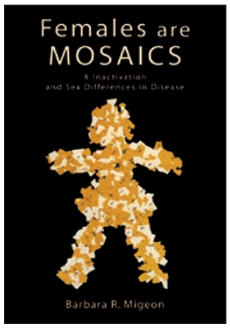
Patchwork women



Females are Mosaics: X Inactivation and Sex Differences in Disease

By Barbara R. Migeon

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Reviewed by Carolyn Brown

If humans had an X-linked biallelic coat color gene, as cats do, then female mosaicism would be as evident in humans as it is in calico cats. This outcome of X inactivation is not immediately visible in humans, however, and its potential importance in sex differences in disease is often overlooked. In the introduction to *Females are Mosaics*, Barbara Migeon states she has been "surprised by the small impact this subject has had in medicine." This book sets out to remedy this deficiency by explaining X inactivation and its importance to the female phenotype.

It is surprising to me that this is the first book-length discussion of the fascinating process of silencing one X chromosome in females. The sex chromosomes themselves have received top billing in the popular science books *The X in Sex* and *Y: The Descent of Man*; however, *Females are Mosaics* is not a popular science book. Rather, as the subtitle suggests, it is a description of a single biological phenomenon, mammalian X inactivation, with a view toward explaining how the choice of which parental X chromosome remains active, and the resulting mosaicism can influence female phenotypes.

The book is true to its title, focusing on X inactivation to explain why females are mosaics and the impact of this on disease in human females. The background section includes chapters on differing disease rates between males and females, the evolution of the sex chromosomes and the means of dosage compensation, followed by an excellent summary of how humans do it—the Lyon hypothesis and the features on which it was based. This section concludes with a discussion of experimental model systems, although in general the book is focused on human X inactivation. The second section on 'Themes and Variations' invokes many current research questions into how the active X is first marked and then how inactivation spreads and is maintained on the inactive X. The variations discussed involve the stability of silencing and the nonrandom choice of an active X. The third section on medical consequences discusses the impact of female X chromosome mosaicism.

Migeon explains how mosaicism provides two cell populations whose proportions can vary by chance or in response to selective pressures, but she also notes that the existence of two populations can lead to interactions resulting in either phenotypic advantages or disadvantages. It seems obvious that having a mosaic population of cells is a benefit when one chromosome carries a mutation, but the disadvantages of mosaicism are sometimes counterintuitive. Migeon describes the fascinating situation of cellular interference for the X-linked dominant craniofrontonasal syndrome in which it is the heterozygous female, not the hemizygous male, who is affected. She also discusses the role mosaicism could have on non–X-linked disorders, notably whether two populations of cells might contribute to the preponderance of autoimmune disease in females.

Who will want to read this book? *Females are Mosaics* is accessible to the non-molecular geneticist, with a full introduction to the evolutionary history of the X that establishes the need for dosage compensation, and it details the current understanding of the process of X inactivation, with considerable emphasis on the resulting mosaicism of females. A glossary is provided to assist those unfamiliar with related terminology, although at its core the book remains a scientific discussion with a thorough reference list and thus should prove useful as a guide for health professionals dealing with families with X-linked disease. An extensive appendix provides brief descriptions of many X-linked genes and their disease manifestations in males and females; however, the relevance of the book to female health goes beyond the classic X-linked disease. As the book jacket emphasizes, health care providers with interests in all aspects of women's health need be aware of the impact of the unique biology of the X chromosome.

I believe the X chromosome expert will also find much of interest in the book. The author has been contributing to the study of X inactivation since shortly after the publication of the Lyon hypothesis of X inactivation in 1961 and thus writes from the perspective of an active observer and participant. She describes not only the results of experiments but also the questions being addressed and concludes each chapter with a section of summary and speculations. This book provides a balanced overview of the field to date, allowing newcomers to the field to concentrate on the recent literature—a necessity, given the current publication rate (in 2006 there were more than 200 PubMed citations for X inactivation). The information in the book is up-to-date and a superb introduction to the entire field for graduate students and fellows.

Overall, this book reminds us that females are not just heterozygous for the X but are in fact mosaics of two different cell populations, and that this unique biology should not be overlooked in considering disease in females.

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