Tumor necrosis factor-α –308 G/A polymorphism in a sample of Egyptian patients with Alzheimer's disease

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Objective
This study was designed to determine whether tumor necrosis factor-a (*TNF-α*) –308 G/A polymorphism was a risk factor for late-onset Alzheimer's disease (LOAD) and/or was associated with a more severe form of LOAD in a sample of Egyptian patients.

Background
LOAD is a neurodegenerative disorder and the most common form of dementia affecting people over 65 years of age. Polymorphisms in the promoter region of the *TNF-α* gene have been reported to increase the transcription rate of the gene and thus might influence the risk for LOAD.

Patients and methods
This study enrolled 31 elderly patients diagnosed with probable Alzheimer's disease. The diagnosis was according to the DSM-IV-TR and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorder Association (NINCDS–ADRDA). Thirty-one cognitively normal elderly controls were included and were subjected to the Clinical Dementia Rating Scale, the Activities of Daily Living scale, and the Instrumental Activities of Daily Living scale.

Results
The presence of the *TNF-α* –308 A allele was associated with an increased risk for LOAD, younger age of onset of LOAD by about 4 years, and statistically significantly more severe form of LOAD in Egyptian patients.

Conclusion
The *TNF-α* –308 A allele was a risk factor for the development of LOAD in Egyptian patients.

Keywords:
Alzheimer's disease; –308 G/A polymorphism; tumor necrosis factor-α

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Introduction

Alzheimer's disease (AD), the most common form of dementia, is a neurodegenerative disorder characterized by progressive cognitive decline associated with functional decline and behavioral disturbances (Kapur *et al.*, 2006).

There are genetic polymorphisms underlying the susceptibility to AD. These polymorphisms are not necessary to cause AD, but they enhance susceptibility in combination with other unknown environmental factors (Bartzokis *et al.*, 2006).

The etiology of late-onset Alzheimer's disease (LOAD) is complex and it has strong genetic heterogeneity: complex because there is no single or simple model explaining the mode of disease transmission, and heterogenous because the gene mutations or polymorphisms may interact with one another and with environmental factors (Tuppo and Arias, 2005).

Serum concentrations of tumor necrosis factor-a (*TNF-α*) were found to be elevated in Alzheimer patients (Bonotis *et al.*, 2008). Polymorphisms in the promoter region of the *TNF-α* gene have been reported to increase the transcription rate of the gene and thus might influence the risk for AD (Tedde *et al.*, 2008). Among them, the polymorphism located on the –308 bp *TNF-α* –308 G/A polymorphism has been shown to be associated with an increased transcriptional activity of the gene (Fargion *et al.*, 2004). The A allele has been reported to be associated with the development of LOAD in a certain section of the population (Wang *et al.*, 2008).

Patients and methods

Forty late-onset Egyptian Alzheimer's patients were chosen from among those admitted or referred to the Department of Geriatric Medicine or Institute of Psychiatry from Ain Shams University Hospitals between 2011 and 2014. Six patients did not complete the interview and three patients' caregivers withdrew their consent. Only 31 cases were enrolled in the study.

The control group included 31 cognitively normal elderly individuals matched in age and sex with cases as much as possible with no evidence of neurological, psychiatric, or medical illnesses that could affect cognition.

Informed consent was taken from the patients or their caregivers. The recruited patients fulfilled both the DSM-IV criteria for AD (American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorder Association (NINCDS–ADRDA) criteria (McKhann *et al.*, 1984) for probable AD. Patients and controls underwent the following assessments:

(1) Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975) and clock drawing test (CDT) for screening of cognitive impairment.
(2) Clinical Dementia Rating Scale (CDRS) (Morris, 1993), Activities of Daily Living (ADL) (Katz *et al.*, 1979), and Instrumental Activities of Daily Living (IADL) (Lawton and Brody, 1969) for detecting the severity of LOAD.

Thereafter, 5–7 ml of blood was drawn into EDTA tubes by means of venipuncture using a vacutainer. The protocol used for the DNA extraction was the one supplied with the InViTek Extraction Kit (Gesellschaft fur Biotechnik & Biodesign mbH). After DNA extraction, PCR had to be performed for the amplification of the extracted DNA, using a specific primer. The primers used are as follows.

Oligonucleotide primers 5'-AGGCA/ATAGGTTTT G/AGGGCCAT-3' (forward) and 5'-TCCTC CCTGCTCCG/ATTCCG-3' (reverse) were used to amplify the 107-bp PCR product of the *TNF-α* promoter polymorphism (rs1800629) (MJ Research PTC-200 Thermal Cycler). Then the PCR products were digested overnight by *Nco*I restriction endonuclease (MBI Fermentas). For proper identification of DNA bands in the PCR products we used gel electrophoresis and for proper identification of DNA bands in the restricted product we used the QIAxcel Advanced System, as shown in the Figs. 1–4.

Statistical design and analysis

Statistical presentation and analysis was conducted using mean, standard error, the Student *t*-test, the χ^2-test, analysis of variance using SPSS (version 17; SPSS Inc., Chicago, Illinois, USA), Tukey's honestly significant difference test, and the Hardy–Weinberg principle.

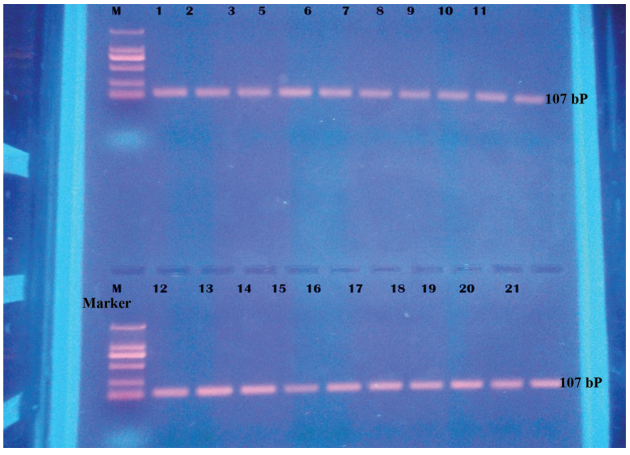
Results

There was a statistically significant difference ($P = 0.034$) between patients and controls regarding their genetic polymorphism as the A allele was significantly more prevalent in patients (25.81%) than in controls (9.68%) and the G allele was significantly more prevalent in controls (90.32%) than in patients (74.19%), as shown in Table 1.

There was a highly statistically significant association between the genetic polymorphism and caregiver complaint of patients ($P < 0.001$) as there was an association between the caregiver's complaint of severe degree of AD with the A allele, repeated quarrels with family members, and impaired awareness of the environment and self, as shown in Table 2.

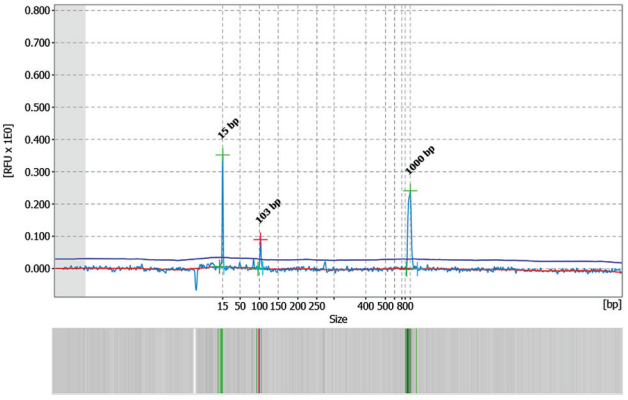
The A allele was statistically significantly associated with younger age of onset of AD compared with the G allele, by about 4 years, as shown in Table 3.

Figure 1



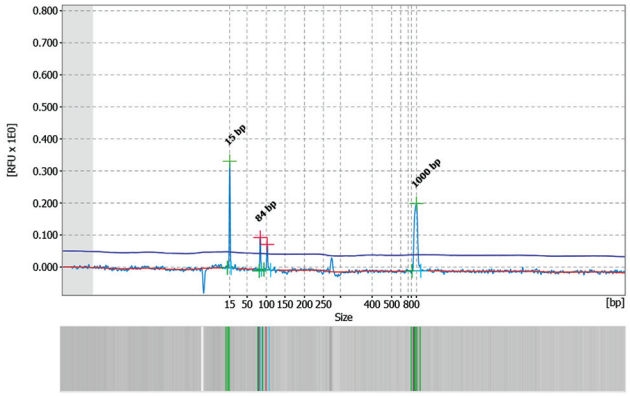
PCR product electrophoresis on agarose gel.

Figure 2



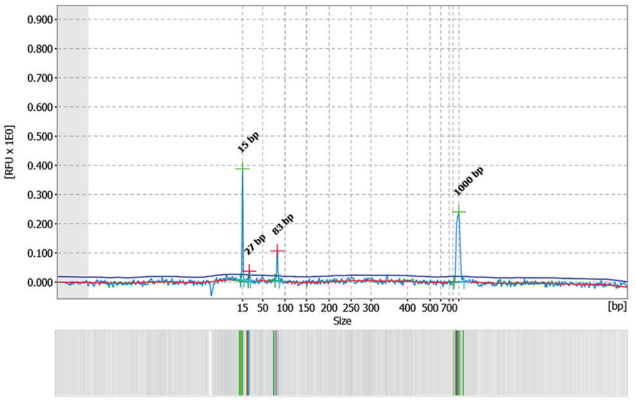
Restricted product with only one band above 100 bp — that is, tumor necrosis factor-α (*TNF-α*) –308 A/A.

Figure 3



Restricted product with two bands, one above 100 bp and one below 100 bp — that is, tumor necrosis factor-α (*TNF-α*) –308 G/A.

Figure 4



Shows restricted product with two bands below 100 bp — that is, tumor necrosis factor-α (*TNF-α*) –308 G/G.

Table 1 Distribution of the tumor necrosis factor-α –308 G/A polymorphism of the entire sample

Genetic polymorphisms	Groups [*N* (%)]		χ^2	*P*-value
	Patients	Controls		
GG	19 (61.29)	25 (80.65)	6.653	0.036***
G/A	8 (25.81)	6 (19.35)		
A/A	4 (12.90)	0		
Hardy–Weinberg 2-allele				
A allele	16 (25.81)	6 (9.68)	4.476	0.034***
G allele	46 (74.19)	56 (90.32)		
P-value	0.0694	0.5508		

The A allele was significantly more prevalent in patients than in controls and the G allele was significantly more prevalent in controls than in patients ($P < 0.001$); *** Highly statistically significant association ($P < 0.001$).

Table 2 Correlation between the caregiver's complaint of the patients and the tumor necrosis factor-α –308 G/A genetic polymorphism

Patients' caregiver complaints	Genetic polymorphism [*N* (%)]			χ^2	*P*-value
	GG	G/A	A/A		
Isolation from the family	4 (40)	0	0	34.502	<0.001***
Repeated falsification of events	3 (30)	0	0		
Repeated losing way to home	3 (30)	0	0		
Repeated quarrels with family members	0	4 (50)	0		
Impaired awareness of environment and self	0	4 (50)	4 (100)		

The A allele was significantly associated with caregiver's complaint denoting severe degree of Alzheimer's disease ($P < 0.001$); *** Highly statistically significant association ($P < 0.001$).

The A allele was statistically significantly associated with longer illness duration of AD compared with the G allele. The mean illness duration of the GG category was 2.737 years, that of the G/A category was 5.875 years, and that of the A/A category was 7 years, as shown in Table 4.

The A allele was statistically significantly associated with lower MMSE score compared with the G allele. The mean score of the GG category was 15.158, that of the G/A category was 5.750, and that of the A/A category was 1.250, as shown in Table 5.

The A allele was statistically significantly associated with lower CDT scores compared with the G allele. The mean score of the GG category was 2.632, that of the G/A category was 0.625, and that of the A/A category was 0, as shown in Table 6.

The A allele was statistically significantly associated with a higher score in the CDRS compared with the G allele. It means that the A allele was statistically significantly associated with a more severe form of AD.

The mean score of the GG category was 9.474, whereas it was 16 in the G/A category and 18 in the A/A category, as shown in Table 7.

The A allele was statistically significantly associated with lower scores in the ADL scale compared with the G allele. The mean score of the GG category was 4.211, whereas it was 0.5 in the G/A category and 0 in the A/A category, as shown in Table 8.

The A allele was statistically significantly associated with lower scores in the IADL scale compared with the G allele. The mean score of the GG category was 4.737, the mean score of the G/A category was 0, and the mean score of the A/A category was 0, as shown in Table 9.

Therefore, the current study revealed that the *TNF-α* –308 A allele was associated with increased susceptibility, early age of onset, and more severe form of LOAD in Egyptians.

Table 3 Correlation between patients' age at onset of Alzheimer's disease and the tumor necrosis factor-α –308 G/A genetic polymorphism

Genetic polymorphisms	Patients' age of onset		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
GG	69–77	73.316 ± 2.678		
G/A	65–71	66.875 ± 2.100	21.534	<0.001***
A/A	66–70	68.500 ± 1.915		
Tukey's test				
GG and G/A	GG and A/A	G/A and A/A		
<0.001***	0.004***	0.538		

The A allele was significantly associated with younger age at onset of Alzheimer's disease compared with the G allele ($P < 0.001$); ANOVA, analysis of variance; *** Highly statistically significant association ($P < 0.001$).

Table 4 Correlation between patients' duration of Alzheimer's disease and the tumor necrosis factor-α –308 G/A genetic polymorphism

Genetic polymorphisms	Patients' illness duration		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
GG	1–5	2.737 ± 1.262	35.094	<0.001***
G/A	5–7	5.875 ± 0.835		
A/A	6–8	7 ± 1.155		
Tukey's test				
GG and G/A	GG and A/A	G/A and A/A		
<0.001***	<0.001***	0.268		

The A allele was significantly associated with longer duration of Alzheimer's disease compared with the G allele ($P < 0.001$); ANOVA, analysis of variance; *** Highly statistically significant association ($P < 0.001$).

Table 5 The correlation between the tumor necrosis factor-α –308 G/A genetic polymorphism and the score of Mini Mental State Examination of patients

Genetic polymorphisms	Patients' MMSE		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
GG	11–19	15.158 ± 2.713	75.284	<0.001***
G/A	2–8	5.750 ± 2.188		
A/A	0–3	1.250 ± 1.500		
Tukey's test				
GG and G/A	GG and A/A	G/A and A/A		
<0.001***	<0.001***	0.017***		

The A allele was significantly associated with lower MMSE score compared with the G allele, denoting a more severe form of Alzheimer's disease ($P < 0.001$); ANOVA, analysis of variance; MMSE, Mini Mental State Examination; *** Highly statistically significant association ($P < 0.001$).

Table 6 Correlation between patients' clock drawing test score and the tumor necrosis factor-α –308 G/A genetic polymorphism

Genetic polymorphisms	Patients' CDT		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
GG	1–4	2.632 ± 0.895	31.893	<0.001***
G/A	0–1	0.625 ± 0.518		
A/A	0–0	0		
Tukey's test				
GG and G/A	GG and A/A	G/A and A/A		
<0.001***	<0.001***	0.387		

The A allele was significantly associated with lower CDT score than the G allele denoting more severe form of Alzheimer's disease ($P < 0.001$); ANOVA, analysis of variance; CDT, clock drawing test; *** Highly statistically significant association ($P < 0.001$).

Table 7 Correlation between patients' Clinical Dementia Rating Scale score and the tumor necrosis factor-α –308 G/A genetic polymorphism

Genetic polymorphisms	Patients' CDRS		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
GG	6–12	9.474 ± 2.816	36.333	<0.001***
G/A	14–18	16 ± 1.069		
A/A	18–18	18 ± 0		
Tukey's test				
GG and G/A	GG and A/A	G/A and A/A		
<0.001***	<0.001***	0.351		

The A allele was significantly associated with higher CDRS score compared with the G allele, denoting more severe form of Alzheimer's disease ($P < 0.001$); ANOVA, analysis of variance; CDRS, Clinical dementia rating scale; *** Highly statistically significant association ($P < 0.001$).

Table 8 Correlation between patients' Activities of Daily Living score and the tumor necrosis factor-α –308 G/A genetic polymorphism

Genetic polymorphisms	Patients' ADL		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
GG	3–6	4.211 ± 1.398	41.908	<0.001***
G/A	0–1	0.5 ± 0.535		
A/A	0	0		
Tukey's test				
GG and G/A	GG and A/A	G/A and A/A		
<0.001***	<0.001***	0.760		

The A allele was significantly associated with lower ADL score compared with the G allele, meaning that the A allele is significantly associated with more functional deterioration among patients, denoting more severe form of Alzheimer's disease ($P < 0.001$); ADL, Activities of Daily Living; ANOVA, analysis of variance; *** Highly statistically significant association ($P < 0.001$).

Discussion

In the present study we found that the presence of the *TNF*-α –308 G/A and A/A polymorphisms – that is, the A allele – was associated with an increased risk for LOAD, younger age of onset of LOAD by about 4 years, and more severe form of LOAD in Egyptians.

Our results agreed with those of several ethnic research studies. A Spanish study (Alvarez *et al.*, 2002) found that the *TNF*-α –308 A allele was significantly associated with a decreased onset age of LOAD. Carriers of the A allele showed an onset age that was 3 years lower than that of noncarriers (72.2 ± 8.6 vs.

Table 9 The correlation between the patients' Instrumental Activities of Daily Living score and the tumor necrosis factor-α −308 G/A genetic polymorphism

Genetic polymorphisms	Patients' IADL		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
GG	3–8	4.737 ± 1.968	33.155	<0.001***
G/A	0	0		
A/A	0	0		
Tukey's test				
GG and G/A	GG and A/A	G/A and A/A		
<0.001***	<0.001***	1.0		

The A allele was significantly associated with lower IADL score compared with the G allele, meaning that the A allele is significantly associated with more functional deterioration among patients, denoting more severe form of Alzheimer's disease ($P < 0.001$); ANOVA, analysis of variance; IADL, Instrumental Activities of Daily Living; *** Highly statistically significant association ($P < 0.001$).

75.1 ± 7.7 years; Kaplan–Meier log-rank 0.019). Interestingly, these results are in agreement with ours. Although our results indicated that the A allele was significantly associated with younger age of onset by about 4 years and not 3 years, we can attribute this difference to the overestimation of illness duration by caregivers.

In an American study, Ramos *et al.* (2006) studied a sample composed of 265 patients meeting the criteria for probable or definite AD, as well as 347 controls. Among patients the frequency of the A/A allele was 4.2%, the frequency of the G/A allele was 27.5%, and the frequency of the A allele was 17.9%. Among controls, the frequency of the A/A allele was 2.3%, the frequency of the G/A allele was 25.4%, and the frequency of the A allele was 15%. They found a trend toward increased risk for AD with each additional −308 A allele – that is, they observed a trend indicating that the minor allele, *TNF*-α −308 A, was associated with an increased risk for AD. Their results reflected a relationship between the risk for LOAD and the *TNF*-α promoter region haplotypes that are associated with higher transcriptional activity. Although these results agreed with ours, their A-allele frequency in cases and controls differed from ours, which could have been due to differences in their sample size, the fact that they did not exclude patients with a first-degree relative with AD, as we did, and due to ethnic differences.

In China Wang *et al.* (2008) found that 3.9% of LOAD patients carried the A/A genotype. The corresponding proportion in controls was 0%. The A-allele frequency in cases (11.1%) was significantly higher than that in controls. There were significant differences between the A/A genotype and the G/A genotype — that is, the A-allele frequency was higher in LOAD patients and in controls in their sample, compared with the G/A phenotype. These results suggested that the *TNF*-α gene −308 G/A polymorphism might be a risk factor for LOAD in the Chinese population. Their A-allele frequency in cases differed from our A-allele frequency, which could be due to differences in their sample size (207 LOAD patients), the fact that they did not exclude patients with a first-degree relative with AD, as we did, and due to ethnic differences.

In another Chinese study, Yang *et al.* (2009) found that 8.1% of sporadic Alzheimer's disease (SAD) patients carried the A/A genotype. The corresponding proportion in controls was 0%. The A-allele frequency in cases (18.3%) was significantly higher than that in controls (7.9%). A significantly increased risk for SAD was observed in the carriers of the A allele. It suggested that the A allele might be closely related to SAD in the southern Chinese population. They found that the serum level of *TNF*-α in the SAD group (567.85 ± 102.43 ng/l) was much higher than that in controls (389.73 ± 56.68 ng/l). The elevation of the serum level of *TNF*-α was closely associated with the risk for SAD. Interestingly, these data were in parallel with the changes of A-allele frequency. These results suggested that the *TNF*-α gene G −308 A polymorphism might be a risk factor for SAD in southern China.

These results agreed with ours; even their A-allele frequency was similar to ours but was not identical, which could have been due to differences in their sample size (112 LOAD patients), the fact that they did not exclude patients with a first-degree relative with AD, as we did, and due to ethnic differences. In addition, we did not measure the serum level of *TNF*-α in our study and thus cannot compare this part, which was also a study limitation.

In an Iranian study, Mohaddes Ardebili *et al.* (2011) excluded patients with a first-degree relative with AD. They found that the presence of the A allele of the −308 G/A polymorphism of the promoter region of the *TNF*-α gene was a genetic marker for susceptibility to AD in the Azeri Turk population. Thus, the *TNF*-α −308 G/A gene polymorphism could affect cerebral inflammatory response and the risk for LOAD. Fortunately, these results were in agreement with ours, although they differed in their A-allele frequency. Allele A frequency in LOAD patients was 44.69% compared with 6.25% in control subjects, which could have been due to differences in their sample size (160 LOAD patients) and ethnic differences.

In another Iranian study, Gharesouran *et al.* (2013) excluded patients with a first-degree relative with AD. The study revealed a significant difference in the

TNF-α –308 G/A genotype and allele frequencies between AD patients and healthy participants. The –308 polymorphism was associated with increased transcriptional activity and *TNF-α* release. The –308 G/A polymorphism was shown to be a genetic marker for susceptibility to AD in the Azeri Turk population. Interestingly these results are in agreement with ours.

In contrast, some studies found a negative association between the *TNF-α* –308 G/A polymorphism and the development of AD. A British study (Culpan *et al.*, 2003) analyzed the individual distribution of two single-nucleotide polymorphisms and two microsatellite loci in AD patients and controls (Fisher's exact test). For each of the four loci (*TNF-α* –308, *TNF-α* 238, *TNF-α*, and *TNF-β*) there was no significant association between any of the loci and the development of AD. Unfortunately, these results were contradictory to ours, which may be due to different sample quality and size (235 post-mortem-confirmed AD and 130 control cases) and ethnic differences (British sample). In addition, they did not exclude patients with a first-degree relative with AD.

In Denmark, Bruunsgaard *et al.* (2004) found that *TNF-α* –308 G/A genotypes were in Hardy–Weinberg equilibrium in centenarians and in 85-year-old and young controls, and there was no difference in the distribution of genotypes or the prevalence of A-allele carriers between any of the age groups. These results were in contrast to ours, which may be due to different quality and size of the investigated sample. The Danish study included 100-year-old Danes (n = 122), octogenarians (n = 174), and healthy volunteers aged 18–30 years (n = 47), there were ethnic differences, and patients with a first-degree relative with AD were not excluded. However, they agreed with us as they concluded that the A/A genotype had greater mortality risk when compared with the other two genotypes (G/G and G/A).

In Italy, Tedde *et al.* (2008) studied five common variations within the promoter region of the *TNF-α* gene in 609 participants (253 AD patients and 356 controls). No positive associations were found. Moreover, they also investigated the combined haplotypes of the five different polymorphisms without finding a positive association. Thus, they did not support the proposal that common nucleotide variations in the *TNF-α* gene can influence the development of AD in an Italian population. These results were contradictory to ours, which may be due to different sample sizes (253 AD patients and 356 controls) and ethnic differences. Further, they did not exclude patients with a first-degree relative with AD.

In Iran, Manoochehri *et al.* (2009) found that the statistical analysis of the patients' genotype and allele frequencies showed that there were no statistically significantly differences in the *TNF-α* –308 G/A genotype and allele frequencies between AD patients and healthy individuals. Next, they stratified the *TNF-α* –308 G/A genotyping results according to their ApoE-ε4 status for synergic effects using logistic regression. After stratifying the ApoE-ε4 genotypes status there was no significant difference between AD patients and healthy controls. They found no statistically significant evidence for the ApoE-ε4 genotypes as a modifier for the *TNF-α* –308 G/A polymorphism. Their results suggested that *TNF-α* –308 G/A was not a risk or protective factor for LOAD in the Iranian population. This contradiction between their results and ours could be explained by different sample sizes (140 AD patients and 158 healthy controls), ethnic differences, and nonexclusion of first-degree relatives with AD, compared with the previously described two Iranian studies, which excluded first-degree relatives with AD.

Thus, there is a discrepancy between studies regarding the role of *TNF-α* –308 G/A polymorphism in the susceptibility of AD as some of these discrepancies might be due to genetic heterogeneity of the populations studied (Tabor *et al.*, 2002). In particular, the *TNF-α* gene may show different effects on different ethnic groups, depending on its interaction with other unknown different susceptibility genes and/or risk factors in another nearby locus, which may vary in different populations. In addition, the *TNF-α* gene was an HLA gene, and in the HLA complex many other genes encode for proteins involved in immune-inflammatory responses (Price *et al.*, 1999; Candore *et al.*, 2004). In this view, for example, the common genetic soil shared between Spanish (Alvarez *et al.*, 2002) and Italian (Lio *et al.*, 2006) populations allows to hypothesize that the HLA 8.1 ancestral haplotype, involving –308 A allele (Candore *et al.*, 2002), might be a disease modifier gene in patients in which AD is rising, bringing to light the importance of genetic variation in the proinflammatory components in the progression of AD pathogenesis.

Limitations of the study

(1) The size of the sample should have been larger.
(2) The geographical distribution of the sample should have covered the whole Arab Republic of Egypt.
(3) A comparative study should have been conducted to cover the entire Arab world.
(4) *TNF-α* level should have been measured both in blood and cerebrospinal fluid and correlated with *TNF-α* –308 G/A polymorphism.

(5) Other risk genes should have been examined to unravel the effects and interactions between different genetic risk genes — for example, APP, PSEN1, PSEN2, and ApoE genes of AD.
(6) More recent markers should have been used in the diagnosis of LOAD to increase reliability of the results — for example, CSF levels of total tau and Aβ-42 plus functional MRI of the brain.
(7) A prospective large study should have been conducted to investigate the effect of anti-*TNF-α* treatment — for example, the effect of thalidomide, enbrel, and remicade on the outcome of AD.

Conclusion

AD is multifactorial in origin. The *TNF-α* −308 A allele is a risk factor for the development of LOAD in Egyptians and is associated with early age of onset and more severe form of AD; however, it is neither necessary nor enough for the disease occurrence as it works as a disease modifier, needing other genetic and/or environmental risk factors to develop AD.

Recommendations

(1) Construction of an Egyptian psychiatric database is mandatory to facilitate accessibility to studies to explore what has been done, thus helping in progression of cumulative work; this may be conducted through the Egyptian Psychiatric Association.
(2) Further studies are needed to explore the genetic and neuroanatomical considerations implicated in the etiology of LOAD. These studies should depend on recent tools such as those of neuroimaging and genetic assessment with a large-sized cross-sectional sample of elders.
(3) We need prospective cohort studies of elders with LOAD to determine the outcome of different strategies in the management.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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