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Sex Bias in Autoimmunity

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Summary

calculated based on prevalence data of a complex interplay of the sex chromosomes, sex hormones, the microbiota, and additional environmental and sociological factors.

Keywords

sex bias; autoimmunity; sex-dependent gene regulation; X chromosome; VGLL3

Introduction

The immune system functions to defend against infection. Responses must be robust and specific enough to ward off or overcome infection without causing undue harm to the organism. Autoimmune disease arises when an exaggerated or misdirected immune response damages native tissues or organs. While individual autoimmune diseases are rare, they are collectively among the most prevalent diseases in Western society (1). Despite intensive investigation, our understanding of the pathogenesis of autoimmune disease is incomplete. A growing body of evidence supports a model wherein environmental and lifestyle factors precipitate development of autoimmunity in genetically susceptible hosts. Cures have been elusive, and lifetime treatment is often required.

Cellular and humoral immunity are generally stronger in women; women have higher levels of circulating antibodies, more circulating CD4 T cells, more robust cytokine production in response to infection, and enhanced rejection of tumors and allografts (2). Many autoimmune diseases show a striking female sex bias (Figure 1) (3). Systemic lupus erythematosus (SLE), Sjogren's syndrome, Grave's disease, and Hashimoto's thyroiditis are seven to ten times more common in women than men; multiple sclerosis (MS), rheumatoid arthritis (RA), and scleroderma are two to three times more common (4). Overall, it is estimated that 78% of people affected with autoimmune diseases are women (5). For many diseases such as SLE, genome-wide association studies and meta-analyses have identified

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Purpose of review

To give an overview of recently published articles addressing the mechanisms underlying sex bias in autoimmune disease.

Conflicts of interest

The authors have no conflicts of interest.

numerous risk variants, yet female sex carries a risk of autoimmunity that dwarfs that of any susceptibility locus noted to date (Figure 2) (6, 7). The biological mechanisms underlying this bias are incompletely understood. Previous inquiry centered on the influence of sex hormones, yet female sex bias is frequently observed even in autoimmune diseases with onset in childhood, when estrogen levels do not differ between the sexes, or in post-menopausal women. More recent work suggests that the sex chromosomes themselves and sex-specific environmental factors such as sexually dimorphic microbiota are also important drivers of sex bias in autoimmunity. In this review, we discuss current and foundational studies addressing mechanisms of sex bias in autoimmunity.

Sex hormones

In the search for drivers of sex-biased autoimmunity, sex hormones represent obvious culprits. Indeed, sex hormone regulation of immunity is extensive, with interconnections to the other mechanisms discussed in this review. Sex hormones act primarily through associating with their respective intracellular receptors and binding their cognate response elements in target genes (8–10). Sex hormone receptors are widely expressed in immune cells, and estrogen and androgen response elements are found in the promoters of several innate immunity genes (11). Variations in autoimmune phenotype across puberty, pregnancy, and menopause demonstrate the complex regulation of immunity by sex hormones. The ease of antagonizing and supplementing these hormones renders them attractive as therapeutic targets and agents, but results have been inconsistent, and exposure to non-physiologic sex hormone levels carries other intrinsic risks (12–14). Thus, identifying and targeting the downstream immunological effectors of sex hormones may hold more therapeutic promise.

Progesterone, which is present at high levels during the luteal phase of the menstrual cycle and in pregnancy, is likely a key promoter of immune tolerance during pregnancy (15). Progesterone is generally immune suppressive, decreasing pro-inflammatory mediators and inhibiting immune cell activation (reviewed in (16)). Progesterone signaling occurs primarily through progesterone receptors, which are expressed in many immune cell types including NK cells, macrophages, dendritic cells, and T cells (17). At high levels, signaling may also occur through glucocorticoid receptors (18). Progesterone decreases activation of NK cells (19), macrophages, and dendritic cells (20, 21) and promotes skewing from Th1 to Th2 type T cell responses (22), which may account for the amelioration of Th1-associated autoimmune diseases such as MS and RA during pregnancy. Studies of human cord blood have shown that progesterone has strong regulatory T cell (Treg) induction activity and suppresses Th17 cell differentiation (15). Some of the effects of progesterone may be mediated by NF-κB inhibition (23).

Regulation of immunity by estrogens is more nuanced. Estrogen levels are high in pregnancy, low in menopause, and variable across the menstrual cycle. Estrogen receptor (ER) subtypes show differential expression in immune cells: ERα is highly expressed in T cells and ERβ in B cells (24). In addition to binding estrogen response elements (EREs) in target genes, ERs also interact with ERE-independent transcription factors in immune cells (25). Estrogens upregulate a number of key immunity factors including interferon (IFN) regulatory factor 5 (IRF5) (26), and IFN-γ (27), as well as the intracellular TLR trafficking

protein UNC93B1 (28). Estrogens also function through ERα to downregulate the autoimmune regulator (AIRE), a critical factor in central tolerance, through promoter methylation(29); AIRE expression is also downregulated by progesterone and upregulated by the androgen dihydrotestosterone (29, 30). The effects of sex hormones on sex-biased DNA methylation and autoimmunity are otherwise as yet unclear (31). Additionally, estrogens regulate miRNAs (32), who in turn regulate estrogen-dependent signaling (33). Estrogens increase neutrophil numbers (34, 35) but overall inhibit their activation and trafficking via multiple mechanisms, some mediated by NF-κB inhibition (reviewed in (36)). Estrogens enhance NK cell cytotoxicity and IFN-γ production (37) but downregulate NK cell granzyme B secretion and cell surface activation markers (38). Effects of estrogen on monocytes and macrophages vary by dose: production of pro-inflammatory cytokines is enhanced at low concentrations and suppressed at high (39). The response of dendritic cells to estrogens is mixed, inducing production of both anti-inflammatory and Th1-type pro-inflammatory cytokines (40–42). At lower concentrations, estrogens have immunostimulatory effects, promoting a Th1 response through enhancing the secretion of IFN-γ (27, 43, 44); in contrast, at high concentrations, estrogens promote a Th2 response (45–47). In pregnant SLE patients, this Th2 shift and consequent increased production of autoantibodies often exacerbates disease (48). Effects on Th17 cells are less clear (36). Treg cells increase with estrogens (49, 50). Estrogens promote B cell survival, maturation, class switching, and antibody production (51–53) and interfere with peripheral negative selection of autoreactive B cells (54, 55). Oophorectomy has been reported to be protective in lupus-prone mice (56); however, recent data suggest that this protection may not rely solely on estrogen-mediated effects, as complete absence of ERα does not delay lupus in prone mice (57).

Androgens predominantly downregulate the immune response (58), decreasing pro-inflammatory mediators and inhibiting the proliferation and activation of a number of immune cell populations (reviewed in (36)). Accordingly, androgens have been shown to exert a protective effect in multiple autoimmune rodent models (30, 59, 60). This appears to be mediated in part by androgen-induced upregulation of AIRE in the male thymus: androgens increase AIRE levels by binding the androgen receptor (AR) and targeting the *AIRE* promoter, and the protective effects of androgens and male sex are lost in AIRE-deficient mice in a model of experimental autoimmune encephalitis (30). Additionally, ARs are broadly expressed in neutrophil-lineage cells, with no difference in male and female expression patterns (61), and act to increase the number and trafficking of neutrophils (62); however, androgens decrease pro-inflammatory responses of neutrophils (63), natural killer (NK) cells (64), and macrophages (65). ARs are not expressed in peripheral lymphocytes but are found in lymphoid and non-lymphoid thymic and bone marrow cells (66), where they limit the number of immature thymocytes and restrain active cell cycling (67). While androgens decrease the activation of Th1 and Th2 cells (68), Th17 cell responses are enhanced (69). Treatment to reduce testosterone decreases Treg count (70). Androgens have also been found to limit the number of immature type 2 innate lymphoid cells in the lung (71). In epidermal cells, androgens were found to modulate the expression of *PRDM1*, a transcriptional repressor involved in thymic T cell apoptosis and other immune cell

processes that is implicated in female-dependent autoimmune risk (72). B cell number is negatively regulated by androgens (62).

Some studies support a role for psychosocial stress in initiation or exacerbation of autoimmune disease, although causation has been challenging to establish (73). Response to stress occurs through the hypothalamus-pituitary-adrenal (HPA) axis, which also exhibits sexual dimorphism in cortisol response to psychosocial stressors (reviewed in (31)). Stress triggers release of glucocorticoids, which generally inhibit immune responses through decreasing production of pro-inflammatory cytokines and inhibiting activation and proliferation of multiple immune cell types. The HPA axis also produces prolactin, another hormone with immunological effects. The prolactin receptor is widely expressed in immune cells (74), and prolactin signaling is largely immunostimulatory (75). In particular, prolactin may promote autoimmunity by inhibiting negative selection of autoreactive B cells, augmenting autoantibody production (76–78). Positive correlations of prolactin levels and disease activity have been identified in SLE patients, but the causality remains to be determined (79).

Sex chromosomes

The presence of two X chromosomes in the female also contributes to sex bias of autoimmunity. While canonically one of the X chromosomes is inactivated in early development, this process is imperfect, with approximately 15% of genes escaping X chromosome inactivation (XCI) (80). A majority of the genes that escape XCI show female expression bias (81–83), and there is variation among individuals in which genes escape (84). Males with Klinefelter syndrome (karyotype XXY) have an increased risk of SLE commensurate with that of females (85), and one male patient with severe pre-pubertal SLE was found to have an XX karyotype due to an X-Y translocation (86), demonstrating the influence of X dosage. In contrast, females with Turner syndrome, who have complete (XO) or partial X chromosome monosomy, are at increased risk of developing autoimmune disease relative even to XX females, but the excess risk may be greater for male-predominant autoimmune conditions such as ankylosing spondylitis (87, 88). In contrast, females with Turner syndrome (karyotype X0) are at increased risk of developing autoimmune disease, but the risk is strongest for male-predominant conditions (87). In most females, XCI is random, resulting in half of cells expressing the maternal and half the paternal X chromosome; however, some females show non-random silencing leading to an 80% or more predominance of one X chromosome. This skewed inactivation is more common in patients with autoimmune diseases (89, 90), although it may be a consequence of autoimmunity rather than a cause (91).

Many genes with established roles in autoimmunity are located on the X chromosome. Several of these have been found to be overexpressed or hypomethylated in female but not male SLE patients (92, 93), and dosage of the X-linked *TLR7* and *TLR8* genes has been shown to influence development of SLE in humans and lupus-prone mice (94–98). Recently, escape of *TLR7* inactivation in a substantial number proportion of immune cells has been described in females and men with Klinefelter syndrome; this biallelic expression of TLR7 primes for increased class switching in activated B cells and increased TLR7 reactivity (99).

The X chromosome is also highly enriched in microRNAs (miRNAs) (100). MicroRNAs, including some located on the X chromosome, are essential for maintenance of immune tolerance (reviewed in (101)), and a subset of X-linked miRNAs was found to be overexpressed in females, but not males, with SLE (93). Finally, the X chromosome can become partially reactivated in lymphocytes in women, resulting in overexpression of immunity genes and possibly contributing to sex bias in SLE (102).

The Y chromosome has garnered much less attention as a driver of sex bias in autoimmunity, but evidence is accumulating. In a mouse model of autoimmune disease, Y chromosome polymorphisms, including gene copy number variation, correlate with disease susceptibility and severity (103–105), although the observed effects may also reflect impaired balancer function in mismatched X and Y chromosomes that evolved in different strains (106). However, data from men with MS suggest the influence of the Y chromosome on autoimmunity may extend to humans (105). Further investigation of male mice with specific Y-linked defects in immunity (107, 108) and examples of human Y-linked immune variation (109) is ongoing and may shed additional light.

Gut immunology and the microbiota

The gut microbiota plays a critical role in maturation and modulation of innate and adaptive immunity (110) yet is itself shaped by the immune system. Both the gut immune system and microbiota exhibit sexual dimorphism. Immune tissues in the gut of male and female rodents differ in representation of immune cells, with an overall trend toward enhanced innate immunity and attenuated adaptive immunity in the male gut relative to the female (111, 112), and many immune genes show sex-biased expression in mouse gut (113, 114). Although some studies have observed no differences in the diversity or composition of male and female gut microbiota, sex differences in the human gut microbiota have been extensively documented (115), raising interest in the gut microbiota as a potential driver of sex bias in autoimmune disease. Additionally, microbiome aberrations have been observed in the vast majority of immune-mediated diseases, although demonstrating causation has proven a significant obstacle thus far (116), with many resorting to animal models for further investigation.

Female mice show increased microbiota diversity relative to male, and many bacterial species show sex-biased enrichment that occasionally varies with strain, age, and diet (reviewed in (115)). Sex hormones likely also play a role. In human twin studies, the microbiota of opposite-sex twins becomes more divergent after puberty relative to same-sex twins (117). Similarly, in the nonobese diabetic (NOD) mouse model of spontaneous autoimmune type I diabetes (T1D), the gut microbiota does not differ in prepubertal male and female mice; however, microbial diversity decreases in intact postpubertal males, while this does not occur in females and castrated males (118). Transfer of male microbiota into germ-free female mice and female microbiota into germ-free male mice revealed that some manifestations of immunological sexual dimorphism appear to depend on sex-specific gut microbiota: regardless of the sex of the recipient, RORγt^{+}Foxp3^{+} cells are increased in gut immune tissues of mice who received male microbiota, and T cell precursors are increased in mice who received female microbiota (113).

There is mounting evidence of a direct role for the gut microbiota in driving sex-biased autoimmunity. Female NOD mice develop spontaneous autoimmune T1D at twice the rate of male mice. Under germ-free conditions, however, incidence of T1D is equal in both sexes (119), indicating that male microbiota may confer protection. Gavage of female NOD weanlings with male NOD intestinal microbiota results in elevated serum testosterone and protects against development of T1D. This effect is abrogated in recipient female mice treated with androgen receptor antagonist, suggesting protection is conferred by a testosterone-dependent mechanism (119). Female MRL/Mp-Fas^{lpr} mice, who develop lupus at far higher rates than males, show significantly higher gut microbiota diversity but lower abundance of *Lactobacillales* species and increased intestinal permeability (120). In female and castrated male Fas^{lpr} mice, *Lactobacillales* gavage restores gut mucosal barrier function, promoting an anti-inflammatory cytokine environment in which autoantibody production decreases and renal disease improves, with increased renal Treg cells and suppression of renal Th17 cells (120). The same benefits were not observed in intact male Fas^{lpr} mice, suggesting that *Lactobacillus* species in the gut attenuate renal disease in lupus-prone mice in a sex hormone-dependent manner. In aggregate, the animal data suggest that sex and androgens appear to regulate gut microbiota composition and function, which reciprocally influences the immune response and development of autoimmunity.

Other factors

Recently, we identified the transcription factor VGLL3 to be critical in orchestrating sex-biased expression of key autoimmune genes in a sex hormone-independent fashion (83). VGLL3 is required for robust expression of genes implicated in autoimmunity and for mounting a full IFN-I response. In healthy skin, VGLL3 shows nuclear localization that is more prominent in women than in men. In lesional skin of patients with cutaneous lupus, however, VGLL3 shows nuclear localization in both sexes, indicating disease-dependent regulation. This suggests VGLL3 governs an autoimmunity pathway that is constitutively active in women but must be triggered by other means in men (83). VGLL3 is located on chromosome 3 and appears to be epigenetically regulated (unpublished observation), and its exact role in driving autoimmune diseases is being actively explored.

Sex bias is prominent in DNA methylation, affecting chromatin accessibility of immune genes (121). The X and Y chromosome may influence DNA methylation, as was shown for an autosomal locus in human cells (122). Prenatal environmental exposures also show sex-specific epigenetic effects on DNA methylation (reviewed in (123)), although the underlying mechanisms remain unknown. Fetal microchimerism, wherein circulating fetal cells travel to the mother and persist for years after pregnancy (124), may predispose to development of autoimmune disease; however, studies disagree on whether autoimmune diseases are more common in women with prior pregnancies, and a definitive connection has not been established (125). Additionally, men and women differ in exposure to environmental endocrine-disrupting chemicals, with estrogenic and anti-estrogenic properties that may affect genetic and epigenetic regulation of immunity (reviewed in (126, 127)). Finally, sociological differences between the sexes, such as rates of smoking in men versus women, may influence the development and manifestations of autoimmune disease (128).

Conclusion

In treating severe autoimmune disease, physicians often must turn to broad immunosuppressive therapies with high side effect burden and inherent risks of infection and malignancy due to decreased immune surveillance activity. The trend toward stratifying immunological research studies by gender and continuous improvements in high-throughput technologies have enabled increasingly sophisticated characterization of the differences between the male and female autoimmune phenotypes; this is evidenced by work such as the recent description of sex bias in the influence of HLA associations on T cell selection and expansion as revealed by TCR immunosequencing of large cohorts (129). These nuanced descriptions are helping to explain observed sex differences in infection susceptibility and autoimmunity, but we must continue to interrogate the mechanistic underpinnings of sex-biased autoimmunity to pave the way toward development of highly specific therapeutics that spare patients the dangers of broad immunosuppression. Targeting the precise pathways that drive the female autoimmune disease burden above the baseline male prevalence will be an immense boon to human welfare, particularly if accompanied only by the relatively modest increased risk of infection and malignancy native to the male immune system.

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Recent findings

Recent studies investigating the origins of sex bias in autoimmune disease have revealed an extensive and interconnected network of genetic, hormonal, microbial, and environmental influences. Investigation of sex hormones has moved beyond profiling the effects of hormones on activity and prevalence of immune cell types to defining the specific immunity-related genes driving these changes. Deeper examination of the genetic content of the X and Y chromosomes and genetic escapees of X chromosome interaction has revealed some key drivers of female-biased autoimmunity. Animal studies are offering further insights into the connections between microbiota, particularly that of the gut, and the immune system.

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Key points

- The mechanisms underlying sex bias in autoimmunity remain incompletely understood.
- The effects of sex hormones on autoimmune disease are mediated in part by direct regulation of key immunity factors such as AIRE, IRF5, and IFN-γ and the intracellular TLR trafficking protein UNC93B1.
- Newly discovered non-hormonally–regulated immune modulators such as VGLL3 may contribute to female-biased autoimmunity.
- The gut microbiota influences the immune response and development of autoimmunity and is itself shaped by androgens.
- These and future investigations may yield targets for more selective and therefore less toxic therapies for autoimmune disease.

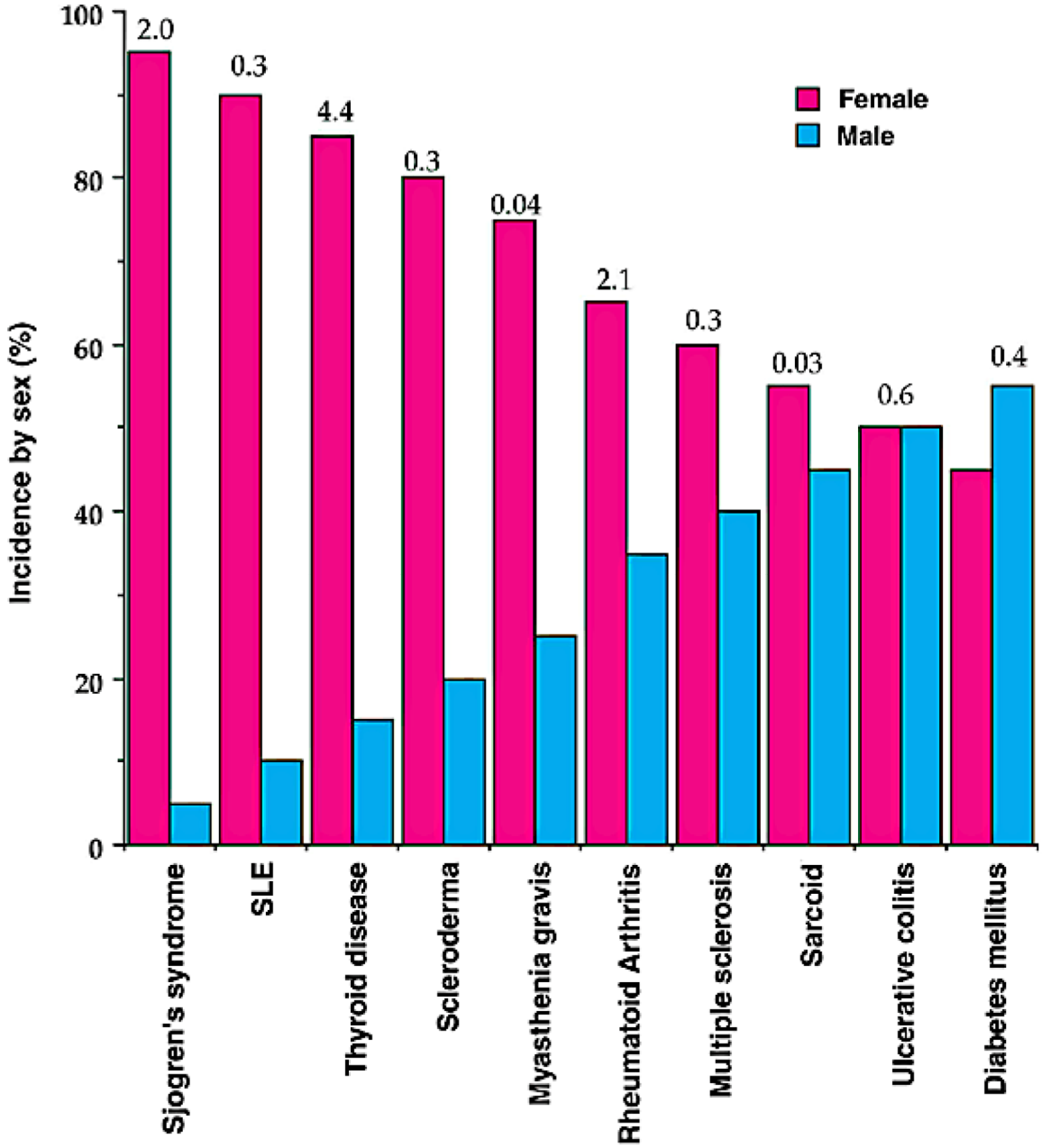

Figure 1. The sex distribution of the major autoimmune diseases.

The numbers above the bars refer to the total number of disease cases (×1,000,000) in the USA (3). SLE: systemic lupus erythematosus.

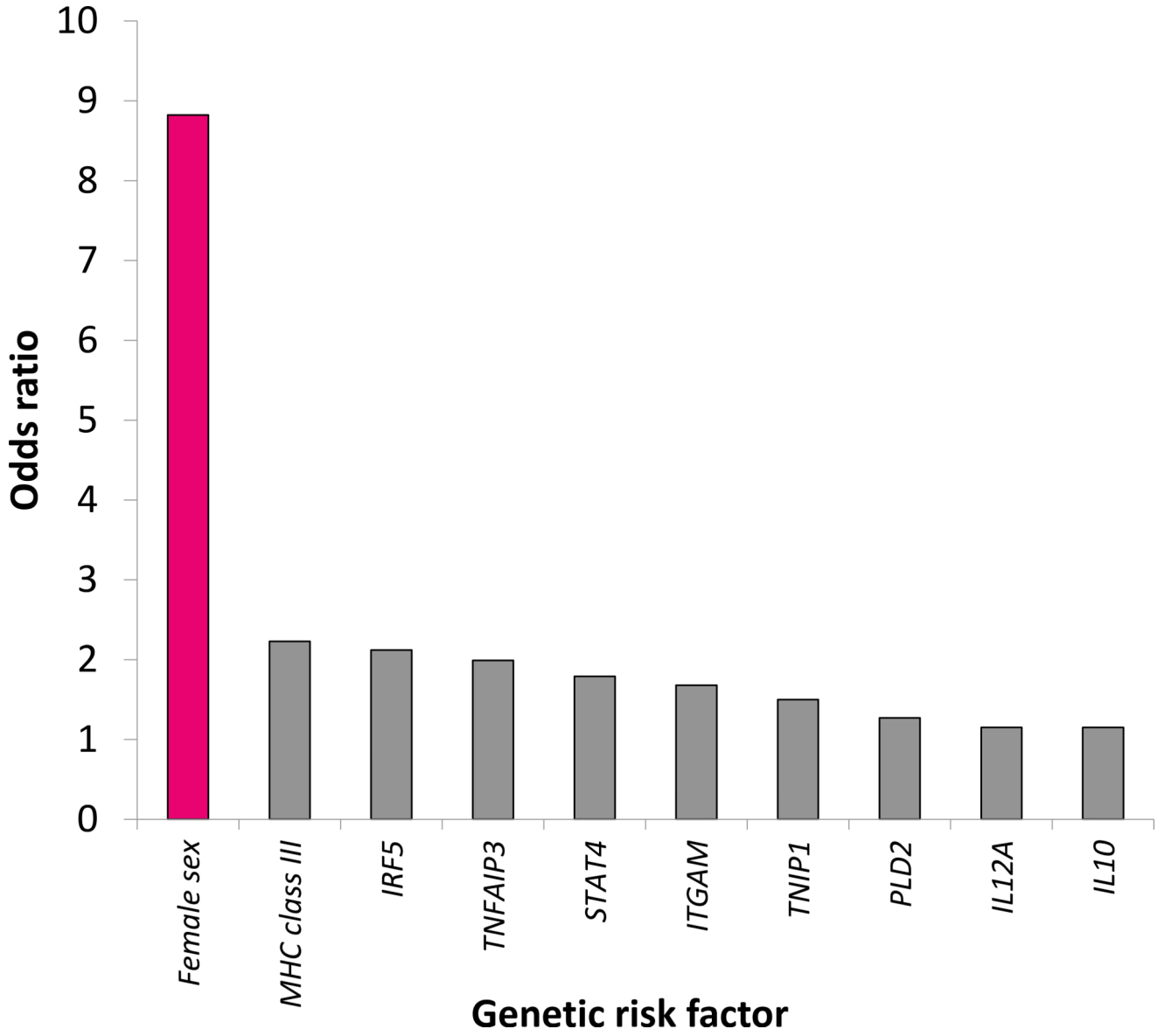

Figure 2. Female sex alone carries a risk of autoimmunity four times greater than any other known genetic risk variant for SLE.

Odds ratio (OR) for female sex was calculated based on prevalence data from the Georgia Lupus Registry from 2002 (6). ORs are shown for allelic associations at SLE susceptibility loci from a genome-wide association replication study (7).