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Parity and HLA alleles in risk of rheumatoid arthritis

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Abbreviations: RA, rheumatoid arthritis; HLA, human leukocyte allele; SE, shared epitope

Specific HLA II alleles are associated with rheumatoid arthritis (RA) risk and others with protection. Risk-associated alleles encode similar amino acid sequences from 70 through 74 of HLA-DRβ1 (QKRAA, QRRAA, RRRAA), referred to as the "shared epitope" (SE) and protective alleles encode DERAA at the same location. Fetal-maternal cell exchange results in long-term microchimerism i.e. harboring small numbers of genetically disparate cells. Women with RA who lack the SE were recently found to harbor microchimerism with the SE more often than healthy women. This finding raises the question whether microchimerism with DERAA confers benefit against RA and is underscored by the observation that overall parity reduces RA risk. While there is currently no test for microchimerism with DERAA, we conducted studies to ask whether parity benefits women at risk for RA, either because they have the SE or lack the protective DERAA sequence. HLA genotyping was conducted for 310 RA and 571 healthy women. Parity was associated with reduced RA risk in women aged <45 years (RR 0.53, 95% CI 0.34-0.82) and further analyses examined this group. RA risk reduction with parity was greater among women with the SE than SE-negative women (RR 0.42, 95%CI 0.22-0.79 vs. RR 0.79, 0.38-1.64). Among women without DERAA, RA risk was significantly reduced with parity (RR 0.44, 95% CI 0.26-0.74) but not among DERAA-positive women (RR 0.95 95% CI 0.34-2.65). In summary, results indicate the effect of parity varied according to a woman's HLA-genotype, and women at increased risk of RA benefited most.

Introduction

We recently found a significantly lower risk of rheumatoid arthritis (RA) in parous women compared to nulliparous women, based on a prospective case-control study of newly diagnosed RA in women.[1] RA risk reduction in parous women was significant for younger women, less than 45 years of age, but not for older women. In addition, we found that shorter time since last childbirth strongly and significantly correlated with RA risk, even after controlling for the mother's age. No correlation was observed with age at first birth or total number of births.

Fetal-maternal cell trafficking during pregnancy has recently been recognized to result in long-term persistence of small numbers of fetal cells in mothers and maternal cells in children, referred to as fetal and maternal microchimerism respectively.[2,3] Fetal microchimerism that persists in the mother offers a potential explanation for an effect of parity on RA risk in women.

HLA-DRβ1 alleles associated with RA susceptibility encode similar HLA-DRβ1 sequences referred to as the "shared epitope" (SE).[4] Nevertheless, depending on the population studied 25% to 75% of RA patients lack the SE.[4,5] Recent evidence indicates that RA patients who do not have the SE in their HLA-genotype can acquire the SE as persistent microchimerism from maternal-fetal cell exchange, and suggest SE-encoding microchimerism could increase RA risk for a subset of women.[6,7] Protection from RA is associated with HLA-molecules that carry the sequence DERAA instead of the SE at the same location of the DRβ1 chain.[8] The purpose of the current study was to ask how the effects of parity and RA-associated HLA alleles interact with respect to risk of RA. Initial analysis was conducted to confirm the reduction of risk in parous compared to nulliparous women with the current dataset and subsequent analyses investigated the impact of parity in combination with effects of RA-associated HLA alleles in patients with RA and healthy controls.

Results

Characteristics of the case and control participants are summarized in **Table 1**. The median age of the cases was 43 years and of the controls was 42 years. Women diagnosed with RA were less likely than controls to be Caucasian and to have been married, and had lower educational levels than control subjects. Sixty-nine percent of cases and 74% of controls were parous. Parity of any number was significantly associated with a lower risk of RA:

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relative risk (RR) 0.66, 95% confidence interval (CI) 0.46-0.95, adjusted for age, race (Caucasian vs. non-Caucasian), education level (college or more vs. less than college) and marital status (married or living as married vs. other). This association did not vary by number of births and gravidity without parity conferred no benefit, similar to our previous report.[1]

The relationship of parity with RA risk varied across age, as revealed by exploratory analysis of interactive effects. The lower risk of RA associated with parity was only evident among women aged less than 45 years and was significantly different between women aged less than 45 years and those 45 and older (p = 0.004 for interaction). The estimates in **Table 2** bear out this interaction, showing a strong association of parity and reduced RA risk in younger women. The relative risk for parity suggested a higher RA risk in the older age group but this effect was not significant.

The established associations of RA risk with specific HLA alleles held true in these data: DRB1*04 and the SE (QKRAA, QRRAA or RRRAA) were associated with higher risk of RA, with increasing trends seen across the number of copies (**Table 2**). Presence of the RA-protective sequence DERAA was significantly associated with decreased risk of RA. The associations of HLA alleles with RA risk were stronger in the younger than in the older age group. The trend of higher RA risk with copy number was statistically significant in both age groups for the SE (and DRB1*04) but steeper among women < 45 compared to women ≥ 45 years old (p = 0.07 and p = 0.12 for interactions, respectively). The inverse association of DERAA with risk of RA was evident in both age groups but statistically significant only among women < 45 years old (p = 0.17 for interaction).

Of primary interest to us was the question of whether the association of parity and RA-risk varied according to a woman's HLA genotype, notably for HLA alleles encoding the SE or encoding DERAA. Because the protective association of parity with RA was observed in younger women (<45 years) further analyses examined this group. Among women with the SE and thus at increased risk for RA (one or two copies), parous women were at significantly lower risk compared to nulliparous women (RR 0.42, 95% CI 0.22-0.79) (**Table 3**). Among women who were SE-negative, RA was somewhat decreased in parous compared to nulliparous women but results were not significant. The relative risks for women with vs. those without the SE were not statistically different from each other (p = 0.25 for interaction).

Parity was significantly associated with lower risk of RA among women lacking the DERAA sequence (RR 0.44, 95% CI 0.26 - 0.74). However, among women who had DERAA there was little association of parity with RA risk (RR 0.95, p = 0.07 for interaction) (**Table 4**). We also considered the impact of parity among women lacking the DERAA sequence within subgroups defined by the presence of SE alleles. Although the sample sizes were small, there was little evidence that the effect of parity varied according to SE status (data not shown). Expressed according to whether a woman was nulliparous or parous, the DERAA sequence was associated with reduced RA risk in the former (RR 0.27, 95% CI 0.12-0.64), but not the latter (RR 0.74, 95% CI 0.39-1.39). Thus if a woman's HLA genotype had DERAA, parity did not result in any additional benefit.

Table 1. Subject characteristics

	Controls (N = 571)	Cases (N = 310)
	N (%)	N (%)
Age in years		
15 – 24	25 (4)	24 (8)
25 – 34	132 (23)	63 (20)
35 – 44	175 (31)	80 (26)
45 – 54	160 (28)	67 (22)
55 – 64	79 (14)	76 (25)
Race		
Caucasian	536 (94)	273 (88)
Black	16 (3)	9 (3)
Asian	11 (2)	16 (5)
Other	8 (1)	12 (4)
Marital status		
Married or living as married	423 (74)	201 (65)
Never married	59 (10)	50 (16)
Divorced or separated	79 (14)	52 (17)
Widowed	7 (1)	7 (2)
Unknown	3 (1)	0
Highest level education		
High school or less	153 (27)	146 (47)
Technical school	36 (6)	49 (16)
College or graduate school	382 (67)	115 (37)

Discussion

Specific HLA alleles are associated with risk and others with protection from RA.[4] HLA alleles that are associated with risk and those associated with protection encode for specific sequences in the third hypervariable region of the HLA-DRβ1 chain, a region that is known for importance both in peptide binding and T-cell recognition. RA-risk associated HLA alleles encode similar sequences referred to as the shared epitope (SE), QKRAA, QRRAA and RRRAA; HLA alleles associated with protection encode the sequence DERAA. The former includes DRB1*0401, *0404, *0405, *0408, *0101, *1402 and *1001 and the latter DRB1*0402, *0103, *1102, *1103, *1301 and *1302. However, many RA patients lack the SE and conversely the SE is not uncommon among healthy individuals without RA.[4,5] This observation points beyond genes inherited in the classical Mendelian fashion to other factors modulating RA risk. Naturally acquired microchimerism is a candidate factor that could potentially modulate RA risk.

Parity provides women with an opportunity to acquire fetal microchimerism that could be beneficial or detrimental depending upon the HLA specificity of the microchimerism and the woman's own HLA genotype.[9] In the current study we investigated the relationship of parity to risk of RA according to a woman's own HLA-genotype. We reasoned that women who lacked the RA-protective sequence DERAA might benefit from parity, presumably through acquisition of microchimerism with DERAA. We also reasoned that women who were at risk of RA because they had the SE could benefit from parity through a similar mechanism.

Table 2. Adjusted relative risks of RA by parity and HLA alleles

	Controls (N = 571)	Cases (N = 310)			
	N (%)	N (%)	RR[a]	95% CI	p-value
Parity					
Subjects < 45 years					
Nulliparous	110 (33)	82 (49)	1.0		
Parous	222 (67)	85 (51)	0.53	0.34 – 0.82	0.005
Subjects ≥ 45 years					
Nulliparous	40 (17)	15 (10)	1.0		
Parous	199 (83)	128 (90)	1.43	0.71 – 2.89	0.31
DRB1*04 copies					
0	389 (68)	133 (43)	1.0		
1	158 (28)	129 (42)	2.38	1.73 – 3.29	
2	24 (4)	48 (15)	5.65	3.22 – 9.92	<0.001[b]
SE copies					
0	337 (59)	103 (33)	1.0		
1	203 (36)	141 (45)	2.28	1.64 – 3.15	
2	31 (5)	66 (21)	6.52	3.92 – 10.85	<0.001[b]
DERAA copies					
0	420 (74)	252 (81)	1.0		
1	138 (24)	51 (16)	0.64	0.44 – 0.91	0.01
2	13 (2)	7 (2)	–[c]		

[a]adjusted for age, race (Caucasian vs. not), education level (college or more vs. less than college) and marital status (married or living as married vs. other). [b]p-value represents test for trend across copy levels. [c]categories for 1 and 2 copies of DERAA were combined for comparison to no copies.

We conducted our study by investigating parity prior to disease onset in women with RA compared to healthy women, according to HLA genotypes. We and others have previously reported that parous women are at reduced risk of RA compared to nulliparous women.[1,10] RA cases for the current study derived from our previous study, however, no HLA-genotyping was available for controls recruited to that study. Recently, HLA-genotyping information became available for a dataset of healthy adult women recruited with the same methods and from the same population as our prior study.[11] Our first analysis for the current study was to confirm the association of parity with risk of RA using the HLA-genotyped controls. A significant reduction of RA risk was observed for parous compared to nulliparous women and this risk reduction was observed for younger and not for older women, similar to our prior report.[1]

We next conducted analyses of parity and HLA-genotypes in women with RA and controls. As expected, having the SE was associated with increased RA risk and having DERAA with decreased RA risk. Further analyses examined parity and HLA-genotypes in women less than 45 as RA risk reduction associated with parity was observed in this group. Women who had the SE, and thus were at risk of RA, showed greater risk reduction with parity than women without the SE, although the relative risks were not significantly different from each other. Fetal microchimerism acquired by women who have given birth could carry either RA-protective or RA-risk associated HLA alleles. While the explanation for our observations is not known one potential explanation is as follows. Women with the SE have increased risk of RA and benefit from RA-protective, DERAA-positive microchimerism. While SE-negative women could also accrue benefit from DERAA-positive microchimerism these women are not at risk of RA. On the other hand if a SE-negative woman acquires SE-positive microchimerism RA risk could increase. However, minimal additional impact may accrue for a woman who is herself SE-positive.

The effects of parity and DERAA varied each according to the other in women younger than 45. Women who lacked DERAA showed significant RA risk reduction with parity whereas any difference among DERAA-positive women was minimal. Thus no additional protection was gained by the combined positivity of DERAA and parity. The explanation for these observations is unknown but a reasonable explanation is as follows. Women who have DERAA in their HLA-genotype already have protection against RA so DERAA-positive microchimerism adds little and they may also be less susceptible to any effect of SE-positive microchimerism. On the other hand DERAA-negative women lack protection and so may benefit from acquiring DERAA-positive microchimerism. Some risk might be anticipated in the latter group, however, in that SE-positive microchimerism could also be acquired.

Our study results indicate it would be of interest to test for DERAA-positive microchimerism in RA patients and controls. This could not be done in the current study because an assay is not currently available for this purpose nor were suitable samples available for microchimerism testing. Two recent studies tested for microchimerism with RA-risk associated HLA alleles. In the first study subjects with RA and controls who were negative for DRB1*04 were tested for microchimerism with DRB1*04 and subjects without DRB1*01 were tested for microchimerism with DRB1*01.[6] Subjects were recruited from a French population where DRB1*04, and to a lesser extent DRB1*01, is increased in RA patients compared to controls. While the specific HLA alleles of the microchimerism were not determined (other than for one subject) a significant increase of microchimerism with DRB1*04 and DRB1*01 was found in RA patients compared to controls. To specifically measure SE microchimerism

Table 3. Adjusted relative risks of RA by parity in subjects < 45 years old by SE positivity

	Controls (N = 332)	Cases (N = 167)			
	N (%)	N (%)	RR[a]	95% CI	p-value
SE negative					
Nulliparous	68 (34)	20 (40)	1.0		
Parous	131 (66)	30 (60)	0.79	0.38 – 1.64	0.53
SE positive					
Nulliparous	42 (32)	62 (53)	1.0		
Parous	91 (68)	55 (47)	0.42	0.22 – 0.79	0.008

[a]adjusted for age, race (Caucasian vs. not), education level (college or more vs. less than college) and marital status (married or living as married vs. other).

Table 4. Adjusted relative risks of RA by parity in subjects < 45 years old by DERAA positivity

	Controls (N = 332)	Cases (N = 167)			
	N (%)	N (%)	RR[a]	95% CI	p-value
DERAA negative					
Nulliparous	76 (32)	73 (53)	1.0		
Parous	161 (68)	65 (47)	0.44	0.26 – 0.74	0.002
DERAA positive					
Nulliparous	34 (36)	9 (31)	1.0		
Parous	61 (64)	20 (69)	0.95	0.34 – 2.65	0.92

[a]adjusted for age, race (Caucasian vs. not), education level (college or more vs. less than college), marital status (married or living as married vs. other) and history of spontaneous abortion.

we developed quantitative PCR assays for the two primary SE sequences QKRAA and QRRAA. Employing these assays to test DNA extracted from peripheral blood mononuclear cells we found a significant increase in SE-positive microchimerism in RA patients compared to controls.[7] If a similar quantitative PCR assay could be developed for DERAA, testing could be conducted for RA patients and controls and on samples collected from high risk individuals who are followed for RA incidence. Such studies could determine whether microchimerism with DERAA provides a "vaccine like" protective effect against RA[1] and if so potentially could be applied to treat high-risk individuals.

The current results might initially appear to be at odds with previous descriptions of SE-positive microchimerism in RA patients.[6,7] However, our study population could contain a subset with increased rather than decreased RA risk as might be hypothesized for women who are DERAA-negative and SE-negative and who acquire SE-positive microchimerism, even though the overall net effect of parity was beneficial. Alternatively, the microchimerism source was not known in studies of SE-positive microchimerism, could have originated from miscarriage or elective termination or another source, and there is no apparent benefit of gravidity without parity against RA risk.[1]

While not the subject of the current studies it is important to add that previous studies have asked whether the non-inherited maternal HLA allele ("NIMA") impacts risk of RA in her progeny.[12,13,14] Earlier studies proposed exposure to maternal antigens during fetal life to explain a "NIMA" effect; however, such an effect could also occur due to persisting maternal microchimerism.[15,16] Interestingly, a recent study investigated HLA alleles in RA patients and their parents and found that the DERAA sequence was significantly underrepresented as a non-inherited maternal HLA allele among RA patients.[17] This observation lends support to the hypothesis that DERAA-positive microchimerism could potentially modulate RA risk, whether of maternal, fetal, or other origin.

A final area of interest for future investigations is to identify the hierarchy (if any) in RA risk that occurs according to parity and with particular combinations of HLA alleles. It is well established that particular combinations of HLA alleles in a person's HLA-genotype generate more risk than others. For example, the HLA-genotype DRB1*0401,*0404 is associated with a particularly high risk of RA, more so than homozygous identity for either HLA DRB1*0401 or *0404.[18] By analogy it may be asked whether parity (or a NIMA effect) occurs with similar combinations of HLA alleles (e.g. a woman with DRB1*0404 acquires microchimerism with DRB1*0401) and whether parity resulting in acquisition of the RA-protective DERAA sequence "trumps" some types of SE sequences but not others.

While other studies will be necessary to address the potential role of parity and of microchimerism in modulating RA risk, a logical hypothesis is that there are inherent trade-offs from parity for women, with the possibility to acquire both protection and risk but with protection dominant in the overall net effect. The biological significance of persistent cells from fetal-maternal exchange during pregnancy is not yet known, but it is likely that the HLA-genotype of a woman and the HLA specificity of any microchimerism she harbors both contribute to the outcome.[9] Additional studies are needed to elucidate the role of parity in RA risk and potentially also in modulating RA severity.

Methods

RA patients data collection. The parent study from which the current study and analyses derive was a prospective case-control study that recruited women between 18 and 64 years old with newly diagnosed RA living in King County, Washington or receiving medical care at Group Health Cooperative, a large, Seattle-based prepaid health plan.[19,20] A surveillance system involving area rheumatologists, family physicians, internists and university-affiliated clinics was used to identify cases diagnosed with RA from November 1986 through February 1991. Each potential case was evaluated in person by a board-certified study rheumatologist, who conducted a standardized clinical history and a joint examination. A rheumatoid factor test was performed by the University of Washington Clinical Immunology Laboratory, and a review of all outpatient medical records was performed. Of potential cases identified 93% agreed to the study examination and personal interview, and of these 87% were found to be eligible. The initial study identified 349 women who met the earlier American College of Rheumatology criteria for definite or probable RA. The current study is limited to 319 of these women who met the 1987 revised American College of Rheumatology criteria for RA[21] following a review of the rheumatologist's physical examination, rheumatoid factor test result and medical record abstracts. Each subject was interviewed in person about events prior to a specified reference date that was defined for cases as the date of the first physician visit for symptoms ultimately diagnosed as RA. Nine participants were excluded from this analysis, four of whom were pregnant at reference date and five were missing relevant data points, yielding 310 cases for analysis for this

study. Subject recruitment was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Control data collection. Controls were identified through random-digit telephone dialing among residents of the 3-county metropolitan Seattle area (King, Snohomish, and Pierce Counties) in Washington State. The response proportion was 66.5%. Controls were interviewed as part of a long-term study (1986–2004) of female cancers, during which all subjects received a similar interview as conducted for RA patients described above.[11] Samples suitable for DNA extraction were collected in the years 1990 through 2004 and 603 control women who were 18-64 years old at the time of interview were available for the current study. In-person interviews covered demographic characteristics as well as reproductive, birth control and smoking histories. After excluding 17 women with a history of RA and 15 women who were pregnant at reference date, 571 control subjects were available for this analysis. Subject recruitment was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

HLA Genotyping. DNA was extracted from whole blood or from peripheral blood mononuclear cells isolated from whole heparinized blood. All subjects were genotyped for HLA-DRB1 and DQB1 loci. DNA-based typing was conducted with sequence-specific oligonucleotide probe panels or, alternatively, DRB1 and DQB1 strip detection (Dynal RELITM SSO, UK) was used for initial determination of DRB1 and DQB1 families followed by identification of specific alleles by sequencing (Applied Biosystems, Foster city, CA).[11,22]

Statistical analysis. The primary outcome for analysis was disease status (RA case vs. control). Logistic regression models were used to estimate the associations between parity, HLA markers and disease status, while adjusting for confounding factors. The resulting odds ratio estimates can be interpreted as relative risks because of the rarity of RA in the population from which cases and controls were drawn. Parity was defined as the number of pregnancies of at least 20 weeks. The HLA variables of interest included copy number of HLA alleles that encode the RA-associated SE (DRB1*0401, 0404, 0405, 0408, 0101, 1402 and 1001) and HLA alleles that encode the amino acid sequence DERAA (DRB1*0402, 0103, 1102, 1103, 1301 and 1302 and other rare alleles). HLA-DRB1*04 was also summarized because it is the most common allele group in our predominantly Caucasian RA population.

Factors examined as potential confounders included age at reference date, race, education level, marital status, body mass index, smoking status, oral contraceptive use (ever or never), age at first birth, time since last birth, history of spontaneous or induced abortion, and menopausal status. A factor was included as a confounder if there was a difference of 10% or more in any of the estimated coefficients of interest between the multivariable model including the factor and the model without it.

Interactive effects on RA risk among the factors parity, HLA alleles and age were also investigated. Tests for differences in risk across subsets were computed via interaction terms in the logistic regression models. P-values from regression models were derived from the Wald test. Analyses were performed on SAS software version 9 (SAS Institute, Inc., Cary, NC).

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