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GENERAL HOSPITAL



Assessing the Genetic Contribution of Drug Response Variability in Selective Serotonin Reuptake Inhibitors From 1,711,695 Purchases in the Finnish National Drug Registry

HSPH Program in Quantitative Genetics Seminar

March 9th, 2021

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#ATGStrong

Drug Response and Efficacy

Pharmacogenomics: *variability of drug response and efficacy is contributed by genetic risk factors*

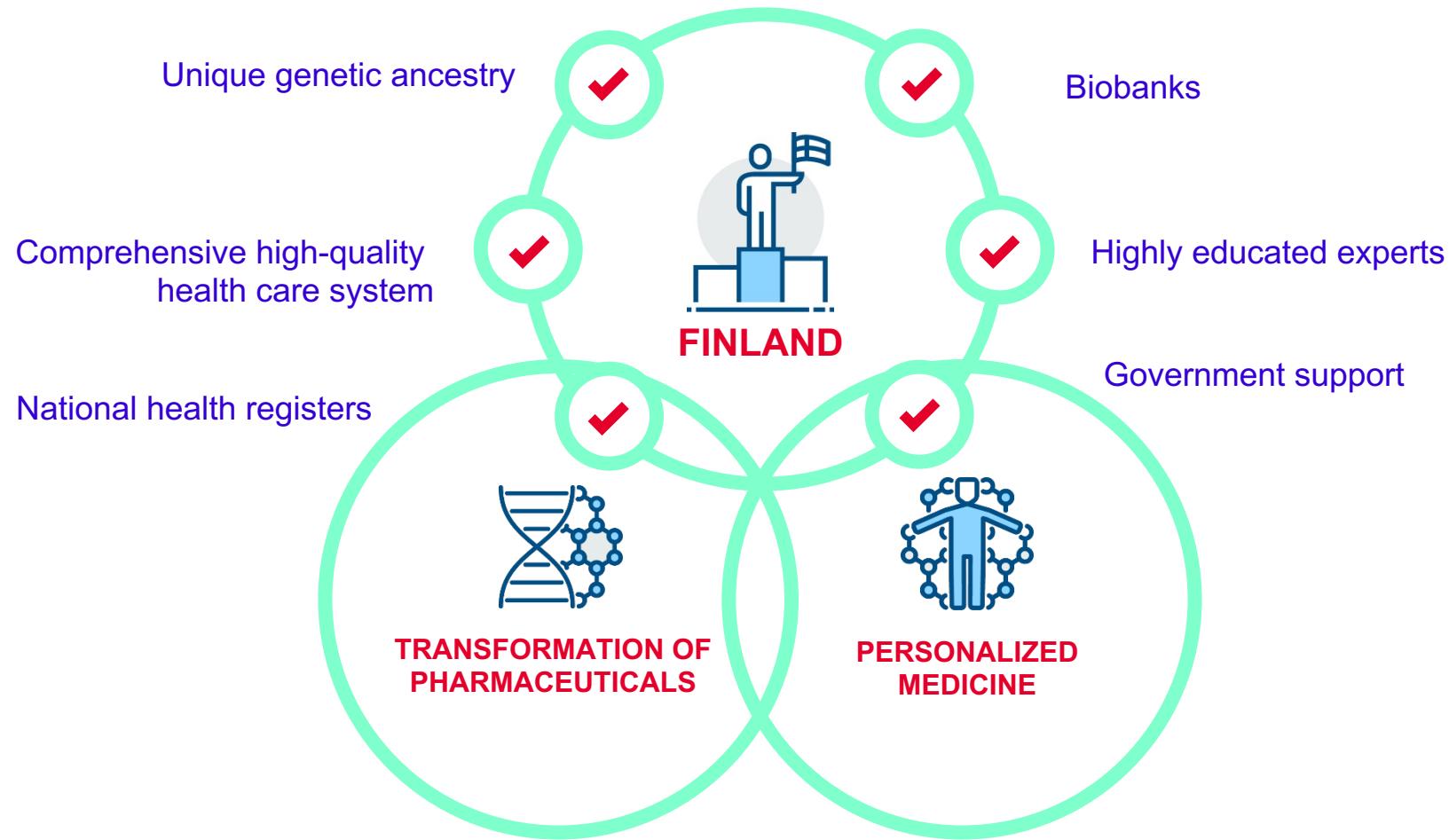
- FDA list of 127 biomarkers in 27 therapeutic areas (mostly *cyp* genes)
 - ADME > Disease >Target (Nelson et al. 2016, *Nat Rev*)
- Poor functional characterization
 - Summary statistics PrediXcan (Gamazon et al. 2005, *Nat Gen*)
 - NIH PGRN and eMERGE – grants for sequencing such as the RIGHT dataset (mostly interrogation in known biomarkers, lack of phenotype)
 - The “druggable” genome -- PharmGKB
- Dosage, use frequency, response, cessation --> Biobanks?

Note

ADME -- drug absorption, distribution, metabolism and excretion

PGRN – Pharmacogenomics Research Network

Why Finland?



Genetic Bottleneck

EARLY SETTLEMENT

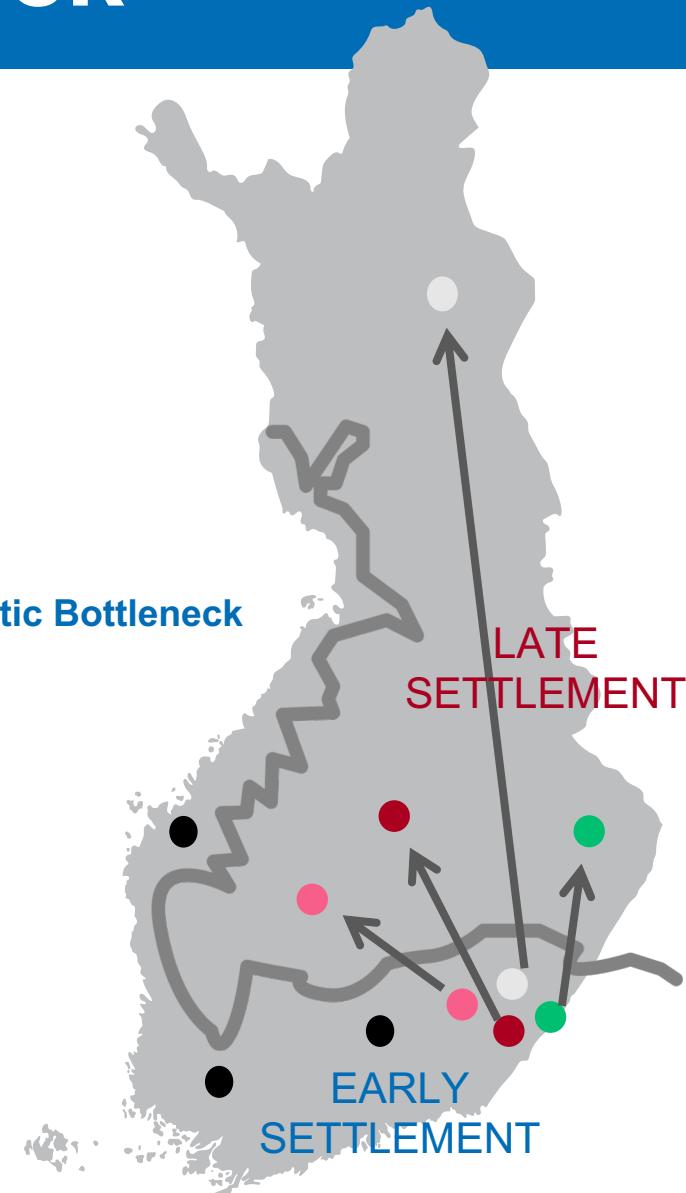
- 2000-10 000 years ago
- South and Coast

LATE SETTLEMENT

- 16th century
- multiple bottle necks

EXPANSION

- 18th century – population 250 000
- Today – population **5.4 million**



Why Finland?



- Countries with Biobanks
- Universal Healthcare
- Unique personal identity code
- Isolated population
- Recalling made easy
(biobank act + social security number)

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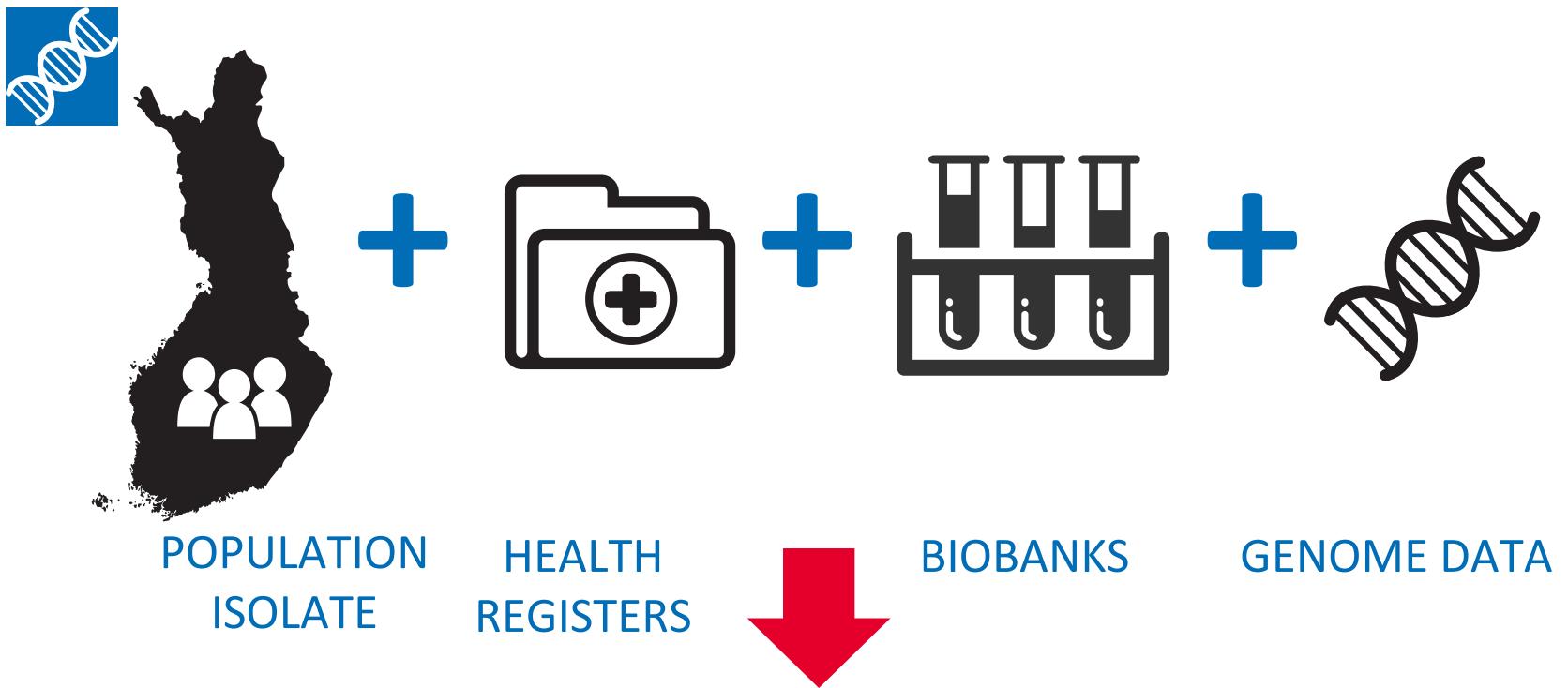


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Why Finland?



- X Countries with Biobanks
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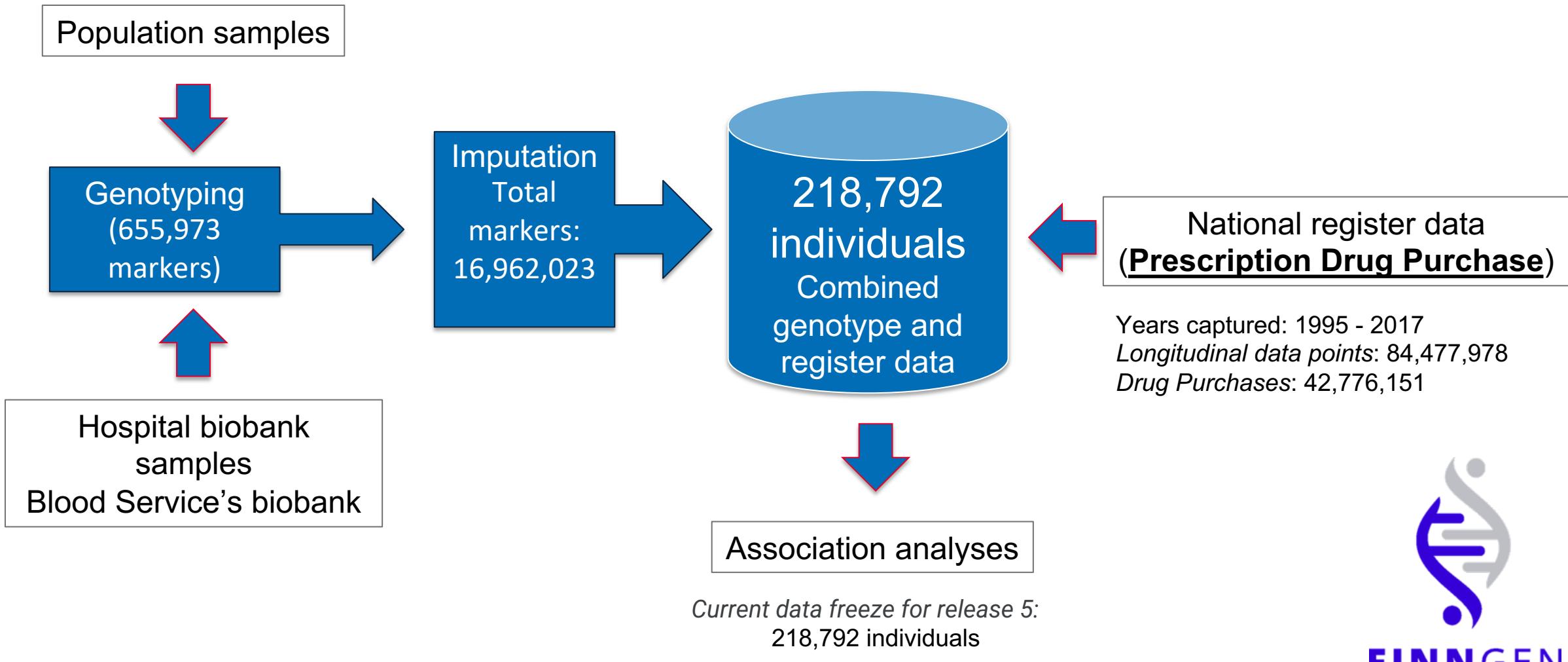


INNOVATIVE STUDY DESIGNS

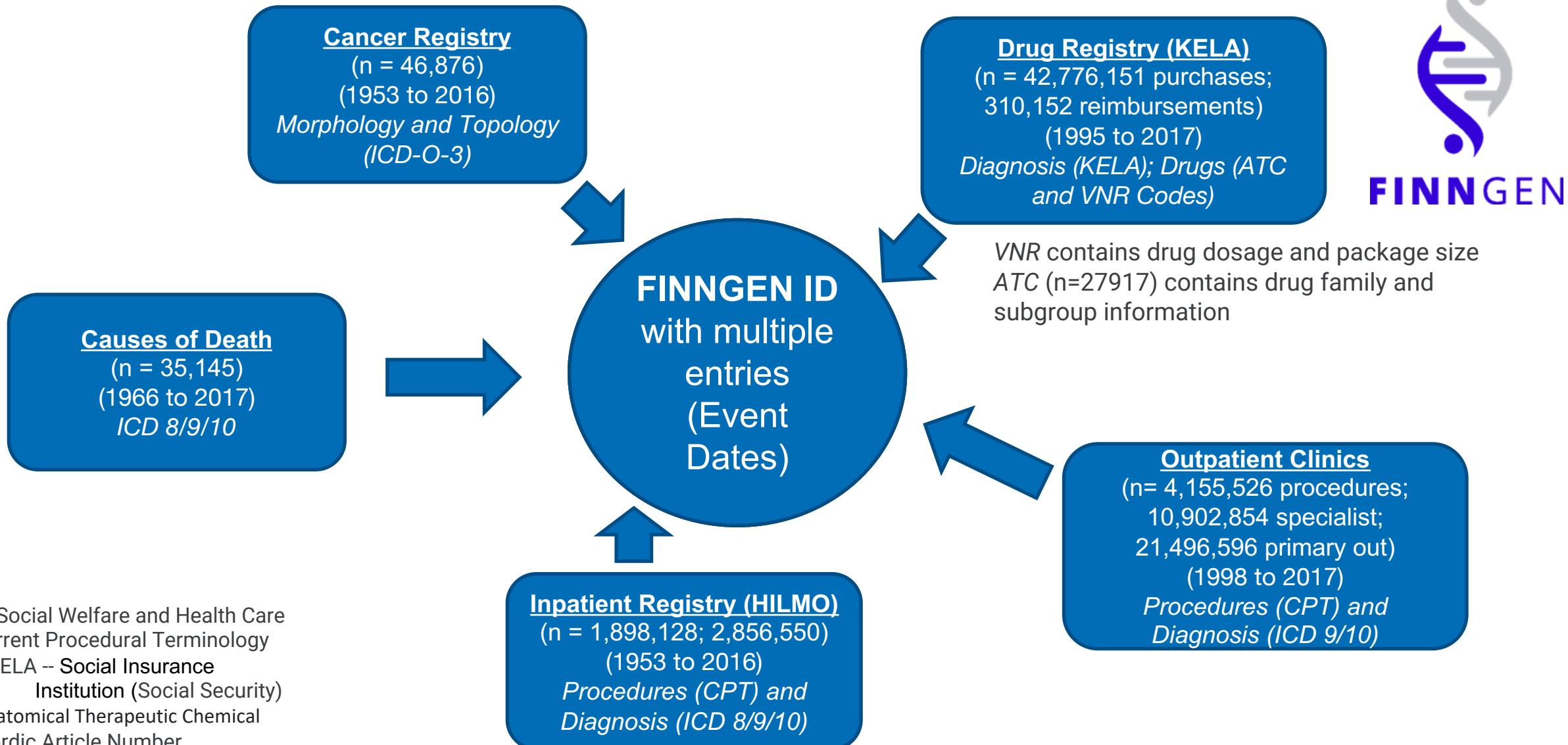


FINN GEN

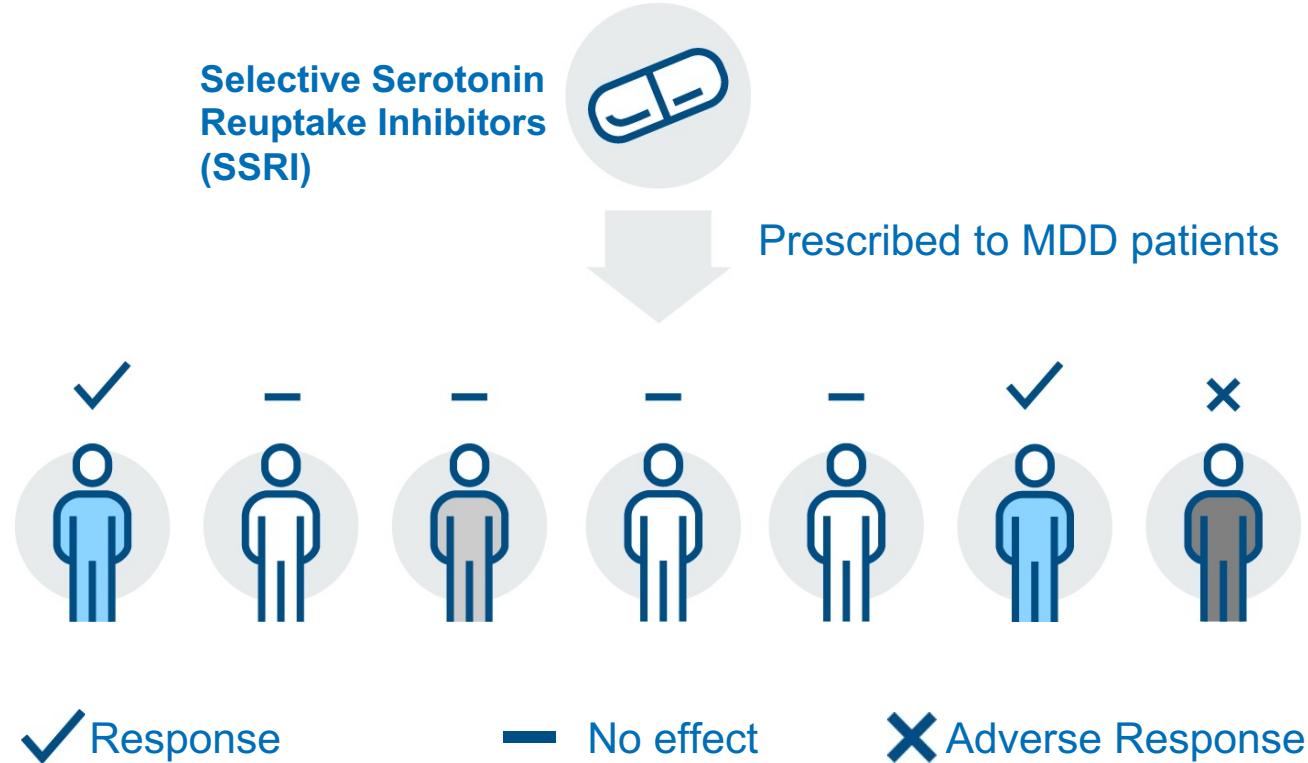
Generating Results from FinnGen



Along with Genotype Data, Many Other Things Make an Endpoint?



SSRI Drug Response Variability



In FinnGen, high correlation between depression and the use of SSRI ($r^2 = 0.518$)

53-65% MDD patients respond to SSRI
(Hamilton Rating Scale for Depression)
(Hirschfeld et al 1999, *J Clin Psychiatry*)

Note:

MDD – Major Depressive Disorder

Objective

To understand the genetic basis of SSRI response variability by leveraging genotype-drug purchase data from 218,792 individuals in FinnGen Release 5.

Analysis Plan

Genotyped and Imputed:

Total markers: 16,962,023



Antidepressant Purchases

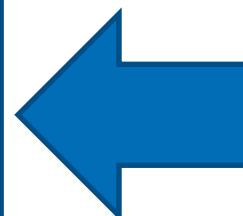
218,792 individuals with
1,711,695 purchases
Years = 1995 to 2017

Association Analysis (SAIGE v0.42.1)

Phenotypes tested adjusting for sex, age,
batch, and first 10 PCs:

- 1) SSRI vs no SSRI purchase
- 2) SSRI Number of Purchases
- 3) SSRI Adherence
- 4) SSRI dosage change over time

Significance threshold: $p < 5 \times 10^{-8}$



Longitudinal SSRI Purchases

51,519 individuals
853,286 purchases

Analysis 1: SSRI vs non-SSRI

Trait type:
Binary



Purchaser vs non-purchaser

VS



Minimum of ONE SSRI purchase

NO / ZERO record of SSRI purchase

$N_{SSRI} = 41,147$

$N_{non-SSRI} = 159,788$

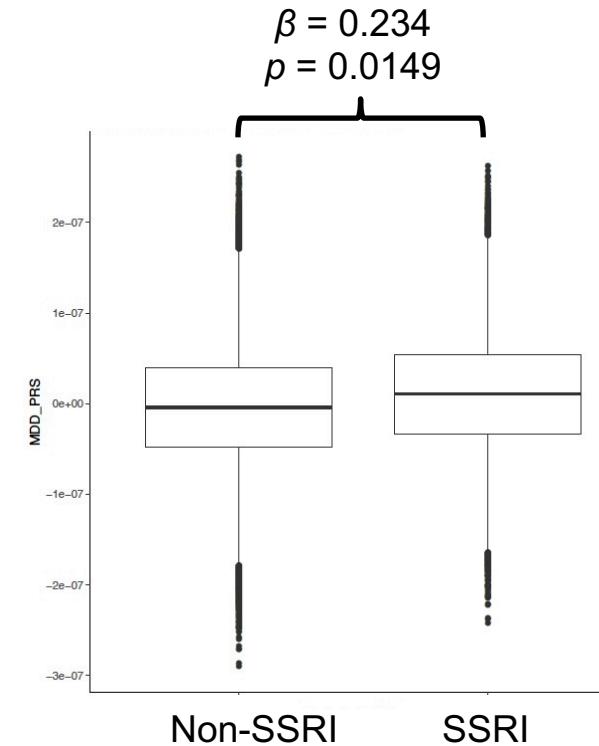
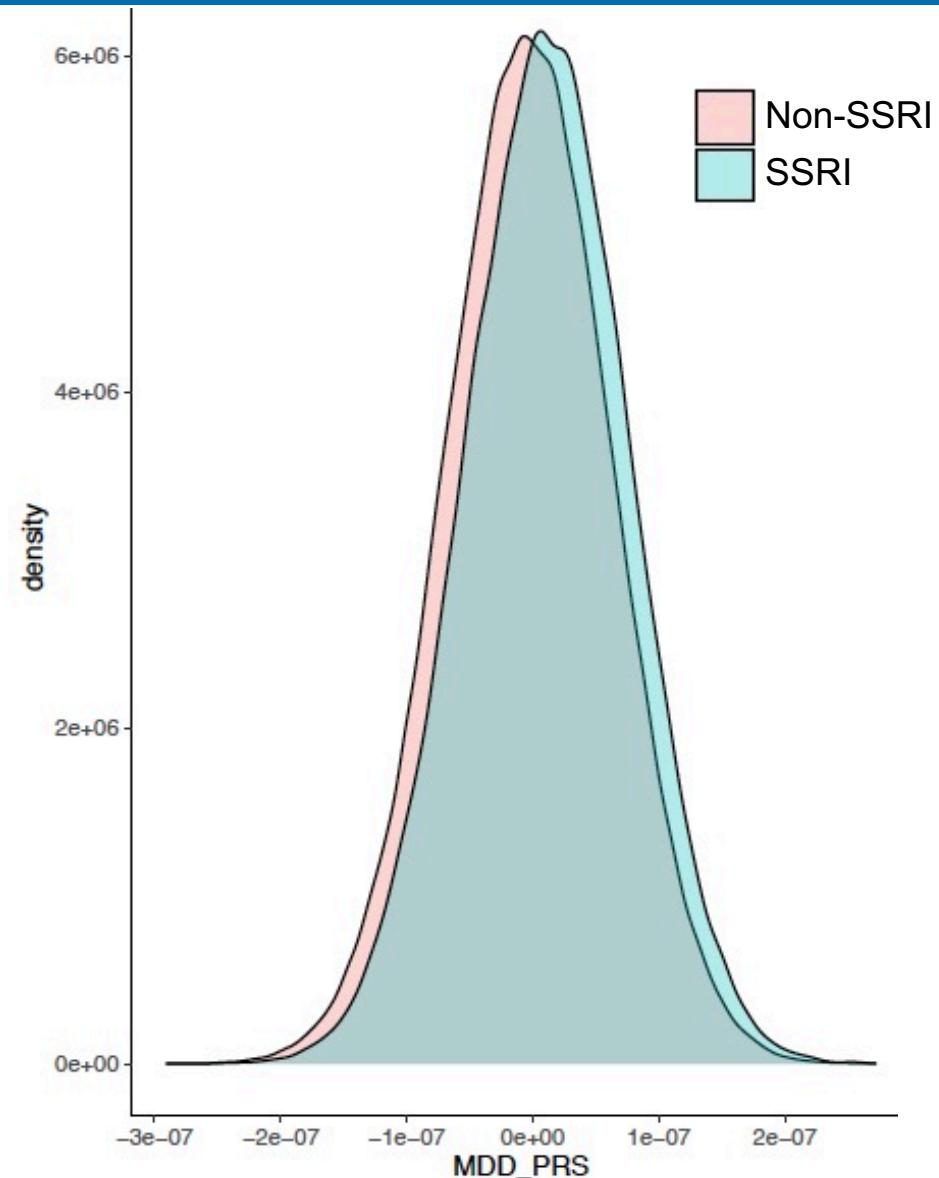
Question:

Are there genetic differences observed with the purchase of SSRI?

MDD Polygenic Risk is different in SSRI vs no-SSRI

MDD to
Antidepressants:
 $r_g = 0.997$

MDD to SSRI:
 $r_g = 0.732$



Note:

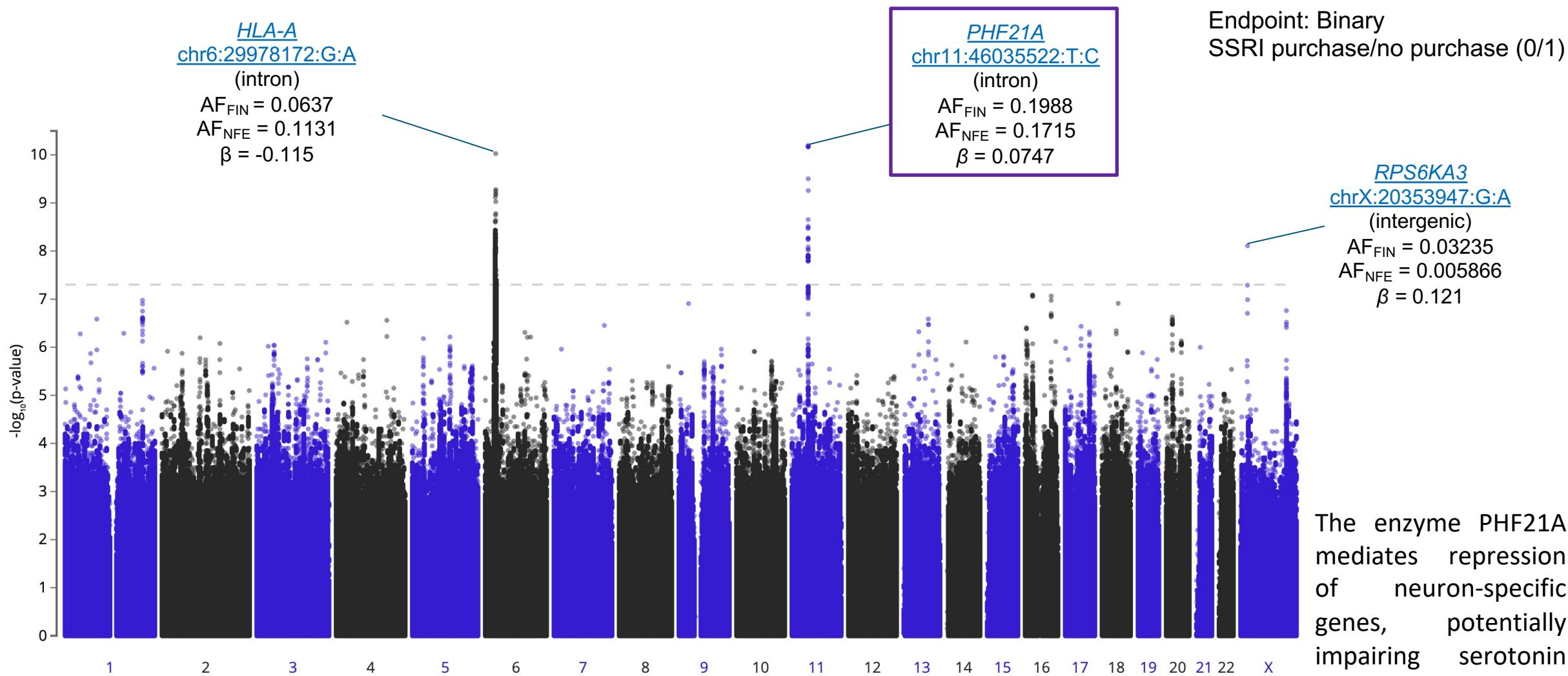
r_g – genetic correlation

MDD – major depressive disorder

SSRI – selective serotonin reuptake inhibitor

Summary statistics for PRS from
Wray et al 2018 Nat Gen

SSRI (N = 41,147) vs non-SSRI purchase (N = 159,788)

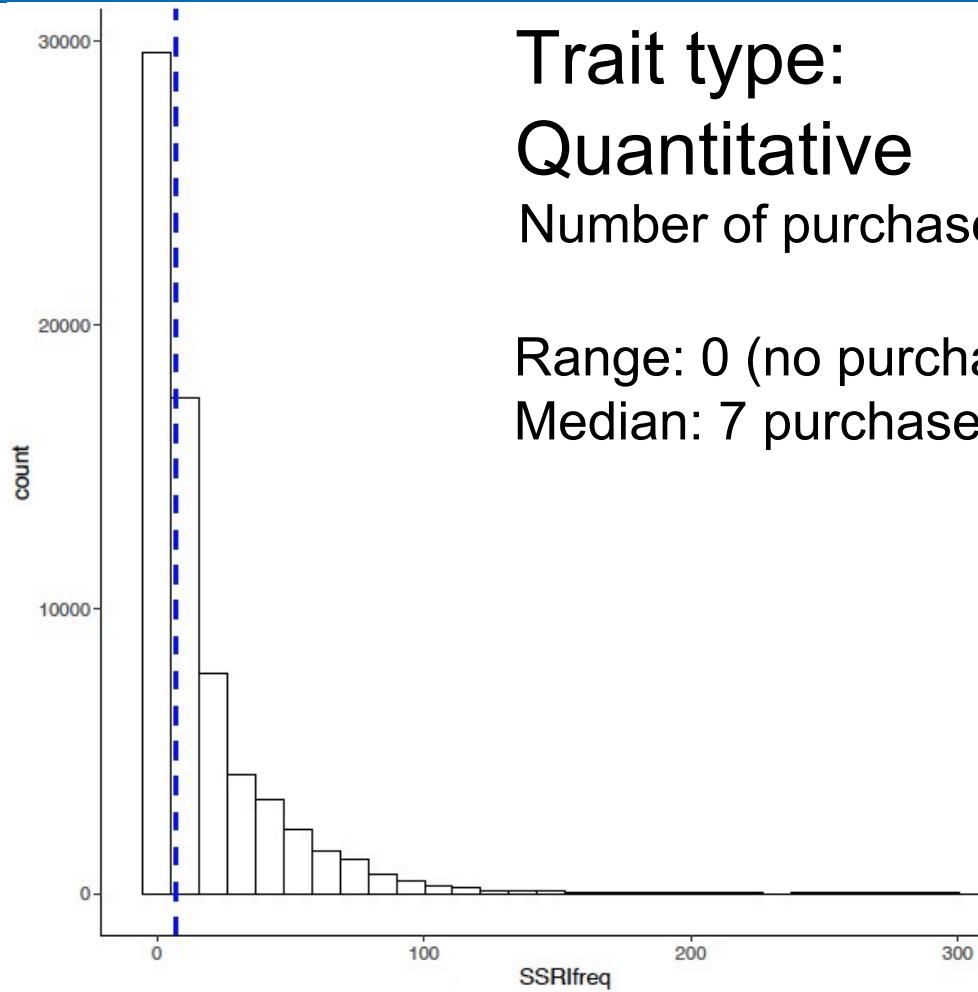


The enzyme PHF21A mediates repression of neuron-specific genes, potentially impairing serotonin metabolism in mice (Garay et al. 2016 *Epigenomics*).

Notes:

AF – gnomAD allele frequencies in Finns (FIN) and Non-Finnish Europeans (NFE)

Analysis 2: Number of SSRI Purchases



Trait type:
Quantitative

Number of purchases per individual

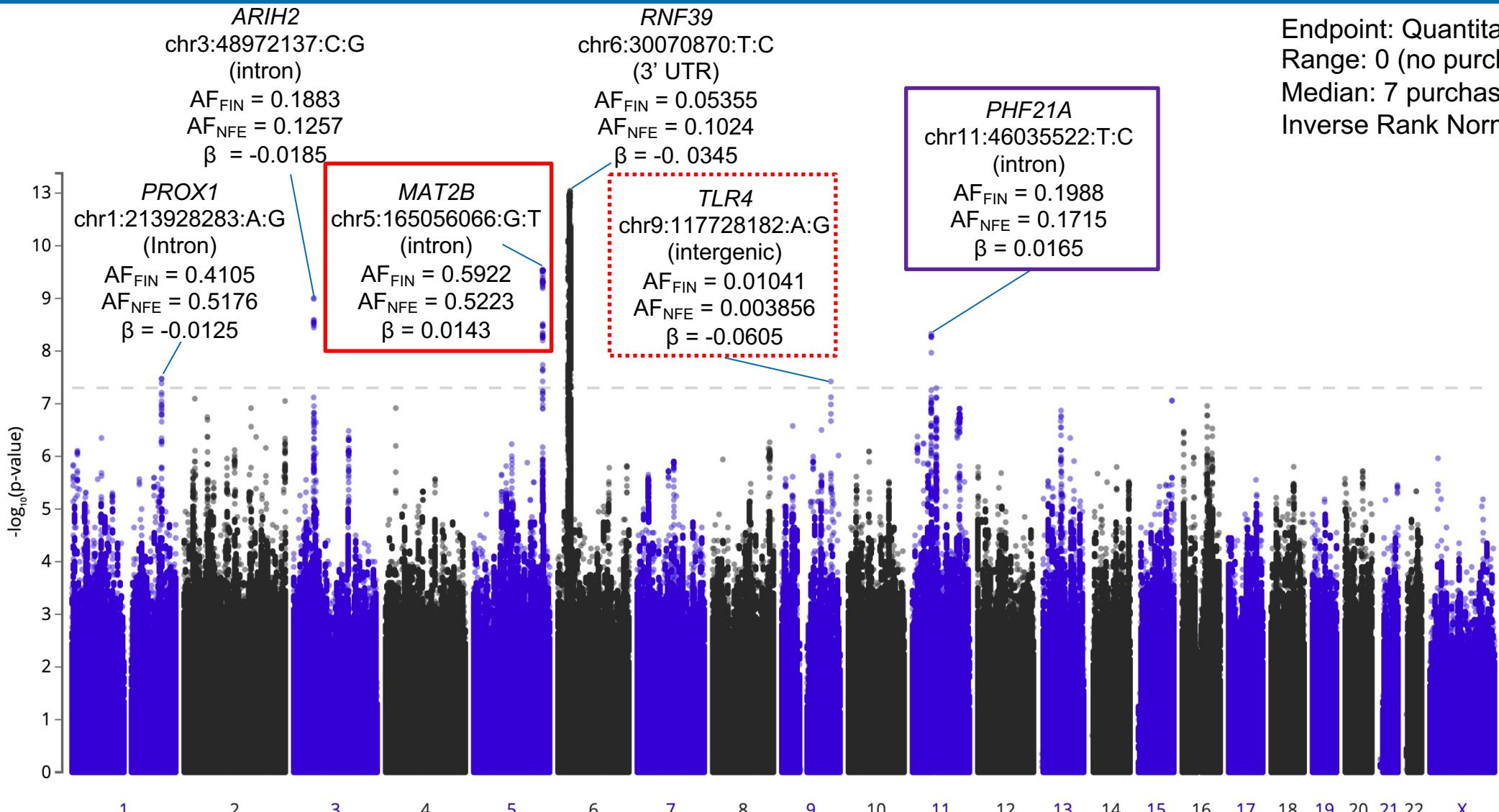
Range: 0 (no purchase record) – 288

Median: 7 purchases per individual

Question:

Are there genetic variants associated with the variability in purchase frequency of SSRI?

SSRI Purchases (Per Individual) (N = 200,935)



Endpoint: Quantitative
Range: 0 (no purchase record) – 288
Median: 7 purchases per individual
Inverse Rank Normalized

S-Adenosyl methionine (SAMe) could be used as a supplement but still remains inconclusive (Cuomo *et al* 2020 *Annals Gen Psych*)

Systemic TLR4 is reduced with SSRI intake (Wang *et al* 2020 *Neuroscience*)

Analysis 3: SSRI Adherence

Note:

NotSSRI includes (based on ATC code)

Non-selective monoamine reuptake inhibitors

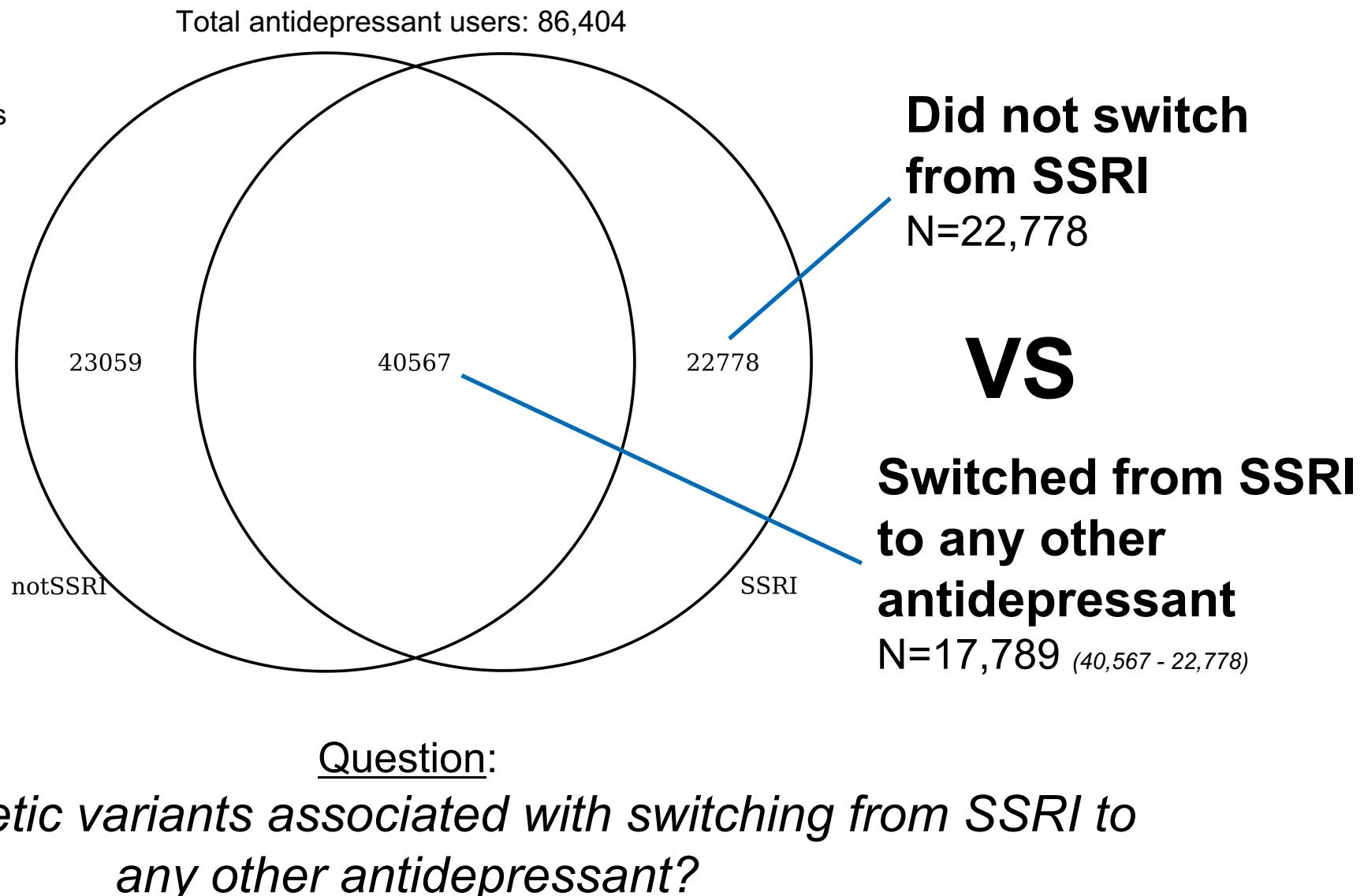
Monoamine oxidase inhibitors

Monoamine Oxidase A inhibitors

Other antidepressants

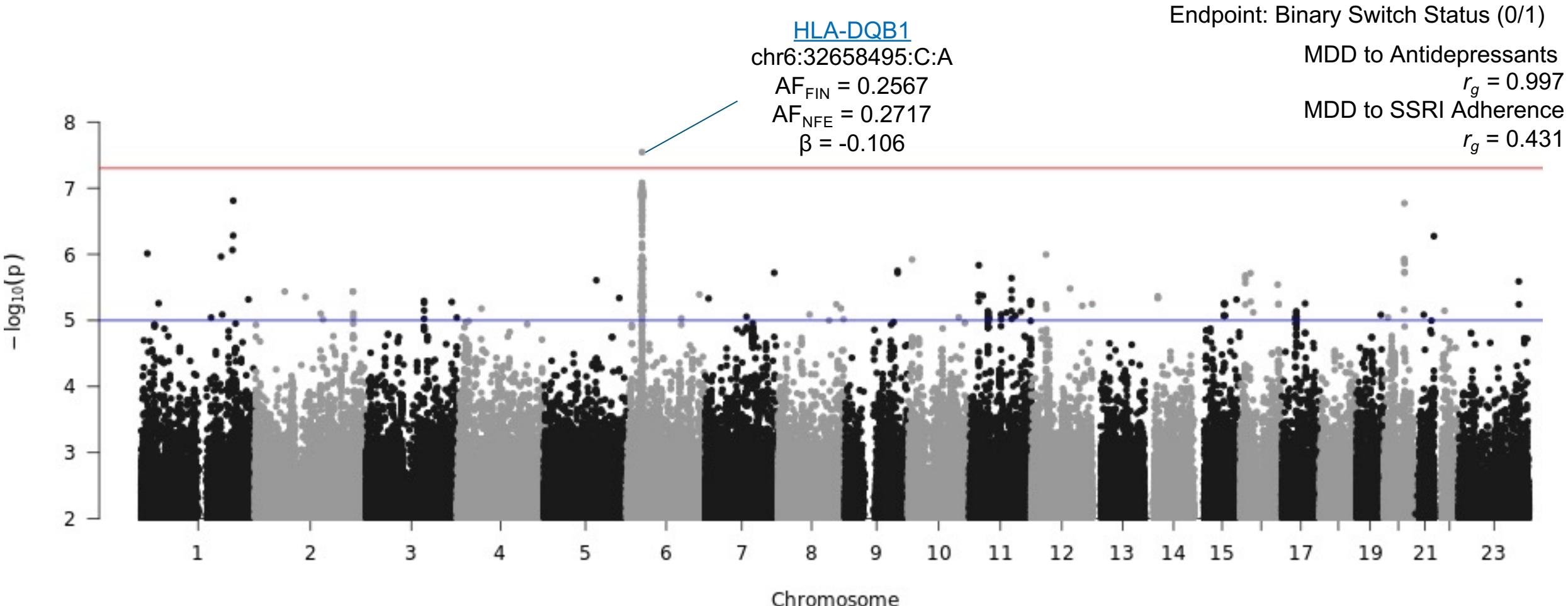
Trait type:
Binary

Purchases SSRI
only vs switched to
another
antidepressant



SSRI Adherence: From SSRI (N=22,778) to Any Other Antidepressant (N=17,789)

Not everyone sticks to SSRI as their effective antidepressant

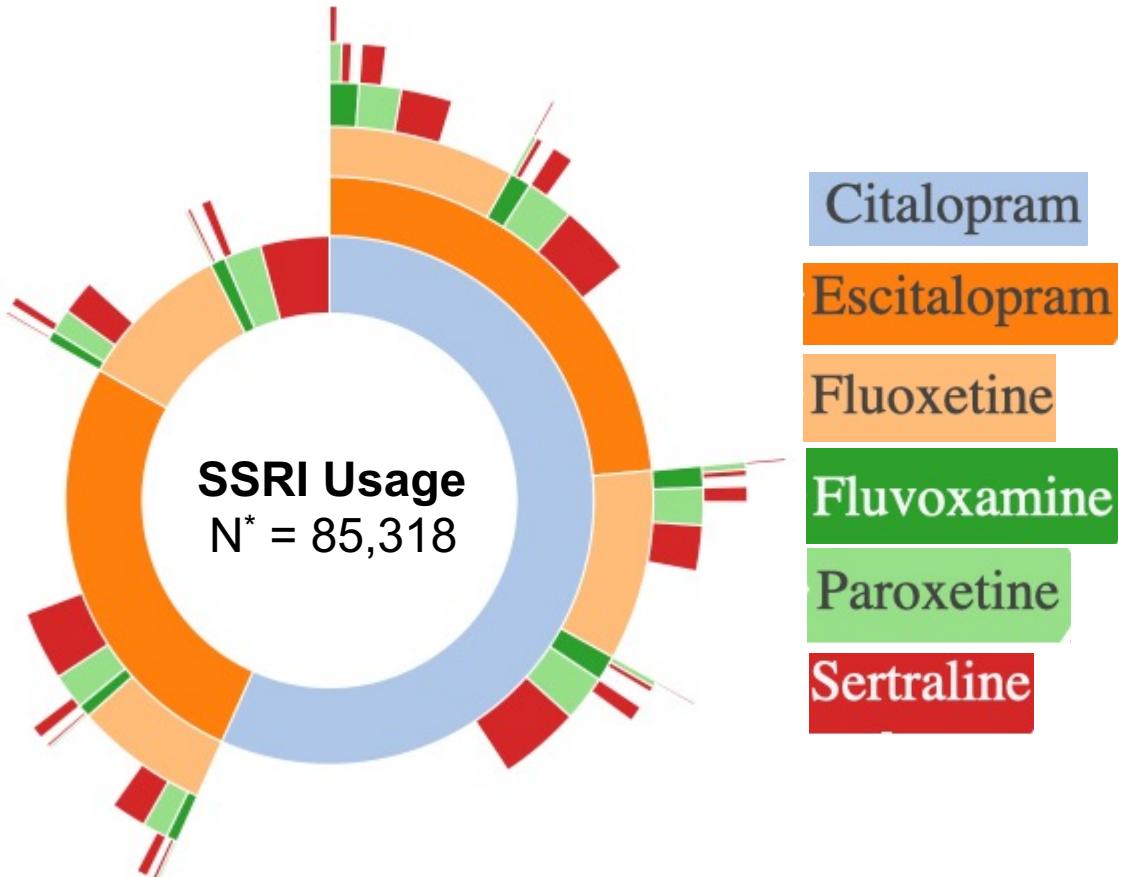


Note:

AF – gnomAD allele frequencies in Finns (FIN) and Non-Finnish Europeans (NFE)

r_g – genetic correlation

SSRI Usage Patterns



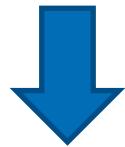
* 28,799 points consume > 1 SSRI

** number of people = 20,430

SSRI	Number of FinnGen IDs	Final count from latest purchases
Citalopram	27,545	18,052
Escitalopram	24,118	20,053
Fluoxetine	13,981	6,791
Fluvoxamine	2,282	933
Paroxetine	5,655	2,957
Sertraline	11,737	7,733
TOTAL	85,318	56,519

Analysis 4: SSRI Dosage Change over Time

$$dosePerDay \text{ (mg/day)} = \frac{\text{package size} \times \text{package dose (mg)}}{\text{difference in days between purchases}}$$



Removal of outliers (<10% and >90%)



Per unit transformation of each drug

$$dosePerDay \text{ (units)} = \frac{\text{dose per day (mg/day)}}{\text{Recommended Drug Daily Dose (mg)}}$$

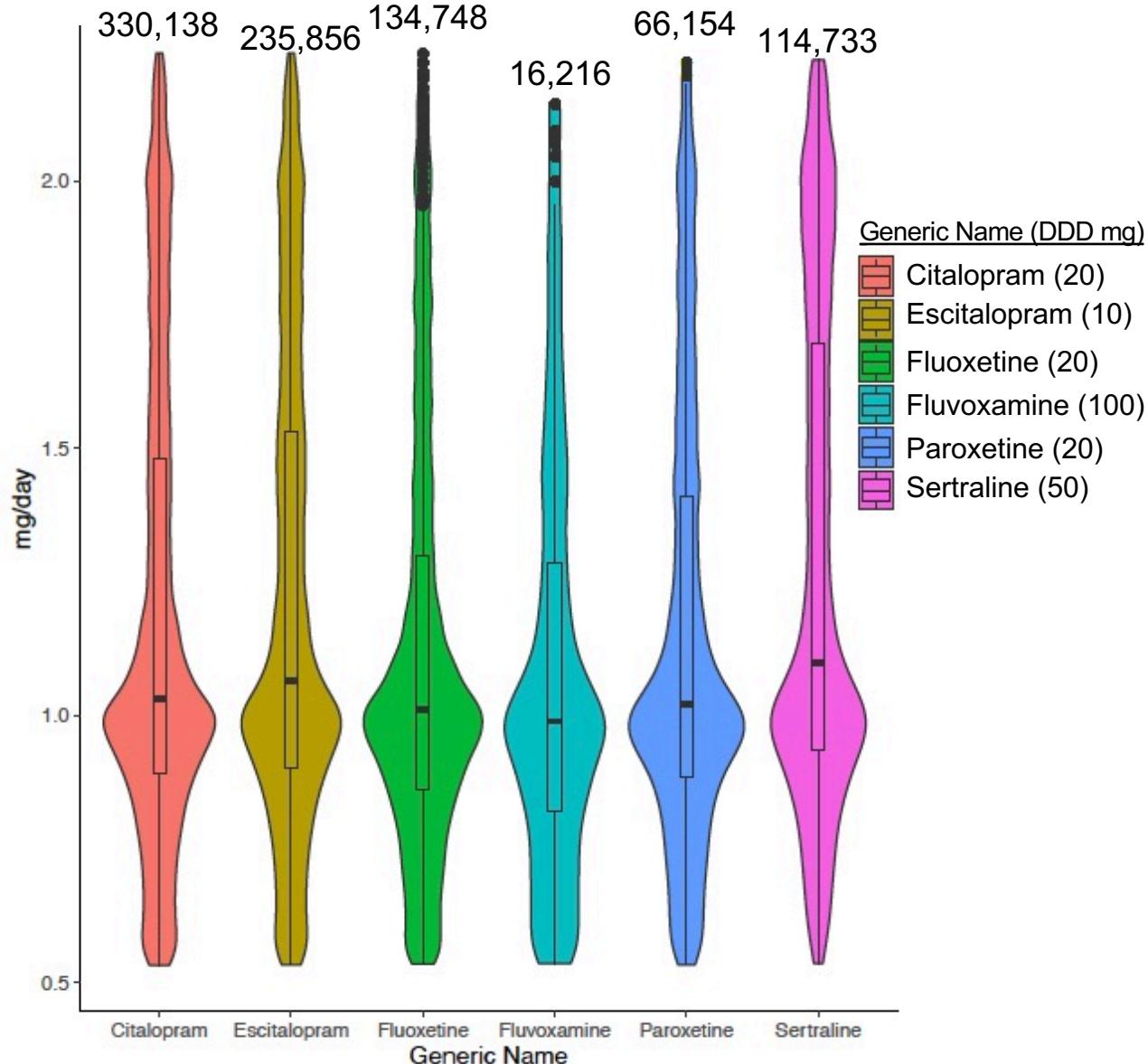


Sum across SSRIs and defined increase/decrease dosage over time

$$\text{Dosage change} = dosePerDay_{t=n} - dosePerDay_{t=0}$$

Increase : positive "Dosage change"

Decrease: negative "Dosage change"

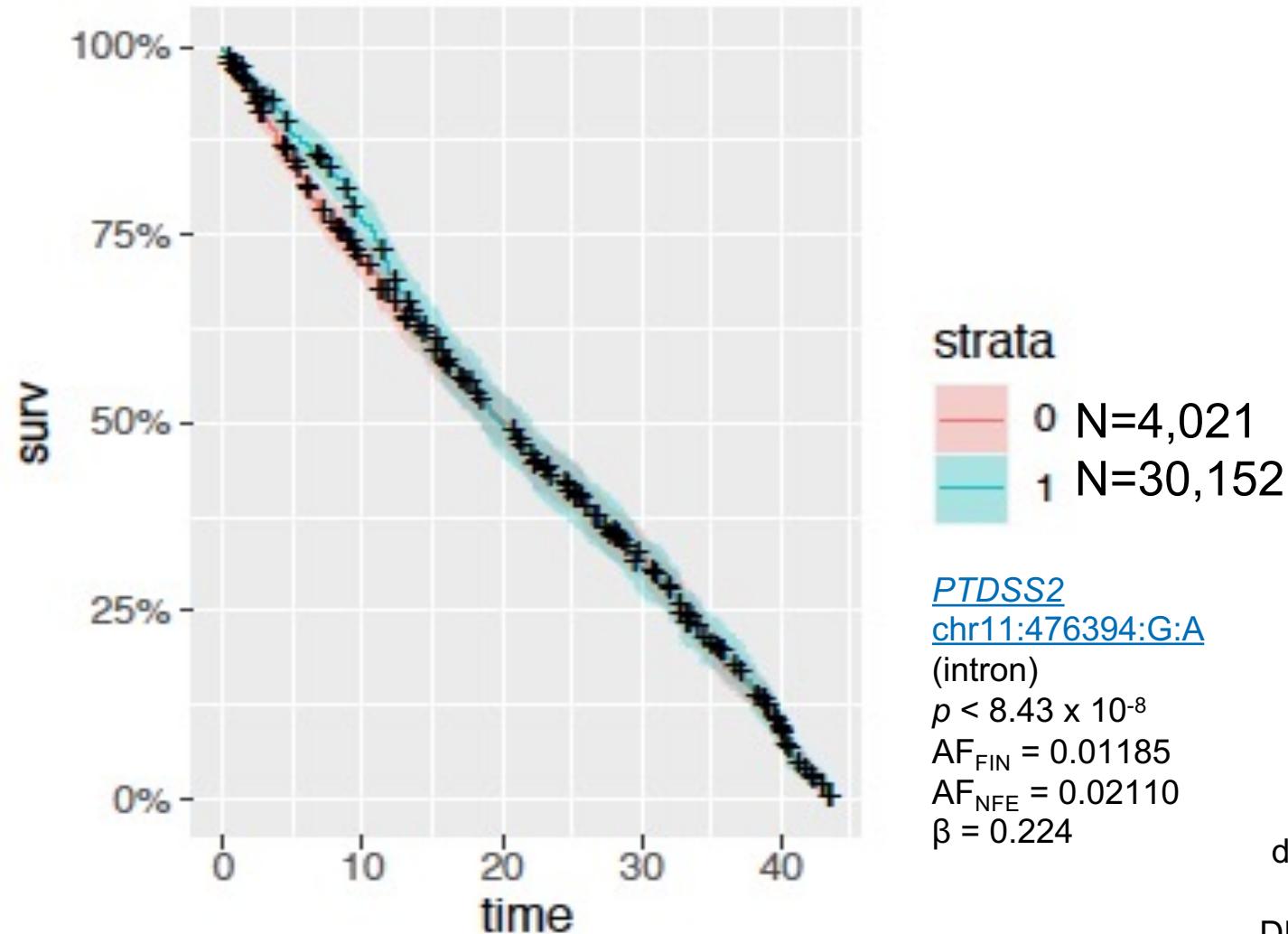


SSRI Dosage: Dosage Increase in per unit SSRI over time

Trait type:
Survival

No dosage change vs
increase in dosage
over time

Question:
*Are there genetic
variants
associated with
SSRI dosage
increase over
time?*



Tracking dosage
per unit of SSRI
increase in months
(median= 40.10)

The protein PTDSS2 has a
high affinity for
docosahexaenoic acid (DHA) :
SSRI can be augmented with
DHA (Li, Fan, and Wang. 2015. *Glycomics
and Lipidomics*)

Note:

AF – gnomAD allele frequencies in Finns (FIN) and Non-Finnish Europeans (NFE)

There is a larger proportion of SSRI purchasers compared to MDD

Were we just testing MDD patients for SSRI variability repeatedly?



Phenotype	Phenotype Correlation (r^2)	Genetic Correlation (r_g)
Antidepressants and MDD	0.444	0.997
SSRI and MDD	0.518	0.731
SSRI switch and MDD	0.00347	0.0443
SSRI increase and MDD	0.00703	0.0270

Conclusion and Future Studies

- To the best of our knowledge, results shown are novel to depression etiology.
- With simple phenotyping, we have shown that there is a genetic basis in SSRI response variability and warrants detailed interrogation.
- *Future studies:*
 - major depressive disorder polygenic risk contributing to SSRI use and dosage changes
 - dosage patterns, and
 - adverse outcomes.

FinnGen Partners

Coordinating partners:



HUS



Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine



HiLIFE UNIT

Funding partners:



Genentech
A Member of the Roche Group



Biobanks:



Hospital District of Southwest Finland
University of Turku
Satakunta Hospital District
Vaasa Hospital District



Hospital District of Helsinki and Uusimaa (HUS)
University of Helsinki
Kymenlaakso Social and Health Services (Carea)
South Karelia Social and Health Care District (Eksote)



Finnish Red Cross Blood Service
Finnish Association of Hematology
Institute for Molecular Medicine Finland (FIMM), HiLIFE,
University of Helsinki



CENTRAL FINLAND
HEALTH CARE DISTRICT
UNIVERSITY OF JYVÄSKYLÄ



Northern Savo Hospital District
University of Eastern Finland
South Savo Social and Health Care Authority
Joint Municipal Authority for North Karelia Social and
Health services (Siun sote)
Eastern Savo Hospital District



Central Finland Health Care District
University of Jyväskylä

Northern Ostrobothnia Hospital District
University of Oulu
Joint Municipal Public Utility for Northern Finland central
laboratory Nordlab
Central Ostrobothnia Joint Municipal Authority for Social
and Health Care
Kainuu Social and Health Care Joint Municipal Authority
Lapland Hospital District
Länsi-Pohja Hospital District



Pirkanmaa Hospital District
University of Tampere
Kanta-Häme Hospital District
South Ostrobothnia Hospital District



Finnish Institute for Health and Welfare (THL)



Funding:

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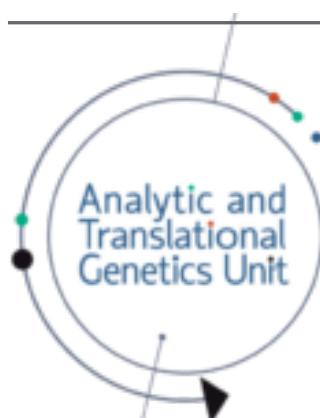
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**HARVARD
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SCHOOL OF PUBLIC HEALTH

Suuri kiitos! Onko kysyttäväää?



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Genetics of use of various drugs correlate with psych traits

LDSC rg

Bonferroni non-significant correlations are 0

	MDD	NRTCSM	INSOMNIA	ADHD	SCZ	BIPOLAR	EDUCATT
Antidepressants (N06A)	0.9969	0.733	0.5595	0.3417	0.4246	0.4698	-0.182
Psycholeptics (N05)	0.788	0.5365	0.5423	0.3281	0.5407	0.5616	-0.1621
Other antidepressants (N06AX)	0.7359	0.533	0.4518	0.2766	0.2926	0.3654	-0.1554
Bicyclic derivatives (N06AB)	0.7312	0.589	0.3268	0.2356	0.3398	0.3881	0
Benzodiazepine derivatives (N05CD)	0.7295	0.4221	0.5838	0.5001	0.3748	0.455	0
Non-selective monoamine reuptake inhibitors (N06AA)	0.7068	0.4554	0.5342	0.4377	0.2077	0	-0.3017
Number of different drugs purchased (UNIQ)	0.649	0.4648	0.5237	0.4474	0	0.1855	-0.3572
Diazepines, oxazepines, thiazepines and oxepines (N05AH)	0.6433	0.4544	0.3776	0	0.6533	0.5805	0
Antiepileptics (N03)	0.6353	0.4044	0.4535	0.4494	0	0.2707	-0.3439
Analgesics (N02)	0.6307	0.3903	0.544	0.5315	0	0	-0.5515
Antipsychotics (N05A)	0.6188	0.4317	0.3486	0.2409	0.6414	0.6354	0
Opioids (N02A)	0.6161	0.3918	0.5715	0.5479	0	0	-0.5268
Sedatives, ATARAKTIKA (N05B)	0.6129	0.4432	0.3513	0.2848	0.358	0.4053	-0.1573
Total number of drug purchases (ALL)	0.6082	0.4489	0.5175	0.382	0	0.2195	-0.3772
Benzodiazepine (N05BA)	0.6074	0.4451	0.3421	0.2723	0.3644	0.3956	-0.1494
Anilides, incl. combinations (N02BE)	0.5953	0.3799	0.4996	0.5326	0	0	-0.6039
Hypnotics and sedatives (N05C)	0.5629	0.3675	0.4609	0.2955	0.2695	0.3279	-0.1163
Tetracyclines (J01A)	0.5438	0.3753	0.3921	0.4544	0	0	-0.3182
Cyclopentolones (N05CF)	0.536	0.3585	0.4392	0.2716	0.2452	0.3088	0
Anti-asthmatics (R03)	0.5201	0.2993	0.4343	0.3971	0	0	-0.2555
Selective beta-2-adrenoceptor agonists (R03AC)	0.5008	0.2874	0.409	0.398	0	0	-0.2742
Antibacterials for systemic use (J01)	0.4984	0.3433	0.3648	0.4236	0	0	-0.28
Other beta-lactam antibacterials (J01D)	0.4828	0.3539	0.3991	0.5098	0	0	-0.3756
Macrolides and lincosamides (J01F)	0.469	0.3086	0.3646	0.398	0	0	-0.215
Acetic acid derivatives and related substances (M01AB)	0.4621	0.2689	0.4475	0.5047	-0.2395	0	-0.5637
Beta-lactam antibacterials, penicillins (J01C)	0.4401	0.312	0.3258	0.3602	0	0	-0.2646
Antiinflammatory and antirheumatic products (M01)	0.4346	0.2975	0.4329	0.4644	-0.2174	0	-0.4875
Propionic acid derivatives (M01AE)	0.418	0.3088	0.4393	0.493	-0.1981	0	-0.5409
Coxibs (M01AH)	0.4163	0.2996	0.4279	0.4	-0.259	0	-0.4209
Glucocorticoids (H02AB)	0.3826	0.2741	0.3263	0.3138	0	0	-0.2731
Corticosteroids for systemic use, plain (H02A)	0.3815	0.2749	0.3277	0.3151	0	0	-0.2717
Corticosteroids (R01AD)	0.374	0.284	0.2684	0	0	0	0
Quinolone antibacterials (J01M)	0.3505	0.2212	0.2617	0.2836	0	0	-0.1525
Other anti-asthmatics, inhalants (R03B)	0.3392	0.1998	0.2897	0.2581	0	0	-0.1556
Beta blocking agents (C07)	0.3152	0.2942	0.3602	0.1896	0	0	-0.3381