Session 2: Leveraging New Methodologies to Interpret Genetic Data in Neurological and Psychiatric Disorders

Danielle Posthuma

d.posthuma@vu.nl

@dposthu

CTGlab – Dept. of Complex Trait Genetics, VU Amsterdam

From Molecular Insights to Patient Stratification for Neurological and Psychiatric Disorders

Oct 5, 2021

Outstanding challenges for GWAS

- Increase diversity: we need more diverse samples, including non-western, non-white populations
- Refine phenotypes: we need more in-depth phenotyping
- Understand pleiotropy and (causal) relationships between phenotypes
- Translate GWAS findings into mechanistic insight

Outstanding challenges for GWAS

- Increase diversity: we need more diverse samples, including non-western, non-white populations
- Refine phenotypes: we need more in-depth phenotyping
- Understand pleiotropy and (causal) relationships between phenotypes
- Translate GWAS findings into mechanistic insight

Translate GWAS findings into mechanistic insight

Challenges:

- Correlation between variants – significant association P-values are distributed over **blocks of correlated genetic variants**: actual causal variant is unclear

Solution: - **functional annotation** (functional variants more likely to be causal than non-functional ones, e.g. tools FUMA, VEP, ANNOVAR)

- **statistical fine-mapping** (the known correlation structure can be modeled against the observed pattern of association values to pinpoint the most likely causal SNPs, can be integrated with functional information (e.g. tools FINEMAP, PAINTOR)

- **local genetic correlation analyses** with molecular traits, e.g eQTLS (incl scRNA), splicing variants etc. Using e..g. LAVA, SUPERgnova, rhoHESS

- Most neuropsychiatric traits are **polygenic**: many genetic variants of small effect, a single genetic variant, even if it is known to be causal, is usually not informative for biology

Solution: look for **convergence** in biological pathways, shared cellular or synaptic function, co-localization, co-expression in tissue or cell types (e.g. tools MAGMA, Ldscore regression, DEPICT)

BRAINSCAPES

A Roadmap from Neurogenetics to Neurobiology

- NWO Gravitation proposal 19.6M€, 2020-2030
- Goal: "… *gain insight into the molecular and cellular basis of complex brain disorders, by closely connecting genetics to neurobiology, facilitating new experimental approaches, and enabling the design of novel treatment strategies*"

Danielle Posthuma - PI
Genetics of Brain Disorders (PI)

Huib Mansvelder
Neurophysiology

Guus Smit
Neurobiology

Jeroen Pasterkamp
Molecular Neurobiology

Elly Hol
Cell Biology

Boudewijn Lelieveldt
Computational Biology

https://brainscapes.nl @BRAINSCAPES1

Brainscapes Rationale

- Computational: Align results from large genetic discovery studies with genetic expression maps of cell types, thereby implicating cell types in disease

- Wet-lab functional experiments: Investigate the role of these **cell types** in disease using the latest neurobiological techniques at single cell resolution

Tools from my lab that aid in interpreting GWAS results

Kyoko Watanabe

Article | Open Access | Published: 28 November 2017

Functional mapping and annotation of genetic associations with FUMA

Kyoko Watanabe, Erdogan Taskesen, Arjen van Bochoven & Danielle Posthuma

Nature Communications **8**, Article number: 1826 (2017) | Cite this article

17k Accesses | **24** Altmetric | Metrics

- *FUMA: For functional annotations, gene-set analyses, visualizations*
- https://fuma.ctglab.nl/
- 6308 current users

Christiaan de Leeuw

PLOS COMPUTATIONAL BIOLOGY

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

MAGMA: Generalized (

Christiaan A. de Leeuw, Joris M. Mooij, Tom

Published: April 17, 2015 • https://doi.org/10.13

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-06022-6 OPEN

Conditional and interaction gene-set analysis reveals novel functional pathways for blood pressure

Christiaan A. de Leeuw[1], Sven Stringer[1], Ilona A. Dekkers[2], Tom Heskes[3] & Danielle Posthuma[1,4]

- *MAGMA: For (conditional) gene-set analyses*
- https://ctg.cncr.nl/software/magma

Josefin Werme

LAVA: An integrated framework for local genetic correlation analysis

J. Werme, S. van der Sluis, D. Posthuma, C. A. de Leeuw

doi: https://doi.org/10.1101/2020.12.31.424652

In press, Nat Genet

- *LAVA: For local genetic correlations*
- https://ctg.cncr.nl/software/lava

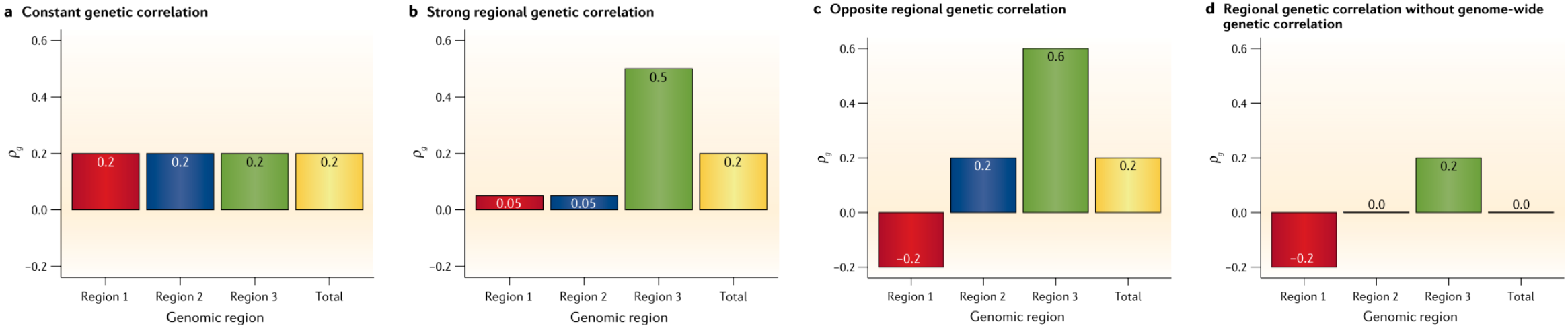
scRNA implementation in FUMA using MAGMA pipeline

- Genetic expression maps of the brain at single cell resolution can be used to map GWAS results more precisely on to cell types
- FUMA now includes cell type enrichment analyses based on GWAS results and 43 publicly available scRNA datasets

Currently working on:

- Adding novel scRNA resources
- Improving statistical methods to determine cell type enrichment

LAVA: Genetic correlation (rg) | Global vs local



van Rheenen et al. (2019), Nat. Rev. Genet.

Existing local r_g methods:

Rho-Hess (Shi, et al., 2016); **SUPERGNOVA** (Zhang et al., 2020); **LOGODetect** (Guo et al., 2019)

Local rg | Overview LAVA

Local **A**nalysis of (co)**V**ariant **A**ssociation

Features / implementation

- R package
- Input: GWAS summary statistics
- Flexible locus definition
- Binary and continuous phenotypes
- Deals with sample overlap
- Bi- and multivariate

Three step procedure

1. **Univariate test**

   Confirm local h^2

2. **Bivariate test**

   Pairwise local r_g

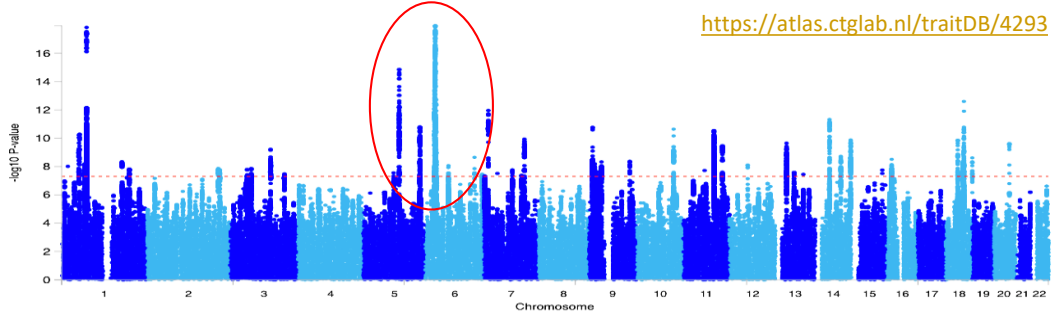
3. **Multivariate test(s)**

   Conditional local r_g

   - Partial cor: **X ~ Y | Z**
   - Mult. reg: **Y ~ X1 + X2 + X3**

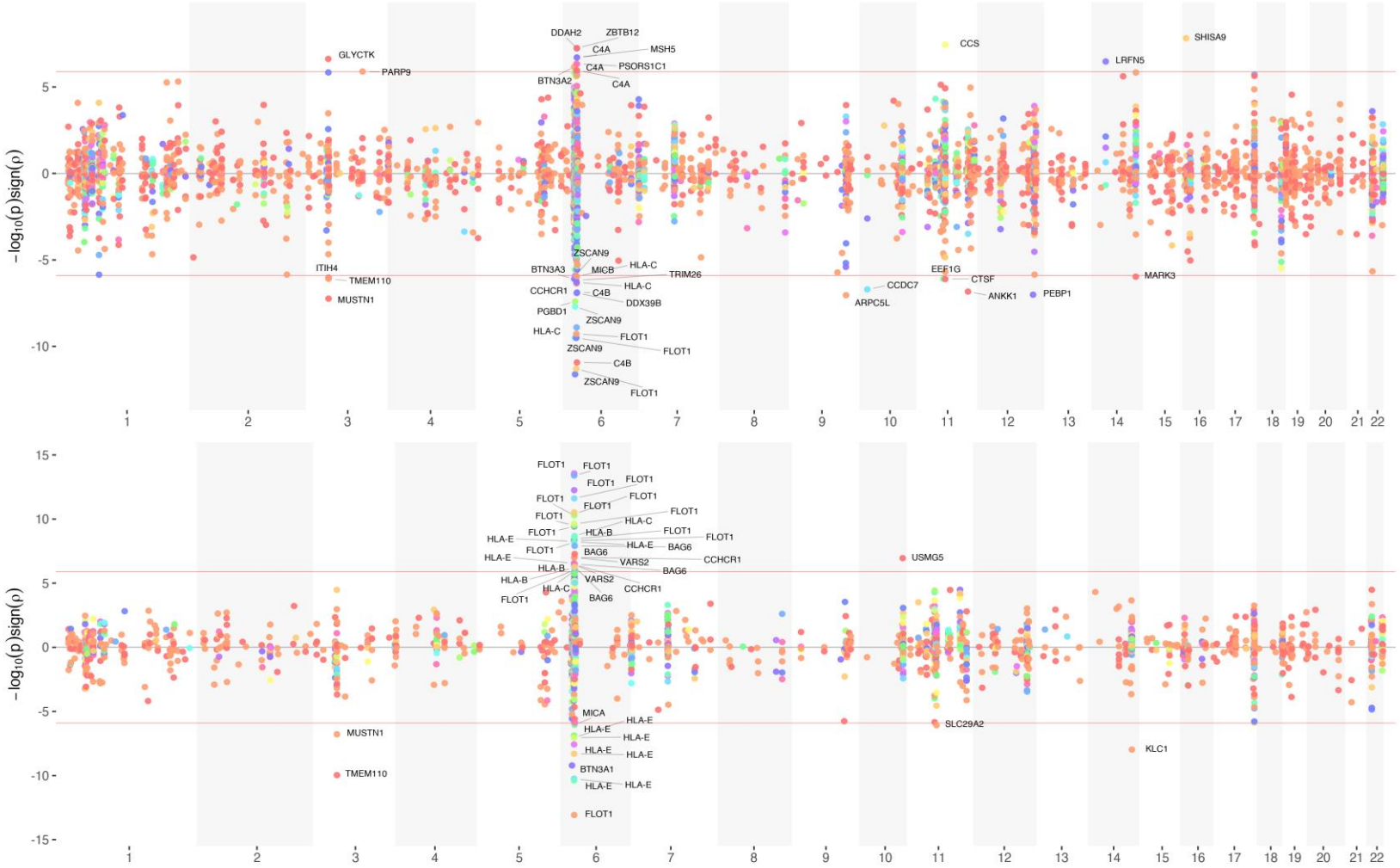
Bivariate LAVA of Depression ~ Expression & splicing

https://atlas.ctglab.nl/traitDB/4293



Expression

Splicing



Tissue

- Adrenal gland
- Amygdala
- Anterior cingulate cortex
- Caudate
- Cerebellar hemisphere
- Cerebellum
- Cortex
- Frontal cortex
- Hippocampus
- Hypothalamus
- Nucleus accumbens
- Putamen
- Spinal cord
- Substantia nigra
- EBV-transformed lymphocytes
- Pituitary
- Thyroid
- Whole blood

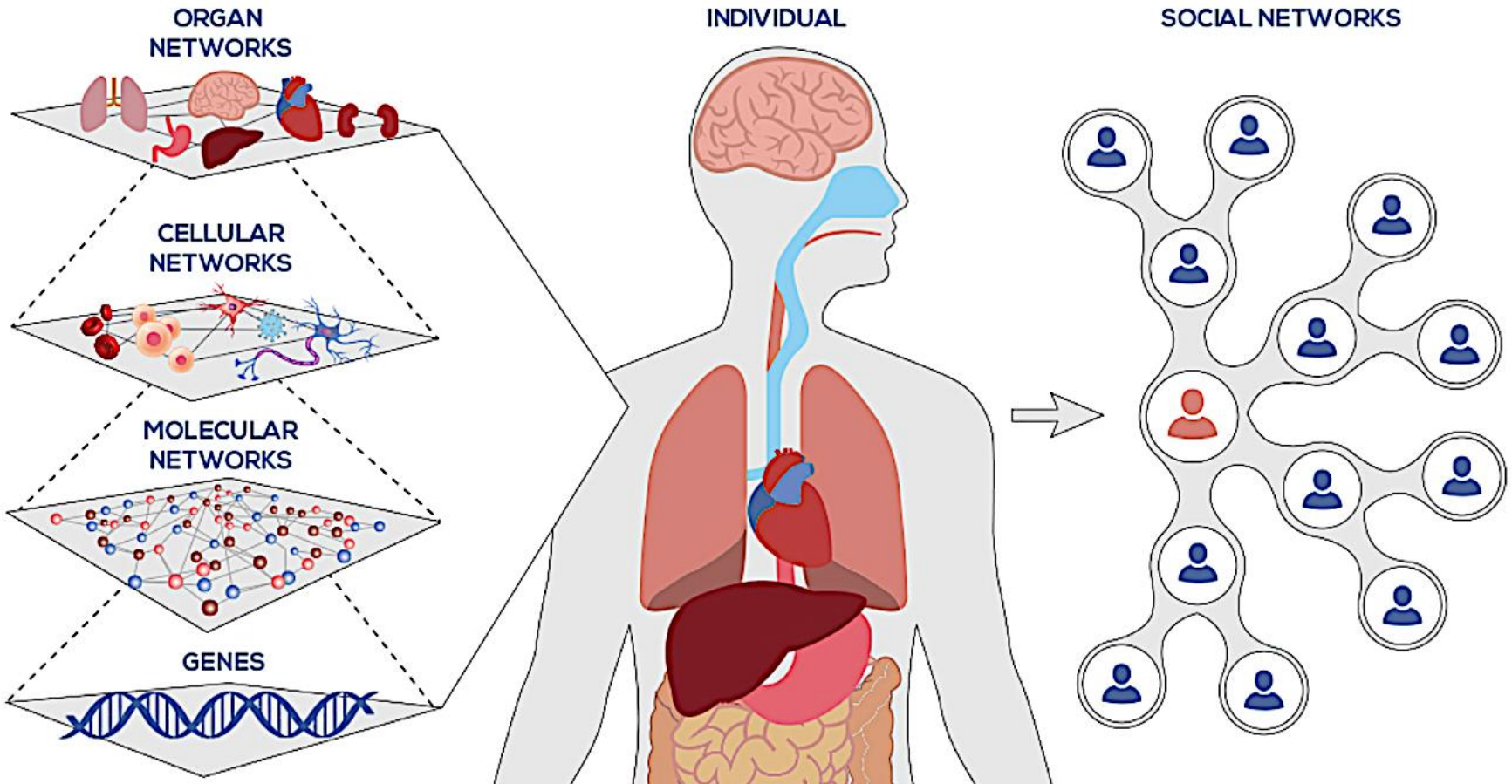
In sum

- Working on addressing polygenicity and looking for convergence of genetic signal from GWAS, by leveraging large scale mapping efforts

- In close collaboration with neuroscientists to facilitate translation of GWAS successes into mechanistic disease insight

Thanks!

Systems biology Approach



https://isbscience.org/about/what-is-systems-biology/