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## Enriched X-chromosome influences on neuroanatomical variation in UK Biobank

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### ABSTRACT:

The X-chromosome has long been hypothesized to have a disproportionate influence on the brain, as genes located on chromosome often show enriched expression in brain tissue relative to other chromosomes (Nguyen & Disteche, 2006). Moreover, it has been demonstrated that the X-chromosome is enriched for genes that cause intellectual disability when mutated (Zechner et al., 2001). Here, we verify this hypothesis through partitioned heritability analysis of X-chromosome influences (XIs) on human brain anatomy in 32,256 individuals from the UK Biobank. We first establish evidence for dosage compensation in XIs on brain anatomy, reflecting larger XIs in males as compared to females. Moreover, we find that the spatial pattern of dosage compensation across the cortex is correlated with that of regional sex-differences in neuroanatomical variance. We then demonstrate that XIs are significantly larger than would be predicted from X-chromosome size for the relative surface area of cortical systems supporting attention, decision making, and motor control. Finally, we report several follow-up analyses that implicate X-linked genes with pleiotropic effects on neuroanatomy and cognition. Taken together, our findings reveal a privileged role for the X-chromosome in human neurodevelopment, and urge greater inclusion of this chromosome in future genetically informative research.

### REFERENCES:

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