**Supplementary Material for**

# The genetic landscape of axonal neuropathies in the middle aged and elderly: focus on *MME*

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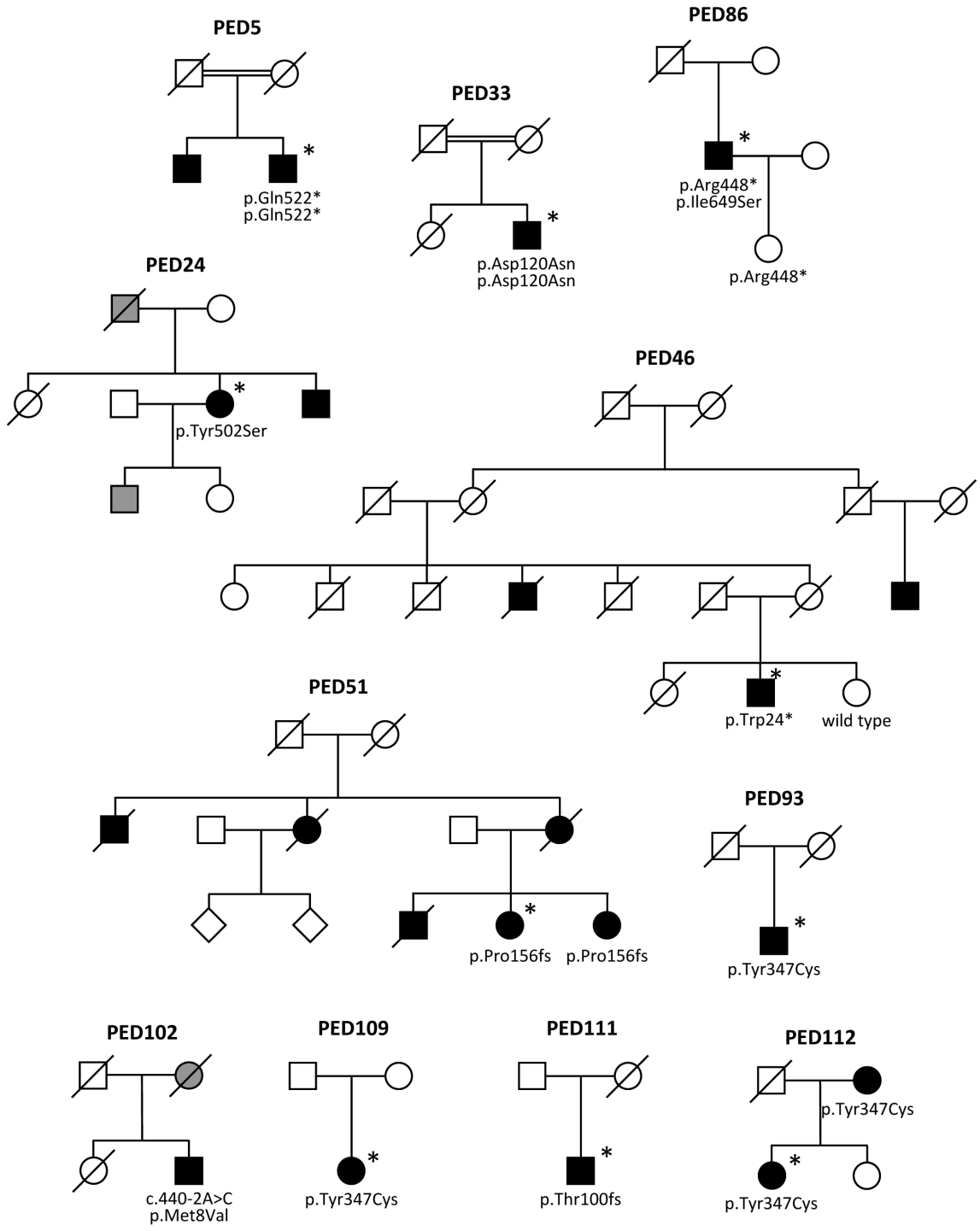


**Figure S1 - Pedigrees of families with serious *MME* variants identified by WES.** Women are represented by circles, men by squares. The symbols of affected individuals are filled (black, clinically affected; gray, probably affected by history or subclinical disease), and those of unaffected individuals are empty. Crossed symbols represent deceased persons. Asterisks indicate index patients whose data are presented in **Table S1**. For PED43 see Figure 2B.

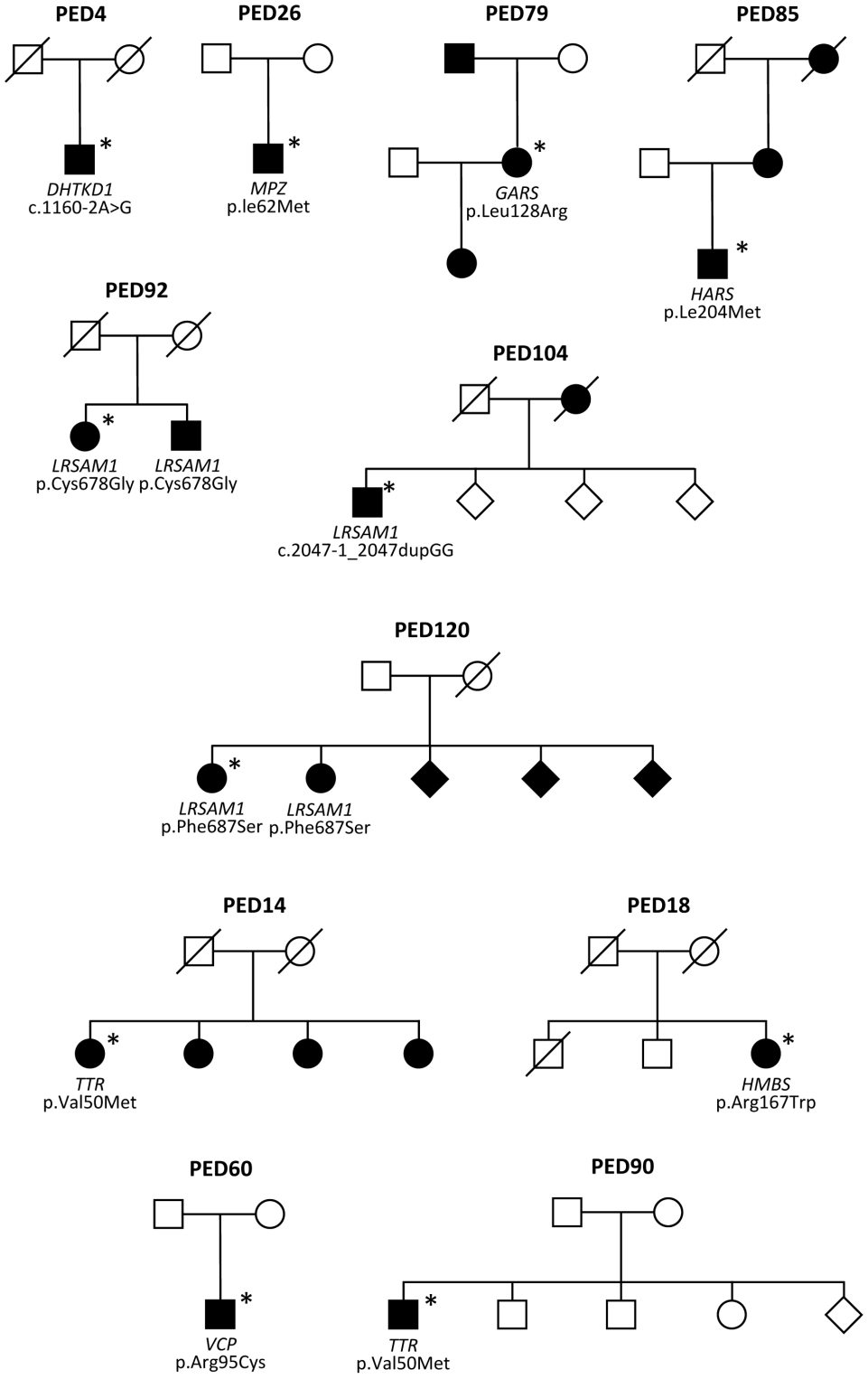


**Figure S2 - Pedigrees of non-*MME* families identified by WES.** Women are represented by circles, men by squares. The symbols of affected individuals are filled (black, clinically affected; gray, probably affected by history or subclinical disease), and those of unaffected individuals are empty. Crossed symbols represent deceased persons. Asterisks indicate index patients whose data are presented in **Table S2**. Note: for some families, pedigrees only incomplete data were available.

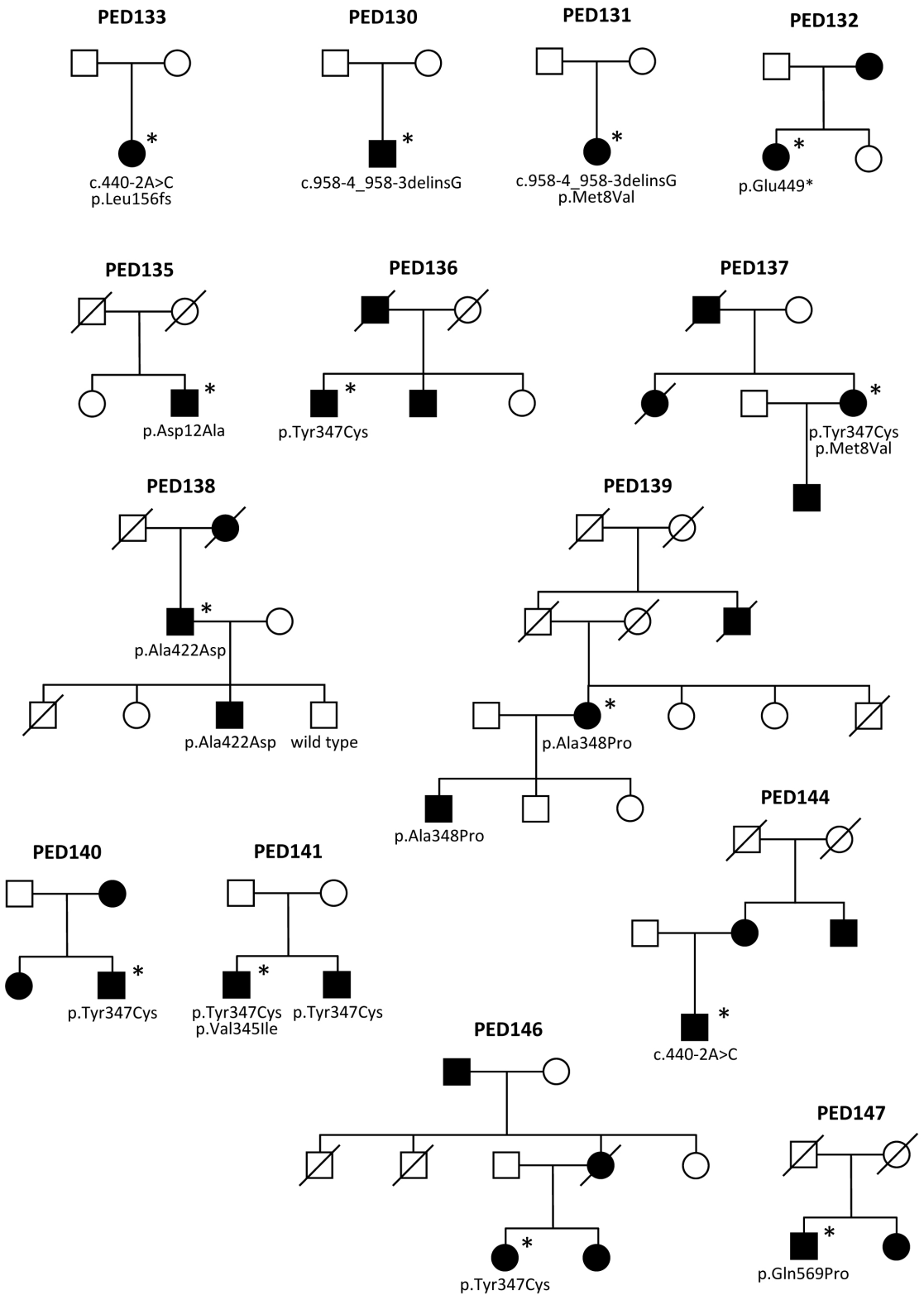


**Figure S3 - Pedigrees of families with serious *MME* variants identified by targeted analysis of the gene.** Women are represented by circles, men by squares. The symbols of affected individuals are filled (black, clinically affected; gray, probably affected by history or subclinical disease), and those of unaffected individuals are empty. Crossed symbols represent deceased persons. Asterisks indicate index patients whose data are presented in **Table S3**.

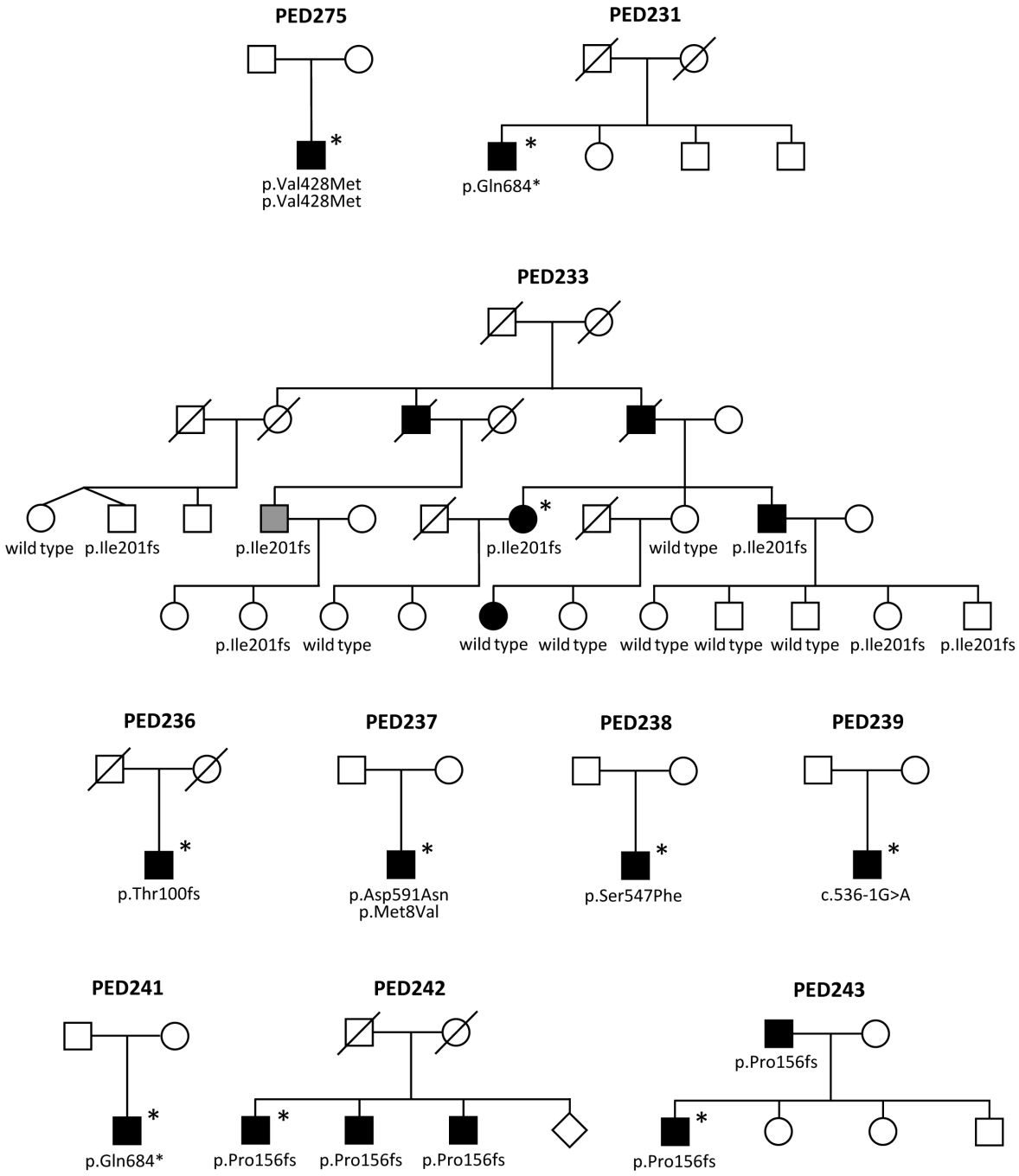


**Figure S4 - Pedigrees of families with serious *MME* variants retrieved from WES repositories and clinical testing laboratories.** Women are represented by circles, men by squares. The symbols of affected individuals are filled (black, clinically affected; gray, probably affected by history or subclinical disease), and those of unaffected individuals are empty. Crossed symbols represent deceased persons. Asterisks indicate index patients whose data are presented in **Table S4**. For PED232 see **Figure 2B**. For PED235 and PED263 see **Figure 2C**. Note: for some pedigrees no sufficient data were available. (continued on the following page)

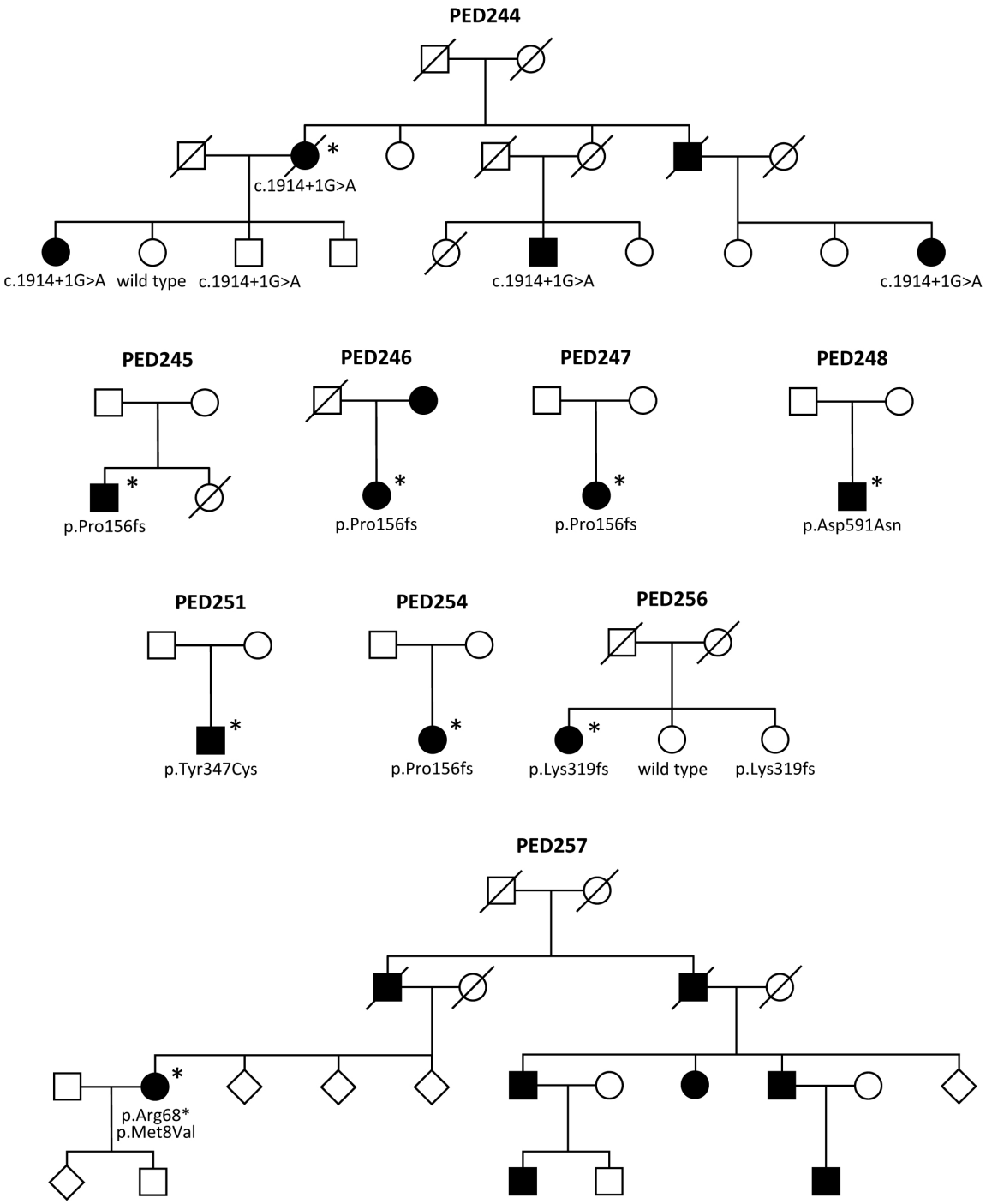


**Figure S4** (continued from previous page)

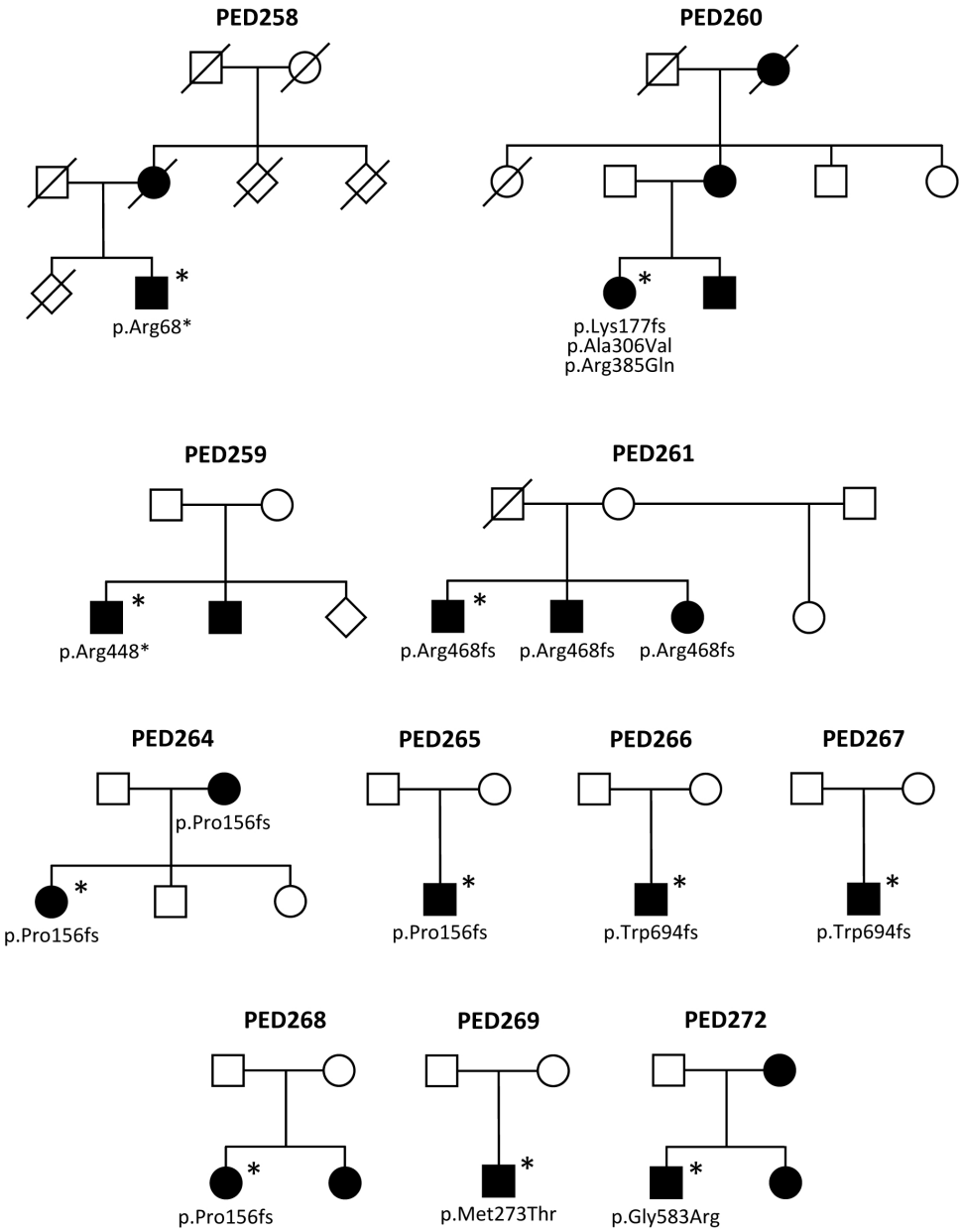


**Figure S4** (continued from previous page)

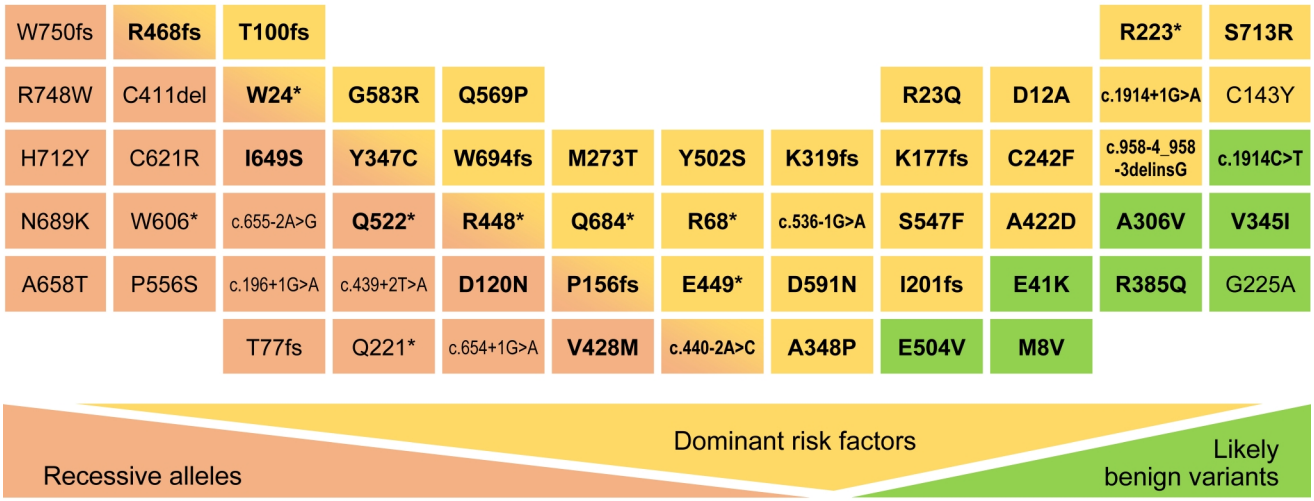


**Figure S5** - Impact of *MME* variants. Graphical overview of *MME* variants identified in patients with late-onset axonal neuropathies in this and previous studies [10-12, 25]. The impact of variants is highlighted by different background colors. Variants printed in bold are reported in this study.

**Table S1 - Cases with *MME* variants among 126 individuals studied by WES.**

| PED No. | Variant(s) | Phenotype | Pedigree | AAD | Score* | First sign(s) | Distal motor deficits UL/LL# | Distal sensory deficits UL/LL# | Pain | PTR | Median MNCV/ CMAP | Peroneal MNCV/ CMAP | Cognitive function (MMSE) | Additional findings/comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Autosomal-recessively inherited *MME* neuropathy** | | | | | | | | | | | | | | |
| 5 (GE) | c.1564C>T (p.Gln522*) hom | LO-CMT2 | F (AR) | 50 | 4 | Abnormal gait | -/++++ | NA/NA | No | NA | NA/NA | NA/NA | Normal | |
| 33 (PL) | c.358G>A (p.Asp120Asn) hom | LO-CMT2 | F (AR) | 46 | 3 | Abnormal gait | +/ +++ | -/+ | NA | 0 | 53.3/3.6 | NR | Normal | |
| 86 (AT) | c.1342C>T (p.Arg448*); c.1946T>G (p.Ile649Ser) | LO-CMT2 | S | 40 | 3 | Abnormal gait | +/+++ | -/- | No | 0 | 44.0/3.5 | NR | Normal | Hoarse voice, elevated CK levels (2.5x) |
| **Autosomal-dominantly transmitted susceptibility to peripheral neuropathy due to heterozygous *MME* loss-of-function variants** | | | | | | | | | | | | | | |
| 43 (AT) | c.467delC (p.Pro156Leufs*14) | LO-CMT2 | F (AD) | 65 | 3 | Abnormal gait, sensory loss in feet | +/+++ | -/+ | No | 0 | NA/NA | NR | Normal (28/30) | Hypacusis; *MME* c.22A>G (p.Met8Val) het; AT1 in ref. 12 |
| 46 (AT) | c.71G>A (p.Trp24*) | LO-CMT2 | F (AD) | 60 | 3 | Abnormal gait | +/+++ | -/++ | No | 0 | 53.5/4.7 | NR | Normal (29/30) | Hypacusis; elevated CK levels (2x); AT3 in ref. 12 |
| 51 (AT) | c.467delC (p.Pro156Leufs*14) | LO-CMT2 | F (AD) | 62 | 3 | Sensory loss & weakness in toes | -/+++ | -/++ | No | 0 | NA/NA | 40.0/0.8 | Normal (27/30) | AT2 in ref. 12 |
| 102 (AT) | c.440-2A>C (p.(?)) | LO-CMT2 | F (AD) | 63 | 3 | Foot drop | -/+++ | -/++ | No | 1 | 49.2/7.1 | NR | Normal | Asymmetric muscle weakness in LL; elevated CK levels (2x); *MME* c.22A>G (p.Met8Val) het |
| 111 (AT) | c.298delA (p.Thr100Profs*11) | LO-CMT2 | S | 65 | 2 | Abnormal gait | +/++ | -/+ | No | 0 | 50.5/8.2 | 37.4/0.3 | Normal | Hypacusis, bulbar speech; elevated CK levels (4x) |
| **Autosomal-dominantly transmitted susceptibility to peripheral neuropathy due to heterozygous *MME* missense variants** | | | | | | | | | | | | | | |
| 24 (CZ) | c.1505A>C (p.Tyr502Ser) | LO-CMT2 | F (AD) | 57 | NA | Foot drop | NA/NA | NA/NA | NA | NA | 55.2/6.0 | NA/NA | Normal | Tremor in UL, cramps in LL |
| 93 (AT) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | S | 70 | 4 | Abnormal gait | -/++++ | -/++ | No | 0 | NA/NA | 31.0/0.1 | Normal | Restless legs syndrome, NIDDM diagnosed at age 85 y |
| 109 (AT) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | S | 64 | 1 | Sensory loss in toes | -/- | -/++ | No | 1 | NA/NA | NR | Normal | Restless legs syndrome |
| 112 (AT) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | F (AD) | 53 | 2 | Sensory loss in feet | -/+ | -/++ | No | 2 | NA/NA | 48.0/6.0 | Normal | |

Abbreviations are as follows: AAD = Age at diagnosis (in years); AD = Autosomal dominant; ALS = Amyotrophic lateral sclerosis; ALS-FTD = Amyotrophic lateral sclerosis with frontotemporal dementia complex; AR = Autosomal recessive; CIDP = Chronic inflammatory demyelinating polyneuropathy; CK levels = Creatine kinase levels (in multiples of upper limit of normal); CMAP = Compound muscle action potential (in mV); CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); CSF = Cerebrospinal fluid; dHMN = Distal hereditary motor neuropathy; F = Familial; (continued on the following page)

**Table S1** (continued from previous page)

HNPP = Hereditary neuropathy with liability to pressure palsies; HSN = Hereditary sensory neuropathy; LL = Lower limbs; LO-CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); MCI = Minimal cognitive impairment; MMSE = Mini-mental state examination; MNCV = Motor nerve conduction velocity (in m/s); NA = Not available; NCS = Nerve conduction studies; NIDDM = Noninsulin-dependent diabetes mellitus, NR = No response; PED No. = Family number (country of recruitment: AT = Austria, AU = Australia; BR = Brazil; CZ =Czech Republic; FR = France; GE = Germany; HU = Hungary; NO = Norway; PL = Poland; SE = Sweden; UK = United Kingdom; US = United States); PTR = Patellar tendon reflex (0 = Areflexic; 1 = Decreased; 2 = Normal; 3 = Brisk); S = Sporadic; UL = Upper limbs; WES = Whole-exome sequencing; y = Years.
*For definition of disease scores, see Materials and Methods section. Only index patients were listed.
[#]Motor and sensory deficits were scored as follows: - = Normal; + = Mild; ++ = Moderate; +++ = Severe; ++++ = Very severe.

**Table S2 - Non-*MME* cases among 126 individuals studied by WES.**

| PED No. | Variant(s) | Phenotype | Pedigree | AAD | Score* | First sign(s) | Distal motor deficits UL/LL# | Distal sensory deficits UL/LL# | Pain | PTR | Median MNCV/ CMAP | Peroneal MNCV/ CMAP | Cognitive function (MMSE) | Additional findings/comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 (AT) | *DHTKD1* c.1160-2A>G (p.(?)) | LO-CMT2 | S | 60 | 3 | Sensory loss in toes | +/+++ | -/ ++ | NA | 1 | 50.9/10.8 | 36.9/0.2 | Normal | |
| 7 (AT) | *HSPB8* c.59C>T (p.Pro20Leu) | LO-CMT2 | S | 69 | 4 | Tingling in great toes | ++/++++ | -/ ++ | NA | NA | 42.2/11.0 | 37.2/2.4 | Normal | |
| 26 (AT) | *MPZ* c.186C>G (p.Ile62Met) | LO-CMT2 | S | 40 | 2 | Sensory loss in feet | -/+ | -/++ | NA | 0 | 50.0/8.3 | NR | Normal | Elevated CK levels (3x) |
| 37 (CZ) | *WARS* c.1228G>A (p.Asp410Asn) | LO-CMT2 | S | 45 | 2 | Complicated wound healing after injury | -/++ | -/+ | NA | NA | 59.7/6.4 | 46.5/1.9 | Normal | |
| 49 (CZ) | *AARS* c.1079C>G (p.Ala360Gly) | LO-CMT2 | F | 45 | 3 | Burning sensation & numbness in feet | -/++ | +/+++ | NA | NA | 49.5/4.2 | 39.5/3.6 | Normal | |
| 79 (GE) | *GARS* c.383T>G (p.Leu128Arg) | LO-CMT2 | F (AD) | 40 | 3 | Abnormal gait, foot drop | +/+++ | -/++ | No | 0 | 48.0/5.0 | NR | Normal | |
| 85 (AT) | *HARS* c.612A>G (p.Ile204Met) | LO-CMT2 | F (AD) | 40 | NA | Foot drop | NA/NA | NA/NA | NA | NA | NA/NA | NA/NA | Normal | |
| 92 (AT) | *LRSAM1* c.2032T>G (p.Cys678Gly) | LO-CMT2 | F | 45 | 4 | Sensory loss in LL | -/+++ | +/++++ | NA | 0 | NA/NA | NR | Normal | |
| 104 (AT) | *LRSAM1* c.2047-1_2047dupGG (p.(?)) | LO-CMT2 | F | 48 | NA | Abnormal gait | NA/NA | NA/NA | NA | NA | NA/NA | NA/NA | Normal | |
| 120 (AT) | *LRSAM1* c.2060T>C (p.Phe687Ser) | LO-CMT2 | F | 40 | 2 | Sensory loss in distal LL | -/+ | -/+++ | NA | NA | NA/NA | NA/NA | Normal | Axonal NCS changes |
| 121 (CZ) | *MPZ* c.181dupG (p.Asp61Glyfs42*) | LO-CMT2 | F (AD) | 45 | 1 | Burning sensation & numbness in feet | -/+ | ++/++ | NA | NA | NA/NA | 35.0/NA | Normal | |
| 14 (GE) | *TTR* c.148G>A (p.Val50Met) | LO-CMT2 | F | 68 | 2 | Abnormal gait | NA/++ | NA/++ | NA | 0 | NA/NA | NA/NA | Normal | Axonal NCS changes in LL |
| 18 (PL) | *HMBS* c.499C>T (p.Arg167Trp) | LO-CMT2 | S | 65 | 1 | Sensory impairment in hands | +/- | +/+ | No | NA | NA/NA | NA/NA | Normal | No history of porphyric attacks |
| 60 (AT) | *VCP* c.283C>T (p.Arg95Cys) | LO-CMT2 | S | 55 | 2 | Pain in LL | -/++ | -/- | Yes | NA | NA/NA | 36.7/7.5 | Normal | Additional proximal muscle weakness in LL; elevated CK levels (3x) |
| 90 (PL) | *TTR* c.148G>A (p.Val50Met) | LO-CMT2 | S | 59 | 1 | Abnormal gait | +/+ | +/+ | NA | NA | NA/NA | NA/NA | Normal | Facial nerve involvement |

Abbreviations are as follows: AAD = Age at diagnosis (in years); AD = Autosomal dominant; ALS = Amyotrophic lateral sclerosis; ALS-FTD = Amyotrophic lateral sclerosis with frontotemporal dementia complex; AR = Autosomal recessive; CIDP = Chronic inflammatory demyelinating polyneuropathy; CK levels = Creatine kinase levels (in multiples of upper limit of normal); CMAP = Compound muscle action potential (in mV); CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); CSF = Cerebrospinal fluid; dHMN = Distal hereditary motor neuropathy; F = Familial; (continued on the following page)

**Table S2** (continued from previous page)

HNPP = Hereditary neuropathy with liability to pressure palsies; HSN = Hereditary sensory neuropathy; LL = Lower limbs; LO-CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); MCI = Minimal cognitive impairment; MMSE = Mini-mental state examination; MNCV = Motor nerve conduction velocity (in m/s); NA = Not available; NCS = Nerve conduction studies; NIDDM = Noninsulin-dependent diabetes mellitus, NR = No response; PED No. = Family number (country of recruitment: AT = Austria, AU = Australia; BR = Brazil; CZ =Czech Republic; FR = France; GE = Germany; HU = Hungary; NO = Norway; PL = Poland; SE = Sweden; UK = United Kingdom; US = United States); PTR = Patellar tendon reflex (0 = Areflexic; 1 = Decreased; 2 = Normal; 3 = Brisk); S = Sporadic; UL = Upper limbs; WES = Whole-exome sequencing; y = Years.
*For definition of disease scores, see Materials and Methods section. Only index patients were listed.
[#]Motor and sensory deficits were scored as follows: - = Normal; + = Mild; ++ = Moderate; +++ = Severe; ++++ = Very severe.

**Table S3 - Cases with *MME* variants among 104 individuals studied by targeted analysis of the gene.**

| PED No. | Variant(s) | Phenotype | Pedigree | AAD | Score* | First sign(s) | Distal motor deficits UL/LL# | Distal sensory deficits UL/LL# | Pain | PTR | Median MNCV/ CMAP | Peroneal MNCV/ CMAP | Cognitive function (MMSE) | Additional findings/comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Autosomal-recessively inherited *MME* neuropathy** | | | | | | | | | | | | | | |
| 133 (CZ) | c.440-2A>C (p.(?)); c.467delC (p.Pro156Leufs*14) | LO-CMT2 | S | 35 | 3 | Pain, muscle cramps | +/+++ | +/++ | Yes | NA | 40.9/10.3 | 28.3/0.3 | Normal | |
| **Autosomal-dominantly transmitted susceptibility to peripheral neuropathy due to heterozygous *MME* loss-of-function variants** | | | | | | | | | | | | | | |
| 130 (PL) | c.958-4_958-3delinsG (p.(?)) | LO-CMT2 | S | 35 | NA | NA | NA/NA | NA/NA | NA | NA | NA/NA | NA/NA | Normal | |
| 131 (CZ) | c.958-4_958-3delinsG (p.(?)) | LO-CMT2 | S | 51 | 2 | Foot drop | ++/++ | NA/NA | NA | NA | 39.0/0.8 | 30.0/0.1 | Normal | *MME* c.22A>G (p.Met8Val) het |
| 132 (CZ) | c.1345G>T (p.Glu449*) | LO-CMT2 | F (AD) | 49 | 3 | Burning sensation in feet | ++/+++ | +/+++ | NA | NA | NA/NA | 27.0/0.2 | Normal | Restless legs syndrome |
| 144 (GE) | c.440-2A>C (p.(?)) | LO-CMT2 | F (AD) | 57 | 3 | Paraesthesia & pain in feet | -/+++ | -/+ | Yes | 0 | NA/NA | 43.7/1.5 | Normal | DE1 in ref. 12 |
| **Autosomal-dominantly transmitted susceptibility to peripheral neuropathy due to heterozygous *MME* missense variants** | | | | | | | | | | | | | | |
| 135 (AT) | c.35A>C (p.Asp12Ala) | LO-CMT2 | S | 69 | 3 | Frequent stumbling | + /+++ | -/+ | No | 0 | 44.0/7.9 | NR | Normal (29/30) | Hypacusis; elevated CK levels (3x); AT4 in ref. 12 |
| 136 (AT) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | F (AD) | 45 | 2 | Tingling in big toe | -/+ | -/+++ | No | 0 | 47.0/12.5 | NR | Normal | AT5 in ref. 12 |
| 137 (AT) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | F (AD) | 55 | 2 | Calf cramps | -/+ | -/ ++ | Yes | 1 | NA/NA | NR | Normal | Mild NIDDM; *MME* c.22A>G (p.Met8Val) het; AT6 in ref. 12 |
| 138 (AT) | c.1265C>A (p.Ala422Asp) | LO-CMT2 | F (AD) | 40 | 3 | Sensory loss in feet | +/+++ | -/+++ | No | 0 | NA/NA | NR | Normal (30/30) | Hypacusis, NIDDM diagnosed at age 50 y; AT8 in ref. 12 |
| 139 (AT) | c.1042G>C (p.Ala348Pro) | LO-CMT2 | F (AD) | 60 | 3 | Frequent stumbling, unsteady gait | +/ +++ | -/+ | No | 0 | 44.0/2.3 | NR | Normal | AT7 in ref. 12 |
| 140 (AT) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | F (AD) | 45 | 3 | Sensory loss in toes | ++/+++ | -/++ | No | 0 | 47.0/8.1 | NR | Normal | Elevated CK levels (3.5x) |
| 141 (AT) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | F | 62 | 2 | Abnormal gait | -/++ | -/+ | No | 0 | NA/NA | NR | Normal | Restless legs syndrome; elevated CK levels (3.5x); *MME* c.1033G>A (p.Val345Ile) het |
| 146 (GE) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | F (AD) | 44 | 3 | Hammer toes, pes cavus | -/+++ | -/+ | No | NA | 39.0/NA | NA/NA | Normal | |
| 147 (GE) | c.1706A>C (p.Gln569Pro) | LO-CMT2 | F | 55 | 2 | Numbness & paraesthesia in LL | +/++ | -/+ | No | 1 | NA/NA | NA//NA | Normal | Axonal sensorimotor NCS changes in LL |

Abbreviations are as follows: AAD = Age at diagnosis (in years); AD = Autosomal dominant; ALS = Amyotrophic lateral sclerosis; ALS-FTD =
(continued on the following page)

**Table S3** (continued from previous page)

Amyotrophic lateral sclerosis with frontotemporal dementia complex; AR = Autosomal recessive; CIDP = Chronic inflammatory demyelinating polyneuropathy; CK levels = Creatine kinase levels (in multiples of upper limit of normal); CMAP = Compound muscle action potential (in mV); CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); CSF = Cerebrospinal fluid; dHMN = Distal hereditary motor neuropathy; F = Familial; HNPP = Hereditary neuropathy with liability to pressure palsies; HSN = Hereditary sensory neuropathy; LL = Lower limbs; LO-CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); MCI = Minimal cognitive impairment; MMSE = Mini-mental state examination; MNCV = Motor nerve conduction velocity (in m/s); NA = Not available; NCS = Nerve conduction studies; NIDDM = Noninsulin-dependent diabetes mellitus, NR = No response; PED No. = Family number (country of recruitment: AT = Austria, AU = Australia; BR = Brazil; CZ =Czech Republic; FR = France; GE = Germany; HU = Hungary; NO = Norway; PL = Poland; SE = Sweden; UK = United Kingdom; US = United States); PTR = Patellar tendon reflex (0 = Areflexic; 1 = Decreased; 2 = Normal; 3 = Brisk); S = Sporadic; UL = Upper limbs; WES = Whole-exome sequencing; y = Years.
*For definition of disease scores, see Materials and Methods section. Only index patients were listed.
[#]Motor and sensory deficits were scored as follows: - = Normal; + = Mild; ++ = Moderate; +++ = Severe; ++++ = Very severe.

## Table S4 - Cases with *MME* variants retrieved from WES repositories and clinical testing laboratories.

| PED No. | Variant(s) | Phenotype | Pedigree | AAD | Score* | First sign(s) | Distal motor deficits UL/LL# | Distal sensory deficits UL/LL# | Pain | PTR | Median MNCV/ CMAP | Peroneal MNCV/ CMAP | Cognitive function (MMSE) | Additional findings/comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Autosomal-recessively inherited *MME* neuropathy** | | | | | | | | | | | | | | |
| 240 (HU) | c.467delC (p.Pro156Leufs*14); c.1400dupA (p.Arg468Glufs*3) | CMT2 | F (AR) | 26 | 3 | Progressive walking difficulty | ++/+++ | -/+ | Yes | NA | 42.0/14.0 | NR | Normal | |
| 275 (NO) | c.1282G>A (p.Val428Met) hom | CMT2 | S | NA | 3 | NA | ++/+++ | ++/++ | NA | NA | NA/NA | NA/NA | Normal | Genetic testing at age 51 y; NIDDM diagnosed at age 50 y; demyelinating & axonal NCS changes |
| **Families compatible with autosomal recessive *MME* neuropathy and autosomal-dominantly transmitted susceptibility to peripheral neuropathy** | | | | | | | | | | | | | | |
| 235 (BR) | c.467delC (p.Pro156Leufs*14) hom | LO-CMT2 | F | 39 | 3 | Abnormal gait | -/+++ | -/- | NA | NA | 44.1/6.9 | NR | Normal | Hand tremor; 3/4 known/obligate heterozygotes affected or likely affected |
| 263 (AU) | c.1040A>G (p.Tyr347Cys) hom | LO-CMT2 | F | 48 | 4 | Foot drop | NA/++++ | NA/NA | NA | NA | NA/NA | NA/NA | Normal | Wheelchair-bound by early 70's; axonal NCS changes; 2/3 known/obligate heterozygotes affected or likely affected |
| **Autosomal-dominantly transmitted susceptibility to peripheral neuropathy due to heterozygous *MME* loss-of-function variants** | | | | | | | | | | | | | | |
| 231 (AU) | c.2050C>T (p.Gln684*) | LO-CMT2 | S | 58 | 3 | Foot drop | -/+++ | -/+ | NA | 0 | 50.0/5.0 | NR | Normal | Mildly elevated CSF protein, elevated CK levels (2x) |
| 232 (AU) | c.1342C>T (p.Arg448*) | LO-CMT2 | F | 68 | 3 | Foot drop | -/ +++ | -/++ | NA | 0 | 44.0/5.0 | NR | Normal | *MME* c.22A>G (p.Met8Val) het |
| 233 (AU) | c.599delT (p.Ile201Leufs*13) | LO-CMT2 | F (AD) | 50 | 3 | Proximal muscle weakness & fatigability | +/+++ | +/++ | NA | 0 | 42.0/2.0 | NR | Normal | Variant not seen in a family member with earlier onset, slowly progressive mild neuropathy |
| 236 (DE) | c.298delA (p.Thr100Profs*11) | ALS | S | 33 | 4 | Fasciculations & weakness in UL | +++/++++ | -/- | No | 3 | NA/NA | NA/NA | Normal | Disease duration >10 years; axonal sensorimotor NCS changes; DE2 in ref. 12 |
| 239 (DE) | c.536-1G>A (p.(?)) | LO-CMT2 | S | 65 | 2 | Pain, paraesthesia & weakness in LL | -/ ++ | -/ ++ | Yes | NA | 38.0/11.5 | NR | Normal | |
| 241 (HU) | c.2050C>T (p.Gln684*) | LO-CMT2 | F | 65 | 2 | Foot drop | -/++ | -/+ | NA | NA | Normal | NR | Normal | |
| 242 (SE) | c.467delC (p.Pro156Leufs*14) | dHMN | F | 47 | 4 | Muscle cramps in legs | -/ ++++ | -/+ | Yes | 1 | NA/NA | NA/NA | Normal | Dysphagia & dysarthria, gynecomastia; , predominant motor NCS changes; elevated CK levels; SE1 in ref. 12 |
| 243 (UK) | c.467delC (p.Pro156Leufs*14) | LO-CMT2 | F (AD) | 70 | 2 | Abnormal/unsteady gait | +/++ | NA/NA | No | 0 | 48.0/6.8 | 24.0/0.6 | Normal | Restless legs syndrome, myeloproliferative disease; UK1 in ref. 12 |
| 244 (AU) | c.1914+1G>A (p.(?)) | LO-CMT2 | F (AD) | 40 | 4 | Toe-walking, abnormal gait | -/++++ | +/+++ | NA | 0 | 37.0/10.0 | NR | Normal | |
| 245 (UK) | c.467delC (p.Pro156Leufs*14) | Sensory ataxia | S | 68 | 2 | Abnormal/unsteady gait, numbness in feet | -/- | -/++ | No | 0 | 44.0/2.3 | NA/NA | MCI | Dysarthria, abnormal smooth-pursuit eye movements, *MME* c.1033G>A, (p.Val345Ile) het; UK2 in ref. 12 |
| 246 (US) | c.467delC (p.Pro156Leufs*14) | LO-CMT2 | F (AD) | 65 | 3 | Sensory disturbances in legs | -/+++ | NA/++ | Yes | 0 | NA/NA | NA/NA | Normal | Initial diagnosis CIDP; axonal NCS changes in LL; US1 in ref. 12 |

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**Table S4** (continued from previous page)

| PED No. | Variant(s) | Phenotype | Pedigree | AAD | Score* | First sign(s) | Distal motor deficits UL/LL# | Distal sensory deficits UL/LL# | Pain | PTR | Median MNCV/ CMAP | Peroneal MNCV/ CMAP | Cognitive function (MMSE) | Additional findings/comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 247 (US) | c.467delC (p.Pro156Leufs*14) | LO-CMT2 | S | 45 | 2 | Impaired balance | -/+ | -/++ | NA | NA | 52.0/9.3 | NA/NA | Normal | |
| 254 (US) | c.467delC (p.Pro156Leufs*14) | ALS | S | 68 | NA | Bulbar-onset ALS-FTD | NA/NA | NA/NA | No | 3 | NA/NA | NA/NA | Dementia | US2 in ref. 12 |
| 256 (US) | c.957+1delG (p.Lys319Asnfs*6) | LO-CMT2 | S | 40 | 3 | Abnormal gait | ++/+++ | +/++ | No | 0 | NA/NA | NR | Normal | US3 in ref. 12 |
| 257 (US) | c.202C>T (p.Arg68*) | LO-CMT2 | F (AD) | 53 | 3 | Numbness, tingling & pain in LL | +/+++ | -/++ | Yes | 2 | NA/NA | NR | Normal | *MME* c.22 A>G (Met8Val) het; US4 in ref. 12 |
| 258 (US) | c.202C>T (p.Arg68*) | CMT2 | F (AD) | 30 | 3 | Weakness and impaired balance | +/+++ | -/++ | Yes | 0 | NA/NA | NA/NA | Normal | Possible history of poliomyelitis at age 6 y; axonal NCS changes; US5 in ref. 12 |
| 259 (US) | c.1342C>T (p.Arg448*) | LO-CMT2 | F | 49 | 3 | Pain in feet, foot drop | +/+++ | +/++ | Yes | 1 | NA/NA | 35.0/1.0 | Normal | Tinnitus, heart disease; US6 in ref. 12 |
| 260 (US) | c.531delA (p.Lys177Asnfs*15) | LO-CMT2 | F (AD) | 35 | 1 | Cramps in LL | +/+ | -/+ | Yes | 0 | NA/NA | NA/NA | Normal | Shooting pain; axonal NCS changes; *MME* c.917C>T (p.Ala306Val) het & c.1154G>A (p.Arg385Gln) het |
| 261 (FR) | c.1400dupA (p.Arg468Glufs*3) | LO-CMT2 | F | 65 | 3 | Steppage gait | +/+++ | -/++ | NA | 0 | 43.0/4.2 | NR | Dementia (12/30) | Elevated CK levels (2x) |
| 262 (US) | c.202C>T (p.Arg68*) | LO-CMT2 | F (AD) | 31 | 2 | Cramps & weakness in LL | -/+ | -/++ | NA | 2 | 49.0/11.9 | NR | Normal | Progressive glomerular kidney disease & proteinuria; elevated CK levels (3-5x) |
| 264 (NO) | c.467delC (p.Pro156Leufs*14) | LO-CMT2 | F (AD) | 63 | 2 | Abnormal gait | +/++ | +/++ | NA | NA | NA/NA | NA/NA | Normal | |
| 265 (NO) | c.467delC (p.Pro156Leufs*14) | CMT2 | S | NA | 2 | Distal muscle weakness | +/++ | -/- | NA | NA | NA/NA | NA/NA | Normal | Genetic testing at age 65 y; axonal NCS changes in LL |
| 266 (NO) | c.2082delG (p.Trp694Cysfs*48) | LO-CMT2 | S | 65 | 2 | Distal sensorimotor disturbances | -/++ | -/++ | NA | NA | NA/NA | NA/NA | Normal | Axonal NCS changes |
| 267 (NO) | c.2082delG (p.Trp694Cysfs*48) | CMT2 | S | 21 | 2 | Distal muscle weakness in UL & LL | +/++ | +/++ | NA | NA | NA/NA | NA/NA | Normal | Congenital aortic stenosis |
| 268 (NO) | c.467delC (p.Pro156Leufs*14) | CMT2 | F | NA | 1 | Distal sensory loss in LL | -/- | -/+ | NA | 0 | NA/NA | NA/NA | Normal | Genetic testing at age 53 y |
| 284 (AT) | c.440-2A>C (p.(?)) | LO-CMT2 | F (AD) | 64 | 2 | Cramps & sensory loss in feet | -/++ | +/++ | No | 0 | 46.7/6.9 | NR | Normal | Intitial diagnosis CIDP; elevated CK levels (2x) |
| 285 (AT) | c.667C>T (p.Arg223*) | LO-CMT2 | F (AD) | 42 | 2 | Foot drop | -/++ | -/- | No | 0 | 42.0/5.5 | 23.5/0.1 | Normal | |
| 286 (AT) | c.440-2A>C (p.(?)) | LO-CMT2 | F (AD) | 42 | 3 | Frequent stumbling | +/+++ | -/++ | No | 0 | 38.5/7.8 | NR | Normal | Elevated CK levels (5x) |

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**Table S4** (continued from previous page)

| PED No. | Variant(s) | Phenotype | Pedigree | AAD | Score* | First sign(s) | Distal motor deficits UL/LL# | Distal sensory deficits UL/LL# | Pain | PTR | Median MNCV/ CMAP | Peroneal MNCV/ CMAP | Cognitive function (MMSE) | Additional findings/comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Autosomal-dominantly transmitted susceptibility to peripheral neuropathy due to heterozygous *MME* missense variants** | | | | | | | | | | | | | | |
| 237 (DE) | c.1771G>A (p.Asp591Asn) | ALS | S | 63 | 3 | Bulbar signs | -/+++ | -/- | NA | 3 | NA/NA | NA/NA | Normal | Dysphagia, dysarthria, respiratory failure; *MME* c.22A>G (p.Met8Val) het |
| 238 (DE) | c.1640C>T (p.Ser547Phe) | Ataxia | S | 47 | 4 | Unsteady gait | -/+++ | -/++++ | NA | 0 | 55.0/11.1 | NR | Normal | Genetically confirmed myotonic dystrophy type 2 (PROMM); elevated CK levels (1.5-4x) |
| 248 (US) | c.1771G>A (p.Asp591Asn) | LO-CMT2 | S | 47 | 3 | Sensory loss in feet | -/++ | -/++ | NA | 1 | NA/NA | NA/NA | Normal | Elevated CK levels (2x) |
| 250 (US) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | F (AD) | 60 | NA | NA | NA/NA | NA/NA | NA | 3 | NA/NA | NA/NA | Normal | |
| 251 (US) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | S | 40 | NA | NA | NA/NA | NA/NA | NA | 3 | NA/NA | NA/NA | Normal | |
| 255 (US) | c.725G>T (p.Cys242Phe) | LO-CMT2 | F | 35 | 2 | Sensory loss in feet | NA/NA | -/++ | Yes | NA | NA/NA | NA/NA | Normal | Ataxia, shooting neuropathic pain, cough, slight upper motor neuron dysfunction |
| 269 (NO) | c.818T>C (p.Met273Thr) | HNPP-like | S | NA | NA | Foot drop | NA/NA | NA/NA | NA | NA | NA/NA | NA/NA | Normal | Genetic testing at age 74 y |
| 272 (NO) | c.1747G>A (p.Gly583Arg) | CMT2 | F (AD) | NA | NA | NA | NA/NA | NA/NA | NA | NA | NA/NA | NA/NA | Normal | Genetic testing at age 61 y; axonal NCS changes |
| 281 (NO) | c.1040A>G (p.Tyr347Cys) | LO-CMT2 | S | 56 | NA | NA | NA/NA | NA/NA | NA | NA | NA/NA | NA/NA | Normal | Elevated CK levels (2x) |
| 282 (AT) | c.68G>A (p.Arg23Gln) | LO-CMT2 | S | 70 | 2 | Par-/dysesthesia in LL | -/+ | -/++ | Yes | 0 | NA/NA | NA/NA | Normal | Hypacusis, carpal tunnel syndrome; axonal NCS changes |
| 283 (AT) | c.2137A>C (p.Ser713Arg) | LO-CMT2 | F (AD) | 58 | 2 | Paresthesia in toes | +/+ | -/+++ | No | 0 | 37.0/7.0 | 35.0/0.5 | Normal | Mild NIDDM, on oral antidiabetic medication; *MME* c.22A>G (p.Met8Val) het |

Abbreviations are as follows: AAD = Age at diagnosis (in years); AD = Autosomal dominant; ALS = Amyotrophic lateral sclerosis; ALS-FTD = Amyotrophic lateral sclerosis with frontotemporal dementia complex; AR = Autosomal recessive; CIDP = Chronic inflammatory demyelinating polyneuropathy; CK levels = Creatine kinase levels (in multiples of upper limit of normal); CMAP = Compound muscle action potential (in mV); CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); CSF = Cerebrospinal fluid; dHMN = Distal hereditary motor neuropathy; F = Familial; HNPP = Hereditary neuropathy with liability to pressure palsies; HSN = Hereditary sensory neuropathy; LL = Lower limbs; LO-CMT2 = Charcot-Marie-Tooth neuropathy type 2 (axonal); MCI = Minimal cognitive impairment; MMSE = Mini-mental state examination; MNCV = Motor nerve conduction velocity (in m/s); NA = Not available; NCS = Nerve conduction studies; NIDDM = Noninsulin-dependent diabetes mellitus, NR = No response; PED No. = Family number (country of recruitment: AT = Austria, AU = Australia; BR = Brazil; CZ =Czech Republic; FR = France; GE = Germany; HU = Hungary; NO = Norway; PL = Poland; SE = Sweden; UK = United Kingdom; US = United States); PTR = Patellar tendon reflex (0

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**Table S4** (continued from previous page)

= Areflexic; 1 = Decreased; 2 = Normal; 3 = Brisk); S = Sporadic; UL = Upper limbs; WES = Whole-exome sequencing; y = Years.
*For definition of disease scores, see Materials and Methods section. Only index patients were listed.
[#]Motor and sensory deficits were scored as follows: - = Normal; + = Mild; ++ = Moderate; +++ = Severe; ++++ = Very severe.