Clinical and epidemiological research

EXTENDED REPORT

Parental history of lupus and rheumatoid arthritis and risk in offspring in a nationwide cohort study: does sex matter?

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ABSTRACT

Objectives To examine the familial risk of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), including juvenile rheumatoid/idiopathic arthritis (JRA), in a population-based setting; and to determine whether patterns of transmission differ according to the sex of the parent or offspring, in order to provide insight into the potential impact of X-chromosomal factors on sex disparities in these autoimmune diseases.

Methods A population-based cohort of parent–offspring triads from Denmark (1977–2010) was established. SLE and RA incidence rates among offspring were calculated, and Cox regression was performed to assess the sex-specific risk of disease in offspring according to maternal or paternal disease history.

Results Among 3 513 817 parent–offspring triads, there were 1258 SLE cases among offspring (1095 female, 163 male) and 9118 cases of RA/JRA (6086 female, 3032 male). Among female offspring, SLE risk was nearly the same according to maternal (HR 14.1) or paternal (HR 14.5) history (p=NS); likewise among male offspring, risk according to maternal (HR 5.5) and paternal (no cases) history were similar (p=NS). For RA, all risk estimates were similar, regardless of the sex of the offspring or parent (HR 2.6–2.9; p=NS).

Conclusions The authors quantified the familial risk of SLE and RA in a nationwide cohort study. For both diseases, transmission was comparable among both female and male offspring of maternal and paternal cases. These data provide evidence at the population level that X-chromosomal factors do not play a major role in sex disparities associated with the risk of SLE and RA.

Like the majority of autoimmune diseases, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) disproportionately affect women, with female to male ratios of up to 9:1.[1] Although sex steroid hormones probably contribute to the increased incidence observed among women, this explanation is simplistic.[2] Genomic differences between men and women may play a role in autoimmune and other immunological diseases, and X-chromosomal factors, including X-linked susceptibility genes or incomplete X inactivation, have been hypothesised to contribute to the female preponderance of these diseases.[3][4] It is estimated that the X chromosome contains close to 6% of genomic DNA in humans, or approximately 1100 known genes.[5] Recent studies have suggested potential alleles on the X chromosome that may be relevant to RA and SLE,[6][7] and investigation of candidate genes on the X chromosome that may be associated with autoimmune disorders is ongoing.

Familial aggregation has been identified for many autoimmune diseases, including SLE and RA.[8–14] For instance, based on data from case–control studies, it has been estimated that offspring of a parent with SLE have more than three times the risk of developing SLE compared with controls with no family history (OR 3.3, 95% CI 1.2 to 8.6);[15] a similar degree of risk for developing RA among offspring with an affected parent has been reported (OR 3.5, 95% CI 1.1 to 10.8).[16] However, familial data for SLE and RA have often been derived from multiplex families recruited for genetics studies, which by definition include families with more than one case of disease. Also, it is unclear whether risk differs for maternal versus paternal transmission, or according to the sex of the offspring. Men have single X chromosomes, with all cells having maternally derived alleles on the X chromosome. While women inherit both maternal and paternal X chromosomes, only a single 'active' X chromosome is normally expressed in each cell (transcription of the inactive X is silenced). Epigenetic mechanisms (gene modifications other than alterations in the DNA sequence), such as DNA methylation, are responsible for inactivation of the second X chromosome. The process of X chromosome inactivation is purportedly random, and therefore is expected to yield approximately equivalent proportions of cells in women who express maternal or paternal X alleles. If there are important risk allele(s) on the X chromosome, male offspring of mothers with SLE or RA would be expected to have a higher risk of disease than male offspring of affected fathers, because sons do not inherit a paternal X chromosome. Female offspring, however, would be expected to experience an equivalent magnitude of familial association regardless of whether the parental proband was maternal or paternal. If such patterns were refuted utilising population-based data, it would suggest that X-linked chromosomes do not play a substantial role in disease risk. Identification of differential risks would provide aetiological clues.

Laboratory research related to the intersection of sex, genetics and epigenetics in autoimmune diseases is ongoing, with a lack of complementary epidemiological data. We conducted this population-based study, utilising Danish registry data, to further understanding of the familial risk of disease and sex disparities in the risk of two major systemic autoimmune diseases—RA and SLE.

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METHODS

Study population

This population-based cohort study used linked Danish health registries for the period 1 January 1977 to 1 January 2010. The Danish Civil Registration System was utilised to produce individual-level data linkages, and also to establish parent–offspring linkages, which are available from 1950 onward. The Danish National Registry of Patients provided diagnostic data, based on the International Classification of Diseases (ICD) coding structure (ICD-8 until 1993; ICD-10 from 1994 onward). This database records hospitalisations since 1977 and outpatient visits since 1995. Further details regarding Danish registry data are described elsewhere.[17–19] This research was approved by the Danish ethical review boards and the Danish Data Protection Agency.

Cases of SLE and RA, including juvenile rheumatoid/idiopathic arthritis (JRA), were identified based on relevant ICD-8 and ICD-10 diagnostic codes (see supplementary appendix, available online only). The date of the first ICD code for a given disease in the patient record was considered the diagnosis date.

Statistical methods

The analysis included all offspring–parent triads followed up during the study period. SLE and RA history, including diagnosis dates, were determined for all offspring and parents. Analyses were carried out separately for female and male offspring, in order to investigate sex-specific effects. Crude incidence rates of disease among the offspring, according to maternal and paternal history of disease, were calculated by dividing the number of cases by person-time at risk, expressed per 100 000 person-years. In order to take into account person-time at risk, Cox proportional hazards regression was performed, using a left-truncated approach and with offspring age as the timescale.[20] [21] Both maternal and paternal disease histories were included as covariates in the primary models. Sensitivity analyses were conducted to account for calendar period, by adjusting for the year of birth, in 5-year groups, in the modelling. Further sensitivity analyses were conducted in which families with more than one affected offspring were excluded, so that these families were not over-weighted in the analyses. The Wald $\chi 2$ statistic was used to compare hazard ratios (HR) between maternal and paternal history. Data management and analysis was performed using SAS v9.2 software.

RESULTS

The study population included 3 513 817 eligible parent–offspring triads. Of these, 1015 female offspring and 1344 male offspring had less than 1 day at risk (due to neonatal death) and were thus excluded from analyses incorporating person-time. There was a total of 1258 cases of SLE among offspring (1095 female, 163 male) and 9118 cases of RA/JRA among offspring (6086 female, 3032 male). Table 1 presents incidence rates and HR with 95% CI corresponding to maternal and paternal history of disease, stratified by the sex of the offspring.

A parental history of SLE was strongly associated with the risk of SLE in offspring (HR >14.0 among female offspring for either maternal or paternal history; HR 5.5 among male offspring for maternal history; HR zero for paternal history due to absence of cases). A parental history of RA was also associated with increased risk of RA among offspring at statistically significant levels, compared with offspring without a parental history of RA. However, magnitudes of association were weaker than those observed for SLE (HR ranging from 2.4 to 2.9 in female and male offspring). When JRA cases were included in the total for RA, HR were similar to those for RA cases alone (HR ranging from 2.4 to 2.7).

As presented in table 1, when HR for maternal versus paternal history of disease were compared according to the sex of

Table 1 Sex-specific incidence rates and HR for SLE and RA, including JRA according to the maternal or paternal history of disease, Denmark, 1977–2010

Parental history of disease	Female offspring					Male offspring				
	No of cases	Person-time at risk	Crude rate/100 000 person-years	HR (95% CI)*	p Value†	No of cases	Person-time at risk	Crude rate /100 000 person-years	HR (95% CI)*	p Value†
Maternal SLE										
No	1078	40 656 405	2.7	Referent	0.9588	162	44 269 324	0.4	Referent	0.9753
Yes	17	44 889	36.3	14.1 (8.7 to 22.8)		1	48 468	2.0	5.5 (0.8 to 39.3)	
Paternal SLE										
No	1090	40 690 357	2.7	Referent		163	44 306 784	0.4	Referent	
Yes	5	10 937	45.3	14.5 (6.0 to 34.9)		0	11 008	–	0 (0)‡	
Maternal RA										
No	4301	40 202 250	10.7	Referent	0.7233	1882	43 767 476	4.3	Referent	0.4651
Yes	203	483 783	42.0	2.7 (2.4 to 3.1)		86	541 077	15.9	2.6 (2.1 to 3.2)	
Paternal RA										
No	4394	40 439 961	10.9	Referent		1916	44 026 469	4.4	Referent	
Yes	110	246 073	44.7	2.8 (2.4 to 3.4)		52	282 083	18.4	2.9 (2.2 to 3.8)	
Maternal RA/JRA										
No	5850	40 190 344	14.6	Referent	0.9823	2931	43 757 816	6.7	Referent	0.5844
Yes	236	485,075	48.7	2.7 (2.4 to 3.1)		101	542 648	18.6	2.4 (2.0 to 2.9)	
Paternal RA/JRA										
No	5964	40 427 902	14.8	Referent		2974	44 017 063	6.8	Referent	
Yes	122	247 517	49.3	2.7 (2.2 to 3.2)		58	283 400	20.5	2.6 (2.0 to 3.4)	

*Adjusted for maternal/paternal history.
†p Value comparing maternal versus paternal history risk estimates.
‡Upper bound not calculated due to no cases among male offspring.
JRA, juvenile rheumatoid/idiopathic arthritis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

Table 2 Sensitivity analyses adjusted for birth year and excluding families with more than one offspring with disease

Parental history of disease	Female offspring				Male offspring			
	Adjusted for birth year		Excluding families with more than one affected offspring		Adjusted for birth year		Excluding families with more than one affected offspring	
	HR (95% CI)*	p Value†	HR (95% CI)*	p Value†	HR (95% CI)*	p Value†	HR (95% CI)*	p Value†
Maternal SLE								
No	Referent	0.9059	Referent	0.7710	Referent	0.9872	Referent	0.9754
Yes	14.1 (8.7 to 22.80)		12.7 (7.6 to 21.2)		5.6 (0.8 to 39.6)		5.6 (0.8 to 39.8)	
Paternal SLE								
No	Referent		Referent		Referent		Referent	
Yes	15.0 (6.2 to 36.1)		14.8 (6.1 to 35.6)		0 (0)‡		0 (0)‡	
Maternal RA								
No	Referent	0.7136	Referent	0.5984	Referent	0.4510	Referent	0.7208
Yes	2.8 (2.4 to 3.2)		2.6 (2.2 to 3.0)		2.6 (2.1 to 3.2)		2.5 (2.0 to 3.1)	
Paternal RA								
No	Referent		Referent		Referent		Referent	
Yes	2.9 (2.4 to 3.5)		2.7 (2.3 to 3.3)		3.0 (2.3 to 3.9)		2.6 (2.0 to 3.5)	
Maternal RA/JRA								
No	Referent	0.9909	Referent	0.7453	Referent	0.5683	Referent	0.7111
Yes	2.9 (2.6 to 3.3)		2.5 (2.2 to 2.9)		2.6 (2.1 to 3.2)		2.3 (1.8 to 2.8)	
Paternal RA/JRA								
No	Referent		Referent		Referent		Referent	
Yes	2.9 (2.4 to 3.5)		2.6 (2.2 to 3.2)		2.9 (2.2 to 3.7)		2.4 (1.8 to 3.2)	

*Also adjusted for maternal/paternal history.
†p Value comparing maternal versus paternal history risk estimates.
‡Upper bound not calculated due to no cases among male offspring.
JRA, juvenile rheumatoid/idiopathic arthritis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

the offspring, magnitudes of risk were similar regarding either parent, both for SLE and RA (all p values NS). Results did not differ appreciably after adjustment for calendar period (in 5-year groups; table 2).

There were 12 families with SLE in more than one offspring (all with SLE in two offspring). For RA, 132 families had the disease in more than one offspring (128 families with two offspring and four families with more than two offspring affected). Results from sensitivity analyses excluding families with more than one affected offspring yielded numbers similar to those from the main models (table 2).

DISCUSSION
While familial aggregation of SLE and RA has long been recognised, our study is unique in its population-based design and focus on intergenerational patterns between parents and their offspring, rather than within more broadly defined first or second degree kinships. In addition, we accounted for the age of the offspring and person-time at risk. We also analysed incident cases, instead of simply reporting proportions of prevalent cases among offspring of affected relatives.

Our data extend former research. We thus showed in the Danish population, that a parental history of SLE is associated with up to a 14-fold increased risk of SLE among offspring, compared with a negative parental history of SLE. The magnitude of this risk is substantially higher than previous reports,[15] suggesting that earlier studies may have underestimated familial risk. In contrast, our estimates for RA (HR ranging from 2.6 to 2.9) correspond more closely to previous data.[22] SLE and RA are both complex diseases with multifactorial aetiologies involving the interplay of genetic and environmental factors. Our data imply that the genetic basis of SLE may be stronger than that for RA. Other lines of epidemiological evidence, such as temporal trends, also lend credence to this theory. For instance, while data indicate that the incidence of SLE has been relatively stable over calendar time,[23] the incidence of RA in recent decades has been

estimated to be decreasing,[24 25] indicating a modulation of RA risk by environmental factors.

When we examined whether a parental history of disease had a differential impact according to the sex of the parent or offspring, we confirmed that female offspring are at greater risk of disease than male offspring. This is consistent with well-recognised higher incidence rates among female offspring. As hypothesised, for both SLE and RA, similar magnitudes of risk were observed among female offspring in association with a maternal or paternal history of disease. However, our data did not support the hypothesis that among male offspring a maternal history of disease would be associated with a greater magnitude of risk compared with a paternal history of disease. Rather, similar levels of risk were also seen among male offspring with maternal versus paternal disease history. Our results remained consistent in sensitivity analyses accounting for calendar time, and after the exclusion of families with more than one affected offspring case.

An overarching question in autoimmune disease research is which factors drive the strong female preponderance of disease. The idea that sex-chromosomal factors are involved is intriguing, and epidemiological research is needed in concert with basic science research in this area. Candidate X-chromosomal genes that may be associated with autoimmune diseases are beginning to be identified. For example, at least two single nucleotide polymorphisms on the X chromosome (variants of TIMP1 and IL9R) have recently been associated with RA in genome-wide linkage and association studies.[6] Sawalha et al[26] demonstrated an association between variants of an X chromosome gene (MECP2) and SLE in two independent populations. Interleukin-1 receptor-associated kinase 1 (IRAK1), another gene located on the X chromosome, may be a disease-susceptibility factor in human lupus, and animal models suggest that blocking IRAK1 can prevent murine lupus.[7] As MECP2 and IRAK1 are located in close proximity to each other (on Xq28), linkage disequilibrium at this locus could underlie the apparent

separate genetic associations. Another line of investigation is the identification of X-chromosomal genes with functional relevance to autoimmune disease. For instance, abnormalities in apoptosis have been observed in autoimmune diseases such as SLE,[27] and at least 17 X chromosome genes, including CD40LG, have apoptosis listed as a gene ontology term.[28] However, our epidemiological findings of similar magnitudes of risk, regardless of the sex of the affected parent, indicate that for both SLE and RA, genetic factors associated with the sex chromosomes do not play a major role in disease risk at the population level. Coupled with the observation that individual single nucleotide polymorphisms recognised as being associated with SLE and RA correspond to small magnitudes of risk (OR individually <2), our findings may imply that epigenetic rather than genetic factors are relevant to the sex disparities observed in the risk of these autoimmune diseases.

Incomplete inactivation of the second X chromosome in women may be one epigenetic mechanism involved in autoimmune disease, by allowing the overexpression of X-chromosomal genes in women. Lu et al[29] provided evidence that demethylation of regulatory sequences on the inactive X chromosome and associated overexpression may be a factor in autoimmune disease. They found that CD40LG (a B-cell co-stimulatory molecule, encoded on the X chromosome) is unmethylated in men, while women have both a methylated and an unmethylated copy. Moreover, they demonstrated in a series of experiments on T cells isolated from lupus patients that CD40LG is overexpressed on CD4 T cells in women, but not men, corresponding to demethylation of CD40LG in women. Research is ongoing to determine if similar findings apply to other genes on the inactive X chromosome. A non-genomic concept that should be considered in the context of the parental origin of effects is the transmission of non-inherited maternal antigens (NIMA), which can occur transplacentally or by breastfeeding.[30] Exposure to NIMA may influence immune modelling,[31] and NIMA have been associated with both an increased[32–34] and decreased[35] risk of RA, whereas data do not support a role for NIMA in association with the risk of SLE.[36]

Our results contrast with those from a US-based registry study of SLE multiplex families, in which 22% of 68 SLE parents with SLE offspring were men. This led the authors to infer that men were overrepresented as parents of offspring with SLE.[37] However, because that study was composed of families with at least two SLE cases rather than being population based, it may have been subject to selection biases, such as the inclusion of cases with greater genetic risk or disease severity, or a greater tendency for men with affected offspring to participate due to the rarity of SLE in men.

A phenomenon termed the 'Carter effect', first described for pyloric stenosis,[38] predicts a greater magnitude of disease transmission in the sex with the lower baseline predisposition for disease (men in the cases of SLE and RA), based on the theory that a greater genetic load would be necessary for disease penetrance in the less affected sex. Support for the Carter effect was reported for multiple sclerosis, another autoimmune disease with a female preponderance,[39] but was refuted in another study.[40] While a higher genetic load has recently been reported for men compared with women with SLE,[41] our results do not provide support for the Carter effect in either SLE or RA.

A number of study limitations should be noted. First, SLE and RA cases included in the analysis were classified based on ICD codes, rather than the fulfilment of formal American College of Rheumatology classification criteria, and it is well known that registry data are not completely accurate. However, American College of Rheumatology criteria also have limitations, and have been shown to have sensitivity and specificity of less than 90% in research populations other than the original test population.[42 43] While there may have been some misclassification of case status, such misclassification would be expected to be non-differential, and would therefore be expected to attenuate the reported risk estimates.[44] Due to the small number of male SLE patients (in particular among male offspring), there may have been insufficient power to detect potential sex-dependent effects for this diagnosis. Another concern is that family linkages were based on administrative data, not permitting us to confirm biological parental status. Also, we were unable to assess the contribution of environmental factors, which may also cluster in families, to disease expression.

A future direction will be to explore the possibility of genetic anticipation in the SLE and RA populations, which would be exhibited by a younger age of onset and increased disease severity among second generation cases. As a simple comparison of age of onset distributions from each generation is inappropriate due to statistical considerations such as right truncation,[45] various methods have been developed for the study of genetic anticipation, including newer methods that incorporate data from unaffected family members.[46–50] Another direction will be to investigate familial autoimmunity in broader terms, rather than focusing on the patterns of single diseases within families. Various combinations of autoimmune diseases have been shown to cluster within families and individuals,[1 51 52] and shared heritable pathogenic factors, such as dysregulation of the interferon-α system in several autoimmune conditions, have been suggested.[53 54] While autoimmune diseases may have genetic and environmental risk factors in common, the interplay of such factors may influence the particular autoimmune phenotypes that are expressed.[55 56]

In conclusion, our study shows a strong familial risk for SLE and a more moderate familial risk for RA. For both diseases, we found equivalent disease transmission among both female and male offspring of maternal compared with paternal cases. These results do not support the concept of the Carter effect in SLE or RA, and provide indirect evidence on a population level that X-chromosomal factors do not play a major role in sex disparities observed for the risk of SLE and RA.

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