Letter to the Editor

A de novo CASK mutation in pontocerebellar hypoplasia type 3 with early myoclonic epilepsy and tetralogy of Fallot

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To the editor:

In a male patient with pontocerebellar hypoplasia (PCH) type 3, previously described in this journal [1], we identified a novel hemizygous frameshift mutation in *CASK* (c.227_228del [p.Glu76Valfs*6]), which occurred *de novo*. *CASK* at Xp11.4 encodes a calcium/calmodulin-dependent serine protein kinase belonging to the membrane-associated guanylate kinase protein family. Heterozygous loss-of-function mutations in *CASK* cause X-linked intellectual disability (ID), microcephaly, and pontocerebellar hypoplasia in female patients [2]. In male patients, hemizygous hypomorphic *CASK* mutations have been found in ID and FG syndrome; cases had developmental delay, a characteristic face, and complete or partial agenesis of the corpus callosum [3, 4]. On the other hand, hemizygous loss-of-function mutations in *CASK* have been reported to cause more severe phenotypes: one case with profound developmental delay, ID, and PCH (c.278 + 1G>A) and two cases showing cerebellar hypoplasia and Ohtahara syndrome (OS) (c.1A>G or deletion of exon 2) [5, 6].

The present case showed a suppression-burst pattern during the infantile period on electroencephalography and frequent myoclonus from the first day of birth, which were compatible with early myoclonic encephalopathy (EME). OS, which is characterized by early-onset seizures, epileptic spasms, and a suppression-burst pattern on electroencephalography, shares some clinical features with EME. Recently, mutations in *STXBPI* have been identified in patients with OS and three patients with EME [7]. Our findings further demonstrate that loss-of-function *CASK* mutations in males cause early-onset epileptic encephalopathy and PCH, and support the idea that OS and EME may share the same genetic basis.

The patient is also complicated with tetralogy of Fallot, which has never been

described in association with *CASK* mutation. Further studies are required to investigate the causal relationship between loss-of-function mutations in *CASK* and congenital heart disease in males.

In summary, a novel frameshift *CASK* mutation was identified in a patient with PCH, EME, and tetralogy of Fallot.

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