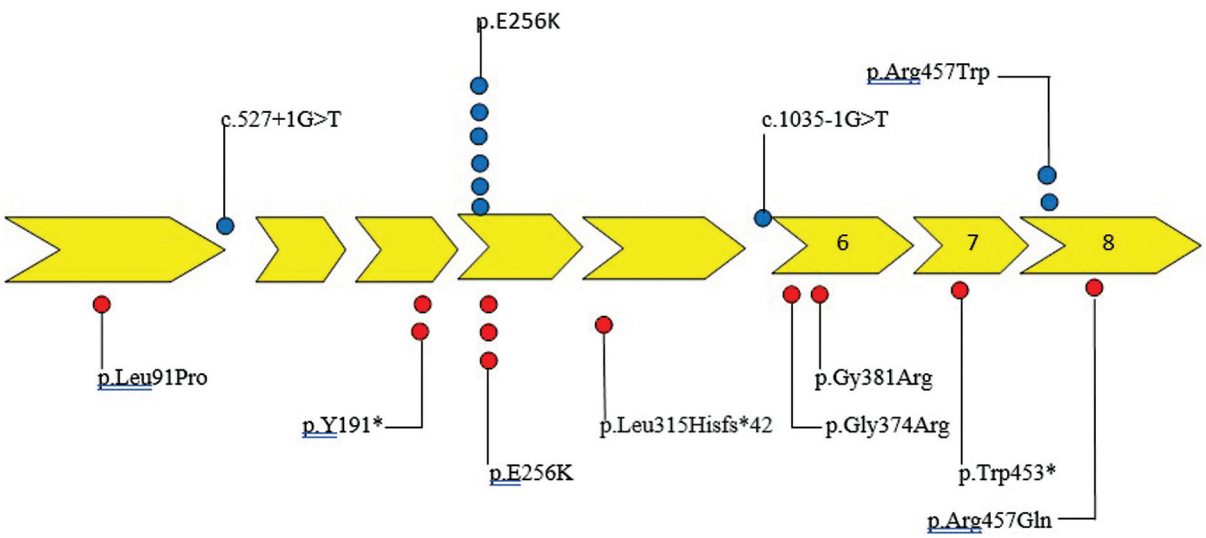

Fig. 4 Schematic view of exons with *SLC1A4* variants. Those on the top are variants without epilepsy, and those on the bottom are variants with epilepsy.

Table 1 Clinical findings of previously reported patients with *SLC1A4* mutation presenting with epilepsy

Patients	Damseh et al	Conroy et al	Pironti et al	Abdelrahman et al	Abdelrahman et al	Teixeira	Sedláčková et al	Sarigecili et al
Age	3–15 y	3 y	7 y	7 y	3 y	9 y	5 y	3.5 mo
Sex	2 females, 1 male	Male	Male	Male	Female	Female	Male	Female
Ethnic group	AJ	Irish	Italian	Pakistani	Pakistani	Portuguese	Czech	Turkish
Dysmorphic features	–	NR	Prominent front face, wide nasal root, anteverted nares, low-set and large ears	Hypertelorism, synophrys, low nasal bridge, large ears	Hypertelorism, synophrys, low nasal bridge, large ears	No dysmorphic facial features, pes valgus (+)	NR	+
Microcephaly	5 primary, 4 acquired, 1 NR	Primary	Acquired	Primary	Primary	Acquired	Acquired	Primary
Epilepsy type	1 Infantile spasm, 2 dialeptic/focal seizure with α awareness	Focal motor and dyscognitive seizures	Tonic extensor spasms with left eye deviation, epileptic nystagmus, and opsoclonus	Generalized tonic-clonic seizures	Generalized tonic-clonic seizures	Myoclonic	Focal seizures with behavioral arrest, epileptic nystagmus	Tonic extensor spasms at the limbs with deviation of eyes
Deep reflexes	Increased	Increased	Increased	Increased	Increased	Increased	Increased	Increased
Tonus	2 hypotonic, 1 hypertonic	Hypotonic	Central hypotonia, peripheral hypertonia	Hypertonic	Central hypotonia, peripheral hypertonia	Peripheral hypertonia	Central hypotonia, peripheral hypertonia	Central hypotonia, peripheral hypertonia
Clonus	–	–	NR	+	+	+	NR	NR
Motor delay	All delayed, variable degrees	No sitting unsupported	No head control	Head control, no sitting and standing	Head control, no sitting and standing	Walking without support, ataxic gait	Only head control	No head control
Speech delay	2 nonverbal, 1 verbal with few word phrases	No babbling	Nonverbal	Babbling	Babbling	Verbal with few word phrases	Nonverbal	No babbling
Abnormal movements	–	NR	NR	+ Stereotypes, hair pulling, irritability	+ Stereotypes, hair pulling, irritability	+ Hyperkinetic behavior	NR	NR
MRI findings	Thin CC, HM, brain atrophy	Thin CC, DM	CC hypoplasia, cerebral and brain stem atrophy	CC and cerebral atrophy	NR	Normal	Cerebral atrophy, thin CC, hypoplastic pons, DM	Thin CC, brain atrophy, DM
Variant	p.E256K and c.945delTT (compound heterozygous), p.E256K	p.Trp453*	p.G381R	p.Tyr191*	p.Tyr191*	p.L91P	p.R457Q	p.G374R

Abbreviations: AJ, Ashkenazi-Jewish; CC, corpus callosum; DM, delayed myelination; HM, hypomyelination; MRI, magnetic resonance imaging; NR, not reported.

Table 2 Clinical findings of previously reported patients with *SLC1A4* mutation presenting without epilepsy

Patients	Damseh et al	Srour et al	Srour et al	Heimer et al	Teixeira	Current
Age	3–15 y	11 y	4 y	6 y	9 y	5 y
Sex	6 females, 2 males	Female	Male	Female	Male	Male
Ethnic group	AJ	AJ	AJ	AJ-Iraqi	Portuguese	Turkish
Dysmorphic features	–	–	–	–	Broad flat philtrum, large mouth, thin upper lip, everted lower lip	Midface retrusion, deep-set eyes, short neck, high palate, pectus carinatum
Microcephaly	3 primary, 4 acquired, 1 NR	Acquired	Acquired	Acquired	Acquired	Acquired
Deep reflexes	Increased	Increased	Increased	Increased	Increased	Increased
Tonus	5 hypotonic, 2 hypertonic, 1 normotonic	Peripheral hypertonia	Mild hypertonia	Peripheral hypertonia	Peripheral hypertonia	Central hypotonia, peripheral hypertonia
Clonus	–	+	–	–	–	–
Motor delay	All delayed, variable degrees	Crawling and standing with support	Crawling and standing with support	Crawling and walking with assistance	Some head control, sitting and standing	Head control and sitting with support
Speech delay	2 nonverbal, 4 babbling, 1 verbal with few words	Nonverbal	Nonverbal	Babbling	Guttural sounds and some monosyllabic words	Nonverbal
Abnormal movements	–	NR	NR	+ Stereotypes, hair pulling, irritability, hyperactivity, and sleep disorder	+ Irritability and sleep disorder	+ Irritability and sleep disorder
MRI findings	Brain atrophy, thin CC, hypomyelination	Thin CC, white matter abnormalities	Thin CC, hypomyelination cerebral atrophy	Mild cerebral atrophy, thin CC	Thin CC	Cerebral atrophy, thin CC
Variant	p.E256K, p.R457W	p.E256K	p.E256K	p.E256K	c.527 + 1G > T intron 2 and c.1035–1G > T intron 6	p.R457W

Abbreviations: AJ, Ashkenazi-Jewish; CC, corpus callosum; MRI, magnetic resonance imaging; NR, not reported.

Of the patients without seizures, six patients were from Damseh et al's report,[1] and two siblings were reported by Srour et al.[13] Also one patient, reported by Heimer et al,[14] who was carrying a homozygous missense p.E256K variant, had repeated febrile seizures; however, epilepsy was not reported.[14] Finally, one case was reported in Teixeira's report.[7] The patient carried splice-site c.527 + 1G > T and c.1035–1G > T variants in compound heterozygous state.[7] A schematic view of the *SLC1A4* exons is shown in ►**Fig. 4**. It is noteworthy that seizures were observed in cases that were compound heterozygous for the p.Glu256Lys and p.Leu315His* 42 variants reported by both Damseh et al[1] and Heimer et al.[14] In vitro functional expression studies in human embryonic kidney cells showed that L-serine and L-alanine transport by the E256K variant were reduced by 25 and 20%, respectively, but there was no measurable substrate transport activity for the R457W variant compared with wild-type.[1] Considering all clinical features of the disease, there is no significant genotype–phenotype correlation. A review of the clinical presentation of all previously described patients with *SLC1A4* variants is summarized in ►**Table 1** (variants with epilepsy) and ►**Table 2** (variants without epilepsy).

Conclusion

Our patient was the second patient presenting with spastic tetraplegia, severe progressive microcephaly, and severe early-onset global developmental delay without seizures, and carrying a biallelic loss-of-function missense p.R457W variant in *SLC1A4*, which has been reported before. We emphasize that the investigation of *SLC1A4* deficiency is important in the patients presenting with unexplained severe early-onset neurodevelopmental delay with spastic tetraparesis and progressive microcephaly with or without epilepsy. As SPATCCM is a relatively rare disorder with phenotypic heterogeneity between patients, even those with the same mutation, reports of each case are valuable to the field and identifying these patients may help identify modifiers of disease in the future.

Statement of Ethics

Samples from the patient were obtained in accordance with the Declaration of Helsinki. The article is exempt from ethical committee approval. Ethical approval was

not required for this study in accordance with local/national guidelines. Written informed consent for genetic testing was obtained from the patient's parents. Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images.

Data Availability Statement

All data generated or analyzed during this study are included in the references. Further inquiries can be directed to the corresponding author.

Conflict of Interest

None declared.

Acknowledgments

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