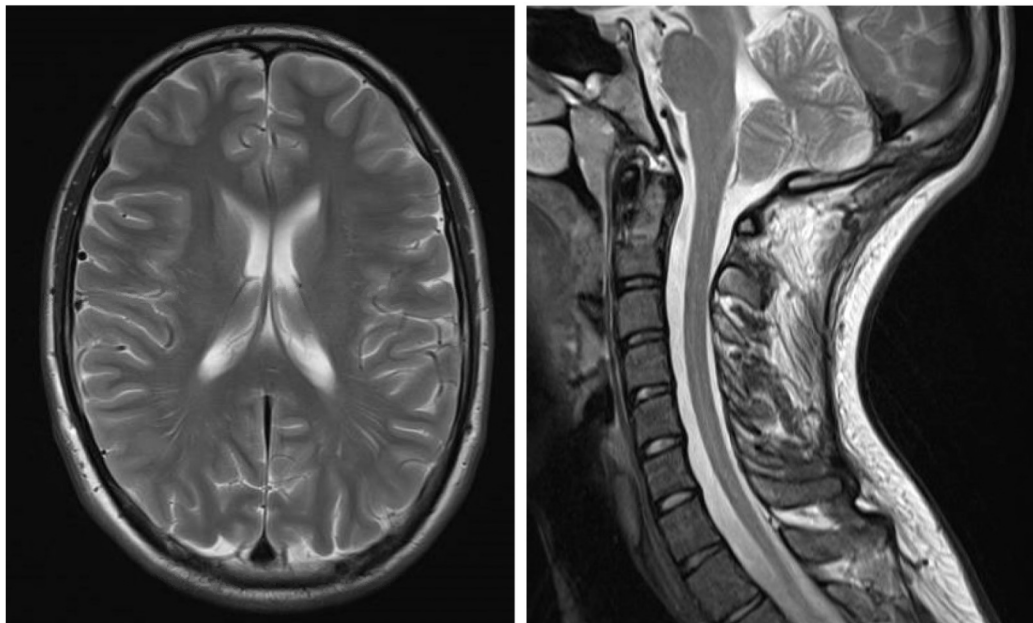


Supplemental Figure 1

| | Proband | Father | Mother |
|---------|-------------|-------------|-------------|
| D6S1552 | 148.9/160.6 | 148.9/162.6 | 150.1/160.6 |
| D6S1624 | 187.8/189.8 | 187.8/193.8 | 185.5/189.8 |
| MOG-CA | 213.6/215.4 | 215.5/221.4 | 209.7/213.5 |

Supplemental Figure 1: RFLP analysis of the proband and her parents (Family 1) confirm the paternity of the father. The following microsatellites markers were used: D6S1552, D6S1624 and MOG-CA. The fragment sizes labeled in red and green correspond to father and mother, respectively.

Supplemental Figure 2



Supplemental Figure 2: MRI of proband from family 3. (A) Transversal T2 section of the brain and (B) sagittal T2 section of the cervical spine showing normal appearance of the brain and cervical spine.

Supplemental Figure 3

Multiple Sequence Alignment

```
CADM1 M---ASVVLPSGSG---CAAAAAA---PPGLRLRLLLLLFSAAALIFTG---D
CADM2 MIWKRSAVL---RFYSVC-----G---LLL-----QGS---Q
CADM3 M-----G-----A-----PAA-SLLLLLLLF-ACCWAPGQANLSQ
CADM4 M-----G-R-----ARRFQWP-----LLLLWAAAA-GE-GA-----

                                         C84
CADM1 G---QNL-----F-----TKDVTVIEGEVATISCVNKS
CADM2 G---Q-----F-----PLTQNVVVEGGTALITCRVDQN
CADM3 GYWQEQDLELGLFAPLDEAIISSVWVSPDMLASQDSQPWTSDETVVAGGTVVLKQVKHD
CADM4 G---QEV-----Q-----TENVTVAEGGVAEITCRLLHQY

                                         C144
CADM1 DDS--VIQLLNPNRQT IYFRDFRPLKDSRFQLL--NFSSSELKVLSTNVSISDEGRYFCQ
CADM2 DNT--S LQWSNPAQQTLYFDDKRALRDNRIELVRASW--HELISISVSDVLSDEGQYTCG
CADM3 EDS--S LQWSNPAQQTLYFGEKRALRDNRIQLVST--PHELSISISNVALADEGEYTCG
CADM4 DGSIVVIQ--NPARQTLFNGTRALKDERFQL--EEFSPRRVRIRLSDARLEDEGGVYFCQ

                                         Y172C C144
CADM1 LYTDP--PQESYTTITVL-V-P--PRNLMD-IQKDTAV-EGEEIEVNTAMASKPATTI
CADM2 LETMPVKTKAY--LTVLGV-PEKPKQ--ISGF--SSPVMGEDMLQITCKTSGSKPAADI
CADM3 IFTMPVTKAKSL--VTVLGI-PQKP--IITG--KSSLREKDTATINQSSGSKPAARL
CADM4 LYTE--DTHHQIATLTVL-VAEPNP--VVE-V-REQAV-EGGEVELSCLVPRSRPAATL

                                         C186
CADM1 RWFKGNTELKCKSE---V---EEWSD---MYTVTSQLMLKVHKEDDG-VEVICQVEH-
CADM2 RWFKNDEKIK---D---VKYLKEE--DANRKTFTVSTLDFRVDRSDDG-VAVICRVDDHE
CADM3 TWRKGDQELHG--EETRI---QE--DPNGKFTVSSVTFQVTRREDDG-ASIVCSVNH
CADM4 RWRDRRELKGG-----VSSS-QE---NGKVWSVASTVRFVRVDRKDDGGI-ICEAQNQ

                                         C243
CADM1 ----PAVTGNLQTRQY-LEVQYKPVVHIQM---T-YPLQGLTREGDALELTCEAIGKP-
CADM2 SLNATPQVA--MQV---LEIHYTPSVKI-I-PSTPFP---QEGQLPILTCESKGPPL
CADM3 SLKGADRS T---SQR--IEVLYTPTA-M-IREDPHP-----REGQKLLHCEGRGNP
CADM4 AL---P--SGHSKQTQYVLVDVQYSPTARI-----HASQAVVREGDTLVLTCAVTGNPR

                                         C333
CADM1 -QFVMVTWVRVD-DE--MPQ--HA-----VLSG----P--N-LFINLNKTDNGTYRC
CADM2 PEPVL--WTK-DGGE--LPDPDRM-----VVSG-----RELNILF---LNKTDNGTYRC
CADM3 PQQYL--WEK-E-GS--VP-PLKMTQESALIF-----P-----F---LNKSDSGTYGC
CADM4 PNQI--RWRN---GNESLPE--RA--EA--V--GETLTLF--G-----LVSADNGTYTC

CADM1 EASNIVG--KAHSDYMLYVD-P-----PTTIPPP-----TTT---TTTTTTTTTIL
CADM2 EATNTIG--QSSAEYVLI VHDVPNTLL--PTTIIPSLTTATVTTVAITTSPTTSATT--
CADM3 TATSNMGSYKAY--YTLNVND-PS-----P--V-PS-----SSSTY-
CADM4 EASNKHG--HARALYVLVYVD-PGAVVEAQTSV-P-----

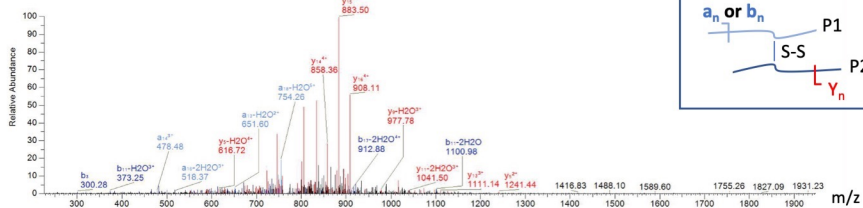
CADM1 TIITDSRA--GEEGSIRAVDHAVI GGVAVVVFAMLLIILGRYF---ARHKGTYFTH
CADM2 SSIRDPNALAGQNGP---DHALIGGIVAVVVFVTLCSIFLLGRYL---ARHKGTYLPN
CADM3 -----HAIIGGIVAFIVFLLLIMLIFLGHYL---IRHKGTYLPN
CADM4 -----YATVGSILALLVFLIIC--VLVG--MWWCSVRQKGSYLTH

CADM1 EAKGADDAADADTAIINAEGGQNNSEKK-EYFI
CADM2 EAKGAEDADPADTAIINAEGSQVNAEKK-EYFI
CADM3 EAKGSDADPADTAIINAEGGQSGDDKK-EYFI
CADM4 EASGLDEQGEAREAFLN--GS--DGHKRKEEFFI
```

Supplemental Figure 3: Multiple sequence alignment between CADM1, CADM2, CADM3 and CADM4 withClustalW. Sequence highlighted in blue indicates membrane signal peptide. The transmembrane region is underlined in orange. Cysteines highlighted in yellow form disulfide bonds of Ig loops. Patients mutation shown in red (Y172C).

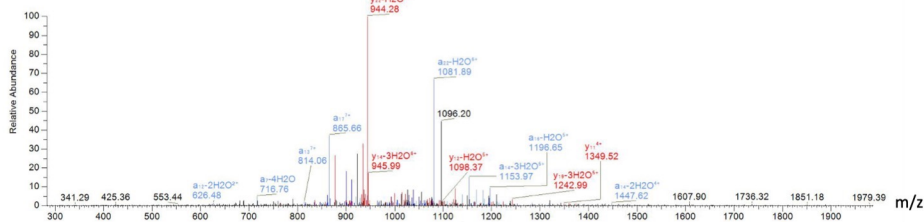
Supplemental Figure 4

C172-C186 disulfide bonds MS/MS spectra



| Identification | 1:S156-K179/S174-R212 = 6878.80a[1ss] SLVTVLGIPOKPIITGCKS | 1:S156-K173/E178-R196 = 3827.028m[1ss] | 1:S156-K173/E178-R196 = 3827.028m[1ss] | 1:D180-R196/S156-K173 = 3569.891m[1ss] | 1:D180-R196/S156-K173 = 3569.891m[1ss] |
|------------------|--|--|--|--|--|
| Peptide Sequence | SLREK/ SSLREKDTATLNCQSSGS KPAARLTWRKGDQELH GEPTR | SLVTVLGIPOKPIITGCK/ EKDQATLNCQSSGSKPA AR | SLVTVLGIPOKPIITGCK/ EKDQATLNCQSSGSKPA AR | DTATLNCQSSGSKPAAR/ SLVTVLGIPOKPIITGCK | DTATLNCQSSGSKPAAR/ SLVTVLGIPOKPIITGCK |
| Enzyme | Trypsin | | | | |
| Firstsite-Site | 1:C172/1:C186 | | | | |
| Delta (ppm) | -1.03 | -1.15 | -1.34 | -2.94 | -5.47 |
| Confidence Score | 99.7 | 100 | 100 | 100 | 100 |
| ID Type | MS2 | MS2 | MS2 | MS2 | MS2 |
| RT | 42.91 | 29.99 | 30 | 31.65 | 31.63 |
| M/Z | 860.937 | 639.177 | 767.014 | 596.154 | 715.382 |
| Charge State | 8 | 6 | 5 | 6 | 5 |
| Mono Mass Theo. | 6878.8216 | 3827.0281 | 3827.0281 | 3569.8911 | 3569.8911 |
| MS Area | 2133297.5 | 280629.91 | 76873.99 | 356203.97 | 215444.12 |

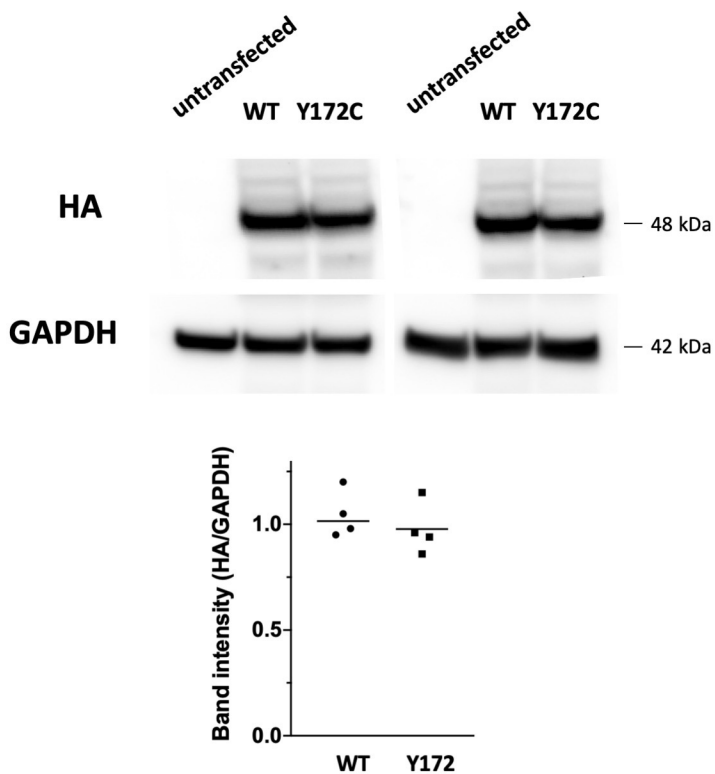
C186-C243 disulfide bonds MS/MS spectra



| Identification | 1:D180-R200/E235-R279 = 7204.527m[1ss] | 1:S174-R196/T221-R260 = 6705.239m[1ss] | 1:S174-R196/T221-R260 = 6705.239m[1ss] |
|------------------|--|---|---|
| Peptide Sequence | DTATLNCQSSGSKPAARLTWR/ EDDGASIVCSNVHESLKGADRSTSRQRIEVLTY PTAMIRPDPPHPR | SSLREKDTATLNCQSSGSKPAAR/ TFTVSSSVTFQVTRREDDGASIVCSNVHESLKG ADRSTSQR | SSLREKDTATLNCQSSGSKPAAR/ TFTVSSSVTFQVTRREDDGASIVCSNVHESLKG ADRSTSQR |
| Enzyme | Trypsin | | |
| Firstsite-Site | 1:C186/1:C243 | | |
| Delta (ppm) | -9.08 | -1.82 | -2.69 |
| Confidence Score | 82.2 | 98.2 | 98.2 |
| ID Type | MS2 | MS2 | MS2 |
| RT | 40.88 | 43.11 | 43.14 |
| M/Z | 801.949 | 959.326 | 1119.211 |
| Charge State | 9 | 7 | 6 |
| Mono Mass Theo. | 7204.5269 | 6705.2388 | 6705.2388 |
| MS Area | 1160911.25 | 2803713.25 | 1614293.5 |

Supplemental Figure 4: MS/MS spectrum of disulfide-linked peptides. Fragments from peptides (P1/P2) are indicated by “a”, “b” or “y” ions derived from trypsin digestion and analyzed on liquid chromatography with tandem mass spectrometry (LC-MS-MS). Top right panel illustrates P1/P2 disulfide bond (S-S) and digested fragments. Raw data was analyzed by BiopharmFinder in order to identify disulfide linked peptide sequences. Table shows detailed information of fragments identified to form disulfide bonds.

Supplemental Figure 5

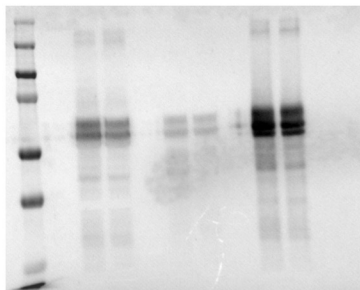


Supplemental Figure 5: Western blot showing relative intensity of CADM3 protein in RT4 Schwann cells transfected with WT-CADM3-HA and Y172C-CADM3-HA. p value >0.5, n=4, unpaired t-test.

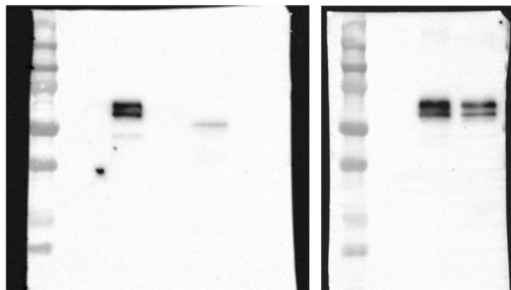
Supplemental Figure 6

Uncropped blots of Figure 3

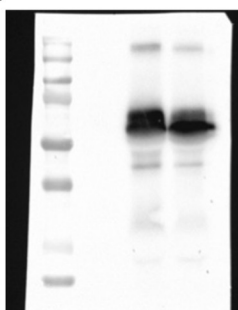
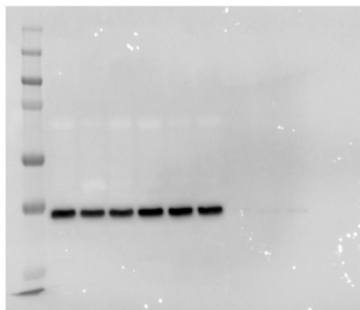
A



B

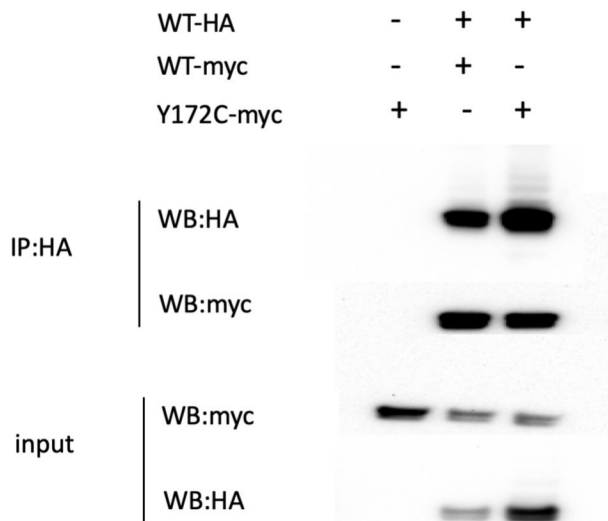
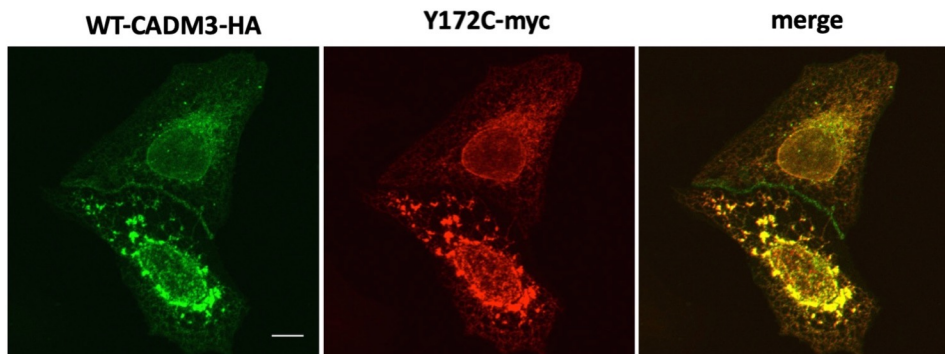


D



Supplemental Figure 6: Uncropped blots of figure 3

Supplemental Figure 7

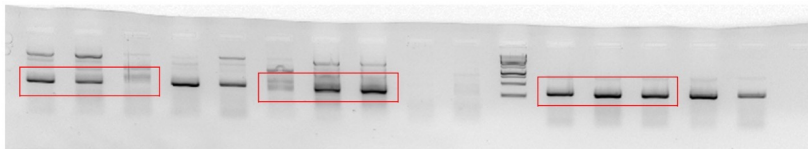


Supplemental Figure 7: Homodimer interaction between WT and mutant CADM3. (A) U2OS cells co-transfected with WT-CADM3-HA and Y172C-myc shows cytoplasmic co-localization between WT and mutant CADM3. (B) Co-immunoprecipitation of WT-CADM3-HA with Y172C-myc indicates homodimer physical interaction.

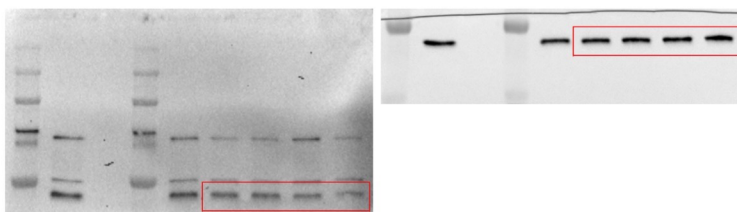
Supplemental Figure 8

Uncropped blots of Figure 6

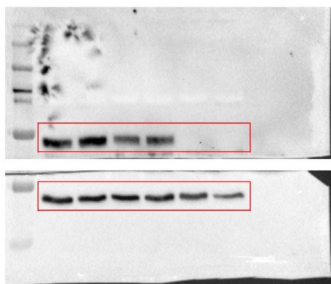
A



B



C



Supplemental Figure 6: Uncropped blots of figure 6

Supplementary Table 1: List of known CMT genes analyzed by whole-exome sequence

| Gene | Associated MIM |
|----------|----------------|
| AARS1 | 613287 |
| ATL1 | 613708 |
| ATL3 | 615632 |
| ATP1A1 | 618036 |
| ATP7A | 300489 |
| BAG3 | 612954 |
| BICD2 | 618291 |
| BSCL2 | 600794 |
| CCT5 | 256840 |
| COX6A1 | 616039 |
| DCAF8 | 610100 |
| DCTN1 | 607641 |
| DHTKD1 | 615025 |
| DNAJB2 | 614881 |
| DNM2 | 606482 |
| DNMT1 | 614116 |
| DST | 614653 |
| DYNC1H1 | 614228 |
| EGR2 | 607678 |
| FBLN5 | 614434 |
| FBXO38 | 615575 |
| FGD4 | 609311 |
| FIG4 | 611228 |
| GAN | 256850 |
| GARS1 | 601472 |
| GDAP1 | 608340 |
| GJB1 | 302800 |
| GNB4 | 615185 |
| HARS1 | 616625 |
| HINT1 | 137200 |
| HK1 | 605285 |
| HOXD10 | 192950 |
| HSPB1 | 606595 |
| HSPB3 | 613376 |
| HSPB8 | 158590 |
| IGHMBP2 | 604320 |
| INF2 | 614455 |
| KARS1 | 613641 |
| KIF1A | 614213 |
| KIF1B | 118210 |
| LITAF | 601098 |
| LMNA | 605588 |
| LRSAM1 | 614436 |
| MARS1 | 616280 |
| MCM3AP | 618124 |
| MED25 | 605589 |
| MFN2 | 601152 |
| MME | 617017 |
| MORC2 | 616688 |
| MPZ | 607736 |
| MTMR2 | 601382 |
| MYH14 | 614369 |
| NAGLU | 616491 |
| NDRG1 | 601455 |
| NEFH | 616924 |
| NEFL | 607734 |
| NGF | 608654 |
| PKD3 | 300905 |
| PLEKHG5 | 615376 |
| PMP2 | 618279 |
| PMP22 | 118300 |
| POLG | 613662 |
| PRDM12 | 616488 |
| PRPS1 | 311070 |
| PRX | 614895 |
| RAB7A | 600882 |
| REEP1 | 614751 |
| RETREG1 | 613115 |
| SACS | 270550 |
| SBF1 | 615284 |
| SBF2 | 604563 |
| SCN11A | 615548 |
| SCN9A | 133020 |
| SETX | 606002 |
| SH3TC2 | 601596 |
| SIGMAR1 | 605726 |
| SLC25A46 | 616505 |
| SLC5A7 | 158580 |
| SPG11 | 616668 |
| SPTLC1 | 162400 |
| SPTLC2 | 613640 |
| SURF1 | 616684 |
| TFG | 604484 |
| TRIM2 | 615490 |
| TRPV4 | 606071 |
| VCP | 616687 |
| WARS1 | 617721 |
| WNK1 | 201300 |
| YARS1 | 608323 |

Supplementary table 2. Fisher's exact test statistic shows a value of $p < 0.01$.

| | Tyr172Cys alleles | Wild-type chromosomes | Total |
|---------------------------|--------------------------|------------------------------|--------------|
| CMT chromosomes (GENESIS) | 3 | 2,508 | 2,514 |
| Controls (GENESIS) | 0 | 16,624 | 16,624 |
| Total | 3 | 19,132 | 19,138 |

Supplementary Table 3: Motor nerve studies

| Individual | Age | Side | Ulnar Nerve | | | | Median Nerve | | | Peroneal Nerve | | | |
|----------------------|-----|------|------------------|-------------------|-------------------|----------------------------|------------------|------------------|-------------------|------------------|-------------------|-------------------|-------------------|
| | | | DML (ms) <3.4 | NCV1 (m/s) >49 | NCV2 (m/s) >50 | CMAP (mV) >2.8 | DML (ms) <3.5 | NCV (m/s) >48 | CMAP (mV) >3.5 | DML (ms) <5.5 | NCV3 (m/s) >40 | NCV4 (m/s) >40 | CMAP (mV) >2.5 |
| Family 1-II:1 | 33 | L | 4.03 | ND | ND | 0.96 | 6.00 | ND | 0.82 | ND | ND | ND | ND |
| Family 2-II:1 | 7 | L | 2.3 | 36 | ND | 0.8 | 4.8 | ND | 0.4 | 4.1 | 30 | ND | 0.3 |
| Family 3-II:1 | 15 | L | 3.1 | 41 | - (dispersion) | 0.3 (dispersion) | 4.6 | 65 | 2.7 | NR | NR | NR | NR |
| Family 3-I:2 | 50 | L | 2.4 | 61 | 40 | 9 | 3.6 | 57 | 7 | 7.2 | 55 | 44 | 0.4 |

Normal values for each nerve in top row under DML, NCV and CMAP. DML – distal motor latency, NCV – Nerve Conduction Velocity; NCV1 – NCV between wrist/elbow; NCV2 – NCV around elbow; NCV3 – NCV between ankle/knee; NCV4 – NCV around knee. CMAP – compound muscle action potential; “ND” indicates measurement was not done. Bold letters signify abnormal values.

Supplementary Table 4: Sensory nerve studies

| Individual | Side | Median Nerve | | | Ulnar Nerve | | | Radial Nerve | | | Lat. (ms) <3.5 | M |
|----------------------|------|-------------------|------------------|------------------|-------------------|------------------|------------------|----------------|----------------|------------------|-------------------|---|
| | | Lat. (ms) <3.5 | NCV (m/s) >44 | SNAP (uV) >20 | Lat. (ms) <3.1 | NCV (m/s) >44 | SNAP (uV) >18 | Lat. (ms) - | NCV (m/s) - | SNAP (uV) >22 | | |
| Family 1-II:1 | L | 2.93 | 47.7 | 13.04 | 3.17 | 44.2 | 13.02 | ND | ND | ND | ND | M |
| Family 2-II:1 | L | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | M |
| Family 3-II:1 | L | | 46 | 6 | | 44 | 7 | | 41 | 6 | | M |
| Family 3-I:2 | L | | 56 | 26 | | 57 | 21 | | 56 | 36 | | 4 |

Normal values listed for each nerve in top row under Lat., NCV, and SNAP., Lat. - latency, NCV – Nerve Conduction Velocity; SNAP-Sensory Nerve Amplitude Potential. “ND” indicates measurement was not done. Bold letters signify abnormal values.