Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common autosomal dominant disorders characterized by progressive weakness of facial, shoulder and upper arm muscles. The disease is caused by transcriptional derepression of DUX4, encoded in the D4Z4 macrosatellite repeat. Two distinct groups of patients expressing DUX4 can be defined: >95% of affected individuals have a contraction of the D4Z4 array at 4q35 (FSHD1) while <5% of the patients do not show contractions (FSHD2). Epigenetic changes like DNA hypomethylation and a decrease of the repressive histone mark H3K9me3 at D4Z4 can be observed in FSHD1 and FSHD2. FSHD patients show a high clinical variability, both between and within families. We tested whether the change in epigenetic modifications at D4Z4 can be used as a measure for disease severity. Our study aimed to correlate the ratio between the transcriptionally permissive marker H3K4me2 and the repressive marker H3K9me3 with clinical parameters and with D4Z4 array length. 7 control, 17 FSHD1 and 9 FSHD2 fibroblast/myoblast samples were included in the study in which we measured the abundance of the histone modifications by cross-linked chromatin immunoprecipitation. Results were analysed statistically by determination of Pearson’s correlation coefficient between the H3K9me3/H3K4me2 ratio and (age-corrected) clinical severity scores (CSS) or D4Z4 array length. We found that the H3K9me3/H3K4me2 ratio is significantly lower ($p < 0.001$) in FSHD1 and FSHD2 patients compared to controls in both fibroblast and myoblast samples. Preliminary data suggests that there is a significant correlation between age-corrected CSS and the H3K9me3/H3K4me2 ratio in the case of FSHD1 and FSHD2 fibroblasts ($n = 15$, $P = 0.05$). Correlation was not significant when we pooled all myoblast and fibroblast data. Finally, FSHD2 myoblast samples showed a significant correlation between the H3K9me3/H3K4me2 ratio and D4Z4 array length. Currently we are expanding our studies in a larger sample set.

EMERY-DREIFUSS MUSCULAR DYSTROPHY: POSTER PRESENTATIONS

P2.41
From Emery-Dreifuss muscular dystrophy to striated muscle laminopathies. A 12 years retrospective

In 1999 we reported the first LMNA gene mutation responsible for the autosomal Emery-Dreifuss muscular dystrophy (EDMD), a gene encoding nuclear envelope proteins lamin A/C. Since a huge number of patients carrying LMNA mutations have been reported in other striated muscle disorders (including LGMD1B and isolated cardiac disease) or in neuro- and lipodystrophies and premature ageing syndromes. These disorders are collectively named laminopathies. We reviewed clinical and genetic data of LMNA mutation carriers (1994 carriers, 961 families) including non published (406 carriers, 219 families, 145 different mutations) and those reported in the literature (737 families, 1583 carriers, 317 different mutations). Using the Universal-Mutation-Database database-LMNA, we looked for molecular epidemiology and phenotype/genotype correlations with a special focus on striated muscle laminopathies (SML). SML has been found in more than 58% of the mutation carriers (1192 patients) either as isolated feature or as part of a multisystem dystrophy syndrome. When isolated (1146 patients, 59.8% of carriers), EDMD, LGMD1B and isolated cardiac disease were found respectively in 19.8% (395 patients), 8.5% (171) and 24.8% (494) of the carriers. LMNA mutations causing SML are spread along the entire gene. 74.8% are missense or in-frame deletion/insertions. Of note, 19% of SML causing mutations are nonsense or out-of-frame deletion/insertions, this mutation type representing only 0.6% of other laminopathies. Different mutations located at different lamin A/C functional domains can give rise to the same clinical condition. Conversely certain mutations can cause completely different diseases even within the same family. These findings suggest important inter- and intra-familial phenotypic heterogeneity in SML and in laminopathies in general.
The molecular bases of this heterogeneity remain to be addressed and represent probably one of the future challenges.

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P2.42
Cys150Arg FH1L mutation in two brothers affected by the Emery-Dreifuss muscular dystrophy phenotype
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Mutations in the four and a half LIM protein 1 (FH1L) gene were recently identified as the cause of four distinct skeletal muscle diseases: reducing body myopathy, X-linked myopathy characterized by postural network atrophy, scapuloperoneal myopathy and Emery-Dreifuss muscular dystrophy (EDMD). FH1L plays multiple roles in the myoblast differentiation. Here we report two male siblings presenting a Emery-Dreifuss muscular dystrophy phenotype. The patients, currently 17 and 14 years old were born from a non consanguineous family. Their mother died from gastric bleeding after having been diagnosed of amyloidosis. However she suffered from a cardiomyopathy and had an increased CK level. Onset of clinical symptoms was at six years of age in both brothers, presenting motor clumsiness, progressive retraction of elbows, hamstring muscles and Achilles tendons contractions. Hyperlordosis and rigid spine were present as well as a restrictive respiratory pattern. CK was increased (N X 100 IU/L). EMG showed a myopathic pattern. Cardiological examination (echocardiogram and Holter studies) were normal. Mild and non specific myopathic features were present. Based on clinical history, physical examination and laboratory tests reminding Emery-Dreifuss phenotype, LMNA/C gene, emerin and SENP1 gene were ruled out. We found an hemizygous mutation c.448 T > C (p.Cys150Arg) in the FH1L gene causing the disease of the brothers. Here we describe for the first time a FH1L mutation not associated with the EDMD phenotype so far in two brothers. The retrospective findings found in their mother would suggest that she could be a carrier. FH1L gene mutation should be rule out in boys with Emery Dreifuss muscular dystrophy phenotype when emerin mutation (EMD) has been excluded.

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P2.43
Revisiting X-linked Emery-Dreifuss muscular dystrophy. New insights into an old story
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In 1966, Emery and Dreifuss reported a large family from Virginia, where affected males showed an unusual type of X-linked condition characterised by muscular dystrophy with early joint contractures and cardiac disease. This report of a new clinical entity later called Emery-Dreifuss muscular dystrophy (EDMD) started a new chapter in muscle diseases.

In 1994, the first mutations were identified in the EMD gene encoding an integral protein of the nuclear envelope, named emerin. Since a huge number of patients and mutations were described. In addition to EDMD, EMD mutations have been also, but rarely, reported to lead to isolated cardiac disease and limb girdle muscular dystrophy. These various phenotypic expressions of emerin mutations are known as emerinopathies. We here reviewed clinical, genetic and protein data of EMD mutation carriers (158 families, 371 carriers) including non published (45 families, 110 carriers) as well as those reported in the literature since 1994 (113 families, 261 carriers). By using the Universal-Mutation-Database database-EMD database tools, we looked for molecular epidemiology and phenotype/genotype correlations. So far, there is only 1 EMD mutation (c.109_111delAAG, p.Lys37del) leading exclusively to isolated cardiac disease in male patients and 2 leading to LGMD with cardiac disease. EMD mutations leading to EDMD are in majority frame shifting mutations (78% of all EMD cases) leading to the absence of emerin. Mutations are spread along the entire gene, exonic mutations having a maximum hit within exon 2, residues 1, 34, 235, 218, 84, 51 and 44 being the most frequently affected (28% of all EMD cases). At the phenotype level, EMD patients presented with similar history with variability in the age of onset of cardiac disease. Cardiac disease complications including high degree conduction defects, sustained arrhythmias, heart failure and ischemic stroke are of high prognosis value.

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OculoPharyngeAL MUSCULAR DYSTROPHY: POSTER PRESENTATIONS

P2.44
Accelerated skeletal muscle ageing is a molecular signature in OPMD
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OculoPharyngeal muscular dystrophy (OPMD) is a dominant late-onset muscle disorder. The disease is typically characterized by progressive ptosis, dysphagia and upper proximal limb muscle weakness. Patients with OPMD carry a trinucleotide repeat expansion mutation that leads to a poly-alanine expansion in the PABPN1 protein. The molecular mechanisms that underlie OPMD are not well understood. Although the mutant protein is ubiquitously expressed, symptoms appear above the age of 40. To identify molecular pathways that are specifically associated with the disease, whole genome expression profiling was performed on RNA from quadriceps of mutant PABPN1 carriers, which were subgrouped into pre-symptomatic and symptomatic. The dataset was complemented with age-matched controls. Three statistical approaches, including Limma, Global test and the literature weighted Global test, were combined in order to indentify OPMD-deregulated pathways. Transcriptome changes in OPMD demonstrate significant similarities to changes observed in normal ageing of skeletal muscles but occur at an earlier age than in healthy controls. Moreover, the majority of the OPMD-deregulated genes can be grouped into molecular pathways that are known to be ageing-associated. In contrast, only minor transcriptome changes were found in pre-symptomatic. We therefore suggest that disease onset in OPMD is triggered by naturally occurring ageing-associated transcriptional changes.

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