NORMENT
Norwegian Centre for
Mental Disorders Research

Mathematical models of the genetic architecture in complex human disorders

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April 7th 2020

UiO : University of Oslo
Oslo University Hospital
UNIVERSITY OF BERGEN
Haukeland University Hospital
Norwegian Centre of Excellence
The Research Council of Norway

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**

Research topics

Genetics

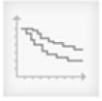
Identify rare genetic variants or expression variation to reveal "missing heritability".

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.

NORMENT

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.

→ Read more about NORMENT

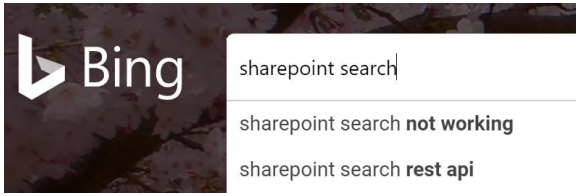
NORMENT in social media

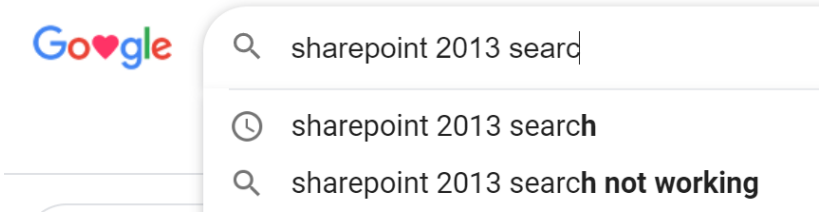
My background

2004 – 2013

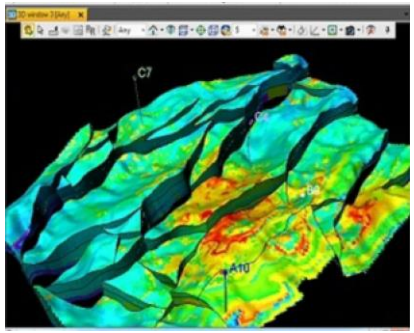
MIPT
MOSCOW INSTITUTE OF PHYSICS AND TECHNOLOGY

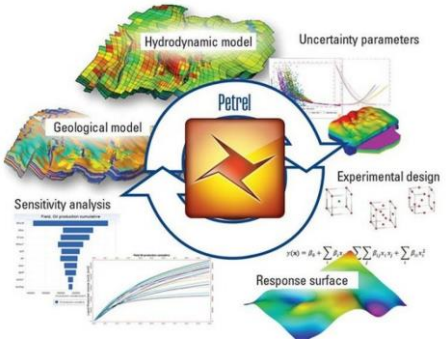
2010 – 2013

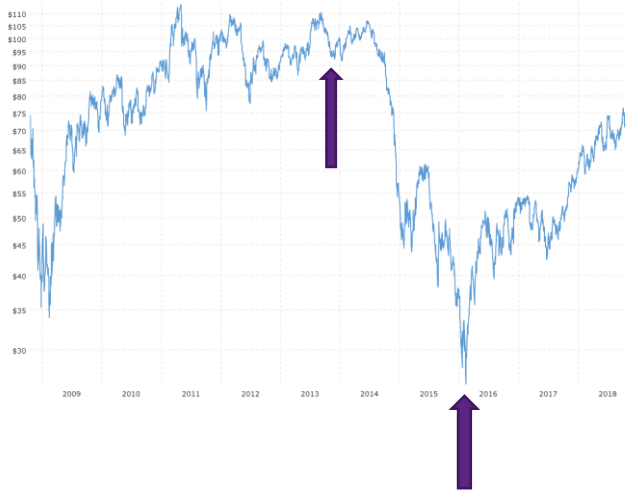




2014 – 2016







2016 - Today

2013-2018
http://bigartm.org/

BigARTM

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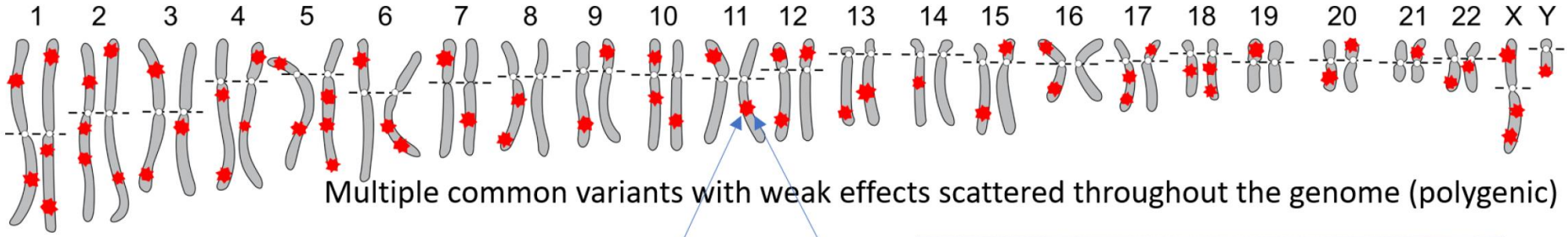
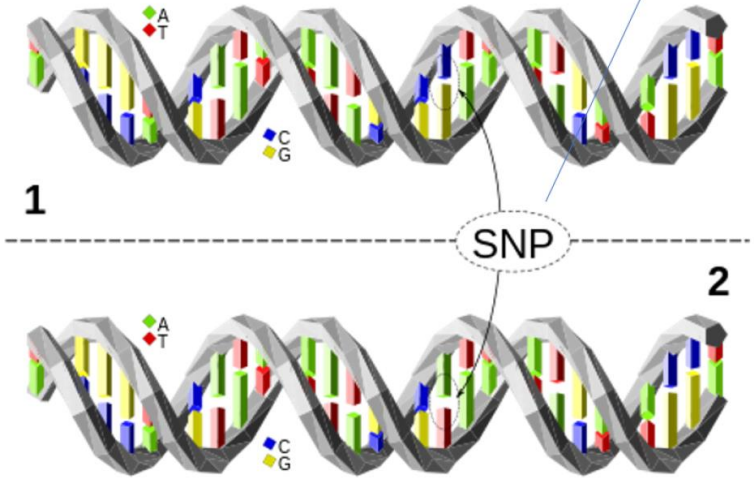
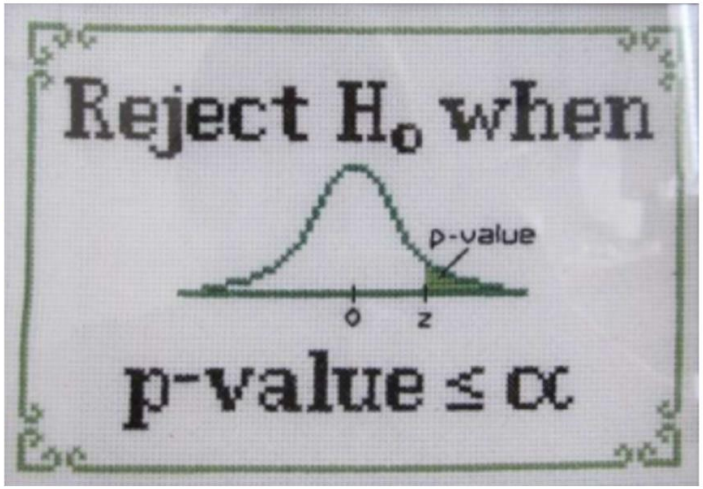
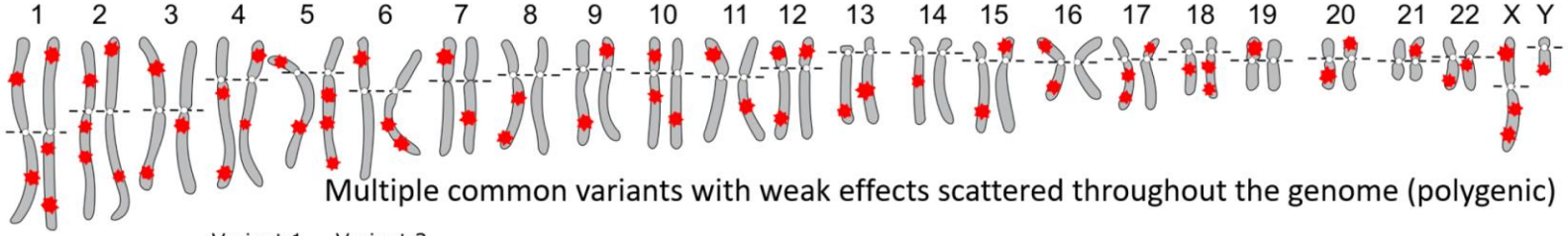
Complex polygenic traits, e.g. height



Multiple common variants with weak effects scattered throughout the genome (polygenic)







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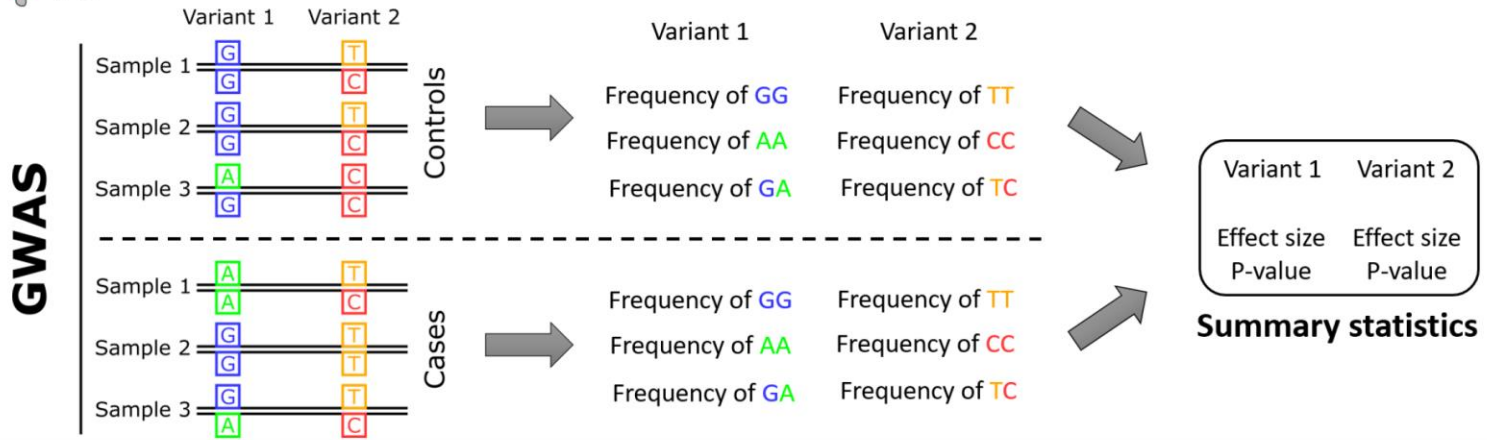


Think of the naïve bayes classifier

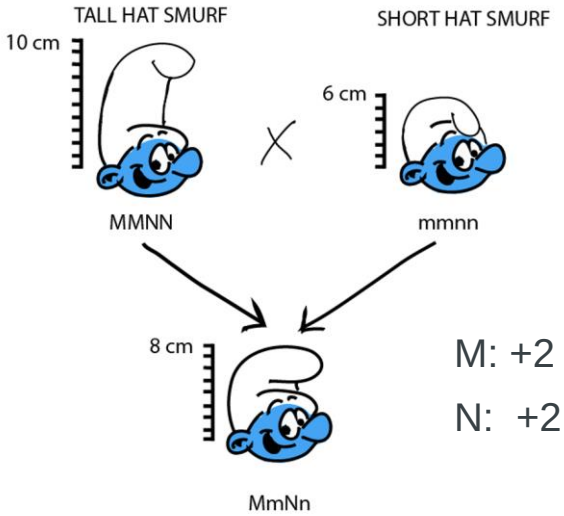
- genetic variants = features
- human trait = output

Simple additive genetic model

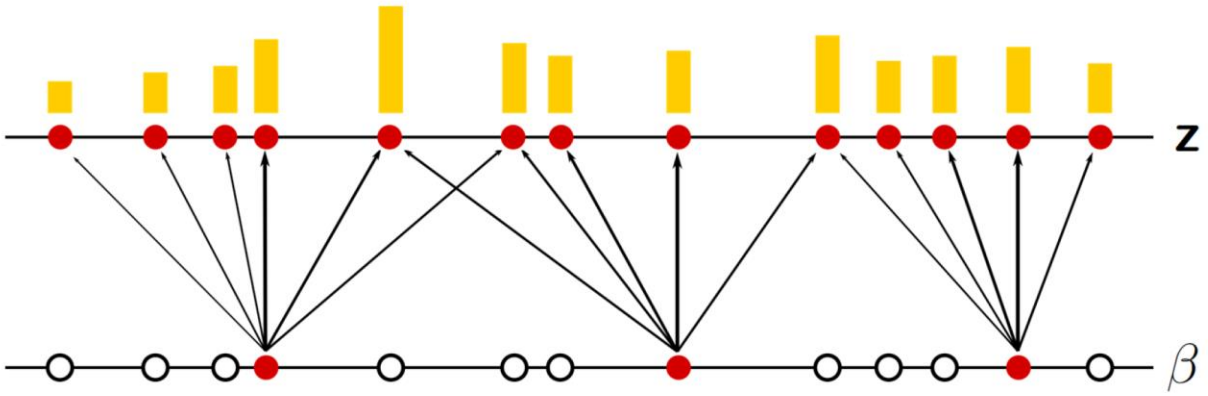
$$y_k = \sum_{i=1}^{M} g_{ki}\beta_i + e \quad \leftrightarrow \quad \mathbf{y} = G\beta + e$$

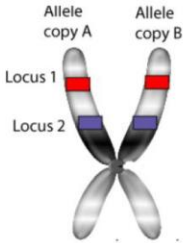
where

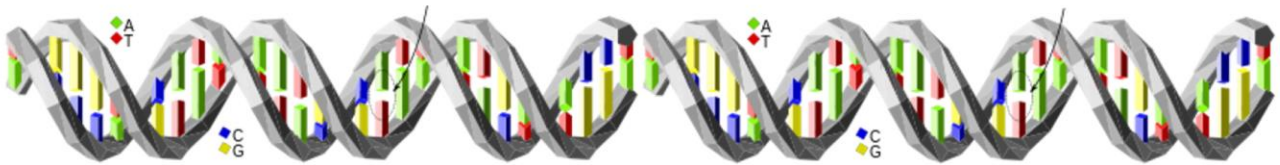
- N - the number of individuals in the dataset
- M - the number of genetic variants
- $\mathbf{y}$ - N-vector, "phenotype" (e.g. human height)
- G - NxM-matrix
- β - M-vector, genetic effects, random variables
- e - non-genetic effects, random variable
- $\mathbf{y}$, G - known; β, e - unknown



LD: Correlation among genetic features







Causal mixture model

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

MiXeR:

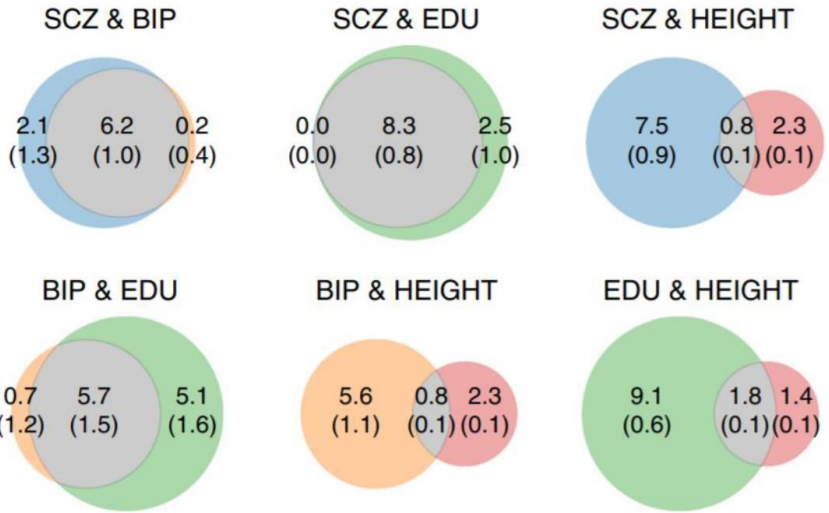
$$\beta_i \sim (1 - \pi_1)N(0, 0) + \pi_1 N(0, \sigma^2_\beta)$$

where

- π_1 - weight in the mixture
- σ^2_β - 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 ✉



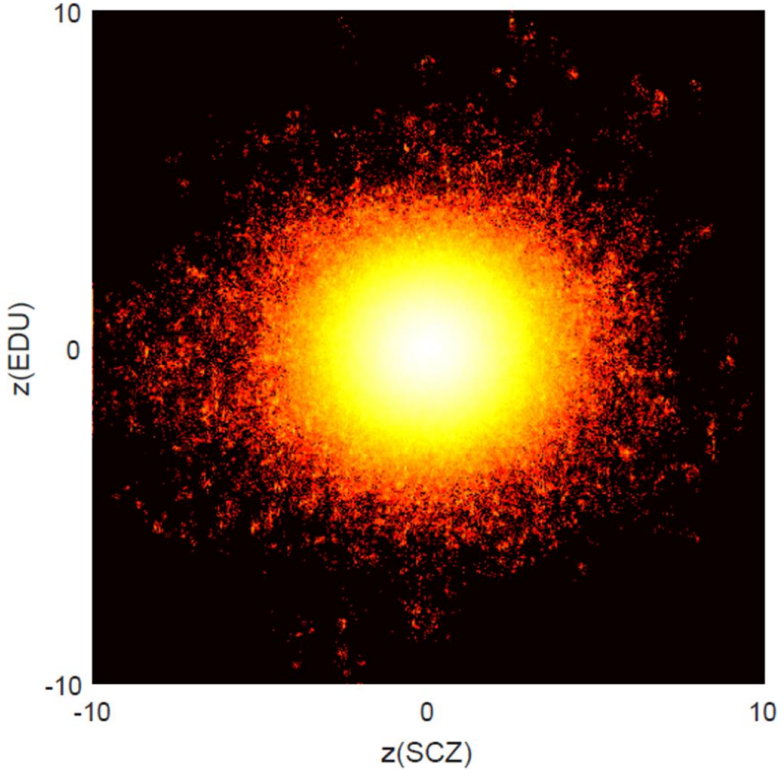
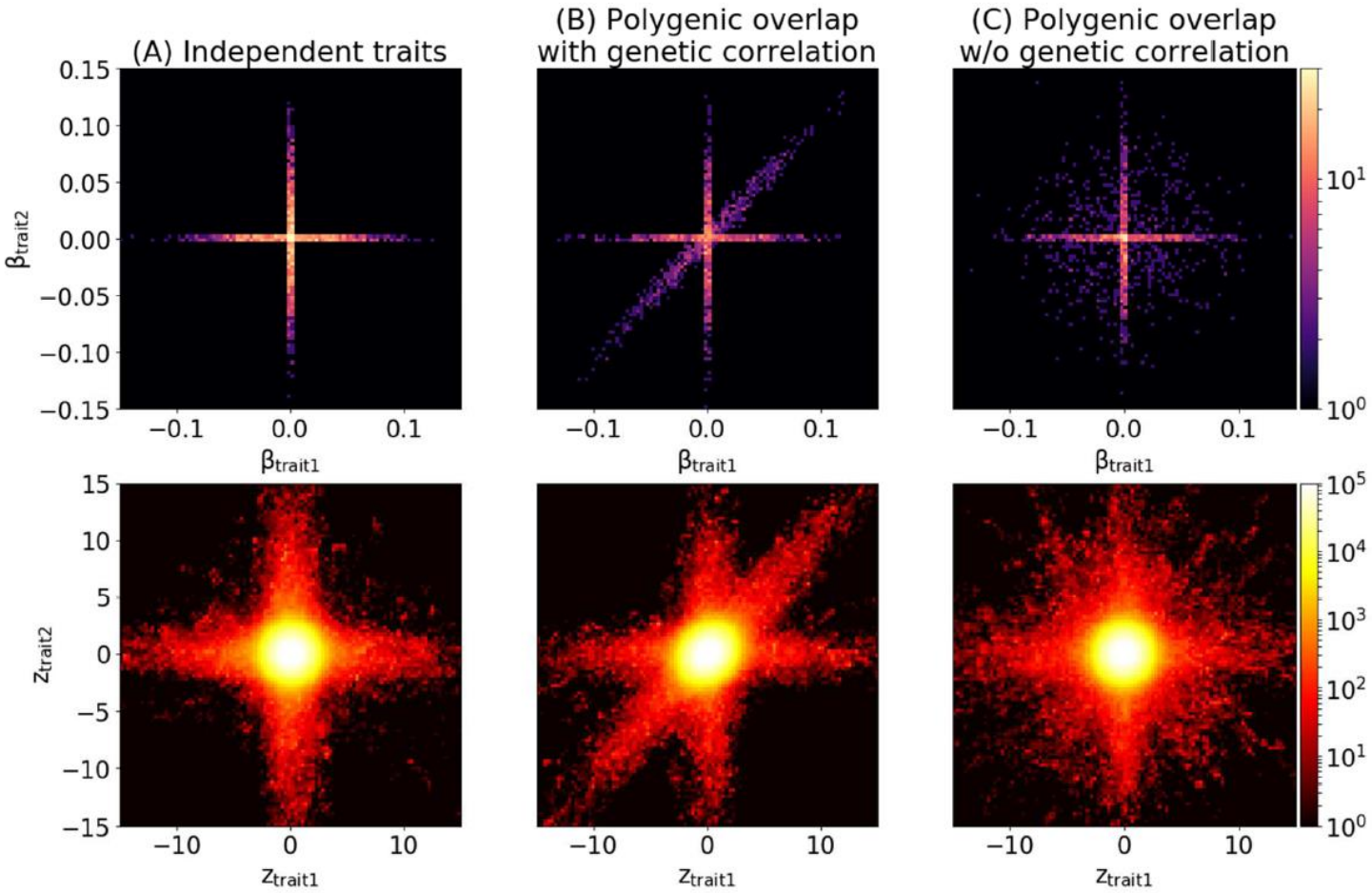
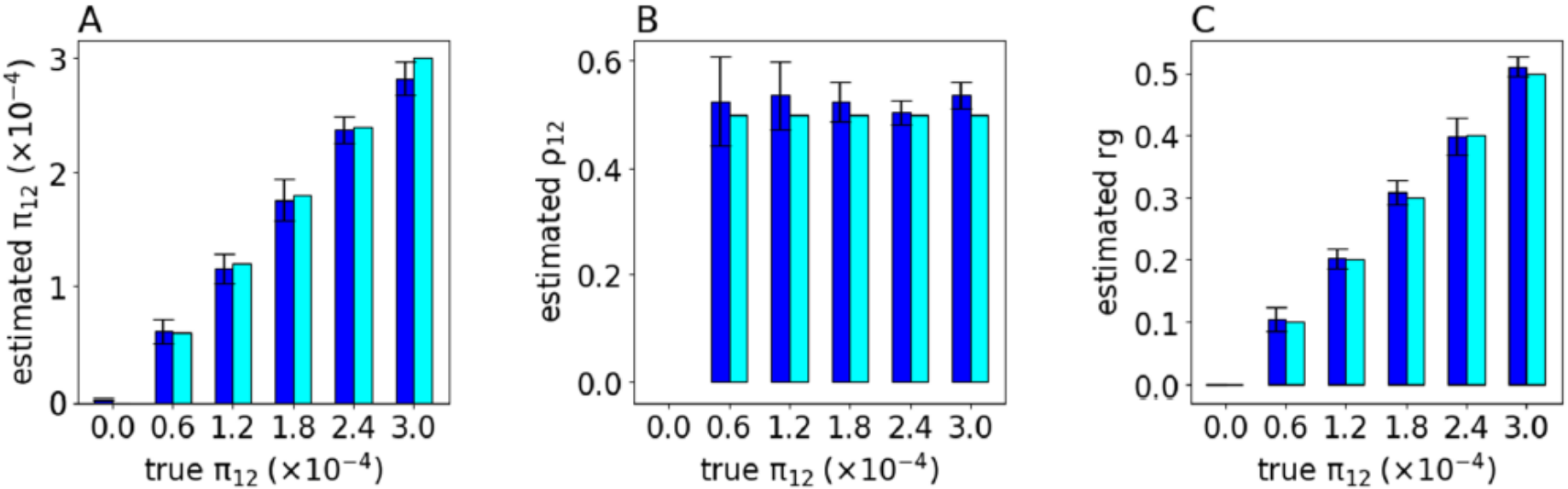


Fig. 3 Venn diagrams of unique and shared polygenic components


(A) Independent traits
(B) Polygenic overlap with genetic correlation
(C) Polygenic overlap w/o genetic correlation
β trait2
β trait1
z trait2
z trait1
Linkage Disequilibrium

Simulations on synthetic data

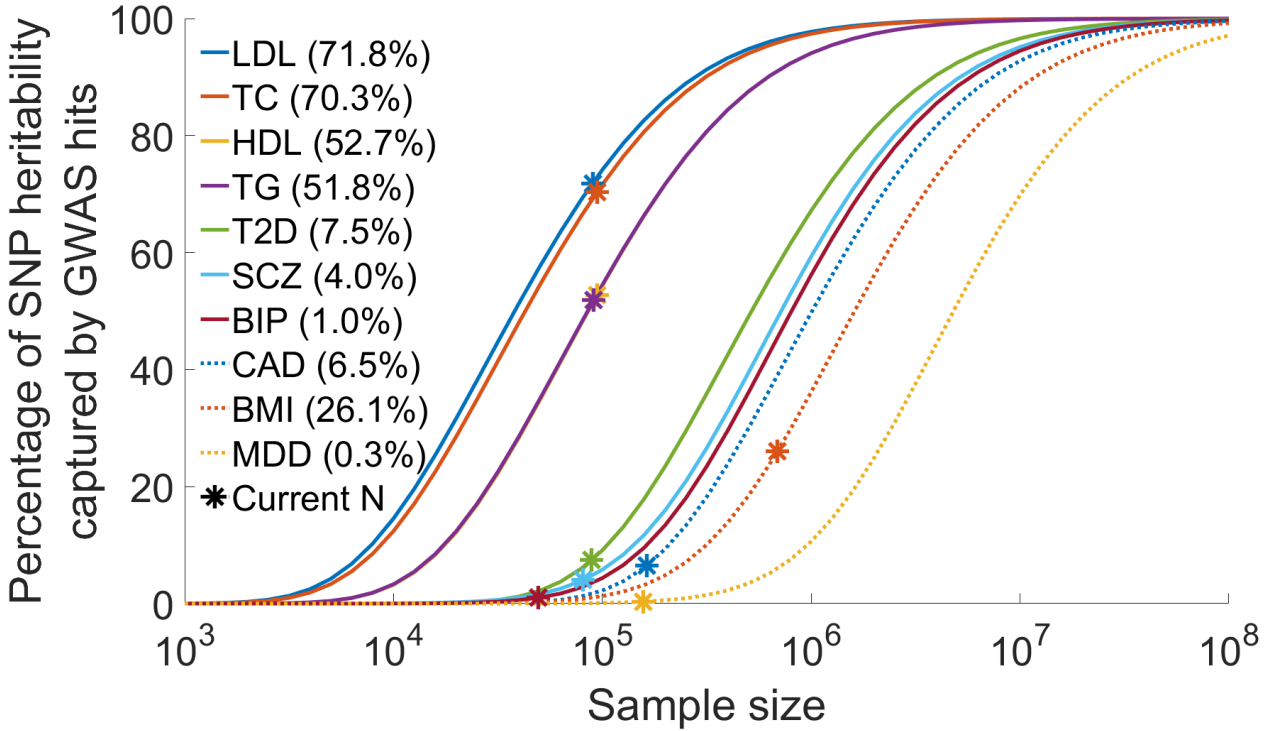


(A) Estimates of polygenic overlap

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

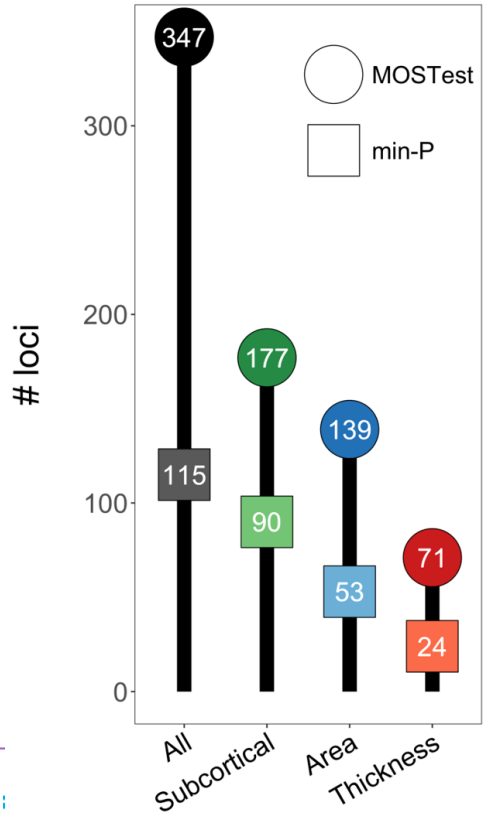
(C) Estimates of genetic correlation

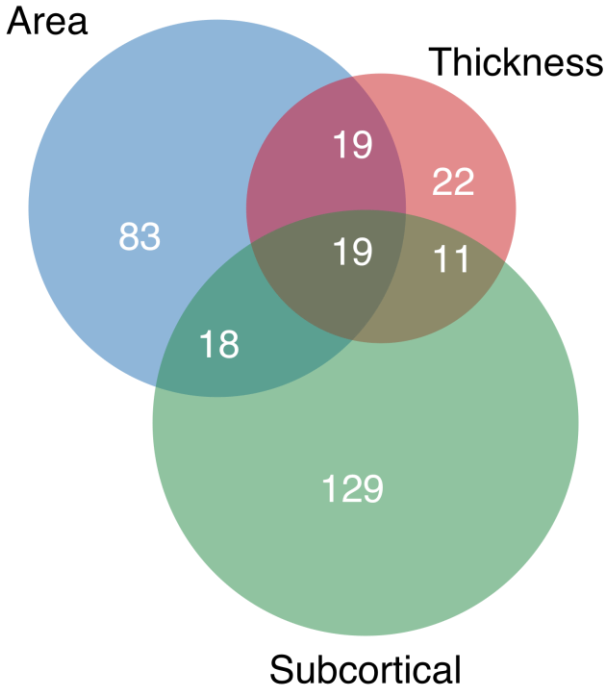
Polygenicity affects power to discover loci in GWAS

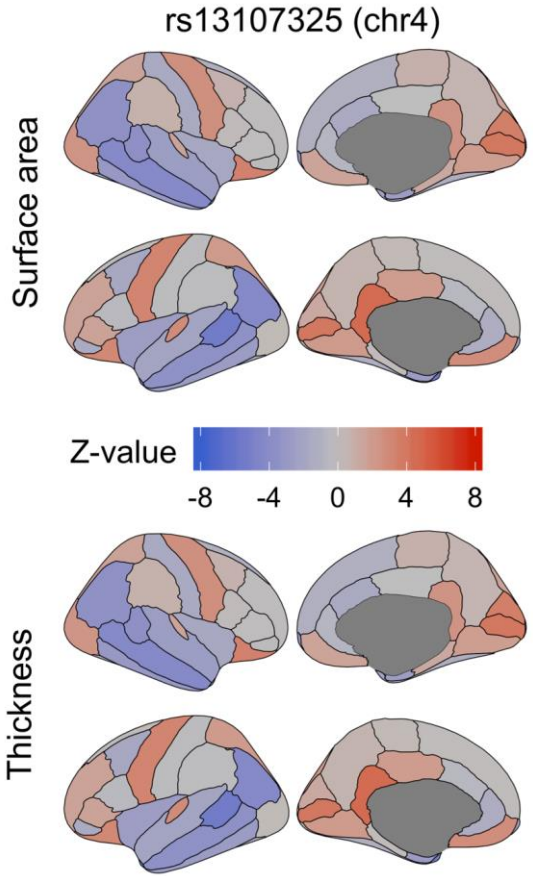


Holland et al. in review

MOSTest – increase discovery (Multivariate Omnibus Statistical Test)

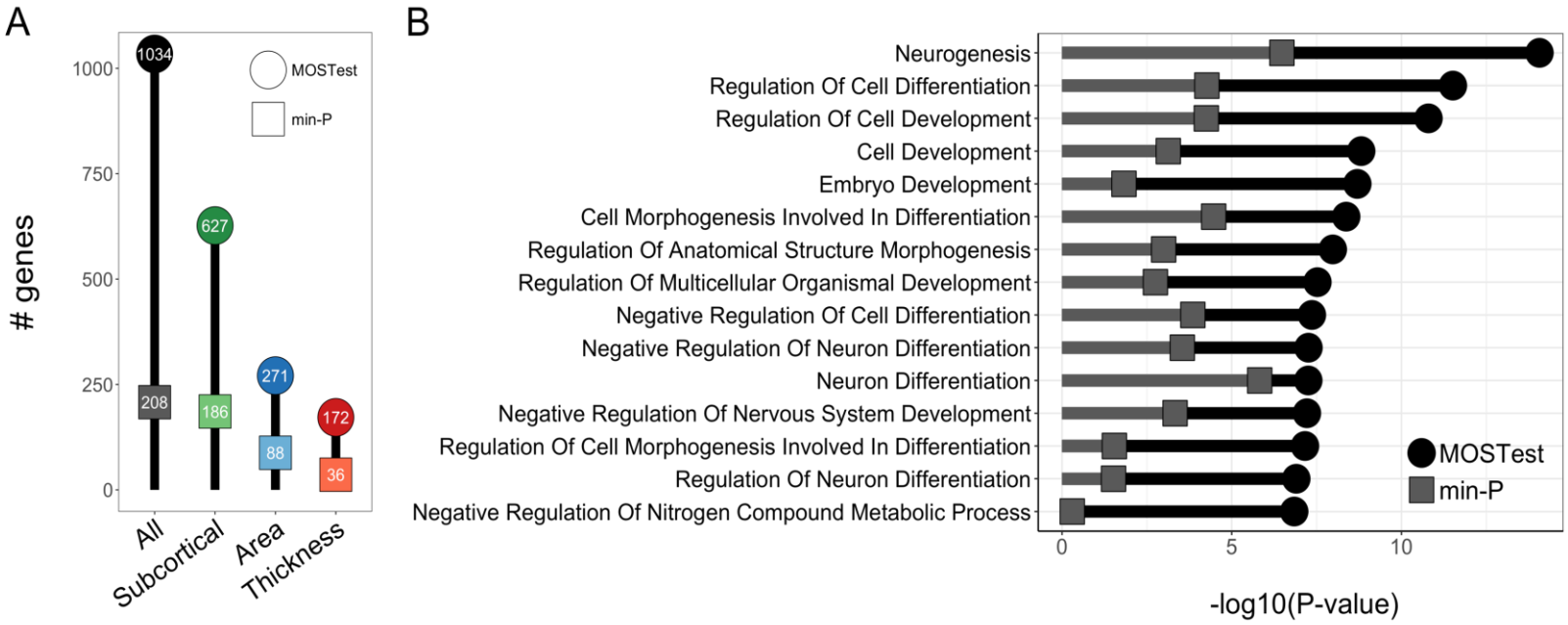






Vd Meer, Frei et al. in review

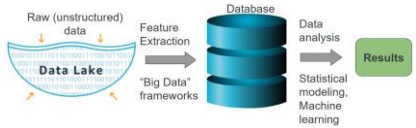
Boost in #genes associated with regional brain morphology



Comparison between tools

	pleioFDR **github.com/precimed/pleiofdr**	**MiXeR** **github.com/precimed/mixer**	**MOSTest** **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



TSD

deCODE genetics

Genotypes → QCed Genotypes → Phased Genotypes → Imputed Genotypes

Reference

Clinical Variables

Polygenic Scores

Neuro-imaging data

EEG Data

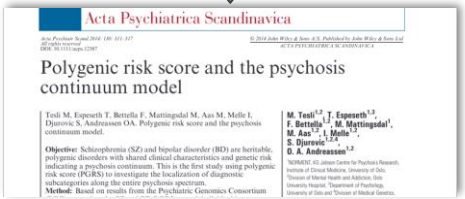
Summary Statistics

SM* + ML**

S3-API

biobank uk

ENIGMA


Acta Psychiatrica Scandinavica

Polygenic risk score and the psychosis continuum model

PGC Psychiatric Genomics Consortium

GWAS

Summary Statistics

*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

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- KG Jebsen Stiftelsen (#SKGJ-Med-008)
- National Institutes of Health.

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Thank you

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