Pharmacogenomics - leveraging genomics data for predicting drug safety and efficacy

Lecture Overview

1. Traditional drug development pathway

2. Using human genomics for preclinical drug target validation and safety evaluation – Mendelian randomization analysis

3. Summary-based MR (SMR) analysis

Acknowledgement of Country

The University of Queensland (UQ) acknowledges the Traditional Owners and their custodianship of the lands on which we meet.

We pay our respects to their Ancestors and their descendants, who continue cultural and spiritual connections to Country.

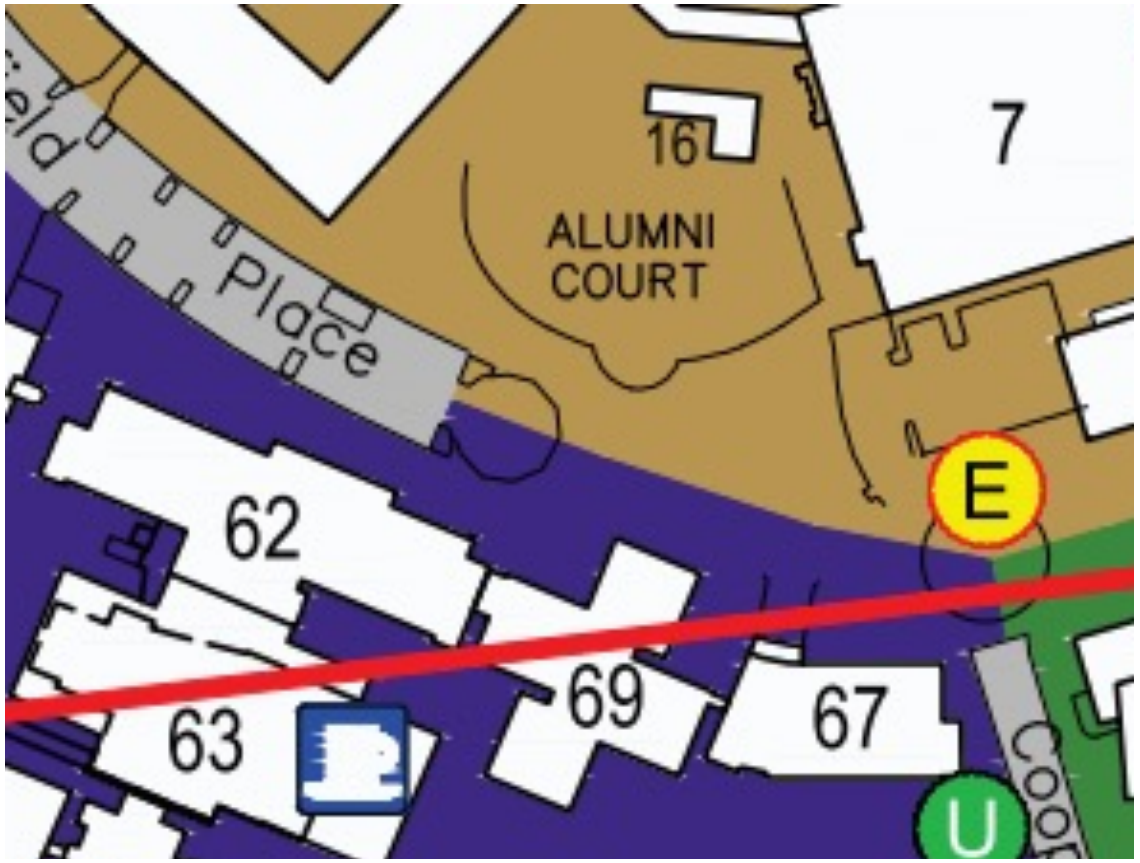
We recognise their valuable contributions to Australian and global society.

Image: Digital reproduction of *A guidance through time* by Casey Coolwell and Kyra Mancktelow

General Information

- We are currently located in Building 69
- Emergency evacuation point 

- Food court and bathrooms are located in Building 63
- If you are experiencing cold/flu symptoms or have had COVID in the last 7 days please ensure you are wearing a mask for the duration of the module



Data Agreement

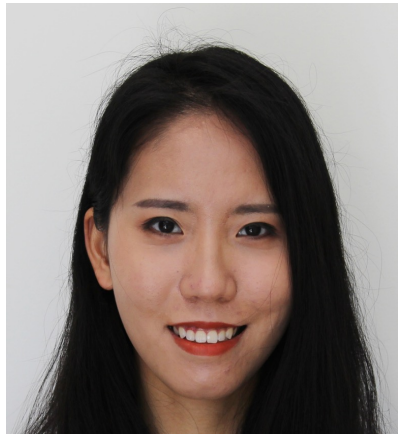
To maximize your learning experience, we will be working with genuine human genetic data, during this module.

Access to this data requires agreement to the following in to comply with human genetic data ethics regulations

Please email pctgadmin@imb.com.au with your name and the below statement to confirm that you agree with the following:

“I agree that access to data is provided for educational purposes only and that I will not make any copy of the data outside the provided computing accounts.”

Systems Genomics and Pharmacogenomics Module



Clara Jiang

Gagandeep Singh

Solal Chauquet

Sonia Shah

Zhihong Zhu

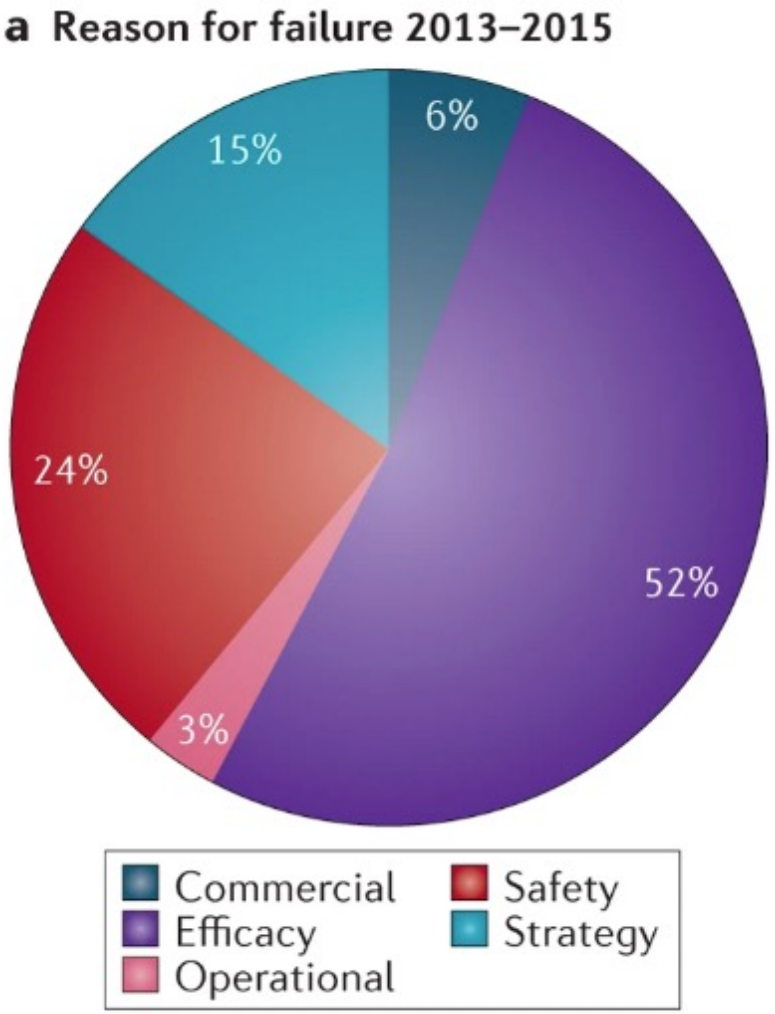
The drug development pipeline

The drug discovery & development pipeline

Basic research (3-6 years)	Preclinical studies (1-2 years)	Clinical Studies (4 – 7 years)	FDA review and approval (1 -2 years)	Post-market monitoring (indefinite)
• Disease biology • Target identification • Compound screening	• Lead identification and optimization • In vitro and • in vivo (in at least 2 different animals) efficacy and toxicology	• Phase 1 – drug safety in healthy volunteers <100 • Phase 2 – efficacy in patients (100-300) • Phase 3 – efficacy compared to placebo or existing treatments (1000+)		• Pharmacovigilance • Observational studies

90% of drugs fail in human clinical trials

- Lack of efficacy
- Unmanageable toxicity
- Poor drug-like properties (solubility, stability, in vivo pharmacokinetics
- Strategic: lack of commercial interest and change in therapeutic focus



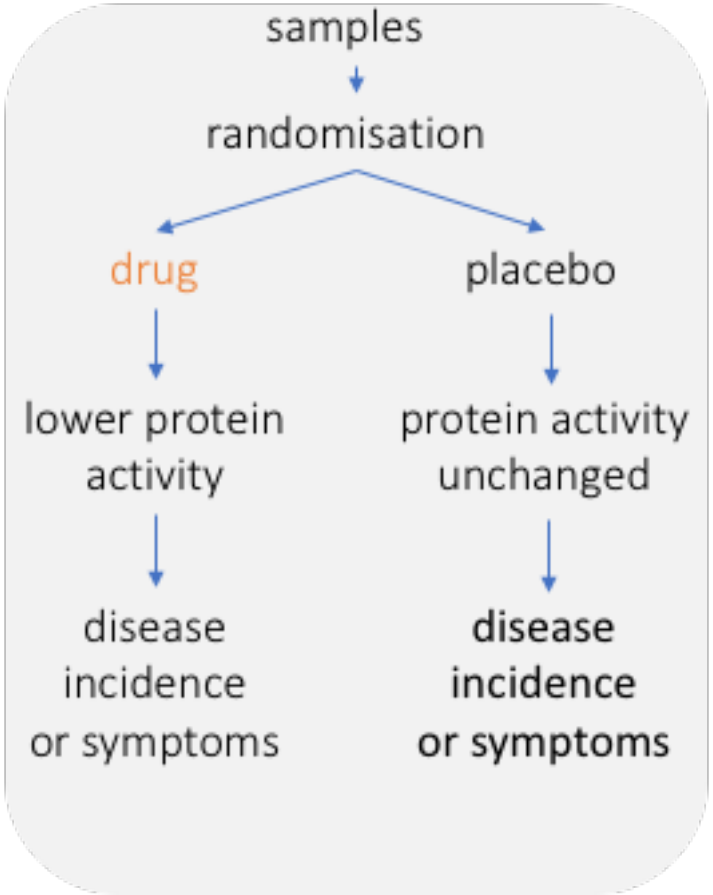
Harrison Nature Reviews Drug Discovery 2016

Lack of efficacy in humans

- Animal studies and isolated systems (cells, tissue preparations) do not always translate to *in vivo* effects in humans
  - Unsuitable drug target
  - Drug pharmacokinetics (drug metabolism, tissue absorption)

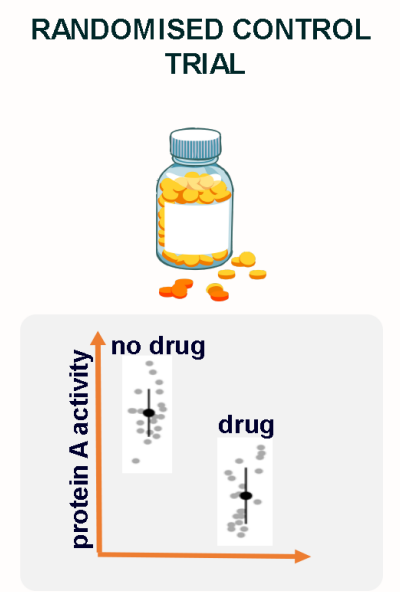
- Gold standard for testing in humans using a randomised control trial (RCT) – final step of the process
  - Costly and high risk
    - Small sample size (esp. Phase 1 and II)
    - Short follow-up time
    - Defined participant criteria (e.g. exclude multimorbid individuals)

- Improved pre-clinical prediction of effects in humans



Mendelian randomisation

Using genetics for drug target validation - Mendelian randomisation (MR)



PCSK9: Genetic mutation to groundbreaking therapy

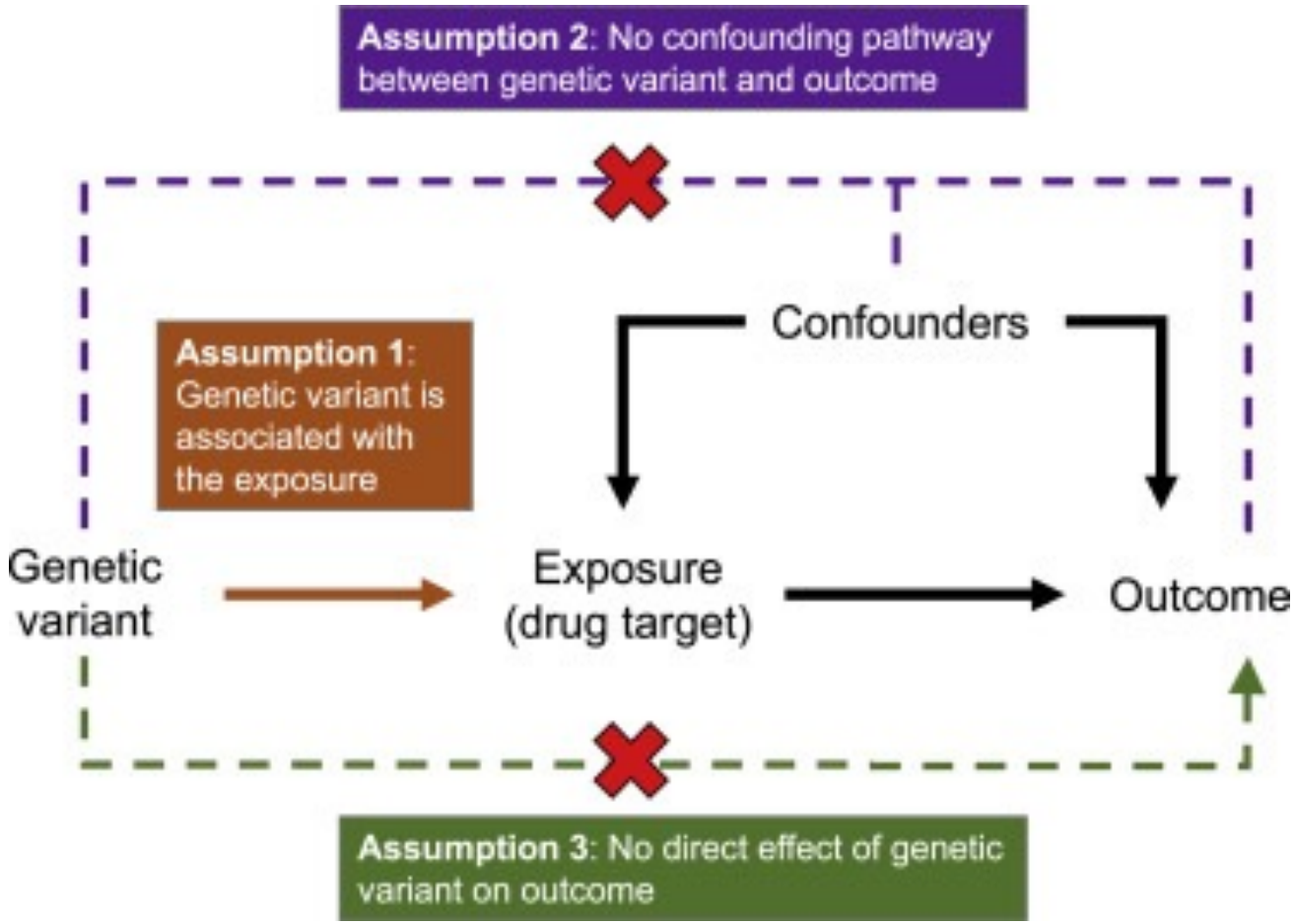
2005 Cohen et al Nature Genetics

Loss-of-function (LOF) mutations in *PCSK9* gene in African-Americans associated with:

- Substantially lower cholesterol
- Reduction in risk of cardiovascular disease

2015 first approved PCSK9 inhibitor

Assumptions of MR

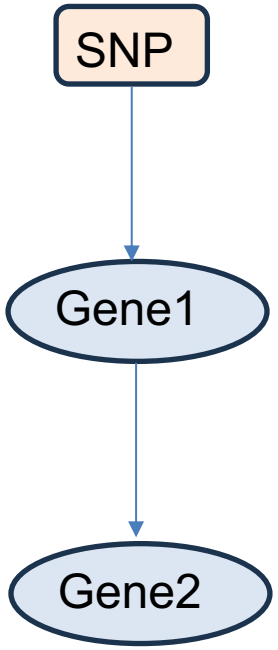


MR assumptions:
1: Genetic variant strongly associates with the exposure (instrument strength: R^2, F-statistics)

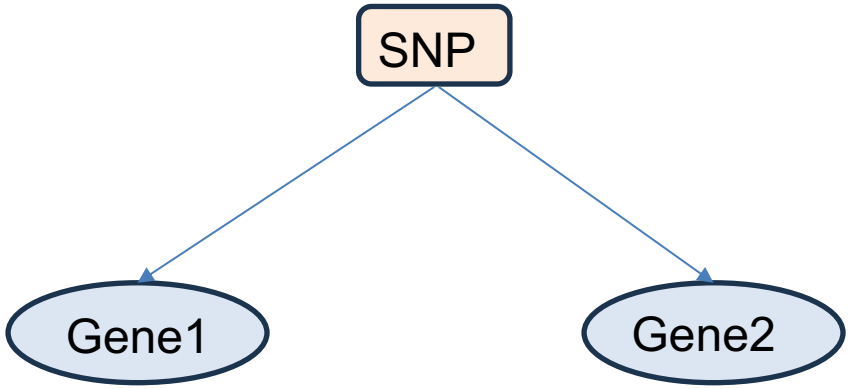
2: Genetic variant does not influence the outcome through a confounding pathway (horizontal pleiotropy or linkage)

Burgess et al Am J Hum Genet 2023

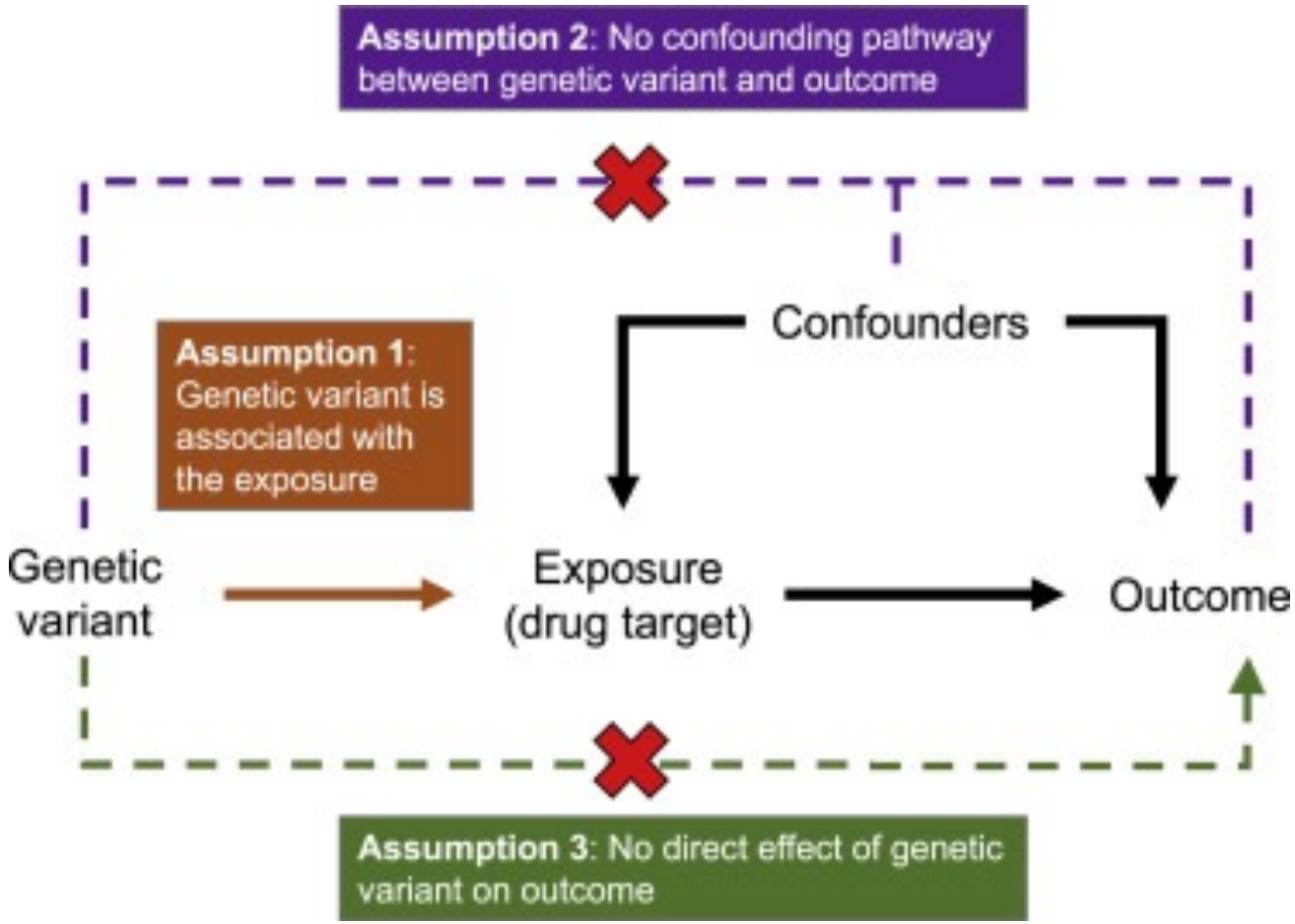
VERTICAL PLEIOTROPY



HORIZONTAL PLEIOTROPY



Assumptions of MR



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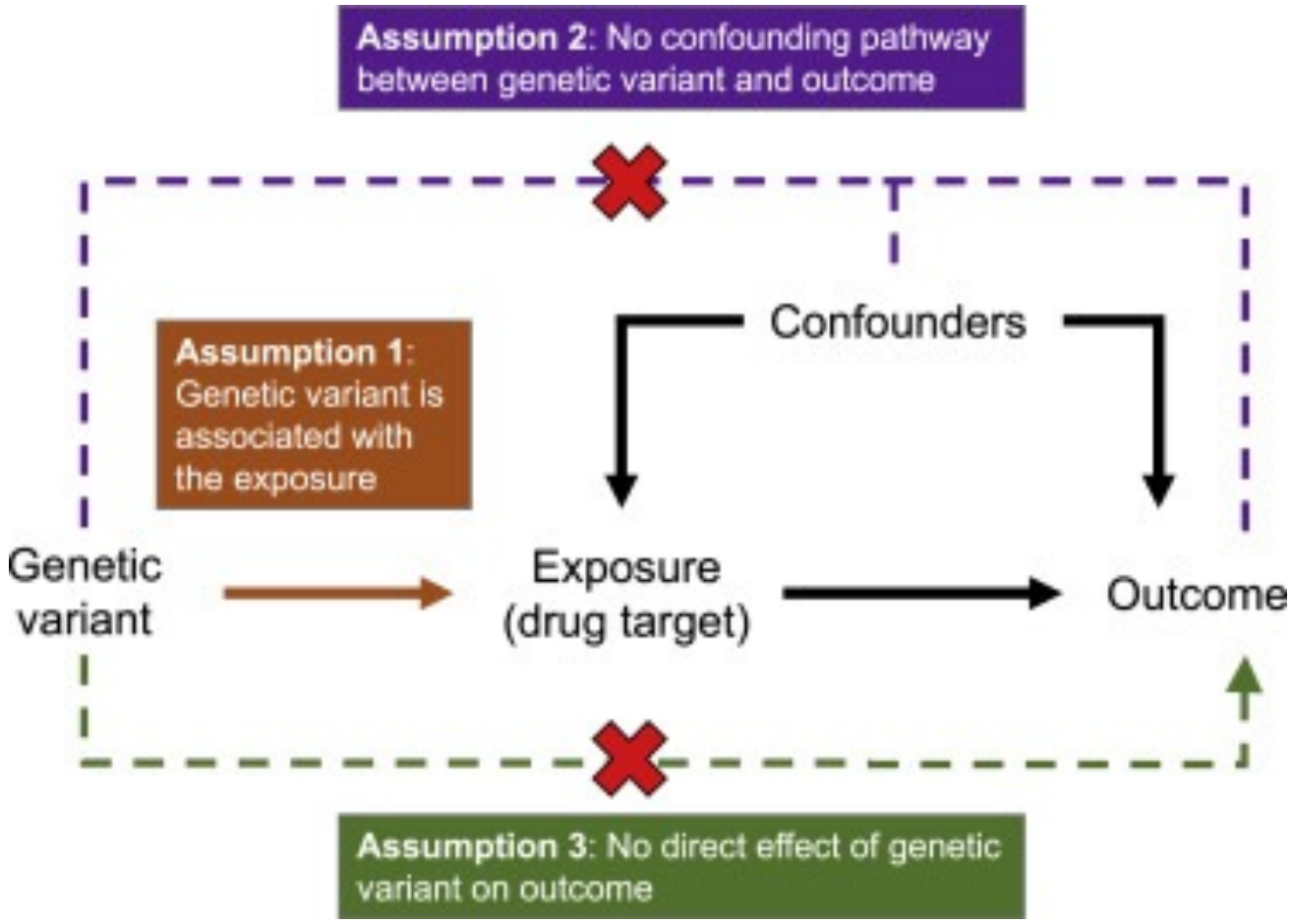
3: Effect of genetic variant on outcome is via effect on drug target

Burgess et al Am J Hum Genet 2023

Assumptions of MR



MR assumptions:
1: Genetic variant strongly associates with the exposure (instrument strength: R^2, F-statistics)

2: Genetic variant does not influence the outcome through a confounding pathway (horizontal pleiotropy or linkage)

3: Effect of genetic variant on outcome is via effect on drug target

- Drug target MR tend to use a genetic variants from a single genomic region near the target gene (cis-MR)
- Multi-SNP analysis when multiple independent cis-variants exist
- Genetic variants need to replicate the effect of the drug

Burgess et al Am J Hum Genet 2023

LOF/GOF as instruments for MR

nature > analyses > article

Analysis | Open Access | Published: 27 May 2020

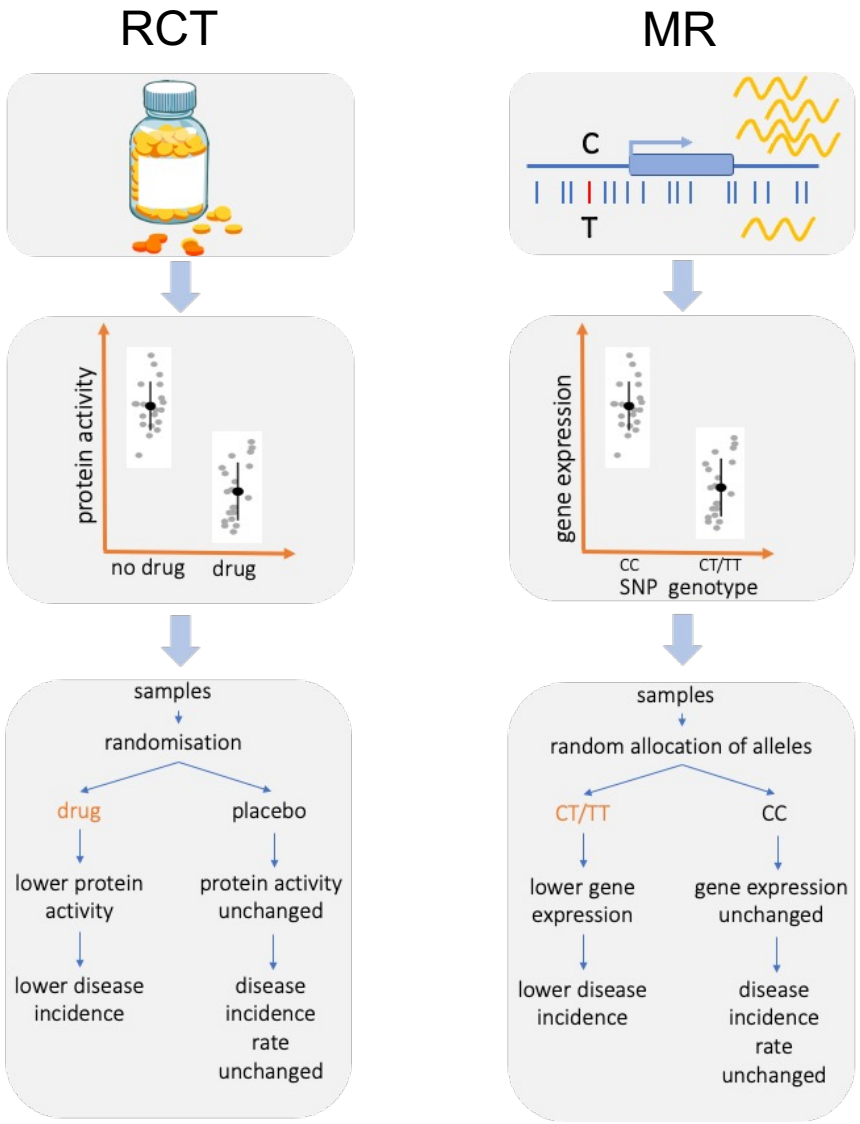
Evaluating drug targets through human loss-of-function genetic variation

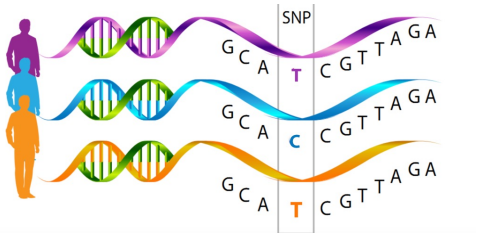
Eric Vallabh Minikel, Konrad J. Karczewski, Hilary C. Martin, Beryl B. Cummings, Nicola Whiffin, Daniel Rhodes, Jessica Alföldi, Richard C. Trembath, David A. van Heel, Mark J. Daly, Genome Aggregation Database Production Team, Genome Aggregation Database Consortium, Stuart L. Schreiber & Daniel G. MacArthur

- Genome Aggregation Database (gnomAD)
- Whole exome data in > 125,000 individuals
- Predicted LOF (nonsense, essential splice site, and frameshift variants)
- Individuals with LOF are very rare

Require sample sizes that are 1000x bigger

eQTLs as instruments for MR analysis





cis-eQTLs as proxies for drug exposure.

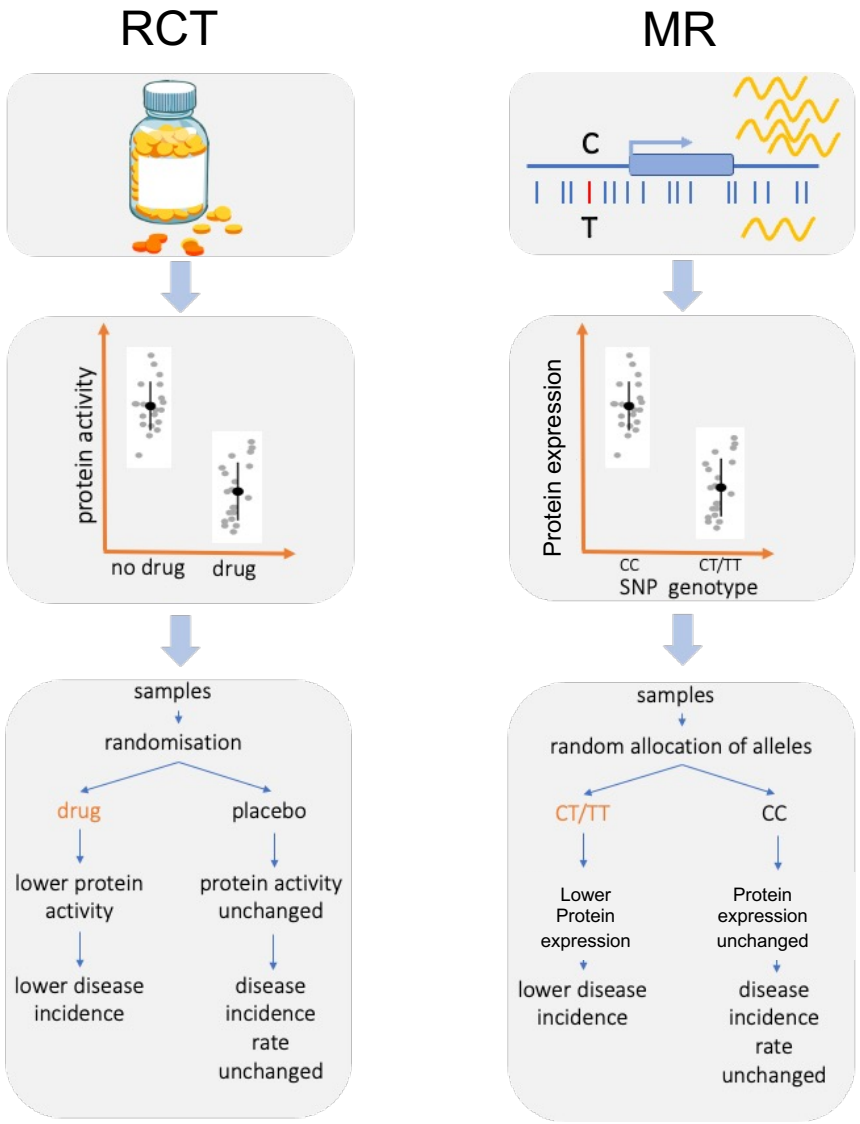
PROS:

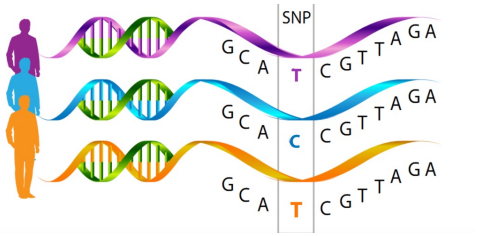
- Gene expression easily measured in different tissues

CONS:

- Gene expression does not always translate to protein levels or activity

pQTLs as instruments for MR analysis





pQTLs as proxies for drug exposure.

PROS:

- Closer phenotype to drug effects

CONS:

- Difficult to measure outside of blood

Example: Darapladib

Published: 01 July 2014

GSK's darapladib failures dim hopes for anti-inflammatory heart drugs

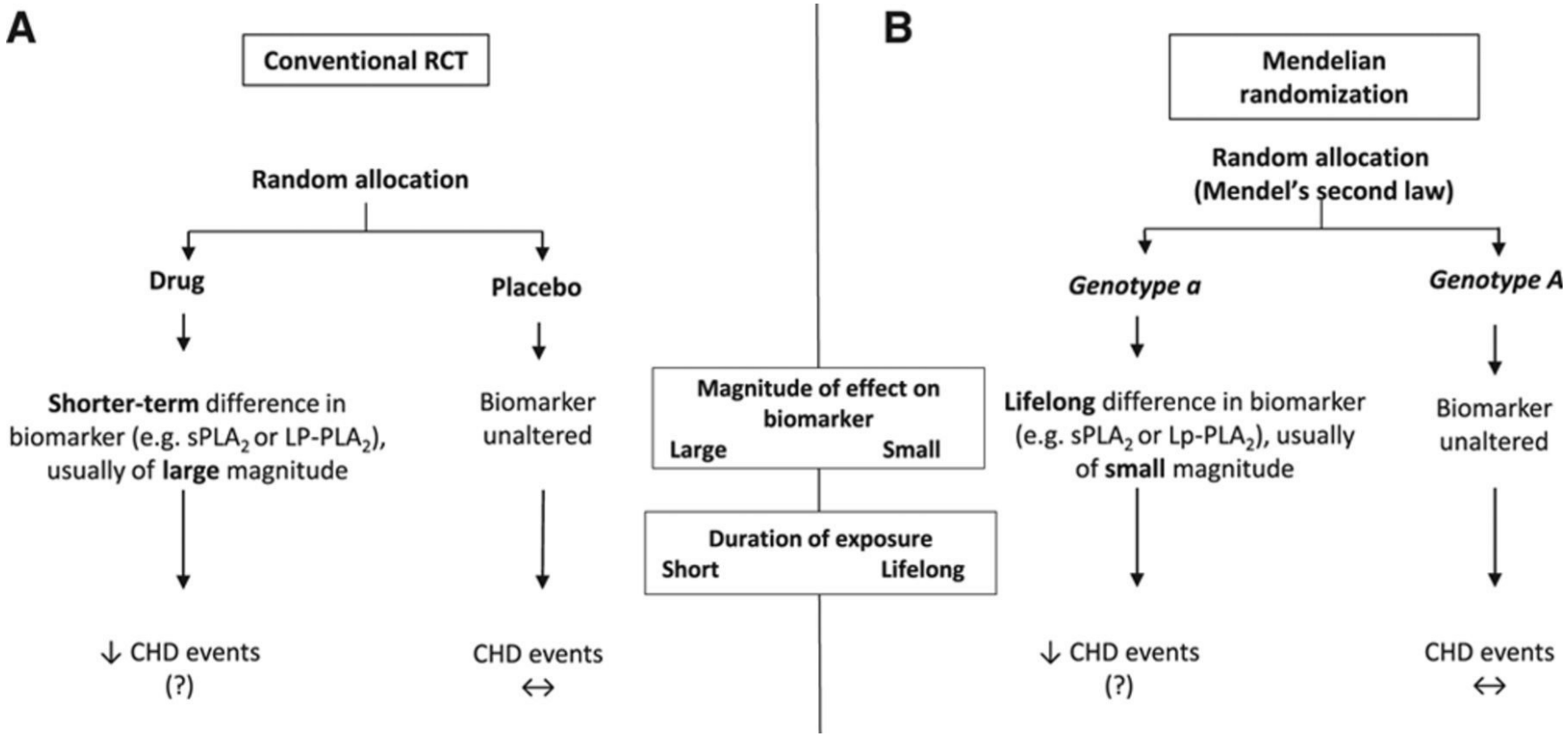
Asher Mullard

Nature Reviews Drug Discovery **13**, 481–482 (2014) | Cite this article

Product	Darapladib
Sponsor	GlaxoSmithKline
Purpose	Add-on to a statin for prevention of cardiovascular disease complications in patients with prior heart attack
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite exciting biomarker evidence in phase 2, in phase 3 trials darapladib failed to reduce the risk of heart attack or cardiac death compared with placebo in patients with chronic cardio vascular disease.

https://www.fda.gov/media/102332/download

MR to Test Causality of Lp-PLA2



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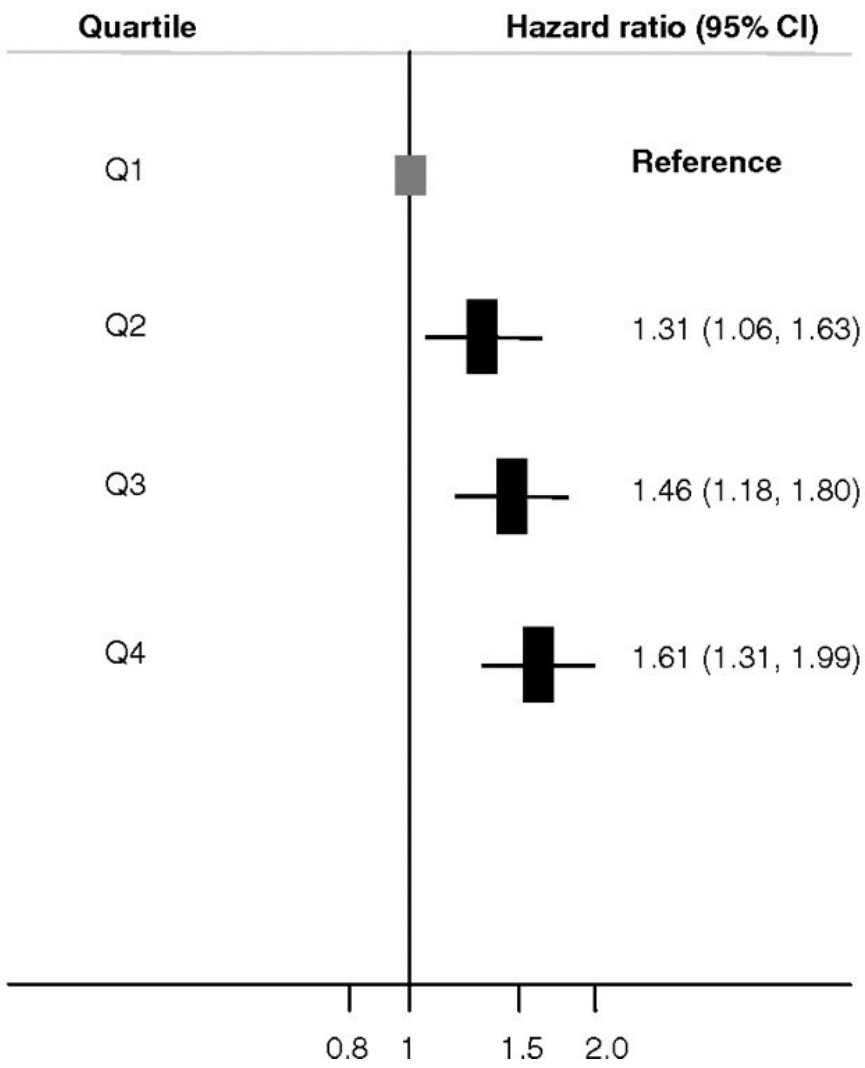
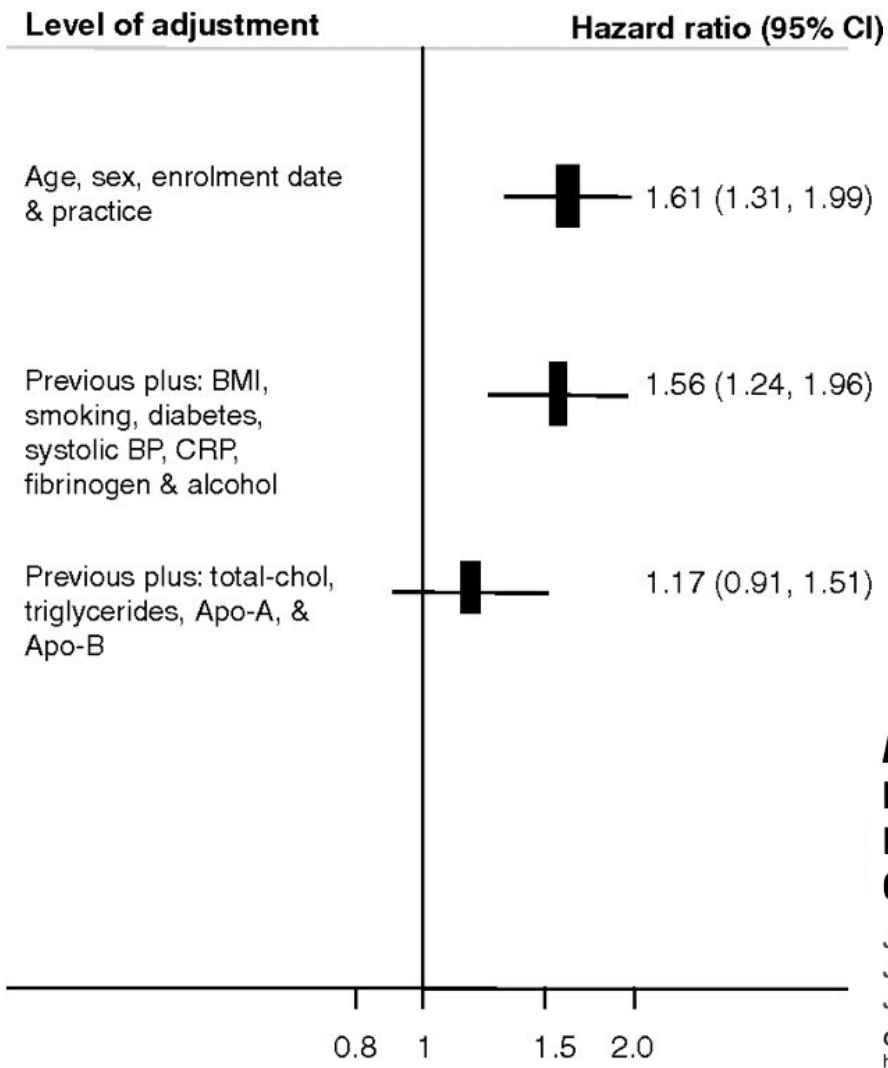
Lp-PLA2 activity and coronary heart disease risk
1030 Cases & 3852 Controls

Model-1:adjusted by age, sex, enrolment date and practice



Effect of the incremental degree of adjustment on the Lp-PLA2-CHD association

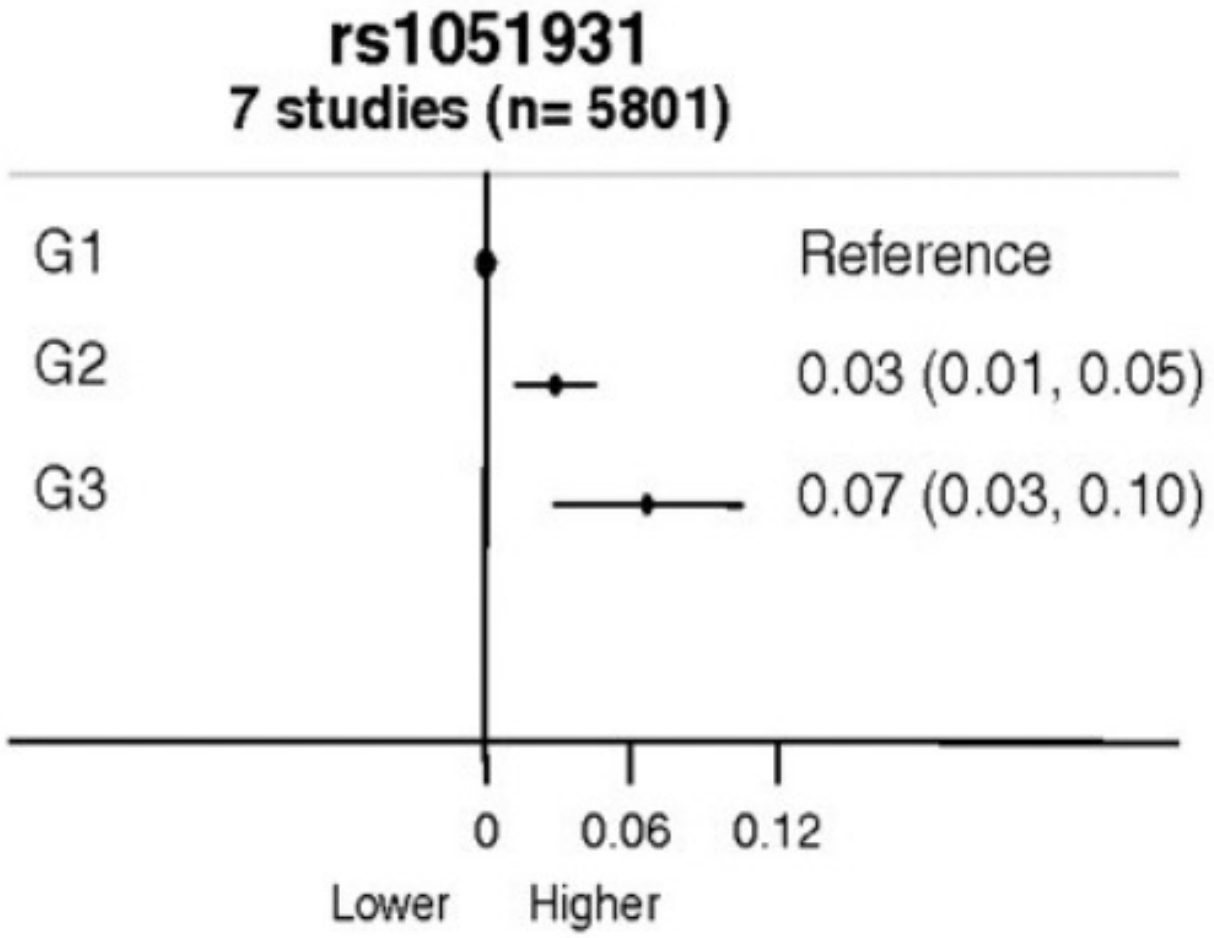
Hazard ratio (95%CI) for Top vs. bottom quartile



PLA2G7 Genotype, Lipoprotein-Associated Phospholipase A_2 Activity, and Coronary Heart Disease Risk in 10 494 Cases and 15 624 Controls of European Ancestry

Juan P. Casas, Ewa Ninio, Andrie Panayiotou, Jutta Palmen, Jackie A. Cooper, Sally L. Ricketts, Reecha Sofat, Andrew N. Nicolaides, James P. Corsetti, F. Gerry R. Fowkes, ... See all authors

Originally published 17 May 2010 | https://doi.org/10.1161/CIRCULATIONAHA.109.923383 | Circulation. 2010;121:2284–2293



Mean difference (95%C) in log-LpPLA2 activity by PLA2G7 variants

G1: Homozygous common-allele;

G2: Heterozygous;

G3: Homozygous rare-allele

***PLA2G7* Genotype, Lipoprotein-Associated Phospholipase A_2 Activity, and Coronary Heart Disease Risk in 10 494 Cases and 15 624 Controls of European Ancestry**

Juan P. Casas, Ewa Ninio, Andrie Panayiotou, Jutta Palmen, Jackie A. Cooper, Sally L. Ricketts, Reecha Sofat, Andrew N. Nicolaides, James P. Corsetti, F. Gerry R. Fowkes, ... See all authors

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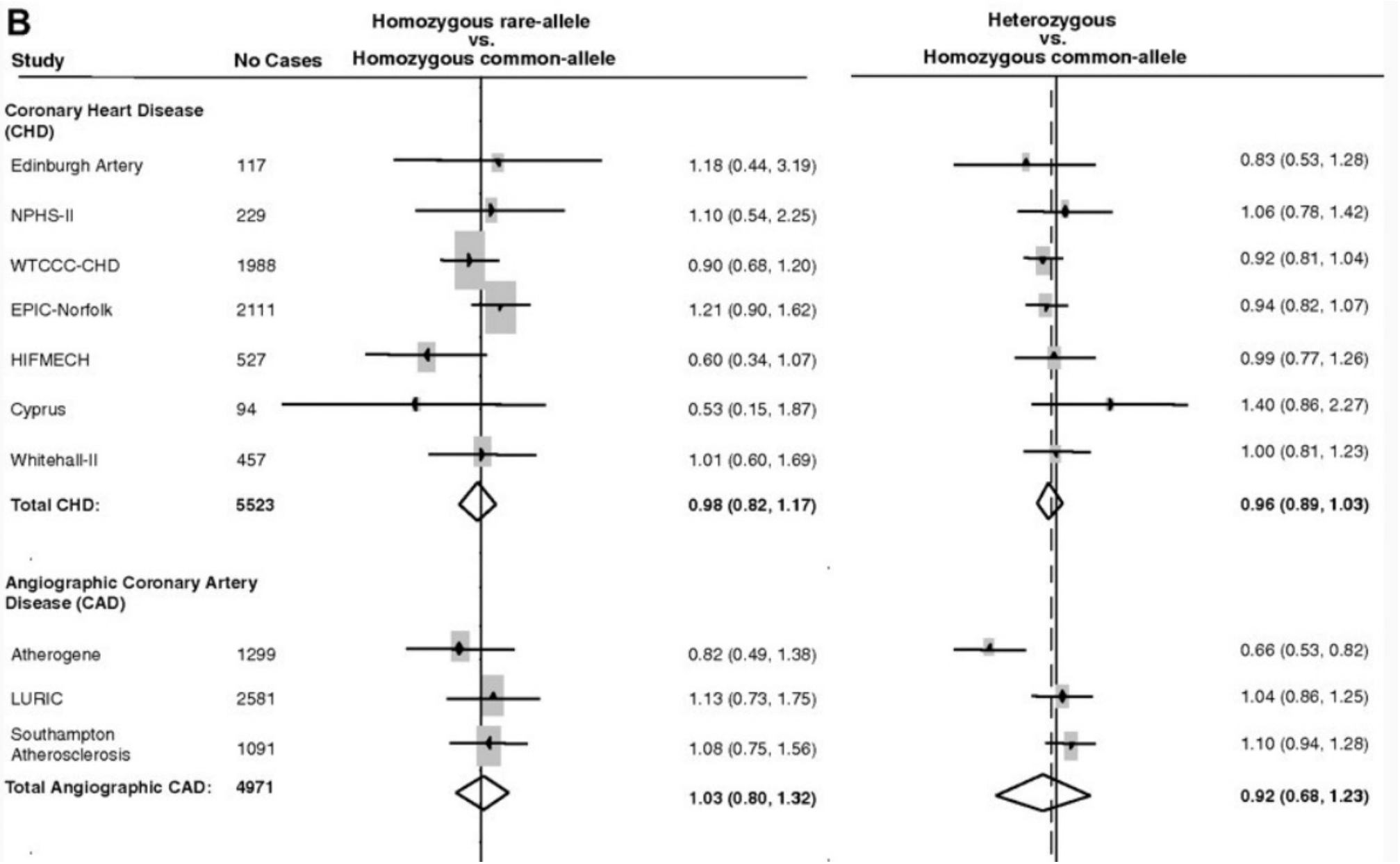


No association of *PLA2G7* variant with risk of CHD

Genetics for drug target validation

nature genetics

Explore content ⌄ About the journal ⌄ Publish with us ⌄

nature > nature genetics > analyses > article

Published: 29 June 2015

The support of human genetic evidence for approved drug indications

Matthew R Nelson ✉, Hannah Tipney, Jeffery L Painter, Judong Shen, Paola Nicoletti, Yufeng Shen, Aris Floratos, Pak Chung Sham, Mulin Jun Li, Junwen Wang, Lon R Cardon, John C Whittaker & Philippe Sanseau

Selecting genetically supported targets could ***double the success rate*** in clinical development

Drug safety

One man is brain-dead and another five people are in hospital after an experimental drug was administered to 90 people in a French clinical trial.

Drug safety

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Original Investigation

May 9, 2017

Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD[1]; Nilay D. Shah, PhD[2]; Jenerius A. Aminawung, MD, MPH[3]; et al

» Author Affiliations | Article Information

JAMA. 2017;317(18):1854-1863. doi:10.1001/jama.2017.5150

FDA announced alerts, warnings, or recalls on about **one-third** of approved drugs

On- vs off-target effects

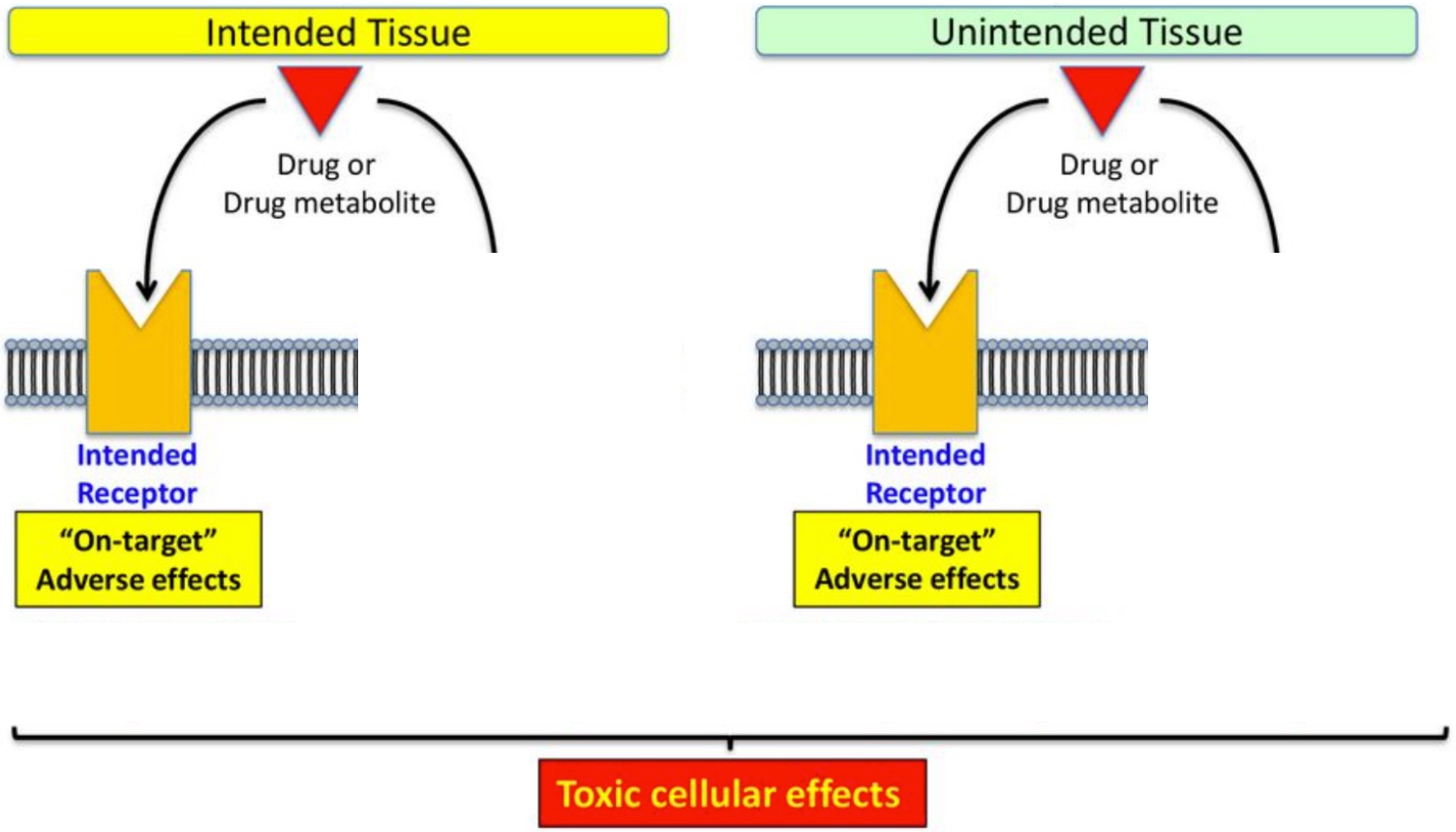


Image from https://www.semanticscholar.org/paper/Drug-Toxicity.-Taniguchi-Armstrong

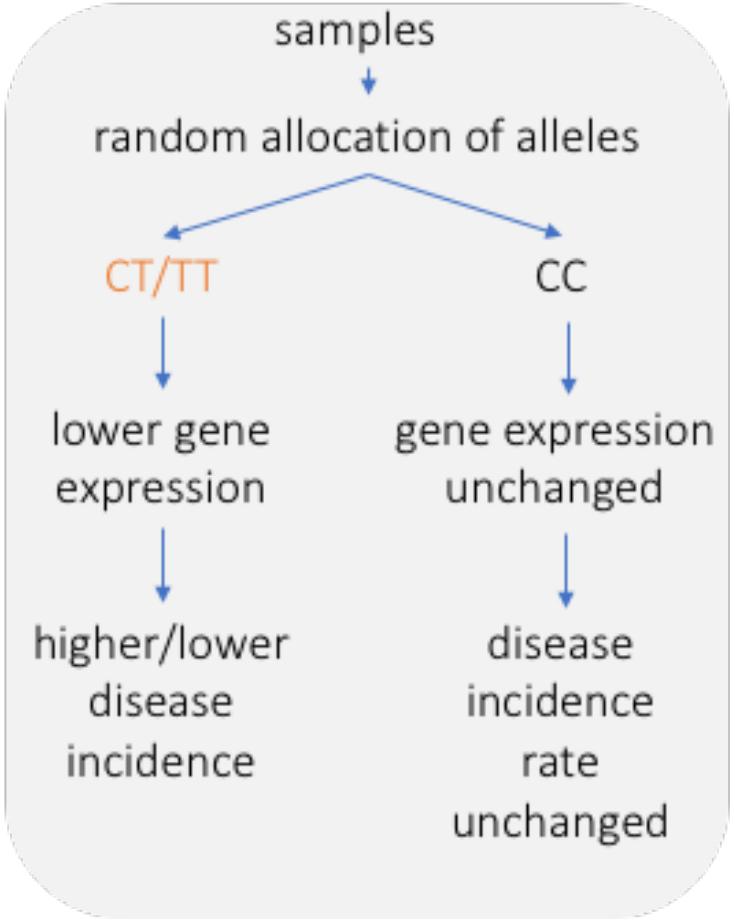
Toxicity

Pharmacogenetics – differences in drug metabolism and clearance can lead to a higher/lower dose

Important to understand if the toxic effect is mediated through intended or unintended target

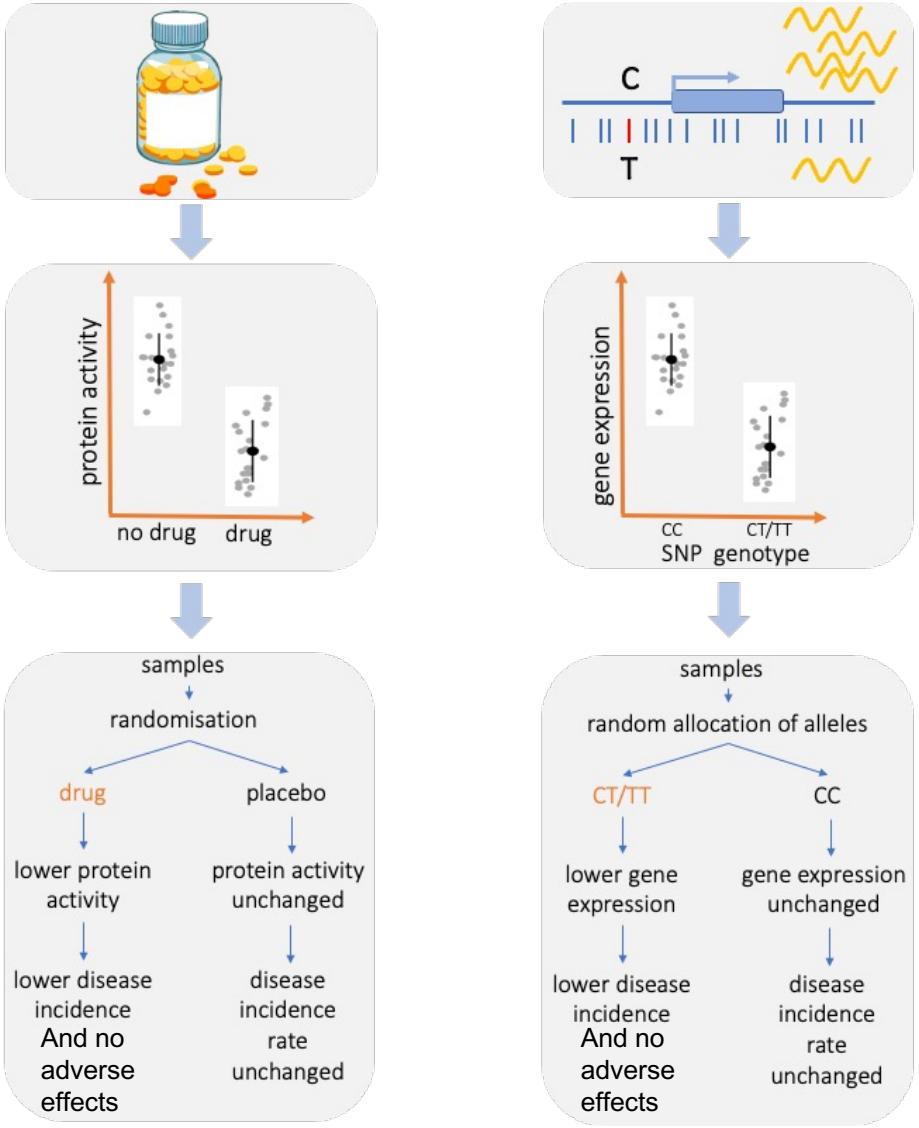
Importance of understanding pleiotropic effects of intended drug target

Testing drug safety and efficacy- Randomised Control Trial (RCT)



- Costly and high risk
  - Small sample size
  - Short follow-up time
  - Defined participant criteria (e.g. exclude multimorbid individuals)
- Only common and large adverse effects may be observed
- Full range of effects (and long term effects) undetected until wider use

MR to assess drug safety - pleiotropic associations



Identifying drug intended and unintended drug targets:

- DrugBank
- CheMBL

Identifying MR instruments for drug exposure:

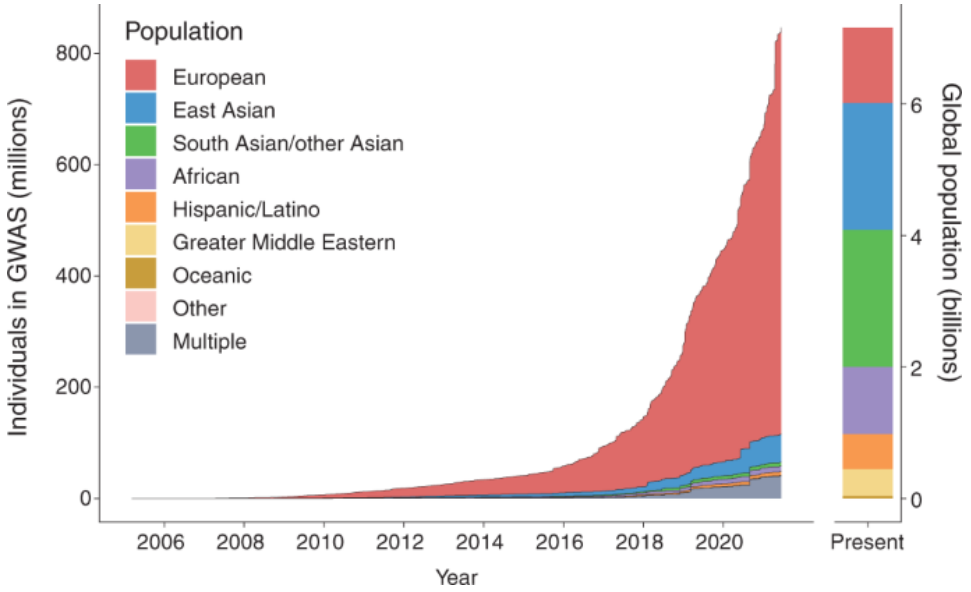
- LOF/GOF
- eQTL
- pQTL

MR for drug target validation and safety

- MR studies **DO NOT** replace RCTs, but together with other pre-clinical evidence can be used to prioritise drug targets.

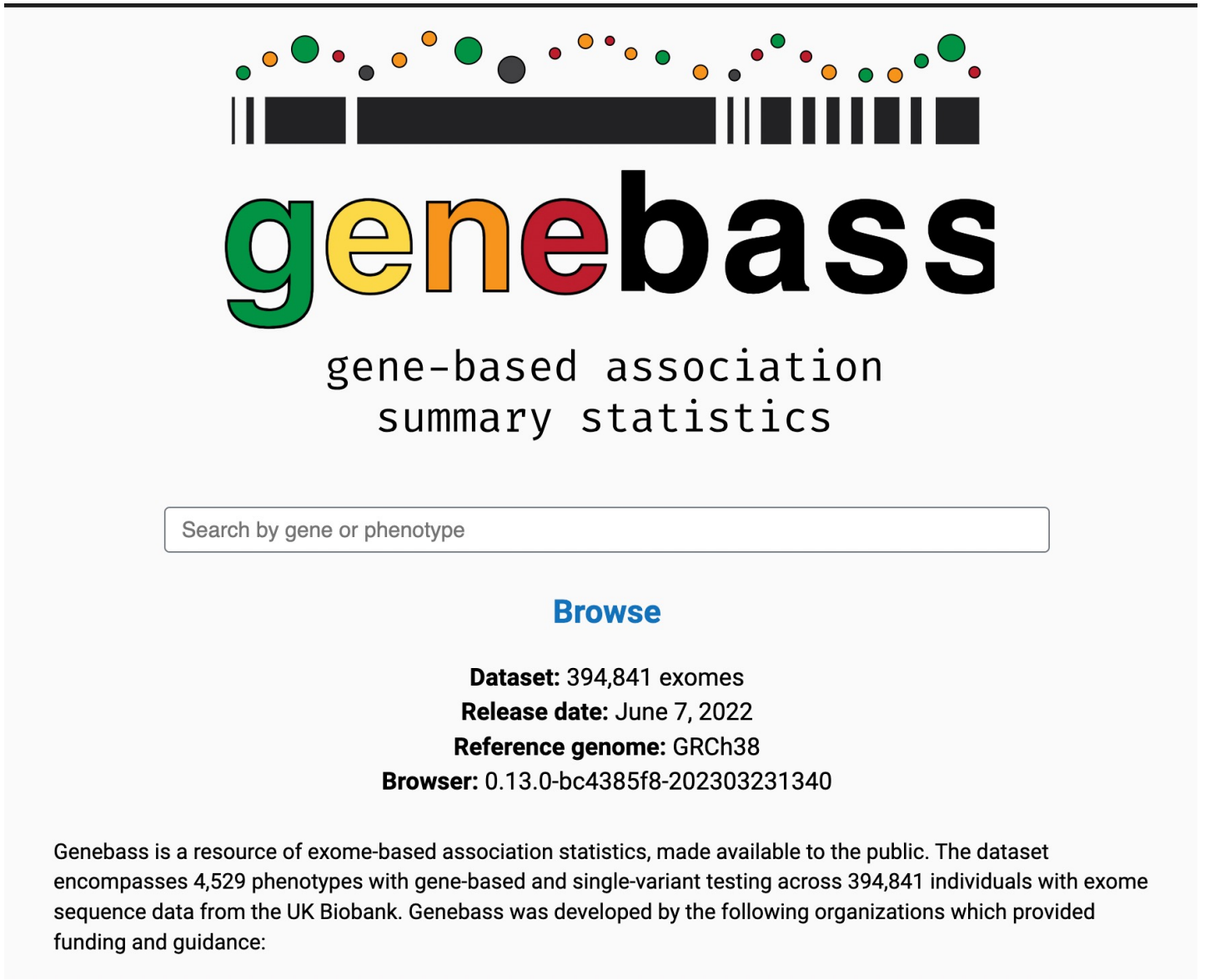
- Only possible due to large, publicly availability GWAS and WGS studies for 1000s of human traits
  - Drug target validation - Test for intended effect
  - Drug target safety - Test for unintended effects (useful for looking at effects in co-morbid individuals)

- Effects in different ancestral groups
  - Comparison of effects sizes
  - Need more data increasing data availability



Fatumo et al Nature Medicine 2021

pLOF Gene-based burden test - Genebass



Gene: PCSK9 (ENSG00000169174) **Burden set:** pLoF

4529 pLoF gene burden associations with PCSK9

Filter phenotypes

Burden test

Burden | SKAT | SKAT-O

Gene P-value coloring

1.0 > 1e-4 > 2.5e-6

-Log$_{10}$P cutoffs

0 — 134

Beta cutoffs

-6.11 — 0.184

Plot options

P-value | Beta | Both

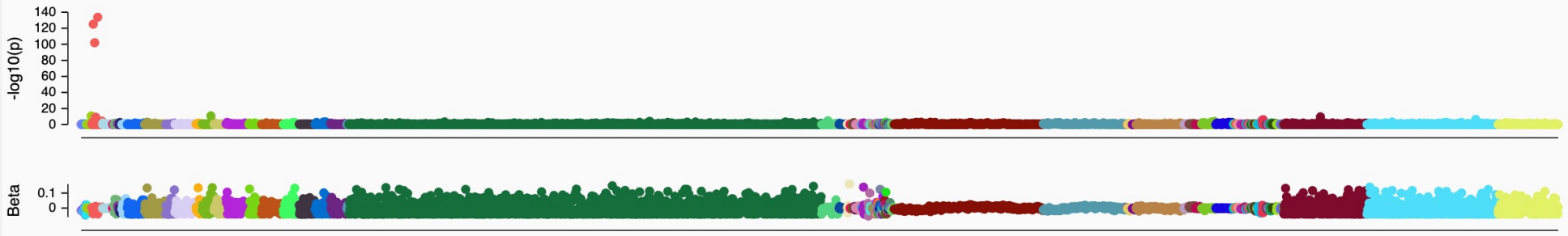
P-value ordered

Log Log Plot

Categories

- Showcase
  - Biological samples (79)
  - Other (45)
  - Health-related outcomes (2232)
  - Online follow-up (108)
  - Population characteristics (1)
  - UK Biobank Assessment Centre (2004)
- No category (52)

SELECT ALL | SELECT NONE



Burden set

pLoF | missense|LC | synonymous

Include filtered

Multi-phenotype selection

Select top | Clear selected

Filter to selected

Description	Phenotype	Trait type	Sex	Category	Info	N cases	N controls	P-Value (SKAT-O)	Beta	Select
LDL direct	30780 irnt	Continuous	Both	Biological samples > Assay results > Bloo...		376106		2e-134	-3.89e-2	
Apolipoprotein B	30640 irnt	Continuous	Both	Biological samples > Assay results > Bloo...		374968		8.21e-126	-3.82e-2	
Cholesterol	30690 irnt	Continuous	Both	Biological samples > Assay results > Bloo...		376808		1.18e-102	-3.34e-2	
E78 Disorders of lipoprotein metabolis...	130814	ICD10	Both	Health-related outcomes > First occurren...		81328	313513	1.29e-11	-2.85e-2	
total fatty acids	total_fatty_a...	Continuous	Both	Biological samples > Assay results > Bloo...		94910		1.82e-11	-2.19e-2	
High cholesterol	20002 1473	Categorical	Both	UK Biobank Assessment Centre > Verbal i...		48438	346345	2.16e-10	-3.1e-2	
Direct bilirubin	30660 irnt	Continuous	Both	Biological samples > Assay results > Bloo...		320418		5.27e-10	1.14e-2	
Simvastatin	20003 1140...	Categorical	Both	UK Biobank Assessment Centre > Verbal i...		45015	349768	3.38e-7	-2.64e-2	
Medication for cholesterol, blood pres...	6153 1	Categorical	Both	UK Biobank Assessment Centre > Touchs...		26921	185712	8.3e-7	-3.07e-2	
Medication for cholesterol, blood pres...	6177 1	Categorical	Both	UK Biobank Assessment Centre > Touchs...		41662	137885	5.22e-6	-2.91e-2	
FH Heart disease custom	FH_Heart_di...	Categorical	Both			176473	204519	1.6e-5	-1.47e-2	
Vitamin D	30890 irnt	Continuous	Both	Biological samples > Assay results > Bloo...		360290		3.94e-5	6.79e-3	
W44.1 Primary total prosthetic replace...	41200 W441	Categorical	Both	Health-related outcomes > Hospital inpati...		304	394537	7.57e-5	1.13e-1	

HOME

Search by gene or phenotype

0.13.0-bc4385f8-202303231340

Gene: HMGCR (ENSG00000113161) **Burden set:** pLoF

4521 pLoF gene burden associations with HMGCR

Filter phenotypes

Burden test
Burden | SKAT | SKAT-O

Gene P-value coloring
1.0 > 1e-4 > 2.5e-6

-Log$_{10}$P cutoffs
0.00 — 4.00

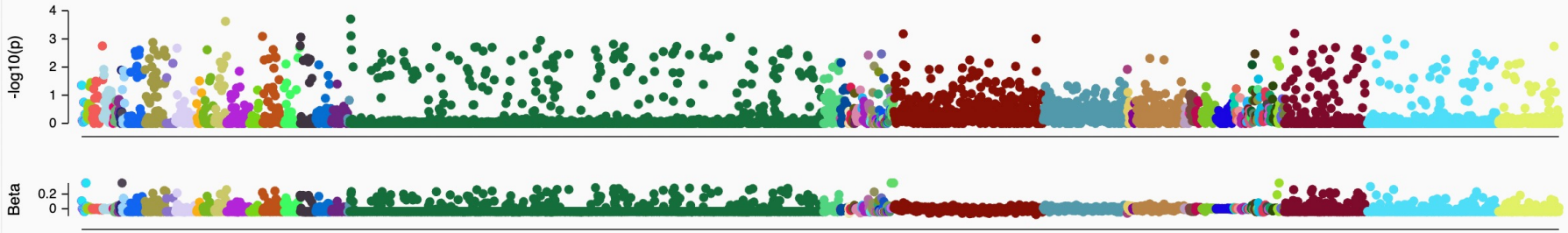
Beta cutoffs
-0.07 — 0.764

Plot options
P-value | Beta | Both

- P-value ordered
- Log Log Plot

Categories
- Showcase
  - Biological samples (79)
  - Other (45)
  - Health-related outcomes (2232)
  - Online follow-up (108)
  - Population characteristics (1)
  - UK Biobank Assessment Centre (2004)
- No category (52)

SELECT ALL | SELECT NONE



Burden set
pLoF | missense|LC | synonymous

- Include filtered

Multi-phenotype selection
Select top | Clear selected

- Filter to selected

Description	Phenotype	Trait type	Sex	Category	Info	N cases	N controls	P-Value (SKAT-O)	Beta	Select
A52.2 Therapeutic sacral epidural injec...	41200 A522	Categorical	Both	Health-related outcomes > Hospital inpati...		2182	392659	1.96e-4	1.22e-1	
H54 Blindness and low vision	131212	ICD10	Both	Health-related outcomes > First occurren...		2016	392825	2.38e-4	1.27e-1	
Cataract	20002 1278	Categorical	Both	UK Biobank Assessment Centre > Verbal i...		5494	389289	6.41e-4	9.45e-2	
Mean FA in posterior limb of internal c...	25075 irnt	Continuous	Both	UK Biobank Assessment Centre > Imagin...		16497		6.61e-4	8.18e-2	
A52.2 Therapeutic sacral epidural injec...	41210 A522	Categorical	Both	Health-related outcomes > Hospital inpati...		305	394536	7.76e-4	2.03e-1	
M00 Pyogenic arthritis	131840	ICD10	Both	Health-related outcomes > First occurren...		546	394295	8.17e-4	2.22e-1	
O02 Other abnormal products of conc...	132166	ICD10	Both	Health-related outcomes > First occurren...		1637	211976	8.72e-4	1.56e-1	
Y53.4 Approach to organ under fluoros...	41210 Y534	Categorical	Both	Health-related outcomes > Hospital inpati...		19562	375279	8.79e-4	4.92e-2	
Mean OD in posterior limb of internal c...	25411 irnt	Continuous	Both	UK Biobank Assessment Centre > Imagin...		16496		9.9e-4	-7.92e-2	
Calcichew 1.25g chewable tablet	20003 1140...	Categorical	Both	UK Biobank Assessment Centre > Verbal i...		850	393933	1.02e-3	1.58e-1	
Q17.8 Other specified therapeutic end...	41200 Q178	Categorical	Both	Health-related outcomes > Hospital inpati...		535	213078	1.13e-3	1.74e-1	
I38 Endocarditis, valve unspecified	131330	ICD10	Both	Health-related outcomes > First occurren...		569	394272	1.33e-3	2.11e-1	
U19.1 Implantation of electrocardiogra...	41200 U191	Categorical	Both	Health-related outcomes > Hospital inpati...		563	394278	1.54e-3	2.13e-1	

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RESEARCH ARTICLE

Association of Common and Rare Genetic Variation in the 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Gene and Cataract Risk

Jonas Ghouse, **Gustav Ahlberg**, **Anne Guldhammer Skov**, **Henning Bundgaard** and **Morten S. Olesen**

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genetically proxied inhibition of the *HMGCR* gene mimicking long-term statin treatment associated with higher risk of cataract. Clinical trials with longer follow-up are needed to confirm these findings