Dear Editor,

Cerebral Dysgenesis, Neuropathy, Ichthyosis, and Keratoderma (CEDNIK) Syndrome with Brain Stem Malformation

She had dysmorphic facial features [Figure 1a]: (depressed nasal bridge, hypertelorism, and synphysis), palmoplantar keratoderma [Figure 1b], ichthyosis, and excessive body hair. Her dentition was normal. Her auditory regard was poor; however, she was able to track objects visually. Ophthalmology assessment showed bilateral esotropia and optic atrophy. Motor system manifestations included generalized hypotonia, weakness, and areflexia.

The motor nerve conduction study showed reduced conduction velocities from bilateral median (20 and 22 m/s) and ulnar nerves (21 and 23 m/s) along with mild prolongation of distal F wave latencies. The compound muscle action potential and F waves of the lower limb nerves were not elicited. The sensory potentials from superficial, sural, and ulnar nerves were not recordable and the peak latencies from median nerves were increased (4.2 and 4.3 ms). Thus, the electroneurographic study was confirmatory for the presence of diffuse sensorimotor demyelinating polyneuropathy. The electromyography from right tibialis anterior and rectus femoris was also suggestive of neurogenic process. Visual evoked potential showed prolonged P100 latency on the left side. Brainstem auditory evoked potential showed prolonged peak latencies of waves III, IV, V bilaterally suggestive of brainstem pathology.

Magnetic resonance imaging (MRI) of the brain [Figure 2] at age 3 years, showed dysgenesis of the corpus callosum, bilateral frontoparietal polymicrogyria with normal cortical folding, T2W diffuse white matter hyperintensity, and hypoplastic intraconal optic nerves. In addition, brain stem malformation in the form of elongated pons and short medulla was seen. We considered Zellweger spectrum disorders, tubulinopathies, congenital disorders of glycosylation, congenital muscular dystrophy and CEDNIK syndrome as possible causes for her condition. Her routine blood investigations including serum creatine phosphokinase (73 U/L) was normal. Clinical exome sequencing identified a homozygous single base pair insertion in exon 3 of the SNAP29 gene [(c.486_487insA)
which was corroborated by Sanger sequencing (variant of uncertain significance). This mutation resulted in shift of the reading frame and premature termination of the protein (p.Ser163LysfsTer6) confirming the diagnosis of CEDNIK syndrome.

The homozygous mutation c.486_487insA (p.ser163LysfsTer6) in the SNAP29 gene identified in this patient was reported previously in 2 Pakistani children and was proved pathogenic by molecular studies. The transfection studies in HeLa cells demonstrated that the c.486insA mutation resulted in production of truncated SNAP29 protein. The loss-of-function of this particular mutation was further confirmed in organotypic cell cultures which showed abnormal differentiation of keratinocytes. Skin biopsy from the affected patient revealed accumulation of clear vesicles in the spinous and granular layers of epidermis as well as in the stratum corneum. Neonatal lethality, acanthosis, hyperkeratosis, abnormal keratinocyte differentiation, and increased proliferation were seen in both total SNAP29 knockout mice and keratinocytes specific knockout mice. The comparable phenotypic findings observed in these animal studies substantiate the pathogenic role of SNAP29 deficiency in CEDNIK syndrome.

Bilateral polymicrogyria, cerebral white matter abnormalities, and dysgenesis of corpus callosum observed in this patient were seen in previously described cases as well. But, the mechanistic process underlying these findings are obscure. The occurrence of polymicrogyria could be due to pial defects, impaired proliferation, and migration of neuroblasts or cortical organization defects that is related to post migrational maturational abnormalities. The causes include congenital cytomegalovirus infection, ischemia, syndromic (Zellweger syndrome, congenital muscular dystrophy, and congenital disorders of glycosylation) or mutations in numerous genes.

The genetic mutations involving TUBB2, GPR56, SRPX2, TBR2, PAX6, KIAA1279, and RAB3GAPI that are required for microtubules, radial glia formation, or transcription can lead to neuronal migration defects including polymicrogyria. But, with the uncovering of SNAP29 gene as a cause of CEDNIK syndrome, the vesicular transport is recognized as a decisive component in the neuronal positioning and migration. SNAP29 located on multiple intracellular membranes including golgi apparatus and synaptic vesicles is critical for neuronal morphogenesis, neuritogenesis, and axon branching. The brainstem malformation in this patient has not been reported previously and it could be due to the neuronal migration defects per se. Hindbrain malformations are also associated with lissencephaly, polymicrogyria, and cerebellar hypoplasia. How exactly, SNAP 29/SNARE proteins are involved in the embryogenesis of hindbrain is vaguely articulated.

In this patient, there is clinical evidence for peripheral neuropathy and through electrophysiological study, demyelination of sensory, and motor nerves was confirmed. The characterization of neuropathy as demyelinating or axonal has not been described in previously reported cases. Mutations involving endosomal trafficking and signaling (LITAF), vesicular transport (RAB7), endocytosis (DNM2), endocytic recycling pathway (SH3TC2) etc., can result in inherited peripheral neuropathies underscoring the importance of the role of vesicular and membrane trafficking for the myelin formation and maintenance of the peripheral nervous system.

We describe the first case of CEDNIK syndrome from South-India caused by a homozygous SNAP29 mutation. The striking observation noted in this case is the brainstem malformation as an additional radiological feature broadening the imaging phenotype of CEDNIK syndrome. Another important finding is the demyelinating pattern of peripheral neuropathy, observed in this case which suggests that SNAP29 has a potential role in peripheral myelin formation and maintenance.

Acknowledgements
We acknowledge the patient’s family for granting permission to publish this information. We thank MedGenome Labs Ltd, Bangalore for genetic testing and analysis.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/
their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

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