The Genetics of the Muscular Dystrophies

by **Christian A Scerri** *MD PhD(Molecular Genetics)*
Clinical and Molecular Geneticist
Clinical and Molecular Genetics Clinic
Speciality Clinics, Mater Dei Hospital

When one mentions muscular dystrophy, the mental picture that emerges is that of Duchene Muscular Dystrophy (DMD). In reality, the term muscular dystrophy refers to around six, heterogenous groups of inherited disorders characterised by progressive muscle wasting and weakness. The common feature of all the dystrophies is the histological picture of muscle biopsy with the typical signs of muscle fibre variation, muscle necrosis and increased fat and connective tissues.

Attempting to classify muscular dystrophy is not easy and straight forward but Walton and Nattrass in 1954 formulated a classification (further elaborated by Walton in 1964) that is based on two principles – mode of inheritance and the predominant affected muscle group (Figure 1). Though this classification is still in use today, the identification of molecular genetics defects underlying particular dystrophies have distorted this clinical classification, Due to editorial constraints, this article shall attempt to give an overview of the molecular pathologies underlying the major classes of muscular dystrophy.

Clinically, the common feature of these disorders is muscle weakness, but the prognosis of the disorders shows great variability.

Duchene-Type Muscular Dystrophy

The commonest form of Muscular Dystrophy is the Duchenne-type. It is inherited as an X linked recessive trait and therefore predominantly affects boys. It is characterised by progressive muscle wasting and weakness and usually results in inability to walk by age 12 and death in the 20's. Some degree of intellectual impairment might be present in up to a third of cases. A similar but clinically milder condition, Becker-type muscular dystrophy (BMD), has an onset in the teenage years or early 20's, with loss of ability to walk occurring much later and survival is beyond middle age.

The gene was localized in 1982, discovered in 1987 with its protein product identified as dystrophin. The gene is the largest gene associated with a disease (2.4 million base pairs) contains 85 exons with the introns making up 98% of the gene. Being a cytoskeletal protein located beneath the sarcolemma, dystrophin is localised at the periphery of muscle fibres. The discovery of the protein, helped in the definition of the pathophysiological difference between Duchenne-type and Becker-type dystrophies, with the former showing complete absence of the protein and the later showing a reduced presence. Dystrophin forms part of a complex of proteins called the Dystrophin-Glycoprotein Complex (DGC) – a complex of five classes of proteins (dystroglycans, syntrophins, dystrobrevins, sarcoglycans and sarcospan) assembled with either dystrophin or its autosomal homologue utrophin (Figure 2). Utrophin is developmentally controlled i.e. it is highly expressed in muscle tissue during the foetal and neonatal period, but is suppressed and confined ot the sarcolemma after birth. This complex binds the cytoskeleton to the sarcolemma and is thought to help maintain the structure of muscle cells.

The DGC proteins have also been found to be expressed in non-muscle tissues especially in the brain and retina, and might explain the abnormalities present in these tissues in DMD patients.

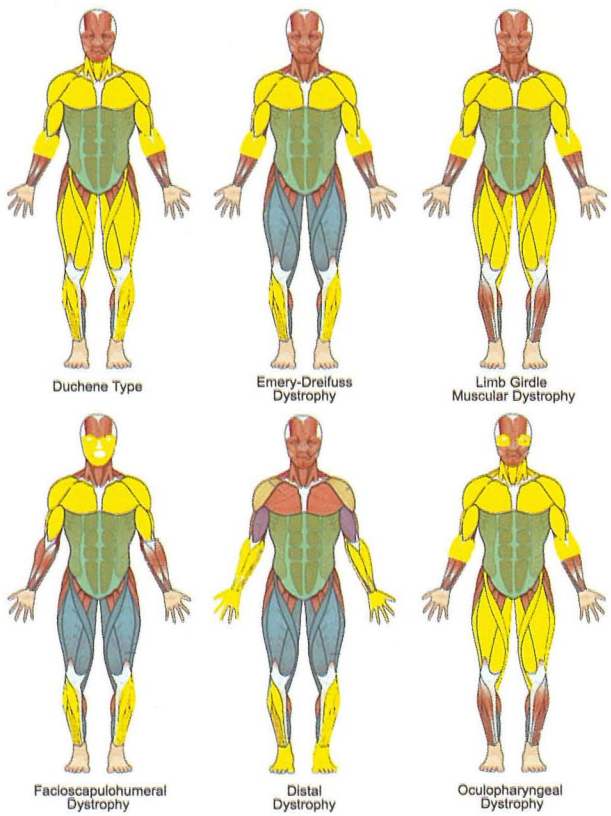

Figure 1: *Distribution of predominant muscle weakness in different types of dystrophy*

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral Muscular Dystrophy (FMD) is characterized by weakness of the facial, scapulohumeral, anterior tibial and pelvic girdle muscles with retinal vascular disease, sensory hearing loss and in some cases, abnormalities of the central nervous system. The responsible gene is located on chromosome 4, and the condition is inherited as an autosomal dominant trait. Individuals suffering of the condition are usually mildly affected though some may later become dependent on wheelchairs.

Almost all the patients with FSHD have been found to have a deletion within the D4Z4 repeat region (chromosome 4q35). However, studies have failed to identify a gene within the region of the D4Z4 repeats and the molecular mechanism is still under study.

continues on page 6

The Genetics of the Muscular Dystrophies

continued from page 4

Limb Girdle Muscular Dystrophy

Though listed under one title, Limb Girdle Muscular Dystrophy (LGMD) is in fact both clinically and genetically a heterogeneous group of conditions. Seven types (around 10% of all LGMD) are inherited in an autosomal dominant trait (named Type 1A to Type 1G) and are relatively mild, characterised by proximal muscle weakness, beginning in the hip girdle region and later progressing to the shoulder girdle region with distal muscle weakness occurring later (if at all). The autosomal recessive form of LGMD shows an even higher degree of heterogeneity than the autosomal dominant form (11 discrete types named Type 2A to Type 2K). Onset is usually in childhood, but can occur in maturity or middle age. The first evidence of the disease is usually the pelvic or, less frequently, the shoulder girdle, often with asymmetry of wasting when the upper limbs are first involved. Spread from the lower to the upper limbs or vice versa occurs within 20 years. The rate of progression is variable, but usually severe disability with inability to walk sets in within 20 to 30 years of onset. Age at death is variable with the largest number of patients dying in middle age. Though in most cases of LGMD the causative gene has been identified, identifying the underlying genetic defect in particular cases can be a daunting task.

Other Dystrophies

The **Dystal Myopathies** are rare forms of dystrophies associated with wasting and weakness of the distal muscles with minor involvement of other muscle groups. Clinically, the disorder follows a mild course though some individuals do suffer from severe mobility problems. At least four genetically distinct types have been identified so far.

The **Oculopharyngeal Muscular Dystrophy** is an autosomal dominant disorder characterised by late adult onset, progressive ptosis and dysphagia. Other cranial and limb muscles can be involved as well. The gene associated with the disease is located on chromosome 14 and it is postulated that a triplet expansion in the PABPN1 gene might be the causative agent.

As the name implies, the relatively uncommon autosomal recessive **Congenital Muscular Dystrophy**, occurs at birth or early infancy. The child presents with hypotonia and generalised weakness with possible joint contractures. Individuals with the disorder tend to have severe muscle weakness, inability to walk and possible respiratory weakness. In most of the cases the disorder is caused by mutations in the merosin gene (chromosome 6) with some cases due to deficiency of its receptor (integrin α 7).

Pathogenesis and Molecular Management

Though muscle weakness is a ubiquitous feature in all cases of muscle dystrophy and even though most of the pathological molecular defects are known, the actual molecular pathogenesis is still not clear. The basic mechanism seems to indicate that the absence of a protein (or the presence of a mutated protein) in the DGC, and thus within the link between the extracellular matrix and intracellular actin molecules, causes a breakdown in the integrity of the muscle membrane that results in muscle weakness. But the actual mechanism by which this weakness occurs is still obscure.

Apart from the use in counseling, molecular biological techniques are promising to produce important developments in the management of the disease. In addition to supportive measures of a good diet, reduction in weight, physiotherapy, controlled exercise and orthotic and surgical corrections, there

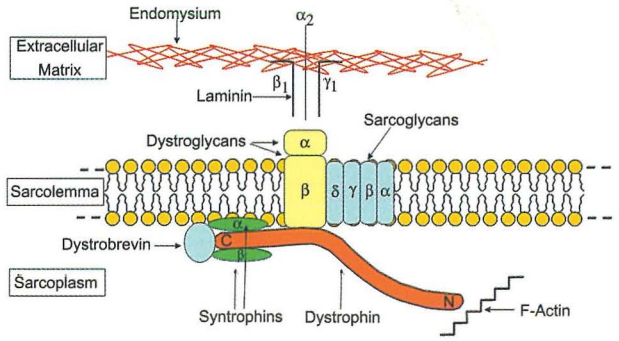

Figure 2: *Dystrophin-Glycoprotein Complex (DGC)*

is the possibility of treating the disease by correcting the underlying defect. It is not surprising to note that as DMD is the most common muscular dystrophy and that the dystrophin gene has been fully characterized and studied, most of the treatment research has been concentrated on this disorder. The observation that the basic molecular pathology difference between DMD and BMD is that the Dystrophin gene is usually either severely truncated or absent in the former, whilst only shortened but partially functioning in the latter, has indicated a possible treatment strategy for DMD cases. There are at present 4 clinical trials (in various phases) that are targeting this approach and are attempting to revert a Duchene-type of mutation into a Becker's type (usually produced by what is known as exon skipping) that should in theory improve the prognosis.

Aminoglycosides have previously been shown to suppress nonsense mutations, allowing translation of full-length proteins in vitro and in animal models. At the moment a number of clinical trials, both in the US as well as in Europe, are underway to determine both the safety and efficacy of Gentamycin IV injections in regenerating dystrophin proteins. Preliminary results have shown that such a treatment can be useful to at least a subset of patients with DMD that can be identified through the type of mutation present. The same approach has been taken through the use of anti-sense oligonucleotides. These are synthetic, short DNA sequences that are complimentary to the area of the DNA that contains the mutation. On binding to this area, the part of DNA is skipped during the translation process. A third clinical trial, that is entering into phase 2, is investigating the use of a small, oral molecule (called PTC124) to induce exon skipping. Preliminary results show that treatment with PTC124 was associated with increases in muscle dystrophin expression.

Other trials include the attempt to introduce the dystrophin gene, initially by direct injection but if successful, by systematic means. Other bio-pharmaceuticals that are at present undergoing clinical trials include the nutritional supplement coenzyme Q10 in conjunction with steroid treatment, creatinine and L-glutamine in steroid naive cases and the 'mast cell stabilizer' oxatomide drug.

Another interesting approach would be to upregulate the dystrophin analogue, utrophin. This approach has been tested in genetically engineered mice with muscular dystrophy with the treated mice showing amelioration. Though this approach offers a novel and relatively safe treatment, the search for a safe compound that upregulates utrophin is still on.

Muscular dystrophy is currently considered to be an incurable disease with an increased degree of morbidity and mortality. Through genetic studies and the use of bio-pharmaceuticals it is hoped that this dim future shall change into one that is brighter and which offers a hope to these patients.