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Reply: X chromosome short arm involvement in autoimmune diseases: comment on the report by Sharma, et al

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Studying Klinefelter's syndrome (male 47,XXY) and triple X (female 4,7XXX), we propose that the number of X chromosomes mediates the female bias of systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Our recent paper described SLE and SS patients with extremely rare X chromosome aneuploidies in which distal Xp was triplicated, implicating genes lying on the short arm of X¹. Brooks points out that X-linked chronic granulomatous disease (X-CGD) can also have gene duplication from Xp21.2 to Xp terminus, and some female carriers of X-CGD have a cutaneous lupus-like illness. In addition, male X-CGD patients have also been described with discoid lupus², but we do not find a reported association of systemic lupus erythematosus with X-CGD disease or carrier state, except for a single case report³. Several other primary immune deficiencies are associated with SLE⁴.

Brooks, et al. also propose that distal Xp genes may be involved in autoimmunity⁵. A central point is that many genes on distal Xp escape X inactivation. This is clearly the case but varies based upon tissue and development⁶. However, escape of X inactivation by some genes in the X-linked regions of the X chromosome, especially Xp, is a part of normal human physiology⁶. Thus, there may be no reason to evoke a disruption of X inactivation as a cause of autoimmune disease. There are several competing hypotheses for how an X chromosome dose effect might operate. For example, skewed X inactivation, acquired X monosomy, fetal chimerism and female X mosaicism, and X chromosome reactivation. We have reviewed the evidence for and against these hypotheses^{1, 7}. Brooks and colleagues propose the X-chromosome-nucleolus nexus, which predicts abnormal X inactivation⁵.

We found excess 47,XXX and 47,XXY in SLE or SS, but not in primary biliary cirrhosis or rheumatoid arthritis^{7–9}. Thus, we conclude that there is more than one path to sex-bias in autoimmunity. Data from Turner's syndrome supports this notion in that these patients have excess type 1 diabetes, autoimmune thyroid disease (AITD) and celiac disease¹⁰, while

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neither RA nor SLE is over-represented^{10, 11}. AITD is in highest excess among Turner's syndrome patients with an Xq isochromosome^{12, 13}. These patients have one copy of Xp but three copies of Xq, in contrast to what we report in SLE and SS, and Brooks hypothesizes for autoimmune disease. Again, suggesting multiple pathways.

As noted by Brooks, there are a number of candidate genes at distal Xp, but only two have shown genetic association with SLE. These are *TLR7* and *CXorf21*¹⁴, both of which escape X inactivation in various immune cells⁶. The associations and this physiology certainly makes these enticing possibilities for mediating an X chromosome dose effect in SLE and SS.

References

1. Sharma R, Harris VM, Cavett J, et al. Rare X Chromosome Abnormalities in Systemic Lupus Erythematosus and Sjogren's Syndrome. *Arthritis & rheumatology* (Hoboken, NJ). 2017; 69:2187–92.
2. Xie C, Cole T, McLean C, Su JC. Association Between Discoid Lupus Erythematosus and Chronic Granulomatous Disease—Report of Two Cases and Review of the Literature. *Pediatr Dermatol*. 2016; 33:e114–20. [PubMed: 27001332]
3. Manzi S, Urbach AH, McCune AB, et al. Systemic lupus erythematosus in a boy with chronic granulomatous disease: case report and review of the literature. *Arthritis Rheum*. 1991; 34:101–5. [PubMed: 1984766]
4. Carneiro-Sampaio M, Liphaus BL, Jesus AA, Silva CA, Oliveira JB, Kiss MH. Understanding systemic lupus erythematosus physiopathology in the light of primary immunodeficiencies. *J Clin Immunol*. 2008; 28(Suppl 1):S34–41. [PubMed: 18404362]
5. Brooks WH, Renaudineau Y. Epigenetics and autoimmune diseases: the X chromosome-nucleolus nexus. *Frontiers in genetics*. 2015; 6:22. [PubMed: 25763008]
6. Tukiainen T, Villani AC, Yen A, et al. Landscape of X chromosome inactivation across human tissues. *Nature*. 2017; 550:244–8. [PubMed: 29022598]
7. Liu K, Kaufman KM, James JA, et al. Sex Bias In Autoimmune Diseases: Increased Risk Of 47,XXX In Systemic Lupus Erythematosus (SLE) and Sjogren's Syndrome (SS) Supports The Gene Dose Hypothesis. *Arthritis Rheum*. 2013; 65:S379–S.
8. Harris VM, Sharma R, Cavett J, et al. Klinefelter's syndrome (47,XXY) is in excess among men with Sjogren's syndrome. *Clin Immunol*. 2016; 168:25–9. [PubMed: 27109640]
9. Scofield RH, Bruner GR, Namjou B, 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. [PubMed: 18668569]
10. Jorgensen KT, Rostgaard K, Bache I, et al. Autoimmune diseases in women with Turner's syndrome. *Arthritis Rheum*. 2010; 62:658–66. [PubMed: 20187158]
11. Cooney CM, Bruner GR, Aberle T, 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. [PubMed: 19458623]
12. Elsheikh M, Wass JA, Conway GS. Autoimmune thyroid syndrome in women with Turner's syndrome—the association with karyotype. *Clin Endocrinol (Oxf)*. 2001; 55:223–6. [PubMed: 11531929]
13. Hamza RT, Raof NA, Abdallah KO. Prevalence of multiple forms of autoimmunity in Egyptian patients with Turner syndrome: relation to karyotype. *J Pediatr Endocrinol Metab*. 2013; 26:545–50. [PubMed: 23446949]
14. Bentham J, Morris DL, Graham DSC, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet*. 2015; 47:1457–64. [PubMed: 26502338]