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Association of human leukocyte antigen alleles and supertypes with immunogenicity of oral rotavirus vaccine given to infants in China

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Abstract

Rotavirus (RV) vaccines show distinct immunogenicity in dozens of clinical trials, which is associated with multiple host and environmental factors. Previous research has demonstrated that the highly polymorphic human leukocyte antigen (HLA) system plays an essential role in regulating immune response to a variety of vaccines. This study aims to investigate the relationship between HLA polymorphisms and immunogenicity of RV vaccine.

A nested case-control study was carried out among infants enrolled in phase III clinical trial of trivalent human-lamb reassortant vaccine (RV3) in Henan province, China. Serum RV specific immunoglobulin A (RV-IgA) was detected before and after a 3-dose vaccination series, followed by calculation of seroconversion rates. Seroconversion was defined as a 4-fold or greater increase in RV-IgA titers between pre-vaccination and 1-month post-dose 3 vaccination. The infants who seroconverted were defined as responders, and the others without seroconversion were considered as non-responders. Their HLA genotypes were obtained by using the sequence-based typing method. The HLA allele and supertype frequencies of 2 groups were analyzed statistically.

Eighty-three of 133 infants seroconverted after vaccination. Twenty-one HLA-A, 45 HLA-B, 24 HLA-Cw, 29 HLA-DRB1 and 16 HLA-DQB1 distinct alleles were detected. The frequency of HLA-B*4001 (corrected $P = .01$, adjusted OR = 0.152, 95% CI = 0.048–0.475) in non-responder group was significantly higher than that in responder group. Furthermore, significant association was found between HLA-B44 supertype (corrected $P = .02$, adjusted OR = 0.414, 95% CI = 0.225–0.763) and RV non-response.

Certain HLA allele (HLA-B*4001) and supertype (HLA-B44) are potentially associated with non-response after immunization with the novel RV3 vaccine in Chinese infants.

Abbreviations: HLA = human leukocyte antigen, RV = Rotavirus, RV3 = trivalent human-lamb reassortant vaccine, RV-IgA = rotavirus specific immunoglobulin A.

Keywords: human leukocyte antigen (HLA), immunogenicity, immunoglobulin A (IgA), rotavirus vaccine

1. Introduction

Rotavirus (RV) is a major cause of severe diarrhea in children under 5 worldwide, leading to an estimated 215,000 children death annually.[1] Vaccination is an essential tool to ease this burden. The World Health Organization (WHO) recommends that RV vaccines should be included in national immunization programs globally.[2] Currently, 2 live oral attenuated RV vaccines, Rotarix (RV1, GlaxoSmithKline Biologics) and RotaTeq (RV5, Merck & Co.), are implemented in national immunization programs of 93 countries.[3] Besides, 4 RV vaccines, Rotavin-M1 (Vietnam), ROTAVAC (India), ROTASIL (India), and LLR (China) are licensed in national market.[4]

Previous studies indicate that RV vaccines showed distinct immunogenicity and efficacy in different clinical trials.[5] Seroconversion rates of Rotarix are 84% to 95% in Finland[6] and France,[7,8] whereas they are 30% to 40% lower in India[9] and South Africa,[7,10] where the vaccine is needed most. In China, the seroconversion rate of Rotarix is 71%,[7] lower than that in Finland and France. Several factors may contribute to this different performance, including maternal antibodies,[10,11] gut microbiota,[12] co-infections with enterovirus,[13] environmental enteropathy,[14] and so on. However, the exact reasons remain uncertain.

Host genetic factors play important roles in vaccine-induced immunity.[15] Human leukocyte antigen (HLA) complex, encoded by highly polymorphic genes that are located on chromosome 6, is indispensable in innate and adaptive immunity.[16] It is well known that HLA molecules are essential in foreign antigen presentation to T-cell receptors (TCRs), and may be crucial in the immune recognition and specific serological response.[17] HLA alleles are more changeable due to genetic variation within the peptide-binding site, so that they may

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influence the ability to bind and present different peptide antigens, affecting the host immune response to antigen.[18]

In this paper, a nested case-control study was carried out among infants enrolled in phase III clinical trial of trivalent human-lamb reassortant vaccine (RV3) in China. Herein, the association of genetic variations in the HLA region with immune response to RV3 was investigated.

2. Methods

2.1. Study design

In this study, samples collected from infants enrolled in the clinical trial of RV3 were used. The trial was performed in Henan province of China, in accordance with protocol, Good Clinical Practice and other relevant regulatory guidelines. The Ethics Committee of the Henan Provincial Centers for Disease Control and Prevention reviewed and approved the protocol. The study is registered at ClinicalTrials.gov with NCT# 01738074. Parents or legal guardians of engaged infants provided written informal consent before the study.

Infants inoculated with other vaccine within7days or received immunosuppressant after birth were ineligible to participate. Besides, infants were excluded from the study if they had an allergy reaction to any of the vaccine components. Infants with any immunosuppressive or immunodeficient condition, congenital disorder or serious chronic illness were also excluded.

All enrolled infants received 3 doses of RV3 from 6 to 13 weeks of age with an interval of 1 month between any 2 consecutive doses. They received routine vaccines according to the national schedule in China 1 week before or after RV vaccination. Blood samples were collected before the administration of the first dose of vaccine and 1 month after the third dose of vaccine. Serum anti-RV IgA were measured by serological assay. IgA titer higher or equal to 30U/mL was considered positive. Otherwise, IgA titer was assigned a value of 1.[19] Vaccine seroconversion was defined as a 4-fold or greater increase in RV specific immunoglobulin A (RV-IgA) titer 1 month after the third dose of vaccination than at baseline. Hereafter, we refer to infants who seroconverted as responders and infants who failed to seroconvert as non-responders.

Following completion of the trial, we conducted a nested case-control study to analyze the association between HLA genetic variation and RV vaccine response. The HLA allele and supertype frequencies were compared between responder group and non-responder group by statistical analysis.

2.2. Vaccine

RV3 is an oral liquid vaccine manufactured by Lanzhou Institute of Biological Products Co., Ltd. in China. It is composed of Lanzhou lamb RV backbone and a segment VP7 contributed by human RV strains to give human-lamb reassortant RVs, which are G2, G3, and G4 types respectively. Each dose of vaccine contained 2.0mL RV of which the titer was$10^{5.5}$ median cell culture infectious dose ($CCID_{50}$) per mL.

2.3. Serological assay

The RV-IgA concentrations were determined using an enzyme-linked immunosorbent assay based on sandwich principle.[6] Briefly, plates were coated with monoclonal antibody of RV, with subsequent RVs and cell mock coated. Dilutions of standard serum assigned an arbitrary value or test sera were added, followed by the addition of biotinylated rabbit anti-human IgA, avidin-biotinylated peroxidase complex, and substrate (ortho-phenylene-diamine/H_2O_2). The reaction was stopped with 1M H_2SO_4, and absorbance was read at 490/620nm with a microplate spectrophotometer. The IgA titer was determined by comparing the optical density values from sample wells with the standard curve.

2.4. HLA genotyping

Genomic DNA was extracted from blood samples using the QIAamp DNA Blood Mini Kit according to the manufacturer's instructions (Qiagen GmbH, Hilden). Five HLA loci (A, B, Cw, DRB1 and DQB1) were determined by SBT method using the BGI HLA-A, -B, -Cw, -DRB1 and -DQB1 SBT kit (Yantian DC, Shenzhen, China) according to the manufacturer's instructions respectively. The sequencing was conducted in forward and reverse directions by a 3730XL DNA Analyzer (Applied Biosystems, Foster City, CA) and BigDye Terminator v3.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA). Soap typing 1.01 software (Beijing Genomics Institute, Shenzhen, China) was used to process the DNA sequence files for analysis and HLA alleles' assignment according to IMGT HLA-database 3.10 (Université de Montpellier, France).

2.5. Statistical analysis

The multiple logistic regression was used to assess the influence of gender, age, height, and weight at the first dose of vaccine on the association between HLA and immune response to RV3. The allele and genotype frequencies were calculated by the direct counting method. Each person contributed 2 observations to alleles, 1 for each allele. HLA class I and class II supertypes were classified based on a shared sequence motif in peptide-binding pockets of HLA molecular.[20,21] The differences of allele and supertype frequencies were compared between the 2 groups by chi-square test. Fisher exact test was applied when expected numbers were smaller than 5. Cornfield's approximation was introduced to calculate odds ratio (OR) with 95% confidence interval (CI) for estimating the relative risk. Bonferroni's corrected P value was also calculated from the formula, (χ^2-test P value) × (the number of alleles or supertypes), to control the overall type I error.[22]P values less than .05 were considered statistically significant. Statistical analysis was performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Characteristics of the study population

Finally, 133 infants including 56 females and 77 males aged 41 to 96 days at the initial inoculation were included in the analysis. All the infants were Han nationality. Only 1 subject was seropositive for RV-IgA before vaccination and showed seroconversion after 1 month of 3 doses of vaccine. Of the 133 infants, 83 infants seroconverted after vaccination. The RV-IgA seroconversion rate was 62% (95% CI=54%–67%), and it was 68% (95% CI=56%–80%) in female infants and 58% (95% CI=47%–69%) in male infants respectively. The relationship between gender (P=.32), age (P=.38), height (P=.25), weight (P=.70), and immune response to RV3 were not statistically significant. (Table 1).

Table 1

General characteristics of the study population.

Characteristics	all the participants (n = 133)	responders (n = 83)	non-responders (n = 50)	*P* value*
Age (days)				.38
Mean ± SD	70 ± 17	71 ± 17	67 ± 17	
Min, Max	41, 96	41, 96	41, 96	
Gender				.32
Girl n (%)	56 (42.11)	38 (45.78)	18 (36.00)	
Boy n (%)	77 (57.89)	45 (54.22)	32 (64.00)	
Height (cm)				.25
Mean ± SD	60 ± 3	60 ± 3	59 ± 3	
Min, Max	52, 70	52, 70	53, 66	
Weight (Kg)				.70
Mean ± SD	6.04 ± 0.93	6.16 ± 0.96	5.84 ± 0.85	
Min, Max	4.20, 8.40	4.20, 8.40	4.30, 7.50	

max = maximum, min = minimum, n = number of subjects, SD = standard deviation.
* Based on multiple logistic regression.

3.2. Association between HLA alleles and seroconversion after RV vaccination

From the 133 infants, 21 HLA-A, 45 HLA-B, 24 HLA-Cw, 29 HLA-DRB1, and 16 HLA-DQB1 distinct alleles were identified (see Table, Supplemental content 1, http://links.lww.com/MD/C536, which illustrates the frequencies of the HLA alleles in the study infants). The results for the association between HLA alleles and seroconversion were shown in Table 2. For HLA-A, Cw, -DRB1, and -DQB1, there was no significant difference in RV seroconversion by the chi-square test. However, significant correlation was observed in HLA-A and -B alleles with seroconversion. The frequency of B*1301 was higher in responders than in non-responders (9.6% versus 3.0%). However, the differences did not reach statistical significance after Bonferroni correction. More frequent B*4001 was observed in non-responders than in responders (14.0% versus 2.4%). Besides, the differences between the 2 groups showed statistical significance after Bonferroni correction (corrected $P = .01$, adjusted OR = 0.152, 95% CI = 0.048–0.475).

3.3. Association between HLA supertypes and seroconversion after RV vaccination

Certain alleles confirmed to be part of the HLA class I and class II supertypes (see Table, Supplemental content 2, http://links.lww.com/MD/C536, which illustrates the frequencies of the HLA supertypes in the study infants). Association between specific HLA supertypes and seroconversion was presented in Table 3. The frequency of class I B44 supertype was significantly higher in non-responder group than in responder group. The statistical association between RV non-response and B44 supertype was observed (corrected $P = .02$, adjusted OR = 0.414, 95% CI = 0.225–0.763). However, the relationship between RV antibody response and HLA class II supertypes was not observed.

4. Discussion

In this study, a low RV-IgA seropositivity before vaccination was found in 1/133 (.75%) of the recruited infants. The low baseline IgA seropositivity indicated that most of the participants were not

Table 2

Association of HLA alleles with rotavirus* seroconversion.

	Responder group		Non-responder group				
HLA allele	n	f (%)	n	f (%)	*P* value†	Corrected *P* value	Adjusted OR (95%CI)
B*1301	16	9.6	3	3.0	.04	>.99	3.449 (0.979–12.150)
B*4001	4	2.4	14	14.0	<.001	.01	0.152 (0.048–0.475)

95% CI = 95% confidence interval, f = positive frequency of each allele, HLA = human leukocyte antigen, n = number of subjects, OR = odds ratio.
* Each subject is represented twice—once for each allele.
† Based on χ^2 tests.

Table 3

Association of HLA supertype with rotavirus* seroconversion.

	Responder group		Non-responder group				
HLA supertype	n	f (%)	n	f (%)	*P* value†	Corrected *P* value	Adjusted OR (95%CI)
B44	24	14.5	29	29.0	<.01	.02	0.414 (0.225–0.763)

95% CI = 95% confidence interval, f = positive frequency of each allele, HLA = human leukocyte antigen, n = number of subjects, OR = odds ratio.
* Each subject is represented twice—once for each allele.
† Based on χ^2 tests.

infected by RV before vaccination, thereby eliminating the effect of pre-infection on the immunogenicity of vaccine, which was observed in south Indian infants.[9] The results of our study show that RV3 is immunogenic in 62% of participants with a seroconversion detected, which is similar to that of Rotarix in China[7] ($P = .06$) but lower than that of Rotarix studies conducted in Finland and France.[6–8]

The lack of immunological response to vaccine is attributed to multiple factors, including the aspect of host and/or vaccine itself. Because various performances showed by the same vaccine in different clinical trials, the host genetic factors should be considered. The highly polymorphic HLA system is vital in presenting antigen and activating immune response.[17] Previous studies have shown that a variety of HLA alleles are involved in regulation of the antibody response to vaccines.[23,24] For example, HLA-DPB1*0501 is found to be associated with poor hepatitis B virus vaccine response in Japanese studies.[25] Besides, HLA-B*5701 allele is identified to be associated with low measles vaccine antibody response.[26]

In our work, the frequencies of each allele or supertype between responder group and non-responder group were studied to investigate the possible association of HLA gene polymorphisms with immune responses to RV vaccine. Our results showed that the frequency of HLA-B*4001 in non-responder group was significantly higher than in responder group. In the study, 6 alleles (B*1302, B*5201, B*1301, B*4001, B*4601, and B*5101) with frequencies were found to be the most common alleles, accounting for 41% of the total B alleles, which are similar to characteristics of HLA-B alleles distribution in Chinese populations.[27] The following evidence are found to be consistent with our association results. In worldwide populations, the frequency of HLA-B*4001 in East Asia is much higher than that in other regions, especially in Europe where there are excellent antibody responses to RV vaccine.[28] In addition, the frequency of HLA-B*4001 in China is higher than that in Japan and South Korea, and RV vaccines have shown better performance in these 2 countries than in China.[7] However, the frequency of HLA-B*4001 is low in India where RV vaccine shows poor performance.[9,28] Thus, it may be 1 of the potential host factors but not the only factor which impacts the immunogenicity of RV vaccines.

The majority of HLA molecules can be grouped into supertypes based on largely overlapping motifs and repertoires in the peptide-binding pockets of HLA. This kind of classification could narrow the types of HLA and eliminate the influence of different areas and ethnic groups to the analysis of HLA. In our study, HLA-B44 supertype was significantly associated with non-response. This observation was similar to the report of measles–mumps–rubella viral vaccine in Minnesota population, where B44 has shown strong association with lower measles vaccine-specific antibodies.[29]

HLA gene polymorphism in RV3 trial shows an obvious relationship with seroconversion, which implies the HLA is instrumental in modulating the immune response to RV. This observation also helps understand variations in immune response to RV vaccine under the fundamental immunologic mechanism. But it is not easy to find out exact factors which are modulated by HLA and influence seroconversion. One possible reason is that HLA molecules encoded by certain alleles may be less efficient in binding and presenting antigens to the immune system, thereby causing a poorer humoral immune response. Studies have shown that there is no binding affinity between HLA-B*4001 and epitopes from Hepatitis C virus envelope 1 protein sequences.[30] There is also evidence that Class I HLA proteins may bind poorly to measles viral vaccine peptides and fail to present the bound antigen to T cells.[31] Similarly, the association of the Class I HLA proteins with poor antibody response was also observed in our study. This result is consistent with previous studies which show different HLA class I alleles or supertypes are associated with lower antibody level of certain pathogens or vaccines.[23,31–33] Although it is not clear how class I HLA proteins would affect humoral immunity, it may be the basis for primary immune failure and affects the whole immune response.

Our study was limited by the lack of vaccine efficacy data due to our small sample size. However, researchers have shown that post-vaccination RV-IgA positivity is associated with the vaccine efficacy.[34] Therefore, studying the association between HLA and seroconversion of vaccine could reflect HLA's relationship with vaccine response so as to explore the influence of HLA on the vaccine efficacy.

The findings show that RV vaccine-induced immune responses are significantly influenced by polymorphisms of HLA alleles and supertypes. This new information would help us better understand the host genetic factors underlying RV vaccine immunogenicity. And it could be useful for the design of vaccine clinical trials and the development of improved RV vaccines.

Author contributions

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