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50 Years Ago in *The Journal of Pediatrics*

Familial Hyperphosphatasia with Mental Retardation, Seizures, and Neurologic Deficits

Mabry C, Bautista A, Kirk RFH, Dublilier LD, Braunstein H, Koepke JA. J Pediatr 1970;77:74-85.

Mabry et al reported the first 4 patients with hyperphosphatasia with mental retardation syndrome (HPMRS) to present with generalized seizures and facial dysmorphism. The syndrome can be distinguished from other developmental disabilities by the stable elevation of alkaline phosphatase without bone disease.[1] Few published reports of the syndrome appeared before we identified a patient whose seizures responded to pyridoxine.[2] Improved syndromology[1] made it possible to use next-generation sequencing to identify the recessive mutations that cause what became known as Mabry syndrome (OMIM 239300).[2] There are at least 6 phenotypes. HPMRS 1, 2, 5, and 6 result from disruption of 4 genes encoding phosphatidylinositol glycan (PIG) anchor biosynthesis enzymes that act in the endoplasmic reticulum: type V (*PIGV*) type O (*PIGO*), type W (*PIGW*), and type Y (*PIGY*). HPMRS 4 and 3 result from disruption of 2 genes encoding postattachment to proteins (PGAP) enzymes that stabilize glycosylphosphatidylinositol attachment to proteins in the golgi: *PGAP3* and *PGAP2*.[3] The report by Mabry et al describes the first of at least 21 inherited glycosylphosphatidylinositol biosynthesis defects (GPIBDs) that together compose approximately 0.15% of all developmental disabilities.[4] The HPMRS3 (GPIBD8 [MIM: 614207]) phenotype presented by Mabry et al, resulting from biallelic inheritance of PGAP2 mutations, is the prototypical HPMRS phenotype among GPIBDs.[5] This work demonstrates the value of case studies to basic science, clinical innovation, and patient follow-up.

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