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Expansion of *PURA*-Related Phenotypes and Discovery of a Novel PURA Variant: A Case Report

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Abstract

Variants in *PURA* have recently been associated with an autosomal dominant form of *PURA*-related neurodevelopmental disorders. Using whole exome sequencing, patients with neurological phenotypes including hypotonia, developmental delay, learning disabilities, and seizures were identified to have de novo variants in *PURA*. We describe a proband with features similar to the previously described cases with *PURA* variants, but including additional features, such as short stature, delayed bone age, and delayed puberty. Exome sequencing revealed a novel pathogenic nonsense variant, c.190A>T (p.Lys64*; NM_005859), in *PURA* that was not inherited from the proband's mother. In the recent literature, a significant number of patients with variants in *PURA* have been described, but to our knowledge, none of these patients have the delayed bone age and growth plateau observed in the proband. It is therefore possible that the above PURA variant may be responsible for the novel features and thus expands the PURA-related phenotype spectrum.

Keywords

PURA, seizures, delayed bone age, next-generation sequencing, developmental delay

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Introduction

Pathogenic variants in the purine rich element binding protein A, *PURA,* are associated with a rare dominant disorder, *PURA*-related neurodevelopmental disorders, characterized by neonatal hypotonia, severely delayed psychomotor development, early-onset feeding difficulties, and significant respiratory insufficiency (MIM# 600473). PURA-syndrome has been described in 73 individuals to date, with either loss-of-function or missense de novo variation in *PURA*.[1–7] Interestingly, these patients have significant phenotypic overlap with the 5q31.3 microdeletion syndrome, the region within which *PURA* resides, suggesting that the loss of *PURA* in the microdeletion syndrome may be the cause of the overlapping phenotypes.[5,8]

We recently pursued WES on an 18-year-old male with multiple features including delayed motor milestones, absent speech, intellectual disability, hypotonia, seizures, short stature, failure to thrive, delayed puberty, cortical blindness, and kyphoscoliosis. Clinical WES revealed a novel variant, c.190A>T (p.Lys64*; NM_005859) in *PURA* that was absent in the proband's mother. In addition to the well-established phenotypes associated with variation in *PURA,* the proband also exhibits delayed bone age and significant short stature. It would be valuable to look for these

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phenotypes in patients with *PURA* variants to determine whether these phenotypes are related, or due to an unidentified cause. Finally, while most patients with PURA variants have delayed walking or are non-ambulatory, with significant therapy, the proband was able to achieve independent walking, which emphasizes that physical therapy for patients with PURA variants may be extremely valuable and can help improve physical symptoms.

Case Presentation

Clinical Presentation

The proband was born at 42 weeks gestation via induction without major complication following an uncomplicated pregnancy with a birth weight of 3.2 kg. APGAR scores were 8, 9, and 10 at 1, 5, and 10 minutes, respectively. Hypoglycemia and hypotonia were noted at birth and in retrospect, his mother noted that fetal movements were decreased compared to his siblings. Placental pathology was not reported. He spent 1.5 weeks in the NICU to be fed by NG tube. Initial EMG and MRI of the brain were normal. During his first month, it was noted that he had nystagmus, and ophthalmology exam identified optic atrophy, hyperopia, amblyopia, and strabismus.

Neurologically, myoclonic and tonic seizures began at 18 months of age. At 10 years of age he started experiencing head drops with corresponding abnormal EEGs. At 16 he was given a diagnosis of Lennox-Gastaut syndrome. At age 19 the patient was noted to have an increase in seizure occurrence. During this time he was admitted to the hospital in status epilepticus with tonic seizures. The addition of valproate and felbatol to his regimen of rufinamide and clobazam was noted to better control his seizures. Currently at age 20 his seizures are being treated with felbamate, valproic acid, clonazepam and rufinamide. Seizures improved from between 5-20 seizures a day to 2-5 per day. His background EEG is consistently abnormal with abundant generalized epileptiform discharges with lack of clear posterior dominant rhythm and generalized slowing. He has recorded myoclonic and tonic seizures. Brain MRI, at age 20, showed no focal abnormality to suggest the cause of epilepsy, and did not show any malformations of cortical or subcortical development.

Due to motor and developmental delays, the proband began receiving PT, OT and speech therapy at a young age. As a result he was able to attain independent ambulation with the assistance of ankle-foot orthoses. At his most recent follow up, his cognitive skills and receptive communication were at a 6-month level, expressive communication and fine motor skills were at an 8 month level, and gross motor skills were at an 11 month level.

From an endocrinology standpoint, the proband had normal growth parameters from birth until 7 years of age, at which time his growth and weight plateaued. Since that time, he has had a slow increase in height with persistently delayed bone age. Extensive gastroenterology and endocrinology workups failed to find a specific issue that could explain his growth delay. Thyroid and adrenal function wer normal. IGF-1 and IGFBP-3 were borderline low but the glucagon-stimulated growth hormone response was robust. Vitamin D levels have been normal on multiple occasions. MRI of brain showed normal pituitary gland. He also had delayed puberty with no pubertal changes noted at 14 years of age. He was diagnosed with hypogonadotropic hypogadism and testosterone injections were started at 14 years of age, which stimulated puberty and growth, however did not improve bone age. At his most recent follow up at age 20, his testes remained prepubertal in size. His height and weight were well below the 3 rd centile at 143 cm and 30.7 kg respectively, and bone age was delayed at 11 years 6 months, unchanged since 17 years of age. Based on parental heights (mother 154 cm and father 158 cm), his predicted height should be 156.7 cm. His brothers have normal height with one brother exhibiting late puberty at age 16.

Family History

The proband has two healthy brothers. Both parents are healthy, and besides a history of malignant hyperthermia in maternal relatives, there are no known neurologic or genetic conditions on either side of the family. There is no history of consanguinity (Figure 1).

Genetic Analysis

Clinical exome sequencing was performed at Baylor on an Illumina HiSeq using 100 base paired-end reads. Variants related to the proband's phenotype were confirmed by Sanger sequencing. A heterozygous c.190A>T (p.Lys64*) variant in *PURA* was detected in this individual. This variant was not found in the proband's mother. This variant has not been reported in the literature, and is truncating. Truncating variants downstream of this position have been identified in many individuals with clinical features of PURA-syndrome.[1,5,7] This variant was reported as pathogenic based on the presence of other truncating pathogenic variants in the literature, the gene's intolerance to loss of function, the highly specific phenotypic features observed in the proband matching PURA-syndrome, and the absence of other pathogenic or likely pathogenic variants in genes related to the phenotype. Additional in vitro functional studies were not performed. A variant of uncertain significance was identified in a mitochondrial gene MTRNR1 (m.650T>C) at 88.5% heteroplasmy in the proband and 72% in his asymptomatic mother and was therefore felt not to be causative of his clinical phenotype. Chromosomal microarray analysis was normal.

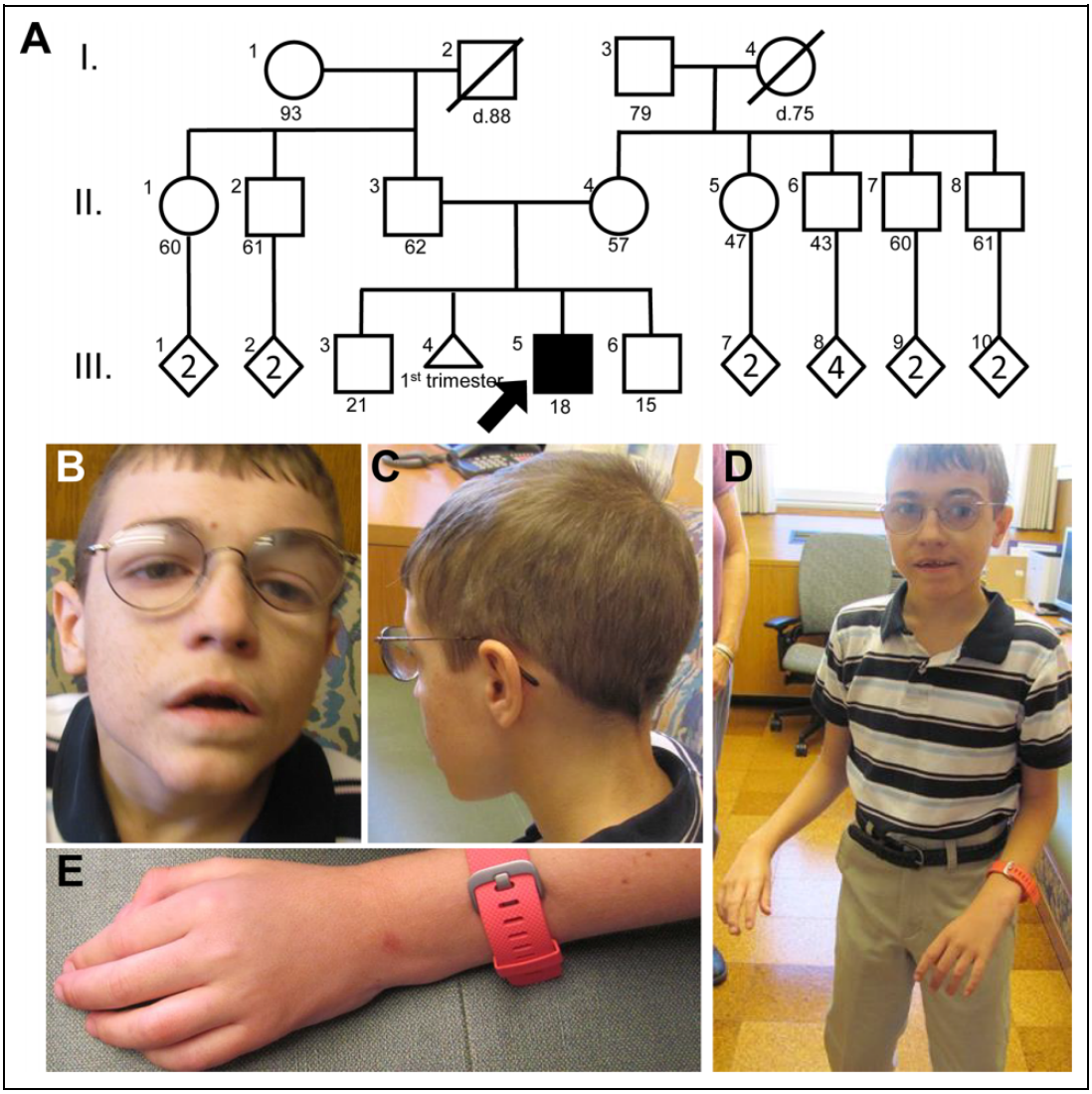

Figure 1. Pedigree and Images of Proband with *PURA* Variant. (A) Pedigree highlighting that the proband (III.5), is affected. (B-E) Representative images of the proband at age 17 years of age showing the patients face, ears, stature, and hand, respectively.

Conclusion

Here we present a patient with a novel truncating variant in *PURA* and a diagnosis of PURA-syndrome. His phenotypic presentation is similar to previously described patients including neonatal hypotonia, severely delayed psychomotor development, absent speech, early-onset feeding difficulties, seizures, and kyphoscoliosis.[1–7] Additional features included short stature, delayed bone age, and delayed puberty which has required testosterone treatment. At age 20, he is one of the oldest PURA-syndrome patients described, adding important natural history about puberty, growth and development for other similarly affected patients.

Short stature has been described previously in PURA syndrome cohorts,[1,6] but to the best of our knowledge has not been as severe as observed in this patient. Delayed puberty was also previously reported in 2 individuals,[6] and is therefore rare in the context of PURA syndrome. Decreased bone density has been previously observed,[1,6] but here we report the first case of delayed bone age. The proband is currently 20, with a bone age of 11 years and 6 months. Also, the proband presented with cortical blindness, which has only been reported in 3 individuals to date.[6] Finally, while most patients with PURA variants have delayed walking or are non-ambulatory, with significant therapy, the proband was able to achieve independent ambulation, emphasizing that physical therapy for patients with PURA variants may be valuable and can help improve physical symptoms. This case adds to our current knowledge of the phenotypic spectrum associated with PURA-syndrome. We present a novel variant as well as some new or rare phenotypic characteristics of patients with PURA-syndrome.

Authors' Note

Drs. Boczek and Macke are co-equal first authors.

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Declaration of Conflicting Interests

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