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X chromosome and female bias in systemic lupus erythematosus: Focus on population-based evidence

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Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disease with strong genetic components. It predominantly affects females, with a female-to-male ratio of approximately 9:1 [1]. Although the gender bias has often been attributed to sex hormones, the fact that male subjects with Klinefelter's syndrome (47, XXY) have approximately a 14-fold higher risk of developing SLE than 46, XY males indicates that X chromosome could contribute to susceptibility of human SLE [2–6]. The substantial contribution of X chromosome is further supported by the current evidence that females having a third X chromosome (47, XXX) also increase the risk of SLE [7]. In this Article, the most recent data regarding potential influence of X chromosome will be discussed. Especially, we will focus on population-based evidence which might provide new insights into the etiology of SLE as well as other female predominant autoimmune diseases.

X-linked susceptibility genes have been recently identified as novel players. *TLR7* plays critical roles in pathogen recognition and activation of innate immunity [8]. Two large-scale studies identified and replicated association of a *TLR7* 3′UTR single nucleotide polymorphism (SNP), rs3853839 (G/C), with risk of developing SLE. They found that G-allele carriers have higher *TLR7* mRNA levels, protein expression levels and more pronounced IFN signature peripheral blood mononuclear cells (PBMCs) than C-allele carriers [9,10]. Of interest, a significant association between the relative copy number variation (CNV) of *TLR7* and the risk of developing SLE was reported in Mexican population [11]. The association was also replicated in an independent cohort of Mexican population [12]. In addition, the *TLR7* CN correlates significantly with *TLR7* mRNA levels [11].

IRAK1 and its adjacent gene *MECP2*, located at Xq28, are strong candidate genes for susceptibility of SLE. To understand which gene is affected by the underlying causal variant(s) conferring risk of SLE, Kaufman et al. fine-mapped *IRAK1-MECP2* region in 15,783 case-control subjects derived from 4 different ancestral groups. They identified rs1059702 (S196F) in *IRAK1* as the most likely causal variant. The data also showed that the SLE-risk genotype of the SNP is associated with lower mRNA levels of *MECP2* [13]. It is worth noting that the neighboring region of *IRAK1-MECP2* on Xq28 also showed distinct signals in multiple populations. It has been reported that three potential signals in the region (rs2071128 in *NAA10*, rs5987175 in *LCA10* and rs17422 in *HCFC1*) are associated with risk of developing SLE [14,15].

Except for the above genes, several X-linked genes also exhibit associations with susceptibility of SLE. A novel variant (rs7062536) in *PRPS2* was previously identified as being associated with SLE susceptibility [14]. Recently, a study in European population identified a prominent signal in *CXorf21* and a study on multiple Chinese cohorts identified *LINC01420* as being associated with risk of SLE [16,17]. More recently, Zhang et al. further identified rs13440883 in *GPR173* as a novel X-linked locus associated with SLE susceptibility. Conditional analyses showed that the SNP is the only independent association signal in this region [15]. All these identified X-linked genes are summaried in Table 1.

Given that females have two X chromosomes and one of them is inactivated by multiple mechanisms including DNA methylation, it has been previously proposed that the reactivation of the inactive X in females, as a result of DNA demethylation, may be at least partially causative to the female predilection of SLE [18]. Using bisulfite sequencing method, Lu et al. has revealed that *CD40LG* is unmethylated in normal males, while the X-linked gene is methylated in one allele and unmethylated in the other allele in normal females. When treated with demethylating agent 5-Azacytidine in vitro, the regulatory sequences of *CD40LG* is demethylated and *CD40LG* expression is doubled on CD4+ T cells from females but not males. Furthermore, *CD40LG* is demethylated and overexpressed in CD4+ T cells from female but not male patients with SLE [19]. Recently, more X-linked mRNAs and miRNAs, including *CXCR3*, *OGT*, miR-98, let-7f-2*, miR 188-3p, miR-421 and miR-503, have been identified to be overexpressed in lupus T cells from females relative to males with active lupus [20]. Together these results further support the previous hypothesis that DNA demethylation may play an important role in pathogenesis of SLE by awakening *CD40LG* and other methylation-sensitive genes on the inactive X chromosome.

Female mammals use X chromosome inactivation to generate a transcriptionally silent inactive X chromosome enriched with heterochromatic modifications and XIST RNA, which equalizes gene expression between the sexes. More recently, Wang et al. identified that unusual maintenance of X chromosome inactivation in lymphocytes

Abbreviations: SNPs, single nucleotide polymorphisms; CNVs, copy number variations

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Table 1
Significant association of genes on X chromosome with SLE.

Position	Genes	Linked SNPs	OR (95%CI)	Associated populations	Refs.
Xp11.21	*LINC01420*	rs5914778	1.31 (unavailable)	Asian	[17]
Xp11.22	*GPR173*	rs13440883	1.16 (1.11–1.23)	Asian/European	[15]
Xp21.2	*CXorf21*	rs887369	1.15 (1.10–1.21)	European	[16]
Xp22.2	*TLR7*	rs3853839	1.27 (1.17–1.36)	Asian	[9,10]
			1.23 (1.13–1.35)	European American	
			1.24 (1.09–1.41)	African American	
			1.26 (1.10–1.43)	Amerindian/Hispanic	
Xp22.2	*PRPS2*	rs7062536	0.84 (0.80–0.89)	Asian	[14]
Xq28	*IRAK1-MECP2*	rs1059702	1.56 (1.35–1.79)	Asian	[13]
			1.35 (1.22–1.48)	European American	
			1.48 (1.17–1.87)	African American	
			1.49 (1.31–1.70)	Amerindian/Hispanic	
Xq28	*HCFC1*	rs17422	0.75 (0.71–0.80)	Asian	[14]
Xq28	*NAA10*	rs2071128	0.81 (0.77–0.86)	Asian	[14]
Xq28	*LCA10*	rs5987175	1.20 (1.05–1.36)	Asian	[15]

Abbreviations: CI: confidence interval, OR: odds ratio, SNPs: single nucleotide polymorphisms.

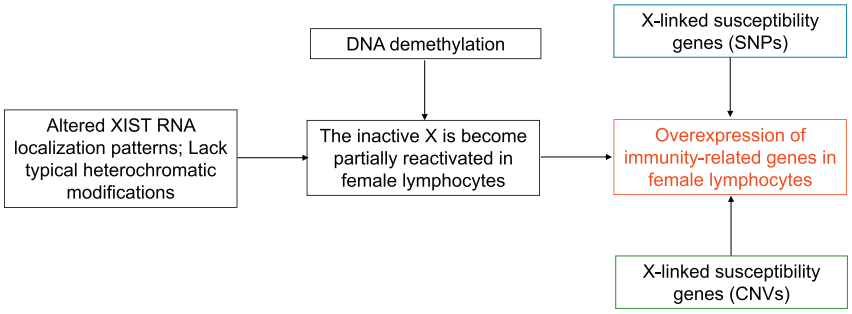

Fig. 1. The potential mechanisms linked X chromosome for gender bias in systemic lupus erythematosus (SLE).

predisposes portions of the inactive X to become reactivated, providing a novel mechanism for why females and individuals with multiple X are more susceptible to autoimmunity. The group observed that mature naïve T and B cells have dispersed patterns of XIST RNA, and they lack typical heterochromatic modifications of the inactive X chromosome. Furthermore, they found that examined B cells from patients with SLE also have altered distributions of XIST RNA localization patterns and these altered distributions are correlated with biallelic expression of immunity-related X-linked genes [21].

The potential mechanisms for gender bias in SLE are presented in Fig. 1. In briefly, since females have two X chromosome, unusual maintenance of X chromosome inactivation (altered XIST RNA localization patterns; lack typical heterochromatic modifications) and DNA demethylation could result in the inactive X is become partially reactivated in female lymphocytes. Due to X chromosome contain many immunity-related genes (such as *TLR7*, *IRAK1*, *CD40LG*, etc.), the reactivation of inactive X could further result in overexpression of these immunity-related genes in female lymphocytes. As a result, females have increased immune responsiveness than males, and they are more likely to develop SLE as well as other autoimmune diseases [21]. Consistently, male subjects may require a higher genetic risk to achieve a lupus flare equal in severity to females in part because of lacking the second X chromosome [22].

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Conflict of interest

The authors declared no competing interests.

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