Analysis of the DYSF mutational spectrum in a large cohort of patients

Martin Krahn, Christophe Bérour, Véronique Labelle, Karine Nguyen, Rafaelle Bernard, Guillaume Bassez, Dominique Figarella-Branger, Carla Fernandez, Julien Bouvenot, Isabelle Richard, et al.

To cite this version:


HAL Id: hal-01681841
https://hal-amu.archives-ouvertes.fr/hal-01681841
Submitted on 10 Apr 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Analysis of the DYSF Mutational Spectrum in a Large Cohort of Patients

Martin Krahn¹,², Christophe Béroud³, Véronique Labelle¹, Karine Nguyen¹,², Rafaëlle Bernard¹,², Guillaume Bassez⁴, Dominique Figarella-Branger⁵, Carla Fernandez⁵, Julien Bouvenot⁶, Isabelle Richard⁷, Elisabeth Ollagnon-Roman⁸, Jorge A. Bevilacqua⁹, Eric Salvo¹, Shahram Attarian¹⁰, Françoise Chapon¹¹, Jean-François Pellissier⁵, Jean Pouget¹⁰, El Hadi Hammouda¹², Pascal Laforêt¹³, Jon Andoni Urtizberea¹⁴, Bruno Eymard¹³, France Leturcq¹⁵, and Nicolas Lévy¹,²*

¹ Département de Génétique Médicale, Hôpital d’Enfants de la Timone, AP-HM, Marseille, France ; ² Inserm UMR910 : "Génétique Médicale et Génomique Fonctionnelle", Faculté de Médecine Timone, Université de la Méditerranée, Marseille, France ; ³ CHU de Montpellier, INSERM U827, and Université Montpellier 1, Montpellier, France ; ⁴ Service de Neurologie, CHU Hôpital Henri Mondor, Créteil, France ; ⁵ Laboratoire d’Anatomopathologie, Hôpital Timone, AP-HM, Marseille, France ; ⁶ Laboratoire de Santé Publique, Faculté de Médecine Timone, Université de la Méditerranée, Marseille, France ; ⁷ Genethon, CNRS FRE 3087, Evry, France ; ⁸ Consultation de Génétique, Hôpital Croix Rousse, CHU, Lyon, France ; ⁹ Departamento de Neurología y Neurocirugía, Hospital Clínico Universitario de Chile, José Joaquín Aguirre, and Programa de Anatomía y Biología del Desarrollo, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile ; ¹⁰ Service de Neurologie, Pôle de Neurosciences Cliniques, Centre de Référence des Maladies Neuromusculaires et de la SLA, Hôpital Timone, AP-HM, Marseille, France ; ¹¹ Consultation de Pathologies neuromusculaires et Laboratoire de Neuropathologie, CHU Côte de Nacre, Caen, France ; ¹² Association Française contre les Myopathies, Evry, France ; ¹³ Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France ; ¹⁴ Hôpital Marin, AP-HP, Hendaie, France ; ¹⁵ Laboratoire de Biochimie Génétique, Hôpital Cochin, Paris, France.

*Correspondence to Pr. Nicolas LEVY, Département de Génétique Médicale, Hôpital Timone Enfants, 264 rue Saint-Pierre, 13385 Marseille Cedex 5, France. E-mail : nicolas.levy@univmed.fr

Contract grant sponsor: This work was supported by the Assistance Publique des Hôpitaux de Marseille, the French Direction de l’Hospitalisation et de l’Organisation des Soins, the Association Française contre les Myopathies and the Jain Foundation.

Communicated by Richard G.H. Cotton

Dysferlinopathies belong to the heterogeneous group of autosomal recessive muscular dystrophies. Mutations in the gene encoding dysferlin (DYSF) lead to distinct phenotypes, mainly Limb Girdle Muscular Dystrophy type 2B (LGMD2B) and Miyoshi myopathy (MM). Here, we analysed the mutational data from the largest cohort described to date, a cohort of 134 patients, included based on clinical suspicion of primary dysferlinopathy and/or dysferlin protein deficiency identified on muscle biopsy samples. Data were compiled from 38 patients previously screened for mutations in our laboratory (Nguyen, et al., 2005; Nguyen, et al., 2007), and 96 supplementary patients screened for DYSF mutations using genomic DHPLC analysis, and subsequent sequencing of detected variants, in a routine diagnostic setting. In 89 (66%) out of 134 patients, molecular analysis identified two disease-

Received 04 March 2008; accepted revised manuscript 17 August 2008.

© 2008 WILEY-LISS, INC.
DOI: 10.1002/humu.20910
causing mutations, confirming the diagnosis of primary Dysferlinopathy on a genetic basis. Furthermore, one mutation was identified in 30 patients, without identification of a second deleterious allele. We are currently developing complementary analysis for patients in whom only one or no disease-causing allele could be identified using the genomic screening procedure. Altogether, 64 novel mutations have been identified in this cohort, which corresponds to approximately 25% of all DYSF mutations reported to date. The mutational spectrum of this cohort significantly shows a higher proportion of nonsense mutations, but a lower proportion of deleterious missense changes as compared to previous series.

KEY WORDS: Dysferlin, DYSF, Dysferlinopathy, Limb Girdle Muscular Dystrophy, LGMD2B, Miyoshi myopathy, Mutation analysis.

INTRODUCTION

Mutations in the gene encoding dysferlin (DYSF; MIM# 603009, 2p13, GenBank NM_003494.2) cause Limb Girdle Muscular Dystrophy type 2B (LGMD2B; MIM# 253601; Bashir, et al., 1998) and Miyoshi myopathy (MM; MIM# 254130)(Liu, et al., 1998). Additionally, mutations in DYSF cause a wide spectrum of phenotypes, ranging from isolated HyperCPKemia to severe disability (Nguyen et al., 2007). Therefore, the generic term of “primary dysferlinopathies” usually defines this heterogeneous group of autosomal recessive muscular dystrophies, caused by mutations in DYSF.

Due to the clinical heterogeneity, initial dysferlin protein analysis on muscle biopsy samples is essential to orientate diagnosis. However, diagnosis should be confirmed by molecular analysis of the DYSF gene (Bushby, 1999).

DYSF is a large-sized gene (>230 kbp, 55 exons, 6243 coding base pairs) (Aoki et al., 2001; Bashir et al., 1998; Liu et al., 1998). Also, more than 300 different sequence variants, including deleterious mutations and non pathogenic polymorphism, have been reported to date (Leiden Muscular Dystrophy pages © www.dmd.nl). These variants are spread along the entire coding sequence, without any apparent mutational “Hotspot” (exception made of founder mutations). Therefore, methods for mutation screening are particularly useful for efficient molecular analysis on a routine basis.

We previously used SSCP (Single Strand Confirmation Polymorphism analysis) or DHPLC (Denaturing High Pressure Liquid Chromatography) for mutational screening in a series of patients (Nguyen, et al., 2005; Nguyen, et al., 2007).

In order to better define the mutational spectrum of DYSF, we here included 96 additional patients and report the results of mutational screening in the largest cohort reported to date. Altogether, we analysed the molecular data of 134 patients included after diagnostic suspicion of primary dysferlinopathy.

PATIENTS, MATERIALS AND METHODS

Patients: Inclusion criteria and definition of the cohort used for mutational data analysis

Inclusion criteria for index patients were: (i) clinical phenotype consistent with LGMD2 or distal myopathy, and (ii) loss or strong reduction of dysferlin expression evidenced by Western-blotting and/or immunohistochemistry on muscle biopsy. When no biopsy was available (patients indicated in Table 1), patients were included after clinical diagnostic suspicion of LGMD2B or MM. Clinical examination was carried out by neurologists from the French Network on LGMD, mainly from the Institut de Myologie, Hôpital de la Pitié Salpêtrière, AP-HP, Paris, and the Service des maladies neuromusculaires, Hôpital Timone, AP-HM, Marseille, France.

DYSF mutational data analysis was carried out on a cohort of 134 patients, for which mutational screening has been performed in our laboratory including 38 patients previously reported by our laboratory (Nguyen, et al., 2005; Nguyen, et al., 2007), and 96 newly included patients. Among the 134 included patients (Table 1), 113 were initial index cases, including 95 sporadic cases, and 18 familial index cases. A total of 21 affected relatives was also
included. The familial cases subdivide as follows: 15 families with one other affected member, and 3 families with two other affected members.

**Protein analysis**

Immunohistochemistry and multiplex Western-blotting on muscle biopsies were carried out as previously described (Anderson and Davison, 1999), using antibodies to dysferlin (NCL-Hamlet antibody, Novocastra Newcastle upon Tyne, UK).

**Genomic mutation screening and mutational data analysis**

After informed consent, genomic DNA was extracted from peripheral blood obtained from all patients. The 55 exons and flanking intronic boundaries of *DYSF* were PCR-amplified, then analysed using DHPLC and subsequent direct sequencing of abnormally eluted fragments, as previously described (Nguyen et al., 2005).

Sequence chromatograms were analysed using the Sequencher® software (Gene Codes Corporation, Ann Arbor, MI, USA) and compared to the human *DYSF* sequence (NM_003494.2). Mutational data are described using the nomenclature of the Human Genome Variation Society (www.hgvs.org/mutnomen). Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines. The initiation codon is codon 1.

Mutational data were compiled and analysed using the bioinformatics algorithms available in the UMD software package (Beroud et al., 2000; Beroud et al., 2005).

Sequence variants identified in this study were determined as deleterious: (i) if pathogenicity had been previously reported in the Leiden Muscular Dystrophy pages database © (www.dmd.nl), based on reports in the literature or direct submission; or (ii) for novel sequence variants, if the type of mutation is *per se* deleterious (nonsense-, frameshifting-, splice-donor-site- or splice-acceptor-site mutations), or for variants of missense-type, a pathogenicity score of $\geq 65$ determined using a novel algorithm, “UMD predictor” (Frederic et al., submitted) and absence of the variant in at least 200 control chromosomes. Selected intronic variants were further analysed using the Splicing Sequences Finder prediction algorithm (www.umd.be/SSF/).

All novel disease-causing mutations identified in this study were submitted to the Leiden Muscular Dystrophy pages database © (www.dmd.nl) (December 2007).

**RESULTS**

*DYSF* mutational data analysis was carried out on a cohort of 134 patients, included for genomic mutational screening following diagnostic suspicion of primary dysferlinopathy.

**Identification of *DYSF* disease-causing mutations and genetic diagnosis of primary dysferlinopathy in the patients (Table 1)**

Altogether, 212 deleterious mutations were identified in the 134 patients included in this study. Two mutations clearly considered as disease-causing were identified in 89 patients (66%), including three patients in whom more than two mutations initially considered as possibly disease-causing were identified (patients F1-18-1-2, F1-47-1-2, and F1-65-1-2). The mutational status of the included patients subdivides as follows.

In 49 index patients, and 8 corresponding relatives, two disease-causing mutations were identified at a compound heterozygous state.

24 index patients, and 8 corresponding relatives, carry homozygous mutations in a context of known familial consanguinity.

In addition, 4 index patients from families with no known consanguinity were found to be homozygous.

In 30 patients (26 index patients and 4 corresponding relatives), only one mutation undoubtedly considered as disease-causing was identified. No disease-causing mutation was found in 10 index patients and 1 corresponding relative.

In the different groups of patients, we identified sequence variants that have been previously reported, but without conclusive information on pathogenicity, and not previously reported sequence variants (listed in Table 1
Identification of novel disease-causing mutations and analysis of the DYSF mutational spectrum

We identified a total of 22 distinct novel mutations, considered as clearly deleterious regarding the type of mutation (nonsense-, frameshifting-, splice-donor-site- or splice-acceptor-site mutations) (Table 2).

Moreover, using bioinformatics predictive algorithms, we analysed variants identified in this study as corresponding to: (i) previously reported disease-causing missense mutations, novel missense and isosemantic exonic variants (Table 3) and (ii) previously reported and novel intronic variants whose pathogenicity is unknown (Table 4).

We identified 8 novel missense variants considered to be pathogenic after bioinformatics analysis (UMD predictor pathogenicity score ≥ 65) (Table 3): c.463G>A (p.Gly155Arg, exon 6); c.851T>C (p.Ile284Thr, exon 8); c.1276G>A (p.Gly426Arg, exon 13); c.2192C>G (p.Pro731Arg, exon 23); c.3086C>T (p.Pro1029Leu, exon 29); c.3683T>C (p.Leu1228Pro, exon 33); c.4577A>C (p.Lys1526Thr, exon 42); c.5908C>T (p.Pro1970Ser, exon 52).

A deleterious effect was excluded for 8 novel exonic variants (7 isosemantic and 1 missense) (Table 3) and 8 novel intronic variants (Table 4).

We analysed the distribution of disease-causing mutations identified in index cases included in this study. The deleterious mutations were distributed along the entire coding sequence, without identified clustering of mutations in a particular exon or domain (Figure 1A). The types of mutations were as follows: 28% of frameshifting mutations, 26% of missense mutations, 26% of nonsense mutations, 18% of intronic mutations and 1% of in-frame deletions (Figure 1B).

Clinical data

Detailed clinical data were available only for 38 patients, indicated in Table 1, and have been reported elsewhere (Nguyen et al., 2005; Nguyen et al., 2007). Briefly, these patients subdivided as: 10 cases of MM, 9 cases of LGMD, 13 cases of proximo-distal myopathy (distal limb-girdle myopathy (Ueyama et al., 2002)), 4 cases of pseudo-metabolic myopathy, and 2 cases of isolated hyperCPKemia.

Regarding the 96 patients additionally included, available clinical information is detailed in Table 1. At onset, 51 patients presented with typical features of MM, 34 with LGMD (including respectively 25 and 21 cases with available results of Western blot analysis showing severely reduced/absence of dysferlin), 6 with isolated hyperCPKemia, and one with myalgia. One additional case initially diagnosed as MM presented normal expression of dysferlin on Western blot. No information on the initial phenotype at inclusion was available for 3 patients, thus included only on the basis of absent dysferlin expression.

Altogether, results from dysferlin Western blot analysis were available for 90 patients. In 89 cases (including 5 affected relatives of index patients) a severely reduced quantity or absence of dysferlin was found.

We compared the type of disease-causing mutations between patients classified respectively as affected with a “MM”, and a “LGMD” phenotype (Figure 1B). No significant difference was evidenced between the two subgroups.

DISCUSSION

The aim of this study was to analyse mutational data from a large cohort of patients, to further characterise the DYSF mutational spectrum. Altogether, we identified 212 mutations clearly considered as disease-causing in our cohort of 134 patients.

As expected from previous reports (Leiden Muscular Dystrophy pages © www.dmd.nl), showing that most of the DYSF disease-causing mutations are private sequence variants, we identified a high proportion of novel
mutations in the newly included patients: we identified 30 not previously reported deleterious mutations (in addition to 34 novel mutations identified in part of this cohort, and already reported (Nguyen et al., 2005; Nguyen et al., 2007)), considered as deleterious either because of the mutation-type, or, in case of missense variants, based on bioinformatics analysis. Among these novel mutations, two were identified each in two non related patients, and may therefore be rare recurrent mutations: c.2217C>A (p.Tyr739X, exon 23) and c.4005+1G>A (IVS 37).

At completion of the present study (February 2008), 352 different DYSF sequence variants (including submissions from our laboratory) were referenced in the Leiden Muscular Dystrophy pages database (database update February 27, 2008) (Leiden Muscular Dystrophy pages © www.dmd.nl), including 82 variants classified as non pathogenic polymorphism. Altogether, the disease-causing mutations identified in this cohort account for ~25% of known pathogenic DYSF variants (30 novel mutations identified in part of this cohort, and 34 already reported (Nguyen et al., 2005; Nguyen et al., 2007)).

A precise determination of the DYSF mutational spectrum is important to better define diagnostic strategies, but also to define possible therapeutic strategies using emerging gene-, cell-, or pharmacological-therapy approaches for autosomal recessive muscular disorders (Daniele et al., 2007). The type and distribution of mutations in this cohort were analysed in index cases by counting both disease-causing mutations for proven or possible compound heterozygotes, and only once for homozygotes (total of 152 mutations analysed). This allows an overview of the different disease-causing alleles to better define the DYSF mutational spectrum (Figure 1B). Moreover, for this autosomal recessive disease, functional restoration of one deleterious allele is expected to have a therapeutic benefit. Therefore, the data from this analysis also allow better determining the mutations to be possibly targeted in the patients, by mutation-specific therapies for primary dysferlinopathies.

As described in previous reports, we found no “mutational hotspot”, mutations being positioned over the entire coding-sequence. However, in comparison to data available from the literature regarding the type of mutations, we found a lower proportion of point mutations (52% vs. 64%; p=0.002). Additionally, we identified a higher proportion of nonsense mutations (26% vs. 18%; p=0.045), but a lower proportion of deleterious missense changes (26% vs. 46%; p<0.001). This difference may at least partially be caused by a mis-interpretation of the pathogenicity for some previously identified missense changes. Interestingly, nonsense mutations, identified in a relatively high proportion in this study, are particular targets for novel therapeutic approaches (Daniele et al., 2007).

From a clinical genetics point of view, our study validated the efficacy of genomic DYSF mutational screening for routine diagnosis. By identifying either compound heterozygous mutations, or homozygous mutations (in cases with known familial consanguinity), diagnosis of primary dysferlinopathy was confirmed on a genetic basis in 89 patients (66%).

However, this value should be considered as a careful underestimation of the actual value. In four (F1-8-1-1, F1-67-1-2, F1-139-1-1 and F1-156-1-2) patients, mutations were identified at a homozygous state, without known consanguinity. A pseudo-homozygous state, correlated to a possible, non identified large genomic deletion in trans, could not be excluded in these patients, due to lack of available samples from their parents. Moreover, in 4 index patients (F1-29-1-2, F1-55-1-1, F1-83-1-2) with only one identified mutation, clearly considered as disease-causing, we found additional possibly deleterious, missense or isosemantic exonic sequence variants. Also, in patient F1-3-1-2 and her affected relative F1-3-2-2, a novel missense variant in exon 52 (c.5899G>A, p.Gly1967Ser) was identified at a homozygous state, and correlates with absence of dysferlin on Western blot in both patients. Bioinformatics analysis predicts a pathogenicity score of 63, just below the predictive pathogenicity threshold of 65. Therefore, the implication of this variant remains unclear, but is yet likely. In patient F1-123-1-1, the intronic variant c.1180+5G>A (Leiden Muscular Dystrophy pages © www.dmd.nl) is predicted to create a cryptic splice donor site. This has to be further validated at the transcriptional level.

We rely on a simple procedure of genomic DHPLC screening (Nguyen et al., 2005). Nonetheless, for all patients, with only one, or no mutation clearly considered as disease-causing, complementary analysis are necessary. We are currently collecting additional samples from these patients, to analyse possible defects at the transcriptional level (de Luna et al., 2006), and screen for large genomic rearrangements, both of which could be missed using genomic DHPLC screening. In our hands, we consider these techniques as valuable complementary approaches, but difficult to use regarding the important number of samples processed, on a routine basis in our laboratory. Exhaustive molecular screening will also allow, in combination with familial analyses, the identification of possible symptomatic heterozygotes (Illa et al., 2007). Finally, differential diagnosis has to be considered in some cases (Bushby, 1999). In particular, patient F1-54-1-1 presented initially with a MM
phenotype, but without dysferlin-deficiency on Western blot analysis. Even if a functional defect, without any related quantitative effect, could result from one or several variants identified in this patient, this hypothesis is unlikely.

Noteworthy, more than two mutations initially considered as possibly disease-causing (as defined in “Patients, Materials and Methods”) were identified in patients F1-18-1-2, F1-47-1-2 and F1-65-1-2.

In patient F1-18-1-2, we previously reported the simultaneous presence in exon 47 of a homozygous non-sense mutation, and a missense change predicted to be pathogenic using bioinformatics analysis. This patient carries in addition a homozygous missense change in exon 6, previously reported as pathogenic (Leiden Muscular Dystrophy pages © www.dmd.nl). Patient F1-47-1-2 is homozygous for a recurrent splice donor site mutation of intron 25 (Leiden Muscular Dystrophy pages © www.dmd.nl), and a novel missence change in exon 42, also predicted to be deleterious. Patient F1-65-1-2 carries a heterozygous frameshifting deletion in exon 50, in addition to two heterozygous missense changes previously reported as pathogenic (Leiden Muscular Dystrophy pages © www.dmd.nl). In these three patients, we could not yet rely on segregation analysis to further evaluate the deleterious, or possibly hypomorphic, implication of the different variants. Even if simultaneous presence of more than two disease-causing mutations cannot be firmly excluded (Drake et al., 2005), further investigation are mandatory before concluding these cases.

Whenever a patient simultaneously carries novel variants, but also two mutations clearly considered as disease-causing, the pathogenicity of the former may be indirectly excluded. In correlation with bioinformatics analyses, this allowed us to exclude in the present series a deleterious effect of 8 exonic variants (7 isosemantic and 1 missense)(Table 3), and 8 intronic variants (Table 4). Two additional novel intronic variants (IVS4: c.343-29A>G, and IVS38: c.4168-40G>A) are candidates for further transcriptional analyses, regarding a possible hypomorphic effect.

As our study was designed for diagnostic purposes, we did not carry out further detailed frequency evaluation of the other variants, classified as most likely non-pathogenic. Such polymorphism analyses are time-consuming and cost-ineffective on a routine basis, and would better suit to large-scale sequencing platforms that should be available in the next future (Mardis, 2006).

Detailed clinical reassessment had been previously done in a subset of the patients described in this study (Nguyen et al., 2007), and identified important variability in the disease phenotype, but without apparent genotype-phenotype correlation. For the 96 additionally included patients, precise clinical data were not available. We therefore compared the types of pathogenic mutations for the two main defined phenotypes, MM and LGMD. In concordance with data from the literature (Glover and Brown, 2007), no significant difference was identified between these two subgroups, further sustaining the possible influence of genetic and/or environmental modifiers on the determination of the primary phenotype. The collection of precise and homogeneous clinical data, and their correlation to genetic findings thus remains an important task, that should take into account the existence of phenotypical “subgroups” among patients affected with primary dysferlinopathy (Nguyen et al., 2007). Moreover, novel large-scale mutational analysis tools, such as genomic micro-array based techniques, should allow to better analyse possible modifying effects of SNPs in the *DYSF* gene, and genes coding for DYSF interacting protein partners.
**Table 1: Genomic mutational findings in the patients included in this study.**

Mutational data are described using the nomenclature of the Human Genome Variation Society (www.hgvs.org/mutnomen). Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence (human DYSF, GenBank NM_003494.2), according to journal guidelines. The initiation codon is codon 1.

*As defined in “Patients, Materials and Methods”.

**Effects on the amino-acid sequence are predicted from the cDNA sequence.

*** Sequence variants previously reported as non pathogenic polymorphism are not listed. If available, SNP accession numbers are indicated in brackets (from dbSNP; www.ncbi.nlm.nih.gov/SNP/)

# Patients included for analysis of the DYSF mutational spectrum, whereas available detailed clinical information and genomic data have been previously evaluated (Nguyen et al., 2007).

Patient identification-data for relatives of index cases are in **bold-italized**. Novel sequence variants are in **bold**.

<table>
<thead>
<tr>
<th>Patient Identification and Gender/Age</th>
<th>Phenotype</th>
<th>DYSF IH or Western blot analysis findings</th>
<th>Genomic mutational findings: Deleterious sequence variants*</th>
<th>Deleterious effect**</th>
<th>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-1-1-1# M 66years</td>
<td>PD#</td>
<td>Absence</td>
<td>IVS8: c.855+1delG HTZ</td>
<td>Abn.Spl.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and ex29: c.3126G&gt;A HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p.Trp1042X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-100-1-1# M 34years</td>
<td>PD#</td>
<td>Absence</td>
<td>ex47: c.5302C&gt;T HTZ</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p.Arg1768Trp)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and ex53: c.5979dupA HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p.Glu1994fsX3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-103-1-1 M 22years</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex2: c.107_108delAA HTZ</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td>(p.Lys36SerfsX11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td>and ex31: c.3389_3399dupTCTCCACCTTG HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td>(p.Phe1135ProfsX3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td>IVS7: c.792+11T&gt;C (rs13428076) HTZ; IVS38: c.4168_40G&gt;A HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-103-2-1 M NA</td>
<td>A: NA</td>
<td>(ND-R)</td>
<td>ex2: c.107_108delAA HTZ</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: HyperCPK</td>
<td></td>
<td>(p.Lys36SerfsX11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td>and ex31: c.3389_3399dupTCTCCACCTTG HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td>(p.Phe1135ProfsX3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


UMD: pathogenicity score analysed using “UMD predictor” (Frederic et al., submitted); indicated for all novel missense or isosemantic changes, and in case of SPDCM.

<table>
<thead>
<tr>
<th>Identification</th>
<th>Patient</th>
<th>Gender/Age</th>
<th>Phenotype</th>
<th>DYSF IH or Western blot analysis findings</th>
<th>Genomic mutational findings: Deleterious sequence variants*</th>
<th>Deleterious effect**</th>
<th>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-1-1-1# M 66years</td>
<td>PD#</td>
<td>Absence</td>
<td>IVS8: c.855+1delG HTZ</td>
<td>Abn.Spl.</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and ex29: c.3126G&gt;A HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p.Trp1042X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-100-1-1# M 34years</td>
<td>PD#</td>
<td>Absence</td>
<td>ex47: c.5302C&gt;T HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p.Arg1768Trp)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and ex53: c.5979dupA HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p.Glu1994fsX3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-103-1-1 M 22years</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex2: c.107_108delAA HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td>(p.Lys36SerfsX11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td>and ex31: c.3389_3399dupTCTCCACCTTG HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-103-2-1 M NA</td>
<td>A: NA</td>
<td>(ND-R)</td>
<td>ex2: c.107_108delAA HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: HyperCPK</td>
<td></td>
<td>(p.Lys36SerfsX11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td>and ex31: c.3389_3399dupTCTCCACCTTG HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------</td>
<td>------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>----------------------</td>
<td>---------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-104-1-2/ M 21years</td>
<td>LGMD#</td>
<td>Absence</td>
<td>IVS5: c.457+1dupG homozygous (CONSANGUINITY)</td>
<td>Abn.Spl.</td>
<td>IVS5: c.457+1dupG homozygous (CONSANGUINITY)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-108-1-1/ F 54years</td>
<td>Absence</td>
<td>ex12: c.1064_1065delAA HTZ (p.Lys355ArgfsX4)</td>
<td>(p.Lys355ArgfsX4)</td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-108-2-2/ F 51years</td>
<td>Absence</td>
<td>ex12: c.1064_1065delAA HTZ (p.Lys355ArgfsX4)</td>
<td></td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-111-1-1/ M 31years</td>
<td>Absence</td>
<td>ex11: c.1020C&gt;A HTZ (p.Ser340Arg)</td>
<td>IVS6: c.664-17C&gt;G homozygous (CONSANGUINITY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-112-1-2/ F 47years</td>
<td>Absence</td>
<td>ex28: c.2975G&gt;A homozygous (CONSANGUINITY)</td>
<td>IVS4: c.265C&gt;T HTZ (p.Arg89X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-112-1-2/ F 19years</td>
<td>Absence</td>
<td>ex4: c.265C&gt;T HTZ (p.Arg89X)</td>
<td>IVS3: c.236+20G&gt;A (rs12470028) homozygous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-113-1-1/ M 64years</td>
<td>Absence</td>
<td>ex6: c.509C&gt;A HTZ (p.Ala170Glu)</td>
<td>ex11: c.1004G&gt;C (p.Gly335Ala) homozygous UMD59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-117-1-1/ M 34years</td>
<td>Absence</td>
<td>ex29: c.3112 C&gt;T HTZ (p.Arg1038X)</td>
<td>IVS37: c.4005+1G&gt;A HTZ (p.Gln1993Gln)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A: NA</td>
<td>B: MM</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td>D: NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A: NA</td>
<td>B: MM</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td>D: NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-12-1-2 F NA</td>
<td></td>
<td></td>
<td>ex39: c.4200dupC homozygous (CONSANGUINITY) (p.Ile140HisfsX8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td>D: NA</td>
<td>IVS12: c.1180+5G&gt;A HTZ; IVS13: c.1285-35G&gt;T HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-123-1-1 M 40years</td>
<td></td>
<td></td>
<td>Ex50: c.5594delG HTZ</td>
<td>(p.Gly1865AlafsX101)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A: NA</td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-125-1-0 (NA)</td>
<td></td>
<td></td>
<td>Exon6: c.591C&gt;G HTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A: NA</td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-13-1-1# M 44years</td>
<td>MM#</td>
<td>Absence</td>
<td>IVS8: c.855+1delG HTZ</td>
<td>Abn.Spl.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and ex52: c.5813_5821del HTZ</td>
<td>(p.Thr1938_Lys1940delinsLys)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-130-1-1 M 37years</td>
<td>(ND-R)</td>
<td></td>
<td>ex34: c.3826C&gt;G HTZ</td>
<td>(p.Leu1276Val)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A: NA</td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: No</td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ex34: c.3826C&gt;G HTZ</td>
<td>(p.Leu1276Val)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and IVS34: c.3843+1G&gt;A HTZ</td>
<td>Abn.Spl.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-130-2-2# F 47years</td>
<td>PD#</td>
<td>Absence</td>
<td>ex34: c.3826C&gt;G HTZ</td>
<td>(p.Leu1276Val)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and IVS34: c.3843+1G&gt;A HTZ</td>
<td>Abn.Spl.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-131-1-1# M 67years</td>
<td>PD#</td>
<td>Absence</td>
<td>ex6: c.490G&gt;T HTZ</td>
<td>(p.Gly164X)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and ex9: c.895G&gt;A HTZ</td>
<td>(p.Gly299Arg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-133-1-1 M 55years</td>
<td></td>
<td></td>
<td>exon 6: c.591C&gt;G HTZ</td>
<td>(p.Tyr197X)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A: NA</td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------</td>
<td>-------------------------------------------------------------</td>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td>(p.Asp1837Asn)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-138-3-1 M NA</td>
<td>A: NA</td>
<td>ex50: c.5594delG homozygous (CONSANGUNITY)</td>
<td>(p.Gly1865AlafsX101)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-139-1-1 M 47years</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex51: c.5698_5699delAG homozygous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td>(p.Ser1900fsX14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-14-1-1 M 72years</td>
<td>A: NA</td>
<td>ex12: c.1157_1168delTCCGGGCGGAGG HTZ and ex19: c.1663C&gt;T HTZ</td>
<td>(p.Phe386_Asp390delinsTyr)</td>
<td>IVS29: c.3175-61G&gt;C HTZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td>(p.Arg555Trp)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td>(p.Arg1046His)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-140-2-1 M 53years</td>
<td>A: 45 years B: MM C: No D: x50N E: Ambulant</td>
<td>Severe reduced</td>
<td>IVS24: c.2511+1G&gt;A HTZ and ex29: c.3137G&gt;A HTZ</td>
<td>Abn.Spl.</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-142-1-2 F 36years</td>
<td>A: NA B: MM C: NA D: NA E: NA</td>
<td>Absence</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-143-1-1 M 36years</td>
<td>A: 20 years B: LGMD C: NA D: x100N E: Ambulant</td>
<td>Absence</td>
<td>ex12: c.1064_1065delAA HTZ (p.Lys1046His)</td>
<td>IVS41: c.4509+40C&gt;T homozygous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-148-1-1 M 59years</td>
<td>A: 24 years B: LGMD C: No D: x5N E: Non ambulant</td>
<td>Absence</td>
<td>IVS51: c.5767+1G&gt;A homozygous (CONSANGUINITY)</td>
<td>ex44: c.4867C&gt;T (p.Leu1623Leu) homozygous UMD23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-150-1-2# F 47years</td>
<td>PD#</td>
<td>Severely reduced</td>
<td>ex4: c.247delG HTZ and ex54: c.6124C&gt;T HTZ (p.Arg1046His)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-150-2-2# F 53years</td>
<td>LGMD# (ND-R)</td>
<td>(ND-R)</td>
<td>ex4: c.247delG HTZ and ex54: c.6124C&gt;T HTZ (p.Arg1042Cys)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-151-1-2# F 65years</td>
<td>LGMD#</td>
<td>Absence</td>
<td>ex42: c.4628G&gt;A HTZ (p.Gly1543Asp)</td>
<td>IVS10: c.938-34T&gt;A HTZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-153-1-1# M 36years</td>
<td>PD#</td>
<td>Absence</td>
<td>ex11: c.1020C&gt;A HTZ and ex50: c.5594delG HTZ (p.Gly1865AalsfsX101)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-154-1-2 F 36years</td>
<td>A: NA B: LGMD C: NA D: NA E: NA</td>
<td>Absence</td>
<td>ex8: c.799_800delTT HTZ and ex33: c.3687C&gt;A HTZ (p.Phe267LeufsX5)</td>
<td>(p.Tyr1229X)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>---------------------</td>
<td>---------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| F1-155-1-2 F 18years               | A: 13 years B: HyperCPK C: NA D: x30N E: NA | Absence | ex7: c.757C>T HTZ  
and ex53: c.5979dupA HTZ | (p.Arg253Trp) | ex43: c.4731G>A (p.Glu1577Glu) HTZ UMD18 |
| F1-156-1-2 F 50years               | A: NA B: MM C: NA D: NA E: NA | Severe reduced | **ex52: c.5805delA homozygous** | (p.Ala1946ProfsX30) | - |
| F1-159-1-0 (NA)                    | A: NA B: LGMD C: NA D: NA E: NA | NA | IVS8: c.855+1delG HTZ  
and IVS28: c.3031+2T>C HTZ | Abn.Spl. | - |
| F1-159-2-0 (NA)                    | A: NA B: LGMD C: NA D: NA E: NA | NA | IVS8: c.855+1delG HTZ  
and IVS28: c.3031+2T>C HTZ | Abn.Spl. | - |
| F1-161-1-1 M 31years               | A: NA B: MM C: NA D: NA E: NA | Severely reduced | IVS26: c.2810+1G>A HTZ | Abn.Spl. | - |
| F1-162-1-2# F 43years              | PM# | NA | ex26: c.2799delG homozygous (CONSANGUINITY) | (p.Ala927LeufsX21) | - |
| F1-163-1-1# M 57years              | LGMD# | Absence | ex20: c.1834C>T HTZ  
and ex37: c.3967C>T HTZ | (p.Gln612X) | - |
<p>| F1-169-1-1 M NA                    | A: NA B: LGMD C: NA D: NA E: NA | NA | ex6: c.509C&gt;A HTZ | (p.Ala170Glu) | - |</p>
<table>
<thead>
<tr>
<th>Patient Identification and Gender/Age</th>
<th>Phenotype</th>
<th>DYSF IH or Western blot analysis findings</th>
<th>Genomic mutational findings: Deleterious sequence variants*</th>
<th>Deleterious effect**</th>
<th>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-17-1-1# M 51 years</td>
<td>PD#</td>
<td>Absence</td>
<td>ex15: c.1392dupA homozygous (CONSANGUINITY)</td>
<td>(p.Asp465ArgfsX9)</td>
<td>-</td>
</tr>
<tr>
<td>F1-170-1-2 F 32 years</td>
<td>A: 15 years</td>
<td>Absence</td>
<td>IVS8: c.855+1delG HTZ</td>
<td>Abn.Spl.</td>
<td>IVS5: c.457+17G&gt;C HTZ</td>
</tr>
<tr>
<td>F1-170-2-2 F 32 years</td>
<td>A: 15 years</td>
<td>(ND-R)</td>
<td>IVS8: c.855+1delG HTZ</td>
<td>Abn.Spl.</td>
<td>IVS5: c.457+17G&gt;C HTZ</td>
</tr>
<tr>
<td>F1-174-1-1 M 46 years</td>
<td>A: 15 years</td>
<td>Absence</td>
<td>ex26: c.2790G&gt;C HTZ</td>
<td>(p.Trp930Cys)</td>
<td>ex33: c.3702T&gt;C (p.Tyr1234Tyr) HTZ UMD18</td>
</tr>
<tr>
<td>F1-179-1-1 M 49 years</td>
<td>A: ~25 years</td>
<td>Absence</td>
<td>ex52: c.5871_5872delGT HTZ</td>
<td>(p.Ser1958ProfsX3)</td>
<td></td>
</tr>
<tr>
<td>F1-183-1-2 F 60 years</td>
<td>A: 40 years</td>
<td>Severe reduced</td>
<td>ex27: c.2894G&gt;A HTZ</td>
<td>(p.Trp965X)</td>
<td></td>
</tr>
<tr>
<td>F1-184-1-2 F 30 years</td>
<td>A: 27 years</td>
<td>NA</td>
<td>ex13: c.1276G&gt;A HTZ</td>
<td>(p.Gly426Arg) UMD100</td>
<td></td>
</tr>
</tbody>
</table>

... (remaining entries continue in a similar format)
<table>
<thead>
<tr>
<th>Patient Identification and Gender/Age</th>
<th>Phenotype A= Age of onset B=initial phenotype C=inflammatory signs on muscle biopsy D=CpK level E=progression after 10 years</th>
<th>DYSF or Western blot analysis findings</th>
<th>Genomic mutational findings: Deleterious sequence variants*</th>
<th>Deleterious effect**</th>
<th>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-187-1-1 M NA</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex32: c.3517dupT HTZ</td>
<td>(p.Ser1173PhefsX2)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td>and ex51: c.5713C&gt;T HTZ</td>
<td>(p.Arg1905X)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-188-1-2 F 47years</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex20: c.1852G&gt;A homozzygous (CONSANGUINITY)</td>
<td>(p.Gly618Arg)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-19-1-1 M 36years</td>
<td>A: NA</td>
<td>Absence</td>
<td>IVS34: c.3702+1G&gt;A HTZ</td>
<td>Abn.Spl.</td>
<td>ex33: c.3702T&gt;C (p.Tyr1234Tyr) HTZ UMD18</td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td>and ex49: c.5509G&gt;A</td>
<td>(p.Asp1837Asn)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-190-1-1 M 30years</td>
<td>A: 18 years</td>
<td>NA</td>
<td>ex21: c.1948delC homozygous (CONSANGUINITY)</td>
<td>(p.Leu650TyrfsX6)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x125N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-192-1-1 M 26years</td>
<td>A: 18 years</td>
<td>NA</td>
<td>ex30: c.3225delT homozygous (CONSANGUINITY)</td>
<td>(p.Phe1075LeufsX45)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x30N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-200-1-1 M 58years</td>
<td>A: NA</td>
<td>Absence</td>
<td>?</td>
<td>-</td>
<td>IVS38: c.4168-20G&gt;A HTZ</td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-201-1-2 F 34years</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex12: c.1117C&gt;T HTZ</td>
<td>(p.Gln393X)</td>
<td>IVS21: c.2055+105_2055+106delAC (rs5832058) HTZ</td>
</tr>
<tr>
<td></td>
<td>B: HyperCpK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-204-1-2 F 36years</td>
<td>A: 33 years</td>
<td>Absence</td>
<td>IVS10: c.937+1G&gt;A HTZ</td>
<td>Abn.Spl.</td>
<td>(p.Tyr586X)</td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td>and ex20: c.1758C&gt;G HTZ</td>
<td>(p.Tyr586X)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C: Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x20N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>F1-205-1-1 M NA</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex9: c.879_883dupGACAG HTZ</td>
<td>(p.Asp295GlyfsX45)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-21-1-2 F 20years</td>
<td>A: 16 years</td>
<td>Absence</td>
<td>ex6: c.490G&gt;T HTZ</td>
<td>(p.Gly164X)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: HyperCPK</td>
<td></td>
<td>and IVS33: c.3703-1G&gt;A HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x25N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-21-2-2 F 19years</td>
<td>A: ~ 16 years</td>
<td>(ND-R)</td>
<td>ex6: c.490G&gt;T HTZ</td>
<td>(p.Gly164X)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: HyperCPK</td>
<td></td>
<td>and IVS33: c.3703-1G&gt;A HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x20N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x40N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-25-2-2 F 40years</td>
<td>A: 20 years</td>
<td>(ND-R)</td>
<td>IVS25: c.2643+1G&gt;A homozygous (CONSANGUINITY)</td>
<td>Abn.Spl.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x25N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-29-1-2 F 64years</td>
<td>A: 25 years</td>
<td>Severe reduced</td>
<td>ex47: c.5302C&gt;T HTZ</td>
<td>(p.Arg1768Trp)</td>
<td>ex12: c.1168G&gt;A (p.Aspr390Asn) HTZ UMD41</td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x11N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>-------------------------------------------------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>F1-30-1-2 F 39years</td>
<td>A: NA</td>
<td>ex26: c.2779delG HTZ (p.Ala927LeufsX21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td>and ex51: c.5713C&gt;T HTZ (p.Arg1905X)</td>
<td>IVS6: c.664-17C&gt;T HTZ; IVS33: c.3703-12C&gt;T HTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-31-1-2# F 36years</td>
<td>MM#</td>
<td>ex9: c.896G&gt;A HTZ (p.Gly299Glu)</td>
<td></td>
<td>IVS6: c.664-17C&gt;T homozygous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-32-1-2 F 28years</td>
<td>A: 14 years</td>
<td>?</td>
<td>Absence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x70N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-34-1-1 M 34years</td>
<td>A: NA</td>
<td>?</td>
<td>Absence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-35-1-2# F 43years</td>
<td>MM#</td>
<td>ex32: c.3516_3517delTT HTZ (p.Ser1173X)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MM#</td>
<td>ex15: c.1368C&gt;G HTZ (p.Cys456Trp)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence</td>
<td>and ex51: c.5713C&gt;T HTZ (p.Arg1905X)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-37-1-1# M 37years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MM#</td>
<td>ex32: c.3477C&gt;A HTZ (p.Tyr1159X)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-38-1-2 F 33years</td>
<td>A: ~ 20 years</td>
<td>ex23: c.2217C&gt;A HTZ (p.Tyr739X)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td>and IVS37: c.4005+1G&gt;A HTZ (p.Ile1401AsnfsX8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x44N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-40-1-2 F 42years</td>
<td>A: NA</td>
<td>ex39: c.4201dupA homozygous (CONSANGUINITY) (p.Ile1401AsnfsX8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x20N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Non ambulant</td>
<td></td>
<td>Absn.Spl.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-44-1-2# F 37years</td>
<td>PD#</td>
<td>ex39: c.4201dupA homozygous (CONSANGUINITY) (p.Ile1401AsnfsX8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-45-1-1 M 49years</td>
<td>A: NA</td>
<td>?</td>
<td>Absence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-45-1-1 M 49years</td>
<td></td>
<td></td>
<td></td>
<td>IVS35: c.3874-30delG homozygous</td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>F1-46-1-2# F 57years</td>
<td>MM#</td>
<td>Absence</td>
<td>ex20: c.1795_1799dupTACTC homozygous (CONSANGUINITY)</td>
<td>(p.Ala601ThrfsX28)</td>
<td>-</td>
</tr>
<tr>
<td>F1-46-2-1# M 43years</td>
<td>MM#</td>
<td>Absence</td>
<td>ex20: c.1795_1799dupTACTC homozygous (CONSANGUINITY)</td>
<td>(p.Ala601ThrfsX28)</td>
<td>-</td>
</tr>
<tr>
<td>F1-48-1-2 F 36years</td>
<td>A: NA B: MM C: NA D: x20N E: Ambulant</td>
<td>ex29: c.3086C&gt;T HTZ</td>
<td></td>
<td>(p.Pro1029Leu) UMD68</td>
<td>-</td>
</tr>
<tr>
<td>F1-48-2-2 F 35years</td>
<td>A: NA B: MM C: NA D: x20N E: Ambulant</td>
<td>ex29: c.3086C&gt;T HTZ</td>
<td></td>
<td>(p.Pro1029Leu) UMD68</td>
<td>-</td>
</tr>
<tr>
<td>F1-5-1-1# M 53years</td>
<td>LGMD#</td>
<td>Severely reduced</td>
<td>ex27: c.2858dupT homozygous (CONSANGUINITY)</td>
<td>(p.Phe954ValfsX2)</td>
<td>-</td>
</tr>
<tr>
<td>F1-50-1-2 F 42years</td>
<td>A: ~25 years B: LGMD C: No D: x10N E: Ambulant</td>
<td>Absence</td>
<td>ex7: c.701G&gt;A HTZ</td>
<td>(p.Gly234Glu)</td>
<td>-</td>
</tr>
<tr>
<td>Patient</td>
<td>Identification and Gender/Age</td>
<td>Phenotype</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------</td>
<td>-----------</td>
<td>------------------------------------------------</td>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>F1-56-1</td>
<td>F 57 years</td>
<td>A: NA</td>
<td>ex8: c.851T&gt;C HTZ (p.Ile284Thr) UMD93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F1-57-1</td>
<td>M 38 years</td>
<td>A: NA</td>
<td>ex18: c.1617C&gt;G HTZ</td>
<td>(p.Tyr593X)</td>
<td>IVS52: c.5947-33G&gt;A HTZ</td>
</tr>
<tr>
<td>F1-58-1#</td>
<td>M deceased</td>
<td>LGMD#</td>
<td>ex19: c.1663C&gt;T HTZ (p.Arg555Trp)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F1-6-1#</td>
<td>M 34 years</td>
<td>MM#</td>
<td>ex19: c.1663C&gt;T homozygous (CONSANGUINITY) (p.Arg555Trp)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F1-61-1</td>
<td>F 45 years</td>
<td>A: 28 years</td>
<td>ex23: c.2192C&gt;G HTZ</td>
<td>(p.Pro731Arg) UMD82</td>
<td>IVS4: c.343-29A&gt;G HTZ</td>
</tr>
<tr>
<td>F1-63-2#</td>
<td>F 36 years</td>
<td>PD#</td>
<td>IVS8: c.855+1delG HTZ</td>
<td>Abn.Spl.</td>
<td>-</td>
</tr>
<tr>
<td>F1-64-1</td>
<td>F 44 years</td>
<td>A: 20 years</td>
<td>ex1: c.120G&gt;C HTZ</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F1-65-1</td>
<td>F 60 years SPDCM</td>
<td>A: NA</td>
<td>ex12: c.1120G&gt;C HTZ</td>
<td>(p.Val374Leu) UMD29</td>
<td>ex4: c.251C&gt;T (p.Ala84Val) HTZ UMD41; ex15: c.1362C&gt;T (p.Ser454Ser) HTZ UMD18</td>
</tr>
</tbody>
</table>

**Notes:**
- AMB: Ambulant
- MM: MM
- PD: PD
- SG: SPDCM
- E: Non ambulant
- A: IGT
- B: MM
- C: NA
- D: NA
- E: NA
- **A**: Age of onset
- **B**: Initial phenotype
- **C**: Inflammatory signs on muscle biopsy
- **D**: CPK level
- **E**: Progression after 10 years
- **NA**: Not available
- **MM**: MM
- **LGMD**: LGMD
- **MM**: MM
- **LGMD**: LGMD
- **ND-R**: (ND-R)
- **CONSANGUINITY**: CONSANGUINITY
<table>
<thead>
<tr>
<th>Patient Identification and Gender/Age</th>
<th>Phenotype</th>
<th>DYSF IH or Western blot analysis findings</th>
<th>Genomic mutational findings: Deleterious sequence variants*</th>
<th>Deleterious effect**</th>
<th>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-65-3-2 F 54years</td>
<td>A: NA</td>
<td>ex50: c.5594delG homozygous (CONSANGUINITY)</td>
<td>(p.Gly1865AlafsX101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-67-1-2 F 43years</td>
<td>A: 25 years</td>
<td>ex34: c.3832C&gt;T homozygous</td>
<td>(p.Gln1278X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x20N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-68-1-2# F 35years</td>
<td>HyperCPK#</td>
<td>ex20: c.1758C&gt;GT HTZ and ex30: c.3321_3324dupAGCT HTZ</td>
<td>(p.Tyr586X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-7-1-2 F 37years</td>
<td>A: 24 years</td>
<td>ex4: c.265C&gt;T homozygous (CONSANGUINITY)</td>
<td>(p.Arg89X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x9N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-70-1-2# F 51years</td>
<td>PM#</td>
<td>ex39: c.4200dupC HTZ</td>
<td>(p.Ile1401HisfsX8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and ex41: c.4433G&gt;A HTZ</td>
<td>(p.Trp1478X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-71-1-2 F 53years</td>
<td>A: ~40 years</td>
<td>ex33: c.3683T&gt;C HTZ</td>
<td>(p.Leu1228Pro) UMD71</td>
<td>IVS29: c.3175-61G&gt;C HTZ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x20N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-73-1-1 M 38years</td>
<td>A: NA</td>
<td>ex54: c.6124C&gt;T HTZ</td>
<td>(p.Arg2042Cys)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-74-1-2# F 49years</td>
<td>PM#</td>
<td>ex8: c.797T&gt;C HTZ</td>
<td>(p.Leu266Pro)</td>
<td>IVS33: c.3521-12C&gt;T HTZ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severeley reduced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and ex44: c.4876delG HTZ</td>
<td>(p.Val1626TyrfsX8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-75-1-1# M 32years</td>
<td>LGMD#</td>
<td>ex29: c.3035G&gt;A homozygous (CONSANGUINITY)</td>
<td>(p.Trp1012X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severely reduced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CONSANGUINITY)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-75-2-1# M 27years</td>
<td>LGMD#</td>
<td>ex29: c.3035G&gt;A homozygous</td>
<td>(p.Trp1012X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severely reduced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype Results of DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>F1-76-1-1# M 34years</td>
<td>MM# Severe muscle weakness and proximal weakness</td>
<td>ex6: c.610C&gt;T HTZ</td>
<td>(p.Arg204X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IVS8: c.855+1delG HTZ</td>
<td>Abn.Spl.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-81-1-1 M 68years</td>
<td>A: NA B: MM C: NA D: NA E: NA</td>
<td>IVS50: c.5668-7G&gt;A homozygous</td>
<td>(p.Asp1890Val6X78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-80-1-0 (NA)</td>
<td>NA</td>
<td>ex29: c.3065G&gt;A HTZ</td>
<td>(p.Arg1022Gln)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-82-1-1# M 38years</td>
<td>PM# Absence</td>
<td>ex52: c.5903G&gt;A HTZ</td>
<td>(p.Trp1968X)</td>
<td>IVS31: c.3442+4A&gt;G HTZ; ex38: c.4089C&gt;T (p.Gly1363Gly) HTZ UMD18</td>
<td></td>
</tr>
<tr>
<td>F1-83-1-2 F 46years</td>
<td>Absence</td>
<td>ex12: c.1177C&gt;T HTZ</td>
<td>(p.Glu393X)</td>
<td>IVS2: c.144+46delG homozygous; ex12: c.1168G&gt;A (p.Asp390Asn) HTZ UMD41; IVS33: c.3703-12C&gt;T HTZ</td>
<td></td>
</tr>
<tr>
<td>F1-84-1-2# F 51years</td>
<td>LGMD# Absence</td>
<td>ex39: c.4200delC homozygous (CONSANGUINITY)</td>
<td>(p.Ile1401SerfsX47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-86-1-2# F 35years</td>
<td>MM# Absence</td>
<td>IVS30: c.3348+1delGTAT HTZ</td>
<td>Abn.Spl.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-88-1-2 F 38years</td>
<td>A: 17 years B: LGMD C: No D: x10 E: Non ambulant</td>
<td>ex26: c.2779delG homozygous (CONSANGUINITY)</td>
<td>(p.Ala927LeufsX21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Identification and Gender/Age</td>
<td>Phenotype</td>
<td>DYSF IH or Western blot analysis findings</td>
<td>Genomic mutational findings: Deleterious sequence variants*</td>
<td>Deleterious effect**</td>
<td>Genomic mutational findings: Sequence variants of undetermined pathogenicity***</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------</td>
<td>----------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>---------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-90-1-0 (NA)</td>
<td>A: NA</td>
<td>Absence</td>
<td>ex29: c.3137G&gt;A HTZ</td>
<td>(p.Arg1046His)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td>and ex32: c.3477C&gt;A HTZ</td>
<td>(p.Tyr1159X)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-91-1-1# M 29years</td>
<td>PD#</td>
<td>Absence</td>
<td>ex50: c.5594delG homozygous (CONSANGUINITY)</td>
<td>(p.Gly1865AlafsX101)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-92-1-2 F 33years</td>
<td>A: 14 years</td>
<td>NA</td>
<td>ex3: c.154 T&gt;C HTZ</td>
<td>(p.Trp52Arg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: LGMD</td>
<td></td>
<td>and ex19: c.1655_1668delATCGTGCCGCGCTT HTZ</td>
<td>(p.Tyr552SerfsX13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x50N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-96-1-2 F 33years</td>
<td>A: 16 years</td>
<td>NA</td>
<td>ex2: c.107_108delAA HTZ</td>
<td>(p.Lys36SerfsX11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: MM</td>
<td></td>
<td>and ex20: c.1758C&gt;G HTZ</td>
<td>(p.Tyr586X)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: x15N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E: Ambulant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA sequence variation</td>
<td>Deleterious effect *</td>
<td>Localisation</td>
<td>Number of alleles</td>
<td>Patient</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>c.457+1insG</td>
<td>Motif: donor site</td>
<td>IVS 5</td>
<td>2</td>
<td>F1-104-1-2 (HOZ)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WT: CAGgtggt (CV 90.50) Mut: CAGgtggt (CV 57.87)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.591C&gt;G</td>
<td>p.Tyr197X</td>
<td>Exon 6</td>
<td>1</td>
<td>F1-133-1-1</td>
<td></td>
</tr>
<tr>
<td>c.799_800delTT</td>
<td>p.Phe267LeufsX5</td>
<td>Exon 8</td>
<td>1</td>
<td>F1-154-1-2</td>
<td></td>
</tr>
<tr>
<td>c.879_883dup</td>
<td>p.As295GlyfsX45</td>
<td>Exon 9</td>
<td>1</td>
<td>F1-205-1-1</td>
<td></td>
</tr>
<tr>
<td>c.1157_1168delTCCGGGCGAGG</td>
<td>p.Phe386_Asp390delinsTyr</td>
<td>Exon 12</td>
<td>1</td>
<td>F1-14-1-1</td>
<td></td>
</tr>
<tr>
<td>c.1617C&gt;G</td>
<td>p.Tyr539X</td>
<td>Exon 18</td>
<td>1</td>
<td>F1-57-1-1</td>
<td></td>
</tr>
<tr>
<td>c.1655_1668delATCGTGCCCGGCTT</td>
<td>p.Tyr552SerfsX13</td>
<td>Exon 19</td>
<td>1</td>
<td>F1-92-1-2</td>
<td></td>
</tr>
<tr>
<td>c.1948delC</td>
<td>p.Leu650TyrfsX6</td>
<td>Exon 21</td>
<td>2</td>
<td>F1-190-1-1 (HOZ)</td>
<td></td>
</tr>
<tr>
<td>c.2511+1G&gt;A</td>
<td>Motif: donor site</td>
<td>IVS 24</td>
<td>2</td>
<td>F1-140-1-2, F1-140-2-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WT: AAAtgagt (CV 87.31) Mut: AAAtgagt (CV 60.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.3225delT</td>
<td>p.Phe1075LeufsX45</td>
<td>Exon 30</td>
<td>2</td>
<td>F1-192-1-1</td>
<td></td>
</tr>
<tr>
<td>c.3389_3399dupTCTCCACCTTG</td>
<td>p.Phe1135ProfsX3</td>
<td>Exon 31</td>
<td>2</td>
<td>F1-103-1-1, F1-103-2-1</td>
<td></td>
</tr>
<tr>
<td>c.3517dupT</td>
<td>p.Ser1173PhefsX2</td>
<td>Exon 32</td>
<td>1</td>
<td>F1-187-1-1</td>
<td></td>
</tr>
<tr>
<td>c.3687C&gt;A</td>
<td>p.Tyr1229X</td>
<td>Exon 33</td>
<td>1</td>
<td>F1-154-1-2</td>
<td></td>
</tr>
<tr>
<td>c.3702+1G&gt;A</td>
<td>Motif: donor site</td>
<td>IVS 33</td>
<td>1</td>
<td>F1-19-1-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WT: TATgtgagt (CV 85.99) Mut: TATatgagt (CV 59.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.4005+1G&gt;A</td>
<td>Motif: donor site</td>
<td>IVS 37</td>
<td>2</td>
<td>F1-40-1-2, F1-114-1-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WT: GAGgtgagc (CV 94.91) Mut: GAGgtgagc (CV 68.07)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.4191C&gt;G</td>
<td>p.Tyr1397X</td>
<td>Exon 39</td>
<td>1</td>
<td>F1-55-1-1</td>
<td></td>
</tr>
<tr>
<td>c.5767+1G&gt;A</td>
<td>Motif: donor site</td>
<td>IVS 51</td>
<td>2</td>
<td>F1-148-1-1 (HOZ)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WT: TGGtaage (CV 90.99) Mut: TGGtaage (CV 64.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.5805delA</td>
<td>p.Ala1936ProfsX30</td>
<td>Exon 52</td>
<td>2</td>
<td>F1-156-1-2 (HOZ)</td>
<td></td>
</tr>
<tr>
<td>c.5871_5872delGT</td>
<td>p.Ser1958ProfsX3</td>
<td>Exon 52</td>
<td>1</td>
<td>F1-179-1-1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Novel nonsense-, frameshifting-, splice-donor-site- and splice-acceptor-site mutations identified in this study.
Mutation numbering is based on cDNA sequence (human DYSF, GenBank NM_003494.2) according to journal guidelines (www.hgvs.org/mutnomen), and as detailed in “Patients, Materials and Methods”.

* Deleterious effects at the protein level are predicted from the DNA sequence variation. Recurrent mutations are in bold.

Table 3: Previously reported disease-causing missense mutations, and novel missense and isosemantic (italized) exonic variants identified in this study.

Mutation numbering is based on cDNA sequence (human DYSF, GenBank NM_003494.2) according to journal guidelines (www.hgvs.org/mutnomen), and as detailed in “Patients, Materials and Methods”.

* Mutations/Variants identified in patients presenting more than two mutations initially considered as possibly disease-causing

** Exclusion based on simultaneous identification of two additional mutations clearly considered as disease-causing, in the same patient

*** Pathogenicity score using UMDpredictor (Frederic et al., submitted)

**** Predicted effect determined as follows depending on the calculated UMDpredictor score:

<50: polymorphism; ≥50 and <65: probable polymorphism; ≥65 and <75: probably pathogenic; ≥75: pathogenic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sequence variation</th>
<th>Predicted amino-acid variation</th>
<th>Exon</th>
<th>Number of patients</th>
<th>Reports of the variant and information on pathogenicity</th>
<th>Domain</th>
<th>Conservation</th>
<th>SIFT score</th>
<th>BLOSUM62 score</th>
<th>Biochemical Value</th>
<th>ESE3 modif</th>
<th>Splice site</th>
<th>Pathogenicity score***</th>
<th>Conclusion of predictive Analysis****</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-92-1-2</td>
<td>c.154T&gt;C</td>
<td>p.Trp52Arg</td>
<td>3</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>C2 Domain</td>
<td>1</td>
<td>0.01</td>
<td>-3.00</td>
<td>0.38</td>
<td>SRp40 [3.60]</td>
<td>No impact</td>
<td>93</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>F1-65-1-2</td>
<td>c.251C&gt;T</td>
<td>p.Ala84Val</td>
<td>4</td>
<td>1</td>
<td>This study</td>
<td>C2 Domain</td>
<td>0.93</td>
<td>0.33</td>
<td>0.88</td>
<td>0.75</td>
<td>No impact</td>
<td>41</td>
<td>Polymorphism</td>
<td></td>
</tr>
<tr>
<td>F1-20-1-2</td>
<td>c.463G&gt;A</td>
<td>p.Gly155Arg</td>
<td>6</td>
<td>1</td>
<td>This study</td>
<td>0.5</td>
<td>0.58</td>
<td>-2.00</td>
<td>0.13</td>
<td>No impact</td>
<td>82</td>
<td>Pathogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-169-1-1, F1-113-1-1</td>
<td>c.509C&gt;A</td>
<td>p.Ala170Glu</td>
<td>6</td>
<td>2</td>
<td>Previously reported* as pathogenic/ unclear</td>
<td>0.5</td>
<td>0.11</td>
<td>-1.00</td>
<td>0.21</td>
<td>No impact</td>
<td>71</td>
<td>Probably Pathogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-18-1-2 (HOZ)</td>
<td>c.565C&gt;G</td>
<td>p.Leu189Val</td>
<td>6</td>
<td>1</td>
<td>Previously reported* as pathogenic/ unclear</td>
<td>0.64</td>
<td>0.09</td>
<td>1.00</td>
<td>0.88</td>
<td>Potential donor splice site [81.82]</td>
<td>29</td>
<td>Polymorphism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-50-1-2</td>
<td>c.701G&gt;A</td>
<td>p.Gly234Glu</td>
<td>7</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>C2 Domain</td>
<td>0.71</td>
<td>0.03</td>
<td>-2.00</td>
<td>0.21</td>
<td>No impact</td>
<td>86</td>
<td>Pathogenic</td>
<td></td>
</tr>
<tr>
<td>F1-155-1-2</td>
<td>c.757C&gt;T</td>
<td>p.Arg253Trp</td>
<td>7</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>C2 Domain</td>
<td>0.79</td>
<td>0.02</td>
<td>-3.00</td>
<td>0.38</td>
<td>SRp55 [4.13]</td>
<td>No impact</td>
<td>93</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>F1-74-1-2</td>
<td>c.797T&gt;C</td>
<td>p.Leu266Pro</td>
<td>8</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>C2 Domain</td>
<td>0.79</td>
<td>0.02</td>
<td>-3.00</td>
<td>0.67</td>
<td>No impact</td>
<td>69</td>
<td>Probably Pathogenic</td>
<td></td>
</tr>
<tr>
<td>F1-57-1-1</td>
<td>c.851T&gt;C</td>
<td>p.Ile284Thr</td>
<td>8</td>
<td>1</td>
<td>This study</td>
<td>C2 Domain</td>
<td>0.79</td>
<td>0.01</td>
<td>-3.00</td>
<td>0.42</td>
<td>SF2/ASF [2.23]</td>
<td>No impact</td>
<td>93</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Patient</td>
<td>Sequence variation</td>
<td>Predicted amino-acid variation</td>
<td>Exon</td>
<td>Number of patients</td>
<td>Reports of the variant and information on pathogenicity</td>
<td>Domain</td>
<td>Conservation</td>
<td>SIFT score</td>
<td>BLOSUM62 score</td>
<td>Biochemical Value</td>
<td>ESE modif</td>
<td>Splice site</td>
<td>Pathogenicity score***</td>
<td>Conclusion of predictive Analysis****</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
<td>-------------------------------</td>
<td>------</td>
<td>--------------------</td>
<td>------------------------------------------------------</td>
<td>--------</td>
<td>--------------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>F1-131-1-1</td>
<td>c.895G&gt;A</td>
<td>p.Gly299Arg</td>
<td>9</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>C2 Domain</td>
<td>0.86</td>
<td>0.01</td>
<td>-2.00</td>
<td>0.13</td>
<td>SRp40 [2.7]</td>
<td>Potential acceptor splice site [91.47]</td>
<td>100</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>F1-31-1-2</td>
<td>c.896G&gt;A</td>
<td>p.Gly299Glu</td>
<td>9</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>C2 Domain</td>
<td>0.86</td>
<td>0.02</td>
<td>-2.00</td>
<td>0.21</td>
<td></td>
<td>Potential acceptor splice site [81.74]</td>
<td>99</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>F1-113-1-1</td>
<td>c.1004G&gt;C</td>
<td>p.Gly335Ala</td>
<td>11</td>
<td>1</td>
<td>This study, exclusion of pathogenicity in patient F1-113-1-1**</td>
<td>Ferlin family domain</td>
<td>0.71</td>
<td>0.00</td>
<td>0.00</td>
<td>0.75</td>
<td>SF2/ASF [3.53]</td>
<td>SC35 [2.84]</td>
<td>No impact</td>
<td>59</td>
</tr>
<tr>
<td>F1-153-1-1, F1-11-1-1</td>
<td>c.1020C&gt;A</td>
<td>p.Ser340Arg</td>
<td>11</td>
<td>2</td>
<td>Previously reported* as pathogenic</td>
<td>Ferlin family domain</td>
<td>0.71</td>
<td>0.10</td>
<td>-1.00</td>
<td>0.29</td>
<td></td>
<td></td>
<td>No impact</td>
<td>71</td>
</tr>
<tr>
<td>F1-65-1-2</td>
<td>c.1120G&gt;C</td>
<td>p.Val374Leu</td>
<td>12</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>Ferlin family domain</td>
<td>0.79</td>
<td>0.40</td>
<td>1.00</td>
<td>0.88</td>
<td></td>
<td></td>
<td>No impact</td>
<td>29</td>
</tr>
<tr>
<td>F1-83-1-2</td>
<td>c.1168G&gt;A</td>
<td>p.Asp390Asn</td>
<td>12</td>
<td>2</td>
<td>Previously reported* as unclear</td>
<td>C2 Domain</td>
<td>0.93</td>
<td>0.28</td>
<td>1.00</td>
<td>0.75</td>
<td>SF2/ASF [4.01]</td>
<td>No impact</td>
<td>41</td>
<td>Polymorphism</td>
</tr>
<tr>
<td>F1-184-1-2</td>
<td>c.1276G&gt;A</td>
<td>p.Gly426Arg</td>
<td>13</td>
<td>1</td>
<td>This study</td>
<td>C2 Domain</td>
<td>1</td>
<td>0.03</td>
<td>-2.00</td>
<td>0.13</td>
<td>SRp55 [3.56]</td>
<td>Potential acceptor splice site [70.48]</td>
<td>100</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>F1-65-1-2, F1-65-2-1 (HOZ), F1-138-1-1 (HOZ)</td>
<td>c.1362C&gt;T</td>
<td>p.Ser454Ser</td>
<td>15</td>
<td>3</td>
<td>This study, exclusion of pathogenicity in patient F1-138-1-1**</td>
<td>C2 Domain</td>
<td>0.86</td>
<td>1.00</td>
<td>4.00</td>
<td>1.00</td>
<td></td>
<td>No impact</td>
<td>18</td>
<td>Polymorphism</td>
</tr>
<tr>
<td>F1-37-1-1</td>
<td>c.1368C&gt;G</td>
<td>p.Cys456Trp</td>
<td>15</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>C2 Domain</td>
<td>0.93</td>
<td>0.03</td>
<td>-2.00</td>
<td>0.38</td>
<td>SRp55 [3.17]</td>
<td>No impact</td>
<td>86</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>F1-58-1-1, F1-6-1-1 (HOZ), F1-113-1-1, F1-114-1-2, F1-14-1-1, F1-49-1-2</td>
<td>c.1663C&gt;T</td>
<td>p.Arg555Trp</td>
<td>19</td>
<td>6</td>
<td>Previously reported* as pathogenic</td>
<td>0.71</td>
<td>0.01</td>
<td>-3.00</td>
<td>0.38</td>
<td></td>
<td>No impact</td>
<td>88</td>
<td>Pathogenic</td>
<td></td>
</tr>
<tr>
<td>F1-188-1-2 (HOZ)</td>
<td>c.1852G&gt;A</td>
<td>p.Gly618Arg</td>
<td>20</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>0.71</td>
<td>0.00</td>
<td>-2.00</td>
<td>0.13</td>
<td></td>
<td>No impact</td>
<td>94</td>
<td>Pathogenic</td>
<td></td>
</tr>
<tr>
<td>F1-54-1-1</td>
<td>c.1980G&gt;A</td>
<td>p.Val660Val</td>
<td>21</td>
<td>1</td>
<td>This study</td>
<td></td>
<td>0.71</td>
<td>1.00</td>
<td>4.00</td>
<td>1.00</td>
<td></td>
<td>No impact</td>
<td>18</td>
<td>Polymorphism</td>
</tr>
<tr>
<td>F1-61-1-2</td>
<td>c.2192C&gt;G</td>
<td>p.Pro731Arg</td>
<td>23</td>
<td>1</td>
<td>This study</td>
<td>Ferlin family domain</td>
<td>0.71</td>
<td>0.45</td>
<td>-2.00</td>
<td>0.17</td>
<td>SRp40 [3.82]</td>
<td>No impact</td>
<td>82</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Patient</td>
<td>Sequence variation</td>
<td>Predicted amino-acid variation</td>
<td>Exon</td>
<td>Number of patients</td>
<td>Reports of the variant and information on pathogenicity</td>
<td>Domain</td>
<td>Conservation</td>
<td>SIFT score</td>
<td>BLOSUM62 score</td>
<td>Biochemical Value</td>
<td>ESE modif</td>
<td>Splice site</td>
<td>Pathogenicity score***</td>
<td>Conclusion of predictive Analysis****</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>-------------------------------</td>
<td>------</td>
<td>-------------------</td>
<td>---------------------------------------------------</td>
<td>--------</td>
<td>--------------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>F1-18-1-2 (HOZ)</td>
<td>c.2283C&gt;A</td>
<td>p.Gly761GLY</td>
<td>23</td>
<td>1</td>
<td>This study, pathogenicity excluded in patient F-18-1-2***</td>
<td></td>
<td>0.64</td>
<td>0.43</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
<td>No impact</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>F1-54-1-1</td>
<td>c.2456G&gt;A</td>
<td>p.Arg819Gln</td>
<td>24</td>
<td>1</td>
<td>This study</td>
<td>Ferlin family domain</td>
<td>0.64</td>
<td>0.60</td>
<td>1.00</td>
<td>0.50</td>
<td></td>
<td>Potential acceptor splice site [98.99]</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>F1-174-1-1</td>
<td>c.2790G&gt;C</td>
<td>p.Trp930Cys</td>
<td>26</td>
<td>1</td>
<td>Previously reported** as pathogenic</td>
<td>Repeated Dysf domain ?</td>
<td>0.71</td>
<td>0.00</td>
<td>-2.00</td>
<td>0.38</td>
<td></td>
<td>No impact</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>F1-80-1-0</td>
<td>c.3065G&gt;A</td>
<td>p.Arg1022Gln</td>
<td>29</td>
<td>1</td>
<td>Previously reported* as unclear</td>
<td>Repeated Dysf domain ?</td>
<td>0.64</td>
<td>0.62</td>
<td>1.00</td>
<td>0.50</td>
<td>SF2/ASF [3.16] SRp55 [3.08]</td>
<td>Potential acceptor splice site [81.31]</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>F1-48-1-2, F1-48-2-2</td>
<td>c.3086C&gt;T</td>
<td>p.Pro1029Leu</td>
<td>29</td>
<td>2</td>
<td>This study</td>
<td>Repeated Dysf domain ?</td>
<td>0.64</td>
<td>0.04</td>
<td>-3.00</td>
<td>0.67</td>
<td></td>
<td>No impact</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>F1-65-1-2</td>
<td>c.3113G&gt;A</td>
<td>p.Arg1038Gln</td>
<td>29</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td>Repeated Dysf domain ?</td>
<td>0.64</td>
<td>0.00</td>
<td>1.00</td>
<td>0.50</td>
<td></td>
<td>No impact</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>F1-90-1-0, F1-140-2-1, F1-140-1-2</td>
<td>c.3137G&gt;A</td>
<td>p.Arg1046His</td>
<td>29</td>
<td>3</td>
<td>Previously reported** as pathogenic/ unclear</td>
<td>Repeated Dysf domain ?</td>
<td>0.64</td>
<td>0.00</td>
<td>0.00</td>
<td>0.58</td>
<td>SF55 [3.17]</td>
<td>No impact</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>F1-71-1-2</td>
<td>c.3683T&gt;C</td>
<td>p.Leu1228Pro</td>
<td>33</td>
<td>1</td>
<td>This study</td>
<td>C2 Domain</td>
<td>1</td>
<td>0.00</td>
<td>-3.00</td>
<td>0.67</td>
<td></td>
<td>No impact</td>
<td></td>
<td>71</td>
</tr>
<tr>
<td>F1-174-1-1, F1-19-1-1</td>
<td>c.3702T&gt;C</td>
<td>p.Tyr1234Tyr</td>
<td>33</td>
<td>2</td>
<td>This study, pathogenicity excluded in patient F1-174-1-1***</td>
<td>C2 Domain</td>
<td>1</td>
<td>1.00</td>
<td>7.00</td>
<td>1.00</td>
<td></td>
<td>No impact</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>F1-130-1-1, F1-130-2-2</td>
<td>c.3826C&gt;G</td>
<td>p.Leu1276Val</td>
<td>34</td>
<td>2</td>
<td>Previously reported* as pathogenic</td>
<td></td>
<td>1</td>
<td>0.02</td>
<td>1.00</td>
<td>0.88</td>
<td></td>
<td>Potential donor splice site [70.91]</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>F1-54-1-1</td>
<td>c.3973A&gt;G</td>
<td>p.Ile1325Val</td>
<td>37</td>
<td>1</td>
<td>This study</td>
<td></td>
<td>1</td>
<td>0.12</td>
<td>3.00</td>
<td>0.88</td>
<td></td>
<td>No impact</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>F1-82-1-1</td>
<td>c.4089C&gt;T</td>
<td>p.Gly1363Gly</td>
<td>38</td>
<td>1</td>
<td>This study</td>
<td>Possible C2 Domain</td>
<td>1</td>
<td>1.00</td>
<td>6.00</td>
<td>1.00</td>
<td>SF2/ASF [3.16] SRp55 [3.08]</td>
<td>Potential donor splice site [76.91]</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>F1-25-1-1 (HOZ), F1-25-3-1 (HOZ)</td>
<td>c.4323G&gt;A</td>
<td>p.Gln1441Gln</td>
<td>39</td>
<td>1</td>
<td>This study, pathogenicity excluded in patient F1-25-1-1 and F1-25-3-1**</td>
<td></td>
<td>1</td>
<td>1.00</td>
<td>3.00</td>
<td>1.00</td>
<td></td>
<td>Potential acceptor splice site [81.04]</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>F1-47-1-2 (HOZ)</td>
<td>c.4577A&gt;C</td>
<td>p.Lys1526Thr</td>
<td>42</td>
<td>1</td>
<td>This study</td>
<td></td>
<td>1</td>
<td>0.04</td>
<td>-1.00</td>
<td>0.21</td>
<td></td>
<td>No impact</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Patient</td>
<td>Sequence variation</td>
<td>Predicted amino-acid variation</td>
<td>Exon</td>
<td>Number of patients</td>
<td>Reports of the variant and information on pathogenicity</td>
<td>Domain</td>
<td>Conservation</td>
<td>SIFT score</td>
<td>BLOSUM62 score</td>
<td>Biochemical Value</td>
<td>ESE modif</td>
<td>Splice site</td>
<td>Pathogenicity score***</td>
<td>Conclusion of predictive Analysis****</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
<td>-------------------------------</td>
<td>------</td>
<td>-------------------</td>
<td>--------------------------------------------------------</td>
<td>--------</td>
<td>--------------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>-------------</td>
<td>---------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>F1-151-1-2</td>
<td>c.4628G&gt;A</td>
<td>p.Gly1543Asp</td>
<td>42</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td></td>
<td>1</td>
<td>0.00</td>
<td>-1.00</td>
<td>0.29</td>
<td>SRp40 [2.88]</td>
<td>No impact</td>
<td>88</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>F1-155-1-2</td>
<td>c.4731G&gt;A</td>
<td>p.Glu1577Glu</td>
<td>43</td>
<td>1</td>
<td>This study, pathogenicity excluded in patient F1-155-1-2**</td>
<td>Possible C2 Domain</td>
<td>1</td>
<td>1.00</td>
<td>5.00</td>
<td>1.00</td>
<td>No impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-148-1-1 (HOZ)</td>
<td>c.4867C&gt;T</td>
<td>p.Leu1623Leu</td>
<td>44</td>
<td>1</td>
<td>This study, pathogenicity excluded in patient F1-148-1-1**</td>
<td>C2 Domain</td>
<td>1</td>
<td>1.00</td>
<td>4.00</td>
<td>1.00</td>
<td>SF2/ASF [3.08]</td>
<td>3C35 [2.51]</td>
<td>No impact</td>
<td>23</td>
</tr>
<tr>
<td>F1-116-1-1</td>
<td>c.5078G&gt;A</td>
<td>p.Arg1693Gln</td>
<td>46</td>
<td>1</td>
<td>Previously reported* as pathogenic</td>
<td></td>
<td>1</td>
<td>0.00</td>
<td>1.00</td>
<td>0.50</td>
<td>Potential acceptor splice site [70.39]</td>
<td>71</td>
<td>Probably Pathogenic</td>
<td></td>
</tr>
<tr>
<td>F1-18-1-2</td>
<td>c.5243A&gt;T</td>
<td>p.Glu1748Val</td>
<td>47</td>
<td>1</td>
<td>Previously reported* as unclear/ polymorphism</td>
<td></td>
<td>1</td>
<td>0.01</td>
<td>-2.00</td>
<td>0.21</td>
<td>Potential donor splice site [85.82]</td>
<td>88</td>
<td>Pathogenic</td>
<td></td>
</tr>
<tr>
<td>F1-29-1-2, F1-100-1-1</td>
<td>c.5302C&gt;T</td>
<td>p.Arg1768Trp</td>
<td>47</td>
<td>2</td>
<td>Previously reported* as pathogenic/ unclear</td>
<td></td>
<td>1</td>
<td>0.00</td>
<td>-3.00</td>
<td>0.38</td>
<td>SF2/ASF [3.16]</td>
<td>SRp40 [1.1]</td>
<td>SRp40 [2.91]</td>
<td>No impact</td>
</tr>
<tr>
<td>F1-135-1-2, F1-19-1-1</td>
<td>c.5509G&gt;A</td>
<td>p.Asp1837Aas</td>
<td>49</td>
<td>2</td>
<td>Previously reported* as pathogenic</td>
<td>Possible C2 Domain</td>
<td>1</td>
<td>0.00</td>
<td>1.00</td>
<td>0.75</td>
<td>No impact</td>
<td>47</td>
<td>Polymorphism</td>
<td></td>
</tr>
<tr>
<td>F1-49-1-2</td>
<td>c.5829C&gt;A</td>
<td>p.Ser1943Ser</td>
<td>52</td>
<td>1</td>
<td>This study, pathogenicity excluded in patient F1-49-1-2**</td>
<td></td>
<td>1</td>
<td>0.79</td>
<td>4.00</td>
<td>1.00</td>
<td>No impact</td>
<td>18</td>
<td>Polymorphism</td>
<td></td>
</tr>
<tr>
<td>F1-137-1-2, F1-3-2-2, F1-3-1-2, F1-55-1-1</td>
<td>c.5899G&gt;A</td>
<td>p.Gly1967Ser</td>
<td>52</td>
<td>4</td>
<td>This study</td>
<td></td>
<td>0.93</td>
<td>0.03</td>
<td>0.00</td>
<td>0.50</td>
<td>No impact</td>
<td>63</td>
<td>Probable polymorphism</td>
<td></td>
</tr>
<tr>
<td>F1-182-1-2</td>
<td>c.5908C&gt;T</td>
<td>p.Pro1970Ser</td>
<td>52</td>
<td>1</td>
<td>This study</td>
<td></td>
<td>0.93</td>
<td>0.00</td>
<td>-1.00</td>
<td>0.38</td>
<td>No impact</td>
<td>76</td>
<td>Pathogenic</td>
<td></td>
</tr>
<tr>
<td>F1-150-1-2, F1-150-2-2, F1-150-2-2</td>
<td>c.6124C&gt;T</td>
<td>p.Arg2042Cys</td>
<td>54</td>
<td>3</td>
<td>Previously reported* as pathogenic</td>
<td></td>
<td>0.86</td>
<td>0.02</td>
<td>-3.00</td>
<td>0.25</td>
<td>No impact</td>
<td>93</td>
<td>Pathogenic</td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Previously reported intronic variants with unknown pathogenicity, and novel intronic variants identified in this study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intronic sequence variant</th>
<th>Reports of the variant and information on pathogenicity</th>
<th>SSF predictive analysis****</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-104-1-2</td>
<td>IVS1: c.89-29C&gt;G</td>
<td>This study, exclusion of pathogenicity in patient F1.104.1**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-65-2-1</td>
<td>IVS2: c.144+46delG</td>
<td>This study, exclusion of pathogenicity in patient F1.65.2.1**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-111-2-2</td>
<td>IVS3: c.236+20G&gt;A</td>
<td>Previously reported in dbSNP*** (rs12470028). Exclusion of pathogenicity in patient F1.111.2.2**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-61-1-2</td>
<td>IVS4: c.343-29A&gt;G</td>
<td>This study, exclusion of pathogenicity in patient F1.61.1.2**</td>
<td>Branch Point inactivation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WT: caccaAc (CV 72.27)</td>
</tr>
<tr>
<td>F1-170-1-2, F1-170-2-2</td>
<td>IVS5: c.457+17G&gt;C</td>
<td>Previously reported* as unclear</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-3-1-2, F1-11-1-1, F1-30-1-2, F1-31-1-2, F1-49-1-2, F1-55-1-1</td>
<td>IVS6: c.664-17C&gt;T</td>
<td>This study, exclusion of pathogenicity in patient F1.30.1.2**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-103-1-1</td>
<td>IVS7: c.792+11T&gt;C</td>
<td>Previously reported in dbSNP*** (rs13428076). Exclusion of pathogenicity in patient F1.103.1.1**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-151-1-2</td>
<td>IVS10: c.938-34T&gt;A</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-123-1-1</td>
<td>IVS12: c.1180+5G&gt;A</td>
<td>Previously reported* as unclear</td>
<td>Donor Site inactivation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WT: AGAgtgct (CV 73.65)</td>
</tr>
<tr>
<td>F1-123-1-1</td>
<td>IVS13: c.1285-35G&gt;T</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-55-1-1, F1-201-1-2</td>
<td>IVS21: c.2055+105_2055+106delAC</td>
<td>Previously reported in dbSNP*** (rs5832058)</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-58-2-2</td>
<td>IVS28: c.3032-16G&gt;A</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-9-1-2, F1-49-1-2, F1-58-2-2, F1-145-1-1</td>
<td>IVS29: c.3175-61G&gt;C</td>
<td>This study, exclusion of pathogenicity in patient F1.9.1.2**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-54-1-1</td>
<td>IVS29: c.3175-31G&gt;G</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-52-1-2</td>
<td>IVS30: c.3349-54T&gt;G</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-82-1-1</td>
<td>IVS31: c.3442+4A&gt;G</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>Patient</td>
<td>Intronic sequence variant</td>
<td>Reports of the variant and information on pathogenicity</td>
<td>SSF predictive analysis****</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------</td>
<td>-------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>F1-52-1-2</td>
<td>IVS31: c.3442+14C&gt;T</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-52-1-2</td>
<td>IVS32: c.3521-12C&gt;T</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-30-1-2</td>
<td>IVS33: c.3703-12C&gt;T</td>
<td>This study, exclusion of pathogenicity in patient F1.30.1.2**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-25-3-1</td>
<td>IVS35: c.3874-30delG</td>
<td>This study, exclusion of pathogenicity in patient F1.25.3.1**</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-103-1-1</td>
<td>IVS38: c.4168-40G&gt;A</td>
<td>This study, exclusion of pathogenicity in patient F1.103.1.1**</td>
<td>Branch Point inactivation WT: CCCAGAG (CV 77.25) Mut: CCCAGGG (CV 47.63)</td>
</tr>
<tr>
<td>F1-200-1-1</td>
<td>IVS38: c.4168-20G&gt;A</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-143-1-1</td>
<td>IVS41: c.4509+40C&gt;T</td>
<td>This study</td>
<td>no effect</td>
</tr>
<tr>
<td>F1-11-1-1</td>
<td>IVS42: c.4639-38A&gt;G</td>
<td>This study</td>
<td>no effect</td>
</tr>
</tbody>
</table>

(With exception of intronic mutations affecting the consensus AG acceptor, or GT donor sites: see Table 1)

Mutation numbering is based on cDNA sequence (human *DYSF*, GenBank NM_003494.2) according to journal guidelines (www.hgvs.org/mutnomen), and as detailed in “Patients, Materials and Methods”. WT: wild type motif. Mut: mutated motif. CV: calculated consensus site value (threshold=70). HOZ: homozygous.

* Leiden Muscular Dystrophy pages database (www.dmd.nl)
** Exclusion based on simultaneous identification of two additional mutations clearly considered as disease-causing, in the same patient

**** Splicing Sequences Finder: www.umd.be/SSF/
Figure 1. A. Distribution of mutations identified in this study on the DYSF coding sequence, and corresponding protein domains. B. Different types of disease-causing mutations identified in index cases included in this study. For heterozygotes, both disease-causing mutations are counted; for homozygotes, the disease-causing mutation is counted once.

ACKNOWLEDGMENTS

We sincerely thank the patients and their families for their invaluable cooperation. We thank all the clinicians who referred patient samples to our laboratory, in particular Drs. R.H. Jr. Brown, M. Dunand, M. Fardeau, X. Ferrer, C. Guiraud-Chaumeil, T. Kuntzer, D. Menard, S. Odent, N. Romero, T. Stojkovic, P. Van den Bergh, and
all clinicians of the French Network on LGMD. We thank the Assistance Publique des Hôpitaux de Marseille, the French Direction de l’Hôpitalisation et de l’Organisation des Soins, the Association Française contre les Myopathies and the Jain Foundation for supporting this work.

REFERENCES


Mardis ER. 2006. Anticipating the 1,000 dollar genome. Genome Biol 7:112.

