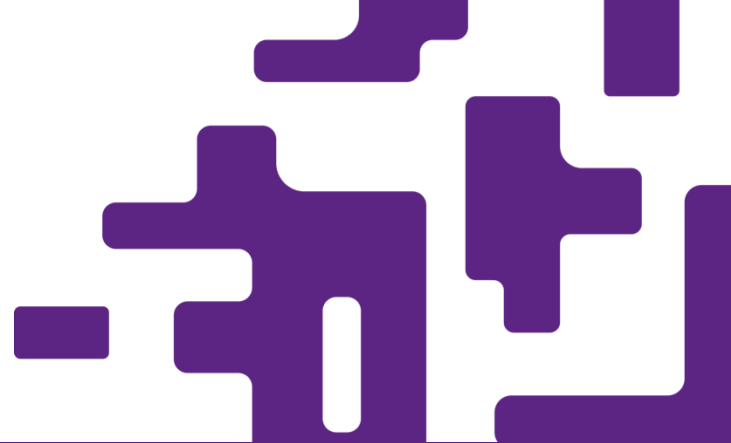




**NORMENT**

Norwegian Centre for  
Mental Disorders Research



# Mathematical models of the genetic architecture in complex human disorders

Oleksandr Frei

April 7<sup>th</sup> 2020

# Outline

- **Introduction**
  - NORMENT
  - My background
- **Genetics of Complex Traits**
  - Mendelian vs polygenic inheritance
  - Genome-wide association studies
  - Simple Additive Genetic Model
- **Modeling genetic architecture with MiXeR**
- **MOSTest – multivariate omnibus statistical test**



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Home

Research

About the centre

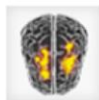
People

## Research topics



### Genetics

Identify rare genetic variants or expression variation to reveal "missing heritability".



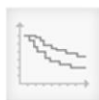
### Brain Imaging

Determine new brain imaging phenotypes linking genes and core clinical phenotypes.



### Antipsychotic Medication

Define new targets to optimize the ratio of beneficial vs. adverse effects of antipsychotics.



### Outcome Predictors

Using genetic and environmental factors to estimate illness course and outcome.



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NORMENT is a Centre of Excellence (CoE) funded by the Research Council of Norway.

Our main goal is to find answers to why some people develop severe mental illness.

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2004 – 2013



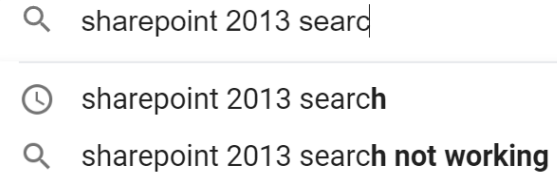
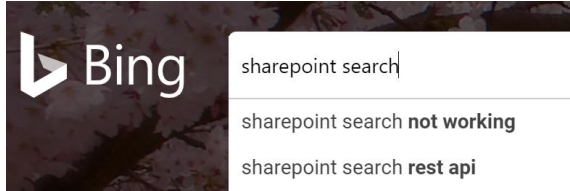
# My background

2004 – 2013



My background

2010 – 2013

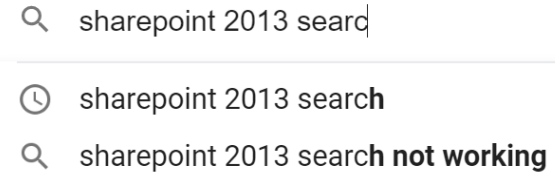
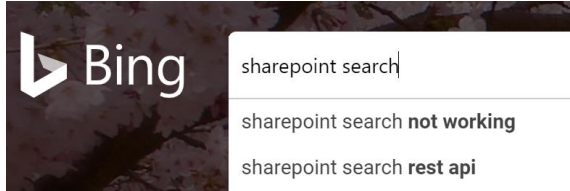


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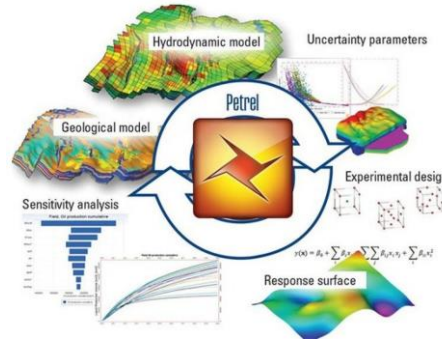
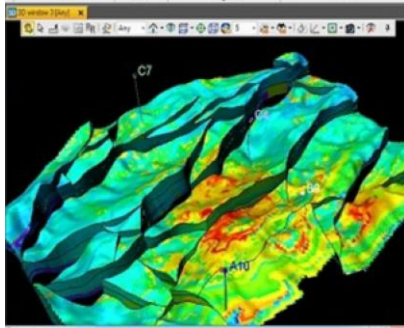


My background

2010 – 2013



2014 – 2016

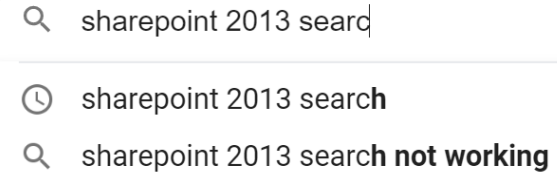
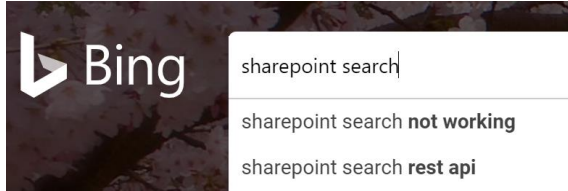


2004 – 2013

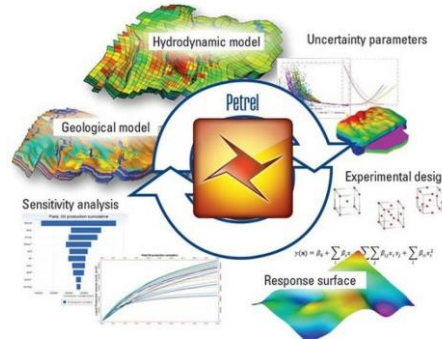
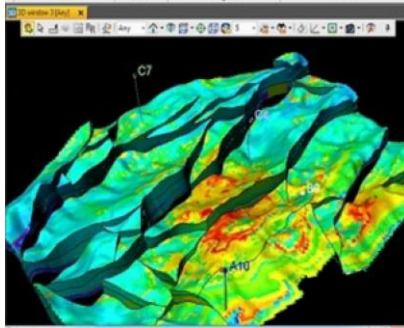


My background

2010 – 2013



2014 – 2016



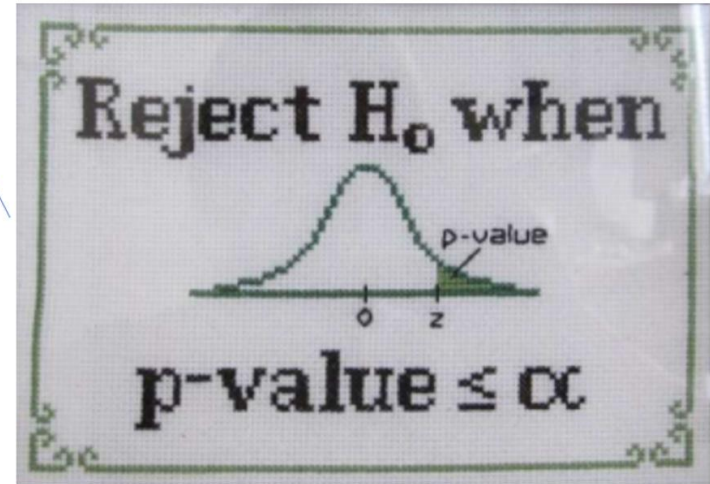
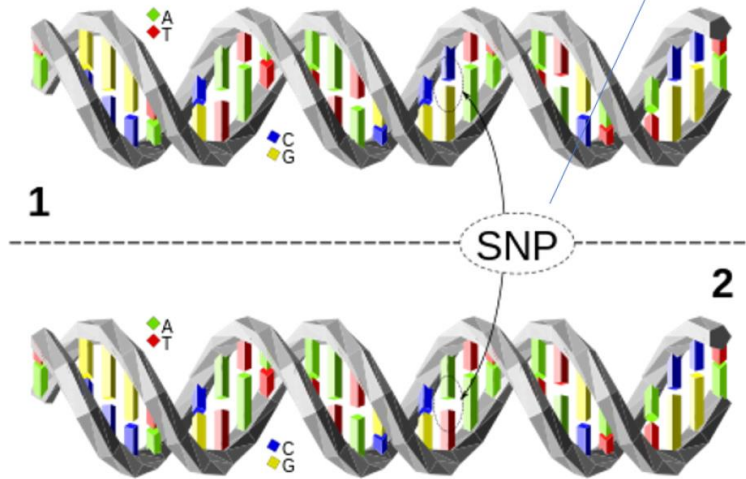
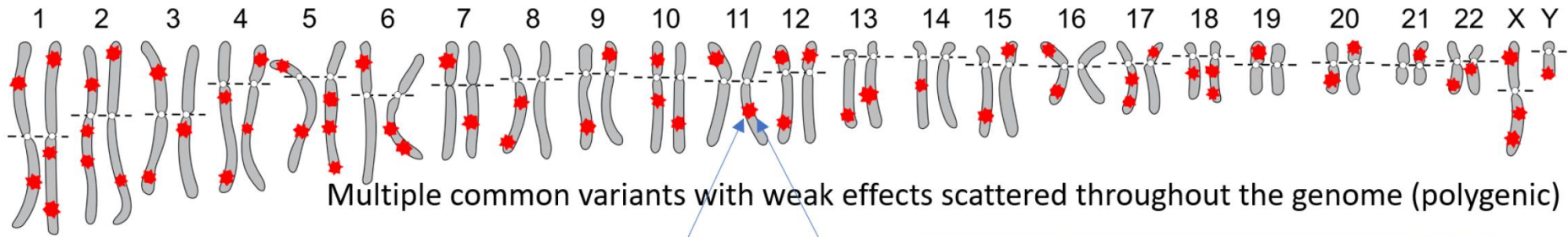
2016 - Today



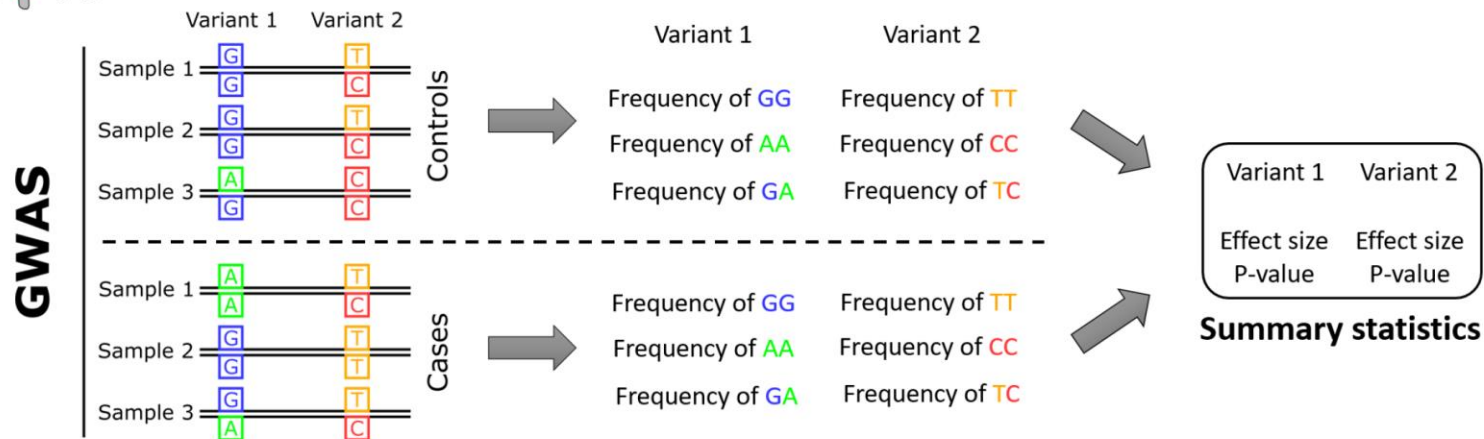
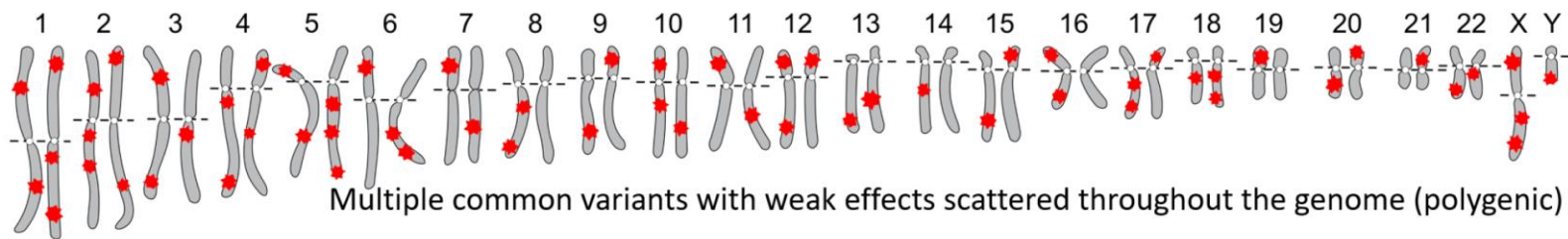
2013-2018  
<http://bigartm.org/>



# Complex polygenic traits, e.g. height







Think of the naïve bayes classifier

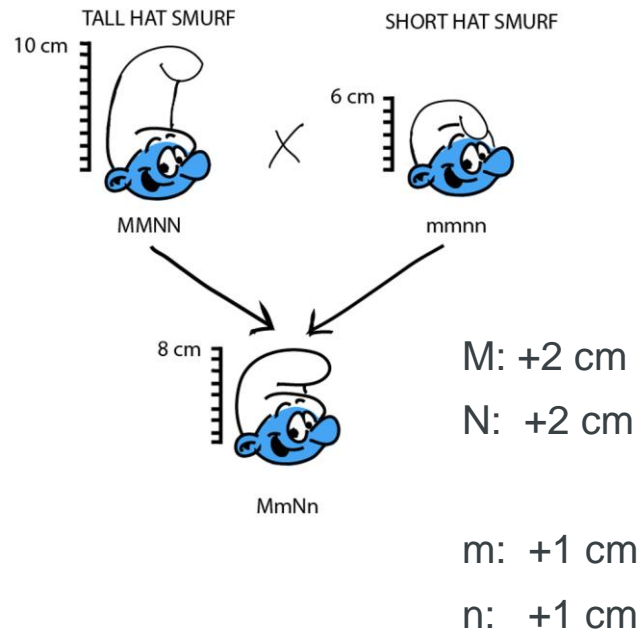
- genetic variants = features
- human trait = output

# Simple additive genetic model

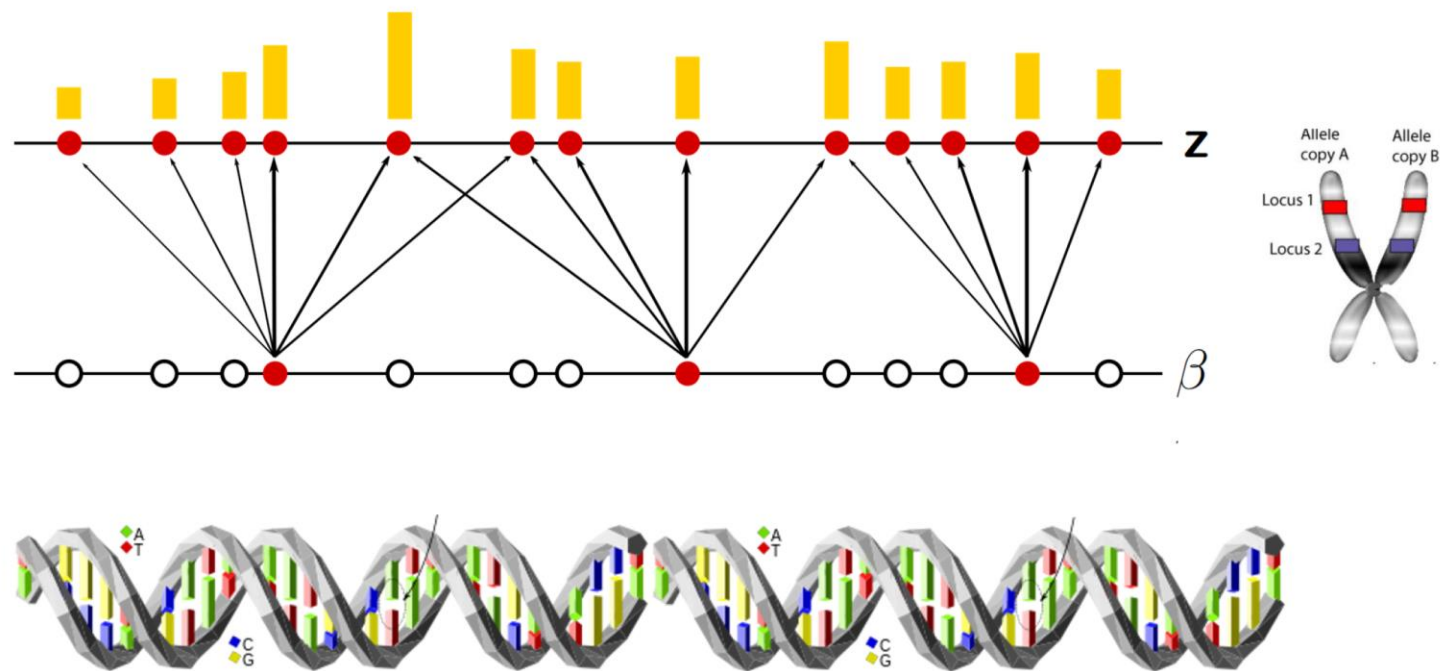
$$y_k = \sum_{i=1}^M g_{ki}\beta_i + e \leftrightarrow \mathbf{y} = \mathbf{G}\boldsymbol{\beta} + \mathbf{e}$$

where

- $N$  - the number of individuals in the dataset
- $M$  - the number of genetic variants
- $\mathbf{y}$  -  $N$ -vector, “phenotype” (e.g. human height)
- $\mathbf{G}$  -  $N \times M$ -matrix
- $\boldsymbol{\beta}$  -  $M$ -vector, genetic effects, random variables
- $\mathbf{e}$  - non-genetic effects, random variable
- $\mathbf{y}$ ,  $\mathbf{G}$  - known;  $\boldsymbol{\beta}$ ,  $\mathbf{e}$  - unknown



# LD: Correlation among genetic features



# Causal mixture model

$$\mathbf{y} = \mathbf{G}\beta + \mathbf{e}, \text{ or}$$

$$\mathbf{z} = \mathbf{A}\beta + \epsilon$$

MiXeR:

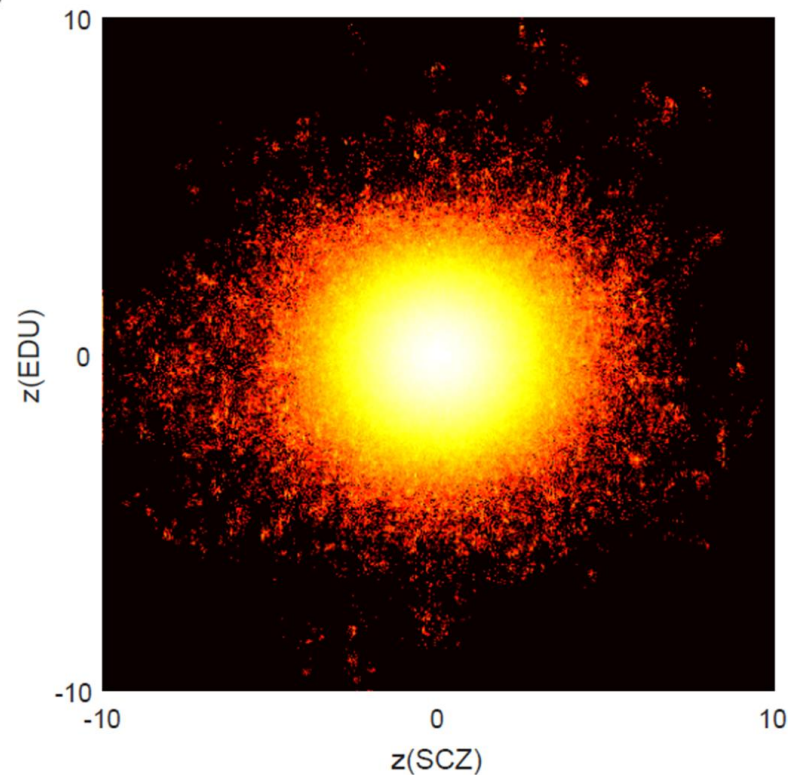
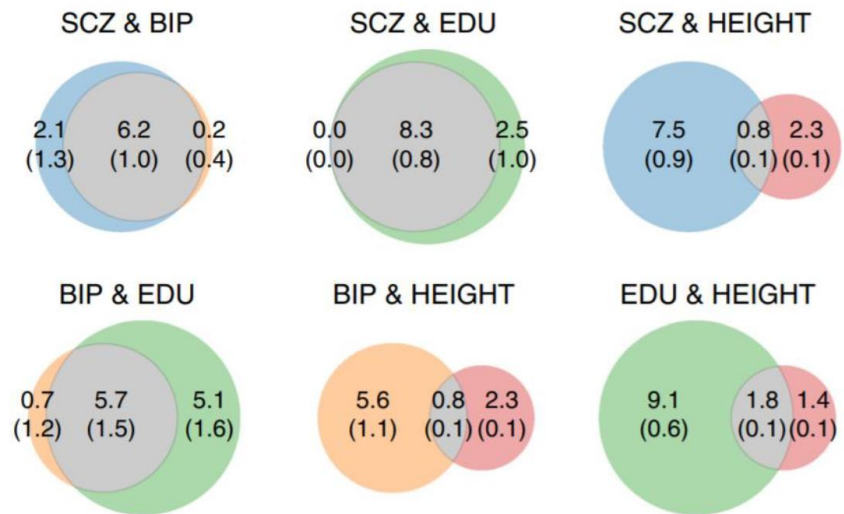
$$\beta_i \sim (1 - \pi_1)N(0, 0) + \pi_1 N(0, \sigma_\beta^2)$$

where

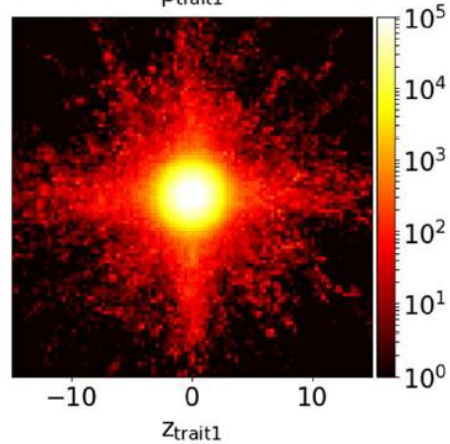
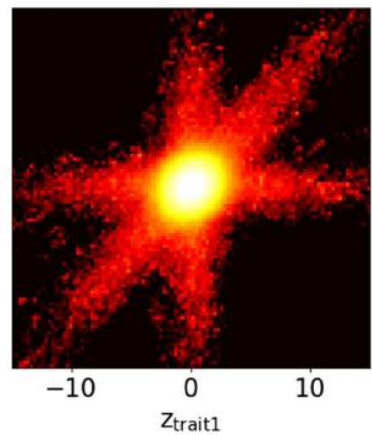
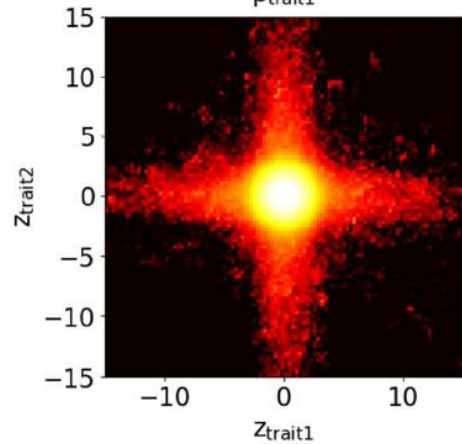
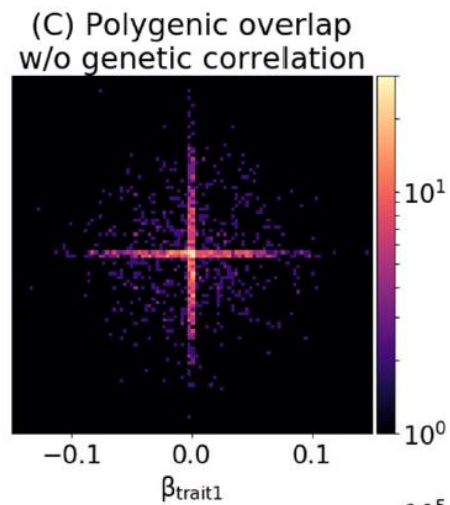
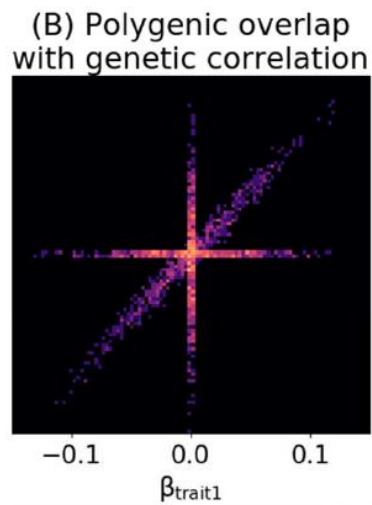
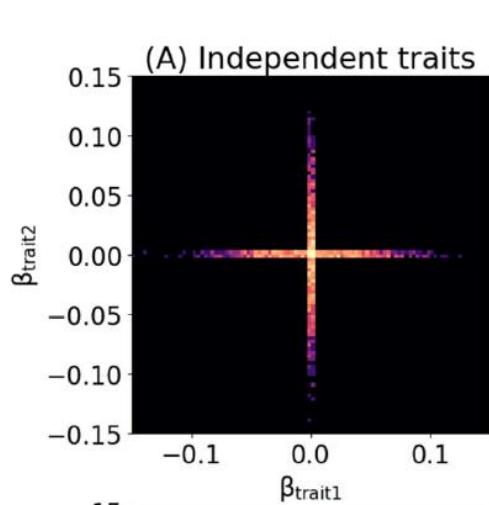
- $\pi_1$  - weight in the mixture
- $\sigma_\beta^2$  - variance
- $N(0, 0)$  - probability mass at zero

# Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation

Oleksandr Frei , Dominic Holland, Olav B. Smeland, Alexey A. Shadrin, Chun Chieh Fan, Steffen Maeland, Kevin S. O'Connell, Yunpeng Wang, Srdjan Djurovic, Wesley K. Thompson, Ole A. Andreassen & Anders M. Dale 

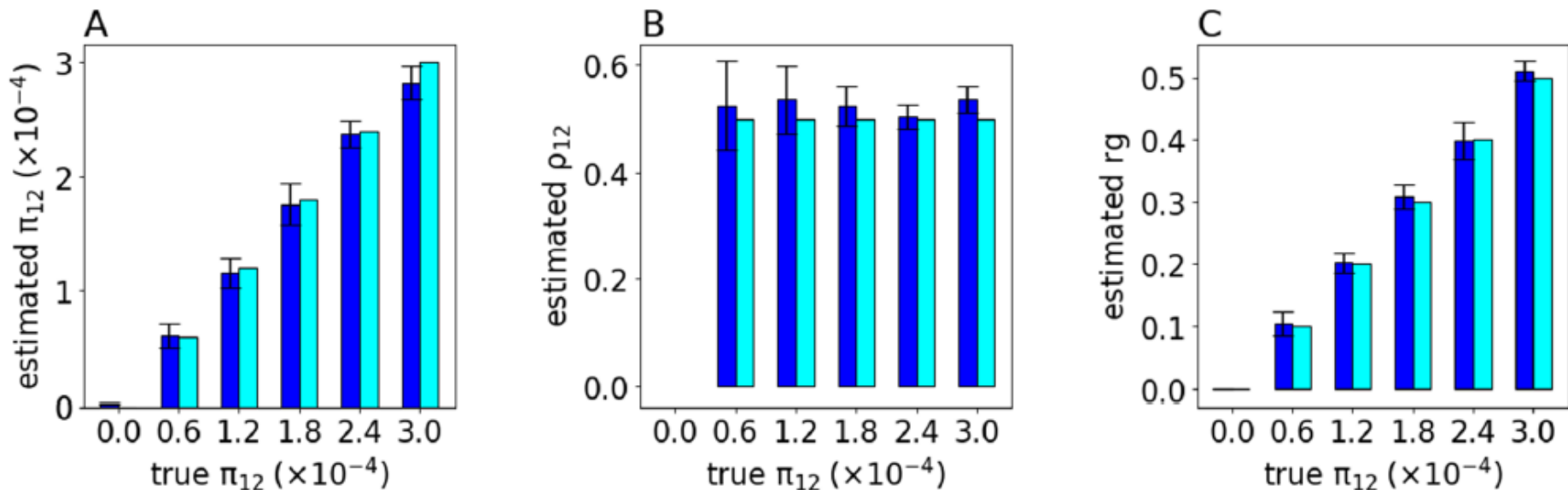


**Fig. 3** Venn diagrams of unique and shared polygenic components



Linkage Disequilibrium

# Simulations on synthetic data



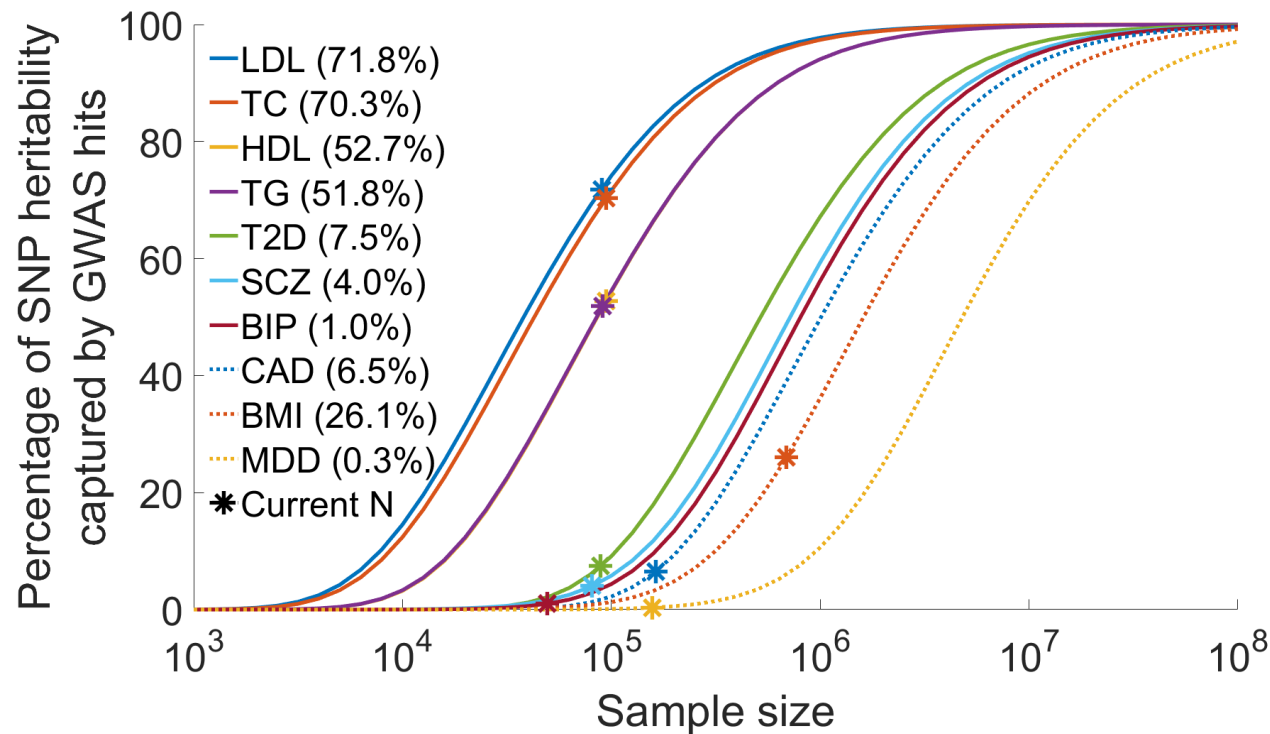
(A) Estimates of polygenic overlap

(B) Estimates of correlation of effect sizes in the shared component

(C) Estimates of genetic correlation

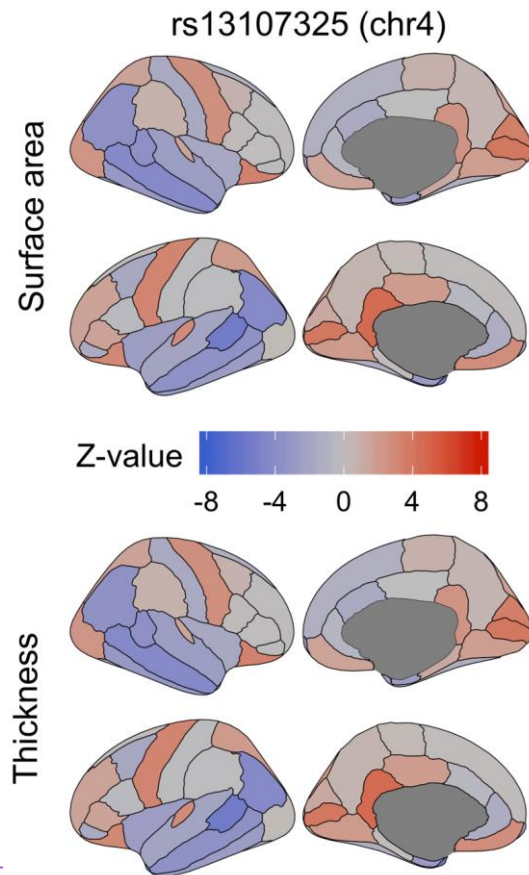
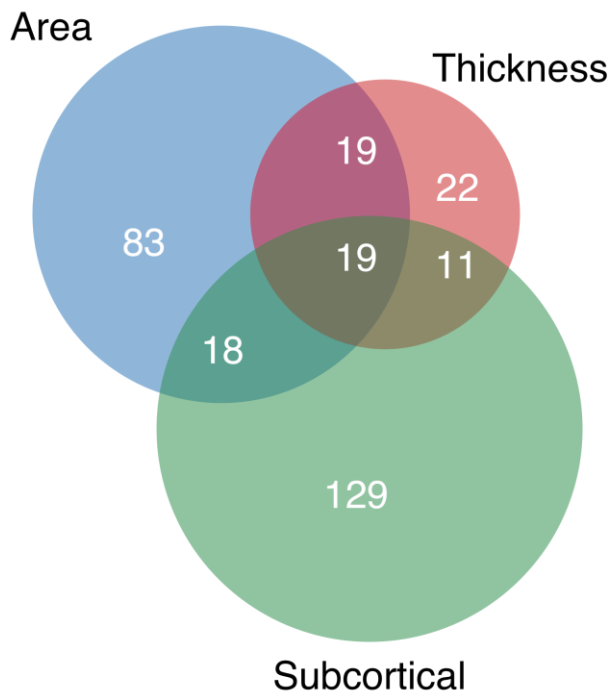
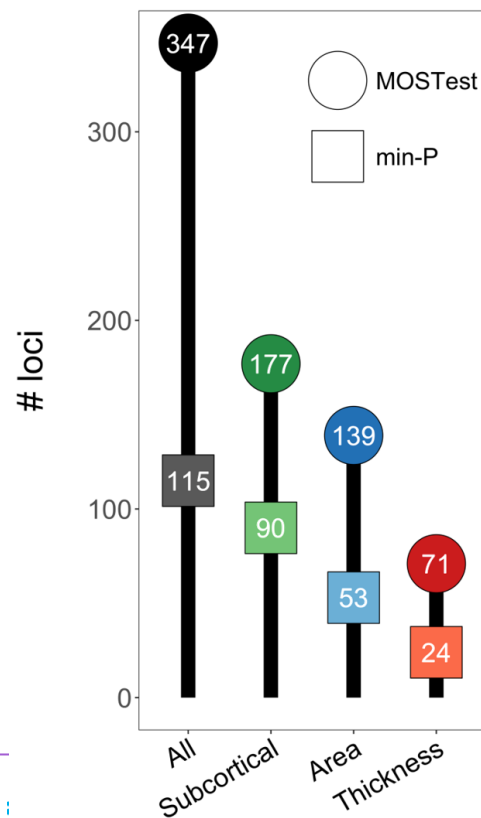


# Polygenicity affects power to discover loci in GWAS

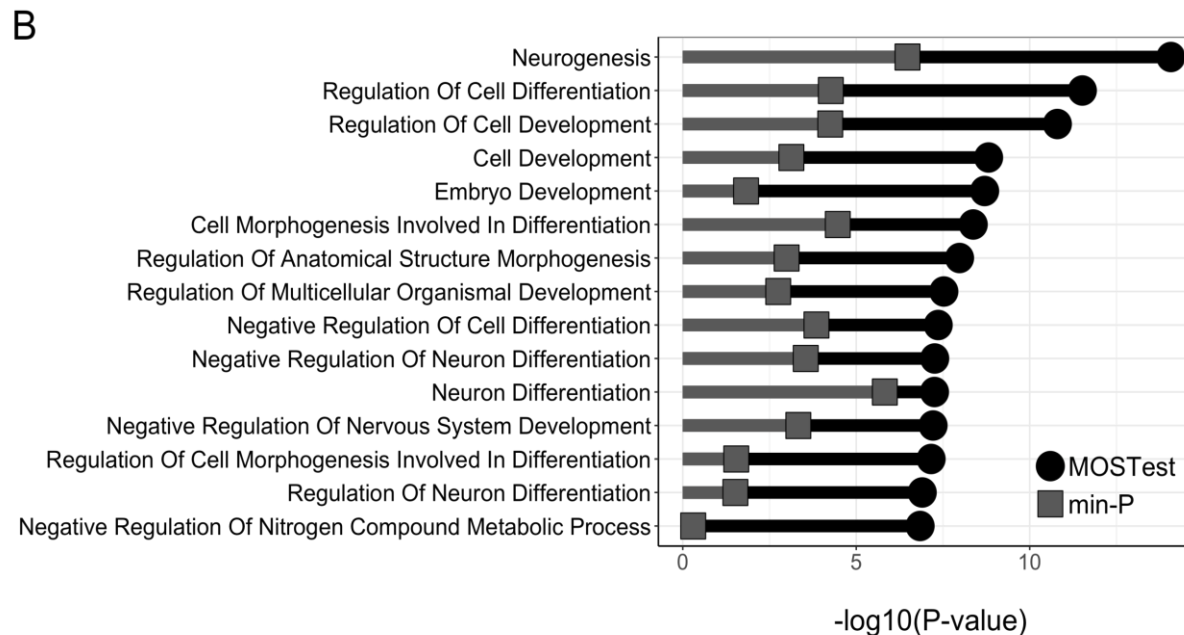
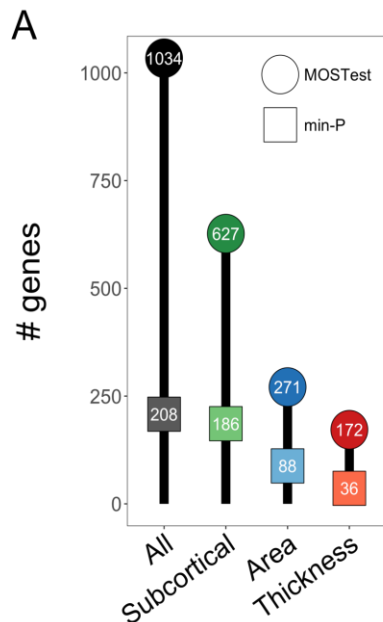




# MOSTest – increase discovery (Multivariate Omnibus Statistical Test)



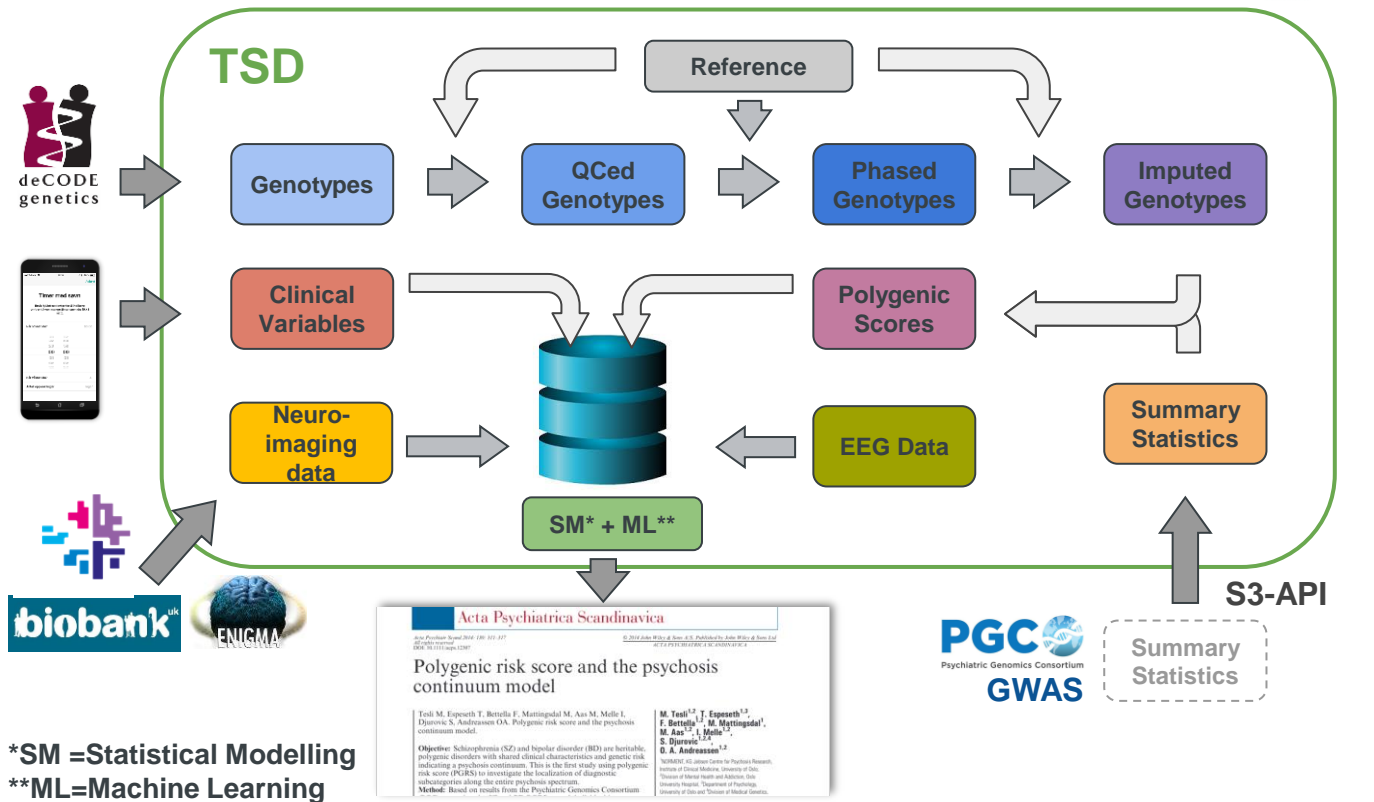
# Boost in #genes associated with regional brain morphology



# Comparison between tools

	<b>pleioFDR</b> github.com/precimed/pleiofdr	<b>MiXeR</b> github.com/precimed/mixer	<b>MOSTest</b> github.com/precimed/mostest
Input	GWAS sumstats for 2 traits + reference	GWAS sumstats for 2 traits + reference	Raw genotypes + N traits
Output	False Discovery Rate per SNP for each trait: condFDR and conjFDR	Genetic architecture: polygenicity, correlation and polygenic overlap	One P-value per SNP H0: none of the N traits are associated with the SNP
Sample overlap?	MUST NOT overlap	CAN overlap	MUST overlap (single cohort – multiple measures)
Tools that address similar questions	MTAG, pw-gwas, GenomicSEM	LDSR, HESS, GenomicSEM (cross-trait analysis)  BayesS, RSS, Genesis (causal mixture model)	MV-PLINK, TATES, MultiPHEN, MultiABEL, MANOVA

# The Big Data pipeline



\*SM =Statistical Modelling  
\*\*ML=Machine Learning

# Acknowledgement

## Study participants

### NORMENT part UiO

- Ole Andreassen
- Srdjan Djurovic
- Lars Westley
- Alexey Shadrin
- Francesco Bettella
- Kevin O'Connell
- Dennis van der Meer
- Tobias Kaufmann
- Olav B. Smeland

### UCSD (University of California in San Diego)

- Anders M. Dale
- Dominic Holland
- Wesley Thompson
- Chun Chieh Fan
- Shan Sundar

### Funding

- Research Council of Norway (#223273, #225989, #248778)
- South-East Norway Health Authority (#2016-064, #2017-004)
- KG Jebsen Stiftelsen (#SKGJ-Med-008)
- National Institutes of Health.





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# Thank you

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