Limb Girdle Muscular Dystrophy Type 2B - Dysferlinopathy

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The muscular dystrophies are a group of inherited muscle disorders that cause weakness and wasting of the skeletal muscles. The ***muscular dystrophies*** represent a subclass of the **myopathies**, which literally means abnormal muscle. Dystrophic muscle is specifically characterized by three main histological features on muscle biopsy; variation in the sizes of the muscle fibres, the presence of fatty or fibrotic infiltrate between the muscle fibres, and the presence of central nuclei within the muscle fibres that signifies degeneration and regeneration.

Mutations in **dysferlin** cause a form of late-onset muscular dystrophy that manifests in teenagers or young adults (Bashir, Britton et al. 1998; Liu, Aoki et al. 1998). Dysferlinopathy is autosomal recessive, meaning that patients require two mutant copies of the dysferlin gene to manifest the disease. Curiously, prior to their presentation, dysferlin patients show no signs of muscle weakness as children, with many patients reporting sporting distinction in their youth (one of our patients represented NSW in under-16's rugby league). This differs to other later onset muscular dystrophies, where tracing back through childhood histories often reveals children who were poor at sports and often naturally veered away from strenuous physical activities. In dysferlinopathy, physically-able young teenagers often suffer an injury that is difficult to recover from, begin to experience unexplained fatigue and muscle pain, followed by progressive muscle weakness. Once dysferlin disease manifests, the physical decline can be rapid, from being able-bodied to non-ambulant (unable to walk) in only 4-8 years (Nguyen, Bassez et al. 2007), with an associated cardiomyopathy in some patients (Kuru, Yasuma et al. 2004; Wenzel, Geier et al. 2007). We don't yet understand why dysferlin's role is so important to muscle function in adulthood, and yet does not affect young muscles of children.

Dysferlinopathy causes two main clinical presentations; **M**iyoshi **M**yopathy (**MM**), initially manifesting as weakness of the distal muscles of the lower arms and lower leg, or, **L**imb **G**irdle **M**uscular **D**ystrophy (**LGMD**) with weakness initially manifesting in the muscles of the hip and shoulder girdle. Dysferlinopathy is characterized by loss (or significant reduction to <10% normal levels) of dysferlin protein in the skeletal muscle of affected patients. Dysferlinopathy patients often have high serum creatine kinase levels, and wasting of the calf-muscles is common in dysferlinopathy.

The mechanism thought to underlie muscle weakness and degeneration in dysferlinopathy centres upon a **defect in muscle membrane repair** (Bansal and Campbell 2004). Dysferlin is a vesicle fusion protein (Lek, Evesson et al. 2012), and cells use vesicle fusion to 'patch' small microtears in the plasma membrane encapsulating each muscle fibre (McNeil and Steinhardt 2003). Because muscle is so active, and contracts under stretch and load, the protective surface membranes of muscle fibres are regularly injured as part of our day-to-day activities. In dysferlinopathy it is thought that a defect in the ability to repair small sites of membrane injury progressively contributes to accrued muscle damage and degeneration of muscle fibres. However, being a vesicle fusion protein, dysferlin also plays an important role in delivery of proteins around the cell, when and where they are needed. Recent research is beginning to suggest that defective membrane repair is only ***one part*** of dysferlin disease, and, other roles that dysferlin plays in the transport of important growth factor receptors may also play a role in disease pathology, influencing how muscle adapts to different requirements in injury and growth (Demonbreun, Fahrenbach et al. 2010).

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