Loss-of-function mutations in RAB39B are associated with typical early-onset Parkinson disease

Suzanne Lesage, Jose Bras, Florence Cormier-Dequaire, Christel Condroyer, Lee Darwent, Rita Guerreiro, Elisa Majounie, Monica Federoff, Peter Heutink, Thomas Gasser, et al.

To cite this version:

HAL Id: hal-01303654
https://hal.sorbonne-universite.fr/hal-01303654
Submitted on 18 Apr 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives| 4.0 International License
Supplemental data at Neurology.org/ng

LOSS-OF-FUNCTION MUTATIONS IN RAB39B ARE ASSOCIATED WITH TYPICAL EARLY-ONSET PARKINSON DISEASE

OPEN

Rab proteins are small molecular weight guanosine triphosphatases involved in the regulation of vesicular trafficking. Three of 4 X-linked RAB genes are specific to the brain, including RAB39B. Recently, Wilson et al. reported that mutations in RAB39B cause X-linked intellectual disability (ID) and pathologically confirmed Parkinson disease (PD). They identified a ∼45-kb deletion resulting in the complete loss of RAB39B in an Australian kindred and a missense mutation in a large Wisconsin kindred. Here, we report an additional affected man with typical PD and mild mental retardation harboring a new truncating mutation in RAB39B.

Methods. We looked for coding and splice site mutations in RAB39B (RefSeq accession number NM_171998.2) using data mining in exomes from a cohort of 1,348 unrelated patients with PD (60% men, mean age at onset 41.7 ± 11.0 years) and 530 controls (65% men, mean age at examination 45.1 ± 10.7 years), mostly of European ancestry, recruited through the International Parkinson’s Disease Genomics Consortium (IPDGC).

Whole exome was sequenced using, for the most part, Illumina TruSeq chemistry and Illumina HiSeq 2000 instrument, using 100 bp paired-end reads, according to the manufacturer’s protocols. A mean of 75% of reads had coverage of at least 30-fold in both patients with PD and controls.

The human reference genome UCSC hg19 was used for sequence alignment and variant calling with the Burrows-Wheeler Aligner (http://bio-bwa.sourceforge.net/) and the Genome Analysis Toolkit (https://www.broadinstitute.org/gatk/). PCR duplicates were removed prior to variant calling using Picard software (http://broadinstitute.github.io/picard/). Variants were annotated with ANNOVAR software (http://www.openbioinformatics.org/annovar/).

Variants of interest were then verified by bidirectional Sanger sequencing using an ABI 3730 automated sequencer (Applied Biosystems, Life Technologies, Carlsbad, CA) with SeqScape v2.6 software (Applied Biosystems). Additional screening of the 2 RAB39B exons by direct sequencing was performed in a cohort of 192 unrelated men with early-onset (EO) parkinsonism (mean age at onset 34.5 ± 7.6 years) recruited through the French network for the study of Parkinson disease genetics and 392 unrelated UK PD cases (mean age at onset 49.8 ± 14.2 years), including 48% men (mean age at onset 49.1 ± 14.4 years).

Results. Among the 1,348 patients with PD, we identified a single man of French origin with parkinsonism who harbored a novel nonsense mutation (c.557G>A in exon 2 [p.Trp186stop] of RAB39B) that was not found in 530 unrelated control individuals of European origin, public databases (dbSNP137) (http://www.ncbi.nlm.nih.gov/SNP/), or in an additional cohort of 61,486 unrelated individuals from the publicly available Exome Aggregation Consortium (http://exac.broadinstitute.org). In addition, this patient was excluded for mutations in all other known PD genes in data from exome analyses. Subsequent screening of RAB39B in 380 additional men with EO parkinsonism failed to identify any additional variants, suggesting that RAB39B is a very rare cause of parkinsonism.

The patient with the RAB39B p.Trp186stop mutation had early disease onset (39 years) and typical parkinsonism with asymmetric rest tremor, an akineto-rigid syndrome, and a good response to levodopa. He had mild mental retardation, which required sheltered employment. No other clinical abnormalities, such as pyramidal, cerebellar, or ocular disorders, were detected. No family history of PD was reported. Brain MRI performed twice was normal.

Eight years after disease onset, the patient developed treatment-related complications, including motor fluctuations, dyskinesia, and limb dystonia, and was thoroughly evaluated in view of possible deep brain stimulation. A neuropsychological examination showed good global cognitive performance (Mattis 138/144) but difficulty concentrating and subcortico-frontal signs. A psychiatric interview revealed dysthyamic disorder with impulsiveness, explaining why surgery was ultimately
not performed. Apomorphine treatment was initiated at age 55. The patient died the same year.

Discussion. Previous studies showed RAB39B to be a rare cause of X-linked ID,1–6 which may be associated with autism spectrum disorder, epileptic seizures, and macrocephaly, but not parkinsonian signs. A recent study reported 2 families with loss-of-function mutations in RAB39B.2 All affected men from the 2 kindreds presented similar clinical phenotypes with variable degrees of ID in their childhood, including developmental delay, cognitive impairment, macrocephaly, and, in some, seizures; EO parkinsonism with tremor appeared subsequently as the presenting symptom. Neuropathologic examination was consistent with α-synuclein pathology. Although we could not exclude the presence of large and complex rearrangements undetectable by the exome sequencing method, we identified an RAB39B p.Trp186stop mutation carried by a 39-year-old man with parkinsonism. The case presented here extends the phenotype caused by loss-of-function RAB39B mutations to include X-linked EO parkinsonism with mental retardation that is mild enough to allow autonomous living. RAB39B plays a role in vesicular trafficking pathway, possibly affecting α-synuclein pathology, as recently reported for another PD-associated gene, VPS35.7

From the Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06 UMR S 1127 (S.L., F.C.-D., C.C., A.N., A.B.), Paris, France; Centre d’Investigation Clinique Pitié Neurosciences CIC-1422 (F.C.-D.); AP-HP, Hôpital de la Salpêtrière (A.B.), Department of Genetics and Cyto genetics, Paris, France; Department of Molecular Neuroscience (J.B., L.D., R.G., M.F., N.W., J.H.), UCL Institute of Neurology, London, United Kingdom; Laboratory of Neurogenetics (E.M., M.F., A.S.), National Institute on Aging, Bethesda, MD; Hertie Institute for Clinical Brain Research (P.H., T.G.), University of Tübingen and DZNE (P.H., T.G.), German Center for Neurodegenerative Diseases, Tübingen, Germany; and Institut des Maladies Neurodégénératives (F.T.), University of Bordeaux and CHU de Bordeaux, Bordeaux, France.

The French Parkinson’s Disease Genetics Study Group (PDG) and the International Parkinson’s Disease Genomics Consortium (IPDGC) coinvestigators are listed at Neurology.org.

Author contributions: Dr. Leage: drafting the manuscript, analysis and interpretation of data, and statistical analysis. Dr. Brice: acquisition, analysis, and interpretation of data. Dr. Cormier-Dequaire: acquisition of clinical data. Mrs. Courdroy: acquisition of genetic data. Dr. Nicolas: bioinformatics analyses. Mrs. Darwent, Dr. Guerreiro, Dr. Majounie, and Mrs. Fedoreff: exome data acquisition and analysis. Dr. Heutink, Dr. Wood, Dr. Gasser, and Dr. Hardy: acquisition and interpretation of data. Dr. Tison: acquisition of clinical data. Dr. Singleton: supervising the exome data acquisition, analysis and interpretation, and obtaining funding. Dr. Brice: drafting/revising the manuscript, study concept or design, study supervision, and obtaining funding. All authors critically reviewed and approved the final manuscript.

Acknowledgment: The authors are grateful to the patients and their families. They thank Merle Ruberg for critical reading of the manuscript and the DNA and Cell Bank of ICM for sample preparation.

Study funding: Supported by the France-Parkinson Association, Roger de Spollерch Foundation, and the French program “Investissements d’avenir” (ANR-10-IAIHU-06). This work was also supported in part by the Intramural Research Program of the National Institute on Aging, NIH, Department of Health and Human Services; project Z01 AG000598 and by MRC Grant G1100643/1.

Disclosure: Dr. Leage, Dr. Bras, Dr. Cormier-Dequaire, Mrs. Courdroy, Dr. Nicolas, Mrs. Darwent, Dr. Guerreiro, Dr. Majounie, and Mrs. Fedoreff report no disclosures. Dr. Heutink has served on scientific advisory boards for Fondation Alzheimer France and Prices Beatrice Fonds; and holds patents for Pathogenic tau mutations, Diagnostics and therapeutics for autosomal dominant hemochromatosis, and a method for diagnosing a neurodegenerative disease. Dr. Wood reports no disclosures. Dr. Gasser has served on scientific advisory boards for joint programming in neurodegenerative disease; has received funding for travel and/or speaker honoraria from MedUp-date, Movement Disorders Society, and the Michael J. Fox Foundation; has served on the editorial boards of Parkinsonism and Related Disorders, Movement Disorders, and Journal of Neurology; holds patents for KASPP (LRK2) Gene, its Production, and Use for the Detection and Treatment of Neurodegenerative Diseases; has served on speakers’ bureaux for Novartis, Merck-Serono, Schwarz Pharma, Boehringer Ingelheim, and Valeant Pharma; and has received research support from Novartis, McFoa, ERA-Net neuron, Multi-syn, Courage-PD, Hemozol Association, and the Michael J. Fox Foundation. Dr. Hardy reports no disclosures. Dr. Tison has served on scientific advisory boards for Novartis, Boehringer-Ingelheim, GlassoSmithKline, ABBOTT, and UCB; has received funding for travel and/or speaker honoraria from Lundbeck, Novartis, UCB, and TEVA; has consulted for Addex Pharma; and has received research support from Novartis, French Ministry of Health, University Hospital Bordeaux, and the Michael J. Fox Foundation. Dr. Singleton has received funding for travel and/or speaker honoraria from 23andMe; has served on the editorial boards of Annals of Neurology, Lancet Neurology, Neurogenetics, Neurodegenerative Diseases, Brain, and Journal of Parkinson’s Disease; has a patent pending for panel of markers to diagnose stroke; and has received research support from NIH. Dr. Brice has received funding for travel and/or speaker honoraria from Lundbeck; and has received research support from Investissements d’avenir, Roger de Spollberch Foundation, and France Parkinson Association. Go to Neurology.org for full disclosure forms. The Article Processing Charge was paid by the Inserm DR Paris 6.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received April 12, 2015. Accepted in final form May 19, 2015.

Correspondence to Dr. Brice: alexis.brice@upmc.fr

5. Giannandrea M, Bianchi V, Mignogna ML, et al. Mutations in the small GTPase gene RAB39B are responsible for


Loss-of-function mutations in \( \textit{RAB39B} \) are associated with typical early-onset Parkinson disease

Suzanne Lesage, Jose Bras, Florence Cormier-Dequaire, et al.

\textit{Neurol Genet} 2015;1;

DOI 10.1212/NXG.0000000000000009

This information is current as of June 18, 2015