In this issue of Brain, three papers (Wallgren-Pettersson et al., Griggs et al. and Walter et al.) expand the horizons of skeletal muscle diseases caused by mutations in sarcomeric proteins.

Two of the papers (Wallgren-Pettersson et al., and Griggs et al.) deal solely with distal myopathies. One of the most unexpected discoveries in the sarcomeric protein disease field has been that mutations in sarcomeric proteins can cause distal myopathies. Each distal myopathy preferentially affects what can be a bizarre collection of specific, restricted muscles. In the early-onset distal myopathy, MPD1, this starts with the tibialis anterior and later extends to the flexor hallucis longus, long finger extensors, sternocleidomastoid and the medial head of the gastrocnemius (Lamont et al., 2006). What sort of gene can do that to a patient? One might think of genes involved in positional information. However, we now know that specific mutations in the rod-domain of the slow myosin heavy chain, the myosin expressed in every slow skeletal muscle fibre and in the heart, cause this disease (Meredith et al., 2004). The pathophysiological cascade from myosin mutation to disease phenotype remains a mystery. Equally, mutations in titin, expressed in every muscle fibre in the body, cause tibal muscular dystrophy—a late onset distal myopathy affecting another restricted group of muscles, including some of the same muscles as MPD1 (Hackman et al., 2002).

In the first paper, Wallgren-Pettersson et al. (page 1465) report that homozygosity for missense mutations in nebulin causes an early onset mild distal myopathy. Wallgren-Pettersson and her colleagues had previously shown that mutations in nebulin are the commonest cause of recessive nemaline myopathy (Pelin et al., 1999). Nebulin nemaline myopathy, like other congenital myopathies, affects proximal muscles more than distal muscles (Wallgren-Pettersson et al., 2004). The nebulin mutations that cause nemaline myopathy are most often nonsense, frameshift or splice site mutations, mutations that should considerably disrupt the nebulin protein (Pelin et al., 2002; Lehtokari et al., 2006). However, in some nemaline myopathy patients, one of these disruptive mutations was found to cause disease in association with a missense mutation (generally less disruptive to protein function) on the other nebulin allele (Pelin et al., 2002; Lehtokari et al., 2006). Wallgren-Pettersson et al. now show that homozygosity for these very same missense mutations causes an early-onset distal myopathy, phenotypically similar to MPD1. This research could only have been accomplished in Finland, where the populations of distal myopathy and nemaline myopathy patients are so well characterized and where the genetic isolate that is the Finnish population, lends itself to such discoveries. Again we do not know how homozygous nebulin missense mutations cause a restricted distal myopathy, while the same missense mutations in conjunction with more deleterious nonsense, frameshift or splice site mutations cause nemaline myopathy, preferentially affecting more proximal muscles.

The second paper by Griggs et al. (page 1477), which also at least in part comes from Finland through the contribution of Bjarne Udd’s laboratory, demonstrates that the seminal Markesbery–Griggs distal myopathy family, first described in 1974 (Markesbery et al., 1974) has the A165V ZASP mutation previously described in myofibrillar myopathy patients (Selcen and Engel, 2005). This result is something of a surprise, since for some time now it has been suggested that the disease in the Markesbery-Griggs family was allelic to tibal muscular dystrophy (Hackman et al., 2002) at the titin locus on chromosome 2. Griggs et al. explain that the linkage to the titin locus proved incorrect and that the identification of a ZASP mutation in this family highlights the difficulties of linkage analysis in late-onset diseases. As Griggs et al. indicate, ‘Relying on linkage results is usually, but not always, good enough.’ Griggs et al. conclude that the muscle pathology findings in the Markesbery–Griggs family were the clue to correcting the molecular genetic approach. Griggs et al. moved to a candidate gene approach instead of further pursuing a borderline linkage result that had caused a fruitless search for a disease-causing mutation in the giant titin gene. Mutations in a number of proteins: ZASP, desmin, myotilin and α-s crystallin are all known to cause myofibrillar myopathy, which may display a distal phenotype (Selcen and Engel, 2005). Sequencing of the ZASP gene in the Markesbery–Griggs patients identified the A165V mutation. Griggs et al. also found the same ZASP A165V mutation in two isolated distal myopathy patients, one from France and one from the UK, that had both been referred for investigation as possible titinopathy patients. Analysis of these patients, one patient from the Markesbery-Griggs family and three patients with the same A165V mutation described by Selcen and Engel (2005), demonstrated a conserved small, ~34 kb, haplotype around the ZASP A165V mutation, indicating a founder mutation.

The third of these papers, by Walter et al. (page 1485), is only partly concerned with distal myopathy but echoes the results of Griggs et al. Walter et al. demonstrate that the scapuloperoneal syndrome in the German family originally described by Kaeser in 1965 (Kaeser, 1965) is caused by the
same R350P mutation in desmin that they had previously identified in a German family with distal myopathy. They found the R350P mutation in three further families all of German descent, making five families in total, and showed a common conserved haplotype around the desmin gene in all five families, again suggesting a founder mutation. In total they examined 15 affected individuals in the five families and found highly variable clinical phenotypes: mostly a limb girdle muscular dystrophy phenotype, or a distal myopathy phenotype in addition to the scapulopel-oneal syndrome. Close to 50% of the patients had cardiomyopathy, and three male patients had gynecomastia. The histopathology was also highly variable in different patients. Walter et al. conclude that the clinical and histopathological phenotypes cannot be due to the desmin R350P mutation alone but must be influenced by other genetic and epigenetic factors including gender. Desmin is the predominant intermediate filament protein of skeletal and heart muscle. It binds to Z-discs and aligns the Z-discs in neighbouring myofibrils. Presumably variations in this environment determine the precise phenotype in each patient.

I think the fact that distal myopathies can be caused by mutations in sarcomeric proteins and sarcomere-associated proteins like desmin is telling us that there are layers of complexity to muscle biology that we know little about. All skeletal muscles are not created equal. Individual skeletal muscles exist in different locations, may contain different proteins (von der Hagen et al., 2005) and are subjected to different environments. The key to understanding the pathophysiology of the distal myopathies must lie in these differences.

There are currently no treatments for the distal myopathies. However, supportive measures including physiotherapy and orthotic appliances can be extremely beneficial. Developing treatments for the distal myopathies originating in the sarcomere, the fundamental unit of muscle contraction, presents a daunting challenge. Take titin as a paradigm for sarcomeric protein diseases. Titin is the giant protein ruler stretching across the entire half sarcomere from Z-line to M-line. There are multiple splice isoforms, each with a coding region greater than 100 kb (10 times the size of dystrophin) and different diseases are caused by different mutations in different parts of titin (Hackman et al., 2003). The other sarcomeric proteins associated with muscle diseases also tend to be large and have different diseases associated with them. Perhaps the best way to overcome the sarcomeric protein diseases may be by muscle transplantation in the form of myoblast or stem cell therapy since these approaches, if successful, could be used to treat multiple mutations in multiple genes (Kunkel et al., 2006). Alternatively, if each step in the pathophysiological cascade from the mutated protein to the disease could be discovered for each of the different diseases, it might be possible to target one or more steps in each of the pathways.

The distal myopathies and their relationship to the mutated proteins that cause them remain fascinating. Other distal myopathies are caused by mutations in the membrane repair protein dysferlin (Liu et al., 1998) and the sialic acid metabolism enzyme (GNE) (Kayashima et al., 2002), but the fact remains that many distal myopathies are caused by mutations in sarcomeric proteins. Interestingly, the gene for Welander distal myopathy, the first definitive distal myopathy described (Welander, 1951), has not yet been found. It will be interesting to see which type of gene causes Welander distal myopathy, with its phenotype so characteristically restricted to hand function. Right now, it is hard to predict what type of mutation or gene that might be.

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