PURA SYNDROME: REFINING THE PHENOTYPE

ABSTRACT

PURA syndrome is a recently described disorder presenting with neonatal hypotonia, feeding difficulties, and frequent apnea and epilepsy. Affected individuals commonly have global developmental delay, intellectual disability, and severe language impairment. We identified 31 new individuals with de novo mutations in PURA. We did not find significant strong clinical associations between PURA mutation type and/or location, however moderate associations were found between presence of a mutation within the PUR-I domain and infantile spasms (Pearson’s correlation = 0.41, p = 0.02), nonrefractory mutations at any location and Lennox-Gastaut syndrome (Pearson’s correlation = 0.52, p = 0.002), and any mutation within the PUR-III domain and Lennox-Gastaut syndrome (Pearson’s correlation = 0.42, p = 0.02). Mutations in the PUR-I domain showed a modest negative correlation with increased clinical severity (Pearson’s correlation = -0.39, p = 0.03). Subjects with epilepsy had a higher mean clinical severity score compared to individuals without epilepsy (p = 0.0005). Individuals who were nonambulatory had a higher mean clinical severity score compared to individuals who could walk (p = 0.02). Although there was a trend in the direction of PUR-I domain mutations being less severe, PUR-I domain mutations showed more heterogeneity, and PUR-III most severe, these differences were not statistically significant. Further studies are indicated in larger cohorts of subjects with PURA syndrome to clarify these genotype-phenotype associations.

METHODS

Whole exome sequencing. Subject DB13-043 and both parents had research whole exome sequencing performed on saliva-derived DNA. All other subjects had clinical whole exome sequencing performed as part of routine care.

Clinical data acquisition. Birth history, medical history, developmental history, and family history were obtained through standardized phone interviews and/or standardized questionnaires with parents of affected individuals. Medical records, including developmental and autism assessments were also reviewed. Routine clinical brain magnetic resonance imaging (MRI) studies were reviewed in 21 of the 31 individuals with PURA syndrome.

RESULTS

Figure 1: Location of pathogenic sequence variations (red) in domains of the PURA protein reported in this series.

Figure 2: Representative facial photographs of individuals with PURA syndrome across the lifespan.

Figure 3: Representative brain MRI findings in individuals with PURA syndrome. (A) Thinning of the corpus callosum and of the subcortical white matter with (B) increased extra-axial fluid spaces. (C) Mildly increased extra-axial fluid in the posterior fossa and (D) Horseshoe of the cortical white matter. (E-G) Subcortical cysts (arrowheads). One patient had cerebellar vermal atrophy (arrows) develop over scans at ages 2 years (K), 6 years (L), and 9 years (M).

CONCLUSIONS

PURA syndrome is the latest neurodevelopmental disorder to emerge where symptoms are attributed to pathogenic sequence variations in a transcription factor expressed during early brain development. Early hypotonia, severe language impairment, variable epilepsy severity, and abnormal patterns of movement are common features. Global developmental delay and significant intellectual disability are usually present in this class of disorders, however there can be considerable variability.

While we observed considerable clinical variability, there are enough core clinical features that this diagnosis should be considered in any individual with severe neonatal hypotonia, feeding difficulties, congenital opalescence, global developmental delay with significant language impairment, as well as frequent occurrence of epilepsy and skeletal abnormalities. The rapid characterization of this previously undescribed disorder, largely through clinically available whole exome sequencing, demonstrates the diagnostic utility of massively parallel sequencing approaches in medical genetics. Further studies to better understand the epilepsy, movement, and other neurologic phenotypes associated with PURA syndrome are indicated.