1. Introduction

Historically, the classification and nomenclature of diseases has not been systematic and diseases were either classified by cause, presenting symptoms and signs, pathological features and organs involved, or they were named after the experts that first described them. An improved understanding of pathomechanisms, the identification of disease genes and an increase in the number of distinct disease entities led to nosological coding systems that are regularly updated and revised. On the one hand, there is a real need to revisit the nomenclature and classification systems of diseases and to update them according to new findings and coding standards; on the other hand, a change in disease names can be confusing for healthcare professionals and affected patients.

The constant increase in the characterisation of new disease genes for rare neuromuscular diseases illustrates the need for improved classification systems and the limb girdle muscular dystrophies (LGMD) form a group of diseases for which the current classification has reached its limits and usefulness. A consortium of clinical experts, experts for disease classifications, patients and representatives of patient organisations came together for the 229th ENMC workshop to address the dilemma of the current LGMD classification and to suggest an improved classification system for this heterogeneous group of disease.

The term ‘limb girdle muscular dystrophy’ was introduced to a wider audience in the seminal paper by Walton and Nattrass in 1954 [1]. The authors identified LGMD as a separate clinical entity from the more common forms: X-linked recessive Duchenne muscular dystrophy, autosomal dominant facioscapulohumeral muscular dystrophy (FSHD) and autosomal dominant myotonic dystrophy. In their description, it is pointed out that the category of LGMD most likely comprises a heterogeneous group of disorders. Due to the first molecular genetic characterisation of a number of LGMDs in the late twentieth century, an ENMC consortium reached a consensus on the classification of LGMD subtypes in 1995 [2]. An alphanumeric system was introduced, thereby avoiding imprecise, often lengthy nomenclature in use contemporaneously, e.g. ‘Severe childhood autosomal recessive muscular dystrophy’ (SCARMD) [2]. In the current classification, the number ‘one’ or ‘two’ is assigned depending on the mode of inheritance: dominant or recessive. A letter is assigned based on the order of discovery of linkage assignment to a certain genetic locus or of a new disease gene. As of today more than 30 different genetic subtypes of LGMD have been identified [3]. The latest autosomal recessive condition that has been suggested to be a LGMD has been classified as LGMD 2Z [4]. Like for other inherited conditions that display huge genetic heterogeneity, nomenclature has become a significant problem with the increased speed in which new...
disease genes are discovered, in part incoherent assignments due to published uncurated data and incorrect linkages in some cases. Because of diagnostic techniques such as exome and genome sequencing, it is likely that many more subtypes of LGMD will be identified in the future. Currently, no consensus exists on nomenclature once the current classification exceeds LGMD 2Z. The default nomenclature system applied by the Online Mendelian Inheritance in Man (OMIM) catalogue would assign the name LGMD 2AA to the next characterized autosomal recessive form of LGMD, a classification system that is not supported by the clinical community. Because of this dilemma, it was time to review and modify the current LGMD nomenclature.

With the exception of autosomal inheritance, the more than 30 different LGMD subtypes listed in the current classification system have little in common. The broad, original definition has led to potential inaccuracies over what is considered a form of LGMD [1]. Over the past sixty years, the original clinical definition of LGMD has been useful, but our increased molecular and pathogenetic understanding of LGMD subtypes is beginning to call into question this definition and subsequent classification by phenotype. Phenotypically LGMD subtypes are highly variable in their age of onset, speed of disease progression and overall severity. They do not share a common pathological mechanism that would distinguish them from other forms of muscular dystrophy and progressive limb girdle weakness is not always the leading clinical feature [3,5]. Advances in genetic medicine and the identification of new genetic loci made the nomenclature increasingly difficult for LGMD, as mutations in a number of genes that have been assigned to subtypes of LGMD can also cause allelic conditions presenting with a different phenotype and be more commonly known under a different name [6]. Mutations in the CAV3, DYSF and especially the TTN gene [7] have e.g. also been associated with distal myopathic phenotypes. Several of the LGMDs are dystroglycanopathies that are also associated with a group of congenital muscular dystrophy syndromes, including Fukuyama congenital muscular dystrophy, Muscle–Eye–Brain disease and Walker–Warburg Syndrome [8]. All dystroglycanopathies, whether considered congenital with severe malformations or the milder forms of LGMD that only affect the skeletal muscle, were grouped together due to the recognition that mutations in at least 18 associated genes all interfere with the glycosylation of α-dystroglycan, and thus dystroglycan’s function as a matrix receptor [9]. Understanding the role of dystroglycan and its carbohydrate moieties as a basement membrane receptor will therefore be relevant for therapy development for a large number of diseases beyond the boundaries of traditional classification systems. Because industry is starting to show increased interest in LGMD, it will be important to have clarity about the classification of diseases caused by mutations in the same gene, as this will affect feasibility studies, inclusion criteria for clinical trials and recruitment strategies. Prevalence data for diseases will also be influenced by the nomenclature.

Nomenclature of disease is an important educational topic for both clinicians and patients and serves as a critical nosological reference point. Widely accepted nomenclature should therefore only be changed with caution and by consulting key clinical opinion leaders and patient advocacy groups. Any change of the classification also needs to take more general reforms of nosology into account (e.g. International Classification of Diseases (ICD)). Patients and their families will often have an emotional link with their diagnosis, identifying with the name of their disease. Changes to nomenclature therefore can have distressing effects for the people living with the disease. It is important to take this and other pragmatic concerns for patients into account. Issues that may arise include: re-explanation of diagnosis to relatives, loss of belief in diagnosis, and resubmission of information for claiming of health related benefits.

The aims of the 2nd ENMC workshop on the classification and nomenclature of the LGMDs were:

- To reach consensus on an updated definition of LGMD and to evaluate current subtypes of LGMD by application of the updated definition.
- To review and evaluate suggestions of potential new classifications of LGMD subtypes.
- To reach consensus on the most useful nomenclature and classification of LGMD subtypes that is accurate, scientific and with capacity to accommodate further discoveries of LGMDs.
- To evaluate and discuss potential implications of a new definition or classification of LGMD for patients.

Session 1: Background of the LGMDs and considerations for new nomenclature

Volker Straub presented the historical aspects of the term LGMD, including quotations from the original paper written by Walton and Natras [1]. The suggestions for the nomenclature from the 30th ENMC workshop were outlined with description of the classification of subtypes of LGMDs [2]. The current issues with the nomenclature of the LGMDs were enumerated, with the list of current LGMDs circulated. Variation of the prevalence of subtypes was seen along ethnic and geographic lines based on founder mutations [10–15]. Alexander Murphy relayed some of his experiences from his introduction to LGMD, concluding that the current classification system causes a great deal of confusion amongst non-experts. Education was highlighted as an important aspect to consider in the development of a new classification system, which should be neither too complicated nor oversimplified. Nina Khianishvili presented her experiences of LGMD from Georgia, a country which has limited access to genetic testing.

Vincenzo Nigro presented the differences in results when using online search engines (‘Google’) and searching for LGMD subtypes and other diagnoses. Whether the subtype or the protein name gave more results was highly variable and dependent on the condition, i.e. LGMD 2A is more commonly referred to than ‘calpainopathy’ (23,600 versus 14,800), whereas the converse is true for LGMD 2B and ‘dysferlinopathy’ (20,800 versus 23,000).
1.1. Online genetic resources and rare disease nomenclature organisations

Ségolène Aymé, a member of the steering group for the revision of rare diseases of the ICD 11 and the founder of Orphanet, discussed the importance of standardised ontologies for disease classification systems. The concept of disease is an artificial construction, a word needed for communication purpose between individuals. The term “disease” is a multi-dimensional, granular concept linked to how it is used. This may be as a recognisable set of signs and symptoms (termed ‘the clinical approach’), as an entity due to a unique mechanism (‘the pathophysiological approach’), as an entity with a unique evolution, prognosis, or a specified aetiology, or as an entity defined by how a group responds to a specific treatment. Diseases are defects of biological systems, some of which cluster into families of diseases in either small nodes, or larger nodes. Existing terminologies are purpose driven; examples include SnoMED which is based on the purpose of health management, whereas ICD has a statistical purpose in public health. To be classed as a ‘rare disease’, the prevalence must be below 1 in 2000 of the population. Orphanet provides both an inventory of rare diseases with all synonyms in use, and a multi-hierarchy classification which has been incorporated into the upcoming version of the ICD 11, which is expected to be released in 2018.

The Orphanet classification system is an ontology, which means that the rules for constructing it are explicitly defined to allow a computer to interpret them. Ontologies are essential, as technology can only operate using well-defined objects and rules.

When designing a classification system, it is also important to consider interoperability issues. Humans are capable of understanding differences in terminology, whereas equivalence needs to be established for computers to allow interoperability between networks. Many phenotype terminology projects exist in a large number of specialised areas and three international generalist systems of nomenclature and classification in the field of rare diseases should be respected: OMIM [16] for Mendelian diseases, Human Phenotype Ontology (HPO) [17] for phenotypic traits and Orphanet [18] for clinical entities. These three nomenclatures are complementary, serve different purposes and are interoperable.

Ségolène Aymé explained that Orphanet uses a typology of phenomes (levels) and that diseases are categorised by their group of phenomes (i.e. system disorder or group), followed by the “disorder level” (i.e. disease, malformation syndrome, morphological anomaly or biological anomaly) and then followed by “subtypes”, which are clinically, histopathologically or genetically defined. The ‘Orphanet inventory of diseases’ is an open source with 4,000 downloads per month. It is revised on a monthly basis, based on published articles from expert groups.

Ada Hamosh, the scientific director of OMIM, outlined the organisation and the process of inclusion of new diseases into OMIM. As of November 2016, there were over 23,000 conditions included in the database, which displays both genes and phenotypes. OMIM has details of over 14,700 autosomal genes, 716 X-linked genes, 49 Y-linked genes and 35 mitochondrial genes. The focus of OMIM is Mendelian disease and should not be considered a mutation database. Diseases are only included based on publications and uncertainty of a mutation is represented by the addition of a question mark. In general, the nomenclature used by OMIM reflects the suggestions of their respective disease communities and experts. OMIM will not use gene-symbols in the top line of disease descriptions due to the likelihood of this being superseded by new gene names. Within OMIM there are currently 39 phenotypic series relating to LGMD (e.g. dystroglycanopathies). Several names can be supported on the OMIM website and former names are retained to assist in recognition [19].

Ségolène Aymé detailed the progress of the WHO ICD 11 classification, which has been supported financially by the Japanese hospital association. ICD originally began in 1953 with 139 diseases included and by 1993 ICD-10-M had grown to a list of 14,473 diseases. The goals of the ICD 11 revision were to evolve a multi-purpose and coherent classification for mortality and morbidity. In ICD 10 there were initially only 240 genetic diseases. Currently 4500 rare diseases are included in ICD 11. WHO is currently in a consultation phase of ICD 11 and aims to launch fully in 2018. In ICD 10, LGMD is under the term ‘muscular dystrophy’, in ICD-11 LGMD is planned to be listed as a separate category.

In order to discuss some of the problems faced in changing nomenclature in heterogeneous inherited diseases, Marianne de Visser outlined the history of the nomenclature of the hereditary neuropathies. Hereditary motor sensory neuropathy (HMSN) was first classified by Dyck in 1968 into six types (HMSN 1–6) [20]. In 1980, Thomas and Harding using a nerve velocity threshold of 38 m/s further distinguished HMSN type 1 and 2 into axonal and demyelinating categories [21]. To add to the complexity some genes can cause axonal, demyelinating, or intermediate phenotypes. De novo cases are seen in approximately a fifth of all hereditary neuropathies with 90% of patients having mutations within one of four genes [22–24]. In 2015, a group led by Jean-Michel Vallat proposed a new nomenclature to deal with the extensive clinical and genetic heterogeneity displayed by hereditary neuropathies [25,26]. It was suggested to include the following factors: mode of inheritance, phenotype, demyelinating or axonal, and genetic mutation. Following this proposal, opinions of experts were surveyed by a questionnaire and of the 107/300 respondents, mainly from France, Italy and the USA, 65% supported the updated nomenclature.

2. Common denominators of the LGMDs

2.1. Clinical denominators of paediatric and adult onset LGMDs

As many congenital muscular dystrophies are allelic with subtypes of LGMDs, Anna Sarkozy presented cases from the UK national referral centre for congenital muscular dystrophy. An important group of conditions that can present in
childhood are the dystroglycanopathies, a group of highly heterogeneous conditions, several of which can display the milder phenotype of LGMD and present in late childhood or adulthood (LGMD 2I, 2K, 2M, 2N, 2O, 2P, 2T, 2U). Conditions that present in early childhood, such as laminin α2 chain-related congenital muscular dystrophy (MDC1A), can also display a typical LGMD phenotype of progressive proximal muscle weakness with elevated serum creatine kinase (CK) levels and dystrophic changes on muscle histology, but are currently not classified as LGMD. A particular challenge is that many patients with LGMD may have symptoms under the age of two which are only appreciated retrospectively.

Carsten Bönemann gave an overview of the common factors between some of the LGMDs, exploring what should be considered part of the definition for LGMD (i.e. non-congenital, proximal muscle weakness, dystrophic appearance on histology). Four factors were outlined by him as important in grouping the phenotypes of several of the LGMDs: cardiac involvement, pattern of muscle weakness (distal phenotype), presence of joint contractures, and congenital onset. Some of the LGMDs present with predominately distal weakness at onset (i.e. myotilinopathy, LGMD1A) and only small numbers of patients with these subtypes may present with proximal muscle weakness.

It is important to clearly define to what degree the features of the definition have to be present, as this is relevant for the phenotypic and even intra-familial heterogeneity seen in subtypes of LGMD. The distribution of weakness as a common denominator excludes several conditions with a predominately distal distribution of weakness at onset (i.e. LGMD 1A), a scapuloperoneal pattern (i.e. FHL1-related myopathy), or facial muscle involvement (i.e. FSHD).

Bjarne Udd suggested that there were two definitions of muscular dystrophy which currently exist, a ‘clinical’ definition as with a genetic disease caused by a progressive loss of muscle tissue, and a ‘pathological’ definition based on the histological features of muscle fibre necrosis, regeneration, and an increase in fibrosis and adipose tissue. A study of the LGMD population of patients in Finland (n = 182) found that the gene prevalence was as follows: 61 ANOS5 (LGMD 2L), 33 CAPN3 (LGMD 2A), 32 FKRP (LGMD2I), 15 SGCA (LGMD 2D), 5 TTN (LGMD 2I), 3 DYS (LGMD 2B), 2 GMPPB (LGMD 2T), 2 SGCD (LGMD 2F), 1 SGCG (LGMD 2C), 16 DNAJB6 (LGMD 1D), 12 LMNA (LGMD 1B), 5 were found to have Becker muscular dystrophy. Twenty patients had a LGMD phenotype but were so far genetically unclassified.

Corrado Angelini discussed the phenotypic presentation of both dominant and recessive LGMD, grouping the subtypes into proximal, distal and pseudo-metabolic phenotypes. The importance of incorporating pathophysiology into the classification was discussed, as this is likely to be the most important factor in future clinical trials. Potential common features that could be used include elements of pathophysiology, i.e. sarcolemmal disorders (sarcoglycans and dysferlin) or enzymatic defects (calpainopathy, enzymes involved in α-dystroglycan glycosylation). Several LGMD subtypes were identified that showed both recessive and dominant modes of inheritance and had other classifications, which are more commonly used (i.e. desminopathies).

Maggie Walter discussed genotype/phenotype correlations along with clinical and genetic heterogeneity. As a common feature progressive, proximal limb weakness was emphasised; however, distal and metabolic myopathy phenotypes also exist within the LGMD group. A common denominator throughout LGMD was the progressive loss of muscle tissue. A recent review by John Vissing identified some of the common denominators of the LGMDs, including the metabolic phenotypes, distal phenotypes, cardiomyopathy, arrhythmias, asymmetric involvement, and muscle magnetic resonance imaging (MRI) appearances [27].

2.2. Common LGMD denominators defined by investigations

Histological findings of the LGMD subtypes were discussed by Pascal Lafourè, who pointed out that the morphological term ‘dystrophy’ implies muscle histopathology showing features of necrosis and regeneration, with subsequent adipose and fibrotic tissue generation. Muscle biopsies may also show additional non-specific signs such as fibre atrophy, hypertrophy, and increased inflammation. Examples of a large spectrum of findings from muscle biopsies were discussed.

John Vissing outlined the results of a study from Denmark, which sought to establish the prevalence of LGMD subtypes within the Danish population. Two hundred and eight patients with a LGMD phenotype were reviewed. In Denmark LGMD 2I was the most common subtype (64), followed by LGMD 2L (27), LGMD 2A (21), LGMD 1B (18), LGMD 2D (12), LGMD 2B (8), LGMD 2E (7), LGMD 2C, 2T, 1C, 2N (each with 3), and LGMD 2M and 2U (each with 1). Twenty patients did not have an identified genetic subtype of LGMD [28].

John Vissing discussed that common features of LGMD can also be identified using muscle MRI; however, there is a variation in the selective pattern of muscle involvement depending on when in the disease process images are acquired. The sarcoglycanopathies (LGMD 2C, 2D, 2E, 2F) can be comfortably grouped together in terms of skeletal muscle involvement and MRI appearances. There is a clear discrepancy in the involvement of proximal and distal leg muscles, with the lower leg muscles only being affected and advanced stages of the disease. Other LGMD subtypes have similar MRI appearances with the hamstrings, medial gastrocnemius and soleus muscles commonly affected early (LGMD 2A, 2I, 2L, 2N, 2M, and 2T). The paraspinal muscles are affected in most subtypes of LGMD. A common denominator of many LGMDs is the frequently unaffected gracilis and sartorius muscle. There are however several differences between LGMD subtypes that are evident on MRI and some forms demonstrate asymmetry of affected muscles (i.e. LGMD 2B and 2L).
3. Results from large scale sequencing projects

To define the prevalence of the different LGMD subtypes, experiences from large sequencing projects were outlined [7,29]. Vincenzo Nigro presented results from the Telethon undiagnosed diseases programme, which has to date genotyped 504 undiagnosed patients with LGMD phenotypes. Roughly 43% received a complete molecular diagnosis applying a large gene panel and a further 31.7% had unproven candidate variants. Seven truncating variants were found in the DMD gene in 500 patients with proximal myopathy. Pompe disease (also known as LGMD 2V) was diagnosed in 11 patients. It is highly likely that massive parallel sequencing approaches will become cheaper as technology advances.

Anna Sarkozy presented results from the United Kingdom whole exome sequencing project (10K UK). The group in London had included 100 patients with genetic muscle diseases of unknown origin and identified disease causing mutation in patients with an LGMD phenotype in the MICU1, ISPD, and GMPPB genes. Patients were also sequenced in a European Union Seventh Framework Programme (FP7/2007-2013) project under grant agreement No. 305121 (Neuromics), using 106 samples from families with congenital muscular dystrophy or congenital myopathy. Several patients were identified with mutations in genes that had been assigned to LGMDs (GMPPB, TTN, and TRAPCC1).

Volker Straub presented results from the MYO-SEQ project, a Europe-wide project using whole exome sequencing to diagnose patients with unexplained limb girdle weakness over the age of 10 years and with raised serum CK levels. Over 1000 patients have been sequenced from over 50 centres. In 50% of the patients disease causing variants were identified in a total of 73 known neuromuscular disease genes. In 333 patients, a diagnosis of muscular dystrophy was suggested, 290 of which had mutations in LGMD genes. In the MYO-SEQ project LGMD 2A (77 patients) was the most frequently diagnosed form of LGMD, followed by LGMD 2B (48), LGMD 2L (31), LGMD 2J (25), and LGMD 2D (10). A total of 24 patients were diagnosed with dystroglycanopathies based on pathogenic variants in 5 of the relevant genes (FKRP, POMT1, POMT2, FKTN, and GMPPB).

Carsten Bönneman presented several cases with anti-HMGCR antibodies mimicking LGMD, highlighting this important and potentially treatable differential diagnosis. Eleven patients with LGMD phenotypes and negative gene panels were investigated, six of which were confirmed to have positive anti-HMGCR antibodies. Immune panels should be included when using gene panels to investigate undiagnosed patients.

4. Proposed definition of LGMD

Following initial discussions, a consensus was reached to retain the term ‘LGMD’, and to revisit and clarify the definition. Several features were identified as important to exclude other conditions such as congenital muscular dystrophies and certain myopathies. The proposed definition for LGMD is as follows:

“Limb girdle muscular dystrophy is a genetically inherited condition that primarily affects skeletal muscle leading to progressive, predominantly proximal muscle weakness at presentation caused by a loss of muscle fibres. To be considered a form of limb girdle muscular dystrophy the condition must be described in at least two unrelated families with affected individuals achieving independent walking, must have an elevated serum creatine kinase activity, must demonstrate degenerative changes on muscle imaging over the course of the disease, and have dystrophic changes on muscle histology, ultimately leading to end-stage pathology for the most affected muscles.”

Proximal muscle weakness and genetic inheritance were kept from the original definition as important factors of LGMD. The term ‘genetic’ was chosen to allow for future discoveries of digenic or polygenic LGMDs. To distinguish LGMD from congenital muscular dystrophies, patients must achieve independent walking, this criteria was felt to be superior to setting a defined age limit (i.e. two years). An elevated serum CK activity is seen in almost all LGMD patients in early stages of the disease process and is related to muscle fibre breakdown, which is considered a hallmark of muscular dystrophy. Degenerative changes on muscle MRI are defined as the replacement of skeletal muscle with adipose tissue as detected on standard T1 weighted axial images. Dystrophic changes on muscle histology include fibre necrosis and regeneration together with an increase in fibrosis and adipose tissue. The term ‘end-stage pathology’ refers to progressive replacement with fibro-adipose tissue seen on histological examination and/or the complete replacement of muscle tissue by fat as detected by MRI. For a newly discovered condition to be considered a LGMD, it must fulfil all of the above criteria and be described in at least two unrelated families within published literature.

Once this definition was applied to the current list of LGMD, ten conditions no longer fulfilled the criteria of LGMD (Table 1). It was proposed that these conditions instead be considered by either their more commonly used names (e.g. ‘myofibrillar myopathy’ for LGMD 1E and LGMD 2R caused by mutations in the DES gene) or as stand-alone entities. It is stressed that conditions that are no longer considered LGMD will still have an identity, usually by which they are more commonly referred to and remain unchanged in terms of diagnosis and treatment. The OMIM catalogue and Orphanet nomenclature will also continue to list previously assigned names in their disease nomenclature records.

5. Implications of a new definition and classification system

Andoni Urtizberea relayed the results of a survey in France and neighbouring French-speaking countries from 20/100 experts that were asked in a questionnaire about
Table 1
Comparison of the previous LGMD nomenclature to the proposed classification system after the definition has been applied to the current list of LGMD. Conditions which are no longer considered LGMDs are highlighted in grey with a reason for their exclusion given.

<table>
<thead>
<tr>
<th>Old name</th>
<th>Gene</th>
<th>Proposed new nomenclature</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGMD 1A</td>
<td>Myot</td>
<td>Myofibrillar myopathy</td>
<td>Distal weakness</td>
</tr>
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<td>LGMD 1B</td>
<td>LMNA</td>
<td>Emery–Dreifuss muscular dystrophy (EDMD)</td>
<td>High risk of cardiac arrhythmias; EDMD phenotype</td>
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<td>CAV3</td>
<td>Rippling muscle disease</td>
<td>Main clinical features rippling muscle disease and myalgia</td>
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<td>DNAJB6</td>
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<td>LGMD 1E</td>
<td>DES</td>
<td>Myofibrillar myopathy</td>
<td>Primarily false linkage; distal weakness and cardiomyopathy</td>
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<td>LGMD 1F</td>
<td>TNP03</td>
<td>LGMD D2 TNP03-related</td>
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</tr>
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<td>LGMD 1G</td>
<td>HNRNPDL</td>
<td>LGMD D3 HNRNPDL-related</td>
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<tr>
<td>LGMD 1H</td>
<td>?</td>
<td>Not confirmed</td>
<td>False linkage</td>
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<tr>
<td>LGMD 1I</td>
<td>CAPN</td>
<td>LGMD D4 calpain3-related</td>
<td></td>
</tr>
<tr>
<td>LGMD 2A</td>
<td>CAPN</td>
<td>LGMD R1 calpain3-related</td>
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<td>LGMD 2B</td>
<td>DYSF</td>
<td>LGMD R2 dysferlin-related</td>
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<td>LGMD 2C</td>
<td>SGCG</td>
<td>LGMD R3 γ-sarcoglycan-related&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>LGMD 2D</td>
<td>SGCA</td>
<td>LGMD R3 α-sarcoglycan-related</td>
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<td>TCP1</td>
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<td>LGMD R8 TRIM 32-related</td>
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<td>FKN1</td>
<td>LGMD R13 Fukutin-related</td>
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<td>LGMD 2P</td>
<td>DAG1</td>
<td>LGMD R16 α-dystroglycan-related</td>
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<td>LGMD R17 plectin-related</td>
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<td>TRAPP11</td>
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<td>GMPPB</td>
<td>LGMD R19 GMPPB-related</td>
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<td>ISP1</td>
<td>LGMD R20 ISPD-related</td>
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<td>Pompe disease</td>
<td>Known disease entity, histological changes</td>
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<td>Reported in one family</td>
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<td>BVES</td>
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<td>TORIAIP1</td>
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<td>Reported in one family</td>
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<td>LGMD 2Z</td>
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<td>COL6A1, COL6A2, COL6A3</td>
<td>LGMD R22 collagen 6-related</td>
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<td>Bethlem myopathy dominant</td>
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</table>

<sup>a</sup> Sarcoglycan-related LGMDs rationalised based on order of gene discovery.

their views on the classification of LGMD. Six proposals of new classification systems were provided and interestingly none of the respondents wanted to keep the current classification. The most popular two proposals included the naming of the affected protein together with the mode of inheritance (n = 8 in each group). A letter from Michel Fardeau, one of the founders of myopathy in France and involved in the characterisation of many LGMD subtypes, outlined how he strongly opposed the current classification and felt it was opaque. He made several recommendations of features that could be included in the new classification.

5.1. The patient view

Changing the established nomenclature and classification system for a large group of diseases will of course have implications for patients and families that are affected by that change. For the workshop discussion, it was therefore important to hear the patient voice, represented by patients diagnosed with LGMD and participants from patient organisations. Several important points were made by the patients and patient organisation representatives. It was emphasised that patients and patient organisations need to be informed about the change in the diagnostic nomenclature and that the
underlying reasons for the change have to be clearly stated and explained. It was felt that re-defining the LGMDs should not merely be an academic exercise, but needs to be justified and understandable to patients. An important consideration is that changing of terminology can have disability welfare funding implications. Any change in nomenclature should be driven by improving care and should also consider the importance of engaging pharmaceutical companies to invest in LGMD. Views were heard from patient organisation representatives and also from a patient group on social media. Some felt that changing the name or classification system could lead to confusion and fragmentation of existing patient communities. Other views included the importance of containing as much detail as possible to allow patients to explain their condition to family and other non-experts.

6. Proposed new LGMD classification

Several different methods of classification of sub-types were discussed, these ranged from replacing the number in the original system with a letter, followed by number (i.e. LGMDA1, LGMDA2, etc. for dominant disease and LGMDB1, B2, etc. for recessive diseases), to adding in more phenotypic features into the name. Consensus was reached on the most important elements to be included.

Due to the importance of genetic counselling, which should be included at diagnosis and revisited as required, it was felt to be important to include the mode of inheritance; this would be represented by the letter ‘D’ for dominant or ‘R’ for recessive, although not currently relevant, the letter ‘X’ would represent the discovery of an X-linked LGMD. In order to facilitate research and to avoid misconceptions it was decided to include details of the affected protein of the LGMD (i.e. Calpain3-related) this allows grouping of LGMDs into cohorts with similar affected proteins and phenotypes for clinical trials. A number will also be assigned based upon the order of discovery of the affected protein; this reflects the history of the LGMDs and allows better differentiation between subtypes. The consortium was aware that assigning numbers based upon the order of discovery may not always be straightforward, as a precise date can be difficult to identify. Due to the wide ethnic variations and large populations in which subtype prevalence has not been fully identified (i.e. China), it was decided not to assign numbers based upon the prevalence of the subtype. The proposed subtype classification therefore follows the formula:

“LGMD, inheritance (R or D), order of discovery (number), affected protein”

An example of this would be: “LGMD R1 Calpain3-related”. See Table 1 for a list of the LGMDs under the proposed definition and classification.

Several of the dystroglycanopathies exhibit a broad clinical phenotype; the majority of patients affected may not fulfil the criteria of the new definition. A consensus was reached on the central importance of α-dystroglycan as a major extracellular matrix receptor and its involvement in muscular dystrophies in general. In light of this, the dystroglycanopathies were retained in the proposed LGMD classification. A decision was made to rationalise the sarcoglycanopathies into alphabetical order as these were previously given numbers based on the date of the discovery of the gene rather than the affected protein.

A considerable group of patients with Bethlem myopathy and milder laminin α2-related muscular dystrophies fulfil the proposed definition of LGMD and have therefore been included as a subtype of LGMD. It was felt that by including these diseases, clinicians will be more inclined to consider them as part of the LGMD differential diagnosis, especially when patients primarily present with limb girdle weakness and an elevated serum CK activity. Another dystroglycanopathy that has been reported to present with a LGMD phenotype, but so far had not been listed in the previous classification, is caused by mutations in the POMGNT2 gene [30]. This form of autosomal recessive LGMD has now been added to the LGMD subtypes (Table 1).

It is suggested that if a patient fulfils the above proposed definition of LGMD with no known pathogenic gene identified, until diagnosis confirmed they should be referred to as ‘LGMD unclassified’. Despite aiming for a robust classification system, workshop participants were aware that there will always be exceptions to the rule and that mutations in LGMD genes may lead to phenotypes that would not meet the suggested criteria of the revised LGMD definition. Due to genetic, epigenetic or environmental modifiers or mutations in more than one known disease gene, patients with clear pathogenic variants in LGMD genes will occasionally show a phenotype deviating from the “typical” clinical presentation. The proposed LGMD classification can therefore only serve as a guideline to assign a specific diagnosis to a patient.

It has been noted that Duchenne muscular dystrophy and Becker muscular dystrophy do fulfil the definition of LGMD, they are however well established entities and have therefore not been included within the proposed classification.

7. Conclusions

The workshop successfully achieved consensus on a proposed updated definition of LGMD and a new system of nomenclature of sub-types. The new definition ensures that LGMD is a clear, distinct entity with several common denominators between sub-types. The proposed classification allows for future discoveries to be added to the list of existing LGMD subtypes. It is emphasised that LGMD subtypes that are now no longer considered to be a LGMD often have a more commonly used name by which they are referred to (i.e. myofibrillar myopathy, Emery–Dreifuss muscular dystrophy) and will not change in terms of diagnosis or treatment. Patients will continue to belong to a specific community and care standards will apply accordingly. Four new LGMDs have been added that fulfil the proposed definition, which should assist clinicians to consider these diagnoses when investigating a patient with LGMD phenotypes. The proposed changes
to the definition of LGMD will have ramifications for patients, researchers and clinicians.

The following key deliverables were achieved:

• A consensus was reached on an updated definition of LGMD and current sub-types were evaluated by application of the updated definition.
• Consensus was reached on the most useful LGMD classification system that also allowed space for further discoveries of new sub-types.
• Potential ramifications of the new definition and classification of LGMD for patients was discussed and several action points around how to disseminate this proposal were identified.

Specific recommendations include:

• The implementation of the proposed definition and classification.
• Implementation of the new definition and classification within ICD 11, OMIM and other international nomenclature systems.
• Dissemination of the proposed classification via lay and formal reports, with presentation at various learned society meetings and patient meetings.
• Genetic counselling should be offered as standard in all new diagnoses of LGMD.
• Immune panel (anti-HMGCR antibodies) should be included alongside gene panels investigating unclassified LGMDs, as this is a potentially treatable cause of proximal muscle weakness.

8. LGMD workshop study group

- Angelini Corrado (Padua, Italy),
- Ségolène Aymé (Paris, France),
- Carsten Bönßneman (Bethesda, USA),
- Marianne de Visser (Amsterdam, Netherlands),
- Ada Hamosh (Baltimore, USA),
- Laura Jacobs (London, UK),
- Nina Khizanishvili (Tbilisi, Georgia),
- Madelon Kroneman (Spierziekten, Netherlands),
- Pascal Laforêt (Paris, France),
- Alex Murphy (Newcastle, UK),
- Vincenzo Nigro (Naples, Italy),
- Laura Rufibach (Seattle, USA),
- Anna Sarkozy (London, UK),
- Volker Straub (Newcastle, UK),
- Shaun Swaneepol (High Wycombe, UK),
- Ivan Torrente (Milan, Italy),
- Bjarne Udd (Tampere, Finland),
- Andoni Urtizberea (Hendaye, France),
- John Vissing (Copenhagen, Denmark),
- Maggie Walter (Munich, Germany).

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Supplementary materials

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References


