present in 9 out of 14 patients. There was no facial or bulbar weakness or respiratory involvement, and only one patient had cardiomyopathy. CK levels were normal to mildly elevated. Muscle MRI (n = 6) and muscle biopsy (n = 6) findings were compatible with a titinopathy. The patients with homozygous mutations did not show significant clinical differences compared to the compound heterozygous patients. Previously, muscular dystrophies caused by mutations in the extreme C-terminus of *TTN* – autosomal dominant tibial muscular dystrophy (TMD) and autosomal recessive LGMD2J – had been primarily described in Finland. The Serbian *TTN* founder mutation explains a sizable portion of distal myopathy patients in this region and may represent the most common single cause of distal myopathies in the Serbian population.

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P.82

Complex processing of titin C-terminus by alternative cleavage of the is7 domain

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The sarcomeric structural protein titin has central mechanistic and developmental functions in striated muscle. Mutations in *TTN* cause a wide spectrum of skeletal and cardiac myopathies. In Finnish patients, the FINmaj mutation causes two different phenotypes, the dominant tibial muscular dystrophy (TMD) in heterozygotes and recessive LGMD2J in homozygotes or compounds with frameshifts, by changing four amino acids in the most C-terminal M10 domain of titin, located in the sarcomeric M-line. The M10 domain harbors binding sites for several ligands, whereas the alternatively spliced is7 domain next to it binds calpain3. In normal muscle the titin C-terminus undergoes proteolytic processing, which is abolished by FINmaj mutation, leading to pathological cleavage and degradation of the titin C-terminal part of the affected titin proteins *in cis*. This was verified by recognition of is7-M10^{FINmaj} construct by the M10-1 antibody. In addition to the previously described cleavage sites within titin is6 and is7 domains, we have shown that is7 can, alternatively, exist as a cleaved isolated domain in muscle. This requires a novel cleavage site near is7-M10 junction. The results suggest that majority of is7+ titin is processed *in situ*, in two different ways. Interestingly, even though in LGMD2J the M10 domain is absent, its ligands N-terminal obscurin, obscurin-like 1 and alpha-synemin showed no gross abnormality in confocal analysis. In addition, the M10 ligands showed multiple sarcomeric localizations. This raises the possibility that some M10-ligand interactions may take place outside the M-line context, involving C-terminal M10-containing fragments, or during development. Our results suggest that the titin C-terminal proteolytic fragments and domains may have independent signaling functions. The processing appears even more complex than previously expected, likely involving different types or proteases, and emphasizing the central role of titin in muscle signaling.

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P.83

Expression of multisystem proteinopathy (MSP) proteins in rimmed vacuolated fibers of tibial muscular dystrophy – Distal titinopathy

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Tibial muscular dystrophy titinopathy (TMD) is an autosomal dominant late-onset distal myopathy caused by mutations in the last exon of the large *TTN* gene. Clinically TMD is characterized by ankle dorsiflexion weakness and atrophy of the lower leg anterior compartment muscles. Previous muscle pathology studies have shown abnormal expressions of autophagy related proteins such as p62 and LC3 in rimmed vacuolated (RV) fibers. Dysfunctions of protein homeostasis and protein accumulations are also connected to multisystem proteinopathy (MSP). MSP is a heterogeneous group of degenerative disorders that can affect muscle, bone and nervous system. One representative is VCP-disease with typical RV-myopathy. Molecular defects in MSP include a range of cell biology mechanisms: chaperone functions, autophagy, protein turnover and RNA processing. How MSP related proteins are involved in TMD RV-pathology is not known. Using a wide range of MSP related protein antibodies applied on TMD muscle biopsies we show that MSP-linked proteins, which accumulate in neurons of the corresponding neurodegenerative diseases, also form aggregates in the TMD muscle fibres with RV-pathology. Our results suggest that altered basic pathways regulating protein and RNA processing in neurodegeneration are at least partly shared with those in RV degenerative changes in the muscle.

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P.84

Desminopathy in Chile, first cases reported

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Patients with desminopathy may present as myofibrillar myopathy, dilated cardiomyopathy or autosomal dominant or recessive limb girdle muscular dystrophy. To date no cases with any form of desminopathy have been reported in Chile. Herein we describe three patients belonging to two unrelated Chilean families harbouring mutations of the desmin gene *(DES)*. Patient 1 is a 36-year-old man with a two-year history of progressive lower limb weakness. He presented distal anterior and posterior leg amyotrophy and bilateral "stepagge", with normal upper limb strength. CK plasma level was elevated 6-fold. A biopsy from the quadriceps showed severe unspecific dystrophic changes and normal immunostaining. Patient 2 is a 48 year-old fit man with a three-year history of progressive distal lower limb weakness. He had a slim phenotype with generalised slightly asymmetric weakness. Osteotendinous reflexes were preserved. CK levels were slightly increased (0.5-fold). His 45-year-old brother (Patient 3) was wheelchair-bound and used a pacemaker. At the age of 40, he started with anterior leg compartment weakness, which later progressed proximally. CK levels were increased 8-fold. In both patients a muscle biopsy had been reported as inflammatory. In the three patients reported, electromyogram was myopathic with normal nerve conduction. Whole body MRI of patients 1 and 2 revealed moderate involvement of the deltoid in the shoulder girdle; severe fatty replacement affecting the anterior and posterior leg compartments and thighs, with complete semitendinosus fatty replacement. The search for mutations in *DES* (NM_001927.3) allowed identification of the missense mutation p.Leu370Pro, in exon 6 of *DES*, in heterozygous state in patient 1, and the variant p. Arg350Pro, in exon 6 of *DES,* in heterozygous state in patients 2 and 3. In both families the particular pattern of MRI of involvement guided the molecular diagnosis, since clinical and biopsy findings were unspecific.

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P.85

A novel homozygous desmin nonsense mutation causes pediatric onset autosomal recessive desminopathy with severe cardiomyopathy

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Desmin is a muscle specific intermediate filament that is important for maintenance of cellular integrity and force transmission. *DES* gene mutations