Rare Cause of West syndrome secondary to Tubulinopathy due to Congenital Symmetric Circumferential Skin Creases (CSCSC) Kunze Type due to a Novel Variant in MAPRE2 Gene

Congenital symmetric circumferential skin creases (CSCSC) is characterized by the ringed creases of limbs and neck with intellectual disability, speech delay, short stature, facial dysmorphism, and various abnormality of fingers and toes. Kunze J et al. described CSCSC in two families and Isrie M et al. identified underlying genetic abnormality due to MAPRE2 or TUBB. The prevalence is not known, and less than 50 cases have been reported. This is the first report of MAPRE2 mutation from Indian subcontinent. West syndrome (WS) was first reported by William James West in 1841. The predominant cause of WS from Indian sub-continent reported was structural. Mutations in MAPRE2 gene cause features of tubulinopathy leading to structural changes in the brain. However, no association has been reported between WS and CSCSC. Hence, we are reporting this case.

A 1-year-old boy born to a non-consanguineous marriage with normal birth history presented with developmental delay, excess skin folds in all four limbs, and epileptic spasms from 7 months of age. He attained partial head control, palmar grasp, social smile, stranger anxiety, cooing, and babbling. He developed epileptic spasms in clusters after awakening from sleep at 7 months of age. Following development of epileptic spasms there was loss of social smile and partial head control. On examination, normal anthropometry, dysmorphism in the form of hypertelorism, microphthalmia, epicanthal folds, depressed nasal bridge, low set, and small ears were noted. There were multiple folds of symmetrical circumferential skin creases noted in all limbs. On neurological examination, he was dull looking, not following light and sound consistently, tone was decreased, complete head lag on pull to sit, power was 3/5, and brisk deep tendon reflexes. On investigations, MRI of the brain showed enlargement of ventricles and irregular ventricular margins, bilateral heterotopia of frontal horns and dysmorphic basal ganglia, hypoplastic corpus callosum, and dysplastic brainstem. EEG was suggestive of hypsarrhythmia. A novel homozygous missense pathogenic variant c.458G>T (p.W153L) noted in exon 4 of the MAPRE2 gene. Treatment with oral prednisolone and rehabilitation, spasms have decreased, and development of the child improved. We advised for antenatal diagnosis for next child to prevent recurrence.

The CSCSC includes two different types, CSCSC1 caused by TUBB gene (OMIM# 156610) and CSCSC2 by MAPRE2 gene (OMIM# 605789), due to different molecular basis. Based on global developmental delay, characteristic skin lesions, and MRI findings, we considered possibility of CSCSC. We also considered following differential diagnosis and excluded; Ehlers-Danlos syndrome (EDS), cutis laxa, Bethlem, and Ullrich congenital muscular dystrophies. The EDS has joint laxity, predominantly motor delay with involvement of eye and heart; however, all these features were absent in the current case. The classical features of cutis laxa are lax skin, isolated motor delay, developmental dysplasia of hip joint, and abnormal skin involvement over limbs and trunk but epileptic spasms and cognitive delay are uncommon that present in the current child. The Bethlem and Ullrich congenital muscular dystrophies usually have distal laxity and proximal muscle contractures with muscle weakness, these features were not present in this child. Hence, finally we diagnosed as CSCSC.
based on classical skin folds and MRI findings and confirmed by pathogenic variant in MAPRE2 gene.

Isrie M et al.\[^{[3]}\] in their report showed that the two individuals with a homozygous MAPRE2 mutation (M2 and M8) had a more severe neurological involvement having severe intellectual disability and seizures, absent in the two individuals with a heterozygous MAPRE2 mutation (M1 and M9). However, the authors were reluctant to conclude the phenotype-genotype correlation and insisted on study of larger allelic series to do so. Feng J et al.\[^{[7]}\] reported a 2-year-old boy with absent expressive speech, normal to mild overgrowth, facial dysmorphic features, remarkable circumferential skin creases on both forearms and ankles, and had a de novo missense MAPRE2 variant, c. 518G > A (p.Arg173Gln.

Berkun L et al.\[^{[8]}\] reported an infant with developmental delay, severe growth delay, dysmorphic features, and multiple congenital anomalies including retinal coloboma, congenital pyloric stenosis, and circumferential skin creases due to homozygous mutations in MAPRE2 and circumferential skin lesions.

A novel homozygous missense variant c. 458G > T (p.W153L) was noted in exon 4 of the MAPRE2 gene. The variant is disease causing by MutationTaster. The variant is damaging by SIFT and probably damaging by Polyphen-2. The variant is not reported in 1000 exome gnomAD or ExAC databases. The mutation is in a mutational hot spot and/or critical and well-established functional domain without benign variation. There is no report of WS reported in association with MAPRE2 gene mutations.

To conclude, any child presenting with WS, global developmental delay, excessive characteristic symmetrical skin creases, dysmorphism, and tubulopathy, CSCSC type 2 to be considered and look for changes in the MRI of the brain and confirmed by genetic testing for MAPRE2 gene variants. Genetic counseling to be done to prevent recurrence.

**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.

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Letters to the Editor

**Conflicts of interest**

There are no conflicts of interest.

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