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Mini Review

The Y Chromosome Increases Risk, and the X Chromosome Exerts Nurture

Kenneth Blum[1,3,10]*, Alireza Sharafshah[2], Kai-Uwe Lewandrowski[3,10], Morgan P Lorio[4], Brian Fuehrlein[5], Albert Pinhasov[1], Abdalla Bowirrat[1], Eliot L Gardner[6], Edward J Modestino[7], Panayotis K Thanos[8], Catherine A Dennen[9], Sergio Luis Schmidt[10], Rossano Kepler Alvim Fiorelli[10], Mark S Gold[11], Marco Lindenau[12], Alexander PL Lewandrowski[13], Thomas Lundquist[14] and Rajendra D Badgaiyan[15]

[1]Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel

[2]Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[3]Center for Advanced Spine Care of Southern Arizona, Tucson, AZ, USA

[4]Advanced Orthopedics, Altamonte Springs, FL. On Behalf of the International Society for the Advancement of Spine Surgery, USA

[5]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

[6]Neuropsychopharmacology Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA

[7]Brain and Behavior Laboratory, Department of Psychology, Curry College, Milton, MA, USA

[8]Behavioral Neuropharmacology and Neuroimaging Laboratory on Addictions (BNNLA), Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York, and Department of Psychology, University at Buffalo, Buffalo, NY, USA

[9]Department of Family Medicine, Jefferson Health Northeast, Philadelphia, PA, USA

[10]Programa de Pós-Graduação em Neurologia, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

[11]Department of Psychiatry, Washington University in St. Louis Euclid Ave, St. Louis, MO, United States

[12]Division of Personalized Genomics, The Blum Institute of Behavior and Neurogenetics, LLC, Austin, Texas, USA

[13]Department of Biological Sciences, Dornsife College of Letters, Arts and Sciences, University of Southern California, Los Angeles, CA, USA

[14]Advanced Pain Modalities, 2320 W Peoria Ave, Building C, Suite 102, Phoenix, AZ, USA

[15]Department of Psychiatry, Texas Tech University Health Sciences, School of Medicine, Midland, TX, USA

***Corresponding Author:** Kenneth Blum, Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel and Center for Advanced Spine Care of Southern Arizona, Tucson, AZ, USA and Programa de Pós-Graduação em Neurologia, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.

Received: May 05, 2025; **Published:** June 12, 2025

Abstract

Globally, women consistently outlive men, regardless of cultural or societal factors. This survival advantage holds true even in times of crisis such as famines or pandemics, underscoring that female longevity and neuroprotection are likely rooted in biology rather than environment alone. In every cell, men carry one X chromosome-always inherited from their mother-and one Y chromosome from their father. Women, by contrast, possess two X chromosomes, one from each parent. However, only one X chromosome is active in any given female cell, due to a biological process known as X inactivation, in which one X effectively shuts down its expression Mice limited to maternal X expression showed signs of accelerated brain aging and significant cognitive decline. In comparison

to their wild-type, mosaic littermates, these mice performed poorly in maze-based tasks, exhibiting impaired learning ability and diminished memory retention with age. In comparison to their wild-type, mosaic littermates, these mice performed poorly in maze-based tasks, exhibiting impaired learning ability and diminished memory retention with age. Understanding these concepts, the RDS Consortium performed in silico pharmacogenomic (PGx) analyses to investigate the roles of sex chromosomes in pre-addiction susceptibility, with a focus on sex-specific genetic expression. Data from the RDS Consortium highlight notable sex-based distinctions in pre-addiction vulnerability, with the Y chromosome appearing to elevate addiction risk in males, while the X chromosome may offer neuroprotective benefits in females.

Keywords: *X and Y Chromosomes; Risk Vs Nurture; Dopaminergic Pathways; Cognition; Aging*

Introduction

Whether individuals inherit their X chromosomes solely from their mother or from both parents may influence cognitive aging, mental health, and susceptibility to early-stage addictive behaviors. These findings highlight possible new avenues for protecting brain health across the lifespan. Although it's well-established that aging processes differ by sex-with women typically enjoying longer lifespans and greater resilience in cognitive decline-the biological underpinnings remain elusive.

From an evolutionary standpoint, the divergence between male (XY) and female (XX) sex chromosomes presents an intriguing puzzle. All great apes-including orangutans, gorillas, chimpanzees, bonobos, and humans-share a common ancestor dating back approximately 13 million years. Since that time, their sex chromosomes have taken markedly different evolutionary routes. The X chromosome has remained relatively stable among great apes, while the Y chromosome has undergone substantial change, reflecting its tendency toward genetic decay and variation across species [1].

New research published January 22 in *Nature* by the Simons Collaboration on Plasticity and the Aging Brain (SCPAB) provides fresh insight into these differences. The study revealed that the maternal X chromosome can adversely impact brain aging by regulating genes linked to cognition. In women, only one of their two X chromosomes is active per cell-so if the paternal X is active, it might provide a cognitive advantage. In contrast, men inherit a single X chromosome exclusively from their mothers, with no such backup.

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In every cell, men carry one X chromosome-always inherited from their mother-and one Y chromosome from their father. Women, by contrast, possess two X chromosomes, one from each parent. However, only one X chromosome is active in any given female cell, due to a biological process known as X inactivation, in which one X effectively shuts down its expression.

This typically results in a balanced activation pattern, where maternal and paternal X chromosomes are each expressed in about half the cells. In some instances, however, this distribution becomes uneven, a condition known as X-skewing. Although complete skewing toward one parent's X is uncommon, most women display a mosaic pattern, with cells expressing a mix of both parental X chromosomes (Figure 1).

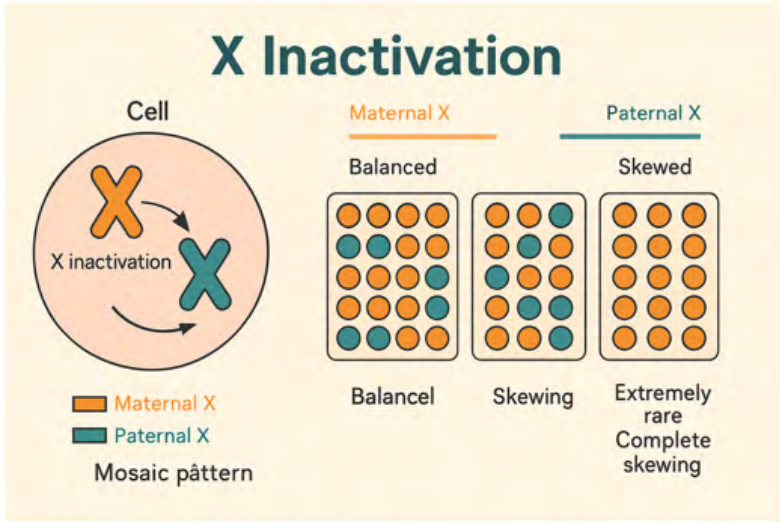

***Figure 1*:** *X-Inactivation and Mosaic Expression in Female Cells is a biological process of X-inactivation in female mammals, wherein one of the two X chromosomes in each cell is randomly silenced. The diagram shows a balanced mosaic pattern of gene expression, with approximately half of the cells expressing the maternal X chromosome (depicted in pink) and the other half expressing the paternal X chromosome (depicted in blue). This mosaicism arises from the random inactivation of one X chromosome early in embryonic development. In some individuals, this distribution becomes skewed toward one parental X chromosome, a phenomenon known as X-skewing. The image highlights both the typical mosaic and the rare skewed expression patterns, emphasizing their relevance to sex-specific traits, brain function, and potential pre-addiction liability.*

To explore how the origin of an active X chromosome influences brain function, researchers from the Simons Collaboration on Plasticity and the Aging Brain (SCPAB) designed a mouse model in which only the maternal X chromosome was expressed. These engineered mice were then subjected to a battery of cognitive assessments targeting memory and learning.

The results were striking: Mice limited to maternal X expression showed signs of accelerated brain aging and significant cognitive decline. In comparison to their wild-type, mosaic littermates, these mice performed poorly in maze-based tasks, exhibiting impaired learning ability and diminished memory retention with age (Figure 2).

Discussion

These findings may also help explain why male brains tend to show greater vulnerability to age-related decline. Unlike women, men possess only one X chromosome-always maternally inherited-since they receive a Y chromosome from their fathers. As a result, male brain cells lack the mosaic expression seen in females and may be disadvantaged by the exclusive reliance on the maternal X, similar to the engineered mouse model discussed earlier.

Figure 2: *Maternal X chromosome expression and cognitive aging in a mouse model showed two genetically distinct mice navigating a maze, representing an experiment conducted to assess cognitive performance based on X chromosome expression. On the left, a mouse engineered to express only the maternal X chromosome demonstrates reduced engagement and impaired navigation, symbolizing accelerated brain aging and memory deficits. On the right, a wild-type littermate with mosaic X expression (both maternal and paternal X chromosomes) displays more efficient cognitive function. A shadowed elderly human figure in the background represents the broader implication for sex-based differences in age-related cognitive decline in humans.*

From an evolutionary perspective, the interplay between sex chromosomes is highly intricate, particularly among humans and other great apes. The Reward Deficiency Syndrome (RDS) Consortium investigated how sex-linked genetic variations influence psychiatric vulnerability, exploring the distinct and overlapping contributions of the X and Y chromosomes to behavior and neurological health.

In an unpublished but submitted study led by Dr. Alireza Sharafshah, our team performed in silico pharmacogenomic (PGx) analyses to investigate the roles of sex chromosomes in pre-addiction susceptibility, with a focus on sex-specific genetic expression. Using a multistep strategy, we examined the Genetic Addiction Risk Score (GARS) panel, which includes ten key reward genes, alongside ZFX-a regulatory gene expressed on the X chromosome-and ZFY, a Y-linked gene crucial for male development.

We further integrated high-scoring sex-linked genes from GeneCard databases and analyzed their biological relevance through protein-protein interactions (PPIs), gene-gene correlations, and related phenotypic traits. This approach offers a novel window into how X and Y chromosome variation may shape gender-specific risk profiles for addiction and related neurobehavioral conditions.

Protein-protein interaction (PPI) analyses revealed fully integrated networks for both sexes, though with distinct gene clusters. In males, PPI mapping connected ZFX and ZFY with USP9Y and SNCA, while in females, the GARS gene set showed associations with ATRX, FMR1, FLNA, and MECP2-genes often implicated in neurodevelopmental and cognitive function.

Gene-gene interaction (GMI) networks further highlighted sex-specific distinctions. In males, significant nodes included SLC6A4, ZFX, OPRM1, COMT, and hsa-miR-26b-5p, interacting with ZFY, DRD3, and GABRA3. Female networks showed more complex interconnec-

tions involving MECP2, SLC6A4, ZFX, FLNA, OPRM1, COMT, and hsa-miR-20a-5p, particularly centered on SLC6A4, MECP2, and FLNA as convergence points.

Transcription factor–microRNA co-regulation (TF-miR CoRegIs) analyses identified REST, CTCF, CREB1, and E2F as dominant transcription factors in both male and female models, reflecting shared upstream regulatory architecture.

Enrichment analyses revealed dopaminergic signaling as the top pathway in both sexes, with higher statistical significance in males (q = 3.83E-11) than in females (q = 1.06E-10). Similarly, the dopamine metabolic process emerged with strong relevance, marked by a q-value of 2.16E-16 in males and 1.08E-15 in females.

Drug-disease association (DDA) results emphasized phenotypes such as substance use disorder, gambling addiction, and heroin dependence-conditions more pronounced in males, consistent with broader Reward Deficiency Syndrome (RDS) frameworks.

Pharmacogenomic profiling identified ZFX, ZFY, USP9Y, SNCA, ATRX, FMR1, FLNA, and MECP2 as key sex-differentiated contributors to dopaminergic imbalance and addiction vulnerability. From an epidemiological standpoint, these genetic findings align with known clinical trends-psychostimulant use disorders being more prevalent in males, while obsessive-compulsive disorder (OCD) appears more frequently in females (Figure 3).

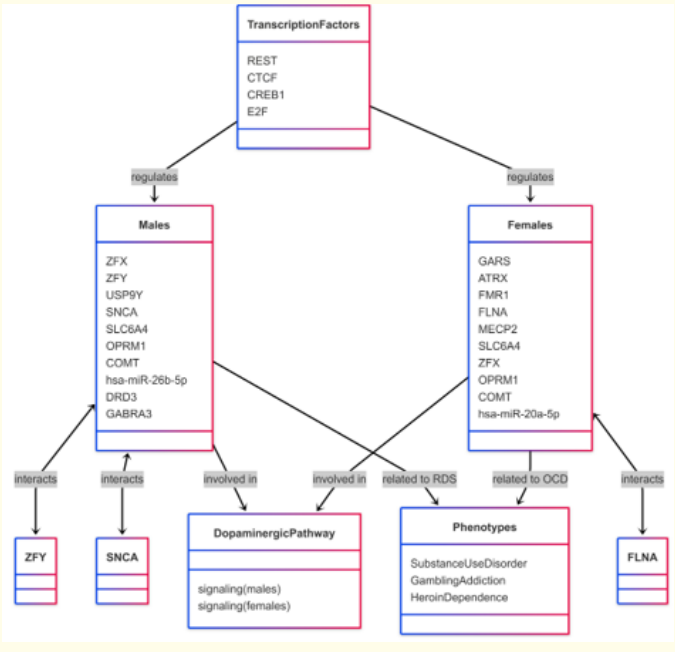

Figure 3: *Sex-specific transcriptional networks involved in reward-related phenotypes and dopamine signaling. This schematic illustrates the regulatory and functional interactions of transcription factors (REST, CTCF, CREB1, E2F) with distinct gene sets in males and females. Male-specific gene clusters include ZFX, ZFY, USP9Y, SNCA, SLC6A4, OPRM1, COMT, hsa-miR-26b-5p, DRD3, and GABRA3, while female-specific gene networks involve GARS, ATRX, FMR1, FLNA, MECP2, SLC6A4, ZFX, OPRM1, COMT, and hsa-miR-20a-5p. These gene sets differentially interact with components of the dopaminergic pathway, influencing signaling in a sex-dependent manner. Notably, male networks are strongly associated with ZFY and SNCA interactions, whereas female-specific interactions prominently involve FLNA. Phenotypic associations differ by sex: male profiles show strong linkage to Reward Deficiency Syndrome (RDS), substance use disorder, gambling addiction, and heroin dependence, while female networks are more closely tied to obsessive-compulsive disorder (OCD). The figure highlights how transcriptional and post-transcriptional regulation contributes to sexually dimorphic expression patterns that may underlie vulnerability to specific neuropsychiatric and addictive disorders.*

Data from the RDS Consortium highlight notable sex-based distinctions in pre-addiction vulnerability, with the Y chromosome appearing to elevate addiction risk in males, while the X chromosome may offer neuroprotective benefits in females. These divergent genetic influences help explain observed differences in disorder prevalence and neurocognitive resilience between sexes, supporting the role of sex-specific genomic factors in both addiction susceptibility and cognitive decline. This distinction also reinforces the importance of incorporating sex-based stratification in preventive strategies and therapeutic interventions.

From an evolutionary perspective, analyzing Y chromosome structure, gene variability, and composition in great apes offers valuable insight into human male-specific traits and the evolutionary pressures associated with sex-biased behaviors and reproductive strategies. The X and Y chromosomes, having diverged significantly in gene content over time, are balanced by regulatory mechanisms that limit gene expression in a sex-specific manner. While these differences predict divergent functional outcomes, large-scale neuroimaging meta-analyses suggest otherwise: dosage effects from sex chromosomes tend to converge on brain regions responsible for social cognition, communication, and executive functioning.

Remarkably, despite minimal sequence overlap and distinct impacts on total brain volume, both the X and Y chromosomes influence the relative size of cortical systems tied to adaptive social behaviors, reinforcing their synergistic role in shaping brain structure and function across sexes [2].

Do distinct genetic disorders lead to varying psychiatric risk profiles? This foundational question carries significant implications for both the biological underpinnings and translational strategies in psychiatry. Schaffer., *et al.* [3] have provided compelling evidence through detailed phenotypic comparisons, highlighting both unique and overlapping influences of the sex chromosomes on human behavior (Figure 4).

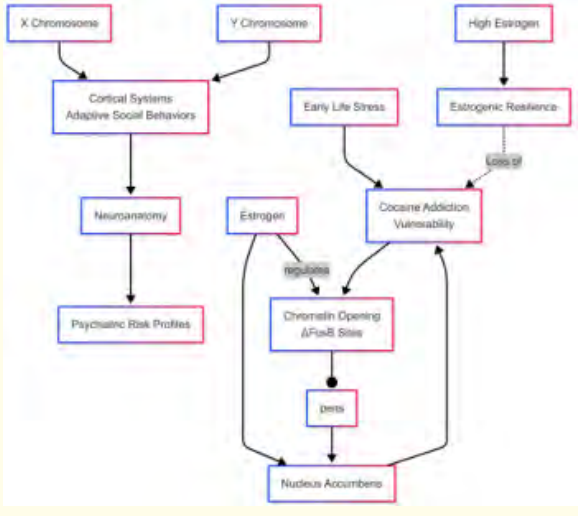

Figure 4: *Sex chromosome, estrogenic, and stress-based modulation of chromatin dynamics and addiction vulnerability illustrating the interaction between X and Y chromosomes, estrogen levels, early life stress, and chromatin remodeling in shaping addiction risk and psychiatric profiles. X and Y chromosomes influence cortical systems involved in adaptive social behaviors, ultimately affecting neuroanatomy and psychiatric vulnerability. High estrogen levels promote estrogenic resilience, offering protection against cocaine addiction. However, early-life stress and estrogen withdrawal diminish this resilience, increasing vulnerability. Estrogen directly regulates chromatin opening at ΔFosB binding sites-a key transcription factor involved in addiction-related plasticity-leading to changes in the nucleus accumbens, the brain's reward hub. These chromatin modifications, when dysregulated, contribute to heightened susceptibility to cocaine addiction, especially under conditions of estrogen loss, chromatin accessibility imbalance, or Y chromosome-driven stress effects. The figure integrates hormonal, genetic, and environmental influences to highlight sex-specific mechanisms contributing to addiction and psychiatric disorders.*

Sex chromosome dosage (SCD) is increasingly recognized as a factor that shapes neuroanatomy and may modulate susceptibility to mental illness. Guma., *et al*. [4] demonstrated that X and Y chromosome copy number differentially impact brain structure and possibly contribute to distinct psychopathological profiles.

One particularly striking example involves how early-life stress and ovarian hormones interact to heighten cocaine addiction vulnerability in females. Research by Rocks., *et al.* [5] revealed that the nucleus accumbens-a key region in reward processing-is influenced by both X chromosome inactivation and estrogen-responsive gene regulation. These molecular interactions underlie increased sensitivity to cocaine cues, particularly in low-estrogen states or after early-life stress. Females in these conditions show chromatin opening enriched for ΔFosB binding sites, a transcription factor associated with persistent drug-related changes. In contrast, high-estrogen states promote chromatin closure, acting as a protective mechanism against synaptic and epigenetic remodeling triggered by cocaine exposure. However, the loss of this estrogenic protection-whether due to hormone withdrawal, early-life adversity, or monosomy X-removes this resilience and exacerbates drug conditioning.

Building upon both the extensive literature [6-29] and findings from the RDS Consortium, we propose a model in which the Y chromosome is linked to heightened addiction risk, whereas the X chromosome contributes protective, regulatory influences-particularly in female neurobiology and psychiatric resilience.

Conclusion

Globally, women consistently outlive men, regardless of cultural or societal factors. This survival advantage holds true even in times of crisis such as famines or pandemics, underscoring that female longevity and neuroprotection are likely rooted in biology rather than environment alone. Data from the RDS Consortium highlight notable sex-based distinctions in pre-addiction vulnerability, with the Y chromosome appearing to elevate addiction risk in males, while the X chromosome may offer neuroprotective benefits in females.

Author Contribution

The initial manuscript was developed by KB, AS., KUL and APL, and each author approved the final manuscript providing comments and edits.

Conflict of Interest

KB owns patents issues and pending worldwide related to genetic testing and pro-dopamine regulation. There are no other conflicts.

Funding Support

R41 MD012318/MD/NIMHD NIH HHS/United States.

I01 CX000479/CX/CSRD VA/United States.

Appendix

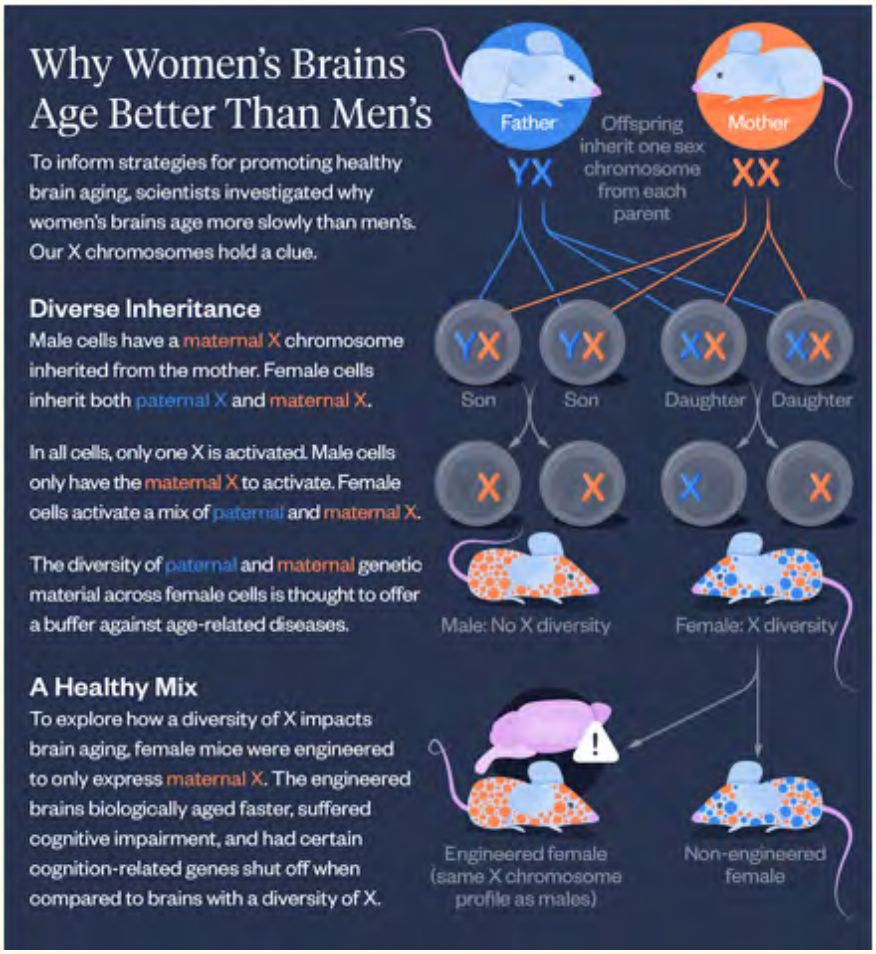

Figure: *X and Y chromosomes linked to aging and cognition.*

Credit: Lucy Reading-Ikkanda/Simons Foundation.

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Volume 17 Issue 7 July 2025