A general overview of Limb-Girdle Muscular Dystrophies

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Introduction

Limb-Girdle Muscular Dystrophy (LGMD) is a progressive inherited disorder characterized by progressive muscular weakness that affects the voluntary muscles, mainly around the pelvic and shoulder regions.

Aims

- Acquire a general knowledge of what is a LGMD.
- Know the different LGMD forms and their major features.
- Name the different genes and proteins that are involved in the LGMDs.
- Explain the current clinical trials and gene therapy used in LGMDs with good perspectives.
- Explain the different existing animal models applied in LGMD.

The major features and model animals in LGMDs

Autosomal recessive forms							
Disease	**Gene locus**	**Affected gene**	**CK level**	**Cardiac complications**	**Respiratory complications**	**Clinical onset**	**Mouse model**
LGMD2A	15q15-q21	CAPN3	Very high	×	✓	Childhood	Capn3$^{-/-}$
LGMD2B	2p13	DYSF	Extremely high	×	×	Early adulthood	SJL
LGMD2C	13q12	SGCG	Very high	✓	✓	Childhood	Sgcg$^{-/-}$
LGMD2B	17q12-q31	SGCA	Very high	✓	✓	Childhood	Sgca$^{-/-}$
LGMD2E	4q12	SGCB	Very high	✓	✓	Childhood	Sgcb$^{-/-}$
LGMD2F	5q33-q34	SGCD	Very high	✓	✓	Childhood	Sgcd$^{-/-}$
LGMD2G	17q11-q12	TCAP	Very high	✓	×	Childhood	-
LGMD2H	9q31-q34	TRIM32	Very high	×	×	Young adult	-
LGMD2I	19q-13	FKRP	Very high	✓	✓	Variable	-
LGMD2J	2q24.3	TTN	Greatly elevated	✓	✓	Childhood	-
LGMD2K	9q34.13	POMTI	Extremely high	×	×	Childhood	-
LGMD2L	11p14.3	ANO5	Greatly elevated	✓	✓	Adulthood	-
LGMD2M	9q31.2	FKTN	Extremely high	×	×	Variable	-
LGMD2N	14q24.3	POMT2	Extremely high	×	×	Childhood	-

Table 1. The different autosomal recessive forms of LGMDs with the major features and their belonging animal model.

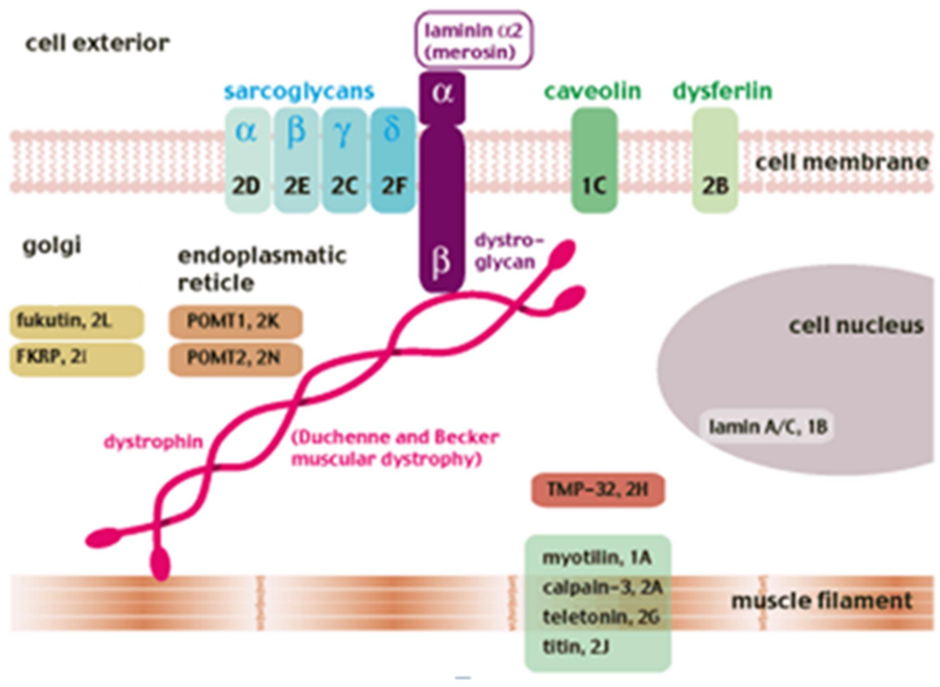

Figure 1. Localization of the different proteins in the dystrophin associated glycoprotein complex (DGC) that are involved in LGMD forms[4].

Autosomal dominant forms							
Disease	**Gene locus**	**Affected gene**	**CK level**	**Cardiac complications**	**Respiratory complications**	**Clinical onset**	**Mouse model**
LGMD1A	5q31	MYOT	Moderately raised	×	×	Adulthood	TgT57I
LGMD1B	1q11-21	LMNA	Moderately raised	✓	✓	Childhood - adult	Lmna$^{-/-}$
LGMD1C	3p25	CAV3	Moderate to very high	×	×	Variable	Cav3$^{-/-}$
LGMD1D	6q23	-	Normal or mildly elevated	✓	✓	Early adulthood	-
LGMD1E	7q	-	Normal or mildly elevated	×	×	Variable	-
LGMD1F	7q31.1-q.32.2	-	Normal or mildly elevated	×	✓	Variable	-

Table 2. The different autosomal dominant forms of LGMDs with the major features and their belonging animal model.

Gene therapy and clinical trials

- Stem cell transplantation therapy to enhance the regenerative ability of damaged and degenerating muscle cells in patients →Different LGMD forms.
- Artificial microRNA vector (miMYOT) to knockdown mutant MYOT in muscles of a LGMD1A mouse model (TgT57I) →LGMD1A.
- restore the α-sarcoglycan using adeno-associated virus serotype1 (AAV1) to transfer the alpha-sarcoglycan gene (SGCA) →LGMD2D.
- Proteasomal inhibition restores function of mis-sense mutated dysferlin →LGMD2B.

Conclusions

- No curative treatment.
- Necessity of monitoring these patients to avoid some cardiac and respiratory complications.
- Follow a specific exercise program to avoid contractures, deformations and maintain the upright position.
- Offer psychological treatment in some cases.
- There are promising clinical trials, gene therapy strategies and animal models.

Relevant bibliography

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