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# The role of the X chromosome in immunity and autoimmunity

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**Abstract**

Primary immunodeficiencies as well as autoimmune diseases have been associated to X chromosome abnormalities. Furthermore, the functional biology of the X chromosome is unique because genes located in this chromosome can undergo inactivation, and subsequently transcriptional silencing. Non-random X chromosome inactivation has been hypothesized to be involved in the development of autoimmunity. Recently X chromosome monosomy has also been proposed as a common etiologic mechanism for some autoimmune diseases. Herein, we review some of these findings above mentioned.


*Keywords:* X chromosome; Immunity; Autoimmune disorders

**Contents**



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In the human being and many other mammals, the X chromosome is one of the two sex chromosomes of the respective species [1]. It has ~5.6% of the human genomic DNA and at present 1098 identified genes. With the exception of genes located in the pseudoautosomal regions (PAR1 and PAR2) in 46,XX females, most of its genes show a hemizygous status due to the X chromosome inactivation and in 46,XY males due to their hemizygotic status. Unfortunately, the clinical relevance of genes that are inactivated and of those that escape inactivation is not clearly understood [2].

The X chromosome is of interest in Rheumatology due to the following statements. First of all, autoimmune diseases are remarkably predominant in females [3] (Table 1), a tendency often ascribed to hormonal differences, i.e. systemic lupus erythematosus (SLE) [4]. Sex-related genes that play a role in the maintenance of physiological sex hormones levels have been mapped to the X chromosome. In addition, an alternative explanation for the female predominance has been recently proposed with the finding of an enhanced X monosomy in peripheral white bloods cells of female patients with primary biliary cirrhosis (PBC) [5]. Secondly, some primary immunodeficiencies and autoimmune diseases have been linked to the X chromosome. Although both conditions might be viewed as opposite features, one as the result of an inadequate response and the other as the consequence of an exaggerated one, in both cases the X chromosome seems to play a special role in the immune response regulation. This review highlights the features that link the X chromosome to immunity and autoimmunity.

Table 1
Female predominance in autoimmune diseases

| Disease | Female/Male ratio |
|---|---|
| Autoimmune thyroid disease | 10:1 |
| Primary biliary cirrhosis | 9:1 |
| Sjögren's syndrome | 9:1 |
| Systemic lupus erythematosus | 8:1[a] |
| Rheumatoid arthritis | 3:1 |
| Scleroderma | 3:1 |
| Myasthenia gravis | 2:1 |
| Multiple sclerosis | 2:1 |

[a] In child-bearing age.

## 1. Specific X chromosome mutations

X-linked gene mutations can affect T cells, B cells or both. Patients with T cell defects, experience an altered immunoregulation that could result in an overactive or a hypoactive T-cell function, and patients with B cell disorders have deficient antibody production and function.

### *1.1. X-linked genes affecting T cells directly*

#### *1.1.1. IPEX syndrome (immunodysregulation, polyendrocrinopathy, enteropathy, X-linked syndrome)*

This disorder is a rare fatal recessive inborn error of immune regulation characterized by the early onset of some autoimmune diseases in boys. Patients can develop type 1 diabetes, enteropathy, eczema, variable autoimmune phenomena and severe infections [6]. Older patients may present sarcoidosis, arthritis, glomerulonephritis, ulcerative colitis and neuropathy. The gene identified as responsible for this disorder is the transcriptional factor *FOXP3* (Table 2), which is mainly expressed in $CD4^{+}CD25^{+}$ T regulatory cells [7]. Murine models with depletion of this T-lymphocyte population spontaneously develop T-cell autoimmune diseases. Although 13 mutations of this gene have been at present identified, no genotype–phenotype correlations have been described [8].

#### *1.1.2. XLP syndrome (X-linked lymphoproliferative syndrome)*

Patients with this abnormality have a defect of the SLAM-associated protein (SAP) (Table 2), a cytoplasmic adaptor that binds signaling of lymphocytic activation molecules (SLAM). T-cells, NK cells and NKT cells predominantly express SAP. This failure results in an uncontrolled proliferation of T cells during an Epstein–Barr infection inducing a fatal mononucleosis. Affected individuals can develop other immunological defects such as lymphoma and hypogammaglobulinemia [9]. These patients also experience a deficiency in memory B cells, plasma cells and antibodies production. This defect is probably due to an impaired T cell help, ensuing an inability to form germinal centers in response to T-cell-dependent antigens [10].