Clinico-genetic spectrum of limb-girdle muscular weakness in Austria: A multicentre cohort study

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Abstract

Background and purpose: Hereditary myopathies with limb-girdle muscular weakness (LGW) are a genetically heterogeneous group of disorders, in which molecular diagnosis remains challenging. Our aim was to present a detailed clinical and genetic characterization of a large cohort of patients with LGW.

Methods: This nationwide cohort study included patients with LGW suspected to be associated with hereditary myopathies. Parameters associated with specific genetic
**INTRODUCTION**

Hereditary myopathies with a limb-girdle pattern of weakness (LGW), also referred to as limb-girdle muscular dystrophies (LGMD), are a group of rare and genetically heterogeneous neuromuscular disorders clinically characterized by weakness of shoulder and pelvic girdle muscles. Disease onset ranges from early childhood to adulthood with slow to rapid progression rates. The clinical spectrum often comprises other manifestations, with respiratory insufficiency and cardiomyopathy representing serious and potentially life-threatening complications [1]. Substantial phenotypic overlaps with other neuromuscular diseases are common [2], and as hereditary myopathies with LGW are rare diseases with a total prevalence of 2–3/100,000 [3,4], in-depth genotype-phenotype correlations are difficult to establish. These factors, together with the vast genetic heterogeneity, pose diagnostic challenges to clinicians, and despite the application of next-generation sequencing (NGS) techniques, a significant proportion of patients with LGW remain genetically undiagnosed [5,6]. Systematic clinico-genetic studies in large cohorts are therefore important, as they have the potential to guide diagnostic testing strategies, optimize the clinical management and improve genetic counselling of patients with LGW [7].

In this cohort study, we provide a detailed clinical and genetic characterization of a large Austrian cohort of patients with LGW. Different parameters associated with specific genetic aetiologies were evaluated, and we further assessed how they predicted the detection of causative variants by conducting genetic analyses.

**Results:** Molecular diagnoses were identified in 62.0% (75/121) of the cohort, with a higher proportion of patients diagnosed by next-generation sequencing (NGS) than by single-gene testing (77.3% vs. 22.7% of solved cases). The median (interquartile range) time from onset to genetic diagnosis was 8.9 (3.7–19.9) and 17.8 (7.9–27.8) years for single-gene testing and NGS, respectively. The most common diagnoses were myopathies associated with variants in CAPN3 (n = 9), FKRP (n = 9), ANOS (n = 8), DYSF (n = 8) and SGCA (n = 5), which together accounted for 32.2% of the cohort. Younger age at disease onset (p = 0.043), >10× elevated creatine kinase activity levels (p = 0.024) and myopathic electromyography findings (p = 0.007) were significantly associated with the detection of causative variants.

**Conclusions:** Our findings suggest that an earlier use of NGS in patients with LGW is needed to avoid long diagnostic delays. We further present parameters predictive of a molecular diagnosis that may help to select patients for genetic analyses, especially in centres with limited access to sequencing.

**Keywords**
Austria, limb-girdle muscular dystrophy, limb-girdle muscular weakness, myopathy, next-generation sequencing
upper limit of normal (ULN); and iii) elevated to >10 times the ULN. Collaborating centres were contacted and asked for data completion in cases of missing data. If available, data on previous genetic tests were collected, and patients with suspected but genetically undiagnosed disease were offered exome sequencing as described previously [6,8]. All genetic variants that were reported prior to study enrolment were re-analysed, and only pathogenic or likely pathogenic variants according to the standards of the American College of Medical Genetics and Genomics [9] were accepted for molecular diagnosis, with the mode of inheritance classified according to the identified variants. Inherent to the multicentric nature of this study and the performance of genetic tests in different laboratories, the sequencing of gene panels and targeted exomes may encompass different sets of genes. The different NGS approaches were therefore pooled and compared as a group to the results obtained by sequential gene-by-gene sequencing.

Evaluation of parameters predictive of the detection of causative variants and clinico-genetic associations

To determine predictive parameters that were associated with the detection of (likely) pathogenic variants, we compared several parameters between patients with and without molecular diagnoses in an unbiased approach. The different methodologies used for genetic testing among the involved national and international laboratories were pooled for this purpose to assess the spectrum of genetic variants in a real-world scenario. To evaluate clinico-genetic associations, the parameters were also analysed across the most common molecular diagnoses that included ≥5 cases.

Statistical analysis

Descriptive statistics were performed using means and standard deviations or medians and interquartile ranges (IQRs). Evaluation of clinico-genetic associations was performed for the most common genetic aetiologies by pairwise comparison with the remainder of the cohort using the chi-squared test for each clinical feature. Bonferroni correction was applied to account for multiple testing. Comparison between more than two means was performed using one-way analysis of variance, and significant main effects were followed by Dunnett’s multiple comparison test. Parameters were compared between patients with and without a molecular diagnosis using the chi-squared test, Mann–Whitney U-test or independent t-test (with Welch’s correction in case of unequal standard deviations between the groups), as appropriate. Binary logistic regression models with molecular diagnosis as the dependent variable were calculated by stepwise inclusion of independent variables as defined by univariate associations with p values <0.1 after adjusting for sex and disease duration. The model’s goodness of fit was tested by the omnibus test of fit, and Nagelkerke’s R-squared was used to assess the contribution of each variable to the explanation of variance within the overall model. All variables were tested for normal distribution by the Lilliefors test and for collinearity by the variance inflation factor (VIF), with exclusion of variables from the regression analysis if the VIF was >2.0, corresponding to an R² of 0.60. Missing values were handled by multiple (20 times) imputation using the missing-not-at-random approach, with pooling of estimates according to Rubin’s rules [10]. Two-sided p values <0.05 were taken to indicate statistical significance, unless otherwise stated. Data processing was performed using the statistical package SPSS v25 (released 2017, IBM Corp.) and Prism, version 9.1.0 (GraphPad Software Inc.).

RESULTS

Demographic and clinical characteristics

A total of 121 patients with LGW were enrolled during the study period (Table 1 and Figure 1a), with females accounting for 52.1% of the cohort. The mean (±SD) age at onset was 28.8 (±17.7) years (Figure 1b), with adult onset (i.e., onset at ≥18 years of age) in the majority of cases (65.8%). Lower limbs were affected more often ($\chi^2(1, n = 120) = 80.6; p < 0.001$) and more severely ($\chi^2(2, n = 121) = 9.4; p = 0.009$ [Figure 1c]) than upper limbs, but the majority of patients (60.3%) could still walk independently at the time of their last visit (Table 1). The most common symptoms associated with LGW were Trendelenburg’s sign (36.8%), winged scapula (34.2%), cardiomyopathy (11.7%), respiratory insufficiency (10.7%) and facial weakness (9.9%; Figure 1d). Three patients (LMNA, DES and RBC2K1) had undergone heart transplantation and five patients depended on non-invasive ventilation (two CAPN3, one FKRP, one SGCA, and one patient without a molecular diagnosis). Contractures were reported in patients with variants in CAPN3 (n = 3), FKRP (n = 2), SGCA (n = 1), FHL1 (n = 1) and COL6A1 (n = 1).

Distribution of molecular diagnoses

Pathogenic or likely pathogenic (i.e., causative) variants in 27 different genes were identified in 75 patients (62.0%; Table 1) with a diagnostic delay of 14.8 years from disease onset (IQR 6.5–26.1 years; genetic variant details provided in Table S1). The majority of molecular diagnoses were established by NGS approaches (77.3%), while only 22.7% of cases were solved by targeted single-gene testing. Prior single-gene analysis was performed in 31% of patients eventually diagnosed by NGS, and 6.9% of patients had had at least three genes sequentially screened before their referral to NGS. Reasons for the application of single-gene analyses included specific muscle biopsy with findings suggestive of immunoblot and immunohistochemistry analyses in eight cases (three CAPN3, three DYSF, one FKRP, one DMD), characteristic phenotypes in two cases (one DUX4, one DMD) and an already known causative variant within the family in one case (DNAJB6).
Variant types in solved cases comprised missense and frameshift variants in 51.6% and 21%, respectively, followed by structural (13.7%), nonsense (7.3%), splice-site (3.2%) and near-splice variants (3.2%). Uncertain findings were reported in 11 individuals (9.1% of the cohort). Ten of these patients harboured one or two variants of uncertain significance (VUSs) in candidate genes, while one patient

### TABLE 1

| | Total cohort (n = 121) | With molecular diagnosis (n = 75) | Without molecular diagnosis (n = 46) | p value |
|---|---|---|---|---|
| **Sex: female, n (%)** | 63 (52.1) | 42 (56.0) | 21 (45.7) | 0.349 |
| **Positive family history, n (%)** | 24 (19.8) | 15 (20.0) | 9 (19.6) | 0.574 |
| **Inheritance pattern, n (%)** | | | | |
| Recessive | 48 (39.7) | 48 (64.0) | - | - |
| Dominant | 20 (16.5) | 20 (26.7) | - | - |
| X-linked | 4 (3.3) | 4 (5.3) | - | - |
| Dual diagnosis | 2 (1.7) | 2 (2.7) | - | - |
| Digenic | 1 (0.8) | 1 (1.3) | - | - |
| **Age at onset in years, n = 118, mean (SD)** | 28.8 (17.8) | 25.4 (16.4) | 34.1 (18.7) | 0.010* |
| **Age group at onset, n (%)** | | | | |
| Infantile, ≤6 years | 7 (5.9) | 6 (8.2) | 1 (2.2) | 0.033* |
| Juvenile, 7–17 years | 34 (28.8) | 23 (31.5) | 11 (24.4) | - |
| Adult, 18–60 years | 73 (61.9) | 44 (60.3) | 29 (64.4) | - |
| Late, >60 years | 4 (3.4) | 0 (0) | 4 (8.9) | - |
| **Disease duration in years, median (IQR)** | 18.1 (13.3) | 19.2 (13.3) | 16.1 (13.3) | 0.227 |
| **Time to genetic diagnosis in years (n = 66), median (IQR)** | | 14.8 (6.5–26.1) | - | - |
| **Single gene testing** | - | 8.9 (3.7–19.9) | - | - |
| **Next-generation sequencing** | - | 17.8 (7.9–27.8) | - | - |
| **Genetic analysis leading to molecular diagnosis, n (%)** | | | | |
| Single gene testing | - | 17 (22.7) | - | - |
| Next-generation sequencing | - | 58 (77.3) | - | - |
| **Creatine kinase (n = 116), n (%)** | | | | |
| Normal | 14 (12.1) | 6 (8.3) | 8 (18.2) | 0.093 |
| Elevated <10× ULN | 62 (53.4) | 37 (51.4) | 25 (56.8) | - |
| Elevated >10× ULN | 40 (34.5) | 29 (40.3) | 11 (25.0) | - |
| **Muscle biopsy with signs of myopathy (n = 82), n (%)** | 64 (78.0) | 37 (72.5) | 27 (87.1) | 0.171 |
| **Myopathic EMG changes (n = 94), n (%)** | 64 (68.1) | 46 (78.0) | 18 (51.5) | 0.011* |
| **Mobility, n (%)** | | | | |
| Independent | 73 (60.3) | 40 (53.3) | 33 (71.7) | 0.098 |
| Walking with aid | 21 (17.4) | 14 (18.7) | 7 (15.2) | - |
| Unable to walk | 27 (22.3) | 21 (28.0) | 6 (13.0) | - |
| **Region of onset (n = 120), n (%)** | | | | |
| Upper limbs | 18 (14.9) | 6 (8.0) | 12 (26.7) | 0.028* |
| Lower limbs | 87 (72.5) | 57 (76.0) | 30 (66.7) | - |
| Other | 15 (12.5) | 12 (16.0) | 3 (6.6) | - |
| Symmetric onset (n = 116), n (%) | 104 (88.1) | 68 (91.9) | 36 (81.8) | 0.141 |

Note: Percentages in brackets refer to absolute subgroup numbers in the corresponding columns. Abbreviations: EMG, electromyography; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal. *Statistically significant.
carried one VUS and one likely pathogenic variant in ANO5 (details provided in Table S2).

The five most common molecular diagnoses (CAPN3, FKRP, ANO5, DYSF and SGCA) accounted for 32.2% of the cohort (Table 2), with a contrasting distribution in children as compared to adults. In patients with disease onset at <18 years of age, CAPN3 was the most commonly mutated gene, accounting for 17.5% of the group, followed by FKRP and SGCA, accounting for 12.5% and 10%, respectively. In adult patients with disease onset at ≥18 years of age, by contrast, ANO5 was the most common diagnosis, at 9.1%, followed by DYSF with 6.5%.

Further clinico-genetic analyses revealed that CAPN3 was associated with significantly earlier disease onset (p = 0.038; Figure 2a) and that these patients were more likely to lose independent ambulation when compared to other aetiologies in the cohort (p < 0.001; Figure 2b). CK activity levels, by contrast, were significantly higher in ANO5 and DYSF (p < 0.001 and p = 0.003, respectively; Figure 2d). Time to molecular diagnosis, disease duration and walking ability were not significantly associated with any of the molecular diagnoses (Figure 2d-f). Moreover, none of the other clinical parameters (listed in Figure 1d) was significantly associated with any of the five common molecular diagnoses.

Parameters associated with the detection of causative variants

Univariate comparison revealed that age at disease onset (p = 0.010), the degree of lower limb weakness (MRC ≤3; p = 0.038) and myopathic EMG changes (p = 0.011) were associated with a molecular diagnosis. After adjusting for sex and disease duration in a multivariate model, however, younger age at onset (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.93–0.99), >10 times elevated CK activity levels (OR 5.3, 95% CI 1.2–10.5) and myopathic EMG changes (OR 3.3, 95% CI 1.4–17.4) were significantly associated with the detection of causative variants in pooled genetic analyses. By contrast, an isolated upper limb manifestation at disease onset predicted the lack of a molecular diagnosis (OR 0.25, 95% CI 0.08–0.94; Table 3).

DISCUSSION

Neuromuscular disorders with LGW represent a challenging entity for molecular diagnosis due to a significant phenotypic overlap and genetic heterogeneity. The implementation of exome sequencing and other NGS techniques in clinical routine has helped to improve
the diagnostic outcome, but these applications are still associated with highly variable hit rates, ranging from 27% to 76% [6,11–16]. Differences in the extent of genetic prescreening and the application of gene panels and exome sequencing covering different numbers of genes have been proposed to contribute to divergent detection rates of causative variants [6,8,14]. The association of founder mutations with specific ethnicities [17] and higher rates of consanguinity in some study populations are additional factors potentially resulting in higher rates of molecular diagnoses [15,18]. In accordance with these data, the vast majority of solved cases (77.3%) in our study could also be diagnosed by NGS-based approaches. However, the time from symptom onset to molecular diagnosis was found to be markedly longer in cases diagnosed by NGS when compared to targeted genetic testing. As NGS has become cost-effective and widely available for an increasing number of Austrian centres in the past few years, most patients in our cohort were initially tested by single-gene analyses before referral to exome sequencing, which might explain the difference in diagnostic latencies.

We further sought to determine parameters that were predictive for the identification of molecular diagnoses, and found younger age at onset, more than 10-fold elevated CK activity levels and myopathic EMG changes to be associated with a higher detection rate of causative variants, whereas isolated upper limb weakness at onset was inversely associated with a molecular diagnosis. The definition of such predictive parameters could be helpful to select patients for genetic analyses in centres with limited access to sequencing.

The NGS applications were performed in different national and international laboratories and thus covered heterogeneous numbers of genes. We were therefore not able to clearly differentiate and perform a direct comparison between gene panel and exome sequencing. However, previous studies compared the diagnostic yield between different NGS applications and found higher yields
associated with sequencing of comprehensive panels or targeted exomes covering large numbers of genes [8,19], while whole-exome sequencing did not further improve the diagnostic yield [15]. Exome sequencing has nevertheless been deemed superior, as it enables both the identification of novel disease genes and the reiteration of analyses when new disease genes are discovered [6]. As exome sequencing has also become cost-effective and thus widely available for an increasing number of centres, we propose that patients with LGW should generally be referred to exome sequencing early in the disease course.

In spite of comprehensive diagnostic efforts, a significant number of patients remain undiagnosed. These unsolved cases could be caused by somatic mosaicism, repeat expansions or by mutations in intronic or intergenic regions that are commonly not detected by gene panel or exome sequencing, while other patients may have acquired disorders such as inflammatory or drug-induced myopathies [6]. A subset of patients may also have monogenic conditions with causative variants in genes not yet associated with human disease. Moreover, some myopathies are increasingly recognized as digenic or oligogenic disorders, in which the combination of multiple variants in different genes contributes to disease pathogenesis [11]. Hence, the clinical presentation could result from the combined effect of variants providing a polygenic background for disease susceptibility with marked inter- and intrafamilial phenotypic variability [11,20,21]. Variants of uncertain significance have also been detected in a significant proportion of unsolved cases in our study and could potentially have contributed to the phenotype in affected individuals.

Causative variants in the five most commonly found genes were identified in 32.2% of cases in our cohort, representing a higher proportion than previously reported. The largest study to date on 1001 undiagnosed patients with LGW reported pathogenic or likely pathogenic variants in the most common eight genes (i.e., CAPN3, DYSF, ANO5, DMD, RYR1, TTN, COL6A2 and SGCA) accounting for 27.1% of their cohort [6], and another study on 504 patients with hereditary myopathies found mutations in six common genes (i.e., RYR1, CAPN3, ANO5, DYSF, SGCA and GAA) accounting for 19.2% of cases [5]. As those studies usually included preselected patients, some of which had undergone extensive testing before being referred to exome sequencing, such studies do not represent the genetic landscape in corresponding populations, as findings from targeted analyses prior to the application of gene panel or exome sequencing would have been missed. Our approach, by contrast, was driven by the clinical phenotype and included all patients irrespective of the applied diagnostic approach and molecular diagnosis, and is therefore considered to provide an overview of the genetic spectrum that is representative of patients with LGW in Austria. As a result, we also identified neuromuscular diseases including facioscapulohumeral muscular dystrophy type 1 (FSHD1) or spinal muscular atrophy that may display LGW but were not
TABLE 3  Likelihood of a molecular diagnosis depending on different parameters

| Parameter                              | OR (95% CI)    | p value | Change in $R^2$ (overall $R^2$) |
|----------------------------------------|----------------|---------|---------------------------------|
| Age at onset (per year)                | 0.96 (0.93–0.99) | 0.043$^*$ | 0.095 (0.115) |
| Region of onset                        |                |         |                                 |
| Lower limbs only                       | Reference category |       | 0.174 (0.289) |
| Upper limbs only                       | 0.25 (0.08–0.94) | 0.039$^*$ |                                 |
| Other                                  | 1.8 (0.34–9.9) | 0.489   |                                 |
| Symmetric onset                        | 1.0 (0.26–4.0) | 0.979   | 0.001 (0.290) |
| Degree of lower limb weakness (KG ≤3)  | 1.3 (0.37–4.5) | 0.694   | 0.003 (0.293) |
| Cardiomyopathy                         | 3.4 (0.57–20.1) | 0.184   | 0.021 (0.314) |
| Mobility                               |                |         |                                 |
| Independent                            | Reference category |       | 0.001 (0.315) |
| Walking with aid                        | 1.1 (0.25–4.5) | 0.949   |                                 |
| Immobile                               | 1.1 (0.28–4.2) | 0.912   |                                 |
| Creatine kinase                        |                |         |                                 |
| Normal                                 | Reference category |       | 0.092 (0.407) |
| Elevated <10x ULN                       | 2.5 (1.1–8.3) | 0.050   |                                 |
| Elevated >10x ULN                       | 5.3 (1.2–10.5) | 0.024$^*$ |                                 |
| Myopathic EMG changes                  | 3.3 (1.4–17.4) | 0.007$^*$ | 0.112 (0.519) |

Abbreviations: CI, confidence interval; MRC, Medical Research Council; OR, odds ratio; $R^2$, regression coefficient; ULN, upper limit of normal.

*Statistically significant.

reported in previous studies with preselected cohorts. These entities should therefore be considered in the diagnostic evaluation of patients with LGW, especially as chromosomal deletions causing inadequate repression of DUX4 that underlie FSHD1 are commonly not detected by exome sequencing. However, it should be noted that our approach could have been limited by reporting bias, as cases with molecular diagnoses could have been more likely to be reported. This would also have contributed to the high rate of molecular diagnoses in our study but is unlikely to have obscured the reported genetic landscape.

Some of the patients with LGW in other cohorts were shown to carry variants in genes that resulted in a specific treatment. Pompe disease with variants in GAA was reported in 1.0%–7.5% of large cohorts of patients with LGW [5,6,22–25], the early treatment of whom has been associated with better clinical outcomes [26]. No causative GAA variants were identified in the present study, which was unexpected as Pompe disease in Austria was proposed to be underdiagnosed considering the low overall prevalence as compared to other European countries [27]. As patients with Pompe disease generally present with limb-girdle or axial weakness and/or hyperCKaemia, we would have expected to identify GAA variants in our cohort as reported in previous studies [22,23]. Highly effective treatments are also available for congenital myasthenic syndromes (CMS). There are now over 30 causative genes described in the context of CMS, 10 of which have been reported to generally present with a limb-girdle pattern of weakness [28]. CMS patients can therefore often be found in large cohorts of patients with LGW [6]. One CMS patient with pathogenic variants in GMP1B was also identified in our study, the subsequent treatment of whom with salbutamol led to a significant clinical improvement. Moreover, although specific therapies were unavailable for the remainder of the cohort, the identification of molecular diagnoses enabled genetic counselling of patients and their families, as well as the inclusion of patients in registries to facilitate trial readiness, or helped to improve the clinical management, for example, by reducing the risk of malignant hyperthermia in RYR1-associated disease.

In conclusion, our study provides the first nationwide clinico-genetic characterization of a large cohort of patients with LGW in Austria. We present parameters predictive of the identification of molecular diagnoses that could be helpful for the selection of patients for genetic analyses in centres with limited access to sequencing facilities. Our data support the early application of NGS-based methods because of the extensive phenotypic overlap and the wide spectrum of different genetic aetiologies associated with LGW.

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CONFLICT OF INTEREST
The authors report no conflict of interest related to this article.

AUTHOR CONTRIBUTION
Martin Krenn: Data curation (supporting); Formal analysis (lead); Methodology (equal); Visualization (supporting); Writing – original draft (equal). Matthias Tomschik: Data curation (supporting); Writing – review and editing (supporting). Matias Wagner: Formal analysis (supporting); Methodology (supporting); Writing – review and editing (supporting). Guadrun Zulehner: Data curation (supporting); Writing – review and editing (supporting). Rosa Weng: Data curation (supporting); Writing – review and editing (supporting). Jakob Rath: Data curation (supporting); Writing – review and editing (supporting). Sigrid Klotz: Data curation (supporting); Methodology (supporting); Writing – review and editing (supporting). Ellen Gelpi: Data curation (supporting); Formal analysis (supporting); Methodology (supporting); Writing – review and editing (supporting). Gabriel Bsteh: Formal analysis (supporting); Methodology (supporting); Writing – review and editing (supporting). Omar Keritam: Data curation (supporting); Writing – review and editing (supporting). Isabella Colonna: Data curation (supporting); Writing – review and editing (supporting).
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