A new patient-derived iPSC model for dystroglycanopathies validates a compound that increases glycosylation of α-dystroglycan.


Centre for Genomics and Child Health, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

Stem Cell Laboratory, National Bowel Research Centre, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

UCL Great Ormond Street Institute of Child Health, London, UK.

Wellcome Sanger Institute, Hinxton, Cambridge, UK.

MRC Laboratory for Molecular Cell Biology, University College London, London, UK.

The Wolfson Institute for Biomedical Research, University College London, London, UK.

NIHR Biomedical Research Centre at Great Ormond Street Hospital, London, UK.

Abstract

Dystroglycan, an extracellular matrix receptor, has essential functions in various tissues. Loss of α-dystroglycan-laminin interaction due to defective glycosylation of α-dystroglycan underlies a group of congenital muscular dystrophies often associated with brain malformations, referred to as dystroglycanopathies. The lack of isogenic human dystroglycanopathy cell models has limited our ability to test potential drugs in a human- and neural-specific context. Here, we generated induced pluripotent stem cells (iPSCs) from a severe dystroglycanopathy patient with homozygous FKRP (fukutin-related protein gene) mutation. We showed that CRISPR/Cas9-mediated gene correction of FKRP restored glycosylation of α-dystroglycan in iPSC-derived cortical neurons, whereas targeted gene mutation of FKRP in wild-type cells disrupted this glycosylation. In parallel, we screened 31,954 small molecule compounds using a mouse myoblast line for increased glycosylation of α-dystroglycan. Using human FKRP-iPSC-derived neural cells for hit validation, we demonstrated that compound 4-(4-bromophenyl)-6-ethylsulfanyl-2-oxo-3,4-dihydro-1H-pyridine-5-carbonitrile
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(4BPPNit) significantly augmented glycosylation of α-dystroglycan, in part through upregulation of LARGE1 glycosyltransferase gene expression. Together, isogenic human iPSC-derived cells represent a valuable platform for facilitating dystroglycanopathy drug discovery and therapeutic development.

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KEYWORDS: CRISPR ; fukutin-related protein; high-throughput screening; human-induced pluripotent stem cells; α-dystroglycan

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