months later corticotherapy were tapered and additional therapy with Azathioprine (100 mg) was initiated with favorable clinical course with no adverse side effects after one year.

In summary we report a case of statin induced autoimmune necrotizing myopathy with a good outcome after treatment suspension and recurrence with gemfibrozil use.

MYOPATHY STATIN FIBRATE

P16- Limb girdle muscular dystrophies / OPMD- N° 238 to N° 255

Limb girdle muscular dystrophies- #2434
P16- 238- A novel mutation in SGCA gene: clinical and genetic analysis of an Iranian family with LGMD2D
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Sarcoglycanopathies constitute a subgroup of autosomal recessive limb girdle muscular dystrophies (LGMDs) which are caused by mutations in sarcoglycan (SG) genes. SG proteins form a core complex consisting of ?, ?, and ? sarcoglycans which are encoded by SGCA, SGCB, SGCG, and SGCD genes respectively. Alpha-SGPs are the most frequent form of SGPs. Muscle biopsy studies in patients with sarcoglycanopathies have indicated that loss of one SG subunit leads to instability of the whole SG complex.

Autozygosity mapping is a gene mapping approach which can be applied in large consanguineous families for tracking the defective gene in most autosomal recessive disorders.

In the present study, proband was a 9 year old girl from consanguineous parents. She was diagnosed at the age of 5 when she had problems climbing stairs. Her creatine kinase level was 16428 U/L. Proximal weakness and ankle contracture were also observed in the patient. Autozygosity mapping, using short tandem repeat (STR) markers linked to the SG genes, showed cosegregation of the phenotype with STR markers linked to the SGCA gene. Her muscle biopsy also suggested alpha sarcoglycanopathy. Mutation analyses revealed a novel homozygous deletion of 11 base pairs in exon 4 of this gene. This deletion causes a frameshift mutation followed by a stop codon at the fourth position after the changed codon. This will eliminate the expression of the downstream part of the extracellular domain of the protein. This domain has a critical role by associating with other molecules of dystrophin-glycoprotein complexes.

IHC studies combined with autozygosity mapping and mutation screening is an efficient diagnostic method in the sarcoglycanopathies.

Alpha-sarcoglycan; Sarcoglycanopathy; Limb girdle muscular dystrophy; Autozygosity mapping; Immunohistochemistry

Limb girdle muscular dystrophies- #2449
P16- 239- Muscular dystrophies in Burkina Faso: a report of one case of dysferlinopathy
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Introduction
Dysferlinopathies encompass a large variety of neuromuscular diseases characterized by the absence of dysferlin in skeletal muscle and an autosomal recessive mode of inheritance. So far, three main phenotypes have been reported: Miyoshi myopathy (MM), limb girdle muscular dystrophy type 2B (LGMD2B), and distal myopathy with anterior tibial onset (DMAT). Although rare, dysferlinopathies occur frequently in the Middle East and the Indian subcontinent. Limb girdle muscular dystrophy is rare in Africa, specifically in Burkina Faso. The objectives of this study is to report a case of dysferlinopathy occur in Burkina Faso.

Clinical observation
It is a case of a burkinabe patient, a teacher, born on 1984 who has consulted on March 2009 in neurology. He was suffering from walk troubles with falls, difficulties to be up, and muscular cramps with a progressive evolution since one year. In the past medical history, three cases of walk troubles have been registred. The neurological examination noticed a tetraparesy with a proximal predominance. The achilleen and osteo-tentinous kneejerk were abolished, so are the idiomuscular reflexes. Serum
It is the first case of dysferlinopathy occurs in Africa and clinical examination noticed proximal dystrophy.

**Conclusion**

It is the first case of dysferlinopathy occurs in Africa and clinical examination noticed proximal dystrophy.

**dysferlinopathies, limb girdle muscular dystrophy, Burkina Faso.**

**Limb girdle muscular dystrophies- #2494**

P16- 240- Alteration of calcium homeostasis in human in vitro models of limb girdle muscular dystrophy type 2A (LGMD2A).

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Limb girdle muscular dystrophy type 2A (LGMD2A) is one of the most frequent forms of recessive muscular dystrophies and it is characterized by primary wasting of scapular and pelvic muscles. LGMD2A is caused by deficiency in Calpain 3, a non-lysosomal Ca2+-dependent cysteine protease. Previous studies suggest that dysregulation of Ca2+ homeostasis is involved in the pathogenic mechanisms of this form of muscular dystrophy. In this study we used human cellular models of LGMD2A in order to determine the effect of Calpain 3 deficiency on Ca2+ homeostasis and the proteins involved in this process. We found abnormally increased cytosolic resting Ca2+ levels in Calpain 3 deficient myotubes when compared to control ones. We also observed reduced expression and function of sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) proteins, which represent the major mechanism of Ca2+ reuptake from the cytoplasm to the sarcoplasmic reticulum. Additionally, we detected indications of sarcoplasmic reticulum stress in Calpain 3 deficient myotubes as shown by gene expression analysis. In conclusion, our findings provide new evidence of the impact of Calpain 3 deficiency on LGMD2A pathological development through destabilization of SERCA proteins, which compromises Ca2+ homeostasis.

* Authors contributed equally to this work.

**Calpain 3, LGMD2A, Calcium homeostasis, muscle dystrophy, SERCA.**

**Limb girdle muscular dystrophies- #2500**

P16- 241- Optimizing antisense oligonucleotide design for achieving exon skipping in dysferlinopathy cell lines

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Background: The dysferlinopathies are a group of adult-onset muscular dystrophies caused by mutations in the dysferlin (DYSF) gene. Some patients with large DYSF deletions have shown remarkably mild symptoms, suggesting some regions of DYSF can be removed without significantly impacting protein function. Antisense-mediated exon skipping therapy uses synthetic molecules called antisense oligonucleotides (AOs) to modulate splicing, allowing exons harboring or near genetic mutations to be removed (?skipped?) and the open reading frame corrected. Which DYSF exons are essential to protein function and which are amenable to exon skipping are unknown. In this study, we utilize a dual in silico and in vitro approach to identify AO sequences that can achieve efficient exon skipping and produce functional dysferlin protein in dysferlinopathy patients' cells. Methods: We first characterized the mutation patterns present in dysferlinopathy patient-derived fibroblasts through PCR and genomic DNA sequencing. After determining which exons would need to be skipped to correct the open reading frame, we utilized a novel software algorithm developed by our lab which predicts the exon skipping efficiency of AO sequences. We then designed phosphorodiamidate morpholino oligomer (PMO) -based AO sequences with the highest predicted skipping efficiencies. PMOs were transfected into patient cells and the efficiency of exon skipping determined based on the presence of exon-skipped mRNA (as shown by RT-PCR and cDNA sequencing) and characterization of protein expression/function based on Western blotting, immunocytochemistry, and membrane resealing assay. Results: Patient cell line mutation patterns have been determined and AOs have been synthesized. We are currently assessing the effectiveness of our AOs at achieving exon skipping and rescuing dysferlin protein expression. Conclusion: While previous investigations in our lab utilizing this dualistic in silico/in vitro approach have provided favorable results in terms of designing effective AOs for use in Duchenne muscular dystrophy, it remains to be seen whether the same approach will be effective in designing AOs for use in dysferlinopathy.

**Dysferlin, Dysferlinopathy, Antisense oligonucleotide, Exon skipping**

**Limb girdle muscular dystrophies- #2507**

P16- 242- Calpainopathy: a survey of novel mutations in Iranian families

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Objectives: Limb girdle muscular dystrophies (LGMDs) are heterogeneous group of muscular disorders characterized by proximal muscle weakness. Calpainopathy or LGMD2A is the most prevalent form of autosomal recessive type of LGMDs which is caused by mutation in CAPN3 gene.

In the present study co-segregation of LGMD with four short tandem repeat (STR) markers linked to CAPN3 gene were analyzed.

Methods: three unrelated Iranian families, having 5 affected patients, were investigated. Haplotype analysis was performed and all coding and non-coding exons and intron boundaries of the CAPN3 gene were sequenced.

Results: DNA sequencing identified 3 novel homozygous mutations including c. 380G>A, c.1894 A>T, and c.567delG.

Conclusions: mutation c. 380G>A was at the first nucleotide of exon 3 resulting in an abnormal splicing. Since this mutation was not observed in 50 ethnically matched healthy controls, it can be regarded as a pathogenic mutation. c.567delG mutation at exon 4 leads to a frame shift, introducing a premature termination codon after the 30th amino acid residues. c.1894 A>T mutation is a nonsense mutation (p.K632 *) observed in exon 16 which yield a truncated protein by elimination of the downstream part of the protein. Searching databases did not revealed similar report therefore it is expected to be a novel mutation.

calpainopathy, autozygosity mapping, novel mutations.

Limbgirdle muscular dystrophies- #2639

**P16- 243- Annexin A2 facilitates skeletal myofiber repair and reduces dysferlinopathic pathology**

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Dysferlinopathies, which include Miyoshi Myopathy (MM) and Limb-Girdle Muscular Dystrophy type 2B (LGMD2B), are autosomal recessive muscular dystrophy caused by inherited mutations of dysferlin gene. Dysferlinopathic patients lack or have reduced expression of dysferlin protein. This results in chronic muscle weakness, high serum creatine kinase activity, muscle inflammation and fatty conversion. Lack of dysferlin has been shown to compromise sarcolemmal repair, which is linked with chronic muscle inflammation. However, the mechanism linking poor sarcolemmal repair to muscle inflammation has not been fully elucidated. Annexin A2 is a dysferlin interacting protein whose levels increase following injury to healthy muscles as well as through the course of disease progression in dysferlinopathy patients. Annexin A2 is a secreted protein and extracellular annexin A2 is known to activate macrophages. We find that Annexin A2 is also needed for successful repair of injured cell membrane. Here we investigated the role of Annexin A2 in regulating myofiber repair and muscle inflammation in healthy and dysferlinopathic mice by using Annexin A2 knockout mice. We find similar to dysferlin deficient, lack of Annexin A2 compromised myofiber repair and resulted in age dependent decline in muscle strength. However, unlike dysferlin deficient, lack of Annexin A2 did not trigger inflammatory gene expression and did not show increased skeletal muscle inflammation or other histopathology. By knockout of Annexin A2 in dysferlinopathic mice we observed reduced muscle inflammation, decreased fatty replacement of muscle fibers, and improved dysferlinopathic muscle function. Our results identify that Annexin A2 is required for efficient sarcolemmal repair, but it also contributes to muscle inflammation and adipogenic status of the dysferlinopathic muscle. These findings suggest that unlinking poor sarcolemmal repair from tissue inflammation and subsequent histopathology is a viable therapeutic target for dysferlinopathy and identifies annexin A2 inhibition as one such potential therapeutic target.

Dysferlinopathy, LGMD2B, Annexin A2, Inflammation, Cell membrane repair

Limbgirdle muscular dystrophies- #2703

**P16- 244- TRIM32 Gene Mutations Detected By Next Generation Sequencing**

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The TRIM32 gene encodes the tripartite motif-containing protein 32, which is known to be associated with a range of diseases including LGMD2H, Bardet-Biedl syndrome and sarcotubular myopathies. LGMD2H is an extremely rare autosomal recessive, mild muscular dystrophy which is characterised by myopathic features. It is typically a late-onset condition with a highly variable phenotype. Initial reports identified a single homozygous mutation to be responsible for causing cases of LGMD2H in the inbred Manitoba Hutterite population. Subsequent studies have shown LGMD2H can be caused by a broader range of mutations including missense mutations, deletions and frameshift mutations. The precise mechanism by which TRIM32 gene mutations result in LGMD2H remains to be elucidated. We present a case report of a 41year old patient who presented with proximal lower limb weakness, atrophy of the quadriceps and calf hypertrophy. He first manifested clinical symptoms at age 30, with waddling
gait and difficulties climbing stairs and walking uphill. Photographic evidence suggests calf hypertrophy was present in his teenage years. His serum CK activity was elevated up to 1844 IU/L. An EMG showed a myopathic pattern and muscle biopsy analysis was consistent with a muscular dystrophy, though no abnormalities were detected following immunohistochemistry and immunoblotting with a panel of antibodies for diagnosis of LGMDs. Muscle MRI showed selective involvement of the posterior compartment of the thigh. Molecular genetic testing was performed for a range of commonly mutated LGMD genes, all of which gave negative results. Next generations sequencing analysis was performed for a panel of 32 genes known to cause LGMD. The patient was found to be heterozygous for the novel pathogenic mutations c.691delG and c.1108delA in exon 2 of the TRIM32 gene. This case report highlights the value of utilising next generation sequencing as a diagnostic tool for rare forms of LGMDs.

**TRIM32, Next Generation Sequencing**

Limburg muscular dystrophies- #2715

P16-245- Screening of mutations in the exon 40a of DYSF

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Dysferlinopathies are disabling muscle diseases caused by mutations in DYSF the gene encoding the dysferlin protein implicated in muscle membrane repair. For an important proportion of patients (19.5%) affected with dysferlinopathy, no second expected disease-causing mutation of DYSF could be identified using sequence analysis of all coding exons and flanking intronic boundaries. It has been recently shown that a mini-dysferlin, cleaved by calpain and named mini-dysferlinC72, has a major role in membrane repair together with the full length dysferlin. The cleavage site by calpain is located in the alternatively spliced exon 40a. Given the functional importance of the region encoded by exon 40a, the probability that the lack of the cleavage site leading to the absence of the mini-dysferlinC72 could be deleterious. To further explore this hypothesis we screened more than 100 patients suspected of dysferlinopathy and no deleterious mutation could be detected. Several explanations could explain this phenomenon. First, the transcript containing the exon 40A are expressed at low level in skeletal muscle. Up to now it is accepted that dysferlinopathies are caused by a loss or strong reduction of dysferlin at the protein level, clinician generally ask for a screening of DYSF only when a large decrease in dysferlin level could be observed. In this hypothesis, patients with mutations in exon 40A are mis-oriented during the diagnosis process. Determining the level of each isoform is of prime importance in order to define which category of patients can carry mutations in this alternative exon. Furthermore, the lack of the cleavage site could lead to a dominant negative effect with dominant transmission, warranting the screen of mutation in this alternative exon even for patients with this kind of transmission.

The generalization of next generation sequencing, allowing the screen of number of genes and exon, could allow the detection of mutations in DYSF exon 40a for patients with no/or limited reduction of dysferlin or for patients with a dominant transmission.

**Dysferlin, exon , splicing, calpain**

Limburg muscular dystrophies- #2738

P16-246- Improved diagnostic in calpainopathies: development of a minigene strategy for detecting splicing mutations

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Calpainopathies are muscular dystrophies caused by recessive mutations in CAPN3. All patients present progressive muscle atrophy leading to walking difficulties up to a total loss of locomotion. As others myopathies, molecular diagnosis of calpainopathies is difficult. To date, there is still 22% of patients for whom the two causative mutations are not defined. It's especially due to the large mutational spectrum of CAPN3. More than 500 different sequence variants have been reported to date, among which 30% are missense mutations. These variants are spread all along the entire coding sequence, without mutational ?hot spot?. The frequent identification of missense variants remains a problem since it always brings us back to the dual possibility of a deleterious or a non-pathogenic effect. Those difficulties of interpretation complicate the diagnosis because a fraction of these mutations may be deleterious by affecting mRNA splicing. To override it, we have developed a functional splicing assay based on a minigene construct that checks, on splicing, the impact of missense variants identified in patients. Each construction contains a genomic segment encompassing one or two exons of interest, flanked with their intronic sequences. After transfection of the vector into cultured cells, the splicing patterns of the transcripts generated from the wild-type and from the variant constructs are compared by reverse transcription-PCR analysis and sequencing. In conclusion, this functional analysis tool could be widely used for the interpretation of missense mutations in CAPN3 or others dystrophies causing genes. Therefore, its use will improve the diagnosis and provide a better understanding of the pathophysiology of calpainopathies.

**Dysferlin, minigene, splicing, diagnostic**

Limburg muscular dystrophies- #2769

P16-247- Beta-sarcoglycanopathy: What's new? The Family Group of Beta-sarcoglycanopathy Onlus towards the first clinical trial for the LGMD2E.

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LGMD2E is a recessive autosomal disease caused by mutation in the gene, located on chromosome 4q12, encoding the beta-sarcoglycan, a major component of the Dystrophin Protein Complex (DPC). Age of onset spans between 2 and the mid-teenage years and the clinical presentation includes progressive limb weakness (mainly of proximal muscles). Cardiac involvement occurs in 20% of the cases. There are no specific treatments for LGMD2E except for some physical therapies that prevent worsening of muscle contractures.

Of interest, sarcoglycans genes are relatively short and with few exons, making sarcoglycanopathies suitable for adenovirus-based gene therapy. Actually, a phase II clinical trial for gene therapy of alpha-sarcoglycanopathy is ongoing in USA.

In 2013 the volunteer organization named Family Group of Beta-sarcoglycanopathy (GFB ONLUS; www.lgmd2e.org) was established for stimulating and supporting both basic and clinical research on this disease. In 2014 GFB ONLUS organized a conference in Venice, where the european network LGMD EuroNET was founded.

Since 2012, the families of the GFB ONLUS are funding a research project of gene therapy for LGMD2E, under the supervision of Prof. J. Mendell, at the Ohio State University (Columbus, Ohio, USA) with two main objectives:

1. pre-clinical experiments to determine the efficacy of the adenov-associated virus-mediated transfer of recombinant human beta-sarcoglycan gene in LGMD2E murine animal model.
2. clinical trial to determine the safety of intramuscular delivery of recombinant adeno-associated virus-human beta-sarcoglycan gene vector, which includes clinical vector production and formal toxicology/biostatistics studies.

This project was completed last summer and the results are under evaluation.

**Limb-girdle muscular dystrophy, LGMD2E, beta-sarcoglycanopathy, orphan disease, website, GFB ONLUS, LGMD EuroNET;**

**Limbgirdle muscular dystrophies- #2888**

**P16-248- Molecular signature in the pathogenesis of Caveolin-3-related Limb-Girdle-Muscular-Dystrophy**

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Caveolin-3 is a muscle specific protein involved in caveolae-formation, signal transduction, lipid metabolism, cell growth, mechanoprotection and cell death. This protein is localized to the sarcolemma, where it interacts with the dystroglycan complex establishing a connection between the extracellular matrix and cytoskeleton. Muscle diseases caused by mutations in the CAV3 gene are called Caveolinopathies. So far more than 40 pathogenic CAV3 mutations related to the have been described leading different disease phenotypes including Limb Girdle Muscular Dystrophy, Rippling Muscle Disease, distal myopathy and hyperCKemia.

A transgenic animal model harboring a Pro104Leu missense mutation (Cav3P104L) was generated in order to study the nature of Caveolin-3-related LGMD. The phenotype of this animal model was already extensively examined within different studies declaring this model as a suitable phenocopy of the human disorder. To understand the molecular aspects of the skeletal muscle impaired by this mutation, we performed unbiased label-free quantitative LC-MS/MS investigations of quadriceps muscles derived from 10 weeks old Cav3P104L animals (age of disease manifestation) and respective wild-type littermates. Our data revealed up-regulation of 130 and down-regulation of 42 proteins most likely leading to clinical manifestation of the Cav3P104L mutation. Altered abundances of paradigmatic proteins was verified by immunoblot and immunohistochemistry studies and correlated with morphological perturbations detected on the ultra-structural level. Notably, several affected proteins localize to the sarcolemma and are thus in accordance with the localization and function of Caveolin-3 (Dystroglycanopathies).

To further elucidate the pathogenic character of Cav3P104L and to identify new binding partners of the wild-type protein, unbiased interaction screening (TAP-assay) was performed. These studies revealed new binding partners for the wild-type protein belonging to the vesicular transport machinery. Interestingly, these interactions are lost by the presence of Cav3P104L.

**Caveolin-3, Limb-Girdle-Muscular-Dystrophy, Proteomics, Protein-Interaction Screening**

**P16-249- Implementation of massively parallel sequencing of a large panel of genes: an efficient diagnostic strategy for myopathies and muscular dystrophies**

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Limbgirdle muscular dystrophies- #2962
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Massively parallel sequencing (MPS) technologies have represented a revolution for molecular characterization of Myopathies and muscular dystrophies (M-MDs). We developed, in collaboration with medical teams of the French South-West Reference Center of neuromuscular disorders, a MPS diagnostic strategy targeted on 137 genes. In addition to 76 genes implicated in M-MD, we added 67 genes involved in other neuromuscular phenotypes (congenital myasthenia?), to detect highly atypical cases. After optimization of the capture, sequencing technology and bioinformatics analyses, we studied a cohort of 40 pediatric and adult patients with M-DM, most of them being sporadic cases. We identified the gene involved or most likely involved (family segregation studies underway) in nearly 50% of cases (19 patients), and potentially in 11 additional patients (discrepancies of the candidate gene with clinical phenotype or immunostaining, additional biochemical studies not finalized). This high diagnostic yield is probably due to the large panel of genes, the high coverage of the targeted regions, the use of two softwares for alignment and variants annotations (improved detection of indel), and transcripts studies for variants potentially affecting splicing. A total of 19 genes were involved, illustrating the genetic heterogeneity of these pathologies. The most frequently implicated genes were nebulin(NEB) and Titin (TTN), in agreement with recent studies. Our results allowed expanding the mutational and phenotypic spectrum of these giant and complex genes, incompletely studied previously. The close interactions with clinicians and pathologists enabled performing phenotype-genotype correlations and to describe atypical phenotypes. We identified a neomutation in LMNA in a pediatric atypical case, enabling implementing a specific cardiac monitoring. A mutation in the recently identified GMPPB gene, implicated in alpha-dystroglycan glycosylation, was identified in a non-specific LGMD patient. For 10 patients (25%), no potentially pathogenic variant was identified. In 5 cases, reevaluation of history and clinical data showed that the disease was probably not a myopathy. For the 5 last patients, whole exome sequencing is planned for searching new genes implicated in these diseases. Our study illustrates the importance of MPS on a large panel of genes in the diagnostic strategy of patients, in particular for those with atypical or aspecific phenotypes.

Lim girdle muscular dystrophies, molecular diagnosis, massively parallel sequencing, phenotype-genotype correlations, large panel

Limb girdle muscular dystrophies- #2966
P16- 250- Muscle water T2 and fat fraction determination by NMRI as well as 31P-NMRS in a global multi-center dysferlinopathy study
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Dysferlinopathy or limb-girdle muscular dystrophy type 2B is a rare neuromuscular disorder caused by mutations in the dysferlin gene. The disease is characterized by progressive muscle wasting. The JAIN foundation is a non-profit organization helping affected patients with a genetic diagnosis of the specific mutation. Quantitative Nuclear Magnetic Resonance Imaging (NMRI) can be used to determine the progression and the activity of the disease. This is performed with dedicated NMRI sequences based on fat/water separation (Dixon techniques) and muscle water T2 mapping (Multi-Slice Multi-Echo, MSME), respectively. Quantitative phosphorus NMR Spectroscopy (31P-NMRS) evaluates phosphate metabolism and pH.

NMRI was obtained bilaterally in the thigh (n= 12) and leg muscles (n=7), of a large subset of 203 enrolled subjects across 14 centres (Europe, USA, Australia, Japan). At three centres, 31P-NMRS was performed in the Tibialis anterior muscle. Subjects are assessed with NMRI/S annually over the course of four years. Medical and physiotherapy assessments are also obtained. Here, an analysis of the NMRI baseline data is performed.

Data was acquired in 124 patients: 62 males (11 to 71 years) and 62 females (15 to 86 years); 16 male and 15 female subjects were non-ambulant. Fat fraction values varied from as low as 1.3 % to as high as 95.1 % in both leg and thigh muscles. Muscle water T2 values were on average 37.4 ± 6.5 ms and 38.9 ± 5.2 ms in leg and thigh muscles, respectively. Muscle water T2 was elevated (? 39 ms) in 59%, 70% and 69% of the cases for Vastus intermedius, Vastus lateralis and Vastus medialis muscles, respectively. Similary, for Tibialis posterior, Adductor magnus, Biceps femoris (Long Head) and Semimembranosus muscles, the percentage of muscles with elevated T2 was also higher than 50%.

In the present work, baseline fat fraction and muscle water T2 values were determined in a large cohort of dysferlinopathy patients, which will serve as a reference for evaluation of disease progression in subsequent years. Phosphorus metabolic information can add value to the evaluation of this neuromuscular pathology. Quantitative NMRI and NMRS can be used to monitor therapeutic efficacy in future clinical trials in dysferlinopathy.
Plectinopathies are orphan diseases caused by mutations of the gene- plectin. Plectin is a cytoskeletal protein that binds components of the cytoskeleton together in various tissues. Polymorphous symptoms, mainly affecting the skin and skeletal muscles, are typical for plectinopathies. We described a patient with limb-girdle muscle dystrophy type 2Q (LGMD2Q) with early childhood onset, who discovered a new homozygous mutation chr8: 145047583C> A, Glu20ter gene PLEC, isoform 1f. Biopsy of vastus lateralis muscle was taken. The aim of the research was histopathological analysis of skeletal muscle biopsy from the patient with LGMD2Q.

Biopsy sections were stained with hematoxylin-eosin (HE), Mallory trichrome, with antibodies to plectin (clone 10F6), desmin, CD34, proliferating cells nuclear antigen (PCNA), heavy chains of fast and slow myosins (MHCfast and MHCslow), Pax7 (resting myosatellites marker), Myf5 and myogenin (differentiation factor and myosatellites terminal differentiation marker) was also performed. Healthy gastrocnemius muscle was taken as a control.

Muscle fibers (MF) of different shape and size (interquartile range of the MF cross-section- 2430.2 vs 788.3 µm2 in the control) were detected in sections stained with HE. At the same time multiple myotubules (MT) (39,37 ± 7,76%, single in the control) were found, lymphocyte and macrophage infiltration was not found. Mallory staining revealed endomysial fibrosis (17,58 ± 0,01% vs 1,64 ± 0,38% in the control). Plectin staining showed loss of membrane staining with aggregates of plectin in cytoplasma of MF (Fig.). Uneven distribution of desmin in the MF with its peripheral accumulation indicates cytoskeleton disorganization due to loss of plectin. Numerous proliferating fibroblasts, clusters of 5-6 MT with PCNA+ nucleus and PCNA+ nuclei in the MF periphery were found. There was an approximately equal number of fast and slow MF in the studied biopsy (52.03% and 47.97%, respectively); while according to M.A. Johnson et al. (1973) normal rate is 67.3% and 37.8% respectively. Multiple Myf5+ nuclei in MT and the only MF with myogenin+ nucleus

Thus, histological analysis of the biopsy revealed myodistrophical pattern of skeletal muscles without macrophage infiltration, with disorganization of the MF cytoskeleton due to loss of plectin and desmin, incomplete reparative rhabdomyogenesis, moderate endomyssial fibrosis and violation of the fast/slow MF ratio.

We thank G. Wiche for providing the plectin 10F6 mAb.

LGMD2Q, plectin, immunohistochemistry, morphometry

Limb girdle muscular dystrophies- 3017

P16- 252- POPDC1S201F causes a new form of autosomal recessive limb girdle muscular dystrophy with atrioventricular block via cAMP binding and membrane trafficking defects.

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The Popeye domain containing 1 (POPD C1) gene encodes a plasma membrane-localized cAMP binding protein. Despite its essential role in regulating the structure and function of cardiac and skeletal muscle in animal models, this gene has never been associated with human cardiac and muscular diseases. We describe a homozygous missense variant (c.602C>T, p.S201F) in POPDC1, identified by whole exome sequencing, in a family-of-four with cardiac arrhythmia and mild limb girdle muscular dystrophy (LGMD). This very rare allele variation was absent in databases, and segregated with the phenotype. Further screening in 104 unrelated patients affected with cardiac rhythm disturbance and mild limb girdle myopathy or high CK resulted negative for other homozygous/compound heterozygous variations, which is consistent with a very rare, family-specific mutation. In skeletal muscle biopsies of two patients, the membrane levels of POPDC1S201F and of the related POPDC2 protein were reduced suggesting impaired membrane trafficking. The mutant protein displayed a 50% reduction in cAMP affinity and displayed deregulation of TREK-1 ion channel gating when injected into Xenopus oocytes. Forced expression of POPDC1S201F in HL-1 cells increased hyperpolarization and upstroke velocity of the action potential. The homologous mutation in zebrafish (popdc1S191F) displayed heart and skeletal muscle phenotypes, which resembled those observed in patients and also affected membrane trafficking. In addition, we showed that POPDC1 interacts with Caveolin 3, acting on membrane compartmentalization and with dystrophin and dyserlin, underlining the common functional circuits these proteins are involved in. Our study therefore identifies POPDC1 as a novel disease gene causing a very rare autosomal recessive cardiac arrhythmia and mild limb girdle muscular dystrophy. POPDC1 expands the heterogeneous genetic landscape of LGMDs with heart disturbances and opens novel pathways underlying these complex genetic disorders. We are currently searching for mutations in POPDC1 gene in other LGMD phenotypes in order to evaluate its causative role also as possible disease modifier.

**LGMD, POPDC1, Cardiomyopathy, Atrioventricular block, WES**

Limb girdle muscular dystrophies- #3020

**P16- 253- Pattern recognition by semiquantitative radiological analysis in a large and multinational cohort of dysferlin patients (JAIN COS Study)**

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Objective
To describe the pattern of pathology by muscle MRI in a large and multinational cohort of patients with dysferlinopathy (JAIN COS Study)

Methods
Muscle MRI was performed in 182 patients with a confirmed diagnosis of dysferlinopathy, 84 of whom had a whole body muscle MRI and 98 a lower limb muscle MRI. Muscle MRI was performed in 14 different centers, using 1.5T or 3T scanners from different manufacturers (Philips, General Electrics, Siemens). The semiquantitative analysis was performed on axial T1 weighted sequences by a blinded neurorologist with experience in muscle MRI using the Mercuri scale modified by Fisher (0 to 4). 81-131
muscles were scored per patient. Statistical analysis was done using SPSS 21.0 and non parametric tests were used to analyze gender and symmetry differences.

Results
Half (50%) of the patients were male and half were female. The mean age at MRI was 38 ± 12.65 years (11-86 years). The mean age of first symptoms was 21.48 ± 8.48 years (1-60 years) and the mean disease duration to MRI was 16.8 ± 10 years (1-51 years). Serum CK activity at the time of the MRI was 4594 ± 4031 IU/L (209-23124). 136 patients (74.7%) were ambulant at the time of the MRI scan. The facial, cervical, pectoralis, trapezius, brachialis, triceps, arm, abdominal, gracilis and popliteal muscles were not usually affected. The femoral quadriceps, peroneus brevis, gastrocnemii and soleus muscle were more affected in female than in male patients (p >0.05). There were statistically significant differences in symmetry in the right long head of the biceps femoris muscle (p<0.0001).

Conclusions
The tensor fasciae latae, hamstrings and peroneus were the most affected muscles in dysferlinopathy patients, followed by the femoral quadriceps and medial gastrocnemius muscles. The facial, popliteal, piriformis and quadratus lumborum muscles were the least affected muscles. The femoral quadriceps and calves muscles were more affected in female patients and differences in symmetry were significant in the long head of the biceps femoris muscle.

Dysferlinopathy, LGMD2B, muscle MRI

Limb girdle muscular dystrophies- #3043
P16- 254- LIMB-GIRDLE MUSCULAR DYSTROPHY 2Q: CASE REPORT
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One of the rare types of autosomal recessive limb-girdle muscular dystrophies is LGMD 2Q (OMIM 613723), caused by mutations in the plectin gene (PLEC), located on 8q24.3 (OMIM 601282). We describe the clinical case of a 26-year-old man from the family with three affected siblings who have the phenotype of LGMD from the highland region of the Republic of Dagestan. Clinical features include a manifestation from an early age, the stability of up to 20 years of age, followed by an active progression, marked atrophy of the axial muscles of the trunk, spine stiffness predominantly in the cervical region, hypertrophy of calf muscles, deltoid and triceps muscle. In 26 years, the patient has appeared intermittent dyspnea. His brother and sister have died from progressive respiratory failure at the age of 29 and 31 years, respectively. None of the family members did not reveal lesions of the skin and mucous membranes. We found a new homozygous mutation located in 1f exon PLEC gene s.145047583 C>A, (p.Glu20ter), using Next-Generation Sequencing. Instrumental examination revealed an increase serum CK to 3500-4100 U/L. Electromyography showed myopathic motor unit potentials, whereas nerve conduction and neuromuscular transmission studies were normal. Lung CT scans showed signs of non-infectious bronchiolitis and atelectasis. Morphological analysis of muscle showed atrophy with disorganization of the cytoskeleton of the muscle fibers, active but not completed reparative myogenesis, moderate endomyal fibrosis and disorder ratio of fast/slow-twitch muscle fibers. Noted marked hyperplasia of endothelial cells in the capillaries of the muscles and skin. Ultrastructural abnormalities included myofibrillar changes such as Z-disc streaming, misalignment of myofilbrils, intermyofibrillar and subsarcolemmal accumulation of filamentous material. Mitochondria presents rare clusters, much smaller, curved shapes and dark colors. The plectin immunostaining with mab-121 showed the cross-striated plectin-staining pattern, but immunostaining with desmin antibodies revealed cytoplasmic and subsarcolemmal desmin-positive deposits. This family observation extends the phenotypic spectrum of the muscle damage and morphological changes caused by mutation plectin isoform 1f and stresses the importance, whole genome sequencing in difficult differential diagnostic LGMD cases.

Keywords: limb-girdle muscular dystrophy, plectinopathy, plectin, intermediate filaments.

Oculo-pharyngeal muscular dystrophy- #2952
P16- 255- A cohort of 354 unrelated patients with oculopharyngeal muscular dystrophy reveals a correlation between polyalanine expansion size and disease severity.
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Oculopharyngeal muscular dystrophy is an autosomal dominant adult-onset disease where typical clinical features are characterized by progressive ptosis of the eyelids, dysphagia, and proximal limb weakness starting in the fourth decade of life. The genetic cause is an expanded (GCN)n mutation in the first exon of the PABPN1 gene encoding for the polyadenylate-binding protein nuclear 1. Normal alleles contain 10 GCN repeats whereas expanded alleles range in size from 11 to 18 GCN repeats. In this study, we explored 354 unrelated index cases recruited since 1999 in several French neuromuscular centers and confirmed with the molecular genotyping of PABPN1. The distribution of the genotypes as well as their correlation with age at diagnosis and phenotypical features are presented. Through analysis of this large cohort, we were able to demonstrate for the first time a strong correlation between the size of the expansion and the mean age of diagnosis, an indicator of disease severity.

To conclude, this large cohort allowed to demonstrate that in heterozygous and homozygous OPMD patients, the mean age at diagnosis and the severity of the clinical symptoms are linked to the number of repeats. Homozygous patients showed the worsened phenotype suggesting a gene-dose effect additionally to the repeat number expansion. Altogether this suggests that the determination of the size of the triplet expansion is an important test to perform in OPMD patients.

triplet expansion disease; OPMD; genotype-phenotype; cohort study; PABPN1

P17 – Miscellaneous- N° 256 to N° 274

Metrology- #2622


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Background: Atlas segmentation is a powerful method for automatic structural segmentation of several sub-structures in many organs. However, no study has used this method so far for skeletal muscle segmentation. In this study, we present an atlas segmentation pipeline we have developed for segmentation of quadriceps muscles from magnetic resonance images obtained in twenty five young healthy males. We also show a few examples for the follow-up of patients.

Materials and Methods: A non-linear registration process based on ANTs algorithm was applied to thigh images initially automatically segmented for bone, muscle and fat tissues. Optimized fusion parameters of STEPS multi-atlas segmentation were determined in order to obtain the highest DICE index as compared to the manual segmentation of quadriceps muscles, considered as the gold standard. Validation and reproducibility of the pipeline was assessed in two other databases of seven healthy male subjects. In a group of dystrophic patients, a single-atlas version of the pipeline was used without the fusion process and a similar validation was performed.

Results: In control subjects, the results for each quadriceps muscle show a mean DICE similarity coefficient higher than 0.85. While the multi-atlas pipeline did not provide satisfactory results in patients due to a massive fat infiltration, the single-atlas version allowed to perform a follow-up for each muscle considering the initial MRI as an atlas.

Conclusion: In the present study we reported two segmentation pipelines based on atlases. The examples provided in a control population and in a few patients demonstrated a robust method which could be useful for muscle quantification and fat infiltration in the fields of neuromuscular disorders, sports medicine and rehabilitation.

MRI, segmentation, atlas

Miscellaneous- #2341

P17- 257- Contribution of neuroacupuncture as a supportive care in neuromuscular diseases. Experience of the Physical Medicine and Rehabilitation department at Rothschild Hospital (Paris, France)

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Introduction

The Physical Medicine and Rehabilitation department at Rothschild Hospital works in partnership with the Neuromuscular Reference Center ?Paris-East?. After the initial consultation, several strategies of care are proposed. For some complex patients with neuromuscular disorders (NMDs), whose pain is not controlled by chemicals or physical techniques, neuroacupuncture is performed by a PM&R physician.