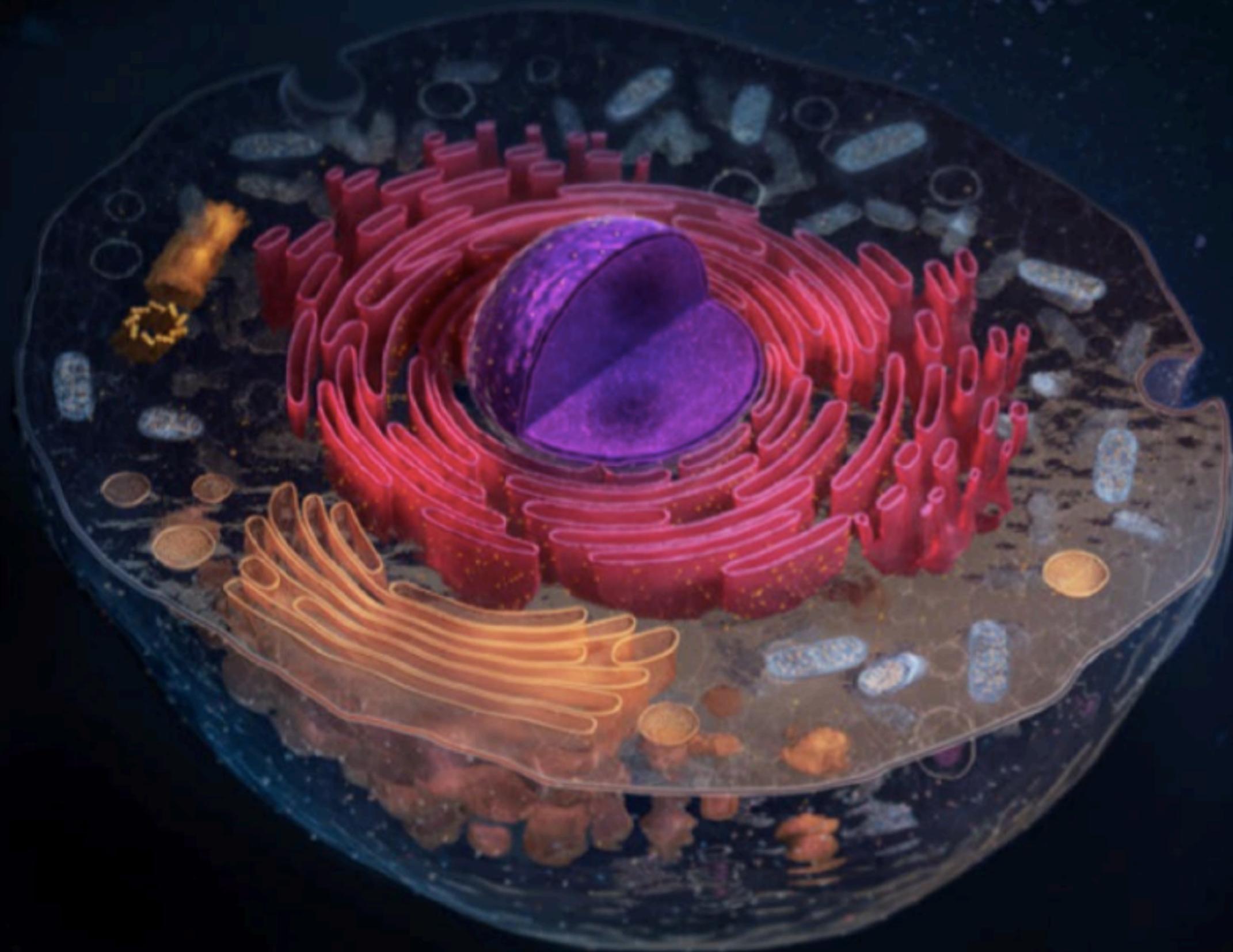


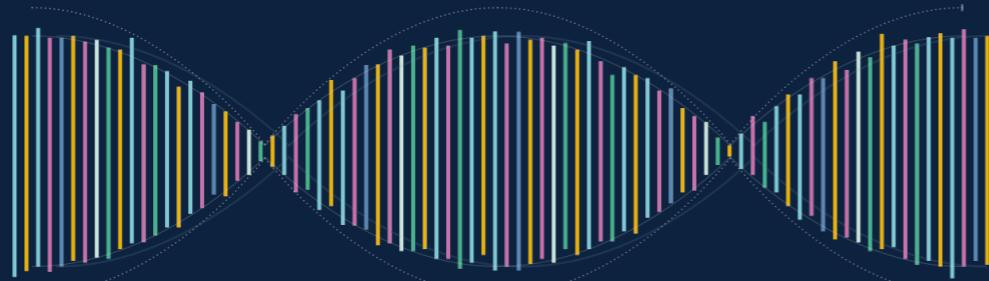
# Генетика здоровья

Ракитъко Александр

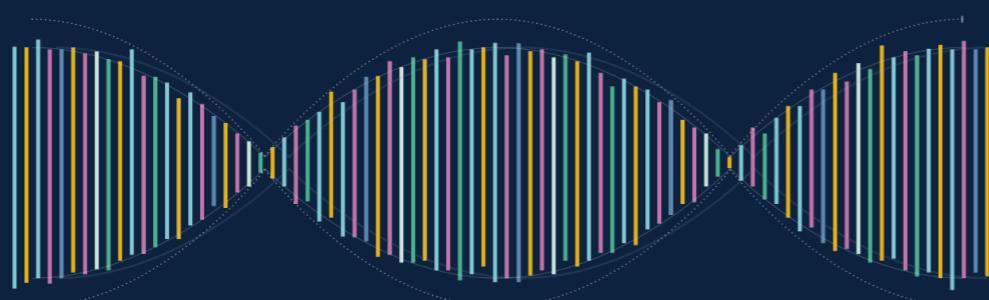




# Что такое генетический полиморфизм?



... A A T G C A A T G C G A ...

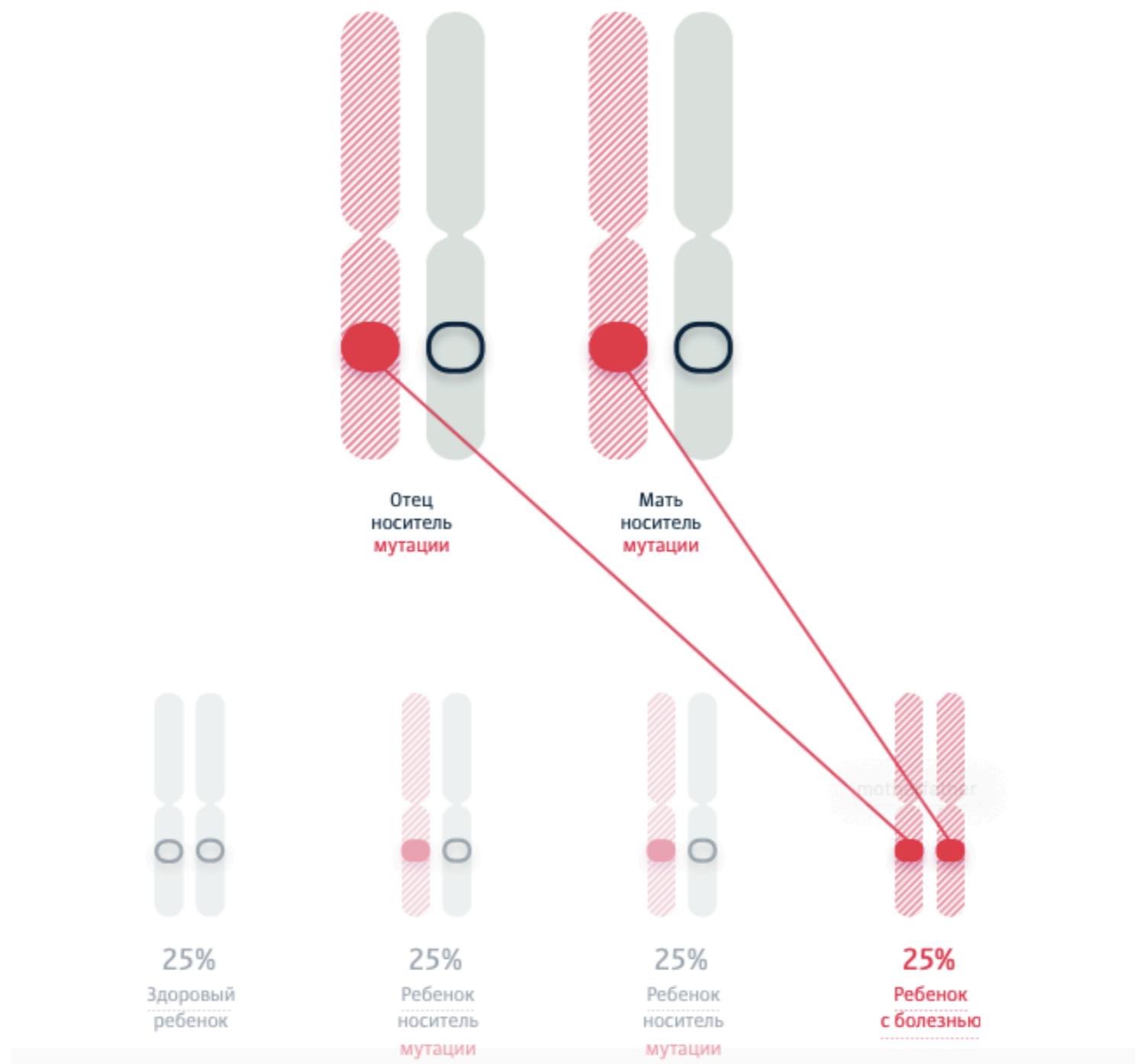


... A A T G C A G T G C G A ...



... A A T G C A C T G C G A ...

# Наследственные заболевания



# Сколько мутаций нужно проанализировать, чтобы оценить риск коронарной недостаточности?

Число известных мутаций,  
ответственных за коронарную  
недостаточность



# Мультифакторные заболевания

Вклад генетики, %

---

Коронарная недостаточность 49

---

Рак молочной железы 25-56

---

Диабет 1-го типа 88

---

Диабет 2-го типа 26

---

Инсульт 32

# Фармакогенетика

- ① Токсичность
  - ② Эффективность
  - ③ Дозировка
- 

80+ лекарственных веществ  
400+ достоверных ассоциаций  
с генетическими маркерами



# Питание и спорт



## Identification of 15 genetic loci associated with risk of major depression in individuals of European descent

Craig L. Hyde<sup>1</sup>, Mike W. Nagle<sup>2</sup>, Chao Tian<sup>3</sup>, Xing Chen<sup>1</sup>, Sara A. Paciga<sup>2</sup>, Jens R. Wendland<sup>2</sup>, Joyce Tung<sup>3</sup>, David A. Hinds<sup>3</sup>, Roy H. Perlis<sup>4</sup>, and Ashley R. Winslow<sup>2,5</sup>

<sup>1</sup>Statistics, Pfizer Global Research and Development, Pfizer, Inc., Cambridge, (MA), USA

<sup>2</sup>Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Pfizer, Inc. Cambridge, (MA), USA

<sup>3</sup>23 and Me Inc., Mountain View, (CA), USA

<sup>4</sup>Center for Experimental Drugs and Diagnostics, Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, (MA), USA

### Abstract

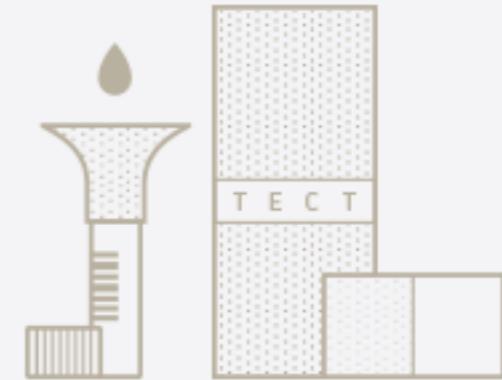
Despite strong evidence supporting the heritability of Major Depressive Disorder, previous genome-wide studies were unable to identify risk loci among individuals of European descent. We used self-reported data from 75,607 individuals reporting clinical diagnosis of depression and 231,747 reporting no history of depression through 23andMe, and meta-analyzed these results with published MDD GWAS results. We identified five independent variants from four regions associated with self-report of clinical diagnosis or treatment for depression. Loci with  $p\text{val} < 1.0 \times 10^{-5}$  in the meta-analysis were further analyzed in a replication dataset (45,773 cases and 106,354 controls) from 23andMe. A total of 17 independent SNPs from 15 regions reached genome-wide significance after joint-analysis over all three datasets. Some of these loci were also implicated in GWAS of related psychiatric traits. These studies provide evidence for large-scale consumer genomic data as a powerful and efficient complement to traditional means of ascertainment for neuropsychiatric disease genomics.

### Keywords

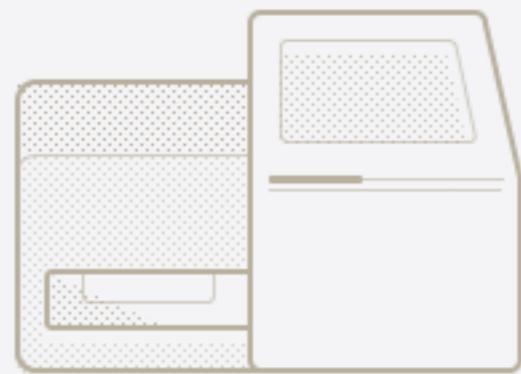
genome-wide; depression; GWAS; single nucleotide polymorphism; SNP; MDD

# How is genetic testing done?

1. Collect saliva



2. Microarray genotyping  
~ 650 000 SNPs



3. Reports (genetics + questionnaire)



# What do we know about the clients?

Age 29

Geolocation Moscow

Diseases Asthma

Height 187 cm

Weight 88 kg

Smoking Never Left Yes Number of cigarettes per day

Alcohol No Per month Per week Almost every day



Valery Ilinsky

stress level



Hospital Anxiety  
and Depression Scale

and other parametres

# Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)					
Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate is best.					
D	A	I feel tense or 'wound up':	D	A	I feel as if I am slowed down:
3		Most of the time	3		Nearly all the time
2		A lot of the time	2		Very often
1		From time to time, occasionally	1		Sometimes
0		Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much	0		Not at all
1		Not quite so much	1		Occasionally
2		Only a little	2		Quite Often
3		Hardly at all	3		Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
3		Very definitely and quite badly	3		Definitely
2		Yes, but not too badly	2		I don't take as much care as I should
1		A little, but it doesn't worry me	1		I may not take quite as much care
0		Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could	3		Very much indeed
1		Not quite so much now	2		Quite a lot
2		Definitely not so much now	1		Not very much
3		Not at all	0		Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
3		A great deal of the time	0		As much as I ever did
2		A lot of the time	1		Rather less than I used to
1		From time to time, but not too often	2		Definitely less than I used to
0		Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all	3		Very often indeed
2		Not often	2		Quite often
1		Sometimes	1		Not very often
0		Most of the time	0		Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
0		Definitely	0		Often
1		Usually	1		Sometimes
2		Not Often	2		Not often
3		Not at all	3		Very seldom

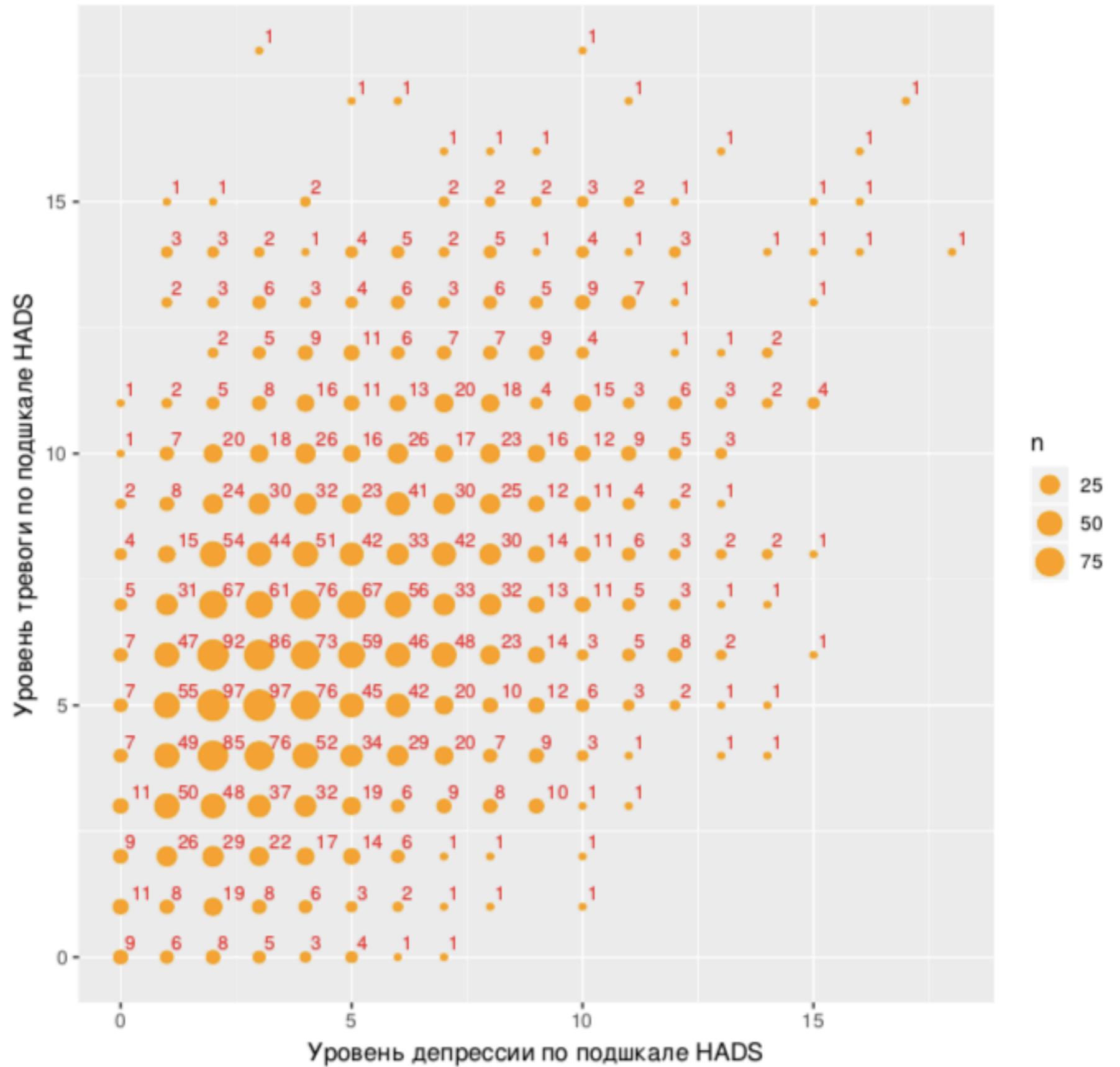
Please check you have answered all the questions

Scoring:  
Total score: Depression (D) \_\_\_\_\_ Anxiety (A) \_\_\_\_\_  
0-7 = Normal  
8-10 = Borderline abnormal (borderline case)  
11-21 = Abnormal (case)

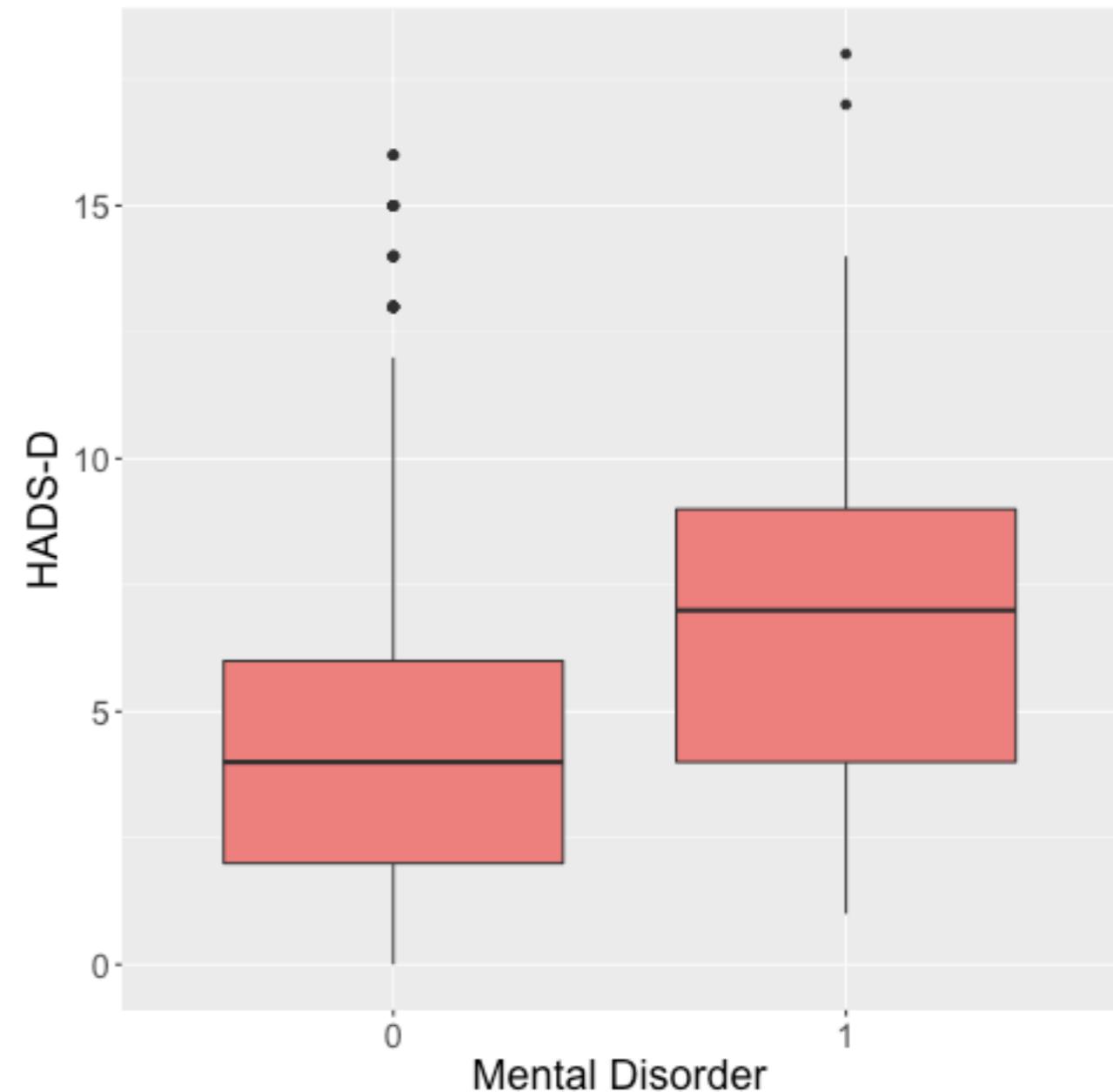
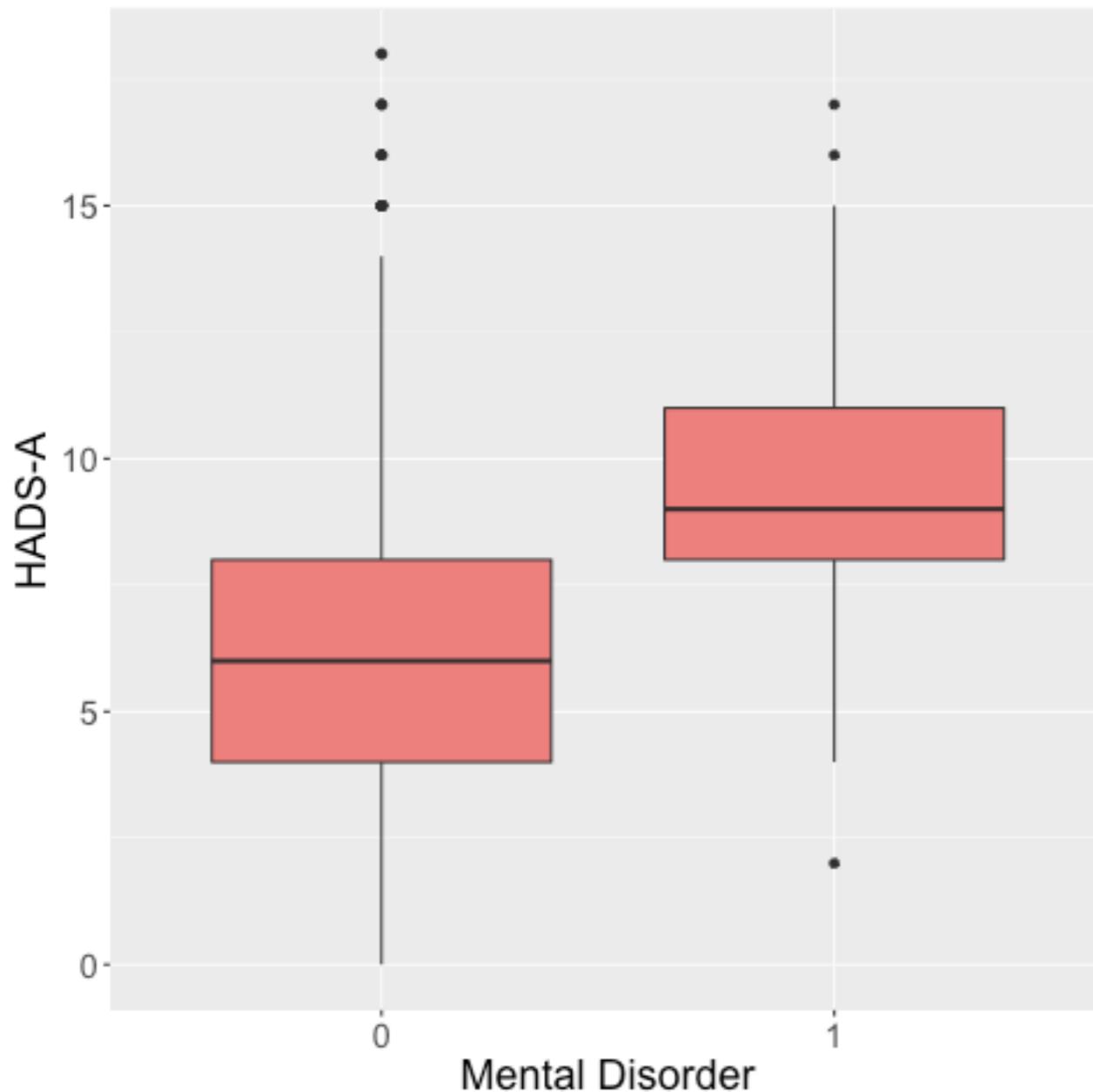
## Cohort

- 3463 samples
- 48.8% females
- 18-65 years
- European ancestry
- Genome-wide genotype data

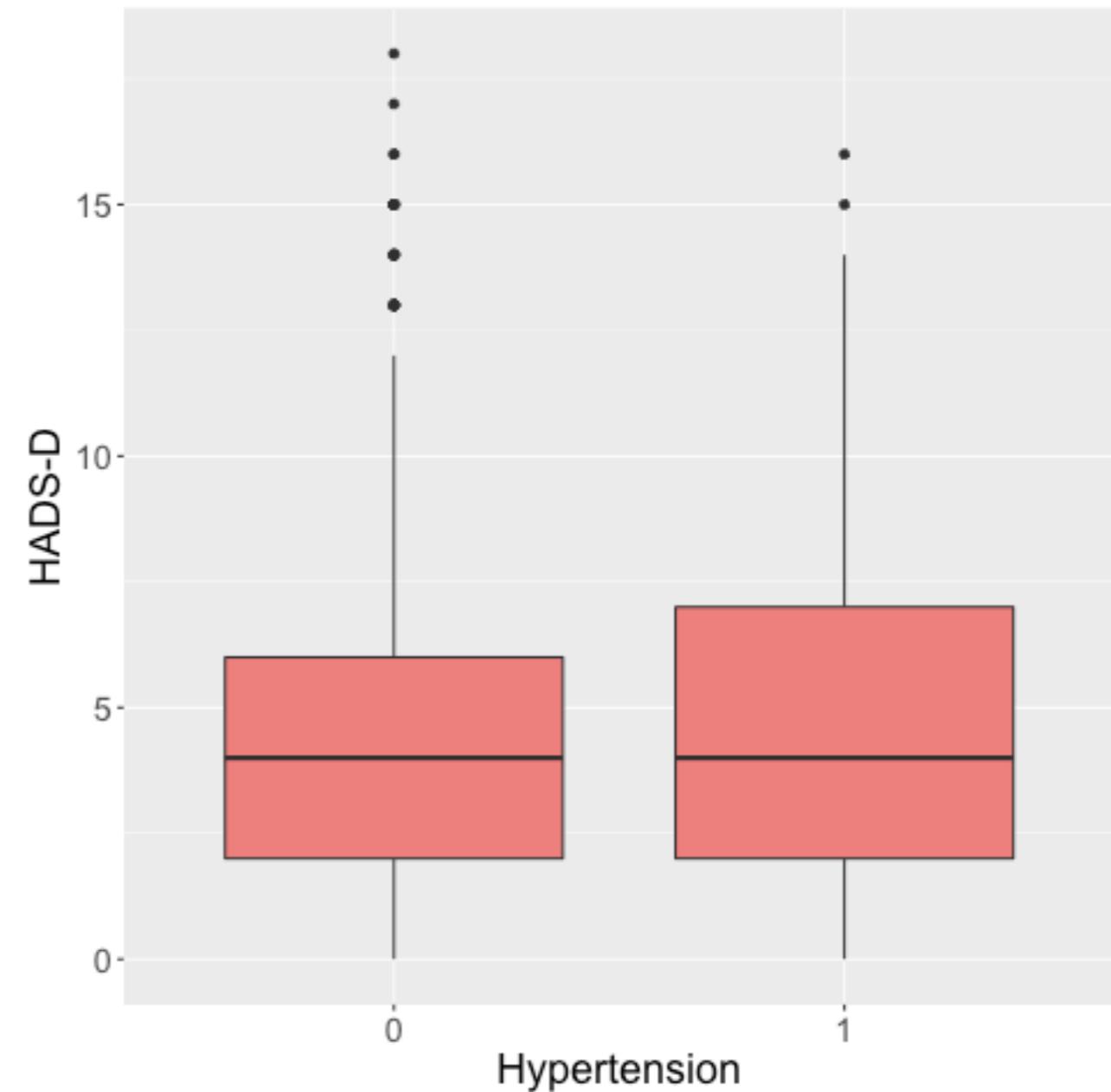
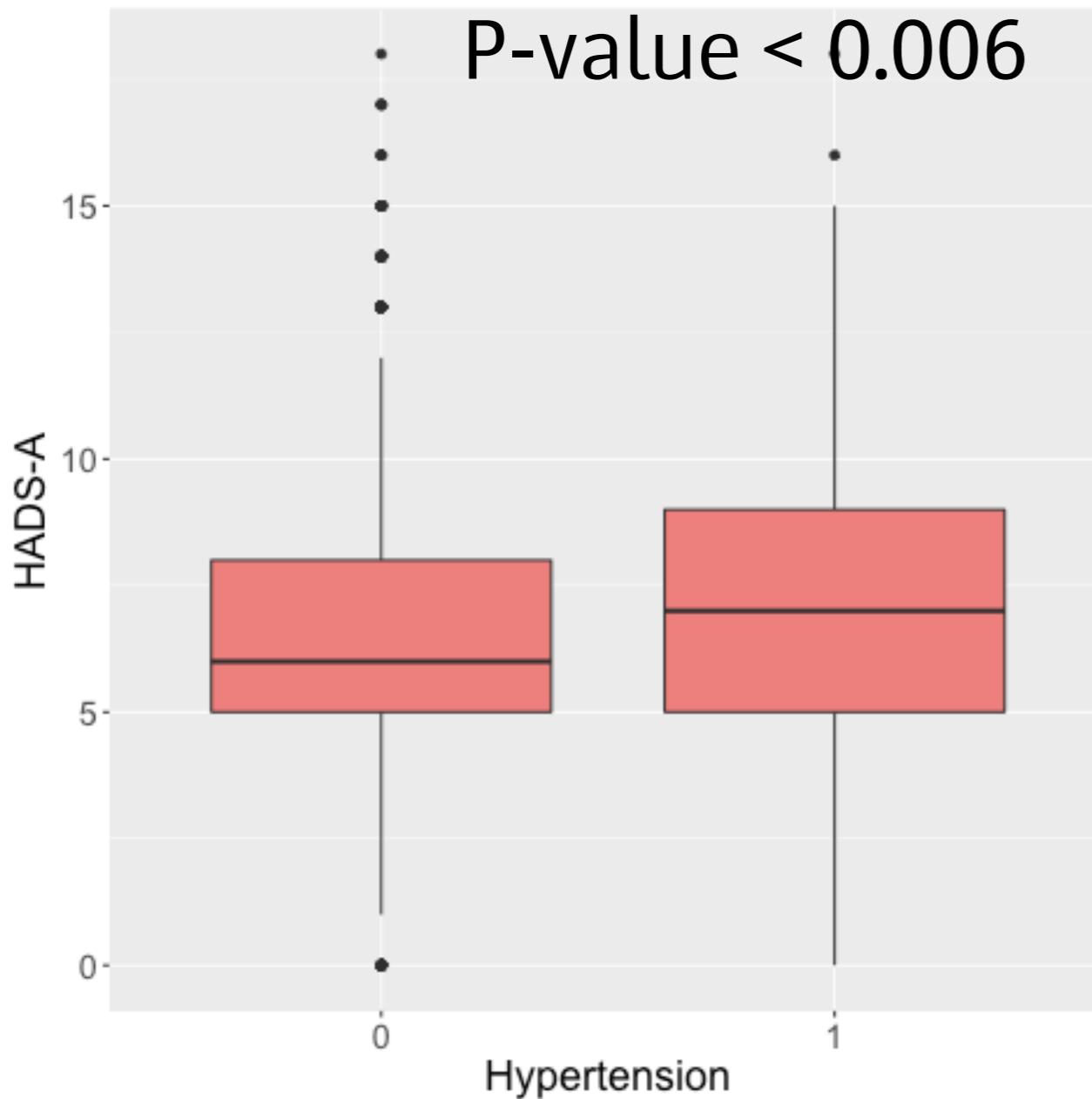




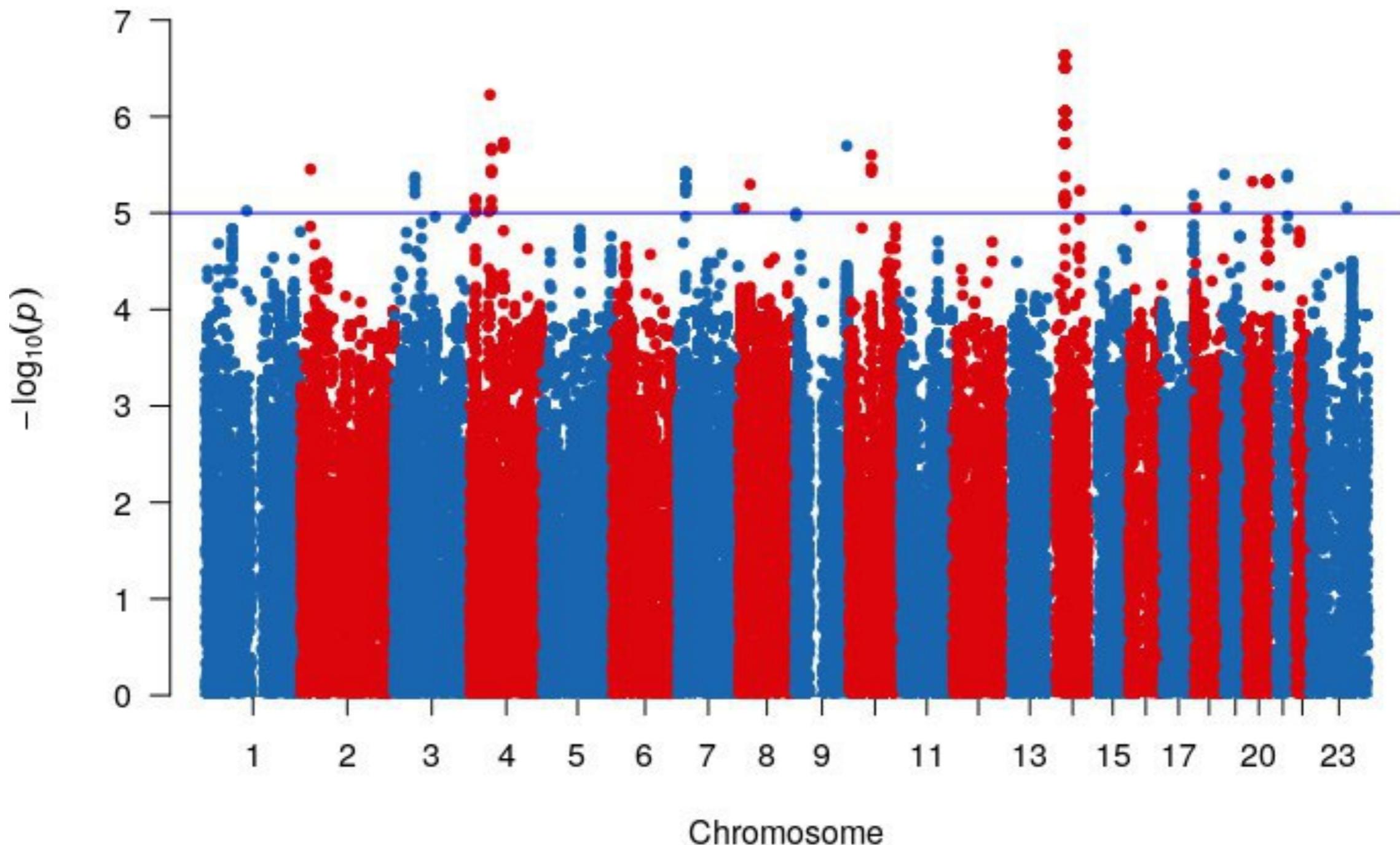
# Mental disorder (105 of 3 463)



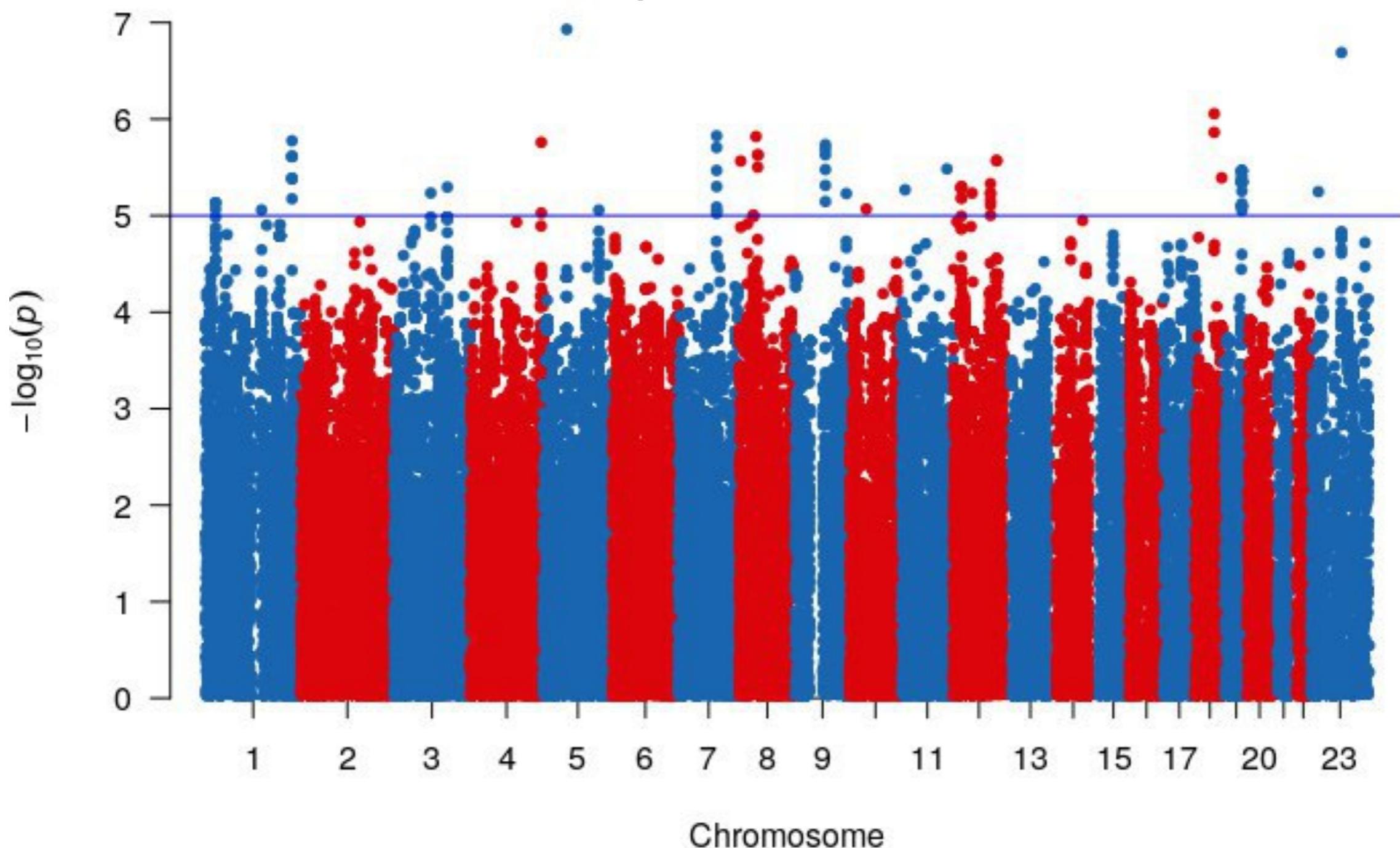
# Hypertension (434 of 3 463)



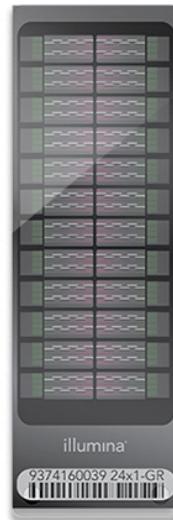
# No associations in anxiety GWAS



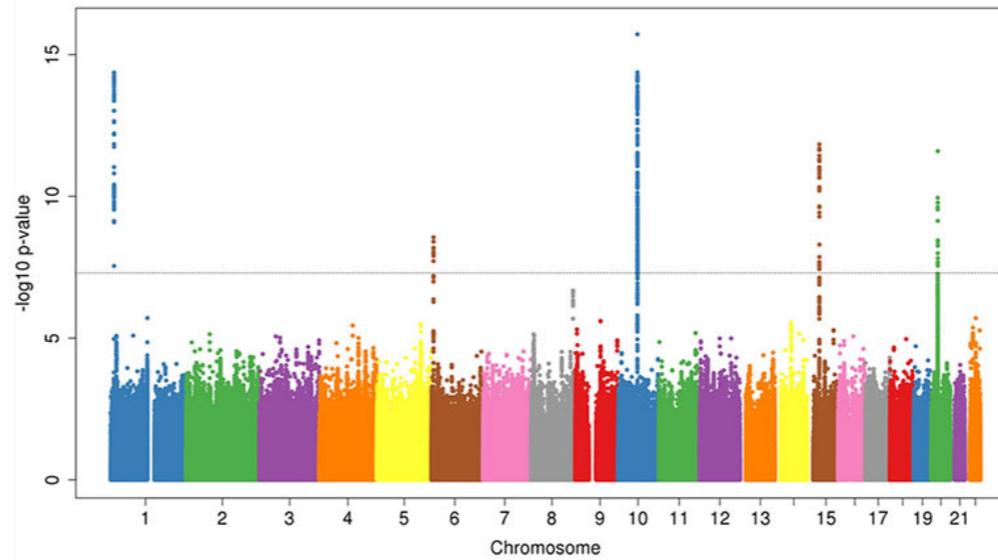
# No associations in depression GWAS



# Polygenic Risk Scores



Microarray Genotyping



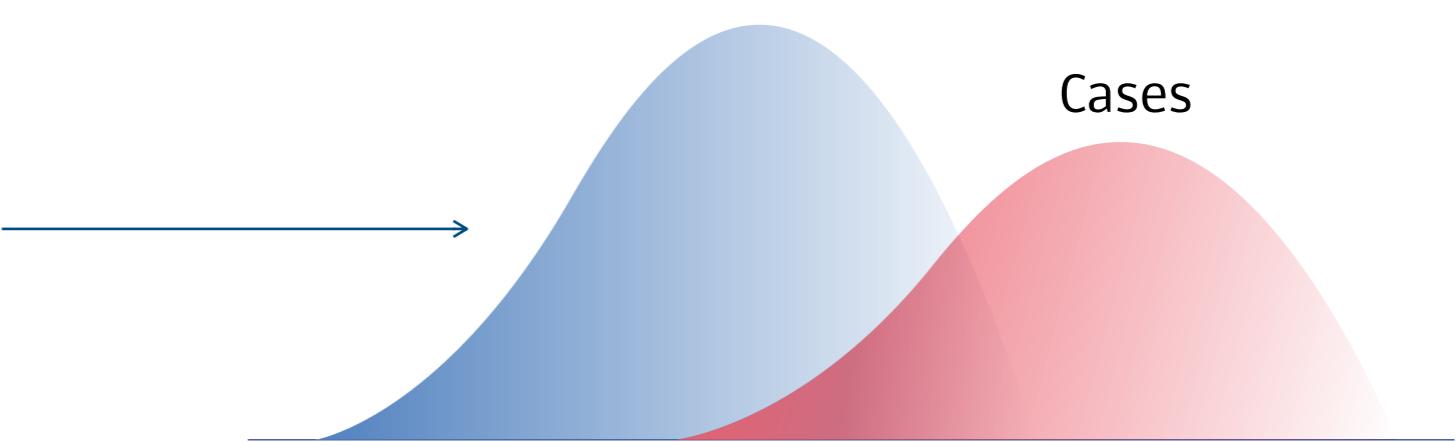
GWAS analysis

$$\text{PRS} = \beta_1 X_1 + \dots + \beta_n X_n$$

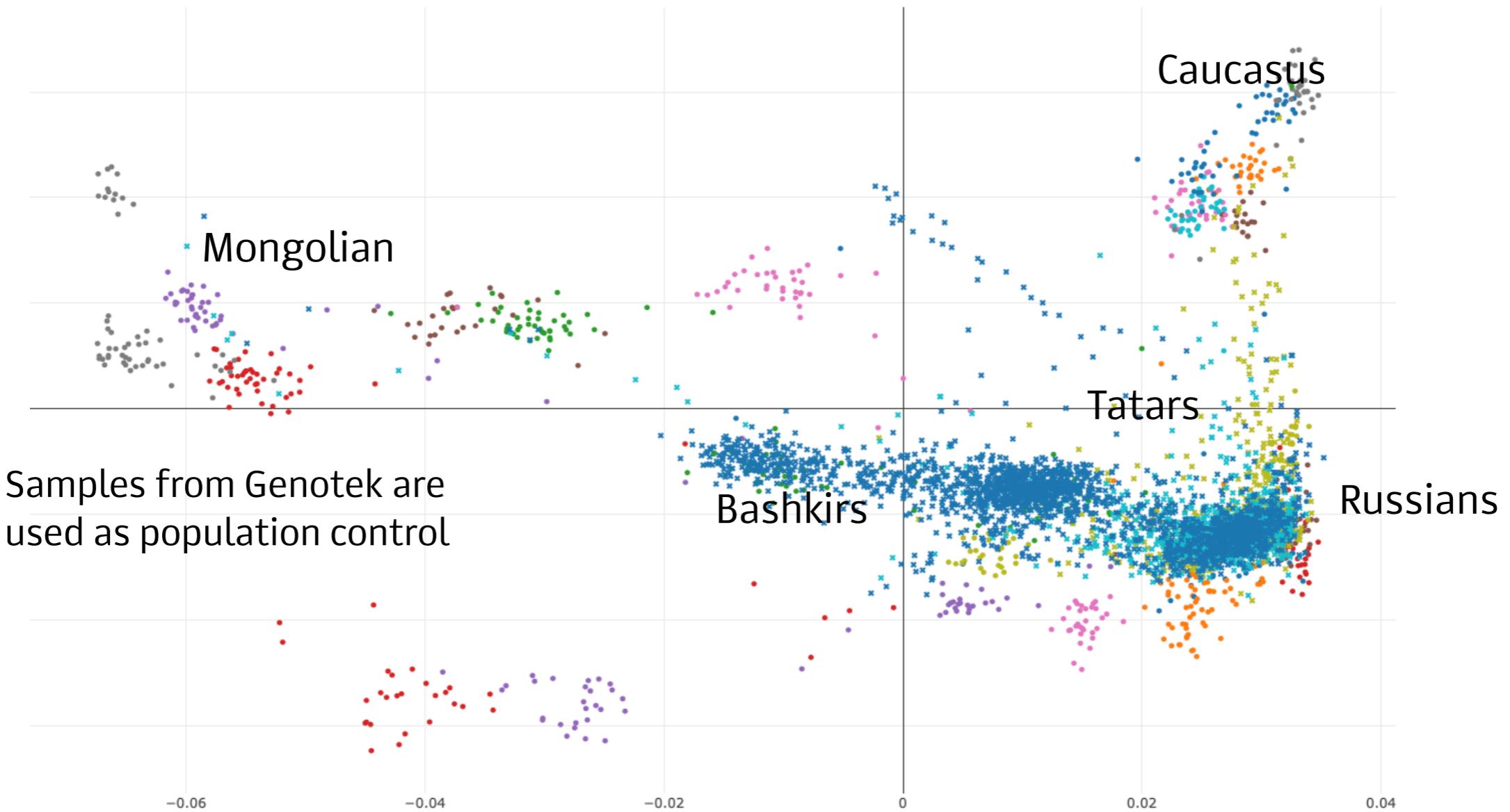
Genome-Wide Polygenic Risk Score

Controls

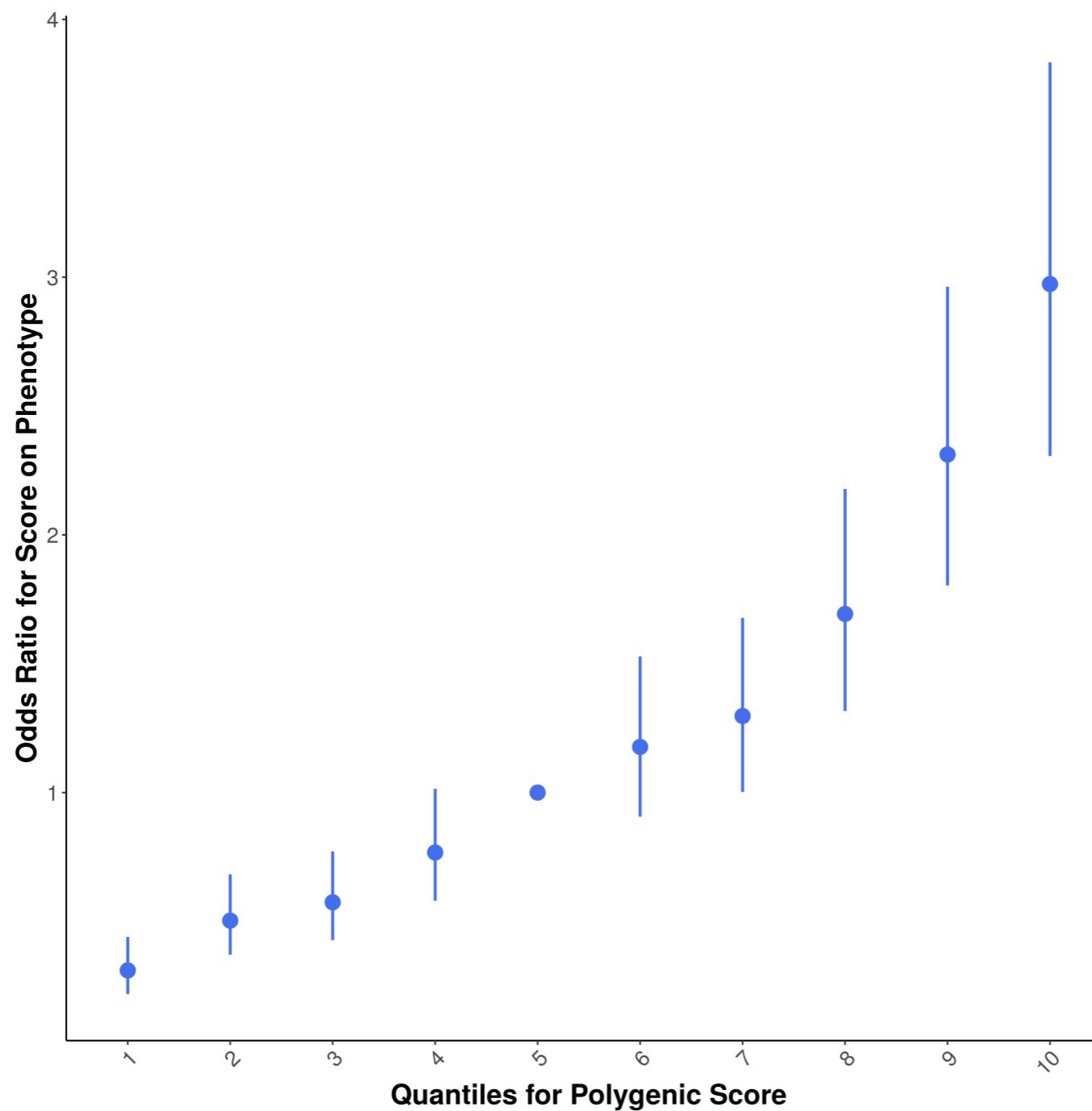
Cases



# GWAS of schizophrenia with Russian National Consortium for Psychiatric Genetics (RNCPG)



Полигенный скор ( $R^2 = 8.5\%$  ,  $h^2 = 17\%$ )



# Коронарная недостаточность

Коронарная недостаточность (КН) — патологическое состояние, характеризующееся частичным или полным прекращением коронарного кровотока и ухудшением снабжения миокарда кислородом и питательными веществами.

## Эпидемиология

В России КН встречается у 10-14.9% населения ([Zhu et al. 2016](#)).  
Наследуемость — 50-60% ([Dai et al. 2016](#)).

## Генетическая модель

В качестве предсказательной модели используется полигенный рисковый скор (polygenic risk score), полученный в ([Khera et al. 2018](#)).

Скор основан на анализе 6 630 150 SNP.

Zhu, Ke-Fu, Yu-Ming Wang, Jin-Zhou Zhu, Qin-Yi Zhou, and Ning-Fu Wang. 2016. “National Prevalence of Coronary Heart Disease and Its Relationship with Human Development Index: A Systematic Review.” European Journal of Preventive Cardiology 23 (5): 530–43.

Dai, Xuming, Szymon Wiernek, James P. Evans, and Marshall S. Runge. 2016. “Genetics of Coronary Artery Disease and Myocardial Infarction.” World Journal of Cardiology 8 (1): 1.

Khera, Amit V., et al. "Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations." Nature genetics 50.9 (2018): 1219.

## Тестовая когорта

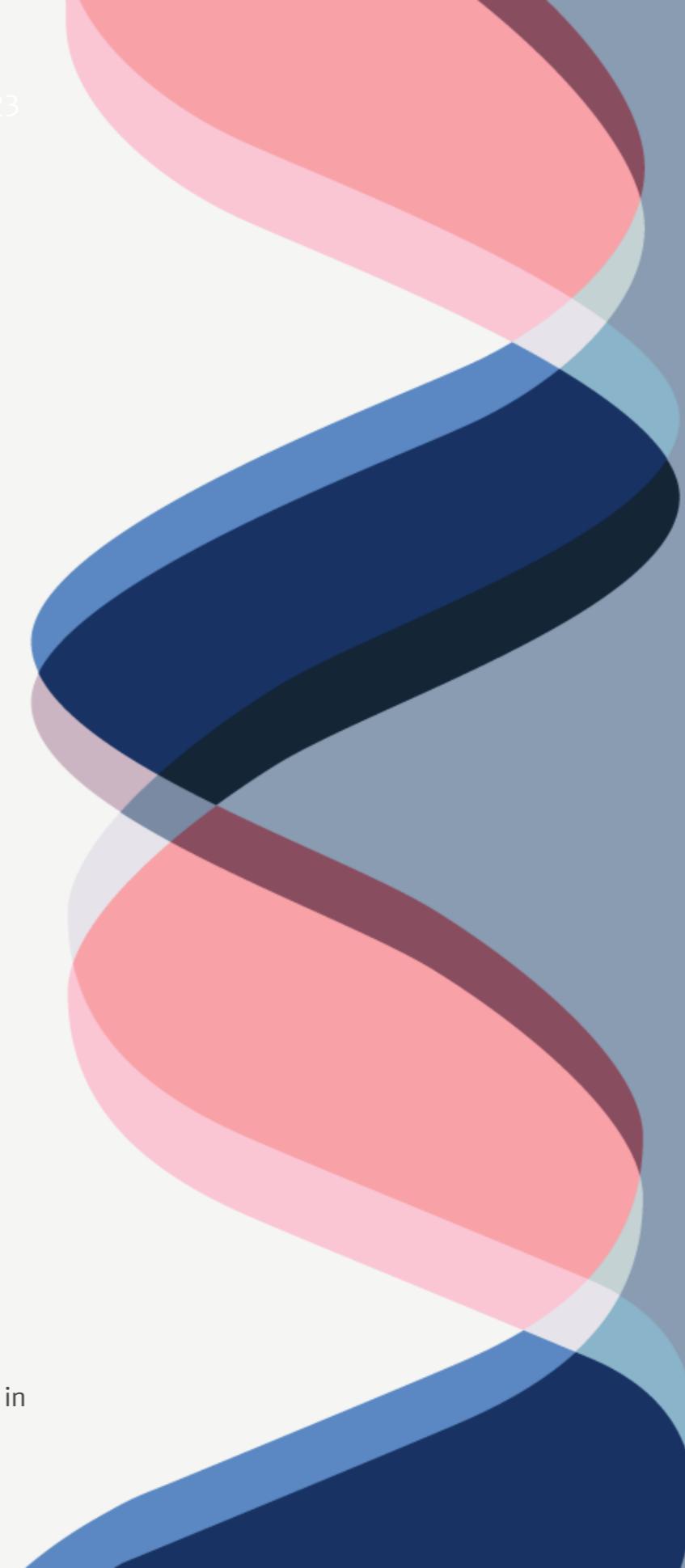
В качестве тестовой выборки использовалась подвыборка из PennCath study (Reilly et al. 2011).

В выборку входило **1401 человека** и **500 000 SNP** из которых **933** больных и **468** здоровых.

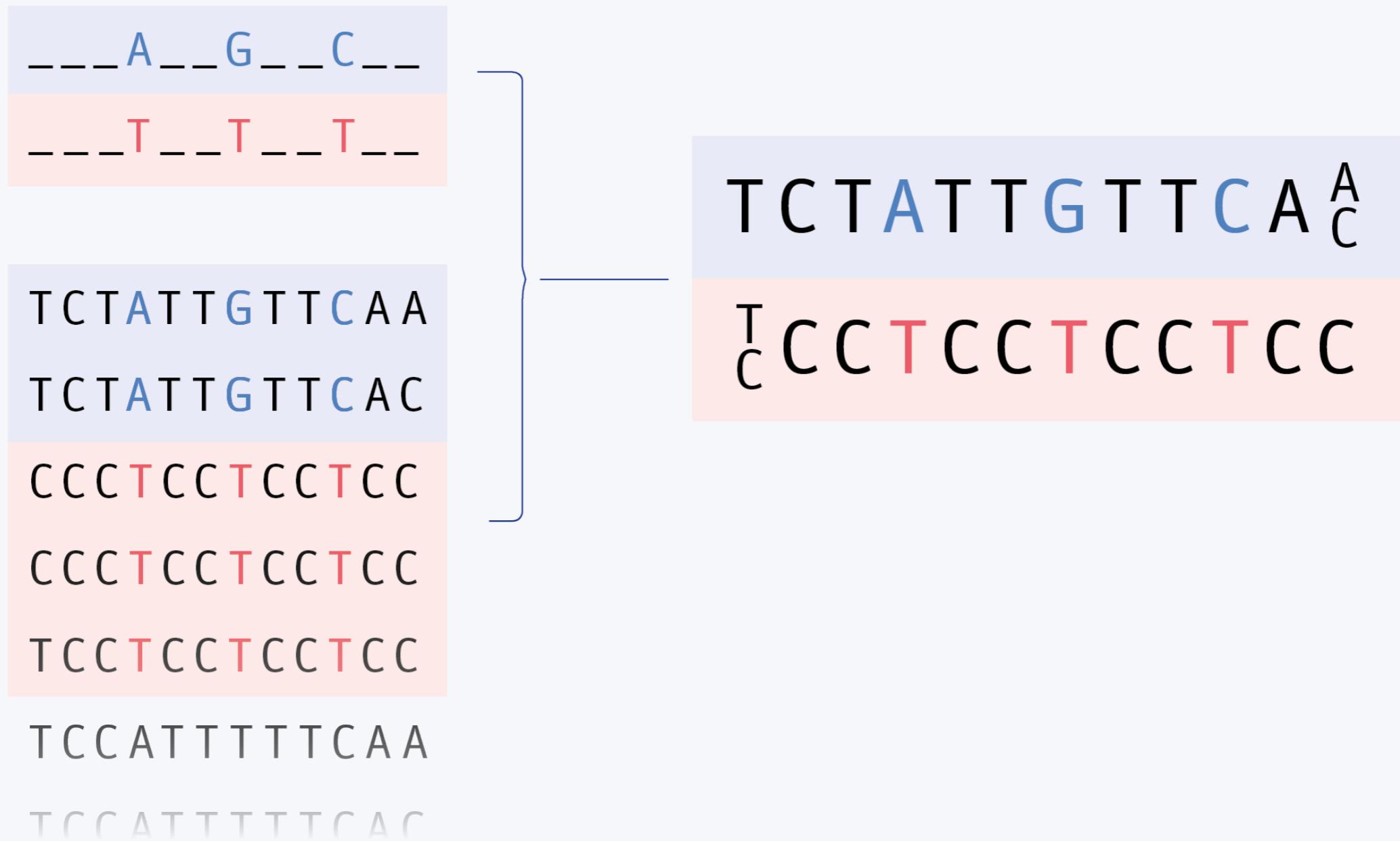
В качестве сопровождающей информации указывались пол, возраст, уровни триглицеридов, ЛПНП и ЛПВП.

[http://www.stat-gen.org/str/Mod1\\_Lab1\\_Data\\_Structure.html](http://www.stat-gen.org/str/Mod1_Lab1_Data_Structure.html)

Reilly, Muredach P., et al. "Identification of ADAMTS7 as a novel locus for coronary atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies." *The Lancet* 377.9763 (2011): 383-392.



# Импьютиинг (восстановление по сцепленности)



# Импьютинг (восстановление по сцепленности)

Импьютирование тестовой выборки производилось с помощью программы BEAGLE 5.0 ([Browning, Zhou, and Browning 2018](#)). В качестве референсной панели для импьютирования использовалась панель HRC ([McCarthy et al. 2016](#)). Для контроля качества импьютирования применялась пост-фильтрация по  $\text{MAF} > 1\%$  и  $\text{DR}_2 > 0.7$ . После импьютирования общее количество SNP составляло **7 450 796** из которых **5 887 713** входит в скор.

---

## Инструменты

Impute 2

BEAGLE 5.0

Minimac 4

---

## Референсные панели

НарМар

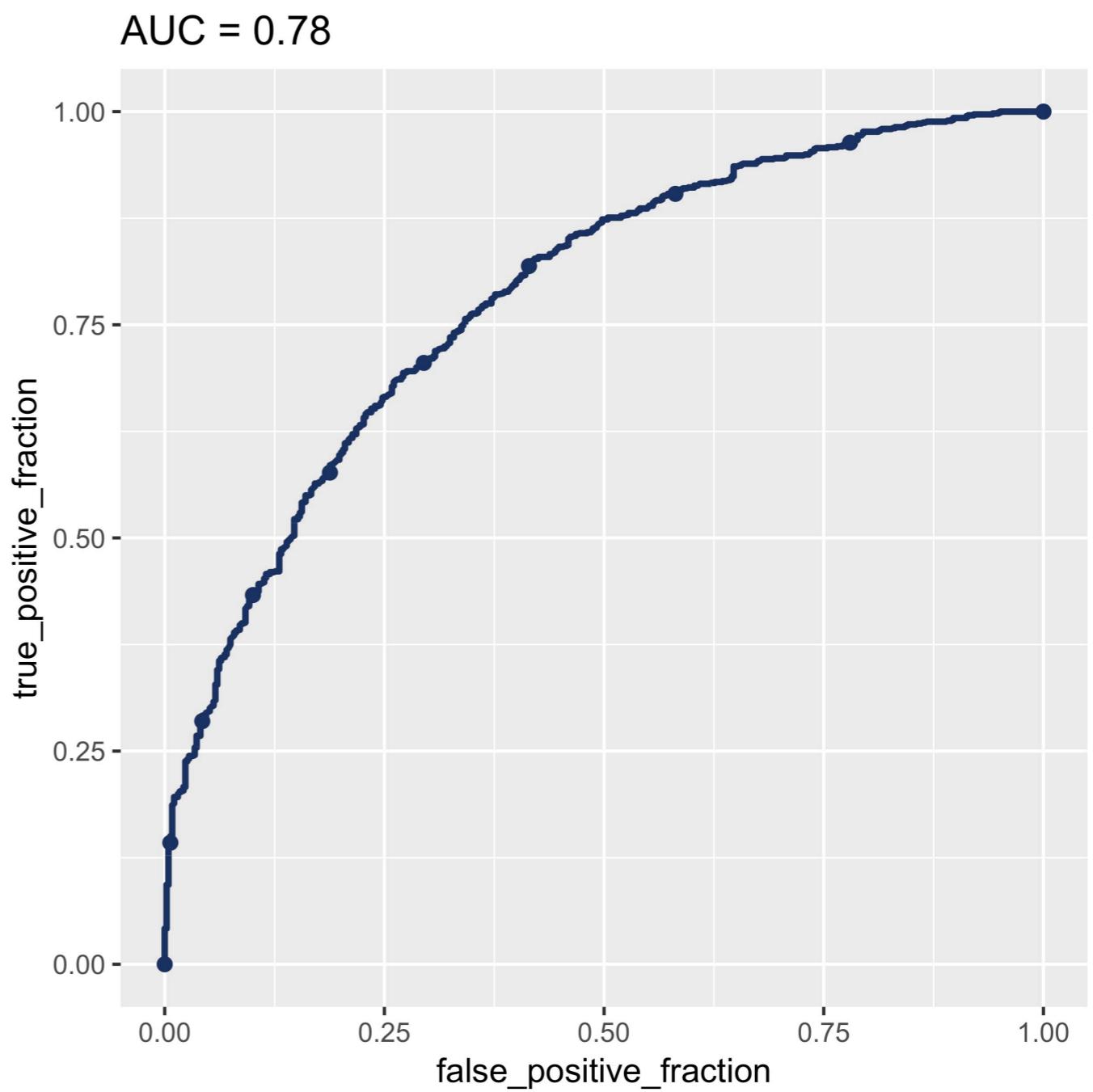
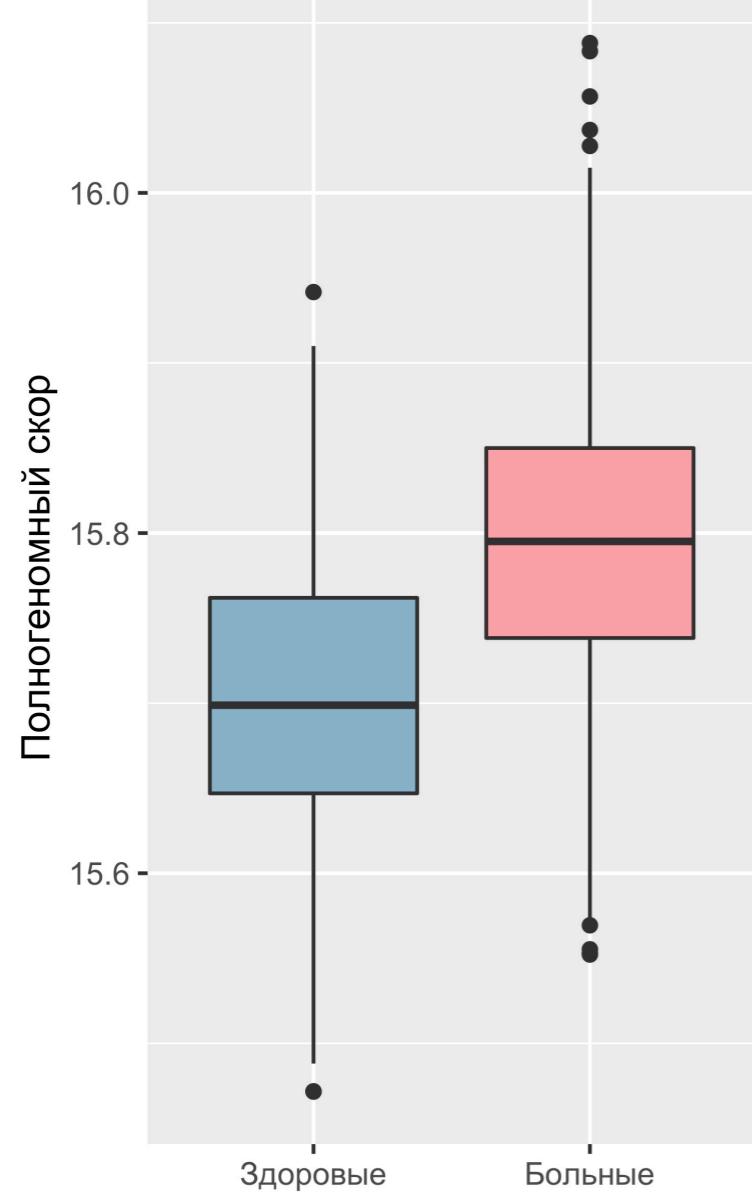
1000 Genomes

Haplotype Reference Consortium

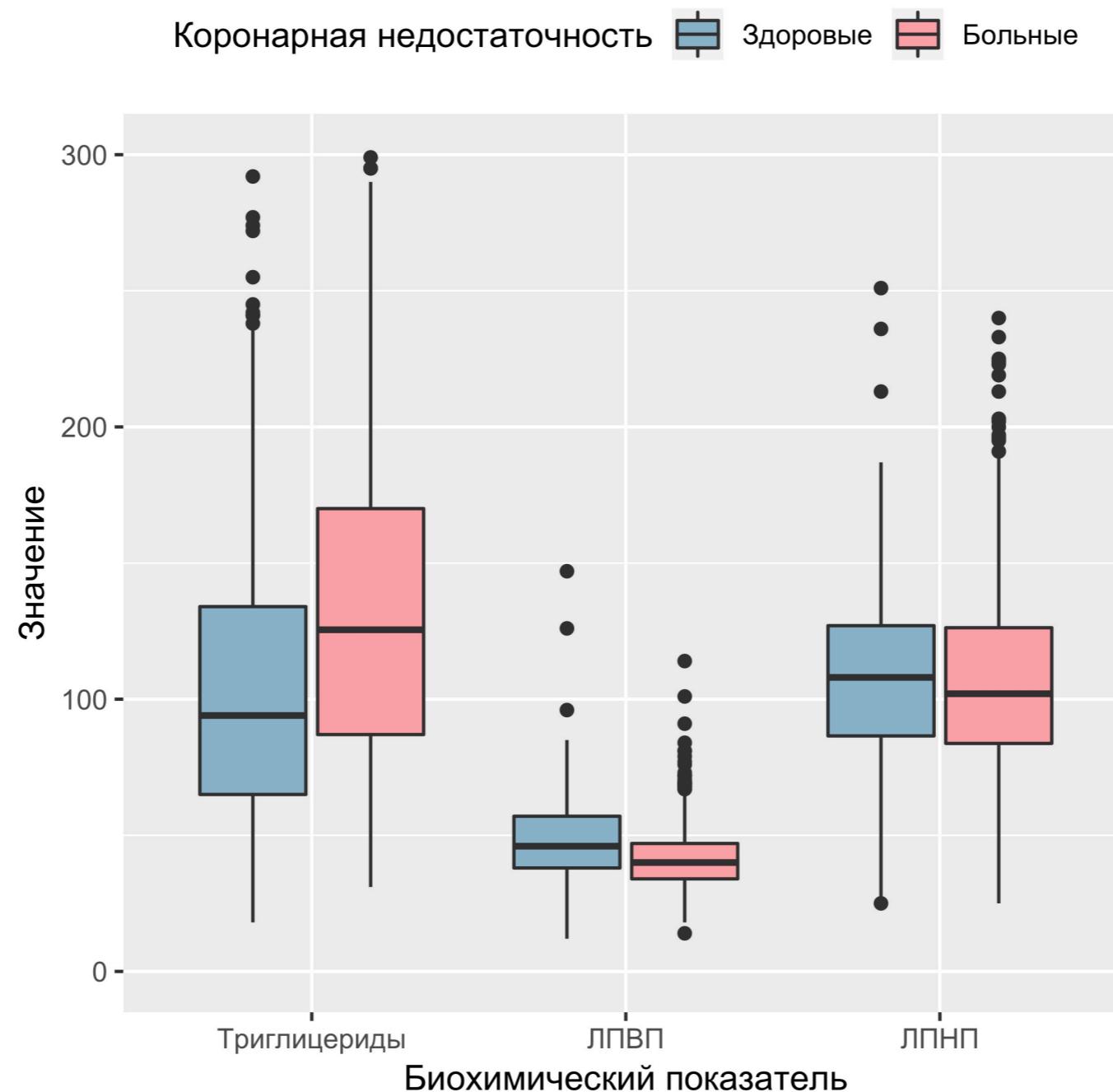
Browning, Brian L., Ying Zhou, and Sharon R. Browning. 2018. “A One-Penny Imputed Genome from Next-Generation Reference Panels.” *American Journal of Human Genetics* 103 (3): 338–48.

McCarthy, Shane, Sayantan Das, Warren Kretzschmar, Olivier Delaneau, Andrew R. Wood, Alexander Teumer, Hyun Min Kang, et al. 2016. “A Reference Panel of 64,976 Haplotypes for Genotype Imputation.” *Nature Genetics* 48 (10): 1279–83.

# Валидирование полногеномного скора



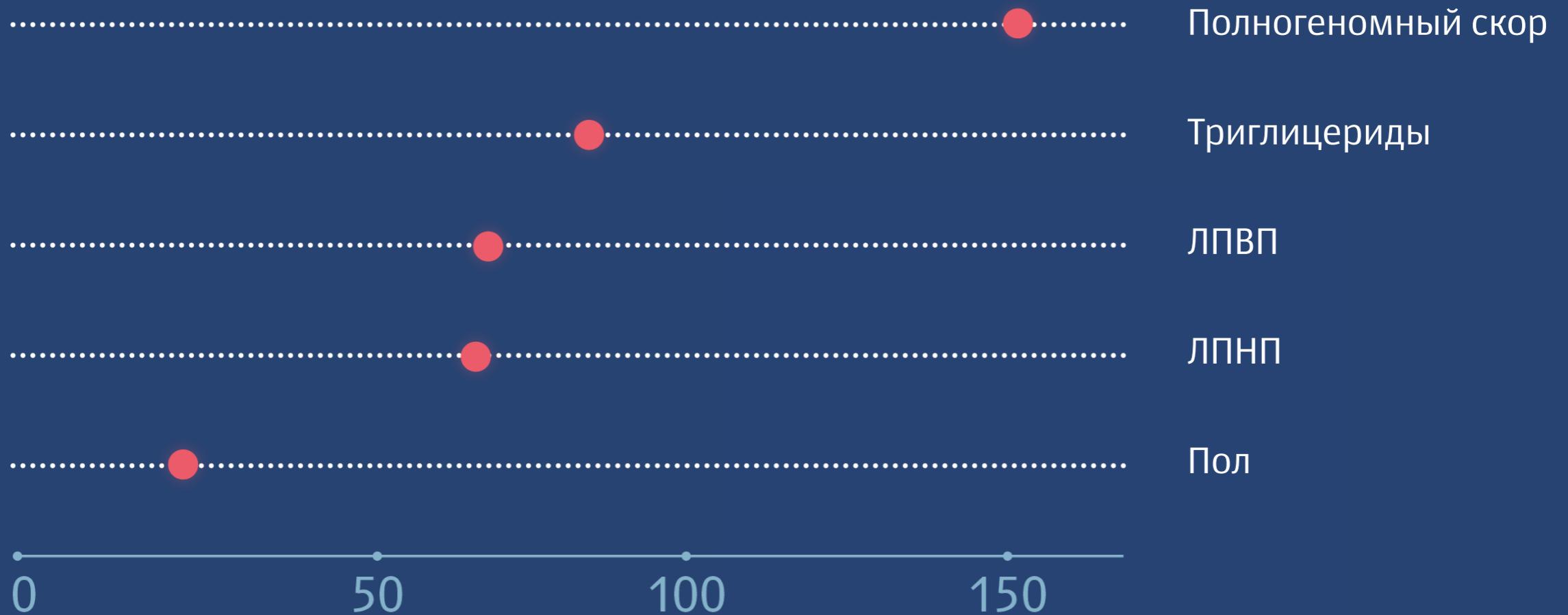
# Негенетические факторы риска



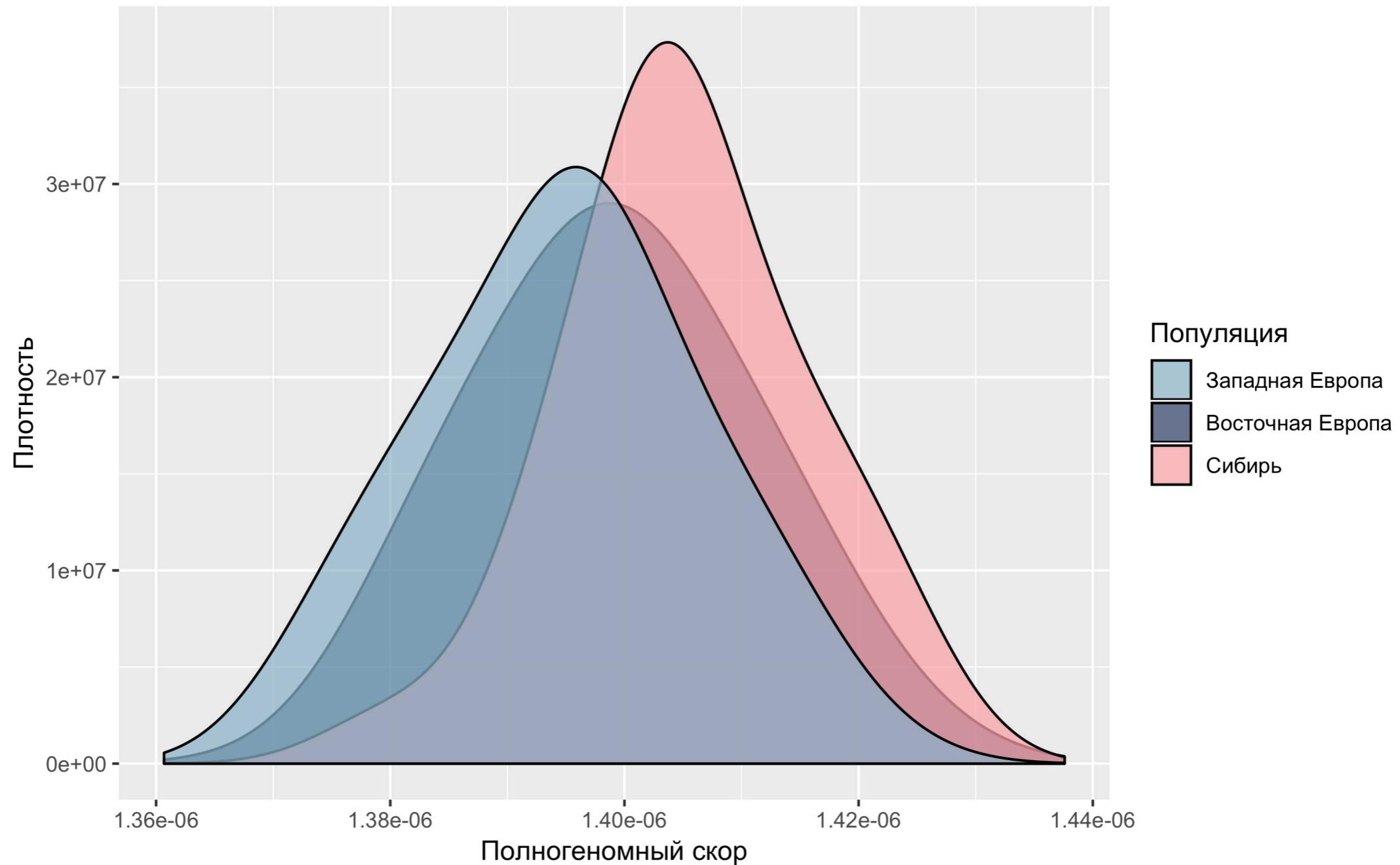
# Сравнение предсказательных моделей

Модель	Внешние факторы	Генетика + внешние факторы
Логистическая регрессия	69,6 % (3)	75,3 % (3,5)
Случайные леса	65,3% (3)	74,5 % (2)
Градиентный бустинг	67,2 % (2)	<b>75,8 %</b> <b>(3)</b>

## Вклад отдельных факторов



# Популяционные различия



# Thank you for your attention!



<https://www.facebook.com/alexrakitko>



<https://t.me/alexrakitko>

[rakitko@gmail.com](mailto:rakitko@gmail.com)

