Increased Stroke Risk in Patients with Parkinson's Disease with *LRRK2* Mutations

Parkinson's disease (PD) is associated with an increased stroke risk, however, no relationship between coronary artery disease (CAD) and PD was found.[1] To date, little is known about the influence of PD-related genes, such as the leucine-rich repeat kinase 2 (*LRRK2*), the parkin (*PRKN*) and the glucocerebrosidase (*GBA*) genes, in the vascular risk of these patients. This work aims to determine whether the vascular risk differs between sporadic/familial PD forms and controls.

We recruited 355 patients with sporadic PD (sPD), 38 with *GBA*-associated PD (*GBA*-PD), 36 with *LRRK2*-associated PD (*LRRK2*-PD), and 23 with *PRKN*-associated PD (*PRKN*-PD) and 620 controls. Demographic, clinical, and vascular risk factors data were collected. The presence of vascular events (ischemic stroke and CAD) were determined by clinical interview and consulting electronic medical records. We applied multivariate logistic regression and Cox regression analyses. In a confirmatory analysis, we repeated our multivariate analysis only with subjects who had a neuroimaging test (computed tomography or magnetic resonance imaging) available in their electronic records. The mutational screening of *PRKN*, *GBA*, and *LRRK2* genes was previously performed using a combination of high-resolution melting and direct DNA resequencing (Appendix S1).[2,3]

Patients with sPD were significantly older than controls and patients with *GBA*-PD. Patients with *PRKN*-PD had a lower rate of arterial hypertension. There were no other differences in vascular risk factors among the groups (Table S1). *PRKN*-PD showed a significantly younger PD onset and longer disease duration than the other groups, and *GBA*-PD had a younger disease onset than sPD (Tables S4–S6). However, there were no differences in other PD features.

The prevalence of ischemic stroke differed among groups, and this difference was statistically significant after controlling for sex, age, and vascular risk factors (Tables S7 and S8). However, no differences in CAD were found among groups. *LRRK2*-PD had the highest proportion of stroke (13.8%), followed by *PRKN*-PD and sPD (8.6% and 5.6%, respectively). *LRRK2*-PD showed a significantly increased risk of stroke compared with controls (odds ratio [OR], 5.1; 95% confidence interval [CI], 1.7–15.3; $P = 0.004$), whereas there were no significant differences in the other PD cohorts (Fig. 1A). In our confirmatory analysis, we corroborated the previous finding. Interestingly, in this analysis sPD also showed a marginally significant increased risk of stroke compared with controls (OR, 1.8; 95% CI, 0.99–3.2; $P = 0.05$; Fig. 1B). There was a statistically significant difference in the survival distribution for ischemic stroke among groups (Fig. 1C). The increased risk of stroke in *LRRK2*-PD was associated with a younger age at stroke compared with controls, a finding supported by our confirmatory analysis (Fig. 1D).

Our results are aligned with previous studies.[4,5] A meta-analysis concluded that the overall PD group had a 1.7-fold increase in the risk of stroke compared with controls, without differences in CAD.[1] In our study, sPD showed a similar increase in the stroke risk, although this association was marginally significant. *LRRK2*-PD showed a 5.1-fold increase in the risk of ischemic stroke after controlling for potential confounding factors. These results might be related to a different pathophysiology of stroke in certain PD subtypes compared with controls. A link between these brain disorders has been proposed, beyond the classical risk factors, considering the role of oxidative stress, neuroinflammation, and altered lipid metabolism among others.[6] Interestingly, it has been suggested that pathogenic variants of *LRRK2* might contribute to postischemic brain damage and neuroinflammation.[7]

In conclusion, patients with *LRRK2*-PD may show an increased risk of ischemic stroke, with no differences in CAD. The sporadic forms of PD might have a higher cerebrovascular risk than controls. Conversely, patients with *GBA*-PD and *PRKN*-PD showed a similar vascular risk to controls. Our results support the idea that mechanisms other than classical vascular risk factors might be involved in the cerebrovascular disease of those patients. Prospective studies are needed to confirm these findings.

Detailed introduction, methods, results, and discussion are included in Appendix S1.

***Correspondence to:** Dr. P. Mir and Dr. P. Gómez-Garre, Unidad de Trastornos del Movimiento, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío, Avda. Manuel Siurot s/n, 41013, Seville, Spain; E-mail: pmir@us.es (P. Mir) and mgomez-ibis@us.es (P. Gómez-Garre)

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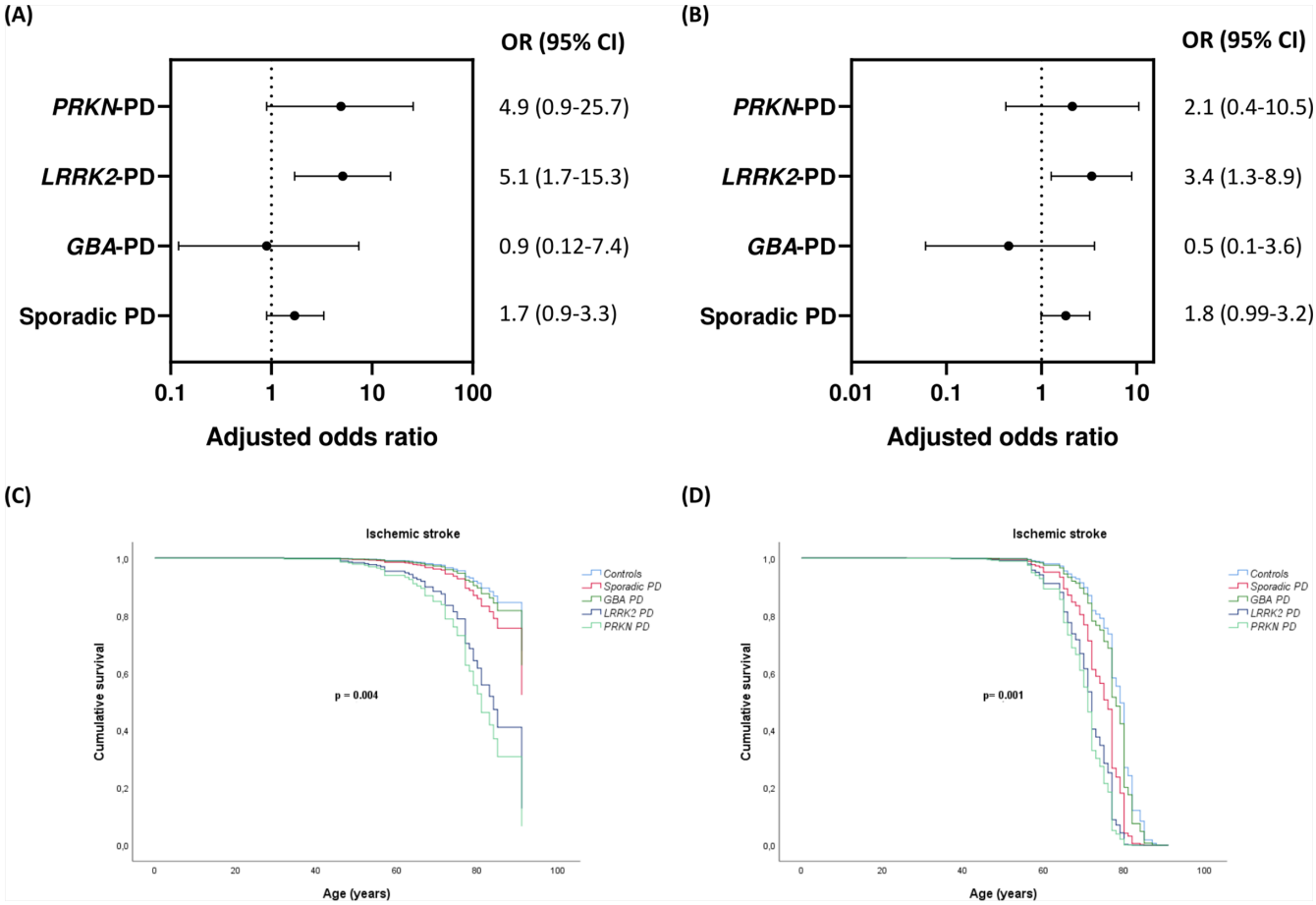

FIG 1. Multivariate logistic regression and Cox regression model to determine the association between the occurrence of ischemic stroke and the study groups. (**A**) Forest plot with adjusted odds ratio and confidence intervals of symptomatic ischemic stroke within the disease groups compared with controls. (**B**) Forest plot with adjusted odds ratio and confidence intervals of neuroimaging-confirmed ischemic stroke within the disease groups compared with controls. (**C**) Survival plots of symptomatic ischemic stroke in the Parkinson's disease groups and controls. Lines represent the cumulative event-free survival in years of age. (**D**) Survival plots of neuroimaging-confirmed ischemic stroke in the Parkinson's disease groups and controls. Lines represent the cumulative event-free survival in years of age. CI, confidence interval; *GBA*-PD, patients with *GBA*-associated Parkinson's disease; *LRRK2*-PD, patients with *LRRK2*-associated Parkinson's disease; OR, odds ratio; *PRKN*-PD, patients with *PRKN*-associated Parkinson's disease; sPD, patients with sporadic Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Daniel Macías-García, MD,[1,2] María Teresa Periñán, MSc,[1,2] Laura Muñoz-Delgado, MD,[1,2] Silvia Jesús, MD, PhD,[1,2] María Valle Jimenez-Jaraba, BSc, MSc,[1] Dolores Buiza-Rueda, MSc,[1,2] Marta Bonilla-Toribio, MSc,[1,2] Astrid Adarmes-Gómez, MD,[1,2] Fátima Carrillo, MD, PhD,[1,2] Pilar Gómez-Garre, PhD,[1,2*] and Pablo Mir, MD, PhD[1,2,3*]

[1]*Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/Consejo Superior de Investigaciones Científicas/Universidad de Sevilla, Seville, Spain,* [2]*Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Madrid, Spain, and* [3]*Departamento de Medicina, Facultad de Medicina, Universidad de Sevilla, Seville, Spain*

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

YY1: A New Gene for Childhood Onset Dystonia with Prominent Oromandibular-Laryngeal Involvement?

The temporal pattern of evolution of dystonia distribution is a clue to genetic etiology. Childhood-onset genetic dystonia frequently begin in a limb and may secondarily generalize, but uncommonly involve the cervical, oromandibular, or laryngeal regions. We report two cases of childhood-onset dystonia with prominent oromandibular-laryngeal involvement with mutation in the *YY1* gene. *YY1* encodes the Yin Yang 1 protein, a transcription factor that has been demonstrated to play a role in neurodevelopment including mediation of myelin gene expression. Clinical manifestations of *YY1* haploinsufficiency typically include intellectual disability and behavioral abnormalities.[1] However, the association of mutation in the *YY1* gene with oromandibular and laryngeal dystonia potentially expands the number of loci associated with this phenotype and implicates convergent molecular pathways that may enhance understanding of dystonia pathophysiology.

Case 1 (*YY1* c.908G > T[p.C303F]) is a 22-year-old male with mild global developmental delay, autism, and progressive gait, speech, and swallowing difficulties. He displayed failure to thrive since infancy attributed to hypersensitivity, oral motor delays, and poor oral coordination. During his early teens, he developed worsening dysarthria, new onset stuttering, dysphagia, gait abnormality, kyphosis, and scoliosis. A G-tube was placed at age 19. Examination (age 22) showed generalized dystonia involving feet, hands, torso, tongue, jaw, pharynx, and larynx. Brain MRI showed scattered foci of T2 hyperintensities in the left anterior temporal, subcortical, and periventricular white matter (Supplementary Videos S1 and S2; Supplementary Figure S1; and Appendix S1).

Case 2 (*YY1* c.385delG[p.D129lfsX127]) previously reported without detail,[1] is a 41-year-old female with mild global developmental delays and progressive gait, speech, and swallowing difficulties. Speech articulation issues were longstanding. Dystonic foot inversion began at age 11 with subsequent progressive gait impairment, dysarthria, dysphagia, lingual, facial, and laryngeal dystonia. A G-tube was placed at age 40. Examination (age 40) showed drooling, severe vocal straining associated with lingual and laryngeal dystonia, diffuse facial dystonia exacerbated by attempted articulation, dystonic postures of the outstretched hands with coarse irregular tremor, and hand and foot dystonia while walking. Brain MRI showed minimal prominence of cortical sulci and lateral ventricles and numerous foci of T2 hyperintensities within the bifrontal subcortical white matter, extending into the periventricular regions. Notably, lymphoma was diagnosed at age 39 (Supplementary Videos S3–S5; Supplementary Figure S2; and Appendix S1).

Oromandibular dystonia of childhood onset is associated with multiple genetic disorders.[2,3] The pathophysiology underlying dystonia and the factors governing onset site and distribution are not well understood. It is uncertain whether genetic dystonias share a common underlying biologic substrate.[4,5]

With this in mind, it is informative to note potential related functions among a subset of genes associated with prominent oromandibular dystonia: *THAP1*, *KMT2B*, *PRKRA*, and now *YY1*. All display high cerebellar expression[6] in line with emerging evidence linking dystonia to the cerebellum. Most interestingly, *YY1*, *THAP1*, *KMT2B*, and *PRKRA* are implicated in regulation of gene transcription[5,7] with striking overlap between YY1 and THAP1 regulated genes.[7] Direct YY1/THAP1 interaction has been demonstrated[7] and an YY1/THAP1 co-regulatory model impairing DNA double-stranded break repair has been suggested as a pathomechanism for *THAP1*-associated dystonia.[8] Additionally, both YY1 and THAP1 play key roles in oligodendrocyte maturation,[7] perhaps relevant to white matter abnormalities on MRI in *YY1* patients[1] and microstructural white matter abnormalities on diffusion tensor imaging in *THAP1* patients.[9,10]

Although speculative at present, these overlapping functions and localizations may provide clues to pathogenesis. We suggest mutation of *YY1* be considered in individuals with prominent oromandibular-laryngeal dystonia of childhood onset. Further investigation is warranted and may give insight into shared mechanisms leading to the genesis and evolution of this unusual phenotype providing a foundation for development of targeted therapies.

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Key Words: dystonia; oromandibular; YY1; laryngeal

***Correspondence to:** J. Friedman, Division of Neurology, Rady Children's Hospital, 3001 Frost St., San Diego, CA, 92123, USA; E-mail: jrfriedman@ucsd.edu

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