

Reply to Karakaya et al.: PRUNE1, a disease-causing gene for secondary microcephaly

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In their Letter to the Editor Karakaya *et al.* present an interesting case report describing the clinical course involving secondary microcephaly of a three year old Turkish boy found to be homozygous for a frameshift mutation in *PRUNE1* identified through whole exome sequencing. The child presented with congenital hypotonia, contractures and global developmental delay. Respiratory insufficiency and seizures developed in the first year of life. The authors note that the affected child's head circumference plotted on the 75th centile at birth, and that by 38 months of age he had developed microcephaly. Neuroimaging at 14 months revealed cerebral and cerebellar atrophy consistent with other patients described with Prune syndrome (Karaca *et al.*, 2015; Zollo *et al.*, 2017; Costain *et al.*, 2017). Although the child had abnormal neurology from birth, there was a period of early developmental regression. Peripheral spasticity in the lower extremities and optic atrophy were not documented until 38 months. In addition to the *PRUNE1* variant Karakaya *et al* also identified a second homozygous variant in the *CCDC14* gene in the Turkish child's whole exome sequencing data which, while listed to have an allele count of 108 in the current Genome Aggregation Database (gnomAD) release, is notably absent in homozygous fashion (Lek *et al.*, 2016). *CCDC14* is known to be expressed in human brain, reported to negatively regulate centriole duplication and interact with proteins previously associated with primary microcephaly (Firat-Karalar *et al.*, 2014). Thus, while it seems likely that the homozygous *PRUNE1* variant is primarily responsible for the clinical presentation in the Turkish child, it is impossible to determine whether there may be any phenotypic contribution from this additional homozygous sequence variant.

Recently, Costain *et al.* described a homozygous consensus splice site variant in *PRUNE1* (c.521-2A>G; NM_021222.1) in a two year old Oji-Cre male who presented with congenital

hypotonia and talipes, whose head circumference was large at birth at birth (+3 standard deviations), but by two years and 2 months plotted on the 50th centile, with a weight and height on the 95th and 75th centiles respectively. However, it should be noted that the child's father is macrocephalic (+4 standard deviations), the published clinical photographs at 2 years 5 months of age illustrate bitemporal narrowing, a sloping forehead and large ears consistent with a developing microcephaly and neuroimaging revealed cortical and cerebellar atrophy. He developed respiratory insufficiency shortly after birth, and infantile spasms in the first year of life (Costain *et al.*, 2017).

As more cases are published the phenotype associated with the autosomal recessive Prune neurodevelopmental disorder is becoming clearer. It is now apparent that while some patients have a small head at birth and others a head circumference in the normal range, the key component of the microcephaly is that it is progressive, and associated with characteristic neuroimaging findings with a thin or hypoplastic corpus callosum and cortical and cerebellar atrophy developing in early childhood. Although all patients with Prune syndrome described to date are neurologically impaired from birth, there also appears to be a neurodegenerative component with progression of the disorder. In our manuscript, we described clinical overlap of Prune syndrome with the neurodegenerative condition associated with homozygous mutations in *TBCD* (Zollo *et al.*, 2017). *TBCD* encodes one of the five tubulin-specific chaperones that are required for α/β -tubulin de novo heterodimer formation and the disorder is characterized by developmental regression, seizures, optic atrophy and secondary microcephaly, cortical atrophy with delayed myelination, cerebellar atrophy and thinned corpus callosum (Edvardson *et al.*, 2016; Flex *et al.*, 2016; Miyake *et al.*, 2016; Pode-Shakked *et al.*, 2016). The neurodegenerative phenotype documented in the

Turkish child by Karakaya *et al.* further demonstrates the similarities with the TBCD disorder, and Prune syndrome and confirms optic atrophy to be a feature of Prune syndrome.

Interestingly, it is also becoming clear that respiratory insufficiency is a common feature of Prune syndrome having been documented by Karakaya *et al.* and in the Oji-Cree child, as well as the youngest affected Omani child described in our manuscript.

Web Sources

The URLs for data presented herein are as follows:

Genome Aggregation Database (gnomAD); <http://gnomad.broadinstitute.org>

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