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Dystroglycanopathies: coming into focus

Caroline Godfrey, A Reghan Foley, Emma Clement and Francesco Muntoni

A common group of muscular dystrophies is associated with the aberrant glycosylation of α-dystroglycan. These clinically heterogeneous disorders, collectively termed dystroglycanopathies, are often associated with central nervous system and more rarely eye pathology. Defects in a total of eight putative and demonstrated glycosyltransferases or accessory proteins of glycosyltransferases have been shown to cause a dystroglycanopathy phenotype. In recent years the systematic analysis of large patient cohorts has uncovered a complex relationship between the underlying genetic defect and the resulting clinical phenotype. These studies have also drawn attention to the high proportion of patients that remain without a genetic diagnosis implicating novel genes in the pathogenesis of dystroglycanopathies. Recent glycomic analyses of α-dystroglycan have reported complex patterns of glycan composition and have uncovered novel glycan modifications. The exact glycan synthesis and modification pathways involved, as well as their role in ligand binding, remain only partially characterised. This review will focus on recent studies that have extended our knowledge of the mechanisms underlying dystroglycanopathies and have further characterised this patient population.

Address
Dubowitz Neuromuscular Centre, UCL Institute of Child Health and the Great Ormond Street Hospital for Children, Guilford Street, University College London, United Kingdom

Corresponding author: Muntoni, Francesco (f.muntoni@ich.ucl.ac.uk)

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Introduction

A reduction in α-dystroglycan's ligand-binding capacity resulting from its aberrant glycosylation is now a well-documented phenomenon characterising a growing subset of muscular dystrophies. The term 'dystroglycanopathies' has been ascribed to these genetically heterogeneous disorders that frequently include central nervous system pathology and encompass a striking range of clinical severity. At the most severe end of the clinical spectrum are the conditions Walker–Warburg syndrome (WWS), muscle–eye–brain disease (MEB) and Fukuyama congenital muscular dystrophy (FCMD) [1–3]. These conditions are characterised by congenital muscular dystrophy (CMD) with severe structural brain and eye abnormalities, which in WWS results in early infantile death [4]. Conversely, individuals at the mildest end of the clinical spectrum may present in adult life with limb girdle muscular dystrophy (LGMD) and without associated brain or eye involvement [5]. A number of intermediate phenotypes between these aforementioned extremes have also been described with the best characterised being MDC1C, due to defects in *FKRP*, in which affected children do not typically have brain or eye involvement despite the relative severe skeletal muscle involvement [5]. Diagnosis of dystroglycanopathies is established upon the detection of hypoglycosylated α-dystroglycan at the sarcolemma of skeletal muscle fibres by immunolabelling and/or on Western blot (Figure 1) [6]. Whereas genetic defects in *DAG1* (encoding dystroglycan) itself have not yet been identified in human disease, defects in eight putative and demonstrated glycosyltransferases, or accessory proteins of glycosyltransferases, implicated in the glycosylation of α-dystroglycan have been shown to cause a dystroglycanopathy phenotype (Table 1) [1–5,7••,8].

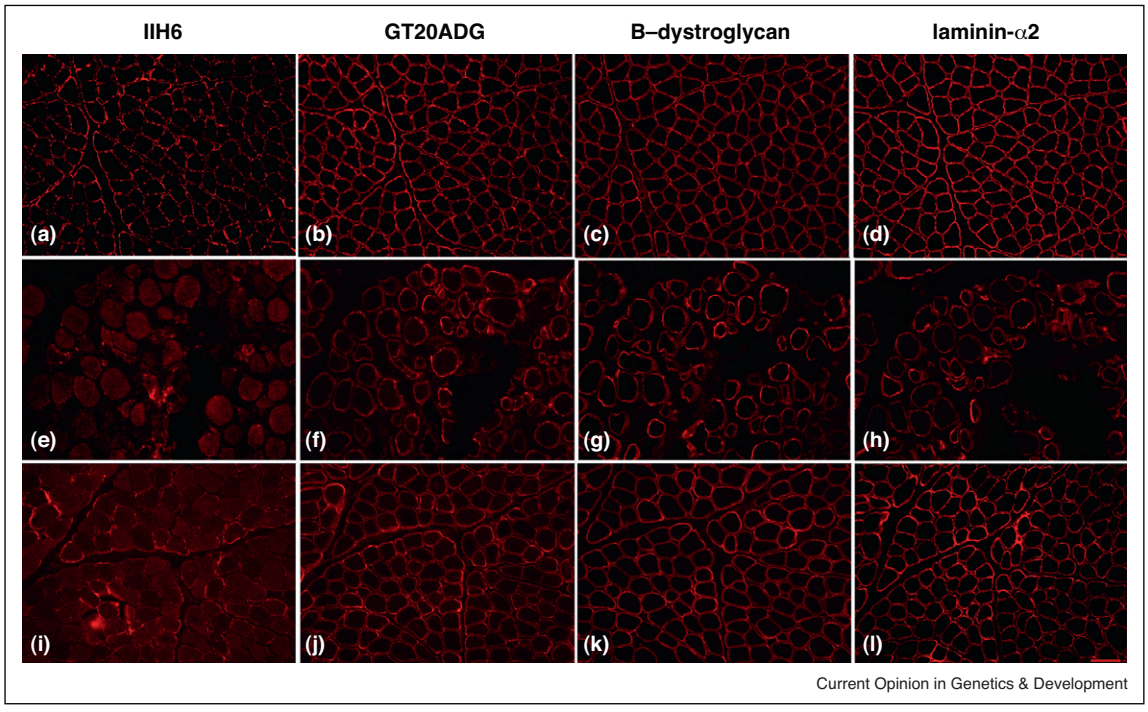
Causative mutations were originally identified in homogenous disease categories in patients from discrete geographic regions. The original data indicated a complete correlation between mutations in specific genes and discrete clinical phenotypes. This is best represented by the research performed on patients with FCMD and MEB. FCMD was described within the Japanese population where, in the majority of cases, it is caused by a 3 kb retrotransposal insertion in the 3′ UTR of the *FKTN* gene, a mutation endemic to Japan [2]. MEB was originally described within an isolated Finnish population in association with mutations in *POMGNT1* [3]. More recently, these tight associations have been blurred as a more complex picture has emerged between gene defect and clinical phenotype.

This review will focus discussion on those studies aimed at characterising the dystroglycanopathy patient population and revealing the molecular and cellular dysfunctions underlying muscular dystrophies with defective glycosylation of dystroglycan.

Genotype–phenotype correlations: additional parameters

Until recently no information has been available regarding the relative contribution of individual causative genes or the genotype–phenotype correlations within large

Figure 1



Pathological features of skeletal muscle in dystroglycanopathies. Common to all these disorders is the reduced glycosylation (*hypo*glycosylation) of α-dystroglycan [6]. The finding that α-dystroglycan glycosylation is perturbed is based on a reduction of immunoreactivity to IIH6 (an antibody specific for α-dystroglycan glycan moieties and gift from Kevin Campbell) (a, e, i) with the retention of immunoreactivity to GT20ADG (an antibody that recognises the core α-dystroglycan peptide) (b, f, j) and β-dystroglycan (c, g, k). A secondary reduction in laminin α-2 labelling is also observed and reflects the reduced capacity of hypoglycosylated α-dystroglycan to bind its extracellular matrix ligands (d, h, l). Immunohistochemical analysis of transverse sections of skeletal muscle from a control normal muscle (a–d) and muscle from three representative dystroglycanopathy patients with mutations in *FKRP* (e–h) and *LARGE* (i–l). Scale bar = 50 μm.

cohorts of dystroglycanopathy patients. Over the past few years, however, a number of studies of large cohorts have been performed by us and others to address this. These studies have firmly established that the clinical spectrum associated with mutations in specific causative dystroglycanopathy genes is in fact far wider than originally appreciated. Hence, in the majority of cases the identity of the defective gene cannot be predicted from the clinical phenotype (Box 1) [9–12,45–48].

One of the major outcomes of establishing the relative frequency of mutation in each gene in these data sets has been to highlight the large proportion of patients who, after the exclusion of the known causative genes, remain without a definitive molecular diagnosis. After the exclusion of *FKRP*, we detected mutations in approximately one third of our cohort consisting of 92 patients [12]. Since this study, results from three other populations have been reported in which mutations in *POMT1*, *POMT2*, *POMGNT1*, *LARGE*, *FKTN* and *FKRP* were systematically screened. Each study analysed a defined clinical presentation and detected mutations in a total of 53%, 40% and 51% of CMD and two WWS patient cohorts respectively [9–11]. Taken together, these studies strongly implicate novel genes in the pathogenesis of the dystroglycanopathies.

More detailed studies of genotype–phenotype correlations focused on additional parameters such as α-dystroglycan epitope staining and clinical severity have also been reported. Jimenez-Mallebrera *et al.* performed a thorough analysis of muscle pathology for a subset of dystroglycanopathy patients [13]. A strong correlation between reduced α-dystroglycan epitope staining and clinical course was observed in patients with mutations in *POMT1*, *POMT2* and *POMGNT1*. This correlation was not consistently found in patients with defects in *FKTN* or *FKRP*, however, as some of the patients with mild LGMD phenotypes and no brain involvement were also found to have a profound depletion in glycosylated α-dystroglycan epitope staining. This study indicated that it is not always possible to correlate clinical severity with α-dystroglycan epitope labelling on immunosections. The evaluation of immunoreactivity on western blot and laminin overlay may provide additional information; however, there is frequently insufficient tissue available to perform these analyses. In a further study focusing on brain involvement in the dystroglycanopathies, brain