

Muscular dystrophies in Arab countries

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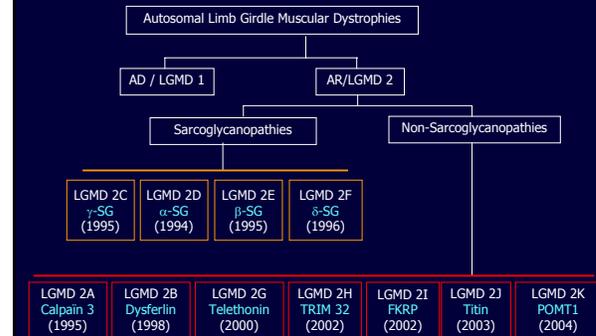
Autosomal Recessive Limb-Girdle Muscular Dystrophies [LGMD2]

- 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 2F δ SG gene identification on Brazilian families
LGMD 2B Myosin gene identification (dysferlin) on Palestinian and Tunisian families (1995-1998)
Mapping of the gene of LGMD2I on Tunisian family (2001)



High prevalence of AR LGMD in Arab Countries

Social and cultural conditions

- High rate of consanguineous marriage; 36 60%
- 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

Reported Muscle disorders

- Muscular Dystrophies:
- Duchenne muscular dystrophies
 - Sarcoglycanopathies.
 - Miyoshi MD, LGMD 2B
 - LGMD 2I
 - Congenital Muscular dystrophies
 - Hereditary Inclusion Body Myopathies

The Sarcoglycans

- 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 :
 - LGMD2C: γ sarcoglycan gene (chr13q).
 - LGMD2D: α sarcoglycan gene (chr17q).
 - LGMD2E: β sarcoglycan gene. (chr4q).
 - LGMD2F: δ sarcoglycan gene. (chr5q).



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

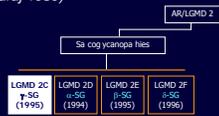


Sarcoglycan expressions in a γ sarcoglycanopathy (LGMD2C)

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 1986; Azibi 1992)
 - Morocco (El Kerch 1992)
 - Egypt (Hachem 1982)
 - Saudi Arabia (Salih and Bohlige)
 - Kuwait (Faraj 1989)



γ -sarcoglycanopathy : LGMD 2C

Molecular genetic findings in Tunisia

- 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

→ Presence of a founder effect

- 582insA mutation first reported in one Libyan family and found in a Tunisian family



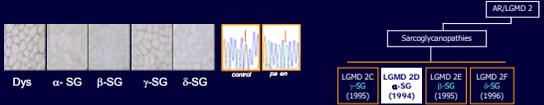
α -Sarcoglycanopathy - LGMD 2D

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 (190G>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=8/2) in outbred populations (26 reported mutations).
- 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



δ – sarcoglycanopathies - LGMD 2F

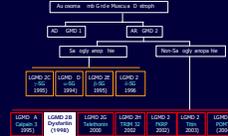
- The rarest sarcoglycanopathy (1/8 compared to LGMD2D)
- Majority of the patients from Brazil (severe phenotype)

Not reported in Arab countries



LGMD 2B/Dysferlinopathy Miyoshi Muscular Dystrophy

- 1987 Report of a distal muscular dystrophy in Japan.
- 1992 Report of one Palestinian family with mild course AR LGMD
- 1995 Linkage of MM to chr. 2p12 in one Tunisian family (Bejaoui *et al.*)
Linkage of LGMD 2B on chr. 2p12 (Bashir *et al.*)
- 1998 Identification of the LGMD 2B gene (Bashir *et al.*)
and of MM (Liu *et al.*): the dysferlin gene, 55 exons
Mutations identified in Palestinian families and not yet in
Tunisian families



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
- Linkage to chr. 19q13.3
- Gene : FKRP gene. (allelic to CMD1C).



Unresolved aspects of LGMD 2

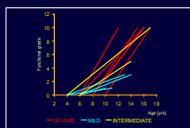
Intrafamilial phenotypic variability

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

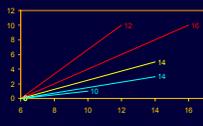
Genetic counseling : intrafamilial genetic heterogeneity

Intrafamilial phenotypic variability

Phenotypic distribution of LGMD 2C deltaT521 patients (128 patients)



	Nb patients	Age exam.	Age onset	Age WCB
Severe	46.9% (n=52)	20.8 ± 7.2	6.1 ± 2.4	14 ± 2.1
Intermediate	28.8% (n=33)	23.8 ± 6.9	6.0 ± 2.4	17.8 ± 3.3
Mild	24.2% (n=32)	21.6 ± 9.9	6.2 ± 2.4	22.7 ± 8.5
Total	100%	21.9 ± 8.0	6.1 ± 2.4	16.3 ± 4.9

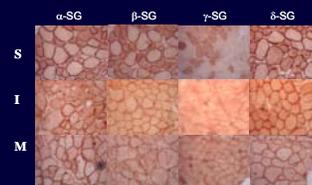


Age	18	6	29	34	32	26
Onset	5	3	6	9	8	9
WCB	13	13	13	24	25	17
SSC	S	M	S	I	I	S

Intrafamilial phenotypic variability

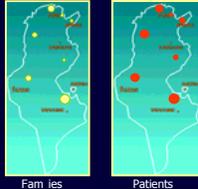
- Clinical variability between siblings is not related to:
 - Age of onset
 - Sarcoglycan expressions
 - Environmental factors: 75 % of families displayed inter siblings variability.
- Probably related to a modifier gene controlling the severity.

Sarcoglycan subunits expression in LGMD 2C



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

Distribution of del521T mutation in Arab countries



- LGMD2C: Most frequent AR LGMD in Tunisia: 81% of sarcoglycanopathies 75 % of all LGMD2
- 1 out of 20 known mutations found in about 99% of Tunisian patients: del521-T mutation



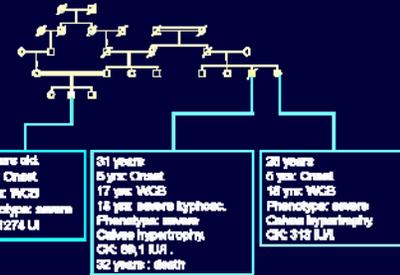
One predominant form (LGMD 2C) and one predominant mutation del521 with founder effect



- 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 ?

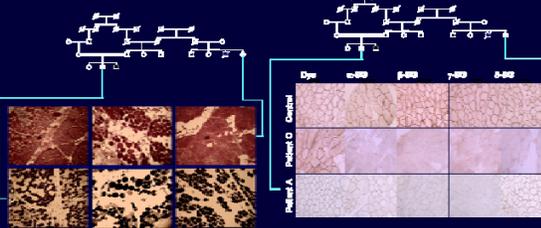
Genetic Counseling: Intrafamilial Genetic heterogeneity

Genetic Counseling: Intrafamilial Genetic heterogeneity



Muscle biopsy: histoenzymological staining

Muscle biopsy: immunostaining

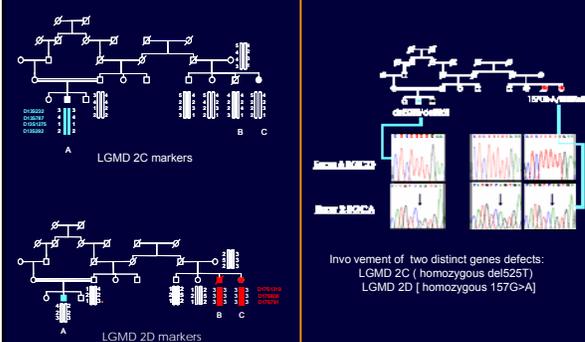


Similar dystrophic changes

Distinct sarcoglycan expressions

Genetic linkage

Mutation analysis



Phenotypic homogeneity and genetic heterogeneity : How?

Patients share a common ancestor

They displayed

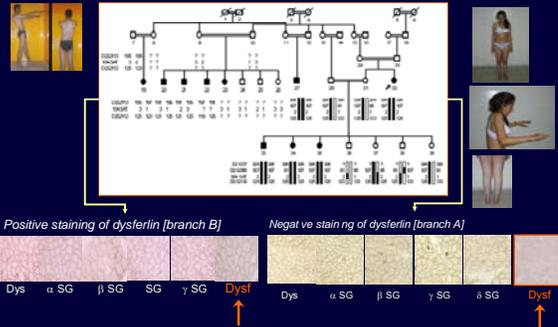
- Similar severe LGMD clinical feature
- Close dystrophic muscle biopsy findings

There was variable muscle sarcoglycans expression

Involvement of two distinct genes defects:

- LGMD 2C (homozygous del525T)
- LGMD 2D [homozygous 157G>A]

Genetic heterogeneity was not an isolated phenomenon



Phenotypic homogeneity and genetic heterogeneity :
What does it mean ?

Two comments:

1. 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 .
2. 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 (γ 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 (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 counseling.

Developing a DNA diagnosis ships including all LGMD2 mutations found in Arab population may be the solution for genetic screening.