

## Supplementary Material

### Next generation sequencing

WES and targeted multigene panel on DNA from blood sample obtained from patient was performed at Neurogenetics Laboratory of UCL Institute of Neurology; Queen Square, London, UK using the Illumina's Nextera rapid capture focused enrichment kit and run on the Illumina HiSeq 2500 instrument. The resulting 100bp paired-end sequence reads were mapped against the human reference genome assembly 19 (GRCh37) with the Burrows-Wheeler Aligner (BWA) package. NGS analysis was performed using in house pipeline.

### *Whole exome sequencing*

WES revealed a total of 22,346 exonic variants. Variants were filtered for non-synonymous, splice-site, and coding indel variants that had a minor allele frequency (MAF) <0.1% in the Exome Variant Server (EVS), 1000 genome project and Exome Aggregation Consortium database (ExAC). 323 variants met these filtering criteria, and one variant was in a gene associated with inherited neuropathies. The c.1325A>G; p.Tyr442Cys, was found in heterozygosity in *IGHMBP2*. This variant has not been previously reported in the literature or to public databases of genetic variation (dbSNP, NHLBI exome variant server, ExAC database). It is located in a high conserved region (phastCons = 1 and phyloP = 4.56), there is a large physiochemical difference between Tyrosin (Tyr) and Cysteine (Cys) and has been predicted to be pathogenic by SIFT (1), MutationTaster (p-value: 1), and Polyphen2 (1).

### *Targeted multigene panel*

Target multigene panel analysis revealed that 99.82% of the coding exons (+/- base pairs, except GJB1, for which the target region is extended 860 bases upstream of the ATG start codon to include the nerve specific promoter region) of all genes in the panel were sequenced to a read depth of 30X or greater. The minimum coverage depth of coverage was 19X for AARS gene. The regions with coverage below 30X were analyzed manually.

### **Sanger sequencing**

PCRs were performed with AmpliTaq Gold 360 Master Mix (Applied Biosystems, Foster City, California, USA), with an annealing temperature of 58°C. Sequencing reactions were performed using M13 primers and BigDye Terminator cycle sequencing chemistry (Applied Biosystems, Foster City, California, USA). Sequences were analyzed on an ABI3730XL automated DNA sequencer and SeqScape software (Applied Biosystems, Foster City, California, USA). Primers are available under request.

**Supplementary table 1.** List of genes related to CMT2 and hereditary motor neuropathy and alignment statistics of depth coverage on WES.

|  | Gene                             | On-target |         |          | Average depth | Median depth | Max depth |
|--|----------------------------------|-----------|---------|----------|---------------|--------------|-----------|
|  |                                  | ≥1X (%)   | ≥10 (%) | ≥30X (%) |               |              |           |
| Alanyl-tRNA synthetase                                     | AARS                             | 100       | 98      | 96       | 99            | 97           | 192       |
| ATPase Cu <sup>(2+)</sup> -transporting, alpha polypeptide | ATP7A                            | 100       | 100     | 88       | 72            | 68           | 185       |
| Bicaudal homolog drosophila 2                              | BICD2                            | 100       | 84      | 54       | 39            | 34           | 114       |
| BSCL2  | BSCL2                            | 98        | 94      | 87       | 88            | 94           | 182       |
| Dynactin 1   | DCTN1                            | 100       | 100     | 87       | 88            | 88           | 194       |
| Dynamamin 2  | DNM2                             | 100       | 100     | 90       | 94            | 97           | 247       |
| Dynein, cytoplasmic heavy chain 1                          | DYNC1H1                          | 100       | 100     | 96       | 101           | 100          | 218       |
| Early growth response 2                                    | EGR2                             | 100       | 74      | 58       | 56            | 45           | 189       |
| FGD1-related actin binding protein                         | FGD4                             | 100       | 99      | 91       | 68            | 70           | 134       |
| SAC domain containing inositol phosphatase 3               | FIG4                             | 100       | 100     | 97       | 77            | 72           | 180       |
| Glycyl-tRNA synthetase                                     | GARS                             | 100       | 100     | 94       | 88            | 88           | 207       |
| Ganglioside-induced differentiation-associated protein 1   | GDAP1                            | 100       | 100     | 100      | 104           | 98           | 208       |
| GAP junction protein, beta-1                               | GJB1 (including promoter region) | 67        | 48      | 32       | 24            | 29           | 115       |
| Histidine triad nucleotide-binding protein 1               | HINT1                            | 100       | 91      | 65       | 47            | 45           | 112       |
| Heat-shock 27-KD protein 1                                 | HSPB1                            | 100       | 84      | 77       | 85            | 85           | 197       |
| Heat-shock 27-KD protein 8                                 | HSPB8                            | 100       | 79      | 73       | 79            | 84           | 182       |
| Immunoglobulin mu-binding protein 2                        | IGHMBP2                          | 100       | 97      | 85       | 71            | 69           | 177       |
| LPS-induced TNF-alpha factor                               | LITAF                            | 100       | 91      | 68       | 52            | 54           | 130       |
| Lamin A/C  | LMNA                             | 99        | 94      | 84       | 76            | 71           | 186       |

|  |         |     |     |     |     |     |     |
|--|---------|-----|-----|-----|-----|-----|-----|
| Leucine-rich repeat and sterile alpha motif containing 1           | LRSAM1  | 100 | 100 | 96  | 98  | 99  | 204 |
| Methionyl-tRNA synthetase  | MARS    | 100 | 93  | 63  | 44  | 41  | 140 |
| Mitofusin 2  | MFN2    | 100 | 100 | 97  | 101 | 101 | 215 |
| Myelin protein zero  | MPZ     | 100 | 100 | 76  | 61  | 57  | 150 |
| Myotubularin-related protein 2                                     | MTMR2   | 100 | 100 | 100 | 90  | 88  | 183 |
| NMYC downstream-regulated gene 1                                   | NDRG1   | 100 | 90  | 78  | 67  | 67  | 146 |
| Neurofilament protein, light polypeptide                           | NEFL    | 100 | 96  | 78  | 60  | 57  | 146 |
| Peripheral myelin protein 22                                       | PMP22   | 100 | 100 | 100 | 104 | 101 | 171 |
| Phosphoribosylpyrophosphate synthetase 1                           | PRPS1   | 100 | 100 | 100 | 95  | 90  | 170 |
| Periaxin   | PRX     | 100 | 92  | 75  | 75  | 63  | 257 |
| Sterile alpha motif domain-containing protein 9                    | RAB7A   | 100 | 94  | 92  | 94  | 104 | 142 |
| SET-binding factor 2   | SBF2    | 100 | 100 | 95  | 73  | 73  | 159 |
| Senataxin  | SETX    | 100 | 98  | 83  | 72  | 67  | 238 |
| SH3 domain and tetratricopeptide repeat domain 2                   | SH3TC2  | 100 | 98  | 87  | 82  | 83  | 219 |
| Solute carrier family 52 (Riboflavin transporter), member 1        | SLC52A1 | 98  | 72  | 41  | 28  | 25  | 92  |
| Solute carrier family 52 (Riboflavin transporter), member 2        | SLC52A2 | 100 | 83  | 50  | 47  | 31  | 175 |
| Solute carrier family 52 (Riboflavin transporter), member 3        | SLC52A3 | 100 | 91  | 76  | 68  | 60  | 208 |
| Transient receptor potential cation channel, subfamily 5, member 4 | TRPV4   | 100 | 93  | 78  | 69  | 67  | 210 |
| Valosin containing protein   | VCP     | 100 | 98  | 95  | 108 | 108 | 231 |
| Tyrosyl-tRNA synthetase  | YARS    | 100 | 100 | 95  | 88  | 86  | 239 |

**Supplementary table 2.** List of genes related to CMT2 and hereditary motor neuropathy and alignment statistics of depth coverage on targeted multigene panel.

| Gene   |                                  | ≥1X (%) | ≥10X (%) | ≥30X (%) | Average depth | Median depth | Max depth |
|--|----------------------------------|---------|----------|----------|---------------|--------------|-----------|
| Alanyl-tRNA synthetase   | AARS                             | 100     | 100      | 99.6     | 328           | 322          | 756       |
| BSCL2  | BSCL2                            | 100     | 100      | 100      | 303           | 263          | 779       |
| Dynamin 2  | DNM2                             | 100     | 100      | 100      | 288           | 280          | 781       |
| Dynein, cytoplasmic 1, heavy chain 1                               | DYNC1H1                          | 100     | 100      | 99.9     | 358           | 329          | 963       |
| Glycyl-tRNA synthetase   | GARS                             | 100     | 100      | 99.8     | 273           | 240          | 741       |
| Ganglioside-induced differentiation-associated protein 1           | GDAP1                            | 100     | 100      | 100      | 472           | 387          | 1170      |
| GAP junction protein, beta-1                                       | GJB1 (Including promoter region) | 100     | 100      | 100      | 329           | 274          | 601       |
| Histidine triad nucleotide-binding protein 1                       | HINT1                            | 100     | 100      | 100      | 405           | 363          | 816       |
| Heat-shock 27-KD protein 1   | HSPB1                            | 100     | 100      | 100      | 366           | 299          | 656       |
| Heat-shock 27-KD protein 8   | HSPB8                            | 100     | 100      | 100      | 303           | 283          | 572       |
| Immunoglobulin mu-binding protein 2                                | IGHMBP2                          | 100     | 100      | 100      | 334           | 333          | 702       |
| Lamin A/C  | LMNA                             | 100     | 100      | 100      | 374           | 352          | 949       |
| Leucin-rich repeat and sterile alpha motif containing 1            | LRSAM1                           | 100     | 100      | 98.2     | 276           | 246          | 784       |
| Methionyl-tRNA synthetase  | MARS                             | 100     | 100      | 100      | 368           | 359          | 704       |
| Mitofusin 2  | MFN2                             | 100     | 100      | 100      | 281           | 278          | 695       |
| Myelin protein zero  | MPZ                              | 100     | 100      | 100      | 327           | 292          | 801       |
| Neurofilament protein, light polypeptide                           | NEFL                             | 100     | 100      | 100      | 292           | 223          | 689       |
| Pheripheral myelin protein 22                                      | PMP22                            | 100     | 100      | 100      | 546           | 545          | 1044      |
| Phosphoribosylpyrophosphate synthetase 1                           | PRPS1                            | 100     | 100      | 100      | 372           | 354          | 645       |
| Sterile alpha motif domain-containing protein 9                    | RAB7A                            | 100     | 100      | 100      | 456           | 395          | 884       |
| SH3 domain and tetratricopeptide repeat domain 2                   | SH3TC2                           | 100     | 100      | 100      | 357           | 381          | 508       |
| Transient receptor potential cation channel, subfamily 5, member 4 | TRPV4                            | 100     | 100      | 100      | 362           | 377          | 676       |

|                                   |             |     |     |       |     |     |     |
|-----------------------------------|-------------|-----|-----|-------|-----|-----|-----|
| <b>Valosin containing protein</b> | <b>VCP</b>  | 100 | 100 | 98.67 | 310 | 278 | 776 |
| <b>Tyrosyl-tRNA synthetase</b>    | <b>YARS</b> | 100 | 100 | 100   | 315 | 322 | 640 |