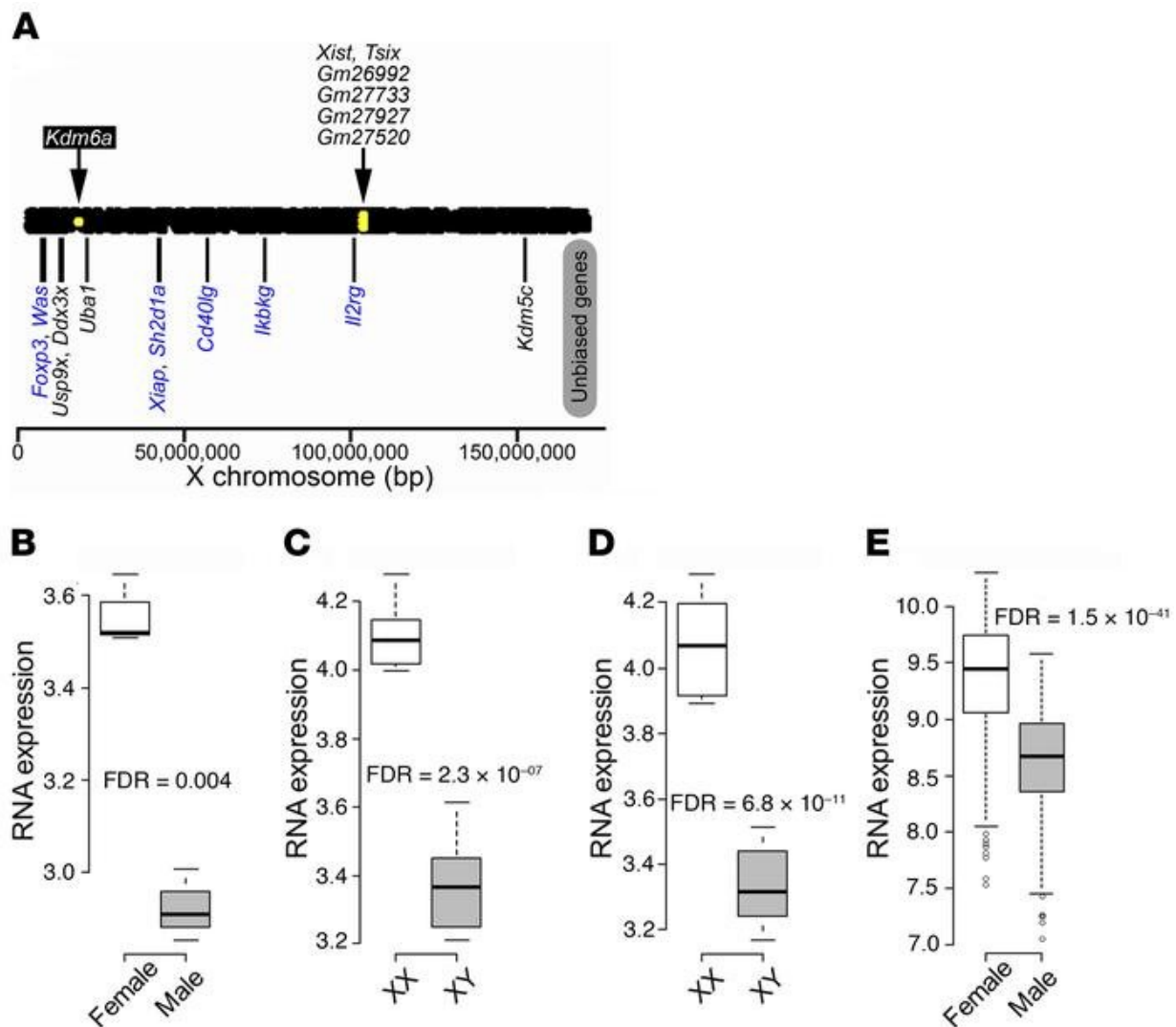


# X chromosome gene may explain why women are more prone to autoimmune diseases

August 20 2019, by Alice Walton



(A) Using the high-throughput sequencing approach, sexually biased X chromosome genes in CD4<sup>+</sup> T cells were determined for C57BL/6J naive CD4<sup>+</sup>

T cells from spleen (GSE94671; 3 males and 3 females). Yellow dots within the bar representing the X chromosome indicate genes with higher expression in females than in males (threshold for significance was  $FDR < 0.05$ ). T cells from females as compared with males. Xist and Tsix, which regulate X inactivation, and 4 predicted genes with unknown functions (Gm26992, Gm27733, Gm27927, and Gm27520) also showed increased expression in females. Shown below the bar representing the X chromosome are previously reported X escapees found in other tissues (black text) as well as X genes not thought to escape X inactivation, but involved in immunity (blue text) (58, 59). None had significantly different expression. (B–E) Expression of Kdm6a in (B) naive  $CD4^+$  T cells from C57BL/6J spleen (GSE94671; 3 males and 3 females); (C) stimulated  $CD4^+$  T cells from C57BL/6J lymph nodes (GSE121292; FCG: 6 XX and 6 XY<sup>−</sup>); (D) stimulated  $CD4^+$  T cells from SJL lymph nodes (GSE121705; FCG: 6 XX and 5 XY<sup>−</sup>); and (E) human naive  $CD4^+$  T cells from healthy control blood (GSE56033; 205 males and 294 females). In box-and-whisker plots, thick lines inside the boxes represent the median of the data. The lower and upper ends of boxes show quantiles (25% and 75%), and whiskers show the minimum and maximum values excluding outliers (circles). FDR was calculated using R package edgeR for A–D. For E, 1-way ANOVA was used.  
<https://www.jci.org/articles/view/126250>

A UCLA study revealed that a gene on the X chromosome may help explain why more women than men develop multiple sclerosis and other autoimmune diseases. Researchers found that a gene known as Kdm6a was expressed more in women's immune cells than in men's, and expressed more in female mice than in males.

When the Kdm6a gene was eliminated in [mice](#) that were bred to mimic a [disease](#) like MS, they had improved symptoms, reduced inflammation and less damage to their spinal cords.

Women's risk of developing MS is about three times greater than men's, and women have stronger immune responses in general. Previous

research has suggested that these differences may be due to differences in sex hormones and/or chromosomes between men and women. Since women have two X [chromosomes](#), they have a "double dose" of genes on the X chromosome, and although there is a natural mechanism to silence the extra genes, some genes elude that mechanism.

The UCLA study set out to determine which X chromosome genes might slip by that silencing mechanism and show increased expression in females' immune systems, and whether those genes might be connected to women's heightened susceptibility to autoimmune disease.

To determine which X chromosome genes were expressed more in the T cells of female immune systems than in males', the team sequenced the RNA of three female and three male mice, and of 294 women and 205 men. (T cells play a central role in [immune response](#).) After finding that the Kdm6a gene showed the greatest difference between males and females, the scientists bred mice that lacked Kdm6a—mice that had previously been bred to develop an autoimmune disease that's similar to MS. The specially bred mice without the Kdm6a gene had fewer symptoms of the disease than the mice who had intact Kdm6a.

The researchers next inspected the animals to assess whether their spinal cords showed any of the damage that's characteristic of MS. In the mice without Kdm6a, there was evidence of reduced autoimmune activity in spinal cord cells, reduced damage to the cells' axons (the long extensions through which neural communication occurs, and which deteriorate in MS), and greater numbers of intact axons. The results suggest that deleting the Kdm6a gene has protective effects.

Finally, the team identified molecular changes that are triggered by the deletion of the gene. In mice lacking Kdm6a, there was evidence of increased activity of multiple genes involved in healthy immune activity, and reduced activity of [genes](#) involved in neuroinflammation.

The results help explain why females are more prone to developing autoimmune disease, and suggest that modulating the activity Kdm6a in T cells might be a potential therapeutic target for MS, and other [autoimmune diseases](#). The findings suggest that drugs like metformin, a diabetes treatment that has been shown to alter Kdm6a activity, might also deserve further study.

**More information:** Yuichiro Itoh et al. The X-linked histone demethylase Kdm6a in CD4+ T lymphocytes modulates autoimmunity, *Journal of Clinical Investigation* (2019). [DOI: 10.1172/JCI126250](https://doi.org/10.1172/JCI126250). [www.jci.org/articles/view/126250](https://www.jci.org/articles/view/126250)

Provided by University of California, Los Angeles

Citation: X chromosome gene may explain why women are more prone to autoimmune diseases (2019, August 20) retrieved 20 March 2024 from <https://medicalxpress.com/news/2019-08-chromosome-gene-women-prone-autoimmune.html>

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