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Research Report

Association study and meta-analysis of Alzheimer's disease risk and presenilin-1 intronic polymorphism

Miguel Rodríguez-Manotas[a], *Manuel Amorín-Díaz*[b,*], *Francisco Cañizares-Hernández*[a], *Francisco Ruíz-Espejo*[a], *Salvadora Martínez-Vidal*[b], *Rogelio González-Sarmiento*[c], *Pedro Martínez-Hernández*[a], *Juan Cabezas-Herrera*[a,*]

[a]*Clinical Analysis Service, University Hospital Virgen de la Arrixaca, Ctra. Madrid-Cartagena s/n, El Palmar, 30120 Murcia, Spain*
[b]*Neurology Service, Hospital Comarcal del Noroeste, C/Miguel Espinosa, 1, Caravaca de la Cruz, 30400 Murcia, Spain*
[c]*Unidad de Medicina Molecular, Departamento de Medicina, Universidad de Salamanca, Campus Miguel Unamuno, 37007 Salamanca, Spain*

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ABSTRACT

Numerous studies have tested for associations between an intronic polymorphism (rs165932) of presenilin-1 (PS-1) gene and the risk of Alzheimer's disease (AD), but results have been conflicting. To throw light on this issue, we investigate the possible involvement of PS-1 genotype in a case–control study based on a relatively stable population in Spain and a meta-analysis of published studies. An examination was conducted of 85 patients with probable or possible AD, along with controls from the same community, by using an χ^2 test for homogeneity and a binary logistic regression model. For comparison purposes, a meta-analysis of data from all available published studies was assessed. In our patients, homozygosity of the allele 2 in the PS-1 gene increased for late-onset AD (OR 2.38, 95% CI 1.07–5.29, $P<0.05$). The presence of at least one allele of apoE was also associated with AD (OR 4.01, 95% CI 1.93–8.34, $p<0.05$). The regression model showed that, overall, the presence of the apoE ε4 allele and the PS-1 2/2 genotype were independent factors for the development of AD in our sample. In our genotype-based meta-analysis, the PS-1 2/2 genotype was probably related with AD for the European sub-group (fixed effects model, OR 1.19, 95% CI 1.02–1.37, $p<0.05$), but there are many confusing factors between different studies. Presenilin-1 2/2 genotype is a risk factor for late onset Alzheimer disease in the Spanish population, and probably, for Europeans.

1. Introduction

The presenilin-1 gene (PS-1), together with the amyloid precursor protein (APP) and presenilin-2 (PS-2), is one of the most widely recognized genes in the development of familial Alzheimer's disease (FAD) (Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995). PS-1 is an integral membrane protein that forms the catalytic core of the γ-secretase complex (De Strooper, 2003), activity related to the accumulation of the Abeta 42 protein in the brain of patients with Alzheimer's disease (AD) (Borchelt et al., 1996).

* *Corresponding authors*. J. Cabezas-Herrera is to be contacted at Clinical Analysis Service, University Hospital Virgen de la Arrixaca, Ctra. Madrid-Cartagena s/n, El Palmar 30120 Murcia, Spain. M. Amorín-Díaz, Neurology Service Hospital Comarcal del Noroeste, C/Miguel espinosa 1, Caravaca de la Cruz, 30400 Murcia, Spain.
E-mail addresses: mdiaza@medynet.com (M. Amorín-Díaz), juan.cabezas@carm.es (J. Cabezas-Herrera).

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Initial studies on the possible relationship between the 1/1 genotype in the PS-1 gene (PubMed reference rs165932), located at intron 8, and late onset Alzheimer's disease (LOAD) started more than 10 years ago (Wragg et al., 1996; Hutton and Hardy, 1997). Later, clinical (Kehoe et al., 1996; Higuchi et al., 1996; Perez-Tur et al., 1996; Isoe et al., 1996; Tysoe et al., 1997; Ezquerra et al., 1997; Brookes et al., 1997; Korovaitseva et al., 1997; Scott et al., 1997; Lendon et al., 1997; Sorbi et al., 1997; Cai et al., 1997; Nishiwaki et al., 1997; Aldudo et al., 1997; Helisalmi et al., 1997; Singleton et al., 1997; Mann et al., 1997; Hu et al., 1998; Kowalska et al., 1998; Taddei et al., 1998; Wang et al., 1998; Scacchi et al., 1999; Wu et al., 1999; Yasuda et al., 1999; Bagli et al., 1999; Van Duijn et al., 1999; Combarros et al., 1999; Romas et al., 2000; Kim et al., 2000; Cui et al., 2000; Rodriguez-Martin et al., 2000; Papassotiropoulos et al., 2000; Dermaut et al., 2001; Chandak et al., 2002; Matsubara-Tsutsui et al., 2002; Jia et al., 2006) and anatomopathological (Yamada et al., 1997; Singleton et al., 1997; Mann et al., 1997; Sodeyama et al., 1998; Liao et al., 1999; Tilley et al., 1999; Yamada, 2002; Jia et al., 2006) studies were not able to confirm these results, and some authors have described histological changes related with intronic polymorphisms (De Jonghe et al., 1999), while others found no such relationship (Liao et al., 1999). Several meta-analyses have been published on the PS-1 1/1 genotype (Yasuda et al., 1999; Dermaut et al., 2001) or allelic frequency (http://www.alzforum.org/res/com/gen/alzgene/meta.asp?geneID=84), analyzing both early (EOAD) and late (LOAD) onset Alzheimer's disease, although a significant relationship was only found for LOAD (Yasuda et al., 1999). Moreover, some clinical studies have even suggested that the 2/2 genotype might be related to the disease (Ezquerra et al., 1997; Brookes et al., 1997; Aldudo et al., 1997).

We present a new study based on clinical cases to ascertain the prevalence of rs165932 PS-1 intronic polymorphism and its relationship with apoE polymorphisms of Alzheimer's disease in a rural area of south-eastern Spain whose population has remained relatively stable. The study was complemented with a meta-analysis focusing on the PS-1 2/2 genotype.

2. Results

The genotypic frequencies of AD and control groups were consistent with the Hardy–Weinberg equilibrium (HWE) and, taking into account the recommendations concerning χ^2 test errors (Terwilliger and Ott, 1994), the Arlequin program was used (Excoffier et al., 2005).

2.1. *Study of the apoE epsilon 4 allele*

As expected, a relationship between the presence of at least one epsilon 4 allele and LOAD (OR 4.01, 1.93–8.34, χ^2 test, $p=0.0001$) was found (Table 1).

2.2. *Study of the PS-1 2/2 genotype*

An OR of 2.38 (1.07–5.29, χ^2 test, $p=0.03$) was found for the 2/2 genotype (Table 1). There were no significant differences for the age of onset of dementia and the different genotypes ([1/1]: 71.05±7.60; [1/2]: 73.18±5.72; [2/2]: 72.95±6.16, ANOVA, $p=0.48$), not even when they were grouped (*t*-test: [2/2] vs. [1/2+1/1], $p=0.81$).

When we analyzed the distribution of the genotypes stratified by the occurrence of at least one allele of apoE epsilon 4, a significant relationship was found between the PS-1 2/2 genoype and the development of LOAD in the absence of apoE epsilon 4 (χ^2 test=3′94, $p=0.047$). When Bonferroni adjustment was applied as a correction for a multiple test, the statistical significance disappeared ($p=0.094$), and so apoE epsilon 4 and PS-1 2/2 can be considered as independent risk factors for LOAD.

2.3. *Relationship between the PS-1 2/2 genotype and the apoE epsilon 4*

As a consequence of the above result, binary logistic regression analysis was carried out, in which the fact of being a patient or a control was established as a dependent variable

Table 1 – Distribution of PS-1 genotypes and stratification by the occurrence of the apoE ε4 allele

		PS-1 GENOTYPE									
		1/1		1/2		2/2		1/1+1/2		2/2	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
	LOAD	18	21.2	45	53.0	22	25.9	63	74.1	22	25.9 (1)
	Control	25	29.1	50	58.1	11	12.8	75	87.2	11	12.8
ApoE stratified (2)											
ApoE ε4–	LOAD	10	20.8	25	52.1	13	27.1	35	73.9	13	27.1 (3)
	Control	20	28.2	42	59.2	9	12.7	62	87.3	9	13.7 (3)
ApoE ε4+	LOAD	7	20.0	20	57.1	8	22.9	27	77.1	8	22.9
	Control	4	30.8	7	53.9	2	15.4	11	84.6	2	15.4

(1) LOAD vs. control×PS-1 2/2 vs. PS-1 (1/1+1/2): $\chi^2=4.71$, $df=1$, $p=0.030$.
(2) ApoE ε4 OR $\chi^2=14.78$, $df=1$, $p=0.0001$.
(3) PS-1 2/2 genotype increases the risk for LOAD in the apoE ε4 negative subjects ($\chi^2=3.94$, $df=1$, $p=0.047$). After Bonferroni adjustment (×2 multiple comparisons) this relationship disappears ($p=0.094$).
Data of apoE epsilon 4 were missed from two patients and two controls.