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X chromosome inactivation in sex disparities to substance use disorder

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Preclinical and clinical studies demonstrate a sex-based disparity associated with substance use disorders (SUDs). Women escalate from initial drug use to compulsive drug-taking behavior (telescoping) more rapidly, and experience greater negative withdrawal effects than men. These biological differences have largely been attributed to sex hormones. However, there is evidence for non-hormonal factors, such as the influence of the sex chromosome, which underlie sex disparities in addiction behavior. However, the mechanisms and genes underlying sex chromosome influences on substance abuse behavior are not completely understood. We hypothesized that escape from X-chromosome inactivation (XCI) in females contributes to sex-associated differences in addiction behavior. Females have two X chromosomes (XX), and during XCI, one X chromosome is randomly chosen to be transcriptionally silenced. However, some X-linked genes escape XCI and display biallelic gene expression. To test our hypothesis and as a proof of concept, we generated an X-linked gene specific bicistronic dual reporter mouse as a tool to visualize allelic usage in a cell specific manner. In these mice, each allele of the gene is linked to a green or red fluorescent reporter via an internal ribosome entry site (IRES) element, which allows for the expression of the downstream cistron (EGFP or RFP) without interfering with endogenous gene expression. Our results reveal a previously undiscovered X-linked gene XCI escaper (CXCR3), which is variable and cell type dependent. This novel approach will facilitate the characterization of allelic usage of X linked genes in models of substance use disorder.