Novel mutations in the C-terminal region of GMPPB causing limb-girdle muscular dystrophy overlapping with congenital myasthenic syndrome.


Abstract

Mutations in the GMPPB gene may underlie both limb girdle muscular dystrophy (LGMD) and congenital myasthenic syndrome (CMS). Forty-one cases have been reported to date and hotspot mutations are emerging in the Caucasian population. Clinical and pathological features of 5 patients with compound heterozygous GMPPB mutations were collected and retrospectively reviewed. In vitro functional analysis was performed to investigate the pathogeneity of GMPPB variants. The patients presented with proximal limb weakness in their first to second decades. Fluctuating muscle weakness, myalgia and calf hypertrophy were the major complaints. Myogenic changes on electromyography and marked attenuation on 3 Hz repetitive nerve stimulation were observed in all patients. Four reported a beneficial response to pyridostigmine. Muscle MRI showed selective involvement in the calf in case 1. Immunolabeling of α-dystroglycan was abnormal for case 1 and case 2. Four novel missense mutations in the C-terminal region of GMPPB were identified, with p.(Arg357His) being present in all the cases. In vitro functional assays demonstrated that these variants did not markedly reduce the amount of GMPPB, but gave rise to an increased propensity for protein aggregation. Increasingly, patients with GMPPB mutations are found to present with an overlapping LGMD/myasthenic syndrome. The mutation spectrum in Chinese patients may differ from that of European populations, with the mutation p.(Arg357His) most frequently found. These mutations may lead to abnormal folding of GMPPB leading to protein aggregates in the cytoplasm rather than an overall loss in protein expression.

KEYWORDS: Congenital myasthenic syndrome; GMPPB; Limb girdle muscular dystrophy; Muscle MRI; Mutation hotspot

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