Evaluating the effects of sex chromosome dosage on autism spectrum disorder risk

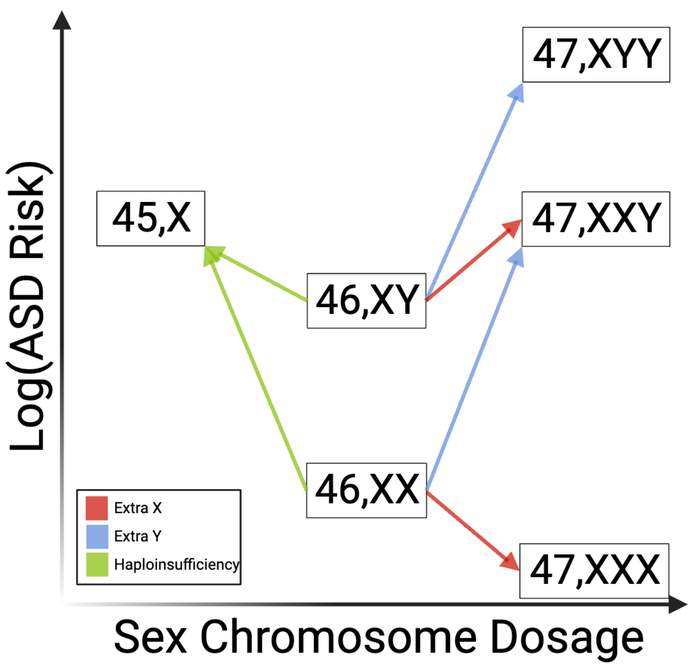
Geisinger

Alexander S.F. Berry[1]; Brenda M. Finucane[1]; Scott M. Myers[1]; John Seibert[1]; David H. Ledbetter[1]; Christa Lese Martin[1]; Matthew T. Oetjens[1]

[1]Autism & Developmental Medicine Institute, Geisinger, Lewisburg, PA

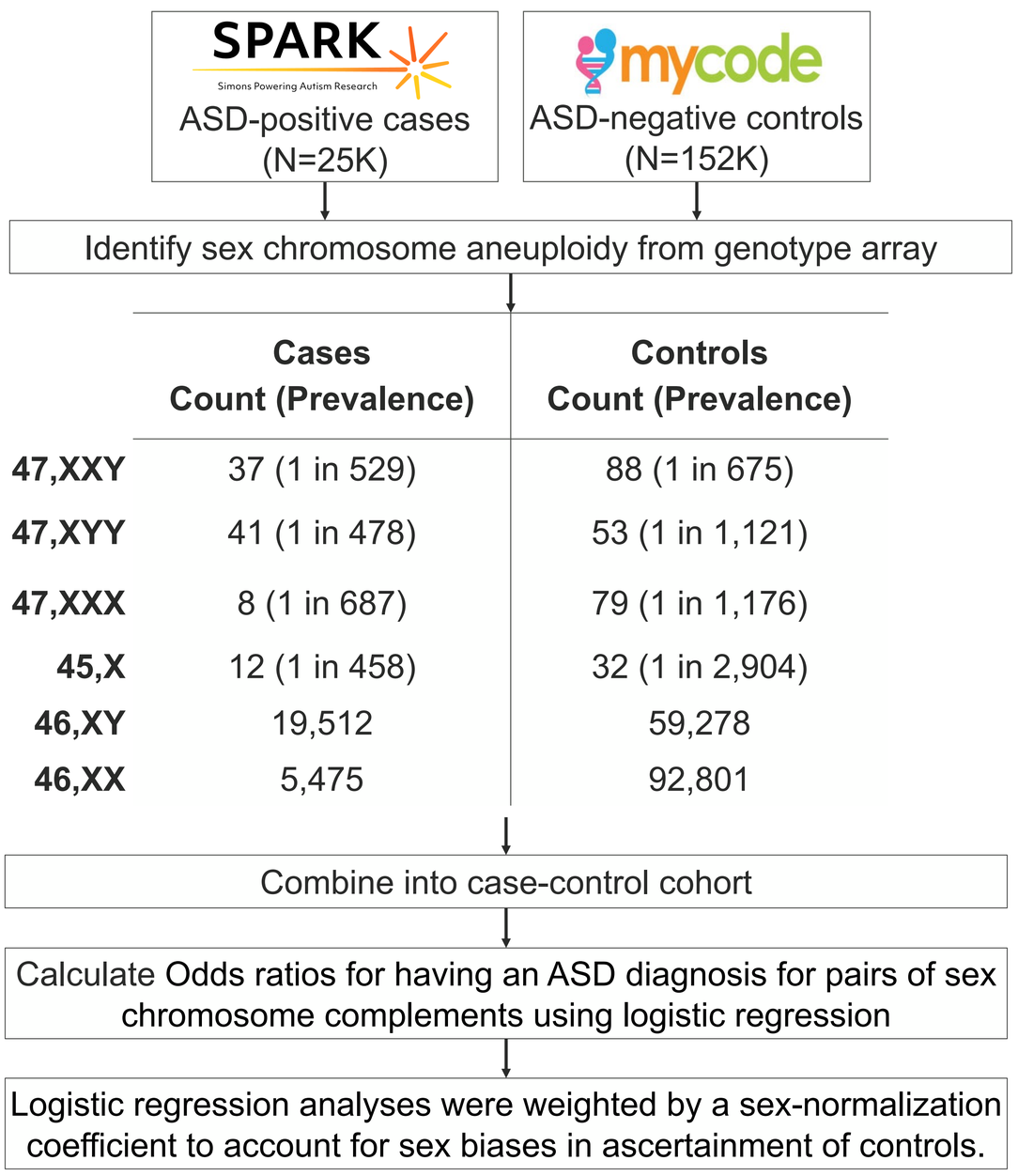
Background

- Autism spectrum disorder (ASD) is 3.8 times more prevalent among males than females, however an explanatory mechanism remains elusive.[1]
- Individuals with an atypical number of X and/or Y chromosomes, a genetic condition called sex chromosome aneuploidy (SCA), can be a useful model to examine the relationship between sex chromosome dosage and human phenotypes.
- The prevalence of ASD reported among the four most common SCAs (45,X, 47,XXX, 47,XXY and 47,XYY) were aggregated from clinical studies and summarized into a model by Green et al.[2]

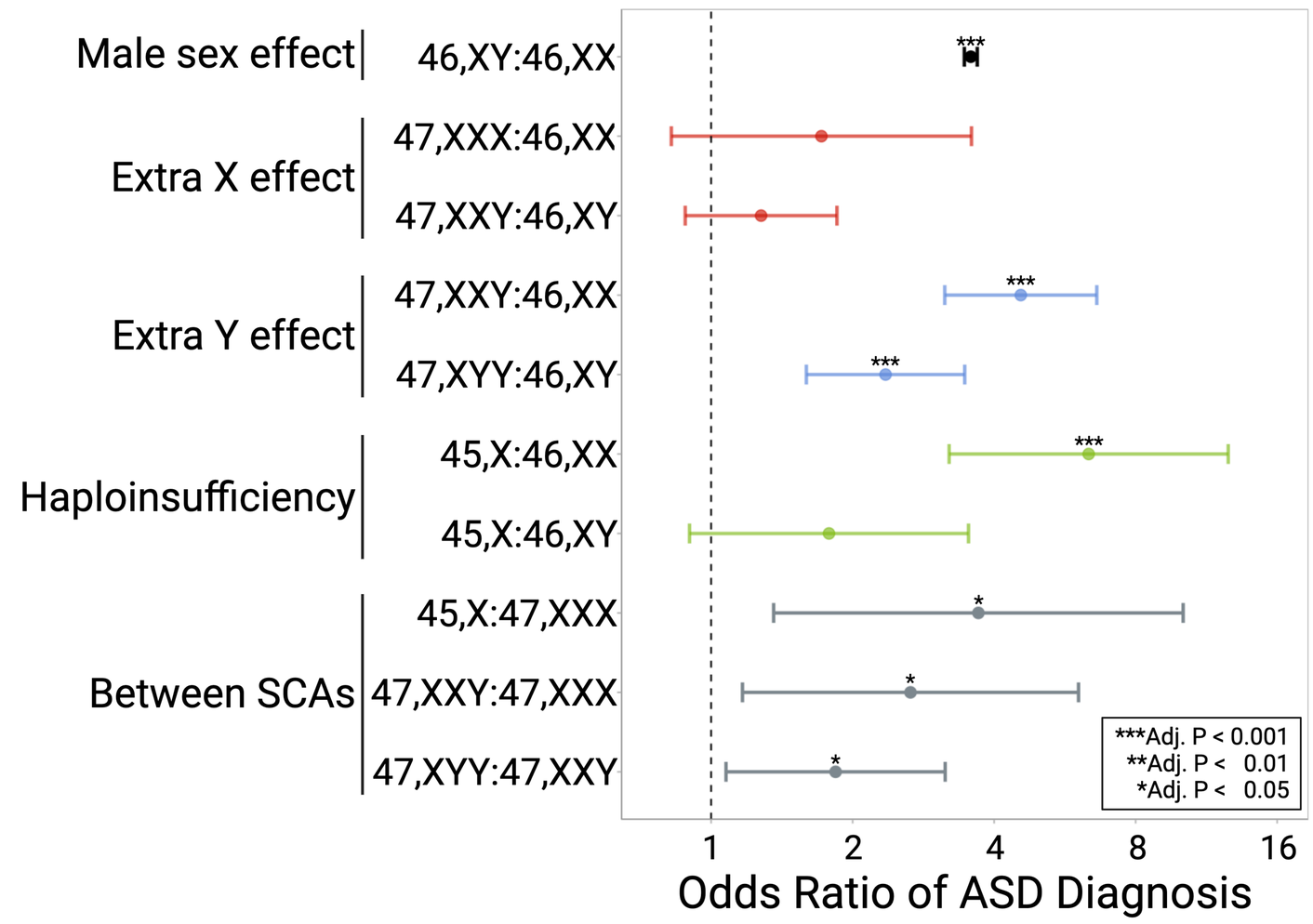


- In this study, we genetically identified individuals with SCA and tested this model of how sex chromosome dosage modulates ASD risk and contributes to the sex difference in ASD prevalence.

Methods



Results



Association between sex chromosome dosage and ASD. Forest plot shows the odds ratios of having an ASD diagnosis for one sex chromosome complement relative to another.

Summary of Results:

1. The Y chromosome increases ASD risk among males
2. No evidence of a dosage sensitive factor on the X chromosome protective of ASD
3. Haploinsufficiency of the X chromosome substantially increases ASD risk.

Conclusions and Future Directions

- By confirming the Green model in a large genetic cohort, this study bridges findings from decades of observational studies of SCA among clinical cohorts with emerging studies of SCA in large scale genetic biobanks.
- Our study provides a framework for using SCA to understand the role of X and Y chromosome dosage on phenotypes with a sex bias.
- Plan to use this framework to study the association between sex chromosome dosage and other phenotypes with sex biases.

Acknowledgements

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References

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