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Research article

Profound human/mouse differences in alpha-dystrobrevin isoforms: a novel syntrophin-binding site and promoter missing in mouse and rat

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Abstract**Background**

The dystrophin glycoprotein complex is disrupted in Duchenne muscular dystrophy and many other neuromuscular diseases. The principal heterodimeric partner of dystrophin at the heart of the dystrophin glycoprotein complex in the main clinically affected tissues (skeletal muscle, heart and brain) is its distant relative, α -dystrobrevin. The α -dystrobrevin gene is subject to complex transcriptional and post-transcriptional regulation, generating a substantial range of isoforms by alternative promoter use, alternative polyadenylation and alternative splicing. The choice of isoform is understood, amongst other things, to determine the stoichiometry of syntrophins (and their ligands) in the dystrophin glycoprotein complex.

Results

We show here that, contrary to the literature, most α -dystrobrevin genes, including that of humans, encode three distinct syntrophin-binding sites, rather than two, resulting in a greatly enhanced isoform repertoire. We compare in detail the quantitative tissue-specific expression pattern of human and mouse α -dystrobrevin isoforms, and show that two major gene features (the novel syntrophin-binding site-encoding exon and the internal promoter and first exon of brain-specific isoforms α -dystrobrevin-4 and -5) are present in most mammals but specifically ablated in mouse and rat.

Conclusion

Lineage-specific mutations in the murids mean that the mouse brain has fewer than half of the α -dystrobrevin isoforms found in the human brain. Our finding that there are likely to be fundamental functional differences between the α -dystrobrevins (and therefore the dystrophin glycoprotein complexes) of mice and humans raises questions about the current use of the mouse as the principal model animal for studying Duchenne muscular dystrophy and other related disorders, especially the neurological aspects thereof.

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