**Supplementary table 1:** genes in CMT NGS panels in London and Iowa. \*Depending on the company offering NGS service and the patient’s clinical features a variable number of genes is sequenced and analyzed as reported in **Table 1**.

|  |
| --- |
| **London** |
| **CMT genes sequenced**  |
| *AARS (NM\_001605.2 ),* *ATL1 (NM\_015915.4), ATP7A (NM\_000052.5), BICD2 (NM\_001003800.1), BSCL2 (NM\_032667.6), CCT5 (NM\_012073.3), DCTN1 (NM\_004082.4), DNM2 (NM\_001005360.2), DNMT1 (NM\_001130823.1), DYNC1H1 (NM\_001376.4), EGR2 (NM\_000399.3), FAM134B (NM\_001034850.2), FGD4)(NM\_139241.2), FIG4 (NM\_014845.5), GARS (NM\_002047.2), GDAP1 (NM\_018972.2), GJB1 (including, promoter) (NM\_000166.5), HINT1 (NM\_005340.6), HSPB1 (NM\_001540.3), HSPB3 (NM\_006308.2), HSPB8 (NM\_014365.2), IGHMBP2 (NM\_002180.2), LITAF (NM\_004862.3), LMNA (NM\_005572.3), LRSAM1 (NM\_138361.5), MARS (NM\_004990.3), MFN2 (NM\_014874.3), MPZ (NM\_000530.6), MTMR2 (NM\_016156.5), NDRG1 (NM\_006096.3 ), NEFL (NM\_006158.4), NGF (NM\_002506.2), NTRK1 (NM\_002529.3), PMP22 (NM\_000304.3), PRPS1 (NM\_002764.3 ), PRX (NM\_181882.2 ), RAB7A (NM\_004637.5 ), SBF2 (formerly MTMR13) (NM\_030962.3), SCN9A (NM\_002977.3), SETX (NM\_015046.5), SH3TC2 (NM\_024577.3), SLC52A1 (NM\_017986.3), SLC52A2 (NM\_024531.4), SLC52A3 (NM\_033409.3), SPTLC1 (NM\_006415.3), SPTLC2 (NM\_004863.3), TRPV4 (NM\_021625.4), VCP (NM\_007126.3), WNK1 (NM\_213655.4), YARS (NM\_003680.3)* |
| **Genes in focused panel for Charcot Marie Tooth disease type 1 / Intermediate CMT (CMT1)**  |
| *EGR2, FGD4, FIG4, GDAP1, GJB1 (including promoter), LITAF, MPZ, MTMR2, NDRG1, NEFL, PMP22, PRX, SBF2, SH3TC2* |
| **Genes in focused panel for Charcot Marie Tooth disease type 2 / Intermediate CMT (CMT2)**  |
| *AARS, BSCL2, DNM2, DYNC1H1, GARS, GDAP1, GJB1, GJB1 (including promoter), HINT1, HSPB1, HSPB8, IGHMBP2, LMNA, LRSAM1, MARS, MFN2, MPZ, NEFL, PMP22, PRPS1, RAB7A, SH3TC2, TRPV4, VCP, YARS* |
| **Genes in focused panel for Distal hereditary motor neuropathy (dHMN)**  |
| *ATP7A, BICD2, BSCL2, DCTN1, DYNC1H1, GARS, HSPB1, HSPB3, HSPB8, IGHMBP2, SETX, SLC52A1, SLC52A2, SLC52A3, TRPV4* |
| **Genes in focused panel for Hereditary Sensory Neuropathy (HSN)**  |
| *ATL1, CCT5, DNMT1, FAM134B, NGF, NTRK1, RAB7A, SCN9A, SPTLC1, SPTLC2, WNK1*  |

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| --- |
| **Iowa** |
| **CMT genes sequenced and analyzed\*** |
| *AARS (NM\_001605.2 ), ABCD1 (NM\_000033.4), ACTA1* (*NM\_001100.3), AIFM1* (*NM\_004208.3), ALDH18A1* (*NM\_002860.3), ALS2* (*NM\_020919.3), ANO5* (*NM\_213599.2), AP4B1* (*NM\_006594.3), AP4E1* (*NM\_007347.4), AP4M1* (*NM\_004722.3), AP4S1* (*NM\_007077.4), AP5Z1* (*NM\_014855.2), ATL1 (NM\_015915.4), ATL3* (*NM\_015459.4), ATP13A2* (*NM\_022089.3), ATP2A1* (*NM\_173201.3), ATP7A (NM\_000052.5), B3GALNT2 (NM\_152490.4), B4GALNT1* (*NM\_001478.4), B4GAT1* (*NM\_006876.2), BAG3* (*NM\_004281.3), BICD2 (NM\_001003800.1), BIN1* (*NM\_139343.2), BSCL2(NM\_032667.6), BVES* (*NM\_001199563.2), C12orf65* (*NM\_152269.4), CACNA1S* (*NM\_000069.2), CAPN3* (*NM\_000070.2), CAV3* (*NM\_033337.2), CCDC78* (*NM\_001031737.2), CFL2* (*NM\_021914.7), CHKB* (*NM\_005198.4), CLCN1* (*NM\_000083.2), CNTN1* (*NM\_001843.3), COL12A1* (*NM\_004370.5), COL6A1* (*NM\_001848.2), COL6A2* (*NM\_001849.3), COL6A3* (*NM\_004369.3), CRYAB* (*NM\_001885.2), CYP2U1* (*NM\_183075.2), CYP7B1* (*NM\_004820.3), CHCHD10* (*NM\_213720.2), DAG1* (*NM\_004393.5), DCTN1 (NM\_004082.4), DDHD1* (*NM\_001160147.1), DDHD2* (*NM\_015214.2), DES* (*NM\_001927.3), DMD* (*NM\_004006.2), DNAJB2* (*NM\_001039550.1), DNM2 (NM\_001005360.2), DNMT1 (NM\_001130823.1), DOK7* (*NM\_173660.4, NM\_001301071.1), DPM1* (*NM\_003859.1), DPM2 (NM\_003863.3), DPM3* (*NM\_153741.1), DST* (*NM\_001723.5; NM\_015548.4), DYNC1H1 (NM\_001376.4), DYSF (NM\_003494.3), EGR2(NM\_000399.3), ELP1* (*NM\_003640.3), EMD* (*NM\_000117.2), ERLIN2* (*NM\_007175.6), FA2H* (*NM\_024306.4), FBXO38* (*NM\_030793.4), FHL1* (*NM\_001449.4), FGD4 (NM\_139241.2), FIG4 (NM\_014845.5), FKRP* (*NM\_024301.4), FKTN* (*NM\_001079802.1, NM\_001079802.1, NM\_001079802​.1), FLNC (NM\_001458.4), GAA* (*NM\_000152.3, NM\_000152.3), GAN* (*NM\_022041.3), GARS(NM\_002047.2), GBA2* (*NM\_020944.2), GBE1* (*NM\_000158.3), GDAP1 (NM\_018972.2), GJB1 (NM\_000166.5), GLA* (*NM\_000169.2; NM\_000169.2), GJC2 (NM\_020435.3; NM\_020435.3), GMPPB* (*NM\_013334.3), GNE* (*NM\_001128227.2), GNB4* (*NM\_021629.3), HARS* (*NM\_002109.5), HEXA* (*NM\_000520.4), HINT1 (NM\_005340.6), HSPB1 (NM\_001540.3), HSPB8 (NM\_014365.2), HSPD1* (*NM\_002156.4), IGHMBP2 (NM\_002180.2), IKBKAP* (*NM\_003640.3), INF2* (*NM\_022489.3), ISPD* (*NM\_001101426.3), ITGA7 (NM\_002206.2), KBTBD13* (*NM\_001101362.2), KLHL40* (*NM\_152393.3), KLHL41* (*NM\_006063.2), KDM5C* (*NM\_004187.3), KIAA0196* (*NM\_014846.3), KIF1A* (*NM\_004321.6), KIF1C* (*NM\_006612.5), KIF5A* (*NM\_004984.2), L1CAM* (*NM\_000425.4), LAMA2* (*NM\_000426.3), LAMP2* (*NM\_002294.2), LARGE* (*NM\_004737.4), LDB3* (*NM\_001080116.1; NM\_001171610.1; NM\_007078.2), LITAF (NM\_004862.3), LMNA (NM\_005572.3), LMOD3* (*NM\_198271.4), LRSAM1 (NM\_138361.5), MATR3* (*NM\_199189.2), MED25* (*NM\_030973.3), MEGF10* (*NM\_032446.2), MFN2 (NM\_014874.3), MICU1* (*NM\_001195518.2), MME* (*NM\_007289.3), MORC2* (*NM\_001303256.2), MPZ (NM\_000530.6), MTM1* (*NM\_000252.2), MTMR2 (NM\_016156.5), MYH2* (*NM\_017534.5), MYH7* (*NM\_000257.3), MYOT* (*NM\_006790.2), NDRG1 (NM\_006096.3), NEB* (*NM\_001271208.1), NEFL (NM\_006158.4), NGF (NM\_002506.2), NIPA1* (*NM\_144599.4), NT5C2* (*NM\_012229.4), NTRK1 (NM\_002529.3), PDK3* (*NM\_001142386.2), PHKA1* (*NM\_002637.3), PLEC* (*NM\_000445.4; NM\_201378.3), PLEKHG5* (*NM\_020631.4), PLP1* (*NM\_000533.4), PMP22 (NM\_000304.3), PNPLA6* (*NM\_020376.3), PRDM12* (*NM\_021619.2), POMGNT1* (*NM\_017739.3), POMK* (*NM\_032237.4), POMT2* (*NM\_013382.5), PRPS1 (NM\_002764.3), PRX (NM\_181882.2), PYGM* (*NM\_005609.3), RAB7A (NM\_004637.5), REEP1* (*NM\_022912.2), REEP2* (*NM\_001271803.1), RETREG1* (*NM\_001034850.2), RTN2* (*NM\_005619.4), RYR1* (*NM\_000540.2), SACS* (*NM\_014363.5), SBF1* (*NM\_002972.4), SBF2 (NM\_030962.3), SCN11A* (*NM\_014139.2), SCN4A* (*NM\_000334.4), SCN9A (NM\_002977.3), SELENON* (*NM\_020451.2; (NM\_20451.2), SGCA* (*NM\_000023.2), SGCB (NM\_000232.4), SCGD* (*NM\_000337.5), SGCG* (*NM\_000231.2), SH3TC2 (NM\_024577.3), SIGMAR1* (*NM\_005866.3), SIL1* (*NM\_022464.4), SLC12A6* (*NM\_001365088.1), SLC16A2* (*NM\_006517.4), SLC25A46* (*NM\_138773.2), SLC52A2 (NM\_024531.4), SLC52A3 (NM\_033409.3), SLC5A7* (*NM\_021815.2), SPART* (*NM\_015087.4), SPAST* (*NM\_014946.3), SPG11* (*NM\_025137.3), SPG20* (*NM\_015087.4), SPG21* (*NM\_016630.6), SPG7 (NM\_003119.3), SPTLC1 (NM\_006415.3), SPTLC2 (NM\_004863.3), SQSTM1* (*NM\_003900.4), SYNE1* (*NM\_033071.3), TCAP* (*NM\_003673.3), TECPR2 (NM\_014844.3), TFG* (*NM\_006070.5), TIA1* (*NM\_022173.2), TMEM5* (*NM\_014254.2), TNNI2 (NM\_003282.4), TNNT1* (*NM\_003283.5), TNPO3* (*NM\_012470.3), TOR1AIP1* (*NM\_001267578.1), TPM2* (*NM\_003289.3), TPM3* (*NM\_152263.3), TRAPPC11* (*NM\_021942.5), TRIM2* (*NM\_001130067.1), TRIM32* (*NM\_012210.3), (TRIP4* *NM\_016213.4), TRPV4 (NM\_021625.4), TTN* (*NM\_001267550.2), TTR* (*NM\_000371.3), UBA1* (*NM\_003334.3), VAMP1* (*NM\_014231.3), VAPB* (*NM\_004738.4), VCP (NM\_007126.3), VPS37A* (*NM\_152415.2), VRK1* (*NM\_003384.2), WASHC5* (*NM\_014846.3), WNK1 (NM\_213655.4), YARS (NM\_003680.3), ZFYVE26 (NM\_015346.3)* |

**Supplementary Table 2. Clinical features of cases with a positive genetic diagnosis.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **#** | ***Patient\_ID#*** | **Center** | **Age (current)** | **Age (onset)** | **Gender** | **CMT subtype** | **family history** | **Symptom onset** | **Additional features** | **CMTNS** | **NCV\_median (or ulnar)** | **Pathogenic variant** | **Class**  | **Novel** |
| 1 | 6 | Iowa | 58 | 18 | Female | Ax/int | Yes | Numbness in calf, foot deformity | None | 10 | 43 m/s | *GJB1* c.283G>A p.(Val95Met) | Pathogenic | No |
| 2 | 16 | Iowa | 35 | 25 | Female | Dem | No | Weakness and poor balance | None | 26 | 25 m/s | *GJB1* c.490C>T p.(Arg164Trp) | Pathogenic | No |
| 3 | 26 | Iowa | 34 | 6 | Male | Dem | Yes | Falls, ankle weakness | None | 17 (CMTES) | 13 m/s | *GJB1* c.163A>G p.(Thr55Ala) | Likely pathogenic | No |
| 4 | 44 | Iowa | 38 | 12 | Female | Ax/int | Yes | Poor balance and sprained ankles | None | 9 | 49 m/s | *GJB1* c.44G>A p.(Arg15Gln) | Pathogenic | No |
| 5 | 48 | Iowa | 20 | 13 | Male | Dem | Yes | Difficulty running | None | 8 | 31 m/s | *GJB1* c.83T>C p.(Ile28Asn) | Pathogenic | No |
| 6 | 50 | Iowa | 48 | 14 | Female | Ax/int | Yes | Poor balance | None | 8 (CMTES) | 39 m/s | *GJB1* c.305A>G p.(Glu102Gly) | Pathogenic | No |
| 7 | 75 | Iowa | 29 | 15 | Male | Dem | Yes | Poor balance | None | 21 | 23 m/s | *GJB1* c.-17G>A p.? (5'UTR) | Pathogenic | No |
| 8 | 90 | Iowa | 59 | 30 | Female | Ax/int | Yes | Falls | None | 18 | 49 m/s | *GJB1* c.283G>A p.(Val95Met) | Pathogenic | No |
| 9 | 116 | London | 57 | 15 | Male | Dem | Yes | Pes planus, poor balance and difficulty walking | None | 11 (CMTES) | 38 m/s | *GJB1*: c.\*15C>T p.? (3'UTR) | Likely pathogenic | No |
| 10 | 148 | London | 40 | 30 | Female | Ax/int | Yes | Difficulty walking | Split hand, motor predominant, plantar flexion weakness | 5 (CMTES) | 46 m/s | *GJB1*: c.491G>A p.(Arg164Gly) | Pathogenic | No |
| 11 | 156 | London | 51 | 15 | Male | Dem | Yes | Ankle sprains, difficulty walking  | Split hand (ALS type, ADM preserved compared to APB and FDIO) | 20 | 36 m/s | *GJB1*: c.-103C>T p.? (promoter) | Pathogenic | No |
| 12 | 147 | London | 50 | 8 | Male | Ax/int | No | Difficulties with handwriting | Split hand, upper limb predominance, upper motor neuron signs  | 15 | 44 m/s | *GJB1*, c.319C>T p.(Arg107Trp) | Pathogenic | No |
| 13 | 15 | Iowa | 37 | 6 | Male | Dem | No | Delayed walking, throbbing pain in ankles | Scoliosis, ventricular arrhythmia  | 14 | 27 m/s | *SH3TC2*: c. 2860C>T p. (Arg954Ter) & c.2128C>T p.(Gln710Ter) | Pathogenic | No, No |
| 14 | 46 | Iowa | 14 | 10 | Female | Dem | No | Difficulty walking | Mild scoliosis | 9 | 33 m/s | *SH3TC2* c.2860 C>T p.( Arg945Ter) (homozygous) | Pathogenic | No |
| 15 | 68 | Iowa | 17 | 13 | Female | Dem | Yes | Scoliosis | None | 16 | 29 m/s | *SH3TC2* c.2860 C>T p.(Arg945Ter) (homozygous) | Pathogenic | No |
| 16 | 122 | London | 29 | 6 | Male | Dem | Yes | Falls, delayed walking  | Scoliosis, facial weakness, hoarseness  | 13 (CMTES) | 20 m/s | *SH3TC2*: c.382-2A>C p.? & Exon 7 deletion | Pathogenic, pathogenic | No, Yes |
| 17 | 125 | London | 59 | 1 | Male | Dem | Yes | Delayed walking, foot drop and falls | Scoliosis, deafness | 20 | 25 m/s | *SH3TC2*: c.2860C>T p.(Arg954Ter) *&* 3303delG p.(Arg1101SerfsTer15) | Pathogenic, pathogenic | No, No |
| 18 | 201 | London | 69 | 6 | Female | Dem | No | Slow runner, unable to wear high heeled shoes | Myasthenia gravis | severe | 25 m/s | *SH3TC2*: c.138G>C p.(Gln46His) & 1797\_1800dupGGCC p.(Cys601GlyfsTer5) | Likely Pathogenic, Pathogenic | Yes, Yes |
| 19 | 213 | London | 31 | 5 | Male | Dem | Yes | Toes walking and Achilles tendon tightness | Scoliosis, prominent sensory loss, ptosis (?) | 16 | 28 m/s | *SH3TC2*: c.2860C>T p.(Arg954Ter) & c.386-2A>C p.? | Pathogenic, pathogenic | No, No |
| 20 | 131 | London | 45 | 5 | Female | Dem | Yes | High foot arches | Facial weakness, kyphoscoliosis, right hip dysplasia | 8 (CMTES) | 32 m/s | *SH3TC2*: c.2860C>T p.(Arg954Ter) (homozygous) | Pathogenic (homozygous) | No |
| 21 | 5 | Iowa | 13 | 6 | Female | Ax/int | Yes | Foot deformity, poor balance  | None | 6 | 50 m/s | *MFN2*: c.436C>T p.(Leu146Phe) | Likely pathogenic | No |
| 22 | 12 | Iowa | 6 | 3 | Female | Ax/int | No | Delayed walking, falls | None | NA | 62 m/s | MFN2: c. 449G>T, p.(Gly150Val) & *MFN2:* deletion exons 7-8 | Pathogenic | No |
| 23 | 18 | Iowa | 63 | 52 | Female | Ax/int | Yes | Sensory loss | None | 15 | 44 m/s | *MFN2*: c.2219G>C p.(Trp740Ser) | Pathogenic | No |
| 24 | 42 | Iowa | 51 | 45 | Female | Ax/int | Yes | Foot deformity | None | 3 | 50 m/s | *MFN2*: c.1091 G>A p.(Arg364Gln) | Pathogenic | No |
| 25 | 59 | Iowa | 39 | 13 | Female | Ax/int | Yes | Foot pain | None | 4 | 56 m/s | *MFN2*: c.311G>T p.(Arg104Leu) | Pathogenic | No |
| 26 | 60 | Iowa | 38 | 5 | Male | Ax/int | Yes | Poor balance | None | 17 | NA | *MFN2*: c.839G>A p.(Arg280His) | Pathogenic | No |
| 27 | 63 | Iowa | 26 | 5 | Female | Ax/int | Yes | Toe walking, poor balance | None | 10 | 54 m/s | *MFN2*: c.2219G>C p.(Trp740Ser) | Pathogenic | No |
| 28 | 181 | London | 56 | 10 | Male | Ax/int | Yes | Difficulty running | Vocal cord paralysis | 23 | 55 m/s | *MFN2*: c.749G>A p.(Arg250Gln) & c.1085C>G p.(Thr362Arg) | Likely pathogenic | No, Yes |
| 29 | 19 | Iowa | 15 | 1 | Male | Dem | No | Hypotonia | None | 15 (CMTES) | NA | *MPZ*: c.292C>T p.(Arg98Cys) | Pathogenic | No |
| 30 | 39 | Iowa | 63 | 32 | Female | Dem | Yes | Distal sensory loss | None | 11 | 23 m/s | *MPZ*: c.584+2T>G p.? | Pathogenic | No |
| 31 | 58 | Iowa | 11 | 2 | Female | Dem | Yes | Delayed walking | None | 14 | 16 m/s | *MPZ*: whole gene duplication | Likely pathogenic | No |
| 32 | 93 | Iowa | 61 | 25 | Male | Ax/int | Yes | Distal sensory loss | None | 14 | 45 m/s | *MPZ*: c.371C>T p.(Thr124Met) | Pathogenic | No |
| 33 | 179 | London | 48 | 43 | Male | Ax/int | Yes | Foot drop, distal sensory loss | None | 9 (CMTES) | 44 m/s | *MPZ*: c.223G>T p.(Asp75Tyr) | Likely pathogenic | Yes |
| 34 | 202 | London | 35 | 1 | Male | Dem | Yes | Delayed walking | None | 17 | 12 m/s | *MPZ*:c.94G>T p.(Val32Phe) | Pathogenic | No |
| 35 | 14 | Iowa | 31 | 1 | Female | Ax/int | No | Delayed walking | Vocal cord paralysis | 28 | NR | *GDAP1*: c.487C>T p. (Gln136Ter) & c.1019dupT p. (Arg341GlnfsTer12) | Pathogenic; likely pathogenic | No |
| 36 | 103 | London | 56 | 10 | Female | Ax/int | Yes | Falls, high foot arches | None | moderate | 56 | *GDAP1*: c.358C>T p.(Arg120Trp) | Pathogenic | No |
| 37 | 124 | London | 43 | 10 | Female | Ax/int | Yes | Delayed walking, slow runner | Upper motor neuron signs | 4 | 58 m/s | *GDAP1*: c.358C>T p.(Arg120Trp) | Pathogenic | No |
| 38 | 170 | London | 20 | 2 | Male | Ax/int | No | Delayed walking | Vocal cord paralysis, mild facial weakness | 17 (CMTES) | NR | *GDAP1*: c.355C>A p.(Pro119Thr) & c.487C>T p.(Gln163Ter) | Pathogenic, likely pathogenic | Yes, No |
| 39 | 1 | Iowa | 33 | 1 | Male | Ax/int | Yes (consanguineity) | Floppy feet, delayed walking | Respiratory failure, recurrent gastric distension | 32 | NR | *IGHMBP2*: c.1325A>G p.(Tyr442Cys) (homozygous) | Likely pathogenic | Yes |
| 40 | 8 | Iowa | 24 | 5 | Female | Ax/int | No | Foot drop | Speech delay | 20 | 40 m/s | *IGHMBP2*: c. 1488C>A p. (Cys496Ter) and c. 2911\_2912delAG p.(Arg971GlufsTer4) | Pathogenic | No |
| 41 | 119 | London | 32 | 1 | Female | Ax/int | Yes (consanguinity) | Floppy feet, delayed walking | Respiratory failure, recurrent gastric distension, autonomic failure, severe scoliosis    | 27 | NR | *IGHMBP2*: c.1325A>G p.(Tyr442Cys) (homozygous) | Likely pathogenic | Yes |
| 42 | 157 | London | 22 | 1 | Female | Ax/int | No | Delayed walking | Scapular winging | 24 | NR | *IGHMBP2*: c.595G>C p.(Ala199Pro) & c.1478C>T p.(Thr493Ile) | Pathogenic,  pathogenic | No, No |
| 43 | 134 | London | 45 | 5 | Male | Ax/int | No | High arches, Achilles Tendon tightness | Erectile dysfunction | 15 | 50 m/s | *LRSAM1*: c. 2086\_2088 delTGC p.(Cys696del) | Likely pathogenic | Yes |
| 44 | 110 | London | 67 | 36 | Male | Ax/int | Yes | Distal sensory loss, poor balance | Prominent  vibratory sensory loss in the lower limbs  | 17 | 56 m/s | *LRSAM1*:c.2087G>A p.(Cys696Tyr) | Likely pathogenic | Yes |
| 45 | 178 | London | 50 | 20 | Male | Ax/int | Yes | High arches, prominent distal sensory loss |  | 13 | 50 m/s | *LRSAM1*: c.1957dupC p.(Gln653ProfsTer5) | Likely pathogenic | Yes |
| 46 | 128 | London | 43 | 3 | Male | Dem | Yes | Poor balance | Kyphoscoliosis, hearing loss, impaired perineal sensation with no erectile dysfunction but impaired ejaculation | moderate | 10 m/s | *FDG4*: 1635+4dup p.? & c.1742A>G p.(His581Arg) | Likely pathogenic, likely pathogenic | Yes, Yes |
| 47 | 139 | London | 32 | 2 | Female | Dem | No | Falls | Recurrent pneumonia, sleep apnoea, scoliosis, prominent vibratory sense loss | 16 | 10 m/s | *FGD4*: c.1056delT p.(Arg354GlyfsTer10) & exon 5 deletion | Likely pathogenic, likely pathogenic | Yes, Yes |
| 48 | 177 | London | 72 | 5 | Female | Dem | No | Falls, unable to run | Deafness, hoarse voice, marked sensory loss, scoliosis | 20 (ES) | 9 m/s | *FDG4*:c.1192-48\_1233del p.? & 1304\_1305delinsAA p.(Arg435Gln) | Likely pathogenic, likely pathogenic | Yes, Yes |
| 49 | 21 | Iowa | 51 | 7 | Male | Ax/int | Yes | Hand weakness and atrophy | None | 7 | 55 m/s | *GARS:* c.880G>C p.Gly294Arg | Pathogenic | No |
| 50 | 57 | Iowa | 46 | 13 | Male | Ax/int | Yes | Tight Achilles tendon and foot drop. | None | 10 | 49 m/s | *GARS:* c.794C>T p.(Ser265Phe) | Likely pathogenic | Yes |
| 51 | 144 | London | 45 | 15 | Male | dHMN | Yes | Hand weakness and atrophy  | None | 11 | 45 m/s | *GARS*: c.1415A>G p.(His472Arg) | Pathogenic | No |
| 52 | 151 | London | 55 | 18 | Female | dHMN | Yes | High arches, ankle sprains | None | 10 (CMTES) | 48 m/s | *AARS*: c.976C>T p.(Arg326Trp) | Pathogenic | Yes |
| 53 | 194 | London | 33 | 15 | Male | Ax/int | No | Poor balance, sprained ankles, distal wasting and sensory loss | Multiple sclerosis | 3 (CMTES) | 44 m/s | *AARS* c.976C>T p.(Arg326Trp) | Likely pathogenic | Yes |
| 54 | 196 | London | 21 | 1 | Male | Dem | Yes | Poor balance, delayed walking | Tremor, mild cerebellar syndrome, mosaicism in mildly affected father | 14 | 23 m/s | *NEFL*: c.65C>T p.(Pro22Leu) |  | Yes |
| 55 | 188 | London | 35 | 8 | Male | Dem | No | Delayed walking, falls | Deafness, vestibular dysfunction, mild cerebellar impairment | 20 (CMTES) | 27 m/s | *NEFL*: c.293A>G p.(Asn98Ser) | Pathogenic | No |
| 56 | 49 | Iowa | 29 | 13 | Male | Dem | Yes | Weakness and poor balance | None | 5 | 38 m/s | *LITAF* c.334G>A p. (Gly112Ser) | Pathogenic | No |
| 57 | 114 | London | 66 | 15 | Male | Dem | Yes | Poor balance, high arches | Diplopia (seronegative ocular myasthenia) | 19 (CMTES) | 20 m/s | *LITAF* c.404C>G p.(Pro135Arg) | Pathogenic | No |
| 58 | 22 | Iowa | 70 | 63 | Male | Dem | No | Left foot drop | HNPP, essential tremor | 7 (CMTES) | 44 m/s | *PMP22* deletion | Pathogenic | No |
| 59 | 111 | London | 49 | 2 | Female | Dem | No | Delayed walking | Pressure palsies, tremor | 15 | 18 m/s | *PMP22:* c.68G>C p.(Thr23Arg) | Likely pathogenic | No |
| 60 | 168 | London | 19 | 2 | Male | Dem | Yes (consanguinity) | Foot deformity, walking difficulties | None | 12 (CMTES) | demyelinating | *MTMR2*: c.1653delC p.(Phe551LeufsTer17) (homozygous) | Pathogenic | Yes |
| 61 | 120 | London | 21 | 2 | Female | Dem | No | Delayed walking, toe walking | Focally folded myelin on sural nerve biopsy (no cataract age 22) | 25 | 29  m/s | *SBF2 (MTMR13)*: c.161G>A p.(Trp54Ter) & c.1718delC p.(Pro573LeufsTer) | Pathogenic | Yes, Yes |
| 62 | 197 | London | 60 | 35 | Male | dHMN | Yes | Lower limb weakness | Proximal weakness, falls  | 12 (CMTES) | 57 m/s | *HSPB8*: c.421A>G p.(Lys141Glu) | Pathogenic | No |
| 63 | 166 | London | 41 | 25 | Female | Ax/int | Yes | Distal sensory loss and lower limb stiffness | None | 12 (CMTES) | 52 m/s | *KIF5A*: c.587 C>A p.(Thr196Asn) | Likely pathogenic | Yes |
| 64 | 164 | London | 35 | 5 | Female | Dem | No | Falls, slow runner | None | 8 | 35  m/s | *NDRG1* c.892-1G>T p.? (homozygous) | Likely pathogenic | Yes |
| 65 | 165 | London | 57 | 8 | Male | HSN | No | Insensitivity to pain, multiple fractures | HNPP-like episodes | moderate | 49  m/s | *SCN9A*: c.3703\_3713del p.(Ile1235LeufsTer2) (homozygous) | Pathogenic | No |
| 66 | 113 | London | 67 | 45 | Male | HSN | Yes | Hyperalgesia, sensory loss and distal weakness | Neuropathic pain | 13 | 52 m/s | *SPTLC2*: c.1276A>T p.(Ile426Phe) | Likely pathogenic | Yes |
| 67 | 220 | London | 62 | 35 | Male | Ax/int | No | Weak hands and later feet | Vocal cord palsy, respiratory insufficiency, scoliosis | 13 (CMTES) | 47 m/s | *TRPV4*: c.694C>T p.(Arg232Cys) | Pathogenic | No |

*Ax/int: axonal or intermediate CMT; CMTES: Charcot-Marie-Tooth examination score; CMTNS: Charcot-Marie-Tooth neuropathy score; Dem: demyelinating CMT; dHMN distal hereditary motor neuropathy; HSN: hereditary sensory neuropathy; NA not available, NR not recordable.*

**Supplementary table 3.** Patients carrying variants of unknown significance identified in the study cohort

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **patientID** | **number of VUS** | **VUS identified**  |
| 1 | 9 | 1 | AARS: c. 1528 C>T, P. Arg510Cys |
| 2 | 7 | 1 | AARS: c. 518 A>G, p.Asp173Gly |
| 3 | 199 | 1 | AARS: c.1375G>A, p.Gly459Arg |
| 4 | 11 | 3 | AARS: c.2552G>A, p. Ser851Asn; FAM134B: c.607G>A, p. Val203Met; NTRK1: c. 865C>A, p. Gln289Lys |
| 5 | 46 | 2 | AARS: c700 C>T, p. Pro234Ser; NDRG1 c.122A>G, p. His41Arg |
| 6 | 40 | 2 | AARS: partial deletion including exon 1; NDRG1: c.122 A>G, p.His41Arg |
| 7 | 63 | 1 | ALDH18A1: c.1015G>A, p. Val339Ile |
| 8 | 96 | 2 | ATL3: c.10C>T, p.Pro4Ser; DCTN1 c.3652A>G, p.Thr1218Ala |
| 9 | 44 | 1 | BSCL2: c.1088T>C, p. Leu363Pro |
| 10 | 43 | 3 | COL6A1: c.1534G>A, p.G512S; COL6A3: c.8270 G>C, p.R2757T; PLEC: c.6046C>T, p.R2016C; ISPD: c.53dupT, p. S19EfsX97 |
| 11 | 65 | 2 | CYP7B1: c.619A>G (p.Lys207Glu; SPG11: c.16G>A, p.Gly6Arg |
| 12 | 20 | 1 | DMN2: c. 1809C>G, p. Ile603Met |
| 13 | 86 | 1 | DNMT1: c.4427A>G, p.His1476Arg |
| 14 | 87 | 1 | DNMT1: c.874G>A, p.Glu292Lys |
| 15 | 100 | 1 | DST: c.6047\_2048dupAG, p.Ile2017ArgfsTer2 |
| 16 | 74 | 1 | DST: c.6319C>G; p.Leu210Val |
| 17 | 53 | 1 | DYNC1H1: c.12113 A>G, p. Asn4038Ser |
| 18 | 134 | 1 | DYNC1H1: c.5326G>A p.Ala1776Thr |
| 19 | 99 | 1 | DYNC1H1: c.8200G>A, p.Val2734Met |
| 20 | 1 | 1 | DYNC1H1:c.12093G>A, p.= |
| 21 | 169 | 1 | DYNC1H1:c.5971G>A p.Asp1991Asn |
| 22 | 198 | 1 | EGR2, c.1337delG, p.Gly446AlafsTer89 |
| 23 | 16 | 3 | EGR2: c.560 C>T p. Ala178Val; SH3TC2: c.2812C>T, p. His938Tyr; PLEKHG5: c.928 G>A p. Asp310Asn |
| 24 | 118 | 1 | FAM134B: c.394A>G, p.Ile132Val |
| 25 | 62 | 2 | GBA2: c.2220C>A p.Ser740Arg; PRX: c.4207G>A, p. Val1403Ile |
| 26 | 32 | 1 | GDAP1: c.614T>C, p. Leu205Ser |
| 27 | 89 | 2 | HSPB1: c.372C>G, p.His124Gln; SCN9A: c.1555G>A, p.Glu519Lys |
| 28 | 215 | 1 | IGHMBP2: c.-4G>A, p.? |
| 29 | 79 | 2 | IGHMBP2: c.165G>C,p.Gln55His; PLEKHG5 c.83C>T, p.Pro28Leu |
| 30 | 209 | 1 | IGHMBP2: c.2036G>A, p.Arg679Gln |
| 31 | 179 | 1 | IGHMBP2: c.596C>G, p.Ala199Gly |
| 32 | 70 | 1 | IKBKAP: c.3398G>A, p.Arg1133His |
| 33 | 34 | 1 | IKBKAP: c.359A>G, p. Asp120Gly |
| 34 | 52 | 1 | INF2: c.3751+5 G>A, IVS22+5G>A |
| 35 | 95 | 1 | LAMA2: c.2288C>T, p.Ala763Val |
| 36 | 60 | 1 | LITAF: c.205C>T, p. Pro69Ser |
| 37 | 130 | 1 | LMNA c.1634G>A p.(Arg545His) |
| 38 | 91 | 2 | LMNA: c.985C>G, p.Arg329Gly; SH3TC2 c.1402\_1403delGCinsTT, p.Ala468Phe |
| 39 | 80 | 1 | MPZ: c.356A>G; p.Tyr119Cys |
| 40 | 187 | 1 | NEFL: c.893\_894delTG, p.Val298fs |
| 41 | 71 | 2 | NGF: c.335C>G, p.Pro112Arg |
| 42 | 54 | 1 | NGF: c.665 T>G, p. Phe222Cys |
| 43 | 94 | 4 | NTRK1: c.1723G>A, p.Glu575Lys; REEP1 deletion of exons 2-7; SLCS2A2 c.342\_344delCTT, p.Phe114del, GDAP1: c.571C>T p.(Arg191Ter) |
| 44 | 68 | 1 | NTRK1: c.53G>A. p.Gly18Glu |
| 45 | 6 | 1 | PLEKHG5 c.1705G>A, p. Asp569Asn |
| 46 | 76 | 1 | PLEKHG5: c.719A>G p.Asp240Gly |
| 47 | 133 | 1 | PMP22: c.353C>T, p.Thr118Met |
| 48 | 206 | 1 | PRX: c.1402G>A p.Val468Met |
| 49 | 42 | 1 | PRX: c.3186G>T, p. Lys1062Asn |
| 50 | 22 | 1 | PRX: c.3373G>A, p. Gly1125Ser |
| 51 | 57 | 1 | SACS: c.13574C>G, p.Thr4525Arg |
| 52 | 93 | 1 | SBF2: c.5205G>C, p.Gln1735His |
| 53 | 37 | 3 | SCN9A: c.2485-10T>G, p. IVS15-10T>G; NTRK1: c.16C>T, p. Arg6Trp; GAN: c.1684C>G, p. Pro562Ala |
| 54 | 45 | 1 | SCN9A: c.684 C>G, p.Ile228Met |
| 55 | 154 | 2 | SETX c.5819A>C p.Lys1940Thr; DCTN1: c.586A>G p.Ile196Val |
| 56 | 110 | 3 | SH3CT2: c.3686A>T, p.Asp1229Val; AARS: c.2385C>G, p.Ile795Met ; MARS: c.491-15C>G, p.? |
| 57 | 28 | 1 | SH3TC2: c.1402\_1403delGCinsTT, p. Ala468Phe |
| 58 | 58 | 1 | SH3TC2: c.1402\_1403delGCinsTT, p. Ala468Phe |
| 59 | 188 | 1 | SH3TC2: c.265C>T, p.Arg89Cys |
| 60 | 31 | 1 | SH3TC2: c.3380G>A, p. Arg1127Gln |
| 61 | 196 | 1 | SH3TC2: c.505T>C p.Tyr169His |
| 62 | 26 | 1 | SH3TC2: c.505T>C, p. Tyr196His |
| 63 | 104 | 1 | SH3TC2: c3686A>T; p.Asp1229Val |
| 64 | 126 | 1 | SLC52A2: c.1016T>C, p.Leu339Pro |
| 65 | 208 | 1 | SPAST: c.131C>T p.Ser44Leu |
| 66 | 155 | 1 | SPLTC2: c.1306A>G p.Lys436Glu |
| 67 | 35 | 2 | SPTLC1: c.208G>T, p. Val70Phe; FGD4: c.1366C>A p. Pro456Thr |
| 68 | 2 | 1 | SPTLC1: c.431T>A,p.Val144Asp |
| 69 | 39 | 2 | SPTLC2: c.508 G>C, p.Val170Leu; KIF1A: c.4604 C>T, p.Ala535Val |
| 70 | 127 | 1 | TRPV4: c.409G>C, p.Ala137Pro |
| 71 | 78 | 1 | WNK1: c.2468A>G, p.His823Arg |
| 72 | 92 | 1 | WNK1: c.2468A>G, p.His823Arg |
| 73 | 59 | 1 | ZFYVE26: c.6194C>T, p. Ala2065Val |