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Minimal Consequences of CMAH and DBA/2J Background on a FKRP Deficient Model

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Abstract

Background: Muscular dystrophies (MD) are a large group of genetic diseases characterized by a progressive loss of muscle. The Latent TGFβ Binding Protein 4 (LTBP4) in the DBA/2 background and the Cytidine Monophosphate-sialic Acid Hydroxylase (CMAH) proteins were previously identified as genetic modifiers in severe MD.

Objective: We investigated whether these modifiers could also influence a mild phenotype such as the one observed in a mouse model of Limb-Girdle MD2I (LGMD2I).

Methods: The FKRPL276I mouse model was backcrossed onto the DBA/2 background, and in separate experiments the Cmah gene was inactivated in FKRPL276I mice by crossing with a Cmah-/- mouse and selecting the double-mutants. The mdx mouse was used as control for these two genome modifications. Consequences at the histological level as well as quantification of expression level by RT-qPCR of genes relevant for muscular dystrophy were then performed.

Results: We observed minimal to no effect of the DBA/2 background on the mild FKRPL276I mouse phenotype, while this same background was previously shown to increase inflammation and fibrosis in the mdx mouse. Similarly, the Cmah-/- deletion had no observable effect on the FKRPL276I mouse phenotype whereas it was seen to increase features of regeneration in mdx mice.

Conclusions: These modifiers were not observed to impact the severity of the presentation of the mild FKRPL276I model. An interesting association of the CMAH modifier with the regeneration process in the mdx model was seen and sheds new light on the influence of this protein on the dystrophic phenotype.

Keywords: Muscular dystrophies; animal models; gene modifiers; genetic background.

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