

# Correlation between visual acuity and human leukocyte antigen (HLA)-DRB1\*04 in patients with Vogt-Koyanagi-Harada disease

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## Research article

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# Abstract

**Background** Human leukocyte antigen (HLA)-DRB1\*04 is well known to be associated with the course of Vogt-Koyanagi-Harada (VKH) disease. The aim of this study was to investigate the relationship between visual prognosis and HLA-DRB1\*04 alleles during systemic corticosteroid therapy in patients with VKH disease. **Methods** This retrospective case series included 47 eyes from 29 consecutive treatment-naïve patients who received systemic corticosteroid therapy. Visual acuity, sex, refractive error, central retinal thickness (CRT), central choroidal thickness (CCT), and duration from onset to treatment were measured at initial and final visits. Mean values of parameters were compared with each visit. Typing was performed by polymerase chain reaction amplification with sequence-specific primers. **Results** Linear regression showed significant differences in logMAR best-corrected visual acuity among the three groups of homozygotes, heterozygotes, and normal subjects between baseline ( $p < 0.01$ ) and final visit ( $p = 0.012$ ). No significant difference was detected between the three groups in age, sex, refractive error, CRT, CCT, or duration from onset to treatment. **Conclusions** The present study revealed a correlation between HLA04 allele type and visual acuity logMAR before and after initiating systemic corticosteroid therapy in treatment-naïve patients with VKH disease.

## Background

Vogt-Koyanagi-Harada (VKH) disease is a systemic disorder considered to represent an autoimmune disease against melanocytes [1]. The human leukocyte antigen (HLA) system is the locus of genes that encode for the major histocompatibility complexes (MHC), cell surface molecules mediating interactions with leukocytes [2]. HLA therefore plays a key role in immune systemic function as well as in the pathogenesis of autoimmune diseases, including VKH, especially HLA-DRB1\*04 [3]. In the eye, the disease presents as acute bilateral granulomatous panuveitis, which responds to systemic corticosteroid therapy and shows a generally good visual prognosis [4]. However, at least among Japanese patients, no reports have investigated correlations between HLA04 allele type and visual outcomes before and after steroid treatment in the real world.

## Methods

This retrospective case series investigated 47 eyes from 29 consecutive patients with treatment-naïve VKH disease who visited the ophthalmology department at Osaka City University Hospital from December 2009 to January 2019 and were followed-up for more than 6 months after starting systemic corticosteroid therapy. VKH disease was diagnosed according to the criteria of Sugiura [5] and the VKH Disease Committee [6]. None of the patients had any medical or ocular history at the initial visit. Central retinal thickness (CRT) and central choroidal thickness (CCT) changes were assessed by vertically and horizontally oriented enhanced depth imaging optical coherence tomography (EDI-OCT) of the macula (Spectralis HRA+OCT Heidelberg Engineering, Heidelberg, Germany) for up to 3 months after treatment. Measurements of CRT and CCT from each eye were then reconfirmed by three experts (NM, MT, and SH) by checking OCT images. Patients received corticosteroid regimens of pulse therapy according to the

timing of the first visit. In 27 patients administered intravenous methylprednisolone at 1,000 mg/day for 3 consecutive days followed by tapering of oral prednisolone (i.e., pulse therapy), as described previously [7]. Oral prednisolone was temporarily increased or restarted if there was an anterior or posterior recurrence of VKH disease. Oral cyclosporine was not administered in the present study. Recurrences were defined as the recurrence of anterior chamber cells and/or posterior segment lesions detected by ophthalmic examinations. The remaining two patients were administered intravenous prednisolone, which was started at and tapered from 100 mg/day (i.e., high-dose therapy), as described previously [8].

HLA typing by polymerase chain reaction amplification with sequence-specific primers (PCR-SSP), typing specificity is part of the amplification step[9].

Approval for this study was obtained prior to the start of the study from the institutional review board at Osaka City University in Japan. Written informed consent for the storage of patient information in the hospital database and use in research was provided by all patients enrolled in the study. The study was performed according to the tenets of the Declaration of Helsinki.

Statistical analyses were performed using SPSS Statistics version 22 software (IBM Japan, Tokyo, Japan). Values of  $P < .05$  were considered statistically significant.

## Results

### Visual outcomes

In terms of visual acuity, mean logMAR best-corrected visual acuity (BCVA) values at baseline and at final visit were  $0.42 \pm 0.59$  and  $0.05 \pm 0.37$  in HLA-DRB1\*04 -/-,  $-0.14 \pm 0.32$  and  $-0.11 \pm 0.10$  in HLA-DRB1\*04 +/-, and  $0.008 \pm 0.14$  and  $-0.13 \pm 0.05$  in HLA-DRB1\*04 +/+, indicating significant visual improvements over time from baseline to final visit in all three groups ( $p = 0.017$ ,  $p < 0.01$ ,  $p = 0.011$ , respectively). In CCT, mean values before treatment and at final visit after treatment were  $489.4 \pm 258.4 \mu\text{m}$  and  $285.2 \pm 159.4 \mu\text{m}$  in HLA-DRB1\*04 -/-,  $557.5 \pm 197.5 \mu\text{m}$  and  $356.1 \pm 135.5 \mu\text{m}$  in HLA-DRB1\*04 +/-,  $517.5 \pm 190.5 \mu\text{m}$  and  $375.8 \pm 211.2 \mu\text{m}$  in HLA-DRB1\*04 +/+, suggesting changes compared with baseline ( $p = 0.110$ ,  $p < 0.01$ ,  $p = 0.173$ , respectively). In only the HLA-DRB1\*04 +/- group, mean post-treatment CCT values were significantly decreased compared with baseline CCT.

### Correlations with HLA-DRB1\*04 allele

HLA-DRB1\*04 typing was performed for 5 patients (10 eyes) among normal subjects (HLA-DRB1\*04 -/-), 16 patients (31 eyes) among heterozygotes (HLA-DRB1\*04 +/-), and 8 patients (16 eyes) among homozygotes (HLA-DRB1\*04 +/+). Baseline patient characteristics are summarized in Table 1. Significant differences were seen from linear regression among the three groups of homozygotes, heterozygotes, and normal subjects in logMAR BCVA at baseline (Figure 1;  $p < 0.04$ ).

Clinical parameters compared to post-treatment among the three groups are summarized in Table 2. First, linear regression showed a significant relationship among the three groups of homozygotes, heterozygotes, and normal subjects and logMAR BCVA at final visit (Figure 2;  $p = 0.016$ ). This was consistent with the finding of no difference among the three groups with regard to choice of treatment regimen according to the period during which the patient visited the clinic (i.e., large dose, earlier; pulse therapy, later). Second, the number of post-treatment recurrences showed no significant difference between groups.

Visual prognosis of the 47 eyes examined was mild to moderate cataract in 4 eyes and drug-controllable glaucoma in 3 eyes after treatment, none of which required surgery during follow-up. No differences in ocular complication rates were seen among groups.

## Discussion

The present study revealed a correlation between HLA04 allele type and visual outcomes before and after initiating systemic corticosteroid therapy in treatment-naïve patients with VKH disease.

Previous studies have reported that HLAs are cell surface molecules mediating interactions with leukocytes. Therefore, HLA plays an important role in immune system function as well as in the pathogenesis of autoimmune diseases, including VKH. Almost 40 years ago, an association of HLA-BW22J and VKH was reported [9]. More articles have since been published on the association of different types of HLA and VKH. Among these, the HLA-DR4 serotype and its corresponding allele HLA-DRB1\*04 have mostly been investigated [10]. A meta-analysis by Shi et al. confirmed the association between VKH and HLA-DR4/DRB1\*04, and found the strength of association differed between different ethnic groups, and identified HLA-DRB1\* 0404, 0405 and 0410 as risk sub-alleles, and 0401 as a protective sub-allele [11,12].

In this study, a significance result was found from linear regression among the three groups of homozygotes, heterozygotes, and normal subjects in logMAR BCVA at baseline.

For groups not having HLA-DR4/DRB1\*04, the diagnosis may be not typical for VKH. However, both homozygous and heterozygous groups were above the regression line, which was considered to have a certain statistical meaning.

In a study of type 1 diabetes in Japanese, disease susceptibility differed between homozygotes and heterozygotes [13]. A similar situation may also apply to VKH patients. Even before and after steroid treatment, homozygotes showed the best post-treatment visual acuity. Normal subjects (no HLA-DRB1\*04 allele) had the poorest visual acuity after treatment. This indicates that therapeutic response and sensitivity to steroid treatment may depend on allele HLA-DRB1\*04. Understanding the pathogenesis underlying these results is difficult. However, previous reports such as haplotype linkage disequilibrium studies have suggested associations with genes closely related to immunity and inflammation, such as IKBL gene and TNFA gene present in HLA class III [14,15,16]. Allele HLA-DRB1\*04 is a disease-associated

gene frequently found in VKH, but this study considered the possibility of disease resistance. On the other hand, another report showed the presence of the HLA-DRB1\*04 allele is related to the prolongation of VKH in previous research in Japanese patients [17]. We know that allele HLA-DRB1\*04 is the key to VKH, but the details remain unclear. According to a previous report, CCT correlates with the vision prognosis in VKH [18]. However, the small number of cases was problematic in this case series, and the correlation between allele HLA-DRB1\*04 and CCT was not determined.

In the future, the complete genetic predisposition of VKH is expected to be elucidated, leading to the development of new treatments and preventions.

We acknowledge these potential issues as well as the need for future worldwide studies into the correlations between allele HLA-DRB1\*04 and visual outcomes and rulein VKH.

## **Conclusion**

The present study revealed a correlation between HLA04 allele type and visual acuity logMAR before and after initiating systemic corticosteroid therapy in treatment-naïve patients with VKH disease.

## **Abbreviations**

Human leukocyte antigen: HLA

Vogt-Koyanagi-Harada: VKH

## **Declarations**

## **Ethics approval and consent to participate**

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

## **Consent for publication**

Not applicable

## **Availability of data and materials**

## **Competing Interests**

The authors declare that they have no competing interests.

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## Authors' contributions

M. T. wrote the main text of the manuscript and prepared the figures. Datasets were prepared by M. T. and N. M. T. K. and S. H. reviewed the manuscript and checked the statistical analysis advice.

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## Authors' information

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## Tables

**Table 1.** Pre-treatment parameters and baseline patient characteristics

HLA-DRB1*04 allele type	HLA- DRB1*04 -/-	HLA- DRB1*04 +/-	HLA-DRB1*04 +/+	p-value
Age (years)	47.83±23.78	50.73±17.53	49.52±14.24	0.793*
Sex (male:female)	3:3	9:5	3:5	0.471**
Refractive error (diopters)	-0.93±17.15	-3.31±2.99	-2.23±2.74	0.81*
CRT (μm)	489.4±258.4	557.5±197.5	517.5 ±190.5	0.867*
CCT (μm)	210±297	310±317	518±191	0.861*
Duration from onset to treatment (days)	18.7±12.68	16.07±11.20	19.25±9.48	0.586*

\* Kruskal-Wallis test

\*\* Fisher's exact test

CRT, central retinal thickness; CCT, central choroidal thickness.

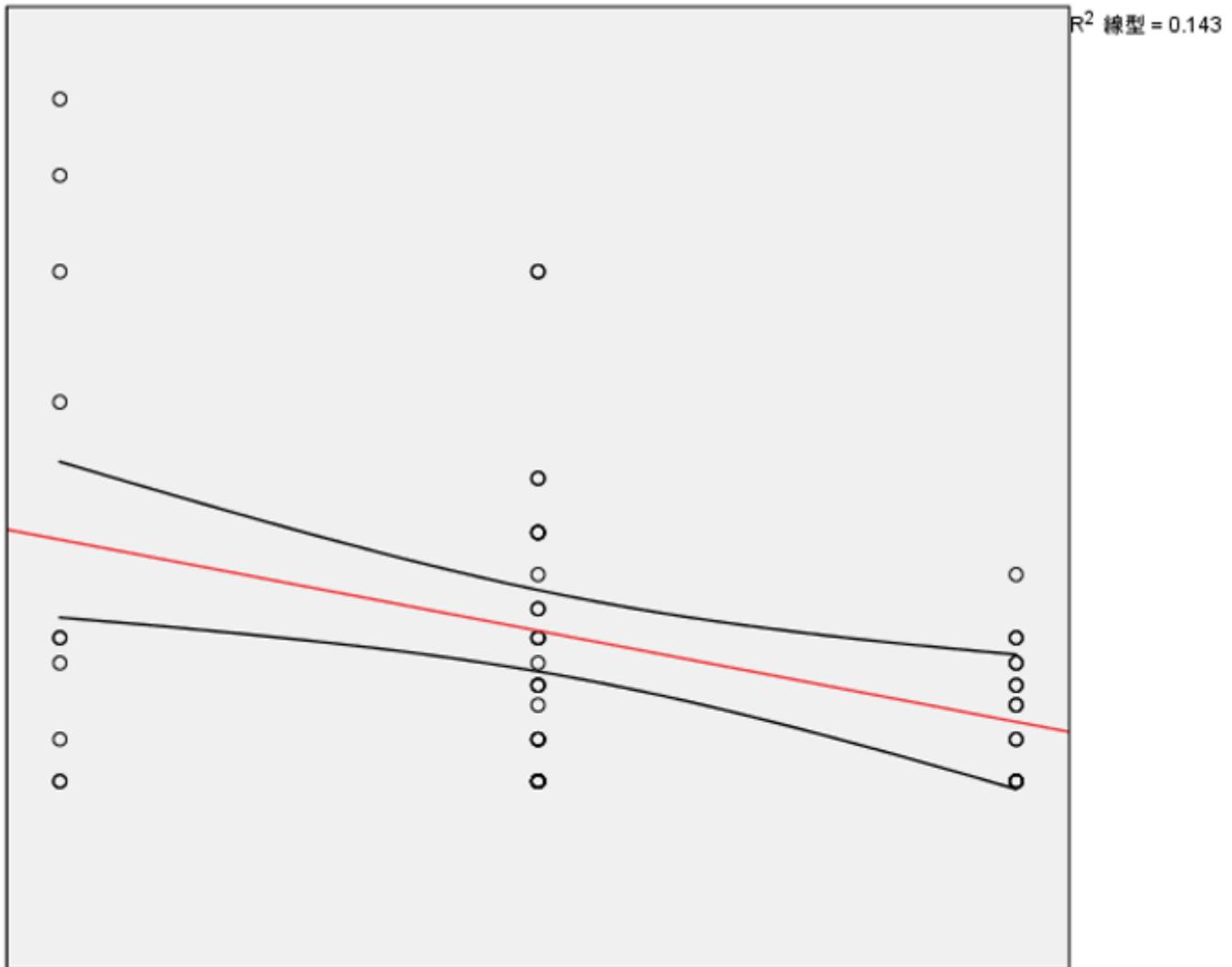
**Table 2.** Clinical parameters compared to post-treatment among the three groups

	Patient ID	Duration from onset to treatment (days)	Follow-up duration (days)	Recurrence (R/L +: 1; +: 0)	Post-treatment ocular complications (R/L +: 1; +: 0)	Treatment
HLA-DRB1*04 +/+	9	37	61	0/0	0/0	pulse
	11	23	114	0/0	0/0	pulse
	13	14	214	0/0	0/0	STTA (40 mg), pulse
	16	11	369	0/0	0/0	pulse
	20	12	1645	0/0	0/0	pulse
	23	25	246	0/0	0/cataract	pulse
	25	9	14	0/0	0/0	pulse
	27	23	1483	0/0	0/0	pulse
HLA-DRB1*04 +/-	2	7	10	0/0	0/0	pulse
	4	14	28	0/0	0/0	STTA (40 mg), pulse
	5	40	546	0/0	0/cataract	pulse
	8	19	77	0/0	0/0	pulse
	10	12	119	-/0	0/0	pulse
	12	21	264	0/0	0/0	pulse
	14	39	251	0/0	0/0	pulse
	17	6	566	0/0	0/0	PSL 40 mg, pulse
	18	11	1755	0/0	0/0	pulse
	19	6	20	0/0	0/0	pulse
	21	8	273	0/0	0/0	pulse
	22	23	407	0/0	0/0	pulse
	26	6	1509	0/0	0/0	pulse
	28	14	222	0/0	0/0	pulse
29	18	3151	0/0	0/0	pulse	
HLA-DRB1*04 -/-	1	16	10	0/0	0/0	pulse
	3	13	315	0/0	cataract/ cataract	pulse
	6	17	42	0/0	0/0	STTA (40 mg), pulse
	7	20	95	0/0	0/0	pulse
	15	6	151	0/0	0/0	PSL 30 mg pulse
	24	42	3051	0/0	0/0	pulse
P-value		0.586*	0.69*			

\* Kruskal-Wallis test

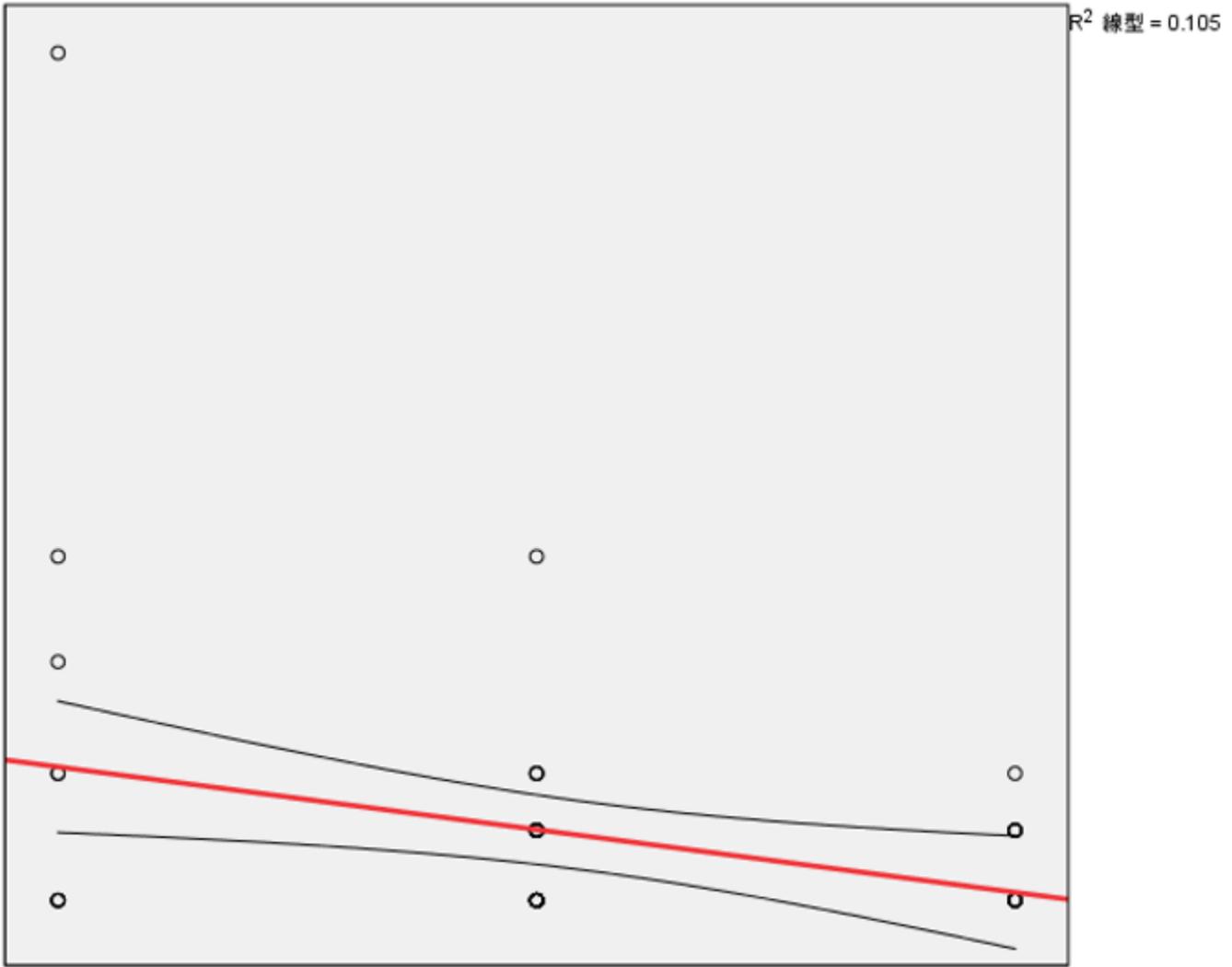
STTA, sub-tenon triamcinolone acetate.

# Figures



**Figure 1**

Linear regression of BCVA at baseline LogMAR best-corrected visual acuity (BCVA) before treatment for Vogt-Koyanagi-Harada (VKH) disease on linear regression among the three groups (homozygotes (HLA-DRB1\*04 +/+), heterozygotes (HLA-DRB1\*04 +/-), and normal subjects (HLA-DRB1\*04 -/-)).



**Figure 2**

Linear regression of BCVA at final visit LogMAR best-corrected visual acuity (BCVA) at final visit after treatment for Vogt-Koyanagi-Harada (VKH) disease on linear regression among the three groups (homozygotes (HLA-DRB1\*04 +/+), heterozygotes (HLA-DRB1\*04 +/-), and normal subjects (HLA-DRB1\*04 -/-)).