Published in final edited form as:

Mov Disord. 2013 February ; 28(2): 248. doi:10.1002/mds.25293.

Novel Lrrk2-p.S1761R Mutation Is Not a Common Cause of Parkinson's Disease in Spain

Ignacio F. Mata, PhD^{1,2,*}, Victoria Alvarez, PhD³, Renee Ribacoba, MD⁴, Jon Infante, MD^{5,6}, María Sierra, MD⁶, Pilar Gómez-Garre, PhD^{5,7}, Pablo Mir, MD, PhD^{5,7}, Sarah Waldherr, BS¹, Dora Yearout, BS¹, Latin American Research Consortium on the Genetics of Parkinson's Disease, and Cyrus P. Zabetian, MD, MS^{1,2}

¹Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA

²Department of Neurology, University of Washington School of Medicine, Seattle, Washington, USA

³Laboratorio de Genetica Molecular, Instituto de Investigacion Nefrologica, Hospital Universitario Central de Asturias, Oviedo, Spain

⁴Department of Neurology, Hospital Universitario Central de Asturias, Oviedo, Spain

⁵Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Barcelona, Spain

⁶Department of Neurology, "Marques de Valdecilla" University Hospital, Santander, Spain

⁷Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain

Using an analysis of shared chromosome 12p11.2-q13.1 haplotypes in 14 Spanish families with late-onset Parkinson's disease (PD), Lorenzo-Betancor et al. recently reported on the discovery of a novel, potentially pathogenic *LRRK2* missense mutation (c.5281A>C).¹ The investigators presented three lines of evidence to support the pathogenicity of this variant. First, it results in the substitution of arginine for a highly conserved serine at amino-acid position 1761 (p.S1761R), which is predicted to disrupt function of the COR domain of the protein *in silico*. Second, there was some suggestion that the mutation segregated with disease in the index family, a multigenerational pedigree from Northeastern Spain. Last, it was not detected in 2,491 healthy white controls (1,024 from Spain). Subsequent screening of p.S1761R in larger samples indicated a possible founder effect, because the mutation was observed in 2 of 1,203 PD patients from Spain (on the same haplotype background), but was not detected in 1,421 patients from Ireland, Poland, and the United States. A similar pattern has been reported on for the Lrrk2-p.R1441G mutation, which is very rarely observed outside of Spain.^{2,3}

We sought to refine the frequency estimate for p.S1761R and identify additional families with the mutation for segregation analysis. We screened the mutation in 1,366 PD patients, including 209 familial cases, and 1,047 healthy controls from three other regions of Spain,

*Correspondence to: Dr. Ignacio F. Mata, Geriatric Research Education and Clinical Center S-182, VA Puget Sound Health Care System, 1660 South Columbian Way, Seattle, WA 98108, USA; nachofm@u.washington.edumailto.

Additional Supporting Information may be found in the online version of this article.

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

two in the North (Asturias and Cantabria) and one in the South (Andalucía). We also genotyped the mutation in 1,217 PD patients and 231 controls from five countries in South America (Argentina, Brazil, Colombia, Peru, and Uruguay) in which substantial Spanish admixture occurs (Supporting Table 1). Genotyping was performed using a TaqMan assay, which included samples from known mutation carriers for quality control (kindly provided by Dr. Lorenzo-Betancor). However, we did not observe p.S1761R in any of these cases or controls. Our failure to detect any mutation carriers further emphasizes the rarity of p.S1761R among patients with PD, but unfortunately does not shed further light on the pathogenicity of this variant. Combining our results with those of Lorenzo-Betancor et al., the observed p.S1761R carrier frequency in PD patients of Spanish ancestry is less than 1 per 1,000.

With the increasing availability of next-generation sequencing technology, the number of “private” mutations discovered in established and new late-onset PD-related genes will grow rapidly in the coming years. However, determining whether such variants are truly pathogenic will likely prove to be challenging because, in most instances, only limited pedigree information will be available, as is the case for Lrrk2 p.S1761R. Though labor-intensive, functional studies in model systems might ultimately be necessary to address this question much of the time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the Parkinson’s disease Foundation; Department of Veterans Affairs (1I01BX000531), National Institutes of Health (P50 NS062684, R01 NS065070 and R25 TW009345), Fondo de Investigacion Sanitaria (FIS, PI11/00228, PFIS, FI 11/00259, IFIMAV, and WLA 04/11), Instituto de Salud Carlos III (PI11/00093 and PI08/0915), Spanish Ministry of Economy and Competitiveness, European Social Fund, and the Asociación Parkinson Asturias.

Membership list of the Latin American Research Consortium on the Genetics of Parkinson’s Disease is provided in the Supporting Information.

References

1. Lorenzo-Betancor O, Samaranch L, Ezquerro M, et al. LRRK2 haplotype-sharing analysis in Parkinson’s disease reveals a novel p.S1761R mutation. *Mov Disord.* 2012; 27:146–151. [PubMed: 22038903]
2. Mata IF, Cosentino C, Marca V, et al. LRRK2 mutations in patients with Parkinson’s disease from Peru and Uruguay. *Parkinsonism Relat Disord.* 2009; 15:370–373. [PubMed: 18980856]
3. Gonzalez-Fernandez MC, Lezcano E, Ross OA, et al. Lrrk2-associated parkinsonism is a major cause of disease in Northern Spain. *Parkinsonism Relat Disord.* 2007; 13:509–515. [PubMed: 17540608]