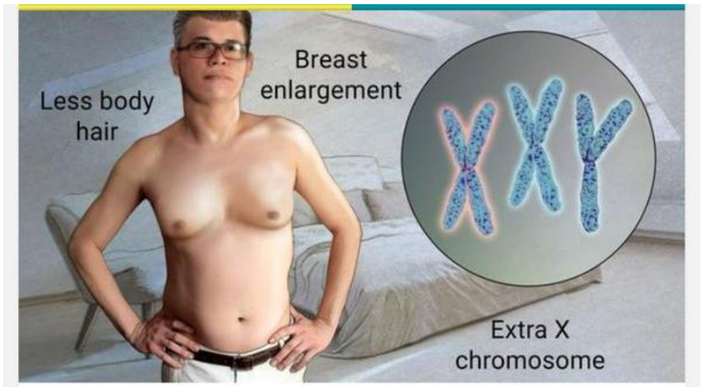
Sex chromosome aneuploidies and risk of neuropsychiatric disorders in two population-based cohorts

Authors: John Seibert[1]; Alexander Berry[1]; Matthew Oetjens[1]
[1]Geisinger Medical Center, Danville, PA

Introduction

- Individuals with sex chromosome aneuploidies, characterized by an atypical number of X or Y chromosomes, collectively comprise a common but under-diagnosed genetic group, with prevalence estimates ranging from 1 in 1400 births to 1 in 650 births.



. Image from https://www.mayoclinic.org/

Figure 1: Clinical features of Klinefelter syndrome

- Individuals with sex chromosome aneuploidies are reported to be at increased risk for neuropsychiatric disorders (NPD). However, this association is not well characterized.

- We leveraged two large population-based cohorts with linked genetic and health data to investigate the relationship between sex chromosome aneuploidy and NPD.

- MyCode, Geisinger's biobank, analyzes consenting patients' DNA and returns clinically actionable findings to them.

- The All of Us research program aims to make advances in tailoring medical care to the individual. Its mission is to accelerate health and medical breakthroughs, enabling individualized prevention, treatment and care.

Materials and Methods

- To assess the frequency of relevant neuropsychiatric disorders, the International Classification of Diseases, Ninth Revision and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision billing codes were extracted from linked EHRs as described Martin et al. 2020.

- Age was calculated based on the last encounter in EHR. Tests of association were performed with logistic regression adjusted for age and sex. Reported P values were 2-sided.

- Sex chromosome aneuploidies were called in MyCode using the protocol reported by Oetjens et al. 2019. In this study, we included four sex chromosome aneuploidies 47,XXY (Klinefelter syndrome); 47, XXX (trisomy X syndrome); 47, XYY (47,XYY syndrome) and 45,X (Turner syndrome).

Results

- Among the most common NPD diagnoses in MyCode, they consisted of anxiety and depression. This finding is similar in the All of Us cohort as well.

Table 1: Prevalence of NPD in MyCode and AllofUs

	MyCode			AllofUs		
NPD	**Controls**	**Cases**	**%**	**Controls**	**Cases**	**%**
ID	170,563	2,208	1.29	98,455	167	0.35
EP	166,360	6,411	3.85	96,792	1,830	3.88
ADHD	166,384	6,387	3.84	97,021	1,601	3.40
ANX	113,724	59,047	51.92	82,202	16,420	34.8
BPD	164,728	8,043	4.88	92,701	5921	12.6
DEP	126,322	46,449	36.77	81,740	16882	35.8
SLP	171,404	1,367	0.80	98,356	266	0.56
SCZ	168,798	3,973	2.35	96,668	1954	4.15
OCD	170,803	1,968	1.15	98,085	537	1.14
COM	169,989	2,782	1.64	98,366	256	0.54
CP	171,356	1,415	0.83	98,540	82	0.17
Motor	171,637	1,134	0.66	97,644	978	2.07
ASD	171,459	1,312	0.77	98,511	111	0.24
OND	172,713	58	0.03	98,510	112	0.24

ID: Intellectual Disability; CD: Communication Disorder; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit and Hyperactivity Disorder; SLD: Specific Language Disorder; MD: Motor Disorder; OND: Other Neurodevelopmental Disorder; SCZ: Schizophrenia and Related Disorder; BPD: Bipolar Disorder; OCD: Obsessive Compulsive Disorder; EP: Epilepsy; CP: Cerebral Palsy;

- The most-rare diagnoses in MyCode are autism, motor disorders, and other neurological disorders. In the All of Us cohort, the most rare diagnoses are cerebral palsy, autism, and other neurological disorders.

- The most common disorders were similar between the All of Us and MyCode cohorts. The rarest disorders were differing, with cerebral palsy in All of Us and motor disorders being in MyCode.

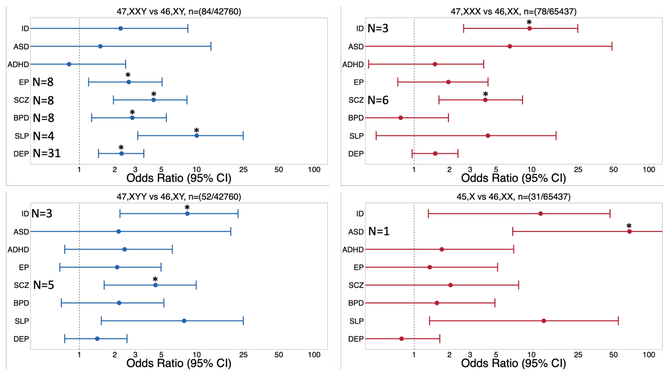


Figure 2: Prevalence of NPD in MyCode and AllofUs

- In MyCode, sex chromosome aneuploidies increased risk of NPD between 5-10x higher compared to individuals with a typical sex chromosome complement

Discussion

- Overall, the prevalence for NPD diagnoses were similar between the MyCode and All of Us cohorts. This was displayed through the proportion of cases.
- Individuals with sex chromosome aneuploidies are at an increased risk of NPDs.

References

C. L. Martin, *et al.*, Identification of Neuropsychiatric Copy Number Variants in a Health Care System Population. *JAMA Psychiatry* (2020)

M. T. Oetjens, M. A. Kelly, A. C. Sturm, C. L. Martin, D. H. Ledbetter, Quantifying the polygenic contribution to variable expressivity in eleven rare genetic disorders. *Nat. Commun.* **10**, 4897 (2019).