**Limb-girdle muscular dystrophy type 2I (LGMD2I) is caused by defects of the fukutin related protein (FKRP) gene. In Caucasian patients, the majority of LGMD2I cases are frequently associated with a single missense mutation of the FKRP gene, namely c.826C > A (p.Leu276ile). We reported two Chinese siblings with adult-onset progressive shoulder and pelvic muscle weakness. They suffered from evident muscle stiffness and myalgia after exercise, but absence of obvious calves hypertrophy. Muscle biopsy showed dystrophic features with numerous rimmed vacuoles in fibers. Immunostaining and immunoblot analysis revealed the reductions of α-dystroglycan (Via4-1) and laminin-α2 (80-kDa C-terminal and 300-kDa N-terminal). Genetic analysis of the FKRP gene revealed novel compound heterozygous mutations (c.208T > A and c.1030G > T). Meanwhile, we summarized the reported cases with LGMD2I in Asian region. To our knowledge, this is first report in Chinese mainland population. Our findings expand the genetic spectrum and geographic distribution of LGMD2I. The findings suggest the pathogenic FKRP mutations may be sporadic compound heterozygous in Asian LGMD2I patients instead of hot-spot c.826C > A mutation in Caucasian population.**

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**P1.29 Expression analysis of N-terminal α-dystroglycan in muscle diseases**

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The dystroglycan complex is composed of two proteins α- and β-dystroglycan (α-and β-DG) encoded by a single gene. α-DG is composed of three distinct domains: N-terminal (α-DG-N), mucin-like and C-terminal (α-DG-C). α-DG-C anchors α-DG at the extracellular surface of the plasma membrane by non-covalent interaction with β-DG. The central mucin-like domain that connects α-DG-N and α-DG-C is highly glycosylated by O-linked sugar chains that bind extracellular ligands such as laminin. It has been shown that α-DG-N is cleaved by furin, a pro-protein convertase. However, the physiological significance of the proteolytic cleavage of α-DG-N remains elusive. In the present study, we used specific antibodies against α-DG-N and α-DG-C, both binding α-DG regardless of its glycosylation status, to characterize their expression in human muscle with LGMD pathologies. Over 30 biopsies including controls and patients with various confirmed molecular diagnosis were analyzed. We observed homogenous expression of α-DG-C in most biopsies. Interestingly α-DG-C labelling was retained even at the periphery of fibres that appeared necrotic by histological analysis and that were lacking expression of sarcolemmal markers such as spectrin and β-DG. Labelling for α-DG-N was less homogenous overall and it was missing around necrotic fibres. These observations suggest that α-DG-N may undergo cleavage concurrently with necrotic events while the remaining of the protein resides into the basement membrane. Seen that α-DG-N has also been detected in human serum it is tempting to speculate that it may play a role in signalling pathways regulating muscle turnover.

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**P1.30 Late-onset limb girdle muscular dystrophy type 2D (LGMD2D)**


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**Background:** LGMD 2D is caused by mutations in gene(SGCA) encoding α-sarcoglycan. LGMD2D is one of sarcoglycanopathies that characterized by a progressive weakness of pelvic and shoulder girdle muscles. The manifestation of LGMD2D varies from mild to severe. The severity is roughly correlated with the residual amount of the protein. Age of onset is from childhood to adulthood. We experienced late-onset mild form of LGMD2D patient showed negative or reduced sarcoglycan complex protein. We aimed to make clinical and pathologic features of late-onset LGMD2D clear. **Methods:** We investigated clinical features and performed histochemical, immunohistochemical and western blotting analyses using biopsied muscle. Mutation screening was done for all four sarcoglycan genes. **Results:** Patient is a 73-year-old female. Her sister was diagnosed as muscular dystrophy and her mother and brother had heart failure. She noticed muscle weakness of lower extremities in her fifties. At the age of 71, she had a medical examination and showed mild muscle weakness of lower extremities, Gowers’ sign and waddling gait. The serum CK level was elevated to 308 IU/L. Muscle CT revealed atrophy and degeneration of posterior femoral muscles. Muscle biopsy showed a few necrotic and regenerating fibers, marked fiber size variation and increase of internal nuclei. Immunostaining and Western blotting analyses revealed negative or reduced sarcoglycan complex. Mutation analysis revealed a compound heterozygous mutation of c.402 C > G (p.Y134X) and c.623 C > T (p.T208I) in SGCA. **Conclusions:** This patient is the most late-onset LGMD2D so far and clinical symptoms were mild. Sarcoglycanopathy patients can show late-onset mild form of LGMD.

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**P1.31 Genetic mutations in sarcoglycanopathies in a Malaysian population**


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Sarcoglycanopathies are a subgroup of autosomal recessive limb girdle muscular dystrophies (LGMD) which are characterized by mutations in one of the sarcoglycan genes, viz., gamma sarcoglycan (LGMD2C), alpha sarcoglycan (LGMD2D), beta sarcoglycan (LGMD2E) and delta sarcoglycan (LGMD2F) genes, respectively. Sarcoglycan immunohistochemistry was performed on muscle biopsies from patients diagnosed as LGMD, and we identified 5 patients with negative or significantly weak staining. Extracted DNA from muscle tissue from these patients was sequenced for all the coding regions of the 4 sarcoglycan genes. Mutational analysis revealed 2 novel mutations.
in the beta sarcoglycan gene in 2 siblings and 1 other unrelated patient. The mutation in the siblings was a homozygous donor splice site mutation, c.621 + 1G > T. Analysis of the cDNA showed two distinct mRNA species: (1) deletion of the whole of exon 3, and (2) 1 bp deletion of the terminal portion of exon 3. In the unrelated patient, there was a homozygous deletion c.570_572TTT > TT of the beta sarcoglycan gene. Two other unrelated patients had the same homozygous missense mutation, c.696C > G (p.Cys232Trp) in the alpha sarcoglycan gene that was not seen in a series of 200 normal chromosomes and published databases. Beta and alpha sarcoglycanopathy appear to be more common than other forms of sarcoglycanopathies in Malaysia. Out of 87 cases of LGMD in our database, they comprise about 5.7%.

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P1.32
A genetic variant within caveolin-3 protects against statin-induced myopathy
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Myopathy is a frequent and potentially life-threatening complication of statin therapy. We hypothesized that there is genetic susceptibility to statin-induced myopathy could be associated with skeletal muscle-related genes. We enrolled a cohort of 400 patients, 250 with muscular symptoms and 150 matched asymptomatic individuals, after due approval. We collected all demographic and laboratory data, including genomic DNA. Muscular symptoms associated with statin intake were defined as muscle pain and/or muscle cramps and/or elevated CK. Laboratory and clinical data were available from all patients, including CK, lipids and liver enzymes. We genotyped single-nucleotide polymorphisms (SNPs) in Caveolin-3, a gene associated with "painful myopathy".

We found a significant effect (p < 0.009) for CAV3 rs1974763 in men. The T allele was protective against statin-induced myopathy, while the C allele appeared as a risk factor. The overall frequency of the alleles was 86% and 13% for C and T respectively. The frequency of the T-allele was 21% in male controls compared to 10% in male cases. In females the T-allele had a frequency of 8% in controls and 13% in cases (n.s.). Caveolae are flask-like plasma membrane invaginations involved in a variety of signal transduction pathways, for example GLUT4 and Sre kinase signalling. In addition, there is emerging evidence of the tight link between caveolae and cholesterol metabolism and the impact of statins on caveola structure and function. To our knowledge, this is the first association study linking genetic variants within a skeletal muscle-related gene, namely Caveolin-3 with statin-induced myopathy.


P1.33
Expression of cavin family members in skeletal muscle
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Background: PTRF (cavin-1) is a caveola protein and is known to have essential roles in caveola formation and stabilize caveolins. We previously reported that PTRF mutations cause muscular dystrophy with generalized lipodystrophy associated with secondary deficiency of caveolins. Up to date, four cavein family members (PTRF/cavin-1, SDPR/cavin-2, SRBC/cavin-3, and MURC/cavin-4) and three caveolins (cavelin-1, -2, and -3) are known. Caveolin-3 and MURC express skeletal and cardiac muscles, whereas other cavin and caveolin members express ubiquitously. Objective: To know the expression of cavin family members in control and diseased skeletal muscles. Method: We examined the expression and interaction of four cavin and three caveolins using immunohistochemistry, immunoblotting, and immunoprecipitation. We used biopsied skeletal muscles from patients with CAV3 or PTRF mutations, muscles showing mosaic caveolin-3 staining with unknown cause, and controls. Results: Muscles from PTRF mutations show negative staining of PTRF with reduced membrane staining of caveolin-3 and MURC. Immunoreaction of caveolins-1 and 2 in the blood vessels are barely detectable. Membrane staining of PTRF and MURC is closely associated with caveolin-3 staining. Immunoprecipitation assay showed caveolin-3 can bind both PTRF and MURC. Conclusion: In skeletal muscle, PTRF and MURC can form a protein complex with caveolin-3 and may have a tissue specific important role at caveola.

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CONGENITAL MYOPATHIES; POSTER PRESENTATIONS

P1.34
A novel homozygous mutation of the selenoprotein gene causes rigid spine syndrome with muscular dystrophy
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Mutations of the selenoprotein gene (SEPN1) cause SEPN1-related myopathy which shares common clinical features characterized by severe weakness and wasting of neck and trunk muscles. SEPN1-related myopathy presents with early-onset and autosomal recessive inheritance. Here we describe a case with rigid spine syndrome due to a novel homozygous SEPN1 mutation.

A 36-year-old male patient was born to nonconsanguineous parents. He appeared to be normal until the age of 18 months when he was delayed to walk. He had difficulty in running and was sometimes easy to fall at the elementary school. He first noticed limitation of flexion in his neck at the high school. In the second to third decades, he developed progressive axial and proximal muscle weakness. Serum CK level had been elevated to 5–10 times the normal upper limit. A muscle biopsy from the vastus lateralis was performed in our hospital at the age of 24 years, which revealed nonspecific dystrophic changes. He had stood with assist and depended on a wheelchair for mobility from the age of 30 years. He had myopathic face, moderate lordoscoliosis, scapula alata, and marked limitation in neck and trunk flexion. Motor exam was significant for weakness in the bilateral shoulder and hip girdle and proximal lower limb. There were no cardiac abnormalities and no limitation of elbow flexion.

We identified in the patient a homozygous T-to-G transition at nucleotide 1574 in the SEPN1 exon 12, which modified Met525, a nonpolar amino acid to Arg, an acidic amino acid. It is noteworthy