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, sternocleidomastoids 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 tibial 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). 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-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
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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