Muscular dystrophies in Arab countries

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Autosomal Recessive Limb-Girdle Muscular Dystrophies

- Primary and progressive muscle disorders usually affecting predominantly the pelvic and then the scapular girdle.
- Autosomal recessive inheritance.
- 11 genes identified: LGMD 2A-2K
- Pathogenic mechanism leading to muscle necrosis unknown.
- Relation between the different proteins involved remains unknown except for the sarcoglycanopathies.

Historical background

Since 19 century: families with AR DLMD reported in Europe, Japan and USA

1977-83 Clinical, epidemiological and muscle biopsy of Duchenne-like MD affecting both sexes and frequent in Tunisia [Ben Hamida et al]

1987 Cloning of the dystrophin gene: starting point of the molecular study of AR LGMDs [Kunkel et al]

1989-2003 α and γ-SG genes identifications on Tunisian, Lebanese and Algerian families (1992-96)
LGMD 2C, δ-SG gene identification on Brazilian families
LGMD 2E, Miyoshi gene identification (dysferlin) on Palestinian and Tunisian families (1995-96)
Mapping of the gene of LGMD2I on Tunisian family (2001)

High prevalence of AR LGMD in Arab Countries

- High rate of consanguineous marriage: 35-50%
- Large sibship size: 5.3 to 7.4
- Improvement of public health indicator:
  - Decrease of infantile mortality
  - Increase of life expectancy
  - Decrease of malnutrition and infectious diseases
  - Improvement of neurological expertise

Muscular Dystrophies:
- Duchenne muscular dystrophies
- Sarcoglycanopathies
- Miyoshi MD
- LGMD 2B
- LGMD 2I

Congenital Muscular dystrophies
- Hereditary Inclusion Body Myopathies

Sarcoglycans

- N-glycosylated transmembrane proteins
- Exclusively expressed in cardiac and skeletal muscle
- Form a tetrameric complex at the muscle cell plasma membrane.
- Stabilizes association of dystrophin with dystroglycans and contributes to the stability of the plasma membrane.
- Four sarcoglycan genes α, β, γ and δ-SG related to each other structurally and functionally.
- Four distinct genetic forms:
  - LGMD2A: γ-sarcoglycan gene (chr13q).
  - LGMD2B: α-sarcoglycan gene (chr17q).
  - LGMD2C: δ-sarcoglycan gene (chr17q).
  - LGMD2D: β-sarcoglycan gene, (chr5q).

Social and cultural conditions

- Reported Muscle disorders

The Sarcoglycans
The Sarcoglycanopathies

Clinical phenotype

- Early-childhood onset.
- Progressive course.
- Muscle weakness and atrophy affecting pelvic followed by shoulder muscle.
- Frequent calves hypertrophy.
- Variable course between siblings with severe Duchenne-like course (wheelchair-bound before 13) to mild course (patients ambulant later than 16 years).
- High CK rate
- Dystrophic feature on muscle biopsy

Sarcoglycans expression

When 1 mutation is present in one of SG-gene:

- The protein encoded by that gene is usually absent
- Secondary and variable reduction in the other SG

The Sarcoglycanopathies

- Linkage to chromosome 13q12
- Linkage disequilibrium with D13S232 marker.
- 1 out of 20 known mutations found in about 99% of Tunisian patients: del521-T mutation.
- The same mutation was reported in other Arab countries
- 582insA mutation first reported in one Libyan family and found in a Tunisian family

γ-sarcoglycanopathies

LGMD2C Epidemiological Data

- Rare in European population (LGMD2D:LGMD2C 8:2 ratio)
- Most frequent LGMD2 in Tunisia: 81% of sarcoglycanopathies; 75% of all LGMD2
- Similar prevalence than DMD in Tunisia: 1/3500 children
- Reported in: Algeria (Masmoudi 1996; Abzi 1992)
  Morocco (El Kerch 1992)
  Egypt (Hachem 1982)
  Saudi Arabia (Salih and Bohlila)
  Kuwait (Faraj 1989)

α-Sarcoglycanopathy - LGMD 2D

in Arab Countries

LGMD2D: α-sarcoglycan gene (chr17q).

- The most frequent Sarcoglycanopathy in Europe (LGMD2D:LGMD2C 8:2)
- Rarely documented in Arab countries.
- Scarcity of publications in Arab countries populations
- Severe to mild phenotype
- 10% of families in Tunisia.
- Various mutation in Tunisian families without founder effect
- New mutation found in a Tunisian family (1900G>A) out of 108 reported mutations.

β - Sarcoglycanopathy – LGMD 2E

LGMD2E: β-sarcoglycan gene (chr4q).

- Less frequent than LGMD 2D (LGMD2D:LGMD2E=8:4) and more frequent than LGMD 2C (LGMD2D:LGMD2C:LGMD2E=4:2) in outbreed populations
- Small families or isolated patients with widespread geographic origins.
- Reported in only one Tunisian family with homozygous missense mutation (G276T) in exon 3
- Reported in Sudan (Salih et al).
- Absence of sarcoglycan expression in muscle biopsy
- Severe phenotype
The rarest sarcoglycanopathy (1/8 compared to LGMD2D)
- Majority of the patients from Brazil (severe phenotype)

Not reported in Arab countries.

LGMD 2I
- Genetic form first described in Tunisian family (Driss et al. 2001).
- The most frequent LGMD2 in Europe
- Remains rare in Tunisia
- Variable age of onset between 1.5 to 27 yrs
- Proximal limb muscle weakness predominantly affecting the pelvic girdle
- Variable course
- High CK rate
- Muscle biopsy: Dystrophic changes
- Gene: FKRP gene. (allelic to CMD1C).

Unresolved aspects of LGMD 2

Intrafamilial phenotypic variability

Epidemiological repartition: one predominant form (LGMD 2C) and one predominant mutation del521 with founder effect.

Genetic counseling: intrafamilial genetic heterogeneity

Clinical variability between siblings is not related to:
- Age of onset
- Sarcoglycan expressions
- Environmental factors: 75 % of families displayed inter-siblings variability.

Probably related to a modifier gene controlling the severity.

Sarcoglycan subunits expression in LGMD 2C

δ – sarcoglycanopathies - LGMD 2F
- The rarest sarcoglycanopathy (1/8 compared to LGMD2D)
- Majority of the patients from Brazil (severe phenotype)

Not reported in Arab countries.
Epidemiological repartition: one predominant form (LGMD 2C) and one predominant mutation del521 with founder effect

- High prevalence not explainable by mutational rate
- DMD
- Disabling disease incompatible with the presence of patient’s progeny: other forms of sarcoglycanopathies remain rare despite high rate of consanguineous marriages
- Distribution correspond to Arabic flux migration
- Presence of a founder effect # genetic heterogeneity of other sarcoglycanopathies.
- Selective advantage of del521T in γ-SG heterozygote?

Genetic Counseling: Intrafamilial Genetic heterogeneity

Distribution of del 521T mutation in Arab countries

- LGMD2C: Most frequent AR LGMD in Tunisia: 61% of sarcoglycanopathies
- 75% of all LGMD
- 1 out of 20 known mutations found in about 99% of Tunisian patients: del521-T mutation

~ Similar dystrophic changes
~ Distinct sarcoglycan expressions

Genetic linkage

- LGMD 2C markers
- LGMD 2D markers
- LGMD 2B markers
- LGMD 2A markers

Mutation analysis

Involvement of two distinct genes: defects
LGMD 2C (homozygous del521T)
LGMD 2D (homozygous 157G>A)
Phenotypic homogeneity and genetic heterogeneity: How?

- Patients share a common ancestor
- They displayed
  - Similar severe LGMD clinical feature
  - Close dystrophic muscle biopsy findings
- There was variable muscle sarcoglycans expression
- Involvement of two distinct genes defects:
  - LGMD 2C \( (\text{homozygous del525T}) \)
  - LGMD 2D \( (\text{homozygous 157G>A}) \)

Genetic heterogeneity was not an isolated phenomenon

Dys Dys α α SG SG β β SG SG γ γ SG SG Dysf Dysf
Positive staining of dysferlin [branch B]

Dys Dys α α SG SG β β SG SG γ γ SG SG δ δ SG SG Dysf Dysf
Negative staining of dysferlin [branch A]

Phenotypic homogeneity and genetic heterogeneity: What does it mean?

- Two comments:
  - Difficulty of genetic counseling in inbreed populations:
    - Paradigm that patients from the same family sharing the same ancestor and similar phenotype carry the same genetic disorder and the same mutation no more accepted?
    - Need to analyze all affected patients within families before giving genetic counseling.
  - Significance of such association:
    - Coincidental association is the most logical hypothesis
    - But does this hypothesis have statistical basis?

Conclusion (1)

- Arab patients had contributed in the identification of a number of genetic forms of LGMD2.
- Some LGMD2 forms are frequent in Arab populations \( (\gamma \text{SG}) \) whereas others seem to be rare, although the high rate of consanguineous marriage.
- Large predominance of one mutation with a founder effect in the most frequent form \( (\text{LGMD 2C}) \) whereas there are various mutations (family private mutations) in rare genetic forms.

Conclusion (2)

- The basis of this epidemiological pattern remain unknown (selective advantage?).
- Variable phenotypes in patients sharing the same mutation is frequent and could be related to a modifier gene.
- Despite the presence of one predominant mutation, the presence of genetic heterogeneity in consanguineous families complicates the genetic counselling.
- Developing a DNA diagnosis ships including all LGMD2 mutations found in Arab population may be the solution for genetic screening.