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Relationship of the Ubiquilin 1 gene with Alzheimer's and Parkinson's disease and cognitive function

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Abstract

Ubiquilin 1 (UBQLN1) is involved in the ubiquitination machinery, which has been implicated in Alzheimer's disease (AD) as well as Parkinson's disease (PD). A polymorphism in the gene encoding for UBQLN1 has been previously associated with a higher risk of AD. We studied the role of the SNP rs12344615 on the UBQLN 1 gene in AD, PD and cognitive function in a population-based study, the Rotterdam Study, and a family-based study embedded in the genetic research in isolated population (GRIP) program. The Rotterdam Study includes 549 patients with AD and 157 patients with PD. The GRIP program includes a series of 123 patients with AD and a study of 1049 persons who are characterized for cognitive function. Data were analysed using logistic and multiple regression analysis. We found no significant difference in risk of AD or PD by the UBQLN1 SNP rs12344615 in our overall and stratified analyses in the Rotterdam Study. In our family-based study, we did not find evidence for linkage of AD to the region including the UBQLN1 gene. In the family-based study we also failed to detect an effect of this polymorphism on cognitive function. Our results suggest that it is unlikely that the SNP rs12344615 of the UBQLN1 gene is related to the onset of AD, PD or cognitive function.

Keywords: Alzheimer's disease; Parkinson's disease; UBQLN1 gene; Cognitive function; Family-based study; Population-based study

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders in western societies. Familial aggregation of these two disorders has been observed suggesting a common genetic cause [7,11,20,39]. The Ubiquilin1 gene (UBQLN1) may be involved in both diseases. An intronic single nucleotide polymorphism (SNP) located downstream of exon 8 (rs12344615) of the UBQLN1 gene has been associated with AD [8]. The ubqln1 protein interacts with presenilin 1 and 2 increasing their level [26], making the gene encoding for this protein, an interesting candidate for AD. UBQLN1 is also involved in the ubiquitination machinery, related with general protein degradation [27] which makes the UBQLN1 gene also of interest for PD [17,19,24,26,31]. Previous studies on the relationship of this gene and AD have shown contradicting results. While some studies found an association with AD or related quantitative traits [22,41], other studies did not find any evidence for association [5,10,40,42]. No studies have been performed so far evaluating the relationship between the UBQLN1 gene and PD. We studied the role of the rs12344615 polymorphism in the UBQLN 1 gene in AD, PD and cognitive function in population and family-based studies.

The Rotterdam Study is a population-based follow-up study of determinants of diseases in the elderly. The study has been previously described [21]. From all subjects, informed consent was obtained and the Medical Ethics committee of ErasmusMC approved the study. The diagnosis of dementia was made following a three-step protocol [3,46] and was previously described [38]. We used a two-step design to identify subjects with PD [12]: if two or more parkinsonian signs were present in a person not taking antiparkinsonian drugs, or if at least one sign had

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improved after medication was started, and when all causes of secondary parkinsonism (dementia, use of neuroleptics, cerebrovascular disease, multiple system atrophy, or progressive supranuclear palsy) could be excluded [13].

The Genetic Research on Isolated Populations (GRIP) program is a family-based study in a genetically isolated community aimed to identify genes involved in complex diseases [2,37]. The Medical Ethics Committee of ErasmusMC approved this study. Patient ascertainment was described previously [39]. AD patients were re-examined by research physicians applying neurological examination and brief neuropsychological testing. A standard interview was performed with close relatives concerning symptoms, disease course, medical, social and family history [39]. Dementia was classified using the clinical dementia rating scale (CDR). Diagnosis was done according to the NINCDS–ADRDA criteria [29].

The ERF study aims to identify susceptibility genes for complex disorders by studying quantitative traits [37]. The Medical Ethics Committee of ErasmusMC approved the study. Five neuropsychological tests were used to evaluate cognitive domains related to neurodegenerative disorders [4,14,15]: the auditory verbal learning test (AVLT) [35,36], the trail making test (TMT) [34], the Stroop Color-word Test [16,18], the verbal fluency test [6,25], and the Block Design subtest of the Wechsler Adult Intelligence Test (WAIS) [47]. Individuals with a previous diagnosis of neurological or psychiatric disorders were excluded ($n = 47$) [37].

DNA was extracted from whole blood using standard methods [30]. All samples were genotyped for SNP rs12344615 with a TaqMan assay using the following primers: forward primer: GCTATCTTGGGTAATGATTTGCTTGAAA, reverse primer: CTCTATTCTATGTTTTGCTATCAGCCAGA. Analysis was done on a Prism 7900HT Sequence Detection System with SDS v 2.1 (Applied Biosystems, Foster City, CA). Based on the analysis of blind duplicates (318 control pairs), there was a 100% concordance in genotyping the rs12344615 SNP. All samples from the GRIP study were genotyped using 18 flourescently labelled microsatellite markers from chromosome 9 following manufacturer instructions (Applied Biosystems, Foster City, CA). The genotyping of APOE in the Rotterdam Study was previously described [48]. APOE in the GRIP and ERF studies was done using TaqMan allelic discrimination Assay-By-Design (Applied Biosystems, Foster City, CA).

Hardy–Weinberg equilibrium (HWE) proportions were estimated and genotype frequencies of the rs12344615 polymorphism were compared between cases and controls using the χ^2-test. For the Rotterdam Study, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariate logistic regression adjusting for age, gender and APOE*4 using the SNP rs12344615 TT genotype as reference. We assessed the effect of the rs12344615 SNP on the age at onset of AD and PD in incident cases only using multiple regression analysis.

For the GRIP study the Quasi-Likelihood Score test of the CC-QLS package [9], was used for the association analysis to correct for familial relationships. For the CC-QLS test, kinship and inbreeding coefficients were calculated using our genealogy database. Individuals with unavailable genealogy used the average kinship and inbreeding coefficients. Parametric linkage analysis was performed under a dominant model using SimWalk2 V.2.91 [43–45]. Age dependent penetrance was estimated using population prevalence [32] and disease gene frequency was set to 1%. Allelic frequencies were estimated from unrelated controls.

We evaluated the association between SNP rs12344615 and cognitive function [37]. Given the skewed distributions of the AVLT-Trial VII, TMT-A, TMT-B, cards I, II and III of the Stroop colour-word and Block design tests, the data were log-transformed. Data were analysed using the linear mixed model implemented in SOLAR [1]. Models were adjusted for age, age^2, sex, inbreeding and general cognitive ability.

Description of the participants of the Rotterdam Study stratified by rs12344615 genotype is shown in Table 1. There were a total of 389 incident and 160 prevalent AD cases available. The total number of available PD cases were 89 incident and 68 prevalent. The distributions of the genotype frequencies were in HWE ($p = 0.70$). The total number of affected individuals with AD or PD was not significantly increased in carriers of the C allele, although the number of PD patients tended to be higher in those homozygous for this allele.

The distribution of rs12344615 in AD and PD cases and controls, overall and stratified by APOE*4, is shown in Table 2. We did not find a statistically significant difference in the distribution of this SNP between patients and controls. There was a non-significant increase in the frequency of CC genotype in AD patients in those without APOE*4 allele. We also found a

Table 1
General characteristics of the Rotterdam Study population stratified by the rs12344615 genotype

	Genotype		
	TT	CT	CC
Total typed (%)	4142 (66.0)	1923 (30.6)	212 (3.4)
Mean age of entry in years (S.D.)	69.3 (9.1)	69.7 (9.3)	68.8 (8.7)
Female (%)	2448 (59.1)	1164 (60.5)	120 (56.6)
APOE*4 carriers (%)	1156 (29.0)	499 (27.3)	59 (28.8)
No. of AD cases[a] (%)	353 (8.5)	178 (9.3)	18 (8.5)
No. of PD cases[b] (%)	105 (2.5)	45 (2.3)	7 (4.5)
No. of parkinsonism cases (%)	171 (4.1)	77 (3.0)	9 (3.5)

Parkinsonism cases include all PD cases.
[a] 389 incident and 160 prevalent.
[b] 89 incident and 68 prevalent.