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Supplemental information

Bi-allelic genetic variants in the translational GTPases GTPBP1 and GTPBP2 cause a distinct identical neurodevelopmental syndrome

Vincenzo Salpietro, Reza Maroofian, Maha S. Zaki, Jamie Wangen, Andrea Ciolfi, Sabina Barresi, Stephanie Efthymiou, Angelique Lamaze, Gabriel N. Aughey, Fuad Al Mutairi, Aboulfazl Rad, Clarissa Rocca, Elisa Calì, Andrea Accogli, Federico Zara, Pasquale Striano, Majid Mojarrad, Huma Tariq, Edoardo Giacopuzzi, Jenny C. Taylor, Gabriela Oprea, Volha Skrahina, Khalil Ur Rehman, Marwa Abd Elmaksoud, Mahmoud Bassiony, Huda G. El Said, Mohamed S. Abdel-Hamid, Maha Al Shalan, Gohun Seo, Sohyun Kim, Hane Lee, Rin Khang, Mahmoud Y. Issa, Hasnaa M. Elbendary, Karima Rafat, Nikolaos M. Marinakis, Joanne Traeger-Synodinos, Athina Ververi, Mara Sourmpi, Atieh Eslahi, Farhad Khadivi Zand, Mehran Beiraghi Toosi, Meisam Babaei, Adam Jackson, SYNAPS Study Group, Aida Bertoli-Avella, Alistair T. Pagnamenta, Marcello Niceta, Roberta Battini, Antonio Corsello, Chiara Leoni, Francesco Chiarelli, Bruno Dallapiccola, Eissa Ali Faqeih, Krishnaraya K. Tallur, Majid Alfadhel, Eman Alobeid, Sateesh Maddirevula, Kshitij Mankad, Siddharth Banka, Ehsan Ghayoor-Karimiani, Marco Tartaglia, Wendy K. Chung, Rachel Green, Fowzan S. Alkuraya, James E.C. Jepson, and Henry Houlden

Supplemental data

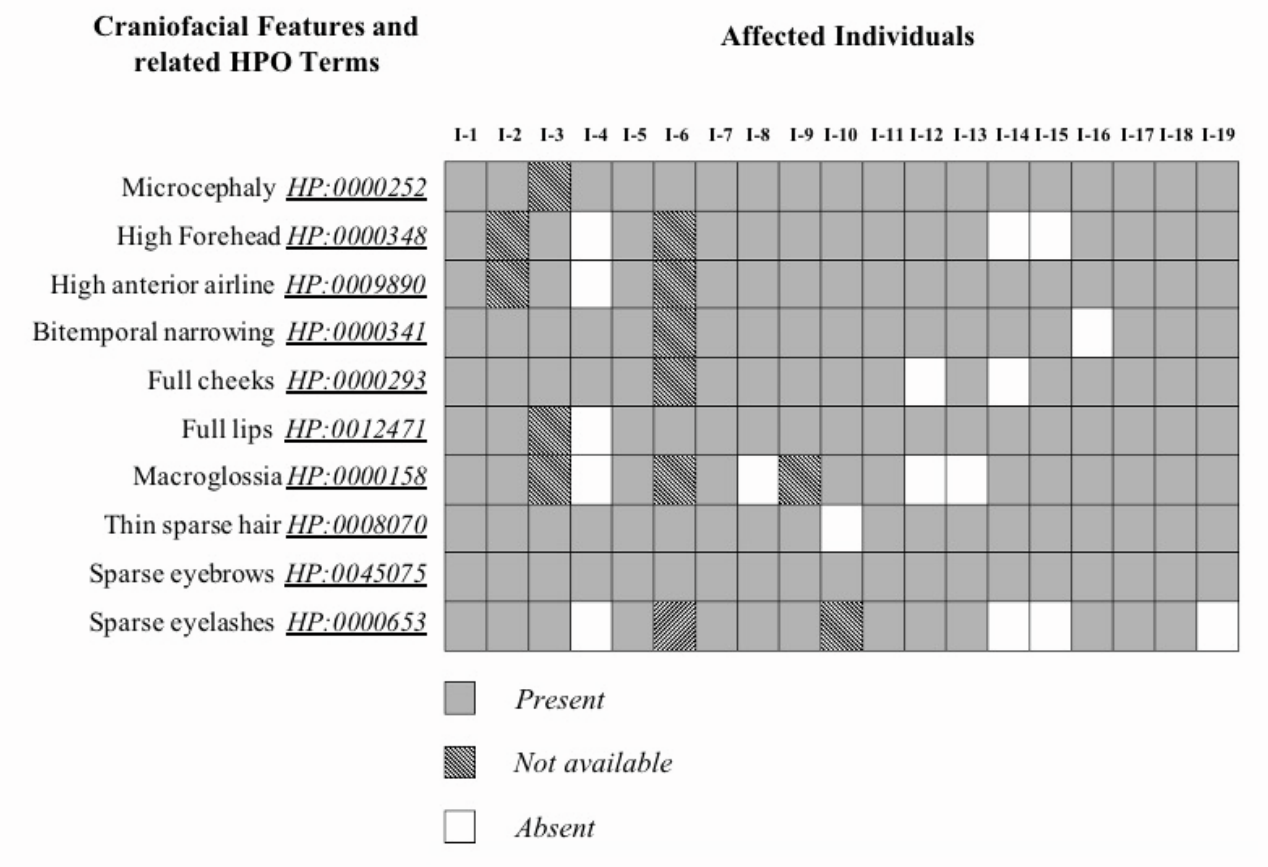

Figure S1: Distinctive craniofacial features in GTPBP1 and GTPBP2 mutation carriers from our cohort. In decreasing order, microcephaly (HPO:0000252), sparse eyebrows (HPO:0045075), thin sparse hair (HPO:0008070), full lips (HPO:0012471), full cheeks (HPO: 0000293) high anterior hairline and bitemporal narrowing are the most consistent craniofacial features across the *GTPBP1*- and *GTPBP2*- mutated individuals from our cohort.

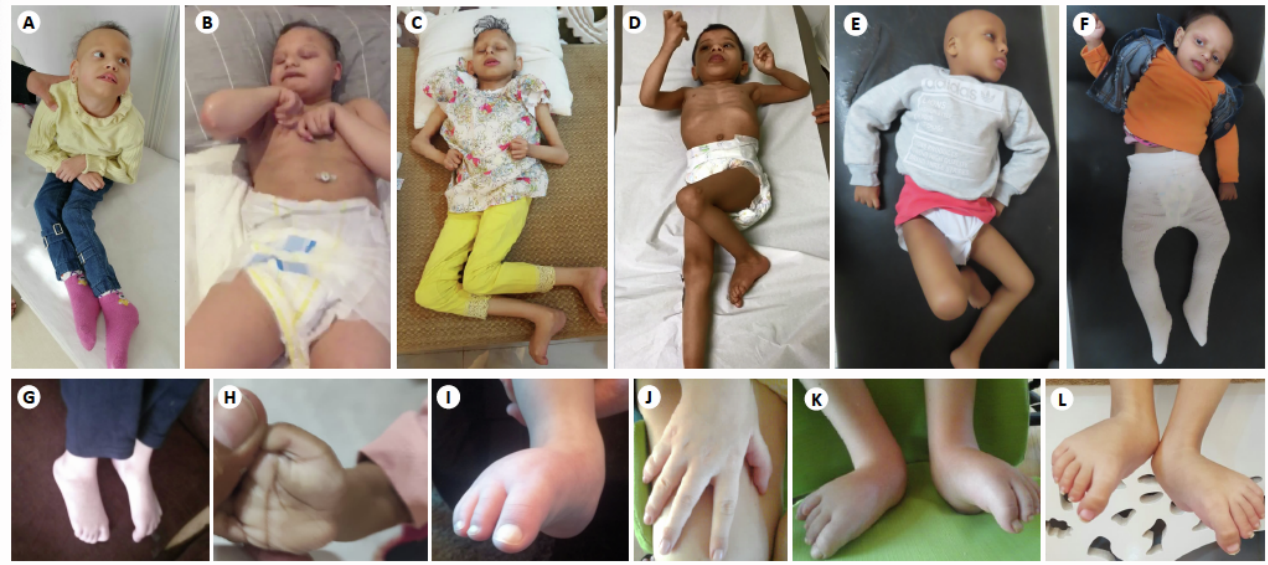

Figure S2: Neurological features associated with *GTPBP1/2*-related disorders. Note spastic tetraparesis and loss of visual fixation of I-1 (A). Note spasticity and dystonic posturing of the upper arms of I-7 (B). Note spastic tetraparesis of I-8 (C). Note spastic tetraparesis and abnormal hand movements of I-10 (D). Note axial hypotonia and lower limbs spasticity of I-16 and I-17 (E-F).

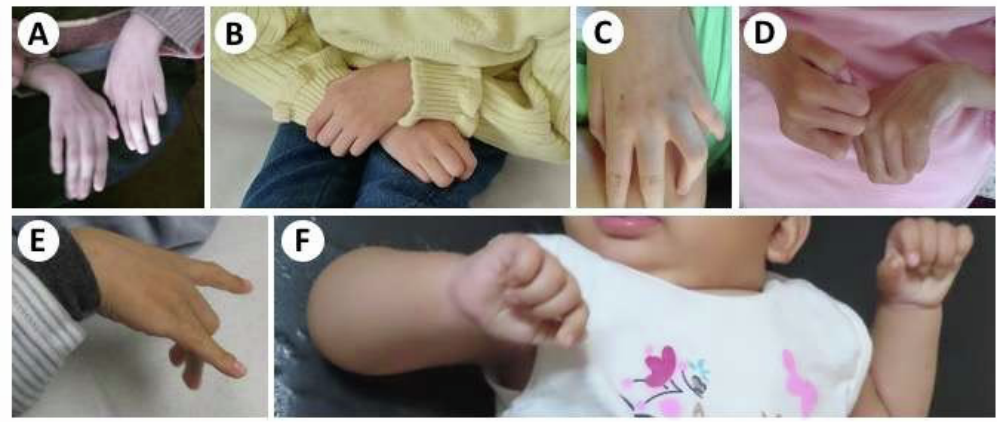

Figure S3: Hand anomalies in GTPBP1 and GTPBP2 mutation carriers from our cohort. Note the proximal (mostly interphalangeal) contractures in individuals I-1 (A-B), I-5 (C), I-8 (D), I-10 (E), I-18 (F) carrying biallelic *GTPBP1* and *GTPBP2* variants.

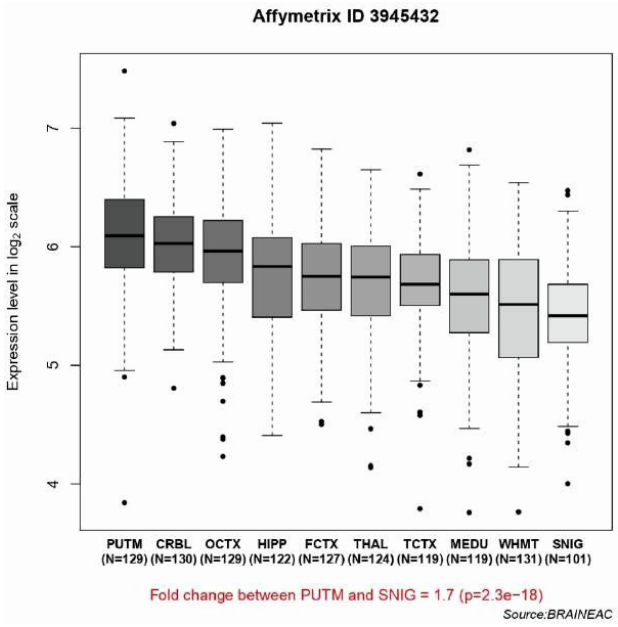

Figure S4: Brain expression values of *GTPBP1*. Brain expression values of *GTPBP1* show higher expression levels in the PUTM (putamen), CRBL (cerebellar cortex), OCTX (occipital cortex), HIPP (hippocampus), FCTX (frontal cortex), THAL (thalamus) and less expression in TCTX (temporal cortex), MEDU (medulla), WHMT (white matter) and SNIG (substantia nigra).

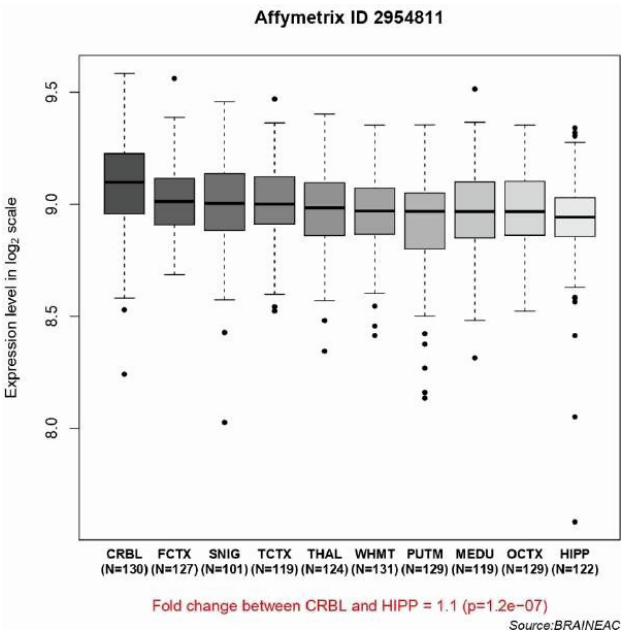

Figure S5: Brain expression values of *GTPBP2*. Brain expression values of GTPBP2 show higher expression levels in the CRBL (cerebellar cortex), FCTX (frontal cortex), SNIG (substantia nigra), TCTX (temporal cortex), THAL (thalamus), WHMT (white matter), PUTM (putamen) and less expression in MEDU (medulla), OCTX (occipital cortex) and HIPP (hippocampus).

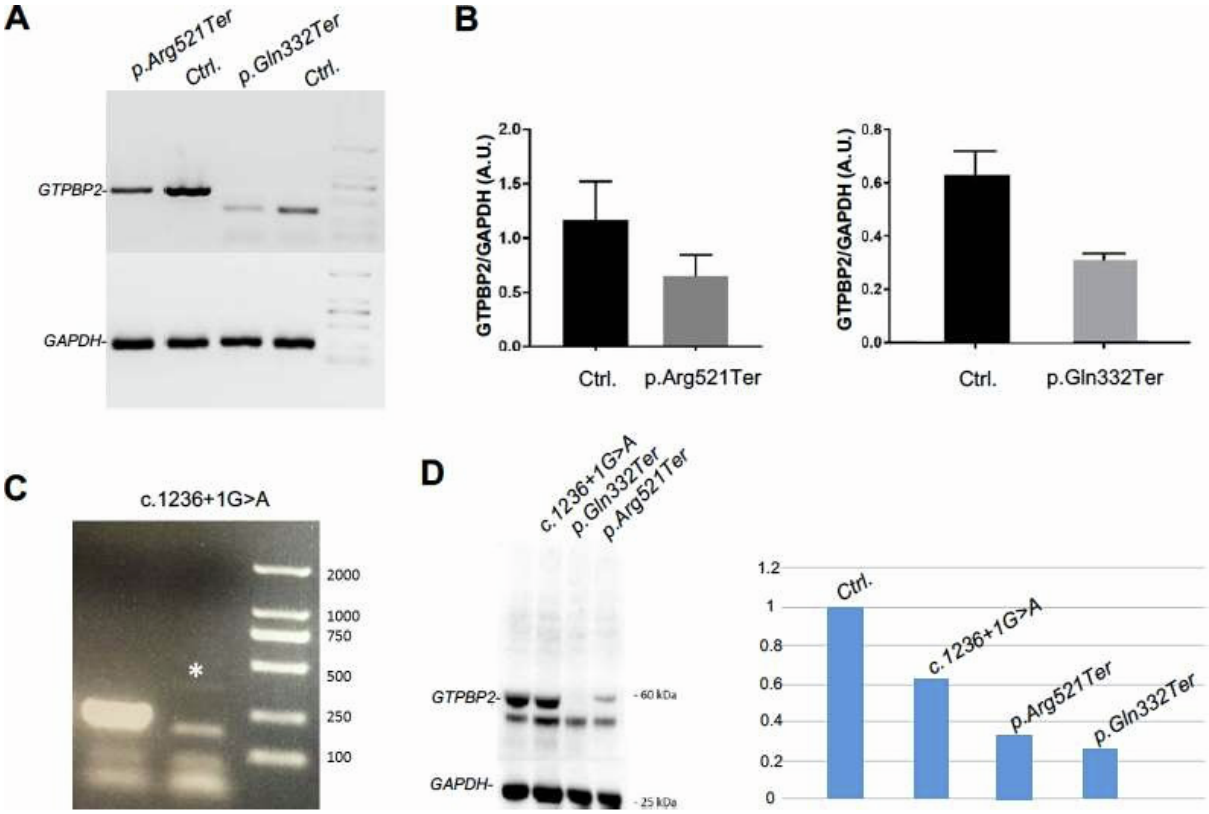

Figure S6. RT-PCR and Western Blot studies in *GTPBP2*-mutated individuals. A significant reduction of mRNA compared to controls in *GTPBP2* mutation carriers is observed (S5A) and is confirmed after normalization using a relative relationship method (Figure S5B). Intron retention products as a result of the splicing c.1236+1G>A homozygous mutation (Figure S5C). Western Blot showed a significant reduction of the Gtpbp2 protein in patient-derived fibroblasts compared to control cell lines (Figure S5D)

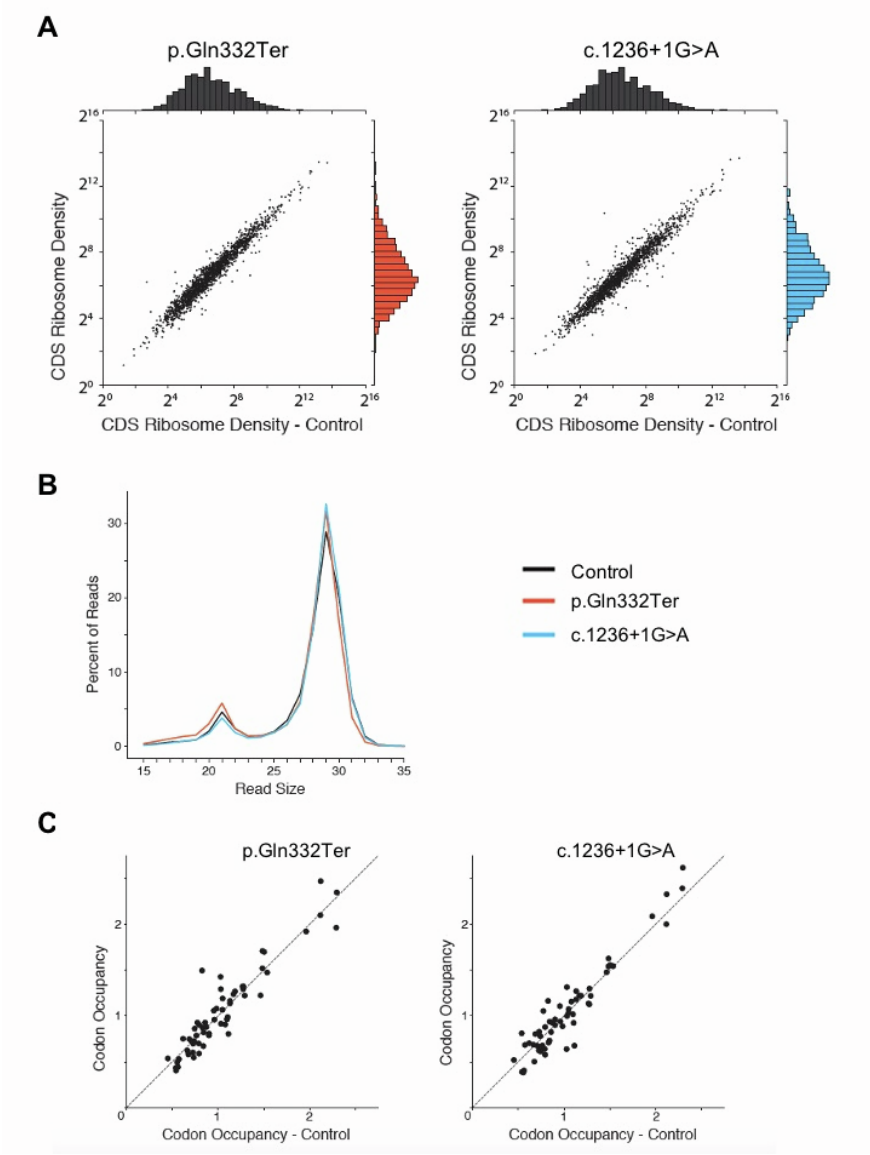

Figure S7. Ribosome profiling in *GTPBP2*-mutated individuals. (A) CDS densities are shown comparing translation of Control fibroblasts to fibroblasts from GTPBP2-mutated Individual carrying the truncating homozygous p.Gln332Ter variant (left) and GTPBP2-mutated Individual carrying the splicing homozygous c.1236+1G>A variant (right). Densities are sorted into histograms with 20 bins each and plotted on the corresponding axis for each sample. Pearson Correlations of log-transformed densities were 0.97 for both comparisons. (B) Read size distributions are shown for Control (Black), p.Gln332Ter (Red), and c.1236+1G>A (Blue) mutated fibroblasts. (C) Codon occupancies are presented for empty A-site ribosomes (21-24 nt reads) comparing relative ribosome occupancy on all 61 sense codons between control and p.Gln332Ter (left) or c.1236+1G>A (right).

Table S1: *GTPBP1* and *GTPBP2* variants identified in this study.

Table S2. Clinical features of patient with biallelic variants in *GTPBP1* NM_004286.5 (light blue) or *GTPBP2* NM_019096.6 (light grey)

Supplemental Methods

Recruitment of research subjects

Individuals and their families were collected prospectively. Informed consent for DNA analysis was obtained from study participants in line with local institutional review board requirements at the time of collection. The study was approved by the ethics committee of University College London (project 06/N076) and additional local ethics committees at the participating centers. Written informed consent for collection of clinical information, neuroimaging, and genetic information was obtained for each study participant.

Reverse-transcriptase polymerase chain reaction (RT-PCR) and Western Blot

To investigate the functional impact of the identified mutations we performed a RT-PCR and WB experiments performed in available fibroblast cell lines from I-7 (Family 5) carrying the p.Gln332Ter homozygous *GTPBP2* variant, I-8 (Family 6) carrying the c.1236+1G>A homozygous splicing *GTPBP2* variant, and I-9 (Family 7) carrying the p.Arg521Ter homozygous *GTPBP2* variant. Control fibroblast cell lines were used from healthy age- and sex-matched individuals. Semi quantitative PCR (semi-qPCR) was performed in 50-µl reaction volume prepared by combining the cDNA template, and gene-specific primers, including two sets for the frameshift variants p.Gln332Ter and p.Arg521Ter: F 5′-CTCACGGACAGCAGAAGAGA -3′ and R 5′- TTGGGTGACTGAGCAAACTG -3′; F 5’-TCTGGAGAGAGTCTGGACCT-3’ and R 5’- GCTTCTCCTGCTGTAATGGC-3’ and intron-intron primers for the c.1236+1G>A splicing variant: F 5’-TGCTCAGTCACCCAATGTCACCCCCAT-3’ and R 3’-ACGGCAAATCCCACTGGAAAGTG-5’), nuclease-free water, and SYBR Green Master Mix. The PCR reaction conditions were: one cycle of 94°C for 4 min, followed by 37 cycles of 94°C for 45 sec, 54°C for 45 sec, and 72°C for 50 sec. For testing the splicing variant, a longer PCR of one cycle of 94°C for 4 min, followed by 37 cycles of 94°C for 45 sec, 54°C for 120 sec, and 72°C for 50 sec was used.

For western blot analysis, protein lysates were obtained from cultured fibroblasts and total protein concentration was measured by means of the Bradford assay. Samples were separated on SDS-PAGE using Bis-Tris gradient gels (4–12% NuPAGE, Invitrogen) according to the

manufacturer's recommendations, electrophoretically transferred into Immobilon-P transfer membranes (Millipore). Membranes were immunoblotted with the antibody: Rabbit polyclonal antibody against the N-terminal portion of human Gtpbp2 protein from Source Bioscience (Nottingham, Uk) at 4°C overnight. Blots were then exposed to horseradish peroxidase-conjugated goat anti-mouse IgG (1706516, Bio-Rad Laboratories, 1:5000) 1 h at room temperature. Blots were developed using ECL-Prime (GE Healthcare), visualized via a ChemiDoc™ Touch Imaging System and analysed using Image Lab 5.2 software (Bio-Rab Laboratories). For the quantifications, the signal intensity of the affected protein bands was normalized to the signal intensity of GAPDH bands.

Ribosome Profiling experiments

Fibroblast cell lines from I-7 and I-8 and age- and sex-matched healthy controls (cultured in 10 cm dishes) were removed from the 37C incubator and washed once with warmed 1X PBS (Thermo Fisher Scientific), to be placed in a shallow bath of liquid nitrogen to flash-freeze the cells. Dishes were transferred to wet ice and thawed in the presence of 500 µL of lysis buffer (20 mM Tris-Cl pH 7.4, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM DTT, 100 µg/mL cycloheximide, 1% Triton X-100, 2.5 U/mL Turbo DNaseI (Thermo Fisher Scientific)). Lysates were transferred to 1.7 mL tubes, incubated on ice for 10 minutes, and clarified by centrifugation at 21,000*g*, 4C, for 10 minutes. The soluble supernatant was removed, and RNA amounts were quantified using the Quant-iT RiboGreen RNA Assay Kit (Thermo Fisher Scientific).

Drosophila studies

The following *Drosophila* stocks were obtained from the Bloomington *Drosophila* Stock Center: w[1118]; pBac{w{+mC]=IT.GAL4}cg2017[0758-G4] (BDSC #63501), w[1118]; pBac{w{+mC]=IT.GAL4}cg2017[0269-G4] (BDSC #62747), y[1]sc[1]sev[21]; P{TRiP.HMS00976}attp2 (BDSC #34097), and w[*]; P{y[+t7.7]w[+mC]=10XUAS-IVS-mCD8::GFP}attP2 (BDSC #32185). Reverse transcription and qPCR reactions were performed using standard protocols. RNA was treated with DNaseI to remove contaminating gDNA (NEB, M0303S) and converted to cDNA using MMLV-RT (Promega, M170A). qPCR reactions were performed using the Power SYBR Green Master Mix (ThermoFisher Scientific) and primers used were as follows (5' – 3'): cg2017-CF – AAACTACGCGCCGAAAAAGG; cg2017-CR-

AGGACTCCATAATGTGTTGCTTC; rp49F:CGATATGCTAAGCTGTCGCACA, rp49R: CGCTTGTTCGATCCGTAACC. PCR reactions were performed in a 96-well Applied Biosystems Step One module using standard thermocycle protocols. For statistical analyses of DAM-derived locomotor values, data were first assessed for normal or non-normal distributions using a Shapiro-Wilk test. Data exhibiting normal distributions were subject to significance testing through one-way ANOVA with Tukey's multiple comparisons tests. Non-normal distributions were subject to significance testing through Kruskal-Wallis with Dunn's multiple comparisons tests.

Consortia involved in this study.

SYNAPS Study Group.

Collaborators	Affiliations
Prof Michael G. Hannah	Affiliation: Department of Neuromuscular Diseases, Queen Square Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK
Dr. Enrico Bugiardini	Affiliation: Department of Neuromuscular Disease, UCL Queen Square Institute of Neurology and The National Hospital for Neurology, London, UK.
Prof. Enrico Bertini	Affiliation: IRCCS "Ospedale Bambino Gesù", Rome, Italy
Prof Yamna Kriouile	Affiliation: Unit of Neuropediatrics, Children's Hospital of Rabat, University of Rabat, Rabat 6527, Morocco Email: dr.kriouile@gmail.com
Prof. Mohamed El Khorassani	Affiliation: Children's Hospital of Rabat, University of Rabat, Rabat 6527, Morocco Email: elkhorassani.mohamed@gmail.com
Prof. Mhammed Aguennouz	Affiliation: Department of Clinical and Experimental Medicine, University of Messina, Messina 98123, Italy Email: aguenoz@unime.it
Prof Stanislav Groppa	Affiliation: Department of Neurology and Neurosurgery, Institute of Emergency Medicine, Chisinau, Republic of Moldova. Email: sgroppa@gmail.com
Dr. Blagovesta Marinova Karashova	Affiliation: Department of Paediatrics, Medical University of Sofia, Sofia 1431, Bulgaria Email: blagovestakarashova@gmail.com
Prof. Jatinder S. Goraya, MD, FRCP	Affiliation: Division of Paediatric Neurology, Dayanand Medical College & Hospital, Ludhiana, Punjab 141001, India Email: gorayajs@gmail.com
Prof. Tipu Sultan	Affiliation: Division of Paediatric Neurology, Children's Hospital of Lahore, Lahore 381-D/2, Pakistan

	Email: tipusultanmalik@hotmail.com
Prof. Daniela Avdjieva	Affiliation: Department of Paediatrics, Medical University of Sofia, Sofia 1431, Bulgaria Email: davdjieva@yahoo.com
Dr. Hadil Kathom	Affiliation: Department of Pediatrics, Medical University of Sofia, Sofia 1431, Bulgaria Email: hadilmk@gmail.com
Prof. Dr Radka Tincheva	Affiliation: Head of Department of Clinical Genetics, University Pediatric Hospital, Sofia 1431, Bulgaria Email: radka.tincheva@gmail.com
Prof. Selina Banu	Affiliation: Neurosciences Unit, Institute of Child Health and Shishu Shastho Foundation Hospital, Mirpur, Dhaka 1216, Bangladesh Email: selinabanu17@gmail.com
Prof. Pierangelo Veggiotti	Affiliation: Unit of Infantile Neuropsychiatry Fondazione Istituto Neurologico "C. Mondino" IRCCS, Via Mondino 2, Pavia 27100, Italy Email: pierangelo.veggiotti@unipv.it
Prof. Alberto Verrotti	Affiliation: University of L'Aquila, L'Aquila, Italy Email: verrottidipianella@univaq.it
Prof. Marcello Lanari	Affiliation: University of Bologna, Bologna, Italy
Dr. Salvatore Savasta	Affiliation: Division of Pediatric Neurology, Department of Pediatrics, University of Pavia, IRCCS Policlinico "San Matteo", Pavia 27100, Italy Email: S.Savasta@smatteo.pv.it
Prof. Alfons Macaya	Affiliation: University Hospital Vall d'Hebron, Barcelona 08035, Spain
Prof. Barbara Garavaglia	Affiliation: IRCCS Foundation, Neurological Institute "Carlo Besta", Molecular Neurogenetics, 20126 Milan, Italy Email: segr.neurogenetica@istituto-besta.it
Dr. Eugenia Borgione	Affiliation: Laboratorio di Neuropatologia Clinica, U.O.S. Malattie, Neuromuscolari Associazione OASI Maria SS. ONLUS – IRCCS, Via Conte Ruggero 73, 94018 Troina, Italy Email: eborgione@oasi.en.it
Prof. Savvas Papacostas	Affiliation: Neurology Clinic B, The Cyprus Institute of Neurology and Genetics, 6 International Airport Road,

	1683 Nicosia, Cyprus Email: savvas@cing.ac.cy
Dr. Michail Vikelis	Affiliation: Iatreio Kefalalgias Glyfadas, 8 Lazaraki str, 3rd floor, 16675, Athens, Greece Email: mvikelis@headaches.gr
Dr Viorica Chelban	Affiliation: Department of Molecular Neuroscience, University College London, London, UK Email: v.chelban@ucl.ac.uk
Dr Rauan Kaiyrzhanov	Affiliation: Department of Molecular Neuroscience, University College London, London, UK Email: rauan.kaiyrzhanov.14@ucl.ac.uk
Dr. Andrea Cortese	Department of Neuromuscular Diseases, University College London, London, United Kingdom Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
Dr. Roisin Sullivan	Affiliation: Department of Molecular Neuroscience, Queen's Square Institute of Neurology, UCL, London, UK. r.sullivan@ucl.ac.uk
Prof Eleni Zamba Papanicolaou	Affiliation: The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus Email: ezamba@cing.ac.cy
Dr Efthymios Dardiotis	Affiliation: University Hospital of Larissa, Neurology Department, Greece Email: edar@med.uth.gr
Prof Shazia Maqbool	Affiliation: Department of Developmental and Behavioral Pediatrics, CH&ICH, Lahore, Pakistan Email: drshazimaq@yahoo.com
Prof Shahnaz Ibrahim	Affiliation: Department of Pediatrics and child health, Aga Khan University, Karachi, Pakistan Email: shahnaz.ibrahim@aku.edu
Prof Salman Kirmani	Affiliation: Department of Paediatrics & Child Health, The Aga Khan University, Karachi , Pakistan Email: salman.kirmani@aku.edu
Dr. Nuzhat Noureen Rana	Affiliation: Department of Paediatric Neurology, Children Hospital Complex and ICH, Multan, Pakistan Email: drnuzhatrana@gmail.com
Dr. Osama Atawneh	Affiliation: Hilal Pediatric Hospital Hebron, Hebron West Bank, Palestine

	Email: osamaat@gmail.com
Prof Shen-Yang Lim	Affiliation: Department of Biomedical Science, Faculty of Medicine, University of Malaya, Malaysia Email: limshenyang@gmail.com
Prof Gian Vincenzo Zuccotti	Affiliation: Department of Pediatrics, University of Milan
Prof Gianluigi Marseglia	Affiliation: Department of Pediatrics, University of Pavia
Prof. Susanna Esposito	Affiliation: Department of Pediatrics, University of Parma
Dr Farooq Shaikh	Affiliation: Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia
Prof. Paola Cogo	Affiliation: Department of Pediatrics, University of Udine
Prof. Giovanni Corsello	Affiliation: Department of Pediatrics, University of Palermo
Prof. Salvatore Mangano	Affiliation: Department of Pediatrics, University of Palermo
Dr. Rosaria Nardello	Affiliation: Department of Pediatrics, University of Palermo
Dr. Donato Mangano	Affiliation: Department of Pediatrics, University of Palermo
Miss. Annarita Scardamaglia	Department of Neuromuscular Diseases, University College London, London, United Kingdom a.scardamaglia@ucl.ac.uk
Prof George Koutsis	Affiliation: Neurogenetics Unit, Neurology Department, Eginition Hospital, National and Kapodistrian University, Athens, Greece Email: marianthibr@med.uoa.gr
Dr Carmela Scuderi	Affiliation: Associazione Oasi Maria SS, 94018 Troina, Italy Email: cscuderi@oasi.en.it
Dr Eugenia Borgione	Affiliation: Associazione Oasi Maria SS, 94018 Troina, Italy Email: eborgione@oasi.en.it
Prof. Pietro Ferrara	Affiliation: Department of Pediatrics, University of Rome "Campus Biomedico"
Dr Giovanna Morello	Affiliation: Institute of Neurological Sciences, National Research Council, Mangone, Italy Email: g.morello@isn.cnr.it
Prof Massimo Zollo	Affiliation: CEINGE, Biotecnologie Avanzate S.c.a.rl., Naples, Italy Email: massimo.zollo@unina.it
Prof. Roberto Berni-Canani	Affiliation: Department of Pediatrics, University of Naples

Prof. Luigi M. Terracciano	Affiliation: Humanitas University, Milan, Italy
Dr. Antonio Sisto	Affiliation: Department of Pediatrics, Teramo University Hospital, Teramo, Italy
Dr. Sandra Di Fabio	Affiliation: Department of Pediatrics, L'Aquila University Hospital, L'Aquila, Italy
Dr. Federica Strano	Affiliation: Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy
Dr. Giovanna Scorrano	Affiliation: Department of Pediatrics, L'Aquila University Hospital, L'Aquila, Italy
Dr. Saverio Di Bella	Affiliation: Department of Pediatrics, L'Aquila University Hospital, L'Aquila, Italy
Dr. Ludovica Di-Francesco	Affiliation: Department of Pediatrics, L'Aquila University Hospital, L'Aquila, Italy
Dr. Ganieva Manizha,	Affiliation: Avicenna Tajik State Medical University, Dushanbe, Tajikistan Email: ganieva.manizha.79@mail.ru
Dr. Maksud Isrofilov	Affiliation: Avicenna Tajik State Medical University, Dushanbe, Tajikistan Email:dr.maks-55@mail.ru
Dr. Ulviyya Guliyeva	Affiliation: Mediclub clinic, Baku, Azerbaijan Email: doctor.ulya@gmail.com
Dr. Kamran Salayev	Affiliation: Azerbaijan State Medical University, Baku, Azerbaijan Email: ksalayev@yahoo.com
Dr. Samson Khachatryan	Affiliation: "Somnus" Neurology Clinic Sleep and Movement Disorders Center, Yerevan, Armenia. Email: drsamkhach@gmail.com
Dr. Georgia Xiromerisiou	Affiliation: Department of Neurology, Medical School, University of Thessaly, Larissa, Greece Email: geoksirom@med.uth.gr, georgiaxiromerisiou@gmail.com
Dr. Cleanthe Spanaki	Affiliation: Department of Neurology, Medical School, University of Crete, Heraklion, Greece Email: kliospanaki@med.uoc.gr
Dr. Chiara Fiorillo	Affiliation: Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genoa, Italy.
Dr. Michele Iacomino	Affiliation: Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health,

	University of Genova, Genoa, Italy.
Prof. Eugenio Gaudio	Affiliation: Sapienza University of Rome, Italy
Dr. Francina Munell	Affiliation: Pediatric Department, Vall d'Hebron Hospital, Barcelona, Spain.
Dr. Antonella Gagliano	Affiliation: Department of Biomedical Sciences, Section Neuroscience and Clinical Pharmacology, University of Cagliari, Cagliari, Italy
Dr. Farida Jan	Affiliation: Department of Paediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan
Prof. Roberto Chimenz	Affiliation: Unit of Pediatric Nephrology, and Rheumatology with Dialysis, Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", University of Messina, "G. Martino" Policlinic, 98124 Messina, Italy.
Prof. Eloisa Gitto	Affiliation: Department of Pediatrics, University of Messina, Messina, Italy.
Prof. Lorenzo Iughetti	Affiliation: Department of Pediatrics, University of Modena, Modena, Italy
Prof. Gabriella Di Rosa	Affiliation: Department of Pediatrics, University of Messina, Messina, Italy.
Prof. Mohamad Maghnie	Affiliation: IRCCS "Giannina Gaslini", University of Genoa, Genoa, Italy
Prof. Massimo Pettoello-Mantovani	Affiliation: University of Foggia, Foggia, Italy.
Prof. Neerja Gupta	Affiliation: Division of Genetics, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, 110029, India. Neerja17@gmail.com.
Prof Madhulika Kabra	Affiliation: Division of Genetics, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, 110029, India.

Dr. Hanene Benrhouma	Affiliation: Child and Adolescent Neurology Department of Neurology, National Institute of Neurology, Tunis, Tunisia.
Dr. Meriem Tazir	Affiliation: Service de Neurologie, University Hospital Mustapha Bacha, Alger, Algeria. Meriem.tazir@sante.dz
Dr. Gabriella Bottone	Affiliation: Department of Pediatrics, University of L'Aquila, 67100, Italy
Dr. Giovanni Farello	Affiliation: Department of Clinical Medicine, Public Health, Life and Environmental Sciences, University of L'Aquila, 67100 L'Aquila, Italy
Prof. Maurizio Delvecchio	Affiliation: Department of Pediatrics, L'Aquila University Hospital, L'Aquila, Italy
Dr Giulio Di-Donato	Affiliation: Department of Pediatrics, University of L'Aquila, 67100, Italy
Prof. Makram Obeid	Affiliation: Division of Child Neurology, Department of Pediatric and Adolescent Medicine, American University of Beirut Medical Center, Beirut, Lebanon. mo21@aub.edu.lb.
Dr. Sophia Bakhtadze	Affiliation: Department of Paediatric Neurology, Tbilisi State Medical University, 0160, Tbilisi, Georgia. Electronic address: s.bakhtadze@tsmu.edu.
Prof. Nebal W Saadi	Affiliation: College of Medicine, Baghdad University, Baghdad, Iraq. Children Welfare Teaching Hospital, Baghdad, Iraq.
Prof. Michele Miraglia Del Giudice	Affiliation: University of Campania "Luigi Vanvitelli", Campania, Italy
Prof. Rita Maccarone	Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, 67100 L'Aquila, Italy
Prof Maha S Zaki	Affiliation: Clinical Genetics Department, Human Genetics and Genome Research Division, National Research Centre, Cairo, Egypt
Prof. Chahnez C Triki	Affiliation: Department of Child Neurology, Hedi Chaker Hospital, LR19ES15 Sfax University, Sfax, Tunisia.
Dr. Majdi Kara	Affiliation: Department of Pediatrics, University of Tripoli, Tripoli, Libya.
Dr. Ehsan G Karimiani	Affiliation: Genetics Research Centre, Molecular and Clinical Sciences Institute, St. George's, University of London, London, UK. Next Generation Genetic Polyclinic, Razavi International

	Hospital, Mashhad, Iran.
Dr. Ahmed M Salih	Affiliation: Molecular microbiology & Immunology, College of Medicine, University of Duhok, Duhok, Kurdistan Region, Iraq.
Prof. Luca A Ramenghi	Affiliation: Neonatal Intensive Care Unit, Giannina Gaslini Children's Hospital, Genova, Italy. Electronic address: lucaramenghi@gaslini.org.
Prof. Marco Seri	Affiliation: IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna 40138, Bologna, Italy
Dr. Giovanna Di Falco	Affiliation: Consorzio Siciliano di Riabilitazione, Sicily, Italy
Dr. Luana Mandarà	Affiliation: Unit of Medical Genetics, Ragusa ASP, Ragusa, Italy
Dr. Giuseppe Barrano	Affiliation: Unit of Medical Genetics, Ragusa ASP, Ragusa, Italy
Dr. Maurizio Elia	Affiliation: Unit of Neurology and Clinical Neurophysiopathology, Oasi Institute for Research on Mental Retardation (IRCCS), Troina, EN, Italy.
Prof. Enrico Cherubini	European Brain Research Institute (EBRI), Rita Levi-Montalcini Foundation, Viale Regina Elena 293-295, 00161 Roma, Italy
Dr. Francesca F. Operto	Affiliation: Department of Pediatrics University of Salerno
Dr. Mariella Valenzise	Affiliation: Department of Pediatrics University of Messina
Prof. Antonino Cattaneo	European Brain Research Institute (EBRI), Rita Levi-Montalcini Foundation, Viale Regina Elena 293-295, 00161 Roma, Italy
Prof. Francesca Zazzeroni	Affiliation: Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, 67100, Italy
Prof. Edoardo Alesse	Affiliation: Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, 67100, Italy
Prof. Sara Matricardi	Child Neurology and Psychiatry Unit, Children's Hospital "G. Salesi", Ospedali Riuniti Ancona, Italy.
Dr. Faisal Zafar	Affiliation: Children's Hospital Multan, Pakistan

Prof Ehsan Ullah	Affiliation: Children's Hospital Multan, Pakistan
Dr Erum Afzal	Affiliation: Children's Hospital Multan, Pakistan
Dr Iram Javed	Affiliation: Childrens Hospital Faisalabad, Pakistan
Dr Fatima Rahman	Childrens Hospital Lahore, Pakistan
Dr Muhammad Mehboob Ahmed	Childrens Hospital Faisalabad, Pakistan
Prof. Pasquale Parisi	Affiliation: Affiliation: Chair of Pediatrics, NESMOS Department, Faculty of Medicine and Psychology, Sapienza University of Rome, Sant'Andrea Hospital.
Prof. Alberto Spalice	Affiliation: Chair of Pediatrics, Umberto I University Hospital, Faculty of Medicine and Psychology, Sapienza University of Rome
Dr. Maria De-Filippo	Affiliation: Department of Pediatrics, University of Pavia
Prof. Amelia Licari	Affiliation: Department of Pediatrics, University of Pavia
Dr. Edoardo Trebbi	School of Public Health, "La Sapienza" University of Rome, 00100 Rome, Italy
Prof. Ferdinando Romano	School of Public Health, "La Sapienza" University of Rome, 00100 Rome, Italy
Dr Gali Heimer	Affiliation: University Hospital of Tel Aviv, Tel Aviv, Israel Email: galih.md@gmail.com
Dr Issam Al-Khawaja	Affiliation: Albashir University Hospital, Amman, Jordan Email: isamkhawaja61@gmail.com
Dr Fuad Al-Mutairi	Affiliation: King Saud University, Riyadh, Saudi Arabia Email: almutairifu@NGHA.MED.SA
Prof Fowzan S Alkuraya	Affiliation: King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia Email: falkuraya@kfshrc.edu.sa
Dr Mie Rizig	Affiliation: Department of neuromuscular diseases, Queen square-Institute of neurology, University College London Email: mie.rizig@uclmail.net
Dr. Chingiz Shashkin	Affiliation: Kazakh National State University, Almaty, Kazakhstan Email: chingizshashkin@gmail.com
Dr. Nazira Zharkynbekova	Affiliation: Shymkent Medical Academy, Kazakhstan
Dr. Kairgali Koneyev	Affiliation: Kazakh National State University, Almaty, Kazakhstan. Email: kairgali@mail.ru