RESEARCH ARTICLE

Association of *PICALM* with Cognitive Impairment in Parkinson's Disease

María Teresa Periñán, MSc,[1,2] Daniel Macías-García, MD,[1,2] Miguel Ángel Labrador-Espinosa, MSc,[1,2] Silvia Jesús, MD, PhD,[1,2] Dolores Buiza-Rueda, MSc,[1,2] Astrid D. Adarmes-Gómez, MD,[1,2] Laura Muñoz-Delgado, MD,[1] Pilar Gómez-Garre, PhD,[1,2*] and Pablo Mir, MD, PhD[1,2*]

[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 (CSIC)/Universidad de Sevilla, Seville, Spain*
[2]*Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain*

ABSTRACT: Background: Cognitive impairment is one of the most disabling nonmotor symptoms in Parkinson's disease (PD). Recently, a genome-wide association study in Alzheimer's disease has identified the *PICALM* rs3851179 polymorphism as one of the most significant susceptibility genes for Alzheimer's disease after *APOE*. The aim of this study was to determine the potential role of *PICALM* and its genetic interaction with *APOE* in the development of cognitive decline in PD. **Methods:** A discovery cohort of 712 patients with PD were genotyped for *PICALM* (rs3851179) and *APOE* (rs429358 and rs7412) polymorphisms. The association of *PICALM* and *APOE–PICALM* genetic interaction with cognitive dysfunction in PD was studied using logistic regression models, and the relationship of *PICALM* with cognitive decline onset was assessed with Cox regression analysis. *PICALM* effect was then replicated in an international, independent cohort (Parkinson's Progression Markers Initiative, N = 231). **Results:** *PICALM* rs3851179 TT genotype was significantly associated with a decreased risk of cognitive impairment in PD (TT vs. CC + CT, $P = 0.041$, odds ratio = 0.309). Replication studies further demonstrated its protective effect on cognitive impairment in PD. In addition, the protective effect of the *PICALM* rs3851179 TT genotype was more pronounced in the *APOE* ε4 (–) carriers from the discovery cohort ($P = 0.037$, odds ratio = 0.241), although these results were not replicated in the Parkinson's Progression Markers Initiative cohort. **Conclusions:** Our results support the fact that *PICALM* is associated with cognitive impairment in PD. The understanding of its contribution to cognitive decline in PD could provide new targets for the development of novel therapies. © 2020 International Parkinson and Movement Disorder Society

Key Words: cognitive impairment; Parkinson's disease; genetics; *PICALM*; *APOE*

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by motor dysfunction.[1] In addition to the defining motor features, a wide variety of nonmotor symptoms including cognitive impairment, hallucinations, and mood disorders are commonly observed in patients with PD. Cognitive decline is one of the most severe and disabling nonmotor symptoms of PD. Almost 25% of newly diagnosed patients with PD experience mild cognitive impairment, and more than 80% of patients with PD develop dementia within 20 years of diagnosis.[2,3] The profile of cognitive dysfunction among patients with PD is heterogeneous in its severity, affected domains, and rate of progression. In particular, the cognitive domains affected by cognitive impairment in PD involve working and semantic memory, executive function, visuospatial skills, attention, and mental processing speed.[4]

***Correspondence to:** Dr. Pablo Mir, 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; or Dr. Pilar 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: mgomez-ibis@us.es

Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 1 June 2020; **Revised:** 7 July 2020; **Accepted:** 17 August 2020

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28283

Neuropathological findings have demonstrated that cognitive impairment in PD correlates with Lewy bodies, cerebrovascular disease, and Alzheimer's disease (AD) pathology (ie, tau neurofibrillary tangles and amyloid-β plaques).[5] Despite the multiple candidate biomarkers being investigated and the ongoing advances in biomarker research, the susceptibility genes involved in cognitive impairment of PD are still unknown. In this regard, genetic polymorphisms may provide additional information on risk and help in the understanding of its biological basis.

Several genetic studies have demonstrated the association of the *APOE* ε4 allele, the major genetic risk factor for AD, with cognitive impairment in PD.[6–9] This finding points to a potential overlap between PD and AD. Indeed, there is increasing evidence showing the similarities in pathological characteristics and clinical features among PD and AD.[10] Recently, a large genome-wide association study in AD has identified a single nucleotide polymorphism, rs3851179, at 5′ to the *PICALM* gene as one of the most significant susceptibility genes of AD after *APOE*.[11] Various studies have considered its minor allele T, which increases the expression of *PICALM*, as a protective allele against AD.[11,12] The *PICALM* gene encodes the clathrin adaptor protein involved in clathrin-mediated endocytosis, which is an essential step in the intracellular trafficking of proteins, lipids, growth factors, and neurotransmitters. In recent years, the potential role of *PICALM* rs3851179 in the pathogenesis of PD has been assessed using ethnically diverse study populations, but the findings have been mixed.[13–18]

Given the importance of cognitive impairment in PD and the effect of *PICALM* on cognition, the aim of the present study was to determine whether *PICALM* rs3851179 and its genetic interaction with *APOE* contribute significantly to the risk of cognitive decline in PD.

Methods

Participants

We included a discovery cohort consisting of 712 patients with PD (59.0% men; mean age of onset, 54.3 ± 12.6 years) recruited from the Movement Disorders Clinic of the Hospital Universitario Virgen del Rocio in Seville, Spain. PD was diagnosed following the Movement Disorder Society clinical diagnostic criteria.[19]

Patients with PD were clinically assessed by movement disorder specialists, and an extensive set of clinical features was obtained. Cognitive impairment was assessed using as screening tools the results of the neuropsychological assessment and the scores in standard scales such as the Mattis Dementia Rating Scale (≤139), Parkinson's Disease Cognitive Rating Scale (≤81), Mini Mental State Examination (≤24), Montreal Cognitive Assessment (≤26), Scales for Outcomes in Parkinson's Disease–Cognition (≤22), and the Parkinson's Disease Dementia Short Screen (≤11).[4,20–24] Consequently, we identified patients with PD who met the diagnostic criteria for mild cognitive impairment or dementia in a long-term review of the medical records. All patients underwent a neuroimage test, and all patients with PD with cognitive impairment underwent brain magnetic resonance as well as biochemical analysis to exclude nondegenerative/metabolic causes of cognitive impairment. Peripheral blood samples were obtained from each participant.

For replicating *PICALM* influence on cognitive impairment in PD, we used the Parkinson's Progression Markers Initiative (PPMI) cohort, an international, multisite, prospective, longitudinal cohort study. Details regarding the PPMI study have been published[25,26] and are available on the PPMI website (http://www.ppmi-info.org). The PPMI data used in this analysis were downloaded on April 2, 2020.

A total of 231 patients with PD (65.4% men; mean age of onset, 61.0 ± 9.6 years) enrolled in the PPMI study were included in the replication study cohort. Participants with PD were required to have (1) an idiopathic PD diagnosis, (2) a dopamine transporter deficit on imaging, (3) genetic material available for analysis, (4) White race, and (5) cognitive assessments done by the site investigators. In this regard, a clinical diagnosis of cognitive impairment (mild cognitive impairment or dementia) was made following the Movement Disorders Task Force Criteria for dementia. Those participants who presented with cognitive complaints but did not fulfill the cognitive impairment criteria during these assessments were excluded from the cognitively healthy group.

The study was approved by the local ethics committee in accordance with the Declaration of Helsinki, and written informed consent was obtained from all the participants in the study. The PPMI study was approved by the local institutional review boards of all participating sites.

Genetics

Genomic DNA was isolated from peripheral blood samples according to established protocols by standard or automated methods (DNA Isolation Kit for Mammalian Blood, Roche Diagnostics, Indianapolis, IN; MagNA Pure LC, Roche Diagnostics). DNA quantification was determined by a NanoDrop2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA).

All participants underwent genotyping for rs3851179 (*PICALM*) as well as rs429358 and rs7412 (*APOE* ε2, ε3, and ε4 alleles). Genotyping was performed using

TABLE 1. Demographic features of the discovery cohort and PPMI replication cohort

	Patients with PD							
	Discovery Cohort				PPMI Replication Cohort			
	Total (N = 712)	Patients with PD with Cognitive Decline (N = 107)	Patients with PD with no Cognitive Decline (N = 605)	*P* Value	Total (N = 231)	Patients with PD with Cognitive Decline (N = 63)	Patients with PD with No Cognitive Decline (N = 168)	*P* Value
Sex, N (% men)	420 (59.0)	58 (54.2)	362 (59.8)	0.275	151 (65.4)	49 (77.8)	102 (60.7)	**0.015**
Age at onset y, mean ± SD	54.3 ± 12.6	58.1 ± 9.1	53.6 ± 13.1	**0.001**	61.0 ± 9.6	65.0 ± 9.3	59.1 ± 9.3	**<0.001**

Abbreviations: PPMI, Parkinson's Progression Markers Initiative; PD, Parkinson's disease; N, number of subjects; SD, standard deviation. Bold values indicate significant Bonferroni-adjusted *P* values.

Taqman SNP Genotyping Assays (Applied Biosystems, Foster City, CA) in a LightCycler480-II (Roche Applied Science, Penzberg, Germany).

In the PPMI replication cohort, the variant rs3851179 (*PICALM*) was genotyped using the ImmunoChip genotyping array as previously described.[27] In addition, the *APOE* ε2/ε3/ε4 genotypes were genotyped using TaqMan genotyping as previously described.[28]

Statistical Analysis

The association of the *PICALM* rs3851179 polymorphism and the *APOE* ε4 allele with the presence of cognitive impairment in PD was investigated in both the discovery and replication cohorts using logistic regression models adjusted for sex and age of onset. All results were corrected for multiple testing using the Bonferroni correction method. A $P < 0.01$ in the Hardy-Weinberg equilibrium test and a minor allele frequency of less than 1% were established as quality controls. Furthermore, an analysis of multiplicative interactions was performed between the *PICALM* rs3851179 polymorphism and the *APOE* ε4 allele in both cohorts. Cox regression was used to examine the association between *PICALM* rs3851179 and the presence of cognitive impairment in PD as a time-dependent outcome. Analysis was adjusted for potential confounding factors including sex and age of onset. All of the analyses were done using PLINK software v.1.07 and R software.[29,30]

Results

Of the 712 patients with PD included in the discovery cohort, cognitive impairment occurred in 15.0% of patients with PD. On the other hand, 27.3% of patients with PD developed cognitive impairment in the PPMI replication cohort. Demographic characteristics of each cohort are shown in Table 1.

The distribution of *PICALM* genotypes in the subset of patients with PD without cognitive impairment was found to be in Hardy-Weinberg equilibrium in the discovery cohort. There were significant differences in genotype frequencies (TT vs. CC + CT, $P = 0.041$, odds ratio [OR] = 0.309) between patients with PD with and without cognitive decline (Table 2).

Of the 712 patients with PD, 107 progressed to cognitive impairment after a mean of 11.3 ± 5.9 years from disease onset. The Cox regression analysis is presented in the Table S1. The *PICALM* rs3851179 TT genotype (hazard ratio = 0.397, $P = 0.044$) was found to have a protective effect against the development of cognitive decline. The survival curve for this polymorphism in the discovery cohort is presented in Figure 1.

Furthermore, the distribution of the *APOE* ε4 allele in the subgroup of patients with PD without cognitive decline was found to be in the Hardy-Weinberg equilibrium. There were significant differences in allele frequencies (ε4− vs. ε4+, $P = 0.008$, OR = 0.516) between patients with PD with and without cognitive decline

TABLE 2. Results for logistic regression of *PICALM* rs3851179 and cognitive impairment in PD in the discovery cohort corrected for sex and age of onset

Polymorphism	Genotype	Patients with PD with Cognitive Decline, N (%)	Patients with PD Without Cognitive Decline, N (%)	OR (95% CI)	*P* Value*
PICALM rs3851179	CC + CT	98 (95.1)	517 (85.7)	Reference	
	TT	5 (4.9)	86 (14.3)	0.309 (0.122–0.785)	**0.041**

Abbreviations: PD, Parkinson's disease; N, number of subjects; OR, odds ratio; CI, confidence interval.
*Bold values indicate significant Bonferroni-adjusted *P* values.

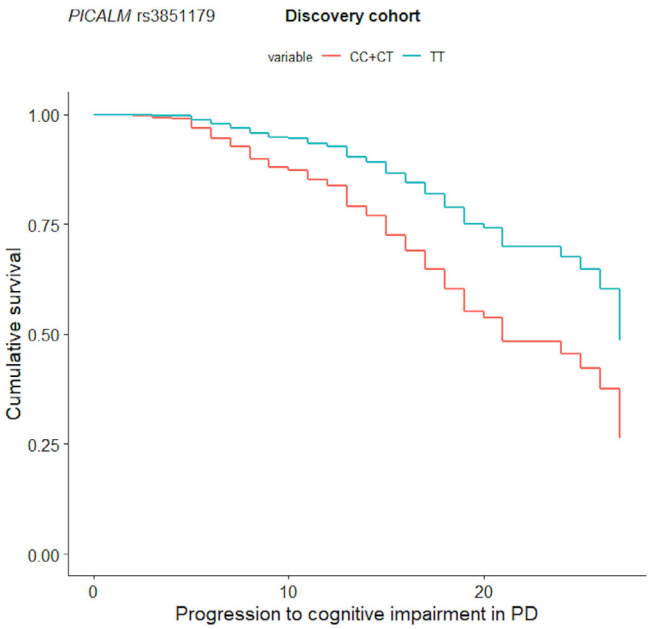

FIG. 1. Survival plot of cognitive impairment onset in PD in the discovery cohort. Lines represent the cumulative dementia-free survival in years from disease onset. PD, Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

(Table S2). After stratification of our PD cohort according to *APOE* ε4 status, a significant association for the rs3851179 TT genotype was found only in the *APOE* ε4 (−) carriers, but not in the *APOE* ε4 (+) subgroup (Table 3).

Having demonstrated that *PICALM* rs3851179 was associated with cognitive impairment in PD in the discovery cohort, we next tested our results for replication in an independent PPMI replication cohort. First, replication studies identified significant differences in *PICALM* rs3851179 genotype frequencies (TT vs. CC + CT, $P = 0.041$, OR = 0.305) between patients with PD with and without cognitive decline (Table S3). Furthermore, the *PICALM* rs3851179 TT genotype (hazard ratio = 0.290, $P = 0.037$) was found to have a protective effect against the development of cognitive decline (Table S4). The survival curve for this polymorphism in the replication cohort is presented in Figure 2. Finally, the stratification of the PPMI replication cohort according to *APOE* ε4 status did not reveal any significant association neither in the *APOE* ε4 (−) carriers nor in the *APOE* ε4 (+) subgroup (Table S5).

Discussion

Our results support the hypothesis that *PICALM* could modulate the risk of cognitive impairment in PD in both the discovery and replication cohorts. Specifically, the *PICALM* rs3851179 TT genotype appeared to have a significant protective effect against cognitive decline in PD. After adjusting for *APOE*, statistical analysis showed that the association between *PICALM* rs3851179 and cognitive decline was only significant among the participants without the *APOE* ε4 allele in the discovery cohort. However, *PICALM*–*APOE* genetic interaction failed to replicate in the PPMI cohort.

Despite the overlap between cognitive impairment in AD and PD, the role of this top hit polymorphism in AD has not yet been widely addressed in cognitive impairment in PD.[14,15] Barret and colleagues[14] suggested that the *PICALM* rs3851179 T allele could increase the risk of cognitive decline in older patients with PD (>70 years old) in the PROGENI/GenePD [Parkinson's Research: The Organized Genetics Initiative (PROGENI); The database of Genotypes and Phenotypes (dbGaP)] cohort (available in dbGaP). Nevertheless, the results in this study were not corrected for multiple testing. These results contrast with our findings that pointed out that the presence of the TT genotype had a significant protective effect against the risk of cognitive decline in both cohorts of patients with PD, expanding the role of *PICALM* not only to older patients with PD.[14]

Furthermore, most studies have focused on the role of *PICALM* in PD; however, none were able to investigate the effect of this gene on cognitive impairment.[13,16–18] Santos-Rebouças and colleagues[13] performed a case-control study in a Brazilian population of 174 patients with late-onset AD, 166 patients with late-onset PD, and 176 controls and showed that the rs3851179 T allele represented a significant

TABLE 3. Analysis of multiplicative interaction between *PICALM* rs3851179 and *APOE* ε4 status in patients with PD with and without cognitive decline in the discovery cohort

APOE Status	*PICALM* rs3851179	PD with Cognitive Decline, N (%)	PD Without Cognitive Decline, N (%)	OR (95% CI)	*P* Value*
ε4−	CC + CT	70 (95.9)	423 (84.9)	Reference	
	TT	3 (4.1)	75 (15.1)	0.241 (0.074–0.788)	**0.037**
ε4+	CC + CT	26 (92.9)	84 (90.3)	Reference	
	TT	2 (7.1)	9 (9.7)	0.580 (0.112–3.003)	1.000

Abbreviations: PD, Parkinson's disease; N, number of subjects; OR, odds ratio; CI, confidence interval.
*Bold values indicate significant Bonferroni-adjusted *P* values.

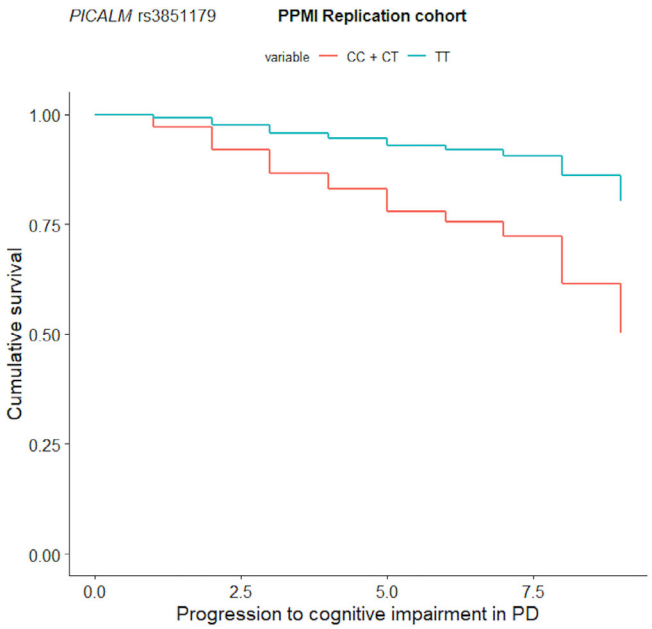

FIG. 2. Survival plot of cognitive impairment onset in PD in the PPMI replication cohort. Lines represent the cumulative dementia-free survival in years from disease onset. PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative. [Color figure can be viewed at wileyonlinelibrary.com]

protective factor for PD with an OR similar to AD. Nonetheless, the plausible interaction of *PICALM* and *APOE* was only assessed in the AD cohort. A significant association for the *PICALM* rs3851179 T allele remained significant only in the *APOE* ε4 (−) subgroup.[13] To the best of our knowledge, our study is the first attempt to analyze the interaction effects of the *APOE* ε4 allele and the single nucleotide polymorphism rs3851179 in PD. Notably, as occurs with AD, a significant association for the *PICALM* rs3851179 TT genotype remained significant only in the *APOE* ε4 (−) subgroup in the discovery cohort.

In recent years, some functional analyses have investigated the relationship between *PICALM* and PD.[13] A clathrin-dependent endocytic mechanism is essential for the maintenance of synaptic transmission because synaptic vesicles need to be recycled after releasing a neurotransmitter.[17] PD predominantly affects the dopamine-producing neurons residing at the substantia nigra, and α-synuclein was found to play a role in regulating dopamine homeostasis through its involvement in clathrin-mediated endocytosis.[31] The role of *PICALM* in vesicle-associated membrane protein-2 trafficking has also been proposed to be crucial to neuronal function.[32]

Our findings suggest another possible explanation for the association of *PICALM* with PD through the *PICALM* rs3851179 polymorphism with cognitive impairment. To date, most longitudinal studies in PD agree that abnormal Aβ is linked to future cognitive decline.[33] Furthermore, *PICALM* is involved in clathrin-mediated endocytosis, which is a component of some metabolic pathways such as formation and clearance on β-amyloid and tau protein clearance by autophagy.[34,35] In line with this, it has been reported that the *PICALM* rs3851179 T allele leads to a modest increase in *PICALM* expression and consequently to an increase in Aβ clearance compared with the nonprotective allele, suggesting a link between *PICALM* and Aβ pathology in PD.[36] This explanation is in accordance with a genetic interaction of *APOE–PICALM* associated with cognitive impairment in PD because *APOE* has also been involved in the regulation of Aβ clearance from the brain.[37]

In terms of study limitations, cognitive dysfunction was not assessed in our discovery cohort at the time of diagnosis of PD, so we were not able to evaluate if this could affect the course of cognitive decline. In addition, cognitive impairment was not assessed with the same standard cognitive scale during follow-up. In this regard, although all the screening scales used to evaluate cognitive status were internationally accepted, statistical adjustment for cognitive scale scores was not possible. Similarly, the level of education was not recorded during the clinical assessments of the participants in our discovery cohort, so we were not able to adjust for this variable when analyzing the associations. Moreover, further studies with larger sample sizes and ethnically diverse populations of patients with PD are needed to confirm the relationship between *PICALM* rs3851179 and cognitive function/dementia in PD in other populations and its possible interaction with *APOE*.

Finally, our results support the fact that the *PICALM* rs3851179 polymorphism is associated with cognitive impairment in PD. The understanding of its contribution to cognitive decline in PD could provide new targets for the development of novel therapies.

Acknowledgments

The authors thank the donors and the Hospital Universitario Virgen del Rocío-Instituto de Biomedicina de Sevilla Biobank (Andalusian Public Health System Biobank and ISCIII-Red de Biobancos PT17/0015/0041) for the human specimens used in this study. Data used in the preparation of this manuscript were obtained from the Parkinson's Progression Markers Initiative database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. Parkinson's Progression Markers Initiative—a public–private partnership—is funded by the Michael J. Fox Foundation for Parkinson's Research. Corporate funding partners include AbbVie, Allergan, Amathus, Avid, Biogen, BioLegend, Bristol-Myers Squibb, Celgene, Denali, GE Healthcare, Genentech, GlaxoSmithKline, Janssen Neurosciene, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Prevail, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, and Voyager, and the philanthropic funding partner is Golub Capital.

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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.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

M.T.P.: 1A, 1C, 2A, 2B, 3A
D.M.-G.: 1C, 3B
M.A.L.-E.: 1C, 3B
S.J.: 1C, 3B
D.B.-R.: 1C, 3B
A.D.A.-G.: 1C, 3B
L.M.-D.: 1C, 3B
P.G.-G.: 1A, 1B, 1C, 3B
P.M.: 1A, 1B, 1C, 3B

Full financial disclosures for the previous 12 months

This work was supported by the Instituto de Salud Carlos III-Fondo Europeo de Desarrollo Regional (PI14/01823, PI16/01575, PI18/01898, PI19/01576), the Consejería de Economía, Innovación, Ciencia y Empleo de la Junta de Andalucía (CVI-02526, CTS-7685), the Consejería de Salud y Bienestar Social de la Junta de Andalucía (PI-0471-2013, PE-0210-2018, PI-0459-2018, PE-0186-2019), and the Fundación Alicia Koplowitz. Pilar Gómez-Garre was supported by the "Miguel Servet" program (MSII14/00018; from the Instituto de Salud Carlos III-Fondo Europeo de Desarrollo Regional) and "Nicolás Monardes" program (C-0048-2017; from the Andalusian Regional Ministry of Health). Silvia Jesús was supported by the "Juan Rodés" program (B-0007-2019) and Daniel Macías-García by the "Río Hortega" program (CM18/00142) (both from the Instituto de Salud Carlos III-Fondo Europeo de Desarrollo Regional). María Teresa Periñán was supported by the Spanish Ministry of Education, Culture and Sports (FPU16/05061).