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THE FUTURE OF HEALTH

Diversity considerations in commercial pharmacogenomic panels for mood disorders: insights from publicly available datasets.

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Disclosure

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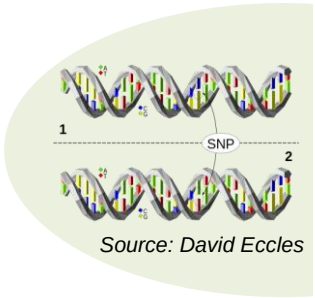
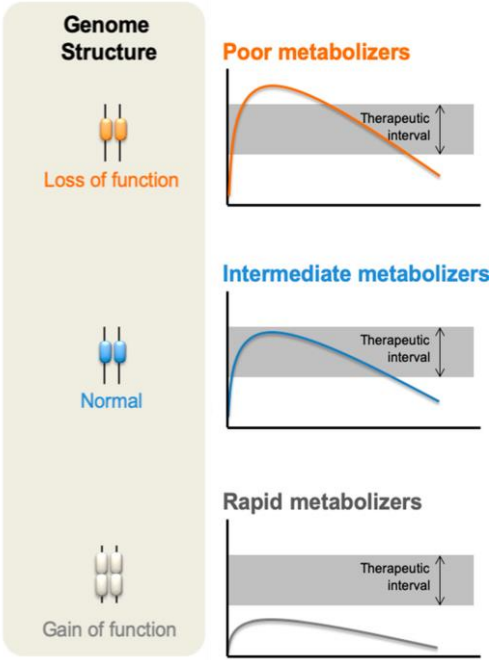
Conflict of interest

No conflict of interest to declare.

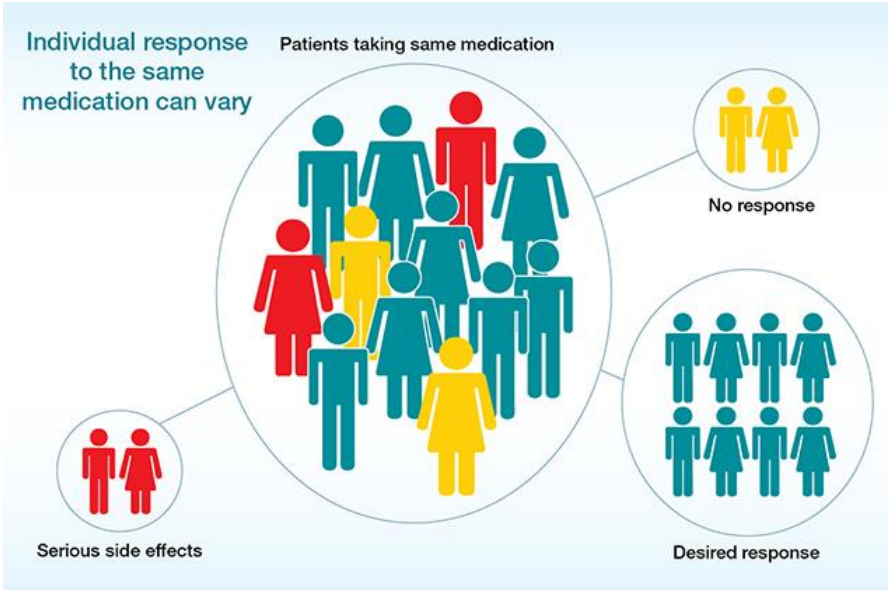
Pharmacogenomics (PGx)



Source: David Eccles



Modified from Reis et al, Medicina, 2019



Source: Mayo Clinic

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Australian Pharmacogenomics Diversity Project

- APDP aims to evaluate the utility of PGx testing for aboriginal and Torres Strait islander people in Australia.
  - Co-design with Aboriginal and Torres Strait Islander representatives.
- Preliminary step: evaluate PGx test available in Australia > *motivates present study*.

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Context of the present study

- 661 new publications per year since 2010 including “pharmacogenomic” or “pharmacogenetic” – only 222 out of 10,049 publications mentioned “ancestry”, “heterogeneity”, or “ethnicity” (as of 1 August 2022).
- $^{1}/_{5}$ new medications approved by FDA (2008-2013) showed differences in exposure and/or response across ethnic groups, translating to population-specific prescribing recommendations (Ramamoorthy et al, *Clin Pharm Therap*, 2015).

Research questions

1. Which genetic variants are included in the PGx tests *specifically advertised for mental health*, currently available in Australia and the U.S.?

2. What is their allele frequency and how does it vary across world populations, as compiled by publicly available reference panels (i.e., ALFA, gnomAD, ExAC and 8.3KJPN)?

3. What is the level of evidence of the associated clinical annotations associated with those variants in the Pharmacogenomics Knowledge Base (PharmGKB)?

Follow-up question:

4. From which ancestry groups does the supporting evidence for PGx recommendations mental health come from?

Quick note

In PharmGKB: ”publicly available, online database responsible for the aggregation, curation, integration and dissemination of knowledge regarding the impact of human genetic variation on drug response

Clinical annotations are unique entries with information about variant-drug pairs which includes prescribing guidance (e.g., FDA), when available.

LEVEL	VARIANT	GENE	DRUGS	PHENOTYPE CATEGORIES
Level 1A	CYP2D6*1, CYP2D6*1xN, CYP2D6*2, CYP2D6*2xN, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*9, CYP2D6*10, CYP2D6*14, CYP2D6*41	CYP2D6	paroxetine	Metabolism/PK

Note: PharmGKB classifies clinical annotations as high level of evidence (1A, 1B), moderate (2A, 2B), low (3), and unsupported (4).

- Which genetic variants are included in the PGx tests *specifically advertised for mental health*, currently available in Australia or the U.S.?

Research Question 1

Previous research (1)

- Previous evaluations of commercial PGx panels for mental health identified lack of consensus on which alleles to test as a threat to translation

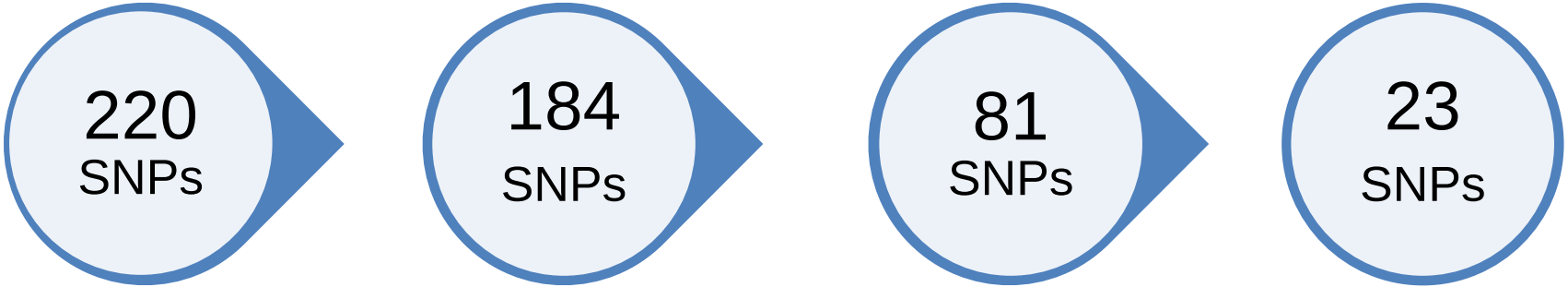
  (Bousman et al., *Pharmacopsychiatry*, 2021).

  - Relevant *CYP2D6* and *CYP2C19* variants are included.
  - HLA-A and HLB-B, involved in carbamazepine metabolization, are not commonly included.

Obtain genetic variants

1. Commercial PGx tests identified via Google search and PubMed (August 2021) – search terms “mental health” and “pharmacogenomics” (available in Australia or the U.S.).
2. Companies were then contacted via email and asked to provide full list of rsIDs included in their array.

Overview of PGx array composition



Included by at least one PGx commercial panel
(range 57-147)

With at least one annotation in PharmGKB

With at least one mental health* annotation

At least one high level of evidence annotation**

* E.g.: Depressive Disorder, Mood Disorders, Fatigue, Bipolar Disorder, etc… Diagnosis or related side effect.

Note: 7/14 companies identified by online search disclosed their rsIDs.

PGx panels and minimum set

Company	N SNPs	*CYP2C19*	*CYP2D6*	Missing*
Sonic (AUS)	66	*2,*3,*4,*17	*2,*3,*4,*6,*7,*9,*10,*14,*17,*41	*HLA-A, HLA-B*
Otogenetics (US)	147	*2,*3,*4,*17	2,*3,*4,*6,*7,*9,*10,*14,*17,*41	*HLA-B*
Genesight (US)	57	*2,*3,*4,*17	2,*3,*4,*6,*7,*9,*10,*14,*17,*41	*HLA-A, HLA-B*
Oneome (US)	77	*2,*3,*4,*17	2,*3,*4,*6,*7,*9,*10,*14,*17,*41	*HLA-A, HLA-B*
RxMatch (US)	77	*2,*3,*4,*17	2,*3,*4,*6,*7,*9,*10,*14,*17,*41	*HLA-A, HLA-B*
Agena (AUS, US)	66	*2,*3,*4,*17	2,*3,*4,*6,*7,*9,*10,*14,*17,*41	*HLA-A, HLA-B*
TaqMan (AUS, US)	56	*2,*3,*4,*17	2,*3,*4,*6,*7,*10,*14,*17,*41	*HLA-A, HLA-B*

- Minimum allele set* for PGx (Bousman et al, *Curr Opin Psychiatry*, 2019) was included by most companies – consensus on *CYP2D6* and *CYP2C19* star alleles.
- Only one company tested for *HLA-A* and no company included *HLA-B* (no changes since review by Fan and Bousman, *Pharmacopsychiatry*, 2020).

- What is their allele frequency and how does it vary across world populations, as compiled by publicly available reference panels (i.e., ALFA, gnomAD, ExAC and 8.3KJPN)?

Research Question 2

Previous research (2)

- **Significant inter-population MAF differences** in 159 drug-response SNPs in 1KG (Ahsan, *PLoS One*, 2020).
- In UK Biobank, **non-European populations carry more** variants predicted to be **functionally deleterious** (McInnes, *Clin Pharm Therap,* 2021).
- ½ functional variants in drug-related genes are unique to only one of the six populations with data available – only 0.1% of functional variants occur with an allele frequency ≥1% across ancestries (Schärfe et al., *Genome Med,* 2017).

Obtain allele frequencies

3. Using dbSNP browser (https://www.ncbi.nlm.nih.gov/snp/) we extracted allele frequencies from:

- Allele Frequency Aggregator (*ALFA*),
- genome Aggregation Database (*gnomAD*),
- Exome Aggregation Consortium (*ExAC*), and
- Japanese Multi Omics Reference Panel (8.3KJPN).

Date of extraction: 23 November 2021

Publicly available datasets

- ✓ *ALFA*: ~100.000 subjects from 12 diverse populations including European, African, Asian, Latin American, and others.
- ✓ *gnomAD*: 125,748 individuals (whole-exome sequence) and 15,708 individuals (whole-genome sequence) from 6 populations.
- ✓ *ExAC*: sequence data for 60,706 from 5 populations.
- ✓ *8.3KJPN*: 14,000 Japanese individuals.

Differences in allele frequency across ancestry

Gene	rsID	Star allele	REF	ALT	ALFA					8.3JKP	Δ
					EUR	AFR	AA	EAS	LAM		
CYP2C19	rs12248560	*17	C	T	0.77	0.77	0.77	0.99	0.84	0.99	0.12
	rs4244285	*2	G	A	0.85	0.83	0.83	0.72	0.84	N/A	0.08
	rs4986893	*3	G	A	0.99	1	1	0.92	1	0.7	0.05
	rs28399504	*4	A	G	1	1	1	1	1	0.87	0.01
											0.07
CYP2D6	rs1065852	*10	G	A	0.78	0.86	0.86	0.43	0.83	N/A	0.16
	rs5030865	*14	C	T	1	1	1	0.99	1	N/A	0.01
	rs16947	*17	G	A	0.68	0.66	0.66	0.97	0.68	N/A	0.15
	rs28371706	*17	G	A	1	0.91	0.91	1	0.97	0.99	0.03
	rs1135840	*2	C	G	0.43	0.38	0.38	0.28	0.43	N/A	0.08
	rs35742686	*3	T	-	0.99	1	1	1	1	N/A	0.01
	rs3892097	*4	C	T	0.81	0.91	0.9	0.99	0.86	0.997	0.12
	rs28371725	*41	C	T	0.9	0.96	0.96	0.95	0.88	N/A	0.05
	rs5030655	*6	A	del	1	1	1	1	1	N/A	0
	rs5030867	*7	T	G	1	1	1	1	1	0.998	0
	rs5030656	*9	CTT	-	0.98	0.99	0.99	1	1	N/A	0.02
											0.06

- *CYP3A5* (average difference=0.331), *ADRA2A* (N=1, 0.312), *GNB3* (N=1,0.238), GRIK4 (N=1, 0.229) and *DRD3* (N=3, 0.183) showed largest cross-ancestry differences.
- *CYP2C19* (N=4, 0.07) and *CYP2D6* (N=12, 0.06) showed lower average differences – some exceptions (*CYP2C19*17*).
- Similar average differences in gnomAD (15 SNPs missing), but 33 SNPs were not present in ExAC – can't directly compare.

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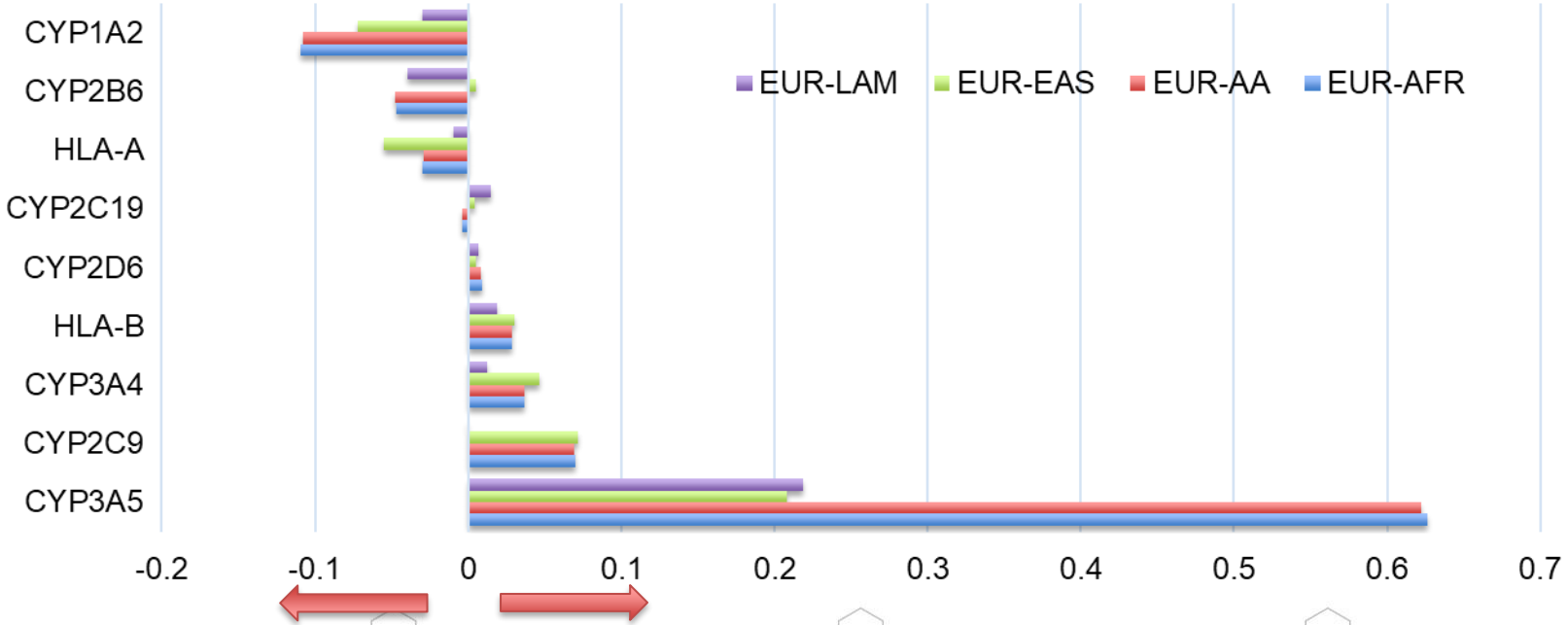
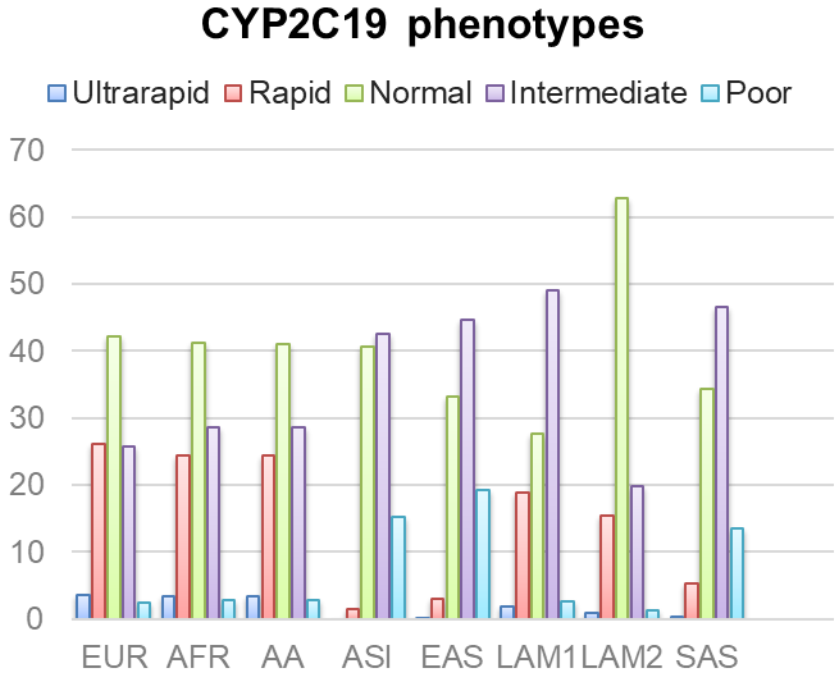
Allele frequency (minimum set) across ancestry

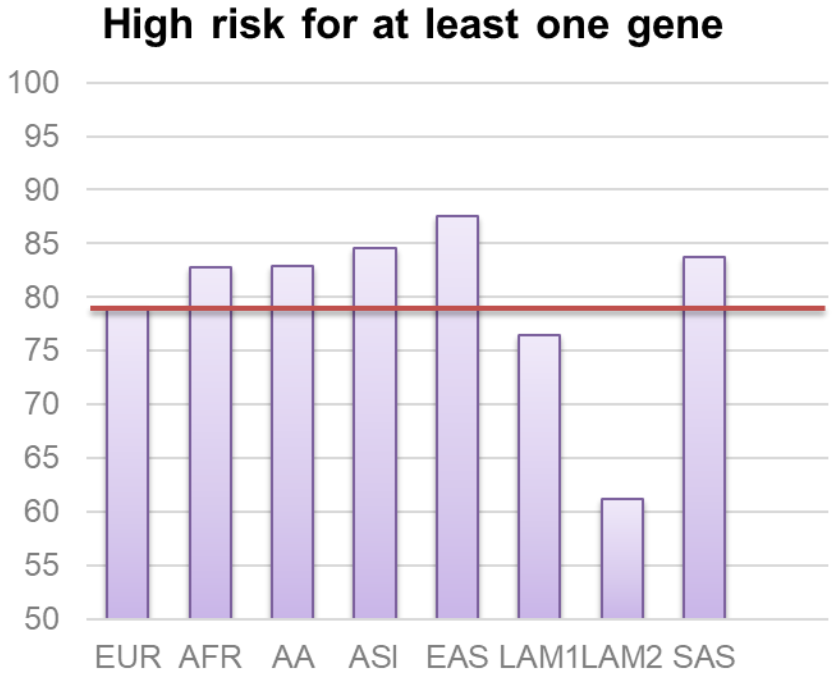
Average difference in key PGx variants allele frequency (in ALFA).



EUR = European; AFR = African; AA = African American; EAS = East Asian; LAM = Latin American with Afro-Caribbean ancestry

Preliminary results from simulation*





* LD was not modelled and simulation assumed that allele frequencies were independent from each other.

✓ **Preliminary results coherent with higher prevalence of actionable variants in non-EUR.**

EUR = European; AFR = African; AA = African American; ASI = Asian; EAS = East Asian; LAM 1 = Latin American with Afro-Caribbean ancestry; LAM2 = Latin American with European and Native American Ancestry; SAS = South Asian.

- What is the level of evidence of the associated clinical annotations associated with those variants PharmGKB?
- From which ancestry groups does the supporting evidence for PGx recommendations mental health come from?

Research Question 3 & 4

“Mining” PharmGKB

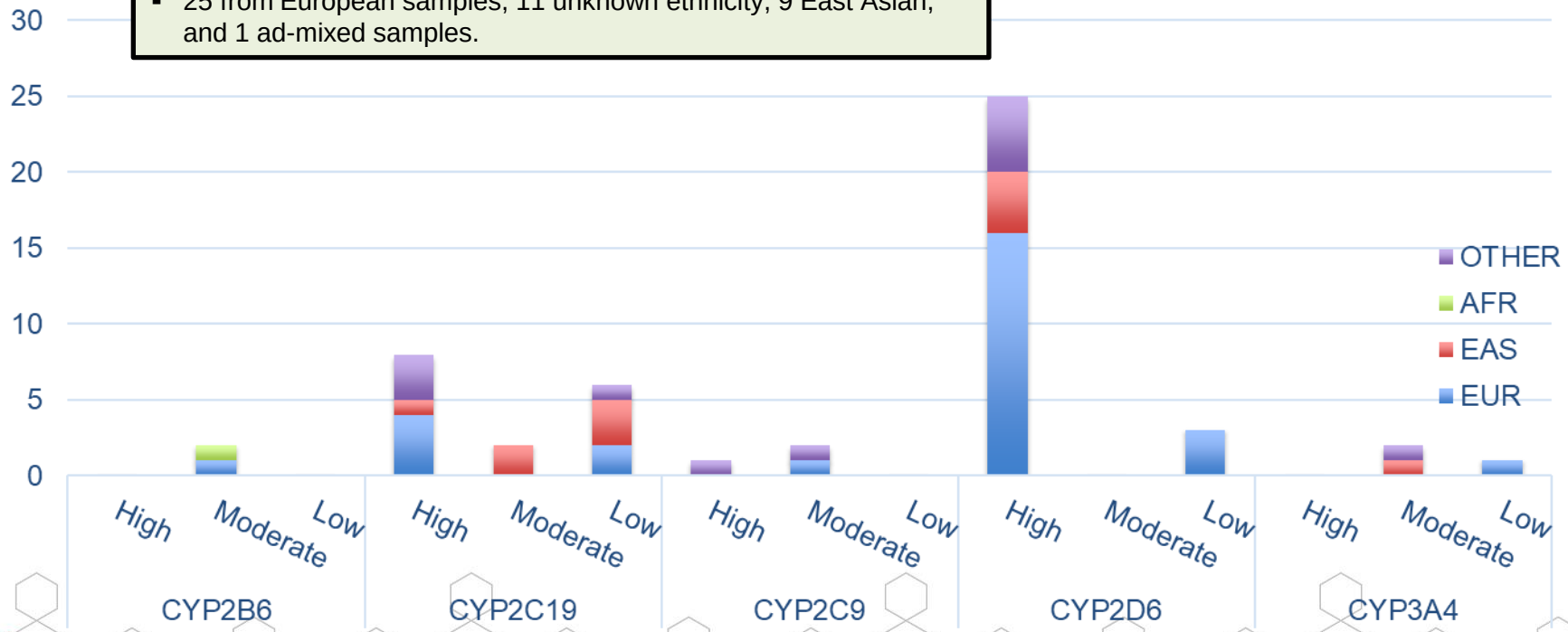
4. PharmGKB provides metafiles with information about level of evidence and biogeographical origin of samples for clinical annotations associated with all SNPs.
    - Each clinical annotation has an associated ID that is linked to a PubMed ID and a genetic variant, which allowed us to describe the characteristics of each supporting evidence (i.e., study) for the SNPs included in PGx panels.

For example: samples size for mental health annotation ranged between [1-4,316] participants (Mdn = 138).

Diversity in PharmGKB annotations

46 gene-drug annotations associated with mental health phenotypes:

- 25 from European samples, 11 unknown ethnicity, 9 East Asian, and 1 ad-mixed samples.



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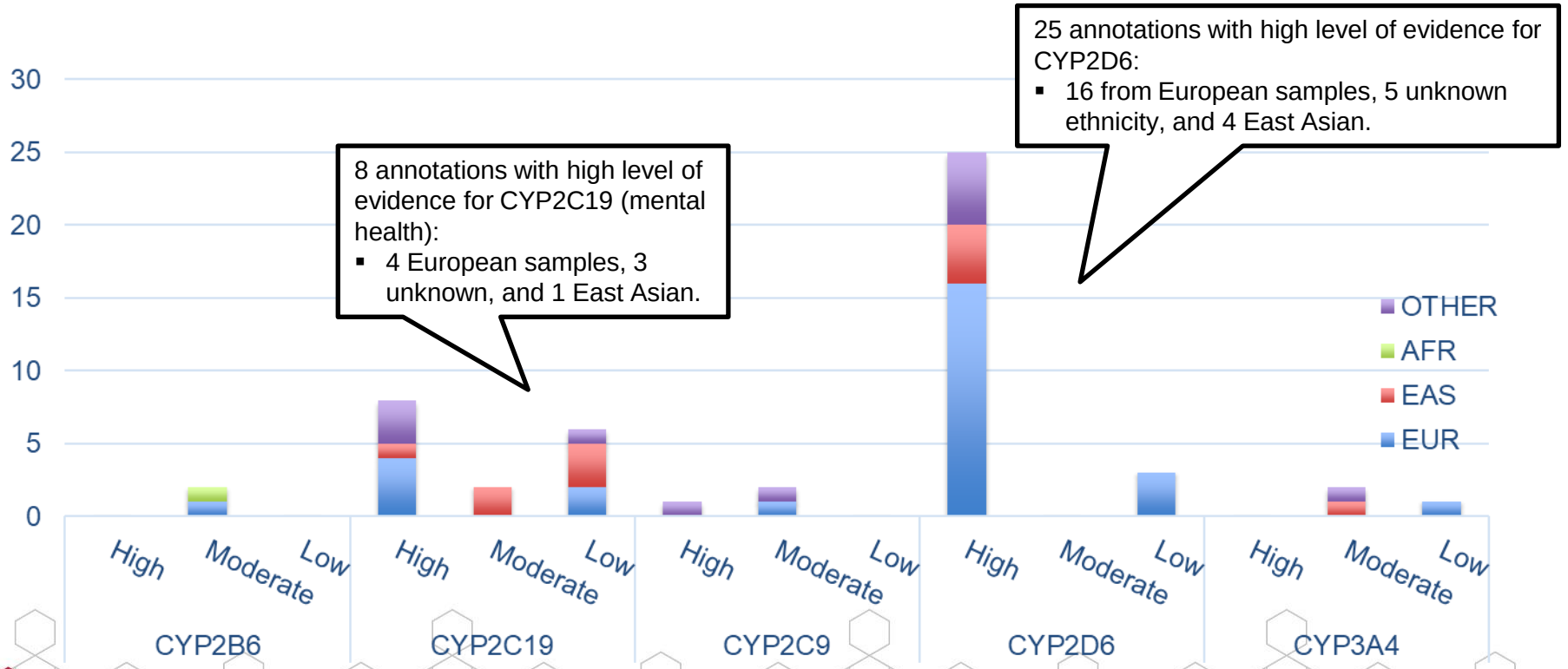
Diversity in PharmGKB annotations



No studies with high level of evidence conducted in African samples.

Conclusions

- **Minimum set** of alleles for PGx in mental health mostly **covered** by products advertised for mental health.
- Publicly available datasets show similar patterns of allele frequency across populations as previous studies (1KG, UKBiobank).
- There is an evident **lack of diversity in evidence** supporting PharmGKB annotations.
  - Potential for more drug targets using pops with different / more genetic variation?
- EUR populations are likely to benefit as much or more from PGx than non-EUR.

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Thank you
for your attention!

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