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# Clinical and Genomic Characteristics of LAMA2 Related Congenital Muscular Dystrophy in a Patients' Cohort From Qatar. A Population Specific Founder Variant

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## Abstract

Congenital LAMA2 related muscular dystrophy (LAMA2-RD), the most commonly recognized type of congenital muscular dystrophies, has been described in patients' cohorts from Europe and the UK but not from Middle-Eastern. This study aimed to reveal the prevalence, clinical and genomic characteristics of congenital LAMA2-RD in a patient's cohort of 17 families (21 patients) from the Gulf and Middle East. Affected subjects exhibited the classic phenotype of generalized hypotonia, developmental delay, and progressive muscular weakness. Despite the homogeneous background of most of our patients, clinical variability was evident; however, none of our patients was able to achieve independent ambulation. The associated features of nephrocalcinosis, infantile-onset osteopenia, and cardiac arrest were first described in this study. LAMA2 mutations constituted 48% of the genetic causes underlying congenital muscular dystrophies (CMDs) in our patients. We estimated a point prevalence of 0.8 in 100.000 for LAMA2-RD in Qatar, relatively higher compared to that described in Europe's studies. The founder mutation and high rate of consanguinity are potential contributors. This study identified five LAMA2 truncating variants, two novel and three recurrent, of which the c.6488delA-frameshift that was found in 12 unrelated Qatari families, highlighting a founder mutation in Qatari patients. The two novel variants involved an acceptor splice site and N-terminus deletion that removes the LAMA2 promoter, exon1, and part of intron1. The "residual" expression of LAMA2 transcript and protein associated with this large N-terminus deletion suggested an alternative promoter that, while seems to be activated, acts less efficiently.

**Keywords:** Genomic modifiers; LAMA2 Founder mutation in Qatar; LAMA2-RD; MDC1A; Merosin deficiency congenital muscular dystrophy; Osteopenia in MDC1A.

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