Abstract. The role of vitamin D in Alzheimer’s Disease (AD) has been studied over the past years. The results from numerous studies have indicated that the molecular pathways involved in the development of AD are closely related to the molecular pathways of the mechanisms of action of vitamin D. However, only a limited number of studies have described the key role of vitamin D receptor (VDR) in the regulation of the functions of vitamin D and the potential effect of single nucleotide polymorphisms (SNPs) of the VDR gene. Thus, the aim of the present study was to investigate the VDR TaqI polymorphism in relation to AD in a Southeastern European Caucasian (SEC) cohort. Further, the present study aimed to compare the results obtained with those of other AD populations. For this purpose, blood samples from 90 confirmed patients with AD [median age, 74 years; median mini-mental state examination (MMSE) score of 21; median frontal assessment battery (FAB) score of 10] and 103 healthy controls (median age, 57 years) were analyzed to determine the genotypes of TaqI (rs731236) using quantitative PCR. The frequencies (%) of the TaqI TT, TC and CC genotypes in the controls/patients were 34/48.9, 47.6/41.1 and 18.4/10.0, respectively. Statistically significant differences were observed for the TaqI C allele [odds ratio (OR), 0.54; 95% confidence interval (CI), 0.30-0.96; P=0.035], the TaqI TT genotype (OR, 1.86; 95% CI, 1.04-3.32; P=0.035) and the TaqI CC genotype (OR, 0.119; 95% CI, 0.014-0.995; P=0.032,) in relation to the MMSE score <21 in the patient’s group. The TaqI TT allele was found to increase the risk of developing AD by 1.86-fold in the SEC population, while the TaqI C allele may act protectively, with a 46% lower risk of developing the disease. Patients with the TaqI CC genotype were found to have an 88% less likelihood of developing severe cognitive impairment based on the MMSE score. On the whole, the present study did not confirm the results of previous studies on the VDR TaqI C allele in patients with AD.

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder contributing to 60-70% of cases of dementia globally, based on the estimations of the World Health Organization (WHO) (1). Vitamin D is an established molecule which is crucial for the development of neural cells and the nervous system (2,3). A number of studies have reported that vitamin D deficiency is associated with a higher risk of developing dementia and neurodegenerative disorders, such as AD (4-8). In parallel, the beneficial effects of vitamin D in neural cells have been reported in a number of studies that have investigated its functions in relation to nerve growth factor, inducible nitric oxide synthase, amyloid β-peptide clearance and calcium homeostasis (9-14). Vitamin D receptor (VDR) is the critical protein involved in the mediation of the functions of vitamin D (15).
Over the past few years, a number of studies have investigated the potential association of vitamin D with the development of late-onset AD (LOAD) in various populations, focusing on the VDR gene single nucleotide polymorphisms (SNPs) (16-22). One reason for which the VDR gene has received increasing attention is that it is included in the risk locus in chromosome 12, which was previously reported by genetic studies to be linked to LOAD (23,24). Vitamin D functions as a transcription factor after binding to VDR and the large number of transcription binding sites, that have been estimated up to 10,000 per cell, are another good basis for researching the potential effects of VDR variants in association with the functions of vitamin D in the nervous system and in the development of LOAD (6,25). However, the initial indication for a potential association of the disease with VDR was described in an older study, which reported lower VDR mRNA levels in hippocampal and pyramidal cells of patients with AD (26).

In addition, to date, only a limited number of studies have been able to provide knowledge regarding the molecular mechanisms or pathways through which vitamin D and VDR affect the development of AD. A previous study concluded that vitamin D and VDR regulated the production of amyloid β, and therefore the development of the disease through the expression of the proteins involved in secretases (25). Information regarding the potential pathways and genes affected by vitamin D and VDR was also provided through an in vivo animal study, which concluded that there was a close connection between vitamin D molecular pathways and Alzheimer’s molecular pathways through certain groups of genes affecting amyloid β production, neuroinflammation or other AD-related molecules (27,28). The molecular pathways involved in the mechanisms of action of vitamin D affect proteins that play a key role in the development of a diverse group of diseases, including diabetes, autoimmune, cardiovascular and malignant diseases, Parkinson’s disease and AD. One indicative example can be described for the protein kinase B (Akt) pathway. Akt phosphorylation is decreased by PTEN in AD, leading to the progression of the disease (29). In parallel, it has been reported that vitamin D through VDR, stimulates the Akt signaling pathway, leading to a potential attenuation of the progression of the disease (29,30). Overall, the molecular pathways of vitamin D and VDR associated with the development of LOAD have not yet been fully investigated. Moreover, the potential effects of the VDR gene SNPs on these pathways have not yet been fully described. VDR polymorphisms have been also investigated in specific neurological diseases and conditions, such as multiple sclerosis, Parkinson’s disease and cluster headaches, with the results indicating possible associations (31-33).

Thus far, the results from studies investigating VDR SNPs and LOAD in various populations have been contradictory. One of the most extensively studied VDR SNP is TaqI (rs731236, c.1056T>C, ATT>ATC, p.Ile, NM_000376.3) which is located in exon 9 and is included in the ligand binding site of the gene. The TaqI polymorphism does not result in an amino acid change of the receptor protein, and has been proposed as a genetic biomarker for AD; however, the results differ according to the ethnic population reported in each study (16,34).

The aim of the present study was to investigate potential associations of the single nucleotide variation TaqI of the VDR gene with the development of LOAD in a Southeastern European Caucasian (SEC) cohort. The present study also wished to compare the observed results with the data from other populations and to evaluate the potential association of this variation with neuropsychometry mini-mental state examination (MMSE) and frontal assessment battery (FAB) assessments.

Subjects and methods

Study subjects. The study sample included 90 patients with well-ascertained LOAD (median age, 74 years; range, 51-92 years; males, 48.9%; females, 51.1%; median MMSE score of 21; median FAB score of 10) and 103 healthy controls (median age, 57 years; range, 51-90 years; males, 49.5%; females, 50.5%). LOAD diagnosis was based on current diagnostic criteria for AD, including a physical examination, MMSE/FAB score, a brain CT/MRI scan and amyloid β, tau and p-tau levels in the cerebrospinal fluid. Patients or healthy control subjects not belonging to the SEC population were not included in the study. Patients were recruited from the Outpatient Clinic of the Cognitive Disorder-Dementia Unit of the Second Department of Neurology at the University General Hospital ‘ATTIKON’ (Athens, Greece). Sample collection took place from January, 2018 to February, 2019. The demographic data of the patient and control groups are presented in Table I. The present study has been approved by the Scientific Council and Bioethics Committee of the University General Hospital ‘ATTIKON’ (Reg. no. 312; December 21, 2017). Written informed consent for participation in the study and the use of their genetic data was obtained from all participants.

DNA isolation and quantitative PCR (qPCR). Blood samples from the patients and controls were analyzed to determine the genotypes of the SNP TaqI (rs731236) of the VDR gene. DNA extraction was performed from 200 μl whole blood samples using the NucleoSpin® Genomic DNA from Tissue kit (Macherey-Nagel GmbH & Co. KG). Genotypes of the TaqI (rs731236) polymorphism were determined using qPCR (using the Light Cycler® 480 system; Roche Diagnostics) with the LightSNiP (SimpleProbe®) assay (TIB Molbiol). For qPCR, an initial polymerase activation and denaturation step at 95°C for 10 min was followed by 45 amplification cycles for each sample in the LightCycler instrument. Cycles included denaturation (95°C for 10 sec), annealing (60°C for 10 sec) and extension (72°C for 15 sec). Fluorescence was measured at the end of the annealing period of each cycle to monitor the progress of amplification. Following amplification, melting curves were created by cooling/holding temperature at 40°C for 30 sec and gradually increasing the temperature up to 95°C. Melting peaks were produced accordingly based on the fluorescence signal using LightCycler® 480 software, version 1.5. Differences in the hybridization between the SimpleProbe® oligonucleotide and the DNA sequence (due to the presence of the polymorphism) result in different melting temperatures, allowing the detection of the alleles. In rs731236, the C allele with three hydrogen bonds is detected at higher temperatures than the T allele with two hydrogen bonds. Homozygous samples (TT or CC) were detected, providing a single melting peak, while heterozygous samples (TC) provided two melting peaks each one corresponding to each allele.
Statistical analysis. Data from the genotyping results were analyzed using SNPstats web-based software, developed by the Catalan Institute of Oncology, 2006 and SPPS® 17.0.0 software (SPPS, Inc.). Logistic regression analysis was applied to analyze the association of the genotypes in each heredity model with the disease and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Fisher's exact test was performed to compare the genotyping results with the MMSE and FAB score within the group of patients. A value of P<0.05 was considered to indicate a statistically significant difference. The results were consistent with the Hardy-Weinberg equilibrium.

Results

The patient group had a median MMSE score of 21 (Fig. 1) and a FAB score of 10. The frequencies (%) of the TaqI TT, TC and CC genotypes in the controls/patients were 34.0/48.9, 47.6/41.1 and 18.4/10.0, respectively (Fig. 2). A statistically significant difference was observed for the TaqI C allele in the dominant model of inheritance TT vs. CT + CC (OR, 0.54; 95% CI, 0.30-0.96; P=0.035) (Table II). On the other hand, a statistically significant difference was observed for the TT genotype in the recessive model of inheritance CC + TC vs. TT (OR, 1.86; 95% CI, 1.04-3.32; P=0.035) (Table II). In the patient group, when analyzing TaqI genotypes in relation to the median value of the MMSE score (21), a statistically significant difference was observed for the TaqI CC genotype and MMSE score <21, CC vs. TC + TT (OR, 0.119; 95% CI, 0.014-0.995; P=0.032) (Table III). No statistically significant difference was observed when analyzing TaqI genotype frequencies and FAB score in the patient group (data not shown).

Discussion

In the SEC cohort examined in the present study, the TaqI TT genotype was associated with a higher risk of developing AD by 1.8-fold. In addition, the TaqI C allele was associated with a potential protective effect against the disease, since it was calculated that TaqI C carriers had a 46% less likelihood of developing AD (Table II). Moreover, in the patient group, the TaqI CC genotype was associated with a 88% less likelihood of developing severe cognitive impairment measured using the MMSE score (Table III). One of the assuming effects of the VDR polymorphism on the molecular level is the affinity of the ligand site of the receptor to vitamin D. It has been previously reported that VDR polymorphisms may decrease the affinity of VDR to vitamin D and may therefore affect the beneficial effects of vitamin D in neural cells as regards calcium homeostasis, neurotrophin levels and inflammation (16,17). Another potential effect of the TaqI polymorphism is on the stability of VDR mRNA expression (17). It can be assumed that the insufficient effects of vitamin D, associated with the TaqI TT genotype, either by decreased affinity to the VDR or reduced mRNA levels in the nervous system may lead to neurodegeneration and cognitive impairment in SECs. On the contrary, the TaqI C allele appears to be associated with enhanced effects of vitamin D in the nervous system in the specific population studied.

The results of the present study in the SEC cohort are not in agreement with those produced by a previous study in the Turkish population, in which the TaqI TT genotype was more frequent in the control group with a statistically significant
difference (16). However, another study in the Asian population reported an association of the Taq I TC genotype with AD with an increased risk of 2.8-fold for the heterozygous carriers (35). By contrast, the Taq I TC frequency in the present study was higher in the control group and no statistically significant association with the disease was observed (Table II). In another study on Northwestern European Caucasians, it was reported that the presence of Taq I C allele in adults <75 years of age resulted in a 3-fold higher risk of developing AD in comparison to the control group with a statistically significant difference (17). On the contrary, the Taq I C allele in the SEC cohort of the present study was associated with a potential protective effect against the disease and a lower likelihood of developing AD (Table II). The VDR Taq I polymorphism has also been investigated in the Iranian population; however, the results of that study did not reveal any statistically significant difference for Taq I genotypes between the patient and control group, and the polymorphism was not associated with the disease (18,20). The results of the present study differ from those reported for the Iranian population in which no risk or protective Taq I allele for AD was detected. The Taq I polymorphism was also previously investigated in a Northeastern European Caucasian cohort and no association with AD was reported (21). Another study on the Spanish population investigated the Taq I polymorphism in relation to serum vitamin D levels (22). However, it was reported that Taq I did not result in any statistically significant difference in the serum vitamin D levels nor was it associated with a higher risk of developing AD (22). These data provide from different studies are presented in the graph depicted in Fig. 3 (16-18,20-22,35).

### Table II. Frequencies of TaqI genotypes in the different inheritance models.

| Model          | Genotype | Controls, n (%) | AD, n (%) | OR (95% CI) | P-value |
|----------------|----------|-----------------|-----------|-------------|---------|
| Codominant     | TT       | 35 (34%)        | 44 (48.9) | 1.00        | 0.064   |
|                | TC       | 49 (47.6)       | 37 (41.1) | 0.60 (0.32-1.11) |         |
|                | CC       | 19 (18.4)       | 9 (10)    | 0.38 (0.15-0.94) |         |
| Dominant       | TT       | 35 (34)         | 44 (48.9) | 1.00        |         |
|                | TC/CC    | 68 (66)         | 46 (51.1) | 0.54 (0.30-0.96) | 0.035   |
| Recessive      | TT/TC    | 84 (81.5)       | 81 (90)   | 1.00        |         |
|                | CC       | 19 (18.4)       | 9 (10)    | 0.49 (0.21-1.15) | 0.092   |
| Recessive (for T allele) | CC/TC | 68 (66%) | 46 (51.1%) | 1.00 |         |
|                | TT       | 35 (34%)        | 44 (48.9%)| 1.86 (1.04-3.32) | 0.035   |

*P<0.05. AD, Alzheimer’s disease; OR, odds ratio; CI, confidence interval.

![Figure 3. Bar chart of frequencies of rs731236 genotypes from the available published studies (16-18,20-22,35).](image-url)
Overall, the results from published studies for each population are contradictory and do not allow for a definite conclusion regarding the association of TaqI with AD (Table IV). The TaqI C allele that appears to increase the risk of developing AD in Northwestern European Caucasians (17) has been shown to exert a protective effect in SECs from the present study. In another study on Northwestern European Caucasians, the TaqI C allele was reported to be associated with the decline in the scoring of tests measuring cognitive performance (36). However, that study did not include patients with AD and therefore a direct comparison to the studies with patients with AD is not applicable. However, the indication of the TaqI C allele that increases the risk of developing cognitive impairment is not confirmed by the results of the present study, in which the TaqI C allele appeared to decrease the risk of developing AD (Table II); homozygous TaqI CC patients also had higher MMSE scores (Table III). The interpretation of the results from different populations should take into account a number of factors, two of which are sun exposure and vitamin D intake. A previous study on Northwestern European Caucasians reported that the activity of VDR may be related to the level of sun exposure of each population (21). That study concluded that AD, Alzheimer’s disease; SD, standard deviation; nAD, number of AD patients; nCO, number of individuals in the control group.
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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ND conceived study and provided the control samples and data. MSK and ML performed the sample analysis. ED obtained the ethics committee study approval, performed the literature review and the statistical and data analyses, and was responsible for the manuscript composition under the supervision of ND, CK and KA. DAS and AT contributed to the editing of the final manuscript. KA and CK reviewed and edited the statistical analysis. DAS, AT, SP, VP and ES contributed to the collection of the clinical data and patient scores. SP, PM and CK also provided the patient samples. All authors discussed the results and agreed on the conclusions of the study and all authors have read and approved the final manuscript. All authors confirm the authenticity of the raw data.

Ethics approval and consent to participate

The present study was approved by the Scientific Council and Bioethics Committee of the University General Hospital ‘ATTIKON’ (Reg. No 312; December 21, 2017). Written informed consent for participation in the study and use of their genetic data was obtained from all participants.

Patient consent for publication
Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. All the other authors declare that they have no competing interests.

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