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Tyrosinase gene family and Vogt-Koyanagi-Harada disease in Japanese patients

Yukihiro Horie,[1] Yuko Takemoto,[1] Akiko Miyazaki,[1] Kenichi Namba,[1] Satoru Kase,[1] Kazuhiko Yoshida,[1] Masao Ota,[2] Yukiko Hasumi,[3] Hidetoshi Inoko,[4] Nobuhisa Mizuki,[3] Shigeaki Ohno[1]

[1]Department of Ophthalmology and Visual Sciences, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo, [2]Department of Legal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano, [3]Department of Ophthalmology, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, [4]Tokai University School of Medicine, Department of Basic Medical Science and Molecular Medicine, Isehara, Kanagawa, Japan

Purpose: The aim of the present study was to examine the genetic background of Vogt-Koyanagi-Harada (VKH) disease in a Japanese population by analyzing the tyrosinase gene family (TYR, TYRP1, and dopachrome tautomerase (DCT)).
Methods: 87 VKH patients and 122 healthy controls were genotyped using seven microsatellite markers on the candidate loci. We analyzed microsatellite (MS) polymorphisms at regions within tyrosinase gene family loci. In addition, the haplotype frequencies were also estimated and statistical analysis was performed. HLA-DRB1 genotyping was performed by the PCR-restriction fragment length polymorphism (RFLP) method.
Results: No significant evidence for an association was found. HLA-DRB1*0405 showed a highly significant association with VKH disease compared with the healthy controls (Pc=0.000000079), as expected.
Conclusions: We concluded that there is no genetic susceptibility or increased risk attributed to the tyrosinase gene family. Our results suggest the need for further genetic study and encourage a search for novel genetic loci and predisposing genes in order to elucidate the genetic mechanisms underlying VKH disease.

Vogt-Koyanagi-Harada (VKH) disease is one of the most frequent forms of uveitis in Japan, and is characterized as a panuveitis accompanied by neurological lesions such as headache and pleocytosis of the cerebrospinal fluid, skin lesions such as vitiligo, alopecia, and inner ear disturbances. This disease is considered to be an autoimmune disease against melanocytes [1]. Numerous studies have shown that about 90% of VKH patients have human leukocyte antigen (HLA) DRB1*0405 [2-4]. However, the true pathogenic gene related to VKH remains unclear. Recently, the genetic contribution of single nucleotide polymorphisms (SNPs) to autoimmune disease has been documented and shown to be consistently associated with numerous diseases, including Graves' disease, type 1 diabetes, and rheumatoid arthritis [5-7].

In earlier studies, melanocyte-specific proteins, tyrosinase-related protein (TRP) 1 and TRP2, induced an experimental autoimmune disease in Lewis rats that resembled human VKH disease [8]. Inflammation induced by TRP1 in Akita dogs also resembled human VKH disease [9]. Lymphocytes extracted from VKH disease patients were reactive to peptides derived from tyrosinase family proteins [10]. These studies suggest that tyrosinase family proteins may be responsible for human VKH disease.

As for the investigation of disease susceptibility genes, association studies are now primarily conducted with single nucleotide polymorphisms or microsatellites because they are ubiquitous in the genome. Microsatellite (MS) polymorphisms show a greater diversity than SNPs and have been widely used in both linkage and association studies of disease. Microsatellite linkage disequilibrium (LD) length is in the approximately 100 kb range [11] when compared with the shorter range for SNPs. Therefore, the advantage of microsatellite analysis is that a collection of relatively small numbers of polymorphic markers can make association analyses an immediate reality [12]. To investigate whether the tyrosinase gene family is responsible for VKH disease or not, we analyzed polymorphisms in MSs among tyrosinase gene family loci.

METHODS

We recruited 87 Japanese VKH patients and 122 healthy Japanese controls for this study. Patients were diagnosed according to the criteria of the American Uveitis Society [13] (at the uveitis clinic of Hokkaido University). All control subjects were healthy volunteers unrelated to each other or to the patients. Informed consent was obtained from all patients and controls, and the procedures used conformed to the tenets of the Declaration of Helsinki.

Genomic DNA was extracted by the QIAamp DNA Blood Mini Kit (Qiagen, Tokyo, Japan) or guanidine method. The tyrosinase gene family was selected as target regions: TYR (11q14-q21), TYRP1 (9q23), and DCT (13q32) [14]. Seven informative microsatellite markers in these regions which had polymorphisms [11] (D9S0128i, D9S0926i, D9S267, D11S0260i, D11S0529i, D13S0450i, and D13S0504i,) were

Correspondence to: Yukihiro Horie, MD, Department of Ophthalmology and Visual Sciences, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo 060-8638, Japan; Phone: +81-11-706-5944; FAX: +81-11-706-5948; email: y-horie@med.hokudai.ac.jp

selected to perform linkage analysis. These makers were distributed at the following distances from the tyrosinase gene family: TRY gene: D11S0529i, located between exon 2 and exon 3, D11S0260i, between exon 4, and exon 5; TYRP1 gene: D9S0128i, 70 kb telomeric, D9S0926i, 4 kb telomeric, D9S267, 200 kb centromeric; and DCT: D13S0450i, 120 kb centromeric, and D13S0504i, 30 kb telomeric.

Oligonucleotide primers for microsatellites were synthesized according to the previously described method [11]. PCR reactions were performed in a total volume of 12.5 µl containing PCR buffer, genomic DNA, 0.2 mM dinucleotide triphosphates (dNTPs), 0.5 µM primers, and 0.35 U Taq polymerase. The reaction mixture was subjected to 5 min at 94 °C, then 35 cycles of 1 min for denaturing at 94 °C, 1 min for annealing, 2 min for extension at 72 °C, and 10 min for final elongation at 72 °C using a PCR thermal cycler, GeneAmp System 9700 (Applied Biosystems, Foster City, CA). PCR annealing temperatures, depending on the primers used, are indicated in Table 1. Each forward primer was labeled at the 5' end with 6-FAM (Sigma, Japan), NED, or VIC (Applied Biosystems). To determine the number of microsatellite repeats, PCR-amplified products were denatured for 2 min at 97 °C mixed with formamide, and electorphoresed using an ABI3130 Genetic Analyzer (Applied Biosystems). Fragment length analysis was performed by an ABI3130 automatic sequencer (Applied Biosystems) with GeneScan software (Applied Biosystems). The number of microsatellite repeats was estimated with GeneMapper v3.5 software (Applied Biosystems) using GS500(-250)Liz (Applied Biosystems) as a size marker.

HLA-DRB1 genotyping by the PCR-RELP method: Genomic amplification of the HLA-DRB1 gene was performed using local primers, as previously described [15]. After PCR amplification, 7 micro liter of PCR products were digested with 2-5 units of allele-specific restriction endonucleases at an appropriate temperature for 3 h in an incubator. These digested products were subjected to electrophoresis in 12% polyacrylamide gels, and HLA genotypes were determined on the basis of the obtained specific band pattern (PCR-RFLP method) [15].

Statistical analysis: Allele frequencies were calculated by direct counting. The significance of association was tested using Fisher's exact method. The probability of an association was corrected with the Bonferroni inequality method, i.e., by multiplying the p-values obtained by the number of alleles compared. The haplotypes frequencies were estimated using the SNPAlyze program version 5.1 software (Dynacom, Yokohama, Japan), which uses the Expectation-Maximization (EM) algorithm. Where there were incomplete genotype data, potential haplotype reconstructions were inferred, given the genotype data observed at the other loci. The Chi-square test was used to detect the difference between VKH patients and healthy controls in haplotype frequencies. Permutation tests were used to assess the significance of VKH patient and healthy control haplotype frequency differences [16].

TABLE 1.

Marker	GenBank accession number	Repeat unit	Primers	Sequences(5' – 3')	Tm(ºC)
D9S0128i	AB133511	TG	5-primer	AGTTAGACAGAACTGATATGGCAC	59
			3-primer	GACTGCTTCCAGACTAAACTGTAG	
D9S0926i	AB133446	TG	5-primer	AGTATTGACCAAATGTCAGTTGTC	58
			3-primer	CAAGCAACTTGTATACGTTTAGAAG	
D9S267	Z23807	TG	5-primer	TTACTGATTGAGGCAACCA	58
			3-primer	GCAATGTTTTGGGCTCT	
D11S0529i	AB143188	AC	5-primer	AACGTGATCTAATTGGCTATTAC	57
			3-primer	TATAAGCCATGAAATAACGAGT	
D11S0260i	AB139945	AC	5-primer	TTCTTAGGTTGCTCAGTATGAT	56
			3-primer	CATTAGAGAACAGCATTTCTAAAT	
D13S0450i	AB146899	CA	5-primer	CTCACTTTACCAGTGAGAACAC	59
			3-primer	GATCCAAGGAGTCTGATTCTAC	
D13S0504i	AB147548	GGAA	5-primer	AAGCCAAAGCATGCTAGTA	60
			3-primer	TTAGTTGCCAGTTGCTGAC	

RESULTS

Table 2 shows the allele frequencies in VKH patients and healthy controls at seven microsatellites. All alleles in each microsatellite marker were named on the basis of the amplified fragment length. Among the seven microsatellite markers, the frequency of allele 162 of D9S267 (55.1% in VKH patients and 65.2% in healthy controls) was shown significant association (p=0.039). However, this increase did not reach significance when the p-value was corrected via multiplication by the number of alleles (pc=0.39). Table 3 displays the results of the estimated haplotype frequency analyses for microsatellite markers at TYR loci. The estimated haplotype frequencies for VKH patients and healthy controls are shown for configurations as well as chi-square, p-value and permutation tests. There was no significant difference between VKH patients and healthy controls in the TYR loci, nor in haplotype frequency.

The phenotype frequency of HLA-DRB1*0405 was 61 (70.1%) in VKH patients, which was remarkably higher than that of healthy controls (35 (28.6%), pc=0.000000079; Table 4).

DISCUSSION

The tyrosinase gene family encodes the enzymes involved in melanin formation and is expressed specifically in melanocytes [17,18]. Yamaki et al. suggested that VKH disease may be induced by tyrosinase family proteins [10]. We speculated that polymorphisms within the tyrosinase gene family may be related to VKH disease. As previously described, the candidate tyrosinase gene family, which codes for melanosome proteins [14], is a class of genes that have been associated with depigmentation and ocular developmental defects. In previous studies, mutations of TYR and TYRP1 caused oculocutaneous albinism (OCA) 1, OCA3, and microphthalmia [19-22]. Recently, it has been reported that mutation of DCT may cause microcoria [23]. These mutations include missense, nonsense, frameshift, and splice site mutations, and deletion of the entire coding sequence [24,25]. At present, six polymorphisms in TYR and seven polymorphisms in TYRP1 have been identified (Albinism Database).

In the present study, we examined 87 VKH patients and 122 healthy controls for tyrosinase gene family loci. None of these regions showed evidence for a significant association with VKH disease. D9S267 showed a marginally significant p-value (p<0.05). However, this did not reach significance when the P-value was corrected (pc=0.39); furthermore, the

Table 2. Genotype frequency of VKH patients and healthy controls at tyrosinase gene family loci

Chromosome	Marker	Allele size	VKH patients (2n=174)	(%)	Healthy controls (2n=244)	(%)	R.R.	P	Pc
Chr 9									
	D9S0128i	257	2	(1.1)	0	(0.0)	0.00	0.09	0.65
		259	117	(67.2)	178	(73.0)	0.76	0.21	1.45
		261	1	(0.6)	3	(1.2)	0.46	0.50	3.49
		263	0	(0.0)	1	(0.4)	0.00	0.40	2.79
		265	9	(5.1)	5	(2.0)	2.61	0.08	0.56
		267	33	(19.0)	40	(16.4)	1.19	0.50	3.46
		269	12	(6.9)	17	(7.0)	0.99	0.98	6.84
	D9S0926i	297	0	(0.0)	1	(0.4)	0.00	0.40	4.77
		301	15	(8.6)	13	(5.3)	1.68	0.18	2.21
		303	2	(1.1)	0	(0.0)	0.00	0.09	1.12
		305	0	(0.0)	1	(0.4)	0.00	0.40	4.77
		307	4	(2.3)	8	(3.3)	0.40	0.13	1.55
		309	10	(5.7)	9	(3.7)	0.91	0.85	10.21
		311	46	(26.4)	60	(24.6)	1.10	0.67	8.03
		313	86	(49.4)	140	(57.4)	0.73	0.11	1.29
		315	7	(4.0)	7	(2.9)	1.42	0.52	6.22
		317	3	(1.7)	4	(1.6)	1.05	0.95	11.36
		319	0	(0.0)	1	(0.4)	0.00	0.40	4.77
		321	1	(0.6)	0	(0.0)	0.00	0.24	2.83
	D9S267	158	0	(0.0)	1	(0.4)	0.00	0.40	3.98
		160	14	(8.0)	14	(5.7)	1.44	0.35	3.52
		162	96	(55.1)	159	(65.2)	0.66	0.04	0.39
		164	6	(3.4)	11	(4.5)	0.76	0.59	5.89
		166	3	(1.7)	5	(2.0)	0.84	0.81	8.11
		168	9	(5.2)	4	(1.6)	3.27	0.04	0.40
		170	41	(23.6)	45	(18.4)	1.38	0.19	1.87
		172	4	(2.3)	3	(1.2)	1.89	0.40	4.01
		174	1	(0.6)	0	(0.0)	0.00	0.24	2.36
		178	0	(0.0)	2	(0.8)	0.00	0.23	2.31
Chr 11									
	D11S0529i	404	1	(0.6)	0	(0.0)	0.00	0.24	2.36
		408	1	(0.6)	2	(0.8)	0.70	0.77	7.70
		410	1	(0.6)	3	(1.2)	0.46	0.50	4.98
		412	18	(10.3)	20	(8.2)	1.29	0.45	4.51
		414	50	(28.7)	60	(24.6)	1.24	0.34	3.43
		416	56	(32.2)	83	(34.0)	0.92	0.70	6.95
		418	16	(9.2)	32	(13.1)	0.67	0.22	2.15
		420	28	(16.1)	40	(16.4)	0.98	0.93	9.34
		422	3	(1.7)	3	(1.2)	1.41	0.68	6.75
		424	0	(0.0)	1	(0.4)	0.00	0.40	3.98
	D11S0260i	232	25	(14.4)	32	(13.1)	1.11	0.71	4.28
		234	20	(11.5)	38	(15.6)	0.70	0.23	1.41
		236	56	(32.2)	59	(24.1)	1.49	0.07	0.43
		238	70	(40.2)	108	(44.3)	0.85	0.41	2.47
		240	2	(1.1)	4	(1.6)	0.70	0.68	4.07
		242	1	(0.6)	3	(1.2)	0.46	0.50	2.99
Chr 13									
	D13S0450	383	0	(0.0)	1	(0.4)	0.00	0.40	3.98
		387	32	(18.4)	51	(20.9)	0.85	0.53	5.26
		389	1	(0.6)	6	(2.5)	0.23	0.14	1.39
		391	2	(1.1)	0	(0.0)	0.00	0.09	0.93
		393	41	(23.6)	43	(17.6)	1.44	0.14	1.35
		395	67	(38.5)	107	(43.9)	0.80	0.27	2.74
		397	15	(8.6)	21	(8.6)	1.00	1.00	9.96
		399	15	(8.6)	10	(4.1)	2.21	0.06	0.55
		401	1	(0.6)	4	(1.6)	0.35	0.32	3.24
		403	0	(0.0)	1	(0.4)	0.00	0.40	3.98
	D13S0504	426	6	(3.4)	11	(4.5)	0.76	0.59	4.12
		430	31	(17.8)	53	(21.7)	0.78	0.33	2.28
		434	85	(48.9)	110	(45.1)	1.16	0.45	3.13
		438	31	(17.8)	38	(15.6)	1.18	0.54	3.80
		442	12	(6.9)	27	(11.1)	0.60	0.15	1.04
		446	7	(4.0)	5	(2.0)	2.00	0.23	1.64
		450	2	(1.1)	0	(0.0)	0.00	0.09	0.65

Chr represents Chromosome. R.R. represents relative risk. Pc represents corrected P-values by Bonferroni's correction.

remaining MS marker (D9S0128i and D9S0926i) at this locus did not yield increased association. To exclude an association with VKH at TYR loci, we also estimated and analyzed haplotype frequencies. This haplotype analysis did not show an association at the level of TYR either (the haplotype 259-313-162; p=0.058). The allele 162 of D9S267 was also included in the haplotype which was the lowest p-value. Considering about the over collection of the p-value, the allele 162 of D9S267 may be associated with VKH disease. According to previous reports, T-cells established from VKH patients responded to peptides derived from tyrosinase family proteins, implying a role in VKH disease [8-10]. Our results did not contradict these reports because VKH disease may be triggered by the breakdown of self-tolerance, in a similar way to other autoimmune diseases [26,27].

We also performed HLA-DRB1 genotyping, and DRB1*0405 was strongly associated with VKH (pc=0.000000079). This result was almost the same as that previously reported [2-4]. We could not identify any association of sites around the tyrosinase gene family loci between VKH patients and healthy controls.

In conclusion, we speculated that polymorphisms in MSs among the tyrosinase gene family loci of VKH patients were different from those of healthy controls, but no significant difference was noted in both single microsatellite marker analysis and haplotype analysis. HLA-DRB1*0405 showed a highly significant association (pc=0.000000079), as expected. The mutational characterization of genes involved in VKH disease will provide additional insight into the molecular mechanisms underlying this common uveitis in the Japanese population.

Table 3. Estimated haplotype frequencies for TYR loci

1 - 2 - 3	All cases (%)	VKH patients (n=87; %)	Healthy controls (n=122; %)	Chi-square	p-value	permutation p-value
259-313-162	32.25	27.43	37.12	4.30	0.038	0.058
259-311-162	7.43	8.25	6.62	0.40	0.528	0.643
259-313-170	7.18	7.02	7.21	0.01	0.941	0.958
267-311-162	4.20	2.18	6.25	3.87	0.049	0.174
259-313-160	3.25	4.97	1.25	5.17	0.023	0.085
267-311-170	3.20	5.52	1.31	6.06	0.014	0.094
269-301-162	2.54	3.19	2.08	0.51	0.477	0.535
259-311-170	2.37	3.02	2.25	0.24	0.624	0.777
265-311-162	2.04	3.30	0.40	5.39	0.020	0.118
267-313-162	2.02	1.92	1.86	0.00	0.964	0.985
259-311-160	1.76	1.65	2.12	0.12	0.730	0.786
259-313-164	1.67	0.34	2.69	4.76	0.029	0.159
267-309-162	1.60	2.08	0.93	0.98	0.323	0.438
259-315-170	1.53	1.51	1.56	0.00	0.967	0.973
259-309-170	1.35	2.52	0.44	3.41	0.065	0.144
259-313-172	1.15	1.95	0.45	2.15	0.143	0.273
259-313-168	1.14	1.28	1.02	0.06	0.804	0.928
267-301-170	1.13	1.66	0.33	2.04	0.153	0.274
259-307-162	1.12	0.57	1.54	0.84	0.359	0.509
259-317-162	1.10	1.15	0.90	0.06	0.800	0.778

Association analysis of haplotype in each candidate loci. All haplotypes with a frequency >1% are displayed. Numbers in the heading are as follows: 1 represents D9S0128i, 2 represents D9S0926i, 3 represents D9S267. p-value based on chi-square distribution. Permutation p-values based on 10,000 permutations.

Table 4. HLA-DR4 phenotype frequency in Japanese VKH patients and healthy controls

DR serotype	DRB1 genotype	VKH patients (n=87)	VKH patients (%)	Healthy controls (n=122)	Healthy controls (%)	R.R.	P	Pc
DR4		71	(81.6)	35	(28.7)	11.03	4.60E-14	1.10E-12
	DRB1*0401	0	(0.0)	4	(3.3)	0	0.09	2.20
	DRB1*0403	3	(3.4)	8	(6.6)	0.51	0.32	8.03
	DRB1*0405	61	(70.1)	35	(28.7)	5.83	3.10E-09	7.90E-08
	DRB1*0406	2	(2.3)	4	(3.3)	0.69	0.68	16.90
	DRB1*0407	0	(0.0)	3	(2.5)	0	0.14	3.52
	DRB1*0408	0	(0.0)	2	(1.6)	0	0.23	5.75
	DRB1*0410	10	(11.5)	2	(1.6)	6.9	0.01	0.13
not DR4		28	(32.2)	115	(94.3)	0.03	1.80E-21	4.40E-20

Not DR4 means the number of the people who have the HLA-DR alleles other than DR4. R.R. represents relative risk. Pc represents corrected P-value by Bonferroni's correction.

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