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Does SCFD1 rs10139154 Polymorphism Decrease Alzheimer's Disease Risk?

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Abstract

A number of genetic variants have been associated with Alzheimer's disease (AD) susceptibility. Sec1 family domain-containing protein 1 (SCFD1) gene polymorphism rs10139154 has recently been implicated in the risk of developing amyotrophic lateral sclerosis (ALS). Similarities in the pathogenetic cascade of both diseases have also been described. The present study was designed to evaluate the possible contribution of SCFD1 rs10139154 to AD. A total of 327 patients with AD and an equal number of healthy controls were included in the study and genotyped for rs10139154. With logistic regression analyses, rs10139154 was examined for the association with the risk of developing AD. In the recessive mode, SCFD1 rs10139154 was associated with a decreased risk of developing AD (odds ratio (OR) (95% confidence interval (CI)) = 0.63 (0.40–0.97), $p = 0.036$). The current study provides preliminary evidence of the involvement of SCFD1 rs10139154 in the risk of developing AD.

Keywords AD · Genetics · SNPs · Polymorphism · SCFD1

Introduction

Alzheimer's disease (AD) is the most prevalent type of dementia and accounts for 60–80% of all dementia diagnoses worldwide (Ashraf et al. 2016). There are almost 44 million individuals suffering from AD worldwide, a number which is expected to exceed 115 million by 2050 (Qiu et al. 2009). AD is more common in Western Europe, with 2 out of 3 patients being women, whereas its main risk factor remains age (2017 Alzheimer's disease facts and figures 2017).

AD is characterized by extracellular deposits of amyloid-β (Aβ), the major component of senile plaques (SPs), alongside the intracellular accumulation of hyperphosphorylated tau protein, namely, neurofibrillary tangles (NFTs) (Scheltens

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et al. 2016). These are the histopathological hallmarks of the disease, and both of these are products of abnormal variants of normally functioning proteins, the Aβ and the tau proteins (Magalingam et al. 2018).

Amyloid-β is a peptide found in the healthy human brain, and it is produced by the cleavage of the amyloid precursor protein (APP) (Tosun et al. 2017). Normally, the cleavage of APP is mediated by α-secretase and γ-secretase in a pathway known as non-amyloidogenic (Hardy 2017; Scheltens et al. 2016). In AD, APP is cleaved by β-secretase instead of α-secretase, through an amyloidogenic pathway, resulting in the formation of the Aβ peptide (Ashton et al. 2018; Hardy 2017; Parihar and Hemnani 2004; Scheltens et al. 2016). The most abundant alloform of the Aβ peptide is Aβ42, which has the tendency to aggregate, forming SPs, thus leading to neurotoxicity and eventually neuronal loss (Carmona et al. 2018).

Tau is a microtubule-binding protein widely expressed in the human brain, particularly in axons and dendrites (Sebastian-Serrano et al. 2018). Tau's primary function is to maintain microtubule stability, thus promoting axonal transport, which is essential for the growth and survival of neurons. It is a phosphoprotein and its phosphorylation is closely regulated. In AD, tau becomes hyperphosphorylated and loses its normal function, resulting in the disruption of microtubules and the interruption of normal axonal transport (Mietelska-Porowska et al. 2014). On the other hand, the hyperphosphorylated tau protein tends to accumulate intracellularly, forming aggregates, NFTs, which are neurotoxic (Alonso et al. 2018).

Approximately 1–6% of all AD cases are familial, all autosomal dominant forms, with a relatively early-onset of AD symptoms (< 65 years of age) (EOAD) (Bekris et al. 2010, O'Brien & Wong, 2011, Haines 2018). Mutations in the APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes have been described in EOAD (Bekris et al. 2010, O'Brien & Wong, 2011, Haines 2018).

Regarding late-onset AD (LOAD), the APOE gene that encodes the APOE protein was the first that was described to confer susceptibility to AD (Raghavan and Tosto 2017). APOE protein exists in 3 allelic variants ε2, ε3, and ε4. From these, ε4 is involved in an increased risk of LOAD, since it seems to interfere with the synthesis, clearance, and aggregation of Aβ (Parihar and Hemnani 2004; Shao et al. 2017).

Over the past decade, thanks to genome-wide association studies (GWASs), several novel risk genes and polymorphisms associated with LOAD have been identified, some linked to the immune response (CR1, CD33, EPHA1, MS4A, TREM2, ABCA7) others to the synaptic function and endocytosis pathways (PICALM, CD2AP, BIN1, SORL1) or to cholesterol and lipid metabolism (CLU, ABCA7) (Karch and Goate 2015; Raghavan and Tosto 2017; Shao et al. 2017). From these, variants in triggering receptor expressed on myeloid cells 2 (TREM2) have been reported to increase the risk of LOAD with its most common variant, R47H, to have almost the same effect as APOEε4, although with a lower impact (Carmona et al. 2018; Van Cauwenberghe et al. 2016). Accounting for EOAD, more than 300 variants have been described to date, all providing weight to the Aβ pathology (Cuyvers and Sleegers 2016; Raghavan and Tosto 2017; Shao et al. 2017).

The pathogenesis of AD is based on the combination of genetic factors and different epigenetic events (Cubinkova et al. 2018). Epigenetic modifications with the major mechanisms being DNA methylation, histone modification, and non-coding RNAs have appeared to be strong contributors to aging and AD (Wang et al. 2013). On the other hand, well defined co-factors of AD pathogenesis are oxidative stress and its subsequent cascade at the level of the mitochondrial, DNA, and endoplasmic reticulum (ER) dysfunction, protein misfolding, and calcium and metal dyshomeostasis (Cubinkova et al. 2018).

Sec1 family domain-containing protein 1 (SCFD1) is a member of the Senc1/Munk 18 (SM) family of proteins which are vesicle-trafficking proteins, functioning with a specific type of SNARE proteins, the syntaxins (Carr and Rizo 2010, Dascher & Balch, 1996, Yamaguchi et al, 2002). SCFD1 is mainly involved in the ER-to-Golgi transport in conjunction with syntaxin 5, assisting in the membrane fusion and allowing the vesicles to pass from one compartment to the other. It may also function in the pre-Golgi intermediates, together with syntaxins 18 and 17, while it has also been proven that it interacts with the conserved oligomeric Golgi complex subunit 4 (COG4) complex, playing an important role in the intra-Golgi-retrograde transport (Hou et al. 2017; Nogueira et al. 2014). Furthermore, it is quintessential in the response to oxidative stress, contributing to protein trafficking in the face of cellular stress (Bando et al. 2005). It exerts anti-apoptotic effects; thus, an increased expression of SLY1 seems to suppress the morphological changes associated with ER due to oxidative stress and prevents cell death (Bando et al. 2005). These have proven to be in a close association with the pathogenesis of Parkinson's disease (PD), another neurodegenerative disease (Bando et al. 2005).

An association of the SCFD1 gene polymorphism rs10139154 with the risk of developing amyotrophic lateral sclerosis (ALS) has recently been described (Chen et al. 2018), particularly with the age of onset of the disease (Chen et al. 2018). The mechanisms underlying possible neurodegeneration have not yet been fully elucidated, although it has been demonstrated that patients with ALS/frontotemporal dementia (FTD) exhibit impaired endosomal trafficking function, the dysfunction of the trans-Golgi trafficking network, and autophagy (Aoki et al. 2017). These effects aggravate under stress conditions, progressively leading to neurodegeneration (Jovičić et al. 2015; Theuns et al. 2014). Abnormal endocytic trafficking has been reported in several neurodegenerative diseases, including ALS and AD (Aoki et al. 2017; Conlon et al. 2018; Haeusler et al. 2014). Additionally, previous studies revealed overlapping pathogenic mechanisms of the two diseases, involving the disruption of a

common axonal transport mechanism of proteins to the synaptic terminal, which is regulated by neurofilaments (Muresan and Ladescu Muresan 2016; Muresan et al. 2014). Considering the similarities in the pathogenetic cascade of both diseases and neurodegeneration (Dardiotis et al. 2019; Jouroukhin et al. 2013), as well as the impact of SCFD1 and particularly of the rs10139154 SNP on ALS, we deemed it useful to determine whether an association exists between AD susceptibility and the rs10139154 SCFD1 gene variant.

Therefore, the aim of this study was to examine the effects of SCFD1 rs10139154 on AD development.

Methods

Participants

In this study, a total of 654 individuals were recruited, 327 patients with a clinical diagnosis of AD (66.9% female, mean age of blood collection ± standard deviation (SD) = 78.90 ± 8.56 years) and 327 cognitively healthy controls. The samples of the patients were collected from the Neurology Department of the University Hospital of Larissa. The diagnosis of probable AD was based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS/ADRDA) criteria for AD (McKhann et al. 1984), and patients were submitted to certain tests, such as Mini-Mental State (MMS) or ADDENBROOKE-ACE-III cognitive examinations. The minimum MMS score obtained was smaller than 5, and for many patients, it was impossible to carry out the tests. The majority of the patients exhibited indicative cortical atrophy in the brain magnetic resonance imaging (MRI) or a reduced blood flow in the HMPO brain scan. A complete neurological examination was performed on each patient. The control samples originated from healthy individuals without a significant medical history and with a normal MMS score, and none fulfilled the criteria of mild cognitive impairment (MCI). The local institutional review board approved the research protocol, and a written informed consent was granted by all the participants or close relatives included in the study.

DNA Isolation and Genotyping Procedure

Peripheral blood samples were collected from all participants. Genomic DNA was extracted from peripheral blood leucocytes, using the method of salting out (Dardiotis et al. 2017; Siokas et al. 2018). Using TaqMan allele-specific discrimination assays on an ABI PRISM 7900 Sequence Detection System, tag SNPs were genotyped and analyzed with SDS software (Applied Biosystems, Foster City, California, USA). The personnel that performed the experimental work was unaware of the information regarding the participants. The genotypic call rate was 97.55%.

Statistical Analysis

Fisher's exact test, with a threshold of p value ≤ 0.05, was indicative of the deviation from the Hardy-Weinberg equilibrium (HWE) (Dardiotis et al. 2014b, 2018a; Katsarou et al. 2018). The study's statistical power was calculated using the CaTS Power Calculator for Genetic Studies (Skol et al. 2006).

Using binary univariate logistic regression analysis, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in order for possible associations between rs10139154 and AD risk to be estimated. Statistical analysis was performed using SNPStats software (http://bioinfo.iconcologia.net/SNPstats/) (Sole et al. 2006), assuming five genetic models (the co-dominant, the dominant, the recessive, the over-dominant, and the additive) of inheritance. A p value < 0.05 was considered to indicate a statistically significant difference.

Results

In total, 654 individuals were included in this study: 327 patients clinically diagnosed with AD (66.9% female, mean age of blood collection ± SD = 78.90 ± 8.56 years) and 327 cognitively healthy controls. Fisher's exact test revealed that rs10139154 was in HWE in both AD cases and healthy controls, with p values equal to 0.079 and 0.71, respectively. Based on the power analysis, this study had a power of 80.0% to detect an association of a variant with a genetic relative risk of 1.33, presuming the multiplicative model, with minor allele frequency (MAF) equal to 37% and type I error level of 0.05.

Analyses performed to assess the genotypic frequencies of SCFD1 rs10139154 demonstrated that genotypes C/C, C/T, and T/T were found in 124 (39%), 137 (43%), and 58 (18%) of the healthy controls, respectively. Concerning the individuals with AD, the results for C/C, C/T, and T/T were 139 (44%), 141 (44%), and 39 (12%), as well. A total of 16 samples (8 cases with AD and 8 healthy controls) failed to be genotyped. Allele and genotype frequencies in AD cases and in healthy controls appear in Table 1.

According to the univariate single-locus logistic regression analysis, SCFD1 rs10139154 was significantly associated with a decreased risk of developing AD, particularly in the recessive mode (OR (95% CI) = 0.63 (0.40–0.97), $p = 0.036$). A non-statistically significant trend for association was also revealed in the co-dominant mode for the T/T genotype (OR (95% CI) = 0.60 (0.37–0.96), $p = 0.097$) and in the log-additive model (OR (95% CI) = 0.81 (0.65–1.01), $p =$

Table 1 Allelic and genotype frequencies of SCFD1 rs10139154 in healthy controls, in AD cases, and in the whole samples

SNP	Genotypes/ alleles	Healthy controls ($n = 327$)	AD ($n = 327$)	Whole sample ($n = 654$)
rs591486		*n* (%)*	*n* (%)*	*n* (%)*
Genotype	C/C	124 (0.39)	139 (0.44)	263 (0.41)
	C/T	137 (0.43)	141 (0.44)	278 (0.44)
	T/T	58 (0.18)	39 (0.12)	97 (0.15)
	Missing	8	8	16
Allele	C	385 (0.60)	419 (0.66)	804 (0.63)
	T	253 (0.40)	219 (0.34)	472 (0.37)

SNP single-nucleotide polymorphism, *SCFD1* Sec1 family domain-containing protein 1, *AD* Alzheimer's disease

*Percentages (%) have been calculated based on successfully genotyped samples

0.056). ORs, CIs, and the *p* values for all modes are presented in Table 2.

Discussion

The current study provides preliminary results for an association between the rs10139154 SCFD1 gene variant and a decreased risk of developing AD, confirming the possible existing theories of overlapping pathologies between neurodegenerative diseases. Of note, at least to the best of our knowledge, no previous study in the existing literature to date has shown any type of association between the SCFD1 gene and AD.

AD represents the most common form of dementia and is characterized by the extracellular deposits of SPs and the intracellular accumulation of NFTs (Singh et al. 2016). Several hypotheses have been postulated to date for the pathogenetic mechanisms of the disease, most of them placing the SPs in the center of the pathology (Cubinkova et al. 2018; Korczyn 2008). However, a plethora of studies have included several factors in the pathogenesis of AD, pointing to the complexity and heterogeneity of the disease. Among these, oxidative stress, mitochondrial dysfunction, ER stress and protein misfolding, calcium dyshomeostasis, inflammatory processes, and environmental and dietary factors all contribute to a vicious cycle leading to amyloidogenesis, hyperphosphorylated tau with neurodegeneration, and eventually cell death (Cubinkova et al. 2018; Luca et al. 2015; Razgonova et al. 2019; Zaganas et al. 2013).

Concerning the wide array of neurodegenerative diseases, various overlapping pathologies may exist, raising the possibility of converging pathogenetic mechanisms among the diseases (Androutsopoulos et al. 2011; Beharry et al. 2014; Friese et al. 2014; Goedert 2015). Previous studies have demonstrated possible common molecular pathways involved in the pathogenesis of ALS and AD (Muresan and Ladescu Muresan 2016; Muresan et al. 2014). This crosstalk is mainly attributed to abnormal endocytic trafficking function, the compromised secretion of extracellular vesicles, and defective intracellular and extracellular vesicle trafficking (Muresan and Ladescu Muresan 2016). All of the above, via cellular stress, aggravate the mechanisms of, and lead to, neurodegeneration (Jovičić et al. 2015). It has also been suggested that the accumulation and aggregation of specific proteins in the central nervous system may lead to neurodegeneration and that specific mutations, different environmental factors, or oxidative stress may engender or aggravate this phenomenon (Bourdenx et al. 2017; Garcia-Gonzalez et al. 2018; Sierra-Fonseca and Gosselink 2018).

The precise mechanism through which the rs10139154 SCFD1 gene variant may influence AD pathophysiology and neurodegeneration has not yet been fully elucidated. A possible assumption is that of the combination of oxidative stress, protein dysfunction, disturbances of vesicle trafficking, and membrane fusion events, which are all enhanced by this variation. However, further studies are required to examine this hypothesis.

Table 2 Single locus analysis for association between SCFD1 rs10139154 and AD in co-dominant, dominant, recessive, over-dominant, and log-additive modes

Mode	Genotype	OR (95% CI)	*p* value
Co-dominant	C/C	1.00	0.097
	C/T	0.92 (0.66–1.29)	
	T/T	0.60 (0.37–0.96)	
Dominant	C/C	1.00	0.23
	C/T-T/T	0.82 (0.60–1.13)	
Recessive	C/C-C/T	1.00	*0.036*
	T/T	0.63 (0.40–0.97)	
Over-dominant	C/C-T/T	1.00	0.075
	C/T	1.05 (0.77–1.44)	
Log-additive	–	0.81 (0.65–1.01)	0.056

SCFD1 Sec1 family domain-containing protein 1, *AD* Alzheimer's disease, *CI* confidence interval, *OR* odds ratio. Statistically significant values are presented in italic font

Despite the aforementioned interesting results, several possible limitations of this study need to be acknowledged. Firstly, some of the patients' data are primarily based on estimates due to the lack of original information since most of them were permanently hospitalized due to advanced AD and were therefore not included in the regression models. Secondly, since APOE ε4 is considered the strongest genetic risk factor for AD (Dardiotis et al. 2014a; Lipnicki et al. 2017; Liu et al. 2013), the interaction between this allele and gene variants may possibly increase the prognostic accuracy or influence the susceptibility of AD. However, in this study, we could not determine the APOE ε4 carriers. Finally, environmental co-factors, such as dietary habits, smoking, alcohol consumption, exercise, companionship, sedentary life style, level of education, stress, and positive family history (Anastasiou et al. 2017; Baltazar et al. 2014; Costa et al. 2017; Dardiotis et al. 2013, 2018b; Gubandru et al. 2013; Lyubartseva and Lovell 2012; Siokas et al. 2019), may be markedly involved in the pathology of AD and should also be considered for a possible association.

Furthermore, epigenetic alterations have been suggested to be a major co-factor of aging, which is considered a main non-modifiable risk factor for AD (Fyfe 2018). It is thought that, inevitably, different epigenetic alterations accumulating through a lifetime could modify gene expression, which may in turn lead to AD (Miller and O'Callaghan 2008). In AD, all of the epigenetic mechanisms have been shown to have an impact to a certain degree, although methylation seems to play the most important role (Argentieri et al. 2017; Danborg et al. 2014; Negoita et al. 2017). For instance, the increased methylation of the BDNF promoter has been associated with MCI-turned-AD (Xie et al. 2017); hypermethylation of regions in the APOE4 gene has been described, even as a marker for LOAD (Corder et al. 1993; Wang et al. 2008). The hypomethylation of the promoter region of APP genes has been shown to lead to increased Aβ production (Tohgi et al. 1999b), and alterations in the methylation of several stops in the tau protein pathway play a role as well (Tohgi et al. 1999a; Zhou et al. 2008). Finally, even the hypermethylation of ribosomal DNA has been shown to be an epigenetic marker of AD (Pietrzak et al. 2011). Considering miRNAs, several have been found to be deregulated in patients with AD, such as miRNA-106, miRNA-146 and miRNA-9, and have been proposed to be used as biomarkers; however, further research is warranted towards this direction (Mushtaq et al. 2016). Finally, epigenetic alterations are also associated with different environmental factors, such as those mentioned further above, as well as with different comorbidities, mostly diabetes mellitus and arterial hypertension, both of those proven to be associated with aging and AD (Gerritsen et al. 2016; Roubroeks et al. 2017).

In conclusion, to the best of our knowledge, the present study is the first to provide a preliminary suggestion of a significant association between the rs10139154 SCFD1 gene variation and a decreased risk of developing AD. However, as a newly associated variant, further studies are required in order to clarify its precise role in AD.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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