47XXY and 47XXX in Scleroderma and Myositis

R. Hal Scofield,1 ID Valerie M. Lewis,1 ID Joshua Cavitt,1 Bijji T. Kurien,1 Shervin Assassi,2 ID Javier Martin,3 Olga Gorlova,4 Peter Gregersen,5 Annette Lee,5 Lisa G. Rider,6 ID Terrance O’Hanlon,6 Simon Rothwell,7 James Lilleker,8 Myositis Genetics Consortium, Xiaoli Liu,9 Yuta Kochi,10 Chikacshi Terao,11 Ann Igoe,12 ID Wendy Stevens,13 Joanne Sahhar,14 Janet Roddy,15 Maureen Rischmueller,16 Sue Lester,16 ID Susanna Proudman,17 Sixia Chen,18 Matthew A. Brown,19 Maureen D. Mayes,2 ID Janine A. Lamb,7 ID and Frederick W. Miller6 ID

Objective. We undertook this study to examine the X chromosome complement in participants with systemic sclerosis (SSc) as well as idiopathic inflammatory myopathies.

Methods. The participants met classification criteria for the diseases. All participants underwent single-nucleotide polymorphism typing. We examined X and Y single-nucleotide polymorphism heterogeneity to determine the number of X chromosomes. For statistical comparisons, we used χ² analyses with calculation of 95% confidence intervals.

Results. Three of seventy men with SSc had 47,XXY (P = 0.0001 compared with control men). Among the 435 women with SSc, none had 47,XXX. Among 709 men with polymyositis or dermatomyositis (PM/DM), seven had 47,XXY (P = 0.0016), whereas among the 1783 women with PM/DM, two had 47,XXX. Of 147 men with inclusion body myositis (IBM), six had 47,XXY, and 1 of the 114 women with IBM had 47,XXX. For each of these myositis disease groups, the excess 47,XXY and/or 47,XXX was significantly higher compared with in controls as well as the known birth rate of Klinefelter syndrome or 47,XXX.

Conclusion. Klinefelter syndrome (47,XXY) is associated with SSc and idiopathic inflammatory myopathies, similar to other autoimmune diseases with type 1 interferon pathogenesis, namely, systemic lupus erythematosus and Sjögren syndrome.

There was no involvement of patients or the public in this work.

Funded in part by the Intramural Research Program of the National Institute of Environmental Sciences as well as grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR-053483 and AR-053734) and the National Institute of General Medical Sciences (GM-104938). Dr. Scofield’s work was supported in part by a grant from the US Department of Veterans Affairs (BX001451).

1R. Hal Scofield, MD, Valerie M. Lewis, PhD, Joshua Cavitt, MS, Bijji T. Kurien, MD, MA, Shervin Assassi, MD, MA, Maureen D. Mayes, MD: University of Oklahoma Health Sciences Center, and Oklahoma City US Department of Veterans Affairs Medical Center, Oklahoma City; 2Shervin Assassi, MD, MA, Maureen D. Mayes, MD: University of Texas Health Science Center at Houston McGovern Medical School, Houston, Texas; 3Javier Martin, MD: Instituto de Parasitología y Biomedicina López-Neyra, Consejo Superior de Investigaciones Científicas, PTS, Granada, Spain; 4Olga Gorlova, PhD: Geisel School of Medicine, Dartmouth College and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; 5Peter Gregerson, MD, Annette Lee, PhD: Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institutes for Medical Research, Manhasset, New York; 6Lisa G. Rider, MD, Terrance O’Hanlon, PhD, Frederick W. Miller, MD, PhD: National Institute of Environmental Health Science, National Institutes of Health, Bethesda, Maryland; 7Simon Rothwell, PhD, Janine A. Lamb, PhD: The University of Manchester, Manchester, UK; 8James Lilleker, PhD: School of Biological Sciences, The University of Manchester, Manchester, UK, and Salford Royal National Health Service Foundation Trust, Salford, UK; 9Xiaoli Liu, PhD: RIKEN Center for Integrative Medical Sciences, Yokohama, Japan; 10Yuta Kochi, MD, PhD: Tokyo Medical and Dental University, Tokyo, Japan, and RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, and Shizuoka General Hospital and School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan; 11Ann Igoe, MD: Oklahoma Medical Research Foundation, Oklahoma City; 12Joanne Sahhar, MD, PhD: Monash Medical Centre, Melbourne, Victoria, Australia; 13Janet Roddy, MD: Fiona Stanley Hospital, Murdoch Western Australia, Australia; 14Maureen Rischmueller, MBBS, Sue Lester, PhD: The Queen Elizabeth Hospital and University of Adelaide, Woodville, South Australia, Australia; 15Susanna Proudman, PhD: Royal Adelaide Hospital, Adelaide, South Australia, Australia; 16Sixia Chen, PhD: College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City; 17Matthew A. Brown, MBBS, MD: Faculty of Life Sciences and Medicine, King’s College London, London, UK. Members of the Myositis Genetics Consortium are listed in Appendix A.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to: R. Hal Scofield, MD, Oklahoma Medical Research Foundation, Arthritis & Clinical Immunology Program, 825 NE 13th Street, Oklahoma City, OK 73104. Email: hal-scofield@omrf.ouhsc.edu.

Submitted for publication July 14, 2021; accepted in revised form January 10, 2022.

DOI 10.1002/acr2.11413

ACR Open Rheumatology
Vol. 4, No. 6, June 2022, pp 528–533
© 2022 The Authors, ACR Open Rheumatology published by Wiley Periodicals LLC on behalf of American College of Rheumatology.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
**Significance & Innovation**
- Autoimmune rheumatic diseases generally impact women more than men.
- A strong component to such bias in systemic lupus erythematosus and Sjögren syndrome is mediated by the sex chromosome complement.
- We find that the number of X chromosomes is also important in the sex bias of systemic sclerosis and idiopathic inflammatory myopathies.
- These diseases all share pathophysiology involving type 1 interferon pathways.

**INTRODUCTION**

Autoimmune diseases are more common among women and girls (1). The sex chromosomes are implicated in autoimmune sex bias (2). Turner syndrome predisposes to some (3) but not all autoimmune diseases (4). Acquired X chromosome monosomy of peripheral blood mononuclear cells is found in primary biliary cirrhosis (PBC) (5), as well as autoimmune thyroid disease and systemic sclerosis (6), but not in systemic lupus erythematosus (SLE) (7). Skewed X inactivation is found commonly among healthy women (8) but may be increased in some but not all autoimmune diseases (9–11).

Klinefelter syndrome (KS) (47,XXY) is found in 1 in 30 men with either SLE or Sjögren syndrome, whereas the known birth rate is about 1 in 500 live-born boys (12–14). Furthermore, women with 47,XXX are also found in excess among those with SLE and Sjögren syndrome (12). In contrast, no increase in X chromosome aneuploidy was found in rheumatoid arthritis (RA) or PBC (12,14). Genes that escape X inactivation (15) are candidates to mediate an X chromosome dose effect and include CD40 (16), TLR7 (17), and CXorf21 (or TASL) (18,19).

We undertook the present study to determine whether X chromosome aneuploidies play a role in the sex bias of scleroderma (systemic sclerosis [SSc]) and idiopathic inflammatory myopathies, both of which are female biased with sex ratios of 5:1 and 3:1 (20,21).

**PATIENTS AND METHODS**

**Participants.** We studied cohorts with SSc or myositis that had undergone genome-wide single-nucleotide microarray genotyping (22–27). All participants met classification criteria for the disease in question (28–32). Diffuse cutaneous SSc was distinguished from limited cutaneous SSc by previously reported schema (23). The discovery cohorts were assembled from large international collaborative efforts, whereas the Japanese confirmatory myositis cohort was a nationwide effort involving 18 institutions (27). No participant was excluded except by failing to meet classification criteria or failure of genetic data in quality control. The control cohort was assembled at the Oklahoma Medical Research Foundation from healthy volunteers. Each control participant was verified not to have an autoimmune disease by a validated questionnaire and had no serum rheumatic disease autoantibodies (12,33). Participants in the discovery cohorts were of European ancestry, with matched control participants of this same origin. Ethics-committee-approved written informed consent was obtained from all participants at the site of recruitment, and the overall study was approved at the University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation.

**Sex chromosome complement determination.** We used the Illumina GenomeStudio Software to examine b allele frequency plots of the X and Y chromosomes to determine the number of sex chromosomes, as previously reported (12–14).

**Statistics.** Descriptive statistics, including frequency and proportion, were calculated for categorical variables. $\chi^2$ Tests were used to examine the association between two categorical variables when no more than 20% of cells had expected frequencies less than five and no one cell had an expected frequency less than one. Otherwise, Fisher’s exact tests were used (34). Wilson type 95% binomial confidence interval (CI) was calculated for the proportion in each group because this test has better performance than other types of binomial confidence intervals (eg, Wald, Clopper-Pearson, and Agresti-Coull intervals; see ref. 35). All calculations were performed by using SAS 9.4 (SAS Institute, Inc.).

**Patient and public involvement.** There was no patient or public involvement in this study.

**Ethical approval information.** Ethics approval was obtained from local committees at the sites of recruitment of the participants. Thus, there were several dozen human investigation committees that approved this work.

**TABLE 1.** X chromosome aneuploidies found among participants with SSc

|          | 46,XY | 47,XXY | 46,XX | 47,XXX |
|----------|-------|--------|-------|--------|
| **Women**|       |        |       |        |
| SSc      | 435   | 0      |       |        |
| Control  | 1345  | 0      |       |        |
| **Men**  |       |        |       |        |
| SSc      | 67    | 3 (4.3%)* |       |        |
| Control  | 1253  | 1 (0.08%) |       |        |

Abbreviation: SSc, systemic sclerosis.

* $P = 0.0001$ by Fisher’s exact test (see text).
The clinical characteristics of the participants with PM/DM with X chromosome aneuploidies are shown in Table 3 and Supplementary Table 1. Five individuals had cancer-associated myositis, and only three of the men with KS had myositis-specific autoantibodies (Table 3).

Finally, we studied participants with inclusion body myositis (IBM). Among 147 men, we found six with 47,XXY (4.1%, 95% CI 1.5%-8.7% or 1 in 66 to 1 in 12; Table 4). The findings were statistically different from those for the controls ($P < 0.00001$ by Fisher’s exact test). Among 114 women with IBM we found one with 47,XXX, which is similar in magnitude to our findings in SLE and Sjögren syndrome (12); further, the 95% CI for this ratio did not include the known prevalence at birth of ~1 in 1000 (0.0481-0.0016 or 1 in 166 to 1 in 21). The clinical features of these participants are given in Supplementary Table 2.

### DISCUSSION

These findings are similar to those in SLE (13,38) and Sjögren syndrome (14) but distinct from RA and PBC. Thus, supernumerary X chromosomes are associated with some but not all sex-biased autoimmune diseases. We conclude that individual autoimmune diseases should be studied for X chromosome abnormalities. The present study adds to the diseases in which an X chromosome dose effect is present. Up to 15% of genes not in the pseudoautosomal regions escape X inactivation (39); therefore, the excess risk in individuals with 47,XXY and 47,XXX is informative concerning the differential risk associated with persons with 46,XX compared with 46,XY. That is, X chromosome biology mediates the sex bias of some autoimmune diseases.

Interferon plays a role in the diseases associated with supernumerary X chromosomes (12,40–43). Two genes lying on Xp, Toll-like receptor 7 (TLR7) and CXorf21, both contain risk alleles for autoimmune disease and escape X inactivation (17,44). TLR7 signaling is initiated by binding of RNA, induces interferon-α as well as other cytokine production, and is involved in the pathogenesis of SLE (45). Our recent data show that the TASN...
some patients with X chromosome abnormalities, and our in about 15% of patients with KS. Thus, we might have missed X chromosome aneuploidies found among participants with IBM

|        | 46,XY | 47,XXY | 46,XX | 47,XXX |
|--------|-------|--------|-------|--------|
| Women  |       |        |       |        |
| IBM    | 113   | 1      | 0.88% |        |
| Control| 1345  | 0      |       |        |
| Men    |       |        |       |        |
| IBM    | 141   | 6      | 4.1%  |        |
| Control| 1253  | 1      | 0.08% |        |

Abbreviation: IBM, inclusion body myositis.
* P < 0.00001 by Fisher’s exact test (see text).

(or CXorf21) protein regulates lysosomal pH as well as interferon and cytokine production in a sexually dimorphic manner (18,46). The SLE-associated haplotype results in a cis expression quantitative trait locus (eQTL) for CXorf21, which is an interferon response gene and whose protein product co-localizes with TLR7 (19). These independent studies find that sexually dimorphic expression of TASL in immune cells regulates innate immunity (18,19). Thus, X chromosome aneuploidies are found in sex-biased autoimmune diseases in which interferon is known to play a role but are not found in diseases without a known role of interferon.

The finding of increased KS among men with IBM is unexpected, in that this disease does not preferentially affect women (47). Although a neurodegenerative pathogenesis has been proposed (48), other studies support an autoimmune mechanism with autoantibodies (49). Highly differentiated CD8+ T cells infiltrating muscle tissue behave similarly to natural killer cells (50). Antigen-driven transformation of CD20+ B cells in clonal CD138+ plasma cells and CD19+ plasmablasts (48) led to the detection of circulating autoantibodies, along with identification of the target antigen as cytosolic 5’-nucleotidase 1A (NT5C1A) (51). Presence of this autoantibody may identify a subset of patients with IBM who are more likely to be female (51,52). Purified anti-NT5C1A antibodies cause modest myodegenerative changes with protein aggregation (53). Thus, these findings implicate an autoimmune etiology for a subset of patients. However, type 2, not type 1, interferon may be a part of IBM pathogenesis (43). Perhaps X chromosome aneuploidies are found among the patients with IBM with autoimmunity, but this has not been borne out in our results thus far.

There are limitations to the present study. Selection bias is a possibility, but patients were recruited without exclusion or inclusion criteria related to X chromosome aneuploidies. There is no clinical phenotype of either 47,XXY or 47,XXX that would lead to misclassification of participants with SSC or inflammatory myopathy. We have studied the heterogeneity of single-nucleotide polymorphisms on the X chromosome to determine 47,XXY or 47,XXX. This approach will miss patients who have a duplicated X chromosome from a nondisjunction in meiosis II, which occurs in about 15% of patients with KS. Thus, we might have missed some patients with X chromosome abnormalities, and our numbers can be considered a lower estimate of X chromosome aneuploidies in these diseases.

We posit that our data demonstrate remarkable complexity in the female sex bias of inflammatory disease as well as sex-based differences in immune function. Thus far, diseases with evidence of pathological involvement of type 1 interferon, or type 2 interferon in the case of IBM (43), show an X chromosome gene dose effect. The present data extend these findings to SSC, PM/DM, and IBM. Further investigation is needed to fully define the mechanisms related to these findings.

ACKNOWLEDGMENTS

We thank Drs. Elaine Remmers and Robert Colbert for their insightful comments on the article.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Scofield had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Scofield, Miller.

Acquisition of data. Martin, Gorlova, Gregerson, Lee, Rider, O’Hanlon, Rothwell, Lamb, Stevens, Sahhar, Roddy, Lilleker, Liu, Kochi, Terao, Rischmueller, Lester, Proudmans, Brown, Mayes, Miller.

Analysis and interpretation of data. Scofield, Lewis, Cavitt, Kurien, Lamb.

REFERENCES

1. Billi AC, Kahlenberg JM, Gudjonsson JE. Sex bias in autoimmunity. Curr Opin Rheumatol 2019;31:53–61.
2. Libert C, Dejager L, Pinheiro I. The X chromosome in immune function: when a chromosome makes the difference. Nat Rev Immunol 2010;10:594–604.
3. Jorgensen KT, Rostgaard K, Bache I, Biggar RJ, Nielsen NM, Tommerup N, et al. Autoimmune diseases in women with Turner’s syndrome. Arthritis Rheum 2010;62:658–66.
4. Cooney CM, Bruner GR, Aberle T, Namjou-Khales B, Myers LK, Fao L, et al. 46,X,del(X)(q13) Turner’s syndrome women with systemic lupus erythematosus in a pedigree multiplex for SLE. Genes Immun 2009;10:478–81.
5. Invernizzi P, Miozzo M, Battezzati PM, Bianchi I, Grati FR, Simoni G, et al. Frequency of monosomy X in women with primary biliary cirrhosis. Lancet 2004;363:533–5.
6. Invernizzi P, Miozzo M, Selmi C, Persani L, Battezzati PM, Zuin M, et al. X chromosome monosomy: a common mechanism for autoimmune diseases. J Immunol 2005;175:575–8.
7. Invernizzi P, Miozzo M, Oertelt-Prigione S, Meroni PL, Persani L, Selmi C, et al. X monosomy in female systemic lupus erythematosus. Ann N Y Acad Sci 2007;1110:84–91.
8. Shvetsova E, Sofronova A, Monajemi R, Gagalova K, Draisma H, White SJ, et al. Skewed X-inactivation is common in the general female population. Eur J Hum Genet 2019;27:455–65.
9. Chitnis S, Monteiro J, Glass D, Apotoff B, Salmon J, Concannon P, et al. The role of X-chromosome inactivation in female predisposition to autoimmunity. Arthritis Res 2000;2:399–406.
10. Santiwatana S, Mahachoklerwattana P, Limwongse C, Khairit P, Pongratanakul S, Roothumrong E, et al. Skewed X chromosome inactivation in girls and female adolescents with autoimmune thyroid disease. Clin Endocrinol (Oxf) 2018;89:863–9.

11. Kanaan SB, Onat OE, Balandraud N, Martin GV, Nelson JL, Azzouz DF, et al. Evaluation of X chromosome inactivation with respect to HLA genetic susceptibility in rheumatoid arthritis and systemic sclerosis. PLoS One 2016;11:e0158550.

12. Liu K, Kurien BT, Zimmerman SL, Kaufman KM, Taft DH, Kottyan LC, et al. X chromosome inactivation with respect to HLA genetic susceptibility in rheumatoid arthritis and systemic sclerosis. Arthritis Rheumatol 2016;68:1290–300.

13. Scofield RH, Bruner GR, Namjou B, Kimberly RP, Ramsey-Goldman R, Petri M, et al. Klinefelter’s syndrome (47,XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome. Arthritis Rheum 2008;58: 2511–7.

14. Harris VM, Sharma R, Cavett J, Kurien BT, Liu K, Koelsch KA, et al. Klinefelter’s syndrome (47,XXY) is in excess among men with Sjögren’s syndrome. Clin Immunol 2016;168:25–9.

15. Tuukainen T, Villani AC, Yan A, Rivas MA, Marshall JL, Satija R, et al. Landscape of X chromosome inactivation across human tissues. Nature 2017;550:244–8.

16. Lu Q, Wu A, Tesmer L, Ray D, Yousif N, Richardson B. Demethylation of CD40LG on the inactive X in T cells from women with lupus. J Immunol 2007;179:6352–8.

17. Souyris M, Cenac C, Azar P, Daviaud D, Canivet A, Grunenwald S, et al. TLR7 escapes X chromosome inactivation in immune cells. Sci Immunol 2018;3:eaap8855.

18. Harris VM, Harlot IT, Kurien BT, Koelsch KA, Scofield RH. Lysosomal pH is regulated in a sex dependent manner in immune cells expressing CXorf21. Front Immunol 2019;10:578.

19. Odhams CA, Roberts AL, Vester SK, Duarte CS, Beales CT, Clarke AJ, et al. Interferon inducible X-linked gene CXorf21 may contribute to sexual dimorphism in systemic lupus erythematosus. Nat Commun 2019;10:2164.

20. D’Amico F, Skarmoutsou E, Mazzarino MC. The sex bias in systemic sclerosis: on the possible mechanisms underlying the female disease preponderance. Clin Rev Allergy Immunol 2014;47:334–43.

21. Meyer A, Meyer N, Schaeffer M, Gottenberg JE, Geny B, Sibilia J. Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatology (Oxford) 2015;54:50–63.

22. Marquez A, Karick M, Zhernakova A, Gutierrez-Achury J, Chen WM, Onengut-Gumuscu S, et al. Meta-analysis of immunochip data of four autoimmune diseases reveals novel single-disease and cross-phenotype associations. Genome Med 2018;10:97.

23. Meyes MD, Bossini-Castillo L, Gorlova O, Martin JE, Zhou X, Chen WV, et al. Immunochip analysis identifies multiple susceptibility loci for systemic sclerosis. Am J Hum Genet 2014;94:47–61.

24. Miller FW, Cooper RG, Vencovsky J, Rider LG, Danko K, Wedderburn LR, et al. Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. Arthritis Rheum 2013;65:3239–47.

25. Miller FW, Chen W, O’Hanlon TP, Cooper RG, Vencovsky J, Rider LG, et al. Genome-wide association study identifies HL A 8.1 ancestral haplotype alleles as major genetic risk factors for myositis phenotypes. Genes Immun 2015;16:470–80.

26. Rothwell S, Cooper RG, Lundberg IE, Miller FW, Gregersen PK, Bowes J, et al. Dense genotyping of immune-related loci in idiopathic inflammatory myopathies confirms HLA alleles as the strongest genetic risk factor and suggests different genetic background for major clinical subgroups. Ann Rheum Dis 2016;75:1558–66.

27. Kochi Y, Kamatani Y, Kondo Y, Suzuki A, Kawakami E, Hiva R, et al. Splicing variant of WDFY4 augments MD5 signalling and the risk of clinically amyopathic dermatomyositis. Ann Rheum Dis 2018;77: 602–11.

28. Subcommittees for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.

29. Bohan A, Peter JB, Bowman RL, Pearson CM. Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. Medicine (Baltimore) 1977;56:255–86.

30. Rose MR, ENMC IBM Working Group. 188th ENMC International Workshop: inclusion body myositis, 2-4 December 2011, Naarden, the Netherlands. Neuromuscul Disord 2013;23:1044–55.

31. Riggs JE, Schochet SS Jr, Gutmann L, McComas CF, Rogers JS II. Inclusion body myositis and chronic immune thrombocytopenia. Arch Neurol 1984;41:93–5.

32. Hilton-Jones D, Miller A, Parton M, Holton J, Sewry C, Hanna MG. Inclusion body myositis: MRC Centre for Neuromuscular Diseases, IBM workshop, London, 13 June 2008. Neuromuscul Disord 2010; 20:142–7.

33. Karlsson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Daltry LH, Katz JN, et al. A connective tissue disease screening questionnaire for population studies. Ann Epidemiol 1995;5:297–302.

34. Bewick V, Cheek L, Ball J. Statistics review 8: qualitative data: tests of association. Crit Care 2004;8:46–53.

35. McGrath O BK. Binomial confidence intervals for rare events: importance of defining margin of error relative to magnitude of proportion. Cornell University Library. September 7, 2021. URL: https://arxiv.org/abs/2109.02516.

36. Nielsen J, Wohiert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Aarhus, Denmark. Human Genet 1991;87:81–3.

37. Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47,XXX). Orphanet J Rare Dis 2010;5:8.

38. Bentham J, Morris DL, Graham DS, Pinder CL, Tombleson P, et al. Dense genotyping of immune-related loci in idiopathic inflammatory myopathies con

39. Cerrelli L, Williams HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 2005;434:400–4.

40. Chen S, Pu W, Guo S, Jin L, He D, Wang J. Genome-wide DNA methylation profiles reveal common epigenetic patterns of interferon-related genes in multiple autoimmune diseases. Front Genet 2019; 10:223.

41. Muskardin TL, Niewold TB. Type I interferon in rheumatic diseases. Nat Rev Rheumatol 2018;14:214–28.

42. van den Hoogen LL, van Roon JAG, Mertens JS, Wienke J, Lopes AP, de Jager W, et al. Galectin-9 is an easy to measure biomarker for the interferon signature in systemic lupus erythematosus and antiphospholipid syndrome. Ann Rheum Dis 2018;77: 1810–4.

43. Pinal-Fernandez I, Casal-Dominguez M, Derfoul A, Pak K, Plotz P, Miller FW, et al. Identification of distinctive interferon gene signatures in different types of myositis. Neurology 2019;93:a1193–204.

44. Morris DL, Sheng Y, Zhang Y, Wang YF, Zhu Z, Tombleson P, et al. Genome-wide association meta-analysis in Chinese and European types. Genes Immun 2015;16:470–80.

45. Clancy RM, Markham AJ, Buyon JP. Endosomal Toll-like receptors in clinically overt and silent autoimmunity. Immunol Rev 2016;269: 76–84.
APPENDIX A: MEMBERS OF THE MYOSITIS GENETICS CONSORTIUM

Additional members of the Myositis Genetics Consortium are as follows:

Robert G. Cooper (Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK), Ingrid E. Lundberg (Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden), Jiri Vencovsky (Institute of Rheumatology and Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic), Katalin Danko (Division of Clinical Immunology, Department of Internal Medicine, University of Debrecen, Debrecen, Hungary), Vidya Limaye (Royal Adelaide Hospital and University of Adelaide, Adelaide, South Australia, Australia), Albert Selva-O’Callaghan (Department of Internal Medicine, Vall d’Hebron Hospital, Barcelona, Spain), Michael G. Hanna (Medical Research Council [MRC] Centre for Neuromuscular Diseases, University College London [UCL] Institute of Neurology, London, UK), Pedro M. Machado (MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK), Lauren M. Pachman (Northwestern University Feinberg School of Medicine and Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, Illinois), Ann M. Reed (Department of Pediatrics, Duke University, Durham, North Carolina), Hazel Platt (Centre for Integrated Genomic Medical Research, University of Manchester, Manchester, UK), Øyvind Mølberg (Department of Rheumatology, Oslo University Hospital, Oslo, Norway), Olivier Berveniste (Pitié-Salpêtrière Hospital, Université Pierre et Marie Curie [UPMC], Assistance Publique – Hôpitaux de Paris [APHP], Paris, France), Permlie Mathiesen (Paediatric Department, Naestved Hospital, Naestved, Denmark), Timothy Radstake (Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, the Netherlands), Andrea Doria (Department of Medicine, University of Padova, Padova, Italy), Jan De Bleecker (Department of Neurology, Neuromuscular Reference Centre, Ghent University Hospital, Ghent, Belgium), Boel De Paepe (Department of Neurology, Neuromuscular Reference Centre, Ghent University Hospital, Ghent, Belgium), Britta Maurer (Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland), William E. Ollier (Centre for Integrated Genomic Medical Research, University of Manchester, Manchester, UK), Leonid Padyukov (Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden), Christopher I. Amos (Geisel School of Medicine, Dartmouth College, Hanover, New Hampshire), Christian Gieger (Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt [GmbH], Neuherberg, Germany), Thomas Meitinger (Institute of Human Genetics, Technische Universität München, Munich, Germany, and Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany), Juliane Winkelmann (NeurologischeKlinik und Poliklinik, Klinikumrechts der Isar, Technische Universität München, Munich, Germany, and Institute of Neurogenomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany), Lucy R. Wedderburn (Versus Arthritis Centre for Adolescent Rheumatology and Institute of Child Health, UCL, London, UK), and Hector Chino (National Institute of Health Research Manchester Musculoskeletal Biomedical Research Unit, Centre for Musculoskeletal Research, University of Manchester, Manchester, UK).