THE INACTIVE X AS A FEMALE PROTECTOR

Autism affects three to four males for every female, and the same male bias runs through a long list of paediatric and congenital autosomal disorders: ADHD, intellectual disability, congenital heart disease, Hirschsprung disease, pyloric stenosis, clubfoot, and others. The underlying mechanism of this Female Protective Effect (FPE) has remained elusive.
In a Nature Genetics Perspective (April 2026), Maya Talukdar and David C. Page (1) propose a simple unifying explanation: the inactive X chromosome (Xi), considered transcriptionally silent since Mary Lyon's 1961 work, is the hidden protector.
The argument rests on three points:

1. Xi is not silent. At least 60 protein-coding genes escape X-inactivation and are transcribed from Xi alongside Xa, giving females a higher total dosage than males (whose Y-linked homologues are often functionally divergent).
2. These Xi-expressed genes are dosage-sensitive global regulators of chromatin (KDM6A, KDM5C), transcription (ZFX), translation (DDX3X), and ubiquitination (USP9X) — the very pathways disrupted in autism.
3. Higher baseline dosage buffers autosomal mutations. Females can tolerate deleterious variants that in males push the system past threshold. Xi acts as a genetic suppressor of autosomal mutations.

The same framework is then applied by the authors to 17 other male-biased paediatric disorders (Table 1 in the paper), each showing consistent FPE signatures (higher familial recurrence when the index case is female; the Carter effect).
The framework remains hypothesis-generating rather than a primary study, but it ties together a remarkable amount of scattered evidence under one experimentally testable mechanism.
It is worth stressing that the disorders discussed here are autosomal, not X-linked. The mechanism proposed is that Xi expression buffers autosomal mutations. It has nothing to do with classical X-linked inheritance.

1. https://www.nature.com/articles/s41588-026-02534-w