**web material and methods**

**Cell cultures.** Schwann cells were cultured from sciatic nerves of neonatal rats as described previously by Brockes et al (Brockes et al, 1979) with minor modifications. We used P3-P4 Wistar rat pups. The sciatic nerves were cut out from just below the dorsal root ganglia and at the knee area. During the extraction and cleaning, the nerves were introduced into a 35 mm cell culture dish containing 2 ml of cold Leibovitz’s F-15 medium (Invitrogen) placed on ice. The nerves were cleaned, desheathed and placed them in a new 35 mm cell culture dish containing DMEM with 1mg/ml of collagenase A (Roche). Subsequently they were cut into very small pieces using a scalpel and left in the incubator for 2 hours. Nerve pieces were homogenized using a 1ml pipette, digestion reaction stopped with complete medium and the homogenate poured through a 40μm Falcon Cell Strainer (Fisher Scientific). We then centrifuged the homogenate at 210 g for 10 minutes at room temperature and resuspended the pellet in complete medium supplemented with 10 μM of cytosine--D-arabinofuranoside (AraC; Sigma) to prevent fibroblast growth. The resuspended cells were then introduced into the PLL-coated 35 mm cell culture dishes. After 72 hours, medium was removed and cell cultures expanded in DMEM supplemented with 3% FBS, 5 μM forskolin and 10 ng/ml recombinant NRG1 (R&D Systems).

RT4D6-P2T rat Schwannoma cells were obtained from Professor Dies Meijer (Centre for Neuroregeneration, University of Edinburgh). HEK293 were obtained from SIGMA. The cells were grown in non-coated flasks with DMEM GlutaMAX, 4.5g/l glucose (Invitrogen) supplemented with 100U/ml penicillin, 100U/ml streptomycin and 5-10% bovine fetal serum. Where indicated, cells were transfected with plasmid DNA using Lipofectamine 2000 (Thermo Fisher Scientific) following the manufacturer’s recommendations.

**Immunofluorescence studies.** For immunofluorescence, cells on cover-slips were fixed in 4% paraformaldehyde/PBS, and blocked for 1 h in 10% horse serum and 0.1% Triton X-100 in PBS. Primary antibodies were diluted in blocking solution and incubated overnight at 4°C. Coverslips were then washed with PBS, and detection was performed by applying the appropriate fluorescent secondary AlexaFluor conjugated antibody. Nuclei were counterstained with bisbenzimide (Hoechst nuclear stain) in PBS. Samples were mounted in Fluoromount G (Southern Biotechnology Associates). Anti-Krox-20 (EGR2) (ABE 1374 Millipore) immunofluorescence was performed as described by Le et al. (Le et al, 2005). Images were obtained using a confocal ultraspectral microscope (Leica TCS SP2). Quantification of fluorescence was performed using Image J and MetaMorph (Molecular Devices) software.

**Immunoprecipitation.** The indicated transfected cells were harvested by centrifugation (210g, 5 min) and washed with PBS twice. Pellets were lysed in 1 ml of 50 mM Tris-HCl pH 7.5, 120 mM NaCl, 0.5 mM EDTA, 0.5 % Nonidet P-40 with phosphatase and protease inhibitors, and centrifuged 20 min at 12000g, 4˚C. Supernatants were recovered and precleared. 100 l of GFP-Trap® agarose beads (Chromo Tek) were added and samples incubated overnight at 4˚C under gentle rotation. Beads were washed three times with TBS including protease and phosphatase inhibitors, eluted with sample buffer, subjected to SDS-PAGE and immunobloted with the indicated antibody.

**SDS-PAGE and immunoblotting.** Cells were homogenized at 4°C in radio-immunoprecipitation assay buffer (PBS, 1% Nonidet P-40, 1% sodium deoxycholate, 0.1% SDS, and 5 mM EGTA) containing protease inhibitors (Complete MINI tablets; Roche) and, where necessary, phosphatase inhibitors (Phospho STOP tablets, Roche). Protein concentrations were determined by the BCA method (Pierce). 10–50 g of total protein was subjected to SDS-PAGE and blotted onto Protran nitrocellulose membrane (Whatman). Membranes were blocked and incubated overnight at 4°C with the indicated primary antibody, washed and incubated with secondary antibodies, and developed with ECLplus (GE Healthcare). The secondary antibodies were conjugated with horseradish peroxidase (1:2000; Sigma).

**Chromatin Immunoprecipitation assays.** The ChIP assay was a modification of the method described by Jang et al (Jang et al, 2006). Briefly, cell cultures were incubated in PBS/1% PFA for 25 min. at room temperature. Cells were harvested by centrifugation (1000g, 3 min) and washed with PBS. The pellet was resuspended in 1.2 ml of buffer A (150 mM NaCl, 10% glycerol, 0.3% Triton, 50 mM Tris-HCl pH8 and protease inhibitors), homogenized and sonicated (20 pulses of 20s separated by 40s on ice between each pulse) to "High Power" in the Bioruptor (Diagenode). Chromatin was clarified by centrifugation at 21000 g for 30 min at 4°C. Protein concentration in the supernatant was quantified by the BCA method (Pierce). An aliquot was saved as input. The volume corresponding to 60-100 g of protein was incubated with the corresponding antibody overnight at 4°C to form immunocomplexes. Next day protein G coupled magnetic beads (Dynabeads, Invitrogen) were added to the immunocomplex and incubated for 1 h at 4°C. Immune complexes were magnetically recovered and washed twice with 1 ml of "low salt buffer" (0.1% SDS, 1% Triton-X100, 2 mM EDTA, 20 mM Tris pH 8.1, 150 mM NaCl, protease inhibitors (Complete Roche)), then washed once with 1 ml of "high salt buffer" (the same but with 500 mM NaCl) and washed three times with 1 ml of LiCl buffer (0.25 M LiCl, 1% IGEPAL, 1% sodium deoxycholate, 1 mM EDTA, 10 mM Tris pH 8.1, protease inhibitors). Chromatin from immunocomplexes and input was eluted with 300 ml of 1% SDS, 0.1 M NaHCO3, 200 mM NaCl and incubated at 65°C for 6 h (to break the DNA-protein complexes). DNA was purified using a column purification kit (GE healthcare) and submitted to SYBR green qPCR with the indicated primers. qPCR was performed using the Applied Biosystems 7500 Real Time PCR System and 5× PyroTaq EvaGreen qPCR Mix Plus (CMB). To avoid genomic amplification, PCR primers were designed to fall into separate exons flanking a large intron when possible. Reactions were performed in duplicates of three different dilutions, and threshold cycle values were normalized to the housekeeping gene 18S. The specificity of the products was determined by melting curve analysis and gel electrophoresis. The ratio of the relative expression for each gene to 18S was calculated by using the 2ΔCT formula. Amplicons were of similar size (≈100 bp) and melting points (≈85°C). Similar amplification efficiency for each product was confirmed by using duplicates of three dilutions for each sample.

**DNA-Protein binding assay.** HEK293 cells weretransfected with the constructs pcDNA3.1-EGR2 and pcDNA3.1-EGR2 P397H and nuclear extracts obtained with the *Nuclear extraction kit* (Abcam) ab113474 following manufacturer’s recommendations. Biotinylated oligonucleotides with the EGR2 binding sequence in tandem (three repeats) were obtained from SIGMA (sense: 5’ [Btn]CGCCCACGCCGCCCACGCCGCCCACGC; antisense: 5’ [Btn]GCGTGGGCGGCGTGGGCGGCGTGGGCG and hybridized. Similar amounts of protein nuclear extracts were incubated with the double stranded oligonucleotide using the DNA-protein binding assay kit form Abcam (ab117139) following manufacturer recommendations. Anti–Krox 20 polyclonal antibody was used to quantify colorimetrically the binding of EGR2 to the oligonucelotide.

**SUPPLEMENTARY CLINICAL DESCRIPTION**

**Clinical studies of the proband.** The proband is a 54-year-old woman with an intermediate hereditary sensory and motor polyneuropathy with chronic axonal damage diagnosed in a neurophysiological study performed at the age of 47. The first symptoms began in the early childhood with frequent falls and stumbles. She had to carry templates because flat feet and special boots. During the adolescence she experienced more falls and repeated ankle sprains, albeit she was still able to run. She suffered a traffic accident at the age of 35 without bone fractures or significant injuries but let her bedridden for a year, developing pain and generalized weakness. Afterwards she noticed severe muscular atrophy, limbs intense pain, cramps and gait instability. Despite doing physical activity, the motor deterioration was getting worse with inability to run or walk long distances without foot orthosis or walking stick. Fine motility in her hands was impaired, without significant sensory alteration. She has been suffering profuse sweating episodes in the last two years, as well as constipation and occasional urine retention. At the most recent examination in April 2018 (Figure 1A), the posterior leg muscle compartment, tibialis anterior and extensor digitorum brevis muscle showed severe atrophy with lower limbs in “inverted champagne bottle”. In the upper limbs hand muscles and tenar eminence were atrophied (Figure 1B). Arched feet and Achilles tendon shortening was noticed (not shown). Medical Research Council (MRC) score on ankle flexion was 1/4, extension 4/5 and toes flexo-extension 2/5 respectively. Upper limbs weakness was modest with 4/5 strength in interosseous and wrist flexion on MRC scale. Reflexes were abolished in lower limbs and decreased in upper ones. All sensory modalities were severely diminished in lower limbs to the knee and partially in upper limbs to the elbow.

In concordance with the physical exploration, motor nerve conduction velocity was slightly decreased in the median nerve but undetectable in the lower limbs (peronal and tibial nerves) (Table 1). On the other hand sensory nerve conduction was decreased in median and sural nerves and undetectable in the peroneal nerve (Table 1). According to the CMT neuropathy score (CMTNS) (Shy et al. 2005), the total value was 20. Neuropathic pain was significant. Cranial nerves were normal, and there was no visual alteration or macular degeneration. Although she performed intense and specialized daily physical activity, she could walk but with apparent instability because of sensitive ataxia and step-page gait, needing feet outhouses and a cane for long distances.