HHS Public Access

Author manuscript

J Neurogenet. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

J Neurogenet. 2018 December ; 32(4): 313–315. doi:10.1080/01677063.2018.1473862.

A *de novo* mutation in *PRICKLE1* associated with myoclonic epilepsy and autism spectrum disorder

Brittany P. Todd[1] and **Alexander G. Bassuk**[1]

[1]The University of Iowa, Department of Pediatrics

Abstract

Homozygous recessive mutations in the *PRICKLE1* gene were first described in three consanguineous families with myoclonic epilepsy. Subsequent studies have identified neurological abnormalities in humans and animal models with both heterozygous and homozygous mutations in *PRICKLE1* orthologues. We describe a 7-year-old with a novel *de novo* missense mutation in *PRICKLE1* associated with epilepsy, autism spectrum disorder, and global developmental delay.

Keywords

PRICKLE1; *de novo* mutation; prickle; epilepsy; autism spectrum disorder

Introduction

Homozygous recessive mutations in the *PRICKLE1* gene were first described in three consanguineous families with myoclonic epilepsy (Bassuk et al., 2008). Subsequent studies have identified neurological abnormalities in humans and animal models with both heterozygous and homozygous mutations in *PRICKLE1* orthologues (Bosoi et al., 2011; Ehaideb et al., 2014; Paemka et al., 2013; Tao et al., 2011). Inherited heterozygous *PRICKLE1* mutations have been reported in several human conditions including epilepsy (Tao et al., 2011) autism (Paemka et al., 2013), and spina bifida (Bosoi et al., 2011). Additionally, *de novo PRICKLE1* mutations have been reported in association with fetal agenesis of the corpus callosum (Bassuk & Sherr, 2015), Charcot Marie Tooth Disease and epilepsy(Pehlivan et al., 2015). We describe a 7-year-old with a novel *de novo* mutation in *PRICKLE1* associated with epilepsy, autism spectrum disorder, and global developmental delay.

Materials and Methods

The family was consented by an IRB approved protocol at the University of Iowa, after informed consent was obtained, clinical whole exome sequencing was performed on DNA isolated from the child and from the parents. Clinical exome sequencing was performed by Gene Dx (Gaithersburg, MD) using standard techniques. Briefly, the clinical exome

Corresponding author: Alexander G. Bassuk, MD, PhD, 2020 Med Labs, 25 S. Grand Avenue, Iowa City, Iowa 52242, 319-356-1851, alexander-bassuk@uiowa.edu.

sequencing begins with massive parallel sequencing using the Illumia HiSeq sequencing system with 100bp paired-end reads. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants using a custom-developed analysis tool (Xome Analyzer). 100% of the coding region was covered at a minimum of 10× coverage.

Results

Case Report

Patient x is a 7-year-old boy. He presented at 11 months with abnormal body movements consistent with myoclonic seizures. EEG demonstrated generalized epileptiform discharges. MRI was normal (Figure 1). The patient was significantly delayed in meeting his motor milestones; he sat up at 18 months, and walked at 2 ½ years. At 6 years of age he was clinically evaluated for behavioral concerns and was diagnosed with autism spectrum disorder and a mild intellectual disability. After informed consent was obtained from an IRB approved protocol from the University of Iowa, clinical whole exome sequencing was performed on DNA isolated from Patient x and from the parents, revealing a *de novo* mutation in the *PRICKLE1* gene c.1444 G>A, D482N (Figure 1). No other *de novo* mutations were identified, nor were any other mutations in known disease-causing genes uncovered, including known global developmental delay, autism spectrum disorder, and epilepsy genes (Supplementary table 1). Genes evaluated include those from the GeneDx epilepsy panel (https://www.genedx.com/test-catalog/available-tests/comprehensive-epilepsy-panel/). The *de novo* mutation was validated by Capillary sequencing. This variant was absent from over 6500 alleles in the Exome Variant Server (http://evs.gs.washington.edu/EVS/)) and absent from the 60,706 individuals from the ExAc Browser (http://exac.broadinstitute.org/). Sequence alignment shows that the D482N encoding *PRICKLE1* mutation alters an amino acid conserved throughout vertebrate evolution.

Discussion

PRICKLE1 mutations in humans were originally described as recessive mutations in families with syndromic myoclonic epilepsy (Bassuk et al., 2008). Subsequently variation in *PRICKLE1* has been described in patients with non-syndromic epilepsy (Tao et al., 2011), autism (Paemka et al., 2013), and spina bifida (Bosoi et al., 2011). Additionally, *de novo PRICKLE1* mutations have been reported in association with agenesis of the corpus callosum and polymicrogyria (Bassuk & Sherr, 2015), Charcot Marie Tooth Disease and epilepsy (Pehlivan et al., 2015). Our description of a novel *de novo PRICKLE1* mutation associated with global developmental delay, autism spectrum disorder, and epilepsy in the absence of any other *de novo* mutation or known disease causing mutation strongly implicates the *PRICKLE1* gene as a causative factor.

Like the original human *PRICKLE1* mutant families (Bassuk et al., 2008) the current patient had normal MRI findings. This is in contrast to our previously reported PRICKLE1 de novo mutation with agenesis of the corpus callosum and polymicrogyria (Bassuk & Sherr, 2015). Thus there seems to be a spectrum of radiological findings among *PRICKLE1* mutant

patients. These findings strengthen and expand the clinical spectrum of abnormalities associated with *PRICKLE1* mutations in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding from NIH 5R01NS098590 (to AGB).

References

Bassuk AG, & Sherr EH (2015). A de novo mutation in PRICKLE1 in fetal agenesis of the corpus callosum and polymicrogyria. J Neurogenet, 29(4), 174–177. doi:10.3109/01677063.2015.1088847 [PubMed: 26727662]

Bassuk AG, Wallace RH, Buhr A, Buller AR, Afawi Z, Shimojo M, … El-Shanti HI (2008). A homozygous mutation in human PRICKLE1 causes an autosomal-recessive progressive myoclonus epilepsy-ataxia syndrome. Am J Hum Genet, 83(5), 572–581. doi:10.1016/j.ajhg.2008.10.003 [PubMed: 18976727]

Bosoi CM, Capra V, Allache R, Trinh VQ, De Marco P, Merello E, Kibar Z (2011). Identification and characterization of novel rare mutations in the planar cell polarity gene PRICKLE1 in human neural tube defects. Hum Mutat, 32(12), 1371–1375. doi:10.1002/humu.21589 [PubMed: 21901791]

Ehaideb SN, Iyengar A, Ueda A, Iacobucci GJ, Cranston C, Bassuk AG, Manak JR (2014). prickle modulates microtubule polarity and axonal transport to ameliorate seizures in flies. Proc Natl Acad Sci U S A, 111(30), 11187–11192. doi:10.1073/pnas.1403357111 [PubMed: 25024231]

Paemka L, Mahajan VB, Skeie JM, Sowers LP, Ehaideb SN, Gonzalez-Alegre P, Bassuk AG (2013). PRICKLE1 interaction with SYNAPSIN I reveals a role in autism spectrum disorders. PLoS One, 8(12), e80737. doi:10.1371/journal.pone.0080737 [PubMed: 24312498]

Pehlivan D, Beck CR, Okamoto Y, Harel T, Akdemir ZHC, Jhangiani SN, Lupski JR (2015). The role of combined SNV and CNV burden in patients with distal symmetric polyneuropathy. Genetics In Medicine, 18, 443. doi:10.1038/gim.2015.124 [PubMed: 26378787]

Tao H, Manak JR, Sowers L, Mei X, Kiyonari H, Abe T, Bassuk AG (2011). Mutations in prickle orthologs cause seizures in flies, mice, and humans. Am J Hum Genet, 88(2), 138–149. doi:10.1016/j.ajhg.2010.12.012 [PubMed: 21276947]

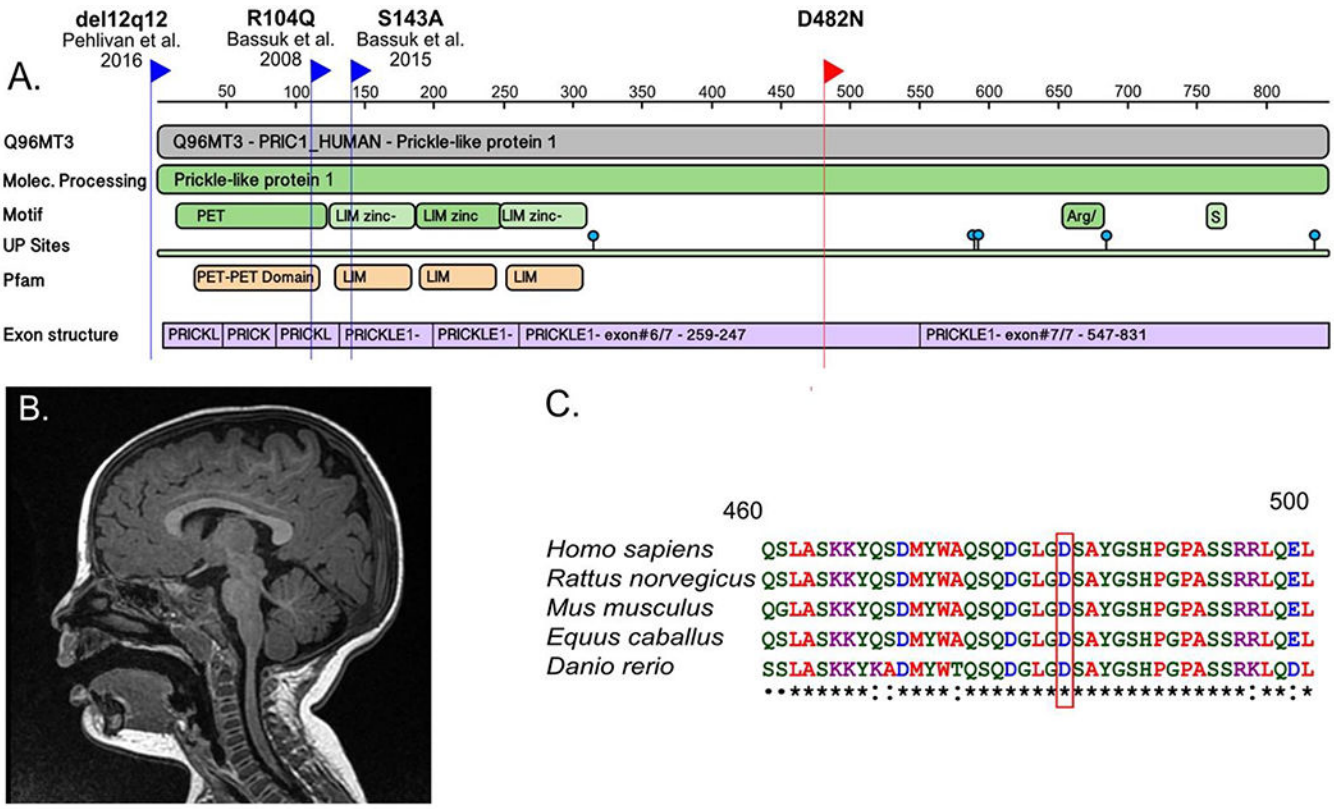

Figure 1:

(a) Protein Feature View for *PRICKLE1* from the RCSB Protein Data Bank (PDB) website. The blue flags indicate the location of human *PRICKLE1* mutations that have been previously reported, including a *de novo* mutation associated with fetal agenesis of the corpus callosum and polymicrogyria (Bassuk & Sherr, 2015), a homozygous recessive mutation associated with myoclonic epilepsy (Bassuk et al., 2008), and a ~30-kb deletion involving the 5' untranslated region and start of the *PRICKLE1* coding sequence associated with Charcot Marie Tooth Disease and epilepsy (Pehlivan et al., 2015). The red flag indicates the novel *de novo PRICKLE1* missense mutation. **(b)** Midline sagittal image from an MRI conducted at 1-year-old showing normal findings. **(c)** Multiple species protein alignment of the region surrounding the amino acid change caused by the novel de novo mutation in PRICKLE1. The red box indicates the reference amino acid, D, in humans and other vertebrates. The amino acid is completely conserved in vertebrates used in the alignment, and is within a highly conserved domain across all species. Peptide sequences were downloaded from UniProt BLAST and the alignment was performed using the Clustal Omega website (http://www.ebi.ac.uk/Tools/msa/clustalo/).