

## Epigenetics and gender

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The morphological and behavioural differences between a man and a woman represent the most evident example of phenotypic diversity among individuals. However, none of these differences allows us to distinguish biologically a male from a female.

### "There is a huge consequence to having two X chromosomes versus an X and a Y"

In fact, while the X chromosome likely contains 800 to 900 genes that provide instructions for making proteins, the Y chromosome likely contains 50 to 60 genes that provide instructions for making proteins. The X chromosome spans about 155 million DNA building blocks (base pairs) and represents approximately 5 percent of the total DNA in cells. The Y chromosome spans more than 59 million building blocks of DNA and represents almost 2 percent of the total DNA in cells. It is therefore clear that differences in the susceptibility of the two sexes to diseases can be influenced by the status of the sex chromosomes at molecular levels. About 80% of people with autoimmune disorders are female. Women tend to have a stronger immune response to infection, and often produce more antibodies in response to vaccination than men. Men are more cancer prone, are twice as likely to die of a malignant disease, and respond differently to cancer therapy. But more women than men die from cardiovascular diseases, and become obese. Males more frequently had developmental abnormalities, and in some types of neuromuscular disorders (e.g. myotonic dystrophy) males show severe myotonia, severe cardiac and respiratory involvement and muscle weakness, as assessed by MRC testing ( $p = 0.001$ ). Females more frequently have cataracts, dysphagia, digestive tract dysfunction, incontinence, thyroid disorder and obesity.

### Cellular processes due to epigenetic mechanisms with implications in gender differences

The differences in susceptibility to diseases observed in the two sexes are not only the direct effects of the expression of the genes mapped on sex chromosomes, but

also of the epigenetic indirect effects epigenetically mediated by them. These include: genomic imprinting (parental effect); X-inactivation in females; differential miRNAs/non-coding RNAs mapping on the X-chromosome. Genomic imprinting occurs when the father and mother contribute different epigenetic patterns for specific genomic loci in their germ cell. These imprintings (or parent-of-origin) mechanisms have been observed for many gender-specific phenotypes. Epigenetic mechanisms can, in fact, regulate gene expression at the molecular level. X-inactivation is a crucial phenomenon in the somatic cells of adult female mammals in order to balance the X-chromosome gene dosage in female XX cells compared to male XY cells. The silenced X-chromosome can be either the paternally or the maternally inherited one, making the adult female a natural mosaic. However, the process of inactivation is not complete and many gene mappings on the X-chromosome escape inactivation. Genes that escape X-chromosome inactivation may account for the differential sensitivity in females to certain diseases. Over 15% of human X-linked genes continue to be expressed from the inactive X-chromosome<sup>2</sup>. The inactive X frequently reactivates in cancers, especially breast cancer, and there are signs that some of its sleeping genes reawaken as women age. Some of the gene escaping X-inactivation code for miRNAs have been implicated in brain health issues, from cognitive decline in normal aging to autism. The human X-chromosome contains 10% of all microRNAs detected so far in the human genome. Several X-chromosome-mapping miRNAs have important functions in immunity and cancer. This explains some of the immunity disadvantage of males and the enhanced survival of females following immunological challenges (e.g., systemic lupus erythematosus).

### Sex-specific expression of metabolic enzymes

Males and females exhibit sex-specific expression in a wide range of genes, including metabolic enzymes, which impact both basic physiology and the response to environmental exposures. Sexually dimorphic gene expression is largely a function of endocrine differences

between males and females, especially in the liver where approximately 1000 genes, including many CYPs, exhibit sexually biased expressions<sup>3</sup>. Differences in the secretion of hormones, such as the growth hormone (GH), control the expression of many transcription factors, particularly the signal transducer and activator of transcription 5 (STAT5). The role of the GH-STAT5 axis, which has been implicated in the regulation of as much as 75-82% of the hepatic sex-biased genes<sup>4</sup>, was recently linked to sex-dependent differences in DNase hypersensitivity (a measure of chromatin accessibility), 6 histone modifications (activating H3K4me3, K27ac, K4me1, K36me3; repressive K27me3, K9me), and the binding of five GH-regulated transcription factors<sup>5</sup>. All of this data confirm and extend the importance of the epigenetic mechanisms in the biological differences observed between sexes. Understanding epigenetics can have important consequences in disease prevention and treatment. In fact, epigenetic modification may alter the response to physiologic, pathologic and pharmacologic triggers. In the future, pharmacoepigenetics will play a crucial role in the pharmacology and clinical medicine for gender-associated diseases.

## References

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