Rare X chromosome abnormalities in systemic lupus erythematosus and Sjögren's syndrome

Sharma, Rohan; Harris, Valerie M; Cavett, Joshua; Kurien, Biji T; Liu, Ke; Koelsch, Kristi A; Fayaaz, Anum; Chaudhari, Kaustubh S; Radfar, Lida; Lewis, David; Stone, Donald U; Kaufman, C Erick; Li, Shibo; Segal, Barbara; Wallace, Daniel J; Weisman, Michael H; Venuturupalli, Swamy; Kelly, Jennifer A; Pons-Estel, Bernardo; Jonsson, Roland

DOI:
10.1002/art.40207

License:
Other (please specify with Rights Statement)

Document Version
Peer reviewed version

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
This is the peer reviewed version of the following article: Sharma, R., et.al. Rare X chromosome abnormalities in systemic lupus erythematosus and Sjögren's syndrome. Arthritis & Rheumatology. Accepted Author Manuscript. doi:10.1002/art.4020, which has been published in final form at 10.1002/art.4020. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• User may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 04. Jan. 2020
Rare X chromosome abnormalities in systemic lupus erythematosus and Sjögren’s syndrome

Rohan Sharma, MBBS1,3,4, Valerie M. Harris, MS1,2,3, Joshua Cavett, MS1,3, Biji T. Kurien, PhD1,3,4, Ke Liu, BS5,6, Kristi A. Koelsch, PhD1,3,4, Anum Fayaaz, MBBS6, Kaustubh S. Chaudhari, MBBS4, Lida Radfar, DDS7, David Lewis, DDS7, Donald U. Stone, MD8, C. Erick Kaufman, MD3, Shibo Li, MD9, Barbara Segal, MD10, Daniel J. Wallace, MD11, Michael H. Weisman, MD11, Swamy Venuturupalli, MD11, Jennifer A. Kelly, MPH1, Bernardo Pons-Estel, MD12, Roland Jonsson, DMD, PhD13,14, Xianglan Lu, PhD9, Jacques-Eric Gottenberg, MD, Phd15, Juan-Manuel Anaya MD, Phd16, Deborah S. Cunninghame-Graham, PhD17, Andrew J.W. Huang, MD, MPH18, Michael T. Brennan, DDS, MHS19, Pamela Hughes, MD, PhD18, Ilias Alevizos, DMD, MMSc20, Corinne Miceli-Richard, MD, PhD21, Edward C. Keystone, MD22, Vivian P. Bykerk, MD22, Gideon Hirschfield, PhD24, Gang Xie, PhD25, Gunnel Nordmark, MD, PhD26, Sara Magnusson Bucher, MD27, Per Eriksson, PhD28, Roald Omdal, MD, PhD29, Nelson L. Rhodus, MPH, DDS30, Maureen Rischmueller, MBBS31,32, Michael Rohrer, DDS18, Marie Wahren-Herlenius, MD, PhD33, Torsten Witte, MD4, Marta Alarcon-Riquelme, MD, PhD35, Xavier Mariette, MD, PhD21, Christopher J. Lessard, PhD1, John B. Harley, MD, PhD5,6,36, Wan-Fai Ng, PhD37, Astrid Rasmussen, MD, PhD1, Kathy L. Sivils, PhD1,2, and R. Hal Scofield, MD1,2,3,4

3Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; Departments of 2Pathology and 4Medicine, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; 4Medical Service, Department of Veterans Affairs Medical Center, Oklahoma City, OK, USA; 5Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA; 6College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA; 7Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 8Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 9Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 10Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 11Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 12Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 13Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 14Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 15Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 16Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 17Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 18Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 19Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 20Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 21Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 22Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 23Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 24Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 25Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 26Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 27Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 28Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 29Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 30Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 31Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 32Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 33Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 34Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 35Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 36Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA; 37Department of Oral Diagnosis and Radiology, College of Dentistry, Cincinnati, Cincinnati, Ohio, USA.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an ‘Accepted Article’, doi: 10.1002/art.40207

© 2017 American College of Rheumatology

Received: Sep 25, 2016; Revised: Apr 10, 2017; Accepted: Jul 06, 2017
University of Oklahoma Health Sciences Center, Oklahoma City, USA; 5Department of Ophthalmology, Johns Hopkins University, Baltimore, MD, USA, and King Khaled Eye Specialist Hospital, Riyadh, KSA; 6Department of Pediatrics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA; 7Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA; 8Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA; 9Sanatorio Parque, Rosario, Argentina; 10Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen 5021, Norway; 11Department of Rheumatology, Haukeland University Hospital, Bergen 5021, Norway; 12Strasbourg University, Strasbourg, France; 13Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia; 14Division of Genetics and Molecular Medicine and Division of Immunology, Infection and Inflammatory Disease, King’s College London, London, UK; 15Department of Developmental and Surgical Sciences, University of Minnesota, Minneapolis, MN, USA; 16Department of Oral Medicine, Carolinas Medical Center, Charlotte, NC 28232, USA; 17Molecular Physiology & Therapeutic Branch, National Institute of Dental and Craniofacial Research, Bethesda, MD, USA; 18Department of Rheumatology, Université Paris-Sud, AP-HP, INSERM U1012, Le Kremlin-Bicêtre, France; 19Department of Medicine, Mount Sinai Hospital and University of Toronto, Toronto, Ontario; 20Hospital for Special Surgery, New York, USA; 21NIHR Biomedical Research Unit, University of Birmingham, Birmingham, UK; 22Samuel Lunenfeld and Toronto General Research Institutes, Departments of Medicine, Immunology and Molecular Genetics, University of Toronto, Toronto Ontario; 23Section of Rheumatology, Department of Medical Sciences and Science for Life Laboratory, Uppsala University, Uppsala, Sweden; 24Department of Rheumatology, Örebro University Hospital, Örebro, Sweden; 25Rheumatology, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; 26Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway; 27Department of Diagnostic and Biological Sciences, School of Dentistry, University
of Minnesota, Minneapolis, USA; 31Rheumatology Department, The Queen Elizabeth Hospital, Woodville South, SA 5011, Australia; 32Discipline of Medicine, University of Adelaide, Adelaide, SA 5000, Australia;
33Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; 34Clinic for Immunology and Rheumatology, Hannover Medical School, 30625 Hannover, Germany; 35Medical Genomics, Centre for Genomics and Oncological Research (GENYO), Pfizer-University of Granada-Andalusian Regional Government, Health Sciences Technology Park, Granada 18016, Spain and Unit for Chronic Inflammatory Diseases, IMM, Karolinska Institutet, Stockholm, 17177, Sweden;
36Medical Service, Department of Veterans Affairs Medical Center, Cincinnati, Ohio, USA;
37Musculoskeletal Research Group, Institute of Cellular Medicine & NIHR Newcastle Biomedical Research Centre, Newcastle University, Newcastle upon Tyne, United Kingdom;

Correspondence to:

Hal Scofield
825 NE 13th Street
Oklahoma City, OK 73104
Phone +1 405 271 7774
Fax +1 405 271 4110
Email hal-scofield@omrf.ouhsc.edu
Abstract

Background. Sjögren’s syndrome and systemic lupus erythematosus (SLE) are related by clinical and serological manifestations as well as genetic risks. Both diseases are more commonly found in women compared to men at a ratio of about 10 to 1. Common X chromosome aneuploidies, 47,XXY and 47,XXX, are enriched among men and women, respectively, in either disease suggesting a dose effect on the X chromosome.

Methods. We examined cohorts of Sjögren’s syndrome or SLE patients with intensity plots of X chromosome single nucleotide polymorphism (SNP) alleles along with karyotype of selected subjects.

Results. Among ~2500 women with SLE we found three patients with a triple mosaic consisting of 45,X/46,XX/47,XXX. Among ~2100 women with Sjögren’s syndrome, one patient had 45,X/46,XX/47,XXX with a triplication of the distal p arm of the X chromosome in the 47,XXX cells. Neither the triple mosaic nor the partial triplication were found among controls. In another Sjögren’s cohort, we found a mother-daughter pair with partial triplication of this same region of the X chromosome. The triple mosaic occurs in approximately 1 in 25,000 to 50,000 live female births, while partial triplications such are even rarer.

Conclusions. Very rare X chromosome abnormalities are present among patients with either Sjögren’s or SLE, and may inform the location of a gene(s) that mediate an X dose effect as well as critical cell types in which such effect is operative.
Introduction

Systemic lupus erythematosus (SLE) and Sjögren’s syndrome are related by common autoimmune serology, clinical manifestations, and genetics, as well as a strong bias towards the female sex. The sex bias for SLE is about 10-to-1\(^1,2\), while among those with Sjögren’s, women are over-represented between 10 and 15-fold.\(^3\)

Aneuploidies of the X chromosome are common in the human population. Klinefelter’s syndrome (male 47,XXY) occurs in about 1 in 500 live male births but 80% of these men are undiagnosed.\(^4\) Meanwhile, 47,XXX is found in about 1 in 1000 live born girls with only about 1% identified.\(^5,6\) We have found excess 47,XXY among men with either SLE\(^7,8\) or Sjögren’s syndrome\(^9\) as well as excess 47,XXX among women with these diseases.\(^10\) On this basis, we have proposed an X chromosome dose effect for the sex bias of SLE and Sjögren’s syndrome. Such a bias might be mediated by specific genes that escape X inactivation, global escape of X inactivation in specific cell types\(^11\) or interference with immune tolerance by increased production of X chromosome gene products\(^12\), or an effect on the immune system by the mosaicism of random X inactivation.\(^13\)

We have previously reported a 46,XX man among 316 men with SLE.\(^14\) This X chromosome abnormality occurs in as few as 1 in 25,000 to 1 in 50,000 live born boys. We undertook the present study to examine women with either SLE or Sjögren’s syndrome for rare X chromosome aneuploidies.

Methods

Subjects. We studied a large cohort of SLE patients with about 60% being of European heritage and 40% of African heritage, gathered for genetic and other studies, which has been described in detail\(^15\) as well as a large cohort of primary Sjögren’s syndrome patients, where all subjects meeting criteria for other
autoimmune rheumatic disease (that is, those with secondary Sjögren’s were excluded). Subjects met the respective research classification criteria for each of the diseases. Women demonstrated to not have SLE or Sjögren’s served as controls. As previously described, controls were screened for autoimmune rheumatic disease, and no such disease was identified.

X chromosome Analyses: The subjects were screened for X chromosome abnormalities by examination of intensity plots of X chromosome single nucleotide polymorphism (SNP) alleles, as we have previously described. In these displays (so-called, b plots) the fluorescent intensity of the b allele is divided by the intensity of the a and b alleles; thus, giving values of 1.0 for homozygous b SNPs, 0.5 for ab heterozygous SNPs and 0.0 for homozygous a SNPs. However, a person with three X chromosomes will have b plot results at 0.33 for aab SNP alleles and 0.67 for abb alleles. Subjects with abnormal b plots were then studied by karyotype of peripheral blood mononuclear cells, or fluorescent in situ hybridization (FISH), as previous described. Some subjects were studied directly with karyotype using standard methods in a Clinical Laboratory Improvements Amendments (CLIA)-approved laboratory.

Statistics. We calculated binomial 95% confidence intervals for ratios. To calculate the prevalence of SLE among individuals with X triple mosaic, we used Bayes’ theorem as previously described. Briefly, 

\[
P(B/A) = P(A/B) \times P(B)/PA,\]

where \( P(B/A) \) = prevalence of SLE among those with the triple mosaic, \( P(A/B) \) = prevalence of the triple mosaic among SLE patients, \( P(B) \) = prevalence of SLE in the population, and \( P(A) \) = prevalence of the X triple mosaic in the population.
Among 2,426 women with SLE, we found three with the rare triple mosaic of 45,X/46,XX/47,XXX based on the b plots; these results were confirmed by G-band karyotyping of 50 cells (Table 1). These SLE patients had approximately the same ratio of cells with the abnormal X chromosome number. Namely, only 3% of cells were either 45,X or 47,XXX, while a large majority (~94%) carried 46,XX. In examination of their clinical records, there was no diagnosis nor clinical evidence of Turner’s syndrome, abnormal sexual development, or infertility. Binomial 95% confidence intervals for the ratio 3 in 2,426 (0.0012 or 1 in 809) were 0.0003 to 0.0036 (or 1 in 3333 to 1 in 278). And, therefore, did not include the estimated birth rate of 45,X/46,XX/47,XXX of 1 in 25,000. Thus, we concluded that there is a statistical increase in the prevalence of the X chromosome triple mosaic among SLE patients.

We used Bayes’ theorem to calculate the prevalence of SLE among women carrying the X triple mosaic. For this calculation we assumed a prevalence for SLE of 1 in 1000 along with a prevalence of the X triple mosaic of 1 in 25,000. The calculation predicted that 1 in 32 individuals with 45,X/46,XX/47,XXX will have SLE.

Among 2,138 women with Sjögren’s syndrome we did not find a subject with the X chromosome triple mosaic described above. Instead, when examining X chromosome b plots, we noted a single subject with a partial triplication of the X chromosome p arm. That is, distal Xp showed 4 intensity bands at 0.0, 0.3, 0.6 and 1.0, indicating three copies of this portion of the X chromosome, but other areas of the X chromosome showed only three bands at 0.0, 0.5 and 1.0. The latter is the pattern for two X chromosomes (Figure 1A). We obtained a blood sample from this subject and performed karyotyping, which showed a triple X chromosome mosaic with 2 of 20 (10%) cells examined carrying 45,X and 13 of 20 (65%) cells carrying 46,XX, while 5 of 20 (25%) of cells had a triplication of the distal portion of the p arm of X (see Figure 1B). This additional, triplicated portion of X consisted of a non-reciprocal
translocation on to one of the X chromosomes, that is, 47,XX\(^{\text{Xp}}\). By karyotype this abnormality was designated 45,X/46,XX/46,X,\(\text{der(X)(pter>q28::p11.4>ppter)}\) (Figure 1).

We have identified another Sjögren’s patient with a rare X chromosome abnormality in a United Kingdom Sjögren’s cohort. The patient was studied by karyotype as a child based on the presence of epilepsy, oligomenorrhea, and thyroid dysfunction. This study showed one normal X chromosome and one isochrome Xp, that is, an X chromosome with 2 p arms (Figure 1C). Her mother had an inverted segment of Xq (Figure 1C). Both the mother and daughter have Sjögren’s syndrome. This entire cohort of 940 Sjögren’s patients has not been systematically studied for X chromosome abnormalities as approximate 700 are included among the 2138 studied above. So, while the identification of this partial triplication of Xp must be considered anecdotal, the triplicated region overlaps with the one found among the systematically studied patients (Figure 1C). Thus, this incidentally found X chromosome abnormality supports the idea that a gene or genes within distal Xp mediate the X chromosome dose effect.

We found no control subject (n=2712) with the X chromosome triple mosaic, or any variant thereof (Table 1).

Discussion

SLE and Sjögren’s syndrome, similar to many other autoimmune diseases, have a marked sex bias with women affected about 10 times more often than men. A number of hypotheses have been proposed, and some of these tested, to explain the marked sex bias in these diseases. An obvious difference is sex hormones, which might include not only estrogen, androgen and progesterone but also prolactin.\(^{22}\)
Several estrogenic effects, including differentiation of T helper cells, induction of interferon, and survival of B cells, may predispose to autoimmune disease as well as recently described effects on the AIRE gene. A counterargument to the hormone hypothesis is that sex hormones are within normal limits at the time of SLE diagnosis and are not different between men with SLE and men with other chronic, non-autoimmune disease. However, men with untreated hypogonadism are reported to be at high risk of SLE. There is no evidence of acquired X monosomy among women with SLE, as there is among those with autoimmune thyroid disease or primary biliary cirrhosis.

Failure to inactivate an X chromosome in activated CD4+ T cells is found in SLE patients and lupus-prone mice with failure to methylate; and, thus silence, X-linked immune genes. A recent study has shown a global difference in X chromosome inactivation in resting lymphocytes, which was associated with bi-allelic expression of genes from lymphocytes of SLE patients. Others have proposed that an overall effect of X reactivation might perturb immune tolerance. Each of these proposed mechanism might underlie a gene dose effect on the X chromosome, which might involve one or more immune-related proteins encoded on the X chromosome.

We have found very rare X chromosome abnormalities among patients with either SLE or Sjögren’s syndrome. Based on karyotypes of consecutive live births, the 45,X/46,XX/47,XXX triple mosaic is found in about 1 in 25,000 live born girls, but was present in about 1 in 800 women with SLE. We did not find and did not expect to find the rare triple mosaic among our controls, which number only just above 2000. But, past studies of more than 25,000 live female births serve as an external validation of the incidence and prevalence of the 45,X/46,XX/47,XXX mosaic. Meanwhile, the 45,X/46,XX/47,XX\(^{Xp}\) found in one of our Sjögren’s syndrome patients is nearly unprecedented.
Finding these X chromosome rarities has several implications. For instance, only a small percentage of cells carried the additional X or portion of the X chromosome in these patients. The data from Wang, et al. are consistent with this finding as the unusual maintenance of X chromosome inactivation in lymphocytes leads to bi-allelic expression of X-linked genes in only a few cells.\textsuperscript{11} In addition, similar to those with 100% of cells carrying 47,XXX\textsuperscript{10}, the 4 patients we described have no evidence of abnormal sex hormones or sexual development. Likewise, hormonal imbalance due to Turner’s syndrome, which is likely under-represented among SLE patients\textsuperscript{7}, is not expected with the low proportion of 45,X cells in our patients. Thus, estrogen, progesterone, or androgen differences cannot be evoked as an explanation of the apparent association of the X triple mosaic with SLE and Sjögren’s syndrome.

Despite the associations we find, increased prevalence of these rare X chromosome aneuploidies does not prove causality. Nonetheless, given the rarity of these X chromosome abnormalities, association by chance alone seems unlikely to us. Determining mechanism by which additional X chromosomes or distal Xp fragments, increase the risk of these diseases remains to be determined, but will provide evidence of causality. Perhaps the findings reported herein give important clues, which can be used to direct and narrow the candidates for genes impacting the X chromosome dose effect. The distal p arm of the X chromosome contains multiple genes that escape X inactivation.\textsuperscript{11} Thus, the finding of a partial trisomy of this portion of the X chromosome in these patients suggests, but does not prove, that the gene or genes mediating this effect are found in this region. There are a number of past examples in which identification of an abnormality on karyotype in an affected individual led to much more rapid identification of the genetic cause of a particular disease. These include Duchenne’s and Becker’s muscular dystrophy, Angelman’s syndrome, and fragile X syndrome. But, perhaps relevant to the findings herein, was the identification of a chromosome X-21 balanced translocation in a girl with
Duchenne's muscular dystrophy. This finding gave the location of the gene on the X chromosome long before identification was possible through reverse genetics studies. In summary, we suspect that these SLE and Sjögren’s with X chromosome abnormalities inform greatly about the common situation, that is, the marked sex bias between 46,XX women and 46,XY men. Future studies, using the localization provided by the very rare patients reported herein, may be able to concentrate on genes within this shared triplicated region of Xp as the mediators of the X chromosome dose effect for sex bias in SLE and Sjögren’s syndrome.
Acknowledgements

This work has been supported in part by NIH grants AR053483, AI082714, AR053734 and GM104938 as well as by a Merit Review Award from the US Department of Veterans Affairs and Lupus Research Institute grant.
Figure 1. A. B plot of the X chromosome of a Sjögren’s syndrome patient. The distal aspect of the p arm demonstrates a 4-band pattern consistent with three copies of this portion of the X chromosome while the centromeric half of Xp and Xq demonstrate a 3-band pattern consistent with two copies of these portions of the X chromosome. B. A karyotype of the X chromosome of all three cells types found in the Sjögren’s patient. One normal X chromosome was found in 10% of cells (B, left), two normal X chromosomes were found in 65% of cells (B, middle), and one normal X chromosome along with an X chromosome with a non-reciprocal translocation of distal Xp was found in 25% of cells (B, right). The arrow shows the junction of Xq with the translocated distal Xp. Cytogenetic designation is given for this patient’s X chromosome complement. C. Diagram of the X chromosome abnormalities found. A normal X is shown on the far left, the pSS-affected mother
Table 1. Patients with an X chromosome triple mosaic were identified in SLE and Sjögren’s syndrome cohorts. The estimated birth rate for the triple mosaic (45,X/46,XX/47,XXX) is 1 in 25,000 to 50,000 live female births.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>X triple mosaic</th>
<th>Binomial 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>2426</td>
<td>3</td>
<td>1 in 278 to 1 in 3333*</td>
</tr>
<tr>
<td>Sjögren’s</td>
<td>2138</td>
<td>1</td>
<td>1 in 385 to 1 in 100,000</td>
</tr>
<tr>
<td>Combined</td>
<td>4564</td>
<td>4</td>
<td>1 in 1111 to 1 in 5000*</td>
</tr>
<tr>
<td>Controls</td>
<td>2712</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Neither 95% CI cross the known birth rate of 45,X/46,XX/47,XXX; and, thus, demonstrate a statistically significant result. NA- not applicable
References


16
Figure 1. A. B plot of the X chromosome of a Sjögren’s syndrome patient. The distal aspect of the p arm demonstrates a 4-band pattern consistent with three copies of this portion of the X chromosome while the centromeric half of Xp and Xq demonstrate a 3-band pattern consistent with two copies of these portions of the X chromosome. B. A karyotype of the X chromosome of all three cells types found in the Sjögren’s patient. One normal X chromosome was found in 10% of cells (B, left), two normal X chromosomes were found in 65% of cells (B, middle), and one normal X chromosome along with an X chromosome with a non-reciprocal translocation of distal Xp was found in 25% of cells (B, right). The arrow shows the junction of Xq with the translocated distal Xp. Cytogenetic designation is given for this patient’s X chromosome complement. C. Diagram of the X chromosome abnormalities found. A normal X is shown on the far left, the pSS-affected mother.

181x215mm (300 x 300 DPI)