thin filaments. Knockdown of lmod3 in the zebrafish replicates this phenotype. These findings define a new genetic subtype of congenital myopathy and demonstrate an essential, previously unrecognised role for Lmod3 in the regulation of sarcomeric thin filaments in skeletal muscle.

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G.O.3

Severe congenital actin related myofibrillar myopathy

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Mutations in *ACTA1* have been associated with nemaline myopathy, intranuclear rod myopathy, actin myopathy, cap myopathy, and congenital fiber type disproportion. Myofibrillar myopathies (MFM) are morphologically distinct but genetically heterogeneous muscular dystrophies arising from mutations in Z-disk related proteins. A 26-month-old boy was hypotonic and weak at birth, had significantly delayed motor development, and was mechanically ventilated and tube-fed since birth. At age 26 months he had cup-shaped low-set ears, a high-arched palate, contractures of the metacarpophalangeal and proximal interphalangeal joints, and facial diplegia with diffuse muscle weakness and reduced tendon reflexes, but had good head control and could sit with support. The EMG showed prominent fibrillation potentials and myopathic motor unit potentials. The muscle biopsy revealed abnormal variation in fiber size, fiber splitting, increased internal nuclei, vacuolar change, myofibrillar disorganization, hyaline structures, focal decreases of oxidative enzyme activity as well as scattered necrotic and regenerating fibers with marked increase of endomysial and perimysial connective tissue. Many structurally abnormal fibers displayed ectopic or abnormal expression of desmin, alphaB-crystallin, myotilin, dystrophin, and NCAM. Whole exome sequencing demonstrated a previously published in-frame insertion of two amino acids in *ACTA1*. The mutant actin was expressed at ~11% of wild-type in COS7 and C2 cells. C2 cells expressing mutant actin displayed cytoplasmic actin aggregates of different sizes whereas cells expressing wild-type actin displayed mostly filamentous actin. We conclude that (1) mutations in *ACTA1* can cause MFM pathology; (2) MFM can be present at birth; (3) mutations in *ACTA1* should be considered in patients with severe congenital hypotonia associated with muscle weakness and MFM pathology.

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G.O.4

The *SMCHD1* mutation spectrum in FSHD2: Novel insight in clinical variability in FSHD

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Fascioscapulohumeral muscular dystrophy (FSHD) is associated with partial chromatin relaxation of the D4Z4 macrosatellite repeat array localized on chromosome 4 and transcriptional derepression of the D4Z4-encoded *DUX4* retrogene in skeletal muscle. In most patients, D4Z4 chromatin relaxation and DUX4 expression results from a contraction of D4Z4 repeat array on a FSHD-permissive allele defined by the presence of a DUX4 polyadenylation signal (autosomal dominant FSHD1). In the rare form of FSHD (FSHD2), D4Z4 chromatin relaxation occurs in the absence of D4Z4 contraction on a FSHD-permissive allele. Recently we reported that mutations in the *structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1)* gene on chromosome 18 can underlie FSHD2. The chromatin modifier SMCHD1 binds to the D4Z4 repeat to maintain a repressed D4Z4 chromatin structure in somatic cells. FSHD2 patients show a reduced binding of SMCHD1 to D4Z4, causing relaxation of the D4Z4 chromatin structure marked by a partial loss of CpG methylation and an increased likelihood of DUX4 expression. *SMCHD1* mutations can also be a modifier of disease severity in FSHD1. We performed a *SMCHD1* mutation screen in 60 unrelated FSHD2 families and identified heterozygous *SMCHD1* mutations in 51 families (85%). Mutations are found throughout the entire *SMCHD1* locus but the mutation spectrum is biased and the damaging potential of the mutation strongly depends on other genetic factors such as the size of the FSHD-permissive D4Z4 repeat array. We also identified a family with autosomal recessive FSHD2 highlighting the variability in *SMCHD1* mutations underlying FSHD2. Collectively, our study identifies novel aspects of repeat-mediated epigenetic repression and provides a molecular basis for the striking clinical variability in disease onset and progression.

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G.O.5

Mitochondrial dysfunction reveals defective poly(A) tail regulation of specific mRNAs as a primary defect in oculopharyngeal muscular dystrophy

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Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant inherited, slow progressing, late onset degenerative muscular disorder where a small group of specific muscles – pharyngeal and eyelid muscles – are primarily affected, leading to dysphagia and ptosis. Its genetic basis is a trinucleotide repeat expansion ranging from (GCG)8 to (GCG)13 in the N-terminus polyalanine domain of the poly(A) binding protein nuclear 1 (PABPN1) gene. Mutated expanded PABPN1 protein accumulates as insoluble nuclear inclusions in muscles of OPMD patients. While the roles of PABPN1 in nuclear polyadenylation and in the regulation of alternative poly(A) site choice are established, the molecular mechanisms behind OPMD remain undetermined. Using a Drosophila model of OPMD, we found that OPMD pathogenesis depends on affected poly(A) tail length regulation of specific mRNAs. We identified a set of mRNAs encoding mitochondrial proteins that are down-regulated during OPMD progression. Reduced levels of these mRNAs correlate with their shortened poly(A) tails. Partial rescue of the levels of these mRNAs when deadenylation is decreased using a deadenylase mutant improves mitochondrial function and reduces muscle weakness. Interestingly, the down-regulation of these mRNAs already occurs in the earliest stages of disease progression, indicating that this defect is one of the first

molecular defects in OPMD. Importantly, the down-regulation of mRNAs encoding mitochondrial proteins has been validated in a transgenic mouse model of OPMD. Moreover, a proteomic approach has also validated the down-regulation of mitochondrial proteins in clinically nonaffected muscles of OPMD patients. We propose a model where one of the primary defect in OPMD corresponds to defective poly(A) tail regulation of specific mRNAs encoding mitochondrial proteins, leading to decreased synthesis of mitochondrial proteins and defective mitochondrial activity.

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G.O.6

Lethal disorder of mitochondrial fission caused by mutations in DNM1L

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We describe two siblings, born to non-consanguineous Filipino parents after 12 years of infertility, with profound hypotonia, absent respiratory effort, hepatic dysfunction and multiple abnormalities on neuropathological studies at autopsy. The first child, a female, died at 3 weeks of age and the second child, a male, died at 5 days of life after withdrawal of care. Array CGH, molecular testing of *SMN1*, *DMPK*, *POLG1*, and metabolic studies (plasma amino acids, urine organic acids, lactate, very long chain fatty acids, transferrin isoforms) were all normal. Neuropathological examination revealed many neurons in the brain and spinal cord with intracytoplasmic hyaline eosinophilic globules. Electron microscopy showed multiple giant mitochondria within hippocampal neurons which contained elongated cristae arranged parallel to each other. Examination of the spinal cord revealed marked reduction in myelin content and neurofilament immunostaining showed decreased numbers of axons. The posterior nerve roots and peripheral nerve also showed poor myelination with a marked reduction in numbers of myelinated axons. Exome sequencing of DNA from all family members revealed both children were compound heterozygous for a c.261dup in exon 3 and a c.385_386del mutation in exon 5 of the *DNM1L* gene. The parents were confirmed heterozygous carriers of one of the mutations. The protein encoded by *DNM1L* is a member of the dynamin superfamily of GTPases and has a critical role in regulating mitochondrial morphology through assembly of fission foci and distribution of mitochondrial tubules throughout the cytoplasm. Drp1 (DNM1L) knock-out mice die shortly after birth and have enlarged, abnormal mitochondria in neuronal cells, defective synaptic development and hepatic dysfunction, similar to our patients. To our knowledge, this is the first report of a mitochondrial fission defect caused by DNM1L deficiency in humans.

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OPMD + OPDM + FSH + BMD

G.P.1

Refinement of diagnosis of Becker muscular dystrophy: Results of re-analysis of DNA samples

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The phenotype of Becker muscular dystrophy (BMD) is highly variable, and thus the disorder might be underdiagnosed. In this study we have reviewed the undiagnosed cases among patients referred for suspected BMD in the period 1985–1995. At that time DNA analysis of the DMD gene was the only routinely available diagnostic test for patients suspected of having muscular dystrophy. Over the last decade sequencing techniques have been developed for the detection of small mutations in the DMD gene. Our aim was to investigate whether BMD had been genetically underdiagnosed in the early decade of DNA analysis and, if so, whether we could improve the diagnostic yield by applying new techniques. Previously, in 79 of 185 referrals for BMD testing no deletions or duplications had been found. The original requisition forms for DNA analysis were re-evaluated; Forty-six cases were excluded because clinical data were lacking or not suggestive for BMD or the patients were known to be deceased. In 33 cases the clinical information was compatible with BMD and those were considered potentially relevant for re-analysis of the DMD gene. Sequencing could be performed on 31 stored DNA samples. Six different mutations, including four novel ones, were found. Long term clinical follow-up in these adult males revealed that one patient was asymptomatic, one had mild symptoms and four had lost ambulation due to progressive limb girdle weakness. *Conclusion:* We conclude that extending DNA analysis by sequencing the DMD gene can be helpful in identifying BMD in male patients in whom previously no deletions or duplications were found. A delayed diagnosis can still be valuable for the proband or the relatives of the BMD patients.

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G.P.2

Clinical profile of pediatric patients with Becker Muscular Dystrophy (BMD)

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Antisense oligonucleotide (AON)-induced exon skipping in Duchenne muscular dystrophy (DMD) patients aim to restore out of frame dystrophin gene mutations to in-frame mutations with resultant dystrophin production and a BMD phenotype. BMD occurs in 1 in 20000 males and is associated with partially functional truncated dystrophin protein. Pending on the amount of truncated dystrophin, the clinical phenotype of BMD patients vary from those with loss of ambulation in the mid-teens to patients with normal skeletal motor function in late adulthood. Natural history data of pediatric BMD patients would provide useful clinical information regarding the potential endpoints of therapeutic efficacy of exon skipping treatment trials. To characterize the clinical profile of pediatric patients with Becker Muscular Dystrophy (BMD) IRB approved retrospective case series' review of BMD patients Clinical profiles of BMD patients: 48 males with clinical and genetic/or histologic diagnosis of Becker's Muscular Dystrophy. Patient characteristics: Mean age at diagnosis – 5.4 years (0.75–12 years); mean CK at time of diagnosis – 8036 (161–40,000); Presenting symptom(s) – elevated LFTs (10/48), gross motor delay (9/48), hypotonia (6/48), exercise intolerance/ myalgias (15/48), abnormal walking/running gait (17/48), family history (6/48), incidental lab finding (9/48), fatigue (1/48); Indices of muscle mass: Pelvic/thigh Muscle MRI – ($n = 33$) normal study to trace fatty infiltration – 16, mild-to-moderate fatty infiltration – 11, diffuse/ significant – 6; mean serum creatinine – 0.41 (0.1–0.8); DEXA mean % lean muscle mass – 70 (51–82); Bone health: mean DEXA distal femur R1 z-score – 0.75 (2.7–3.8); Cardiac function: mean left ventricular