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Biallelic PIGB variants are a cause of childhood-onset, motor-predominant neuropathy with conduction blocks and neuromyotonia

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Glycosylphosphatidylinositol (GPI)-anchored proteins (GPI-AP) play crucial roles in the nervous system and biallelic variants in phosphatidylinositol glycan (PIG) genes cause severe neurodevelopmental disorders in infants. We report the first adult patients carrying mostly novel PIGB variants, presenting with childhood-onset, motor-predominant neuropathy with conduction blocks and neuromyotonia.

Genotyping was performed via exome/genome sequencing. Clinical data were collected retrospectively. GPI-AP expression was analyzed in blood cells by flow cytometry. Variant validation using a PIGB KO/KI K562 model is ongoing.

One known [p.(Arg232His)] and seven novel [p.(Leu112Pro), p.(Trp182Leu), p.(Val295Met), p.(Val414Ile), p.(Met436Ile), p.(Met454Thr), de novo inversion inducing a PIGB(E1–E9):Rab7(E7) fusion] PIGB variants were identified in 6 adults from 5 families (3 females, median age 35.5 years). All had pes cavus and distal lower-limb weakness from childhood, and walked independently on last visit. ENMG showed motor-predominant neuropathy with conduction blocks in five patients and one had demyelinating sensorimotor neuropathy. Four showed electrical neuromyotonia and muscle hypertrophy, 2 only muscle hypertrophy. One had episodic proximal weakness with diffuse decrements in repetitive nerve stimulation responsive to pyridostigmine. All but one patient had mild psychomotor delay or

behavioral problems and two had transit epilepsy during childhood. One had mild dysmorphic features and five had elevated alkaline phosphatase. GPI-AP expression in blood cells was mildly to moderately reduced in all patients. The p.(Leu112Pro) and p.(Met436Ile) have been validated in vitro.

PIGB is a novel cause of slowly progressive, motor-predominant neuropathy with conduction blocks. Neuromyotonia, more common in acquired neuropathies, was frequent, reminiscent of HINT1-associated CMT. PIGB should be screened in unexplained neuropathies with conduction block and neuromyotonia.