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ORIGINAL ARTICLE

Associations between Polymorphisms within Interferon Gamma and Tumor Necrosis Factor Genes and *Toxoplasma* Retinochoroiditis in Ghanaian Patients

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ABSTRACT

Purpose: To evaluate associations between IFN-γ +874T/A and TNF-α-308G/A polymorphism with the development of *Toxoplasma* retinochoroiditis.

Methods: By ARMS–PCR, a cross-sectional genetic study involving 30 patients with *Toxoplasma* retinochoroiditis and 87 controls was carried out.

Results: IFN-γ +874: by comparing with the AA genotype, individuals with the TT genotype had a 3.4 odds ratio (OR); AT had a 1.6 OR; and the T allele had a higher OR (1.6), indicating a likely susceptibility of IFN-γ +874T to the infection, though the overall distribution was not significant ($p = 0.259$). For TNF-α-308G/A, individuals with both GA and AA genotypes had lower ORs when compared with the GG genotype, implying the A allele could confer protection against *Toxoplasma* ocular lesions.

Conclusions: IFN-γ +874T allele may increase the risk of ocular lesions in *Toxoplasma* infection. The principle of natural selection seems to also play a role. The less common TNF-308A allelic form could be protective against the development of *Toxoplasma* ocular infection.

Keywords: Genes, Ghana, interferon gamma, retinochoroiditis, *Toxoplasma*, tumor necrosis factor

Ocular toxoplasmosis (OT) is a major cause of posterior uveitis and visual impairment in many parts of the world.[1] There is a disproportionate occurrence of ocular toxoplasmosis in different populations with comparable seroprevalence findings. The outcome of OT depends on the interaction of many factors, including functions of the host immune system, as well as host and parasite genetic factors.[2] Immune reactions to *Toxoplasma gondii* infection are associated with a strong T-helper 1 response, though a study among Colombian OT patients showed a T-helper 2 dominant immune response to SAG1 and ROP18 peptides.[3,4] Susceptibility to the development of ocular lesions seems to be associated with the production of proinflammatory cytokines, including interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) that contribute to the inflammatory responses responsible for damaging the choroid and retina.[4] Functional polymorphisms in the promoter regions of TNF-α and IFN-γ genes regulate their production levels and the outcome of infections.[5–9] Thus, a T to A single nucleotide polymorphism (SNP) of IFN-γ at +874 and a G to A SNP of TNF-α at position -308, have been implicated in many disease outcomes.[10–13] Associations between these gene polymorphisms and the outcome of OT have, however, been contradictory and inconclusive. While previous studies in Brazilian patients did not associate TNF-α-308G/A polymorphism with the outcome of *Toxoplasma* retinochoroiditis,[14] the IFN-γ +874T allelic form seemed

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to confer some protection against the disease.[15,16] A closer observation also gives a trend of diverse genotypic distribution profile of these cytokine gene polymorphisms (particularly of IFN-γ +874T/A) in different populations. This could also be a determining factor to the disease outcome in such populations. The aim of the current study was to evaluate the distribution of IFN-γ +874T/A and TNF-α-308G/A genotypes and their associations with the occurrence of *Toxoplasma* retinochoroiditis in patients from Ghana, West Africa.

MATERIALS AND METHODS

Sample Size Determination

A sample size of 39 was estimated, based on the expression $N = Z^2 (1 - p)(p)/b2$, where

N = estimated sample size,
Z = the standard score at 95% confidence interval (1·96),
b = desired error bound taken as 5% and
p = prevalence of ocular toxoplasmosis in this population being 2.6%[17]

Study Participants

The study included 30 patients with *Toxoplasma* retinochoroiditis (ocular group) and 87 individuals without ocular lesions (control group). The ocular group consisted of 20 consecutive patients with *Toxoplasma* retinochoroiditis, who visited the University of Cape Coast Eye Unit, plus 10 patients from an earlier population-based survey, all in the Central Region of Ghana.[17] The control group comprised 87 healthy individuals matched by age and sex, who were positive for anti-*Toxoplasma* IgG antibodies but had no ocular lesions and no history of uveitis. The study was conducted in accordance with the Helsinki Declaration on research regarding human subjects. The protocol for this study was reviewed and approved by the Ghana Health Services' Ethical Review Committee (ID: GHSERC: 21/11/12). Participants signed consent forms after the study protocol had been explained to them.

Ophthalmic examination was conducted by trained ophthalmologists and optometrists. The examination included slit-lamp biomicroscopy and dilated funduscopy by binocular indirect ophthalmoscopy. Fundus photographs were taken for cases of retinochoroiditis. Clinical diagnosis of OT was based on characteristic ocular lesions consistent with *Toxoplasma* retinochoroiditis, in addition to a positive serologic result and in the absence of other identifiable ocular morbidities. The criterion for positive serologic result was a positive test for any of the two anti-*Toxoplasma* IgG or IgM antibodies, or a combination of both. Serologic results were obtained using the commercial ELISA test kit (VEDALAB, Alencon, France), following the manufacturer's instructions.

DNA Extraction

Genomic DNA was extracted from whole blood using DNA blood mini kit (QIAgen, Hilden, North Rhine-Westphalia, Germany) by strictly following the manufacturer's protocol.

IFN-γ +874T/A Polymorphism Determination

The IFN-γ +874T/A polymorphism was determined using an amplification refractory mutation system by polymerase chain reaction (ARMS-PCR), as described previously.[15,18] The ARMS-PCR was carried out in a total volume of 25 µL containing 12.5 µL of GoTaq® Green Master Mix (Promega Corporation, Fitchburg, WI), 5 µM of generic primer (100 pmol/µL; 5′ - TCA ACA AAG CTG ATA CTC CA -3′), 5 µM of specific A primer (100 pmol/µL, 5′ - TTC TTA CAA CAC AAA ATC AAA TC**A** -3′), or 5 µM of specific T primer (100 pmol/µL, 5′ - TTC TTA CAA CAC AAA ATC AAA TC**T** -3′); 0.5 µM of internal control 1 (10 pmol/µL, 5′ - GCC TTC CCA ACC ATT CCC TTA -3′); 0.5 µM of internal control 2 (10 pmol/µL, 5′ - TCA CGG ATT TCT GTT GTG TTTC -3′); 3 µL of genomic DNA, and nuclease free water (Fitchburg, WI, USA). ARMS-PCR was performed in a thermocycler (GeneAmp® PCR System 9700, USA) consisting of an initial denaturation step (95ºC for 3 min); 10 cycles of 95ºC (15 s), 65ºC (50 s), and 72ºC (40 s), followed by 20 cycles of 95ºC (20 s), 55ºC (50 s), and 72ºC (50 s), with a final extension time of 7 min at 72ºC.

TNF-α-308G/A Polymorphism Determination

The polymorphism for TNF-α-308G/A was also determined using ARMS-PCR as described by Gupta and Sehajpal.[19] The optimized reaction conditions consisted of 3 µL of genomic DNA in a total volume of 25 µL of reaction mixture containing 0.16 µM of each primer, 12.5 µL of GoTaq® Green Master Mix (Promega). The reaction was amplified for 35 cycles, each cycle consisted of denaturation at 94ºC for 30 s, annealing at 57ºC for 20 s, extension at 72ºC for 20 s, and finally a 3 min extension at 72ºC.

All PCR products were analyzed in 2% agarose gel electrophoresis stained with ethidium bromide and visualized on UV transillumination.

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Data Analysis

All the data obtained were analyzed using the Statistical Package for Social Sciences (version 16; SPSS Inc, Chicago, IL). Allele and genotype frequencies were compared between cases and controls using multivariate logistic regression analysis (with 95% confidence intervals, CI). Hardy–Weinberg equilibrium was tested using the control group by comparing the observed values with expected values. A p value ≤0.05 was considered statistically significant. The Fisher's exact test was used when any expected frequency was <5.

RESULTS

Genotype frequencies of the polymorphisms studied were in Hardy–Weinberg equilibrium (IFN-γ: $\chi^2 = 0.55$, $p = 0.46$; TNF-α: $\chi^2 = 199$, $p = 0.58$).

IFN-γ Gene Polymorphism

All 117 individuals (30 cases and 87 controls) were tested by ARMS–PCR at the IFN-γ +874T/A polymorphic site. In total, 88 individuals (75.2%) showed AA homozygosity, 25 (21.4%) were AT heterozygous, while four (3.4%) were TT homozygous. Genotype frequency analysis showed that AA genotypes were the majority in both the ocular and the control groups [20 (67%) and 68 (78%), respectively)]. There was a similar distribution of the AT genotypes between cases and controls (27 and 20%, respectively). By logistic regression analysis, the TT homozygous individuals had ORs of 3.4 when compared with the AA genotype, though the overall distribution was not statistically significant (Fisher's exact test value = 2.46, $p = 0.259$). Similarly, the AT heterozygous individuals had 1.6 OR when compared with the AA genotype. Analysis of allele carriage indicated that the presence of a T allele in either the homozygous or the heterozygous forms gave higher ORs, indicating a likelihood of developing toxoplasmic ocular lesions. There was no significant difference in the distribution of alleles between cases and controls ($p = 0.18$) though the T allele had a higher OR, also signifying susceptibility to the infection. The lack of significant association could be due to the small number of cases (as *Toxoplasma* ocular infection is rare in Ghana[17]). Table 1 presents the genotype, allele, and allele carriage distributions of IFN-γ +874T/A polymorphism in cases and controls.

TNF-α Gene Polymorphism

After genotyping was performed for all 30 cases and 87 controls at TNF-α-308 by ARMS–PCR, the GG genotype was the largest group in both cases and controls [29 (97%) and 78 (90%), respectively]. This was followed by the GA genotype (3% in cases and 9% in controls) and finally the AA genotype (0% in cases and 1% in controls). There was no significant difference in the distribution of both genotypes and alleles between the cases and controls ($p = 0.59$; 0.16). However, both GA and AA genotypes had lower ORs when compared with GG, indicating that the presence of the A allele could confer some protection against the development of toxoplasmic ocular lesions. Allele carriage analysis (AA vs GA+GG) also indicated that the presence of the G allele may increase susceptibility to ocular lesions. Similarly, when compared with the G allele, the A allele gave a lower OR. Table 2 presents the distribution of TNF-α-308G/A genotype, allele, and allele carriage between cases and controls. Table 3 compares the distributions of IFN-γ and TNF-α genotypes in different populations.

DISCUSSION

The current study sought to evaluate the distribution profile of IFN-γ +874T/A and TNF-α-308G/A

TABLE 1. Distribution of genotype and allele frequencies of IFN-γ +874T/A polymorphism in cases of ocular toxoplasmosis and controls.

	Ocular group (n = 30)		Control group (n = 87)				
IFN-γ +874T/A	n	(f)	n	(f)	OR	95% CI	p value
Genotypes							
AA	20	0.67	68	0.78	Reference	Reference	Reference
AT	8	0.27	17	0.20	1.600	0.602–4.251	0.35
TT	2	0.07	2	0.02	3.400	0.450–25.691	0.24
Allele carriage							
AA	20	0.67	68	0.78	Reference	Reference	Reference
AT+TT	10	0.33	19	0.22	3.036	0.408–22.565	0.28
Alleles							
A	48	0.80	153	0.88	Reference	Reference	Reference
T	12	0.20	21	0.12	1.600	0.802–3.193	0.18

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TABLE 2. Distribution of genotype and allele frequencies of TNF-α-308G/A polymorphism in cases of ocular toxoplasmosis and controls.

	Ocular group (n = 30)		Control group (n = 87)				
TNF-α-308G/A	n	(f)	n	(f)	OR	95% CI	p value
Genotypes							
GG	29	0.97	78	0.90	Reference	Reference	Reference
GA	1	0.03	8	0.09	0.336	0.040–2.807	0.31
AA	0	0.00	1	0.01	1.0×10^{-8}	1.0×10^{-8} to 1.0×10^{-8}	
Allele carriage							
GA+GG	30	1.00	86	0.99	Reference	Reference	Reference
AA	0	0.00	1	0.01	0.30	0.036–2.464	0.26
Alleles							
G	59	0.98	164	0.94	Reference	Reference	Reference
A	1	0.02	10	0.06	0.336	0.075–1.508	0.16

TABLE 3. Comparison of IFN-γ and TNF-α genotypes in different populations.

		IFN-γ genotype		
Study	Population	AA	AT	TT
This study	Ghanaian	88 (75.2%)	25 (21.4%)	4 (3.4%)
Rekha et al. (2006)[20]	Indian	46.2%	35%	18.8%
Albuquerque et al. (2009)[15]	Brazilian	27%	63.7%	8.9%
Neves et al. (2012)[16]	Brazilian	40%	42.5%	17.5%
Visentainer et al. (2005)[22]	Brazilian	31.6%	54%	14.4%
Hussein et al. (2009)[11]	Egyptian	14%	33%	53%
		TNF-α genotype		
		GG	GA	AA
This study	Ghanaian	107 (91.5%)	9 (7.6%)	1 (0.9%)
Cordeiro et al. (2008)[14]	Brazilian	79%	18%	3%
Pujhari et al. (2012)[32]	Japanese	57.7%	42.3%	0%
Mishra et al. (2015)[33]	Indian	71.4%	28.6%	0%
Parikh et al. (2004)[34]	Ugandan	84.1%	15.9%	0%

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genotypes and also to determine their associations with *Toxoplasma* retinochoroiditis in Ghanaian patients.

IFN-γ Gene Polymorphism in the Study Population

Similar to this study, which found the AA genotype as the predominant group (75.2%) in the population, a report by Rekha et al.[20] in India also observed that the AA genotype was more frequent (46.2%), followed by the AT genotype (35%), and TT genotype (18.8%). In contrast to the current finding, the AT genotypes were found as the predominant group in Brazilian populations. Albuquerque et al.[15] reported a profile of 27% of AA genotype, 63.7% of AT genotype and 8.9% of the TT genotype. Neves et al.[16] also reported a similar profile of 40% of the AA genotype, 42.5% of the AT genotype, and 17.5% of the TT genotype in a population of Rio de Janeiro, Brazil. Two other studies from Brazil found similar patterns of genotype frequency distribution.[21,22] A study in Egypt by Hussein et al.[11] however, found the TT genotype as the predominant group (53%) followed by the AT genotype (33%) and the AA genotype (14%). IFN-γ +874T/A polymorphism has been shown to associate with several diseases. For instance, the AA genotype was found to be associated with tuberculosis in Iran,[10] Brazil,[21] and Spain[5]; hepatitis B in China[13]; *Helicobacter pylori* gastritis in Italy[23]; type 2 diabetes mellitus in Greece[24]; Wegener's granulomatosis in Germany[25]; atopic patients in Egypt.[11] Similarly, the AT and TT genotypes were found to associate with breast cancer in Iran;[26] hepatitis C in Taiwan;[6] and Hashimoto's disease in Japan.[27] The current findings do not seem to corroborate the only two earlier studies that investigated associations between IFN-γ +874 T/A polymorphism and the occurrence of ocular lesions caused by *Toxoplasma gondii*. Those studies, which were all conducted in Brazilian

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populations, suggested that individuals with the A allele in its homozygous form had the tendency to develop ocular lesions.[15,16] The current study suggests that the T allele is associated with susceptibility to ocular lesions in 3.4- and 1.6-fold, respectively. Polymorphisms at the IFN-γ +874T/A position is known to associate with different levels of IFN-γ production. The TT genotype is associated with high levels of IFN-γ production, the AT with medium levels and the AA with lower levels.[5–7] The finding that the TT genotype (higher IFN-γ production) was associated with susceptibility to developing ocular lesions in this study may be related to severe inflammatory responses following increased cytokine production. Exacerbation of inflammatory reactions is known to result in retinochoroidal tissue destruction.[16] It was reported in the Brazilian patients regarding the scale of morbidity where the presence of the A allele seemed to confer protection against the development of clinical symptoms, although this did not result in ocular lesions.[16] The pathophysiologic mechanisms that underlie retinal damage in ocular toxoplasmosis are not yet fully understood, as the role of proinflammatory and immunoregulatory factors remain unclear.[28] Lahmar et al. reported increased levels of proinflammatory cytokines including IFN-γ and particularly IL-12 in patients with ocular toxoplasmosis than in other ocular diseases.[29] Again, IFN-γ was found to associate with the development of severe intraocular inflammatory disease in transgenic mice.[30] Stanford et al. also reported an association between high IFN-γ production and the outcome of ocular disease, where the presence of the T allele in either the heterozygous or homozygous forms was significantly higher in cases compared with controls.[31] The differences in IFN-γ genotype distribution profile in different populations may also determine which allele is associated with susceptibility or otherwise to developing ocular lesions. A careful observation of the pattern of genotype distribution seems to suggest the role of natural selection in relation to the T allele being associated with susceptibility to ocular infection in the current study as opposed to the AA genotype in the Brazilian studies. The genotypes occurring in fewer proportions seem to be associated with susceptibility to developing ocular lesions. That is, 24.8% of AT + TT in this Ghanaian population and 27% of AA genotype in a Brazilian population.[15] Neves et al. also reported 40% of the AA genotype in another Brazilian population.[16] For instance, if the AA homozygous individuals (75.2%) were to have an increased risk of developing ocular lesions in the current study, the implication would be that the prevalence of *T. gondii* retinochoroiditis in the population would be higher than the current state of 2.6%.[17] Conversely, if the T allele was to be associated with susceptibility to ocular infection in the Brazilian populations (73 and 60%, respectively), we would expect a higher prevalence of retinochoroiditis in those populations than is currently reported (31.8 and 5.8%, respectively).

TNF-α Gene Polymorphism in the Study Population

As in the current study, many studies have shown that at the TNF-α-308 polymorphic site, the GG genotype is the most frequent, while the AA genotype is the least common in all populations studied.[14,32–34] The only previous study that sought to investigate the association between TNF-α-308 polymorphism and the development of toxoplasmic retinochoroiditis did not find any association.[14] That finding was unexpected as the role of TNF-α in the pathophysiology of OT is very relevant. For instance, pretreatment of rat retinal vascular endothelial cells with TNF-α was found to inhibit the growth of *T. gondii* tachyzoites within these cells. This cytokine appeared to restrict parasite replication by starving the parasites of the amino acid L-tryptophan.[35] Similar to the current finding, several studies have associated the A allele with a protective effect against many diseases, including infectious and non-infectious uveitis. From Australia, El-Shabrawi et al. observed that the frequency of A allele in patients suffering from a human leukocyte antigen (HLA)-B27-associated uveitis was significantly lower than those in HLA-B27-negative control subjects.[36] Kuo et al. also described a reduced A allele frequency (6.6%) in their HLA-B27-positive uveitis patients in the UK.[37] A similar protective outcome with the A allele was associated with the development of ankylosing spondylitis in a population of Taiwan.[38] The less common TNF-308A allelic form has been found to associate with the binding of transcription factor, either by increasing promoter activity or by inhibiting the repressor of transcription and thereby increasing the production of TNF.[8,9] Contrary to the current finding, Sen et al. found a significant association of the A allele and the AA genotype with the occurrence of Eales disease.[12] Their explanation for this observation was that high expression of TNF-α could be responsible for the inflammation-associated angiogenesis in the proliferative stage of Eales disease, thus influencing susceptibility of the individual to the disease. The A allele was also associated with susceptibility to a non-infectious intermediate uveitis in the UK.[39]

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In conclusion, the results suggested that the presence of the IFN-γ +874T allele either in the homozygous (TT) or heterozygous (AT) forms may increase susceptibility to developing ocular lesions. The concept of natural selection seemed to play a role in determining which genotype or allele of IFN-γ +874 is associated with susceptibility or otherwise of developing ocular lesions. Also, the presence of the less common TNF-308A allelic form could be protective against the development of ocular infection in the present study. It is important to indicate that, due to considerations of unique cytokine genotypic profile for different populations, these results are valid for our study population and may not be applicable to the whole of Africa.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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