Protein aggregate myopathies

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PROTEIN AGGREGATE MYOPATHIES

Muscle disorders morphologically defined by the presence of protein aggregates in muscle cells.
PAM

- Hereditary (AD; X-linked; AR) or sporadic (IBMs)
- Marked clinical and genetic heterogeneity
- Onset from the neonatal period to late adulthood
- Both sexes
- Pleomorphic clinical presentation:
  - congenital myopathies
  - scapuloperoneal and oculopharyngeal phenotypes
  - distal, limb girdle, generalized patterns of muscle weakness
Protein aggregate myopathies – why do they occur?

Disturbances in the systems responsible for:
- Folding of proteins
- Refolding (molecular chaperones)
- Degradation of misfolded proteins

**External stresses**
- Mutations

**Native quaternary structure**

**Native**

**Misfolded protein**

**Dimer nm**

**Oligomer <0.1µm**

**Linear/ordered aggregates**
- 0.1-100µm

**Amorphous/disordered aggregates**
- 0.1-100µm

**Visible protein aggregates**
- >100µm

**Protein aggregate myopathies – why do they occur?**
### Proteins/Genes associated with PAMs

<table>
<thead>
<tr>
<th>Localisation</th>
<th>Protein</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myofibrillar apparatus</strong></td>
<td>a-actin</td>
<td>ACTA1</td>
</tr>
<tr>
<td></td>
<td>myosins</td>
<td>MYH2; MYH7</td>
</tr>
<tr>
<td></td>
<td>titin</td>
<td>TTN</td>
</tr>
<tr>
<td></td>
<td>filamin C</td>
<td>FLNC</td>
</tr>
<tr>
<td></td>
<td>myotilin</td>
<td>MYOT</td>
</tr>
<tr>
<td></td>
<td>Protein cypher</td>
<td>ZASP</td>
</tr>
<tr>
<td></td>
<td>Bag3 (Bcl-2–associated athanogene-3)</td>
<td>BAG3</td>
</tr>
<tr>
<td></td>
<td>FHL1</td>
<td>FHL1</td>
</tr>
<tr>
<td><strong>Filamentous extra-sarcomeric network</strong></td>
<td>Desmin</td>
<td>DES</td>
</tr>
<tr>
<td></td>
<td>Plectin</td>
<td>PLEC</td>
</tr>
<tr>
<td></td>
<td>αB-crystalline</td>
<td>CRYAB</td>
</tr>
<tr>
<td><strong>Proteins involved quality control</strong></td>
<td>VCP</td>
<td>VCP</td>
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<tr>
<td></td>
<td>DNAJB6</td>
<td>DNAJB6</td>
</tr>
<tr>
<td></td>
<td>BAG-3</td>
<td>BAG3</td>
</tr>
<tr>
<td></td>
<td>αβ-crystallin</td>
<td>CRYAB</td>
</tr>
<tr>
<td><strong>Enzymes</strong></td>
<td>GNE</td>
<td>GNE</td>
</tr>
<tr>
<td><strong>DNA-binding proteins</strong></td>
<td>PABPN1</td>
<td>PABPN1</td>
</tr>
</tbody>
</table>
Morphological aspects of PAM

PAM are morphologically heterogeneous

2 main subgroups:

➢ Myopathies with sarcoplasmic and/or nuclear protein aggregates
➢ Myofibrillar Myopathies (+frequent)
Myopathies with sarcoplasmic or nuclear aggregates

• Desmin-negative inclusions
  (e.g., thin filaments, caps, rods, zebra bodies, hyaline bodies, tubulo-filamentary inclusions)

OPMD
Myofibrillar Myopathies (MFM)

- **Desmin-positive** sarcoplasmic aggregates

- Degenerative changes of the myofibrillar structure:
  - myofibrillar disorganization beginning at the Z-disk
  - accumulation of myofibrillar degradation products
  - ectopic expression of multiple proteins

- With or Without Intracytoplasmic vacuoles
Abnormally accumulated proteins

- Cytoskeletal and Sarcomeric
- Autophagy markers
- Ubiquitin-proteasome system
- Others...
- Neuronal proteins
- Kinases
- Nuclear
- Intermediate filaments
- DESMIN
- Alzheimer-disease-related
- Oxidative and nitrosative stress
- Chaperones

MFM
Immunohistochemical study

Z-disc proteins

- filamin C
- myotilin
- ZASP
- XinR
- XinC
- XIRP2
- α-actinin
- myopodin (central)
- myopodin (N-term.)
- tritopodin
- titin
Immunohistochemical study
Z-disc associated, M-band and other proteins

desmin  $\alpha$-crystallin  M-protein  myomesin

NCAM  gelsolin
## Genes causing MFM

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Class</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmin</td>
<td>DES</td>
<td>Intermediate filament</td>
<td>Skeletal, Cardiac, smooth m,</td>
</tr>
<tr>
<td>aB-crystalline</td>
<td>CRYAB</td>
<td>Small heat-shock protein</td>
<td>Skeletal, Cardiac, lens, kidney, lung</td>
</tr>
<tr>
<td>Myotilin</td>
<td>MYOT</td>
<td>Sarcomere protein</td>
<td>Skeletal, Cardiac</td>
</tr>
<tr>
<td>Protein cypher</td>
<td>ZASP</td>
<td>Sarcomere protein</td>
<td>Skeletal, Cardiac</td>
</tr>
<tr>
<td>BAG3</td>
<td>BAG3</td>
<td>BAG family</td>
<td>Skeletal, Cardiac, smooth m.</td>
</tr>
<tr>
<td>Filamin C</td>
<td>FLNC</td>
<td>Filamin family</td>
<td>Skeletal, Cardiac</td>
</tr>
<tr>
<td>FHL1</td>
<td>FHL1</td>
<td>FHL family</td>
<td>Skeletal, Cardiac</td>
</tr>
<tr>
<td>Titin</td>
<td>TTN</td>
<td>Third filament system</td>
<td>Skeletal, Cardiac</td>
</tr>
<tr>
<td>Plectin</td>
<td>PLEC *</td>
<td>Intermediate filament</td>
<td>Skeletal, Skin</td>
</tr>
<tr>
<td>DNAJB6</td>
<td>DNAJB6 *</td>
<td>DNAJ family</td>
<td>Skeletal, Brain</td>
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<tr>
<td>α-actin</td>
<td>ACTA1 *</td>
<td>thin filament</td>
<td>Skeletal, Cardiac</td>
</tr>
<tr>
<td>HSPB8</td>
<td>HSPB8 *</td>
<td>Small heat-shock protein</td>
<td>Skeletal muscle, heart, placenta</td>
</tr>
</tbody>
</table>

*New MFM disease genes
MFM – Clinical aspects

- **Onset:** from infancy to late adulthood
- **Clinical features:**
  - Progressive distal to proximal weakness or LGMD pattern (25%)
  - Respiratory failure
  - Cardiomyopathy (50%)
  - CK: Normal, or Elevated < 5x
DESMINOPATHY

AR, AD, de novo
Mean age at onset **32 years**

- Distal lower limb weakness
- Proximal weakness (LGMD like)
- Scapulo-peroneal

- Cardiomyopathy (75%)
- Respiratory insufficiency

- Trunk, neck and bulbar weakness
Desmin mutations

Clemen CS, Herrmann H, Strelkov SV, Schröder R.
Functional analysis of mutant desmin

DES (missense mutation p.S21)
DES (missense mutation p.S21)
**DES** (missense mutation p.S21)
DES (missense mutation p.S21)
αB-CRYSTALLINOPATHY

CRYAB, 11q22.3q23.1

• AD, AR (infantile)
• Mean age at onset 36.8 years
• Onset: Distal to proximal weakness or cardiac failure
• Trunk, neck and bulbar
• Respiratory insufficiency
• Cardiomyopathy

HSP with chaperone-like activity – prevents protein aggregation, inhibits apoptosis
Major role in keeping the intracellular architecture
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0137973
CRYAB p.Arg120Gly
CRYAB p.Arg120Gly
CRYAB p.Arg120Gly
ZASP related myopathy

ZASP, 10q22-q23.3
• Autosomal dominant/sporadic
• Age at onset: 40-73 (mean 59)
• Early involvement of hand muscles
• Distal/proximal weakness lower limbs
• Cardiomyopathy in some patients
ZASP mutation p.A165V
ZASP mutation p.A165V
Titin

• **skeletal and cardiac muscles**

• located in the sarcomere

• from the Z-disc to M-line

• maintenance of the sarcomere structure during contraction
TTN - muscle diseases and phenotypes

• Late-onset autosomal dominant tibial muscular dystrophy (TMD) (MIM #600334),
• Limb-girdle muscular dystrophy type 2J (LGMD2J; MIM#608807)
• **Hereditary myopathy with early respiratory failure (HMERF;MIM #603689)**
• Early-onset myopathy with fatal cardiomyopathy, EOMFC(MIM #611705)

• Congenital Centronuclear Myopathy (CNM)
• Multi-minicore Disease with Heart Disease (MmD-HD) including clinical variations
• Young adult onset AR distal titinopathy
• Early onset AR Emery-Dreifuss-like without cardiomyopathy
• Adult onset AR proximal lower limb muscular dystrophy

Skeletal muscle disease mutations in titin

FIGURE 6. Histochemistry from P21, Group 4 (HMERF)
FIGURE 5. Electron microscopy studies from Group 3 (AR-DM). (A) P15. Loss of myofilaments with M-line dissolution (in ...
Digenic inheritance

TIA1 variant drives myodegeneration in multisystem proteinopathy with SQSTM1 mutations

Myopathy With SQSTM1 and TIA1 Variants: Clinical and Pathological Features

Zhiyu Niu, Carly Sabine Pontefex, Sarah Berini, Leslie E. Hamilton, Elie Naddaf, Eric Wieben, Ross A. Aleff, Kristina Martens, Angela Gruber, Andrew G. Engel, Gerald Pfeffer, and Margherita Milone

PMCID: PMC5824866
PMID: 29457785
**FLNC**

- AD
- Age at onset: 34-60 (mean 47)
- Proximal weakness
- Neck and trunk involvement
- Winging of scapula
- Cardiomyopathy in 30% of cases
- Respiratory insufficiency in 45% of cases
Biopsie: MS, deltoïde, 19 ans (asymptomatique) FLNC
Biopsie: MS, deltoïde, 19 ans (asymptomatique) FLNC
Biopsie: MS, deltoïde, 19 ans (asymptomatique) FLNC
A novel FLNC frameshift and an OBSCN variant in a family with distal muscular dystrophy
MFM as oligogenic disorders

MFM are starting to be seen as **oligogenic disorders**:

- Variable clinical presentation (combined effect of mutations in different genes)
- Inter- and intrafamilial variability (specific genetic background, sets of phenotype-modifying co-causal mutations (variant burden))
- The concept of non-monogenic inheritance will influence:
  - gene identification
  - genetic testing and counselling
Therapeutic approaches

- Exogenous stress
- Antioxidant (NAC, tocopherols)?
- Protein synthesis
- Aggregate formation
- Antioxidant
  - NAC, Vitamin E?
  - Oxypurinol

- Glucocorticoids?
- 4-phenylbutyrate?
- Geranylgeranylacetone

- HSP activation
  - HSPB1
  - HSPB8
  - alphaBCE
  - HSP90

- Autophagy or UPS degradation
  - Pp242?
  - Rapamycin?
  - AMPK?

- Mitochondrial dysfunctions
  - Anti-apoptotic
    - bcl2 overexpression

References:
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