



Case Report

Hyperphosphatasia with mental retardation syndrome, expanded phenotype of *PIGL* related disordersRuqaiyah Altassan^a, Stephanie Fox^a, Chantal Poulin^b, Daniela Buhas^{a,c,*}^a Department of Medical Genetics, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada^b Department of Pediatric, Division of Neurology, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada^c Department of Human Genetics, McGill University, Montreal, Quebec, Canada

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ABSTRACT

Hypomorphic mutations in six different genes involved in the glycosylphosphatidylinositol (GPI) biogenesis pathway are linked to Mabry syndrome (hyperphosphatasia with mental retardation syndrome, HPMRS). This report on the third affected family with a HPMRS phenotype caused by mutations in *PIGL*, confirming the seventh GPI biogenesis gene linked to HPMRS. Two siblings presented with the main features of HPMRS; developmental delay, cognitive impairment, seizure disorder, skeletal deformities, and high alkaline phosphatase. We identified two heterozygous mutations in the *PIGL* gene (P.Trp20Ter and p.Arg88Cys). *PIGL* mutations have been linked to another distinctive neuroectodermal disorder: CHIME syndrome. The clinical picture of our patients expands the spectrum of *PIGL*-related phenotypes.

1. Introduction

Glycosylphosphatidylinositol (GPI) glycolipids play a critical role in the post-translation modification and cell membrane anchoring of > 150 eukaryotic proteins which ultimately affect the sorting, trafficking, and dynamics of those proteins. Also, they participate in the process of embryogenesis, neurogenesis, immune responses, and fertilization. The biogenesis of mature GPI involves > 20 genes and occurs in eukaryotes via a conserved post-translational pathway [1].

In animal studies, complete deletion of the GPI pathway results in embryonic lethality. However, complete deletion has not been reported in humans. Hypomorphic mutations in the genes encoding the GPI biogenesis pathway result in partial reduction of GPI-anchored proteins, which leads to phenotypically heterogeneous clinical presentations, with global developmental delay a common feature. This element supports the notion that GPI-anchored proteins play a vital role in neurogenesis [2,3].

PIGL encodes the endoplasmic phosphatidylinositol glycan anchor biosynthesis class L, which is involved in the second step of GPI biosynthesis: the de-n-acetylation of n-acetylglucosaminyl-phosphatidylinositol (GluNAc-PI), generating glucosaminyl-phosphatidylinositol (GlcN-PI) on the cytoplasmic side of the endoplasmic reticulum [4].

Mutations in *PIGL* have been linked to two rare distinctive

syndromes: CHIME syndrome (Zunich neuroectodermal syndrome) and Mabry syndrome (hyperphosphatasia with mental retardation syndrome, HPMRS) [5,6].

2. Clinical data

The proband is a 10-year-old West African male who is the first offspring of a non-consanguineous couple. He was delivered spontaneously at term after an uneventful pregnancy weighing 2665 g (5th percentile) with a head circumference of 32 cm (5th percentile) and Apgar score of 9. At the age of 6 months, he presented with myoclonic seizures that were partially controlled with medications. By the age of 12 months, he had surgical correction of inguinal hernia, hydrocele, and strabismus. His developmental milestones were globally delayed, including cognitive, language, gross and fine motor functions, with no major improvement despite intensive rehabilitation. His first available baseline physical examination was documented at 4 years of age. Growth parameters were normal with weight, height and head circumference on the 75th percentile. The facial features were coarsely dysmorphic, including prominent forehead, high arched eyebrows and sparse on the outer third, nystagmus, mild telecanthus, uplifted ear lobes, and open mouth with intermittent drooling. In addition, he had mild pectus excavatum and clinodactyly involving the fifth digits, 4th

Abbreviations: GPI, glycosylphosphatidylinositol; HPMRS, hyperphosphatasia with mental retardation syndrome; CHIME, ocular colobomas, heart defect, ichthyosis, mental retardation, and abnormal ears or epilepsy; *PIGL*, phosphatidylinositol glycan anchor biosynthesis class L; ALP, alkaline phosphatase; CSS, Coffin-Siris syndrome

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Fig. 1. X-ray hands showed deformity of the middle phalanx of the 5th finger bilaterally with the lateral aspect of the phalanx being shorter than the medial aspect.

and 5th toes bilaterally. (Fig. 1, hand X-ray). No skin abnormalities were noted. Other features included reducible umbilical hernia, mild hepatomegaly, and ataxic gait. Audiology and heart evaluations were normal. Brain MRI showed symmetrical bilateral patchy signal abnormalities in the periventricular zones in the parietal, occipital and frontal regions, white matter loss, and thin corpus callosum. Liver enzymes showed mildly elevated transaminases with significantly elevated ALP 968 U/L (normal: 135–320 U/L). Vitamin E and alpha-feto-protein were normal. All metabolic tests were unremarkable, including but not limited to purines/pyrimidines, glycosaminoglycans, creatine panel, carbohydrate transferrin, homocysteine, sterol profiles, and creatine kinase. Array CGH and Coffin-Siris molecular testing were normal.

Evaluation of the patient's younger 4-year-old brother revealed a very similar presentation. He had unremarkable antenatal and perinatal history. His developmental milestones were globally delayed. He developed his first onset of partially controlled tonic-clonic seizures at the age of 4 months. Strabismus was surgically corrected at the age of 1 year. On examination, he was inattentive with coarse facial features including high hairlines, hypertelorism, epicanthal folds, horizontal nystagmus, depressed nasal bridge, delayed teeth eruption, everted and partially bifid lower lip, folded ears, and irregular hypopigmented skin margins surrounding the eyes and the nose. His head circumference was 51 cm (75th percentile). Systemic examination revealed spastic lower limbs, bilateral brachydactyly, severe clinodactyly of both fifth fingers and toes and dry eczematous skin. No chest deformity or organomegaly was noted. His ALP was 454 U/L.

3. Molecular data

A commercially available multigene panel for intellectual disability (GeneDx) was performed in the proband and revealed two variants in *PIGL* gene, a nonsense (c.60G > A; p.Trp20Ter; W20X) pathogenic variant and missense (c.262C > T; p.Arg88Cys; R88C) variant. Neither variant was observed in approximately 65,000 individuals of European and African American ancestry in the NHLBI Exome Sequencing Project. The first variant was interpreted as pathogenic as it causes loss of normal protein function through truncation or nonsense-mediated mRNA decay. For the second variant, in silico analysis predicted it as likely damaging the protein structure and function. Parental analyses

were done by Sanger sequencing and confirmed *in trans* mutations. Targeted genetic testing for the brother detected the same variants.

4. Discussion

In 1970, Mabry et al. described a unique syndrome comprised of severe cognitive impairment, seizures, various neurologic deficits, and elevated serum ALP [6]. This syndrome was acronymed HPMRS-1 (OMIM: 239300) [7] and linked to mutations in the *PIGV* gene, which is involved in the early steps of GPI anchor assembly [8]. Subsequently, other pathogenic defects in genes involved in either GPI anchor assembly or maturation were linked to the same phenotype. [Table 1].

The *PIGL* gene is responsible for the second step of GPI biosynthesis. Mutations in this gene were initially reported in seven cases presenting with CHIME syndrome. CHIME (OMIM: 280000, ocular Colobomas, Heart defect, Ichthyosis, Mental Retardation, and abnormal Ears or Epilepsy) was first described clinically by Zunich et al. in 1983, acronymed by Shashi et al. in 1995, and linked to *PIGL* mutations by Ng et al. in 2012. All patients presented the main features of CHIME syndrome plus a variable combination of facial dysmorphism such as brachycephaly, flat and broad nasal root, short philtrum, hypertelorism, cloudy corneas, overfolded helices, wide mouth, full lips, cleft palate, and abnormal dentation. Mildly elevated alkaline phosphatase was reported in only one patient who presented with a clinical phenotype of CHIME syndrome (not molecularly confirmed) in the setting of acute lymphocytic leukemia [5,9–12].

Recently, in addition to its association with CHIME syndrome, mutations in *PIGL* have been linked to HPMRS in two cases [13,14]. We are reporting the third family with a HPMRS phenotype secondary to *PIGL* mutations supported by the clinical presentations of cognitive delay, seizures, skeletal deformities, and elevated ALP. Our patients had some overlapping features between CHIME and HPMRS, particularly in the characteristic facial features, seizures, and global developmental delay. However, the absence of coloboma, heart defect and hearing impairment, in addition to the distinctive skeletal phenotype of short terminal phalanges and the high ALP made the presentation more suggestive of HPMRS.

The phenotypic difference between HPMRS and CHIME syndromes could be related to the type of *PIGL* mutation. All the reported cases with a HPMRS phenotype, including our patients, presented at least one

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