Dear Editor,

Trappopathies are a group of disorders related to the TRAnsport Protein Particle (TRAPP) associated proteins, which have critical roles in cellular trafficking events, autophagy and TRAPP proteins are essential for dendritic spine morphogenesis.\(^1\)\(^2\) TRAPPC4 is one of the core proteins of the TRAPP complex and the number of diseases associated with mutations of the genes encoding the TRAPP complex is increasing.\(^1\) Different mutations affecting the TRAPP complex may share some overlapping features, like microcephaly, seizures, intellectual disability, neurodevelopmental regression and abnormal cranial magnetic resonance imaging (MRI).\(^1\)

Reported features of trappopathies include skeletal disorder, spondyloepiphyseal dysplasia tarda and a febrile illness-induced encephalopathy and neurodevelopmental delay in TRAPPC2 and TRAPPC2L, intellectual disability, microcephaly, and thin corpus callosum (TCC) in both TRAPPC6 and TRAPPC9, autosomal recessive mental retardation 13 due to TRAPPC9, elevated creatinine kinase (CK) and lactate, liver disease and muscular disorders (either myopathy or limb-girdle muscular dystrophy and alpha-dystroglycanopathy) in TRAPPC11 related diseases, and microcephaly, severe developmental delay, seizures, and brain abnormalities such as brain atrophy, agenesis of corpus callosum or pons hypoplasia in TRAPPC12.\(^1\)

Van Bergen et al.\(^2\) recently described a pathogenic homozygous c.454+3A>G variant (MIM: 610971) in the TRAPPC4 gene which encodes the trafficking protein particle complex, subunit C4 (TRAPPC4) which resulted in a common phenotype in three unrelated families. Patients all had progressive microcephaly due to severe brain atrophy, spastic quadriparesis, early-onset seizures, profound developmental delay, and common facial dysmorphic features including bitemporal narrowing, thick eyebrows, full cheeks, long filtrum, wide mouth, thin and tinted upper lip, and pointed chin.\(^2\)\(^3\) This phenotype was described by Van Bergen et al.\(^2\)\(^3\) is also known as NEDESBA (MIM: 618741); Neurodevelopmental Disorder with Epilepsy, Spasticity and Brain Atrophy.\(^4\)\(^5\) Herein, we report a patient with the same homozygous c.454+3A>G variant of TRAPPC4, diagnosed by whole-exome sequencing (WES) after rapid deterioration of electroencephalogram (EEG) and MRI findings.

**Case Report**

A three and half month-old girl was admitted to the pediatric neurology clinic because of small head size, restlessness and staring attacks. She was born at 37 weeks with a birth weight of 2500 g, after an uneventful pregnancy, as the first child of second-degree consanguineous Turkish parents. On physical examination, her weight was 5745 g (-0.44 standard deviations [SDs]), and head circumference (HC) of 36 cm (-4.2 SDs).\(^6\) She had atopic dermatitis on her cheeks due to multiple food allergy and subtle dysmorphic features, including bi-temporal narrowing, thick eyebrows, long eyelashes, strabismus, long filtrum, thin upper lip, pointed chin, low set ears, and high arched palate; overriding on the right foot was also noted. Neurological examination revealed spasticity in all extremities. She had fixation to the face without visual pursuit while no optic atrophy was detected. Informed patient consent had been obtained from the parents both for genetic workup and patient’s photograph.

On laboratory examination, routine blood tests, including total CK, aspartate transaminase (AST), alanine aminotransferase (ALT) and serum lactate levels were all normal. Immunoglobulin (Ig) levels showed low IgA, suggesting partial deficiency of IgA. Thorough metabolic workup including serum amino acid and acylcarnitine analysis, urine organic acid profile, serum lysosomal enzymes for GM1 and GM2 gangliosidosis, Krabbe disease, metachromatic leucodystrophy (MLD), and enzyme levels for neuronal ceroid lipofuscinosis (NCL) type 2 did not reveal any pathology. Karyotype analysis and microarray analysis were normal. Her newborn hearing-screening test was reported to be normal. Electroencephalography during sleep showed epileptiform activity over the posterior regions of her brain [Figure 2a] and enlarged subarachnoid spaces were reported on cranial MRI [Figure 1b]. She was put on levetiracetam (LEV) treatment, although infrequent clonic

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**Figure 1:** (a) Typical facial appearance of TRAPPC4 trappopathy with bitemporal narrowing, thick eyebrows, full cheeks, long filtrum, wide mouth, thin and tinted upper lip, and pointed chin. Atopic dermatitis, spastic fisting are also noted. (b) T1 weighted MRI slice showing enlarged subarachnoid spaces at presentation. (c and d) Severe cerebral atrophy is more prominent over the frontotemporal regions; lateral ventricles and subarachnoid spaces are enlarged, secondary to atrophy at the age of 5.5 months.
seizures occurred despite LEV therapy of 40 mg/kg/day. At the age of five and a half months, a home video showed spasms. Her EEG during sleep showed excessive voltage suppression at 10 and 7 microvolts with slow and sharp waves persisting over the posterior regions [Figure 2b and c]. Cranial MRI showed brain atrophy [Figure 1c and d]. Levetiracetam was replaced by topiramate. Whole exome sequencing revealed a homozygous splicing change in the TRAPPC4 gene (hg19:chr11:g. 118890966A>G; TRAPPC4: ENST00000533632.1: c. 454+3A>G). Segregation analysis by Sanger sequencing showed both healthy parents were heterozygous for the same variant.

At 13 months of age she had a weight of 5800 g (-5.27 SDs) and HC of 36.5 cm (-7.49 SDs). Severe cognitive and motor disability, no eye-tracking or visual pursuit, exotropia, bilateral optic atrophy, and persistent spasticity in spite of baclofen treatment and a physical rehabilitation program were noted. She had had no obvious seizure on topiramate treatment of 5 mg/kg/day.

**DISCUSSION**

Patients with a homozygous c.454+3A>G variant in the TRAPPC4 gene may present with early-onset seizures, microcephaly, sensory neural hearing loss, visual problems and spastic quadriplegia. Increased serum CK levels, indicating muscle involvement in an Indian family with the c.454+3A>G variant and two Indian families with a novel missense variant NM_0161146.6:C191T>C p. (Leu64Pro) in TRAPPC4 have
recently been reported, while elevated CK has been reported in other trappopathies.

However, our patient had normal serum CK and lactate levels without any muscle involvement. Some patients exhibit frequent infections, which can lead to death in the first decade, at a mean age of 8.8 years. In addition to atopic dermatitis, our patient had low levels of IgA, which has not previously been reported as part of the syndrome. Searching for immunodeficiency in these patients exhibiting frequent infections might expand the phenotype.

A variety of seizures, including spasms, occur early in NEDESBA. Epileptiform abnormalities, generalized disorganization and very low voltage background activity are reported. Brain MRI findings show a variable degree of progressive cerebral atrophy with an increased severity in older age. Enlarged subarachnoid spaces, loss of white matter, enlarged ventricles and cerebellar atrophy have also been reported frequently. However, brain involvement with early-onset seizures, and spasticity are the main presenting symptoms of many neurodegenerative disorders in infancy.

Early-onset epileptic encephalopathies, lysosomal storage diseases, such as NCL, and mitochondrial encephalopathies present with prominent gray matter involvement, whereas white matter involvement occurs in disorders with demyelination, such as MLDD and Krabbe disease. Basal ganglia and cerebellum involvement is present in leuco-axonopathies, like GM1 and GM2 gangliosidoses, mitochondrial encephalopathies, organic acidurias and Lesch Nyhan syndrome. Before proceeding to next-generation sequencing, a thorough metabolic workup in order to exclude neurodegenerative diseases, which may present with a similar phenotype is advisable. This metabolic workup did not detect any abnormalities in our patient.

In the presented patient, spasms and very low voltage activity on EEG early in the course, led to a second MRI showing severe cortical atrophy, indicating the progressive course of the disease. Our patient also developed optic atrophy, which was not present at the first ophthalmological examination. Eye problems occur in most of the TRAPPC4 patients with absence of pursuit and optic atrophy.

Many new and rare developmental disorders have been described as a result of development in next-generation sequencing technology. Whole-exome sequencing and whole-genome sequencing tests provide a diagnostic yield rate of between 25% and 65% and reduce the ‘diagnostic odyssey’. Phenotype-guided genetic tests are reported to achieve a diagnostic confirmation of up to 94%. One of the families reported by Van Bergen et al. as having a homozygous c.454+3A>G variant in TRAPPC4 was from Turkey. Currently, patients with a homozygous c.454+3A>G variant of TRAPPC4 have been reported from European, Mediterranean, Middle Eastern and Indian ancestries, not only in relatives but also in unrelated families. Carrier frequency of this neurodevelopmental and neurodegenerative disorder, NEDESBA, has been reported to be relatively high, varying from 2.4-5.4 per 10,000 individuals worldwide, and mostly frequent in Mediterranean and European ancestries. It is likely, given the relatively high carrier frequency, more patients with NEDESBA will be diagnosed. In patients presenting with severe microcephaly, typical dysmorphic facial features, early-onset seizures with very low voltage, abnormal EEG and progressive cortical atrophy, a TRAPPC4-related neurodevelopmental disorder should be considered in the differential diagnosis of neurodegenerative diseases.

**Abbreviations**

ALT: alanine aminotransferase
AST: aspartate transaminase
CK: Creatine kinase
EEG: Electroencephalography
HC: Head circumference
Ig: Immunoglobulins
LEV: Levetiracetam
MLD: metachromatic leucodystrophy
MRI: Magnetic resonance imaging
NCL: neuronal ceroid lipofuscinosis
NEDESBA: Neurodevelopmental Disorder with Epilepsy, Spasticity and Brain Atrophy
SDs: Standard deviations
TCC: Thin corpus callosum
TRAPP: TRAnsport Protein Particle
TRAPPC4: TRAnsport Protein Particle complex, subunit C4
WES: Whole exome sequencing.

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**Conflicts of interest**

There are no conflicts of interest.

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