

Short Communication

Evaluation of *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$ Alleles in a Cohort of Individuals Affected by Developmental Topographical Disorientation

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Abstract. The three common alleles of the *APOE* gene, $\epsilon 2/\epsilon 3/\epsilon 4$, have been linked to human spatial orientation. We investigated the genetic role of *APOE* in developmental topographical disorientation (DTD), a lifelong condition that results in topographical disorientation. We genotyped the *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$ alleles in a cohort of 20 unrelated DTD probands, and found allele frequencies not statistically different from the those seen in the population as a whole. Therefore, we found no evidence that DTD occurs preferentially on a genetic background containing any particular *APOE* allele, making it unlikely that these *APOE* alleles are contributing to the development of DTD.

Keywords: Cognition disorders, genotype, memory, navigation, spatial learning

INTRODUCTION

The gene *APOE* codes for the lipid-binding protein apolipoprotein E (ApoE), which binds to cholesterol and other lipids, and transports them between various cell and tissue types. ApoE is known to be involved in a wide range of processes, including lipoprotein metabolism, immunoregulation, and, importantly, cognition [1–3]. ApoE is associated with Alzheimer disease (AD), representing the main genetic factor determining individuals' risk of occurrence of AD [2, 4–8]. There are three common

isoforms of ApoE (ApoE2, ApoE3, and ApoE4), corresponding to three alleles of *APOE* ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$), as defined by two single nucleotide polymorphisms at positions 2059 and 2179, affecting the amino acids encoded at positions 112 and 158 of the ApoE protein (Table 1; [3, 9, 10]). These polymorphisms affect the structure and function of the ApoE protein, with the different isoforms exhibiting altered lipid association and receptor binding characteristics [9]. E3 is the isoform most commonly seen in the population, while the E4 and E2 isoforms are associated with an increased and decreased risk for AD, respectively [5] (see [2] for a comprehensive review of *APOE*/ApoE).

One important characteristic of AD is that patients get lost in familiar surroundings [11]. Such impairment is distinct from the general memory issue that is

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Table 1
Details of APOE alleles and corresponding ApoE isoforms

APOE allele	DNA base at position 2059 of APOE	DNA base at position 2179 of APOE	ApoE Isoform	Amino acid at position 112 of ApoE	Amino acid at position 158 of ApoE	Frequency in Caucasian controls [5]
ϵ 2	T	T	E2	Cys	Cys	8.4%
ϵ 3	T	C	E3	Cys	Arg	77.9%
ϵ 4	C	C	E4	Arg	Arg	13.7%

hallmark of the disease [12] and is present in nearly all AD patients from early on in the disease course [13]. This peculiar behavioral defect in AD patients raised the issue of specific effects that the E2/E3/E4 ApoE isoforms may have on the ability of the individuals to orient and navigate in the environment. Indeed, it has been shown that the E4 allele has an effect on brain activation during memory tasks in healthy adults [14], as well as on spatial memory behavior in healthy children, decades before AD might occur [15]. In searching for early indicators and mechanisms of AD's neurocognitive pathology in young adults carrying the ϵ 4 APOE allele (individuals who are therefore at risk of developing AD later in life), Kunz and colleagues [16] found evidence of a dysfunction of grid cells in the entorhinal cortex, a cell type well-known to be involved in the representation of a spatial layout and especially critical for effective orientation and navigation [17]. Specifically, in the ϵ 4 carriers, the authors observed a reduction of grid-cell-like representations while undergoing a functional magnetic resonance imaging (fMRI) study, and a declined performance in spatial orientation while navigating a virtual arena. These authors also found that both of these changes were related to impaired spatial memory performance, although, as a group, the ϵ 4 carriers did not exhibit reduced spatial memory when compared to participants homozygous for the ϵ 3 allele.

In a different study, Konishi and colleagues also provided evidence of a significant link between the ApoE isoforms and spatial orientation, in which navigational behavior and functional and structural brain properties appeared to be influenced by APOE genotype in healthy young adults [18, 19]. Specifically, these authors found that ϵ 2 carriers favored a navigation strategy dependent on the hippocampus (i.e., a spatial over a non-spatial/response strategy), and had increased gray matter volume of the hippocampus, as compared to ϵ 4 carriers or participants homozygous for ϵ 3, i.e., non- ϵ 2 and non- ϵ 4 carriers [18]. Later, in comparing ϵ 4 carriers who favored a spatial navigation strategy (ϵ 4-spatial) to ϵ 4 carriers who favored a non-spatial navigation strategy (ϵ 4-response), the

authors found that ϵ 4-response participants had a decreased gray matter volume compared to non- ϵ 4 carriers, whereas ϵ 4-spatial participants did not (i.e., their gray matter volumes were comparable to non- ϵ 4 carriers). In addition, ϵ 4-response participants had a decreased blood-oxygen-level-dependent signal (i.e., the indirect fMRI measure of neural activity) when compared to ϵ 4-spatial participants [19]. Taken together, these studies suggest that the APOE gene might be a critical genetic determinant of spatial orientation abilities in the healthy population as well as among AD patients. Here, we sought to investigate the APOE ϵ 2/ ϵ 3/ ϵ 4 genotypes in a group of individuals who suffer from a lifelong inability to orient and navigate in familiar surroundings, that is, individuals affected by developmental topographical disorientation (DTD) [20].

DTD refers to a highly-selective lifelong impairment in the ability of an individual to find their way around in extremely familiar surroundings such as the neighborhood where they live, the building where they have worked for many years, or in extreme cases, their own house [20–25]. This disability, which can be devastating, is present despite the fact that these individuals have well-preserved cognitive functions, no other neurological impairments and no brain injuries [26–28]. This behavioral defect appears most commonly to result from the inability of the individuals to form cognitive maps [21, 24, 26, 29]. A cognitive map is a mental representation of the environment including the landmarks within it and their spatial relationships and is formed as individuals familiarize themselves with their spatial surroundings, enabling them to reach any location from anywhere within the environment [30, 31]. Individuals affected by DTD are unable to form cognitive maps, and therefore never gain the ability to orient within a given environment, no matter how long they live in it [29]. Importantly, there is evidence found in a cohort of individuals with DTD of familial clustering of this trait, suggesting that genes might play a role in the development of DTD [20, 32].

The evidence that the three common APOE alleles may play a role in determining spatial orientation

ability marks them as potential candidates for genetic variants contributing to the occurrence of DTD. Specifically, DTD may be more common among $\epsilon 4$ carriers, given the evidence of their grid cell dysfunction [16] and increased risk of developing AD. Also, DTD may be less common in $\epsilon 2$ carriers, given the evidence of a more likely use of a hippocampal effective spatial navigation strategy [18]. To test these hypotheses, we genotyped the common *APOE* alleles in a cohort of DTD individuals and their families.

MATERIALS AND METHODS

Participants

The cohort included 20 unrelated DTD probands, and 22 relatives of those probands (both with and without the DTD trait; see Table 2). Given that we reported participants' *APOE* genotype status, which could pose a risk of harm in terms of worry and emotional distress, if such information were delivered without appropriate consent and counselling, it was important to mitigate the risk of participants identifying themselves. Therefore, age and sex are not reported. Since the outcome measure in our study is genotype—something participants were born with—age and sex does not affect the interpretation of results. The probands had either been part of one of two previous studies on DTD [24, 26], or were self-referred, having contacted us after hearing about DTD in the media or online. Each proband described getting lost in environments that most people would consider to be very familiar, such as the neighborhood where they grew up and/or had lived for many years, or their workplace, even after having worked there for several years. For all participants included in the study (probands and relatives), the DTD phenotype was confirmed using the online assessment adopted in a previous study [32], evaluating the four key inclusion criteria for DTD diagnosis [24]. The inclusion criteria consist of: (a) getting lost frequently in very familiar surroundings, (b) experiencing orientation difficulties consistently from childhood or adolescence (i.e., the stage at which one would expect an individual to begin independently navigating), (c) having no other cognitive complaints, and (d) having suffered no brain injuries or neurological conditions. In some cases, an interview was used in place of the online assessment to evaluate these same criteria. In addition, most participants completed the Cognitive Map Formation Test [32–36], which assesses an individual's ability to form cognitive maps [35, 37] and

Table 2
The cohort of unrelated DTD probands and their 22 relatives

Family/Proband Number	Relationship to Proband*	DTD Phenotype	<i>APOE</i> genotype
1	Proband	DTD	$\epsilon 2/\epsilon 3$
2	Proband	DTD	$\epsilon 4/\epsilon 4$
	Mother	DTD	$\epsilon 3/\epsilon 4$
	Father	Not DTD	$\epsilon 3/\epsilon 4$
	Sister	Not DTD	$\epsilon 3/\epsilon 4$
	Daughter	Not DTD	$\epsilon 3/\epsilon 4$
	Son	Not DTD	$\epsilon 3/\epsilon 4$
3	Proband	DTD	$\epsilon 2/\epsilon 3$
	Daughter	DTD	$\epsilon 2/\epsilon 4$
	Daughter	Not DTD	$\epsilon 2/\epsilon 3$
4	Proband	DTD	$\epsilon 3/\epsilon 3$
	Brother	Not DTD	$\epsilon 2/\epsilon 3$
	Sister	Not DTD	$\epsilon 2/\epsilon 3$
	Paternal First Cousin	DTD	$\epsilon 3/\epsilon 3$
	Husband	Not DTD	$\epsilon 3/\epsilon 3$
	Daughter	Not DTD	$\epsilon 3/\epsilon 3$
5	Proband	DTD	$\epsilon 3/\epsilon 3$
6	Proband	DTD	$\epsilon 3/\epsilon 3$
7	Proband	DTD	$\epsilon 3/\epsilon 4$
8	Proband	DTD	$\epsilon 3/\epsilon 3$
9	Proband	DTD	$\epsilon 3/\epsilon 3$
	Sister	DTD	$\epsilon 3/\epsilon 3$
	Proband	DTD	$\epsilon 3/\epsilon 3$
10	Brother	DTD	$\epsilon 3/\epsilon 3$
	Brother	Not DTD	$\epsilon 3/\epsilon 3$
	Son	Not DTD	$\epsilon 3/\epsilon 3$
11	Proband	DTD	$\epsilon 3/\epsilon 3$
12	Proband	DTD	$\epsilon 3/\epsilon 3$
13	Proband	DTD	$\epsilon 3/\epsilon 3$
14	Proband	DTD	$\epsilon 3/\epsilon 3$
15	Proband	DTD	$\epsilon 3/\epsilon 3$
16	Proband	DTD	$\epsilon 3/\epsilon 3$
17	Proband	DTD	$\epsilon 3/\epsilon 3$
	Mother	DTD	$\epsilon 3/\epsilon 3$
	Brother	Not DTD	$\epsilon 3/\epsilon 3$
	Sister	DTD	$\epsilon 3/\epsilon 3$
	Son	Not DTD	$\epsilon 3/\epsilon 3$
18	Proband	DTD	$\epsilon 3/\epsilon 3$
19	Proband	DTD	$\epsilon 3/\epsilon 3$
20	Proband	DTD	$\epsilon 3/\epsilon 3$

*Participant age and sex were not included so as to limit the potential for participants to be identified.

which has been used in the past to confirm that individuals with DTD are indeed unable to form cognitive maps [20, 26, 36]. In our sample, 18 of the 20 probands failed to solve the Cognitive Map Formation Test in the 20 trials provided. One did not complete the test because it caused them to experience motion sickness, while another was eventually able to solve the test after 18 attempts (while the mean number of attempts required for non-DTD individuals is less than 10 [33, 34]). The study was approved by the local Ethics Research Board.

ApoE isoforms

To determine the particular ApoE isoforms present in individuals with DTD, we genotyped using a PCR method which detects the sequence variants at nucleotide positions 2059 and 2079 of *APOE* (Table 1), which are present in allele combinations to form haplotypes that correspond to the three common ApoE isoforms ($\epsilon 2/\epsilon 3/\epsilon 4$), as previously described [38].

The allele frequencies in the DTD cohort were compared to the allele frequencies observed in a large group of Caucasian controls (without dementia), as well as that expected in AD [2, 5], to determine whether or not any allele occurred more or less often in the DTD group than would be expected in a random sampling of individuals from the larger population. Statistical significance of allele frequency differences was evaluated using a chi-squared analysis as implemented in JASP Version 0.14.3. When possible, we also looked for co-segregation of the *APOE* alleles with the DTD trait within family members.

RESULTS

Among the 20 unrelated DTD probands, we observed 16 individuals with the $\epsilon 3/\epsilon 3$ genotype; two with $\epsilon 2/\epsilon 3$; one with $\epsilon 3/\epsilon 4$; and one with $\epsilon 4/\epsilon 4$ genotypes (Table 2). This pattern of allele frequencies did not appear to differ from that expected in the general population ($\chi^2(2)=2.340, p=0.309$), but were distinct from that expected in an AD population ($\chi^2(2)=15.642, p<0.001$), see Table 3 and Fig. 1. Additionally, when the less common $\epsilon 2$ and $\epsilon 4$ alleles were observed within a family, they did not co-segregate with either the DTD or non-DTD phenotype (Table 2).

DISCUSSION

To investigate whether *APOE* genetics was involved in the development of DTD, we determined the $\epsilon 2/\epsilon 3/\epsilon 4$ genotype in 20 unrelated individuals with DTD and found that the allele frequencies in

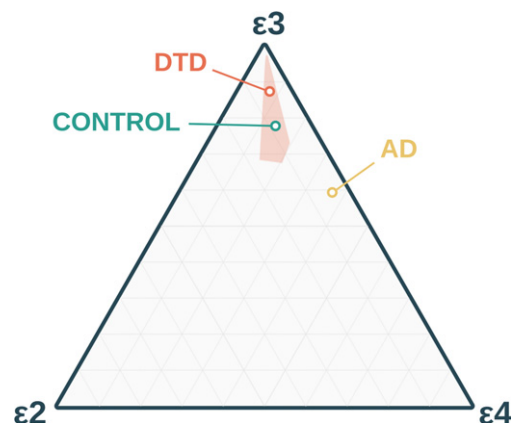


Fig. 1. Allele proportions of the present developmental topographical disorientation (DTD) cohort, as well as reference proportions from Caucasian control and Alzheimer's disease (AD) populations [5]. The shaded area about the DTD point estimate represents a 95% confidence interval, estimated from independent binomial distributions.

this DTD group were similar to those seen in the general population (Table 3). These results indicate that the three major *APOE* isoforms do not determine DTD status, suggesting that if there is a genetic component to DTD, this would involve some other gene(s). Therefore, while evidence exists that *APOE* is involved in the development of spatial orientation abilities [16, 18, 19], other proteins/genes are likely involved as well. Our findings show that DTD can occur against a genetic background containing any of the three $\epsilon 2/\epsilon 3/\epsilon 4$ alleles. In other words, individuals with any of the three major *APOE* isoforms can have a total lack of developed spatial orientation abilities. Additionally, in an exome sequencing study of nine of these DTD probands, we did not identify rare protein-altering variants in *APOE* [39]. Therefore, *APOE* cannot be the single major genetic determinant of spatial orientation abilities in humans. This is not at all surprising since most gene products work together with several (or many) other gene products in complex interaction networks in order to carry out their biological functions. This would especially be expected when looking at such a complex function as spatial orientation, which is already known to involve several brain regions and several cognitive processes.

Table 3
APOE $\epsilon 2/\epsilon 3/\epsilon 4$ allele frequencies in DTD cohort and reference populations

Allele	<i>n</i>	Chromosomes tested	Allele frequency in DTD cohort	Reference allele frequencies in Caucasian controls [5]	Reference allele frequencies in Caucasians with AD [5]
$\epsilon 2$	2	40	5.0%	8.4%	3.9%
$\epsilon 3$	35	40	87.5%	77.9%	59.4%
$\epsilon 4$	3	40	7.5%	13.7%	36.7%

If a major genetic determinant of DTD is discovered in the future, it may be important to identify whether or not it interacts with *APOE* in any way.

Another way to investigate a possible relationship between *APOE* genetics and DTD would be to document the incidence of DTD and the $\epsilon 2/\epsilon 3/\epsilon 4$ genotype in a large population of individuals. In the future, such a large-scale study could eventually allow for a more definitive statement about whether $\epsilon 2/\epsilon 3/\epsilon 4$ genotype contributes to DTD risk. Indeed, such a large-scale study would allow for the investigation of all potential genetic contributors to the development of DTD. Here, in a small study of a DTD population, we have seen that the pattern of $\epsilon 2/\epsilon 3/\epsilon 4$ genotypes does not appear to differ from what would be expected in any population of this size, indicating, preliminarily, that $\epsilon 2/\epsilon 3/\epsilon 4$ genotype is at least not the major genetic determinant of DTD.

Interestingly, among individuals with the $\epsilon 4$ allele, brain changes appeared to be linked to navigation strategy [19]. $\epsilon 4$ carriers who used a non-spatial strategy were more likely to have the brain changes expected to be indicative of AD risk [19]. Individuals with DTD, being impaired in their ability to form cognitive maps, must rely on a non-spatial (e.g., a response) strategy to navigate. Therefore, future studies may focus on investigating the frequency of developing AD in DTD individuals, as well as the use of navigational strategies aimed at improving the spatial orientation skills in those with DTD, which may protect against AD-type brain changes in $\epsilon 4$ carriers. It would be critical to answer these questions in order to start defining the relationship between AD and the presence of a lifelong condition such as DTD.

Our study was limited by the sample size. Indeed, even if no DTD probands had the $\epsilon 2$ allele, our sample size would not be big enough to say that the $\epsilon 2$ allele frequency was significantly lower in our cohort than in the general population. However, our results show a similar pattern of *APOE* alleles in the DTD group as is seen in the general population, and, as such, any effect, if present, is going to be subtle. Therefore, future studies in a larger DTD cohort will be beneficial to continue exploring the genetics of the DTD trait, and will reveal whether or not such a subtle effect does indeed exist.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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