doi:10.1093/brain/awx199 BRAIN 2017: 140; 1–2 | e62

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Reply: *PRUNE1*: a disease-causing gene for secondary microcephaly

Emma L. Baple,[1] Henry Houlden,[2] Massimo Zollo[3,4,5] and Andrew H. Crosby[1]

1 Medical Research (Level 4), RILD Wellcome Wolfson Centre, University of Exeter Medical School, Royal Devon and Exeter NHS Foundation Trust, Barrack Road, Exeter, EX2 5DW, UK
2 Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK
3 Dipartimento di Medicina Molecolare e Biotecnologie Mediche DMMBM, Università di Napoli Federico II, Via Sergio Pansini 5, Naples, 80131, Italy
4 CEINGE Biotecnologie Avanzate, Via Gaetano Salvatore 486, Naples, Italy
5 European School of Molecular Medicine, SEMM, University of Milan, Italy

Correspondence to: Dr Emma L. Baple,
Medical Research (Level 4),
RILD Wellcome Wolfson Centre,
Royal Devon and Exeter NHS Foundation Trust,
Barrack Road, Exeter, EX2 5DW, UK
E-mail: E.Baple@exeter.ac.uk

Sir,

In their Letter to the Editor, Karakaya *et al.* (2017) present an interesting case report describing the clinical course involving secondary microcephaly of a 3-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 with respiratory insufficiency and seizures developing 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; Costain *et al.*, 2017; Zollo *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 that, 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 phenotypical contribution from this additional homozygous sequence variant.

Recently, Costain *et al.* (2017) described a homozygous consensus splice site variant in *PRUNE1* (c.521-2A > G; NM_021222.1) in a 2-year-old Oji-Cre male who presented with congenital hypotonia and talipes, whose head circumference was large at birth (+3 standard deviations), but by 2 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

Advance Access publication August 23, 2017

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).

It remains to be determined how the phenotypical outcomes stemming from proposed loss-of-function mutations defined by Karakaya *et al.* and Costain *et al.*, relate to missense mutations published by Karaca *et al.* and also Zollo *et al.*, which are likely to involve at least partial gain-of-function outcomes in PRUNE1 activity. However, as more cases are investigated and published, the phenotype associated with autosomal recessive Prune neurodevelopmental disorder, and the functional outcomes of PRUNE1 mutation, are 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.*, 2017). 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-Cre child, as well as the youngest affected Omani child described in our manuscript.

Web resources

The URLs for data presented herein are as follows: Genome Aggregation Database (gnomAD); http://gnomad.broadinstitute.org

References

Costain G, Shugar A, Krishnan P, Mahmutoglu S, Laughlin S, Kannu P. Homozygous mutation in PRUNE1 in an Oji-Cree male with a complex neurological phenotype. Am J Med Genet A 2017; 173: 740–3.

Edvardson S, Tian G, Cullen H, Vanyai H, Ngo L, Bhat S et al. Infantile neurodegenerative disorder associated with mutations in TBCD, an essential gene in the tubulin heterodimer assembly pathway. Hum Mol Genet 2016; 25; 4635–48.

Firat-Karalar EN, Rauniyar N, Yates JR 3rd, Stearns T. Proximity interactions among centrosome components identify regulators of centriole duplication. Curr Biol 2014; 24: 664–70.

Flex E, Niceta M, Cecchetti S, Thiffault I, Au MG, Capuano A et al. Biallelic mutations in TBCD, encoding the tubulin folding cofactor D, perturb microtubule dynamics and cause early-onset encephalopathy. Am J Hum Genet 2016; 99: 962–73.

Karaca E, Harel T, Pehlivan D, Jhangiani SN, Gambin T, Coban Akdemir Z, et al. Genes that affect brain structure and function identified by rare variant analyses of Mendelian neurologic disease. Neuron 2015; 88: 499–513.

Karakaya M, Yilmaz S, Storbeck M, Hoelker I, Heller R, Serdaroglu G, et al. *PRUNE1*: a disease-causing gene for secondary microcephaly. Brain 2017; 140: e61.

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016; 536: 285–91.

Miyake N, Fukai R, Ohba C, Chihara T, Miura M, Shimizu H et al. Biallelic TBCD mutations cause early-onset neurodegenerative encephalopathy. Am J Hum Genet 2016; 99: 950–61.

Pode-Shakked B, Barash H, Ziv L, Gripp KW, Flex E, Barel O et al. Microcephaly, intractable seizures and developmental delay caused by biallelic variants in TBCD: further delineation of a new chaperone-mediated tubulinopathy. Clin Genet 2017; 91: 725–38.

Zollo M, Ahmed M, Ferrucci V, Salpietro V, Asadzadeh F, Carotenuto M, et al. PRUNE is crucial for normal brain development and mutated in microcephaly with neurodevelopmental impairment. Brain 2017; 140: 940–52.