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A Child's *HLA-DRB1* Genotype Increases Maternal Risk of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) disproportionately affects women of reproductive age. During pregnancy, women are exposed to various sources of fetal material possibly constituting a significant immunologic exposure relevant to the development of SLE. The objective of this study was to investigate whether having any children who carry *DRB1* alleles associated with SLE increase the risk of maternal SLE.

This case-control study is based on the University of California, San Francisco Mother-Child Immunogenetic Study and from studies at the Inova Translational Medicine Institute. Analyses were conducted using data for 1,304 mothers (219 cases/1,085 controls) and their respective 1,664 children. We selected alleles based on their known association with risk of SLE (*DRB1*03:01*, **15:01*, or **08:01)* or Epstein-Barr virus (EBV) glycoproteins (**04:01*) due to the established EBV association with SLE risk. We used logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) for each allele of interest, taking into account maternal genotype and number of live births.

We found an increase in risk of maternal SLE associated with exposure to children who inherited *DRB1*04:01* from their father (OR 1.9; 95% CI, 1.1-3.2), among **04:01* allele-negative mothers. Increased risk was only present among mothers who were positive for one or more SLE risk-associated alleles (**03:01, *15:01* and/or **08:01*). We did not find increased risk of maternal SLE associated with any other tested allele.

These findings support the hypothesis that a child's alleles inherited from the father influence a mother's subsequent risk of SLE.

Keywords

systemic lupus erythematosus; genetic epidemiology; human leukocyte antigen genes; pregnancy

1. Introduction

Systemic lupus erythematosus (SLE) has one of the most striking sex ratios ranging from 4-13 females per every male affected and a peak in incidence during the reproductive years [1]. Fetal microchimerism has been previously proposed to contribute to female-predominant autoimmune diseases [2, 3]. Microchimerism, or the presence of a small number of cells from one individual present in another, is a natural consequence of bi-directional cellular trafficking that takes place between mother and fetus. Previous studies have found a higher prevalence of fetal microchimerism in SLE cases compared to controls [4, 5].

These observations support the hypothesis that fetal material such as fetal cells, fetal cell free DNA or the contents of placental vesicles, may constitute a significant immunologic exposure to the mother that contributes to an increased incidence of SLE among women. Fetal material enters the maternal circulation during normal pregnancy and has immunomodulatory effects [6]. Fetal DNA, lipids and proteins are released into the maternal circulation by the syncytiotrophoblast of the placenta [7]. The contents of placental exosomes are believed to be an important source of fetal-maternal communication [8]. To date, little is known about how the exposure to fetal material shapes the long-term health of the mother.

It has previously been reported that SLE autoantibodies precede diagnosis, diversify and accumulate [9, 10]. Exposure to fetal material through the maternal circulation may contribute to the development of autoantibodies. We hypothesize that risk of maternal SLE is increased depending on the characteristics of the fetal material the mother is exposed to during pregnancy. Using a genetic approach, we investigated whether having any children who carry SLE-associated HLA alleles *DRB1*03:01*, **15:01*, or **08:01* [11-13] increases the risk of maternal SLE. It is also possible that fetal material may act through molecular mimicry of certain infections [14]. Therefore, we also investigated the relationship between having any children who carry *DRB1*04:01* and maternal SLE due to the association between Epstein-Barr virus (EBV) and SLE [15] and the amino acid sequence similarity between EBV glycoproteins and *DRB1*04:01* [16].

2. Materials and methods

2.1 Study population

We conducted a case control study of 1,304 mothers and their children using data from the UC San Francisco (UCSF) Mother-Child Immunogenetic Study (MCIS) and research studies conducted at the Inova Translational Medicine Institute (ITMI), Inova Health System, Falls Church, Virginia. White females of European ancestry with at least one living child were eligible to participate. Cases were identified from patients enrolled in genetic studies of

autoimmunity at UCSF. All SLE cases met the 1997 revised criteria of the American College of Rheumatology [17, 18] and had at least one live birth prior to diagnosis. Control mothers had no prior history of autoimmune disease and had at least one live born child. Controls were recruited from various sources including blood donors at the Blood Centers of the Pacific and the Institute for Transfusion Medicine in Pittsburgh, PA and from families who enrolled in studies at the Inova Women's Hospital, Inova Fairfax Medical Center, Falls Church, Virginia. Only participants with genotype data for both mother and at least one child were included in this study. All participants provided written informed consent. The study protocol is in accordance with the Declaration of Helsinki and was approved by the UCSF and UC Berkeley Institutional Review Boards (IRB). ITMI studies were approved by the Western IRB and the Inova Health System IRB.

2.2 Clinical and questionnaire data

For cases, we obtained the date of diagnosis and clinical characteristics from medical records. The MCIS collected data from case and control mothers on reproductive history and potential confounders through a self-administered questionnaire. For ITMI control mothers, reproductive history, mother's and child's date of birth were obtained from electronic medical records (EMR).

2.3 HLA allele imputation

We used SNP2HLA [19] to impute HLA alleles using post-QA/QC genotype and whole genome sequencing data. In order to minimize confounding by ancestry, we selected participants of European ancestry for inclusion in this study. Using ancestry informative markers for Northern and Southern Europeans [12], we adjusted for ancestry proportions estimated using STRUCTURE (version 2.3.4) [20]. A detailed description of genotyping, QA/QC steps and imputation methods are found in the Supplementary material section.

2.4 Statistical analyses

We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between mother's SLE status and a child's *DRB1* genotype. For each eligible mother, we included data from all children (n=1,664; 386 from cases/1,278 from controls) who participated in the study. We created a binary variable for each *DRB1* allele of interest (**03:01, *15:01, *08:01* and **04:01*) to indicate whether any child carried one or two alleles vs. none and constructed a model for each allele. We addressed three main questions: a) is the *DRB1* allele associated with SLE; b) is a child's *DRB1* allele associated with maternal SLE; and c) is a child's *DRB1* allele associated with maternal SLE among mothers who were not carriers of the same allele. Using directed acyclic graphs we identified our sufficient adjustment set of variables that met the definition of a confounding variable. Maternal genetic ancestry was considered in all models but it was not included in final models since it did not affect our estimates. The number of live births was included in models for the second and third questions. In order to isolate the independent effect of a child's genotype and maternal SLE, we adjusted for maternal carrier status of each tested allele for the second set of models and excluded mothers with the allele in the third set. To correct for multiple testing, we applied a Bonferroni correction to each of

the three questions investigated [21]. Statistical analyses were conducted using Stata 13 (StataCorp, College Station, Texas) and R [22].

2.4.1 Interaction and sensitivity analyses—We investigated potential mother-child genotype interaction between a child's **04:01* carrier status and maternal *DRB1* risk-allele carrier status of at least one allele of **03:01*, **15:01*, or **08:01*. We conducted the analysis among **04:01* allele-negative mothers. In addition, we performed sensitivity analyses to rule out alternative explanations for our findings. Due to the case control difference in the number of participating children, we conducted a sensitivity analysis where we only included mothers with one participating child. We also adjusted our models to account for the difference in the number of live births between cases and controls using total number of children included in the study instead of total number of live births, as this may affect the probability of exposure. We reclassified our exposure of having allele-positive children to only include children born pre-diagnosis rather than including all children.

Since the results of mother-child allele combinations could be a surrogate for a genetic effect of allele combinations, we tested statistically significant combinations in a larger dataset of SLE cases and controls (n=12,935). Data for the analysis was obtained from a previously published study that includes our 219 cases [13]. Furthermore, to investigate whether the time of exposure to the pregnancy was within a plausible time period for the development of autoantibodies [10], we conducted an analysis excluding cases diagnosed more than 10 years after their last pregnancy.

3. Results

Controls were younger at study enrollment and had fewer births (1.9 vs. 2.3) due to the inclusion of ITMI pregnancy cohorts (Table 1). Genotype data were available for some but not all children. The average number of children included in the study was slightly greater for SLE cases than controls (1.8 vs. 1.2). The average age at SLE diagnosis among cases was 38.6 ± 12.6 and 18% had a lupus nephritis diagnosis. Antibody test results were available for 91% to 97% of cases, depending on the antibody. Antibodies to double stranded DNA (anti-dsDNA) and Ro (anti-Ro) were present in 40% and 30% of all cases, respectively. Frequencies for other antibodies are in Table 1. The frequency of each of the 1997 ACR revised criteria for SLE [17, 18] is available in Supplementary Table 1.

3.1 DRB1 and maternal SLE

For comparison to published reports, we first investigated the association between presence of each *DRB1* allele and SLE by comparing mothers in a traditional case control manner. Our results were consistent with previously reported associations between **03:01*, **15:01*, and **04:01* and SLE (Table 2). The association between **08:01* and SLE was in the expected direction but estimates lacked precision.

3.2 Child's DRB1 genotype and maternal SLE

We investigated the association between having any children who carried one or two copies of each *DRB1* allele and maternal SLE in separate models (Table 3). We found a two-fold

increase in risk of maternal SLE among women who had an **04:01* allele-positive child compared to controls (OR 2.1; 95% CI, 1.4-3.1). Models were adjusted for maternal **04:01* status and number of live births. The association was stronger when comparing cases with lupus nephritis to controls (OR 2.7; 95% CI, 1.2-6.1). We did not find an association between any other *DRB1* allele investigated and maternal SLE. Our study had more than 80% power to detect a 20% increase in risk associated with having any children positive for the **03:01* allele and maternal SLE, but power was lower for detecting the observed level of increase in risk associated with **15:01* (67%) and **08:01* (32%).

To rule out the possibility that the effect was limited to children who inherited the allele from their mother, we conducted the analysis excluding mothers who carried each allele (Table 4). Among **04:01* allele-negative mothers (177 cases / 920 controls), having any **04:01* allele-positive children was associated with maternal SLE (OR 1.9; 95% CI, 1.1-3.2); an attenuated but significant result compared to allele-positive mothers (n= 42 cases /165 controls; OR 2.4; 95% CI, 1.1-4.9). The increase in risk is present regardless of whether the child inherited the allele from his or her father or mother.

In order to determine whether the effect of a child's genotype on maternal disease was modified by the mother's own genetic susceptibility, we stratified on whether mothers carried one or more *DRB1*03:01, *15:01,* or **08:01* alleles. We found that the association between **04:01* allele-positive children and maternal SLE was restricted to mothers who carry one or more risk-associated *DRB1* alleles (Table 5; *p-interaction* = 0.09). Our study was not adequately powered (n=134, 27% power) to test if having any children positive for one or more alleles of **03:01*, **15:01* and/or **08:01* and negative for **04:01* among mothers who were **04:01*-positive and negative for the other three alleles increased the risk of maternal SLE. We found a slightly stronger association between having **04:01* allele-positive children and maternal SLE among mothers diagnosed within 10 years of a child's birth compared to controls (n= 978; OR 2.7; 95% CI, 1.3-5.7).

Our estimates remained consistent in analyses where we only included mothers with one participating child (n=455, OR 2.6; 95% CI, 1.1-6.0), or when we adjusted for number of participating children rather than number of live births. As it was possible that our results could have been affected by our method of classifying the genotype of children born at any time independent of date of diagnosis, we reclassified exposure by limiting to those born prior to diagnosis; results were similar (n=585, OR=2.1; 95% CI, 1.1-4.1). Due to the difference in age at interview of ITMI and MCIS mothers, we compared the frequency of having any **04:01*-allele positive children between the two control groups. We did not find a statistically significant difference (p=0.18). The age at interview for MCIS control mothers did not differ compared to case mothers (55 vs. 54 years, respectively; p=0.14).

Furthermore, among mothers we did not find strong evidence of additional risk associated with carrying *DRB1*04:01* in combination with any one of the *DRB1* risk-associated alleles **03:01, *15:01*, and/or **08:01* relative to mothers who were **03:01, *15:01* and/or **08:01* positive and **04:01*-negative in this study (OR 1.7; 95% CI, 1.0-3.0, p=0.05) or in our larger dataset (OR 0.9; 95% CI, 0.8-1.0, p=0.15).

4. Discussion

To our knowledge, this is the first report of an association between a child's genotype and maternal SLE risk. We found that having children who are *DRB1*04:01* allele-positive is associated with a two-fold increase in risk of SLE among mothers who carry at least one *DRB1* risk allele (*03:01, *15:01, and/or *08:01). The association is present among women who are positive as well as negative for the allele. Among allele-negative mothers this means that *04:01* was inherited from the father, suggesting that *DRB1* alleles may also increase risk of disease through non-genetic effects. We did not find evidence of increased risk of SLE associated with carrying *04:01* in combination with *03:01, *15:01, or *08:01. The increase in risk of maternal SLE associated with *04:01* is only present when exposure occurs through the allele of the child. These findings support the hypothesis that exposure to fetal material during pregnancy may contribute to the development of SLE. There are several plausible explanations for our findings based on current understanding of the biology of pregnancy as well as the natural history of SLE.

One possibility is that fetal material that enters the maternal circulation during pregnancy mediates the production of autoantibodies that contribute to the development of SLE. During pregnancy, mothers can make antibodies against placental material and specifically against the paternal HLA of the fetus [23-26]. Antibodies to fetal paternally inherited HLA molecules have been detected in nearly a third of pregnant women [26]. Memory T-cells against paternal HLA can persist for up to 10 years after birth, even in the absence of antibodies [24], suggesting that transient exposure to paternal HLA via the fetus can shape the maternal T-cell repertoire. Among susceptible women, the interaction between maternal and paternal antigens could contribute to the break in tolerance leading to the production of autoantibodies.

Our findings are intriguing because *DRB1*04:01* is not an allele associated with overall risk of SLE, although it may be associated with a subset of autoantibodies [27-29]. In rheumatoid arthritis patients, *DRB1*04:01* is one of the alleles that comprise the strongest genetic risk factor referred to as the “shared epitope” which are associated with anti-citrullinated protein antibody production [30-32]. Our rationale for including *DRB1*04:01* in the current study was due to its association with an EBV glycoprotein previously identified in a study of rheumatoid arthritis [16]. The association between exposure to a child who carries *DRB1*04:01* and SLE may be due to a form of molecular mimicry, where components of a child's DNA may mimic an infectious agent that leads to the initiation or propagation of an immunologic process that results in SLE. Both molecular mimicry and epitope spreading have been hypothesized to contribute to SLE [33, 34]. Longitudinal studies on the natural course of SLE have shown that autoantibodies appear years before diagnosis and they accumulate and change over time, possibly due to epitope spreading [9, 10, 14].

Exposure to fetal material may also affect the maternal immune system through other pathways. It is estimated that fetal DNA makes up 3% to 6% of total maternal plasma DNA in early and late pregnancy, respectively [35]. Fetal material, including fetal DNA, can contribute to systemic inflammation leading to pregnancy complications such as

preeclampsia [36, 37]. Levels of fetal DNA are higher in preeclamptic pregnancies compared to controls [38]. It is possible that shared mechanisms may be involved in some aspects of SLE and preeclampsia. SLE patients suffer have higher rates of preeclampsia compared to the general population [39]. Fetal-maternal genotype combinations of HLA-C and maternal KIR are associated with increased risk of preeclampsia [40]. These findings support the hypothesis that the fetal genotype may affect the development of SLE through immunologic pathways.

Another possible explanation is that fetal cells trigger an immune response by maternal immune cells or that fetal lymphocytes attack maternal cells. Microchimerism, of presumed fetal origin, has been found more frequently among SLE cases compared to controls. One study identified fetal microchimerism in 68% of SLE cases compared to 33% of controls [5]. Similarly, another study found evidence of microchimerism in 31% of cases compared to only 4% among controls [4]. Two post-mortem studies [41, 42] and a study using renal biopsies [43] found evidence of microchimerism in SLE affected organs compared to controls or to normal tissue in cases. Phenotypically, microchimeric cells have demonstrated multilineage capacity [44] and may resemble hematopoietic stem cells but their function remains unknown.

We were unable to confirm the underlying assumption that fetal genotype affects the characteristics or function of microchimeric cells or any other type of fetal material since we did not quantify either exposure. Fetal microchimerism is associated with some, but not all, female predominant autoimmune diseases [45]. Our study cannot directly elucidate the role of microchimerism in female predominant autoimmune diseases, although it has informed our hypothesis. The association between microchimerism and autoimmune diseases may be due to a variety of factors. Female predominant autoimmune diseases are a heterogeneous group of conditions with complex etiology. The association of a single factor with each disease may vary depending on its relative importance among the many factors that lead to a specific disease [46], despite sharing common causes. We have identified evidence for association between a child's genotype and maternal SLE, which may or may not be mediated by microchimerism. Studies using functional approaches are needed to understand potential biological effects.

Our study has a number of strengths. We have investigated fetal-maternal genetic interactions in a large sample of mothers and their children. We have performed QA/QC measures that increase our confidence in the quality of our data. We have taken into account potential sources of bias in our models by adjusting for confounding variables and by conducting various sensitivity analyses. We minimized the probability that results are false positives by testing a limited number of candidate alleles and by correcting for multiple comparisons.

Some limitations must also be considered. Although our sample size was large, we were unable to rule out chance as an explanation for some results. We tested a limited number of candidate alleles and our study would benefit from a more thorough investigation using a larger sample. The ITMI controls were younger at age at study entry and had fewer live births compared to our cases. The difference in age could impact our results through

misclassification of disease status (future cases in the younger control group) and by a reduced exposure to live births. However, our results are unlikely due to these differences for a number of reasons. SLE is a rare condition, and we expect that if any controls subsequently develop the disease, the number is likely to be very small. Further, inclusion of potential cases in our control group would result in a bias towards the null. Differences in maternal age at interview could influence the number of live births and subsequently the number of allele-positive children. However, we did not find evidence that maternal age affected the proportion of **04:01* allele-positive children when older and younger control groups were compared.

Potential confounding variables for ITMI controls were extracted from electronic medical records, which differed from direct collection methods used for MCIS participants. Although differences in exposure measurement can be a source of bias in case-controls studies, the impact on results are likely to have been minimal. As a genetic study, confounding can result from differences in population structure between cases and controls. Our study was conducted among non-Hispanic white individuals and models were adjusted for genetic ancestry. The validity and reliability of maternal report of live births compared to medical records has previously been reported to be very high (kappa=1.0) [47, 48], therefore minimizing concern that the method of collection contributed to the results.

Our study was conducted in a subset of female patients who had given birth to a child prior to diagnosis, and are therefore not generalizable to the entire SLE patient population. In order to minimize confounding by ancestry, white women of European ancestry were investigated, which also affected the generalizability of study findings. SLE disproportionately affects African Americans who suffer from more severe disease [52-54] and additional populations need to be examined. Compared to white cases from a population-based study, we observed a similar frequency of lupus nephritis, an indicator of disease severity [54]. The similarities increase our confidence that our cases are representative of European-ancestry women with SLE in the United States.

In conclusion, these findings support the hypothesis that exposure to the fetus influences a mother's risk of disease. This is the first study to demonstrate an association between a child's *DRB1* genotype and risk of SLE in the mother.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- A child's *DRB1* genotype is associated with increased risk of maternal SLE.
- *DRB1*04:01* inherited from the father is associated with a 2-fold risk of SLE.
- Risk was only increased among mothers who carry *DRB1 *03:01, *15:01* and/or **08:01*.

Table 1

UCSF Mother-Child Immunogenetic Study (MCIS) and Inova Translational Medicine Institute (ITMI) participant characteristics

	Cases	Controls
	Mean ± SD or *N* (%)	**Mean ± SD or *N* (%)**
Mothers, n	219	1,085
Age at study enrollment [1,2]	53.8±11.0	37.7±10.4
Number of live births [2]	2.3±1.2	1.9±1.0
Ever smoker [2]	103 (47.0)	271 (25.0)
Age at diagnosis, per medical records	38.6±12.6	--
Autoantibodies [3]		
Anti-dsDNA	87 (39.7)	--
Missing	7 (3.2)	
Anti-Ro	65 (29.7)	--
Missing	13 (5.9)	
Anti-La	28 (12.8)	--
Missing	14 (6.4)	
Anti-Sm	20 (9.1)	--
Missing	14 (6.4)	
Anti-RNP	33 (15.1)	--
Missing	19 (8.7)	

[1] ITMI controls age at study enrollment is mother's age at birth of child.

[2] *p*-value <0.001 for the difference between cases and controls.

[3] Patients may have more than one autoantibody.

Table 2

Association between carrying 1 or more known *DRB1* risk alleles and systemic lupus erythematosus among mothers in the Mother-Child Immunogenetic Study (MCIS)

HLA-DRB1 alleles **(Mothers)**	***N*** **=1,304 (cases/controls)**	**SLE OR (95% CI)** [1]	**Bonferroni corrected *p*-value**
**03:01*			
None	139/832	Reference	0.0004
1 or 2	80/253	1.9 (1.4-2.6)	
**15:01*			
None	156/831	Reference	0.36
1 or 2	63/254	1.3 (1.0-1.8)	
**08:01*			
None	201/1,038	Reference	0.07
1 or 2	18/47	2.0 (1.1-3.5)	
**04:01*			
None	177/920	Reference	0.56
1 or 2	42/165	1.3 (0.9-1.9)	

[1] OR = odds ratio; 95% CI = 95% confidence interval for the association between carrying one or more of each listed *DRB1* allele compared to none and SLE among mothers.

Table 3

Association between children carrying *DRB1* alleles of interest and mothers' systemic lupus erythematosus status

***HLA-DRB1* allele-positive children**	***N* =1,304 (cases/controls)**	**SLE (mother) OR (95% CI)** [1]	**Bonferroni corrected *p*-value**
**03:01*			
None	147/836	Reference	*1.0*
1 or more	72/249	1.2 (0.8-1.7)	
**15:01*			
None	141/787	Reference	*0.48*
1 or more	78/298	1.3 (0.9-1.9)	
**08:01*			
None	204/1,035	Reference	*1.0*
1 or more	15/50	1.0 (0.5-2.2)	
****04:01***			
None	168/941	Reference	***0.004***
1 or more	51/144	**2.1 (1.4-3.1)**	

[1] OR = odds ratio; 95% CI = 95% confidence interval for the association between having one or more children with the specified *DRB1* alleles compared to none and SLE among mothers. Each model is adjusted for number of live births and maternal carrier status of the same allele.

Table 4

Association between children carrying *DRB1* alleles of interest and mothers' systemic lupus erythematosus status among allele-negative mothers

***HLA-DRB1* allele-positive children**	***N* Allele-negative mothers (cases/controls)**	**SLE (mother) OR (95% CI)** [1]	**Bonferroni corrected *p*-value**
**03:01*			
None	118/729	Reference	*1.0*
1 or more	21/103	1.1 (0.7-1.9)	
**15:01*			
None	127/688	Reference	*1.0*
1 or more	29/143	1.0 (0.7-1.6)	
**08:01*			
None	195/1,014	Reference	*1.0*
1 or more	6/24	1.4 (0.5-3.4)	
****04:01***			
None	155/852	Reference	*0.08*
1 or more	22/66	**1.9 (1.1-3.2)**	

[1] OR = odds ratio; 95% CI = 95% confidence interval for the association between having one or more children with the specified *DRB1* alleles compared to none and SLE among mothers. Each model is for mothers negative for the allele and is adjusted for number of live births.

Table 5

Association between *DRB1 *04:01* allele-positive children and maternal SLE according to maternal carrier status of any SLE risk-associated *DRB1* allele **03:01, *15:01*, and/or **08:01*

***DRB1 *04:01* allele-negative mothers**				
	SLE risk allele-positive		**SLE risk allele-negative**	
****04:01* allele-positive children**	***N* (cases/controls)**	**OR (95% CI) [1]**	***N* (cases/controls)**	**OR (95% CI) [1] n = 510**
None	100/439	Reference	55/415	Reference
1 or more	17/30	**2.6 (1.4-4.9)**	5/36	1.0 (0.4-2.6)

[1] Adjusted for number of live births. Risk allele-positive is defined as carrying at least one *DRB1 *03:01, *15:01*, and/or **08:01* allele and risk allele-negative as not carrying any.