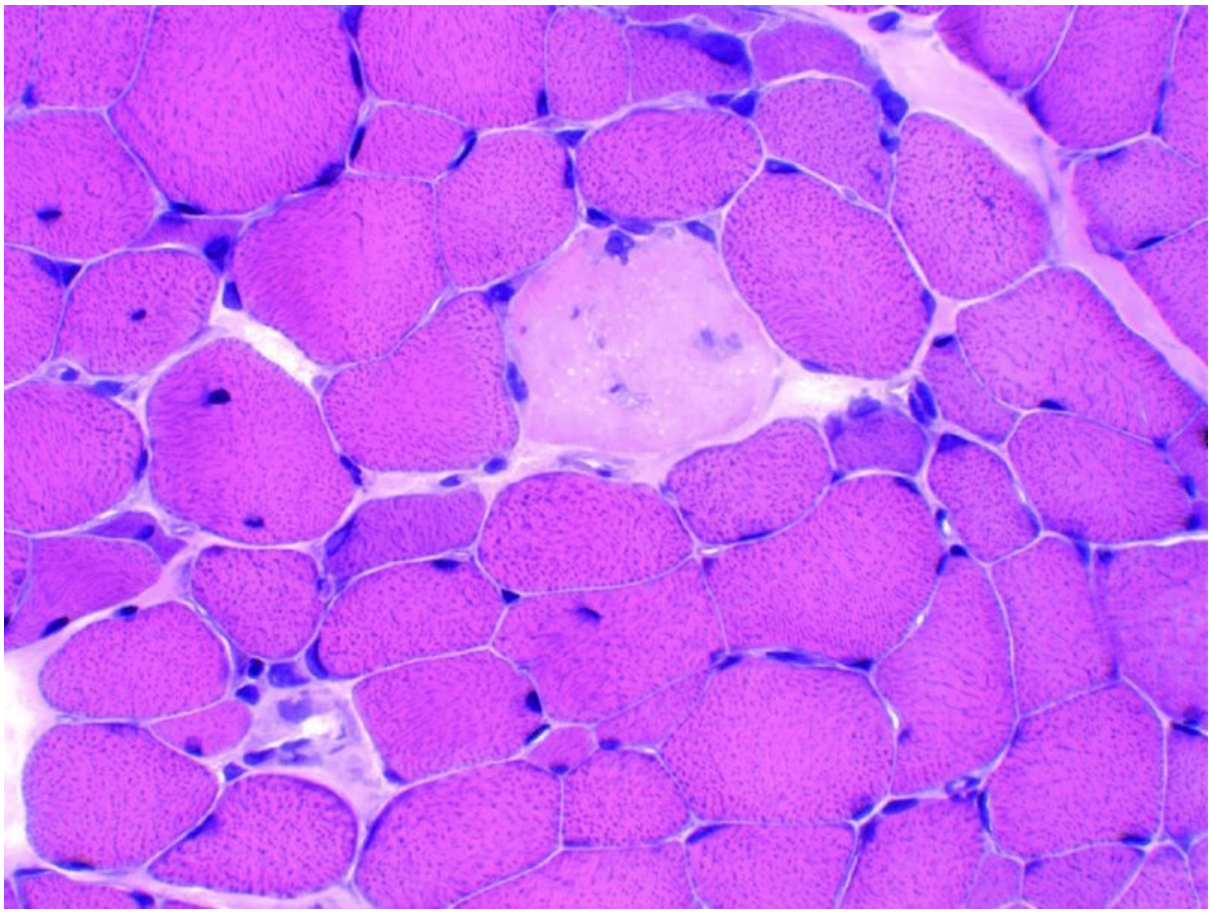
Whole Exome Analyses of Congenital Muscular Dystrophy and Congenital Myopathy Patients from India Reveal a Wide Spectrum of Known and Novel Mutations

Wednesday, 4 Nov 2020



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Published in *European Journal of Neurology* on 30 October 2020
https://doi.org/10.1111/ene.14616

Abstract

Background

Congenital muscular dystrophies (CMD) and congenital myopathies (CM) are a group of genetically and clinically heterogeneous degenerative primary muscle disorders with onset at birth or during infancy. Due to vast heterogeneity, clinical examination and protein-based analyses often fail to identify the genetic causes of these diseases.

Methods

Whole Exome Sequencing (WES) was done to identify pathogenic mutations and genetically diagnose a cohort of 36 difficult-to-diagnose CMD and CM cases of Indian origin, using variant calling and stringent variant filtration process. Subsequently, *in silico* molecular modelling and dynamics (MD) studies were undertaken for a number of novel and missense variants.

Results

A total of 33 and 21 rare and deleterious mutations were identified in 28 genes previously reported in CMD and CM based on OMIM, ClinVar and Orphanet, respectively. We could accurately diagnose 54% patients (n=12/22) in the CMD group and 35% patients (n=5/14) in the CM group. Furthermore, MD studies for mutations located in LMNA, LAMA2 and RYR1, suggest that the wild type proteins are more stable than their mutant counterparts, implying a potential mechanism of pathogenesis.

Conclusion

The WES findings have led us to identify reported as well as novel variants for the first time in Indian CMD and CM patients. This has allowed us to achieve an accurate genetic diagnosis which was otherwise difficult using conventional diagnostic tools. Transferring these WES findings to clinical practice will help guided clinical care of the affected patients and informed genetic counselling.

Figure

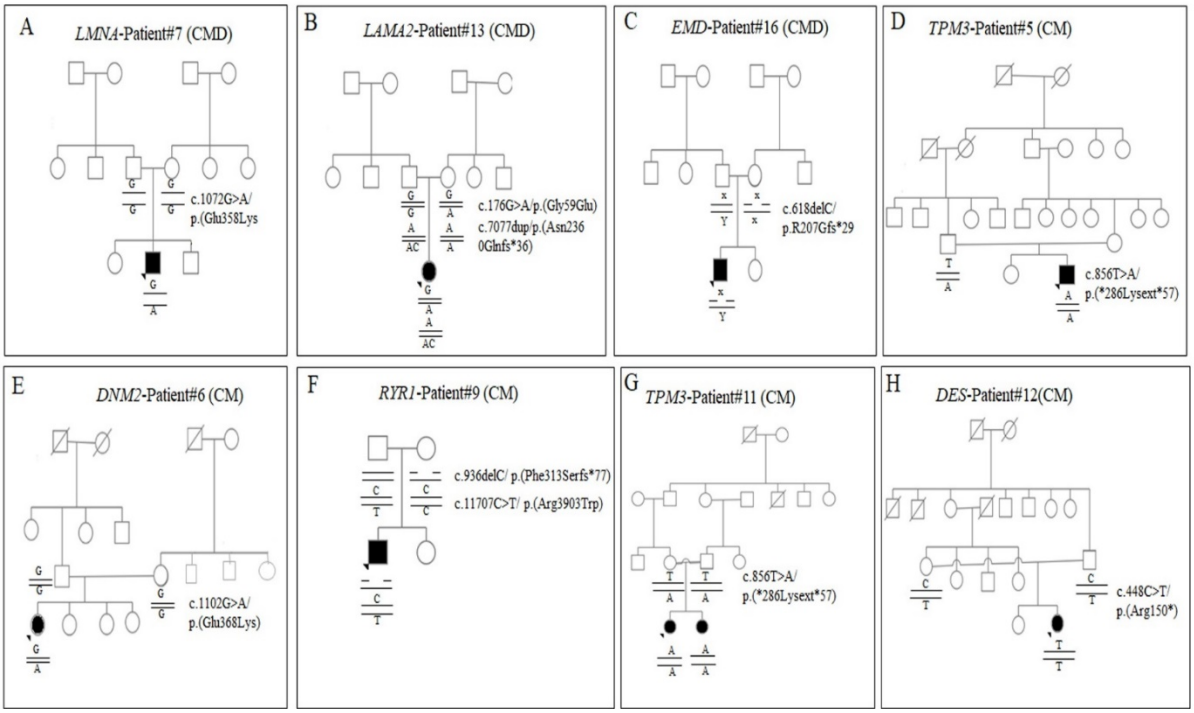

Figure legend: Segregation analysis of mutations in representative CMD and CM genes.