International Conference on Spinocerebellar degenerations

Held by

- ***The Network of hereditary forms of SPAstic paraplegias and cerebellar ATAXias*** **(SPATAX)**

- ***The Ataxia Study Group*** **(ASG)**

- ***The European Friedreich's Ataxia consortium for Translational Studies*** **(EFACTS)**

Brain and Spine Institute (ICM),

Pitié-Salpêtrière Hospital, Paris (France)

June 11-13, 2013

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PROGRAM

June 11, 2013

18.30 Welcoming session and presentation of the conference (Alexandra Durr, Holm Graessner, Alexis Brice and Giovanni Stevanin)

18.40-19.30 Plenary conference by Huda Zoghbi (Baylor College of Medicine, Houston, USA) on cerebellar ataxias

*From **19.40 Cocktail buffet** offered by ENP (Ecole des Neurosciences Paris Ile-de-France)*

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June 12, 2013

8.30-10.00 Session on dominant ataxias
(Chairs: Thomas Klockgether, Germany; Bart Van de Warrenburg, The Netherlands)

Plenary conferences *(25'+5' questions)*

- **Henry Houlden** (*University College London Institute of Neurology, London, UK*) "Diagnostic exome sequencing for the spinocerebellar ataxias"
- **Willeke van Roon-Mom** (*Leiden University Medical Center, Leiden, The Netherlands*) "Using antisense oligonucleotides to reduce or modify the disease causing proteins in autosomal dominant spinocerebellar ataxias"
- **Peter Breuer** (*University of Bonn Medical Center, Bonn, Germany*) **"**A functional role for calpains in the aggregation of Ataxin 3"

10.00-10.30 Coffee break and posters session

10.30-12.00 Abstract session on dominant ataxias
(Chairs: Thomas Klockgether, Germany; Bart Van de Warrenburg, The Netherlands)

10.30 Jacobi H., Reetz K., Tezenas du Montcel S., Bauer P., Mariotti C., Nanetti L., Rakowicz M., Sulek A., Durr A., Charles P., Filla A., Antenora A., Schöls L., Schicks J., Infante J., Kang J.S, Timmann D., Di Fabio R., Masciullo M., Baliko L., Bela M., Boesch S., Bürk K., Peltz A., Schulz J.B., Dufaure-Garé I., Klockgether T. (*University of Bonn, Bonn, Germany*): Prospective study of individual at-risk for SCA1, SCA2, SCA3 and SCA6 (RISCA)
10.45 Di Gregorio E, Borroni B., Giorgio E., Lacerenza D., Calcia A., Mura I., Coviello D., Mitro N., Gaussen M., Vaula G., Lagroua I., Orsi L., Durr A., Costanzi C., Padovani A., Brice A., Boccone L., Hoxha E., Tempia F., Caruso D., Stevanin G., Brusco A. (*University of Torino, Torino, Italy*): A novel form of Spinocerebellar Ataxia (SCA) linked to chromosome 6
11.00 Raskind W.H., Chen D.H., Below P., Sul Y., Matsushita M., Wolff J., Bonkowski E., Bird T.D. (*Psychiatry University of Washington School of Medicine, Seattle, USA*): A novel spinocerebellar ataxia with hematologic cytopenias: linkage analysis and exome sequencing identifies a candidate gene
11.15 Chen D-H., Poorkaj Navas P., Oda K., Wolff J., Sul Y., Matsushita M., Bonkowski E., Bird T.D., Raskind W.H. (*University of Washington School of Medicine, Seattle, USA*): Pathogenesis and disease course of spinocerebellar ataxia type 14 in a mouse model
11.30 Alves S., Cormier-Dequaire F., Marinello M., Marais T., Beaumatin F., Muriel M.P, Charbonnier F., Tahiri K., den Dunnen W., Seilhean D., El Hachimi K., Stevanin G., Barkats M., Priault M., Brice A., Durr A., Corvol J.C, Sittler A. (*CRicm, Paris, France*): Selective autophagic-lysosome deregulation in spinocerebellar ataxia 7.

11.45 Pereira MC., Morais S., Sequeiros J., Alonso I. (*University of Porto, Porto, Portugal*): Large scale functional RNAI screen in C.elegans reveals candidate modifier genes for Cacna1a.

12.00-13.00 Buffet and posters session

13.00-15.00 Session on recessive and spastic ataxias
(Chairs: Filippo Santorelli, Italy; Alexis Brice, France)

Plenary conferences *(25'+5' questions)*

- **Peter Bauer** (*University of Tübingen, Tübingen, Germany*) "Gene panel sequencing for hereditary ataxias: A tool for research and diagnostics"
- **Tiziano Verri** (*University of Salento, Italy*) "Comparative analysis, functional mapping of SACS mutations and novel insights into sacsin architecture"
- **Sacha Vermeer** (*University Medical Centre Nijmegen, Nijmegen, The Netherlands*) "ANO10 and beyond"
- **Mathieu Anheim** (*CHU de Strasbourg, Strasbourg, France*) "Algorithm for the diagnosis of autosomal recessive cerebellar ataxia"

15.00-15.30 Coffee break and posters session

15.30-17.00 Abstract session on recessive ataxias
(Chairs: Filippo Santorelli, Italy; Alexis Brice, France)

15.30 Ali-Pacha L., Hamza W., Nouioua S., Lagier-Tourenne C., Benhassine T., Assami S., Koenig M., Tazir M. (*CHU Mustapha Bacha, Algiers, Algeria*): Autosomal recessive cerebellar ataxias: clinical and genetic study of 188 patients

15.45 Mallaret M., Lee J., Sagum C.A, Drouot N., Renaud M., Klein F.A.C, Anheim M., Mignot C., Mandel J.L, Bedford M., Salih M.A, C. Aldaz M., Koenig M. *(Hôpital de Hautepierre, Strasbourg, France*): The tumor suppressor gene WWOX is mutated in autosomal recessive cerebellar ataxia with epilepsy and mental retardation

16.00 Di Gregorio E., Bianchi F.T, Schiavi A., Chiotto A.M.A, Rolando M., Verdun di Cantogno L., Grosso E., Cavalieri S., Calcia A., Lacerenza D., Zuffardi O., Retta S.F, Stevanin G., Marelli C., Durr A., Forlani S., Chelly J., Montarolo F., Tempia F., Beggs H.E, Reed R., Squadrone S., Abete M.C, Brussino A., Ventura N., Di Cunto F., Brusco A. (*University of Torino, Torino, Italy*): A de novo X;8 translocation creates a PTK2-THOC2 gene fusion with THOC2 expression knockdown in a patient with psychomotor retardation and congenital cerebellar hypoplasia

16.15 Tingaud-Sequeira A., Raldùa D., Mathieu G., Rambeau P., Knoll-Gellida A., André M., Goizet C., Babin P.J. (*University of Bordeaux, Talence, France*): Transient knockdown of zebrafish abhd12 provides a new genetic for the study of neurodegenerative disease PHARC

16.30 Synofzik M., Schatton C., Schicks J., Giese M.A, Schöls L., Ilg W. (*Hertie Institute for Clinical Brain Research Tübingen, Germany*): Videogame-based coordinative training improves motor performance in children with degenerative ataxia

16.45 Salih M.A, Mundwiller E, Khan A.O, AlDrees A, Elmalik S.A, Hassan H.H, Al-Owain M, Alkhalidi H.M.S, Katona I, Kabiraj M.M, Chrast R, Kentab A.Y, Alzaidan H, Rodenburg R.J, Bosley T.M , Weis J., Koenig M., Stevanin G., Azzedine H. (*College of Medicine, King Saud University, Riyadh, Saudi Arabia*): PLA2G6 gene mutation cause evolving spinocerebellar ataxia influenced by the genotype

17.00-17.30 Posters session

17.30-18.00 Plenary conference by Giorgo Casari (San Raffaele University, Milan, Italy), "More SCA28, indeed…"

*From **20.15 Cocktail dinner** at the Institut du Monde Arabe (IMA), Welcome to all! with Musical ambiance by Jérome Yelnik and the Monday's quartet (offered by EUROSCA)*

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June 13, 2013

9.00-10.30 Session on spastic paraplegias (1)
(Chairs: Ludger Schöls, Germany; Giovanni Stevanin, France)

Plenary conferences *(25'+5' questions)*

- **Stephan Züchner** (*University of Miami, Miami, USA*) "Exome approach in the identification of new genes"
- **Elena Rugarli** (*University of Cologne, Cologne, Germany*) "Novel insights on spastin function"
- **Fanny Mochel** (*CRicm, Paris, France*) "Spastic paraplegia and metabolic disorders: a focus on lipid metabolism"

10.30-11.00 Coffee break and posters session

11.00-12.30 Abstract session on spastic paraplegias

11.30 Coutinho P., Ruano L., Loureiro J.L, Cruz V.T, Barros J., Assunção Tuna3, Barbot C., Guimarães J., Alonso I., Silveira I., Sequeiros J., Marques Neves J., Serrano P., Silva M.C. (*UnIGENe IBMC, Universidade do Porto, Portugal*): Hereditary Ataxia and Spastic Paraplegia in Portugal: a population-based prevalence study
11.45 Ordóñez-Ugalde A., Quintáns B., Cacheiro P., Grandas F., Pascual S.I, Sanz I., Bautista J.D, Pardo J., Carracedo Á., Sobrido M.J. (*Fundación Pública Galega de Medicina Xenómica, Instituto de Investigaciones Sanitarias Santiago de Compostela (IDIS)-SERGAS, Spain*): Our experience with next generation sequencing of target genes in hereditary spastic paraplegias and spastic ataxias
12.00 Lavie J., Melser S., Solé G., Hannequin D., Lyonnet S., Forlani S., Brice A., Stevanin G., Durr A., Goizet C., Rossignol R., Giovanni G. (*University of Bordeaux, Talence, France*): Role of REEP1 (SPG31) in mitochondrial structure and energetic function
12.15 O'Sullivan N.C, Stofanko M., Yalçın B., Xu L., O'Kane C.J. (*University of Cambridge, Cambridge, UK*): REEP and reticulon mutant phenotypes in Drosophila
12.30 Wedding, I.M, Koht J., Tuong Tran G., Misceo D., Selmer K., Holmgren A., Frengen E., Bindoff L., Tallaksen C.M.E, Tzoulis C. (*Oslo University Hospital, Oslo, Norway*): Paraplegin mutations cause progressive external ophtalmoplegia with multiple mitochondrial DNA deletions in skeletal muscle
12.45 Di Bella D., Sarto E., Mariotti C., Plumari M., Nanetti L., Baranello G., Chiapparini L., Taroni F. *(Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy*): Molecular analysis of FA2H gene mutations in patients with spastic paraplegia

12.45-14.00 Buffet and posters session

14.00-16.00 Session on spastic paraplegias (2)
(Chairs: Jamilé Hazan, France; Evan Reid, UK)

Plenary conferences *(25'+5' questions)*

- **Margaret Robinson** (*University of Cambridge, Cambridge, UK*) "AP-4 and AP-5: two related protein complexes mutated in spastic paraplegias"
- **Craig Blackstone** (*National Institutes of Health, Bethesda, USA*) "Defects in lipid/sterol metabolism as a common theme"
- **Christian Beetz** (*University of Jena, Jena, Germany*) "A novel model for hereditary spastic paraplegia"
- **Evan Reid** (*University of Cambridge, Cambridge, UK*) "Co-ordination of endosomal recycling with degradation via an ESCRT-spastin interaction"

16.00-16.30 Coffee break and posters session

16.30-18.00 Abstract session on spastic ataxias and X-linked forms
(Chairs: Paola Giunti, UK; Alexis Brice, France)

16.30 Pilliod J., Lavie J., Coupry I., Maurat E., Anheim M., Barth M., Guichet A., Rooryck-Tambo C., Arveiler B., Forlani S., Lesne F., Mochel F., N'Guyen K., Lesca G., Brice A., Lacombe D., Stevanin G., Durr A., Rossignol R., G Benard G., Goizet C. (*University of Bordeaux, Talence, France*): Genetic and functional studies of autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)
16.45 Soehn A.S, Synofzik M., Gburek-Augustat J., Schicks J., Karle K.N, Schüle R., Haack T.B, Schöning M., Biskup S., Rudnik-Schöneborn S., Senderek J., Hoffmann K.T, MacLeod P., Schwarz J., Bender B., Krüger S., Kreuz F., Bauer P., Schöls L. (*University of Tübingen, Tübingen, Germany*): Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS): expanding the genetic, clinical and imaging spectrum
17.00 Larivière R., Gaudet R., Chang P., Conte T., Gentil B., Leclerc-Désaulniers K., Dicaire M.J, Durham H.D, Shoubridge E.A, McBride H.M, Gehring K., McPherson P.S, McKinney R.A, Brais B. (Laboratory of neurogenetics of motion, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada): Sacsin knockout mice amnifest clinical and pathological features of ARSACS
17.15 Coutelier, M., Monin M.L, Gautier C., Tesson C, Esteves T., Koskelainen S., Charbonnier-Beaupel F., Labussière M., Mundwiller E., Valleix S., Tahiri K., Langui D., Corvol J.C, Kiuru- Enari S., El Hachimi K., Brice A., Darios F., A. Durr A., Stevanin G. (*CRicm, Paris, France*): *GSN*, a new candidate gene in autosomal dominant spastic cerebellar ataxia
17.30 Zanni G., Calì T., Kalscheuer V.M, Ottolini D., Barresi S., Lebrun N., Montecchi-Palazzi L., Hu H., Chelly J., Bertini E., Brini M., Carafoli E. (*Bambino Gesù Children's Hospital, (IRCCS), Roma, Italy*): Mutation of plasma membrane Ca2+ ATPase isoform in a family with X-linked congenital cerebellar ataxia repairs Ca2+ homeostasis
17.45 Chen A., Shi Y.T, Sun Z.F, Wang J.L, Hu, Z.M, Pan Q., Xia K., Tang B.S, Hong Jiang, H. (*Xiangya Hospital, Central South University, Changsha, Hunan 410008, P.R. China*): A gene identified as a novel causative gene of X-linked ataxia using LEC strategy

18.00-18.15 Presentation awards
The awards (500€) will be granted based on votes by all participants.

Platform award, offered by the Tom Wahlig Stiftung
Poster award, offered by GATC Biotech
Student award, offered by Ecole Pratique des Hautes Etudes (EPHE)

18.15 End of the SPATAX/ASG conference.
Removal of posters

18.15-19.45 EFACTS board meeting (board members of EFACTS only)
18.15-19.45 LIGENAX meeting (members of LIGENAX only)

ABSTRACTS SELECTED FOR PLATFORM PRESENTATIONS

(1) Prospective study of individuals at risk for SCA1, SCA2, SCA3 and SCA6 (RISCA)

H. Jacobi[1,*], K. Reetz[1,*], S. Tezenas du Montcel[2], P. Bauer[3], C. Mariotti[4], L. Nanetti[5], M. Rakowicz[6], A. Sulek[7], A. Durr[8,9], P. Charles[9], A. Filla[10], A. Antenora[10], L. Schöls[11,12], J. Schicks[11,12], J. Infante, J-S. Kang, D. Timmann, R. Di Fabio, M. Masciullo, L. Baliko, M. Bela, S. Boesch, K. Bürk, A. Peltz, J.B. Schulz, I. Dufaure-Garé, T. Klockgether[1]

[1]Department of Neurology, University of Bonn and German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [2]AP-HP, Groupe Hospitalier Pitie-Salpetrière, Biostatistics Unit, Paris, 75013, France ; [3]Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany; [4]Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [5]Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy; [6]Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland; [7]Department of Genetic, Warsaw, Poland ; [8]Université Pierre et Marie Curie-Paris 6, UMR-S975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Groupe Hospitalier Pitié-Salpêtrière ; Inserm, U975 ; Cnrs, UMR 7225, Paris, France ; [9]APHP, CHU Pitié-Salpêtrière, Fédération de Génétique, Paris, France ; [10]Dipartimento di Scienze Neurologiche, Università Federico II, Napoli, Italy; [11]Department of Neurodegeneration, Hertie Institute for Clinical Brain Research and Centre of Neurology, Tübingen, Germany ; [12]German Research Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Germany; Department of Neurology, University of Duisburg-Essen, Essen, Germany; Department of Neurology, Philipps-University of Marburg, Marburg, Germany; Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; Department of Neurology, Medical University Innsbruck, Austria; Department of Neurology, University Hospital Aachen, Aachen, Germany.
*Both authors contributed equally

Rationale

SCA mutation carriers provide a unique research opportunity to prospectively study the preclinical phase of SCAs and to identify the earliest and most sensitive clinical signs and biological markers that precede disease onset. This information is of critical importance for the development of future therapeutic interventions aimed at postponing the clinical onset of ataxia.

Study design

RISCA is a prospective, multicentric, international, observational study of non-ataxic adult individuals that descend from an SCA1, SCA2, SCA3 or SCA6 individual (offspring and sibs).
Both, individuals who were aware of their carrier status, and individuals who were not aware of their carrier status were included. All genetic tests were done anonymously under an arrangement that guarantees that no party including clinical investigators and study participants will be informed about the results.

Inclusion criteria

• Direct descendance from an SCA1, SCA2, SCA3 or SCA6 patient (offspring and sibs)
• Age 18 to 50 years for descendants of SCA1, SCA2 or SCA3 patients and 35 to 70 years for descendants of SCA6 patients
• Absence of ataxia (SARA < 3)
• Written, informed consent

Summary

• SCA1, SCA2 carriers had higher SARA scores; SCA1, SCA2, SCA3 carriers performed worse on timed tests.
•Prevalence of non-ataxia symptoms was increased in SCA1 carriers, gaze-evoked nystagmus in SCA3 carriers, spontaneous cramps in SCA2 carriers.
•In SCA1, SCA2 carriers confidence rating, SARA and timed-tests increased with TFO.
•Quantitative MRI showed cerebellar and brainstem volume loss in SCA1 and SCA2.

Conclusion

Our data suggest the presence of functional and brain structural alterations in preclinical SCA1 and SCA2 mutation carriers. The extent of a number of these alterations increased with decreasing interval to the predicted time of ataxia onset.

(2) A novel form of Spinocerebellar Ataxia (SCA) linked to chromosome 6

Eleonora Di Gregorio[1,2], Barbara Borroni[3], Elisa Giorgio[1], Daniela Lacerenza[1], Alessandro Calcia[1], Isabella Mura[4], Domenico Coviello[4], Nico Mitro[5], Marion Gaussen[6], Giovanna Vaula[7], Isabelle Lagroua[6], Laura Orsi[7], Alexandra Durr[6,8], Chiara Costanzi[3], Alessandro Padovani[3], Alexis Brice[6,8], Loredana Boccone[9], Eriola Hoxha[10], Filippo Tempia[10], Donatella Caruso[5], Giovanni Stevanin[6,8], Alfredo Brusco[1,2]

[1]University of Torino, Department of Medical Sciences, Italy; [2]S.C.D.U. Medical Genetics, Città della Salute e della Scienza, Torino, Italy; [3]University of Brescia, Department of Neurology, Brescia, Italy; [4]Laboratory of Human Genetics, Galliera Hospital, Genova, Italy; [5]University of Milano, Department of Pharmacological Sciences, Italy; [6]Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (INSERM / UPMC Univ. Paris 6, UMR_S975 ; CNRS 7225, EPHE), Pitié-Salpêtrière Hospital, Paris, France ; [7]S.C.D.U. Neurology, Città della Salute e della Scienza, Torino, Italy ; [8]APHP, Fédération de génétique, Pitié-Salpêtrière Hospital, Paris, France ; [9]Ospedale Regionale Microcitemie, ASL 8, Cagliari, Italy ; [10]University of Torino, Neuroscience Institute Cavalieri Ottolenghi (NICO), Torino, Italy.

Spinocerebellar ataxias (SCA) are a highly heterogeneous group of autosomal dominant neurodegenerative disorders phenotypically characterized by gait ataxia, incoordination of eye movements, speech, and hand movements, and usually associated with cerebellar atrophy. More than 30 SCAs have been identified, whose genes may be classified into two main categories: repeat expansion disorders – among which the most common forms SCA 1-3, 6, and 7 – and genes with conventional mutations.
Here we report the identification of a novel SCA gene. Genome-wide linkage analysis identified a 92 Mb region on chromosome 6 in an Italian family affected by a pure form of ataxia with disease onset in the 4th decade of life. Next generation sequencing of all coding genes in the smallest interval identified only one possible mutated gene, with a Gly to Val amino acid change. Screening of over 450 SCA independent patients identified this same mutation in two further unrelated Italian families. Haplotyping proved that at least two of the three families shared a common ancestor. Two further missense variants, in three independent families, affected the same exon involved in the Italian families, suggesting this may be a mutational hot-spot. All changes hit conserved amino acids, and were not common polymorphisms.
The gene encodes an ubiquitously expressed enzyme involved in fatty acid biosynthesis. *In situ* hybridization on mouse and human brain demonstrated that Purkinje cells have a peculiar high expression of the enzyme.
In agreement with the function of this gene, we showed a reduced level of a subgroup of fatty acids in the serum of three patients with the Gly to Val amino acid change. Furthermore, we found an upregulation of the gene expression at the messenger RNA and protein levels in the patients' lymphoblasts vs. controls. We hypothesize that a positive feedback loop, activated by the functional impairment of the enzyme, may lead to an increase of protein expression that in turn may accumulate within cells leading to a toxic gain of function.
In conclusion, we suggest that our mutated gene, highly expressed in Purkinje cells, is a good candidate for a new form of pure autosomal dominant cerebellar ataxia and join the group of CNS diseases involving fatty acids metabolism.

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(3) A novel spinocerebellar ataxia with hematologic cytopenias: linkage analysis and exome sequencing identifies a candidate gene

Wendy H. Raskind[1,2,5], Dong-Hui Chen[3], Piper Below[4], Youngmee Sul[1], Mark Matsushita[1], John Wolff[1], Emily Bonkowski[1], Thomas D. Bird[1, 5, 3]

[1]Departments of Medicine/Medical Genetics, University of Washington School of Medicine, Seattle, WA, USA; [2]Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA; [3]Neurology, University of Washington School of Medicine, Seattle, WA, USA; [4]Genome Sciences, University of Washington School of Medicine, Seattle, WA, USA; [5]the GRECC and MIRECC, Veterans Administration Puget Sound Veterans Health Care Center, USA.

We report a new member of the continuously enlarging group of genetically heterogeneous spinocerebellar ataxias (SCAs). We identified a family of European ethnic background segregating an autosomal dominant disorder characterized by both cerebellar ataxia and variable hematologic cytopenias, a feature not present in other described SCAs. Affected individuals manifest early onset nystagmus and imbalance that slowly progresses to a full cerebellar syndrome. The age of onset

ranged from 8 to 55, with a mean of 25 years. The spectrum of hematologic abnormalities is broad, ranging from totally normal cell counts to severe decreases in multiple cell lines. Autopsy on one person who died in adolescence of retroperitoneal hemorrhage revealed predominant Purkinje cell loss. The known genes or loci for SCA or pancytopenia were excluded by sequence analysis or targeted linkage analysis. To identify candidate genes, we exploited a combination of new genomic technologies, including massively parallel exome resequencing, SNP-based linkage and identity-by-descent (IBD) analyses, and bioinformatics. After stepwise filtering to remove common and non-functional variants, heterozygous variants shared by the exomes of two affected subjects were prioritized and examined by Sanger sequencing for confirmation and to evaluate co-segregation in the family; none of these variants co-segregated appropriately. Subsequent SNP-based linkage analysis using all available family members detected four shared regions that were also found by IBD analysis. In one of the samples used for exome sequencing, derived from a lymphocyte cell line, the array revealed a region of loss of heterozygosity (LOH) that overlapped with one of the linkage regions. When this sample was excluded, we identified a variant in the region of LOH that cosegregated with disease. This variant is not reported in the dbSNP, 1000 Genomes or Exome Variant Server databases; both Polyphen and SIFT programs predict it to be damaging; and PhastCons indicates high conservation of the residue. The causative gene is not well characterized but is thought to be involved in control of cell proliferation and has been associated with myeloid leukemia. Ongoing functional studies on the effect of this mutation will be presented.

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(4) Pathogenesis and disease course of spinocerebellar ataxia type 14 in a mouse model

Dong-Hui Chen[1], Parvoneh Poorkaj Navas[2], Kaori Oda[3], John Wolff[2], Youngmee Sul[3], Mark Matsushita[c], Emily Bonkowski[1], Thomas D. Bird[1,2,4], Wendy H. Raskind[2,3,4]

[1]Departments of Neurology, University of Washington School of Medicine, Seattle, WA 98195, USA; [2]Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA 98195, USA; [3]Medicine/Medical Genetics, University of Washington School of Medicine, Seattle, WA 98195; [4]the GRECC and MIRECC, Veterans Administration Puget Sound Veterans Health Care Center, USA.

Spinocerebellar ataxia type 14 (SCA14) shares many clinical and pathologic features with other autosomal dominant SCAs, but the phenotype has been broadened to include myoclonus and a variety of cognitive impairments. SCA14 is caused by mutations in protein kinase C gamma (*PRKCG,* PKCγ). To date, 24 distinct mutations in *PRKCG*, including missense mutations and two in-frame deletions, have been reported. In vitro studies suggest that mutant PKC□ is susceptible to aggregation, which leads to apoptosis and impairment of the ubiquitin-proteasome system. While *PRKCG*-null mice and rat models exist, the phenotypes are not identical to that of SCA14 in humans, and both animal models are recessive. There are preliminary reports of SCA14 mouse models either with human *PRKCG* cDNA driven by a CMV promoter or through direct injection into Purkinje cells of lentivirus vector bearing human *PRKCG* cDNA. Neither model is likely to be a full recapitulation of human SCA14. A more appropriate biological model of SCA14 would be extremely useful for investigations of disease pathogenesis, potential therapies and possible common pathways with other neurodegenerative diseases.
We have developed bacterial artificial chromosome (BAC) transgenic mice with either the human wild type *PRKCG* gene (WT) or a mutant form (H101Y and F643L). These transgenic lines were tested for neurological and pathological deficits. Behavioral testing by rotarod and the Composite Phenotype Scoring System, an assessment of coordination in mouse models, demonstrated that 101Y and 643L mice performed significantly worse than WT mice from 6 months of age. IHC staining revealed cerebellar abnormalities including aggregation of PKCγ in Purkinje cell bodies and dendrites in 101Y mice, and disorganized dendrites in 643L mice as early as 12 wks. Interestingly, the pathologic changes found are mutation specific and mimic what we observed in *in vitro* mutant PKCγ transfection studies. These mouse models will be invaluable in future studies to clarify potential pathogenesis in SCA14 related to mutations in different domains of PKCγ and to investigate therapeutic options.

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(5) Selective autophagic-lysosome deregulation in Spinocerebellar ataxia 7

Sandro Alves[1,2,3], Florence Cormier-Dequaire[1,2,3,6*], Martina Marinello,[1,2,3*], Thibaut Marais[4,5], Florian Beaumatin[9], Marie-Paule Muriel[1,2,3], Fanny Charbonnier[1,2,3,6], Khadija Tahiri[1,2,3,6], Wilfred den Dunnen[7], Danielle Seilhean[10], Khalid El Hachimi[1,2,3,8], Giovanni Stevanin[1,2,3,8], Martine Barkats, Muriel Priault[9], Alexis Brice[1,2,3], Alexandra Durr[1,2,3], Jean-Christophe Corvol[1,2,3,6] and Annie Sittler[1,2,3]

[1]Université Pierre et Marie Curie-Paris 6, UMR_S 975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM), Pitié-Salpêtrière Hospital, 75013 Paris, France ; [2]CNRS, UMR 7225, 75013 Paris, France ; [3]INSERM, U975, 75013 Paris, France ; [4]INSERM, U974, 75013 Paris, France
[5]UPMC-AIM UMR S974, CNRS UMR 7215, Institut de Myologie, 75013 Paris, France ; [6]Clinical Investigation Center (CIC-9503), Pitié-Salpêtrière Hospital, 75013 Paris, France ; [7]Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [8]Laboratoire de Neurogénétique, Ecole Pratique des Hautes Etudes, Institut du Cerveau et de la Moelle épinière, Pitié-Salpêtrière Hospital, 75013 Paris, France ; [9]CNRS, Université de Bordeaux, Institut de Biochimie et de Génétique Cellulaires, UMR5095, 33000 Bordeaux, France ; [10]Laboratoire de neuropathologie Escourolle, Hôpital de la Pitié Salpêtrière, 75013 Paris, France.

There is still no treatment for polyglutamine disorders, but clearance of the mutant proteins is a potential therapeutic strategy. Autophagy, responsible for degrading long-lived proteins and organelles, has been implicated in these diseases. In this study, we investigated the implication of the autophagy-lysosome system, the major pathway for organelle and protein turnover, in the pathophysiology of Spinocerebellar ataxia type 7.
We looked for biochemical, histochemical and transcriptomic abnormalities in components of the autophagy-lysosome-pathway *in vitro*, in knock-in and lentiviral-induced mouse models of SCA7, and postmortem brain and lymphocytes from patients.
In the mouse models, mutant ataxin-7 accumulated in inclusions immunoreactive for the autophagic proteins mTOR, beclin-1, p62 and ubiquitin; the autophagosome/lysosome markers LC3, LAMP-1, LAMP2 and cathepsin-D accumulated in the cerebellum. Autophagic markers were also abnormally expressed in the cerebellum and cerebral cortex of patients, but not the striatum, which is spared in the disease, suggesting that autophagy is impaired by the selective accumulation of mutant ATXN7. Importantly, i*n vitro* overexpression of the proteins beclin-1 and ATG7 proteins reduced the accumulation of both soluble and insoluble mutant ATXN7. Moreover, the early autophagy-associated gene *ATG12* was upregulated in lymphocytes from SCA7 patients and was correlated with disease severity.
The autophagosomal/lysosomal-pathway is selectively impaired in neurons undergoing degeneration in SCA7. Macroautophagy-lysosome-associated molecules might be useful markers in tests of potentially therapeutic autophagy modulators in models. ATG12, which is accessible in blood, might be a first indicator of disease progression in SCA7 in patients.

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(6) Large scale functional RNAi screen in *C. elegans* reveals candidate modifier genes for *Cacna1a*

Pereira Maria C[1,2], Morais Sara[1,2], Sequeiros Jorge[1,2,3], Alonso Isabel[1,2]
[1]UnIGENe, IBMC, Porto, Portugal;[2]ICBAS, University of Porto, Porto, Portugal; [3]CGPP, IBMC, Porto, Portugal.

Mutations in the *CACNA1A* gene that encodes the pore-forming α_1 subunit of human voltage-gated $Ca_v2.1$ (P/Q-type) Ca^{2+} channels cause several autosomal-dominant neurologic disorders, including familial hemiplegic migraine type 1 (FHM1), episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6).
In order to identify modifiers of uncoordination in movement disorders, we performed a large scale functional RNAi screen using the *C. elegans* strain CB55, which carries a truncating mutation in the *unc-2* gene, the worm ortholog for the human *CACNA1A*.
The screen was carried out by the feeding method in a 96-well liquid culture format using the ORFeome v1.1 feeding library of ORFs (Source Bioscience) as previously described. We used time-lapse imaging of worms in liquid culture to assess changes in thrashing behaviour. Raw imaging data was analysed with open source Image J, and the thrashing analysis results were loaded on CellHTS2 for further exploration.
We looked for genes that when silenced either ameliorated the slow and uncoordinated phenotype of unc-2 or interacted to produce a more severe phenotype. Raw data was collected for the full library and the primary screen has been analysed by CellHTS2. During the primary screen we found 142 candidate genes improving CB55 motor function, and 148 candidate genes increasing *unc-2* impairment, through interaction with *Cacna1a*. Gene ontology revealed an overrepresentation of genes involved in development, growth, locomotion, signal transduction and vesicle mediated transport.
We are now finishing collection of raw data for the secondary screen and will follow with more detail the genes that score again by expanding the panel of behavioural and neurodegeneration assays. Overall the *unc-2* mutant is a very attractive model to study neuronal dysfunction and movement

disorders as mutations in the human gene give rise to at least three different disorders with overlapping phenotypes.

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(7) Autosomal recessive cerebellar ataxias : cinical and genetic study of 188 patients

Lamia Ali-Pacha[1], W Hamza[2,3], S Nouioua[1], C Lagier-Tourenne[3], Traki Benhassine[2], S Assami[1], Michel Koenig[3], Meriem Tazir[1]

[1]Laboratoire de Neurosciences, Service de Neurologie, CHU Mustapha Bacha, Algiers, Algeria ; [2]Laboratoire de biologie moléculaire, Université H. Boumediène, BEZ, Algiers, Algeria ; [3]Institut de génétique et de biologie moléculaire et cellulaire(IGBMC) Illkirch, France.

Autosomal recessive cerebellar ataxias (ARCA) are heterogeneous hereditary and neurodégénérative diseases. They are characterized by involvement of cerebellum, brainstem, and spinocerebellar tracts. Currently, this group of diseases contains more than 20 clinical entities and an even larger number of associated genes.
We retrospectively and prospectively studied 188 cases belonging to 117 families suspected of ARCA, coming from different regions of Algeria, between 2001 à 2012.
Complete clinical examination, laboratory, imaging and electrophysiological investigations allowed us to obtain a detailed phenotype for each patient with cerebellar ataxia. The initial molecular investigation for each patient was the FRDA GAA expansion test. The non-Freidreich patients were then explored genetically according to their detailed phenotype.
Finally**,** the molecular diagnosis could be established in 67% of ARCA patients (126 patients belonging to 75 families): 52 patients (32 families) were affected with Friedreich ataxia (FRDA), 21 (11 families) with ataxia with oculomotor apraxia type 2 (AOA2),16 (9 families) with Ataxia with isolated vitamin E deficiency (AVED), 12 (10 families) with Ataxia-Telangiectasia (AT), 9 (4 families) with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), 9 (5 families) with Joubert syndrome (JS), 5 (2 families) with autosomal recessive ataxia type 2 (ARCA2), and 2 (2 families) with ataxia with oculomotor apraxia type 1 (AOA1). Sixty two patients have no identified mutation.
In conclusion this study in a large Algerian cohort of ARCA patients allowed us to determine the frequency of 8 ARCA entities. Friedreich ataxia was the most frequent entity, as found in the majority of studies, followed by AOA2 and AVED. Ataxia with Vit E deficiency with a founder effect mutation in North-Africa is one of the few ARCA that can be treated and therefore must be looked for in first instance after FRDA in Friedreich-like patients. Two families contributed to identify ARCA2 a new cerebellar ataxia entity. However 32 % of ARCA patients remained not linked to known genes, such that new ARCA forms are expected in the near future.

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(8) The tumor suppressor gene *WWOX* is mutated in autosomal recessive cerebellar ataxia with epilepsy and mental retardation

Martial Mallaret[1,2], Jaeho Lee[3], Cari A. Sagum[3], Nathalie Drouot[2], Mathilde Renaud[1,2], Fabrice A.C. Klein[2], Mathieu Anheim[1,2], Cyril Mignot[4], Jean-Louis Mandel[2,5], Mark Bedford[3], Mustafa A. Salih[6], C. Marcelo Aldaz[3], Michel Koenig[2,5]

[1]Department of Neurology, Hôpital de Hautepierre, Strasbourg, France ; [2]Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), INSERM-U964/CNRS-UMR7104/Université de Strasbourg, Collège de France, 67404 Illkirch, France ; [3]Department of Molecular Carcinogenesis, University of Texas M. D. Anderson Cancer Center, Smithville, TX, USA ; [4]APHP, Groupe Hospitalier Pitié Salpêtrière, Unité Fonctionnelle de Génétique Médicale, Paris, France ; [5]Laboratoire de Diagnostic Génétique, Nouvel Hôpital Civil, 67091 Strasbourg, France ; [6]Division of Pediatric Neurology, Department of Pediatrics, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

We previously localized a new form of recessive ataxia with generalized tonic-clonic epilepsy and mental retardation to a 19 Mb interval in 16q21-q23 by homozygosity mapping of a large consanguineous Saudi Arabia family. We now report the identification by whole exome sequencing of the missense mutation changing proline 47 into threonine (p.Pro47Thr) in the first WW domain of the WW oxido-reductase gene, *WWOX*, located in the linkage interval. Proline 47 is a highly conserved residue that is part of the WW motif consensus sequence and is part of the hydrophobic core that stabilizes the WW fold. We demonstrate that proline 47 is a key amino-acid essential for maintaining the WWOX protein fully functional, with its mutation into a threonine resulting in a loss of peptide interaction for the first WW domain. We also observed that the short lived *Wwox* KO mice display spontaneous and audiogenic seizures, a phenotype previously observed in the *Ide* rat spontaneous *Wwox* mutant presenting with ataxia and epilepsy (Suzuki et al, 2007 and Suzuki et al, 2009),

indicating that homozygous WWOX mutation in different species causes cerebellar ataxia associated with epilepsy.

Key words: ataxia, tonic-clonic epilepsy, WWOX, WW domain, exome sequencing

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(9) A *de novo* X;8 translocation creates a *PTK2-THOC2* gene fusion with *THOC2* expression knockdown in a patient with psychomotor retardation and congenital cerebellar hypoplasia

Eleonora Di Gregorio[1,2], Federico T. Bianchi[3], Alfonso Schiavi[4,5], Alessandra M.A. Chiotto[3], Marco Rolando[6], Ludovica Verdun di Cantogno[7], Enrico Grosso[2], Simona Cavalieri[2] , Alessandro Calcia[1], Daniela Lacerenza[1], Orsetta Zuffardi[8,9],Saverio Francesco Retta[10], Giovanni Stevanin[11,12], Cecilia Marelli[11,12], Alexandra Durr[11,12], Sylvie Forlani[11], Jamel Chelly[13], Francesca Montarolo[14], Filippo Tempia[14], Hilary E. Beggs[15], Robin Reed[16], Stefania Squadrone[17], Maria C. Abete[17], Alessandro Brussino[1], Natascia Ventura[4,5], Ferdinando Di Cunto[3], Alfredo Brusco[1,2*]

[1]University of Torino, Department of Medical Sciences, Italy; [2]S.C.d.U. Medical Genetics, Città della Salute e della Scienza, Torino, Italy; [3]University of Torino, Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Centre, Via Nizza 52, 10126, Torino, Italy; [4]University of Roma "Tor Vergata", Department of Biomedicine and Prevention, Italy; [5]Institute of Clinical Chemistry and Laboratory Medicine of the Heinrich Heine University, and the IUF - Leibniz Research Institute for Environmental Medicine, Duesseldorf, Germany; [6]S.C. Neuropsichiatria Infantile, ASL TO3, Pinerolo, Italy; [7]S.C.d.U. Anatomia Patologica, Città della Salute e della Scienza, Torino, Italy; [8]Department of Molecular Medicine, University of Pavia, Pavia, Italy; [9]IRCCS "National Neurological Institute C. Mondino" Foundation, Pavia, Italy; [10]Department of Clinical and Biological Sciences, University of Turin, Orbassano, Italy; [11]Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (INSERM / UPMC Univ. Paris 6, UMR_S975 ; CNRS 7225, EPHE), Pitié-Salpêtrière Hospital, Paris, France ; [12]APHP, Fédération de génétique, Pitié-Salpêtrière Hospital, Paris, France ; [13]Université Paris Descartes, Institut Cochin - Hôpital Cochin, Paris, France ; [14]University of Torino, Neuroscience Institute Cavalieri Ottolenghi (NICO), Torino, Italy; [15]Department of Ophthalmology, University of California San Francisco, San Francisco, CA 94122, USA; [16]Department of Cell Biology, Harvard Medical School, Boston, USA; [17]Istituto Zooprofilattico Sperimentale del Piemonte, Liguria e Valle d'Aosta, CReAA- National Reference Centre for Surveillance and Monitoring of Animal Feed, Lab. Contaminanti Ambientali, Torino, Italy.

We identified a balanced *de novo* translocation involving chromosomes Xq25 and 8q24 in an eight year-old girl with a non-progressive form of congenital ataxia, cognitive impairment and cerebellar hypoplasia. Breakpoint definition showed that the promoter of the *Protein Tyrosine Kinase 2* (*PTK2*, also known as *Focal Adhesion Kinase, FAK*) gene on chromosome 8q24.3 is translocated 2 kb upstream of the THO complex subunit 2 (*THOC2*) gene on chromosome Xq25. *PTK2* is a well-known non-receptor tyrosine kinase whereas *THOC2* encodes a component of the evolutionarily conserved multiprotein THO complex, involved in mRNA export from nucleus. The translocation generated a sterile fusion transcript under the control of the *PTK2* promoter, affecting expression of both *PTK2* and *THOC2* genes. PTK2 is involved in cell adhesion and, in neurons, plays a role in axonal guidance, and neurite growth and attraction. However, *PTK2* haploinsufficiency alone is unlikely to be associated with human disease. Therefore, we studied the role of THOC2 in the CNS using three models: 1) *THOC2* ortholog knockout in *C.elegans* which produced functional defects in specific sensory neurons; 2) *Thoc2* knockdown in primary rat hippocampal neurons which increased neurite extension; 3) *Thoc2* knockdown in neuronal stem cells (LC1) which increased their in vitro growth rate without modifying apoptosis levels. We suggest that *THOC2* can play specific roles in neuronal cells and, possibly in combination with *PTK2* reduction, may affect normal neural network formation, leading to cognitive impairment and cerebellar congenital hypoplasia.

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(10) PLA2G6 gene mutations cause evolving spinocerebellar ataxia influenced by the genotype

Mustafa A. Salih[1], Emeline Mundwiller[2], Arif O. Khan[3], Abdulmajeed AlDrees[4], Salah A. Elmalik[4], Hamdy H. Hassan[5], Mohammed Al-Owain[6], Hisham M. S. Alkhalidi[7], Istvan Katona[8], Mohammad M. Kabiraj[9], Roman Chrast[10], Amal Y. Kentab[1], Hamad Alzaidan[6], Richard J. Rodenburg[11], Thomas M. Bosley[12,13], Joachim Weis[8], Michel Koenig[14], Giovanni Stevanin[2,15,16, 17, 18, 19, a], Hamid Azzedine[10, a]

[1]Division of Pediatric Neurology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [2]Institut du Cerveau et de la Moelle épinière (ICM), Genotyping and Sequencing Facility, Groupe Hospitalier Pitié-Salpêtrière, 75013 Paris, France ; [3]Division of Paediatrics Ophthalmology, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia; [4]Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [5]Department of Radiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [6]Department of Medical Genetics, King Faisal specialist Hospital & Research Centre, Riyadh, Saudi Arabia; [7]Department of Pathology, College of

Medicine, King Saud University, Riyadh, Saudi Arabia; [8]Institut für Neuropathologie, Universitätsklinikum der RWTH, 52074 Aachen, Germany; [9]Department of Neurosciences, Armed Forces Hospital, Riyadh, Saudi Arabia; [10]Department of Medical Genetics, Faculty of Biology and Medicine, University of Lausanne, CH-1005 Lausanne, Switzerland; [11]Radboud University Medical Center, Nijmegen Center for Mitochondrial Disorders, Department of Pediatrics, Department of Laboratory Medicine, 774 Laboratory for Genetic, Endocrine and Metabolic disorders (LGEM), Nijmegen, The Netherlands; [12]Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [13]Neurology Division, Cooper University Hospital, Camden, USA; [14]Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), CNRS/INSERM/Université de Strasbourg, et Collège de France, 67404 Illkirch, France; [15]Ecole Pratique des Hautes Etudes (EPHE) [16]INSERM-U975, Paris, France ; [17]CNRS-UMR7225, Paris, France ; [18]Université Pierre et Marie Curie – Paris 6, UMRS_975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (cricm), F-75013 Paris, France ; [19]APHP, Département de Génétique et Cytogénétique, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.

[a]These Authors contributed equally

Mutations in *PLA2G6* gene have variable phenotypic outcome including infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (NAD), idiopathic neurodegeneration with brain iron accumulation (NBIA) and Karak syndrome. The cause of this phenotypic variation is so far unknown which impairs both genetic diagnosis and appropriate family counseling. We report detailed clinical, electrophysiological, neuroimaging, histologic, biochemecial and genetic characterization of 11 patients, from 6 consanguineous families, who were followed for a period of up to 17 years. Cerebellar atrophy was constant and the earliest feature of the disease preceding brain iron accumulation, leading to the provisional diagnosis of a recessive progressive ataxia in these patients. Ultrastructural characterization of patients' muscle biopsies revealed focal accumulation of granular and membranous material possibly resulting from defective membrane homeostasis caused by disrupted PLA2G6 function. Enzyme studies in one of these muscle biopsies provided evidence for a relatively low mitochondrial content, which is compatible with the structural mitochondrial alterations seen by electron microscopy. Genetic characterization of 11 patients led to the identification of six underlying *PLA2G6* gene mutations, five of which are novel. Importantly, by combining clinical and genetic data we have observed that while the phenotype of neurodegeneration associated with *PLA2G6* mutations is variable in this cohort of patients belonging to the same ethnic background, it is influenced by the genotype, considering the age at onset and the functional disability criteria. Molecular testing for *PLA2G6* mutations is, therefore, indicated in childhood-onset ataxia syndromes, if neuroimaging shows cerebellar atrophy with or without evidence of iron accumulation.

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(11) Transient knockdown of zebrafish abhd12 provides a new genetic model for the study of neurodegenerative disease PHARC

Angèle Tingaud-Sequeira, Demetrio Raldùa, Guilaine Mathieu, Pierre Rambeau, Anja Knoll-Gellida, Michèle André, Cyril Goizet, Patrick J. Babin

University of Bordeaux, Maladies Rares: Génétique et Métabolisme (MRGM), EA 4576, F33400 Talence, France

Recent studies linked several ABHD12 mutations to the neurodegenerative disease PHARC (Polyneuropathy, Hearing loss, Ataxia, Retinitis pigmentosa, Cataract), identified as a progressive and autosomal recessive disease. Although ABHD12 is suspected to play a role in lysophosphatidylserine and/or cannabinoid pathways, its precise role(s) leading to PHARC disease remain to be characterized.

Zebrafish abhd12 was identified on the basis of high overall protein sequence identity and conservation of gene synteny. RT-PCR approach demonstrated abhd12 ubiquitous expression during embryonic and larval development and in several adult tissues. However, in situ hybridization approach on adult histological sections demonstrated high abhd12 transcript levels in the nervous system, particularly concentrated in optic tract and spinal cord. By immuno-colocalization with the myelin basic protein, abhd12 appeared to be expressed by oligodendrocytes but not Schwann cells. Moreover, phenotype of abhd12 knockdown morphants exhibited clear resemblance with some of the PHARC hallmarks.

A strong disruption of the retina architecture and defects in the lens were observed. Neuromasts, mechanosensory receptors very similar in structure and function to the sensory patches of the human inner ear, were severely impaired in abhd12 morphants.

Defect in the cerebellum development and myelination were also induced. Finally, abhd12 morphants presented impairment at different levels of the motor system and a concomitant to functional deficits characterized by progressive dyskinesia and decrease in mobility.

Our results show that both the expression pattern of zebrafish abhd12 and the phenotype of the zebrafish morphants are consistent with the human PHARC symptoms.

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(12) Videogame-based coordinative training improves motor performance in children with degenerative ataxia

Matthis Synofzik[1,2], Conny Schatton[3,4], Julia Schicks[1,2], Martin A. Giese[3,4], Ludger Schöls[1,2], Winfried Ilg[3,4]

[1]Department of Neurodegeneration, Hertie Institute for Clinical Brain Research and Centre of Neurology, Tübingen, Germany
[2] German Research Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Germany
[3]Department of Cognitive Neurology, Hertie Institute for Clinical Brain Research, Tübingen, Germany
[4]Centre for Integrative Neuroscience (CIN), Tübingen, Germany

Degenerative ataxias in children present a rare condition where effective treatments are lacking. Intensive coordinative training based on physiotherapeutic exercises improves degenerative ataxia in adults, but such exercises have drawbacks for children, often including a lack of motivation for high-frequent physiotherapy. Recently developed whole-body controlled video-game technology might present a novel treatment strategy for highly interactive and motivational coordinative training for children with degenerative ataxias.
We examined the effectiveness of an 8-week coordinative training in a piloting cohort of children suffering from progressive spinocerebellar ataxia. Training was based on three commercial Xbox Kinect® video-games particularly suitable to exercise whole-body coordination and dynamic balance. Training was started with a lab-based two-week training phase and followed by six weeks training in children's home environment.
Rater-blinded assessments were performed two weeks before lab-based training, immediately prior to and after the lab-based training, as well as after home training. These assessments allowed for an intra-individual control design, where performance changes with and without training were compared.
Here we present the piloting results of this study. Ataxia symptoms were significantly reduced (decrease in SARA score, p=0.0078) and balance capacities improved (DGI, p=0.04) after intervention. Quantitative movement analysis revealed improvements in gait (reduced lateral sway: p=0.01; step length variability: p=0.01) and in goal-directed leg placement (p=0.03).
Our study demonstrates that - despite progressive cerebellar degeneration – children with ataxia are able to benefit from whole-body controlled video-game based training. This might present a highly motivational, cost-efficient and home-based rehabilitation strategy to train dynamic balance and interaction with dynamic environments in a large variety of young-onset neurological conditions.

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(13) Hereditary ataxia and spastic paraplegia in Portugal: a population-based prevalence study

Paula Coutinho[1], Luís Ruano[2], J.L. Loureiro[2], Vítor T. Cruz[2], José Barros[3,4], Assunção Tuna[3], Clara Barbot[5], João Guimarães[6], Isabel Alonso[1], Isabel Silveira[1], Jorge Sequeiros[1,4], José Marques Neves[7], Pedro Serrano[7], M. Carolina Silva[4]

[1]UnIGENe and Centro de Genética Preditiva e Preventiva, IBMC – Instituto de Biologia Molecular e Celular, Universidade do Porto, Portugal; [2]Hospital de São Sebastião, CHEDV, Santa Maria da Feira, Portugal; [3]Hospital de Santo António, CHP, Porto, Portugal ; [4]ICBAS -Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal ; [5]Hospital Maria Pia, CHP, Porto, Portugal ; [6]British Hospital XXI, Lisboa, Portugal ; [7]Ministério da Saúde, Coordenação de Formação em Saúde Pública, Portugal.

Epidemiological data on the hereditary ataxias (HCA) and spastic paraplegias (HSP) are scarce. Our aim is to estimate the prevalence of HCA and HSP and describe the main clinical groups found in a Portuguese population-based survey.
A nationwide, population-based, systematic survey was conducted in Portugal from 1994 to 2004. Multiple sources of information were used (review of clinical files, active collaboration of neurologists and geneticists, and investigation of affected families), but the main source was active collaboration of general practitioners. Patients were examined by the same team of neurologists, using homogeneous inclusion criteria. The clinical data were registered, and appropriate genetic testing was performed. Families without identified mutation were clinically reviewed and grouped by phenotypes for further clinical and genetic research. From 2724 referred patients, 1336 patients were diagnosed with HCA or HSP.

The overall prevalence was 12.9/105 in a population of 10,322 millions. The prevalence of HCA was 5.6/105 for dominant and 3.3/105 for recessive forms. The HSP are less prevalent, 2.4/105 for dominant and 1.6/105 for recessive forms. Machado-Josephdisease (MJD/SCA3) was the most frequent, with a prevalence of 3.1/105. In the dominant HCA group, it was followed by dentatorubro-pallidoluysian atrophy (DRPLA) (0.3/105). Friedreich ataxia and ataxia with oculomotor apraxia (AOA) were the most prevalent recessive HCA, 1.0/105 and 0.4/105 respectively. The most prevalent HSP forms were SPG4 (0.9/105), SPG3 (0.1/105) and SPG11 (0.3/105). This population-based survey covered all the Portuguese territory and mobilized most general practitioners and health centers. To our best knowledge, it was the largest ever performed for HCA and HSP. Prevalence of autosomal dominant ataxias was high, particularly for MJD/SCA3. New disease clusters and multiple undiagnosed families were identified, setting the basis for assistance, prevention and counselling programs. The genetic cause has not been identified in 39.7% of the patients studied.

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(14) Our experience with next generation sequencing of target genes in hereditary spastic paraplegias and spastic ataxias

Andrés Ordóñez-Ugalde[1,2,3], Beatriz Quintáns[1,2], Pilar Cacheiro[1], Francisco Grandas[4], Samuel I Pascual[5], Irene Sanz[6], Juan D Bautista[7], Julio Pardo[8], Ángel Carracedo[1,3], María-Jesús Sobrido[1,2]

[1]Fundación Pública Galega de Medicina Xenómica, Instituto de Investigaciones Sanitarias Santiago de Compostela (IDIS)-SERGAS, Spain; [2]Centro Investigación en Red de Enfermedades Raras (CIBERER), Spain; [3]Instituto de Biología Molecular y Celular (IBMC), Porto, Portugal; [4]Movement Disorders Unit, Instituto Investigación Sanitaria-Hospital General Universitario Gregorio Marañón, Madrid, Spain; [5]Department of Pediatric Neurology, Hospital Universitario La Paz, Madrid, Spain; [6]Neurology Department, Hospital Universitario La Paz, Madrid, Spain; [7]Asociación Española de Paraparesia Espástica Familiar (AEPEF), Spain; [8]Neurology Department, Hospital Clínico Universitario Santiago de Compostela, Spain.

Next generation sequencing (NGS) is moving from research to diagnostic setting. The ability to generate enormous amount of data at an affordable cost is revolutionizing analysis of hard-to-diagnose genetic disorders. In order to establish routine diagnostic protocols, more data on the performance and efficiency of NGS - both target and whole exome/genome analysis - are still needed. Hereditary spastic paraplegias (HSP) and spastic ataxias (SA), characterized by broad genetic and clinical heterogeneity, currently demand laborious gene-by-gene analyis.
Target gene NGS of HSP/SA patients using solution-based enrichment (SureSelect®) and the SOLiD® platform. We included 98 patients with unknown etiology in whom SPAST and BSCL2 mutations had been ruled out, and controls with known mutations. Hybridization probes for all exons (~200 Kb) of 30 genes causing HSP and overlapping phenotypes were designed with SureDesign® (Agilent), paired-end sequencing was carried out in the SOLiD5500xl®. Reads were aligned to hg19 with LifeScope® and GATK using default parameters, variants were annotated with ANNOVAR and exonic/splicing variants with MAF ≤0.02 were filtered against dbSNP135 and 1000 Genomes data using an in-house R script. The IGV viewer was used for further selection of changes to be validated by Sanger sequencing and co-segregation. The resulting variants were divided into likely pathogenic (including previously known), likely non-pathogenic and of unknown significance.
The hybridization step failed for 22 samples. Positive control changes were correctly annotated. Coverage ≥40X was obtained for 89% of the target regions, ranging from 51% (GJC2) to 99% (ZFYVE26). With the described filtering criteria we obtained 6 (sd 2) variants per patient. Subsequent manual curation left an average of 2 variants per case, 10 cases with no candidate variant. Pathogenic variants were detected in 15 out of 76 cases finally analyzed (20%): ATL1 (3), SPG 11 (1), SPG7 (1), ABCD1 (3), CYP7B1 (3), REEP1 (2), KIF5A (1), SACS (1). Potentially causal variants were present in 7 additional patients: ABCD1 (1), SACS (2), SPG11 (2), SPG8 (1), L1CAM (1), leaving 54 (71%) of patients with still unknown etiology.
Target NGS is a cost-efficient diagnostic approach for HSP/SA, enabling simultaneous screening of genes causing overlapping syndromes. Performance is heterogeneous across genomic regions and may depend on enrichment and sequencing protocols, as well as on parameters applied for variant detection and filtering. The identified genetic alterations must be validated with other methods and the correct interpretation of the observed variants remains a main challenge. The high frequency of mutations in ABCD1 indicates that adrenoleukodystrophy is not sufficiently ruled out during routine diagnostic workup, and highlights the need to include this gene in NGS protocols for HSP and SA.

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(15) Role of REEP1 (SPG31) in mitochondrial structure and energetic function

Julie Lavie[1], Su Melser[1], Guilhem Solé[1,2], Didier Hannequin[3], Stanislas Lyonnet[4], Sylvie Forlani[5,6,7], Alexis Brice[5,6,7,8], Giovanni Stevanin[5,6,7,8], Alexandra Durr[5,6,7,8], Cyril Goizet[1], Rodrigue Rossignol[1], Giovanni Bénard[1]

[1]Laboratoire Maladies Rares : Génétique et Métabolisme (MRGM)- EA 4576 Université Bordeaux Segalen, Bordeaux, France ; [2]CHU Bordeaux, Pôle des Neurosciences Cliniques, Pessac, France ; [3]INSERM, U614, Service de Neurologie, CHU Rouen, France Neurologie, CHU Rouen ; [4]Université Paris Descartes and APHP, Département de Génétique, Hôpital Necker-Enfants Malades, Paris, France ; [5]INSERM, U675, Paris, France ; [6]Université Pierre et Marie Curie - Paris 6, UMR-S975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, F-75013 Paris, France ; [7]CNRS, UMR7225, Paris, France ; [8]APHP, GHU Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Fédération de Génétique, France.

Mutations in REEP1 are associated with an autosomal dominant HSP, SPG31. In a previous study, we showed that fibroblasts and muscle biopsies from one patient with a heterozygous truncative mutation of REEP1 (c.106delG ; p.V36SfsX4) displayed defective mitochondrial energy production as well as altered structure of mitochondrial network.We now confirme an alteration of mitochondrial function and architecture using fibroblasts from additional patients with missense mutations (c.166G>A, p.D56N and c.124T>C, p.W42R, respectively). Interestingly, we also find that SPG31 patients reveal higher level of mitochondrial DNA (around 3-fold increase) compared to controls. To analyze whether REEP1 is involved in mitochondrial physiology, we have expressed different isoforms of REEP1 in HeLa cells and we demonstrate different localization profiles for REEP1. We observed that one pool of REEP1 strongly locates to mitochondria inducing the organelle fragmentation. Our results validate the role of REEP1 in mitochondrial functions.

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(16) REEP and reticulon mutant phenotypes in *Drosophila*

Niamh C. O'Sullivan, Martin Stofanko, Belgin Yalçın, Liwen Xu, Cahir J. O'Kane

Department of Genetics, University of Cambridge, Cambridge, UK.

Several causative genes for hereditary spastic paraplegia encode proteins with intramembrane hairpin loops that contribute to curvature of the endoplasmic reticulum (ER), but the relevance of this function to axonal degeneration is not understood. These genes include *reticulon2* and *REEP1*. In contrast to mammals, *Drosophila* has only one widely expressed reticulon ortholog, *Rtnl1*, and two REEP othologs, ReepA and ReepB. We therefore used *Drosophila* to test the importance of these proteins in ER organization and axonal function. Rtnl1 and ReepB distribution overlapped with that of ER, but in contrast to rough ER, was enriched in axons. Commonly used ER markers gave at best only weak labeling of axons, likely due to their association with the protein traffic or folding characteristic of rough ER. In contrast, proteins thought to be localised in smooth ER showed strong labeling in axons. Loss of Rtnl1 or *reepA*, *reepB* double mutants led to expansion of sheet ER in larval epidermis. Loss of Rtnl1 also caused abnormalities specifically in the distal portions of longer motor neuron axons and terminals, including in smooth ER, the microtubule cytoskeleton, and mitochondria. In contrast proximal axon portions and shorter axons appeared unaffected. Our results show a preferential requirement for reticulon function in distal longer axons, analogous to the preferential susceptibility of distal long axons to degeneration in HSP, and support a model in which spastic paraplegia can be caused by impairment of axonal smooth ER. Our experimental paradigm will allow us to test the requirements for any HSP genes that are conserved in Drosophila, for roles in organisation of axonal ER.

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(17) Paraplegin mutations cause progressive external ophthalmoplegia with multiple mitochondrial DNA deletions in skeletal muscle

Iselin Marie Wedding[1, 2], Jeanette Koht [2, 6], Gia Tuong Tran[4, 5], Doriana Misceo [2,3], Kaja Selmer[2,3], Asbjørn Holmgren[2,3], Eirik Frengen[2,3], Laurence Bindoff[4, 5], Chantal ME Tallaksen[2, 1], Charalampos Tzoulis[4, 5]

[1]Department of Neurology, Oslo University Hospital, Ullevål, 0407 Oslo, Norway; [2]Department of Medical Genetics, Oslo University Hospital, Ullevål, 0407 Oslo, Norway; [3]University of Oslo, Faculty of Medicine, Oslo, Norway; [4]Department of clinical Medicine, University of Bergen, Bergen, Norway;

[5]Department of Neurology, Haukeland University Hospital, Bergen, Norway; [6]Department of Neurology, Drammen Hospital, Vestre Viken Health trust.

Spastic paraplegia 7 (SPG7) is an autosomal recessive form of Hereditary Spastic Paraplegia (HSP) caused by mutations in the SPG7 gene, which encodes paraplegin, a member of the AAA family of ATPases, located at the inner mitochondrial membrane. Paraplegin is involved in the processing of mitochondrial proteins. Respiratory chain dysfunction has been reported in muscle in SPG7 patients, but its molecular aetiology and pathogenic role remains unknown. We report a novel SPG7 mutation in two Norwegian families presenting with a phenotype consistent with mitochondrial disease, and study the disorder`s molecular pathogenesis.
Four patients from two Norwegian families with a phenotype of progressive external ophthalmoplegia (PEO) and spastic paraplegia were examined clinically. Muscle histology and molecular mitochondrial DNA studies were performed in one of the index patients, an additional SPG7 patient from an unrelated family and ten controls.
We found a novel SPG7 missense mutation, c.2102A>C, p.H701P, which was homozygous in the first family and compound heterozygous in trans with the known pathogenic mutation c.1454_1462del in the second family. Molecular studies showed multiple mitochondrial DNA (mtDNA) deletions and deficiency of respiratory complexes I, III and IV in skeletal muscle.
We report a novel SPG7 mutation causing a complex HSP phenotype with PEO, a common mitochondrial disease phenotype. Moreover, our findings reveal novel aspects of the molecular pathogenesis of SPG7. We show that SPG7 mutations lead to respiratory dysfunction by causing secondary mtDNA damage and therefore link paraplegin to the homeostasis of the mitochondrial genome.

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(18) Molecular analysis of FA2H gene mutations in patients with spastic paraplegia

D. Di Bella[1], E. Sarto[1], C. Mariotti[1], M. Plumari[1], L. Nanetti[1], G. Baranello[2], L. Chiapparini[3], F. Taroni[1]

[1]Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [2]Unit of Developmental Neurology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [3]Unit of Neuroradiology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy.

Hereditary spastic paraplegias (HSP) are a clinically and genetically heterogeneous group of neurodegenerative disorders. Pure and complicated forms of the disease have been described. SPG35 is an autosomal recessive HSP (AR HSP) caused by mutations in the gene encoding fatty-acid 2-hydroxylase (FA2H), an enzyme that produces free 2-hydroxy fatty acids, which are incorporated into ceramide, the precursor of galactosylceramides, essential lipid components of normal myelin. FA2H mutations have recently been associated not only to complicated forms of spastic paraparesis, but also to leukodystrophy and Neurodegeneration with Brain Iron Accumulation (NBIA). The objective is to screen for FA2H mutations a group of Italian patients with HSP
One hundred and eighty-six (186) HSP index patients, including sporadic and patients from families with autosomal recessive pattern of inheritance, were investigated for SPG35 mutations by direct sequencing of the FA2H gene. A subgroup of patients were also screened for micro-rearrangements in the FA2H gene by real-time quantitative PCR to assess the frequency of deletions/duplications. Four novel FA2H mutations were detected in 4 probands from 3 families. Two novel missense mutations (Y34C, T207M) were detected in one family, with 2 affected sibs carrying both variations and 2 healthy brothers heterozygous for the Y34C only or homozygous for the normal allele, respectively. The 2 affected brothers presented with adult-onset (@ 32 and 40 yrs) HSP and manifested, a few years later, speech impairment and cognitive decline. Disease course was slowly progressive and neurological examination at age 48 and 51 demonstrated severe lower-limb spasticity, Babinski sign, pes cavus, distal muscle weakness, dysarthria, ophthalmoplegia, and dementia. Electroneurography showed normal conduction velocities. MRI demonstrated prominent global atrophy (including cerebellum, brainstem, cerebral hemispheres, and corpus callosum) with enlarged ventricles. Notably, no iron deposits were present. One missense (P148L) and one nonsense (W226X) homozygous mutations were identified in 2 sporadic patients, one of whom born to consanguineous parents. Both patients had a childhood onset with spasticity and showed a severe disease progression. MRI demonstrated initial cerebellum atrophy, followed by global atrophy and mild leukodystrophy. There was no hypointensity of globus pallidus nor evidence of brain iron deposits. None of the sequence variants was present in 300 unrelated control chromosomes. No CNVs were identified.
We have identified compound heterozygosis for two missense FA2H mutations in one adult-onset AR family, and 2 homozygous mutations in 2 childhood-onset patients with complicated form of HSP. Our findings indicate that, although it represents a rather rare form, SPG35 should be considered in complicated AR-HSP phenotypes even in the absence of brain iron accumulation.

(19) Genetic and functional studies of autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)

Julie Pilliod[1], Julie Lavie[1], Isabelle Coupry[1], E Maurat, Mathieu Anheim[2], M Barth[3], A Guichet[3], C Rooryck-Tambo[1], B Arveiler[1], Sylvie Forlani[2], Fabien Lesne[2], Fanny Mochel[2], Karine N'Guyen[4], Gaétan Lesca[5], Alexis Brice[2], Didier Lacombe[1], Giovanni Stevanin[2], Aalexandra Durr[2], Rodrigue Rossignol[1], G Benard[1], Cyril Goizet[1]

[1]Univ. Bordeaux, Maladies Rares : Génétique et Métabolisme (MRGM), EA 4576, F-33000, Bordeaux, France ; [2]Pitié-Salpêtrière Hospital, INSERM/UPMC UMR_S975, F-75013, Paris, France; [3]CHU Angers, Service of Genetics, F-49100, Angers, France; [4]Timone Hospital, Department of Medical Genetic, F-13000, Marseille, France; [5]CHU Lyon, Service of Genetics, F-69677, Lyon, France.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is the second most frequent form of hereditary spastic ataxia and is caused by mutations in the *SACS* gene encoding sacsin. Previous subcellular localization studied demonstrated that 30% of sacsin is localized to the mitochondria but its specific function is still unknown.
We have searched for mutations by direct sequencing and customized CGH array in *SACS* in a series of 315 patients affected by progressive spastic ataxia with age at onset < 45 years. We identified 39 mutations (13 missenses and 26 truncating) in 29 ARSACS' patients (9% of the tested patients). A search for phenotype-genotype correlations is in progress.
We obtained primary cultures of three patients' fibroblasts in order to perform functional analyses of sacsin. Two patients, P51-3 and P02-6, carries two heterozygous nonsense mutations (p.L1180LfsX8; p.K3747X and p.V3545EfsX3; p.R3792X, respectively) and the other, P16-5, is homozygous for a missense mutation (p.R272H). The mitochondrial network appeared quantitatively altered (with a decrease of 50% of the global mitochondrial mass) and revealed hyperfused tubules. We observed an abnormal mitochondrial shape with the presence of rackets and bubbles in the three patients. We also began to study potential interactions of sacsin with partners, particularly with proteins involved in the control of mitochondrial dynamics such as DRP1.

(20) Autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS): expanding the genetic, clinical and imaging spectrum

AS Soehn[3,14], M Synofzik[1,2,14], J Gburek-Augustat[4,14], J Schicks[1,2,14], KN Karle[1,2,14], R Schüle[1,2,14], TB Haack[5], M Schöning[4,14], S Biskup[1,2,6,14], S Rudnik-Schöneborn[7], J Senderek[7,8], K-T Hoffmann[9], P MacLeod[10], J Schwarz[11]; B Bender[12,14], S Krüger[13], F Kreuz[13], P Bauer[3,14], L Schöls[1,2,14]

[1]Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, University of Tübingen, Germany; [2]German Research Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany; [3]Institute of Medical Genetics and Applied Genomics, University of Tübingen, Germany; [4]Department of Neuropediatrics, University of Tübingen, Germany; [5]Institute of Human Genetics, Technische Universität München, Germany; [6]CeGaT GmbH, Center for Genomics and Transcriptomics, Tübingen, Germany; [7]Institute of Human Genetics, RWTH Aachen University, Aachen, Germany; [8]Department of Neurology, Friedrich-Baur Institute, Ludwig-Maximilian University Munich, Germany; [9]Department of Neuroradiology, University of Leipzig, Germany; [10]Medical Genetics Clinic, Victoria General Hospital, Canada; [11]Hospital Mühldorf am Inn, Germany; [12]Department of Neuroradiology, University of Tübingen, Germany; [13]Gemeinschaftspraxis für Humangenetik, Dresden, Germany; [14]Rare Disease Center Tübingen, Germany.

Mutations in *SACS*, leading to autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), have been identified as a frequent cause of recessive early-onset ataxia around the world. Here we aimed to enlarge the spectrum of *SACS* mutations outside Quebec, to establish the pathogenicity of novel variants, and to expand the clinical and imaging phenotype. We identified 11 index patients harbouring 17 novel *SACS* variants. 9/11 patients harboured two variants of at least probable pathogenicity which were not observed in controls. These 9 patients accounted for 11% in our series of unexplained early onset ataxia subjects. While most patients (7/9) showed the classical ARSACS triad (ataxia, spasticity and peripheral neuropathy), we demonstrate that each feature of this triad might be missing in ARSACS. Nevertheless, characteristic MRI features – which also extend to supratentorial regions and involve the cerebral cortex – will help to establish the diagnosis in most cases.

(21) Sacsin knockout mice manifest clinical and pathological features of ARSACS

R. Larivière[1], R. Gaudet[1], P. Chang[3], T. Conte[1], B. Gentil[2], K. Leclerc-Désaulniers [1], M.J. Dicaire[1], H.D. Durham[2], E.A. Shoubridge[2], H.M. McBride[2], K. Gehring[4], P.S. McPherson[2], R.A. McKinney[3], B. Brais[1]

[1]Laboratory of neurogenetics of motion, Departments of Neurology and Neurosurgery and Human Genetics, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada; [2]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada; [3]Department of Pharmacology, McGill University, Montréal, Quebec, Canada; [4]Department of Biochemistry, McGill University, Montréal, Quebec, Canada.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early-onset neurodegenerative disorder caused by mutations in the *SACS* gene. Over 140 mutations have now been identified world-wide in *SACS* and are thought to cause a loss of sacsin function. To better understand the course of the disease, we generated and characterized sacsin knockout (KO) mice. On behavioral testing, KO mice display a clinical phenotype attributable to motor and cerebellar dysfunction, including a balance deficit, loss of coordination and distal limb weakness. KO mice also display an ataxic gait and tremor later in life. This evolving clinical phenotype is accompanied by a progressive loss of Purkinje cells mostly in the anterior cerebellar lobules, a feature also observed in patients. The absence of sacsin results in a distinct histological staining of many neuronal populations, most notably the Purkinje cells, deep cerebellar neurons, cortical pyramidal cells, thalamic and spinal motor neurons. These neurons present abnormal neurofilament protein distribution, reminiscent of the human pathology. This line of sacsin knockout mice therefore is an excellent model for ARSACS that can be used for preclinical trials and to explore the pathophysiology of this increasingly diagnosed recessive ataxia.

(22) GSN, a new candidate gene in autosomal dominant spastic cerebellar ataxia

M. Coutelier[1,2], M-L. Monin[1], C. Gautier[1], C. Tesson[1,3], T. Esteves[1], S. Koskelainen[4], F. Charbonnier-Beaupel[1], M. Labussière[1], E. Mundwiller[1], S. Valleix[5], K. Tahiri[1], D. Langui[1], J. C. Corvol[1], S. Kiuru-Enari[4], K. El Hachimi[1,3], A. Brice[1,6], F. Darios[1], A. Durr[1,6], G. Stevanin[1,3,6]

[1]Université Pierre et Marie Curie-Paris 6, UMR-S975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, F-75013 Paris, France ; Inserm, U975, F-75013 Paris, France ; Cnrs, UMR 7225, Paris, France ; [2]Institut de Duve, Brussels, Belgium; [3]Ecole Pratique des Hautes Etudes, Paris, France ; [4]Biomedicum, Helsinki, Finland; [5]APHP, Groupe Hospitalier Cochin, Paris, France; [6]APHP, CHU Pitié-Salpêtrière, Fédération de Génétique, Paris, France.

Autosomal dominant (AD) cerebellar ataxias (CA) are severe neurodegenerative disorders, characterized by movement incoordination, variably associated with other neurological signs. As of today, 35 loci and 20 genes have been described in ADCA, but the causative gene is still unknown in half of the patients. We report a large French family with adult-onset rapidly progressive ataxia, associated with pyramidal signs, spasticity, decreased pallaesthesia and ophthalmoplegia. After exclusion of polyglutamine expansions or mutations in the commonest causative genes, susceptibility loci including about 450 genes were identified through linkage analysis. Analysis of variants obtained from exome sequencing in two patients, filtered with data from 2 healthy controls and 6 patients with other neurodegenerative disorders, and cosegregation verification, lead to the identification of a missense mutation in the *GSN* (gelsolin) gene that was shown to appear *de novo* in the affected grandfather. The variant was not found in 380 healthy controls or in online databases. A point mutation in *GSN* is already responsible for Finnish amyloidosis. However, the mutation described here differs, and the phenotype was excluded in our family through immunohistochemistry of patient skin sample. Mutation screening in 39 patients with AD spastic ataxia revealed two new potential variants. Further screening is ongoing for another 95 patients, with a broader clinical picture. Functional studies aiming at the cytoskeleton function of fibroblasts, including immunofluorescent staining and migration tests are ongoing to validate and understand the causative nature of the mutations.

(23) Mutation of plasma membrane Ca2+ ATPase isoform 3 in a family with X-linked congenital cerebellar ataxia impairs Ca2+ homeostasis

Ginevra Zanni[1], Tito Calì[2], Vera M. Kalscheuer[3], Denis Ottolini[4], Sabina Barresi[1], Nicolas Lebrun[5], Luisa Montecchi-Palazzi[6], Hao Hu[3], Jamel Chelly[5], Enrico Bertini[1], Marisa Brini[2], Ernesto Carafoli[7]

[1]Unit of Molecular Medicine for Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital,(IRCCS), Rome, Italy; [2]Department of Comparative Biomedicine and Food Science, University of Padua, Italy; [3]Max Planck Institute for Molecular Genetics, Department of Human Molecular Genetics,Berlin, Germany; [4]Department of Biomedical Sciences, University of Padua, Italy; [5]Department of Genetic and Development, Institut Cochin, Université Paris Descartes, CNRS-UMR8104, Paris, France; [6]European Bioinformatics Institute (EBI), Wellcome Trust Genome Campus, Hinxton, Cambridge UK; [7]Venetian Institute for Molecular Medicine, 35129 Padua, Italy.

Ca2+ in neurons is vital to processes such as neurotransmission, neurotoxicity, synaptic development, and gene expression. Disruption of Ca2+ homeostasis occurs in brain aging and in neurodegenerative disorders. Membrane transporters, among them the calmodulin (CaM)-activated plasma membrane Ca2+ ATPases (PMCAs) that extrude
Ca2+ from the cell, play a key role in neuronal Ca2+ homeostasis. Using X-exome sequencing we have identified a missense mutation (G1107D) in the CaM-binding domain of isoform 3 of the PMCAs in a family with X-linked congenital cerebellar ataxia.
PMCA3 is highly expressed in the cerebellum, particularly in the presynaptic terminals of parallel fibers–Purkinje neurons. To study the effects of the mutation on Ca2+ extrusion by the pump, model cells (HeLa) were cotransfected with expression plasmids encoding
its mutant or wild-type (wt) variants and with the Ca2+-sensing probe aequorin. The mutation reduced the ability of the PMCA3 pump to control the cellular homeostasis of Ca2+. It significantly slowed the return to baseline of the Ca2+ transient induced by an inositol-trisphosphate (InsP3)-linked plasma membrane agonist. It also compromised the ability of the pump to oppose the influx of Ca2+ through the plasma membrane capacitative channels.

Reference: **Zanni G** et al Proc Natl Acad Sci (PNAS) U S A. 2012 Sep 4;109(36):14514-9.

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(24) *A* gene identified as a novel causative gene of X-linked ataxia using LEC strategy

Zhao Chen[1*], Yu-ting Shi[1*], Zhan-fang Sun[1], Jun-ling Wang[1], Zheng-mao Hu[2], Qian Pan[2], Kun Xia[2], Bei-sha Tang[1,2,3], Hong Jiang[1,3]

[1]Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, P. R. China; [2]State Key Laboratory of Medical Genetics, Central South University, Changsha, Hunan 410078, P. R. China; [3]Neurodegenerative Disorders Research Center, Central South University, Changsha, Hunan 410008, P. R. China.

** Contributed equally to this work.*

To date, more than 30 causal genes responsible for X-linked ataxias have been identified. Recently, we applied a combined strategy of Linkange Analysis/Exome sequencing/CNV Analysis (LEC) to have found a novel causative gene of X-linked ataxias, *A*(It is still kept secret before publication). We sequenced the whole exome of three patients in a Chinese three-generation family with X-linked ataxias that was characterized by progressive ataxia and hearing loss, and found a novel missense mutation, c.1213G>A transition (E405K), in exon 12 of *A* gene. This base substitution occurred at a highly conserved region of *A* gene and completely co-segregated with the phenotype in this kindred. The novel putative pathogenic variation, predicted to have a functional impact, was then verified via Sanger sequencing and not detected in 500 healthy control individuals. The exome sequencing results were also validated by linkage analysis as well as CNV analysis. In sum, our finding of the novel potential causative variant is driving us to undergo the functional investigation to reveal important roles of *A* gene and its related pathogenesis.

Key words: X-linked ataxias; exome sequencing; linkage analysis; CNV analysis; *A* gene mutation

ABSTRACTS SELECTED FOR POSTER PRESENTATION

(25) Addressing Mitochondrial Function in a mouse model of Friedreich's Ataxia (FRDA)

Rosella Abeti[1], Michael Parkinson[1], Chiranjeevi Sandi[2], Mark Pook[2], Andrey AY Abramov[1] and Paola Giunti[1]

[1]Department of Molecular Neuroscience, UCL, Institute of Neurology, Queen Square, London, UK; [2]Biosciences Division School of Health Sciences & Social Care, Heinz Wolff Building, Brunel University, Kingston Lane, Uxbridge, UK.

Friedreich's ataxia (FRDA) is an autosomal recessive disorder caused by GAA repeat expansion mutation within intron 1 of the FXN gene (Campuzano et al, 1996). The effect of the GAA expansion mutation reduces the expression of frataxin leading towards dramatic changes at the cellular level (Pandolfo and Pastore, 2009). Frataxin is a mitochondrial protein involved in iron-sulphur cluster and heme biosynthesis (Pandolfo and Pastore, 2009).
Its loss of function leads to crucial changes in iron metabolism that inhibits mitochondrial respiration and promotes production of reactive oxygen species (ROS), causing mitochondrial dysfunction, oxidative stress and subsequent mitochondrial iron accumulation (Pandolfo and Pastore, 2009), resulting in neuronal atrophy. Since the cerebellum is one of the primary sites of the pathology (Koeppen et al, 2007), we now investigate the mitochondrial activity in granular and glial cells, taken from the cerebellum of a FRDA mouse model. The FRDA mouse model used was generated by the Pook lab (Al Madhawi, 2004) based upon expression of human FXN transgene containing two GAA repeat expansions (90 and 190) within a mouse frataxin null background which exhibited features of FRDA-like disease (Al-Mahdawi et al, 2006), making this model extremely useful for investigations in the pathophysiology of FRDA disease. Confocal microscopy was used to investigate an array of functional assays to characterize the possible difference in mitochondrial activity between control and FRDA cells. Here we studied mitochondrial membrane potential ($\Delta\Psi_m$) and its maintenance, mitochondrial NADH redox state, FAD+ pool, and lipid peroxidation in co-culture of granular and glial cells. These assays showed that FRDA granular cells have a decreased basal level of $\Delta\Psi_m$, which cannot be maintained during acute oligomycin treatments, compared to Control and FRDA cultures. This may be caused by the lack of substrates, for the electron transport chain (ETC) and/ or the reverse activity of the F1F0ATPase (complex V; Nicholls, 1981). Our studies show mitochondrial dysfunction in granular cells of the FRDA mouse model used. This will help the understanding of the frataxin role in in mitochondrial physiology.

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(26) Modelling Spinocerebellar ataxia type 7 in the mouse brain

Sandro Alves[1,2,3,4], Thibaut Marais[5], Martina Marinello[1,2,3,4], Khalid El Hachimi[1,2,3,4], Giovanni Stevanin[1,2,3,4], Alexis Brice[1,2,3,4], Annie Sittler[1,2,3,4], Martine Barkats[5]

[1]Université Pierre et Marie Curie-Paris 6, UMR_S 975, 75013 Paris, France; [2]Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, F-75013 Paris, France; [3]Institut National de la Santé et de la Recherche Médicale, U 975, 75013 Paris, France; [4]Centre National pour la Recherche Scientifique, UMR 7225, 75013 Paris, France; [5]UPMC-AIM UMR S974, INSERM U 974, CNRS UMR 7215, Institut de Myologie, Université Pierre et Marie Curie Paris 6, 75013 Paris, France.

Spinocerebellar ataxia type 7 is a dominantly inherited neurodegenerative disorder. The mutation has been identified as a CAG-trinucleotide repeat expansion in the coding region of the *ATXN7* gene, which encodes the ataxin-7 (ATXN7) protein.
In the present work we engineered lentiviral vectors (LV) encoding either wild-type or mutant truncated human ATXN7. The goal is to develop a SCA7 *in vivo* model, to study the effects of human ATXN7 overexpression in the mouse cerebellum known to be affected in SCA7.
LV encoding mutant or wild-type human ATXN7 were injected in the brain of 4-week-old C57/BL6 adult mice and the animals were tested for behavioral deficits and neuropathological abnormalities 2, 8 and 12 weeks after injection.
We showed that human mutant ATXN7 was expressed in the cerebellum (preferentially in Purkinje cells and granule cells) and mediated within a short time frame (8 weeks), the development of a behavioral phenotype including reduced balance and motor coordination.
Cerebellar neuropathology was confirmed with loss of calbindin, MAP-2 and neurofilaments expression, associated to the presence of misfolded ATXN7 immunoreactive for ubiquitin, heat-shock proteins (Hsp40, Hsp70, Hsp90 and Hsc70) and the RNA-binding proteins FUS/TLS and TDP-43.

Expression of the pathological protein was accompanied with increase of the GFAP and Iba1 neuroinflammation markers. No neuropathological changes were observed upon wild-type ATXN7 overexpression, highlighting the specificity of the mutant ATXN7 induced pathological features.
The cerebellar dysfunction triggered by mutant ATX7 was confirmed in SCA7$^{266Q/5Q}$ knock-in mice and postmortem tissue from SCA7 patients, also showing robust loss of neuronal markers (calbindin and neurofilaments), formation of pycnotic nuclei associated to increased expression of neuroinflammation markers.
This study demonstrates that LV can mediate high and sustained (3-4 months) expression of mutant ATXN7 in the adult mouse cerebellum, thus allowing to better understand the specific contribution of this brain region without interference of other regions in SCA7 neuropathology.

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(27) Disruption of Drp1 mediated mitochondrial fission underlies Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

Teisha Bradshaw[1], Emma Duncan[1], David Parfitt[1], Sascha Vermeer[2] and J Paul Chapple[1]

[1]Centre for Endocrinology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [2]The Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early onset neurodegenerative disease resulting from mutations in the *SACS* gene. Prominent features include pyramidal spasticity and cerebellar ataxia. *SACS* encodes sacsin, a large modular protein with domains linking it to molecular chaperone and protein degradation systems (Parfitt et al., 2009). We have shown that sacsin localizes to the cytosolic face of mitochondria in non-neuronal cells and primary neurons (Parfitt et al., 2009, Girard et al., 2012). Sacsin knockdown leads to an overly interconnected and functionally impaired mitochondrial network, with accumulation of mitochondria in the soma and proximal dendrites of neurons (Girard et al., 2012). Importantly, ARSACS patient fibroblasts also have altered mitochondrial networks that appear collapsed and more interconnected. Sacsin interacts with dynamin-related protein 1 (Drp1), a large GTPase that is essential for mitochondrial fission in mammalian cells. At sites of fission Drp1 self-assembles into oligomers that wrap around mitochondria and cause scission of the mitochondrial membrane by a GTP hydrolysis dependent process. In cells lacking sacsin, including ARSACS patient fibroblasts, we have observed a reduction in the incidence of mitochondrial associated Drp1 foci, this phenotype persists even when fission is induced by drug treatment. Our data identifies disrupted mitochondrial dynamics as the likely cellular basis for ARSACS and suggests sacsin may function as a chaperone in the recruitment, stabilisation or activation of Drp1 at sites of mitochondrial division. Interestingly, disrupted mitochondrial dynamics is a feature of more common neurodegenerative diseases such as Alzheimer's and Parkinson's.

References : Parfitt DA et al (2009) Hum Mol Genet 18:1556-1565.

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(28) Ataxia caused by a new mutation in the gene TTBK2: first Portuguese family with spinocerebellar ataxia type 11?

Ana Filipa Brandão[1], Ana Paula Sousa[2], Isabel Alonso[1,3], Jorge Sequeiros[1,3,4]

[1]CGPP, Instituto de Biologia Molecular e Celular (IBMC), University of Porto, Porto, Portugal; [2]S. Neurologia, Hosp. Santo António dos Capuchos, Portugal; [3]UnIGENe, IBMC, University of Porto, Porto, Portugal; [4]ICBAS, University of Porto, Porto, Portugal.

The autosomal dominant spinocerebellar ataxias (SCAs) are a group of neurodegenerative disorders, clinically and genetically heterogeneous, characterized by uncoordinated gait, resulting from cerebellar degeneration, and may be associated with other signs and symptoms. SCA11 is a rare subtype of ataxia, representing around 2% of cases. Clinically, in addition to cerebellar signs, is characterized by eye movement abnormalities, including ophthalmoparesis and horizontal and vertical nistagmus. SCA11 presents with early onset and slow progression. It is caused by mutations in the *TTBK2* gene, located on chromosome 15q24-21, which encodes a serine/threonine kinase that phosphorylates tau and tubulin proteins.
We report a male patient presenting with progressive gait imbalance with onset at 48 years old. Neurological examination revealed ataxia, dysmetria, abnormal proprioception and nystagmus. Brain MRI showed cerebellar atrophy. This patient sister is also affected with ataxia and neuropathy.
In this patient, acquired ataxias, dominant ataxias caused by triplet expansions, as well as recessive ataxias (AOA1, AOA2 and Friedreich's ataxia), were excluded. *TTBK2* mutation analysis was

performed by PCR amplification of all exons and flanking intronic regions, followed by direct sequencing.
A novel missense mutation in exon 8 of the *TTBK2* gene, consisting on the substitution of a leucine for a phenylalanine at position 209, was detected. The bioinformatic analysis suggests it is pathogenic as this is a highly conserved residue.
According to the literature, this would be the first SCA11 mutation reported in Portuguese patients and it is therefore important to confirm familial segregation of the mutation. The molecular diagnosis will allow appropriate genetic counseling to this patient and at-risk relatives.

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(29) Screening for mutations in ARSACS Portuguese patients

Ana Filipa Brandão[1], Carmen Costa[2], Teresinha Evangelista[3], Isabel Alonso[1,4], Jorge Sequeiros[1,4,5]

[1]CGPP, Instituto de Biologia Molecular e Celular (IBMC), University of Porto, Porto, Portugal; [2]S. Neurologia, Hosp. Pediátrico de Coimbra, Centro Hosp. e University of Coimbra, Coimbra, Portugal; [3]S. Neurologia, Hospital de Santa Maria, Lisboa, Portugal; [4]UnIGENe, IBMC, University of Porto, Porto, Portugal; [5]ICBAS, University of Porto, Porto, Portugal.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a complex neurodegenerative disorder and is clinically characterized by a progressive cerebellar syndrome, peripheral neuropathy and spasticity. Disease onset is usually in early childhood, often leading to delayed walking due to gait unsteadiness in very young infants. *SACS* is the only gene responsible for ARSACS and is located on chromosome 13q12. This gene encodes *sacsin* suggested to be involved in protein quality control. Mutations in this gene include deletions/insertions, missense, nonsense and splice-site mutations.
We have clinically ascertained 17 Portuguese patients presenting ataxia and spastic paraplegia and performed *SACS* mutation analysis. PCR amplification of all exons and flanking intronic regions was performed, followed by bidirectional direct sequencing.
We have identified three different *SACS* mutations, all novel: one nonsense and two deletions that result in frameshift mutations. The nonsense mutation replaces an arginine by a stop codon at position 1645 and the deletions are located at positions 3066 (one base deleted) and 6633 (two bases deleted).
In this study, we enlarge the *SACS* mutational spectrum. We have identified *ARSACS* mutations in 18% of the studied cases. The 3 positive cases clinically present ataxia and spastic paraplegia with an early age at onset. Additionally, molecular confirmation of the clinical diagnosis in patients with ARSACS allows proper genetic counselling to patients and their relatives.

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(30) Molecular analysis of KIF5A gene mutations in patients with spastic paraplegia

S. Caldarazzo[1], E. Sarto[1], C. Mariotti[1], L. Nanetti[1], D. Pareyson[2], G. Lauria[3], E. Salsano[2], D. Di Bella[1], F. Taroni[1]

[1]Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [2]Unit of Neurology 8, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [3]Unit of Neuromuscular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy.

Hereditary spastic paraplegias (HSP) are a clinically and genetically heterogeneous group of neurodegenerative disorders. Pure and complicated forms of the disease have been described. About half of HSP cases result from autosomal dominant mutations in spastin (SPG4), atlastin-1 (SPG3A), or REEP1 (SPG31) genes. Mutations in the KIF5A gene have been reported to be a rather frequent cause (approx. 10%) of autosomal dominant (AD) pure or complicated HSP phenotypes (SPG10) in French and Italian population. The KIF5A gene encodes the neuronal kinesin heavy chain implicated in the anterograde axonal transport. Most mutations identified so far (all missense except one deletion) are located into the motor domain, with the exception of one mutation identified in the neck region and one in the stalk domain of the protein. We screened a large cohort of Italian patients with spastic paraplegia for mutations in the motor domain of KIF5A. The motor domain (exon 1-11) of KIF5A was analysed by high-resolution melting (HRM) analysis and/or direct sequencing in 350 unrelated HSP index cases, including 185 AD and 165 sporadic cases, negative for SPG4 mutations.
We identified 10 different missense mutations, 4 of which are novel, in 11 HSP probands. All novel mutation are not present in more than 350 normal alleles. In silico analysis revealed that all mutations are predicted to damage protein structure or function. Six mutations were identified in AD-HSP probands, but segregation could be assessed only in two families. Of the remaining cases, 3 were apparently sporadic while for 2 probands family-history was either not available or unclear. Our

patients showed a wide-range of age-at-onset with 3 patients exhibiting a childhood onset and the others in the 3rd-4th decade, with 2 patients with a later onset (>50 yrs). Interestingly, 7/11 patients had a complex phenotype with axonal neuropathy, parkinsonism, and deafness as variably associated symptoms. Conclusions: In our study, KIF5A mutations account for 3.5% of cases with both autosomal dominant inheritance and sporadic HSP patients, a frequency lower than that observed in Italian and French patients, but similar to that (4%) found in a mixed European population.
Our findings indicate that, SPG10 should be considered in the molecular analysis of HSP phenotypes, even in the absence of clearly positive family-history. Clinically, the probands of our SPG10 families present with a rather broad range of phenotypes, from pure HSP to complicated forms.

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(31) Interferon-beta induces clearance of mutant ataxin-7 and improves locomotion in SCA7 knock-in mice

Alice Chort,[1,2,3,4a] Sandro Alves,[1,2,3,4a] Martina Marinello,[1,2,3,4] Béatrice Dufresnois,[1,2,3,4] Jean-Gabriel Dornbierer,[1,2,3,4] Christelle Tesson,[1,2,3,4,5] Morwena Latouche,[1,2,3,4] Darren P. Baker,[6] Martine Barkats,[7] Khalid H. El Hachimi,[1,2,3,4,5] Merle Ruberg,[2] Alexandre Janer,[2b] Giovanni Stevanin,[1,2,3,4,5] Alexis Brice,[1,2,3,4,8], Annie Sittler[1,2,3,4]

[1]Université Pierre et Marie Curie-Paris 6, UMR_S 975, 75013 Paris, France ; [2]Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Hôpital de la Pitié-Salpêtrière, 75013 Paris, France ; [3]Institut National de la Santé et de la Recherche Médicale, U 975, 75013 Paris, France ; [4]Centre National pour la Recherche Scientifique, UMR 7225, 75013 Paris, France ; [5]Ecole Pratique des Hautes Etudes (EPHE), 75007 Paris, France ; [6]BiogenIdec Inc., 12 Cambridge Center, Cambridge, USA ; [7]UPMC-AIM UMR S974, INSERM U 974, CNRS UMR 7215, Institut de Myologie, Université Pierre et Marie Curie Paris 6, 75013 Paris, France ; [8]Département de Génétique et Cytogénétique, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, 75013 Paris, France.

We showed previously, in a cell model of spinocerebellar ataxia SCA7 that interferon-beta induces the expression of promyelocytic leukemia protein (PML) and the formation of PML nuclear bodies that degrade mutant ataxin-7, suggesting that the cytokine, used to treat multiple sclerosis, might have therapeutic value in SCA7. We now show that interferon-beta also induces PML-dependent clearance of ataxin-7 in a preclinical model, SCA7$^{266Q/5Q}$ knock-in mice, and improves motor function. Interferon-beta, administered intraperitoneally three times a week, was internalized with its receptor in Purkinje and other cells and translocated to the nucleus. The treatment induced PML expression and the formation of PML nuclear bodies and decreased mutant ataxin-7 in neuronal intranuclear inclusions, the hallmark of the disease. No reactive gliosis or other signs of toxicity were observed in the brain or internal organs. The treatment also significantly improved the performance of the SCA7$^{266Q/5Q}$ knock-in mice on two behavioral tests sensitive to cerebellar function: the Locotronic test of locomotor function and the beam-walking test of balance, motor coordination and fine movements, which are affected in patients with SCA7. Finally, since neuronal death does not occur in the cerebellum of SCA7$^{266Q/5Q}$ mice, we showed in primary cell cultures expressing mutant ataxin-7 that interferon-beta treatment improves Purkinje cell survival. This treatment might apply to all polyglutamine diseases in which PML associates, in cell nuclei, with the mutant proteins responsible for the disease.

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(32) Late onset oculomotor apraxia type 2: a new *SETX* mutation

Criscuolo C, Marsili A, Guacci A, Carbone R, De Michele G, Filla A

Dipartimento di Scienze Neurologiche, Università Federico II, Napoli, Italia

Ataxia with oculomotor apraxia type 2 (AOA2) is an autosomal recessive disorder characterized by onset between 10 and 22 years, cerebellar atrophy, peripheral neuropathy, oculomotor apraxia and elevated alpha-fetoprotein (AFP) serum levels. The gene responsible for this disease (*SETX*) maps to chromosome 9q34, and encodes for senataxin, a 2677 amino acid protein. The C-terminal domain of senataxin corresponds to the helicase domain, the loss of function of which has been speculated to cause abnormal processing of RNA.
The objective was to to screen for *SETX* in ataxic patients with high alpha-fetoprotein (AFP)
Three patients with high AFP, from two unrelated families were analysed for *SETX*. All underwent an accurate neurological examination, brain MRI and nerve conduction study. Routine laboratory tests, including vitamin E and serum creatine kinase (CK) were performed. The presence of GAA expansion triplet, responsible of Friedrich ataxia, was excluded. The coding sequence and the intron-exon junctions of *SETX* were directly sequenced.
We identified the same new missense mutation in the three patients in homozygote state. The mutation cosegregates with the disease in the two families. It was absent in 200 Italian controls originating from the same geographic areas. The patients were from Campania. All the patients had

cerebellar features, axonal neuropathy, cerebellar atrophy. Oculomotor apraxia was absent in all. No patients showed extrapyramidal signs or cognitive decline. Serum CK, albumin and cholesterol were normal. The parents of two affected sibs were consanguineous. These two patients had onset age at 40 years old. One patient became weelchair-bound after 17 years of disease. The other needs unilateral help for walking. Age at onset of the third patient was 22 years old with diplopia, ataxia appeared after four years. After 12 years of disease she is still able to walk without help.
We report previously unidentified missense mutations that map to the DNA/RNA helicase domain, emphasizing the importance of this region to the pathogenesis of AOA2.We identified the same mutation in two different families suggesting a founder effect in Campania. The mutation is associated with a late onset and a slow progression of disease underlying the importance of screening *SETX* in patients with ataxia and high AFP even in those with very late onset.

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(33) Course & life expectancy of SPG11

Susanne T. de Bot[1], Rogier C. Burggraaff[2], Johanna C. Herkert[2], Helenius J. Schelhaas[1], Bart Post[1], Reinout O. van Vliet[3], Marjo S. van der Knaap[4], Erik-Jan Kamsteeg[5], Hans Scheffer[4], Bart P. van de Warrenburg[1], Corien C. Verschuuren-Bemelmans[2], Hubertus P.H. Kremer[6]

[1]Department of Neurology, RUNMC, Nijmegen, Netherlands; [2]Department of Genetics, UMCG, Groningen, Netherlands; [3]Het Roessingh, Centre of Rehabilitation, Enschede, Netherlands; [4]Department of Child Neurology, VUmc, Amsterdam, Netherlands; [4]Department of Genetics, RUNMC, Nijmegen, Netherlands; [6]Department of Neurology, UMCG, Groningen, Netherlands.

The objective is to describe the course and prognosis of spastic paraplegia 11 (SPG11), with retrospective chart analysis of all known SPG11 patients in the Netherlands.
SPG11 is the most frequent complicated form of hereditary spastic paraplegia.
Although the clinical spectrum (i.e. spastic paraplegia with cognitive decline and thin corpus callosum on brain MRI, +/-polyneuropathy, cerebellar ataxia, parkinsonism or anterior horn cell degeneration signs) is well recognized, data on the long-term prognosis and life-expectancy are lacking.
We identified 9 different SPG11 mutations, 4 of which are novel, in 9 index patients. The mean age at onset in 18 SPG11 patients from 9 families was 7.9 years (range: 4 months14 years), starting with either gait impairment (61%) or learning disabilities (39%). Brain MRI showed a thin corpus callosum in 8/9 patients and periventricular white matter changes in the frontal horn region (known as the “ears-of the lynx”-sign) in all patients (fig. 1). In 2 out of 6 patients (33%) fundus photographs revealed retinal pigment epithelium lesions, compatible with Kjellin syndrome (Fig. 2). Most patients became wheelchair bound after a disease-duration of 1 to 2 decades. End-stage disease consisted of loss of spontaneous speech/mutism, severe dysphagia, spastic tetraplegia with peripheral nerve involvement, and contractures. Lifespan was restricted in five patients who died at ages 30 to 48 years, 26 to 47 years after onset of gait impairment, due to complications such as pneumonia. Other relevant features during the disease were urinary and fecal incontinence, obesity and psychosis. No extrapyramidal signs were noted, apart from mild arm rigidity in one patient.
SPG11 has a childhood-onset with either gait or learning disabilities and a progressive, complicated course with a restricted lifespan. Death may occur in the third to fifth decades.

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(34) Spastic paraplegia with thin corpus callosum (SPG11) share clinical and histological similarities with juvenile amyotrophic lateral sclerosis

K.H. El Hachimi[1,2,3,4], P.S. Denora[1,2,3], C. Casali[5], F. Zolfanelli[5], E. Mundwiller[6], E. Bertini[5], A. Brice[1,2,3,7], F. Darios[1,2,3], G. Stevanin[1,2,3,4]

[1]Université Pierre et Marie Curie-Paris 6, UMR_S 975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM), Pitié-Salpêtrière Hospital, 75013 Paris, France ; [2]CNRS, UMR 7225, 75013 Paris, France ; [3] INSERM, U975, 75013 Paris, France ; [4]Groupe de neurogénétique, Ecole Pratique des Hautes Etudes, Institut du Cerveau et de la Moelle épinière, Groupe Hospitalier Pitié-Salpêtrière, Paris, France ; [5]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [6]Institut du Cerveau et de la Moelle Epinière, 75013 Paris, France
[7]APHP, Fédération de génétique, Pitié-Salpêtrière Hospital, Paris, France.

Spastic paraplegia 11 (SPG11), the most frequent (21%) clinico-genetic entity of autosomal recessive spastic paraplegia, is essentially characterized by the degeneration of the pyramidal tract, thinning of the corpus callosum (TCC) and white matter abnormalities (WMA) at brain MRI, leading to spasticity in lower limbs, mental impairment and peripheral neuropathy in patients. The disease is predominantly associated with loss of function mutations in the *SPG11* gene, coding for Spatacsin. We report the first

neuropathological analysis of a 27 years-old woman presenting with a severe progressive disability and mental deterioration, TCC, periventricular WMA, marked frontal and parietal cortical, cerebellar and medullar atrophy. Mutational analysis revealed two heterozygous stop mutations in SPG11 gene. The mutations in the Spatacsin gene cause a wide spectrum of clinical and pathological features. We show that the neuropathological profile overlaps with amyotrophic lateral sclerosis (ALS).

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(35) Genetic delineation of early onset cerebellar ataxia phenotypes in India through next generation sequencing

Mohammed Faruq, Ankita Narang, Renu Kumari, Achal Kumar Sriavstava, Debasis Dash, Mitali Mukerji

Genetic characterization has lead to the identification of nearly 60 causal loci in ataxias. The prevalence of ataxia types with respective genetic defect vary geographically. The genetic testing of each known ataxic associated variation for uncharacterized phenotype is challenging and cost/time expensive.
In our ataxic cohort (n=1000) majority being North-Indian families, more than half of the cases (~57%) are genetically uncharacterized (UC). We aimed to delineate genetic defect in uncharacterized cases using next generation sequencing platform.
We carried out exome-sequencing for 12 individuals from three uncharacterized families of recessive inheritance manifesting typical FRDA or unique phenotype such as infantile onset ataxia with hearing loss or seizures.
Clinical investigations and exome sequencing in one family reveals association of GAA expansion negative FRDA phenotype with novel homozygous frame-shift mutation in *SACS* (Autosomal recessive ataxia of Charlevoix-Saguenay) locus. In second family with infantile onset ataxia and hearing loss we identified a novel homozygous missense mutation in *c10orf2*. In remaining family with juvenile onset ataxia and generalized seizures we identified novel compound heterozygous mutations in *CLN6* (Ceroid-Lipofuscinosis Neuronal 6).
We have identified novel mutation loci in typical known recessive ataxic phenotype and compound novel heterozygous mutations in *CLN6* a known locus for seizures-dementia-visual failure being associated with atypical manifestation of predominant ataxia and seizures. Further, this study emphasizes the prudent role of exome sequencing technology in delineation of genetic etiology in a rare and other genetically heterogeneous ataxic disorders.

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(36) Gait adaptability training improves obstacle avoidance capacities and dynamic stability in patients with degenerative cerebellar ataxia

Ella M.R. Fonteyn[1,2], Anita J. Heeren[3], Jasper-Jan C. Engels[3], Jasper J. Den Boer[3], Bart P.C. van de Warrenburg[1], Vivian Weerdesteyn[3],

[1]Department of Neurology, Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition, and Behaviour, Nijmegen, The Netherlands; [2]Department of Neurology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; [3]Department of Rehabilitation, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Balance and gait problems in patients with degenerative cerebellar ataxia lead to reduced mobility, loss of independence, and frequent falls. It is currently unclear, however, whether balance and gait capacities can be improved by training in this group of patients.
The objective is to examine the effects of gait adaptability training on obstacle avoidance capacities and dynamic stability during adaptive gait.
Ten patients with degenerative cerebellar ataxia received 10 protocolised gait adaptability training sessions of 1 hour each during a period of 5 weeks. Training was performed on a treadmill instrumented to project visual cues on the belt's surface. Main outcome measures were an obstacle avoidance task while walking on a treadmill, and clinical tests including the Scale for the Assessment of Ataxia (SARA), the 10 meter walking test (10MWT), Timed Up-and-Go Test (TUG), Berg Balance Scale (BBS), and the obstacle subtask of the Emory Functional Ambulation Profile (EFAP). To measure changes in gait parameters and dynamic stability, 3D motion analysis was used. Participants' levels of confidence in balance and physical activity were evaluated using questionnaires.
SARA scores and the clinical subtasks involving obstacle avoidance improved significantly. No significant improvements were found in the other clinical tests or levels of confidence in balance and physical activity. The observed clinical benefit was supported by the kinematic data, as success rates on the obstacle avoidance task on the treadmill significantly increased, and participants more frequently used a short step strategy to cross obstacles with earlier stabilisation after crossing the obstacle.

This pilot study provides evidence of a beneficial effect of gait adaptability training on obstacle avoidance capacity and dynamic stability in patients with degenerative cerebellar ataxia. Future research will focus on the neuronal substrate of this improvement as well as on the sustainability of these improvements.

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(37) Autosomal recessive hereditary spastic paraplegia: *SPG11* and *SPG15* mutational spectrum in Portuguese patients

Gama M[1], Lopes AM[1], Loureiro JL[2,3], Pereira MC[3], Coutinho P[1,3], Sequeiros J[1,2,4], Alonso I[1,2,4]

[1]CGPP, IBMC, Porto, Portugal; [2]Serviço de Neurologia, Centro Hospitalar entre Douro e Vouga, Portugal; [3]UnIGENe, IBMC, Porto, [4]ICBAS, University of Porto, Porto, Portugal.

Hereditary spastic paraplegias (HSPs) are a group of rare neurodegenerative disorders, clinically and genetically highly heterogeneous. Clinically, they can be divided into two clusters: pure, characterized mainly by slowly progressive lower extremity spasticity and weakness, and complex, characterized by the presence of additional neurological and other non-neurological features. Genetically, have been described three modes of inheritance: autosomal dominant, autosomal recessive and X-linked. We focus on *SPG11* (spatacsin) and *SPG15* (spastizin) genes, both responsible for autosomal recessive HSP with a similar phenotype comprising spastic paraplegia, thin corpus callosum (TCC) and cognitive deficits.
Sixty patients were screened for mutations in the *SPG11* gene, 12 for *SPG15* gene and 72 for both genes. All coding regions and intron-exon boundaries were PCR amplified, followed by bidirectional direct sequencing. Large gene rearrangements were screened by MLPA.
By molecular analysis, we identified 15 patients with mutations in *SPG11*, 9 of them with TCC and 6 patients with mutations in *SPG15*, 2 of them with TCC (brain MRI data was not available for all patients).
In *SPG11*, we found 1 novel missense mutation, 4 large deletions, 1 of which is novel, 3 nonsense mutations, 1 of which is novel, 4 frameshift and 1 splice site mutation. In *SPG15*, we found 3 frameshift mutations, 2 of which are novel.
In a cohort of Portuguese patients with clinical diagnosis of autosomal recessive spastic paraplegia, SPG11 was confirmed in 10,4% and SPG15 in 4,2% of the cases. TCC is a good predictor for SPG11 as well as for SPG15.
As autosomal recessive HSP present a variable phenotype, mutation screening in these genes and in others HSP genes can be invaluable to establish a genetic diagnosis, in addition to allowing proper genetic counselling.

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(38) Interaction between AP-5 and the Hereditary Spastic Paraplegia proteins SPG11 and SPG15

Jennifer Hirst[1], Georg H.H. Borner[1], James Edgar[1], Marco Y. Hein[2], Matthias Mann[2], Frank Buchholz[3], Robin Antrobus[1], Margaret S. Robinson[1]

[1]University of Cambridge, Cambridge Institute for Medical Research, Cambridge, UK; [2]Max Planck Institute of Biochemistry, 82152 Martinsried, Germany; [3]Medical Systems Biology, UCC, 01307 Dresden, Germany.

Adaptor proteins form part of a vesicle coat machinery involved in sorting transmembrane proteins to different destinations in the cell. Using structural homology searching we identified a fifth adaptor complex, and named it AP-5 (**Hirst J** et al., 2011 PLoS Biol. Oct;9(10):e1001170). In order to identify proteins that associated with AP-5 we performed native immunoprecipitations and found two proteins stably associated with AP-5. These proteins were identified as SPG15 (FYVE-CENT/ ZFYVE26/spastizin) and SPG11 (spatacsin), which are mutated in patients with hereditary spastic paraplegia. Indeed, SPG11 and SPG15 had already been genetically linked through similar patient phenotypes, characterised by an autosomal recessive form of hereditary spastic paraplegia with thin corpus callosum. Here, we provide further evidence for the association of SPG11 and SPG15 with AP-5, and investigate the stoichiometry and interdependence of this association. In addition, we show that knockdowns of SPG11 or SPG15 phenocopy knockdowns of any one of the AP-5 subunits, perturbing the trafficking of the cation-independent mannose 6-phosphate receptor. Our working hypothesis is that SPG11 and SPG15 may act as components of the AP-5 ‘coat machinery’ to provide a scaffold (analogous to clathrin), and a means to regulate its membrane association.

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(39) PolyQ-ataxin-7 toxicity activates endogenous neurogenic response in the SCA7 mouse retina

A. Karam[1], C. Weber[1], S. Alves[2], A. Sittler[2], M.G. Yefimova[3], Y. Trottier[1]

[1]IGBMC, Illkirch, France ; [2]Université Pierre et Marie Curie-Paris 6, UMR_S 975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM) ; CNRS, UMR 7225 ; INSERM, U975, 75013 Paris, France ; [3]S.I.E.P.B., St-Petersburg, Russia.

Patients affected by Spinocerebellar ataxia 7 (SCA7) suffer from cone-rod dystrophy that leads to visual impairment. SCA7-R7E trangenic mice express polyQ-ataxin-7 specifically in photoreceptors and show progressive loss of visual function, due to photoreceptor dedifferentiation and cell death. Surprisingly, cell death does not cause massive reduction of the photoreceptor cell layer. We now show, using bromodeoxyuridine (BrdU) and mitotic markers, that cell death activates proliferation of Müller glial (MG) cells, which migrate from the inner retina to populate the photoreceptor cell layer of SCA7-R7E retina. Similarly, we found a large amount of proliferating MG cells in the photoreceptor cell layer of SCA7266Q/7Q knock-in mouse model. We further show that most proliferating MG cells express Pax6, indicating that they acquire progenitor properties. Finally, using BrdU pulse-chase experiments, we traced the fate of proliferating MG cells over time and found that one third of them expresses rod specific markers and survives for at least several weeks in the SCA7R7E retina.
These results suggest that cell death induces conversion of MG cells into new rod photoreceptors to compensate for cell loss. Similar endogenous neurogenic activation involving MG cells has been reported in lesioned retina of lower vertebrates, but it is rarely observed in mammal. The activation of endogenous neurogenic response in SCA7 retina is reminiscent to the situation in Huntington's disease where increased adult neurogenesis was reported in patient brains. The similarity suggests that polyQ toxicity may activate common molecular pathways leading to neurogenic response in diverse tissues. Identification of these pathways may provide therapeutic strategies to activate endogenous regeneration to slow down polyQ pathologies.

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(40) Friedreich's and other hereditary ataxias in Greece: an 18-year perspective

Georgios Koutsis[1], Athina Kladi[1], Georgia Karadima[1], Henry Houlden[2], Nicholas W. Wood[2], Kyproula Christodoulou[3], Marios Panas[1]

[1]Neurogenetics Unit, 1st Department of Neurology, University of Athens Medical School, Eginition Hospital, Athens, Greece; [2]Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK; [3]Neurogenetics Department, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus.

Limited data exist at present on the spectrum of heredoataxias in the Greek population, including the prevalence and phenotype of Friedreich's ataxia (FRDA) and the prevalence and subtypes of dominant spinocerebellar ataxias (SCAs). The Athens Neurogenetics Unit is the only one of its kind in Greece, acting as referral center for patients with inherited ataxias from all over the country. The Cyprus Institute of Neurology and Genetics occasionally provides molecular diagnosis for patients from Greece.
We analyzed clinically and investigated genetically for FRDA and triplet repeat expansion SCAs a consecutive series of 186 patients with suspected heredoataxia presenting over an 18-year period. For estimates of minimum prevalence we included patients with molecular diagnosis from Cyprus that were absent from the Athens cohort.
The minimum prevalence of FRDA was ~0.9/100,000, with clusters of high prevalence in Aegean islands. FRDA was diagnosed in 73 probands. The genotypic and phenotypic spectrum of FRDA was similar to other populations, with one patient compound heterozygote for a known point mutation in *FXN* (Asn146Lys). Undiagnosed recessive ataxias included FRDA-like and spastic ataxia cases. The minimum prevalence of dominant SCAs was ~0.7/100,000. SCA1 (4), SCA2 (4), SCA6, SCA7 and SCA17 (1 each) expansions were identified in 11 probands (31% of dominant cases). Undiagnosed dominant patients included a majority of type III autosomal dominant cerebellar ataxias.
FRDA is the commonest heredoataxia in the Greek population with prevalence towards the lower end of other European populations. Dominant SCAs are almost as prevalent. SCA1, SCA2, SCA6, SCA7 and SCA17 patients complete the spectrum of cases with a specific molecular diagnosis.

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(41) Sensory ataxia as prominent clinical presentation in two families with SPG5

L. Leonardi[1], C. Marcotulli[1], A.Tessa[2], R. DiFabio[1], M. Serrao[2], F. Pierelli[1], FM. Santorelli[2], C. Casali[1]

[1]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [2]Molecular Medicine & Neurodegenerative Diseases, IRCCS Fondazione Stella Maris, Pisa, Italy.

Hereditary spastic paraparesis (HSP), are highly heterogeneous disorders affecting primarily the pyramidal tracts, resulting in spastic gait, abnormal reflexes and hyperreactive bladder. Even though

SPG5 was the first ARHSP locus to be mapped on chromosome 8q12.3 in early 1990s [1], pathogenetic mutations in the *SPG5/CYP7B1* gene were only described in 2009 [2]. Herein we describe two Italian kindreds with sensory ataxia as initial and most prominent clinical presentation.
In the first kindred, a brother and a sister, now aged 60 and 57 respectively, born to consanguineous healthy parents, first developed unsteady gait after age 30, with slowly progressive course. Recent neurological examination in the woman showed marked impairment of position and vibration sense over her lower limbs, positive Romberg sign, mild spasticity with brisk tendon reflexes and bilateral extensor response. The second kindred included three sibs, two sisters and a younger brother, now aged 58, 54 and 50 years, born to healthy apparently non consanguineous parents. They all reported experiencing unsteady gait exclusively in the darkness or after closing their eyes, since from childhood. The symptoms progressed slowly and after age 20 weakness and spasticity ensued, leading to frank spastic paraparesis only after 35 years. The two elder sisters are now both wheelchair-bound, while the younger brother is still able to walk with bilateral support. The neurological examination showed marked posterior column signs and pyramidal signs in their lower limbs.
Biochemical (including extensive studies of Vitamin B12 levels and B12 carrier proteins in serum), genetic (including FRDA, ARSACS, SPG4 and SPG7) and neuroimaging evaluation failed to detect any notable abnormality, until recently we found a homozygous c.889A>G (p.T297A) mutation in *SPG5/CYB7B1* gene in all affected members of both kindreds, which come from different areas of Central Italy.
Families with ARHSP associated with *SPG5/CYP7B1* mutations are increasingly being reported. The clinical phenotype is generally described as "pure", with variable age at onset (range 1–40 years). Additional neurological features have occasionally been reported in SPG5-linked families, however [3], suggesting that even complicated patients might harbor variants in *SPG5/CYP7B1*.
Conclusions: We report two Italian kindreds harboring the same homozygous *SPG5/CYP7B1*mutation with a similar, rather unusual, clinical presentation characterized by early severe involvement of posterior columns, with severe sensory ataxia followed by spastic paraparesis, adding to clinical variability of this form of ARHSP.

References: Depienne C, Stevanin G, Brice A, Durr A. Hereditary spastic paraplegias: an update. Curr Opin Neurol 2007;20:674–80.
Tsaousidou MK, Ouahchi K, Warner TT, et al. Sequence alterations within CYP7B1 implicate defective cholesterol homeostasis in motor-neuron degeneration. Am J Hum Genet 2008;82:510–5.
Klebe S, Durr A, Bouslam N, et al. Spastic paraplegia 5: Locus refinement, candidate gene analysis and clinical description. Am J Med Genet B Neuropsychiatr Genet 2007;144:854–61.

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(42) Israeli hereditary spastic paraplegia (HSP) database update 2013

A. Lossos[1], V. Meiner[2], B-E. Zimmerman[2], M. Asulin[2], H. Marreed[3], L. Dov-Chamma[2], G. Stevanin[4], A. Durr[4], A. Brice[4], I. Lerer[2]

[1]Departments of Neurology, Hebrew University-Hadassah Medical Center, Jerusalem, Israel; [2]Human Genetics, Hebrew University-Hadassah Medical Center, Jerusalem, Israel; [3]Hebrew University-Hadassah School of Medicine, Jerusalem, Israel; [4]INSERM/UPMC, UMR-S679, Hopital Pitie-Salpetriere, Paris, France.

HSP is a clinically and genetically heterogeneous group of pure and complex forms with more than 48 reported loci and with 10 identified autosomal dominant (AD) and 12 recessive (AR) genes. Because molecular characterization of HSP may yield efficient local diagnostic strategy, identify demographic clustering, and enable phenotype-genotype correlation, we have established clinical and molecular HSP database in 2005.
Sixty-eight non-related centrally ascertained Israeli HSP pedigrees of various ethnic background currently form the database. Genotyping was performed on genomic DNA using PCR amplified polymorphic markers followed by sequencing candidate genes. Since 2011, we have started using genome-wide homozygosity mapping for homozygous candidate regions in informative AR families. Instances with the large size of homozygous stretches with consequent high number of candidate genes are further subjected to whole-exome sequencing.
The apparent mode of inheritance is AD in 18 families, AR in 44, and six cases are sporadic. As expected, AD-HSP mainly present with early-onset pure clinical phenotype, whereas AR-HSF usually manifest additional neurological features. So far, eight SPG4 and six SPG3A mutations were characterized among the AD pedigrees, and five SPG11, two SPG15, one SPG30 and two *FA2H* -related families were identified among the AR pedigrees. Several AR families have been analyzed using exome sequencing with identification of novel HSP genes and with extension of the phenotype in previously reported genes.

We present the clinical and molecular findings in the largest Israeli HSP cohort. Despite apparent referral bias, the observed increased frequency of AR-HSP forms (65%) seems important and may be related to the common local preference of parental consanguinity. However, the relative proportion of the main AD forms grossly resembles their worldwide distribution. The new molecular methodology enhances identification of novel genes, provides accurate genetic counseling, and enables better understanding of the pathophysiology of HSP.

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(43) Concurrent mutations in AFG3L2 and paraplegin cause mitochondrial dysfunction in patients with spinocerebellar degeneration

S. Magri[1], V. Fracasso[1], M. Plumari[1], S. Caldarazzo[1], E. Sarto[1], C. Gellera[1], C. Mariotti[1], C. Pantaleoni[3], P. Giunti[4], F. Lazzaro[2], M. Muzi-Falconi[2], D. Di Bella[1], F. Taroni[1]

[1]Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [2]Department of Biomolecular Sciences and Biotechnology, University of Milan, Italy; [3]Unit of Developmental Neurology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [4]Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK.

Autosomal dominant spinocerebellar ataxias (SCA) are a heterogeneous group of neurological disorders characterized by cerebellar dysfunction mostly due to Purkinje cell degeneration. We have discovered that heterozygous AFG3L2 (ATPase family gene 3-like 2) mutations cause SCA type 28. AFG3L2 and its partner protein paraplegin, which causes recessive spastic paraparesis SPG7, are components of the m-AAA complex, involved in mitochondrial protein quality control. Mutation analysis in a large cohort of patients demonstrated that AFG3L2 mutations account for ~3% of SCA with unknown defect. Functional analysis in an m-AAA-deficient yeast cellular model (yta10del/yta12del) demonstrated that the mutations (>20) located in the ATPase or in the protease functional domains of the protein cause respiratory deficiency and defective processing of m-AAA substrates. Since yeast functional studies showed that paraplegin coexpression can complement AFG3L2 mutations in some cases, we investigated the possible coinheritance of AFG3L2 and SPG7 mutations in patients with spinocerebellar syndromes. We identified 4 probands with heterozygous mutations in both the AFG3L2 and the SPG7 genes. Three ataxic patients carry AFG3L2 mutations affecting highly conserved amino acids located in the ATPase or in the proteolytic domains of the protein along with a paraplegin loss-of-function mutation. In one family, double heterozygosity for AFG3L2R702Q and parapleginA510V results in a full-blown ataxic phenotype, while AFG3L2R702Q heterozygotes manifest only moderate cerebellar atrophy at MRI and parapleginA510V heterozygous carriers are completely unaffected. In the fourth family, the proband carries a de novo AFG3L2 mutation in the highly conserved SRH region of the ATPase domain along with the inherited heterozygous deletion of SPG7 exons 4-6. The clinical presentation of this patient is characterized by early-onset optic atrophy and a L-dopa-responsive spastic-ataxic syndrome with extrapyramidal signs. A muscle biopsy revealed an isolated complex I deficiency. Moreover, analysis of substrates processing in patient's fibroblasts showed a abnormal processing pattern of OPA1 and evaluation of mitochondrial morphology revealed a severe fragmentation of mitochondrial network. In conclusion, our data indicate that the presence of a loss-of-function mutation in the AFG3L2 partner paraplegin may act as a disease modifier for heterozygous AFG3L2 mutations. Furthermore, concurrent mutations in both components of the mitochondrial m-AAA complex may result in a complex phenotype, thus expanding the clinical spectrum of AFG3L2-associated mutations. Finally, biochemical and cell biology studies demonstrated the crucial role of the m-AAA complex in the processing of OPA1 and the maintenance of mitochondrial morphology and dynamics in human cells.

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(44) Resting and free-living energy expenditure in Spinocerebellar Ataxia Type 1

Anja Mähler[1,2], Jochen Steiniger[1], Matthias Endres[2,3,4], Friedemann Paul[1,2], Michael Boschmann[1], Sarah Stricker[2,3]

[1]Experimental & Clinical Research Center, a joint cooperation between Charité University Medicine Berlin and Max Delbrueck Center for Molecular Medicine, Berlin, Germany; [2]Excellence Cluster NeuroCure, Charité University Medicine, Berlin, Germany; [3]Department of Neurology, Charité University Medicine, Berlin, Germany; [4]Center for Stroke Research Berlin, Charité University Medicine, Berlin, Germany.

Autosomal dominant spinocerebellar ataxia type 1 (SCA1) is a genetic movement disorder with neuronal loss in cerebellum, brainstem and other cerebral regions. There is clinical evidence for

progressive weight loss and amyotrophia within the course of the disease, the causes of which are still unknown.
The objective was to test the hypothesis that a disturbed energy balance contributes to weight loss in SCA1 patients.
Anthropometric measures, energy intake (food records), and resting (calorimetry) and free-living (accelerometry) energy expenditure were determined in 10 patients with genetically proven SCA1 and 10 healthy control subjects closely matched for age, sex, and body composition.
At rest, energy expenditure was 9% and fat oxidation rate 28% higher in patients vs. controls. Under free-living conditions, total energy expenditure and daily step counts were significantly lower in patients vs. controls. However, most patients were able to maintain energy intake and expenditure in a balanced state.
Resting energy expenditure and fat oxidation is higher whereas total 24h energy expenditure is lower in SCA1 patients vs. healthy controls. An altered autonomic nervous system activity and a decreased physical activity might contribute to this outcome.

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(45) Genome-wide expression analysis identified defects in cell growth, proliferation and viability in SCA28 lymphoblastoid cell lines

Cecilia Mancini[1], Paola Roncaglia[2,3], Alessandro Brussino[1], Giovanni Stevanin[4,5,6], Nicola Lo Buono[1], Helena Krmac[3], Francesca Maltecca[7], Elena Gazzano[8], Anna Bartoletti Stella[9], Maria Antonietta Calvaruso[10,11], Luisa Iommarini[10], Claudia Cagnoli[1], Sylvie Forlani[4], Isabelle Le Ber[4], Alexandra Durr[4,5], Alexis Brice[4,5], Dario Ghigo[8], Giorgio Casari[7], Anna Maria Porcelli[10], Ada Funaro[1], Giuseppe Gasparre[9], Stefano Gustincich[3], Alfredo Brusco[1,11*]

[1]University of Torino, Department of Medical Sciences, Italy; [2]European Bioinformatics Institute, Cambridge, UK; [3]Neurobiology Sector, SISSA/ISAS, Trieste, Italy; [4]Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (INSERM / UPMC Univ. Paris 6, UMR_S975 ; CNRS 7225), Pitié-Salpêtrière Hospital, Paris, France ; [5]APHP, Fédération de génétique, Pitié-Salpêtrière Hospital, Paris, France ; [6]Neurogenetics team, Ecole Pratique des Hautes Etudes, Institut du Cerveau et de la Moelle épinière, Paris, France ; [7]San Raffaele Scientific Institute, Vita-Salute San Raffaele University and Center for Translational Genomics and Bioinformatics, Milan, Italy; [8]University of Torino, Department of Oncology, Italy; [9]University of Bologna, Department Medical and Surgical Sciences, Medical Genetics, Bologna, Italy; [10]University of Bologna, Department of Pharmacy and Biotechnologies (FABIT), Bologna, Italy; [11]Medical Genetics Unit, "Città della Salute e della Scienza" Hospital, Torino, Italy.

SCA28 is an autosomal dominant ataxia associated with *AFG3L2* gene mutations. We performed a whole genome expression profiling using lymphoblastoid cell lines (LCLs) from four SCA28 patients, and six unrelated healthy controls matched for sex and age. We found 66 genes whose expression was statistically different, 35 of which were up-regulated (Fold Change - FC = 2.5-10) and 31 down-regulated (FC = 0.1-0.3). The differentially expressed genes were clustered in five functional categories: (1) regulation of cell proliferation; (2) regulation of programmed cell death; (3) response to oxidative stress; (4) cell adhesion, and (5) chemical homeostasis. To validate these data, we performed functional experiments that proved an impaired SCA28 LCLs growth compared to controls ($p < 0.005$), an increased number of cells in the G0/G1 phase ($p < 0.001$), and an increased mortality of patients' cells due to apoptosis ($p < 0.05$). We also showed that respiratory chain activity and reactive oxygen species levels were not altered, although lipid peroxidation in SCA28 LCLs was increased in basal conditions ($p < 0.05$). We did not detect mitochondrial DNA large deletions. An increase of TFAM, a crucial protein for mtDNA maintenance, and a decrease of DRP1, a key regulator of mitochondrial dynamic mechanism, suggested an alteration of mitochondrial network pathways.
In conclusion, whole genome expression profiling in SCA28 LCLs allowed the identification of several altered pathways that may be related to the disease.

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(46) Spinocerebellar ataxia type 10 in a Peruvian woman in Italy

C. Marcotulli[1], L. Leonardi[1], A.Tessa[2], R. DiFabio[1], M. Serrao[1], FM. Santorelli[2], C. Casali[1]

[1]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [2]Molecular Medicine & Neurodegenerative Diseases, IRCCS Fondazione Stella Maris, Pisa, Italy

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant neurodegenerative disorder manifested by ataxia and seizures, caused by a large expansion of an intronic ATTCT pentanucleotide repeat in the ATXN10 gene on 22q13.3. Normal alleles have from 10 to 29 repetitions while affected

people's alleles have up to 4500 repetitions (1). Herein we report on the first patient with SCA10 in Italy.
A 45-year-old woman from Lima (Peru), living in Italy since, had started complaining at age 35 of slowly progressive unstable gait, dysarthria and dysphagia. Family history was apparently unremarkable. On clinical examination she presented mild dysarthria, unsteady and broad-based gait needing for occasional support, upright posture oscillations, lateral nystagmus and fragmentation of slow gaze movements, hypotonia, adiadochokinesia and poor segmental limb coordination prevalent in her upper limbs. Brain MRI revealed mild atrophy of cerebellar vermis. Screening for anti-cerebellar, anti-GAD 65, anti-gliadin autoantibodies and genetic tests for SCA1, SCA2, SCA3 all gave negative results. During hospitalization she experienced an episode of transient loss of consciousness. Upon deeper enquiry she reported frequent similar episodes since a few years. An EEG showed diffuse epileptiform discharges with occipital and temporal prevalence. Antiepileptic therapy with Levetiracetam (500 mgs b.i.d) was followed by prompt clinic response and EEG normalization.
Prompted by the unusual association of cerebellar ataxia and epilepsy and her South American origin we decided to perform genetic investigation for SCA 10 which identified a pathologic expansion (> 280) of ATTCT pentanucleotide in the ATXN10 gene.
SCA 10 is the second most frequent genetic ataxia in Brazilian and Mexican families. It has recently been shown to have a more widespread occurrence in other Latin American countries, but not in Peru so far, in patients with Amerindian ancestry (2).Conclusions: Even though SCA10 has never been reported outside Latin America and East Asia it should be considered in patients living in Europe with suitable genetic background. The clinical phenotype is usually characteristic, but the occurrence of absence seizures can be overlooked by patients and their families and should be carefully investigated.

References:

Matsuura T, Yamagata T, Burgess DL, Rasmussen A, Grewal RP, Watase K, et al. Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nat Genet 2000;26:191e4.
Almeida T, Alonso I, Martins S, Ramos EM, Azevedo L, Ohno K, et al. Ancestral origin of the ATTCT repeat expansion in spinocerebellar ataxia type 10 (SCA10). Plos One 2009;4:e4553.

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(47) Implication of ATXN7 SUMOylation in degradation of nuclear aggregates

Martina Marinello[1,2,3], Sandro Alves[1,2,3], Alexis Brice[1,2,3], Annie Sittler[1,2,3]

[1]Université Pierre et Marie Curie-Paris 6, UMR_S 975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM), 75013 Paris, France ; [2]CNRS, UMR 7225, 75013 Paris, France ; [3]INSERM, U975, 75013 Paris, France

The post-translational proteins modifications are critical for the spatial and temporal regulation of signaling cascades. This is especially important in the CNS where the processes affecting differentiation, growth, targeting and communication between neurons, are highly complex and very tightly regulated. Recently, the idea has emerged that protein modification by members of the SUMO proteins family plays key roles in neuronal functions. Therefore, our team demonstrated that SUMOylation plays a role in Spinocerebellar ataxia type 7 (SCA7). Numerous ATXN7 positive nuclear inclusions, colocalizing with SUMO1 and SUMO2, were observed in cortex and cerebellar cells. In particular, in a disease cellular model we found that preventing SUMOylation of expanded ATXN7 leads to higher amounts of SDS-insoluble aggregates. These results demonstrate that SUMOylation influences aggregation of polyQ expanded ATXN7, which is likely a key event during progression of pathogenesis. In order to identify potential ATXN7 SUMOylation actors, we analyzed the expression and subcellular distribution of proteins that we think may be implicated in this pathway. We focused on the enzyme RanBP2, which we recently hypothesized to be the SUMO E3 ligase for ATXN7. The aim was to investigate if RanBP2 couples the post-translational modification of the target protein, as ATXN7, with the entry of these protein into the nucleus. The first step was determining the physical interaction between ATXN7 and RanBP2. Secondly, in order to confirm that RanBP2 was an actor in the SUMOylation pathway of ATXN7, we used a siRNA approach to decrease its expression and evaluated the silencing consequences. Preliminary results show us a deficit in the degradation of nuclear insoluble aggregates, pointing to the direction that RanBP2 could influence ATXN7 SUMOylation. The structural data for the SUMO E3 enzyme RanBP2 in complex with the other components of the SUMO pathway is now available, making possible the structure-based design of specific inhibitors or activators. For this reason, the principal aim is to elucidate the mechanisms regulating ATXN7 degradation via SUMOylation to identify the useful target for therapeutic intervention.

(48) Survival in autosomal dominant cerebellar ataxias differs according to the mutational mechanism: prognostic implications

Marie-Lorraine Monin[1,2,3,4], Sophie Tezenas du Montcel[5], Cecilia Marelli[1,2,3,4], Cécile Cazeneuve[4], Perrine Charles[4], Alexis Brice[1,2,3,4,6], Giovanni Stevanin[1,2,3,4], Alexandra Durr [1,2,3,4], on behalf of the SPATAX network

[1]INSERM, UMR_S975 - CRICM, F-75013 Paris, France; [2]UPMC University Paris 06, UMR_S975, F-75013, Paris, France; [3]CNRS 7225 - CRICM, F-75013 Paris, France ; [4]AP-HP, Hôpital Pitié-Salpêtrière, Département de Génétique et de Cytogénétique, Centre de Génétique Moléculaire et Chromosomique, F-75013 Paris, France ; [5] AP-HP, Groupe Hospitalier Pitie-Salpetrière, Biostatistics Unit, Paris, 75013, France ; [6]AP-HP, Hôpital Pitié-Salpêtrière, Fédération des maladies du système nerveux, F-75013 Paris, France.

Autosomal dominant cerebellar ataxias are a group of diseases affecting the cerebellum and its afferent/efferent tracts, characterized by genetic heterogeneity (SCA1 - 34). We studied 1013 index cases and estimated survival in 461 index cases and 224 affected relatives with known mutations. Median age at death (n=461) was 68 years [28-97]. Comparison of 409 subjects with SCA due to CAG expansions (SCA1, 2, 3, 6, 7, 17, DRPLA) and 52 subjects with non-polyglutamine SCAs (SCA 11, 13, 14, 15, 23, 25, 28, 31, 32, 36) showed that survival was significantly shorter in the former (67 years [28-97] versus 83 years [45-95], p< .0001). SCA with polyglutamine expansions died 16 years earlier and have a significantly reduced survival. Among polyglutamine SCA median age at death in SCA1 was 63 years [58-65], significantly earlier than SCA 2, 3, 6 and 7 (Log Rank 34.0, p= .0001). Death occurred 8.1 years earlier in the offspring of polyglutamine SCA (p< .001) indicating anticipation. Despite significantly earlier age at onset in non-polyglutamine SCA (37.8 years ± 13.3 versus 29.0 years ±17.7, p< .001), the disease progression was faster in polyglutamine SCA (duration between age at onset and first examination 21.9± 14.6 years and 8.9± 6.9 years respectively, p< .0001). Duration between age at onset and death was 18 years in index cases with polyglutamine SCA.
These results showed that survival and severity among SCAs were significantly different according to the underlying mutational mechanism.

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(49) Mast Syndrome (SPG21): Clinical presentation of an Austrian family harbouring a mutation in the ACP33 gene

Wolfgang Nachbauer*, Anna Hussl*, Elisabeth Wolf, Sylvia Boesch

Department of Neurology, Medical University Innsbruck, Austria

**These authors contributed equally to work.*

Mast syndrome (SPG21) is an autosomal recessive spastic paraplegia with causative mutations in the ACP33 gene on chromosome 15. ACP33 codes for maspardin which is located in intracellular endosomal/trans-Golgi vesicles and is thought to function in protein transport and sorting. Mast syndrome is highly prevalent among Amish people. We here report on clinical features of the first Austrian family harbouring a mutation in the ACP33 gene.
Two out of seven siblings are clinically affected and were followed up at the neurological department for more than 5 years. Clinical assessment consisted of repeated clinical evaluation including ataxia rating scales, magnetic resonance imaging (MRI), as well as neurophysiological and neuropsychological testing. Genetic testing was done in a certified laboratory by standard procedures (Centogene, Rostock). Patients gave written informed consent for video recording and presentation.
The 37 year old male index patient developed unsteadiness of gait and impaired fine motor skills at the age of 10 years. In the further course of the disease he displayed cognitive deficits and slurred speech. Neurological assessment at the age of 30 revealed spasticity of the lower limbs in combination with a mild cerebellar syndrome. Neuropsychological testing showed impairment in verbal and visual tasks, as well as in frontal executive functions. Cerebral imaging exhibited a thin corpus callosum, calcifications of the basal ganglia, cortical and cerebellar atrophy. Neurophysiological examination did not reveal evidence of neuropathy. His 55 year old sister displayed a disease onset at the age of 20 with slowly progressive spasticity, dementia and ataxia becoming wheelchair bound at the age of 40. Both patients showed mutations on exon 3 of the ACP33 gene leading to a STOP- and frameshift mutation.
In our family Mast syndrome is defined by a slowly progressive, complicated phenotype of spastic paraplegia in combination with thin corpus callosum and cortical atrophy. In families compatible with autosomal recessive inheritance the clinical diagnosis can be suspected also in absence of Amish ancestors.
Video of the index patient will be presented.

(50) *SETX* gene mutational screening and differential diagnosis in patients with ataxia, sensory neuropathy, and increased alpha-fetoprotein

L. Nanetti[1*], S. Cavalieri[2], V. Pensato[1], A. Erbetta[1], D. Pareyson[1], M. Panzeri[1], G. Zorzi[1], C. Antozzi[1], I. Moroni[1], C. Gellera[1], A. Brusco[2,3], C. Mariotti[1].

[1]Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy; [2]SCDU Medical Genetics, S Giovanni Battista Hospital, Turin, Italy; [3]Department of Medical Sciences, University of Turin, Turin, Italy.

Ataxia with oculomotor apraxia represents a group of genetically distinct autosomal recessive ataxias: ataxia telangectasia (AT), AT-like disorder (ATLD), ataxia with oculomotor apraxia type 1 (AOA1) and ataxia with oculomotor apraxia type 2 (AOA2). The causative disease genes encode for proteins involved in DNA single or double-strand breaks repair. These rare neurodegenerative diseases show overlapping clinical and biochemical caracteristics, including abnormalities in eye movements, progressive cerebellar degeneration, and sensory axonal peripheral neuropathy. A-T patients, AOA2, and occasionally AOA1 patients, present a specific biochemical marker consisting in elevated serum levels of alpha-fetoprotein (AFP).
We selected a cohort of Italian subjects with progressive cerebellar ataxia, axonal neuropathy, and elevated serum concentrations of AFP (>7 ng/ml). A total of 22 patients (9 men, 13 women), from 21 families, were included in this study. Mean age at examination was 37.2±14.3years (± SD, range 14-71), mean age at onset was 18.6 ± 15.3 (range 3-67). All cases were negative for Friedreich ataxia and Spinocerebellar Ataxia type 1 and 2. Mutational screening in the genes associated with A-T, AOA1, and AOA2, was perfomed. We performed DHPLC, direct sequence analyses of coding regions and exon-intron boundaries, and MLPA analysis. Clinical, neurophisiological and neuroimaging data of mutated subjects were collected.
We identified: two A-T patients, three AOA1 patients, and thirteen AOA2 patients (12 families) with *SETX* gene mutations (57%). In addition, in one patient we found a homozygous *SETX* variant of uncertain pathogenic significance, while in three patients we could not find pathogenic mutations in all the screened genes. This small group of subjects had a late onset (mean 44,5 years), and mildly increased AFP serum level (mean 27,35 ng/ml). Molecular findings in the patients with the diagnosis of AOA1 were previously described (Castellotti, 2011). The *SETX* gene mutations were: ten truncating mutations, one splice site mutation causing the in-frame skipping of exon 7, one trinucleotide deletion causing an in-frame skipping of a lysine codon, one 36-nucleotide in-frame insertion, and 4 were missense mutations. Six patients had homozygous *SETX* mutations, and six index patients were compound heterozygous. All the described mutations were novel, except the nonsense p.R2414X mutation and the missense p.P2213L mutation that were previously described (Moreira 2004; Anheim 2009). The novel missense mutations were not reported as SNPs, and were highly conserved in evolution.
The age at onset of *SETX* mutated individuals ranged from 5 to 19 years (mean 15±4 years). Mean age at examination was 35±8, and disease duration was 20±8 years. All patients, but one, had a sporadic presentation. First symptom was gait ataxia in 9 patients, and facial and upper limb dyskinesia in two patients. None of the subjects had obvious oculomotor apraxia at the latest examination. Mean AFP serum level was 89.5±78 ng/ml. Albumin level was normal, while serum cholesterol was slightly increased in four cases. Brain MRI showed severe cerebellar atrophy, predominantly of the vermis.
In our survey, *SETX* mutations were responsible of approximately 60% of juvenile-adult onset cases with cerebellar atxia, sensory neuropathy and increased AFP. The AOA2 phenotype was consistent with previous reports, except for a higher frequency of strabismus and choreoathetosis, and for the absence of overt OMA. The observation of late onset cases, for which a genetic diagnosis could not be achieved, suggests further clinical and genetic heterogeneity.

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(51) The role of interruptions in the polyglutamine tract in SCA1 pathology

Suran Nethisinghe[1], Rajesh P. Menon[2], Serena Faggiano[2], Tommaso Vannocci[2], Human Rezaei[3], Sally Pemble[4], Mary G. Sweeney[4], Nicholas W. Wood[1], Annalisa Pastore[2], Paola Giunti[1]

[1]Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK; [2]MRC NIMR, The Ridgeway, London, UK; [3]INRA, France; [4]Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.

At least seven dominant spinocerebellar ataxias (SCAs) are caused by anomalous expansion of CAG triplet repeats in coding regions of specific genes which results in abnormal lengths of polyglutamine (polyQ) tracts in the corresponding gene products. When above a threshold that is specific for each disease the expanded polyQ repeats promote protein aggregation, misfolding and neuronal cell death.

The length of the polyQ tract inversely correlates with the age at disease onset. It has however been observed that interruption of the CAG tract by silent (CAA) or missense (CAT) mutations may strongly modulate the effect of the expansion and significantly delay the age at onset. By extensive cloning of both normal and expanded SCA1 alleles taken from our cohort of ataxia patients we have determined sequence variations not detected by fragment sizing. We show that pathogenic alleles can be interrupted by histidines with relatively high frequency and that the age at disease onset and the aggregation properties of polyQ inversely correlate linearly with the longer uninterrupted CAG stretch. The correlation between individual clone sequence lengths and their fragment sizes will also be discussed. This study contributes to the understanding of the role of polyQ expansion in the SCA1 phenotype.

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(52) Optical Coherence Tomography Studies of Retinal Changes in Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) and Other Genetic Ataxias

Michael H Parkinson[1], Ana Bartmann[2], Lisa Clayton[2], Suran Nethisinghe[1], Mary Reilly[1], Fion Bremner[2], Paola Giunti[1]

[1]Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK; [2]Department of Neuro-ophthalmology, National Hospital for Neurology & Neurosurgery, London, UK.

The objective is to investigate the usefulness of optical coherence tomography (OCT) in measuring changes in retinal nerve fibre layer (RNFL) thickness in patients with ARSACS and other genetic ataxias.
ARSACS (OMIM 270550) is a rare, early-onset hereditary ataxic syndrome which presents with a slowly progressive cerebellar ataxia, spasticity, peripheral neuropathy, dysarthria, nystagmus, pes cavus and hammer toes. The syndrome is caused by mutations in the SACS gene on chromosome 13q12.12. It is known that patients with ARSACS have thickening of the peripapillary RNFL which is demonstrable by OCT. RNFL thickening on OCT has not been described in other ataxic disorders, although thinning of the RNFL has been seen in Friedreich's ataxia and other ataxias. OCT is a cheap, fast, widely available, non-invasive technique, whereas the genetic test for ARSACS is expensive and not routinely available in most UK hospitals. OCT might therefore be a useful screening test for these genetic conditions.
We performed a full ophthalmological evaluation including OCT in a consecutive series of patients presenting to a genetic ataxia clinic with a variety of genetic ataxias including ARSACS. OCT demonstrated marked RNFL thickening in cases of ARSACS, but not in patients with other hereditary ataxias.
OCT appears to be a sensitive tool for identifying retinal changes in patients with ARSACS. We advocate the use of OCT in evaluating patients with suspected ARSACS.

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(53) Spinocerebellar ataxia type 36 (SCA36): expanding the genotype and phenotype

Masato Obayashi[1], Giovanni Stevanin[2,3,4,5,6], Matthis Synofzik[7,8], Marie-Lorraine Monin[2,3,4], Charles Duyckaerts[2,3,4,9], Nozomu Sato[), Nathalie Streichenberger[10], Alain Vighetto[11], Virginie Desestret[12], Christelle Tesson[2,3,4,6], H-Erich Wichmann[13,14], Sylvie Forlani[2,3,4], Thomas Illig[15], Ludger Schöls[7,8], Johanna Huttenlocher[16], Yasushi Kita[17], Yuishin Izumi[18], Nobuo Sanjo[1], Hidehiro Mizusawa[1], Peter Bauer[16], Thomas Klopstock[19], Alexis Brice[2,3,4,5], Kinya Ishikawa[1], Alexandra Dürr [2,3,4,5].

[1]Department of Neurology and Neurological Sciences, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan; [2]Université Pierre et Marie Curie-Paris 6, UMR-S975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Paris, France ; [3]Inserm, U975, Paris, France ; [4]Cnrs, UMR 7225, Paris, France ; [5]AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Paris, France ; [6]Groupe de neurogénétique, Ecole Pratique des Hautes Etudes, Institut du Cerveau et de la Moelle épinière, Paris, France ; [7]Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, Tübingen, Germany; [8]German Centre of Neurodegenerative Diseases, University of Tübingen, Germany; [9]Laboratoire de Neuropathologie R. Escourolle, Groupe Hospitalier Pitié-Salpêtrière, Paris, France ; [10]Pathology and Biochemistry, Groupement Hospitalier Est, Hospices Civils de Lyon/Claude Bernard University, Lyon, France ; [11]Neurology Department, Hôpital Pierre Wertheimer, Lyon, France ; [12]Fédération de recherche Santé Lyon Est, CNRS UMS3453/INSERM US7 Louis Léopold Ollier, Université Claude Bernard Lyon 1, Lyon, France ; [13]Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center

for Environmental Health, Neuherberg, Germany; [14]Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany; [15]Unit for Molecular Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany; [16]Institute of Medical Genetics and Applied Genomics, University of Tübingen, Germany; [17]Neurology service, Hyogo Brain and Heart Center at Himeji, Himeji, Hyogo, Japan; [18]Department of Clinical Neuroscience, The University of Tokushima Graduate School, Tokushima, Japan; [19]Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-Universität München, Munich, Germany; [20]German Network for mitochondrial disorders (mitoNET); [21]DZNE - German Center for Neurodegenerative Diseases, Munich, Germany; [22]German Center for Vertigo and Balance Disorders, Munich, Germany.

Spinocerebellar ataxia type 36 (SCA36) is an autosomal dominant neurodegenerative disorder caused by a hexanucleotide GGCCTG repeat expansion in intron 1 of the *NOP56* gene. SCA36 has been reported from some regions of Japan and Spain, but its occurrence in different populations is unknown. We here performed a large-scale trans-continental assessment of this repeat in a cohort of 676 families excluded for previously known SCAs and originating mostly from France, Germany and Japan. We found SCA36 expansions in nine French and five Japanese index patients, as well as in one each from China, Portugal and Spain, thus accounting for 1.9% of all French, 1.5% of Japanese and 0% of German SCAs. Besides long expansions ranging between approximately 800 and 2,000 repeats, we found short GGCCTG expansions ranging between 23 and 30 repeats. The expansion was highly unstable as two individuals, one with a long and the other with a short expansion, existed in the same family. Clinically, the cardinal feature was slowly progressive cerebellar ataxia, frequently accompanied by hearing and cognitive impairments, tremor, ptosis, reduced vibration sense and sensory axonal neuropathy with the age at onset ranging between 39 and 65 years. Neuropathology in one asymptomatic French individual disclosed mild losses of Purkinje cells and hypoglossal neurons, suggesting that these neurons are consistently affected from an early stage. We conclude that SCA36, caused by a highly unstable GGCCTG repeat expansion in *NOP56*, is a rare but global disease with various extra-cerebellar symptoms.

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(54) SPG11 and SPG15 are the most frequent genotypes causing spastic paraplegia with thin corpus callosum, white matter changes and mental retardation in Italian patients

V. Pensato[1], B. Castellotti[1], E. Sarto[1], D. Di Bella[1], L. Nanetti[1], D. Pareyson[2], E. Salsano[2], M. Eoli[3], C. Ciano[4], F. Taroni[1], C. Mariotti[1], C. Gellera[1]

[1]Unit of Genetics of Neurodegenerative and Metabolic Diseases, Milan, Italy; [2]Unit of Clinic of Central and Peripheral Degenerative Neuropathies, Milan, Italy; [3]Unit of Molecular Neuro-Oncology, Milan, Italy; [4]Clinical Neurophysiology Department, IRCCS - Fondazione Istituto Neurologico Carlo Besta, Milan, Italy.

Hereditary Spastic Paraplegias (HSPs) are clinically and genetically heterogeneous diseases characterized by the presence of lower limb spasticity and weakness. Based on clinical presentation, HSPs are distinguished in “pure” and “complicated” forms. The genetic of HSPs is complex and all types of transmission have been described. To date, 58 HSP loci have been classified and for 38 of these forms the causative gene has been identified. A subgroup of complicate autosomal recessive HSPs (ARHSP) has been recently distinguished for the presence, of thin corpus callosum (TCC) and mild white matter lesions (WML). The ARHSP-TCC phenotype has been recognized in association with at least seven loci, SPG11 (15q13), SPG15 (14q24), SPG18 (8p12), SPG21 (15q22), SPG32 (14q12), SPG46 (9p13), and SPG47 (1p13). Causative mutations have been most frequently found in the *KIAA1840* gene (SPG11) and in the *ZFYVE26* gene (SPG15).
We selected a cohort of 53 unrelated Italian patients with complicated spastic paraplegia presenting with at least one of the following clinical/radiological features: mental retardation, TCC and/or WML at brain MRI. DNA samples from the patients were analyzed for mutations in *SPG11*, *SPG15*, *SPG21* and *SPG5A* genes. Informed consent was obtained from all patients included in this study. All exons and intron-exons boundaries of *KIAA1840* (SPG11, exons 1-40), *ZFYVE26* (SPG15, exons 1-42), *CYP7B1* (SPG5, exons 1-6) and *ACP33* (SPG21 exons 1-8) genes were analyzed for mutations by direct sequence analysis.
Patients included in this survey were 19 men and 34 women, age at onset of neurological symptoms was 14.6 ± 10 years (mean±SD), and the age at examination was 25.9 ± 11years. In 10 cases family history was compatible with a recessive inherited disorder, while the remaining were sporadic cases. Molecular investigations allowed the genetic diagnosis in 21 index cases: 15 patients, from 14 families, were found to carry pathogenic mutations in the *KIASA1840* gene (SPG11), and 7 unrelated patients were found to carry mutations in the *ZFYVE26* gene (SPG15). The remaining 32 cases were negative also for mutations in *SPG21* and *SPG5A* genes.

The SPG11 subjects (11F and 4M) had a mean age at onset of 21.2 years (range 12-40). At neurological examination all SPG11 patients presented spastic paraplegia, muscle weakness at lower limbs, 14/15 had mental retardation or cognitive decline, 7/15 dysarthria. All subjects had TTC and WML at MRI examination, and 5/15 had a sensory axonal peripheral neuropathy.
The 7 patients positive for SPG15 mutations were all sporadic cases. Their age at onset was 16.7 years (range 11-23). All subjects had lower limb spasticity, hyperreflexia, and TCC and WNL at brain MRI. Three out of 7 patients had a sensory-motor peripheral neuropathy.
SPG11 mutations were found in homozygous form in 4 cases and in compound heterozygous form in the remaining 10 patients. Overall, we found 19 different mutations with a large prevalence (14/19; 74%) of nonsense mutations (stop and frameshift). Only, 7 mutations have been previously reported. SPG15 mutations were all newly identified mutations. They have been found in homozygous form in 6 cases (five carried a stop mutation and one carried a missense mutation), while one patient was compound heterozygous for a frameshift and a stop mutation. In all cases we could demonstrated the segregation of the identified mutations within families.
In our cohort of Italian patients with complicated HSP we found SPG 11 mutations in 26% of the cases, and SPG15 mutations13%. The majority of mutations are predicted to cause absence of the protein. In this study we report the identification of 18 new mutations associated with SPG11 and SPG15 phenotype. By contrast, in our series we did not find SPG21 and SPG5A genes mutations. We observed a consistent clinical phenotype in SPG11 and SPG15 patients, always associated with characteristic findings at MRI evaluations.
Negative molecular results in at least 60% of cases in our cohort, suggests further genetic heterogeneity among the patients with similar clinical presentation.

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(55) Oculodentodigital dysplasia: variable neurological phenotype associated with the p.V85M mutation in connexin 43

Beatriz Quintáns[1,2], Paloma Martínez-Montero[2,3], Andrés Ordoñez-Ugalde[1,2,4] Jesús Esteban-Pérez[2,5], Irene Sanz[6], Adela Escudero[3,7], Jesús Molano[2,3], Justo García de Yébenes[8], Ángel Carracedo[1,2], Luis C. Barrio[7], María-Jesús Sobrido[1,2.]

[1]Fundación Pública Galega de Medicina Xenómica, Instituto de Investigaciones Sanitarias de Santiago de Compostela (IDIS)-SERGAS, Spain; [2]Centro para Investigación en Red Enfermedades Raras (CIBERER), Spain; [3]Molecular Genetics Unit-INGEMM, La Paz Hospital (IDIPAZ), Madrid, Spain; [4]Instituto de Biología Molecular y Celular (IBMC), Porto, Portugal; [5]Neurology Department, Instituto de Investigación Biomédica, Hospital 12 de Octubre, Madrid, Spain; [6] Neurology Department, Hospital Universitario La Paz, Madrid, Spain; [7]Experimental Neurology Unit, Ramón y Cajal Hospital (IRYCIS), Madrid, Spain. [8]Neurology Department, Ramón y Cajal Hospital, Madrid, Spain.

Oculodentodigital dysplasia (ODDD, OMIM #164200) is a rare syndrome characterized by craniofacial, neurologic, limb and ocular abnormalities. ODDD is typically caused by heterozygous mutations in the *GJA1* gene, which encodes the gap junction protein connexin 43 (Cx43). Cx43 is expressed throughout multiple human tissues, including bone, heart and central nervous system, in which Cx43 is the primary gap junction constituent in astrocytes.
We describe a three generation family with ODDD. Sequencing of the coding region of *GJA1* gene was carried out by the Sanger method.
A 47 year old woman from Southern Spain came for evaluation with a 10 year history of spastic paraplegia (SP) with autosomal dominant inheritance. Upon examination, she had bilateral syndactyly of the 4th and 5th fingers, microphtalmia, hypertelorism, epicanthal folds, hypoplastic alae nasi and small teeth with enamel hypoplasia. Her mother also had adult-onset SP but without syndactyly, while the patient´s sister and one of her children both manifested as a childhood-onset SP and syndactyly. One of the patients, who had low-borderline IQ and never achieved an independent walk, had been diagnosed with cerebral palsy. The *GJA1* mutation c.253G>A (NM_000165.3);p.V85M (NP_ 000156) co-segregated with the SP in this ODDD family. The pathogenicity of this missense variant is further supported by another ODDD family previously reported with the p.V85M change, although no description of the neurological phenotype was provided.
The characteristic feature combination of ODDD cannot be missed and should prompt to the analysis of *GJA1* in patients with hereditary spastic paraplegia. We describe the variable severity of the neurological phenotype that can be caused by this point mutation. Whether one or diverse dysfunctional molecular mechanisms underlay the pleiotropic manifestations of Cx43 mutations remains to be elucidated.

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(56) Balance assessment in premanifest gene carriers and symptomatic SCA1 and SCA2 patients

Maria Rakowicz[1], Anna Sobańska[1], Leszek Czerwosz[2], Anna Sułek[3], Rafał Rola[4], Iwona Stępniak[3], Jakub Antczak[1]

[1]Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland;[2]Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland; [3]Department of Genetic, Warsaw, Poland; [4]First Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland.

Disequilibrium is one of the first signs of spinocerebellar ataxias (SCAs). The mechanisms leading to spinocerebellar degeneration are still not clearly understood. There is
no pharmacological treatment. Evaluation of first signs of gait and trunk ataxia and early rehabilitation assigned specifically for SCA patients seems to be crucial in long term disability prevention.
To assess objectively the alterations of balance in premanifest gene carriers and in symptomatic SCA patients. A total of 106 subjects underwent static posturography: 25 SCA1 and SCA2 premanifest gene carriers (RISCA) in mean age 26.3 ± 5.4 y., and 26 symptomatic SCA1 and SCA2 patients, aged 41.9 ± 13.9 y., from 32 families. The 55 healthy volunteers enrolled as a control group were divided into: younger group – 25 subjects with average age of 26.0 ± 4.3 y. and an older group - 30 cases aged 44.6 ± 10.2 y. All subjects were evaluated on a force plate and the sway of centre of gravity in standing position with open (EO) and closed eyes (EC) was recorded. We calculated from each stabilogram the basic parameters of motion trajectory of centre of feet pressure (COP): mean radius (R), developed surface area (A), and mean COP movement velocity (V). Ataxia was clinically evaluated with the Scale for Assessment and Rating of Ataxia (SARA).
All stabilogram measures expressed highly significant differences among investigated groups. In SCA patients the mean values were as follows: R_{EO} = 8.1 ± 2.7 mm, A_{EO} = 2.4 ± 2.1 cm^2, V_{EO} = 27.1 ± 13.6 mm/s in eyes open conditions and R_{EC} = 12.6 ± 5.2 mm, A_{EC} = 9.6 ± 1.1 cm^2, V_{EC} = 70.6 ± 56.7 mm/s with eyes closed. The corresponding values in RISCA group were: R_{EO} = 4.9 ± 2.6 mm, A_{EO} = 0.89 ± 0.99 cm^2, V_{EO} = 14.9 ± 8.8 mm/s and R_{EC} = 6.3 ± 3.3 mm, A_{EC} = 1.5 ± 1.9 cm^2, V_{EC} = 21.1 ± 14.2. The more pronounced influence of vision was found in symptomatic SCA patients, less evident in RISCA group. Young controls did not show any differences between sways with eyes open and closed. Older controls expressed small but statistically significant differences related to visual control. RISCA cases were different to the lesser degree from healthy volunteers. Statistical significant correlation of mean sway radius R_{EC} with SARA was found r= 0.69, if calculated in combined groups SCA and RISCA, whereas the correlation coefficient in SCA patients was r=0.49 and in RISCA group r=0.33. Remaining analyzed parameters of stabilogram correlated with SARA similarly.
All sway parameters did not correlated with number of CAG repeat.
Posturography is an objective measure of instability that correlates with the commonly used SARA test and reveals even slight balance abnormalities in the RISCA cases. In symptomatic SCA patients, the visual control is an important compensatory mechanism of posture stability.
Static posturography can be used as a sensitive evaluation tool of disease progression and rehabilitation effects as well as in clinical trials of patients with SCAs.

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(57) Double capture and next-generation sequencing as a diagnostic tool in hereditary spastic paraplegia

Laure Raymond[1,2,3], Emeline Mundwiller[4], Christel Depienne[1,2,3,5], Célia Gauthier[1,2,3], Cécile Cazeneuve[5], Eric Leguern[1,2,3,5], Yannick Marie[4], Giovanni Stevanin[1,2,3,5,6]

[1]Université Pierre et Marie Curie-Paris 6, UMR_S 975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM), 75013 Paris, France ; [2]CNRS, UMR 7225, 75013 Paris, France ; [3]INSERM, U975, 75013 Paris, France ; [4]Institut du Cerveau et de la Moelle Epinière, 75013 Paris, France ; [5]APHP, Fédération de génétique, Pitié-Salpêtrière Hospital, Paris, France ; [6]Laboratoire de Neurogénétique, Ecole Pratique des Hautes Etudes, Institut du Cerveau et de la Moelle épinière, 75013 Paris, France.

Hereditary spastic paraplegia (SPG) is a group of neurodegenerative disorders clinically characterized by progressive spasticity and weakness of the lower limbs. There is a considerable phenotypic heterogeneity, and mutations in more than 40 genes were involved to date, making genetic diagnosis by conventional molecular testing long and arduous.
We investigated whether targeted capture (Roche NimbleGen) of 34 SPG genes (532 exons), combined with next-generation sequencing (Roche GS Junior), are suitable for molecular diagnostics of SPG. 18 patients (10 with unknown genetic basis and 8 positive controls) were screened in 7 runs, in which cost and efficiency improvements was pursued by developing protocols of multiplexing and

double capture. Reads mapping and variant calling was performed using the Genomics Workbench software (CLC Bio).
Analysis of sequencing metrics showed a strong increase of the “on target” rate, from 5% in the simple capture assay to 80% in the double capture assay. The mean and minimum coverage remained reliable when multiplexing up to 4 patients. Less than 5% of exons had at least one base covered lower than 10X, meaning that these exons may need a Sanger resequencing. In all patients, ~40 variants compared to the Hg19 sequence were identified in exons and flanking intronic sequences. In positive controls, all the 26 known variations, distributed among 10 genes and including deletions up to 29 base pairs, were accurately detected. In patients with unknown mutations, further analyses are in process to determine which variations could be causative.
In conclusion, double capture combined with NGS seems to meet sensitivity, specificity and cost-effectiveness requirements for the genetic diagnosis of SPG, and a new capture is under design to target 42 SPG genes.

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(58) *ANO10* mutations define a significant fraction of cerebellar ataxias

Mathilde Renaud[1,2], Mathieu Anheim[1,2], Jean Pouge.[3], Mathias Mallaret[1,2], Kamsteeg E-J.[4], Drouot N.[2], Redin C.[2], Fanny Mochel[5,6], Salort-Campana E.[4], Muller J.[2], Scheffer H.[4], Alexandra Durr[5,6], Christine Tranchant[1,2], Michel Koenig[2,8]

[1]Département de neurologie, hôpitaux universitaires de Strasbourg, hôpital de Hautepierre, 67098 Strasbourg cedex, France ; [2]Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), INSERM-U964/CNRS-UMR7104/Université de Strasbourg, 67404 Illkirch, France ; [3]Département de neurologie, hôpitaux universitaires de Marseille, hôpital de la Timone, 13385 Marseille cedex 5, France ; [4]Department of Human Genetics, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands; [5]Université Pierre et Marie Curie Paris 6, Centre de recherche de l’institut du cerveau et de la moelle épinière, UMR-S975, 75005 Paris, France ; [6]AP-HP, Hôpital de la Salpétrière, Département de Génétique et Cytogénétique, 75013 Paris, France ; [8]Laboratoire de Diagnostic Génétique, Nouvel Hôpital Civil, 67091 Strasbourg, France.

Inherited cerebellar ataxias are heterogeneous disorders. We reported *ANO10* mutations as the genetic basis of a novel form of autosomal recessive cerebellar ataxia (ARCA, Vermeer et al. Am J Hum Genet 87:813-9, 2010). We have since then sequenced *ANO10* in 46 patients with pure cerebellar ataxia defined by presence of cerebellar atrophy and absence of peripheral neuropathy. Fifteen patients were sequenced by the Sanger method and 31 were sequenced by exon capture of 57 ataxia genes followed by high throughput sequencing. We identified 6 new *ANO10* mutations in 4 independent patients. Pyramidal features were variably present. Brain MRI demonstrated isolated, diffuse and severe cerebellar atrophy. Comparison with the eleven previously published patients revealed a clear genotype/phenotype correlation. The complete loss of function mutations were associated with juvenile/adolescent onset and mental retardation while the presence of at least one predicted partial loss of function mutation was associated with adult onset, slow progression and persistence of ambulation over a long disease duration. These observations indicate that *ANO10* defect is a relatively frequent cause of ARCA with severe cerebellar atrophy and absence of peripheral neuropathy. We suggest naming this entity ARCA3, following the description of patients with SYNE1 and ADCK3 mutations, causing respectively ARCA1 and ARCA2, and also prominently associated with cerebellar atrophy and absence neuropathy.

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(59) Characterization of families from Southern Italy with autosomal dominant spastic paraplegia and recessive ataxia with myoclonic epilepsy

Carlo Rinaldi[1], Chiara Criscuolo[2], Filippo M. Santorelli[3], Janel O. Johnson[4], Giuseppe De Michele[2], Alessandro Filla[2], Bryan J. Traynor[4], Kenneth H. Fischbeck[1]

[1]Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA; [2]Dipartimento di Scienze Neurologiche, Università Federico II, Napoli, Italy; [3]Unità complessa di medicina molecolare, IRCCS Fondazione Stella Maris, Pisa, Italy;
[4]Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA.

We are studying two families from Southern Italy with respectively a dominantly inherited pure form of spastic paraplegia (family 1) and an autosomal recessive disease characterized by progressive myoclonus, epilepsy, and ataxia (family 2). Gene identification studies with exome sequencing and candidate evaluation are in progress.
Twelve subjects across 3 generations from family 1 were clinically assessed, and DNA was collected from 10 (5 affected and 5 unaffected), with informed consent. All affected subjects had a progressive

spastic gait abnormality, with bilateral extensor-plantar reflex, and sustained ankle or knee clonus. The mean ± SD age of symptom onset was 36 ± 12 (range 19–48) years. Disease progression was rapid, leading to wheelchair use and walking only with assistance in less than 10 years. Brain MRI scans were generally normal, and motor evoked potential studies showed prolongation of central conduction time. No mutations were found in SPG3A, SPG4, NIPA1, SPG13, KIF5A, REEP1, and ZFYVE27.
The four affected members of family 2 had onset of generalized tonic clonic seizures between 8 and 12 years of age; the onset of myoclonus and ataxia was difficult to establish with accuracy. Myoclonic jerks were marked, and affected the head, trunk, and upper and lower extremities. The jerks were sometimes observed at rest, but appeared primarily during action and when the arms or the legs were in an outstretched position. The ocular fundi were normal, and visual acuity was not impaired. Cognitive impairment was present in all patients. Routine laboratory examination, ceruloplasmin, lactate, hexosaminidases A and B, arylsulfatase, urine sialyloligosaccharides, and anti-gliadin and anti-endomysial antibodies levels were normal. MRI brain scans showed cerebellar atrophy in all subjects, with associated with cerebral atrophy. EEG back-averaging, triggered by myoclonus in wrist flexor muscles, showed a large positive-negative biphasic EEG discharge in the contralateral hemisphere, time-locked to the muscle contraction, in both patients examined. A muscle biopsy specimen showed normal morphology and histochemistry, without ragged red fibers. No Lafora bodies or 'fingerprint' inclusions were observed at skin biopsy. The clinical picture of our patients suggests the diagnosis of Unverricht Lundborg disease. However, genetic analysis showed no mutation in CSTB. Neither were mutations found in EPM2A or NHLRC1.

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(60) The global epidemiology of hereditary ataxias and spastic paraplegias: a systematic review of prevalence studies

Luis Ruano[1], Cláudia Melo[2], M. Carolina Silva[3], Paula Coutinho[4]

[1]Hospital de São Sebastião, CHEDV, Santa Maria da Feira, Portugal ; [2]Centro Hospitalar do Médio Ave, Famalicão, Portugal ; [3]UNIFAI, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal ; [4]CGPP – Centro de Genética Preditiva e Preventiva, IBMC – Instituto de Biologia Molecular e Celular, Universidade do Porto, Porto, Portugal.

There is great uncertainty regarding the global distribution and prevalence of hereditary cerebellar ataxia (HCA) and hereditary spastic paraplegia (HSP). Our aim is to systematically review and perform meta-analysis of HCA and HSP prevalence studies.
We searched the MEDLINE, ISI Web of Science and SCOPUS databases for studies providing a prevalence estimate of a defined population and geographical region for at least one of the following groups: autosomal dominant (AD) HCA, autosomal recessive (AR) HCA, AD-HSP or AR-HSP published from 1 of January of 1983 to 3 of February of 2013. Relevant
methodological parameters and data were extracted using an assessment grid. Random-effects meta-analysis was performed for each one of the above-mentioned groups and for combined HSP and HCA prevalence
Overall, 22 studies were included, reporting 14,539 patients from 16 different countries with a reference population of around 347 million people. The overall prevalence average for HCA and HSP is 9.8/105 (95% CI, 6.7-12.8). AD-HCA prevalence ranged from 0.0 to 5.6/105, with a pooled average of 2.7/105 (95% CI, 1.5-4.0). MJD/SCA3 is the most common dominant ataxia, followed by SCA2 and SCA6, the three with a worldwide geographical distribution. The AR-HCA prevalence ranges from 0.0 to 7.2/105, with an average of 3.3/105 (95%CI, 1.8-4.9). Friedreich ataxia is the most frequent AR-HCA in every country except Japan, followed by ataxia with oculomotor apraxia or ataxia-telangiectasia. The prevalence of AD-HSP ranges from 0.5 to 5.5/105 and of AR-HSP from 0.0 to 5.3/105, with pooled averages of 1.8/105 (95%CI, 1.0-2.7) and 1.8/105 (95%CI, 1.0-2.6) respectively. The most common AD-HSP form in every population was SPG4 followed by SPG3A, while SPG11 is the most frequent AR-HSP followed by SPG15. In population-based studies, the number of families without genetic diagnosis after systematic testing ranges from 33% to 92% in the AD-HCA, 40-46% in ARHCA, 45-67% in the AD-HSP and 71-82% in the AR-HSP.
HCA and HSP are present in multiple populations across the world with variable prevalence values. This variation reflects in part the different genetic background of the surveyed populations, but also the methodological heterogeneity of the studies. The overall average prevalence in the surveyed areas is around 1:10.000 inhabitants. Multisource population-based studies yielded higher prevalence values than genetic centres or hospital based studies. In spite of the advances in genetic research, most families in population-based series persist without identified genetic mutation, even after extensive testing.

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(61) Autophagy involvement in retinal degeneration in a SCA7 Knock-In mouse model

Anais Sapienza[1,2,3], Martina Marinello[1,2,3], Sandro Alves[1,2,3], Huda Zoghbi[4], Alexis Brice[1,2,3,6], Giovanni Stevanin[1,2,3,6,7], Annie Sittler[1,2,3,6], Khalid H. El Hachimi[1,2,3,6,7]

[1]Université Pierre et Marie Curie-Paris 6, UMR-S975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Paris, France ; [2]Inserm, U975, Paris, France ; [3]Cnrs, UMR 7225, Paris, France
[5]Departments of Pediatrics - Neurology and Developmental Neuroscience, Molecular and Human Genetics, and Neuroscience, Jan and Dan Duncan Neurological Research Institute, Houston, USA ; [6]AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Paris, France ; [7]Groupe de neurogénétique, Ecole Pratique des Hautes Etudes, Institut du Cerveau et de la Moelle épinière, Paris, France.

Spinocerebellar ataxia type 7 (SCA7) is a neurodegenerative disorder of dominant inheritance, associated with neuronal degeneration in cerebellum and retina. It is caused by an expansion of a trinucleotide CAG repeat, leading to a polyglutamine expansion in the ataxin 7 protein (ATXN7). The time course of retinal degeneration of a KI mouse model of the disease presenting 100 glutamines in ATXN7, generated by H. Zoghbi, was carried out. Mutated ATXN7 accumulated early (4-6 months) in intranuclear inclusions in every retinal layers; then the gliosis (astrocytic and microglial) was evidenced at 7 month and increased with disease progression and photoreceptor degeneration. KI mouse span life was 14 months. Chromatin decondensation in the photoreceptor cell nucleus was evident and also associated with atrophic outer segments. Many photoreceptor cells showed “dark cell” features. This substantial neuronal loss in this mouse is apparently associated with many autophagic and lysosomal vesicles in the residual retinal neurons. Lastly, autophagy was abundant but fails to eliminate the inclusions and/or to protect against neuronal death. In conclusion, the KI mouse model presents with severe neuronal death and activated autophagy processes in an attempt to compensate for the accumulation of mutated ATXN7.

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(62) SCA36 molecular analysis in patients with spinocerebellar ataxia

E. Sarto, S. Magri, C. Mariotti, L. Nanetti, C. Gellera, D. Di Bella, F. Taroni

Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy.

Autosomal dominant spinocerebellar ataxias (SCA) are a heterogeneous group of neurological disorders characterized by cerebellar dysfunction mostly due to Purkinje cell degeneration. Recently, a novel form of spinocerebellar ataxia (SCA36) with motor neuron involvement was described in Japanese and Galician patients. It is caused by a GGCCTG repeat expansion in intron 1 of NOP56 gene. This gene encodes a component of the ribonucleoprotein complex and plays a role in transcription and splicing. The objectives is to
screen a large cohort of Italian unrelated patients with familiar (n=142) or sporadic/unknown (n=254) spinocerebellar ataxia for GGCCTG repeat expansion in NOP56 intron 1. All patients were negative for the common SCA1 and SCA2 mutations.
The NOP56 repeat was analysed by fluorescent triplet repeat-primed PCR (TPPCR) analysis, using three primers including one fluorescent-dye-conjugated forward primer, a first reverse primer consisting of 4 repeat units and a 5’ anchor tail, and a second reverse anchor primer. Results: NOP56 intron1 repeat expansion was detected in 5 probands from 4 different unrelated Italian families with dominant ataxia and also in one sporadic patient and, subsequently, in his affected brother. Normal alleles in the SCA populations ranged from 6 to 14 repeats, with the 9-repeat allele being the most frequent. Interestingly, all probands originated from a relatively small area in central Italy, suggesting a common ancestor and a founder effect for this mutation. Conclusions: SCA36 accounts for approximately 3% of Italian autosomal dominant SCA families negative for the common SCA mutations, a frequency lower than that (6.9%) observed in Galician patients but similar to that (3.6%) found in the Japanese population. Clinically, mutated patients presented with slow progressive gait ataxia with late onset (40-60 yrs) with pyramidal signs, eye movement abnormalities and, in some cases, motor neuron involvement (tongue atrophy). Neuroimaging revealed prominent cerebellar atrophy affecting the vermis, with minor involvement of cerebellar hemispheres and brainstem in later stages

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(63) Analyzing potential genetics modifiers of Spinocerebellar ataxia type 3

Thorsten Schmidt[1,2], Katrin Gross[1,2], Laura Dengler[1,2], Theocharis Tsoleridis[1,2], Jonasz Weber[1,2], Hjörvar Pétursson[3], Peter Bauer[1,2], and Olaf Riess[1,2]

[1]Institute of Medical Genetics & Applied Genomics, University of Tuebingen, Tuebingen, Germany; [2]Center for Rare Diseases (ZSE), University Hospital Tuebingen, Tuebingen, Germany; [3]Statistics Iceland, Reykjavík, Iceland.

Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease (MJD) is an autosomal-dominantly inherited, neurodegenerative disorder caused by the expansion of a CAG repeat in the *MJD1 gene* leading to an expanded polyglutamine repeat in the encoded ataxin-3 protein. Statistically, a correlation between the number of CAG repeats and the age at onset of SCA3 patients exists and patients with more CAG repeats have an earlier onset of symptoms. However, this statistical correlation is not perfect and the number of CAG repeats contributes only about 55 % to the age at onset. Therefore, the remaining 45 % are influenced by other factors, which we aim to identify in this study. Aside from the CAG repeat itself, the *MJD1 gene* contains several polymorphisms within the coding region which lead to amino acid changes or even a premature stop in the encoded ataxin-3 protein.
Here, we assume that the amino acid changes within ataxin-3 resulting from these polymorphisms influence the function of normal and expanded ataxin-3 and/or its interaction with other proteins and therefore modify the age at onset, the pathogenesis and disease progression of SCA3 patients. We, therefore, genotyped more than 500 samples of SCA3 patients for these polymorphisms and generated haplotypes comprising the CAG repeat length and the polymorphisms located downstream. Two haplotypes turned out to be most common among SCA3 patients and additional haplotypes have a possible impact on the age at onset in SCA3. We hope that our results will improve the prediction of clinical symptoms and contribute to the understanding of pathogenic processes in SCA3.

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(64) *AFG3L2* partial deletions can cause spinocerebellar ataxia type 28

Katrien Smets[1,2,3], Tine Deconinck[1,2,3], Jonathan Baets[1,2,3], Jean-Jacques Martin[2,3], Anne Sieben[3,4], Iris Smouts[1,2,3], Elena Rugarli[5,6], Shuaiyu Wang[5,6], Franco Taroni[7,8], Daniela Di Bella[7,8], Wim Van Hecke[9,10], Paul Parizel[9,10], Christina Jadoul[11], Robert De Potter[12], Fran Couvreur[13], Peter De Jonghe[1,2,3]

[1]Neurogenetics Group, Department of Molecular Genetics, VIB, University of Antwerp, Antwerp, Belgium; [3]Department of Neurology, Antwerp University Hospital, Edegem, Belgium; [3]Neurogenetics Laboratory, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; [4]Department of Neurology, Ghent University Hospital, Ghent, Belgium; [5]Biocenter , University of Cologne, Cologne, Germany; [6]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; [7]Unit of Genetics of Neurodegenerative and Metabolic Disease, Milan, Italy; [8]Fondazione Istituto Neurologico Carlo Besta, Milan, Italy; [9]Department of Radiology, Antwerp University Hospital, Antwerp, Belgium; [10]Icometrix, Leuven, Belgium; [11]Department of Neurology, Hospital AZ Nicolaas, Sint Niklaas, Belgium; [12]Department of Neurology, Hospital AZ Saint-Lucas, Gent, Belgium; [13]Department of Neurology, Hospital AZ Klina, Brasschaat, Belgium.

Spinocerebellar ataxia type 28 (SCA28), first described in 2006, represents one of 11 autosomal dominant (AD) SCA subtypes currently known to be caused by point mutations. The culprit gene *AFG3L2* on chromosome 18p11 encodes a mitochondrial protein. So far 11 missense mutations and one small indel mutation have been observed in SCA 28. SCA 28 has a juvenile onset and is a slowly progressive disease with eye movement disturbances and ptosis as hallmark features, although pyramidal signs can be present too. A total of 15 families of Italian, French and German origin have been published to date and missense mutations in the *AFG3L2* proteolytic domain account for 1,5% of European Autosomal Dominant Cerebellar Ataxias. By contrast, autosomal recessive spastic ataxia (SPAX5) is caused by a homozygous mutation in the *AFG3L2* and is reported in a single family worldwide. It is however still questionable whether SPAX5 is due to a true recessive trait or the result of co-dominant alleles. Here we report the clinical findings of 19 patients belonging to two SCA28 families harboring an identical heterozygous partial deletion of exon 14-15-16 in the proteolytic domain of *AFG3L2.* In the largest pedigree we obtained conclusive linkage to the SCA28 locus but mutation analysis failed to detect a point mutation in *AFG3L2*. Multiplex Amplicon Quantification (MAQ) subsequently detected the genomic rearrangement. Both Belgian families share a common haplotype suggesting a common founder. Although the nature of the mutation could suggest haploinsufficiency as the underlying pathomechanism, RNA and Western Blot analysis showed the presence of a *AFG3L2* RNA and the corresponding truncated protein, suggesting that this partial deletion escapes

nonsense mediated decay. Functional studies are ongoing to elucidate the consequences of this truncated protein. A brain autopsy in one patient showed severe olivo-cerebellar atrophy.
In six patients we performed MRI with Diffusion Tensor Imaging (DTI) and a Cerebellar Volumetric Measurements, confirming the presence of a superior vermis atrophy in SCA 28. Our study adds to the phenotype characterization of SCA28 but most importantly demonstrates that specific testing for rearrangements is warranted since these DNA alterations escape detection by classical PCR-based Sanger sequencing.

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(65) The clinical phenotype of Polish patients with *ATL1* gene point mutations: preliminary description

I. Stępniak[I], E. Elert-Dobkowska[I], M. Rakowicz[2], W. Łojkowska[3], M. Rajkiewicz, W. Krysa[I], E. Zdzienicka[I], J. Zaremba[I], A. Sułek[I]

[I]Department of Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland; [2]Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland; [3]First Neurological Department, Institute of Psychiatry and Neurology, Warsaw, Poland.

Hereditary spastic paraplegias (HSP) are a group of clinically and genetically heterogeneous, neurodegenerative disorders characterized by progressive spasticity of the lower limbs. Mutations in the *SPAST* and *ATL1* genes are responsible for the most frequent forms of AD-HSP.
The majority of patients with mutations in the *ATL1* gene, encoding atlastin 1, present pure form of HSP with early onset and slow progression, the additional features occur rarely.
In a group of 128 index patients (66 with AD-HSP family history and 62 isolated cases) clinically diagnosed as HSP, in whom *SPAST* mutations were previously excluded, we identified 5 different missense mutations in *ATL1* gene in six families (2 mutations not described to date). All mutations carriers and their family members (not yet genetically analyzed) underwent a detailed neurological examination. The diagnostic criteria for HSP were used according to Fink. Functional impairment was assessed by the Spastic Paraplegia Rating Scale (SPRS) and classification used by Dürr.
In a group of 20 patients clinically examined, the age at onset ranged 1 - 32 years (mean 7±3.5), disease duration 1-47 years, SPRS scores 0 – 25 (mean 12±8.4). Seventeen patients had gait disturbances but could move without walking aids (disability score 2 or 3). One patient didn't complain of gait problems, but neurological examination detected evident signs of spasticity. The results of neurological assessment in two obligate mutations carriers (their children and siblings affected) were normal.
The present study revealed early onset and slow progression of SPG3. The clinical picture in our patients was consistent with pure HSP. All individuals had family history of AD-HSP. These results are in agreement with previously described SPG3 cases. In two families (with different mutations in exon 12, replacing arginine with tryptophan) incomplete penetrance was observed. Mutation R415W was reported previously as having the lowest penetrance.

Key words: hereditary spastic paraplegia, ATL1 gene, disability

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(66) Recessive dystonia-ataxia syndrome in a Turkish family caused by a FAM36A (COX20) mutation

Sarah Stricker[1], Björn Arns[2], Thomas Klopstock[3], Christine Zühlke[4], Alfredo Ramirez[2,5], Susen Winkler[2], Matthias Endres[1,6,7], Christine Klein[2], Katja Lohmann[2]

[1]Department of Neurology, Charité – University Medicine Berlin, Berlin, Germany; [2]Institute of Neurogenetics, University of Lübeck, Lübeck, Germany; [3]Department of Neurology with Friedrich-Baur-Institute, Ludwig-Maximilians-University, Munich, Germany; [4]Institut für Humangenetik, Universität zu Lübeck, Lübeck, Germany; [5]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany; [6]Center for Stroke Research Berlin (CSB), Charité – University Medicine Berlin, Berlin, Germany; [7]NeuroCure Cluster of Excellence, Charité – University Medicine Berlin, Berlin, Germany.

A combination of dystonia and cerebellar ataxia is referred to as DYTCA syndrome. In a few cases with sporadic or autosomal dominantly inherited disease, the disorder has been explained by mutations in selected spinocerebellar ataxia (SCA) genes including SCA1 (ATXN1), SCA2 (ATXN3), SCA3 (ATXN3), SCA6 (CACNA1A), SCA7 (ATXN7), or SCA12 (PPP2R2B).
We here describe two affected siblings with consanguineous parents of Turkish descent. Detailed clinical and biochemical investigations were performed and included a muscle biopsy. After exclusion of known genetic causes, we carried out exome sequencing in both affected siblings. For validation, we chose those variants that were (1) homozygous in both patients (2) considered to change the protein sequence, and (3) reported at a frequency of <1% in public databases. We prioritized genes

for follow-up with a reported function linked to movement disorders and/or mitochondrial dysfunction. The best candidate variant was re-sequenced by Sanger sequencing and tested for heterozygosity in the parents. Its frequency was estimated by genotyping 427 healthy controls of Turkish, Pakistani, and German background. All exons of the FAM36A gene were sequenced in another 80 early-onset dystonia and 49 early-onset ataxia patients.
The affected brother presented with leg dystonia, cerebellar ataxia, and sensory axonal neuropathy, while his sister had a torticollis, gait ataxia, and a sensory axonal neuropathy on a background of developmental delay. Onset was in early childhood. The muscle biopsy revealed a mitochondrial respiratory chain complex IV deficiency. Exome sequencing identified a homozygous missense mutation (c.154A>C; p.Thr52Ser) in both patients in the FAM36A gene. FAM36A shows homology to the fungal complex IV assembly factor COX20. Both unaffected parents carried the mutation in the heterozygous state, while it was absent in 854 control chromosomes. We did not detect any other patient with homozygous or compound heterozygous mutations in FAM36A. Notably, the same mutation was recently described in 1 of 40 patients with complex IV-deficiency who presented with early-onset cerebellar ataxia, intention tremor, and pyramidal signs.
Mutations in FAM36A/COX20 are a novel cause of recessively inherited, early-onset dystonia-ataxia syndrome and reduced complex IV-activity.

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(67) Spinocerebellar ataxias (SCAs) and hereditary spastic paraplegias (HSP) - rare movement disorders prevalence in Poland

A. Sulek[1], W. Krysa[1], E. Elert-Dobkowska[1], M. Rajkiewicz[2], I. Stepniak[1], M. Rakowicz[1], R. Rola, M. Dusza-Rowinska[??], J. Zaremba[1]

[1]Department of Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland; [2]Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland; [3]First Neurological Department, Institute of Psychiatry and Neurology, Warsaw, Poland.

Hereditary movement disorders represent a large group of heterogenic diseases diversified in terms of mode of transmission - dominant, recessive or X linked, molecular causative defect - numerous genes harbouring pathogenic mutations and clinical presentation.
This category of disorders, among the others, includes 40 types of spinocerebellar ataxias (SCAs) (10 SCAs caused by dynamic mutations) and hereditary spastic paraplegias (HSP) resulting from point mutations and micro-rearrangements in respective genes - 48 HSP loci known so far.
The aim of the retrospective study was to assess the relative prevalence of rare hereditary movement disorders: spinocerebellar ataxias caused by dynamic mutations and spastic paraplegias molecularly confirmed in Poland.
During 15 years of testing for SCAs resulting from dynamic mutations, performed for 9 types of SCAs: SCA 1, 2, 3, 6, 7, 8, 12, 17 and 36; amongst 2845 individuals in 531 subjects pathogenic expansions were detected. The identified 531 mutation carriers belong to the following pedigrees: 172 SCA1, 28 SCA2, 1 SCA3 (of German origin) 2 SCA7, 48 SCA8, 3 SCA17 and the most recent finding 5 SCA36 families.
The molecular investigation on hereditary spastic paraplegias (HSP, SPG) performed until now for 221 probands revealed 47 mutation carriers, among those 33 were found to be affected with SPG4 (19 point mutations, 14 micro-rearrangements), which stands for 70% of all detected cases. In the remaining 14 subjects two other autosomal dominant HSPs caused by point mutations were found: SPG3 – 6 cases and SPG31 – 2 cases and two autosomal recessive types: SPG11 – 5 cases, SPG7 – 1 case resulting from micro-rearrangements in respective genes.
Contrary to the highest worldwide SCA3 incidence, among Polish patients only 1 SCA3 family was found, whereas SCA1 is the commonest genetic type of SCA in Poland with relative frequency of 67% (among all genetically confirmed SCAs). In accordance to published data on specific SPG types frequencies, SPG4 was also the most prevalent within Polish group of patients tested till now.

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(68) Deciphering early-onset ataxias: an international multicenter registry (*EOA registry*)

Matthis Synofzik[1,2] , Maja Steinlin[3], Peter Baxter[4], Ludger Schöls[1,2], EOA study group
[1]Department of Neurodegeneration, Hertie Institute for Clinical Brain Research and Centre of Neurology, Tübingen, Germany; [2]German Research Center for Neurodegenerative Diseases (DZNE), University of Tübingen,Germany; [3]Department of Neuropaediatrics, Development and Rehabilitation, University Children's Hospital, Inselspital, Bern, Switzerland; [4]The Ryegate Children's Centre, Sheffield, UK.

Early onset ataxias (EOA) are a highly heterogeneous group of degenerative and metabolic diseases, mostly due to genetic causes with autosomal-recessive inheritance. Although an increasing number of recessive ataxia genes is currently identified, more than 50% of all EOA still remain genetically

undefined, thus warranting collaborative efforts to identify and validate novel EOA gene candidates in joint EOA cohorts. Moreover, knowledge about the comparative frequencies, phenotypic spectra, biomarkers and natural history progression of the respective EOAs is still missing. This is largely due to the fact that – in contrast to the successful EUROSCA registry for dominant ataxias - an orchestrated systematic multi-center registry has still been missing for the even rarer recessive ataxias.
We established a pseudoanonyminised, web-based registry collecting data on subjects with congenital or early onset (start <40years of age) ataxias that allows to systematically aggregate and study EOA subjects with both unexplained and genetically defined ataxia across Europe. Data include a standardized, systematic assessment of: demographics, evolution of ataxia and non-ataxia disease features, disease progression determined by SARA, serum biomarkers, electrophysiological features, MRI and genetic analyses.
A first analysis of registry entries shows that data entry is readily feasible for different centers across Europe. It allows for an extensive phenotypic and serum characterization of subjects with so far unexplained EOA, which can be easily assessed for screening and validating novel ataxia genes or for forming well-defined subgroups that can be jointly investigated by whole exome sequencing to identify new EOA genes. In subjects with previously genetically defined ataxia, it allows to compare to compare regional frequency of genotypes, to define the respective phenotypic spectrum and to perform a comparative analysis of electrophysiological characteristics, neuroimaging findings and metabolic markers.
This registry allows large-scale genetic and phenotypic studies in EOA, thus preparing the ground for comprehensive international cooperations and applications (e.g. to the EU). It provides the basis for comparative natural history studies in EOA subtypes, which are essential for upcoming interventional studies.

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(69) Alteration of fatty-acid-metabolizing enzymes affect mitochondrial form and function in Hereditary Spastic Paraplegia

C. Tesson[1,20], R. Rossignol[13], M.A.M. Salih[3], M. Zaki[7], F. Fellmann[4], R. Schule[9], C. Mignot[2], M. Nawara[1], E. Obre[13], C. Durand[13], A. Bouhouche[10], F. Santorelli[11], A. Caballero Oteyza[9], K.H. El-Hachimi[1,20], F. Lamari[16], T. Esteves[1], M. Gaussen[1], M-L. Monin[1], G. Gyapay[15], D. Lechner[14], M.A. Gonzalez[18], C. Depienne[1,2], F. Mochel[1,2,], J. Lavie[13], L. Schols[9], D. Lacombe[13], S. Zuchner[18], A. Yamashita[19], A. Benomar[10], J. Gleeson[8], C. Goizet[13], A. Brice[1,2,], A. Durr[1,2,], F. Darios[1], G. Stevanin[1,2,20]

[1]Institut du Cerveau et de la Moelle épinière (INSERM / UPMC UMR_S975, CNRS 7225, NEB), Pitié-Salpêtrière Hospital, Paris, France ; [2]APHP, Fédération de Génétique, Hôpital Pitié-Salpêtrière, Paris, France ; [3]King Saud University, Riyadh, Saudi Arabia; [4]Département de Génétique Médicale, CHUV, Lausanne, Suisse ; [7]National Research Institute in Cairo, Egypt; [8]University of California, San Diego. USA; [9]Hertie-Institute for Clinical Brain Research and Center for Neurology, Germany; [10]Hôpital des Spécialités, Rabat, Morocco ; [11]IRCCS Fondazione Stella Maris, Calambrone, Pisa, Italy ; [13]Université de Bordeaux, France ; [14]Centre National de Génotypage, Evry, France ; [15]Genoscope, Evry, France ; [16]Service de Biochimie, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, 75013 Paris, France ; [18]Department of Human Genetics and Hussman Institute for Human Genomics, Miller School of Medicine, University of Miami, USA; [19]Department of Life and Health Sciences, Faculty of Pharmaceutical Sciences, Teikyo, University, Tokyo, Japan; [20]Ecole Pratique des Hautes Etudes, Paris, France.

Hereditary spastic paraplegia (HSP) is considered one of the most heterogeneous group of neurological disorders, both clinically and genetically. It comprises pure and complex forms that clinically include slowly progressive lower-limb spasticity resulting from degeneration of the corticospinal tract. At least 50 loci accounting for these diseases have been mapped to date, and mutations have been identified in 29 genes, most of which playing a role in intracellular trafficking. Here, we identified mutations in two functionally related genes (DDHD1 and CYP2U1) in individuals with autosomal recessive forms of HSP by using either the classical positional cloning or a combination of whole-genome linkage mapping and next-generation sequencing. Interestingly, three subjects with CYP2U1 mutations presented with a thin corpus callosum, white-matter abnormalities, and/or calcification of the basal ganglia. Furthermore, we recently identified a new mutation of *CYP2U1* in a Switzerland family: c.1A>C/ p.M1L. This mutation is also present in an asymptomatic sister aged of 50 years; suggesting an incomplete penetrance or a metabolic compensation in this individual. These genes code for two enzymes involved in fatty-acid metabolism, and we have demonstrated in human cells that the HSP pathophysiology includes alteration of mitochondrial architecture and bioenergetics with increased oxidative stress. Our combined results focus attention

on lipid metabolism as a critical HSP pathway with a deleterious impact on mitochondrial bioenergetic function.

Keywords: Hereditary spastic paraplegia, *arachidonic acid, lipid metabolism*

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(70) Impaired eyeblink conditioning in preclinical carriers of a spinocerebellar ataxia type 3 (SCA3) mutation

J. van Gaalen[1], R.P.P.W.M. Maas[1], K.Y van Spaendonck-Zwarts[3], E.F. Ippel[4], C.C. Verschuuren-Bemelmans[5], S. Vermeer[2], B.P. van de Warrenburg[1]

[1]Department of Neurology & Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands; [2]Department of Human Genetics Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; [3]Department of Clinical Genetics, Amsterdam Medical Centre, Amsterdam, the Netherlands; [4]Department of Medical Genetics, University Medical Centre Utrecht, Utrecht, the Netherlands; [5]Department of Genetics, University Medical Centre Groningen, Groningen, the Netherlands.

There are suggestions that in dominant spinocerebellar ataxias (SCAs), cerebellar dysfunction is present before the actual clinical onset of ataxia. The cerebellum plays an essential role in classic eyeblink conditioning (EBC) and it has been generally established that cerebellar pathology affects this form of motor learning. We here explore whether abnormal EBC can be demonstrated in preclinical carriers of a CA3 mutation, which would provide an objective marker for cerebellar dysfunction in this disease stage.
We performed EBC experiments in 14 SCA3 mutation carriers and 11 age-matched controls.
A standard delay EBC procedure was performed in which paired trials of a conditioned stimulus (CS; auditory tone) and an unconditioned stimulus (US; electrical stimulus) were administered to acquire conditioned eyeblink responses (CRs). As outcome measures the number of CRs was counted manually. Percentages of CRs between blocks were analyzed with Friedman-ANOVA en Mann-Whitney-U-tests.
Mutation carriers demonstrated a lower percentage of CRs per block than controls. And whereas the percentage of CRs significantly increased across the six learning blocks in controls, no such block effect was observed in carriers.
Significant differences between both groups could not be found in any of the blocks. However, there was a significant subdivision in the carrier group: one subgroup showed normal to strong acquisition, while the other subgroup demonstrated hardly any acquisition of CRs.
As we are currently testing more subjects, these results are preliminary.
The first data of this ongoing study provides evidence of abnormal EBC and thus cerebellar dysfunction in preclinical carriers of a SCA3 mutation. In particular, there is a subgroup of carriers with very poor acquisition of CRs, and in them it is likely that the pathological process has reached a certain threshold that can be picked up as reduced cerebellar learning.

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List of the SPATAX members (research laboratories and clinical departments)

Dr. Alexandra DURR (coordinator)
Pr. Giovanni STEVANIN (co-coordinator)
Pr. Alexis BRICE
Dr. Annie SITTLER
Dr. Frédéric DARIOS
Cricm U975
Pitié-Salpêtrière Hospital
47 boulevard de l'Hôpital
75013 Paris, France
alexandra.durr@upmc.fr
giovanni.stevanin@upmc.fr
alexis.brice@upmc.fr
annie.sittler@upmc.fr
frederic.darios@upmc.fr

Pr. Jean-Philippe AZULAY
Service de Neurologie et Pathologies du Mouvement
Hôpital d'Adultes de la Timone
264, rue Saint-Pierre
13385 Marseille cedex 5, France
jazulay@ap-hm.fr

Pr. Ali BENOMAR
Service de Neurologie B
Laboratoire de Neurogénétique
Hôpital des Spécialités
Rabat Instituts
BP 6402 Rabat, Morocco
ali.benomar@hotmail.com

Pr. Enrico BERTINI
Molecular Medicine & Dept. of Neurosciences
Osp. Bambino Gesù, Piazza S. Onofrio, 4
00165 Rome, Italy
ebertini@tin.it

Pr. Odile BOESFPLUG-TANGUY
Inserm U676
Hôpital Robert Debré
48 boulevard Sérurier
75019 Paris, France
odile.boespflug-tanguy@rdb.aphp.fr

Dr. Alfredo BRUSCO
Department of Medical SCiences
University of Turin
via Santena, 19
10126 Torino, Italy
alfredo.brusco@unito.it

Pr. Giorgio CASARI
Vita-Salute San Raffaele University and
Human Molecular Genetics Unit
San Raffaele Scientific Institute
DIBIT, Via Olgettina 58
20132 Milano, Italy
casari.giorgio@hsr.it

Pr. Paula COUTINHO
UnIGENe and Centro de Genetica Preditiva e Preventiva, Institute for Molecular and Cell Biology, Universidade do Porto
Rua do Campo Alegre, 823
4150-180 Porto, Portugal
paula.coutinho@ibmc.up.pt

Pr. Alessandro FILLA
Dipartimento Di Scienze Neurologiche
Clinica Neurologica, Università Degli Studi Di Napoli Federico II
Via Pansini 5
80131 Napoli, Italy
afilla@unina.it

Pr. Cyril GOIZET
Consultation de Neurogénétique
CHU de Bordeaux, Hôpital Pellegrin
Place Amélie Raba-Léon
33076 Bordeaux cedex, France
cyril.goizet@chu-bordeaux.fr

Pr. Hamri ABDELMADJID
Service de Neurologie
Hôpital Benbadis
Constantine, Algeria
hamrimadjid@yahoo.fr

Pr. Didier HANNEQUIN
Unité de Génétique Clinique
Hôpital Charles Nicolle
1 rue de Germont
76031 Rouen, France
Didier.Hannequin@chu-rouen.fr

Dr. Jamilé HAZAN
INSERM UMR 952
Université Pierre et Marie Curie
7 Quai Saint Bernard, Bâtiment A 3ème étage
75252 Paris cedex 05, France
jamile.hazan@snv.jussieu.fr

Pr. Michel KOENIG
INSERM U964
Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC)
Parc d'innovation, 1 rue Laurent Fries
BP 10142
67404 Illkirch cedex, France
mkoenig@igbmc.fr

Pr. Vladimir S. KOSTIC
Institute of Neurology
Clinical Centre of Serbia
str. Dr. Subotica 6A
Belgrade 11000, Serbia
vkostic@sbb.co.yu

Dr. Berry KREMER
Department of Neurology
University Medical Centre Groningen
Hanzeplein 1
9700 RB Groningen, The Netherlands
h.p.h.kremer@umcg.nl

Pr. Pierre LABAUGE
Service de neurologie
Pôle Neurosciences Tête et Cou
CHU de Montpellier
Hôpital Gui de Chauliac

80, avenue Augustin Fliche
34295 Montpellier cedex 5, France
labauge@yahoo.fr

Dr. Alexander LOSSOS
Department of Neurology
Hadassah-Hebrew University Medical Centre Hospital
Ein Kerem, Jerusalem 91120, Israel
alos@hadassah.org.il

Dr. André MÉGARBANÉ
Unité de génétique Médicale
Université Saint-Joseph Faculté de Médecine
Campus des Sciences Médicales, Rue de Damas
BP 11-5076 Riad El Solh, 1107 2180 Beirut, Lebanon
megarbane@usj.edu.lb

Pr. Chokri MHIRI
Unité de Neurogénétique
Service de Neurologie
Hôpital Habib Bourguiba
Rue El Ferdaous, CP 3029
Sfax, Tunisia
chokri.mhiri@tunet.tn

Dr. Karine N'GUYEN
Département de Génétique Médicale
Unité de Génétique Clinique
Hôpital d'Enfants de la Timone
264, rue Saint-Pierre
13385 Marseille cedex 05, France
karine.nguyen@ap-hm.fr

Pr. Jørgen E. NIELSEN
Institute of Cellular and Molecular Medicine
Section of Neurogenetics,
University of Copenhagen, Blegdamsveij 3
DK 2200 Copenhagen, Denmark
jnielsen@sund.ku.dk

Pr. Massimo PANDOLFO
Service de Neurologie
Université Libre de Bruxelles, Hôpital Erasme
Route de Lennik 808
1070 Brussels, Belgium
massimo.pandolfo@ulb.ac.be

Dr. Olga Lucia PEDRAZA LINARES
Departamento Neurociencias
Hospital Universitario de San Ignacio,
Pontificia Universidad Javeriana
Bogota, Colombia
olgalp@etb.net.co

Pr. Evan REID
Department of Medical Genetics
University of Cambridge, Box 134,
Addenbrooke's Hospital
Cambridge CB2 2QQ, UK
ealr4@cam.ac.uk

Pr. Diana RODRIGUEZ
Service de Neuropédiatrie et Pathologie du Développement
Hôpital Armand Trousseau-La Roche-Guyon
28 avenue du Docteur Arnold Netter
75012 Paris, France
diana.rodriguez@trs.aphp.fr

Dr. Samir ROUMANI
Service of Neurology
PO Box 5764
Damaseus, Syria
swlhb@net.sy

Pr. Mustapha M.A. SALIH
Department of Pediatrics (39)
College of Medicine and KKUH, King Khalid University Hospital
PO Box 2925
Riyadh 11461, Saudi Arabia
mustapha@ksu.edu.sa

Pr. Filippo M. SANTORELLI
Molecolare e Malattie Neuromusculari,
Neurogenetics Laboratory
UOC Neurodegenetic e Medicina
Istituto di Neuropsichiatria Infantile (INPE),
IRCCS Fondazione Stella Maris
Via dei Giacinti 2
56018 Calambrone (PI), Italy
filippo3364@gmail.com

Pr. Lüdger SCHÖLS
Department of Neurology and Hertie-Institute for Clinical Brain Research
University of Tübingen, Hoppe-Seyler-Str. 3,
D-72076 Tübingen, Germany
ludger.schoels@uni-tuebingen.de

Pr. Jorge SEQUEIROS
Instituto de Biologia Molecular e Celular
University of Porto
Rua do Campo Alegre, 823
4150-180 Porto, Portugal
jsequeir@ibmc.up.pt

Pr. Chantal TALLAKSEN
Department of Neurology
Ullevål University Hospital
0407 Oslo, Norway
chantal.tallaksen@medisin.uio.no

Pr. Meriem TAZIR
Service de Neurologie
CHU Mustapha, Place du 1er Mai
16000 Algiers, Algeria
meriemtazir@yahoo.com

Pr. Christophe VERNY
Service de Génétique
Département de Neurologie, Unité Charcot,
CHU d'Angers
4, rue Larrey, 49000 Angers, France
chverny@chu-angers.fr

Pr. Thomas T. WARNER
Reta Lila Weston Institute of Neurological Studies
UCL Institute of Neurology
1 Wakefield Street
London WC1N 1PJ, UK
t.warner@ucl.ac.uk

Pr. Nicholas WOOD
Neurogenetics, Institute of Neurology
University Department of Clinical Neurology
The National Hospital, Queen Square
London WC1N 3BG, UK
N.Wood@ion.bpmf.ac.uk

List of the Ataxia Study Group –ASG- members (research laboratories and clinical departments)

Pr. Isabel ALONSO
Instituto de Biologia Molecular e Celular
University of Porto
Rua do Campo Alegre, 823
4150-180 Porto, Portugal
ialonso@ibmc.up.pt

Pr. Georg AUBURGER
Experimental Neurology
Department of Neurology
Goethe University Medical School
Senckenberganlage 31
D-60325 Frankfurt am Main, Germany
auburger@em.uni-frankfurt.de

Dr. Laszlo BALIKO
Department of Neurology and Stroke
County Hospital
H-8200 Veszprém, Hungary
ldegstroke@freemail.hu

Pr. Clara BARBOT
UnIGENe and Centro de Genetica Preditiva e Preventiva, Institute for Molecular and Cell Biology, Universidade do Porto
Rua do Campo Alegre, 823
4150-180 Porto, Portugal
cgpp@ibmc.up.pt

Pr. Jose BERCIANO
Department of Neurology
University Hospital "Marqués de Valldecilla,"
CIBERNED
Avda. Valdecilla, s/n.
Cantabria, 39008
Santander, Spain
jaberciano@humv.es

Dr. Sylvia BOESCH
Department of Neurology
University of Innsbruck
Innrain 52
A-6020 Innsbruck, Austria
Sylvia.Boesch@i-med.ac.at

Dr. Katrin BÜRK
Department of Neurology
Philipps-University of Marburg
Biegenstraße 10 / 12
D-35037 Marburg, Germany
buerk@ngi.de

Dr. Carlo CASALI
Department of Medico-Surgical Sciences and Biotechnologies
University of Rome ''Sapienza'
Via Faggiana 34
40100 Polo Pontino, Latina, Italy
carlo.casali@uniroma1.it

Pr. Paula COUTINHO
UnIGENe and Centro de Genetica Preditiva e Preventiva, Institute for Molecular and Cell Biology, Universidade do Porto
Rua do Campo Alegre, 823
4150-180 Porto, Portugal
paula.coutinho@ibmc.up.pt

Pr. Stefano DIDONATO
Divisione di Biochimica e Genetica
Istituto Nazionale Neurologico Carlo Besta - IRCCS
Via Celoria 11
20133 Milan, Italy
didonato@istituto-besta.it

Dr. Alexandra DURR
Cricm U975 and Department of Genetics and Cytogenetics
Pitié-Salpêtrière Hospital
47 boulevard de l'Hôpital
75013 Paris, France
alexandra.durr@upmc.fr

Pr. Richard FESTENSTEIN
Clinical Professor of Molecular Medicine
Department of Medicine
Imperial College London
South Kensington Campus
London SW7 2AZ, UK
r.festenstein@imperial.ac.uk

Pr. Alessandro FILLA
Dipartimento Di Scienze Neurologiche
Clinica Neurologica, Università Degli Studi Di Napoli Federico II
Via Pansini 5
80131 Napoli, Italy
afilla@unina.it

Pr. Paola GIUNTI
Department of Molecular Neuroscience
Institute of Neurology, Queen Square
University College London
Gower Street
London - WC1E 6BT, UK
p.giunti@ucl.ac.uk

Dr. Ilaria Anna GIORDANO
Klinik und Poliklinik für Neurologie
Universitätsklinikum Bonn
Sigmund-Freud-Straße 25
D-53105 Bonn, Germany
Ilaria_Anna.Giordano@ukb.uni-bonn.de

Dr. Jon INFANTE
Department of Neurology
University Hospital "Marqués de Valldecilla,"
CIBERNED

Avda. Valdecilla, s/n.
Cantabria, 39008
Santander, Spain
jinfante@humv.es

Pr. Thomas KLOCKGETHER
Department of Neurology
University Hospital of Bonn
Sigmund-Freud-Straße 25
D-53105 Bonn, Germany
Thomas.Klockgether@ukb.uni-bonn.de

Pr. Michel KOENIG
INSERM U964
Institut de Génétique et de Biologie
Moléculaire et Cellulaire (IGBMC)
Parc d'innovation, 1 rue Laurent Fries
BP 10142
67404 Illkirch cedex, France
mkoenig@igbmc.fr

Dr. Wioletta KRYSA
Zakład Genetyki
Instytut Psychiatrii i Neurologii w Warszawie ul.
Sobieskiego 9
02-957 Warszawa, Poland
krysa@ipin.edu.pl

Dr. Caterina MARIOTTI
Department of Biochemistry and Genetics
Fondazione-IRCCS
Istituto Neurologico Carlo Besta
Via Celoria 11
20133 Milan, Italy
mariotti@istituto-besta.it

Pr. Antoni MATILLA DUEÑAS
Investigator of the Spanish National Health System
Department of Neuroscience
Health Sciences Research Institute Germans Trias i Pujol (IGTP)
Universitat Autònoma de Barcelona
Carretera de Can Ruti, Cami de les escoles s/n
08916 Badalona, Spain
amatilla.igtp.germanstrias@gencat.cat

Pr. Bela MELEGH
Department of Medical Genetics and Child Development
University of Pécs
Pécs, Hungary
bela.melegh@aok.pte.hu

Pr. Massimo PANDOLFO
Service de Neurologie
Université Libre de Bruxelles, Hôpital Erasme
Route de Lennik 808
1070 Brussels, Belgium
massimo.pandolfo@ulb.ac.be

Dr. Jorge PINTO BASTO
Instituto de Biologia Molecular e Celular
University of Porto
Rua do Campo Alegre, 823
4150-180 Porto, Portugal
jpbasto@ibmc.up.pt

Dr. Hélène PUCCIO
INSERM U964
Institut de Génétique et de Biologie
Moléculaire et Cellulaire (IGBMC)
Parc d'innovation, 1 rue Laurent Fries
BP 10142
67404 Illkirch cedex, France
hpuccio@igbmc.fr

Dr. Maria RAKOWICZ
Department of Clinical Neurophysiology
Institute of Psychiatry and Neurology
02-957 Warsaw, Poland
rakowicz@ipin.edu.pl

Pr. Olaf RIESS
Department of Medical Genetics
University of Tübingen
Calwerstrasse 7
D-72076 Tübingen, Germany
olaf.riess@med.uni-tuebingen.de

Dr. Carlo RINALDI
Dipartimento Di Scienze Neurologiche
Clinica Neurologica, Università Degli Studi Di Napoli Federico II
Via Pansini 5
80131 Napoli, Italy

Dr. Rafal ROLA
Institute of Psychiatry and Neurology
ul. Sobieskiego 9
02-957 Warsaw, Poland
rafal.rola@wp.pl

Dr. Udo RUEB
Dr. Senckenberg Chronomedical Institute, Goethe-University
Theodor-Stern-Kai 7
D-60590 Frankfurt/Main, Germany
u.rueb@em.uni-frankfurt.de

Dr. Eniko SAFRANI
Pecs, Hungry
eniko.safrany@aok.pte.hu

Dr. Tanja SCHMITZ-HUEBSCH
Department of Neurology
University Clinic Bonn
Sigmund-Freud-Straße 25
D-53105 Bonn, Germany
Tanja.Schmitz-Huebsch@ukb.uni-bonn.de

Pr. Lüdger SCHÖLS
Department of Neurology and Hertie-Institute for Clinical Brain Research
University of Tübingen, Hoppe-Seyler-Straße 3
D-72076 Tübingen, Germany

ludger.schoels@uni-tuebingen.de

Pr. Jorge SEQUEIROS
Instituto de Biologia Molecular e Celular
University of Porto
Rua do Campo Alegre, 823
4150-180 Porto, Portugal
jsequeir@ibmc.up.pt

Pr. Jörg B. SCHULZ
Department of Neurology
University Hospital Aachen
Pauwelsstraße 30
52074 Aachen, Germany
jschulz4@gwdg.de

Dr. Jun-Suk KANG
Department of Neurology
University of Frankfurt
Senckenberganlage 31
60325 Frankfurt am Main, Germany
Jun-Suk.Kang@em.uni-frankfurt.de

Dr. Anna SULEK
Zakład Genetyki
Instytut Psychiatrii i Neurologii w Warszawie ul. Sobieskiego 9
02-957 Warszawa, Poland
suleka@ipin.edu.pl

Pr. Chantal TALLAKSEN
Department of Neurology
Ullevål University Hospital
0407 Oslo, Norway
chantal.tallaksen@medisin.uio.no

Dr. Franco TARONI
SOSD Genetics of Neurodegenerative and Metabolic Diseases
Fondazione IRCCS
Istituto Neurologico “Carlo Besta,”
Via Celoria 11
20133 Milan, Italy
ftaroni@istituto-besta.it

Dr. Dagmar TIMMAN-BRAUN
Department of Neurology
University Hospital of Essen
Hufelandstraße 55
D-45147 Essen, Germany
dagmar.timmann-braun@uni-duisburg-essen.de

Pr. Yvon TROTTIER
Département de neurobiologie et génétique
Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC)
Parc d'innovation, 1 rue Laurent Fries
BP 10142
67404 Illkirch cedex, France
yvon@titus.u-strasbg.fr

Pr. Bart VAN DE WARRENBURG
Department of Neurology
Donders Centre for Neuroscience
Radboud University Nijmegen Medical Center
PO Box 9102
6500 HC Nijmegen, the Netherlands
B.vandeWarrenburg@neuro.umcn.nl

Pr. Ullrich WUELLNER
Department of Neurology
University of Bonn
Sigmund-Freud-Straße 25
D-53105 Bonn, Germany
Ullrich.Wuellner@ukb.uni-bonn.de

Dr. Jacek ZAREMBA
Zakład Genetyki
Instytut Psychiatrii i Neurologii w Warszawie ul. Sobieskiego 9
02-957 Warszawa, Poland
zaremba@ipin.edu.pl

List of the European Friedreich's Ataxia Consortium for Translational Studies - EFACTS
(research laboratories, clinical departments and biotechs)

Pr. Massimo PANDOLFO (coordinator)
Service de Neurologie
Université Libre de Bruxelles, Hôpital Erasme
Route de Lennik 808
1070 Brussels, Belgium
massimo.pandolfo@ulb.ac.be

Pr. Jörg B. SCHULZ
Department of Neurology
University Hospital Aachen
Pauwelsstraße 30
52074 Aachen, Germany
jschulz4@gwdg.de

Pr. Gunnar BUYSE
University Hospitals Leuven and Katholieke Universiteit Leuven
Child Neurology Department
Herestraat 49
Leuven
B – 3000 Belgium
gunnar.buyse@uzleuven.be

Dr. Caterina MARIOTTI
Department of Biochemistry and Genetics
Fondazione-IRCCS
Istituto Neurologico Carlo Besta
Via Celoria 11
20133 Milan, Italy
mariotti@istituto-besta.it

Dr. Sylvia BOESCH
Department of Neurology
University of Innsbruck
Innrain 52
A-6020 Innsbruck, Austria
Sylvia.Boesch@i-med.ac.at

Pr. Paola GIUNTI
Department of Molecular Neuroscience
Institute of Neurology, Queen Square
University College London
Gower Street
London - WC1E 6BT, UK
p.giunti@ucl.ac.uk

Pr. Richard FESTENSTEIN
Clinical Professor of Molecular Medicine
Department of Medicine
Imperial College London
South Kensington Campus
London SW7 2AZ, UK
r.festenstein@imperial.ac.uk

Dr. Mark POOK
Biosciences
Heinz Wolff Building 231
Brunel University
Uxbridge UB8 3PH, UK
mark.pook@brunel.ac.uk

Pr. David GILBERT
Centre for Intelligent Data Analysis (CIDA)
School of Information Systems, Computing and Mathematics
St John's Building
Brunel University
Uxbridge, Middlesex UB8 3PH, UK
david.gilbert@brunel.ac.uk

Pr. Annalisa PASTORE
Medical Research Council (MRC)
National Institute of the Medical Research
The Ridgeway, Mill Hill
London NW7 1AA , UK
apastor@nimr.mrc.ac.uk

Pr. Richard WADE-MARTINS
University of Oxford
Department of Physiology, Anatomy and Genetics (DPAG)
Le Gros Clark Building, South Parks Road
Oxford OX1 3QX, UK
richard.wade-martins@dpag.ox.ac.uk

Pr. Francesc PALAU
Instituto de Biomedicina de Valencia (IBV)
Spanish Council for Scientific Research (CSIC)
University of Valencia
Jaime Roig, 11
46010 Valencia, Spain
fpalau@ibv.csic.es

Dr. Hélène PUCCIO
INSERM U964
Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC)
Parc d'innovation, 1 rue Laurent Fries
BP 10142
67404 Illkirch cedex, France
hpuccio@igbmc.fr

Dr. Alexandra DURR
Cricm U975
Pitié-Salpêtrière Hospital
47 boulevard de l'Hôpital
75013 Paris, France
alexandra.durr@upmc.fr

Pr. James R. RUSCHE
Repligen Corporation
41 Seyon Street
Building #1, Suite 100
Waltham, MA 02453, USA
JRusche@repligen.com

List of participants to the International Conference on Spinocerebellar ataxias (SPATAX / Ataxia Study Group / European Friedreich's Ataxia Consortium for Translational Studies)

Dr. Rosella ABETI
Department of Molecular Neuroscience
Institute of Neurology
University College London
London, UK
r.abeti@ucl.ac.uk

Dr. Lamia ALI PACHA
Department of Neurology
CHU Mustapha
Algiers, Algeria
miapacha@yahoo.fr

Dr. Rachel ALLISON
Department of Medical Genetics
University of Cambridge
Addenbrooke's Hospital
Cambridge, UK
rja45@cam.ac.uk

M. Céline AMET
Brain and Spine Institute
Paris, France
celine.amet@icm-institute.org

Pr. Isabel ALONSO
Instituto de Biologia Molecular e Celular
University of Porto
Porto, Portugal
ialonso@ibmc.up.pt

Dr. Mathieu ANHEIM
Service de Neurologie
Hôpital de Hautepierre
CHU de Strasbourg
Strasbourg, France
Mathieu.ANHEIM@chru-strasbourg.fr

Dr Michaela AUER-GRUMBACH
Division of Endocrinology and Metabolism
Department of Internal Medicine
Medical University of Graz
Graz, Austria
michaela.auergrumbach@medunigraz.at

Dr. Hamid AZZEDINE
Department of Medical Genetics
University of Lausanne
Lausanne, Switzerland
azzedine.hamid@yahoo.fr

Dr. Peter BAUER
Department of Medical Genetics
University of Tübingen
Tübingen, Germany
peter.bauer@med.uni-tuebingen.de

Pr. Patrick BABIN
Laboratoire MRGM-EA4576
University of Bordeaux
Talence, France
p.babin@gpp.u-bordeaux1.fr

M. Claudie BALEYDIER
Association Française de l'Ataxie de Friedreich
France (AFAF)
cbaleydier@numericable.fr

Dr. Guillaume BANNEAU
Department of Genetics and Cytogenetics
Pitié-Salpêtrière Hospital
Paris, France
guillaume.banneau@psl.aphp.fr

Dr. Maria Teresa BASSI
Laboratory of Molecular Biology
E. Medea Scientific Institute
Lecco, Italy
mariateresa.bassi@bp.lnf.it

M. Claude BAYER
Association Connaitre les Syndromes Cérébelleux (CSC)
France
cscsecretariat@gmail.com

Dr. Christian BEETZ
Institut für Klinische Chemie und Laboratoriumsdiagnostik
University of Jena
Jena, Germany
christian.beetz@med.uni-jena.de

M. Nadège BELLANCE
Laboratoire MRGM-EA4576
University of Bordeaux
Talence, France
nbellance@gmail.com

M. Jean BENARD
Association Strümpell-Lorrain
France (ASL)
jeanbenard46@yahoo.fr

Dr. Giovanni BENARD
University of Bordeaux
Laboratoire MRGM-EA4576
Talence, France
giovanni.benard@inserm.fr

Dr. Julia Katharina BICKMANN
Department of Medical Genetics
University of Tübingen
Tübingen, Germany
julia.bickmann@med.uni-tuebingen.de

Pr. Craig BLACKSTONE
Neurogenetics Branch, NINDS
National Institutes of Health
Bethesda, MD, USA
blackstc@ninds.nih.gov

M. Magali BORDIER
Laboratoire MRGM-EA4576
University of Bordeaux
Talence, France
lapianiste78@hotmail.fr

Pr. Bernard BRAIS
Department of Human Genetics
Montreal Neurological Institute
McGill University
Montreal, Canada
bernard.brais@mcgill.ca

Dr. Peter BREUER
Department of Neurology
University Bonn Medical Center
Bonn, Germany
peter.breuer@ukb.uni-bonn.de

Dr. Sylvia BOESCH
Department of Neurology
Medical University Innsbruck
Innsbruck, Austria
Sylvia.Boesch@i-med.ac.at

Pr. Odile BOESFPLUG-TANGUY
Inserm U676
Hôpital Robert Debré
Paris, France
odile.boespflug-tanguy@rdb.aphp.fr

Dr Teisha BRADSHAW
Centre for Endocrinology
William Harvey Research Institute
Queen Mary University London
London, UK
t.y.bradshaw@qmul.ac.uk

Dr. Ana Filipa BRANDÃO
CGPP, Instituto de Biologia Molecular e Celular
University of Porto
Porto, Portugal
ana.brandao@ibmc.up.pt

Dr. Erika BRIGHINA
Laboratory of Molecular Biology
E. Medea Scientific Institute
Lecco, Italy
erika.brighina@bp.lnf.it

Pr. Alexis BRICE
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
alexis.brice@upmc.fr

Dr. Alfredo BRUSCO
Department of Medical Sciences
University of Turin
Torino, Italy
alfredo.brusco@unito.it

Dr. Lydie BURGLEN
Department of Genetics
Trousseau Hospital
Paris, France
lydie.burglen@trs.aphp.fr

Dr. Serena Maria CALDARAZZO
SOSD Genetics of Neurodegenerative and Metabolic Diseases
Fondazione IRCCS
Istituto Neurologico “Carlo Besta,”
Milan, Italy
serena.caldarazzo@istituto-besta.it

Dr. Paola CAROPPO
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
paolacaroppo@libero.it

Pr. Giorgio CASARI
Vita-Salute San Raffaele University and
Human Molecular Genetics Unit
San Raffaele Scientific Institute
Milano, Italy
casari.giorgio@hsr.it

Dr. Anne CASTRIOTO
Department of Psychiatry and Neurology
CHU Grenoble
Grenoble, France
acastrioto@chu-grenoble.fr

Dr. Cécile CAZENEUVE
Department of Genetics and Cytogenetics
Pitié-Salpêtrière Hospital
Paris, France
cecile.cazeneuve@psl.aphp.fr

Dr. Paul CHAPPLE
Centre for Endocrinology
William Harvey Research Institute
Queen Mary University London
London, UK
j.p.chapple@qmul.ac.uk

Dr. Perrine CHARLES
Department of Genetics and Cytogenetics
Pitié-Salpêtrière Hospital
Paris, France
perrine.charles@psl.aphp.fr

Dr. Dong-Hui. CHEN
Department of Neurology
University of Washington
Seattle, WA, USA
cdhui@u.washington.edu

Dr. Karine CHOQUET
Department of Human Genetics
Montreal Neurological Institute
McGill University
Montreal, Canada

karine.choquet@mail.mcgill.ca

Dr. James CONNELL
Cambridge Institute for Medical Research
University of Cambridge
Cambridge, UK
jwc36@cam.ac.uk

Dr. Marie COUTELIER
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
marie.coutelier@etu.upmc.fr

Dr. Chiara CRISCUOLO
Dipartimento Di Scienze Neurologiche
Clinica Neurologica, Università Degli Studi Di
Napoli Federico II
Napoli, Italy
sky569@hotmail.com

Dr. Frédéric DARIOS
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
frederic.darios@upmc.fr

Dr. Susanne DE BOT
Department of Neurology
Radboud University Nijmegen Medical Center
Nijmegen, The Netherlands
st.bot@neuro.umcn.nl

Dr. Tine DECONINCK
Department of Molecular Genetics
Neurogenetics Group
University of Antwerp
Antwerp, Belgium
tine.deconinck@molgen.vib-ua.be

M. Marie DEHEM
GATC Biotech AG
Konstanz, Germany
m.dehem@gatc-biotech.com

Pr. Peter DE JONGHE
Departement of Molecular Genetics
Neurogenetics Group
University of Antwerp
Antwerp, Belgium
peter.dejonghe@molgen.vib-ua.be

Dr. Christel DEPIENNE
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
christel.depienne@upmc.fr

Dr. Daniela DI BELLA
SOSD Genetics of Neurodegenerative and
Metabolic Diseases
Fondazione IRCCS
Istituto Neurologico “Carlo Besta,”
Milan, Italy
daniela.dibella@istituto-besta.it

Dr. Eleonora DI GREGORIO
Department of Medical Sciences
University of Turin
Torino, Italy
ele.digregorio@gmail.com

Dr. Emma DUNCAN
Centre for Endocrinology
William Harvey Research Institute
Queen Mary University London
London, UK
e.j.duncan@qmul.ac.uk

Dr. Alexandra DURR
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
alexandra.durr@upmc.fr

Dr. Ewelina ELERT-DOBKOWSKA
Genetics Department
Institute of Psychiatry and Neurology
Warsaw, Poland
elerte@ipin.edu.pl

Dr. Khalid Hamid EL HACHIMI
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
khalid.el_hachimi@upmc.fr

Dr. Liena ELSAYED
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
liena.elsayed@icm-institute.org

M. Typhaine ESTEVES
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
typhaine.e@gmail.com

Dr. Claire EWENCZYK
Department of Genetics and Cytogenetics
Pitié-Salpêtrière Hospital
Paris, France
claire.ewenczyk@psl.aphp.fr

Dr. Coralie FASSIER
INSERM UMR 952
Université Pierre et Marie Curie
Paris, France
Coralie.Fassier@snv.jussieu.fr

Dr. Augusto FERREIRA
Novartis Portugal

Pr. Richard FESTENSTEIN
Department of Medicine
Imperial College London
South Kensington Campus

London, UK
r.festenstein@imperial.ac.uk

Pr. Alessandro FILLA
Dipartimento Di Scienze Neurologiche
Clinica Neurologica, Università Degli Studi Di Napoli Federico II
Napoli, Italy
afilla@unina.it

Dr. Ella FONTEYN
Department of Neurology
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands
e.fonteyn@gmail.com

M. Sylvie FORLANI
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
sylvie.forlani@upmc.fr

Dr. Christos GANOS
Sobell Department of Motor Neuroscience and Movement Disorders
UCL Institue of Neurology
London, UK
cganos@gmail.com

Dr. Maria GAMA
Instituto de Biologia Molecular e Celular
University of Porto
Porto, Portugal
maria.gama@ibmc.up.pt

Dr. Cinzia GELLERA
Dipartimento di Diagnostica e Tecnologia Applicata
Fondazione IRCCS
Istituto Neurologico Carlo Besta
Milan, Italy
gellera@istituto-besta.it

M. Marion GAUSSEN
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
Marion.gaussen@upmc.fr

Dr. Ilaria Anna GIORDANO
Klinik und Poliklinik für Neurologie
Universitätsklinikum Bonn
Bonn, Germany
Ilaria_Anna.Giordano@ukb.uni-bonn.de

Pr. Paola GIUNTI
Department of Molecular Neuroscience
Institute of Neurology
University College London
London, UK
p.giunti@ucl.ac.uk

Pr. Cyril GOIZET
Consultation de Neurogénétique
CHU de Bordeaux, Hôpital Pellegrin
Bordeaux, France
cyril.goizet@chu-bordeaux.fr

Dr. Holm GRAESSNER
Department of Neurology and Hertie-Institute for Clinical Brain Research
University of Tübingen
Tübingen, Germany
holm.graessner@med.uni-tuebingen.de

M. Philippe HANRIAT
Association Strümpell-Lorrain France (ASL)
asl-secretariat@orange.fr

Dr. Jamilé HAZAN
INSERM UMR 952
Université Pierre et Marie Curie
Paris, France
jamile.hazan@snv.jussieu.fr

Dr. Delphine HERON
Department of Genetics and Cytogenetics
Pitié-Salpêtrière Hospital
Paris, France
delphine.heron@psl.aphp.fr

Dr. Jennifer HIRST
Cambridge Institute for Medical Research
University of Cambridge
Cambridge, UK
jh228@cam.ac.uk

Pr. Henri HOULDEN
Department of Molecular Neuroscience
UCL Institute Neurology
London, UK
h.houlden@ucl.ac.uk

M. Simon HUBBARD
Hereditary Spastic Paraplegia Support Group UK
si@sjhubbard.com

M. Cécile HUCHET
Association Connaitre les Syndromes Cérébelleux (CSC)
France
cscpresidence@gmail.com

M. Vincent HUIN
Inserm U837
Lille, France
vincent.huin@inserm.fr

Dr. Kinya ISHIKAWA
Department of Neurology and Neurological Sciences
Tokyo Medical and Dental University
Tokyo, Japan
pico.nuro@tmd.ac.jp

Dr. Karin IVAN
Friedrich-Baur-Institut an der Neurologischen Klinik und Poliklinik
Klinikum der Universität München - Campus Innenstadt
München, Germany
Ivan.Karin@med.uni-muenchen.de

Dr. Heike JACOBI
Department of Neurology
University Hospital of Bonn
Bonn, Germany
heike_jacobi@ukb.uni-bonn.de

Pr. Albena JORDANOVA
Department of Molecular Genetics
University of Antwerp
Antwerp, Belgium
albena.jordanova@molgen.vib-ua.be

M. Alice KARAM
Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC)
Illkirch cedex, France
alice@igbmc.fr

Pr. Thomas KLOCKGETHER
Department of Neurology
University Hospital of Bonn
Sigmund-Freud-Straße 25
Bonn, Germany
Thomas.Klockgether@ukb.uni-bonn.de

Pr. Michel KOENIG
INSERM U964
Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC)
Illkirch, France
mkoenig@igbmc.fr

Dr. Jeanette KOHT
Department of Neurology
Drammen Hospital
Drammen, Norway
jeanette.koht@vestreviken.no

Dr. Giorgio KOUTSIS
1st Department of Neurology
Eginition Hospital
University of Athens Medical School
Athens, Greece
gkoutsi2@otenet.gr

Dr. Berry KREMER
Department of Neurology
University Medical Centre Groningen
Groningen, The Netherlands
h.p.h.kremer@umcg.nl

Dr. Wioletta KRYSA
Genetics Department
Institute of Psychiatry and Neurology
Warsaw, Poland
krysa@ipin.edu.pl

M. Julie LAVIE
University of Bordeaux
Laboratoire MRGM-EA4576
Talence, France
julielavie@hotmail.com

Dr. José LEAL LOUREIRO
Instituto de Biologia Molecular e Celular
University of Porto
Porto, Portugal
leal.loureiro@chedv.min-saude.pt

M. Claire LECOCQ
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
lecocq.claire@gmail.com

Dr. Luca LEONARDI
Department of Medical-Surgical Sciences and Biotechnologies
Rome Sapienza University
Rome, Italy
carlo.casali@uniroma1.it

Dr. Israel LERER
Department of Neurology
Hadassah-Hebrew University Medical Centre Hospital
Jerusalem, Israel
lereris@hadassah.org.il

M. Wei Nee LIM
Department of Molecular Neuroscience
Institute of Neurology
University College London
London, UK
w.lim@ucl.ac.uk

Dorthe LYKKE
Euro HSP
dorthelykke@youmail.dk

Dr. Anja MÄLHER
Klinik und Poliklinik für Neurologie
University Medicine Berlin
Berlin, Germany
Anja.Maehler@charite.de

Dr. Stefania MAGRI
SOSD Genetics of Neurodegenerative and Metabolic Diseases
Fondazione IRCCS
Istituto Neurologico “Carlo Besta,”
Milan, Italy
stefania.magri@istituto-besta.it

Dr. Martial MALLARET
Service de Neurologie
Hôpital de Hautepierre
CHU de Strasbourg
Strasbourg, France

martial.mallaret@gmail.com

Dr. Cecilia MANCINI
Department of Medical Sciences
University of Turin
Torino, Italy
cecilia.mancini@unito.it

M. Graziella MANGONE
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
gra.mangone@yahoo.it

Dr. Christian MARCOTULLI
Department of Medical-Surgical Sciences and Biotechnologies
Rome Sapienza University
Rome, Italy
carlo.casali@uniroma1.it

Dr. Cecilia MARELLI
Service de neurologie
Pôle Neurosciences Tête et Cou
CHU de Montpellier
Hôpital Gui de Chauliac
Montpellier, France
c-marelli@chu-montpellier.fr

M. Vavla MARINELA
"E. Medea" Scientific Institute Conegliano-Pieve di Soligo Research Centre
Conegliano, Italy
mvavla@yahoo.it

M. Martina MARINELLO
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
Martina.marinello@upmc.fr

Dr. Caterina MARIOTTI
Department of Biochemistry and Genetics
Fondazione-IRCCS
Istituto Neurologico Carlo Besta
Via Celoria 11
Milan, Italy
mariotti@istituto-besta.it

Dr. Ana Rita MARQUES
UnIGENe - Instituto de Biologia Molecular e Celular
University of Porto
Porto, Portugal
ana.fernandes@ibmc.up.pt

Dr. Elodie MARTIN
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
elodie.martin@upmc.fr

Dr Andrea MARTINUZZI
"E. Medea" Scientific Institute Conegliano-Pieve di Soligo
Conegliano, Italy
andreamartinuzzi@hotmail.com

Dr. Faruq MODH
CSIR-IGIB
India
faruq.mohd@igib.res.in

Dr. Fanny MOCHEL
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
Fanny.mochel@upmc.fr

M. Marie-Lorraine MONIN
Department of Neurology
Hôpital Central, CHU de Nancy
Nancy, France
mlmonin@live.fr

M. Sara MORAIS
Instituto de Biologia Molecular e Celular
University of Porto
Porto, Portugal
sara.morais@ibmc.up.pt

Dr. Wolfgang NACHBAUER
Department of Neurology
University of Innsbruck
Innsbruck, Austria
wolfgang.nachbauer@i-med.ac.at

Dr. Lorenzo NANETTI
Dipartimento di Diagnostica e Tecnologia Applicata
Fondazione IRCCS – Istituto Neurologico Carlo Besta
Milano, Italy
Lorenzo.Nanetti@istituto-besta.it

Dr. Suran NETHISINGHE
Department of Molecular Neuroscience
Institute of Neurology, Queen Square
University College London
Gower Street
London, UK
s.nethisinghe@ucl.ac.uk

Dr. Gaël NICOLAS
Inserm U1079
Faculté de Médecine et Pharmacie
Rouen, France
gaelnicolas@hotmail.com

Pr. Jørgen E. NIELSEN
Institute of Cellular and Molecular Medicine
University of Copenhagen
Copenhagen, Denmark
jnielsen@sund.ku.dk

Dr. Troels T NIELSEN
Institute of Cellular and Molecular Medicine
University of Copenhagen
Copenhagen, Denmark
troelsn@sund.ku.dk

Dr. Esther NIBBELING
Department of Genetics
University Medical Center Groningen
Groningen, The Netherlands
e.a.r.nibbeling@umcg.nl

Pr. Cahir O'KANE
Department of Genetics
University of Cambridge
Cambridge, UK
cahiro@gmail.com

Dr. Laura ORSI
S.C.D.U. Neurology
Città Della Salute e Della Scienza di Torino
Torino, Italy
lorsi@cittadellasalute.to.it

Pr. Massimo PANDOLFO
Service de Neurologie
Université Libre de Bruxelles, Hôpital Erasme
Brussels, Belgium
massimo.pandolfo@ulb.ac.be

Dr. Michael PARKINSON
Department of Molecular Neuroscience
Institute of Neurology
University College London
London, UK
m.parkinson@ucl.ac.uk

Pr. Annalisa PASTORE
Medical Research Council (MRC)
National Institute of the Medical
Research
London, UK
apastor@nimr.mrc.ac.uk

Dr. Alex PATTO
University of Cambridge
Cambridge, UK
alexpatto1@gmail.com

M. Kåre PEDERSEN
Euro HSP
kaare500@gmail.com

Dr. Olga Lucia PEDRAZA LINARES
Departamento Neurociencias
Hospital Universitario de San Ignacio,
Pontificia Universidad Javeriana
Bogota, Colombia
olgalp@etb.net.co

Dr. Viviana PENSATO
Dipartimento di Diagnostica e Tecnologia
Applicata
Fondazione IRCCS – Istituto Neurologico
Carlo Besta
Milano, Italy
viviana.pensato@istituto-besta.it

Dr. Maria PEREIRA
UnIGENe - Instituto de Biologia Molecular e
Celular
University of Porto
Porto, Portugal
maria.pereira@ibmc.up.pt

M. Julie PILLIOD
Laboratoire MRGM-EA4576
Talence, France
juliepilliod@aol.com

Pr. Stephan PULST
Department of Neurology
University of Utah
Salt Lake City, UT, USA
stefan.pulst@hsc.utah.edu

Dr. Beatriz QUINTANS
Fundacion Publica Galega Medicina Xenomica
Instituto de Investigaciones Sanitarias (IDIS)-
SERGAS
Santiago de Compostela, Spain
beaquintans@gmail.com

Dr. Myriam RAI
Laboratory of Experimental Neurology
Université Libre de Bruxelles, Hôpital Erasme
Brussels, Belgium
myriam.rai@ulb.ac.be

Dr. Maria RAKOWICZ
Department of Clinical Neurophysiology
Institute of Psychiatry and Neurology
Warsaw, Poland
rakowicz@ipin.edu.pl

Dr. Wendy RASKIND
Psychiatry and Behavioral Sciences University
of Washington
Seattle, WA, USA
wendyrun@uw.edu

M. Laure RAYMOND
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
laurefloriane@wanadoo.fr

Pr. Evan REID
Department of Medical Genetics
University of Cambridge
Addenbrooke's Hospital
Cambridge, UK
ealr4@cam.ac.uk

Pr. Olaf RIESS
Department of Medical Genetics

University of Tübingen
Tübingen, Germany
olaf.riess@med.uni-tuebingen.de

Dr. Carlo RINALDI
Dipartimento Di Scienze Neurologiche
Clinica Neurologica, Università Degli Studi Di Napoli Federico II
Napoli, Italy
carlo.rinaldi@nih.gov

Pr. Margaret ROBINSON
Cambridge Institute for Medical Research
University Cambridge
msr12@cam.ac.uk

Dr. Luis RUANO
UnIGENe and Centro de Genetica Preditiva e Preventiva, Institute for Molecular and Cell Biology, Universidade do Porto
Porto, Portugal
lmruano@gmail.com

Pr. Elena RUGARLI
Biocenter
University of Cologne
Cologne, Germany
elena.rugarli@uni-koeln.de

Pr. Bernard SABLONNIERE
Inserm U837
Lille, France
bernard.sablonniere@inserm.fr

Pr. Mustapha M.A. SALIH
Department of Pediatrics (39)
College of Medicine and KKUH, King Khalid University Hospital
Riyadh, Saudi Arabia
mustapha@ksu.edu.sa

Pr. Filippo M. SANTORELLI
Molecolare e Malattie Neuromusculari,
Neurogenetics Laboratory
UOC Neurodegenetic e Medicina
Istituto di Neuropsichiatria Infantile (INPE),
IRCCS Fondazione Stella Maris
Calambrone (PI), Italy
filippo3364@gmail.com

Dr. Irene SANZ GALLEGO
Departments of Neurology, IdiPAZ Hospital Universitario La Paz
Madrid, Spain
irenesanzgallego@gmail.com

Dr. Elisa SARTO
Dipartimento di Diagnostica e Tecnologia Applicata
Fondazione IRCCS – Istituto Neurologico Carlo Besta
Milano, Italy
elisa.sarto@istituto-besta.it

Pr. Lüdger SCHÖLS
Department of Neurology and Hertie-Institute for Clinical Brain Research
University of Tübingen
Tübingen, Germany
ludger.schoels@uni-tuebingen.de

Dr. Gumeni SENTILJANA
"E. Medea" Scientific Institute Conegliano-Pieve di Soligo
Conegliano, Italy
sentiljana@yahoo.com

Dr. Mariano SERRAO
Department of Medico-Surgical Sciences and Biotechnologies
University of Rome ‘‘Sapienza’
Polo Pontino, Latina, Italy
carlo.casali@uniroma1.it

Dr. Annie SITTLER
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
annie.sittler@upmc.fr

M. Madeleine SCHMEDER
Association Française de l’Ataxie de Friedreich France (AFAF)
madeleine.schmeder@orange.fr

Dr. Thorsten SCHMIDT
Institute of Medical Genetics & Applied Genomics
University of Tübingen
Tübingen, Germany
thorsten.schmidt@med.uni-tuebingen.de

Dr. Katrien SMETS
Departement of Molecular Genetics
Neurogenetics Group
University of Antwerp
Antwerp, Belgium
katrien.smets@molgen.vib-ua.be

Dr. Anna SOBANSKA
Zakład Genetyki
Instytut Psychiatrii i Neurologii w Warszawa, Poland
suleka@ipin.edu.pl

Dr. Anne SOEHN
Department of Medical Genetics
University of Tübingen
Tübingen, Germany
anne.soehn@med.uni-tuebingen.de

Pr. Maria-Jesùs SOBRIDO
Fundacion Publica Galega Medicina Xenomica
Instituto de Investigaciones Sanitarias (IDIS)-SERGAS
Santiago de Compostela, Spain
ssobrido@telefonica.net

Dr. Iwona STEPNIAK
Genetics Department
Institute of Psychiatry and Neurology
Warsaw, Poland
istepniak@ipin.edu.pl

Pr. Giovanni STEVANIN
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
giovanni.stevanin@upmc.fr

Dr. Sarah STRICKER
Klinik und Poliklinik für Neurologie
University Medicine Berlin
Berlin, Germany
sarah.stricker@charite.de

Dr. Isabelle STRUBI-VUILLAUME
Pôle Biochimie et Biologie moléculaire
Centre de Biologie Pathologie
CHRU de Lille
Lille, France
isabelle.vuillaume@chru-lille.fr

Dr. Anna SULEK
Genetics Department
Institute of Psychiatry and Neurology
Warsaw, Poland
suleka@ipin.edu.pl

Dr. Kirsten SVENSTRUP
Institute of Cellular and Molecular Medicine
University of Copenhagen
Copenhagen, Denmark
ksvenstrup@sund.ku.dk

Dr. Matthis SYNOFZIK
Department of Neurodegeneration
Hertie Institute for Clinical Brain Research and
Centre of Neurology
Tübingen, Germany
matthis.synofzik@uni-tuebingen.de

M. Khadija TAHIRI
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
khadija.tahiri@upmc.fr

Pr. Chantal TALLAKSEN
Department of Neurology
Ullevål University Hospital
Oslo, Norway
chantal.tallaksen@medisin.uio.no

Dr. Franco TARONI
SOSD Genetics of Neurodegenerative and
Metabolic Diseases
Fondazione IRCCS
Istituto Neurologico “Carlo Besta,”
Milan, Italy
ftaroni@istituto-besta.it

Pr. Meriem TAZIR
Service de Neurologie
CHU Mustapha
Algiers, Algeria
meriemtazir@yahoo.com

M. Christelle TESSON
Cricm U975
Pitié-Salpêtrière Hospital
Paris, France
Christelle.tesson@upmc.fr

Dr. Vannocci TOMMASO
National Institute of the Medical
Research
Medical Research Council
London, UK
tvannoc@nimr.mrc.ac.uk

Pr. Yvon TROTTIER
Département de neurobiologie et génétique
Institut de Génétique et de Biologie
Moléculaire et Cellulaire (IGBMC)
Illkirch cedex, France
yvon@titus.u-strasbg.fr

Pr. Bart VAN DE WARRENBURG
Department of Neurology
Donders Centre for Neuroscience
Radboud University Nijmegen Medical
Nijmegen, the Netherlands
B.vandeWarrenburg@neuro.umcn.nl

Dr. Judith VAN GAALEN
Department of Neurology
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands
j.vangaalen@neuro.umcn.nl

Dr. Willeke VAN ROON-MOM
Center for Human and Clinical Genetics
Leiden University Medical Center
Leiden, The Netherlands
w.m.c.van_roon@lumc.nl

Dr. Liana VENEZIANO
Institute of Translational Pharmacology
C.N.R.
Rome, Italy
liana.veneziano@ift.cnr.it

Dr. Sasha VERMEER
Department of Human Genetics
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands
s.vermeer@antrg.umcn.nl

Dr. Tiziano VERRI
Department of Biological and Environmental
Sciences and Technologies University of
Salento
Lecce, Italy
tiziano.verri@unisalento.it

Pr. Thomas T. WARNER
Reta Lila Weston Institute of Neurological Studies
UCL Institute of Neurology
London, UK
t.warner@ucl.ac.uk

Dr. Iselin Marie WEDDING
Department of Neurology
Ullevål University Hospital
Oslo, Norway
i.m.wedding@medisin.uio.no

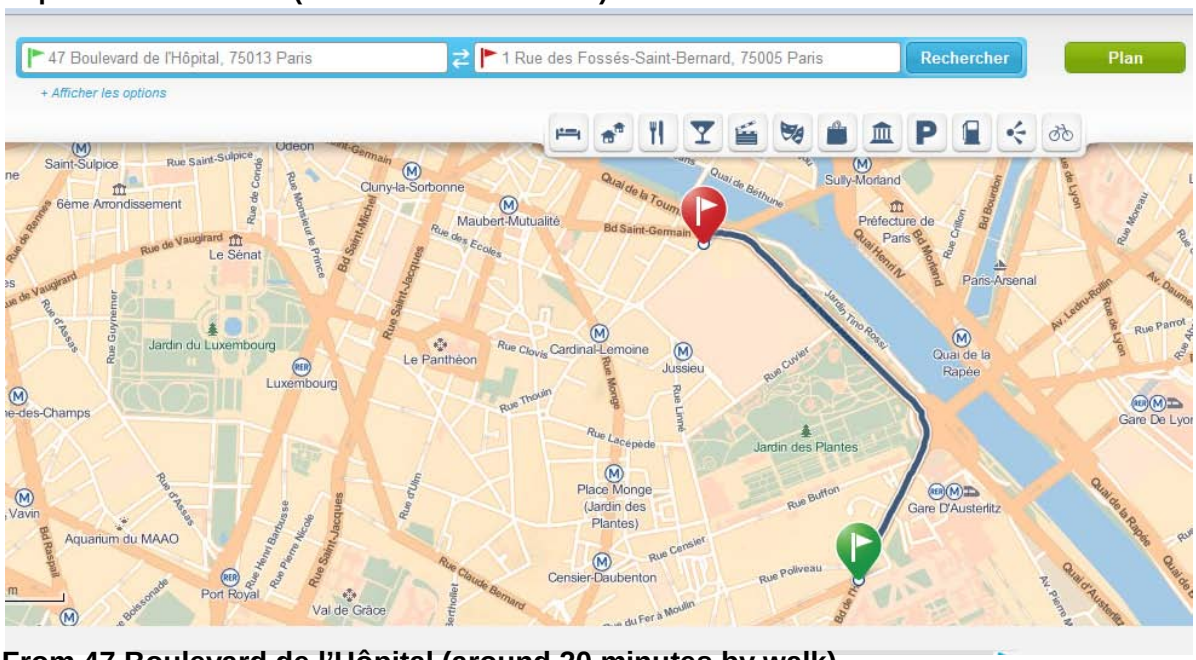
Dr. Belgin YALCIN
Department of Genetics
University of Cambridge
Cambridge, UK
by226@cam.ac.uk

Pr. Ginevra ZIANNI
Molecular Medicine & Dept. of Neurosciences
Osp. Bambino Gesù Rome, Italy
ginevra.zanni@opbg.net

Pr. Huda ZOGHBI
Departments of Pediatrics - Neurology and Developmental Neuroscience, Molecular and Human Genetics, and Neuroscience
Jan and Dan Duncan Neurological Research Institute
Houston, USA
hzoghbi@bcm.edu

Pr. Stephan ZÜCHNER
Center for Human Molecular Genomics
John P. Hussman Institute for Human Genomics
University of Miami Miller School of Medicine
University of Miami
Miami, FL, USA
SZuchner@med.miami.edu

Map Noura Restaurant (Insitut du Monde Arabe)



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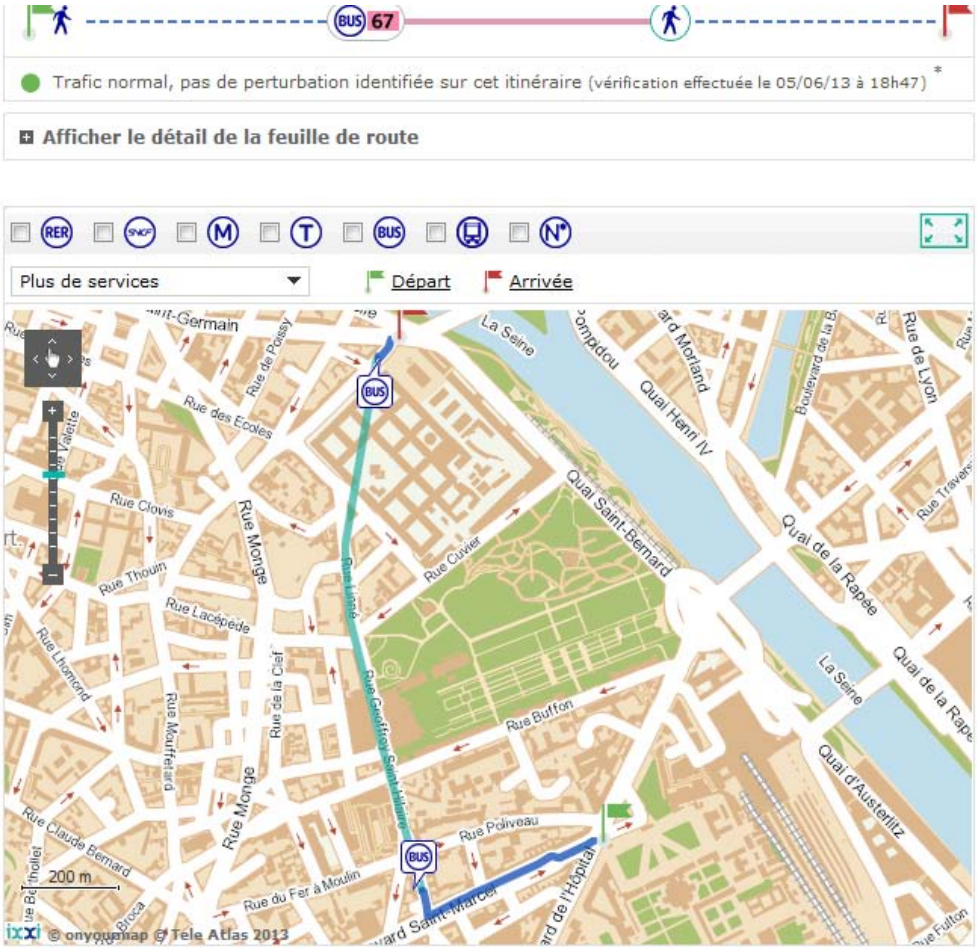
- Go down on the boulevard de l'Hôpital until the Jardin des Plantes (in front of Austerlitz train station)
- Turn left on Quai Saint Bernard and walk straight along the Jardin des Plantes until Boulevard Saint Germain.
- Turn left at Mohammed V place

By bus (from Saint-Marcel - Jeanne d'Arc Line 7, direction Pigalle; stop Institut du Monde Arabe) 15 minutes



Association Connaitre les Syndromes Cérébelleux

Ecole Pratique des Hautes Etudes

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Tom Wahlig Stiftung

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Association Française Ataxie de Friedreich

Associazione Italiana Vivere la Paraparesi Spastica Onlus (A.I. Vi.P.S. Onlus)

Hereditary Spastic Paraplegia Support Group UK

Eurosca

Mairie de Paris

DIM Cerveau &Pensée

Institut Carnot-ICM

The symposium will take place at the Brain and Spine Institute (Pitié-Salpêtrière Hospital, Paris, France)