

Why are autoimmune diseases more prevalent in women?

PERSPECTIVES

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Women are less susceptible to infectious diseases than men, but are more often prone to autoimmune diseases. This higher prevalence is partly attributable to the X chromosome, which has many genes relating to the immune system. It is advantageous for women to have two X chromosomes, but the price is a greater tendency to develop autoimmunity.



Illustration: Ørjan Jensen/Superpop

Women are healthier and live longer than men. They are less susceptible to infectious diseases (1), but on the other hand 80% of individuals with autoimmune diseases are women. These diseases affect 5–10% of the population, are often chronic, and represent a considerable burden on healthcare budgets (2, 3).

The autoimmune diseases are a heterogeneous group with multifactorial causes. The common denominator is an immunological reaction that leads to the breakdown, either systemic or organ-specific, of tolerance for the subject's own tissue. Most autoimmune diseases are far more prevalent among women than among men. Women account for 80–95% of patients with primary Sjögren's syndrome, systemic lupus erythematosus (SLE), primary biliary cirrhosis, autoimmune thyroid disease and systemic sclerosis, and about 60% of arthritis and multiple sclerosis patients are women. Some autoimmune diseases, like ankylosing spondylitis, are more common among men (4) (Table 1).

Table 1

Percentage of women and abnormalities of the X chromosome in autoimmune diseases.
+ Higher prevalence found. - Higher prevalence not found.

Autoimmune disease	Percentage women (%) ¹	Skewed X chromosome inactivation	Monosomy X in peripheral blood	Increased prevalence of triple X syndrome	Reference
Primary Sjögren's syndrome	95	-	Not studied	+	4, 3, 16
Systemic lupus erythematosus	90	-	Not studied	+	4, 13, 16
Primary biliary cirrhosis	90	-	+	-	4, 3, 18
Autoimmune thyroid disease	85.	+	+	Not studied	4, 11
Systemic sclerosis	80	+	+	Not studied	4, 10
Rheumatoid arthritis	65	+	Not studied	-	4, 12
Multiple sclerosis	60	-	Not studied	Not studied	4, 13, 14

¹ The percentage will vary depending on the age group studied (4)

It is advantageous for women to have two X chromosomes. Women are protected against X-linked hereditary diseases. A woman with a defective gene on one X chromosome will most often be unaffected as long as she has a normal copy of the gene on the other X chromosome. The presence of two X chromosomes may be one of the reasons that women generally live longer than men (5, 6). However, the price of having two X chromosomes is a higher risk of autoimmune disease.

Sex hormones have a bearing on the difference between women and men in the prevalence of autoimmune diseases (7). Oestrogens stimulate and androgens provide protection against autoimmunity. The effect of female hormones is manifested by the fact that many autoimmune diseases in women start shortly after puberty and often change during pregnancy. However, pregnancy may have the opposite effect on the symptoms. The symptoms of rheumatoid arthritis and multiple sclerosis often improve, while those of systemic lupus erythematosus are exacerbated.

In recent years it has become clear that the X chromosome plays an important part in the development of autoimmunity (5). The purpose of this paper is to discuss the significance of factors related to the X chromosome for the gender difference in the prevalence of autoimmune diseases. The paper is based on the author's own research, research reports and review articles.

The X chromosome

The X chromosome contains over 1 000 genes, while the Y chromosome only has about a hundred. Many of the X-linked genes relate to the immune system, such as *CD40L*, *CXCR*, *OGT*, *FOXP3*, *TLR7*, *TLR8*, *IL2RG*, *BTK*, and *IL9R*, and women produce more immunoglobulins than men (5).

The X chromosome is the only chromosome that does not occur in a pair in both genders. In order for women not to have double the expression of genes on the X chromosome compared with men, one of the two X chromosomes is inactivated (8). This inactivation takes place early in the development of the embryo. It is permanent for the individual cell, and it is a matter of chance which X chromosome – mother's or father's – is inactivated in an individual. All women are therefore cellular mosaics. They have two cell lines: one in which the X chromosome from the father is the active one, and one in which the X chromosome from the mother is the active one. Most women have an approximately 50:50 distribution of the two cell types. A skewed inactivation pattern is a substantial deviation from a 50:50 distribution, and is often defined as a distribution of 80:20 or more skewed. Since the X chromosome inactivation is a stochastic process, skewed inactivation may occur randomly, but also as a result of selection favouring one of the two X chromosomes. The X chromosome inactivation pattern can be determined by means of a PCR based method, and for practical reasons this is usually performed on peripheral blood cells.

X chromosome inactivation is a complex and only partially understood process (9). Inactivation of the one X chromosome has proved incomplete, as a full 10–15% of the genes are not inactivated. Women therefore have a double dose, i.e. double expression, of certain X-linked genes, which has a bearing on the development of autoimmunity. Moreover, inactivation is incomplete for a further 10% of the genes. The degree of inactivation varies from one woman to the next and across different tissues in the same woman. This allows extensive genetic diversity, which may be of benefit for women's immune defences (5).

Skewed X chromosome inactivation and autoimmunity

Women who are carriers of X-linked hereditary disease are usually healthy, but may occasionally exhibit signs of disease. The explanation is often that they have skewed X chromosome inactivation (8). Recent research has shown a higher prevalence of skewed X chromosome inactivation in some autoimmune diseases; this was first found for systemic sclerosis (10). Skewed X chromosome inactivation has been found in autoimmune thyroid disease, both Hashimoto's thyroiditis and Grave's disease (11) and in rheumatoid arthritis (12), but not in primary Sjögren's syndrome, systemic lupus erythematosus, primary biliary cirrhosis or multiple sclerosis (2, 13, 14) (Table 1).

It is assumed that it is the skewed X chromosome inactivation that causes the disposition to autoimmunity, and not the reverse (3). Skewed X chromosome inactivation may lead to women mainly having cells that only express X-linked genes from one X chromosome. One explanation for the relationship between skewed X chromosome inactivation and autoimmune disease may be that X-linked autoantigens on the one X chromosome are not sufficiently presented in the thymus or other tissues involved in the induction of tolerance – whereas the expression in peripheral tissues is large enough to trigger the development of autoantibodies (3, 5).

Deviant number of X chromosomes and autoimmunity

Abnormalities in chromosome numbers are usually serious. The exception is abnormalities in the number of sex chromosomes. Men who have an extra X chromosome (Klinefelter syndrome, 47, XXY), and women who have an extra X chromosome (triple X syndrome, 47, XXX), may have minor symptoms or signs, and be unaware that they have an extra X chromosome. A missing chromosome is not normally consistent with viability, but here, too, the sex chromosomes are an exception. Women who lack part of or a whole X chromosome (Turner syndrome) are short, have gonadal dysgenesis and a number of other characteristic features. Common to these three X chromosomal anomalies is a high prevalence of autoimmune disease.

Systemic lupus erythematosus is a rare and serious autoimmune disease that most frequently affects women (Table 1). Men with Klinefelter syndrome have the same high prevalence of systemic lupus erythematosus as women (15), and also have a high prevalence of autoimmune thyroid disease, primary Sjögren's syndrome, Addison's syndrome, diabetes, multiple sclerosis and rheumatoid arthritis compared with men without a known chromosomal anomaly (3). Women with systemic lupus erythematosus and primary Sjögren's syndrome have a higher prevalence of triple X syndrome than women without these syndromes (16) (Table 1).

Women with Turner syndrome had twice as much risk of autoimmune disease as women in a control group (17). They have a high prevalence of Hashimoto's thyroiditis, but otherwise the autoimmune diseases that predominate in Turner syndrome are different from those that predominate in Klinefelter syndrome. Turner syndrome is particularly associated with autoimmune diseases where there is no pronounced gender difference, such as diabetes, and systemic lupus erythematosus is very rare (17).

While Turner syndrome is rare, loss of an X chromosome in peripheral blood cells (monosomy X) occurs frequently in women, particularly elderly women. A higher prevalence of monosomy X, most pronounced in T and B lymphocytes, has been found in autoimmune thyroid disease, systemic sclerosis and primary biliary cirrhosis (18) (Table 1).

A higher prevalence of autoimmune disease, in cases of both too many and too few X chromosomes, indicates that it is the dose of certain X-linked genes that is critical. A double expression of genes on the X chromosome may also arise in

women with a normal number of X chromosomes, since 10–15% of the genes on the X chromosome are not inactivated. An example of this has been found in a mouse model of systemic lupus erythematosus. The female mice had overexpression of the immune-related X-linked gene toll-like receptor 8 (*Tlr8*) due to incomplete inactivation (19). Double expression of genes may also arise due to reactivation of genes on the inactive X chromosome. There is evidence that the inactive X chromosome in lymphocytes is disposed to partial reactivation, which may result in overexpression of immune-related genes (20). Not only overexpression, but also the absence of expression of genes on the X chromosome results in a higher risk of autoimmunity, as seen in Turner syndrome and acquired monosomy X in peripheral blood cells.

Micro-RNA (miRNA) can regulate gene expression. X-linked miRNA-mediated suppression of immunosuppressive genes is a new field of research that may contribute to a better understanding of why so many women are affected by autoimmune diseases (21).

Most studies of gender differences and autoimmunity have been conducted on women, particularly women with an autoimmune disease in which the gender difference is most pronounced. It has been maintained that attention should also be directed at why men so seldom are affected, with focus on possible protective factors in men (22).

Conclusion

There are probably many reasons why most autoimmune diseases are far more prevalent in women than in men. Some of these reasons are associated with the X chromosome, where the dose of certain X-linked genes appears to be critical. Few genes are known to date. Future studies of the X chromosome may identify new genes and provide more knowledge of the complex mechanisms underlying the development of autoimmunity.

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