Polygenic epilepsies

September 13, 2020

Epilepsy Genetics Update 2020

Cleveland Clinic

Every life deserves world class care.

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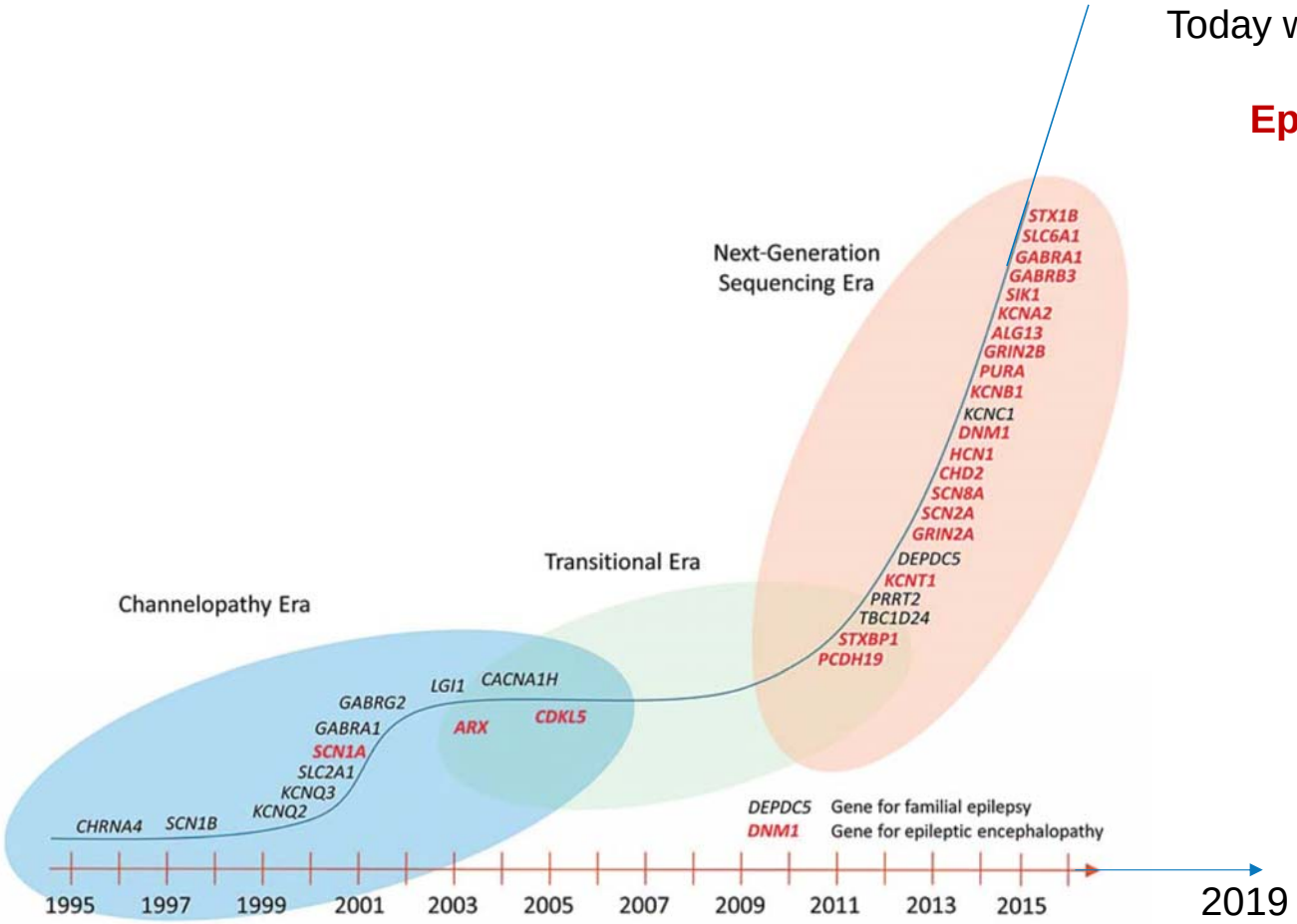
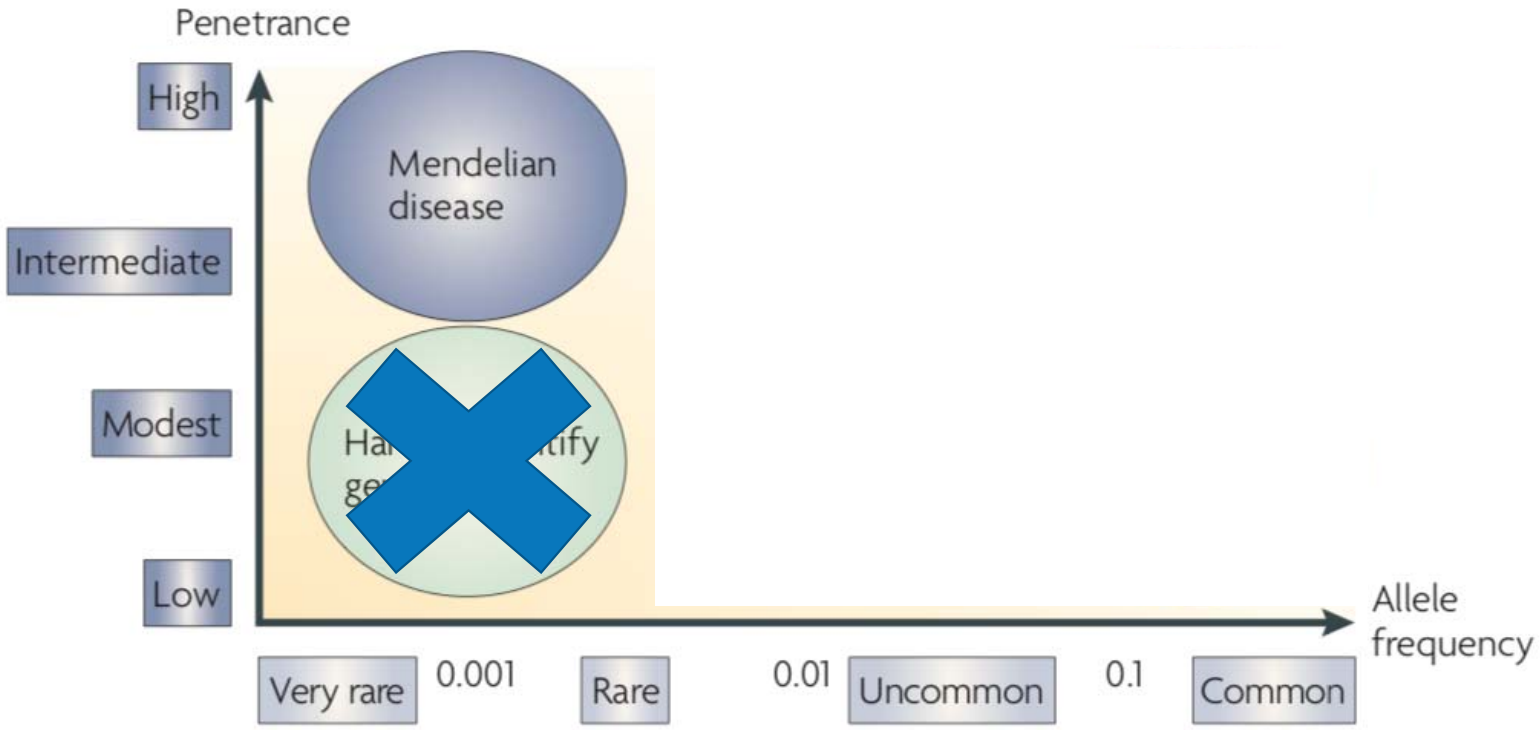
The number of known genes for rare (monogenic) epilepsies is growing



Today we know with high confidence about **30 – 100** genes associated with **Epilepsy – Neurodev. disorder with seizures**

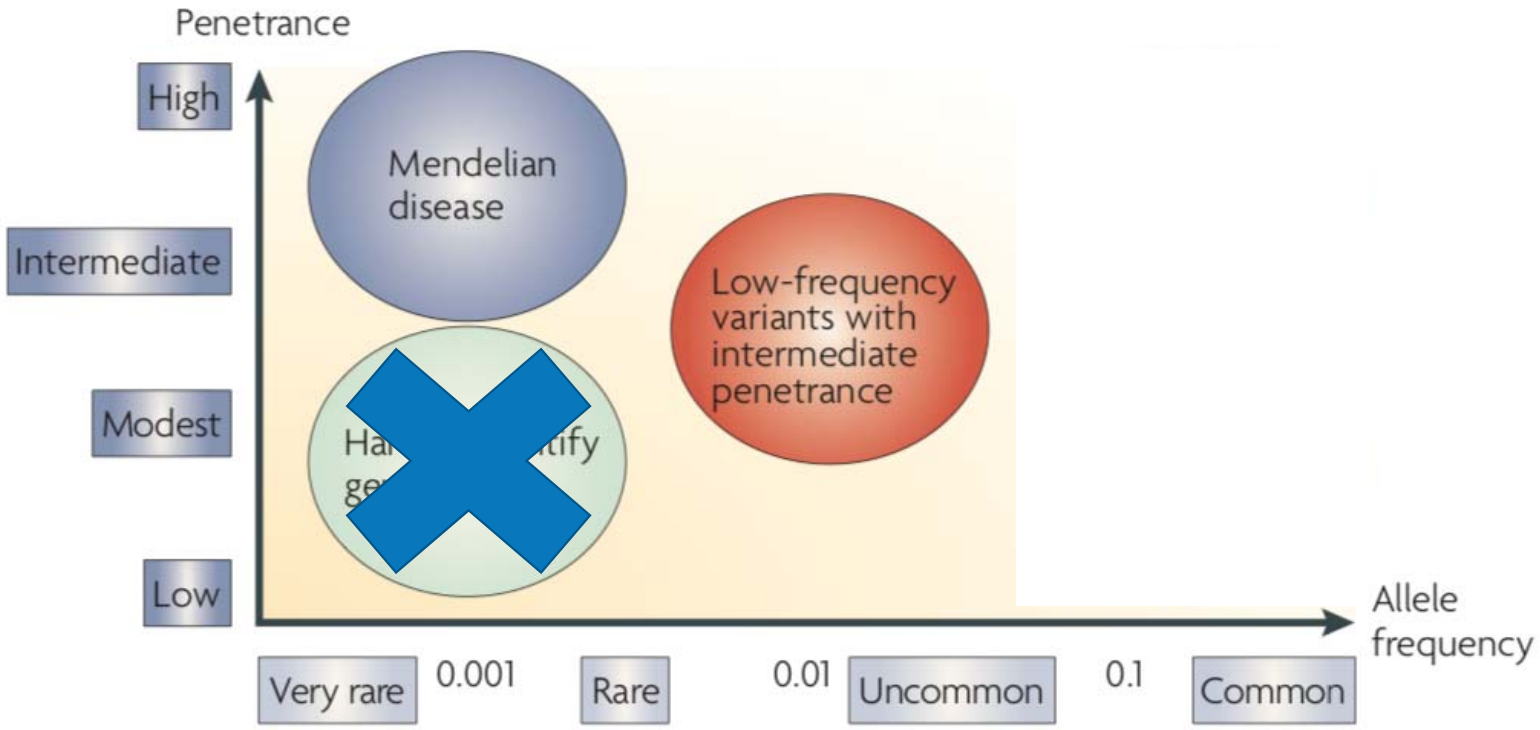
Modified from Helbig et al., 2016
PMID: 27781027

All types of causal variants



Modified from McCarthy et al., 2008
PMID: 18398418

All types of causal variants



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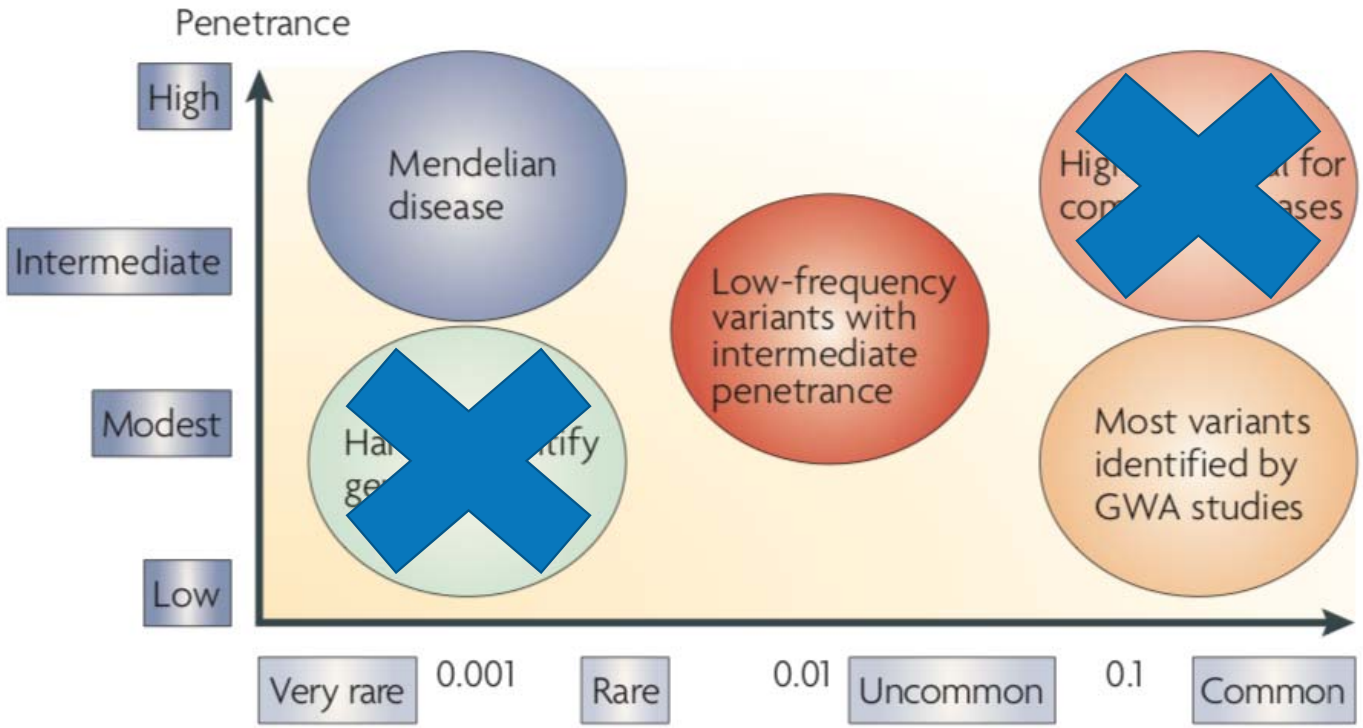
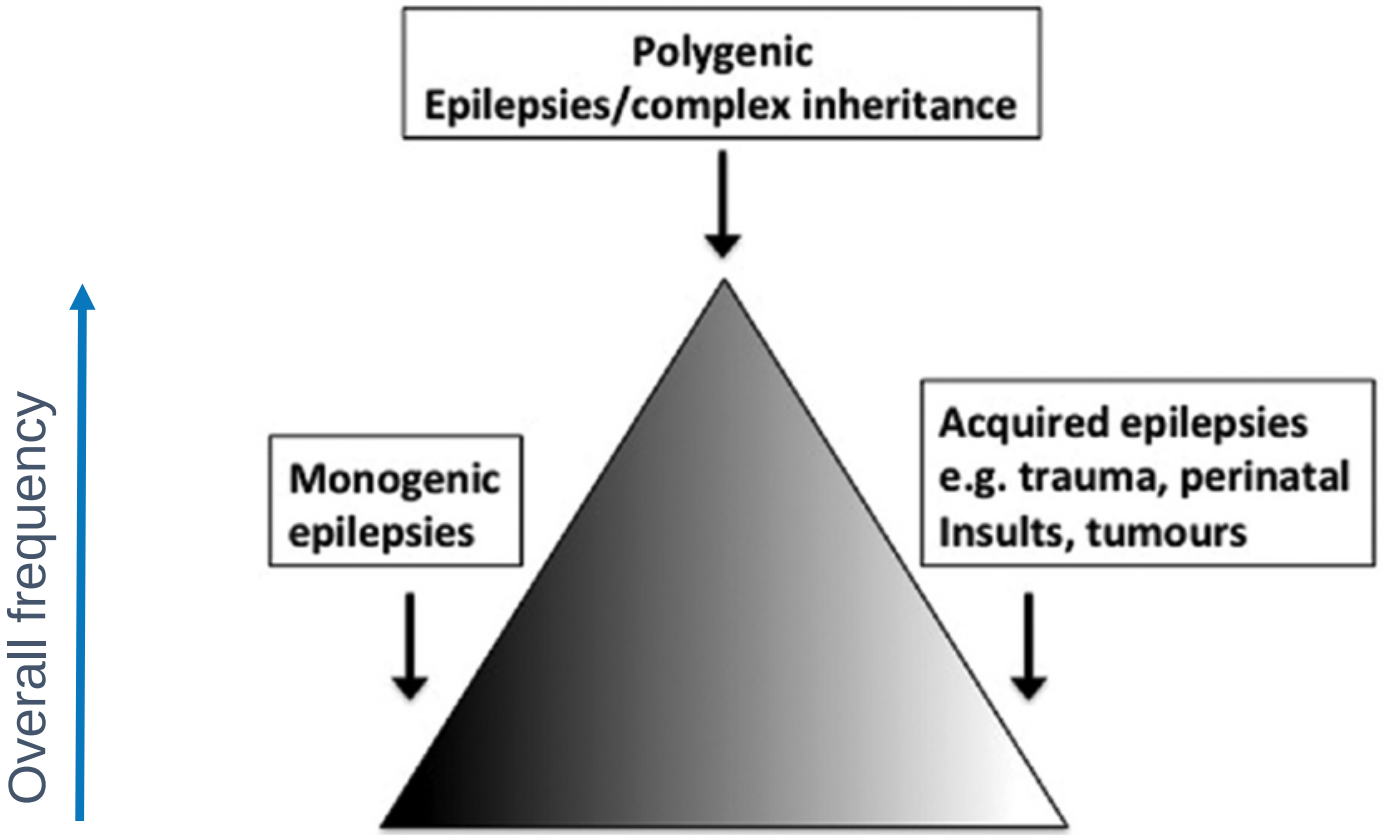


APOE

Alzheimer's disease and cardiovascular disease

Modified from McCarthy et al., 2008
PMID: 18398418

Monogenic vs. polygenic epilepsies



from Dhiman, 2017
PMID: 28615892

Genes known to cause Mendelian forms of epilepsy play only minor roles for common forms of epilepsy.

There is an unmet need for predictive genetic markers for the common epilepsies.

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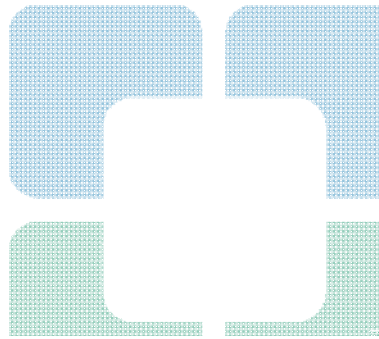
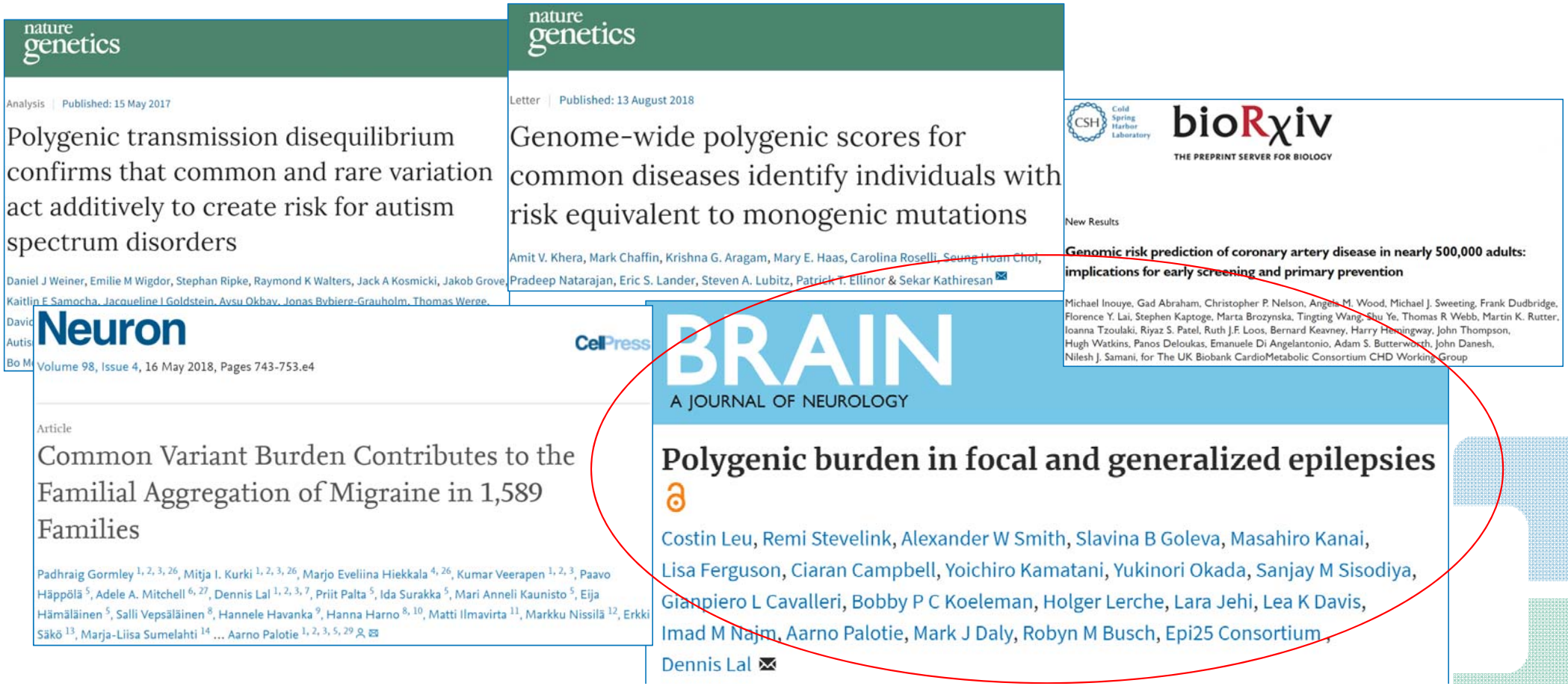


Polygenic risk scores

- The **utility of PRS as biomarkers** has been demonstrated virtually all complex traits and diseases, including neuropsychiatric disorders



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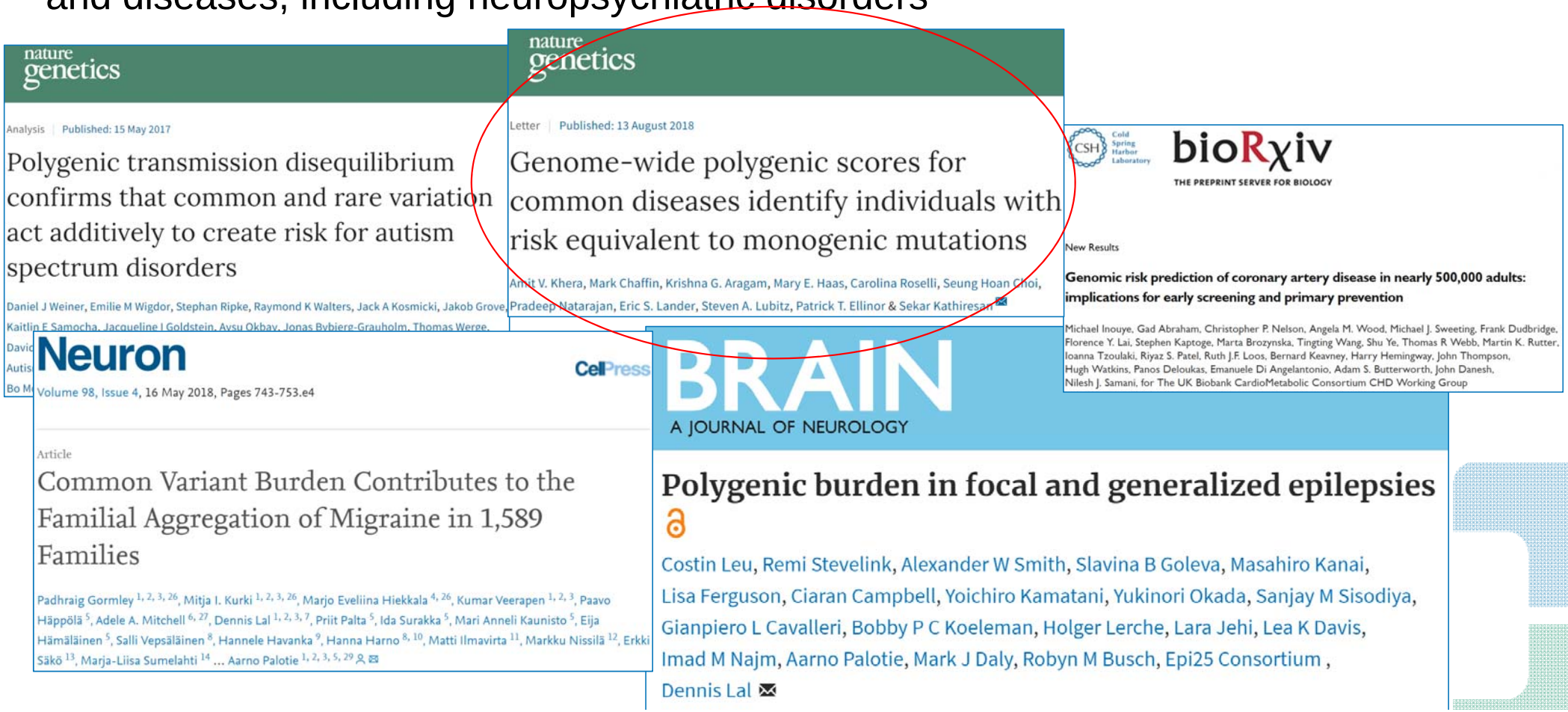
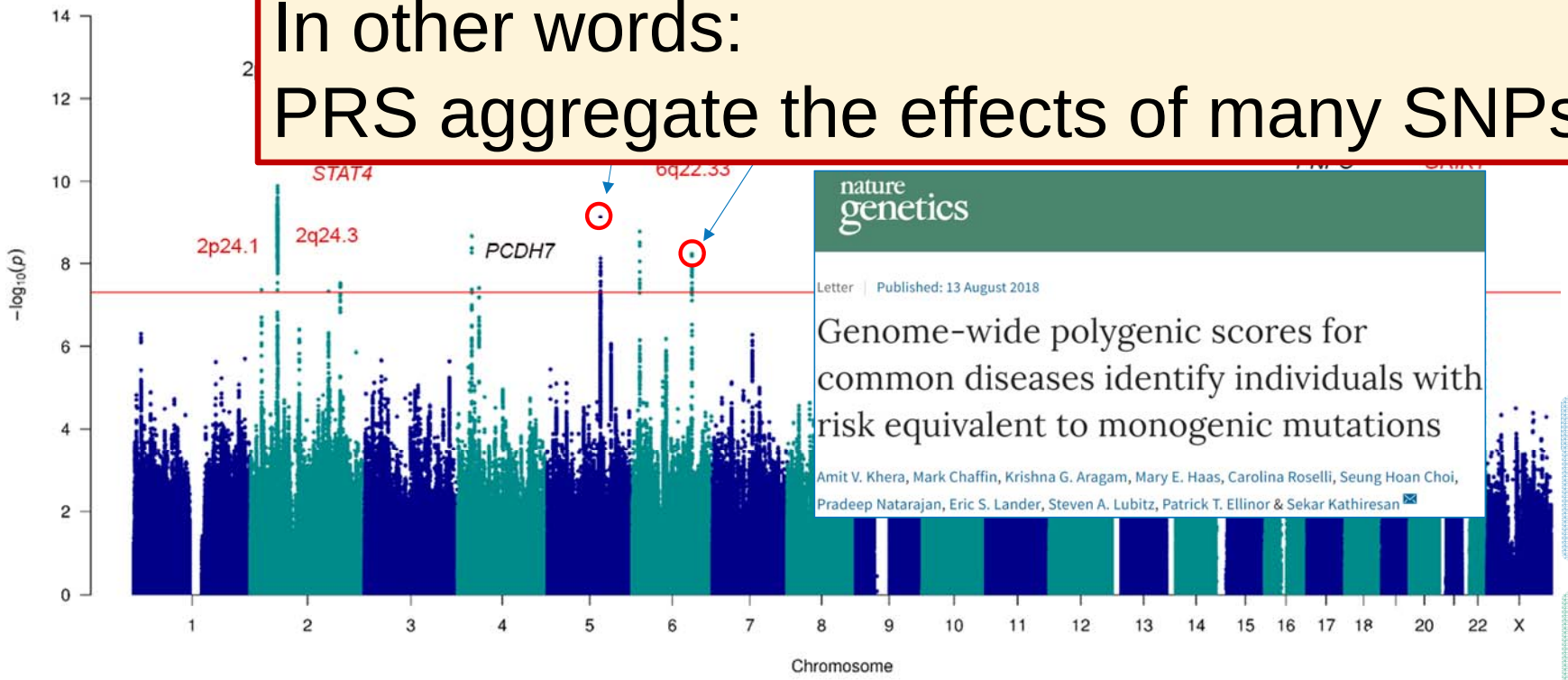


ILAE2 Genetic Generalized Epilepsy (GGE) GWAS – 3708 cases vs. 24218 controls

PRS = Number (Alleles) * $\log(OR_{SNP1})$ + Number (Alleles) * $\log(OR_{SNP2})$ + Number (Alleles) * $\log(OR_{SNP3})$ = $\sum [\log(OR_i) * N_{alllele}i] / \text{Number SNP}_i$

Per person

In other words:
PRS aggregate the effects of many SNPs



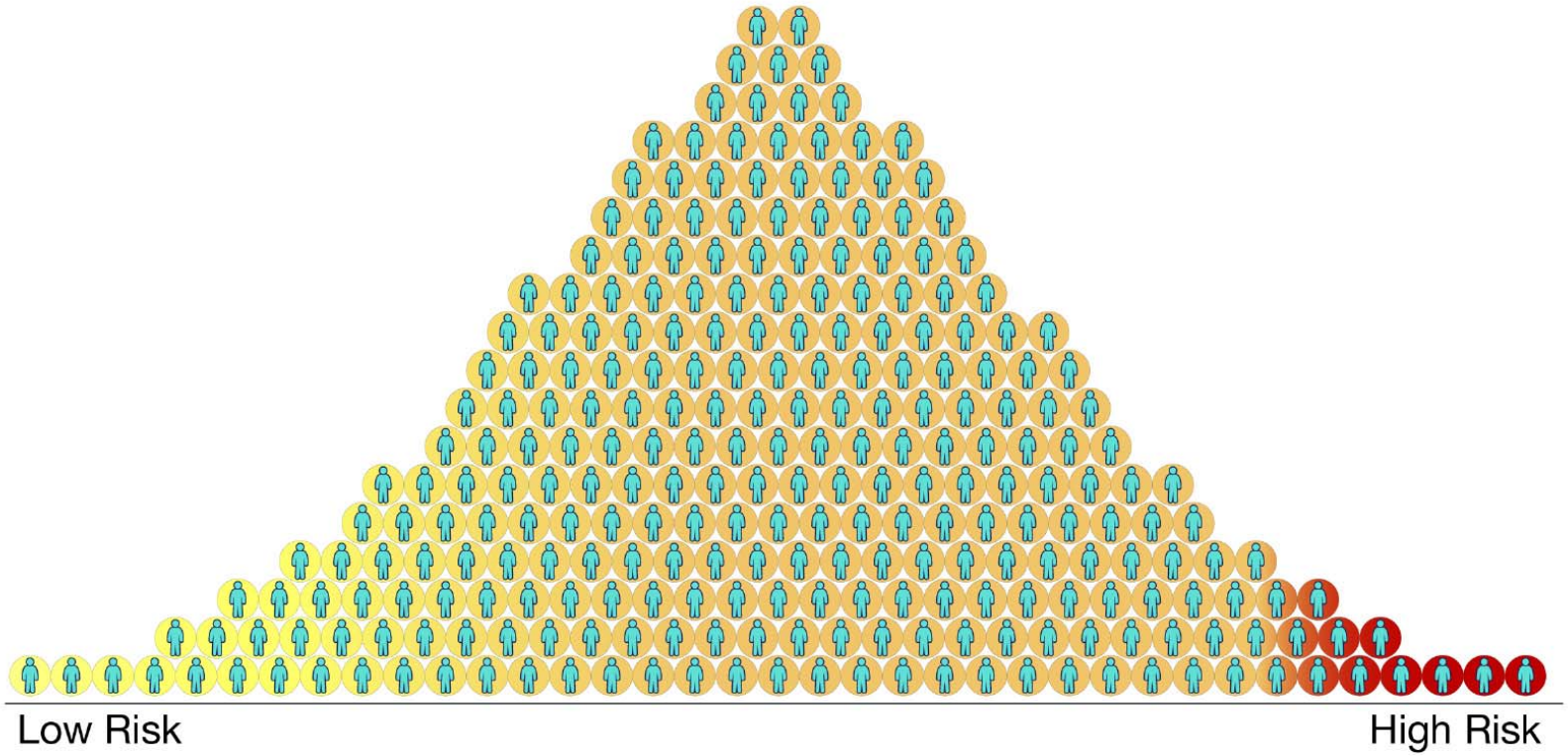
nature genetics

Letter | Published: 13 August 2018

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

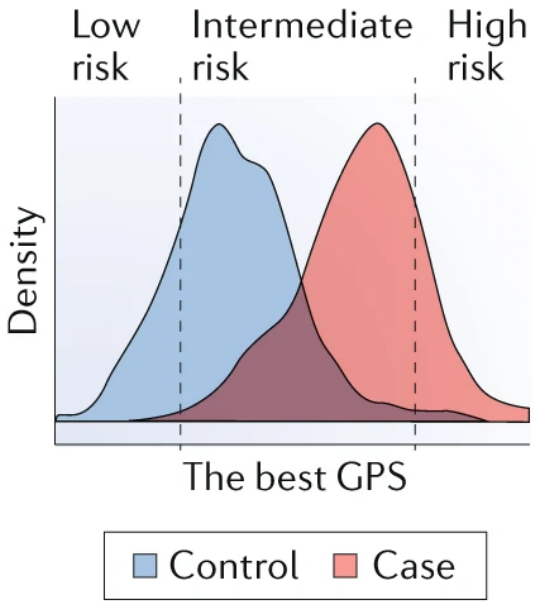
Amit V. Khera, Mark Chaffin, Krishna G. Aragam, Mary E. Haas, Carolina Roselli, Seung Hoan Choi, Pradeep Natarajan, Eric S. Lander, Steven A. Lubitz, Patrick T. Ellinor & Sekar Kathiresan

Polygenic risk scores are normally distributed



From https://www.genome.gov

Evaluation of the Polygenic Risk Scores



Polygenic score for relative risk stratification

Modified from Liu and Kiryluk, 2018
PMID: 30279535

Can epilepsy PRS be used as genetic biomarkers ?

PRS are derived from a GWAS and can only be generated in independent samples

1. Genome-wide association study (GWAS) for risk score generation

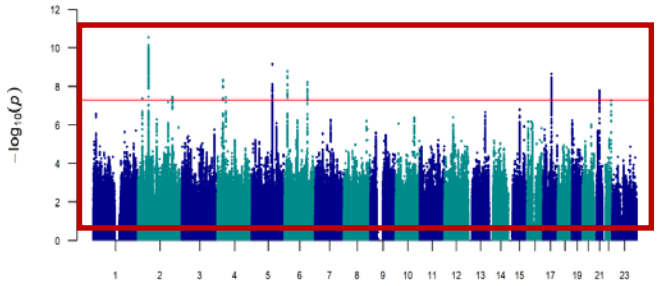
ILAE 2018 analysis
12,803 cases

VS.

24,218 controls

GWAS: Genetic Risk

variants

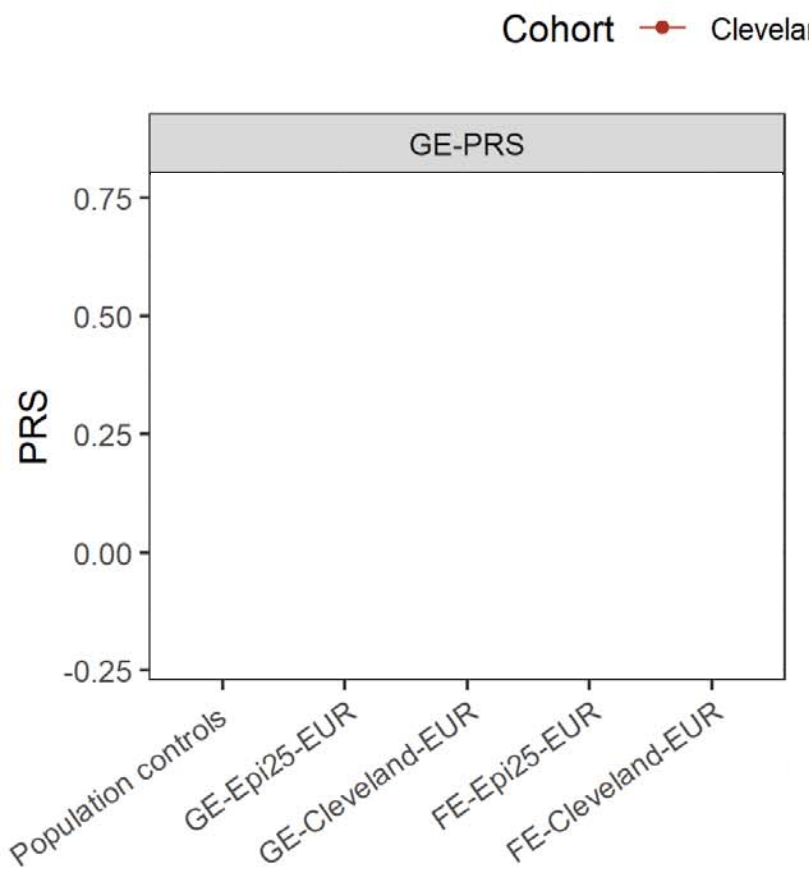


Epi25-EUR = 5,705	***Cleveland-EUR*** = 620	EUR controls = 20,435	***Epi25-FIN*** = 449	FINRISK = 1,559

UK biobank (UKB) = 459 = 383,197	**Vanderbilt biobank (BioVU)** = 829 = 48,670	**BioBank Japan (BBJ)** = 324 = 168,356

8,386 people with epilepsy and 622,217 population controls available across six cohorts

Polygenic risk scores for focal (FE) and generalized (GE) epilepsy



PRS = Polygenic risk score; GE = Generalized epilepsy; FE = Focal epilepsy; T2D = Type 2 diabetes; CC = Cleveland Clinic cohort, Epi25 = Consortium cohort

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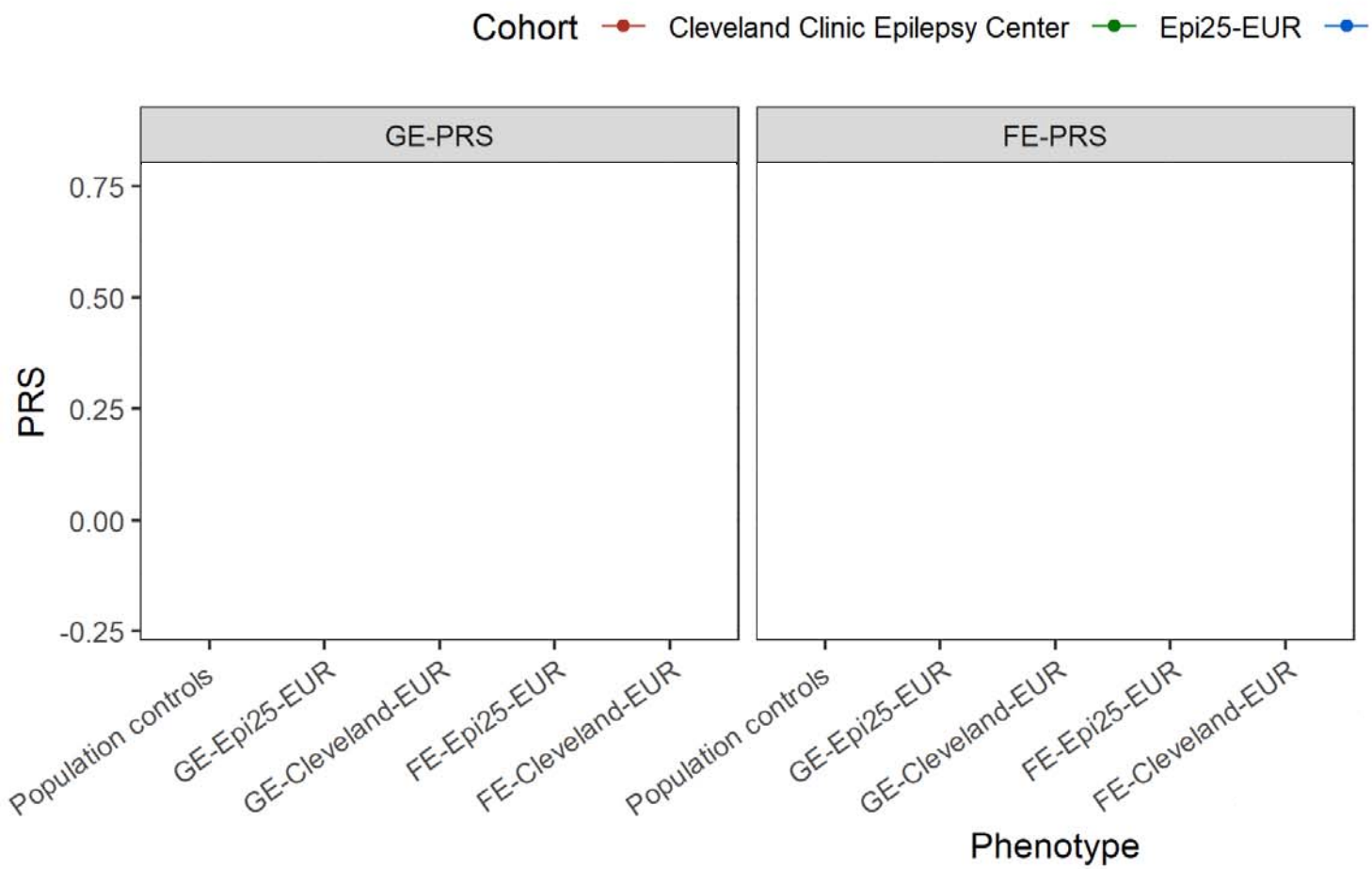

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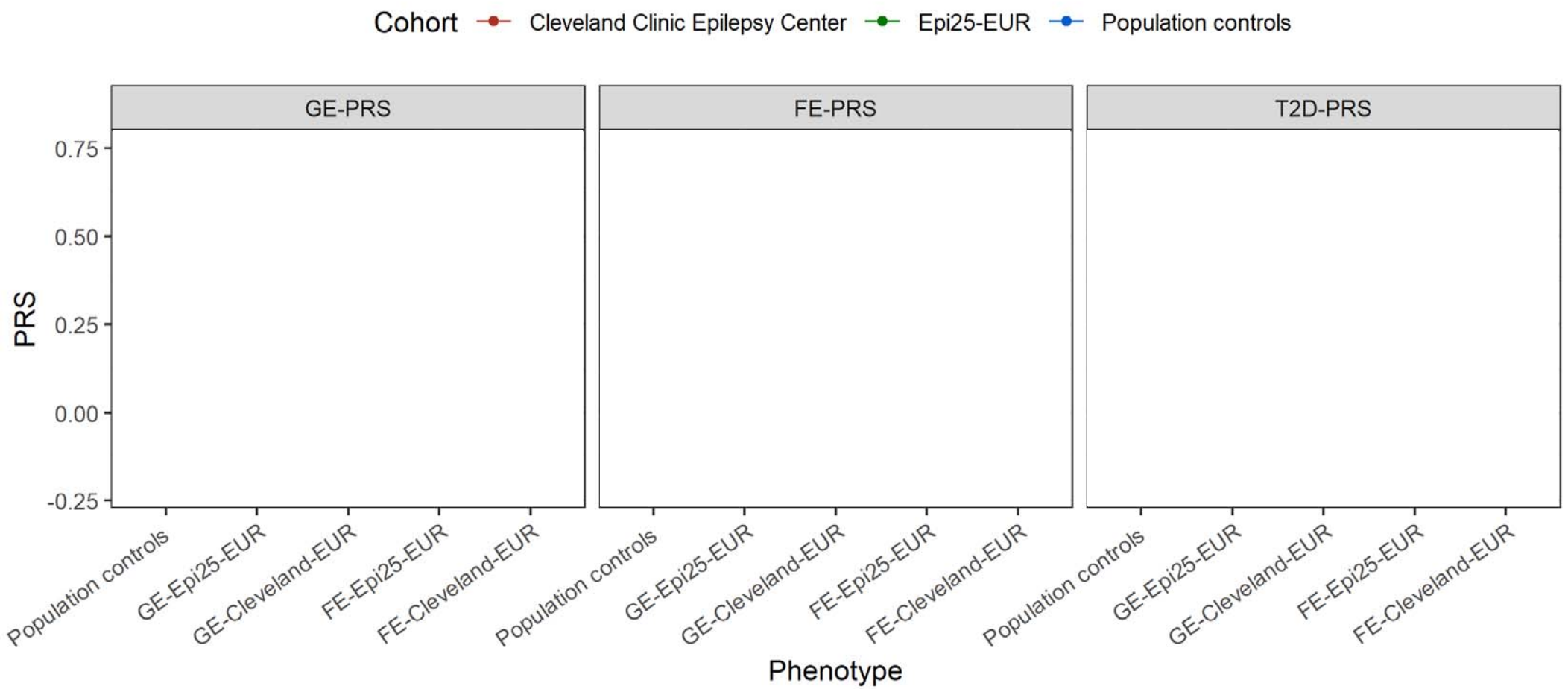

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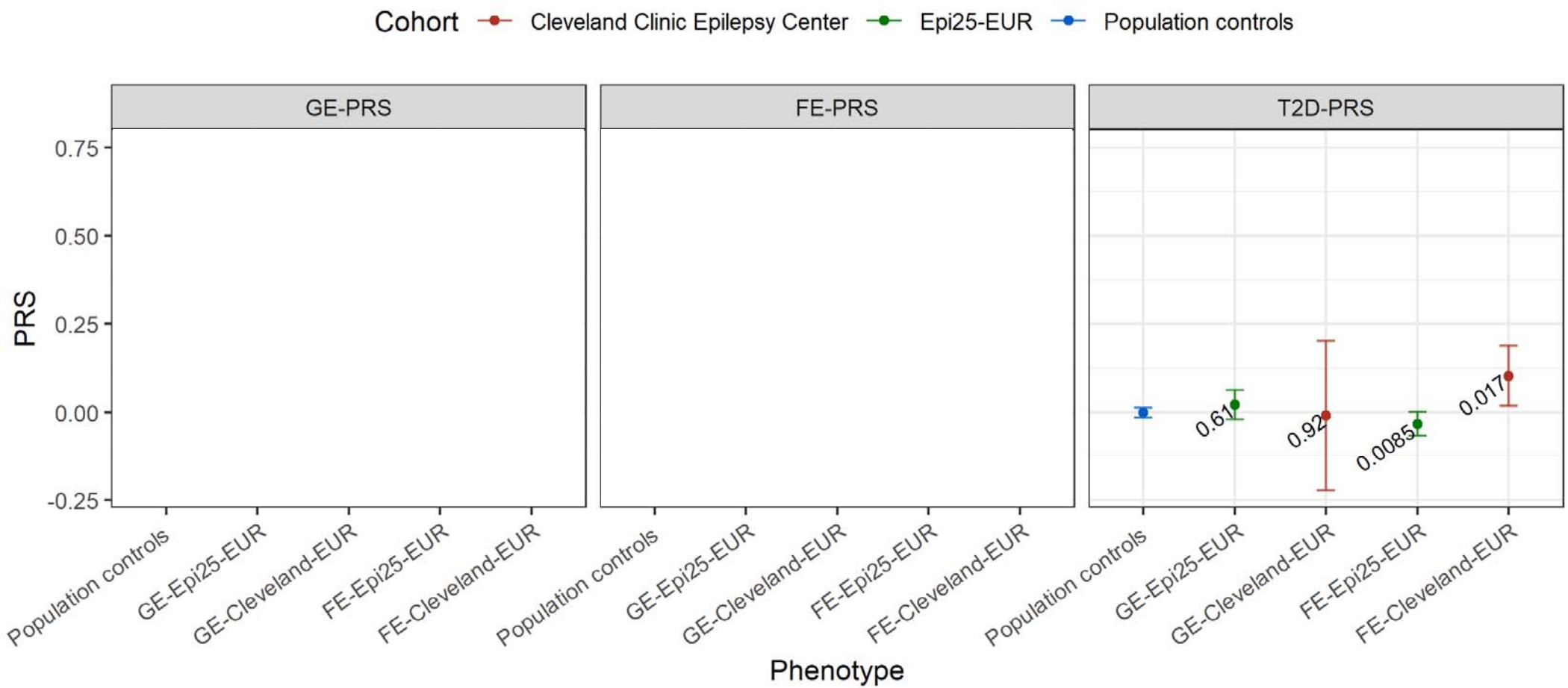

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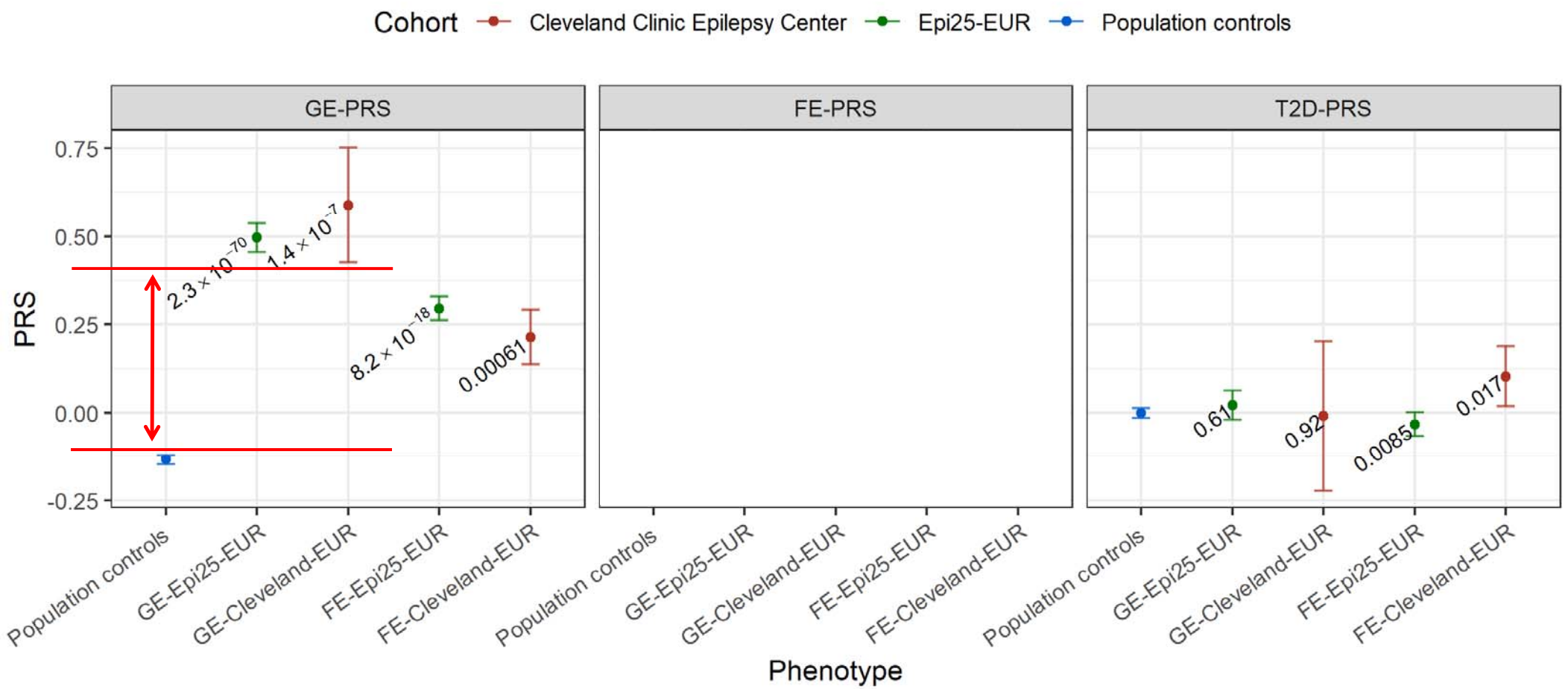

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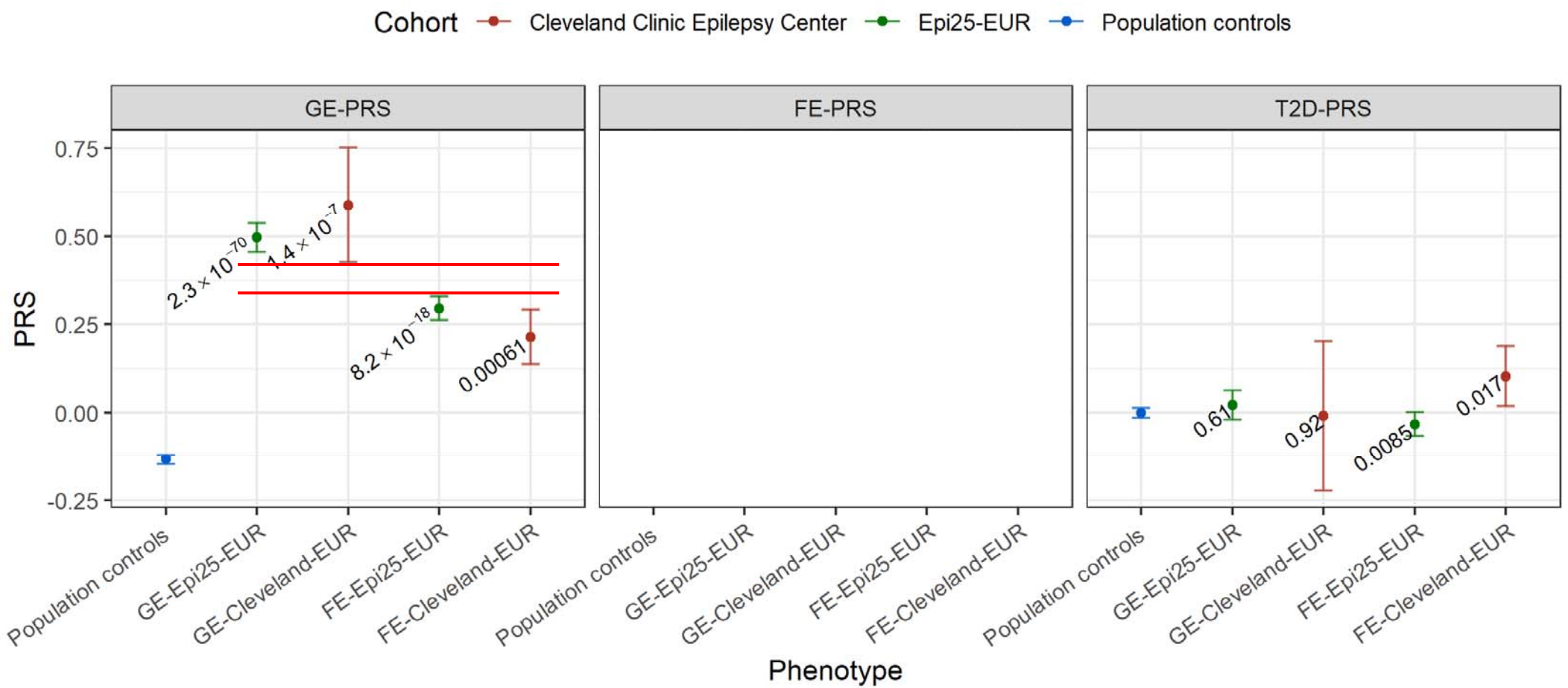

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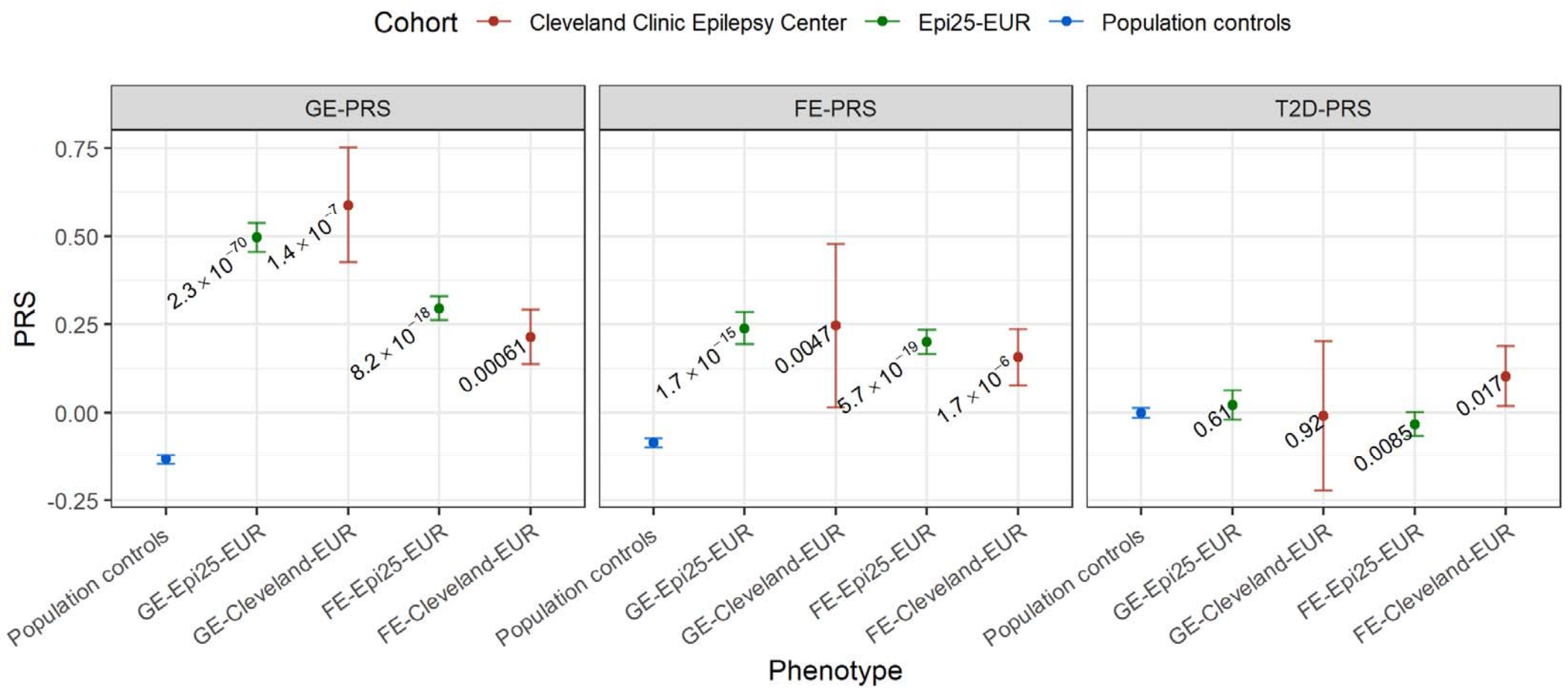

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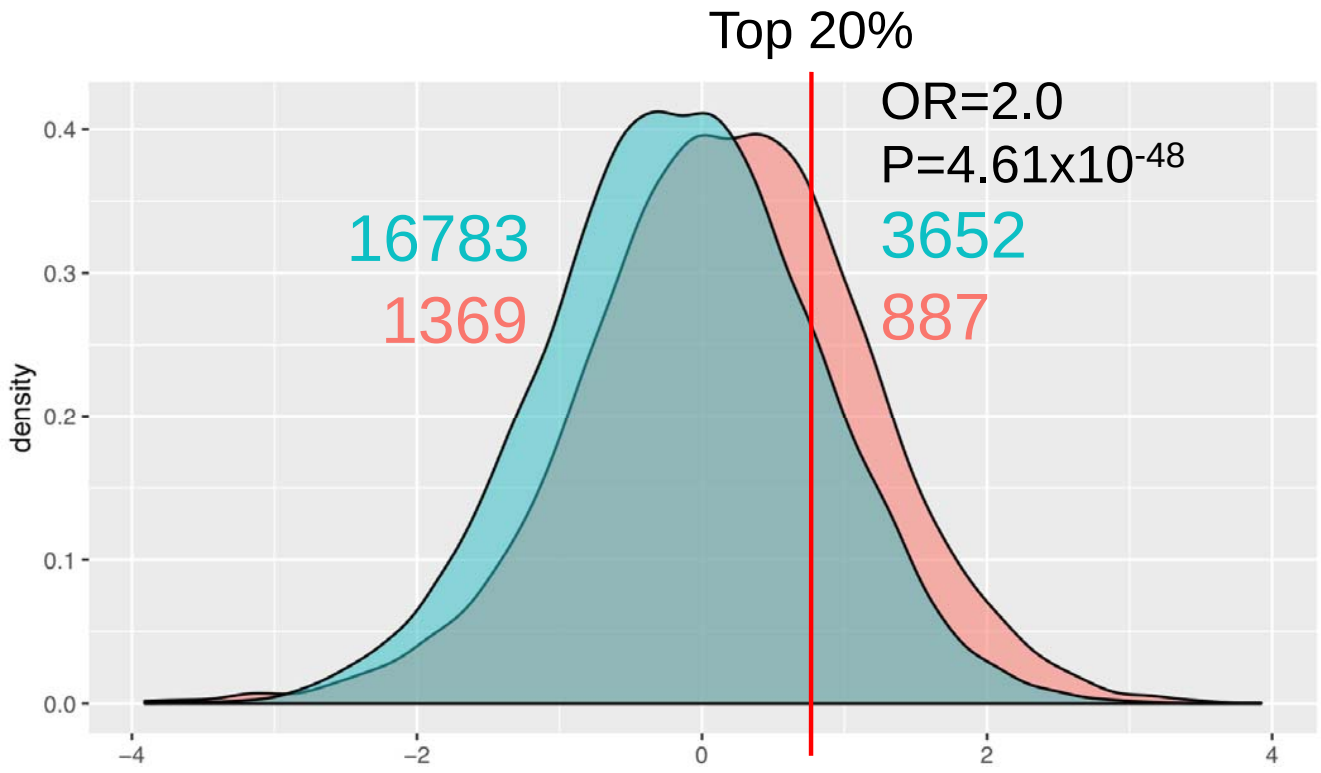
How are the PRS distributed

- Few patients with very high PRS burden
- Slight shift toward higher PRS burden in all patients

?

Individuals with GE are enriched in the extreme tail of the PRS distribution

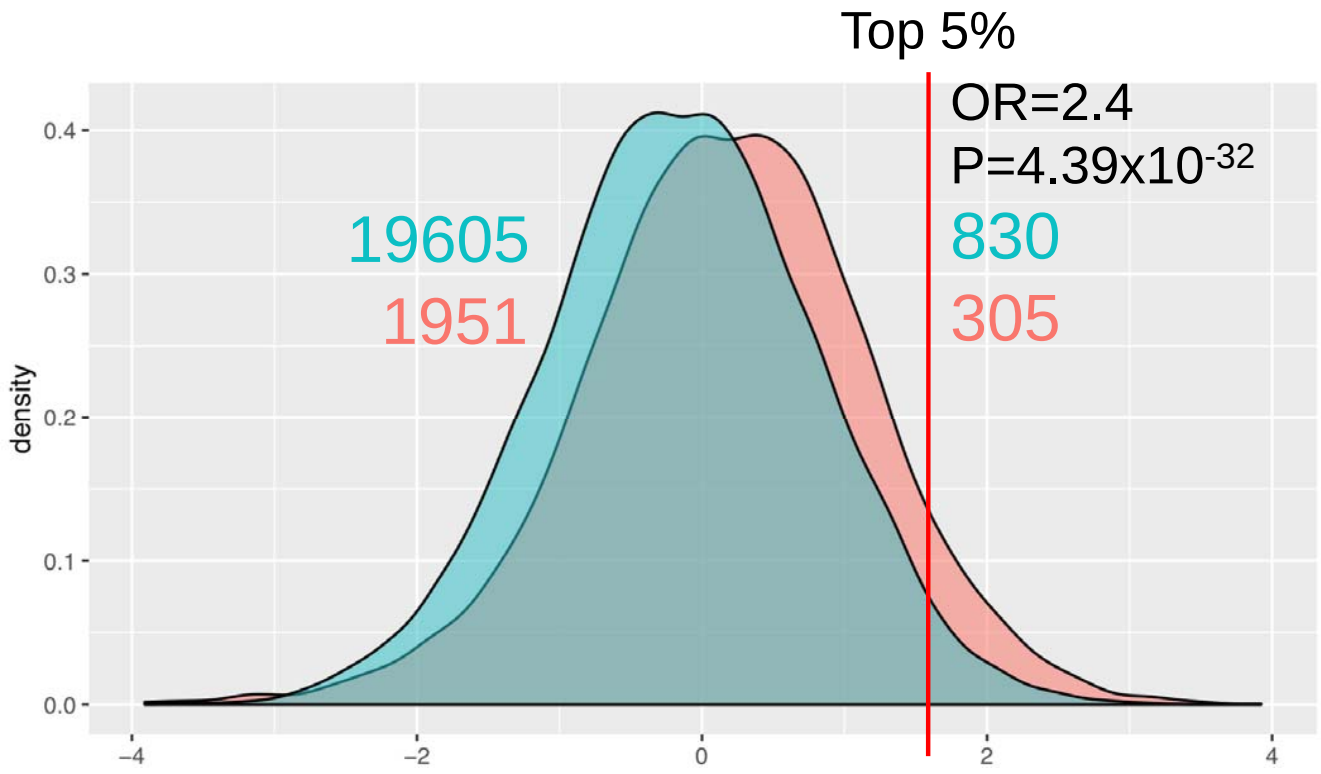


Sensitivity: 0.39
Specificity: 0.82

Generalized epilepsy
Controls

Low ← **Polygenic risk score** → **High**

Individuals with GE are enriched in the extreme tail of the PRS distribution

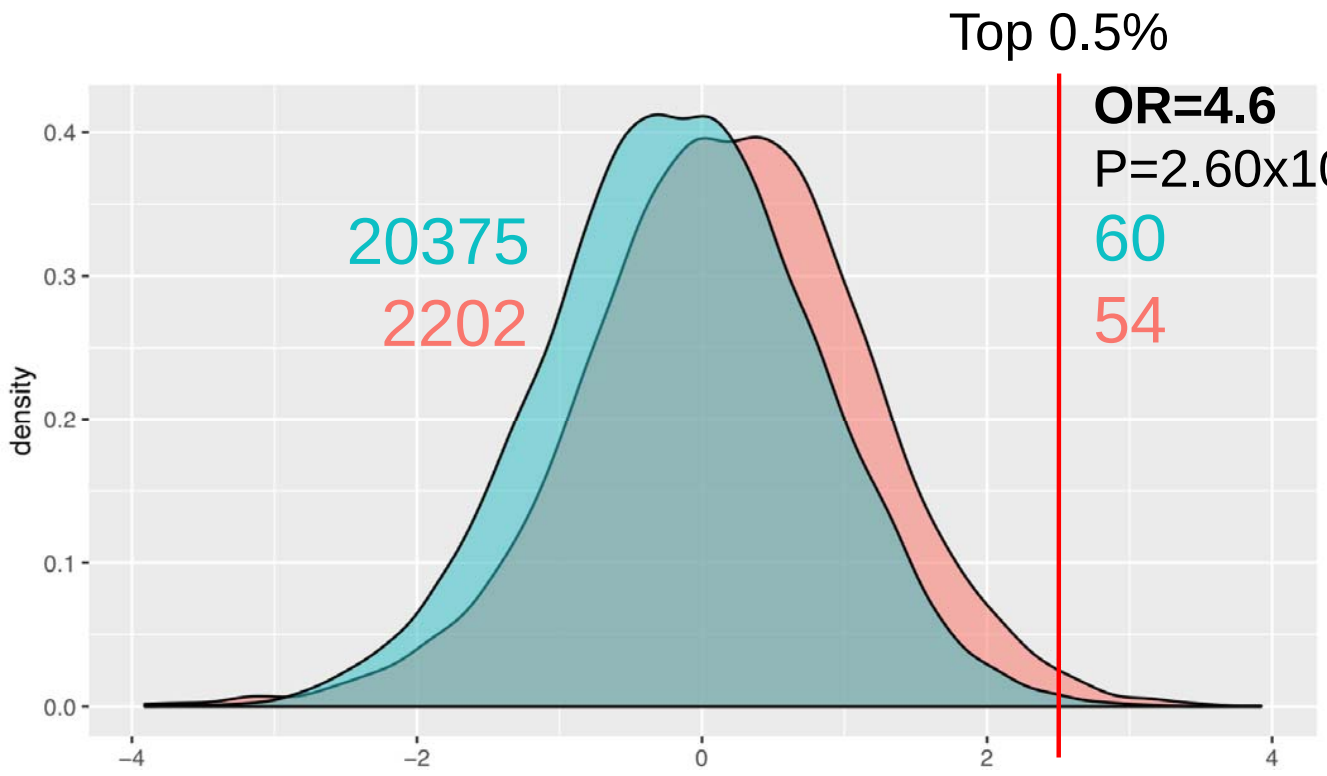


Sensitivity: 0.14
Specificity: 0.96

Generalized epilepsy
Controls

Low ← **Polygenic risk score** → **High**

Individuals with GE are enriched in the extreme tail of the PRS distribution



Sensitivity: 0.024
Specificity: 0.997

Generalized epilepsy
Controls

Low ← **Polygenic risk score** → **High**

Polygenic risk score in large datasets

To learn more about genetics of complex disorders

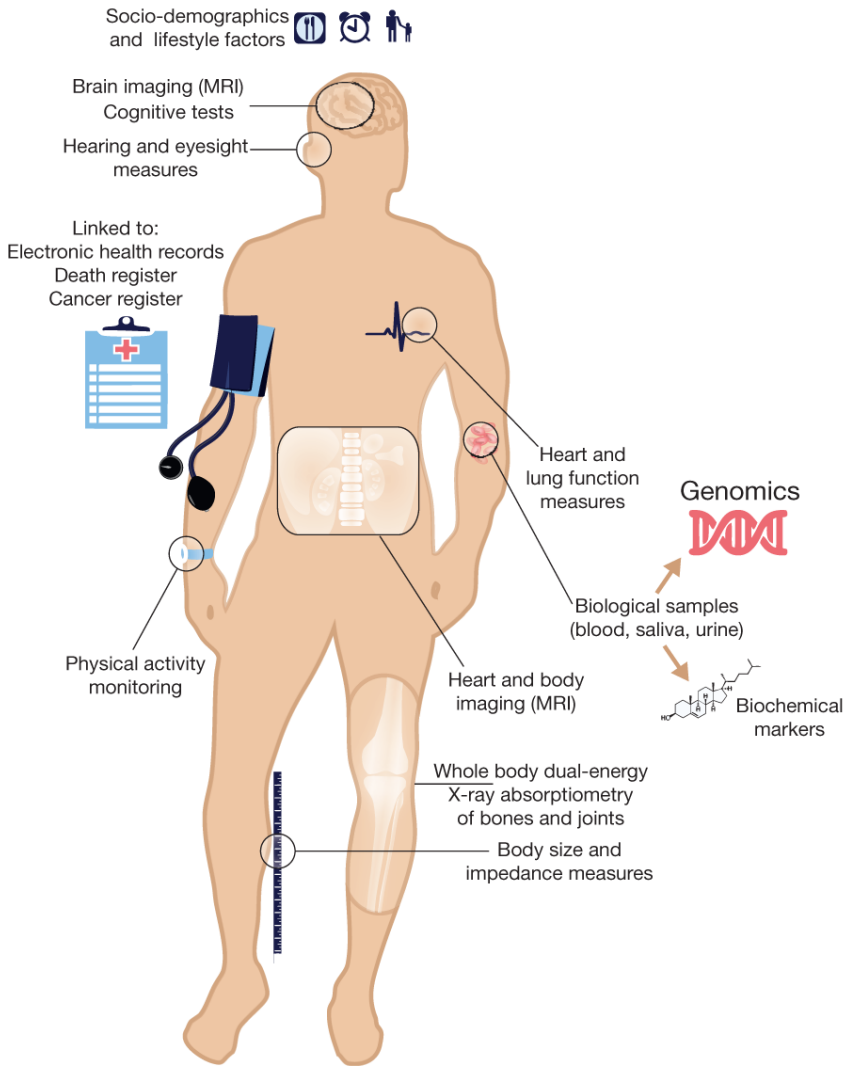
PLOS ONE

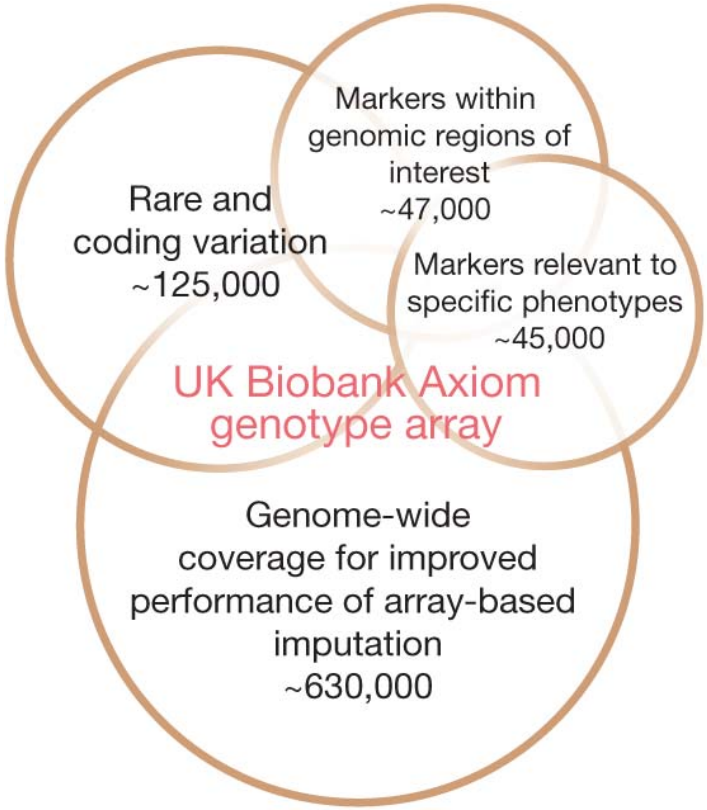
Pleiotropy of polygenic factors associated with focal and generalized epilepsy in the general population

Costin Leu, Tom G. Richardson, Tobias Kaufmann, Dennis van der Meer, Ole A. Andreassen, Lars T. Westlye, Robyn M. Busch, George Davey Smith, Dennis Lal

Published: April 28, 2020 • https://doi.org/10.1371/journal.pone.0232292

UK Biobank





biobank uk

Improving the health of future generations

PRS brain-focused PheWAS in the UKB

PRS for generalized and focal epilepsy

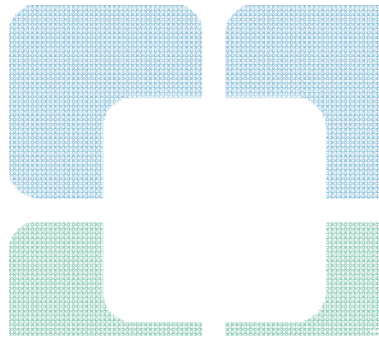
in

UK biobank (UKB)
= 334,398 without epilepsy

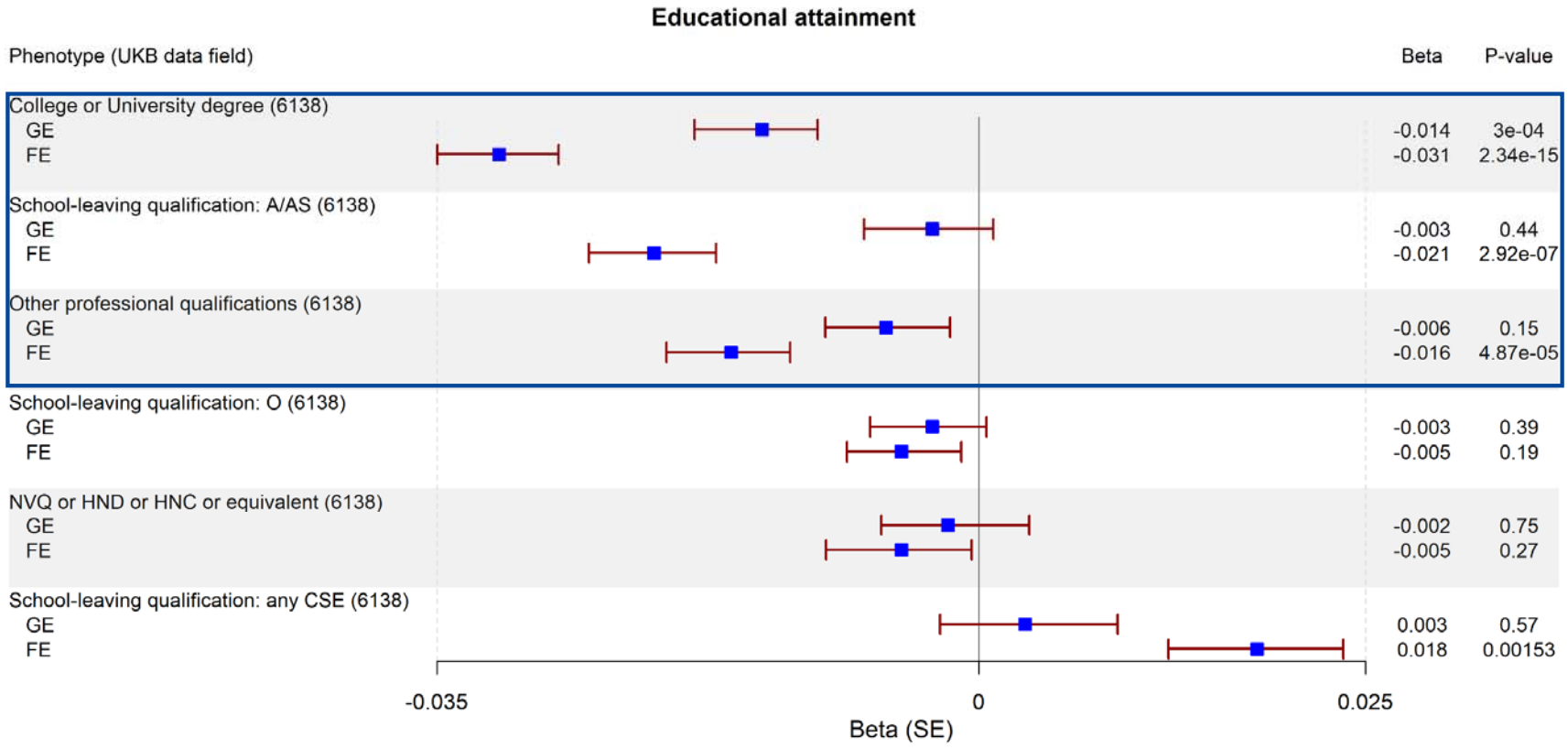
with

42 conditions, categorized six groups:

1. Educational attainment
2. Neuroticism
3. Mood [affective] disorders
4. Substance use/abuse/dependence
5. Diseases of the nervous system
6. Nonpsychotic mental disorders

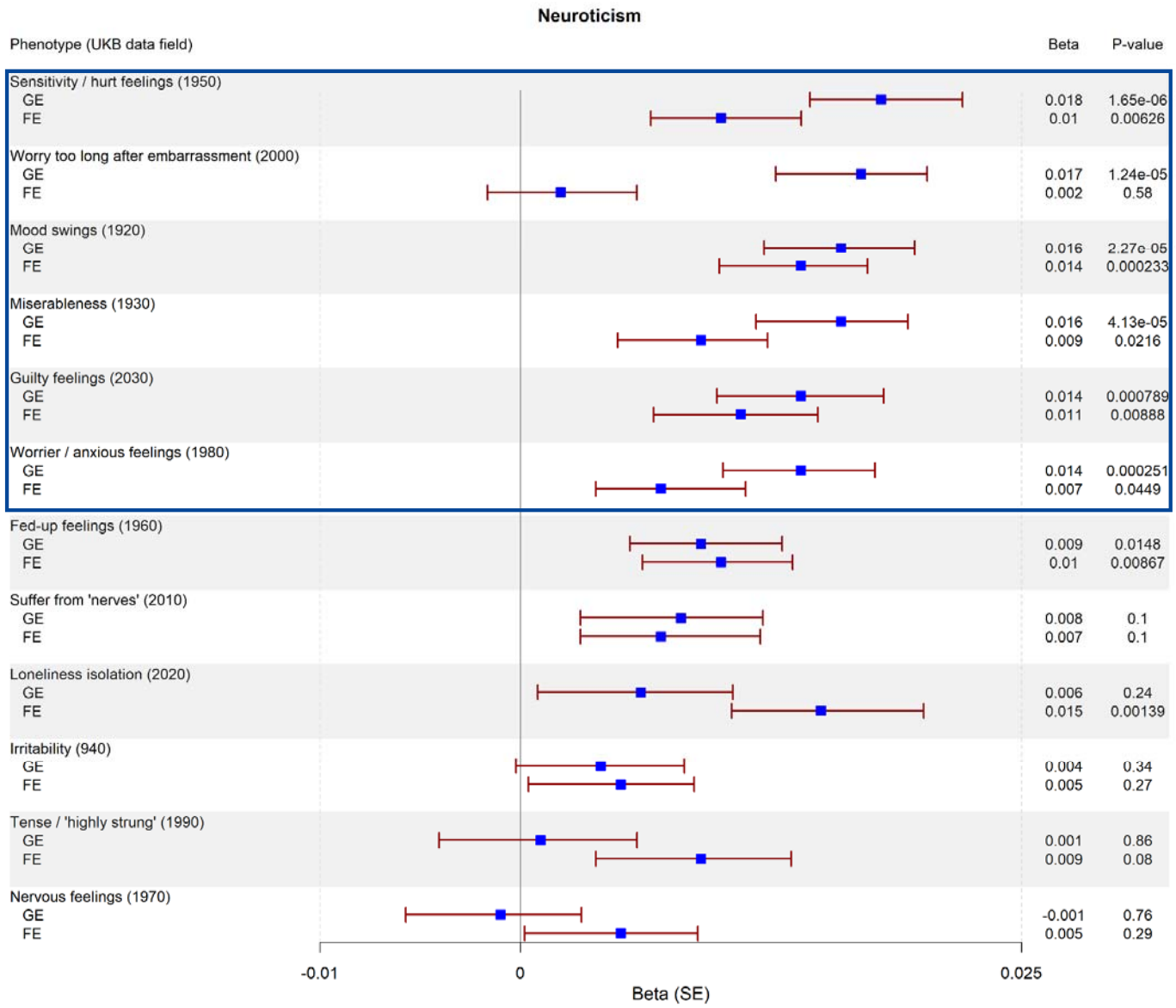


Educational attainment



Significant association if $P<5.95x10E^{-4}$

Neuroticism



Significant association if $P<5.95x10E^{-4}$

Polygenic risk score to evaluate
clustering algorithms for improved patient classification

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Epilepsia®
Official Journal of the International League Against Epilepsy

Polygenic risk heterogeneity among focal epilepsies
Gramm*, Leu* et al., 2020 (accepted)

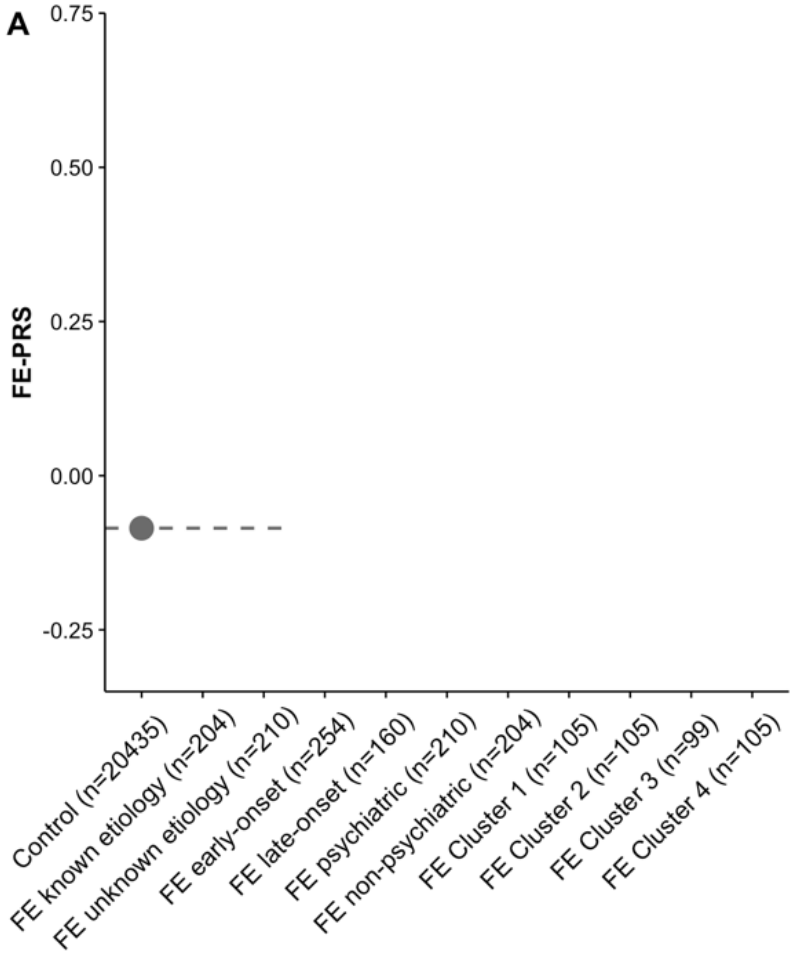
Cluster analysis can improve classifications

A Study cohort

Cleveland Clinic

414 individuals with focal epilepsy (FE)
- Phenotype data
- Genotype data
- European ancestry

20,435 population controls
- Genotype data
- European ancestry



1 Known etiology (n=204)

2 Unknown etiology (n=210)

3 Early seizure onset (n=254)

4 Late seizure onset (n=160)

5 Psychiatric Comorbidity (n=210)

6 No psychiatric comorbidity (n=204)

Summary

- Most epilepsy cases are not monogenic
- Polygenic factors are shown for other diseases to confer risk equivalent to monogenic risk variants
- Polygenic risk factors also play a role in epilepsy and can be measured
- Polygenic risk factors for epilepsy are associated with neurological and psychiatric traits in healthy individuals
- Polygenic risk factors can be used to test and potentially improve the genetic homogeneity within phenotype subgroups

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