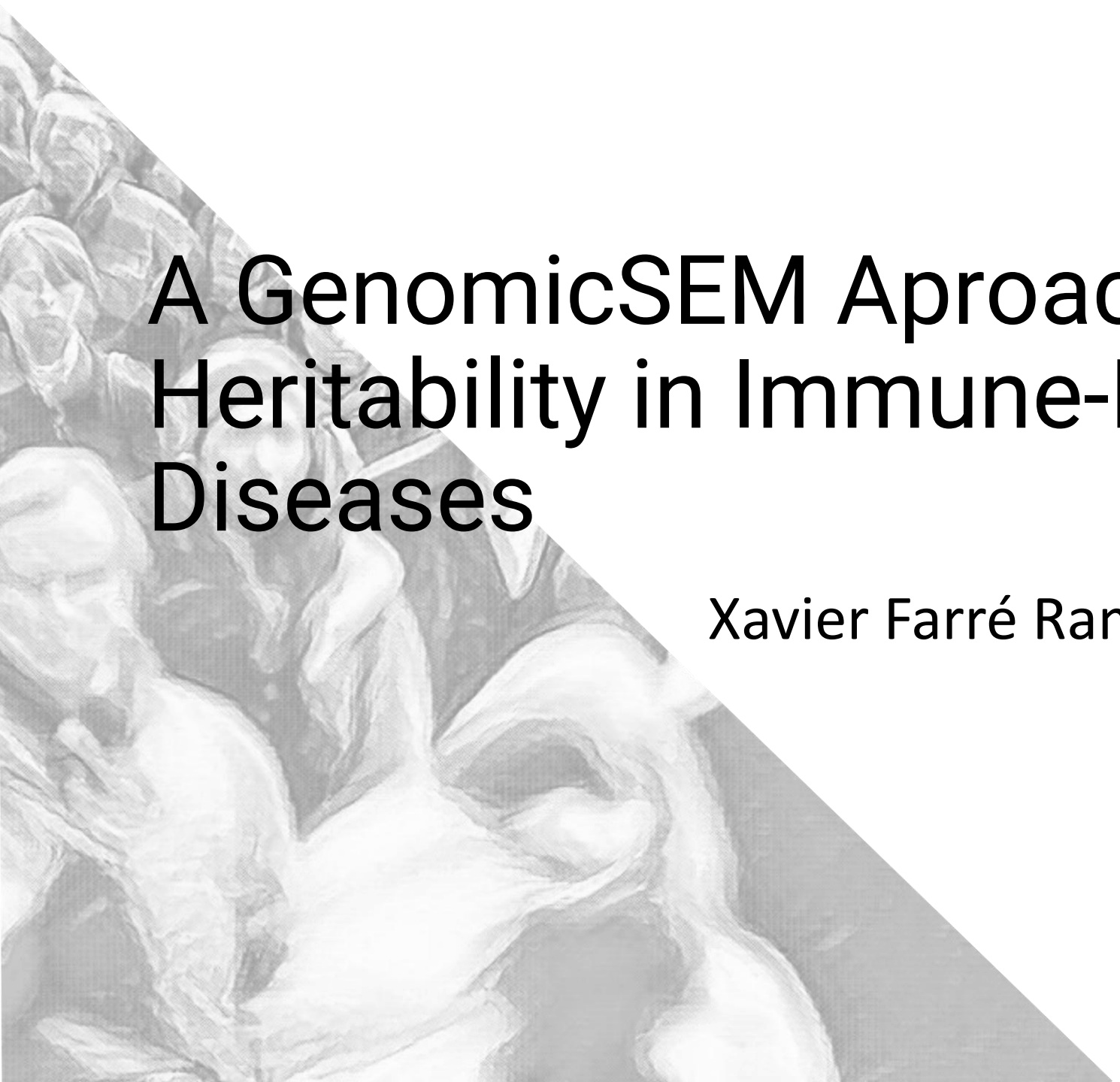


A GenomicSEM Aproach to Shared Heritability in Immune-Related Diseases

Xavier Farré Ramon

GCAT Genomes for Life

IGTP Institut de Recerca Germans Trias i Pujol

In the beginning was the GWAS

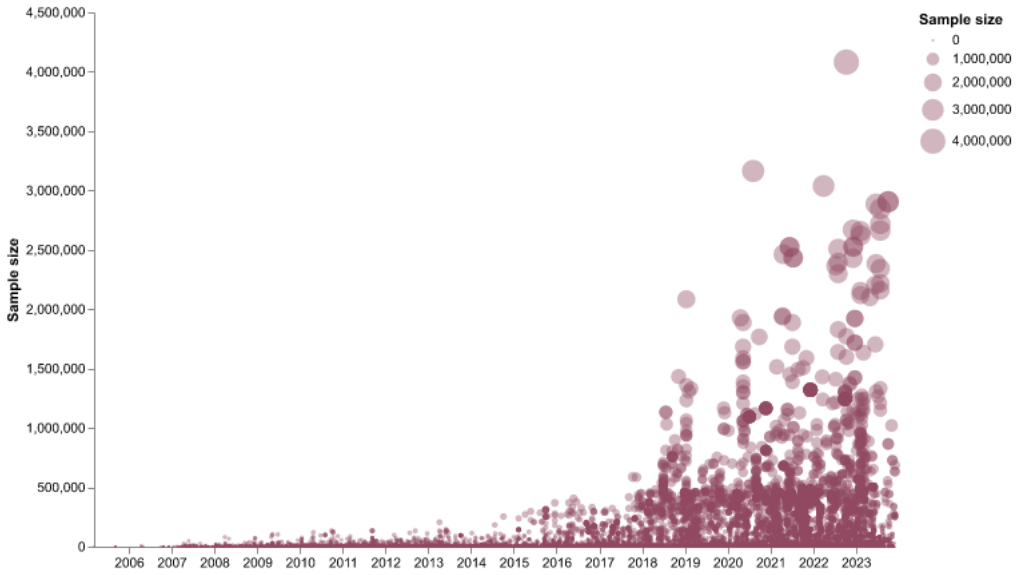
Vol 447|7 June 2007|doi:10.1038/nature05911 nature

ARTICLES

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

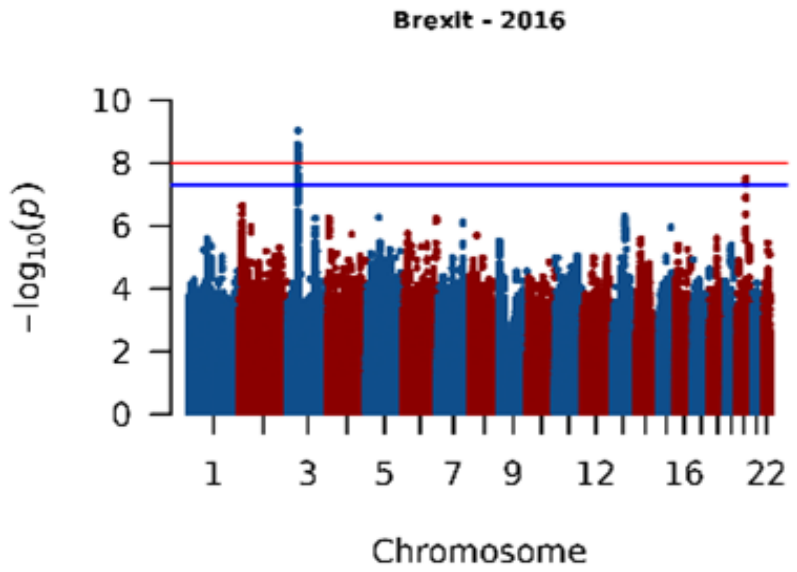
and researchers went crazy



Data from:

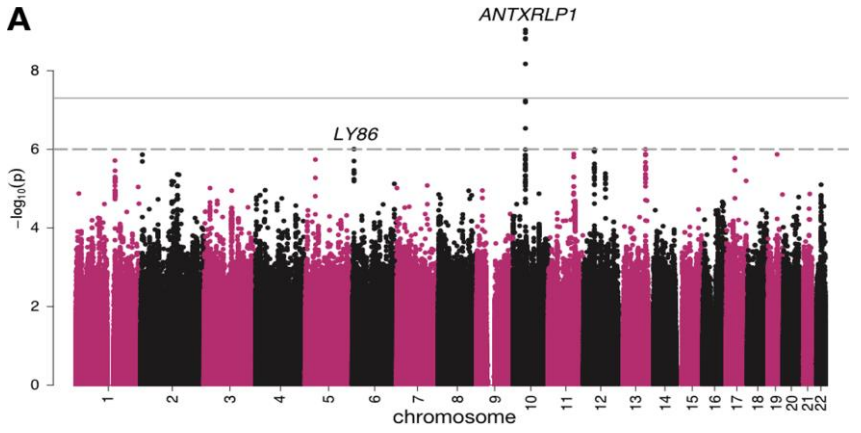
Mills, M.C., Rahal, C. The GWAS Diversity Monitor tracks diversity by disease in real time. *Nat Genet* **52**, 242–243 (2020). https://doi.org/10.1038/s41588-020-0580-y

Maybe too crazy?



Abdellaoui, A., Hugh-Jones, D., Yengo, L. *et al.* Genetic correlates of social stratification in Great Britain. *Nat Hum Behav* **3**, 1332–1342 (2019). https://doi.org/10.1038/s41562-019-0757-5

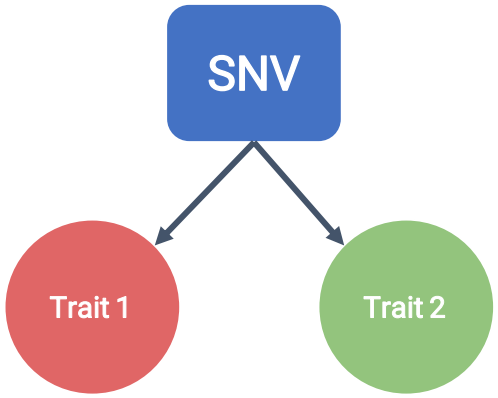
Facial attractiveness ranked by female coders



Hu B, Shen N, Li JJ, Kang H, Hong J, Fletcher J, Greenberg J, Mailick MR, Lu Q. Genome-wide association study reveals sex-specific genetic architecture of facial attractiveness. PLoS Genet. 2019 Apr 4;15(4):e1007973. doi: 10.1371/journal.pgen.1007973. PMID: 30946739; PMCID: PMC6448826.

Pleiotropy

The presence of pleiotropy, a locus that influences multiple traits, is common if not ubiquitous



Associations reported in the GWAS catalog 2007

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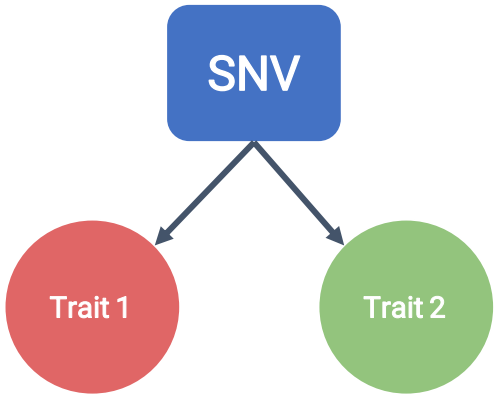

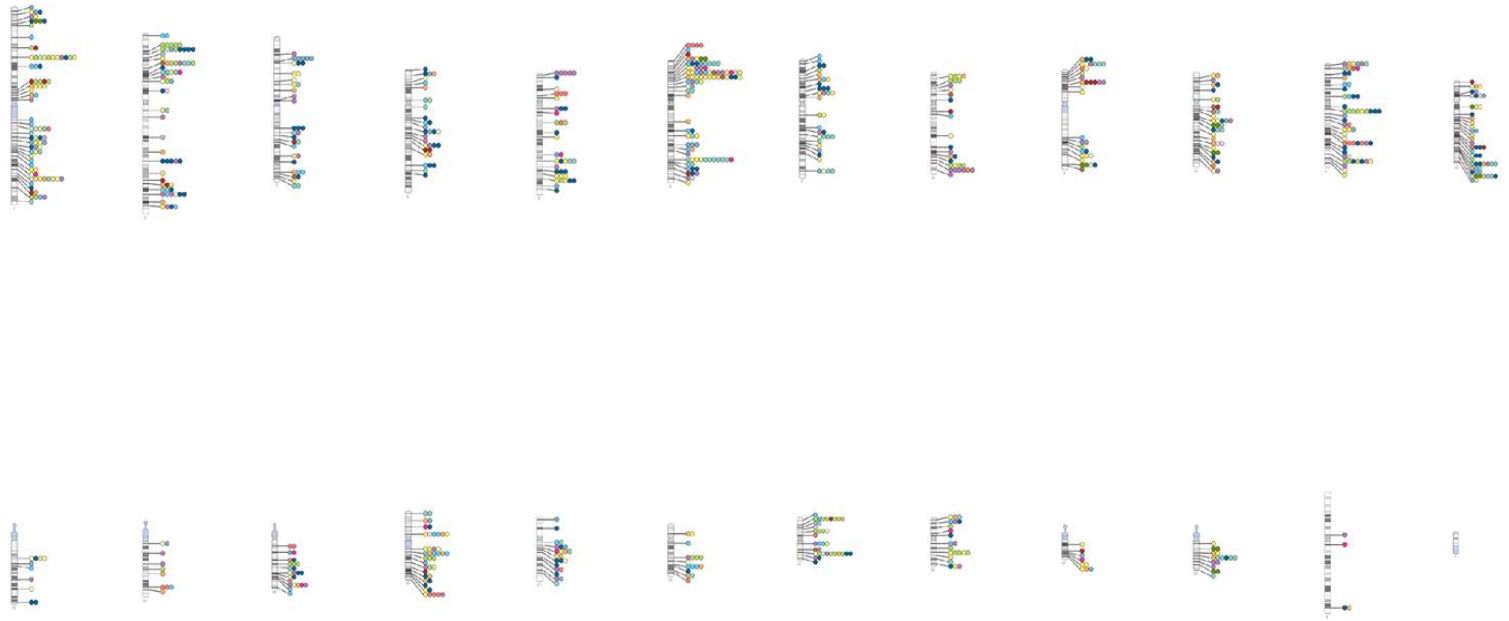

Associations reported in the GWAS catalog 2009

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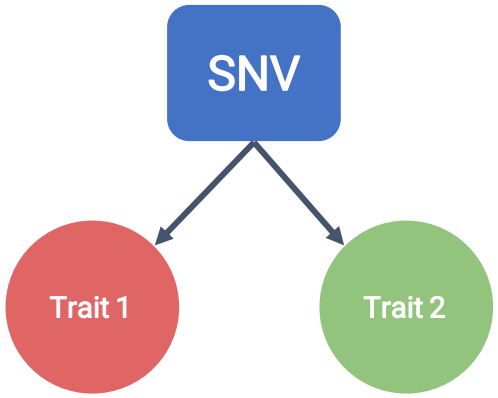


Associations reported in the GWAS catalog 2019

Shared Genetics Detection Tools

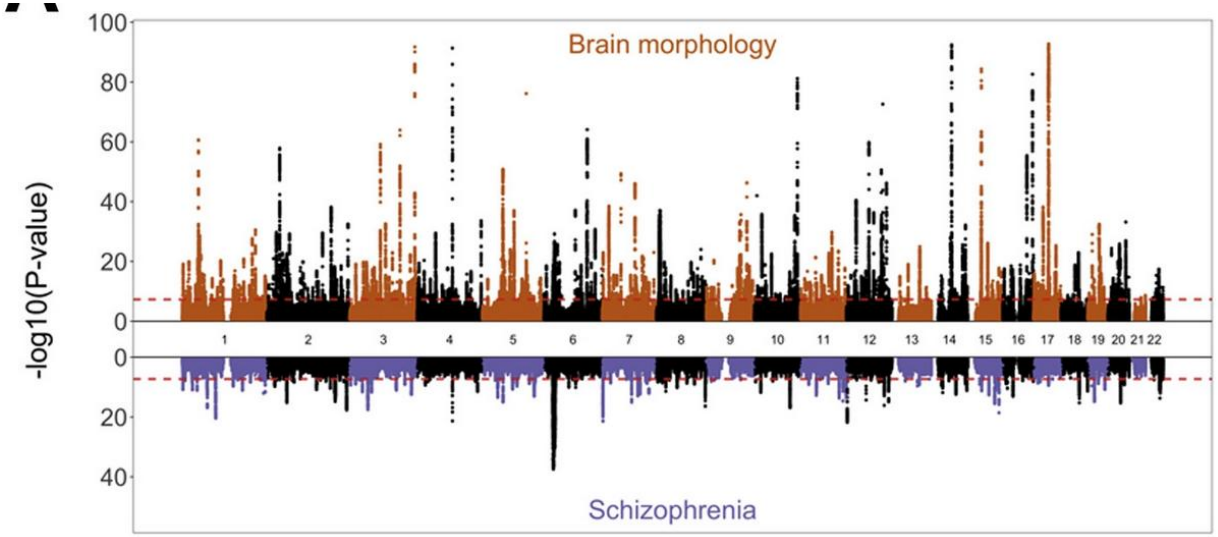
	Individual-level Data	GWAS Summary Statistics
Global pleiotropy	PRS Bivariate-GREML	LDSC SumHer HESS Popcorn GNOVA
Local pleiotropy	Bivariate-GREML GCTA-COJO	LAVA PleioFDR ρ-HESS PLACO SUPERGNOVA

Detect Pleiotropies with Summary Statistics

Improved Detection of Common Variants Associated with Schizophrenia and Bipolar Disorder Using Pleiotropy-Informed Conditional False Discovery Rate

Ole A. Andreassen, Wesley K. Thompson, Andrew J. Schork, Stephan Ripke, Morten Mattingsdal, John R. Kelsoe, Kenneth S. Kendler, Michael C. O'Donovan, Dan Rujescu, Thomas Werge, Pamela Sklar, The Psychiatric Genomics Consortium (PGC), Bipolar Disorder and Schizophrenia Working Groups, [···], Anders M. Dale
[view all]

Published: April 25, 2013 • https://doi.org/10.1371/journal.pgen.1003455



Boosting Schizophrenia Genetics by Utilizing Genetic Overlap With Brain Morphology. van der Meer, et al. 2022 Biological Psychiatry

- **pleioFDR (pleiotropy-informed False Discovery Rate)** is a statistical method to improve GWAS discovery

- Start with two GWAS datasets
  - For each SNP:
    - Look at p-value in Trait A
    - Look at p-value in Trait B
  - Estimate enrichment:
    - Are low p-values in A more frequent when B is also low?
  - Adjust FDR based on this enrichment

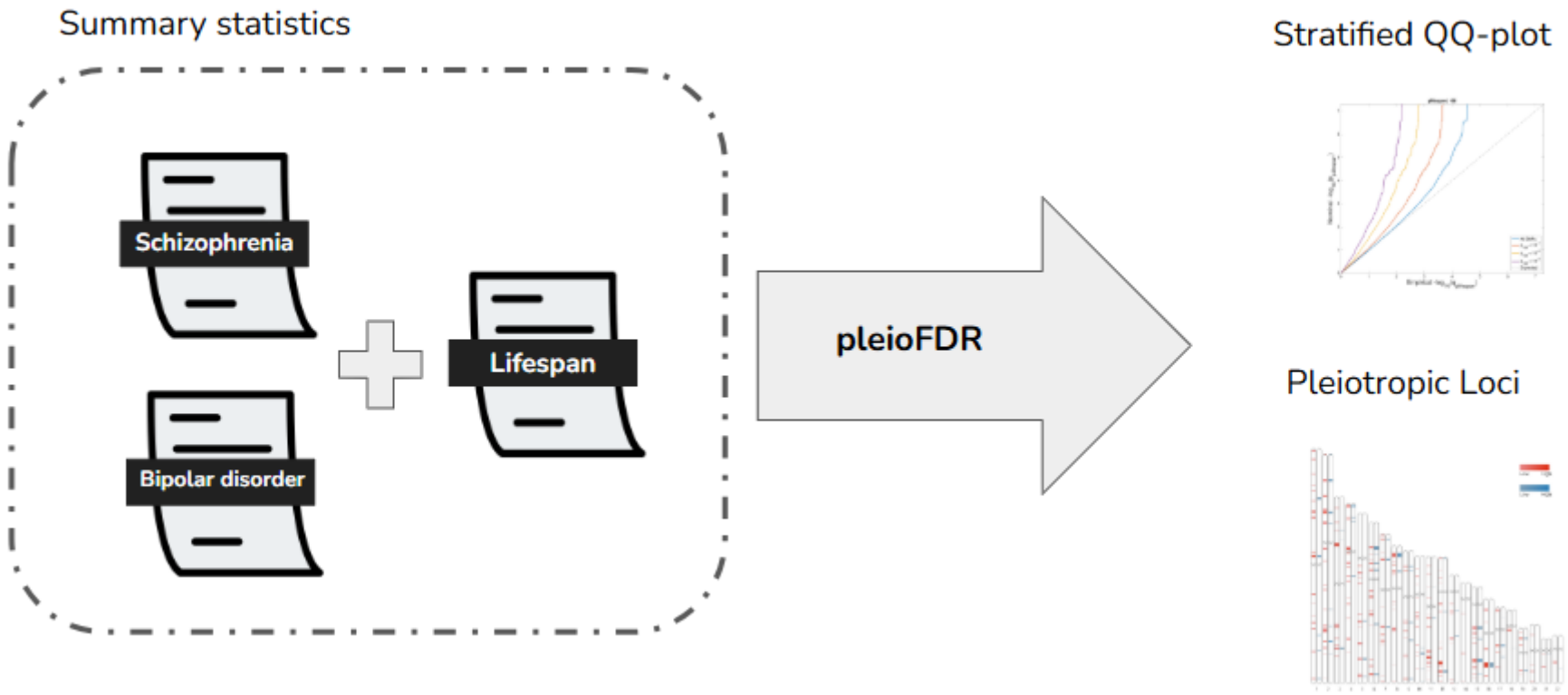
PleioFDR: Schizophrenia, Bipolar Disorder and Lifespan

Original Investigation | Published: 09 August 2020

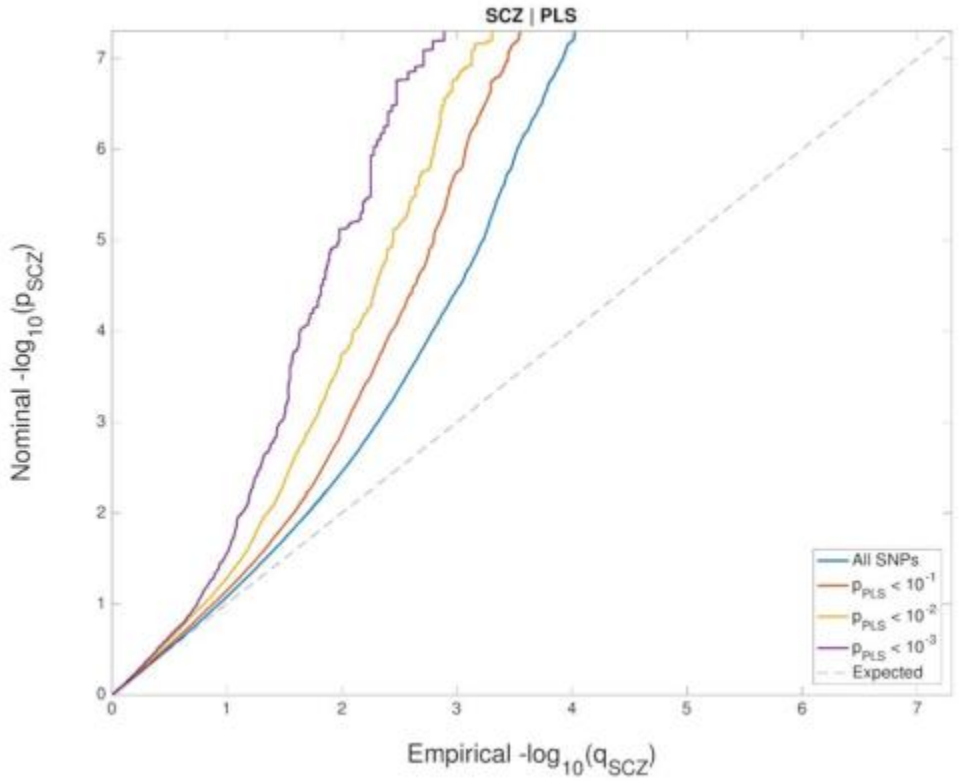
The shared genetic architecture of schizophrenia, bipolar disorder and lifespan

Gerard Muntané ✉, Xavier Farré, Elena Bosch, Lourdes Martorell, Arcadi Navarro & Elisabet Vilella

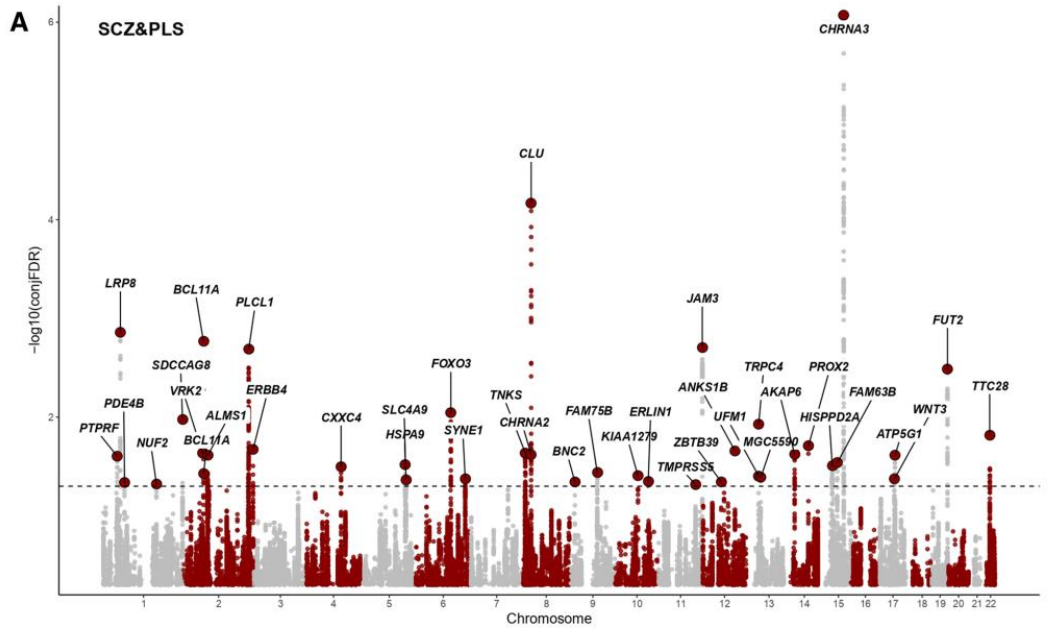
Human Genetics **140**, 441–455 (2021) | Cite this article



PleioFDR: Schizophrenia, Bipolar Disorder and Lifespan



Presence of **shared genetic architecture between SCZ and lifespan**



39 pleiotropic loci were jointly associated with SCZ and lifespan
17 of which were novel SCZ risk loci

If multiple traits are genetically correlated, can we model that structure explicitly?

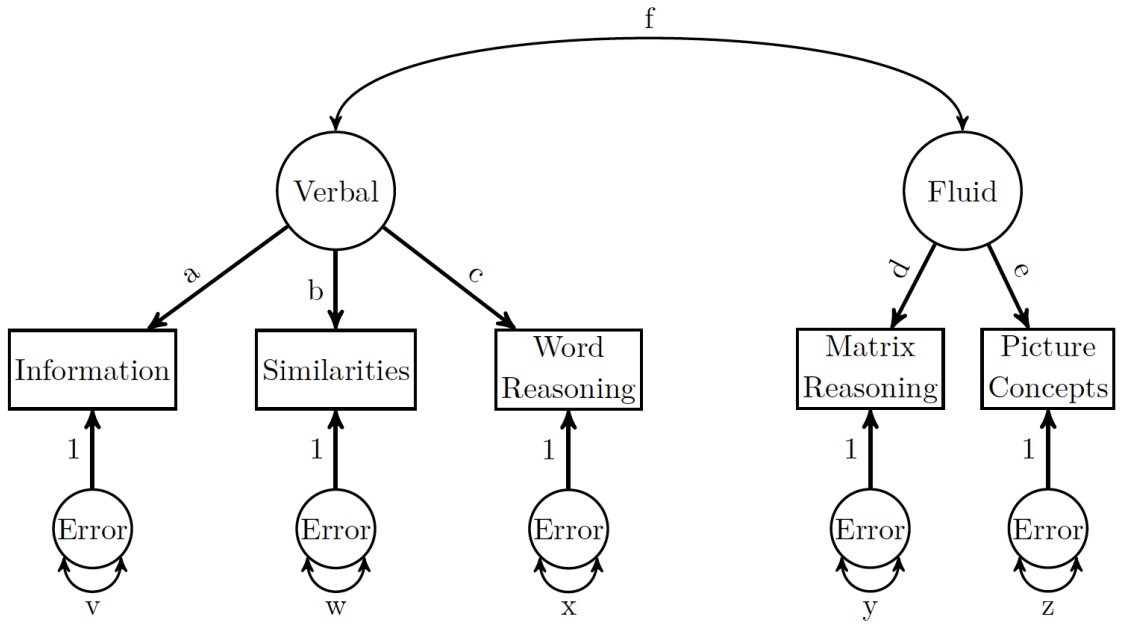
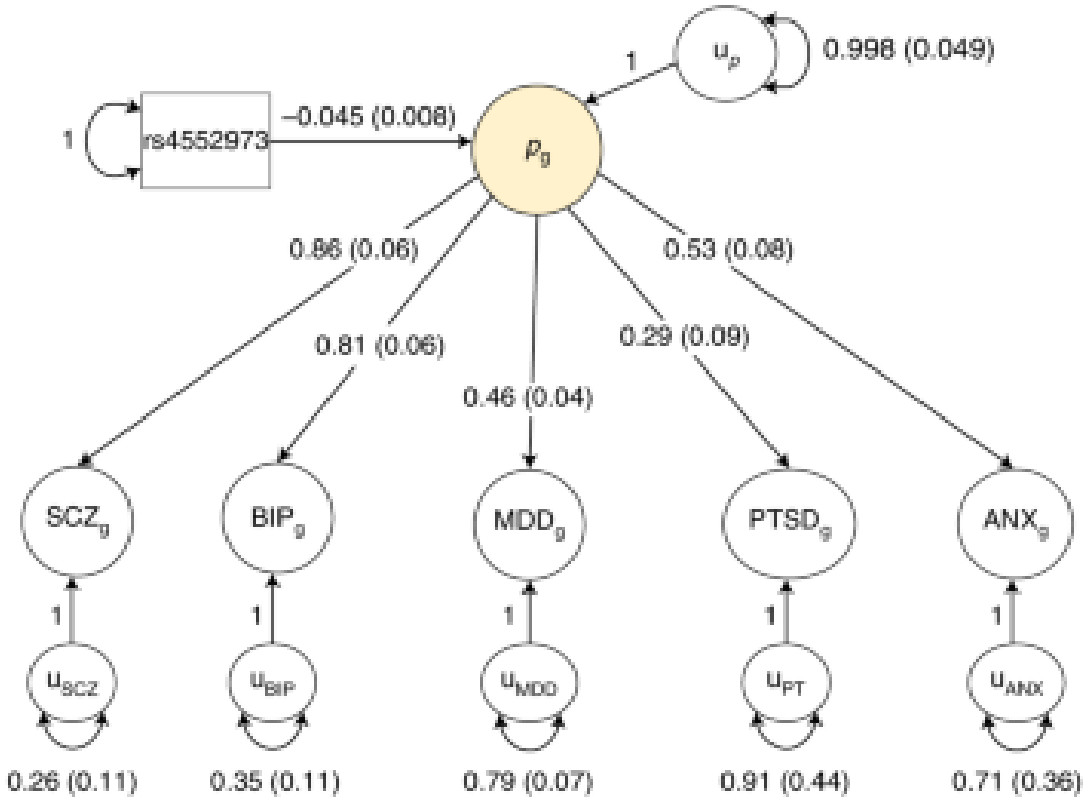


Figure 3.9 Model of five subtests from the Wechsler Intelligence Scale for Children-Fourth Edition with two latent variables.

SEM is a framework to model **unobserved variables** using observed data

- How strongly each test reflects the latent trait (loadings)
- How strongly the latent traits are correlated
- And how well the model explains the observed covariance



In a traditional SEM, your observed variables are phenotypes (like a score on a test). In Genomic SEM, the "observed" variables are the GWAS summary statistics for those phenotypes.

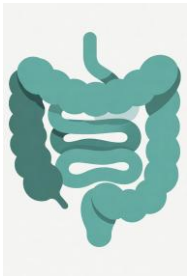
The Latent Factor: Just as a latent factor in psychology represents a "hidden trait" (like Intelligence), a latent factor in Genomic SEM represents a shared genetic liability (like a "General Psychopathology" factor).

The "Input" Shift: You move from a covariance matrix of phenotypes (how people's scores correlate) to a covariance matrix of genetics (how the DNA-based risks for those traits correlate).

Latent Genetic Structure Underlying Immune-related Diseases

Latent Immune-related Factor

IBD



Psoriasis

Rheumatoid arthritis

Multiple Sclerosis

Asthma

T1D/T2D

CKD

Coronary atherosclerosis

Lupus

Latent Genetic Structure Underlying Immune-related Diseases

Model	chi-square	df	P-value	CFI	SRMR	AIC
Common Factor	354.8999	35	0.0000	0.6200	0.1116	394.8999

Fit Index	Good Fit	Acceptable Fit	Poor Fit
CFI (Comparative Fit Index)	≥ 0.95	≥ 0.90	< 0.90
SRMR (Standardized Root Mean Square Residual)	≤ 0.05	≤ 0.10	> 0.10
χ^2 p-value	> 0.05 (non-significant)	Often ignored	—
AIC	Lower is better	—	—

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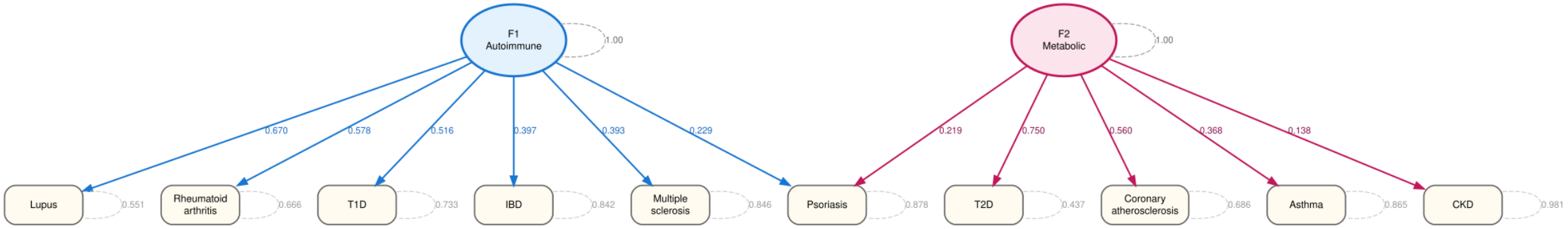
χ^2 p-value	> 0.05 (non-significant)	Often ignored	—
AIC	Lower is better	—	—

Not Good!

Exploratory Factor Analysis

	Factor 1	Factor 2
IBD	0.308	
Psoriasis	0.156	0.251
Rheumatoid Arthritis	0.697	
Asthma		0.334
Multiple Sclerosis	0.316	
T1D	0.472	
Lupus	0.773	
Coronary Atherosclerosis	-0.146	0.670
T2D		0.687
CKD	-0.157	0.236

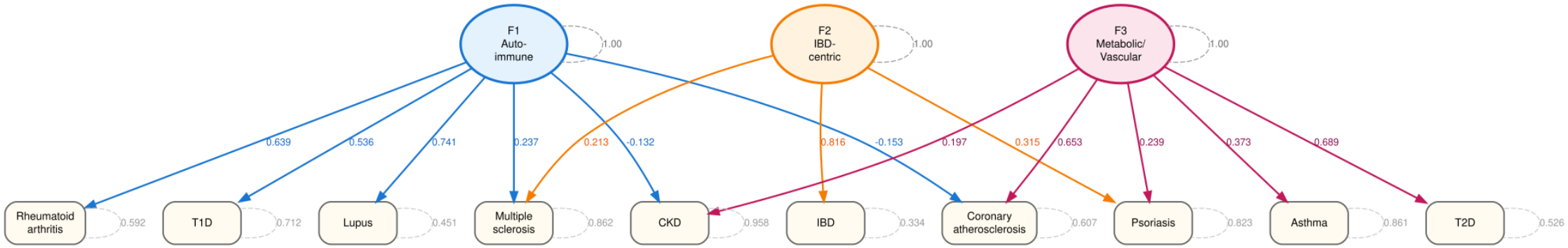
	Factor 1	Factor 2
SS loadings	1.576	1.173
Proportion Var	0.158	0.117
Cumulative Var	0.158	0.275



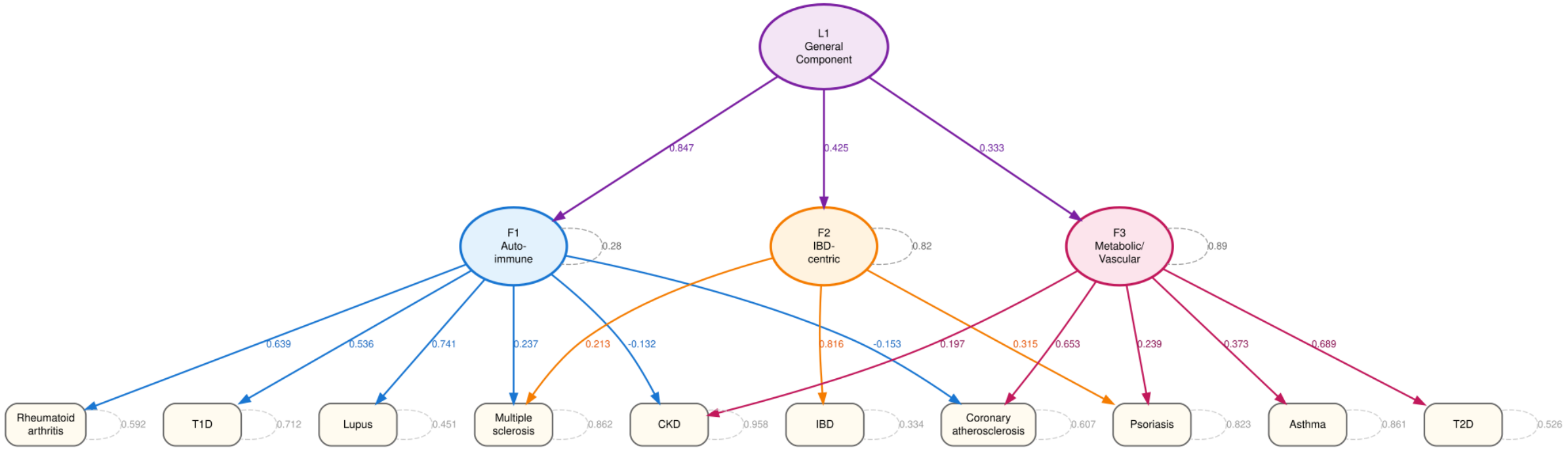
Exploratory Factor Analysis

	Factor 1	Factor 2	Factor 3
IBD		1.040	
Psoriasis		0.243	0.226
Rheumatoid Arthritis	0.690		
Asthma			0.328
Multiple Sclerosis	0.239	0.166	
T1D	0.459		
Lupus	0.810		
Coronary Atherosclerosis	-0.123		0.633
T2D			0.733
CKD	-0.120		0.230

	Factor 1	Factor 2	Factor 3
SS loadings	1.440	1.173	1.170
Proportion Var	0.144	0.119	0.117
Cumulative Var	0.144	0.263	0.380



Hierarchical Model



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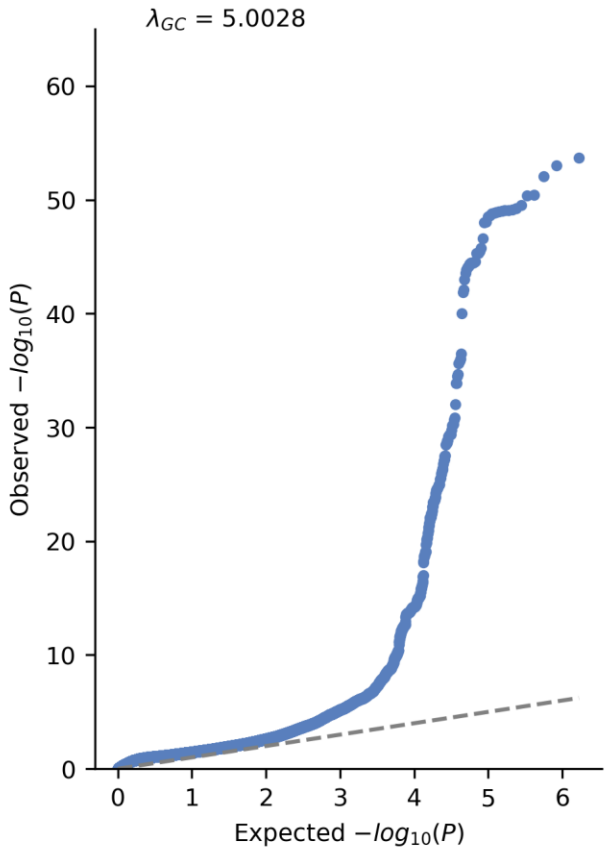
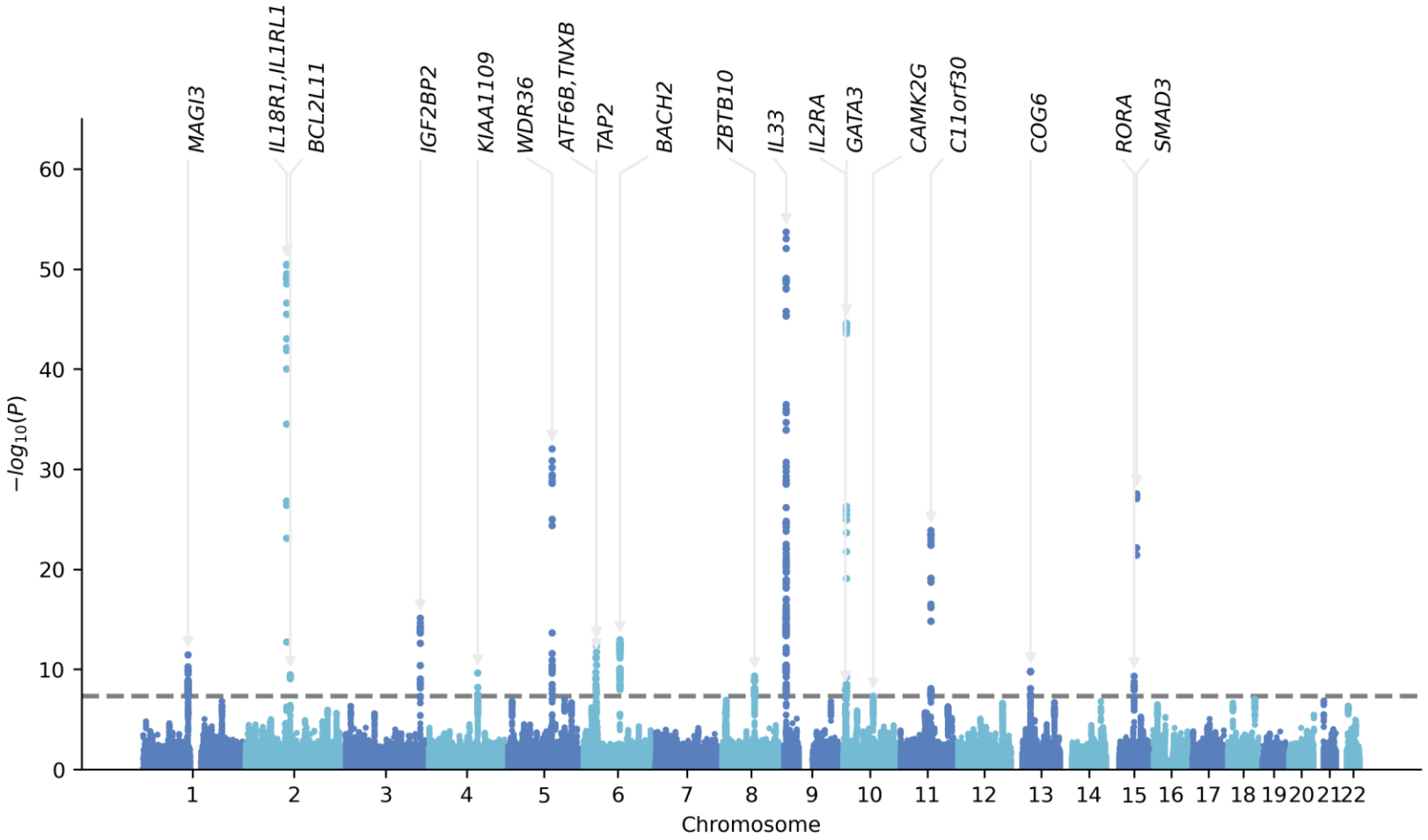
Model	chi-square	df	P-value	CFI	SRMR	AIC
Common Factor	354.8999	35	0.0000	0.6200	0.1116	394.8999
2-Factor	121.7142	33	0.0000	0.8946	0.0548	165.7142
3-Factor	51.2361	28	0.0047	0.9724	0.0317	105.2361
3-Factor + Hierarchical	51.2360	28	0.0047	0.9724	0.0317	105.2360

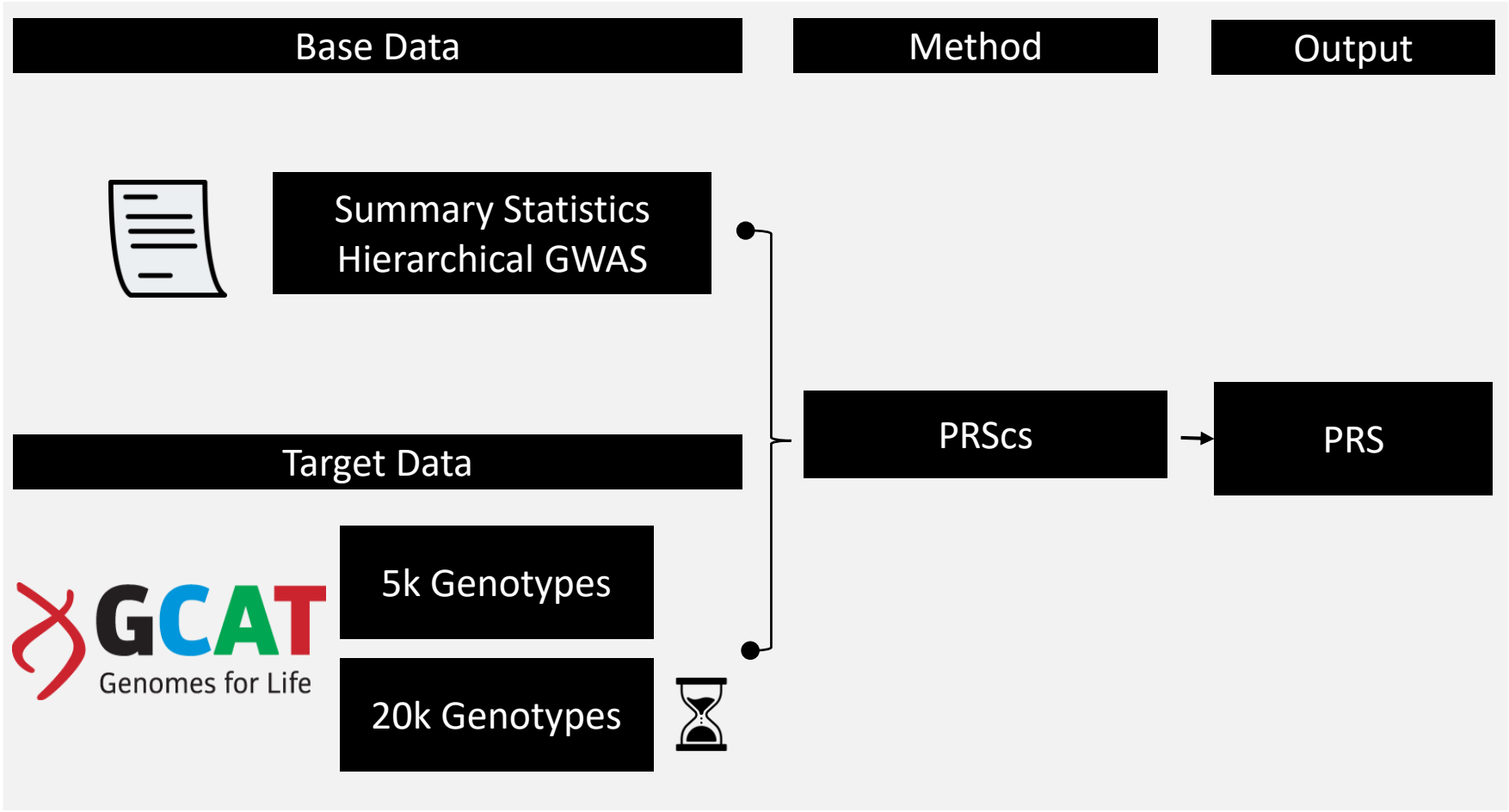
Hierarchical Model GWAS





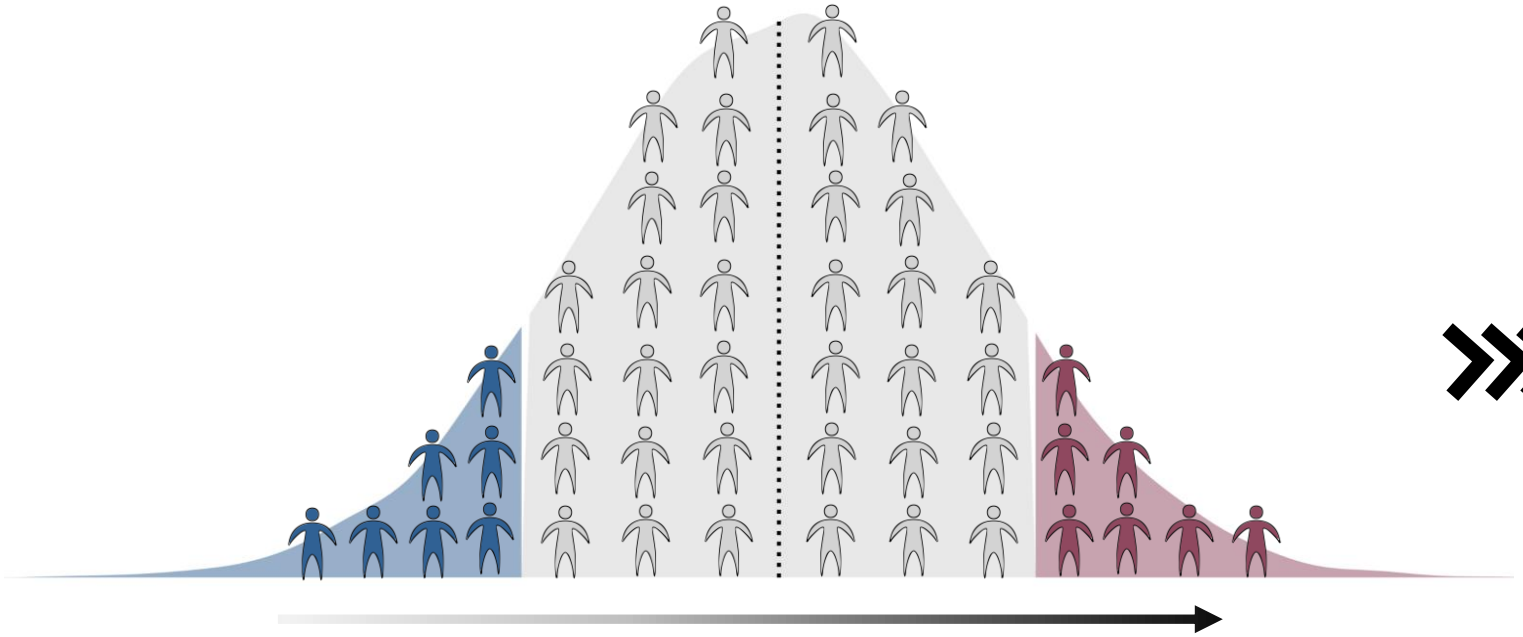
Hierarchical Model PRS

Is the genetic liability of the immune related disorders with other diseases?

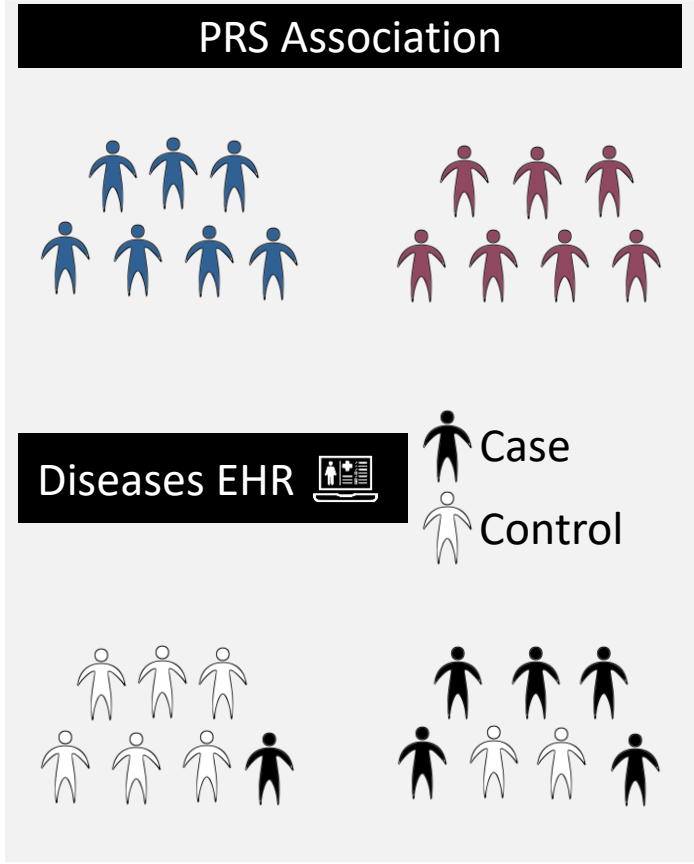


Hierarchical Model GWAS PRS

Is the genetic liability of the immune related disorders with other diseases?



Deciles of the PRS on Immune related disorders



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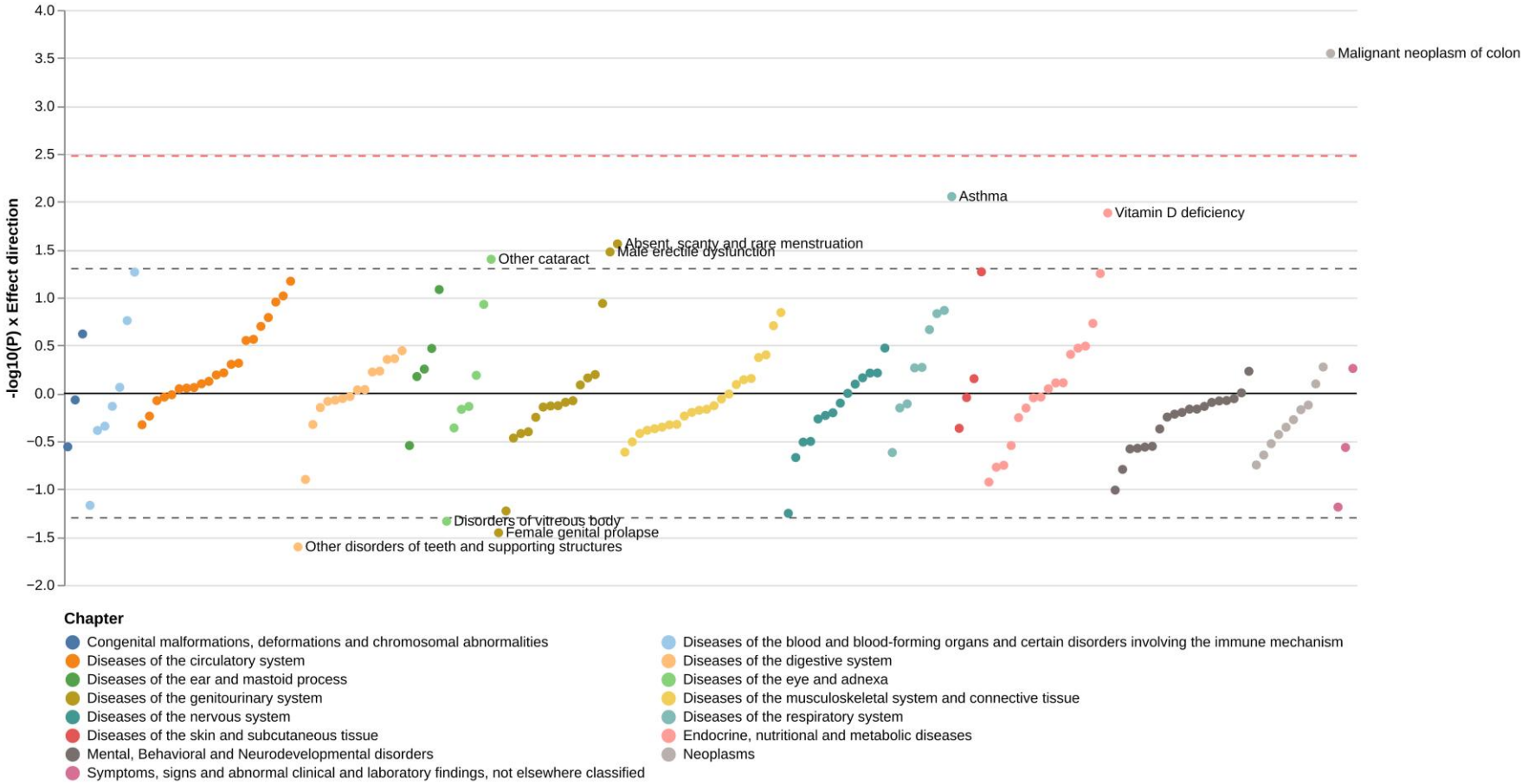
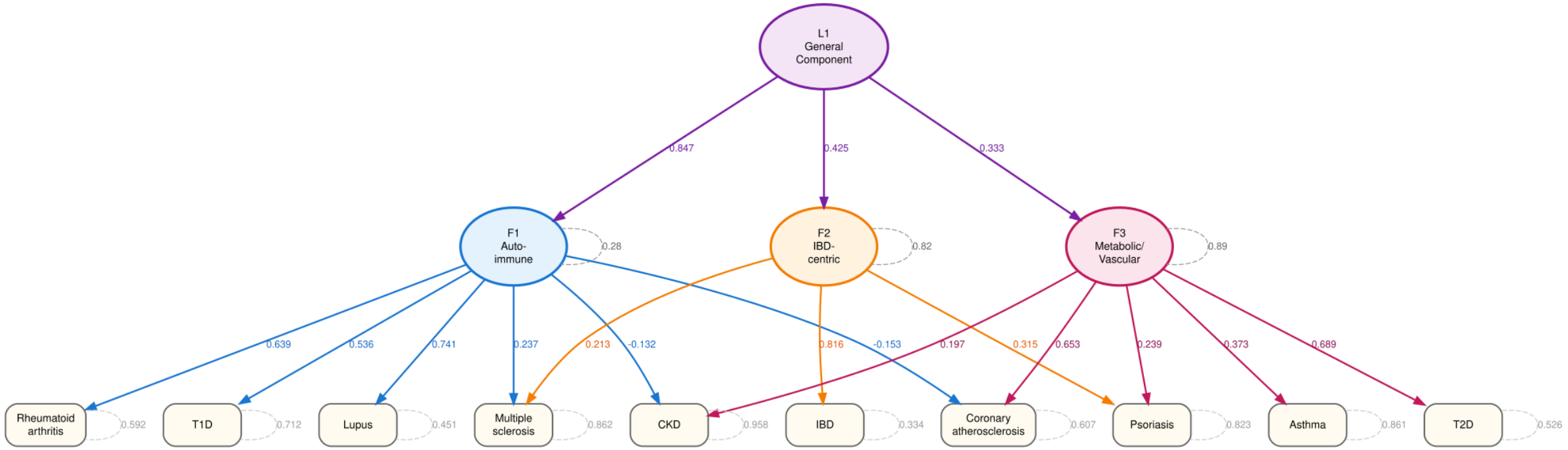
Hierarchical Model GWAS PRS

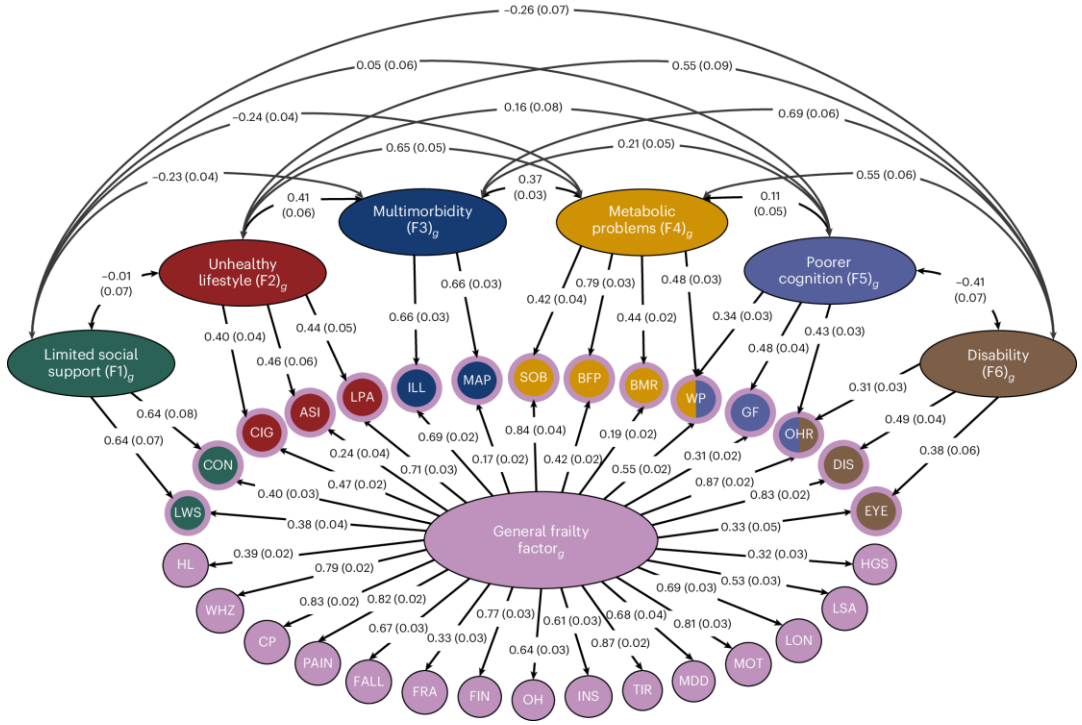


Hierarchical Model

The hierarchical model is difficult to interpret...



The Bifactor Model Joins the Fight



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Article | Open access | Published: 04 August 2025

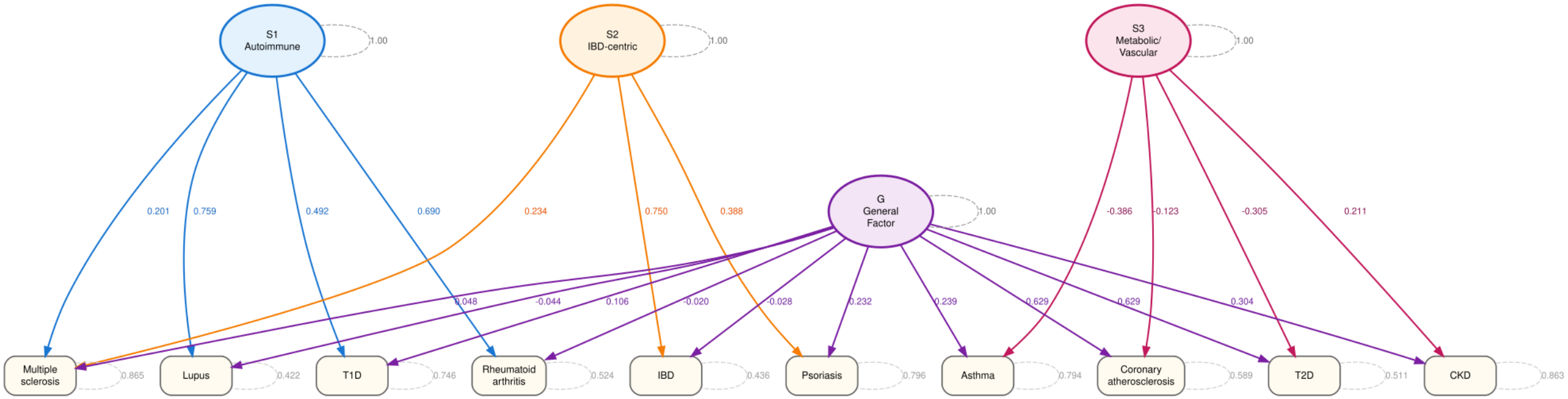
Uncovering the multivariate genetic architecture of frailty with genomic structural equation modeling

Isabelle F. Foote, Jonny P. Flint, Anna E. Fürtjes, Jeremy M. Lawrence, Donncha S. Mullin, John D. Fisk, Tobias K. Karakach, Andrew Rutenberg, Nicholas G. Martin, Michelle K. Lupton, David J. Llewellyn, Janice M. Ranson, Simon R. Cox, Michelle Luciano, Kenneth Rockwood & Andrew D. Grotzinger

Nature Genetics **57**, 1848–1859 (2025) | Cite this article

- Provides a direct GWAS target for shared genetic liability, rather than an indirect (mediated) estimate.
- Separates global and disease-specific genetic effects through orthogonal factors, improving interpretability.
- Enhances power and biological clarity by aggregating shared signal while controlling for trait-specific variation.

The Bifactor Model



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3-Factor + Hierarchical	51.2360	28	0.0047	0.9724	0.0317	105.2360
Bifactor	23.0959	21	0.3389	0.9975	0.0205	91.0959

Bifactor-to-Phenotype Correlations

•**Cross-trait LDSC**: Estimate genetic correlation (r_m) between bifactor and:
- Individual component diseases (should be high)
- Non-component traits (sanity check: should be lower)
- Complex behavioral/metabolic traits

•**Visualize correlation matrix**: Heatmap of bifactor vs. external traits

Shared vs. Specific Genetic Architecture

•**Variance partitioning**: What % of each disease's heritability is explained by:
- The bifactor (shared)
- Disease-specific factors

•**Comparison with hierarchical model**: Why bifactor is more interpretable

Take Home Messages

- The Bifactor Model Solves a Real Problem:
  - GWAS treats diseases in silos; ignores shared genetic liability
  - Bifactor solution: Decomposes shared (general) and specific genetic effects
  - Advantage over hierarchical SEM: Direct GWAS target for shared factor; easier interpretation
- Pleiotropy is Ubiquitous and Biologically Meaningful
  - GWAS catalog: 2007 → 2009 → 2019 shows explosive growth in detected pleiotropy
  - Many SNPs influence multiple traits; this isn't noise, it's real biology
  - Immune diseases share genetic risk → suggests shared biological mechanisms

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