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ORIGINAL ARTICLE

ATP5H/KCTD2 locus is associated with Alzheimer's disease risk

M Boada[1,2,15], C Antúnez[3,15], R Ramírez-Lorca[4,15], AL DeStefano[5,6], A González-Pérez[4], J Gayán[4], J López-Arrieta[7], MA Ikram[8], I Hernández[1], J Marín[9], JJ Galán[9], JC Bis[5], A Mauleón[1], M Rosende-Roca[1], C Moreno-Rey[4], V Gudnasson[10], FJ Morón[4], J Velasco[4], JM Carrasco[4], M Alegret[1], A Espinosa[1], G Vinyes[1], A Lafuente[1], L Vargas[1], AL Fitzpatrick[5], for the Alzheimer's Disease Neuroimaging Initiative[15], LJ Launer[11], ME Sáez[4], E Vázquez[4], JT Becker[12], OL López[12], M Serrano-Ríos[13], L Tárraga[1], CM van Duijn[8], LM Real[4], S Seshadri[5,6,14] and A Ruiz[1,4]

To identify loci associated with Alzheimer disease, we conducted a three-stage analysis using existing genome-wide association studies (GWAS) and genotyping in a new sample. In Stage I, all suggestive single-nucleotide polymorphisms (at $P<0.001$) in a previously reported GWAS of seven independent studies (8082 Alzheimer's disease (AD) cases; 12 040 controls) were selected, and in Stage II these were examined in an *in silico* analysis within the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium GWAS (1367 cases and 12 904 controls). Six novel signals reaching $P<5\times10^{-6}$ were genotyped in an independent Stage III sample (the Fundació ACE data set) of 2200 sporadic AD patients and 2301 controls. We identified a novel association with AD in the adenosine triphosphate (ATP) synthase, H+ transporting, mitochondrial F0 (*ATP5H*)/Potassium channel tetramerization domain-containing protein 2 (*KCTD2*) locus, which reached genome-wide significance in the combined discovery and genotyping sample (rs11870474, odds ratio (OR) = 1.58, $P=2.6\times10^{-7}$ in discovery and OR = 1.43, $P=0.004$ in Fundació ACE data set; combined OR = 1.53, $P=4.7\times10^{-8}$). This *ATP5H/KCTD2* locus has an important function in mitochondrial energy production and neuronal hyperpolarization during cellular stress conditions, such as hypoxia or glucose deprivation.

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia. It is expected that AD prevalence will be quadrupled by 2040, reaching a worldwide number of 81.1 million affected individuals.[1] In spite of the knowledge that genetic factors may account for about 60–80% of AD susceptibility,[2] the *APOE* epsilon 4 allele was, until very recently, the only accepted risk factor for late-onset AD (LOAD).[3] Fortunately, genome-wide association study (GWAS) technologies are rapidly transforming our knowledge of important in determining the risk of LOAD.[10] However, researchers are intensively looking for direct relationships between these novel loci and amyloid deposition speculating that new genes might have effects on amyloid metabolism or through previously unsuspected pathophysiological pathways, and indeed preliminary evidence for relationships between the amyloid hypothesis and some of the novel loci is rapidly emerging.[11]

Specifically, it has been reported that *PICALM* has a role in beta-amyloid membrane trafficking in yeast models[12] Furthermore