Human leukocyte antigen type and progression from onset of symptoms to development of asthma

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ABSTRACT

*This study investigated the influence of human leukocyte antigen (HLA) genes on the progression of asthma, from the initial onset of symptoms to when criteria for asthma are met. Study subjects were a subsample (n = 340) of 838 healthy children, aged 5–12 years, who participated in a previous study, and who had HLA data and asthma status. The duration in time from the initial onset of asthma symptoms documented in each subject's medical records to the index date when the subject first met criteria for asthma was determined. The time duration was compared between carriers and noncarriers of HLA genes of interest of the 340 original subjects with HLA data available, 114 children (33.5%) met criteria for asthma before 18 years of age. The median ages at onset of asthma symptoms and at the index date of asthma were 4.4 years and 7.2 years, respectively. The median time intervals between onset of symptoms and index date for HLA DRB1*11 carriers and noncarriers were 552 versus 61 days, respectively (p = 0.004). The same time intervals for HLA DQB1*0301 carriers and noncarriers were 420 versus 59 days, respectively (p = 0.012). However, HLA DQB1*0302 or DRB1*03 carriers had shorter median intervals, when compared with noncarriers (119 versus 266 days, respectively, p = 0.20; and 86 versus 258 days, respectively, p = 0.38) but they did not reach statistical significance. HLA type appears to influence the progression of asthma from initial symptoms to disease. Thus, genetic factors may affect the natural history of asthma.*

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There are two important time intervals that precede the establishment of the diagnosis of asthma: (1) the time between the initial onset of asthma symptoms and the index date of asthma (*i.e.*, when a patient first meets criteria for asthma) and (2) the time between the index date of asthma ascertainment based on meeting predetermined criteria and the date of diagnosis of asthma given by health care providers. We defined the index or incidence date of asthma as the earliest constellation of symptoms that met predefined criteria for asthma, regardless of whether health care providers had diagnosed the patient with asthma. The time interval between the onset of asthma symptoms and the index date of asthma may be more closely related to the disease of asthma and is important in understanding the natural history of asthma. The second interval, between the index date of asthma and the diagnosis of asthma by health care providers, may be related to the diagnosis of asthma and is important for determining access of asthmatic patients to therapeutic and preventive health services.

Characterization of the duration between onset of asthma symptoms and the index date of asthma will help clinicians better identify and monitor children who have rapid progress to the development of asthma and prompt researchers to assess this duration as another potential phenotype of asthma. Therefore, it is important to address questions as to why some individuals exhibit slow asthma progression while others rapidly progress, and what immunogenetic factors, such as human leukocyte antigen (HLA) genotypes, predict these differential rates of asthma disease progress.

In addressing these questions, along with environmental influences, genetic factors are likely to play an important role.[1-5] Most genetic studies in asthma have focused on the etiologic aspects of asthma or pharmacogenetics (as discussed in a recent review on genetics in asthma[6]), and few genetic studies are available that assess the role of genetic factors in the duration between onset of asthma symptoms and the index date of asthma. HLA class II genes are an important immuno-

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genetic factor in the pathogenesis of atopy and asthma, affecting genetic predisposition and clinical expression of disease.[7–18] Thus, we conducted a retrospective cohort study that assessed the influences of HLA class II genes on the duration of time between onset of asthma symptoms and the development of asthma.

METHODS

Study Design and Setting

This study was a retrospective cohort study. Rochester, MN, is an excellent setting to conduct a retrospective cohort study such as this, because medical care is virtually self-contained within the community with a unified medical record system for research.[19–24]

Study Subjects

Study subjects were obtained from a sample of 876 children who were enrolled in the Rochester Family Measles Project, which was a convenience sample recruited from the Rochester School District. Details about the original subjects were described in a previous study.[25] The original study cohort consisted of children between the ages of 5 and 13 years, who were enrolled in the study from schools in Rochester, MN, in 1993. At the time of our study between 2002 and 2006, the study subjects were ≥14 years of age. We excluded subjects who did not authorize research review of their medical records and those who were not Olmsted County residents.

Ascertainment of Asthma Cases

We conducted comprehensive medical record reviews to determine the asthma status of study participants between July 2002 and June 2006 by applying predetermined criteria for asthma that are detailed in Table 1. These criteria were developed during a previous study, and numerous previous studies on asthma epidemiology research have used these criteria to define asthma.[19,21–33] A previous study that analyzed interobserver reliability and agreement rates between abstractors found a high degree of concordance.[21] Briefly, for criterion 1, we reviewed the entire medical record to identify a history of cough with wheezing and/or shortness of breath documented by physicians or documented wheezing episodes on examination with cough and/or shortness of breath. Criterion 2 was considered to be met when an episode occurred at least twice or more in 3-year periods within the first episode, with documented interim periods without asthma symptoms. When two of eight items of the third criterion were documented in the medical record, we considered the third criterion to be met.

Table 1 **Asthma criteria**

Patients were considered to have *definite* asthma if a physician made a diagnosis of asthma and/or if each of the following three conditions were present. They were considered to have *probable* asthma if only the first two conditions were present:
History of cough, dyspnea, and/or wheezing OR history of cough and/or dyspnea plus wheezing on examination,
Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent
Two or more of the following:
Sleep disturbed by nocturnal cough and wheeze
Nonsmoker (≥14 years of age)
Nasal polyps
Blood eosinophilia of >300/uL
Positive wheal and flare skin tests OR elevated serum IgE
History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
Pulmonary function tests showing one FEV_1 or FVC of <70% predicted and another with at least 20% improvement to an FEV_1 of >70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
Favorable clinical response to bronchodilator
Patients were excluded from the study if any of these conditions were present:
Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity
Tracheobronchial foreign body at or about the incidence date
Hypogammaglobulinemia (IgG of <2.0 mg/mL) or other immunodeficiency disorder
Wheezing occurring only in response to anesthesia or medications
Bullous emphysema or pulmonary fibrosis on chest radiograph
α1-Antiprotease phenotype ZZ α_1-antitrypsin
Cystic fibrosis
Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

FVC = forced vital capacity; FEV_1 = forced expiratory volume at 1 s.

Onset of Symptoms of Asthma

Asthma status, as defined previously, was determined first. Subsequently, the specific date of onset of symptoms of asthma was determined. The date of onset of asthma symptoms was defined as the date of

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the earliest symptoms of asthma in the medical record. We considered symptoms of asthma to include wheezing (exercise or infection induced), spasmodic cough, bronchospasm (exercise or infection induced), shortness of breath or dyspnea, and chest tightness. An example of the onset of asthma symptoms would be a patient who had a wheezing episode associated with exposure to a cat. The point in time at which a physician listed this episode as the first episode of wheezing for this subject was considered to be the date of symptom onset, although at the time of symptom onset, this subject would not meet the predetermined criteria for asthma diagnosis.

Index Date of Asthma

Asthma index date was defined as the earliest constellation of symptoms, including cough, dyspnea, and/or wheezing, found in the medical record that met the predetermined criteria for asthma in Table 1. We also developed specific criteria to estimate an approximate index date in cases where the onset of asthma was described in general terms.

Dependent Variable

Asthma status as defined previously, date of onset of asthma symptoms, and the index date of asthma were defined as mentioned earlier. The dependent variable of this study was the duration of time between onset of asthma symptoms and the index date of asthma.

Independent Variables

The independent variables in this study were HLA class II allele types that have been reported to be associated with asthma or related phenotypes, *e.g.*, atopy.

HLA Typing

The detailed procedures for HLA typing in this study have been described elsewhere.[33–35] A subsample of 340 subjects had HLA typing performed. We explored the association between HLA alleles and the rate of the progress of asthma from the onset of asthma symptoms to the index date of asthma using the HLA alleles reported to be associated with asthma or asthma-related phenotypes that are listed in Table 2.[7–11,18,36,37]

Statistical Analysis

The dependent variable in this study was the duration of time between the onset of asthma symptoms and the index date (when a subject met the criteria for asthma summarized in Table 1). The Wilcoxon rank sum test was used to compare the median duration between carriers and noncarriers of each HLA allele. All calculated p values were two-sided and values of $p < 0.05$ were considered statistically significant.

RESULTS

Of the 876 children enrolled in the Rochester Family Measles Project, 839 had provided research authorization for medical record review. Of the 839 children, 276 met the predetermined criteria for asthma before 18 years of age, and 340 children had HLA data available. Of the 276 children with asthma, 114 had HLA information available. Data on both date of onset of asthma symptoms and index date were available for 86 of the 114 children. Of the study cohort of 86 children, 48 were boys 38 were girls. The median ages at onset of asthma symptoms and at the index date for the 86 children were 4.4 years (interquantile range [IQR], 1.1–9.0 years) and 6.6 years (IQR, 2.6–11.0 years), respectively. The median and mean durations between onset of asthma symptoms and the index date were 149 days (IQR, 10–742 days) and 682 days, respectively.

Table 2 shows the relationship between HLA-DQB1 and HLA-DRB1 alleles and the time interval between onset of asthma symptoms and the index date of asthma. The median intervals between onset of symptoms and index dates for HLA DRB1*11 carriers and noncarriers were 552 versus 61 days, respectively ($p = 0.004$). Likewise, the time intervals for HLA DQB1*0301 carriers and noncarriers were 420 versus 59 days, respectively ($p = 0.012$). On the other hand, HLA DQB1*0302 and DRB1*03 carriers had a shorter median time interval compared with noncarriers, but this did not reach statistical significance. Other HLA haplotypes were studied but did not show significant influence on progression of asthma from symptom onset to index date.

DISCUSSION

Our study results suggest that HLA class II genes may play an important role in determining the course of asthma from the onset of symptoms to phenotypic development of disease. There is a high degree of polymorphism between most of the HLA loci, and many previous studies have shown associations between specific HLA alleles or haplotypes and asthma or related phenotypes.[2,7–11,14–18,29,36,38] The HLA alleles analyzed in this study were chosen based on these studies. In this study, we found that DRB1*11 and DQB1*0301 carriers had significantly slower progress from onset of asthma symptoms to the index date of asthma, compared with noncarriers. Both median and mean time intervals from the onset of asthma symptoms to the index date of asthma for DRB1*11 carriers were 1560 and 552 days, whereas those for noncarriers were 465 and 61 days, respectively. Similarly, the intervals for DRB1*0301 carriers were 1155 and 420 days, whereas those for noncarriers were 412 and 59 days, respectively. These results suggest that these HLA allele carriers were three to seven times slower in the

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Table 2 **HLA class II genes and the duration between onset of asthma and index date**

HLA Type	Carrier	*n*	Mean	SD	25th Percentile	Median	75th Percentile	*p* Value¶
DQB1*0301	Negative#	49	412.0	788.1	7.0	59.0	365.0	0.012
	Positive§	30	1155.2	1542.9	62.0	419.5	2027.0	
DQB1*0302	Negative	56	808.9	1282.8	15.0	265.5	1204.0	0.20
	Positive	23	415.0	855.4	0.0	119.0	344.0	
DQB1*0501	Negative	59	687.9	1222.2	7.0	119.0	712.0	0.44
	Positive	20	712.8	1087.9	34.0	286.0	1006.0	
DQB1*0603	Negative	71	741.3	1231.8	16.0	204.0	809.0	0.33
	Positive	8	276.0	439.8	3.5	60.0	403.0	
DRB1*11	Negative	63	465.4	834.7	5.0	61.0	424.0	0.004
	Positive	18	1560.3	1783.2	119.0	551.5	2810.0	
DRB1*02	Negative	57	913.7	1361.5	10.0	258.0	1292.0	0.22
	Positive	24	221.9	305.3	18.5	60.0	344.0	
DRB1*03	Negative	57	799.8	1322.9	21.0	258.0	742.0	0.38
	Positive	24	492.6	792.2	5.0	85.5	865.0	
DRB1*04	Negative	53	775.3	1292.7	21.0	119.0	1203.0	0.42
	Positive	28	582.8	990.0	0.0	214.0	468.5	
DQA1*0101	Negative	62	807.1	1267.9	16.0	227.0	1203.0	0.40
	Positive	17	455.6	910.0	10.0	119.0	365.0	
DQA1*0301	Negative	52	791.0	1281.7	18.5	127.5	1204.0	0.49
	Positive	27	616.8	1049.6	0.0	250.0	461.0	
DQA1*0401	Negative	74	614.2	981.5	10.0	170.0	742.0	0.21
	Positive	5	2467.6	2576.1	48.0	2795.0	3316.0	
DQA1*0501	Negative	39	561.4	940.6	5.0	119.0	742.0	0.49
	Positive	40	897.3	1406.1	13.0	254.0	1240.0	

Not all 86 subjects had complete HLA types available.
#Negative means noncarriers.
§Positive means carriers.
¶Two-sided p value for the Wilcoxon rank sum test.
HLA = human leukocyte antigen.

progression of asthma from the onset of asthma symptoms to the development of asthma.

Previous studies reported that DRB1*11 had inconsistent results in relation to the risk of atopic asthma (*i.e.*, increased risk[14] versus decreased risk[39]). Likewise, the relationship between HLA DQB1*0301 and asthma incidence has been reported to be inconsistent as well (*i.e.*, increased risk[14] versus decreased risk[40]). Gao *et al.*, suggested that different phenotypic definitions of asthma and different methodologies of HLA typing might contribute to the discrepant results between their study and that of Lara-Marquez *et al.*[40] We previously reported that HLA DRB1*03 was associated with an increased asthma incidence in this study cohort (hazard ratio,1.8; 95% CI, 1.1–2.9; $p = 0.02$),[29] but in this present study, carriers of this allele did not have a statistically significant tendency for more rapid progression to the disease of asthma compared to noncarriers. At present, although there are studies that showed the association between HLA class II genes and asthma incidence, there is no study that shows the potential influence of HLA II genes on the duration from the onset of asthma symptoms to index date and with which we can compare our study results.

Non-HLA genes that affect asthma susceptibility, severity, and response to treatment have been reported, but much of the literature focuses on etiology and severity of asthma and pharmacogenetics, as discussed in the recent review on genetics in asthma by Guerra and Martinez.[41] Little is known about how genetic factors affect the natural history of asthma progression. A recent study by Inoue *et al.* found evidence that UGRP1, a secretory protein found in the airways, may be one of the genetic factors affecting asthma severity.[42] Halloway *et al.*, also recently examined the effect of interpatient genetic variability on asthma progression. Their study suggested that the severity and natural history of an individual patient's asthma disease may be the result of multiple environmental factors interacting with a susceptible genotype. There are a number of genes previously identified in the literature that are associated with asthma severity, including the

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β_2-adrenergicreceptor, *TNFA*, and *CCL5* (RANTES).[43] However, the influences of these genes associated with asthma severity on asthma progression from onset of asthma symptoms to the development of phenotypically full-blown asthma disease have not been investigated, thus, the role of genes in such progression is yet to be determined.

For nongenetic factors, we previously reported that children with a history of fewer upper respiratory tract infections, younger ages at index date of asthma, more severe asthma, exercise-induced asthma symptoms, and pets in the household were more likely to have a shorter time interval between the onset of asthma symptoms and the index date of asthma.[5] As in the etiology of asthma, both genetic and environmental factors may interact in a way that determines the speed of progress from onset of symptoms to the development of asthma disease. In this study, because of our limited sample size, we did not explore the complex interaction between the studied HLA genes and environmental factors. Given the complexity of asthma, it may be challenging to understand how our study findings are related to the complex nature of asthma. Our current study is not suitable to address this question. However, our study findings highlight that genes such as HLA type might influence the rapidity of the progression from the onset of asthma symptoms to index date of asthma.

The strengths of our study include ascertainment of asthma status and index date by predetermined, well-established criteria for asthma. Because our study assessed the time interval between first asthma symptoms documented in the medical record to the point at which the patient met criteria for asthma (index date), we did not have to rely on a physician diagnosis or parental report alone. Also, our study setting has a self-contained health care environment with a unified medical records system for research that allowed us to capture all asthma-related inpatient and outpatient events, including clinic visits or evaluations, tests, medications, and hospital admissions.

There are also limitations to the retrospective study design we used. Ascertainment of asthma and determination of the progress from the onset of asthma symptoms to the development of asthma may not have been perfect and entirely accurate. However, the errors from this inaccuracy are likely to be subject to nondifferential misclassification bias. Another limitation was that as a result of the lack of available dates of asthma symptoms, only 86 subjects of the 114 children with HLA data and asthma were available for the present study. The small sample size tends to be more problematic for a negative study supporting the null hypothesis. Despite the small sample size in our study, we were able to accomplish the study but our study findings need to be confirmed by a larger study. We compared sociodemographic characteristics among included subjects, excluded subjects, the eligible original cohort, and a population-based sample of asthmatic children in our study setting.[24] We found no significant differences in ethnicity, and our study subjects were closest to the population-based sample of asthmatic children in our study setting with regard to gender and age at the onset of asthma (data not shown). Because our study cohort was predominantly white (93.8%), our results may not be generalized across other ethnic populations.

In conclusion, HLA class II genes may influence the rapidity of progression from initial asthma symptom onset to full-blown asthma disease. This information may help clinicians and researchers better characterize asthma for patient care (*e.g.*, early identification and treatment) and research (*e.g.*, the different degree of the progression of asthma as a potential phenotype of asthma). These research findings deserve further investigation.

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