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GENETIC MODIFIERS OF SEVERITY IN COLLAGEN VI-RELATED MUSCULAR DYSTROPHY

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Collagen VI-related muscular dystrophies (COL6-RD) display phenotypic heterogeneity that includes mild Bethlem myopathy (BM), intermediate (INT), and severe Ullrich congenital muscular dystrophy (UCMD) phenotypes. COL6-RD are characterized by mutations within the collagen VI genes (COL6A1, COL6A2, and COL6A3) that lead to improper formation of collagen VI protein. Resulting symptoms may include progressive muscle weakness, joint contractures, loss of ambulation, and premature death. Variation in phenotypic severity is not fully explained by primary collagen VI gene mutations alone, suggesting the presence of genetic modifier loci that control the level of pathogenic response. Previous studies have shown that the gene encoding latent transforming growth factor β binding protein 4 (*LTBP4*) plays a role in genetically modifying the severity of phenotypes in other muscular dystrophies including sarcoglycanopathy in mice and Duchenne muscular dystrophy (DMD) in humans.

We sought to test the hypothesis that *LTBP4*, a regulator of TGF- β signaling, is a modifier of clinical severity of COL6-RD. Genotyping of one of the four single nucleotide polymorphisms (SNPs) that define the IAAM haplotype of the *LTBP4* gene was performed in a cohort of comprehensively phenotyped COL6-RD patients.

The *LTBP4* haplotype was determined in 45 individuals with COL6-RD and associated with clinical severity outcomes using chi-squared (χ^2) tests. We did not find a statistically significant association between the *LTBP4* genotypes and observed phenotypic classes. Our results do not support the initial hypothesis that *LTPB4* is a genetic modifier of clinical severity in patients with COL6-RD.

Although results did not support the initial hypothesis, our research outcomes still provide important insights into the phenotypic heterogeneity seen in patients with COL6-RD. While our findings indicate that *LTBP4* may not act as a broadly applicable genetic modifier to target in the treatment of all existing forms of muscular dystrophy, COL6-RD remain an important group of muscle diseases to study. These results exemplify the need to consider the influence of genetic factors outside of *LTBP4* and primary COL6A genes in the pursuit of understanding variations in clinical severity.