Introduction to drug target Mendelian randomization

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CHARGE Mendelian Randomization Workshop

9 May 2023

UNIVERSITY OF COPENHAGEN

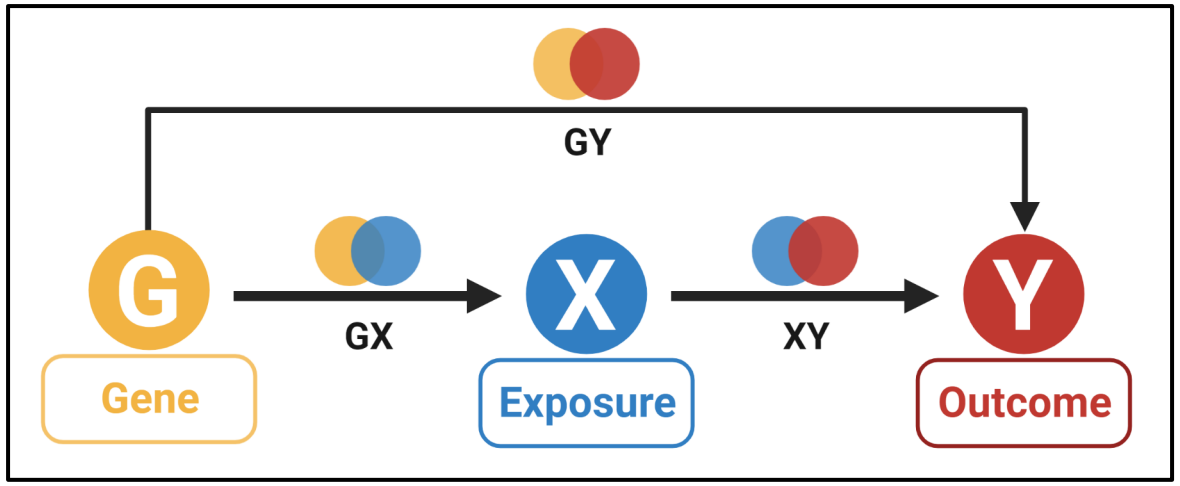
Imperial College London

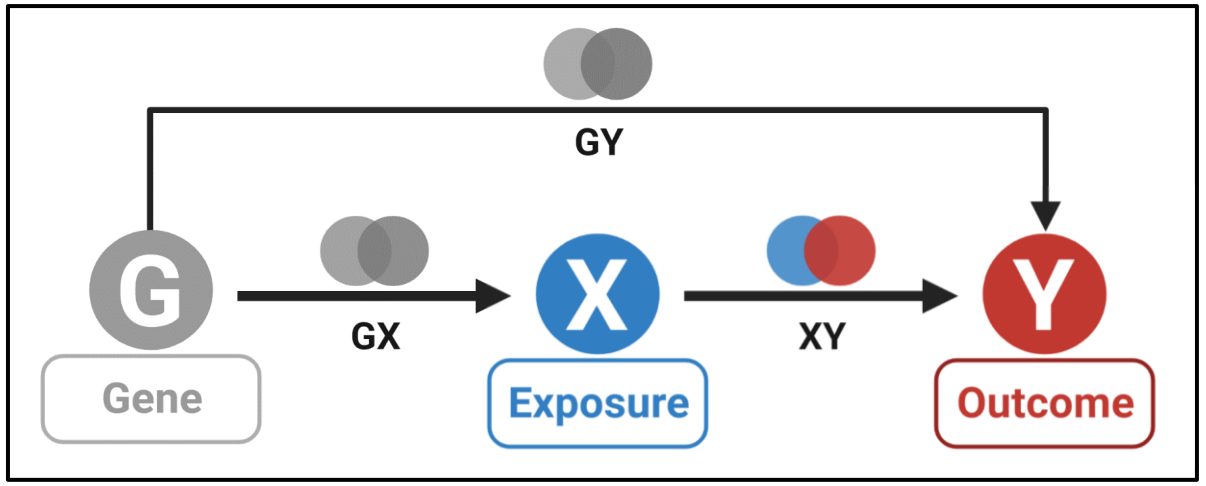
Agenda

- What is Mendelian randomization?
- Application of Mendelian randomization for studying drug effects
- Instrument selection for drug target perturbation
- Interpretation of drug target Mendelian randomization
- Example
- Questions and comments

What is Mendelian randomization?

Mendelian randomization

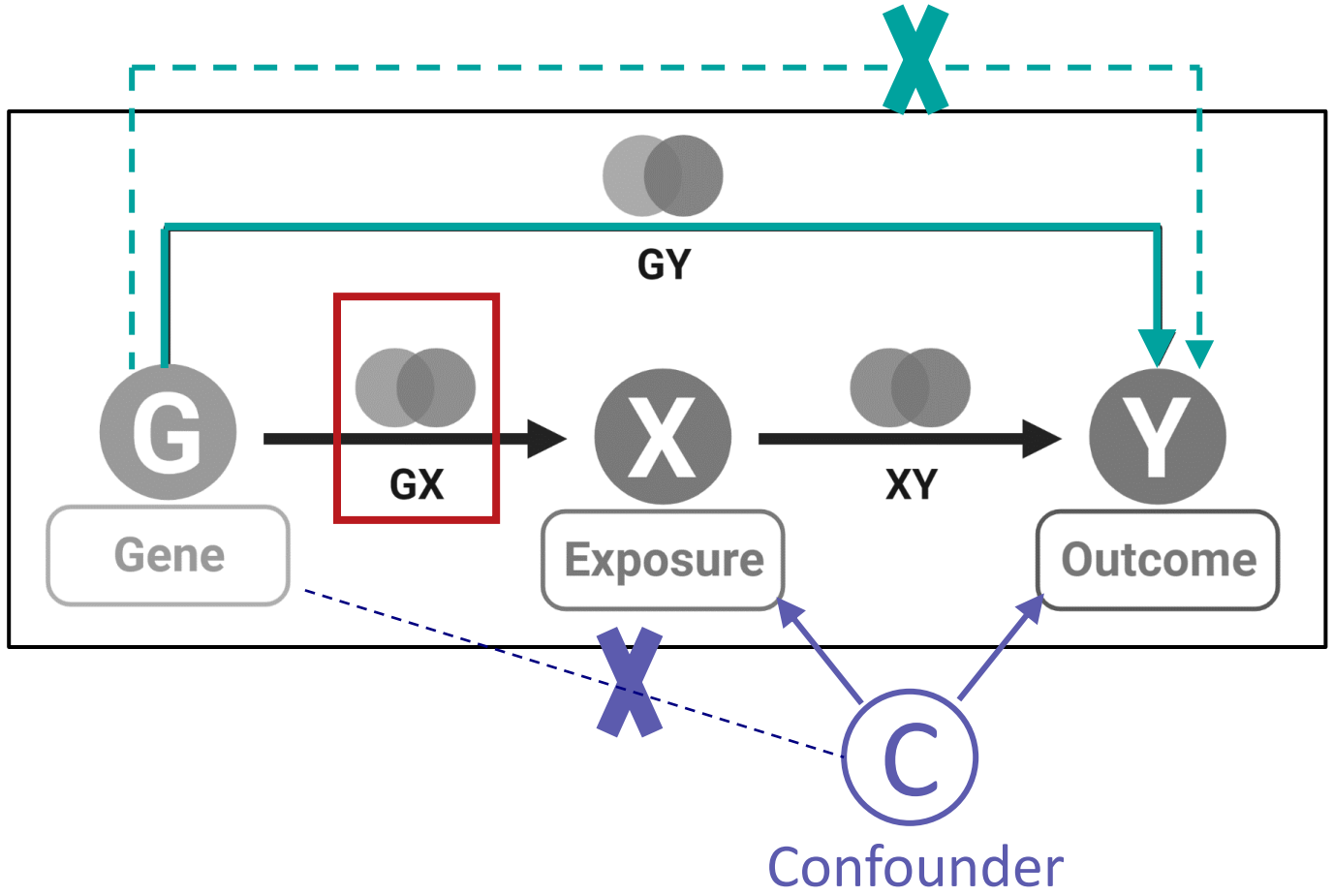




$$GY = GX \times XY$$

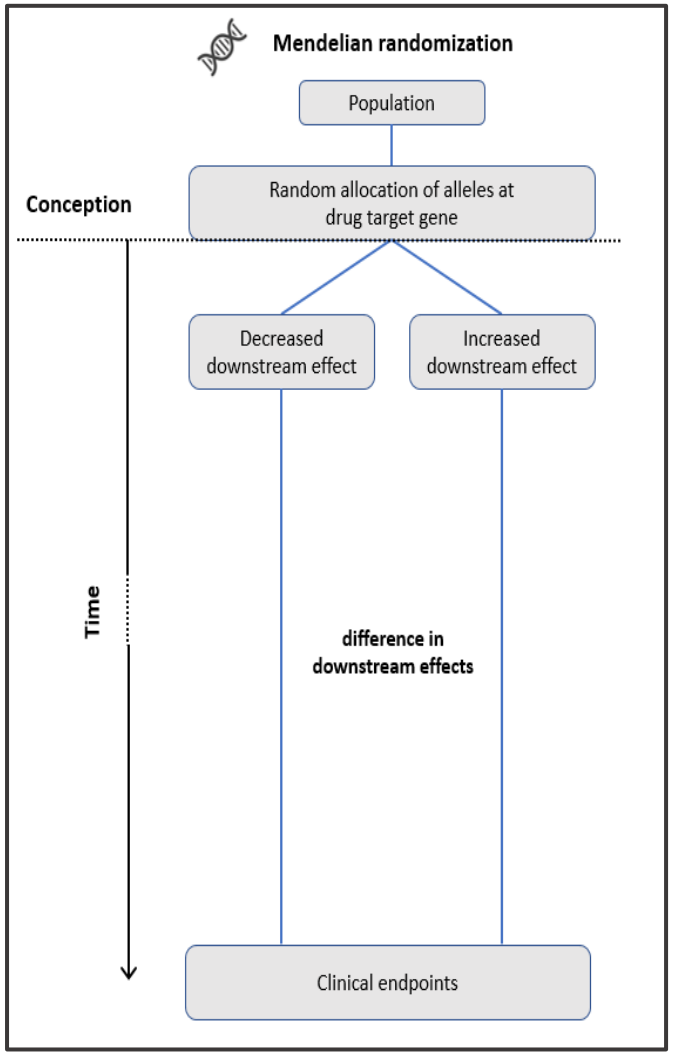
$$XY = \frac{GY}{GX}$$

Key instrumental variable assumptions



1. **Relevance**
   - Strong GX (testable)
2. **Independence**
   - Not fully testable
3. **Exclusion-restriction**
   - Not fully testable

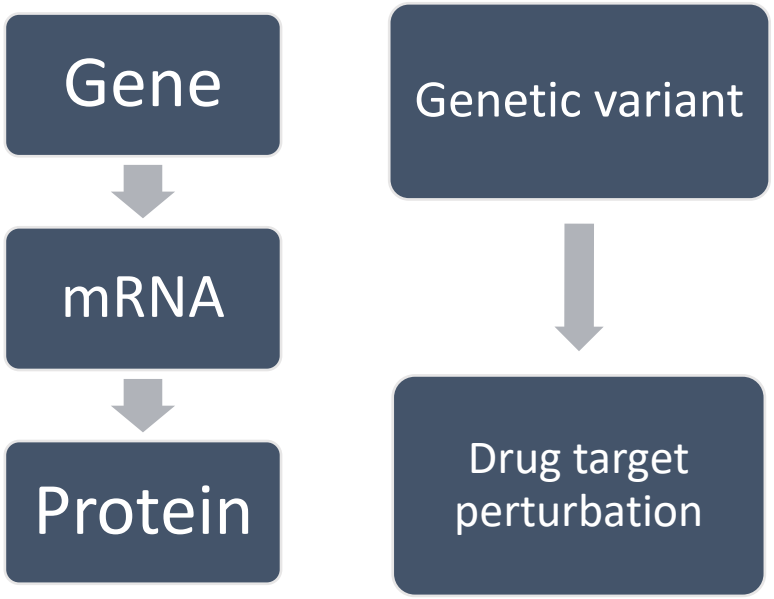
Comparison with Randomized Clinical Trials

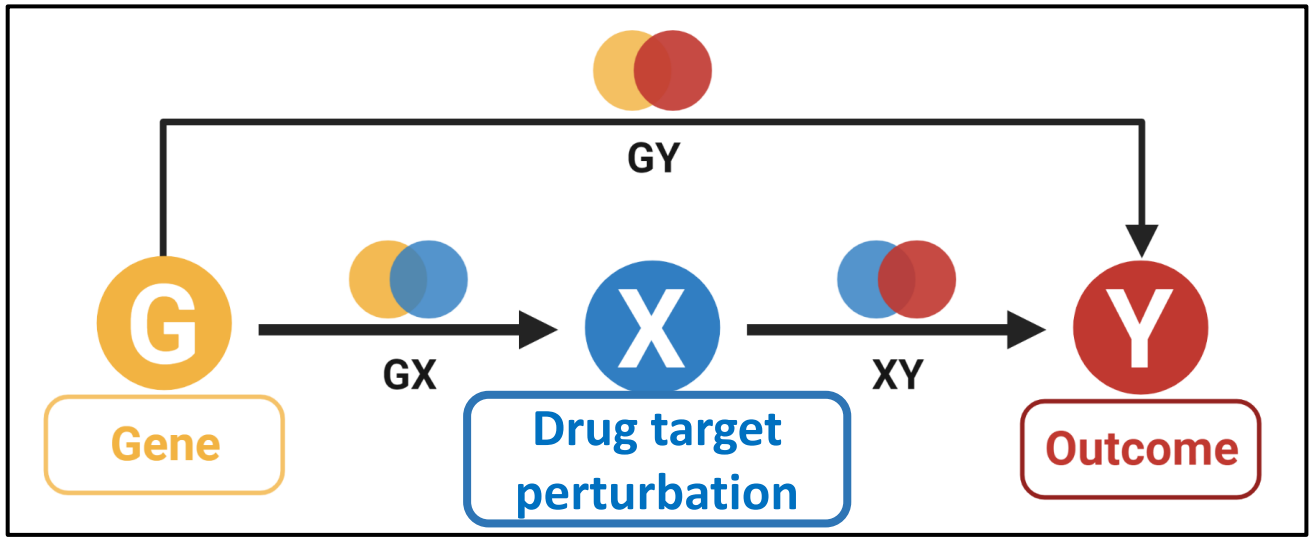


Mendelian Randomization	Randomized Clinical Trial
• Genetic risk variants randomized at conception	• Therapy or placebo randomized upon initiation of trial
• No confounding factors	• Could be multiple confounding factors
• Fixed for life	• Not fixed even during the trial
• Design enables one to determine whether the risk factor is causative	• Design does not necessarily enable one to determine causation
• Safety and efficacy assessed from birth (lifetime of exposure)	• Safety and efficacy assessed for duration of trial (3 to 5 yrs)
• Relatively inexpensive	• Invariably costs millions
• Markedly less time-consuming	• Invariably 3 to 5 yrs

Application of Mendelian randomization for studying drug effects

How is MR used to investigate drug effects?



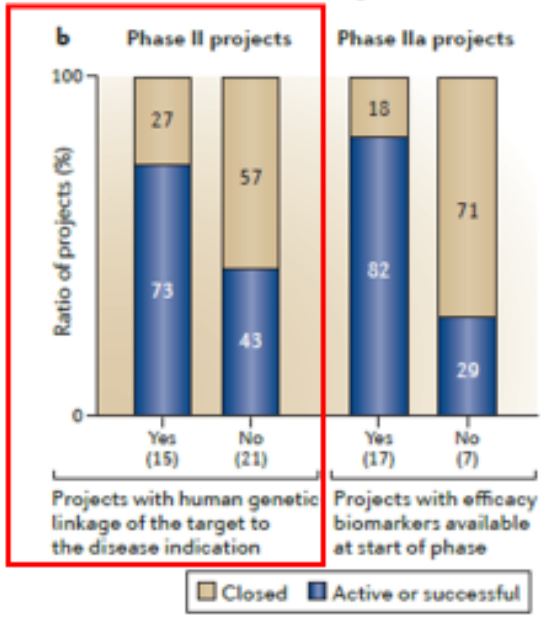


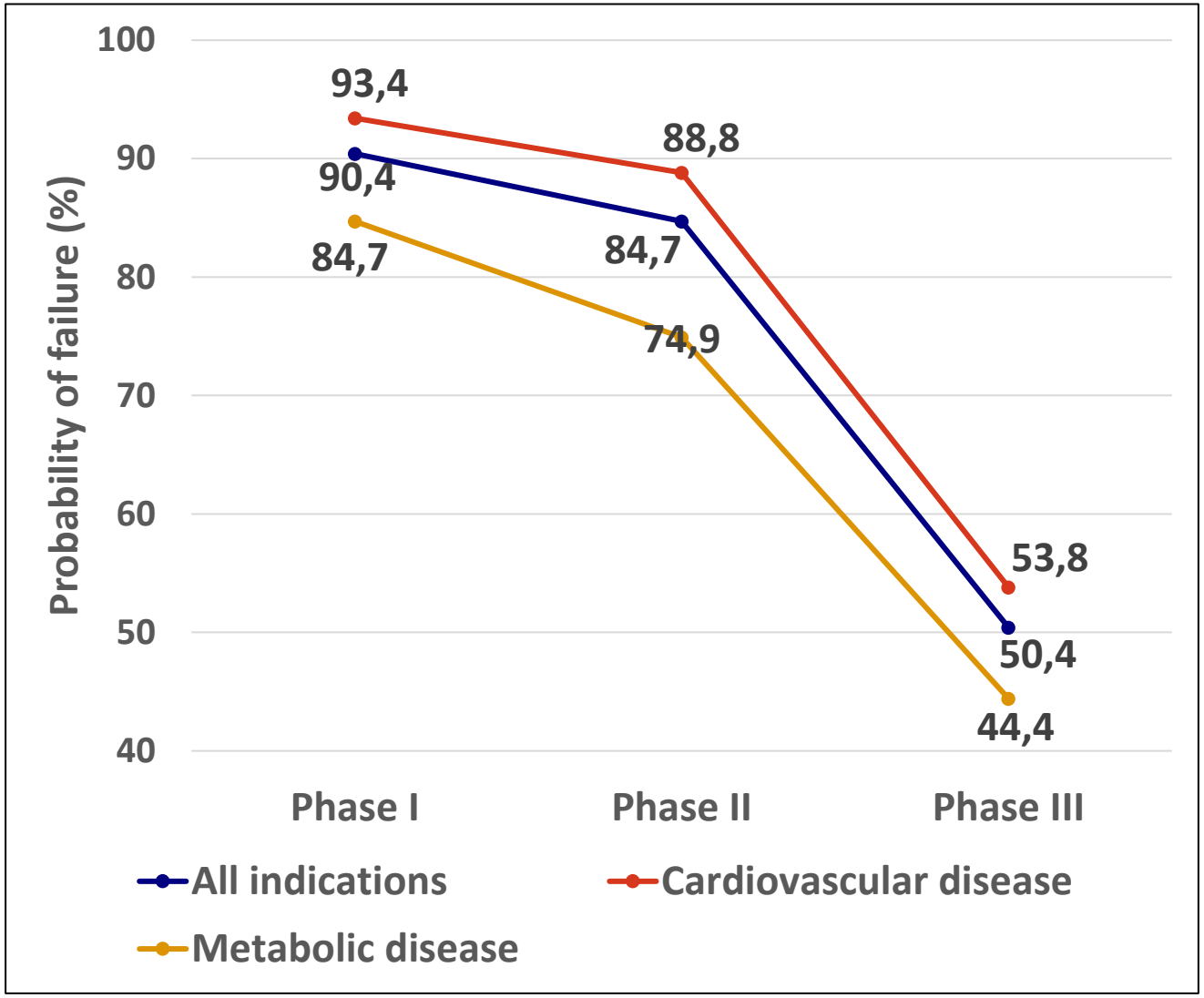
Where the exposure under study is perturbation of a drug target, MR can be used to explore drug effects

Why MR is useful for studying drug effects

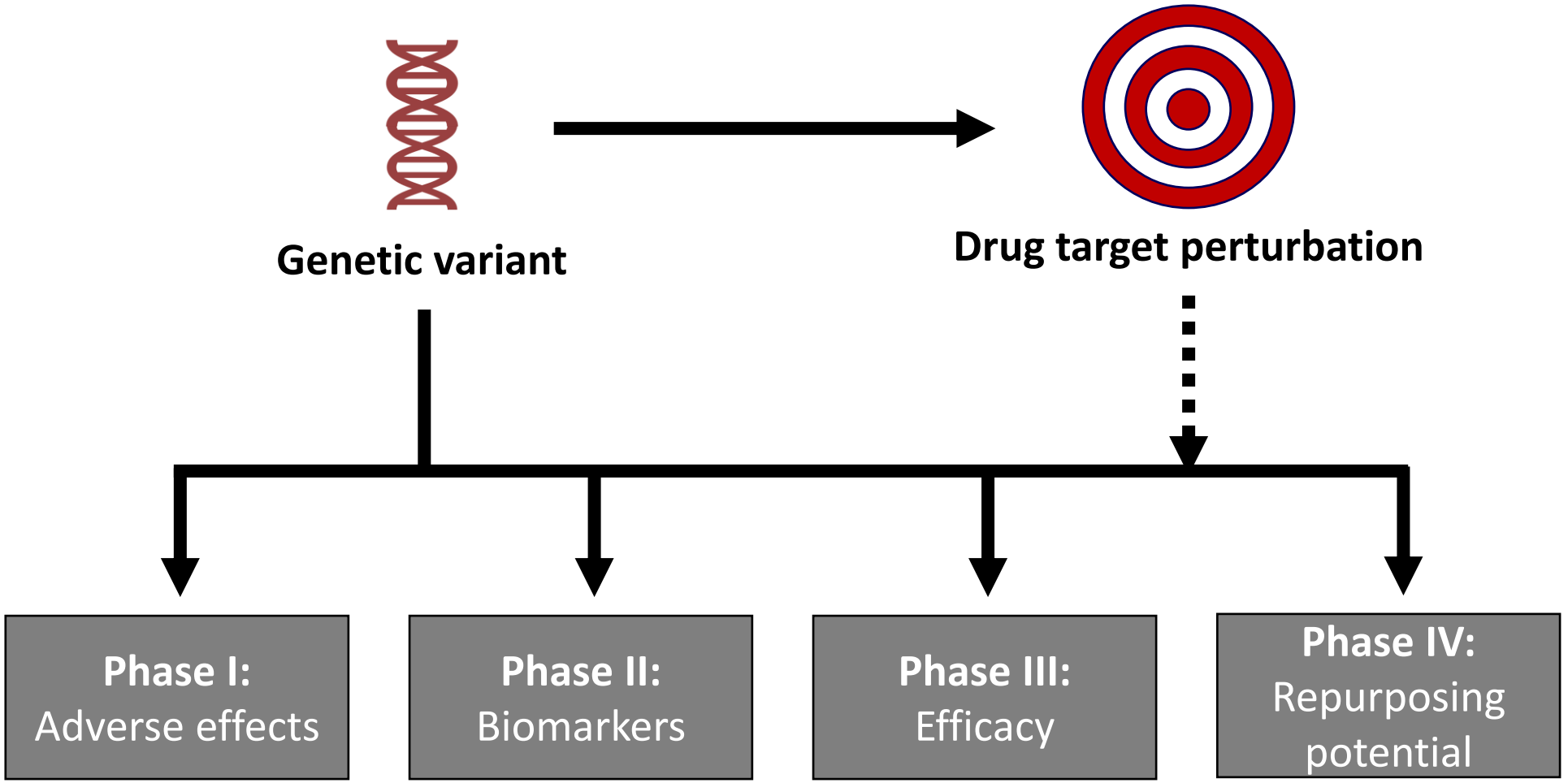
Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos





Genetic variants to proxy drug target perturbation can be leveraged to facilitate all stages of drug development

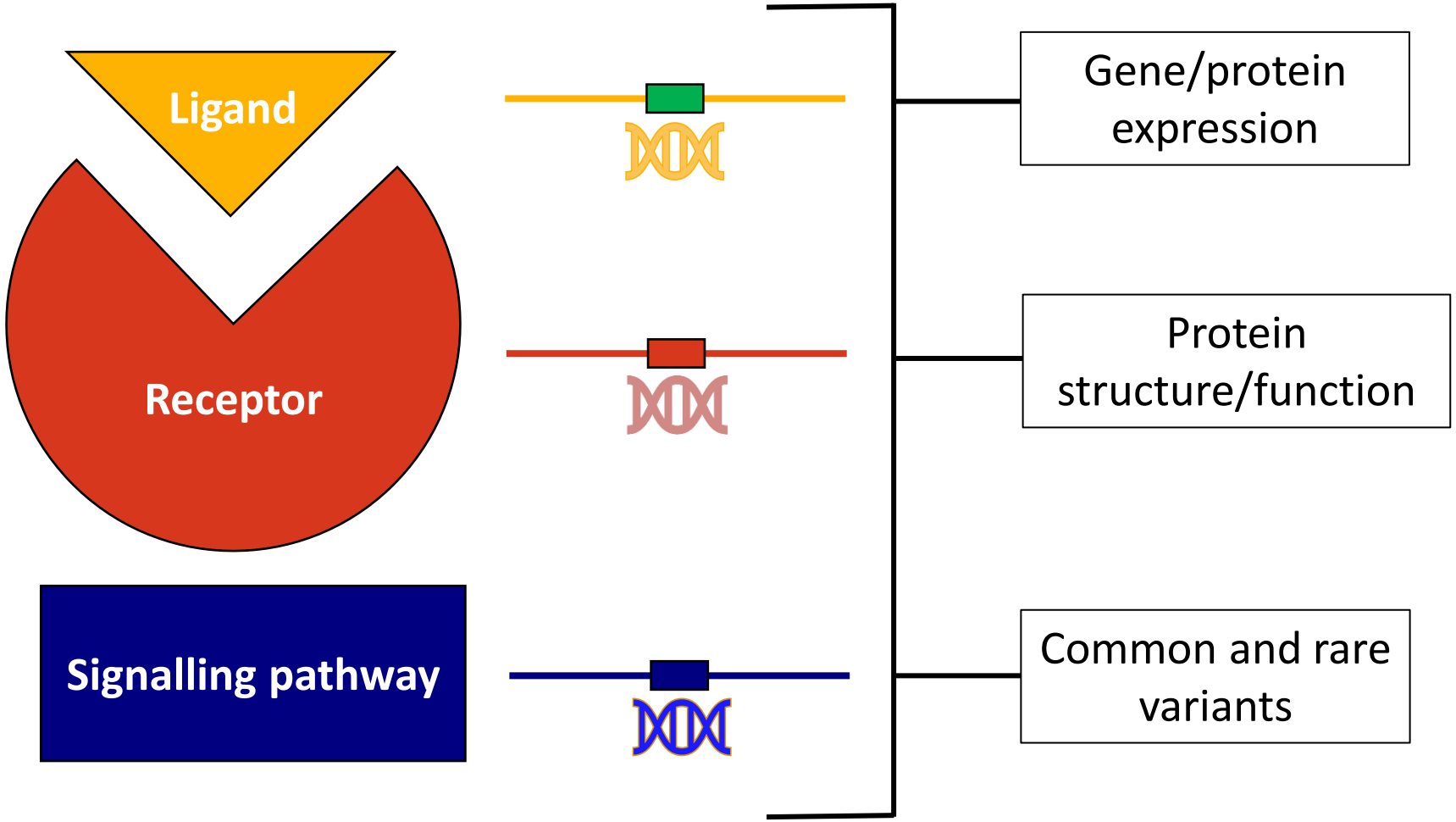


MR to investigate drug effects?

	Conventional MR	MR investigating drug effects
Aim of the analysis	To investigate the effect of an exposure on an outcome	To investigate the effect of perturbing a drug target on an outcome
Genomic location of instruments	Genome-wide	Often restricted to the locus of the gene encoding the drug target under study
Selection of genetic instruments	Variants associated with the exposure under study	Variants associated with perturbation of the drug target under study
Statistical analysis	Typically uses uncorrelated variants; higher risk of pleiotropic effects on the outcome through pathways unrelated to the exposure	More frequent use of methods to account for correlation between instrument variants; lower risk of pleiotropic effects on the outcome through pathways unrelated to the drug target

Instrument selection for drug target perturbation

Genetic variants to proxy drug target perturbation identified through relational to functionally relevant traits



Phenotypes that can be used to weight the effect of a genetic proxy for a drug target

Gene Expression Levels

eQTLs in disease-relevant tissue

Protein Levels

pQTLs in disease-relevant tissue

Downstream Biomarkers

Molecular measures of **target engagement**

Clinical Outcomes

Disease **risk factors** and **outcomes**

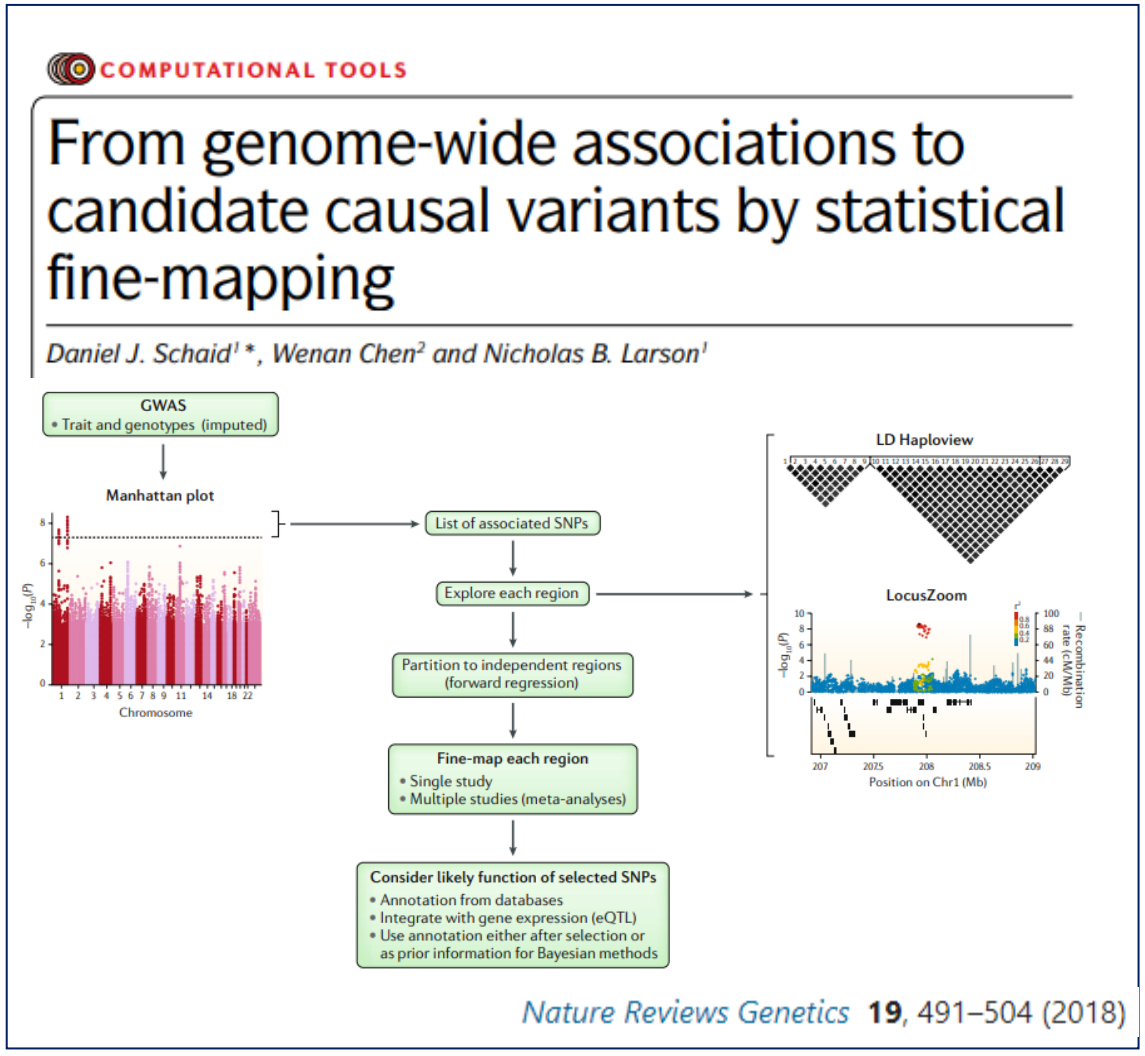
ACE: ACE expression

IL1RA: inflammatory cytokine

IL6R: Serum CRP levels

ADRB1: Blood pressure

Selection of instrumental variables

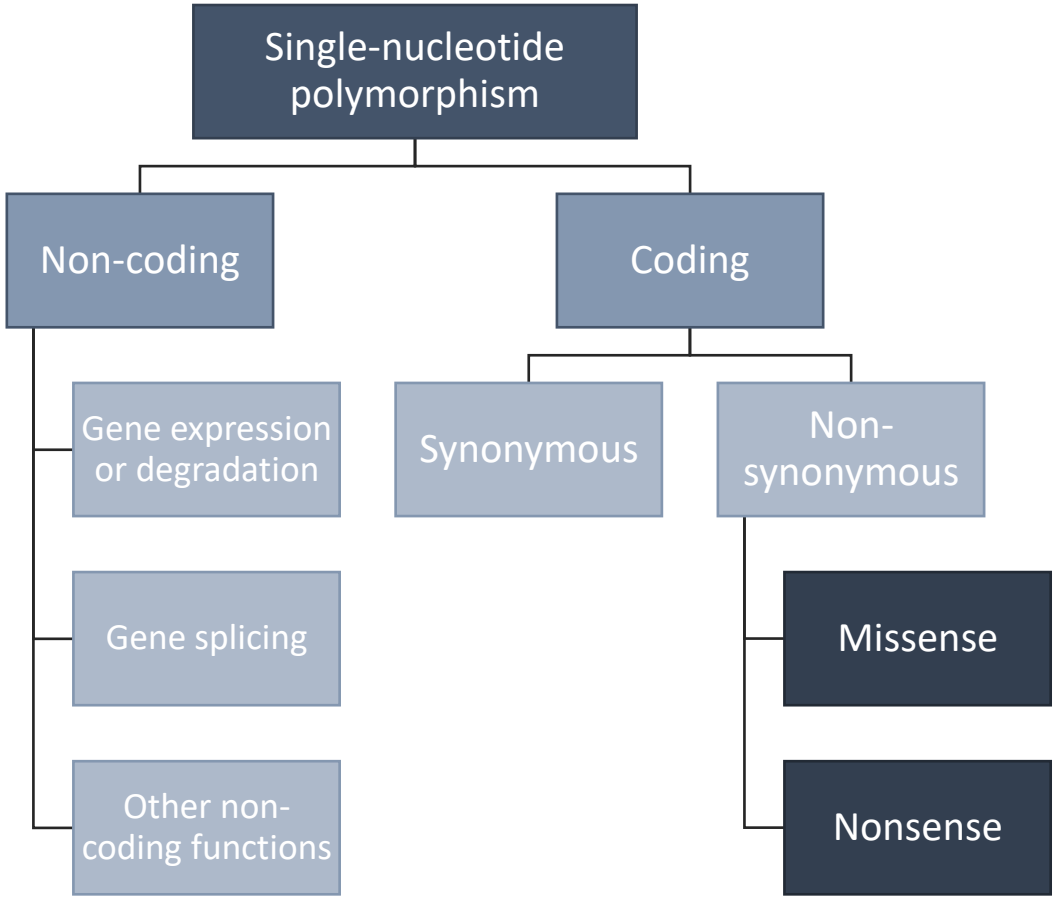


COMPUTATIONAL TOOLS

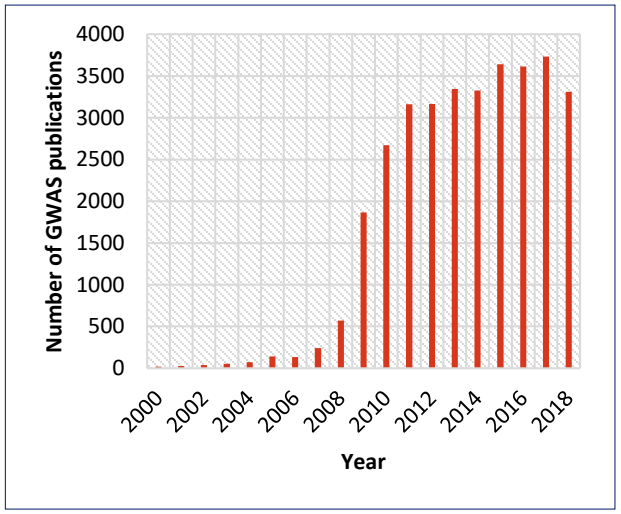
From genome-wide associations to candidate causal variants by statistical fine-mapping

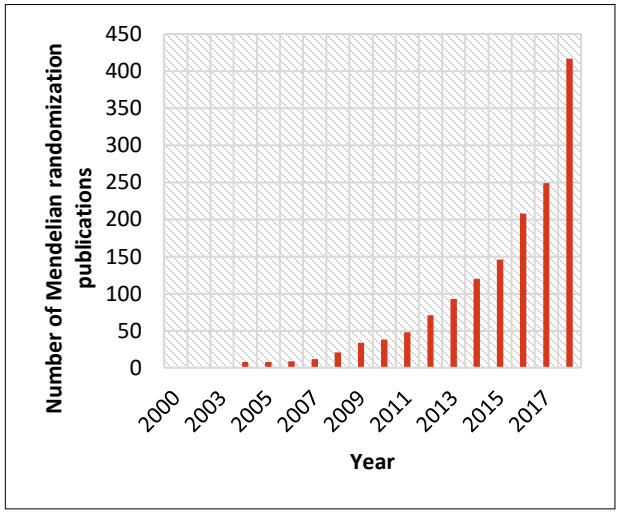
Daniel J. Schaid[1], Wenan Chen[2] and Nicholas B. Larson[1]*

Nature Reviews Genetics **19**, 491–504 (2018)



Public resources for data access





COMMON METABOLIC DISEASES KNOWLEDGE PORTAL

CARDIOVASCULAR DISEASE KNOWLEDGE PORTAL
Powered by the AMP-T2DKP platform

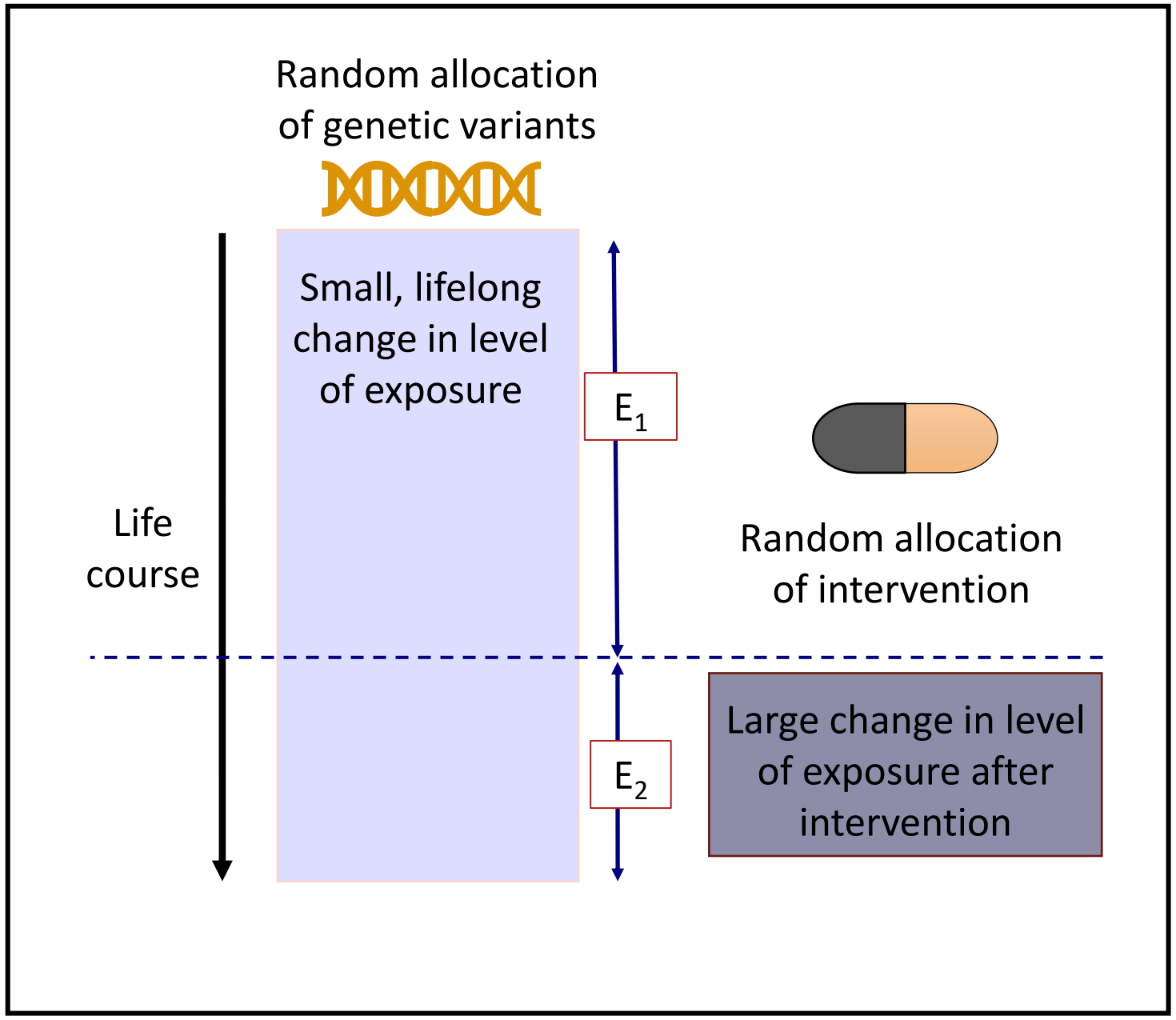
CEREBROVASCULAR DISEASE KNOWLEDGE PORTAL
Powered by the AMP-T2DKP platform

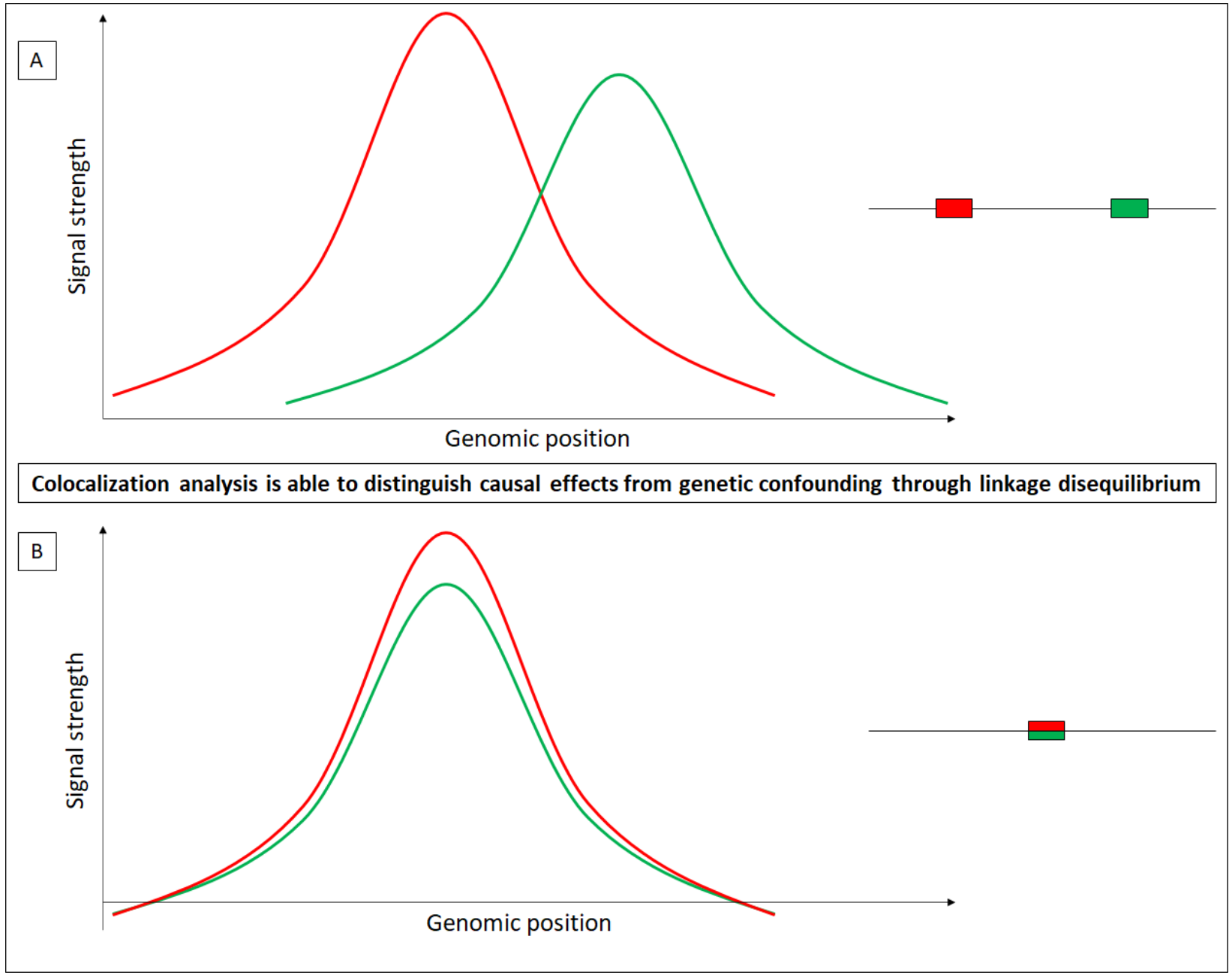
DRUGBANK Online

GTEx Portal

Open Targets Genetics
Explore **variant-gene-trait** associations from UK Biobank and GWAS Catalog

Interpretation of drug target Mendelian randomization

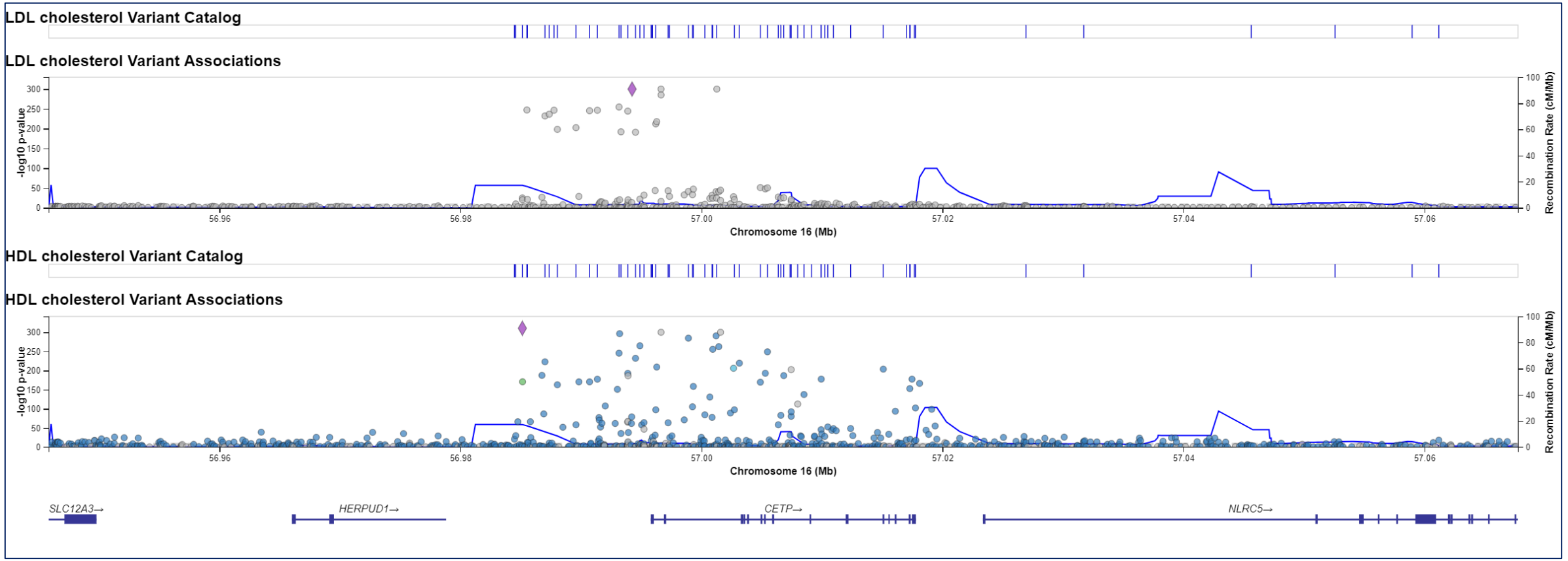

Random allocation
of genetic variants
Small, lifelong
change in level
of exposure
E_1
Life
course
Random allocation
of intervention
E_2
Large change in level
of exposure after
intervention


A
Signal strength
Genomic position
Colocalization analysis is able to distinguish causal effects from genetic confounding through linkage disequilibrium
B
Signal strength
Genomic position

Brief example

Genetic variation as instrumental variables

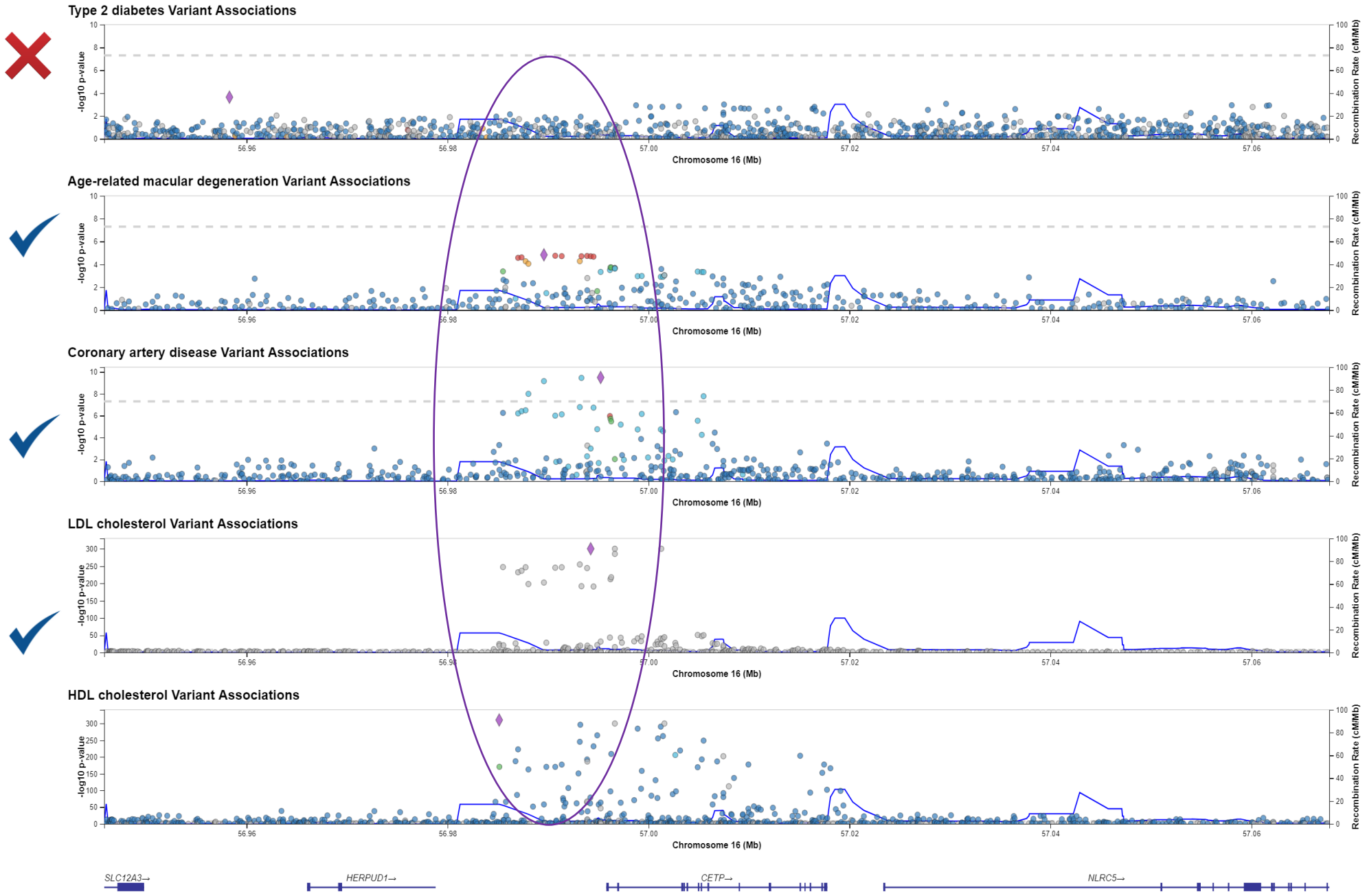
Gene to genetic proxy: example of CETP



COMMON METABOLIC DISEASES KNOWLEDGE PORTAL

Genetic variant is causal for more than one trait:

Colocalization



Thank you!