SUPPLEMENTARY MATERIAL FOR:

**Lamin mutation location predicts cardiac phenotype severity–combined analysis of the published literature**

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**SUPPLEMENTARY METHODS**

**In silico predictive algorithms**

To permit classification of variants using the American College of Medical Genetics and Genomics (ACMG) standards each reported variant was examined by the following in silico predictive algorithms:

**MutationTaster**1 available at: http://www.mutationtaster.org/

**PolyPhen-2**2 available at: http://genetics.bwh.harvard.edu/pph2/

**SIFT**3 available at: http://sift.jcvi.org/

**PROVEAN**3 available at: http://provean.jcvi.org

**Condel**4 available at: http://bg.upf.edu/condel

**Manual search strategy**

First we identified a concept table of all free-text terms and controlled vocabulary terms pertinent to lamin heart disease organized as 4 concepts.

|  |  |  |  |
| --- | --- | --- | --- |
| **Concept 1** | **Concept 2** | **Concept 3** | **Concept 4** |
| #1 lamin | #1 dilated cardiomyopathy | #1 sudden cardiac death | #1 atrioventricular block |
| #2 laminopathy | #2 congestive dilated cardiomyopathy | #2 sudden cardiac arrest | #2 implantable cardioverter defibrillator |
| #3 LMNA | #3 hypokinetic non-dilated cardiomyopathy | #3 ventricular arrhythmia | #3 cardiac conduction system disease |
| #4 nuclear envelope | #4 heart failure | #4 malignant ventricular arrhythmia |  |
|  |  | #5 heart transplant |  |

In line with Cochrane guidance, we searched for each identified search term individually, then used the correct Boolean operators to combine the terms. This helped reduce human error and allowed us to see which search terms added value to the search and whether a particular search term produced too many irrelevant results. Here we provide one example of how we approached the search in PubMed:

**1.** Carried out separate searches for each free-text term (Text Words) and controlled vocabulary term (MeSH) in Concept 1 of Concept Table.

**2.** Combined all individual searches for Concept 1 with OR (used the Add link in the History to bring the individual searches back up into the Builder).

**3.** Repeated steps 1 and 2 for all other concepts.

**4.** Combined the OR searches for each concept with AND (used the Add link in the History to bring the individual searches back up into the Builder).

**SUPPLEMENTARY TABLE 1. Genetic variants reported to date in association with lamin A/C heart disease, classified by MOGE(S) nosology**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variant (nucleotide change, predicted amino acid change)** | **Location: Variant type, molecular consequence\*** | **Summative MOGE(S) classification**∞ | **ClinVar Clinical Significance** | **ACMG Assertion of Pathogenicity** | **Ref.#** |
| c.1\_356del, p.Met1? | Exon 1: Large deletion (5’ region including exon 1), predicted protein truncation | MD(SA, CCD, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (Ia) | van Tintelen et al. 20075 |
| c.5delA, p.Glu2GlyfsX94 | Exon 1: Single nucleotide insertion, frameshift and premature termination of translation | NA | N/A | Likely pathogenic (I) | van Rijsingen et al. 20136 |
| c.16C>T, p.Gln6Ter | Exon 1: Single nucleotide substitution, nonsense | MD(SA, CCD, eHF, VA, MVA, ↑CK, <25) OH(LV)+M GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Bécane et al. 20007 |
| c.28insA, p.Thr10AsnfsX31 | Exon 1: Single nucleotide insertion, frameshift and premature termination of translation | MD(SA, CCD, VA, MVA, <40) OH(LV)+M GAD EG SC-IV | Not provided | Likely pathogenic (I) | Sébillon et al. 20038 |
| c.31delC, p.Arg11AlafsX85 (reported as p.Thr10fs85X) | Exon 1: Single nucleotide deletion, frameshift and premature termination of translation | MD(SA, CCD, eHF, VA, MVA, ↑CK, <25, ≥25) OH(LV)+M GAD EG SC-NA | Not Provided | Pathogenic (Ia) | Pasotti et al. 20089 |
| c.46\_49dup, p.Ser18GlnfsX24 | Exon 1: Duplication (4 nucleotides), frameshift and premature termination of translation | MD(CCD, MVA, <40) OH(LV) GAD EG SC-NA | N/A | Pathogenic (Ib) | Ho JCY et al. 201110 |
| c.65C>T, p.Ser22Leu | Exon 1: Single nucleotide substitution, missense | MD(eHF, VA, ≥25) OH(LVRV) GNA EG SC-IV | N/A | Likely pathogenic (II) | Pethig et al. 200411 |
| c.73C>T, p.Arg25Cys | Exon 1: Single nucleotide substitution, missense | MD(eHF, VA, ≥25) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | van Tintelen et al. 200712~ |
| c.73C>G, p.Arg25Gly | Exon 1: Single nucleotide substitution, missense | MD(CCD, eHF, MVA, ↑CK, <25) OH(LV)+M GAD EG SC-IV | Conflicting interpretations of pathogenicity: Pathogenic(1);Uncertain significance(1) | Likely pathogenic (II) | Yuan et al. 200913 |
| c.80C>G, p.Thr27Ser | Exon 1: Single nucleotide substitution, missense | MD(CCD, VA, ↑CK, ≥25) OH(LVRV, A) GAD EG SC-I | Uncertain significance | Likely pathogenic (II) | Parnham et al. 201514 |
| c.82C>T, p.Arg28Trp | Exon 1: Single nucleotide substitution, missense | MD(CCD, eHF, <40) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | Pasotti et al. 20089 |
| c.106C>T, p.Gln36Ter | Exon 1: Single nucleotide substitution, nonsense | MD(CCD, VA, MVA, ≥25) OH(LV) GAD EG SC-III | Not provided | Likely pathogenic (II) | Arbustini et al. 200915 |
| c.134A>G, p.Tyr45Cys | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD) OH(LV)+M GAD EG SC-NA | Uncertain significance | Likely pathogenic (II) | Arola et al. 200416 |
| c.154C>G, p.Leu52Val | Exon 1: Single nucleotide substitution, missense | NA | Likely pathogenic | Likely pathogenic (II) | https://www.ncbi.nlm.nih.gov/clinvar/variation/48042/ |
| c.155T>C , p.Leu52Pro | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, VA, MVA, ↑CK, <25) OH(LV) GAD EG SC-III | Not provided | Likely pathogenic (II) | Rudenskaya et al. 200817 |
| c.158A>T, p.Glu53Val | Exon 1: Single nucleotide substitution, missense | MD(CCD, eHF, ≥25) OH(LV) GDN EG SC-IV | Not provided | Likely pathogenic (II) | Song et al. 200718 |
| c.165delG, p.Asn56ThrfsX40 | Exon 1: Single nucleotide deletion, frameshift and premature termination of translation | MD(CCD, ≥25) OH(LV) GAD EG SC-II | N/A | Likely pathogenic (I) | Verga et al. 200319 |
| c.176T>G, p.Leu59Arg | Exon 1: Single nucleotide substitution, missense | MD(MVA, <25) OH(LV) + L + E GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | McPherson E et al. 200920 |
| c.178C>G, p.Arg60Gly | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, eHF, MVA, ↑CK, ≥25) OH(LV) GAD EG SC-IV | Pathohenic | Pathogenic (II) | Fatkin et al. 199921 |
| c.184C>G, p.Arg62Gly | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, ↑CK, ≥25) OH(LV, A)+M+L+E GAD EG SC-IV | Pathogenic: Familial partial lipodystrophy 2, not provided | Likely pathogenic (II) | Garg et al. 200222 |
| c.201C>G and 202delC, p.Thr64SerfsX32(reported as c.291C>G and 292delC) | Exon 1: Single nucleotide substitution and single nucleotide deletion, frameshift and premature termination of translation | NA | N/A | Likely pathogenic (I) | van Rijsingen et al. 20136 |
| c.203\_208delAGGTGG, p.Glu68\_Val69del | Exon 1: Deletion (6 nucleotides), inframe deletion of 2 amino acids | ME(CCD, ↑CK, ≥25) OH(LV)+M GAD EG SC-I | Not provided | Likely pathogenic (II) | Arbustini et al. 200723 |
| c.215G>T, p.Arg72Leu | Exon 1: Single nucleotide substitution, missense | MD(eHF, VA) OH(LV) GAD EG SC-IV | Uncertain significance | VUS - not enough evidence | Kumar et al. 201624 |
| c.232A>G, p.Lys78Glu (reported as c.444A>G) | Exon 1: Single nucleotide substitution, missense | MD(CCD, VA, ≥25) OH(LV) GAD EG SC-IV | Uncertain significance | VUS - not enough evidence | Kourgiannidis et al. 201325 |
| c.244G>A, p.Glu82Lys | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, eHF, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (III) | Wang et al. 200626 |
| c.250G>A, p.Glu84Lys | Exon 1: Single nucleotide substitution, missense | NA | N/A | Likely pathogenic (II) | van Rijsingen et al. 20136 |
| c.254T>G, p.Leu85Arg | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, eHF, MVA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Fatkin et al. 199921 |
| c.266G>T, p.Arg89Leu | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Taylor et al. 200327 |
| c.273C>A, p.Thr91Thr | Exon 1: Single nucleotide substitution, missense | NA | N/A | VUS - not enough evidence | Fokkema et al. 200528 |
| c.274C>T, p.Leu92Phe | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA< ≥25) OH(LV) GAD EG SC-NA | Not provided | Likely pathogenic (II) | Millat et al. 200929, Chami et al. 201230 |
| c.289A>G, p.Lys97Glu | Exon 1: Single nucleotide substitution, missense | MD(CCD, eHF, VA, ↑CK, ≥25) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | Arbustini et al. 200231 |
| c.302G>C, p.Arg101Pro | Exon 1: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Uncertain significance | Likely pathogenic (II) | Parks et al. 200932 |
| c.328C>A, p.Arg110Ser | Exon 1: Single nucleotide substitution, missense | MD OH(LV) GAD EG SC-NA | Uncertain significance | VUS - not enough evidence | Botto et al. 201133 |
| c.331G>T, p.Glu111Ter | Exon 1: Single nucleotide substitution, nonsense | MD(CCD, eHF, VA, ≥25) OH(LV) GAD EG SC-IV | N/A | Pathogenic (Ia) | Arbustini et al. 200231 |
| c.336\_340delGTTTA, p.Phe113GlyfsX12 | Exon 1: Deletion (5 nucleotides), frameshift and premature termination of translation | NA | N/A | Pathogenic (Ic) | van Rijsingen et al. 20136 |
| c.348dupG, p.Lys117GlufsX10 | Exon 1: Single nucleotide duplication, frameshift and premature termination of translation | MD(SA, CCD, VA, MVA, ≥25) OH(LV) GAD EG SC-NA | Pathogenic | Pathogenic (Ia) | Pan et al. 200934 |
| c.350A>G, p.Lys117Arg | Exon 1: Single nucleotide substitution, missense | NA | Conflicting interpretations of pathogenicity: Likely pathogenic(1);Uncertain significance(1) | VUS - not enough evidence | van Rijsingen et al. 20136 |
| c.356+1G>C | Intron 1: Single nucleotide substitution, predicted abnormal splicing | NA | Likely pathogenic | VUS - not enough evidence | van Rijsingen et al. 20136 |
| c.357−1G>T | Intron 1: Single nucleotide substitution, predicted abnormal splicing | MD(SA, CCD, eHF, VA, <25) OH(LV) GAD EG SC-IV | Not provided | VUS - not enough evidence | Parks et al. 200932 |
| c.367–369delAAG, p.Lys123del | Exon 2: Deletion (3 nucleotides), inframe deletion of single amino acid | MD(SA, CCD, VA, MVA, ↑CK, <25) OH(LV) GAD EG SC-IV | Likely pathogenic | Likely pathogenic (II) | Keller et al. 201235 |
| c.373G>A, p.Gly125Ser | Exon 2: Single nucleotide substitution, missense | ME(SA) OH(LV) GDN EG SC-NA | Not provided | VUS - not enough evidence | Brauch et al. 201036 |
| c.383\_384ins24bp, p.Ile128-Ala129insRVTLISSR | Exon 2: Insertion (24 nucleotides), inframe insertion of 8 amino acids | MD(CCD) OH(LV) GAD EG SC-III | N/A | Pathogenic (Ic) | Millat et al. 200929 |
| c.394G>C, p.Ala132Pro | Exon 2: Single nucleotide substitution, missense | MD(SA, CCD, eHF, ≥25) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | Kärkkäinen et al. 200637 |
| c.397C>G,p.Arg133Gly | Exon 2: Single nucleotide substitution, missense | MD(eHF, VA) OH(LV) GNA EG SC-IV | N/A | VUS - not enough evidence | Kumar et al. 201624 |
| c.418–438dup, p.Leu140\_Ala146dup | Exon 2: Duplication (21 nucleotides), inframe duplication of 7 amino acids | MD(SA, CCD, eHF, VA, MVA, <25) OH(LVRV)+M GAD EG SC-IV | N/A | Pathogenic (II) | Forleo et al. 201538 |
| c.424\_425ins21nt, p.Leu141\_Asn142insLysAspLeuAspAlaLeuLeu | Exon 2: Duplication (21 nucleotides), inframe duplication of 7 amino acids | MD(SA, CCD, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | N/A | VUS - not enough evidence | Perrot et al. 200639 |
| c.427T>C, p.Ser143Pro | Exon 2: Single nucleotide substitution, missense | MD(CCD, eHF, VA, MVA) OH GNA EG SC-IV | Pathogenic | Pathogenic (II) | Kärkkäinen et al. 200440 |
| c.435delG, p.Ala146ProfsX2 | Exon 2: Single nucleotide deletion, frameshift and premature termination of translation | MD(CCD, eHF, VA, <25) OH(LV)+M GAD EG SC-IV | N/A | Pathogenic (Id) | Simms-Williams et al. 201341 |
| c.436\_446delGCCGCACTGAG, p.Ala146HisfsX5 | Exon 2: Deletion (11 nucleotides), frameshift and premature termination of translation | ME(CCD, VA, MVA) OH(LV) GAD EG SC-I | N/A | Pathogenic (Ib) | Nishi et al. 201642 |
| NM\_005572.3:c.449C>T, p.Thr150Ile | Exon 2: Single nucleotide substitution, missense | MD OH(LV) GNA EG SC-NA | N/A | VUS - not enough evidence | Hirlte-Lewis et al. 201343 |
| c.459\_462delTGAG, p.Ser153ArgfsX22 | Exon 2: Deletion (4 nucleotides), frameshift and premature termination of translation | NA | N/A | Pathogenic (Ic) | van Rijsingen et al. 20136 |
| c.481G>A, p.Glu161Lys | Exon 2: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (II) | Sébillon et al. 20038 |
| c.485T>C, p.Leu162Pro | Exon 2: Single nucleotide substitution, missense | MD(SA, VA, MVA, CCD, eHF, ↑CK, <25) OH(LV)+M GAD EG SC-IV | Likely pathogenic | Likely pathogenic (II) | Brodsky GL et al. 200044 |
| c.497G>C, p.Arg166Pro | Exon 2: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, <25) OH(LV) GAD EG SC-IV | Pathogenic/Likely pathogenic | Likely pathogenic (II) | Parks et al. 200932 |
| NM\_005572.3:c.513+1G>C | Intron 2: Single nucleotide substitution, predicted abnormal splicing | MD(SA, MVA, CCD, ↑CK, ≥25) OH(LV, RV, A)+M+N GAD EG SC-II | Likely pathogenic | Likely pathogenic (II) | Chen C et al. 201345 |
| c.514-1G>A | Intron 2: Single nucleotide substitution, predicted abnormal splicing | MD(VA, MVA, <40) OH(LV) GDN EG SC-IV | Not provided | VUS - not enough evidence | Pasotti et al. 20089 |
| c.514\_1995del, p.Leu172fsX22 | Exon 3: Deletion from exon 3 to 12, frameshift and premature termination of translation | MD(VA, ≥25) OH(LV) GDN EG SC-II | N/A | Pathogenic (Ic) | Gupta et al. 201046 |
| c.548T>C, p.Leu183Pro | Exon 3: Single nucleotide substitution, missense | MD(CCD, <40) OH(LV) GDN EG SC-NA | Not provided | Likely pathogenic (II) | Pasotti et al. 20089 |
| c.556G>A, p.Glu186Lys | Exon 3: Single nucleotide substitution, missense | MD(CCD, eHF, ≥25) OH(LV) GDN EG SC-IV | Not provided | Pathogenic (II) | Song et al. 200718 |
| c.565C>T, p.Arg189Trp | Exon 3: Single nucleotide substitution, missense | MD(VA, MVA, ≥25) OH(LV) GAD EG SC-II | Uncertain significance | Pathogenic (II) | Botto et al. 201047 |
| c.[1699 to 183\_1699–160inv24; 568\_1699–184del; 1699 to 159\_1995+6997del] | Exon 3 + 10: Complex double deletion with break point (24-bp inversion flanked by 3.8-kb deletion upstream & 7.8-kb deletion downstream) | MD(SA, CCD, VA, MVA, <25) OH(LV, A) GAD EG SC-NA | N/A | Pathogenic (Ia) | Marsman et al., 201148 |
| c.568C>T, p.Arg190Trp | Exon 3: Single nucleotide substitution, missense | MD(SA, CCD, VA, MVA, ↑CK, <25) OH(LV) GAD EG SC-NA | Pathogenic | Pathogenic (IIIb) | Arbustini et al. 200231 |
| c.569G>A, p.Arg190Gln | Exon 3: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Parks et al. 200932 |
| c.575A>T, p.Asp192Val | Exon 3: Single nucleotide substitution, missense | MD(eHF, MVA, <25) OH(LV) GAD EG SC-IV | Not provided | Pathogenic (II) | Subramanyam et al. 201049 |
| c.575A>G, p.Asp192Gly | Exon 3: Single nucleotide substitution, missense | MD(CCD, eHF, MVA) OH(LV) GAD EG SC-IV | Not provided | Pathogenic (II) | Sylvius et al. 200550 |
| c.585C>A, p.Asn195Lys | Exon 3: Single nucleotide substitution, missense | MD(CCD, eHF, MVA, ≥25) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | van Tintelen et al. 200712 |
| c.585C>G, p.Asn195Lys | Exon 3: Single nucleotide substitution, missense | MD(SA, CCD, eHF, MVA, <25) OH(LV, A) GAD EG SC-IV | Pathogenic | Pathogenic (II) | Fatkin et al. 199921 |
| c.607G>A, p.Glu203Lys | Exon 3: Single nucleotide substitution, missense | MD(SA, CCD, eHF, MVA) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (II) | Jakobs et al. 200151 |
| c.608A>G, p.Glu203Gly | Exon 3: Single nucleotide substitution, missense | MD(SA, CCD, eHF, MVA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (II) | Fatkin et al. 199921 |
| c.608A>T, p.Glu203Val | Exon 3: Single nucleotide substitution, missense | MD(CCD, eHF) OH(LV) GAD EG SC-IV | Not provided | Pathogenic (II) | Perrot et al. 200952 |
| c.624\_626delAAG, p.Lys208del | Exon 3: Deletion (3 nucleotides), inframe deletion of single amino acid | MD(VA, MVA, ↑CK, ≥25) OH(LV)+M GAD EG SC-NA | Pathogenic | Pathogenic (IIIb) | van Tintelen et al. 200712~ |
| c.629T>G, p.Ile210Ser | Exon 3: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Uncertain significance | Likely pathogenic (II) | Parks et al. 200932 |
| c.639+1G>A | Intron 3: Single nucleotide substitution, predicted abnormal splicing | NA | N/A | VUS - not enough evidence | van Rijsingen et al. 20136 |
| c.640-10A>G | Intron 3: Single nucleotide substitution, predicted abnormal splicing | MD(SA, CCD, eHF, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic/Likely pathogenic | Likely pathogenic (II) | Otomo et al. 200553 |
| c.643C>G, p.Leu215Val | Exon 4: Single nucleotide substitution, missense | NA | Uncertain significance | VUS - not enough evidence | van Rijsingen et al. 20136 |
| c.644T>C, p.Leu215Pro | Exon 4: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (II) | Hershberger et al. 200254 |
| c.646C>T, p.Arg216Cys | Exon 4: Single nucleotide substitution, missense | MD(CCD, VA, ≥25) OH(LV) GAD EG SC-I | Conflicting interpretations of pathogenicity: Likely pathogenic(1);Uncertain significance(4) | VUS - not enough evidence | van Rijsingen et al. 20136, Rasmussen et al. 201755 |
| c.656A>C, p.Lys219Thr | Exon 4: Single nucleotide substitution, missense | MD(CCD, <40) OH(LV) GAD EG SC-NA | Uncertain significance | Likely pathogenic (II) | Pasotti et al. 20089 |
| c.657G>C, p.Lys219Asn | Exon 4: Single nucleotide substitution, missense | MD(SA, CCD, eHF, MVA, ≥25) OH(LV) GAD EG SC-NA | N/A | Pathogenic (IIIb) | Arbustini et al. 200723 |
| NM\_005572.3(LMNA):c.673C>T, p.Arg225Ter | Exon 4: Single nucleotide substitution, nonsense | MD(SA, CCD, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (Ia) | Jakobs et al. 200151 |
| c.700C>T, p.Gln234Ter | Exon 4: Single nucleotide substitution, nonsense | MD(CCD, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic/Likely pathogenic | Likely pathogenic (II) | Parks et al. 200932 |
| c.706delG, p.Glu236SerfsX262 | Exon 4: Single nucleotide deletion, frameshift and premature termination of translation | NA | N/A | Pathogenic (Ic) | van Rijsingen et al. 20136 |
| c.725C>T, p.Ala242Val | Exon 4: Single nucleotide substitution, missense | MD(MVA, ≥25) OH(LRV) GAD EG SC-IV | Pathogenic/Likely pathogenic | Likely pathogenic (II) | https://www.ncbi.nlm.nih.gov/clinvar/variation/48076 |
| c.736C>T, p.Gln246Ter | Exon 4: Single nucleotide substitution, nonsense | MD(CCD, ≥25) OH(LV) GAD EG SC-NA | Pathogenic | Pathogenic (Id) | Pasotti et al. 20089 |
| c.746G>A, p.Arg249Gln | Exon 4: Single nucleotide substitution, missense | ME(SA, <25) OH(A)+M GDN EG SC-IV | Likely pathogenic | Likely pathogenic (II) | Bonne G et al. 200056 |
| c.751dup, p.Gln251ProfsX3 | Exon 4: Single nucleotide duplication, frameshift and premature termination of translation | MD(CCD) OH(LV) GNA EG SC-NA | Conflicting interpretations of pathogenicity: Likely pathogenic(1);Uncertain significance(1) | Pathogenic (Id) | Arola et al. 200416 |
| c.763delC, p.Gln255Argfs | Exon 4: Single nucleotide deletion, frameshift and premature termination of translation | NA | N/A | Pathogenic (Ic) | https://www.ncbi.nlm.nih.gov/clinvar/variation/48079 |
| c.768G>A, p.Val256Val | Exon 4: Single nucleotide substitution, missense | MD(CCD) OH(LV) GAD EG SC-NA | Likely pathogenic | VUS - not enough evidence | Ito et al. 201457 |
| c.775T>C, p.Tyr259His | Exon 4: Single nucleotide substitution, missense | MD(SA, CCD, VA, ≥25) OH(LV) GAD EG SC-I | Pathogenic | Likely pathogenic (II) | Saga et al. 200958 |
| c.777T>A, p.Tyr259Ter | Exon 4: Single nucleotide substitution, nonsense | ME(SA, CCD, ↑CK, ≥25) OH GAD EG SC-I | Not provided | Pathogenic (Ia) | van Tintelen et al. 200712~ |
| c.780G>C, p.Lys260Asn | Exon 4: Single nucleotide substitution, missense | MD(CCD) OH(LV) GAD EG SC-NA | Pathogenic | Pathogenic (IIIb) | Arbustini et al. 200559 |
| c.781\_783delAAG, p.Lys261del | Exon 4: Deletion (3 nucleotides), in-frame deletion | MD(SA, MVA, ↑CK, <25) OH(LV)+M GAD EG SC-I | N/A | Pathogenic (Id) | Felice K et al. 200060 |
| c.799T>C, p.Tyr267His | Exon 4: Single nucleotide substitution, missense | MD(SA, CCD, VA, ≥25) OH(LV, A)+M GAD EG SC-NA | Pathogenic/Likely pathogenic | Pathogenic (IIIb) | Carboni et al. 201261 |
| c.800A>G, p.Tyr267Cys | Exon 4: Single nucleotide substitution, missense | MD(CCD) OH(LV)+M GAD EG SC-NA | Pathogenic | Likely pathogenic (II) | Pasotti et al. 20089 |
| c.810+63C>A | Intron 4: Single nucleotide substitution, not predicted to cause cryptic splicing | ME(SA) OH GAD EG SC-I | Not provided | VUS - not enough evidence | Brauch et al. 200936 |
| c.815\_818delinsCCAGAC, p.Asp272AlafsX208 | Exon 5: Deletion + insertion, frameshift and premature termination of translation | MD(SA, CCD, VA, MVA, ≥25) OH(LV) GAD EG SC-II | Not provided | Pathogenic (Ia) | Saga et al. 200958 |
| c.825\_832delGCAGTCTG, p.Arg275SerfsX1 | Exon 5: Deletion (8 nucleotides), frameshift and premature termination of translation | NA | Not provided | Pathogenic (Ia) | van Rijsingen et al. 20136 |
| c.832G>A, p.Ala278Thr | Exon 5: Single nucleotide substitution, missense | MD(SA, VA, MVA, ≥25) OH(LV)+M GAD EG SC-I | N/A | Likely pathogenic (II) | Beckman et al. 201062 |
| c.859insC, p.Ala287ArgfsX44 | Exon 5: Single nucleotide insertion, frameshift and premature termination of translation | MD(SA) OH(LV) GAD EG SC-III | N/A | Pathogenic (Ic) | Millat et al. 200929 |
| c.860delC, p.Ala287ValfsX193 | Exon 5: Single nucleotide deletion, frameshift and premature termination of translation | MD(CCD) OH(LV) GNA EG SC-NA | N/A | Pathogenic (Ic) | Karrouz et al. 200963 |
| NM\_005572.3: c.863C>G, p.Ala288Gly | Exon 5: Single nucleotide substitution, missense | MD(SA, ≥25) OH(LV) GAD EG SC-NA | Likely pathogenic | Likely pathogenic (II) | https://www.ncbi.nlm.nih.gov/clinvar/variation/48089 |
| c.868G>A, p.Glu290Lys | Exon 5: Single nucleotide substitution, missense | MD(CCD, MVA, ≥25) OH(LV)+E GAD EG SC-I | Conflicting interpretations of pathogenicity | Likely pathogenic (II) | Finsterer et al. 201664 |
| c.871G>A, p.Glu291Lys | Exon 5: Single nucleotide substitution, missense | MD(CCD, eHF, MVA, <25) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Perez-Serra et al., 201565 |
| c.892C>T, p.Arg298Cys | Exon 5: Single nucleotide substitution, missense | MD(SA, CCD, VA, MVA, ↑CK, <25) OH(LV) GAD EG SC-NA | Pathogenic | Likely pathogenic (II) | Ben Yao et al. 200766 |
| c.908\_909delCT, p.Ser303CysfsX27 | Exon 5: Deletion (2 nucleotides), frameshift and premature termination of translation | MD(SA, CCD, VA, MVA) OH(LV)+M GAD EG SC-NA | Pathogenic: Dilated cardiomyopathy 1A, Dilated cardiomyopathy 1S, Charcot-Marie-Tooth disease, type 2 | Pathogenic (Ia) | Antoniades et al. 200767 |
| c.936G>C, p.Gln312His | Exon 5: Single nucleotide substitution, missense | MD(CCD, eHF) OH(LV)+M GAD EG SC-NA | N/A | Likely pathogenic (II) | Ben Yao et al. 200568 |
| c.936+1delG | Intron 5: Single nucleotide deletion, predicted abnormal splicing | MD OH(LV) GAD EG SC-NA | N/A | VUS - not enough evidence | van Rijsingen et al. 20136, |
| c.936+2T>G | Intron 5: Single nucleotide substitution, predicted abnormal splicing | MD OH(LV) GAD EG SC-NA | N/A | VUS - not enough evidence | van Spaendonck-Zwarts et al. 201369 |
| c.936+1G>T | Intron 5: Single nucleotide substitution, predicted abnormal splicing | MD(CCD, VA, MVA, ≥25) OH(LV) GAD EG SC-III | Not provided | Likely pathogenic (II) | Arbustini et al. 200723 |
| c.937-11C>G | Intron 5: Single nucleotide substitution, predicted abnormal splicing | MD(SA, CCD, VA, ≥25) OH(LV, LVRV, A)+M GAD EG SC-NA | N/A | Likely pathogenic (II) | Carboni et al 201170 |
| c.937-46A>G | Intron 5: Single nucleotide substitution, predicted abnormal splicing | MD(SA, eHF) OH GDN EG SC-NA | N/A | VUS - not enough evidence | Brauch et al. 200936, Banerjee A et al. 201571 |
| c.949G>A, p.Glu317Lys | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, eHF, ≥25) OH(LV) GAD EG SC-NA | Pathogenic/Likely pathogenic | Likely pathogenic (II) | Arbustini et al. 200231 |
| c.952G>A, p.Ala318Thr | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, ≥25) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | Parks et al. 200932 |
| NM\_005572.3:c.959delT, p.Arg321GlufsX159 | Exon 6: Single nucleotide deletion, frameshift and premature termination of translation | MD(SA, CCD, eHF, VA, MVA, ↑CK, <25) OH(LV)+M GAD EG SC-III | Pathogenic | Pathogenic (Ia) | Brodsky et al. 200044 |
| c.961C>T, p.Arg321Ter | Exon 6: Single nucleotide substitution, nonsense | MD(CCD, VA, <25) OH GAD EG SC-NA | Pathogenic | Likely pathogenic (II) | Hasselberg et al. 201472 |
| c.992G>A, p.Arg331Gln | Exon 6: Single nucleotide substitution, missense | MD(≥25) OH GAD EG SC-NA | Pathogenic | Likely pathogenic (II) | Benedetti et al. 200773, Hoorntje et al. 201774 |
| c.1001G>A, p.Ser334Asn | Exon 6: Single nucleotide substitution, missense | NA | Pathogenic/Likely pathogenic | VUS - not enough evidence | van Spaendonck-Zwarts et al. 201369 |
| c.1003C>T, p.Arg335Trp§ | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, ≥25) OH(LV) GAD EG SC-IV | N/A | Likely pathogenic (II) | Stallmeyer et al. 201275 |
| c.1004G>A, p.Arg335Gln | Exon 6: Single nucleotide substitution, missense | MD(CCD) OH(LV) GDN EG SC-NA | Pathogenic/Likely pathogenic | VUS - not enough evidence | Ehlermann et al. 200976 |
| c.1039G>A, p.Glu347Lys | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, ↑CK, MVA, ≥25) OH(LV)+M GAD EG SC-NA | Uncertain significance | Likely pathogenic (II) | Vytopil et al. 200377 Bollati et al. 201278 |
| c.1044G>T, p.Met348Ile | Exon 6: Single nucleotide substitution, missense | MD(CCD) OH(LV) GAD EG SC-NA | Likely pathogenic | Likely pathogenic (II) | Meinke et al. 201179 |
| c.1045C>T, p.Arg349Trp | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, eHF, ↑CK, <25) OH(LV)+M+L+E GAD EG SC-IV | Not provided | Likely pathogenic (II) | van Tintelen et al. 200712~ |
| c.1046G>T, p.Arg349Leu | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, eHF, <25) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Hermida-Prieto et al. 200480 |
| c.1048G>C, p.Ala350Pro | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, VA, ↑CK, <25) OH(LV)+M GAD EG SC-II | Not provided | Likely pathogenic (II) | Rudenskaya et al. 200817 |
| c.1057C>A, p.Gln353Lys | Exon 6: Single nucleotide substitution, missense | MD(VA, ↑CK, ≥25) OH(LV)+M GAD EG SC-IV | Not provided | Pathogenic (II) | Gupta et al. 201046 |
| c.1063C>T, p.Gln355Ter | Exon 6: Single nucleotide substitution, nonsense | MD(SA, CCD, eHF, ≥25) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | Pethig et al. 200511 |
| c.1069G>C, p.Asp357His | Exon 6: Single nucleotide substitution, missense | MD(CCD, MVA) OH(LV) GAD EG SC-NA | Pathogenic | Likely pathogenic (II) | Fujimori et al. 200881 |
| c.1070A>C, p.Asp357Ala | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | Not provided | VUS - not enough evidence | Stallmeyer et al. 201275 |
| c.1072G>A, p.Glu358Lys | Exon 6: Single nucleotide substitution, missense | MD(CCD) OH(LV)+M GNA EG SC-NA | N/A | Likely pathogenic (II) | Dittmer et al. 201482 |
| c.1072G>T, p.Glu358Ter | Exon 6: Single nucleotide substitution, nonsense | ME(CCD, VA, MVA, ≥25) OH(LV) GAD EG SC-I | Pathogenic | Pathogenic (Ia) | De Backer et al. 201083 |
| c.1085delT, p.Leu363TrpfsX117 | Exon 6: Single nucleotide deletion, frameshift and premature termination of translation | MD(SA, CCD, VA, eHF, ≥25) OH(LV) GAD EG SC-IV | Not provided | Pathogenic (Ia) | Kärkkäinen et al. 200637 |
| c.1112\_1115dupTGGA, p.Glu372Aspfs | Exon 6: Duplication (4 nucleotides), frameshift and premature termination of translation | MD(SA, CCD, MVA, ≥25) OH(LV) GAD EG SC-NA | Likely pathogenic | Pathogenic (Ic) | Parks et al. 200932 |
| c.1114delG, p.Glu372ArgfsX108 | Exon 6: Single nucleotide deletion, frameshift and premature termination of translation | MD(SA, CCD, eHF, VA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Parks et al. 200932 |
| c.1128C>A, p.Tyr376Ter | Exon 6: Single nucleotide substitution, nonsense | NA | Pathogenic/Likely pathogenic | Likely pathogenic (II) | van Rijsingen et al. 20136 |
| c.1129G>A, p.Arg377Gly (erroneously reported as p.Arg377His)) | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, ≥25) OH(LV) GAD EG SC-NA | Not provided | Likely pathogenic (II) | Perrot et al. 200639 |
| c.1129C>T, p.Arg377Cys | Exon 6: Single nucleotide substitution, missense | MD(eHF, <25) OH(LV)+M GAD EG SC-IV | N/A | Likely pathogenic (II) | Komaki et al. 201184, Anselme et al. 201385, Kumar et al. 201624 |
| c.1130G>A, p.Arg377His | Exon 6: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA, <25) OH(LV)+M GAD EG SC-IV | N/A | Likely pathogenic (II) | Charniot et al. 200386 |
| c.1130G>T, p.Arg377Leu | Exon 6: Single nucleotide substitution, missense | ME(SA, CCD, MVA, ↑CK, <25) OH(LV)+M GAD EG SC-NA | Pathogenic/Likely pathogenic | Likely pathogenic (II) | van Tintelen et al. 200712~ |
| c.1142delA, p.Glu381GlyfsX99 | Exon 6: Single nucleotide deletion, frameshift and premature termination of translation | MD(eHF, VA) OH(LV) GNA EG SC-IV | Pathogenic | Pathogenic (Ic) | Kumar et al. 201624 |
| c.1146C>T, p.Gly382Gly | Exon 6: Single nucleotide substitution, synonymous; predicted creation of new splice donor site resulting in deletion of the last 13 nucleotides of exon 6 and frameshift | MD(MVA) OH GNA EG SC-NA | Uncertain significance | Pathogenic (Ic) | Benedetti et al. 200773, Quenin et al. 201787 |
| c.1150G>T, p.Glu384Ter | Exon 6: Single nucleotide substitution, nonsense | MD OH(LV) GNA EG SC-NA | N/A | Pathogenic (Ic) | Hirlte-Lewis et al. 201343 |
| c.1157G>C, p.Arg386Thr | Exon 6: Single nucleotide substitution, missense | MD(CCD, VA, ≥25) OH(LV)+M GAD EG SC-NA | Pathogenic/Likely pathogenic | Likely pathogenic (II) | Bonne G et al. 200056 |
| c.1157+1G>A | Intron 6: Single nucleotide substitution, predicted abnormal splicing | MD(eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | N/A | VUS - not enough evidence | Pasotti et al. 20089 |
| c.1157+1G>T, p.Arg386SerfsX21 | Intron 6: Single nucleotide substitution, frameshift and premature termination of translation | MD(eHF, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (Ic) | Stallmeyer et al. 201275 |
| c.1158-44C>T | Intron 6: Single nucleotide substitution, predicted abnormal splicing | NA | Not provided | VUS - not enough evidence | Fokkema et al. 200528 |
| c.1163G>A, p.Arg388His | Exon 7: Single nucleotide substitution, missense | MD(SA, CCD, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Parks et al. 200932 |
| c.1173dup, p.Ser392GlnfsX34 | Exon 7: Single nucleotide duplication, frameshift and premature termination of translation | MD(eHF, VA) OH(LV) GNA EG SC-IV | Benign | VUS - not enough evidence | Kumar et al. 201624 |
| c.1189C>T, p.Arg397Cys | Exon 7: Single nucleotide substitution, missense | MD OH(LV) GNA EG SC-NA | Not provided | VUS - not enough evidence | Narula et al. 2012, van Rijsingen et al. 20136 |
| c.1195C>T, p.Arg399Cys | Exon 7: Single nucleotide substitution, missense | MD(CCD, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | N/A | Likely pathogenic (II) | Parks et al. 200932 |
| c.1243G>A, p.Val415Ile | Exon 7: Single nucleotide substitution, missense | ME(SA) OH GDN EG SC-I | Uncertain significance | VUS - not enough evidence | Brauch et al. 200936 |
| c.1294C>T, p.Gln432Ter | Exon 7: Single nucleotide substitution, nonsense | MD(SA, CCD, VA, ≥25) OH(LV) GAD EG SC-NA | Conflicting interpretations of pathogenicity | Pathogenic (Ia) | Møller et al. 200988 |
| c.1303C>T, p.Arg435Cys | Exon 7: Single nucleotide substitution, missense | MD(eHF, <25) OH(LV)+M GAD EG SC-IV | Uncertain significance | Likely pathogenic (II) | Vytopil et al. 200377 |
| c.1307\_1308insGCAC, p.Ser437HisfsX2 | Exon 7: Duplication (4 nucleotides), frameshift and premature termination of translation | MD(SA, CCD, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | Pathogenic/Likely pathogenic | Pathogenic (Ia) | Parks et al. 200932 |
| c.1318G>A, p.Val440Met | Exon 7: Single nucleotide substitution, missense | MD(CCD) OH(LV) GNA EG SC-NA | Conflicting interpretations of pathogenicity | Likely pathogenic (II) | Dittmer et al. 201482 |
| c.1322C>T, p.Ala441Val | Exon 7: Single nucleotide substitution, missense | MD OH GNA EG SC-NA | Pathogenic | VUS - not enough evidence | Perrot et al. 201089 |
| c.1380+1G>T | Intron 7: Single nucleotide substitution, predicted abnormal splicing | MD(VA) OH(LV) GNA EG SC-NA | Conflicting interpretations of pathogenicity | Likely pathogenic (II) | Kumar et al. 201624 |
| c.1380+1G>A | Intron 7: Single nucleotide substitution, predicted abnormal splicing | MD(SA, CCD, MVA, ≥25) OH(LV) GAD EG SC-NA | N/A | Likely pathogenic (II) | van Tintelen et al. 200712 |
| c.1381G>T, p.Asp461Tyr | Exon 8: Single nucleotide substitution, missense | MD(CCD) OH(LV) GAD EG SC-NA | N/A | Likely pathogenic (II) | Scharner et al 201390 |
| c.1397delA, p.Asn466IlefsX14 | Exon 8: Single nucleotide deletion, frameshift and premature termination of translation | MD OH GNA EG SC-NA | Pathogenic | Pathogenic (Ia) | Genschel et al. 200091 |
| c.1412G>A, p.Arg471His | Exon 8: Single nucleotide substitution, missense | MD(SA, eHF, VA, MVA, <25) OH(LV) GAD EG SC-IV | Not provided | Likely pathogenic (II) | Parks et al. 200932 |
| c.1424\_1425insAGA, p.Gly474\_Asp475insGlu | Exon 8: Duplication (3 nucleotides), inframe insertion of single amino acid | MD(VA, ≥25) OH(LV) GAD EG SC-NA | Not provided | Likely pathogenic (II) | Parks et al. 200932 |
| c.1443C>G, p.Tyr481Ter | Exon 8: Single nucleotide substitution, nonsense | MD(SA, CCD, eHF, <25) OH(LV) GAD EG SC-IV | Conflicting interpretations of pathogenicity | Pathogenic (Ia) | Sylvius et al. 200550 |
| c.1462A>C, p.Thr488Pro | Exon 8: Single nucleotide substitution, missense | ME(SA, ≥25) OH GNA EG SC-I | N/A | VUS - not enough evidence | Brauch et al. 201036 |
| c.1489-1G>T, p.Ile497\_Glu536del | Intron 8: Single nucleotide substitution, inframe deletion of 40 amino acids | MD(SA, CCD, VA, ↑CK, <25) OH(LV)+M GAD EG SC-NA | Not provided | VUS - not enough evidence | Stallmeyer et al. 201275 |
| c.1489-2A>G | Intron 8: Single nucleotide substitution, predicted abnormal splicing | NA | Not provided | VUS - not enough evidence | van Rijsingen et al. 20136 |
| c.1492T>A, p.Trp498Arg | Exon 9: Single nucleotide substitution, missense | MD(CCD, VA, MVA, ↑CK, <40) OH(LV)+M GAD EG SC-NA | N/A | Likely pathogenic (II) | Pasotti et al. 20089 |
| c.1493delG, p.Ala499LeufsX49 | Exon 9: Single nucleotide deletion, frameshift and premature termination of translation | MD(SA, VA, ≥25) OH(LV) GAD EG SC-NA | Likely pathogenic | Pathogenic (Ia) | Kärkkäinen et al. 200637 |
| c.1496delC, p.Ala499ValfsX49 | Exon 9 Single nucleotide deletion, frameshift and premature termination of translation | MD(SA, CCD, eHF, ↑CK, ≥25) OH(LVRV)+N+M GAD EG SC-IV | Not provided | Pathogenic (Ia) | Duparc et al. 200992 |
| c.1512–1513insAG, p.Thr505ArgfsX44 | Exon 9: Insertion (2 nucleotides), frameshift and premature termination of translation | MD(SA, CCD, eHF, VA, MVA, ≥25) OH(LV) GAD EG SC-IV | Not provided | Pathogenic (Ia) | van Tintelen et al. 200712 |
| c.1526insA, p.Thr510TyrfsX42 | Exon 9: Single nucleotide insertion, frameshift and premature termination of translation | MD(SA, CCD, eHF, MVA, <25) OH(LV) GAD EG SC-IV | Not provided | Pathogenic (Ia) | Chen et al. 201393 |
| c.1526insC, p.Thr510TyrfsX41 | Exon 9: Single nucleotide insertion, frameshift and premature termination of translation | MD(SA, CCD, CK, eHF, VA, MVA, <25) OH(LV)+M GAD EG SC-IV | Not provided | Pathogenic (Ia) | Saj et al. 201394, van Rijsingen et al. 20136 |
| c.1542G>A, p.Trp514X | Exon 9: Single nucleotide substitution, nonsense | NA | N/A | Pathogenic (Ic) | van Rijsingen et al. 20136 |
| c.1549C>T, p.Gln517Ter | Exon 9: Single nucleotide substitution, nonsense | MD(SA, CCD, VA, MVA, ≥25) OH(LV)+M GAD EG SC-NA | Pathogenic/Likely pathogenic | Pathogenic (Ic) | Stallmeyer et al. 201275 |
| c.1560G>A, p.Trp520Ter | Exon 9: Single nucleotide substitution, nonsense | MD(CCD, ≥25) OH(LV) GAD EG SC-NA | N/A | Likely pathogenic (II) | Stallmeyer et al. 201275 |
| c.1567G>A, p.Gly523Arg | Exon 9: Single nucleotide substitution, missense | MD OH(LV) GAD EG SC-NA | N/A | Likely pathogenic (II) | Millat et al. 200929 |
| c.1576\_1579dup, p.Arg527ProfsX26 (reported as c.1579\_1580insCTGC, p.Ile527fsX23) | Exon 9: Duplication (4 nucleotides), frameshift and premature termination of translation | MD(CCD, eHF, MVA, <40) OH(LV) GAD EG SC-IV | Pathogenic | Pathogenic (Ia) | Pasotti et al. 20089 |
| c.1580G>C, p.Arg527Pro | Exon 9: Single nucleotide substitution, missense | MD(CCD) OH(LV) GNA EG SC-NA | Uncertain significance | Pathogenic (II) | Dittmer et al. 201482 |
| c.1608+4A>G | Intron 9: Single nucleotide substitution, predicted abnormal splicing | MD(eHF) OH(LV) GAD EG SC-IV | N/A | VUS - not enough evidence | te Rijdt et al. 201795, van Spaendonck-Zwarts et al. 201369 |
| c.1608+14G>A | Intron 9: Single nucleotide substitution, predicted abnormal splicing | NA | Pathogenic | Likely pathogenic (V) | van Rijsingen et al. 20136 |
| c.1609-12T>G, p.Glu536fsX14 | Intron 9: Single nucleotide substitution, frameshift and premature termination of translation | MD(SA, CCD, VA, MVA, ↑CK, ≥25) OH(LV)+M GAD EG SC-NA | N/A | Pathogenic (Ic) | Renou et al. 200896 |
| c.1609-3C>G | Intron 9: Single nucleotide substitution, predicted abnormal splicing | MD(CCD, eHF, VA, MVA) OH(LV)+M GAD EG SC-IV | N/A | Likely pathogenic (V) | Chrestian N et al. 200897, Fokkema et al. 200528 |
| c.1621C>T, p.Arg541Cys | Exon 10: Single nucleotide substitution, missense | MD(SA, CCD) OH(LV) GNA EG SC-NA | Pathogenic | Likely pathogenic (II) | Dittmer et al. 201482 |
| c.1621C>G, p.Arg541Gly | Exon 10: Single nucleotide substitution, missense | MD(CCD) OH(LV) GNA EG SC-NA | Pathogenic/Likely pathogenic | Likely pathogenic (II) | Dittmer et al. 201482 |
| c.1621C>A, p.Arg541Ser | Exon 10: Single nucleotide substitution, missense | MD(SA, eHF, ↑CK, <25) OH(LV)+M GAD EG SC-IV | Pathogenic | Likely pathogenic (II) | Sylvius et al. 200550 |
| c.1622G>A, p.Arg541His | Exon 10: Single nucleotide substitution, missense | MD(SA, CCD, VA, <25) OH(LV) GAD EG SC-II | Pathogenic | Likely pathogenic (II) | Rudenskaya et al. 200817 |
| c.1622G>C, p.Arg541Pro (erroneously reported as p.Arg541Lys) | Exon 10: Single nucleotide substitution, missense | MD(CCD, eHF, VA, ↑CK, <25) OH(LV)+M GDN EG SC-IV | Not provided | Likely pathogenic (II) | van Tintelen et al. 200712 |
| c.1634G>A, p.Arg545His | Exon 10: Single nucleotide substitution, missense | ME(CCD) OH(LV)+M GDN EG SC-I | Conflicting interpretations of pathogenicity | VUS - not enough evidence | van Rijsingen et al. 20136, Olaopa et al. 201898 |
| c.1657G>A, p.Asp553Asn | Exon 10: Single nucleotide substitution, missense | MD(VA) OH(LV) GNA EG SC-NA | Likely pathogenic | VUS - not enough evidence | Kumar et al. 201624 |
| c.1698+83G>A | Intron 10: Single nucleotide substitution, predicted abnormal splicing | MD(CCD) OH(LV) GAD EG SC-NA | Conflicting interpretations of pathogenicity | VUS - not enough evidence | Benedetti et al. 200499 |
| NM\_005572.3:c.1713C>A, p.Ser571Arg (erroneously reported as c.1711C>A, p.Arg571Ser) | Exon 11: Single nucleotide substitution, missense | MD(SA, CCD, ↑CK, ≥25) OH(LV) GAD EG SC-NA | Uncertain significance | VUS - not enough evidence | Fatkin et al. 199921 |
| c.1714insCTGC, p.Ser572LeufsX8 | Exon 11: Insertion (4 nucleotides), frameshift and premature termination of translation | MD(CCD, eHF, VA, ≥25) OH(LV) GAD EG SC-IV | N/A | Pathogenic (Id) | Arbustini et al. 200231 |
| c.1718C>T, p.Ser573Leu | Exon 11: Single nucleotide substitution, missense | MD(VA, ≥25) OH(LV) GDN EG SC-III | Pathogenic | Pathogenic (IIIb) | Taylor et al. 200327 |
| c.1839\_1840insC, p.Arg614GlyfsX89 | Exon 11: Single nucleotide insertion, frameshift and premature termination of translation | NA | N/A | Pathogenic (Id) | van Rijsingen et al. 20136 |
| c.1851C>T, p.Ala617Ala | Exon 11: Single nucleotide substitution, missense | NA | Conflicting interpretations of pathogenicity | VUS - not enough evidence | Fokkema et al. 200528 |
| c.1904G>A, p.Gly635Asp | Exon 11: Single nucleotide substitution, missense | MD(CCD) OH(LV) GNA EG SC-NA | N/A | Likely pathogenic (II) | Dittmer et al. 201482 |
| c.1912G>A, p.Gly638Arg | Exon 11: Single nucleotide substitution, missense | NA | Conflicting interpretations of pathogenicity | VUS - not enough evidence | van Rijsingen et al. 20136, Pugh et al. 2014100 |
| c.1930C>T, p.Arg644Cys | Exon 11: Single nucleotide substitution, missense | MD OH(LV) GAD EG SC-NA | Not provided | Likely pathogenic (III) | Genschel et al. 2001101 |
| c.1960C>T, p.Arg654Ter | Exon 11: Single nucleotide substitution, nonsense | MD(SA, CCD, VA, MVA, ≥25) OH(LV) GAD EG SC-NA | Conflicting interpretations of pathogenicity | Likely pathogenic (II) | Parks et al. 200932 |
| c.1975dup, p.Gln659delinsSer | Exon 12: Single nucleotide duplication, inframe deletion and insertion of single amino acid | MD(VA, MVA) OH(LV) GNA EG SC-NA | Conflicting interpretations of pathogenicity | VUS - not enough evidence | Moller et al. 2010102 |

\* Mutations are ordered by exonic location.

∞ The summative (overall) MOGE(S) class for each mutation was derived using available data reported for the mutation-positive proband or affected family members in the published literature (of which at least 1 citation is reproduced here). If phenotypic heterogeneity existed between reported probands/families, the descriptor was taken as the most severe manifestation reported or the youngest reported age of presentation. Mutations with missing phenotype information are labeled NA. **MOGE(S)** nosology103 used throughout this table is as follows:

**M, morphofunctional phenotype with main descriptors**:

**D**, dilated cardiomyopathy

**E**, early phenotype not fulfilling criteria for DCM (e.g. mild LV dilatation with preserved/low-normal systolic function or normal LV cavity size and function but other clinical features consistent with subclinical cardiac disease e.g. CCD/Arrhythmia/Atrial dilatation)

**NA**, not available

To ‘**D**’ or ‘**E**’ we have added the following **key clinical red flags**:

**SA**, supraventricular arrhythmia

**CCD**, cardiac conduction system disease

**eHF**, end-stage heart failure defined as heart transplantation or death from end-stage heart failure

**VA**, ventricular arrhythmia defined as any type of non-life threatening VA including ventricular ectopy

**MVA,** malignant ventricular arrhythmia defined as the potentially life-threatening VA, sudden cardiac death, resuscitation or appropriate defibrillator therapy

**↑CK,** elevated creatine phosphokinase

**<25** or **≥25**, to differentiate between mutations of early versus late phenotypic penetrance, considering the earliest reported age of phenotypic expression in the proband or affected family members. Where age of phenotypic penetrance was not indicated by authors in the cited work the denomination is omitted from the MOGE(S). Where authors only reported ages as </≥30 or </≥40 a similar cut off was used. If age was not reported it is omitted from the table.

**O, organ system involvement with main descriptors:**

**H**, heart

**M**, skeletal muscle (any report of even mild symptomatic myopathy is counted as skeletal muscle involvement but isolated high CPK with no symptoms or confirmatory muscle tests is not)

**N**, nervous

**L**,lipid (lipodystrophy)

**E**, endocrine (e.g. insulin abnormalities)

**NA**, not available

To ‘**H**’ we have added the following denominators:

**LV**, left ventricle involvement

**RV**, right ventricle involvement

**LRV**, biventricular involvement

**A**, atrial involvement

**G, genetic inheritance pattern with main descriptors:**

**AD**, autosomal dominant where the cited publication suggests other likely affected family members

**DN**, de novo disease-causing mutation where the cited publication includes indicates a patient who is the uniquely affected member of the family, and in the absence of a family history of CM

**NA,** not available

**E, etiology with main descriptor:**

**G**, genetic (applies to all cases here)

**S, functional status with main descriptor:**

**CI-IV**, as the most severe New York Heart Association Functional class (NYHA I-IV) reported in the patient or in the affected family members in the cited paper. If NYHA functional class was not specified in the cited paper but reported phenotype included **eHF**, then the most severe NYHA functional class was assumed to be class IV.

**NA**, not available

**Note-1:** *LMNA* mutations linked primarily to LGMD, EDMD, FPLD or progeroid syndromes, where DCM is reported as an associated, but not the primary clinical manifestation, have not been included in this table.

*ACMG, American College of Medical Genetics and Genomics; EDMD, Emery-Dreifuss muscular dystrophy; FPLD, Familial partial lipodystrophy, Dunnigan variety; LAP2-α, Lamin associated protein; LGMD, Limb-girdle muscular dystrophy; NLS, nuclear localisation signal.*

**SUPPLEMENTARY TABLE 2. Solutions from the various clustering algorithms.** All 7 cluster algorithms consistently generate a 2-branch dendrogram with 4 contained subclusters.

|  |  |  |
| --- | --- | --- |
| **Cluster Algorithm** | **Output** | **Cophenetic Correlation with method ‘Ward’** |
| Ward\* | Dendrogram with 2 branches and 176 members total, at height 90.3 | – |
| Single | Dendrogram with 2 branches and 176 members total, at height 2.1 | 0.84 |
| Complete | Dendrogram with 2 branches and 176 members total, at height 4.0 | 0.90 |
| Average | Dendrogram with 2 branches and 176 members total, at height 3.1 | 0.91 |
| Mcquitty | Dendrogram with 2 branches and 176 members total, at height 3.1 | 0.77 |
| Median# | Dendrogram with 2 branches and 176 members total, at height 1.2 | 0.43 |
| Centroid# | Dendrogram with 2 branches and 176 members total, at height 1.6 | 0.46 |

Seven cluster objects, including our chosen method (\*) were tested using ‘hclust’ chained together as a single dendlist object.

# Cluster methods ‘Median’ and ‘Centroid’ are less meaningful when applied to ordinal categorical data like ours, where use of the other methods is more appropriate.

**SUPPLEMENTARY TABLE 3. Cluster conformity test results.** When data was cut to k=4 clusters using the Fowlkes-Mallows Index (excluding methods ‘Median’ and ‘Centroid’), all cluster solutions retained good agreement with the chosen method ‘Ward’ (\*, FM indices > 0.7).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Algorithm** | **Ward\*** | **Single** | **Complete** | **Average** | **McQuitty** |
| **Ward\*** | 1.00 | NA | 1.00 | 0.74 | 0.87 |
| **Single** | NA | 1.00 | NA | NA | NA |
| **Complete** | 1.00 | NA | 1.00 | 0.74 | 0.87 |
| **Average** | 0.74 | NA | 0.74 | 1.00 | 0.84 |
| **McQuitty** | 0.87 | NA | 0.87 | 0.84 | 1.00 |

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