MIF Gene Polymorphisms Confer Susceptibility to Vogt-Koyanagi-Harada Syndrome in a Han Chinese Population

Chunxia Zhang,[1] Shouli Liu,[1] Shengping Hou,[2] Bo Lei,[2] Xiuyun Zheng,[1] Xiang Xiao,[2] Aize Kijlstra,[3] and Peizeng Yang[2]

[1]Jinan Mingshui Eye Hospital, Jinan, People's Republic of China
[2]The First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Ophthalmology, and Chongqing Eye Institute, Chongqing, People's Republic of China
[3]University Eye Clinic Maastricht, Maastricht, Limburg, The Netherlands

Correspondence: Peizeng Yang, The First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Ophthalmology, and Chongqing Eye Institute, Chongqing, People's Republic of China, 400016; peizengycmu@126.com.

CZ and SH contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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Purpose. The aim of the study was to determine the association of macrophage migration inhibitory factor (*MIF*) gene polymorphisms with Vogt-Koyanagi-Harada (VKH) syndrome.

Methods. A total of 600 Han Chinese VKH patients and 600 healthy controls were genotyped for rs755622 and rs2096525 of MIF by PCR-restriction fragment length polymorphism (PCR-RFLP) assay. Data were analyzed by χ^2 analysis.

Results. Genotype distribution in controls was in Hardy-Weinberg equilibrium. The frequencies of the rs755622 GG genotype and G allele were significantly lower in VKH patients compared with controls ($P_c = 0.006$ and 0.016). Stratification analysis showed decreased frequencies of the rs755622 GG genotype and G allele in patients, respectively with headache, tinnitus, alopecia, poliosis or vitiligo compared with controls (all $P_c < 0.05$). rs2096525 genotype and allele frequencies were not different between VKH patients and controls. However, a lower frequency of the rs2096525 TT genotype was observed in patients with headache compared with controls ($P_c < 0.05$). The frequencies of the rs2096525 T allele in patients with headache or vitiligo were significantly decreased compared with controls ($P_c = 8.54 \times 10^{-4}$ and 0.012). In addition, the results showed a significantly increased frequency of the combined rs755622/rs2096525 CT haplotype and a decreased frequency of the GT haplotype in VKH patients compared with controls.

Conclusions. Our study identified a strong association of rs755622 with VKH syndrome and certain clinical features. rs2096525 was associated with certain clinical features of VKH syndrome. The results also suggested that the CT and GT haplotypes were associated with VKH syndrome.

Keywords: Vogt-Koyanagi-Harada (VKH) syndrome, macrophage migration inhibitory factor (*MIF*), disease association, gene polymorphism

Vogt-Koyanagi-Harada (VKH) syndrome is a systemic autoimmune disease characterized by a bilateral granulomatous panuveitis, frequently accompanied by poliosis, vitiligo, alopecia, and central nervous system and auditory signs.[1–2] Although the precise etiology of VKH syndrome remains unknown, an autoimmune response, possibly in combination with an innate immune response, has been presumed to be implicated in its pathogenesis. A variety of studies have showed that genes in the human leukocyte antigen (*HLA*) region, such as *HLA-DR4*[3–5] and *HLA-DRw53*,[5,6] are the most powerful genetic disease risk factors for VKH syndrome in China, Japan, and other countries. Several non-*HLA* genes—including interleukin (*IL*)-17,[7] *STAT4*,[8] programmed cell death 1 (*PDCD1*),[9] and Fc receptor-like 3 (*FCRL3*)[6]—have been identified to be associated with VKH syndrome.

The macrophage migration inhibitory factor (*MIF*) gene is located on chromosome 22q11.2 and expressed mainly in macrophages and T cells. It has proinflammatory, enzymatic, and hormonal activities.[10,11] Recently, many studies have revealed that single nucleotide polymorphisms (SNPs) in the *MIF* gene are associated with immune-related diseases, including juvenile idiopathic arthritis,[12–14] multiple sclerosis,[15] systemic lupus erythematosus (SLE),[16] psoriasis,[17] and ulcerative colitis.[18] These studies suggest that *MIF* may play a role in a variety of autoimmune diseases. Recent studies provided evidence that *MIF* may be involved in the pathogenesis of VKH syndrome.[19–21] We recently reported that MIF gene polymorphisms are associated with Behçet's disease,[22] but whether these polymorphisms are also associated with other uveitis entities has not yet been addressed. Since VKH syndrome is a relatively common uveitis entity in China, we decided to extrapolate our earlier studies to this patient group. The results showed a strong association of the rs755622 MIF SNP with VKH syndrome and certain clinical features. SNP rs2096525 was also shown to be associated with VKH in the patient subgroup presenting with headache and vitiligo. Furthermore, we found that the combined rs755622/rs2096525 CT and GT haplotypes were associated with VKH syndrome.

Table 1. Primers and Restriction Enzymes Used for RFLP Analysis of the *MIF* Gene

RS Number	Primers	Restriction Enzyme
rs755622	5′ TGGGGAAGTCACCGCCTGCCTC 3′	ALUI
	5′ TGGCCCAAAGACAGGAGGTACA 3′	
rs2096525	5′ GGTGCCCACCGGACGAGGGAT 3′	MBOI
	5′ GTCGGGCCCCGAACGTCCACT 3′	

Methods

Study Populations

A total of 600 unrelated patients and 600 age-, sex-, and ethnicity-matched healthy controls were investigated in this study. The group of healthy controls was the same as the one we used for our study on the association of MIF gene polymorphisms and Behçet's disease.[22] The blood samples were obtained from the First Affiliated Hospital, Chongqing Medical University (Chongqing, China), or the Uveitis Study Center of the Sun Yat-sen University (Guangzhou, China). All patients fulfilled the First International Workshop criteria for VKH syndrome.[23] The clinical characteristics of VKH patients were assessed at the time of diagnosis and are summarized in Table 3 and Table 4. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local institutional ethics committee of The First Affiliated Hospital of Chongqing Medical University. Written informed consent was also obtained from all the subjects. Blood samples were collected in EDTA tubes and kept at −70°C until use.

Gnomic DNA Extraction and Genotyping

Genomic DNA was extracted by using a commercial kit (QIAamp DNA Blood Mini Kit; Qiagen, Valencia, CA). Amplification of the target DNA in the *MIF* gene was performed by the PCR using primers presented in Table 1. Each PCR reaction was carried out in a 10-μL reaction mixture containing 5 μL commercial PCR kit (Premix Taq, Ex Taq Version; Takara Biotechnology, Co., Ltd., Dalian, China), 20 pmol primers, and 0.2 μg of genomic DNA for amplification of the DNA. Its conditions were as follows: initial denaturation at 95°C for 5 minutes followed by 39 cycles of denaturation at 95°C for 30 seconds, annealing at 65°C for 30 seconds, extension at 72°C for 30 seconds, and a final extension at 72°C for 5 minutes. The two SNPs were genotyped by PCR-RFLP analysis. PCR products of rs755622 and rs2096525 polymorphisms were respectively digested with 2 U restriction enzyme (ALUI; Fermentas, Shengzhen, China) and MBOI (Fermentas) in a 10-μl reaction volume overnight. Digestion products were visualized on a 4% agarose gel and stained with a commercial stain (GoldView; SBS Genetech, Beijing, China). Direct sequencing was also performed by the Majorbio Biotechnology Company (Shanghai, China), using randomly selected subjects (20% of all samples) to validate the method used in this study.

Statistical Analysis

Hardy-Weinberg equilibrium was tested using the χ^2 test. Genotyping results were estimated by direct counting. Allele and genotype frequencies were compared between patients and controls by the χ^2 test using statistical software (SPSS version 17.0; SPSS, Chicago, IL). The *P* values were corrected (P_c) with the Bonferroni method by multiplying with the number of analyses performed. $P_c < 0.05$ was considered significant.

Results

The VKH cohort consisted of 600 subjects (348 male, 252 female), which were all Han Chinese. The average age of the VKH patients was 35.2 ± 9.2 years. The healthy control cohort included 600 subjects (360 male, 240 female), in which the average age was 34.1 ± 11.3 years. No statistical difference was observed between VKH patients and controls in the distribution of age and sex ($P > 0.05$).

Two SNPs of *MIF* (rs755622 and rs2096525) were successfully genotyped in 600 VKH patients and 600 controls. The results showed that the distribution of genotypes did not deviate from the Hardy-Weinberg equilibrium in controls. The genotype and allele frequencies of the two SNPs examined in VKH patients and normal controls are summarized in Table 2. The frequencies of the rs755622 genotype GG and G allele in VKH patients were significantly decreased compared with controls ($P_c = 0.006$, odds ratio [OR] 1.519, 95% confidence interval [CI] 1.197–1.928; $P_c = 0.016$, OR 1.351, 95% CI 1.099–1.659, respectively). A comparison of the allele and genotype frequencies of rs2096525 showed no significant differences between VKH patients and healthy controls.

We further performed a stratification analysis for certain clinical findings of VKH syndrome with both tested SNPs, including headache, tinnitus, alopecia, poliosis, and vitiligo. The results showed that the frequencies of the rs755622 GG genotype and G allele were significantly decreased in the patient subgroup with either headache, tinnitus, alopecia, poliosis, or vitiligo compared with controls (Table 3). In the tested SNP rs2096525, a significantly decreased prevalence of the T allele was found in patients with headache or vitiligo compared with controls ($P_c < 0.05$). A significantly lower frequency of the TT genotype of rs2096525 was also observed

Table 2. Frequencies of Alleles and Genotypes of *MIF* Polymorphisms in VKH Patients and Controls

SNP	Genotype/ Allele	VKH (%), $n = 600$	Controls (%), $n = 600$	χ^2	*P* Value	P_c Value	OR (95% CI)
rs755622	GG	360 (60.0)	417 (69.5)	11.862	0.001	0.006	0.66 (0.52–0.84)
	GC	226 (37.7)	167 (27.8)	13.171	2.84×10^{-4}	1.70×10^{-4}	1.57 (1.23–2.00)
	CC	14 (2.3)	16 (2.7)	0.137	0.712	NS	0.87 (0.42–1.80)
	G	946 (78.8)	1001 (83.4)	8.231	0.004	0.016	0.74 (0.60–0.91)
	C	254 (21.2)	199 (16.6)	8.231	0.004	0.016	1.35 (1.10–1.66)
rs2096525	TT	435 (72.5)	437 (72.8)	0.017	0.897	NS	0.98 (0.76–1.27)
	TC	144 (24.0)	150 (25.0)	0.162	0.687	NS	0.95 (0.73–1.23)
	CC	21 (3.5)	13 (2.2)	1.937	0.164	0.656	1.64 (0.81–3.30)
	T	1014 (84.5)	1024 (85.3)	0.325	0.568	NS	0.94 (0.75–1.17)
	C	186 (15.5)	176 (14.7)	0.325	0.568	NS	1.07 (0.85–1.34)

Table 3. Frequencies of Alleles and Genotypes of rs755622 in VKH Patients With Clinical Features

	VKH Patients	Genotype				Allele		
Clinical Features	**Total, $n = 600$ (%)**	**GG (%)**	**GC (%)**	**CC (%)**	**P_c***	**(%)**	**C (%)**	**P_c**
Age at onset, y ± SD	35.2 ± 9.2							
Male	348 (58.0)	209	131	8	0.998	549	147	0.963
Female	252 (42.0)	151	95	6	0.998	397	107	0.963
Uveitis	600 (100)	360 (60.0)	226 (37.7)	14 (2.3)	0.012	946 (78.8)	254 (21.2)	0.048
Headache	103 (17.2)	53 (51.5)	46 (44.7)	4 (3.9)	3.91×10^{-3}	152 (73.8)	54 (26.2)	0.012
Tinnitus	240 (40.0)	140 (58.3)	90 (37.5)	10 (4.2)	0.024	370 (77.1)	110 (22.9)	0.024
Alopecia	271 (45.2)	140 (51.7)	115 (42.4)	16 (5.9)	4.62×10^{-6}	395 (72.9)	147 (27.1)	4.0×10^{-6}
Poliosis	233 (38.8)	129 (55.4)	96 (41.2)	8 (3.4)	1.40×10^{-3}	354 (76.0)	112 (24.0)	5.51×10^{-3}
Vitiligo	138 (23.0)	66 (47.8)	64 (46.4)	8 (5.8)	1.40×10^{-3}	196 (71.0)	80 (29.0)	2.50×10^{-5}

P_c, Bonferroni corrected P value; NS, no significance.

* Stratification analysis of genotype GG in subgroups of VKH syndrome according to clinical features as compared with normal controls.

in the headache subgroup compared with controls. We failed to find an association in the tinnitus, alopecia, or poliosis subgroup with rs2096525 SNPs ($P_c > 0.05$; Table 4).

Haplotypes were reconstructed and analyzed using genetic software (Haploview version 3.32; Broad Institute, Cambridge, MA). The results showed that the combined rs755622/rs2096525 CT haplotype frequency was significantly increased in VKH syndrome compared with controls ($P_c = 2.42 \times 10^{-10}$, OR 4.203, 95% CI 2.664–6.632). A significantly lower GT haplotype was also observed in VKH syndrome compared with controls ($P_c = 0.015$, OR 0.722, 95% CI 0.587–0.887; Table 5).

Discussion

In this study, we identified a strong association of rs755622 with VKH syndrome and certain clinical features. The present study also showed an association between rs2096525 and certain clinical features of VKH syndrome. The results furthermore suggest that the combined rs755622/rs2096525 CT and GT haplotypes are associated with VKH syndrome.

Although the cause and pathogenesis of VKH are still not completely understood, *MIF* is thought to be an important cytokine in the pathogenesis of VKH syndrome and its polymorphisms have been shown to be associated with a number of autoimmune diseases.[12–18,24–27] In this study, we investigated whether its polymorphism was also associated with VKH syndrome, a typical autoimmune disease. The choice of tested SNPs was principally based on earlier reports.[12–18,24–27] The SNP rs755622 appears to have a consistent association with multiple autoimmune diseases.[12–18,24–27] Furthermore, this SNP has been shown to influence the level of *MIF* expression in juvenile idiopathic arthritis patients and controls,[28,29] suggesting its functional role in the development of disease. Previous studies showed that SNP rs5844572 was associated with autoimmune disease such as autoimmune liver disease[30] and that SNPs rs755622 and rs5844572 were in linkage disequilibrium in Chinese Han[31] or Caucasian populations.[30,32,33] SNP rs755622 is located 621 bp upstream from rs5844572, suggesting that it most likely has an effect on MIF promoter functionality on the basis of linkage disequilibrium.[34] Additionally, our group has previously shown that rs755622 affects its gene expression in PBMCs.[22] Based on the aforementioned information, SNP rs5844572 was not chosen in the present study.

Because numerous factors have been reported to influence the results of a study on the association of gene polymorphisms with disease, we made a number of efforts to ensure the correctness of the obtained data. We strictly selected the VKH patients included in our study according to the revised criteria as set up by an international committee on the nomenclature of this disease.[23] If there was any doubt about the diagnosis, we excluded the patient from the study. Unrelated healthy individuals were sex-, age-, and ethnicity-matched with patients and all the controls and patients were taken from a Han Chinese population to avoid a possible influence of ethnicity. Furthermore, 20% of the samples were randomly chosen and analyzed by direct sequencing in an attempt to validate the methods used in our study.

In this study, we found a decreased frequency of the GG genotype and G allele in VKH patients, suggesting that both may be protective factors for this disease. Interestingly, in a recent study we also found a similar result concerning MIF

Table 4. Frequencies of Alleles and Genotypes of rs2096525 in VKH Patients With Clinical Features

	VKH Patients	Genotype				Allele		
Clinical Features	**Total (%), $n = 600$**	**GG (%)**	**GC (%)**	**CC (%)**	**P_c***	**G (%)**	**C (%)**	**P_c**
Age at onset, y ± SD	35.2 ± 9.2							
Male	348 (58.0)	252	84	12	0.993	588	108	0.985
Female	252 (42.0)	183	60	9	0.993	426	78	0.985
Uveitis	600 (100)	435 (72.5)	144 (24.0)	21 (3.5)	NS	1014 (84.5)	186 (15.5)	NS
Headache	103 (17.2)	59 (57.3)	35 (34.0)	9 (8.7)	0.012	153 (74.3)	53 (25.7)	8.54×10^{-4}
Tinnitus	240 (40.0)	168 (70.0)	63 (26.3)	9 (3.8)	NS	399 (83.1)	81 (16.9)	NS
Alopecia	271 (45.2)	185 (68.3)	68 (25.1)	18 (6.6)	NS	438 (80.8)	104 (19.2)	0.204
Poliosis	233 (38.8)	171 (73.4)	53 (22.7)	9 (3.9)	NS	395 (84.8)	71 (15.2)	NS
Vitiligo	138 (23.0)	87 (63.0)	39 (28.3)	12 (8.7)	0.264	213 (77.2)	63 (22.8)	0.012

* Stratification analysis of genotype TT in subgroups of VKH syndrome according to clinical features, as compared with normal controls.

Table 5. Frequencies of the Haplotypes Formed by rs755622 and rs2096525 SNP in VKH Patients and Controls

Haplotype	Case Control Ratio	χ^2	*P* Value	P_c Value	OR (95% CI)
CC	0.314, 0.146	0.387	0.534	NS	0.93 (0.74–1.17)
CT	0.077, 0.020	44.229	3.03×10^{-11}	2.42×10^{-10}	4.20 (2.66–6.63)
GT	0.768, 0.833	9.682	0.002	0.016	0.72 (0.59–0.89)

* Frequencies < 0.03 will be ignored in analysis.

polymorphisms with Behçet's disease,[22] an autoinflammatory disease caused by environmental factors in genetically susceptible individuals. In that study we performed a series of functional studies and provided evidence that an individual carrying the CC genotype of rs755622 would show a significantly higher MIF mRNA level than those carrying the GC or GG genotype. Previous studies showed that the deletion of MIF in animal models leads to a decreased production of IL-1beta and IL-12[33] and that gene knockout prevents disease development in the collagen- and the adjuvant-induced arthritis models.[33,35] These observations confirm that MIF plays an important and upstream role in the inflammatory cascade by promoting the release of other inflammatory cytokines. The combined data suggests that SNP rs755622 GG genotype may play a protective role (anti-inflammatory response) by down-regulating MIF expression and thereby regulating the production of inflammatory cytokines. Stratification analysis showed an association between certain clinical findings such as vitiligo, alopecia, tinnitus, and headache with SNP rs755622.

Although we did not observe an association between rs2096525 with susceptibility to VKH syndrome, a stratification analysis according to certain clinical findings showed an association of rs2096525 with the headache or vitiligo subgroup, suggesting that this SNP may be a risk factor for both manifestations in this disease. VKH syndrome is thought to be caused by an autoimmune response directed against melanocytes and the clinical symptoms observed are found in certain organs containing melanocytes. Apart from the skin, neural crest-derived melanocytes are found in noncutaneous places such as the eye (choroid, iris, ciliary body), ear (vestibular organ, cochlea), and in the meninges of the brain, which may explain the association of MIF polymorphisms with disease expression at these various locations. In this study, the number of patients with certain clinical findings in subgroups are limited. Further studies with more patients in subgroups are needed to analyze MIF expression and genotype, to help understand etiology of clinical manifestations in VKH syndrome.

A combined rs755622/rs2096525 haplotype analysis revealed that the haplotype GT conferred a reduced risk of VKH syndrome, whereas the haplotype CT was associated with susceptibility to VKH syndrome, suggesting that there are VKH syndrome associated SNPs present in a locus between SNPs rs755622 and rs2096525.

It has been reported that VKH occurs most commonly in individuals who are Asian, Latino, Native American, or Asian Indian.[36] As the VKH patients tested only came from a Han Chinese population, the identified association in this study needs to be verified in other populations. On the other hand, we only examined the association of rs755622 and rs2096525 with VKH syndrome and didn't eliminate the possibility that other gene polymorphisms of MIF are associated with this syndrome.

In conclusion, our study identified a strong association of *MIF* polymorphisms with VKH syndrome. The GG genotype and G allele of rs755622 were defined as protective factors for the development of VKH and manifestation of certain clinical features. The mutant allele C of rs2096525 may be a susceptibility factor to headache and vitiligo in VKH syndrome. In addition, CT and GT haplotypes were also associated with VKH syndrome. Further studies are needed to investigate whether a manipulation of the MIF response in patients with a certain genotype may alter the course of their disease.

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