found only in 2.25% of all muscle biopsies analyzed at Siriraj Hospital.
DMRV is by far the most common distal myopathy in Thai population
accounting for 50% of all cases and 80% of Thai DMRV patients carry
GNE gene mutations. Dysferlinopathy is the second common distal
myopathy in Thailand but only 25% of patients carry DYSF mutation.
Many novel mutations of GNE and DYSF genes are identified.

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NUCLEAR ENVELOPATIES; POSTER PRESENTATIONS

G.P.4.01
Rare congenital presentation of Emery-Dreifuss muscular dystrophy due
to a novel de-novo LMNA mutation R249W
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We report an 8-year-old girl with congenital onset of Emery-Drei-
 fuss muscular dystrophy (EDMD) with a novel LMNA gene mutation.
The patient is the 2nd child born to non-consanguineous parents after
a full-term uneventful pregnancy with normal intra-uterine growth.
Mild ankle and knee contractures were present at birth. Her hypotonia
did not come to medical attention until 4 months of age when persis-
tent head lag was noted. Her head control worsened between 3 and 6
months of age. CK levels were 1050 and 1430. First neurologic evalu-
ation at 8 months of age revealed generalized hypotonia and weakness
with diminished reflexes. Genetic testing for SMA was normal. Muscle
biopsy at 9 months showed only mild disparity in the size and shape of
individual myofibers, normal immunohistochemistry stains and nor-
mal immunostaining for dystrophin, z-sarcoglycan and merosin.
EMG at 2 years was essentially normal in distal lower limb but showed
a lack of motor unit potentials without acute or chronic denervation
signs in proximal upper extremity, paraspinal muscles and tibialis an-
terior. Brain MRI was normal. At 7 years of age the patient presented
to our center for a repeat diagnostic evaluation. She had overall wasted
appearance with almost no subcutaneous fat, in particular around her
neck. There was no antigravity strength in the neck; no to minimal
antigravity strength in proximal upper extremities; and barely present
antigravity strength in proximal lower extremities. Multiple flexion
contractures were present, including fingers, wrists, hips, knees and
ankles. Spine showed mild scoliosis with rigidity. She has minimal
facial weakness. Her cognitive skills were age appropriate. Her echo-
cardiogram and Halter monitor studies have been normal. LMNA
gene sequencing revealed R249W missense mutation that was not
found in either of her parents. While R249W is a novel mutation,
R249Q has been previously reported in multiple affected individuals
with more classic EDMD. Mutations in the LMNA gene are known
to cause a very broad phenotypic spectrum leading to nine distinct con-
ditions. Congenital onset of EDMD is rare and has been reportedly
only a few times. Given the lack of specific findings on muscle biopsy
along with normal immunostaining results, this report further supports
the need to consider LMNA gene mutations in merosin positive
congenital muscular dystrophy cases with normal cognitive
development.

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G.P.4.02
Pathophysiologi cal mechanisms of lamin A/C associated Charcot-
Marie-Tooth disease (CMT2B1/ARCMT2)
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Lamins, a class of intermediate filaments, are major components of
the nuclear lamina, a filamentous network underlying the inner face of
the nuclear membrane. A-type lamins are encoded by the same gene:
LMNA, as a result of alternative splicing. Up to date, at least nine
pathologies, described as laminopathies, have been associated with
mutations in LMNA. One of these, Charcot-Marie-Tooth disease, type
2B1, is an autosomal recessive form of axonal hereditary motor and
sensory peripheral neuropathy caused by the mutation c892C>T in exon
5 of the gene. In order to progress towards understanding the
pathophysiological mechanisms underlying CMT2B1, we studied two
different models for the disease: human patient’s cells homozygous
for the c892C>T mutation, and a murine Knock-In model. First,
the role of LMNA in maintenance of nuclear integrity was assessed
by immunofluorescent studies. Interestingly, no nuclear abnormalities
were observed. Second, gene expression studies performed on microflu-
idic plates (Low Density Array) evidenced significant decreased expres-
sion levels for several genes, including LMNA. These observations
were confirmed by Low Density Array experiments on brain, muscle
and heart murine cDNA. Finally, in Knock-In models, behavioral,
morphological and functional analyses are still in progress.

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G.P.4.03
Mutations in the lamin A/C gene: An emergent cause of fatal arrhyth-
mias in congenital muscular dystrophies
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Mutations in laminas A and C, nuclear intermediate-filament pro-
teins, cause a variety of diseases that primarily affect striated muscle,
adipocytes, or peripheral nerves or cause features of premature aging.
Muscle involvement is generally variable in severity, from congenital
onset with severe phenotype to milder classic Emery-Dreifuss variant.
There is no clear correlation between the clinical phenotype and type
or localization of the mutations in proteins, which are generally amino
acid substitutions or short deletions throughout the sequences. We
report 2 patients (N2862, male and N4127, female) affected by congen-
tal muscular dystrophy who developed cardiac arrhythmias due to a
heterozygous de novo LMNA mutation. Both patients – born from
non consanguineous marriages – presented with severe and diffuse
hypotonia associated with delayed motor milestones, weakness, absent
tendon reflexes, equinus and wrist contractures, very poor spontaneous
activity, moderately increased serum CK levels. Mental development
was normal as brain NMR. Muscle biopsy showed signs of mixed mus-
Phenotypic clustering of lamin A/C mutations in neuromuscular patients

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Mutations in the LMNA gene, encoding human lamin A/C, have been associated to an increasing number of disorders involving skeletal and cardiac muscle, peripheral nerve and more complex syndromic forms. We have screened a large cohort of patients for mutations in the LMNA gene. Our analysis identified 26 variants, eleven of which had not been previously described. By clustering LMNA mutated patients according to the age at onset of symptoms, we identified some interesting clinical and genetic correlations: (1) Patients with childhood onset displayed mainly neuromuscular disorder with scapuloperoneal distribution, while 63% of patients with onset in or after the third decade presented isolated cardiac dysfunction. These initial differences tended however to decrease with disease progression, as the coexistence of cardiac and skeletal muscle disorders was significant in both groups. Interestingly, the interval between the onset of neuromuscular and cardiac symptoms was correlated to the distribution of muscular weakness. (2) Most early onset patients were sporadic, whereas 75% of the adult-onset cases had a positive family history. (3) Frameshift LMNA mutations occurred almost exclusively in adult-onset patients with cardiopathy, while 93% of infantile cases carried in frame variations. In addition, the distribution of missense substitutions along the gene was different in the two groups. (4) Lamin A/C molecular structure analysis suggested that missense variations could alter either lamin filaments assembly at different levels or interactions with other ligands. These observations lead us to hypothesize that different pathogenetic mechanisms may determine the diverse disease phenotypes in the two groups. Moreover, our data sustain the necessity for a combined neurologic and cardiologic evaluation of patients as soon as LMNA defects are diagnosed, especially because the risk of sudden death due to malignant ventricular arrhythmias is high and symptoms may be underestimated.