SKEWED X-INACTIVATION: CAUSES AND ITS IMPACT ON DISEASE

Skewed X inactivation can lead to the manifestation of X-linked disorders in heterozygous females. But what actually drives this skewing? A review in Nature Reviews Genetics (1) proposes that heterozygous variants can give cells a competitive advantage or disadvantage, that creates clonal competition between cells expressing one or the other X chromosome. The paper explores how these selective forces shape development and influence disease expression.

Reported examples
• STAG2 variants: In mouse models, STAG2-variant clones contribute normally to many tissues but are excluded from the lymphoid lineage when competing with wild-type clones. Notably, these same variants can produce full lymphocyte lineages when no wild-type competitors are present, showing that the disadvantage is relative, not intrinsic .
• HDAC8 and STAG2 in humans: Female carriers of heterozygous mutations frequently show strong skewing in blood in favor of the X chromosome with the wild-type allele, consistent with selection against clones expressing the mutant variant .
• Immunodeficiency genes (IL2RG, BTK, WAS, NEMO): These X-linked mutations impair the survival or maturation of specific immune cell types. In heterozygous females, only clones expressing the wild-type allele can complete lymphocyte development, producing dramatic skewing driven by cell-intrinsic fitness differences .
• ABCD1 (X-linked adrenoleukodystrophy): Interestingly, in this case blood cells skew toward the mutant allele, even though the disease manifests in the brain. This shows that competition and skewing are tissue-specific, and that selection in one compartment (blood) does not predict disease risk in another (brain microglia) .

Overall, the article argues that skewed X inactivation often reflects underlying competitive interactions between clones with different X-linked alleles. Rare variants, tissue-specific fitness effects, and developmental bottlenecks collectively determine which clones dominate. These processes may modulate the severity of X-linked diseases in females and shape X-linked genetic diversity in human populations.

1. https://www.nature.com/articles/s41576-025-00840-3