

Male-only Systemic Lupus

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ABSTRACT. Objective. Systemic lupus erythematosus (SLE) is more common among women than men, a ratio of about 10 to 1. We undertook this study to describe familial male SLE within a large familial SLE cohort.

Methods. SLE families (2 or more patients) were identified from the Lupus Multiplex Registry and Repository. Genomic DNA and blood samples were obtained using standard methods. Autoantibodies were determined by multiple methods. Medical records were abstracted for SLE clinical data. Fluorescent *in situ* hybridization (FISH) was performed with X and Y centromere-specific probes, and a probe specific for the Toll-like receptor 7 gene on the X chromosome.

Results. Among 523 SLE families, we found 5 families in which all the SLE patients were male. FISH found no *yaa* gene equivalent in these families. SLE-affected primary female relatives from the 5 families with only-male SLE patients had a statistically increased rate of positive antinuclear antibodies compared to SLE-affected female relatives in other families. White men with SLE were 5 times more likely to have an offspring with SLE than White women with SLE, but there was no difference in this likelihood among Black men.

Conclusion. Because women in the all-male families had positive antinuclear antibodies, and men are more likely to have children with SLE, these data suggest genetic susceptibility factors that act only in men. (J Rheumatol First Release May 15 2010; doi:10.3899/jrheum.090726)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS MEN AUTOANTIBODIES GENETICS

Interplay between genetics and environmental factors has been implicated for human autoimmune diseases¹. Collectively, autoimmune diseases are one of the 10 leading causes of death among women under 65 years of age in the US². Autoimmune diseases predominately affect women, with an estimate that patients with systemic lupus erythematosus (SLE), Sjögren's disease, systemic sclerosis, and thyroiditis are at least 85% women³.

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SLE is an autoimmune disorder characterized by production of autoantibodies that react with nuclear components^{4,5}. SLE has a female predominance > 90% in general³, and even more so in the childbearing years, where the female-male ratio has been reported as high as 12:1⁶. Men and women with SLE present with different clinical and serological profiles, men having more severe disease⁷. The influence of hormones and chronobiology has been explored, but the nonhormonal influences of menstrual cycles and other unrecognized variables are only just being determined⁸. Recent data suggest that number of X chromosomes rather than sex may be critically important for the sex predilection of SLE^{9,10}.

Familial aggregation of SLE has been demonstrated in the general population, with 7%–12% of patients with SLE having a first-degree relative with SLE in comparison to an average prevalence of 1 lupus patient per 2000 population in Europe¹¹. A high concordance rate of up to 20% among monozygotic twins also suggests a strong genetic component in the development of SLE^{11,12}. Multiple susceptibility genes have been identified by genetic linkage or association^{13,14}.

Genetics in animal models of lupus have also contributed to knowledge of disease susceptibility. Multiple loci for susceptibility to lupus have been mapped for inbred strains of mice that consistently develop the disease¹⁵. One such strain is BxSB, in which the lupus-like illness is both more common and more severe in males¹⁶. Susceptibility to lupus in this strain has been mapped to the Y chromosome

and the locus denoted *yaa* (y-associated autoimmunity) since 1994. Recently, 2 independent reports have shown that an unequal crossover between the X and Y chromosomes has resulted in translocation of a syntenic 4-megabase region of the X chromosome to the Y chromosome, and this region contains the Toll-like receptor 7 (TLR7) gene. Therefore, male mice of this strain have a 2-fold overexpression of TLR7, which was found to be sufficient to dysregulate TLR7-mediated activation of innate immune responses. Thus, these studies demonstrate that the *yaa* gene responsible for susceptibility to a lupus-like illness in these mice is in fact an overexpression of TLR7. However, a recent investigation of 44 men and 55 women with SLE did not find an increased copy number of the TLR7 gene compared to matched controls¹⁷.

Even though mouse models provide important insight into human immune function and disease, their mechanisms require careful validation, since many known immunological differences exist between the 2 species¹⁸. TLR7 is located in a syntenic region of the X chromosome in humans and mice; thus, an unequal crossover between X and Y in humans could result in a *yaa* equivalent. The study of TLR7 copy number was in unrelated patients with SLE¹⁷. We hypothesized that if a *yaa* equivalent exists in humans with SLE, then the most likely scenario in which to find this putative susceptibility gene would be families where men sharing a Y chromosome had SLE.

Thus, we undertook this study to describe families in which the SLE patients are males. In particular, we wished to determine clinical differences in SLE among these men and to determine the presence of a *yaa* gene equivalent.

MATERIALS AND METHODS

Patient collection. Families for this study were obtained from the collection of patients with SLE from the Lupus Family Registry and Repository (LFRR) at the Oklahoma Medical Research Foundation (OMRF)^{7,19,20}. Recruitment is conducted following protocols approved by institutional review boards of both OMRF and the University of Oklahoma Health Sciences Center. Informed consent is obtained from all participants before collection of relevant materials including medical charts and blood samples. A patient is recruited following a telephone interview and an extensive review of medical records by a reviewer with a medical background. A patient thus enrolled must meet at least 4 of the 1982 American College of Rheumatology (ACR) classification criterion to qualify^{21,22}. Recruiting efforts also involve enrolment of affected family members of the proband. To increase the capacity of studying genetic linkage or association, grandparents, parents, and siblings without lupus are also recruited. A blood sample is collected from all participants. Genomic DNA is isolated by use of standard methods as described²⁰. A second set of families with SLE meeting the 1982 ACR criteria was studied as a confirmatory cohort²³.

We identified all families in which the SLE-affected individuals were males and only males, and where there were at least 2 SLE-affected male patients. An alleged SLE-affected patient is one for whom the diagnosis could not be confirmed. In the case of Family C in Figure 1, the alleged SLE patient, who was a man, was deceased when the proband was recruited to the study; thus, confirmation as SLE could not be obtained. The Institutional Review Board of the OMRF has approved the use of the family tree diagrams of these families for this report. In addition to these male-

only families, we also studied families with affected male identical twins.

Healthy family members in these families reported no known history of SLE and had no symptoms suggestive of the diagnosis of SLE as assessed by questionnaire.

Serology. Serology was performed at the OMRF Clinical Immunology Laboratory. Indirect immunofluorescence²⁴ was used to analyze antinuclear antibody (ANA) titers using HEP-2 substrate. Anti-double-stranded DNA (anti-dsDNA) was determined by Farr assay²⁵, and confirmed by *Criethidia lucilliae* kinetoplast immunofluorescence method²⁶. Antibodies to extractable nuclear antigens were determined by Ouchterlony agar gel immunodiffusion²⁷. ELISA was used to assay anticardiolipin IgM and IgG²⁸. Medical records were also abstracted for preexisting laboratory results for these antibodies and used for determining the ACR criteria these patients met.

Autoantibody analysis was also done using the Bio-Rad BioPlex 2200 ANA device (Bio-Rad, Hercules, CA, USA), a fully automated clinical laboratory analysis tool. The BioPlex ANA Screen utilizes multiplex technology and dyed magnetic beads to simultaneously perform automated measurements of 13 autoantibodies. Undiluted sera samples were loaded onto the BioPlex 2200 following the recommendations of the manufacturer. This method was used to detect antibodies against any of the following antigens: 60 kDa Ro (or SSA 60), 52 kDa Ro (SSA52), La (SSB), SmRNP complex, Sm, RNP 68, RNP A, centromere B, Scl-70 (topoisomerase 1), Jo-1, chromatin, dsDNA, and ribosomal P. The centromere B, Jo-1, nRNP 68, nRNP A, Scl-70 (topoisomerase 1), and 52 kDa Ro were produced recombinantly, while dsDNA was synthesized by polymerase chain reaction, and the remaining antigens were affinity purified. The BioPlex 2200 ANA Screen reports a semiquantitative value from 0 to 8, termed the antibody index (AI), for each autoantibody. The positive cutoff for each assay is established by the manufacturer to equal 1.0 AI for each assay, except for dsDNA, which is a quantitative assay reporting IU/ml (normal cutoff 10 IU/ml).

This analysis was also performed upon available sera of 12 healthy first-degree female relatives from the male-only SLE families. Further, these 12 healthy family members were matched on basis of ethnicity, sex, and age within 5 years with 4 additional sets or 48 individual healthy family members not belonging to these male-only families.

Fluorescent in situ hybridization (FISH). FISH was performed with X and Y centromere-specific probes and a probe specific for the TLR 7 gene on the X chromosome (Vysis Inc., Downers Grove, IL, USA). Typing was done at 256 single-nucleotide polymorphism (SNP) from the non-pseudoautosomal regions of the X chromosomes, using the 10K GeneChip Array (Affymetrix Inc., Santa Clara, CA, USA).

RESULTS

We have been identifying and collecting material on families with 2 or more SLE patients as part of the LFRR for 20 years²⁰. Among 523 of these families, there are 1146 patients with SLE, of whom 115 (10%) are males. There are 245 families consisting of SLE-affected siblings, while the remaining families are multigenerational. Of the 523 families, we find that 5 (0.96%) are made up of only male SLE patients (Figures 1 and 2). Three of the families are multigenerational, while 2 contain sibling brothers (Figure 1), one of which contains identical twins (Figure 2). Three of the male-only SLE families were self-identified as White, one as Black, and one as American Indian.

We also examined male twins in our collection of SLE families. There is one male-only SLE family that consists of identical twin brothers, and there is a second family with identical twin brothers as well as an SLE-affected sister

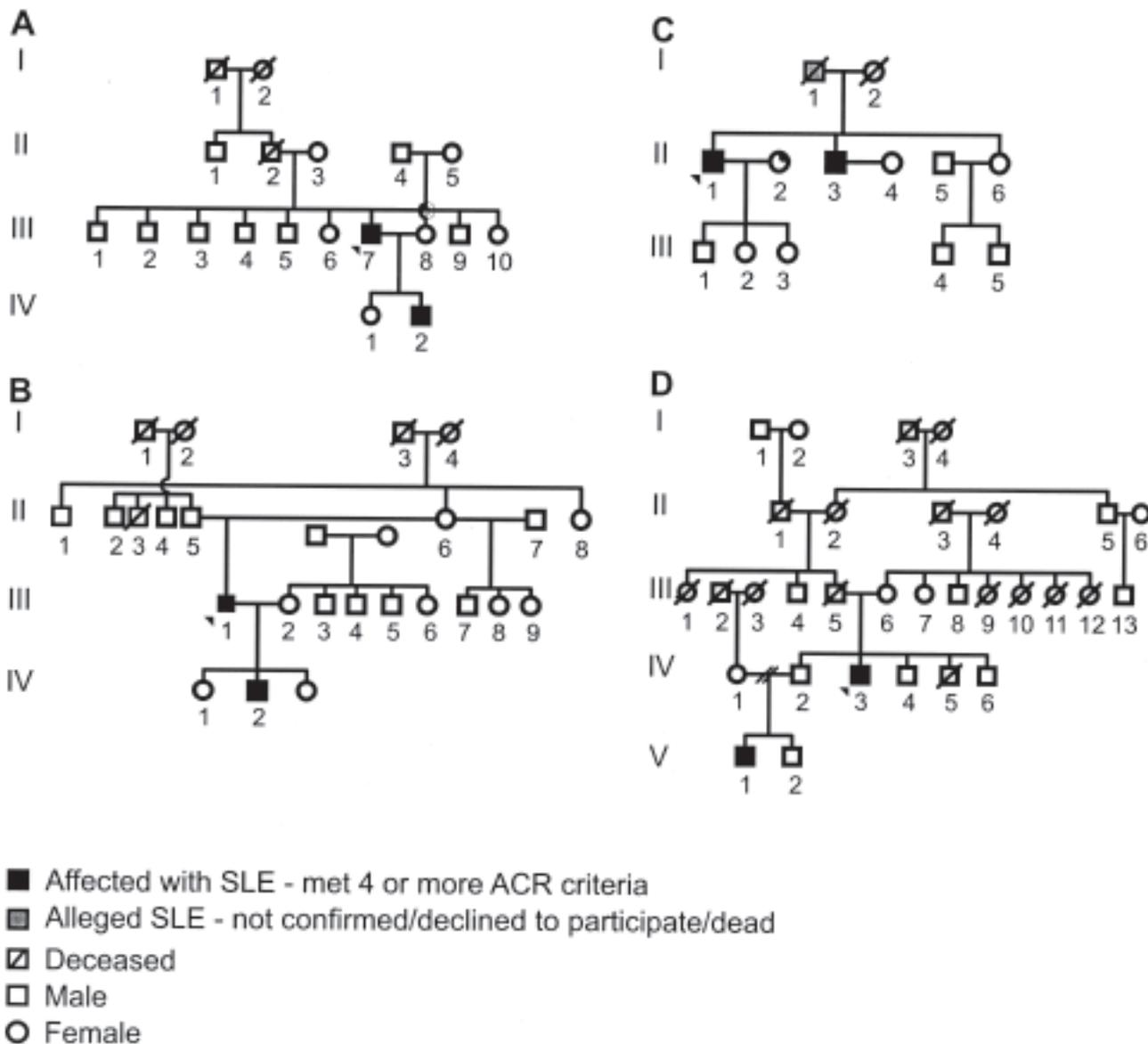


Figure 1. Tree diagrams of families with male-only member SLE.

(Figure 2). Of note, these are the only sets of identical twin boys with SLE in our cohort, and both sets are concordant for disease. There are 13 sets of female identical twins in which at least one of the pair met criteria for SLE. Among these 13 sets of twins, 6 are concordant for SLE and 7 are discordant for disease. All but one set of previously reported identical twins with SLE are female, and the concordance rate is about 15% on aggregate²⁹.

We examined another set of families with 2 or more SLE patients for families in which only males have SLE. Among a total of 428 families, there are 4 where all the SLE patients were male. This included 2 sets of SLE-affected brothers and 2 father-son pairs. Thus, in this second group of SLE families, approximately 1% contained male-only SLE-affected members. This finding is similar to that in our

cohort, where 5 (0.96%) of 523 families had only males affected with SLE.

We next examined the clinical features of SLE among the patients and their relatives in the all-male families. The clinical features of disease (Table 1) show no clear pattern of more serious or worse disease among these men compared to men from families with SLE-affected women. Autoantibodies were determined by an automated analysis procedure as well as traditional methods in the female first-degree relatives in the 5 all-male SLE families. We found that all 12 of these female first-degree relatives without SLE had a positive ANA by indirect immunofluorescence. Among 48 age and ethnicity matched SLE-unaffected female first-degree relatives from families with female SLE patients, only 19 had a positive ANA (chi-square = 11.7, p =

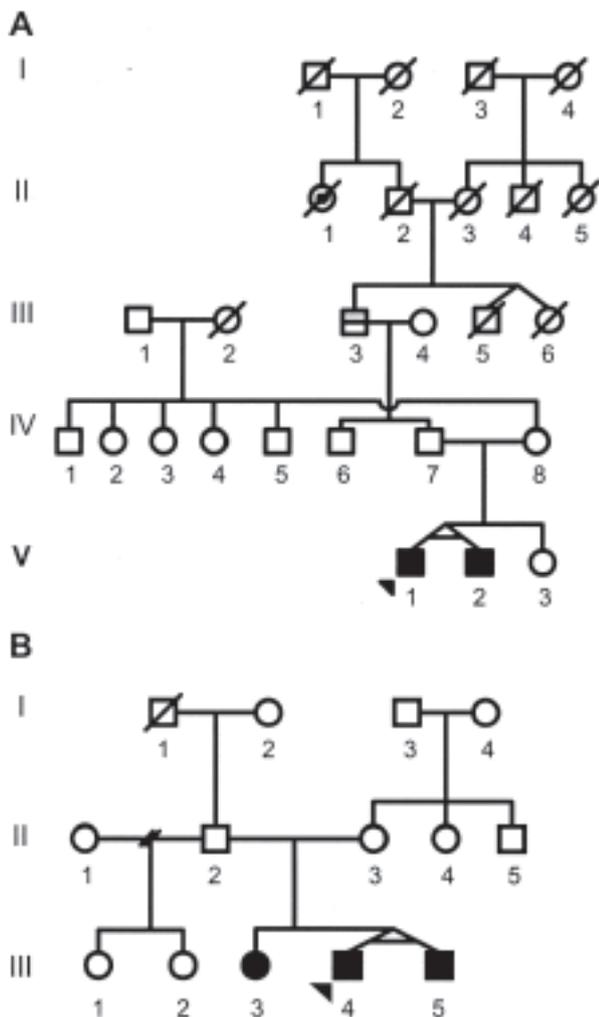


Figure 2. Families with identical male twins with SLE.

0.0006). Antibodies to specific extractable nuclear antigens were uncommon in both groups, and there was no difference between the female first-degree relatives from the all-male SLE families and those from the families with female SLE. Among the male SLE patients in these families, anti-dsDNA was very common, while renal disease was found in only 2 of these men (Table 1).

Next, using the entire LFRR cohort of families with more than one SLE patient, we examined parent-offspring sets to determine sex differences. There were 82 mother-daughter pairs, 10 mother-son pairs, 17 father-daughter pairs, and 6 father-son pairs. In total, there were 924 patients, of which 78 had a child with SLE. Fifteen of these were fathers and 53 were mothers. Thus, 22% of SLE patients who had children with SLE were fathers. White fathers are 4.9 times more likely to have a child with SLE compared to White women, but there was no difference between Black men and women (Table 2). Also, there was a trend toward fathers with SLE having sons with SLE compared to daughters, in that of 23 offspring of SLE men, 6

(26.7%) were male. These data demonstrate that men are overrepresented as parents of SLE patients, and tend to have male children with SLE.

These data suggest a susceptibility factor specific for males. One such factor, already defined in the BxSB mouse, is the *yaa* gene as discussed above. We hypothesized that if such a *yaa* gene equivalent exists in human SLE, it would most likely be found in families with male SLE patients who share a Y chromosome. Therefore, we assessed the men in the all-male SLE families for translocation of the TLR7 gene onto the Y chromosome. For this purpose, we developed a FISH probe that hybridizes to the region of the X chromosome that contains the TLR7 gene. We found that no patient had hybridization of the probe to the Y chromosome, while this probe did bind all X chromosomes studied (Figure 3). Thus, no male SLE patient in these all-male SLE families had the TLR7 gene translocated to the Y chromosome.

DISCUSSION

Efforts to examine the genetics of SLE have resulted in large collections of families in which more than one person is affected with the disease. We have identified over 500 such families and our colleagues at University of California Los Angeles have collected nearly 450 such families. Among both these cohorts of SLE families, about 1% consist of only SLE-affected men. Considering the rarity of men with SLE, that there are families with only men is initially unexpected. On the other hand, in an idealized situation, if men represent 10% of SLE patients and each family has 2 SLE patients, then by chance alone one expects 1% of families to be male only. Nevertheless, even if not greater than expected by chance, study of families with only males with SLE may be fruitful.

In addition to the 5 male-only SLE families in the LFRR, we also found one family where we could confirm one SLE patient who had a brother with incomplete lupus (that is, less than 4 criteria), and yet another family with a patient with confirmed SLE who had a brother with reported SLE. This brother declined to participate in the study, however. No women in either family had a putative or a confirmed diagnosis of SLE. While interesting, these 2 families with putative all-male SLE were not considered further, and were not included in the analyses.

SLE in men is different than that in women, although all studies do not agree on this³⁰. In general, SLE is more severe in men, with renal disease and serious hematological disease such as thrombocytopenia and autoimmune hemolytic anemia as well as neurological disease more likely in men than women³¹⁻³⁵. Several studies have found that SLE in men is more likely to present with serositis than SLE in women^{33,36-39}. An explanation of why SLE is more severe in men has not been achieved, but genetics may play a role. Stein and colleagues found that women with SLE

Table 1. Clinical features of SLE-affected subjects in the all-male SLE families.

Family	Individual	Clinical Features of Pedigree Members with SLE
1 A	III 7	Discoid rash, photosensitivity, arthritis, hematologic disorder immunologic disorder, ANA. Antibodies positive are anti-dsDNA, anti-Sm, anti-Ro, anti-La, anti-RNP, and aPL
	IV 2	Malar rash, oral ulcers, immunologic disorder, ANA. Antibodies positive are anti-dsDNA, anti-Sm, and anti-RNP
1 B	III 1	Malar rash, photosensitivity, hematologic disorder, immunologic disorder, ANA. Antibodies positive are anti-dsDNA, anti-Sm, anti-Ro, anti-RNP and aPL
	IV 2	Serositis, hematologic disorder, immunologic disorder, ANA. Antibodies positive are anti-dsDNA and aPL
1 C	II 1	Photosensitivity, arthritis, serositis, hematologic disorder immunologic disorder, ANA. Antibodies positive are anti-dsDNA, anti-Ro and anti-La
	II 3	Malar rash, discoid rash, photosensitivity, arthritis, serositis hematologic disorder, immunologic disorder, ANA. Antibodies positive are anti-dsDNA, anti-Ro, anti-La and aPL
1 D	IV 3	Malar rash, photosensitivity, arthritis, serositis, hematologic disorder, immunologic disorder, ANA. Antibodies positive are anti-Sm, anti-Ro, anti-La, anti-RNP and aPL
	V 1	Malar rash, arthritis, immunologic disorder, ANA. Antibodies positive are anti-dsDNA and aPL
2 A	III 3	Photosensitivity, arthritis
	V 1	Malar rash, photosensitivity, renal disorder, ANA. Antibodies positive are anti-dsDNA and aPL
2 B	V 2	Malar rash, photosensitivity, arthritis, immunologic disorder, ANA. Antibodies positive are anti-dsDNA and aPL
	III 3	Arthritis, renal disorder, immunologic disorder, ANA. Antibodies positive are anti-dsDNA and aPL
	III 4	Oral ulcers, renal disorder, hematologic disorder, immunologic disorder, ANA. Antibodies positive are anti-dsDNA, anti-Sm and aPL
	III 5	Malar rash, oral ulcers, renal disorder, immunologic disorder, ANA. Antibodies positive are anti-dsDNA and aPL

ANA; antinuclear antibody; aPL: antiphospholipid antibody.

Table 2. Men with SLE are more likely than women with SLE to have SLE-affected offspring.

SLE-affected Parent	Child with SLE, n	No Child with SLE, n
All families		
Father	15	71
Mother	53	785
Chi-square = 14.4, p < 0.0001		
White families only		
Father	12	35
Mother	29	413
Chi-square = 19.9, p < 0.00001. Odds ratio = 4.9 for men to have SLE-affected child compared to women.		

who had an SLE-affected male relative had more severe disease than women without an SLE-affected male relative⁷. This finding was made in the LFRR cohort, which we examined in our study.

There are only a few reports of male SLE families. Lahita and colleagues described 3 families in which there were father-son pairs and no other SLE-affected members⁴⁰. In 1973, 2 sets of brothers with SLE were described⁴¹. While that study predated the 1982/1997 revised ACR classification criteria^{21,22}, upon review, the men described here had convincing SLE by the current criteria⁴¹. Arnett and Shulman's classic report from 1976 described a father-son pair with SLE⁴². One set of identical male twins concordant for SLE has been described⁴³. Thus, the twins reported here bring the total to 3 sets, all concordant for disease. While the number is low, this SLE concordance rate is far above that found for female identical twins.

SLE is a complex genetic disease where a large number

of genes contribute to the risk, but each of these individual susceptibility genes imparts only a small increase in relative risk (reviewed by Rhodes and Vyse⁴⁴). In genetic association studies using SNP typing, the relative risk for SLE associated with the presence of a specific SNP allele may be only 1.2 to 1.4 (see Sestak, *et al*⁴⁵). The men in our families share a Y chromosome, but we did not find a *yaa* gene equivalent⁴⁶⁻⁴⁸ among these families (Figure 3). These results confirm a recent finding in a cohort of unrelated men with SLE, where no significant concordance was found between the number of relative TLR7 gene copies and the SLE phenotype¹⁷. Further, those investigators did not find any difference in variation by ethnic group. These data suggest that the murine genomic segmental duplication in the TLR7 gene and the translocation of this segment to produce the *yaa* gene cannot be translated directly to humans with SLE. The contributory role of genetic variants in TLR7 gene in the human SLE phenotype remains to be determined.

The genetics of autoimmune disease may act at several levels. This has been suggested by study of mice with a lupus-like illness in that an individual susceptibility gene may act by breaking tolerance to self-antigens, by affecting lymphocyte activity, or by increasing likelihood of certain manifestations⁴⁹. The associations of HLA are stronger for specific autoantibodies than for SLE itself (see Scofield, *et al*⁵⁰ and reviewed in Schur⁵¹). So there may be genetics imparting risk for autoimmune disease in general, for specific diseases, or for specific manifestations of a given disease^{19,50,52}.

Could there be genetic factors that contribute to autoimmune disease that operate in only one sex or the other? The

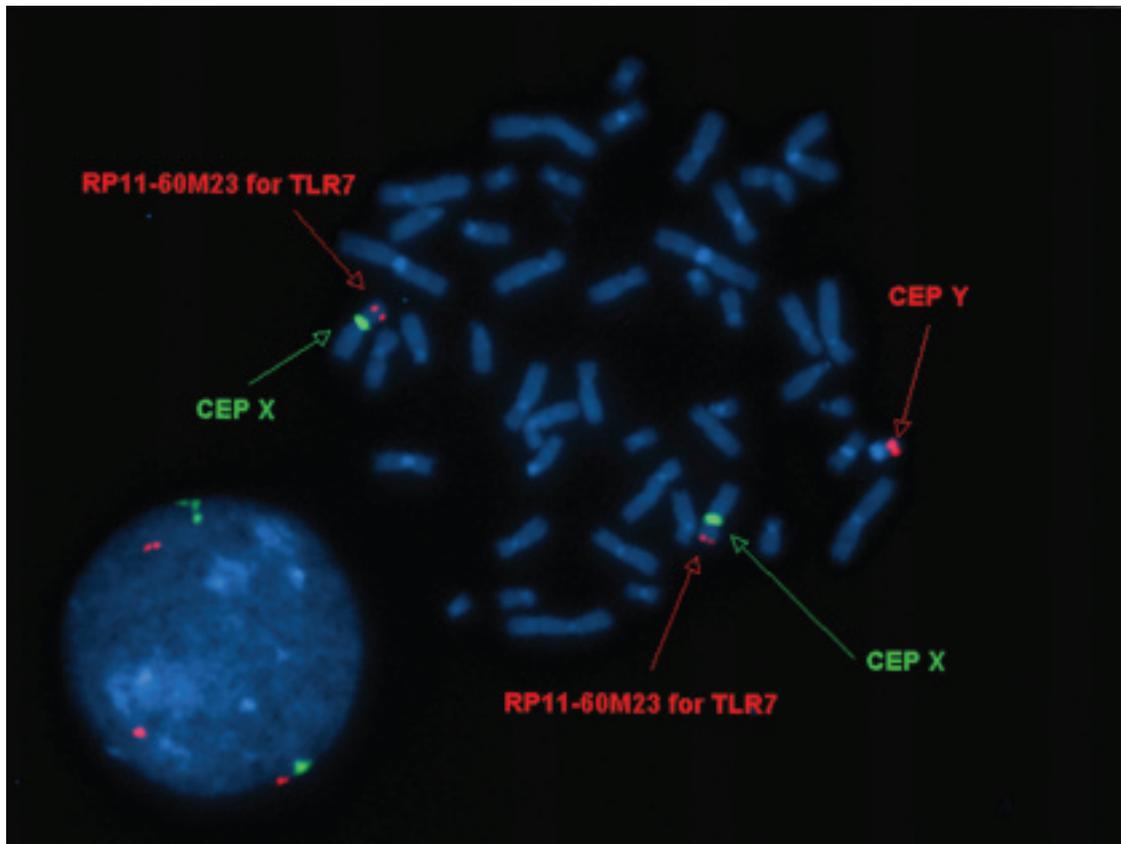


Figure 3. Representative fluorescent *in situ* hybridization (FISH) result in which one probe (RP11-60M23) hybridizes with TLR7-containing portion of the X chromosome. Meanwhile, probes labeled CEP X and CEP Y hybridize with the X and Y chromosomes, respectively. This demonstrates the presence of only one copy of the TLR7 gene on the X chromosome, while there is no evidence of a gene segment containing the TLR7 gene on the Y chromosome. This was the finding in all the SLE men studied.

data are clear that this is the case for type 1 diabetes mellitus, in which men with the disease are much more likely to have offspring with the disease than are women with type 1 diabetes⁵³. This effect may be mediated through genetic imprinting on chromosome 11 at the susceptibility locus IDDM2, for which allelic variations of the insulin-like growth factor-2 have been implicated⁵⁴.

Our data demonstrate that men with SLE are more likely than expected to be the parents of children eventually affected by SLE. There are several possible reasons to explain this observation. Women with SLE may have infertility problems because of recurrent spontaneous abortion associated with antiphospholipid antibodies^{55,56}. Because of lupus nephritis, women may be told by their physician not to have children, but this is obviously not the case for men with SLE. Conversely, there may be genetic causes for an increase in SLE-affected men fathering children with SLE. There is at least one example of an SLE genetic effect that operates in men but not in women⁵⁷. However, not all studies agree on which sex is affected by alleles within this gene⁵⁸. In a linkage study the effect was seen only in families with a male SLE patient⁵⁹. That men with SLE are more

likely to be parents of SLE-affected offspring than women may also be explained by the so-called Carter effect, defined as a polygenic inheritance model with a sexual dimorphic threshold such that the lesser-affected sex is more likely to have children with the phenotype^{60,61}. The Carter effect is known to operate in multiple sclerosis⁶².

Our data suggest that there are factors, genetic or otherwise, that contribute risk to SLE only for men. First, the SLE-unaffected women in the male-only SLE families almost universally had a positive ANA. Their rate of ANA positivity was higher than that found in SLE-unaffected relatives among families with female SLE patients. One can interpret this finding to mean that the break in tolerance that leads to autoimmunity is common between men and women in these male-only families. However, the factor or factors leading to disease are acting only in the men within these families. In addition, we examined parent-offspring pairs with SLE in the LFRR collection of over 600 families with SLE. We found that men are more likely than women to be parents of SLE-affected offspring, but that this difference was present only among American White men and was not found among American Black men. It is possible that SLE

in men is more genetic than in women. That is, men need to have more susceptibility genes than women because male-ness is protective. One such protective factor might be the presence of one X chromosome instead of 2¹⁰. Determining that there are male-specific genetics may be difficult, in that the number of men with SLE needed for such a study will be large. Notwithstanding, the data we present, along with previous reports⁵⁷⁻⁵⁹, suggest that genetic susceptibility factors act in a sex-specific manner. Sorting this out in a genetically complex human disease will be challenging.

In summary, we report that in about 1% of families with SLE all the SLE patients are men. SLE-unaffected women in these families universally have autoantibodies. Along with data that SLE men tend to have more children with SLE compared to women with SLE, these data imply that there are susceptibility factors operating in men but not in women in these families.

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