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CORRESPONDENCE

Genetic variant rs613872 in transcription factor 4 (*TCF4*) is not associated with primary open-angle glaucoma

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To the Editor:

Transcription factors play a key role in transcriptional gene regulation in both physiological and pathophysiological mechanisms of human diseases. Genes encoding transcription factors have been associated with glaucoma [1]. A genetic variation, rs613872 in transcription factor 4 (*TCF4*) gene, has been consistently reported to increase the risk of Fuchs's corneal endothelium dystrophy (FCD) [2]. TCF4 has been reported to be expressed in the human trabecular meshwork [3]. Multiple studies have proposed an association between FCD and the various subsets of glaucoma with inconsistent findings [4, 5], indicating an unconfirmed but plausible relationship between FCD and glaucoma. Besides, oxidative stress and apoptosis are often cited as common etiologic disease mechanisms. Based on a shared etiology and considering a common genetic predisposition between FCD and glaucoma, we hypothesized that the *TCF4* variant rs613872 might have a role in glaucoma as well. Thus, we investigated an association between rs613872 and primary open-angle glaucoma (POAG) in a Saudi cohort of 359 subjects, consisting of 186 POAG cases (102 men and 84 women) with no corneal abnormalities, and 173 controls (96 men and 77 women). Rs613872 genotyping was done using the TaqMan® real-time assay (C___3016617_10; Applied Biosystems Inc., Foster City, CA, USA). There was no significant difference between age, gender distribution, systemic disease status, and smoking habits among patients and controls. The minor "G" allele frequency was 0.11 and 0.14 among POAG cases and controls, respectively (odds ratio (OR) = 0.84, 95% confidence interval (CI) = 0.53–1.31, p = 0.446). Likewise, the allele frequencies between cases and controls did not vary significantly in men (OR = 0.65, 95% CI = 0.35–1.22, p = 0.184) and women groups (OR = 0.90, 95% CI = 0.48–1.68, p = 0.751). Besides, there was no significant deviation from the Hardy–Weinberg Equilibrium (p > 0.05). The codominant, dominant, recessive, overdominant, and log-additive genetic models with Akaike's information criterion and Bayesian information criterion values to indicate the best-fit model were used to test for association between rs613872 in the *TCF4* gene and POAG risk using SNPStats online tool (Table 1). The overall analysis showed no significant association of this variation with POAG. A similar gender-stratified genotype analysis also showed no significant association in men or women groups (Table 1). These associations remained nonsignificant after adjustment for age and sex. Furthermore, binary logistic regression analysis exhibited no significant effect of age (p = 0.124), sex (p = 0.912), and genotype (p = 0.418) on the disease outcome. Besides, within the POAG group, there was no significant genotype effect of rs613872 on different demographic and clinical markers used to assess disease severity such as intraocular pressure (IOP; p = 0.240), cup/disc ratio (p = 0.790), and the number of antiglaucoma medications (p = 0.322). The genetic basis of POAG in middle-eastern Saudi Arabs is still unknown. The data show that the *TCF4* variant is not associated with POAG or its related clinical phenotypes such as IOP and cup/disc ratio in the Saudi cohort. The results are also suggests a lack of common pathogenetic link between FCD and POAG etiology. However, the role of genetic determinants influencing corneal cell density cannot be ruled out [6].

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Table 1 Association analysis of rs613872 variant in *TCF4* with POAG.

Group	Genetic model	Genotype	CONTROL, *n* (%)	POAG, *n* (%)	OR (95% CI)	*p*	AIC	BIC	p^a
Overall	Codominant	T/T	128 (74.0)	148 (79.6)	1.00	0.44	501.6	513.2	0.39
		G/T	41 (23.7)	34 (18.3)	0.72 (0.43–1.20)				
		G/G	4 (2.3)	4 (2.1)	0.86 (0.21–3.53)				
	Dominant	T/T	128 (74.0)	148 (79.6)	1.00	0.21	499.6	507.4	0.18
		G/T-G/G	45 (26.0)	38 (20.4)	0.73 (0.45–1.19)				
	Recessive	T/T-G/T	169 (97.7)	182 (97.8)	1.00	0.92	501.2	509	0.91
		G/G	4 (2.3)	4 (2.1)	0.93 (0.23–3.77)				
	Overdominant	T/T-G/G	132 (76.3)	152 (81.7)	1.00	0.21	499.6	507.4	0.18
		G/T	41 (23.7)	34 (18.3)	0.72 (0.43–1.20)				
	Log-additive	–	–	–	0.78 (0.51–1.20)	0.26	499.9	507.7	0.23
Men	Codominant	T/T	71 (74.0)	85 (83.3)	1.00	0.17	276.8	286.7	0.16
		G/T	24 (25.0)	15 (14.7)	0.52 (0.25–1.07)				
		G/G	1 (1.0)	2 (2.0)	1.67 (0.15–18.81)				
	Dominant	T/T	71 (74.0)	85 (83.3)	1.00	0.11	275.7	282.3	0.10
		G/T-G/G	25 (26.0)	17 (16.7)	0.57 (0.28–1.13)				
	Recessive	T/T-G/T	95 (99.0)	100 (98.0)	1.00	0.59	278	284.6	0.56
		G/G	1 (1.0)	2 (2.0)	1.90 (0.17–21.30)				
	Overdominant	T/T-G/G	72 (75.0)	87 (85.3)	1.00	0.07	275	281.5	0.06
		G/T	24 (25.0)	15 (14.7)	0.52 (0.25–1.06)				
	Log-additive	–	–	–	0.66 (0.35–1.23)	0.19	276.6	283.2	0.19
Women	Codominant	T/T	57 (74.0)	63 (75.0)	1.00	0.86	228.6	237.8	0.85
		G/T	17 (22.1)	19 (22.6)	1.01 (0.48–2.13)				
		G/G	3 (3.9)	2 (2.4)	0.60 (0.10–3.74)				
	Dominant	T/T	57 (74.0)	63 (75.0)	1.00	0.89	226.9	233	0.85
		G/T-G/G	20 (26.0)	21 (25.0)	0.95 (0.47–1.93)				
	Recessive	T/T-G/T	74 (96.1)	82 (97.6)	1.00	0.58	226.6	232.7	0.57
		G/G	3 (3.9)	2 (2.4)	0.60 (0.10–3.70)				
	Overdominant	T/T-G/G	60 (77.9)	65 (77.4)	1.00	0.93	226.9	233	0.97
		G/T	17 (22.1)	19 (22.6)	1.03 (0.49–2.17)				
	Log-additive	–	–	–	0.91 (0.50–1.66)	0.76	226.8	233	0.72

OR (*95% CI*) odds ratio (95% confidence interval), *AIC* Akaike's information criterion, *BIC* Bayesian information criterion.

[a]*p* value adjusted for age and sex in overall group and by age in men and women groups.

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Compliance with ethical standards

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

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