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Original Article

Genetic associations of *FCRL3* polymorphisms with the susceptibility of Graves ophthalmopathy in a Chinese population

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Abstract: Background: Graves ophthalmopathy (GO) is a form of autoimmune thyroid disease commonly found in approximately 25-50% patients with Graves' disease. Both the thyroid-specific genes and immune-modulating genes are involved in susceptibility to GO. However, even though *FCRL3* polymorphisms were also autoimmune-associated genes, no study has been performed regarding the association of *FCRL3* with GO. Therefore, the objective of the current study was to conduct a basic case-control study in a Chinese population. Methods and materials: Seven SNPs were selected in this case-control study and 577 GD patients and 608 controls were recruited. Odds ratio and 95% confidence interval were used to assess the association between susceptibility of GO and *FCRL3* polymorphisms with Stata software (Version 11.0, Stata Corp LP, USA). Results: The case-control analysis showed that three polymorphisms, FCRL3_3C, FCRL3_5C, FCRL3_6A, were significantly associated with raised risk of GO in a Chinese Han population in the allelic model [OR = 1.28, 95% CI: 1.09-1.51, *P* = 0.003; OR = 1.26, 95% CI: 1.07-1.48, *P* = 0.005; OR = 1.25, 95% CI: 1.06-1.47, *P* = 0.007]. Conclusions: This case-control analysis confirmed that the FCRL3_3, FCRL3_5 and FCRL3_6 polymorphisms were associated with significantly increased risk of GO in a Chinese population.

Keywords: *FCRL3*, graves ophthalmopathy, single-nucleotide polymorphisms

Introduction

Graves' ophthalmopathy (GO), also called thyroid-associated ophthalmopathy (TAO), appears to be the most common extrathyroidal disorder, which could be found in 25-50% of patients suffering from Graves' disease (GD) [1]. Individuals clinically diagnosed as GO usually manifest as periorbital oedema, proptosis, lid retraction, diplopia and they would be plagued by sight-threatening corneal ulceration and even blindness [2]. Actually, the occurrence of GO has been demonstrated as a consequence of cumulative effects of both genetic and environmental factors [3, 4]. People at an older age or with poor habits of smoking and excessive iodine consumption, for instance, are more inclined to suffer from GO [5]. Furthermore, since GO appears as an autoimmunity-related disease and the significance of T cells in progression of GO has been confirmed by previous investigations [6], it could be hypothesized that genetic polymorphisms associated with regulation of T cells in autoimmune disorders could potentially account for the underlying etiology behind GO. Such promising candidate genes were displayed in previous studies as *SOCS3*, *HLA*, *CTLA4*, *IL12B*, *CD80*, *CD86*, *CD103* and so on [2, 7-11]. Additional studies demonstrated that thyroid-specific *TSHR* might also serve to dysregualte GO development partly owing to the association of GO with thyroid [12, 13].

Besides the above etiological factors of GO, another gene linked with the autoimmune system, *FC receptor-like-3 (FCRL3)*, should be emphasized in possible association with GO. *FCRL3* encoded one member of the immunoglobulin receptor superfamily, containing immunoreceptor-tyrosine activation and inhibitory motifs in its cytoplasmic domain which may be

involved in regulation of the immune systems [14]. Especially, polymorphisms in *FCRL3* were found to affect nuclear factor-κB (NF-κB) signaling pathway, which is not only associated with the innate immune response through up-regulation of anti-inflammatory factors, antimicrobial peptides and components of the complement system, but also with the adaptive response via controlling expression of antigen presentation components as well as recognition pathways of T cells and B cells [15]. Based on the complicated influence of *FCRL3* on NF-κB and the pivotal role of NF-κB in the immune response, *FCRL3* has been considered as a candidate locus for multiple autoimmune disorders with both human and murine models, such as rheumatoid arthritis, systemic lupus erythematosus and AITD [16-19].

However, there has been no study investigating about the possible correlation between *FCRL3* polymorphism and GO. Thus, the present study was aimed to estimate a more specific association of *FCRL3* polymorphisms with GO.

Methods and materials

Subjects

Unrelated Chinese patients diagnosed with GO were recruited from Ningbo No. 2 Hospital from April 2013 to May 2014. Patients diagnosed with GO should satisfy the following criteria: biochemical hyperthyroidism, dysthyroid eye disease, diffuse goiter, thyroglobulin, microsomal, and thyroid stimulating hormone receptor (TSHR) autoantibodies [20]. Matched control subjects without genetic relations were healthy individuals after routinely clinical and physical examinations in the outpatient departments during the same period and they were confirmed to be individuals without history of GO or any other autoimmune diseases. All these participants have signed informed consent and the project was approved by Ningbo No. 2 Hospital research ethics committee.

SNP selection and genotyping

Single-nucleotide polymorphisms (SNPs) were selected via HaploView software (version 4.2) and the International HapMap project database (HapMap Data Rel 24/phaseII Nov08, on NCBI B36 assembly, dbSNP b126) which included the genotyped data from Chinese Han individuals without genetic association. The criteria for SNP selection were listed as follows: (1) minor allele frequency was larger than 0.05; (2) the threshold *P* value of Hardy-Weinberg equilibrium (HWE) was 0.1; and (3) r^2 was greater than 0.8.

DNA was extracted from all the participants' 10 ml venous blood using the Blood DNA Extraction kits II (Beijing Bioteke Co.Ltd). Subsequently, TaqMan Mior Groove Binder (MGB) chemistry (Applied Biosystems, Foster City, CA, USA) was used to conduct the polymerase chain reaction (PCR) assay, following the manufacture's instruction. Finally, the PCR products were directly sequenced with a DNA sequencing Kit and the Big Dye Terminator on an automated ABI prism 3100 DNA sequence detection system (Applied Biosystem, Forster City, CA, USA). Moreover, the genotyping accuracy was confirmed with random selected samples.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was calculated to measure the genotype distribution between GO patients and healthy subjects with HaploView software (Version 4.2). Chi-square test, combined with its odds ratio (OR) and 95% confidence intervals (95% CIs), were utilized to estimate the association between selected SNPs and risk of GO in their allele or genotype frequencies. T-tests and chi-square tests were performed to tell the differences between cases and controls in patients' clinical variables, such as age, sex, thyroxine level, triiodothyronine and thyroid stimulating hormone level. All the statistical tests were performed with Stata software (Version 11.0, StataCorp LP, USA).

Results

Participants' characteristics

A total of 577 GO patients and 608 healthy controls were enrolled in this case-control study and the average ages of the two groups were 40.41 and 40.88, respectively. There was no significant association observed between cases and controls in terms of age, sex ratio, the thyroid stimulating hormone and triiodothyronine levels. However, the thyroxine level were significantly lower and the smoking habits were

Table 1. Comparison of GO patients and controls by selective characteristics

Clinical characteristics	GO patients (n = 577)	Controls (n = 608)	*P* value
Age (years)	40.41 ± 9.96	40.88 ± 9.24	0.399
Sex (male/female)	88/489	97/511	0.739
Smoking status			
Smoking	75	13	
Non-smoking	502	595	< 0.001
Free T4 (ng/dL)	1.43 ± 0.36	0.83 ± 0.31	< 0.001
Free T3 (pg/mL)	1.61 ± 0.38	1.57 ± 0.36	0.063
TSH (μIU/mL)	0.73 ± 0.24	0.71 ± 0.21	0.154
TRAb (IU/L)	7.32 ± 11.72	< 1.75	-
TgAb (2^n*100)	2.78 ± 2.81	Negetive	
McAb (2^n*100)	4.65 ± 2.51	Negetive	
Age at diagnosis of GO in years (mean ± sd)	37.44 ± 10.27	None	-
Disease duration in years (mean ± sd)	2.74 ± 3.67	None	-
Treatment time	12.1 ± 6.8	None	-
Current dose of anti-thyroid drug (mg/day)	13.2 ± 11.27	None	-
Goitre			
Grade 1	243	None	
Grade 2	228	None	
Grade 3	106	None	
Nodular hyperplasis			
Yes	63	None	
No	514	None	
Myxedema			
Yes	31	None	
No	546	None	
Vitiligo			
Yes	6	None	
No	571	None	

GO, Graves' ophthalmopathy; T4, thyroxine; T3, triiodothyronine; TSH, thyroid stimulating hormone; TRAb, anti-thyrotropin receptor antibody; McAb, anti-thyroid microsomal antibody; TgAb, anti-thyroglobulin antibody.

remarkably less found in healthy control subjects, compared to GO patients. More detailed features of other clinical variables are presented in **Table 1**.

Genotype frequency and its association with risk of GD

Seven SNPs, rs7528684 (*FCRL3_3*), rs11264799 (*FCRL3_4*), rs945635 (*FCRL3_5*), rs3761959 (*FCRL3_6*), rs2210913 (*FCRL3_7*), rs2282284 (*FCRL3_8*) and rs2282283 (*FCRL3_9*), have been selected. Among these polymorphisms, only three of them (*FCRL3_3*, *FCRL3_5*, *FCRL3_6*) were exhibiting significantly increased relationships with GO. More specifically, *FCRL3_3*C, *FCRL3_5*C, *FCRL3_6*A allelic frequencies were significantly higher in case group than control group (OR = 1.28, 95% CI: 1.09-1.51, *P* = 0.003; OR = 1.26, 95% CI: 1.07-1.48, *P* = 0.005; OR = 1.25, 95% CI: 1.06-1.47, *P* = 0.007). Moreover, their dominant models also

revealed significant associations between the genetic variants with increased risk of GO. Nontheless, after allowing for the potential affects imposed by certain parameters as free triiodothyronine level, participants' smoking habits and other SNPs, numeber of subjects carrying TC and CC of *FCRL3_3* as well as GC and CC of *FCRL3_5* remained pronouncedly larger than the carriers of TT (*FCRL3_3*) as well as GG (*FCRL3_5*), respectively, while *FCRL3_6* was no longer correlated with higher risk of GO. Intriguingly, *FCRL3_8* appeared significant associations with susceptibility to GO when the collective influences were incorporated (CC+TC vs. TT, OR = 1.73, 95% CI: 1.12-2.66, *P* = 0.014). More detailed results of genotype and allele frequencies in both dominant and allelic models were shown in **Table 2**.

Discussion

This case-control study was performed to investigate the association between *FCRL3* polymorphisms and susceptibility of GO in a Chinese population, indicating that *FCRL3_3* (rs7528684), *FCRL3_5* (rs945635) and *FCRL3_6* (rs3761959) were significantly correlated with increase risk of GO.

FCRL3 belongs to the immunoglobulin receptor superfamily, which acts directly against myelin-derived antigens on surface of immune cells [21]. Furthermore, although the precise function of *FCRL3* still remains unknown, the contained immunoreceptor-tyrosine inhibitory motifs (ITIMs) and immunoreceptor-tyrosine activation motifs (ITAMs) are believed to be involved in regulation of the immune system [22]. The signaling pathways are activated and inhibited by *FCRL3*, indicating that *FCRL3* has been playing a great role in cellular signaling thresholds regulation [23, 24]. The polymorphism in *FCRL3* was found to be responsible for affecting the binding affinity of nuclear factor-κB (NK-κB) and regulating the *FCRL3* expression [17]. As NK-κB is a significant stimulator to various immunological genes, the regulation of NK-κB activity proves to be pivotal to the autoimmune disease, leading to a deviant process that presents self-antigens as non-self. According to above basic features of *FCRL3*, plenty of studies have revealed the association between polymorphisms in this gene and susceptibility of autoimmune disorders [25-28].

It is the first study that focus on the correlation of *FCRL3* genetic polymorphisms with GO, indicating the novelty and originality of our study. However, a series of studies that studied on correlation of *FCRL3* polymorphisms with GD were conducted before. Because GO is one of the most common complications of GD, the micromolecular pathogenesis between GO and GD is similar and analogical. Hence, the association between genetic polymorphisms and GD progression may act as the reference value to evaluate the similar association between the genetic polymorphisms and GO. It showed that the *FCRL3* genetic polymorphisms related to the high risk of GO in Asian (Chinese and Japanese), while contradictory results remained in Caucasians. It suggested the factors affecting susceptibility to GO maybe different among two ethnicities. The results were expected for similar situation also found in other autoimmune disease, such as rheumatoid arthritis (RA). Study showed that the *FCRL3_3* polymorphism was found to be associated with an increased risk of RA in Asian population, while no significant association was observed in European populations [29]. Moreover, other genetic variants, for instance, the *PTPN22* and *PAD14* were also observed with inconsistent relations with RA in Caucasians and Asians [29, 30]. In those complex diseases, the causal genetic regions are various in different racial and ethnic groups [29, 31], indicating the susceptibility of each specific disease dependent on race and ethnicity of their participants [31]. Furthermore, studies performed on associations between different populations and diseases would highlight the importance of different genetic origins of ethnicity specific.

Both of the clinical heterogeneity and different participants' structures could lead to this difference. Thus, the standard diagnosis criteria and the patients' structure need to be confirmed in future analysis. Then, the polymorphism in linkage disequilibrium with a nearby causal variant may exist in one ethnic population, but not in another one, which was largely relied on the different linkage disequilibrium patterns [31]. Moreover, the whole-genome linkage studies needed to confirm the genetic susceptibility with GO in different ethnicities. This association study was only performed in Asian group, and both of previous studies confirmed the genetic susceptibility to GO [14, 32], thus other

Table 2. Allele and genotype distributions of *FCRL3* SNPs in Graves' ophthalmopathy (GO) patients and controls

SNP	dbSNP rs# (W>M)	Population	Genotype (n, %)			Dominant model				Allele (n, %)		Allelic model	
			WW	WM	MM	OR (95% CI)	*P*	Adjusted OR (95% CI)	Adjusted *P*	W	M	OR (95% CI)	*P*
FCRL3_3	rs7528684 (T>C)	GO	130	306	141	1.38 (1.06-1.79)	0.017	1.47 (1.01-2.13)	0.045	566	588	1.28 (1.09-1.51)	0.003
		Control	174	324	110					672	544		
FCRL3_4	rs11264799 (C>T)	GO	279	239	59	1.08 (0.86-1.35)	0.533	1.17 (0.85-1.63)	0.341	797	357	1.08 (0.90-1.29)	0.403
		Control	305	249	54					859	357		
FCRL3_5	rs945635 (G>C)	GO	140	299	138	1.31 (1.01-1.70)	0.038	1.48 (1.02-2.14)	0.037	579	575	1.26 (1.07-1.48)	0.005
		Control	180	320	108					680	536		
FCRL3_6	rs3761959 (G>A)	GO	132	299	146	1.34 (1.03-1.74)	0.028	1.05 (0.73-1.51)	0.788	563	591	1.25 (1.06-1.47)	0.007
		Control	173	315	120					661	555		
FCRL3_7	rs2210913 (C>T)	GO	142	284	151	0.96 (0.74-1.25)	0.760	1.25 (0.85-1.83)	0.251	568	586	1.05 (0.90-1.24)	0.536
		Control	145	324	139					614	602		
FCRL3_8	rs2282284 (T>C)	GO	477	94	6	1.15 (0.84-1.56)	0.384	1.73 (1.12-2.66)	0.014	1048	106	1.07 (0.80-1.52)	0.653
		Control	514	90	4					1118	106		
FCRL3_9	rs2282283 (A>C)	GO	374	168	35	0.90 (0.71-1.14)	0.375	1.23 (0.88-1.72)	0.224	916	238	0.99 (0.81-1.21)	0.952
		Control	379	196	33					964	252		

FCRL3, Fc receptor-like protein 3; SNP, single nucleotide polymorphism; W, wildtype allele; M, minor allele; GO, Graves' ophthalmopathy; OR, odds ratio; CI, confidence interval; Adjusted OR: OR after considering the collaborative effects of smoking status, free thyroxine level and other SNPs; Adjusted P: P after considering the collaborative effects of smoking status, free thyroxine level and other SNPs.

ethnicities were still in need. The susceptibility of other autoimmune disease, such as RA, was confirmed with genetic heterogeneity in previous whole-genome linkage studies [33].

Although the case-control study was firstly performed to investigate the association between *FCRL3* and GO, several limitations still existed. Firstly, the association may not be applied to people living in other regions within China because the limited number of patients might have distorted the analysis results and we cannot rule out the possible personal and regional particularities in our analysis. Secondly, there were limited ethnic groups included in the study. For example, considering multiple Asian countries, only Chinese population was included in Asian group in our study, let alone the Caucasian population, Latin Americans and Africans. Therefore, besides Asians, the Caucasians, Latin Americans and Africans are also needed to be studied to validate the association of *FCRL3* with risk of GO in their own ethnic groups in future research.

In conclusion, the case-control study indicated that *FCRL3_3* and *FCRL3_5* polymorphisms were associated with significantly increased risk of GO in a Chinese population. Nevertheless, more large cohort analysis are also required to further confirm the functional role of *FCRL3* polymorphisms in GO among other ethnicities, aiding in development of new treatments for GO.

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Disclosure of conflict of interest

None.

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