**Supplementary information**

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*DNA isolation*

Extraction of genomic DNA was performed from whole blood from nine family members (III:1, IV:2, IV:1, V:1, V:2, V:3, V:4, IV:8, and IV:9), using DNeasy Blood & Tissue kit (Qiagen, Hilden Germany), according to the manufacturer’s instructions.

*Genetic analysis*

*Next Generation sequencing*

*Neuromuscular sub-exomic sequencing (NSES)*

NSES was performed on DNA from the index case V:2, using the Ion ProtonTM sequencer (Life Technologies), as previously described 1, 2. The NSES panel comprised of 336 known and candidate neurogenic disease genes, including those listed within the December 2012 freeze of the Neuromuscular Disorders gene table 3. NSES data were analysed using the Cartegenia software package (Agilent Technologies). Only variants with a minor allele frequency of <2% in control population databases ExAC, 1000 Genome Project and dbSNP 4 were retained.

*Whole exome sequencing (WES)*

WES was performed on DNA from the unaffected and affected individuals in the family (V:1, V:2 and V:3), as previously described 5. Briefly, target enrichment was performed with 3 μg genomic DNA using the SureSelectXT Human All Exon Kit version 5 (Agilent Technologies, Santa Clara, CA, USA) to generate barcoded whole-exome sequencing libraries. Libraries were sequenced on the HiSeq2000 platform (Illumina, San Diego, CA, USA) as paired-end 2 ×100-bp reads with 60x coverage. Quality assessment of the sequence reads was performed by generating QC statistics with FastQC (http://www.bioinformatics.bbsrc.ac.uk/projects/fastqc). Read alignment to the reference human genome (hg19, UCSC assembly, February 2009) was done using BWA 6 with default parameters. After removal of PCR duplicates (Picard tools, http://picard.sourceforge.net) and file conversion (SAMtools) 7, quality score recalibration, indel realignment and variant calling were performed with the HaplotypeCaller algorithm in the GATK package 8 based on established best practices 9.

*Variant annotation and selection*

Variants were annotated with ANNOVAR 10 using a wide range of databases such as dbSNP build 135, dbNSFP, KEGG, the Gene Ontology project and tracks from the UCSC. A filtering strategy, directed to disease gene candidates, was performed by QIAGEN’s Ingenuity® Variant Analysis™ software (www.qiagen.com/ingenuity). Ingenuity Variant Analysis combines analytical tools which annotates variants and displays data including Polyphen, SIFT and CADD scores. We focused initially on coding variants in known neurogenetic disease genes, e.g. where the mutation produced a missense change, stop gain or stop loss, frameshift or essential splicing change. For this family with known consanguinity, the initial filtering strategy was also focused on homozygous variants. Only those changes that were predicted to be damaging or with unknown impact were analysed. We excluded variants that were frequent in control datasets (>1% in dbSNP 4, the Exome Variant Server (EVS) (NHLBI) (<http://evs.gs.washington.edu/EVS/>), the 1000 Genome Project Database (<http://browser.1000genomes.org/index.html)>, the Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/) and the Human Background Variant Database (<http://neotek.scilifelab.se/hbvdb/>).

*Polymerase chain reaction (PCR) and Sanger sequencing*

PCR and bi-directional Sanger sequencing of *MRE11* was performed on patients and relatives. Primer details and conditions are available upon request.

*Histochemical and Immunohistochemical analyses of* *muscle biopsy*

An open muscle biopsy specimen was obtained from the biceps brachii in the index patient (V:2), after informed consent. The sample was embedded in paraffin. For conventional histochemical techniques 10 µm thick cryostat sections were stained with haematoxylin and eosin (H&E). Cryostat sections, 6-μm-thick, were processed for immunohistochemistry with the streptavidin-biotin Super Sensitive TM IHC detection system (BioGenex, San Ramon, CA, USA), using a polyclonal rabbit anti-MRE11A (1:250, Sigma) for examination of nuclear staining of MRE11A homolog, double-strand break repair nuclease. Sections from paraffin-embedded muscle tissues (the biceps brachii) from two individuals without neurodegenerative diseases were used as controls. Muscle sections were examined under a microscope. Images were processed using Photoshop (Adobe, USA).

*cDNA analysis*

Total RNA was extracted from paraffin-embedded muscle tissue sections of the index patient (V:2) and controls using a Qiagen total RNA Isolation System kit (RNeasy DSP FFPE Kit), according to the manufacturer’s instructions. Synthesis of first-strand complementary DNA (cDNA) was performed using Ready-To-Go You-Prime First-Strand Beads (Amersham Pharmacia Biotech, Uppsala, Sweden) according to the manufacturer’s instructions. To analyse the splicing of exon 7 of *MRE11* in the index case, PCR was performed on cDNA with primer pairs covering exon 1 through 8 (1168 bp). Beta actin was used as control. PCR primers are available on request.

1. **e-References**

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