Patient information leaflet on new names for LGMD

New names for limb girdle muscular dystrophies

Recently, the naming system (nomenclature) of limb girdle muscular dystrophies has changed. This paper describes why this was deemed necessary and what the changes are. At the end, we will address the consequences for people that already have a confirmed diagnosis of a specific type in the old system.

The old system

The term 'limb girdle muscular dystrophy' (LGMD) is used for the first time in 1954 by two British neurologists, Walton and Natrass. Both were experts on neuromuscular diseases. However, LGMD became a recognized disease name only after the development of molecular-genetic research, resulting in the discovery of several genes related to specific types of LGMD. A simple naming system was chosen to distinguish the LGMD types: LGMD1 represented the autosomal dominantly inherited types (one of the parents has the gene defect and children have a 50% chance of inheriting the disease) and LGMD2 the autosomal recessively inherited types (both father and mother need to have the gene defect to pass it onto their children, children have a 25% of inheriting the disease). Specific gene defects were assigned a letter of the alphabet in the order that they were discovered, for example, LGMD2A was caused by a gene defect in the calpain 3 gene and was the first recessive gene (hence the 2) defect to be discovered (hence the A).

The end of the alphabet is reached: a workshop on how to proceed

In the last decades, a large number of gene defects were found, resulting in the fact that the last letter in the alphabet was reached with the discovery of LGMD2Z. To solve the problem how to name the next discovered gene defect, an international workshop was organized in 2017 by the European NeuroMuscular Centre (ENMC). Another reason for the workshop was that over time, diseases were included that are actually no LGMDs. For instance, Pompe disease also received a LGMD name (LGMD2V), whereas it is now known that this disease is not a muscular dystrophy but a metabolic disease.

A new definition of limb girdle muscular dystrophy

The experts who participated in the workshop started with the formulation of a definition of limb girdle muscular dystrophy (LGMD), since this did not exist yet. At the end of the workshop, agreement was reached about the following:

"Limb girdle muscular dystrophy is a hereditary disease that leads to progressive (over time increasing) muscle weakness of especially the proximal muscles (shoulder and pelvic girdle, upper arms and thighs). The term LGMD can only be assigned when a specific type is

described in at least two non-related families, if it concerns patients that have acquired the ability to walk (so they do not have the muscle disease starting from birth), if the activity of the muscle enzyme Creatine Kinase is elevated, when degenerative changes (cells look different compared to healthy tissue) are found in the muscle biopsy or if muscle tissue is replaced by fatty tissue, which is visible on MRI."

All current subtypes of LGMD were carefully evaluated for their compliance to the definition. If not, they were removed from the list. Five diseases that were not yet part of the LGMD family but appeared to fulfill the criteria, were added to the list..

New names

At the workshop, the experts and patient representatives have extensively discussed the naming system, in order to establish a more logical system. Finally consensus was reached on the following: LGMD is followed by the letter "D" when the disease is inherited in an autosomal dominant manner and by an "R" if it is inherited in a recessive manner. Subsequently, the disease is given a number in the order in which the disease is discovered over time and finally, the name of the protein that is not or incorrectly produced. To give some examples: the name "LGMD D5 collagen6-related" stands for the disease that we currently know as Bethlem MD and which is caused by a mutation in the collagen6 gene, leading to a shortage of the collagen6 protein. "LGMD R3 calpain3-related" stands for LGMD caused by mutations in the calpain3 gene and "LGMD R3 alpha-sarcoglycan-related" for LGMD as a result of mutations in the alpha-sargoclycan gene.

The advantage of still having a number is that some genes have unpronounceable names (such as 2-C-methyl-D-erythritol 4-phosphate). The advantage of having the protein name in the disease name is that even for physicians it was difficult to remember which number was related to which gene, so now it is part of the name. The reason to use the name of the affected protein and not of the gene where the mutation exists is that protein names have proven to be more stable over time as compared to gene names.

Consequences of the new names

During the workshop, where also patient representatives were present, the consequences for patients were extensively discussed. For instance, some patients who were diagnosed with LGMD, now suddenly learn that they do not have LGMD anymore. This can be psychologically challenging. Therefore, it is important to stress that you do not have to switch to the new name. The old name can still be used. There is an international database, called OMIM (www.omim.org) in which all names ever assigned to a disease are listed. It will also take some time before everyone gets used to the new names. As a result old and new names will be used simultaneously for quite some time in the near future. However, you can easily see whether the old name or the new name is used: if it starts with a letter, the new name is used, if it starts with a number, the old name is used. The new names may cause confusion when for instance looking for fellow patients, for instance on social media. New patients may hear only the new name and already existing patients may not know that this new name is the same as their own diagnosis. That is why it is important that you know

about the new names, how they were established and how they differ from the old names. For patients whose disease is no longer a LGMD but an other type of disease: please realize that the variation in the disease that they are now part of can be very large as well and therefore you may have the feeling that you do not fit into the description of that disease. The reason why you are part of the other disease now is that you share a defect in the same gene as the other disease. However, symptoms may vary considerably between different mutations of the same gene and exactly this was the reason why some types were misdiagnosed as LGMD. And remember: if you do not feel at home with the new disease, just continue to use you old diagnosis.

Tabel 1. Overview of old and new names of LGMD-subtypes

Old name	Protein	New name	Reason why it is not a LGMD or a New LGMD subtype
Autosomal dominant LGMD			
LGMD 1A	*Myot*	Myofibrillar myopathy	Not LGMD: Mainly weakness of the lower legs
LGMD 1B	*LMNA*	Emery-Dreifuss muscular dystrophy	Not LGMD: High risk on heart rhythm disorders, muscle weakness not according to the LGMD pattern
LGMD 1C	*CAV3*	Rippling muscle disease	Not LGMD: Most important symptoms are rippling muscles and muscle pain
LGMD 1D	*DNAJB6*	LGMD D1 DNAJB6-related	
LGMD 1E	*DES*	Myofibrillar myopathy	Not LGMD: Mainly weakness of the lower legs and cardiomyopathy
LGMD 1F	*TNP03*	LGMD D2 TNP03-related	
LGMD 1G	*HNRNPDL*	LGMD D3 HNRNPDL-related	
LGMD 1H	Gene not known	-	Not LGMD: Is described in one family only
LGMD 1I	*CAPN*	LGMD D4 Calpain3-related	*New*
Autosomal recessive LGMD			
LGMD 2A	*CAPN*	LGMD R1 Calpa¡n3-related	
LGMD 2B	*DYSF*	LGMD R2 Dysferlin-related	

Old name	Protein	New name	Reason why it is not a LGMD or a New LGMD subtype
LGMD 2C	*SGCG*	LGMD R5 Gamma-sarcoglycan-related	The order of these LGMD diseases has changed for logical reasons: alpha, bèta, gamma, delta now have consecutive numbers
LGMD 2D	*SGCA*	LGMD R3 Alfph-sarcoglycan-related	
LGMD 2E	*SGCB*	LGMD R4 Bèta-sarcoglycan-related	
LGMD 2F	*SGCD*	LGMD R6 Delta-sarcoglycan-related	
LGMD 2G	*TCAP*	LGMD R7 Telethonin-related	
LGMD 2H	*TRIM32*	LGMD R8 *Tripartite motif containing protein* 32-related	
LGMD 2I	*FKRP*	LGMD R9 Dystroglycan-related	
LGMD 2J	*TTN*	LGMD R10 Titin-related	
LGMD 2K	*POMT1*	LGMD R11 Dystroglycan-related	
LGMD 2L	*ANO5*	LGMD R12 Anoctamin5-related	
LGMD 2M	*FKTN*	LGMD R13 Dystroglycan-related	
LGMD 2N	*POMT2*	LGMD R14 Dystroglycan-related	
LGMD 2O	*POMGnT1*	LGMD R15 Dystroglycan-related	
LGMD 2P	*DAG1*	LGMD R16 Dystroglycan-related	
LGMD 2Q	*PLEC*	LGMD R17 Plectin-related	
LGMD 2R	*DES*	Myofibrillar myopathy	Weakness of the distal limb muscles (lower leg, forearm)
LGMD 2S	*TRAPPC11*	LGMD R18 TRAPPC11-related	
LGMD 2T	*GMPPB*	LGMD R19 GDP-mannose pyrophosphorylase-related	
LGMD 2U	*ISPD*	LGMD R20 2-C-methyl-D-erythritol 4-phosphate cytidylyltransferase-like protein-related	
LGMD 2V	*GAA*	Pompe disease	Not LGMD: metabolic disease
LGMD 2W	*PINCH2*	PINCH-2 related myopathy	Is described in one family

Old name	Protein	New name	Reason why it is not a LGMD or a New LGMD subtype
			only
LGMD 2X	*BVES*	BVES-related myopathy	Is described in one family only
LGMD 2Y	*TOR1AIP1*	TOR1AIP1-related myopathy	Is described in one family only
LGMD 2Z	*POGLUT1*	LGMD R21 *POGLUT1*-related	
Bethlem myopathy recessive	Collagen-6	LGMD R22 Collagen 6-related	*New*
Bethlem myopathy dominant	Collagen-6	LGMD D5 Collagen 6-related	*New*
Laminin α2-related muscular dystrophy	LAMA2	LGMD R23 Laminin α2-related	*New*
POMGNT2-related muscular dystrophy	POMNGT2	LGMD R24 POMNGT2-related	*New*

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