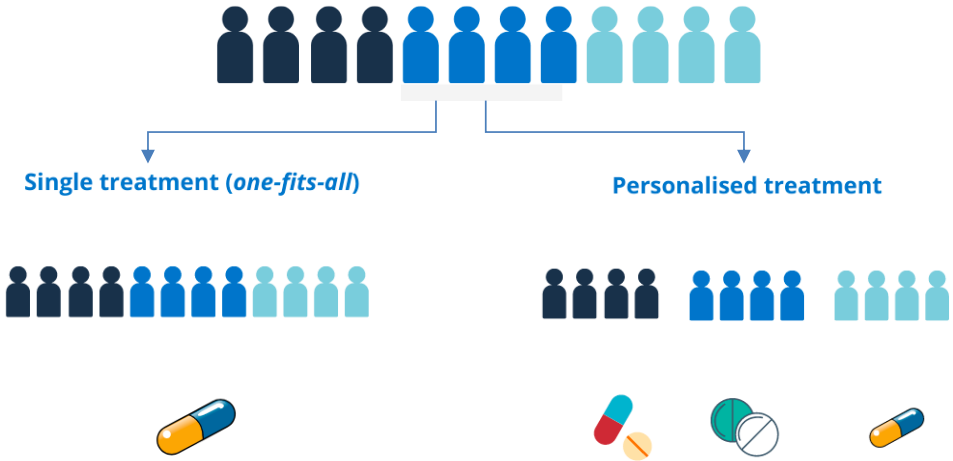
UQ Genetics and Genomics Winter School 2026

Systems Genomics and Pharmacogenomics Module 6 Day 2

From genetic maps to medicine – Using human genomics for preclinical drug target validation and safety evaluation

Pharmacogenomics

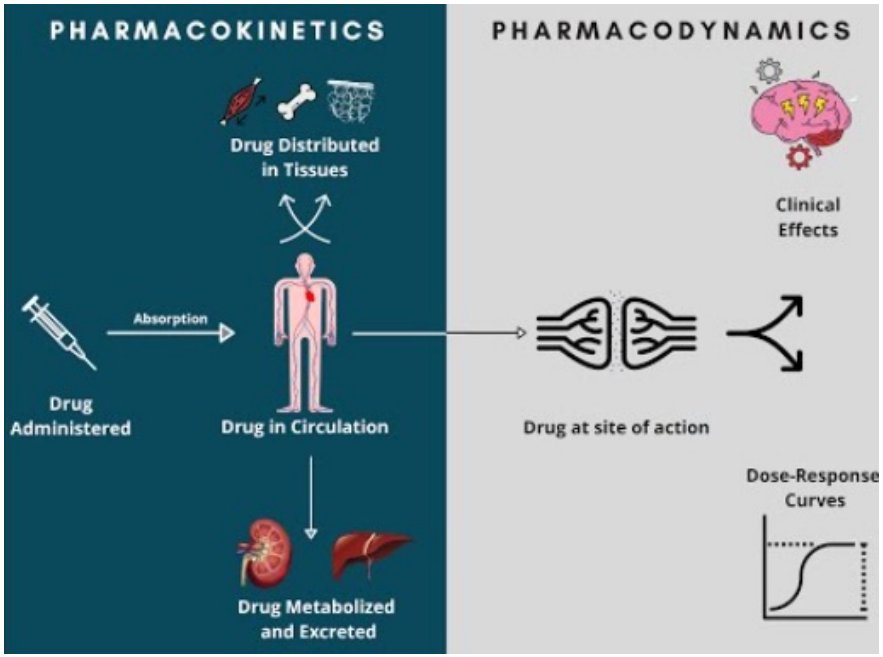
Study of how an individual's genetic makeup affects their response to medications



Pharmacokinetics vs pharmacodynamics

What the body does to the drug

ADME
Absorption
Distribution
Metabolism
Excretion



What the drug does to the body

(mechanism of their action)

https://images.app.goo.gl/pFwBhCtdrmhxe6rb6

The drug discovery & development pipeline

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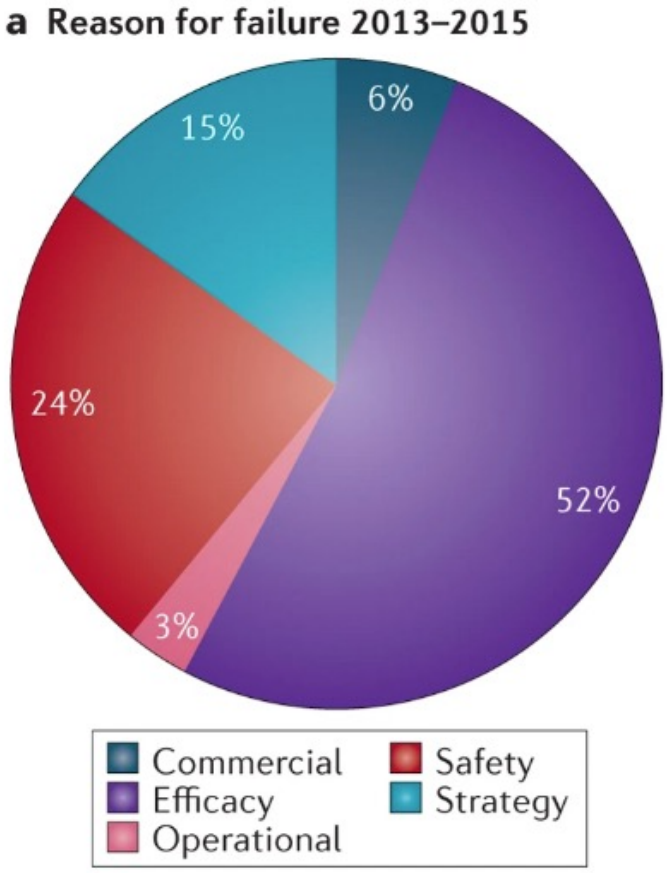
Basic research (3-6 years)	Preclinical studies (1-2 years)	Clinical Studies (4 – 7 years)	FDA review and approval (1 -2 years)	Post-market monitoring (indefinite)
• Disease biology • **Gene target identification** • Compound screening	• Lead identification and optimization • *In vitro* and *in vivo* (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

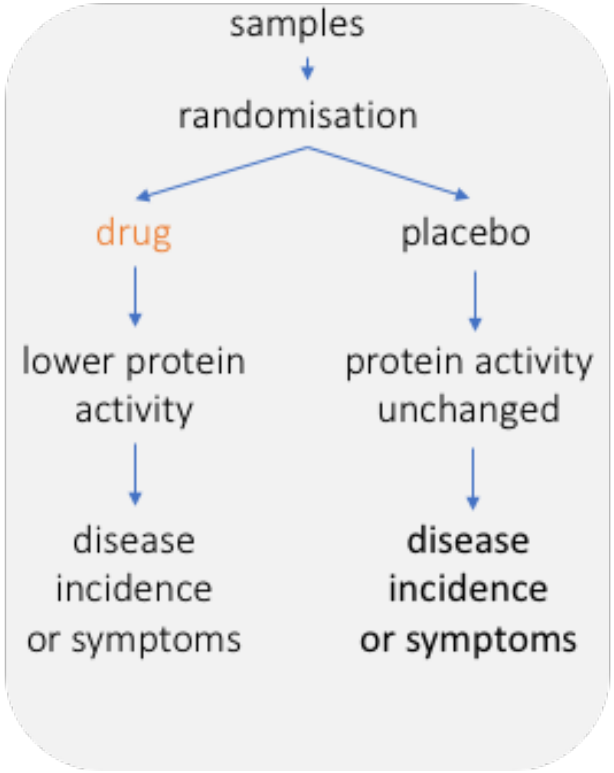


Harrison Nature Reviews Drug Discovery 2016

Extrapolating drug effects in humans

- Animal studies and isolated systems (cells, tissue preparations) do not always translate to *in vivo* effects in humans
  - Unsuitable drug target in humans
  - Drug pharmacokinetics (drug metabolism, tissue absorption) – genetic variation may also play a role

- Gold standard for testing in humans using a randomised control trial (RCT) – the final step of the process is the most costly and highest risk



Reducing risk of failure

1. Identification of a drug target whose modulation in humans would be beneficial for disease treatment

Predicting drug effects using human genetic studies

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

nature genetics

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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

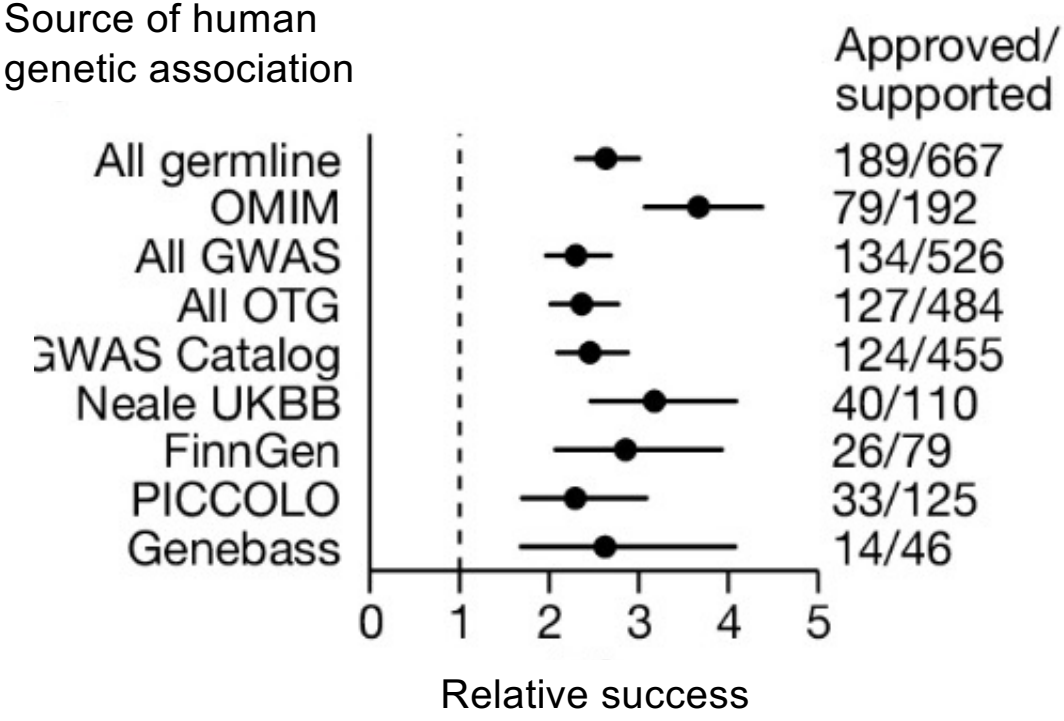
nature › analyses › article

Analysis | Open access | Published: 17 April 2024

Refining the impact of genetic evidence on clinical success

Eric Vallabh Minikel, Jeffery L. Painter, Coco Chengliang Dong & Matthew R. Nelson

Nature **629**, 624–629 (2024) | Cite this article



Using genetics to select drug targets

PCSK9: Genetic mutation to groundbreaking therapy

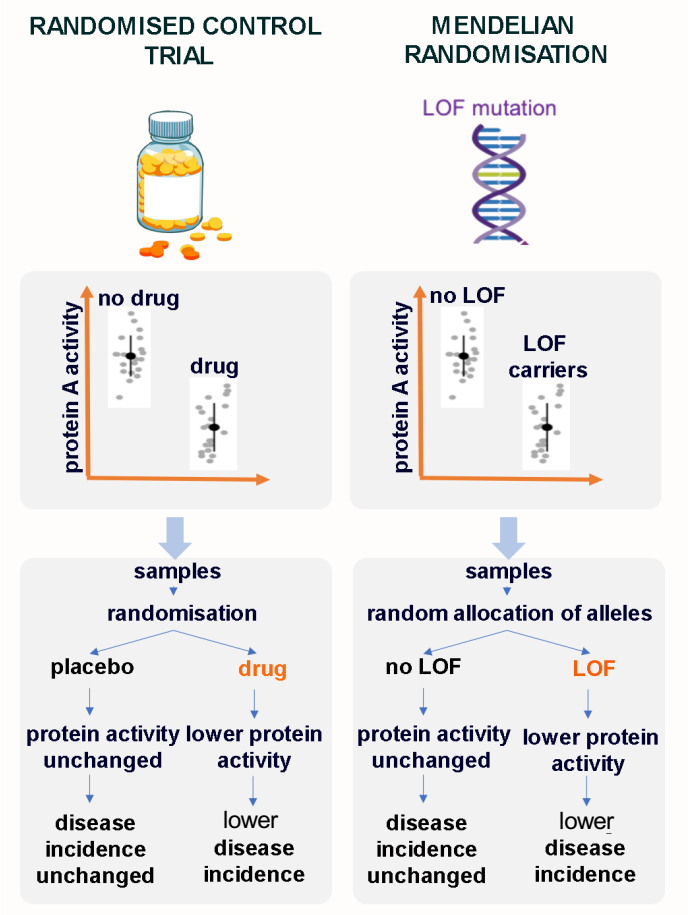
2005 Cohen et al Nature Genetics

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

- Substantially lower cholesterol
- Reduction in risk of cardiovascular disease
- No other health problems - safety

2015 first approved PCSK9 inhibitor

Mendelian randomisation (MR) analysis



LOF/GOF as instruments for MR

The University Of Queensland
AUSTRALIA

nature › analyses › article

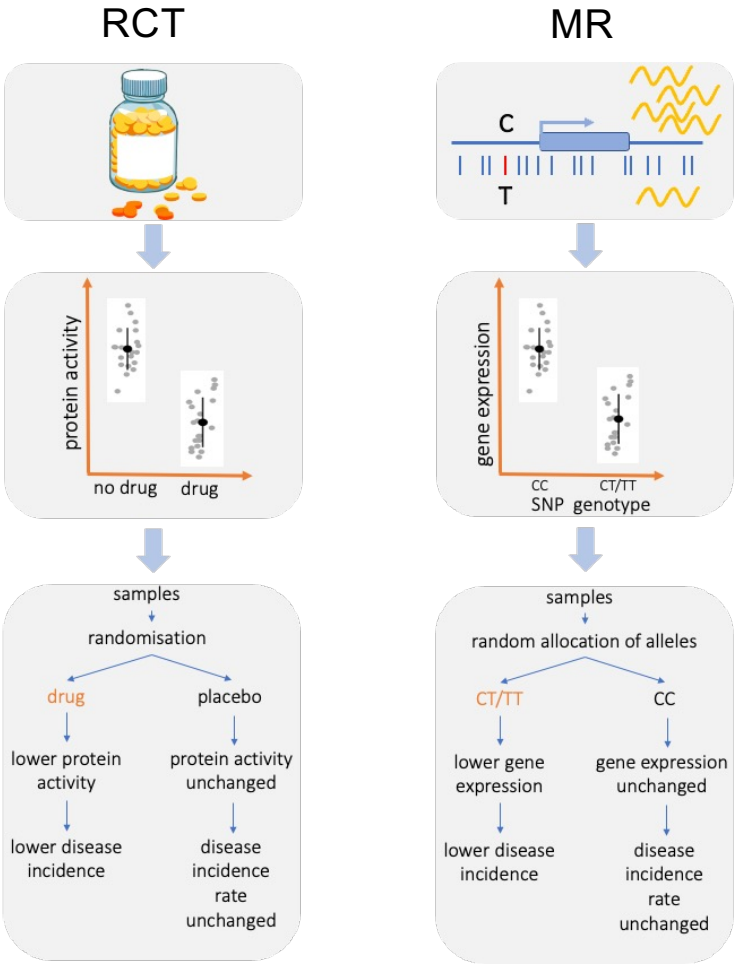
Analysis | Open Access | Published: 27 May 2020

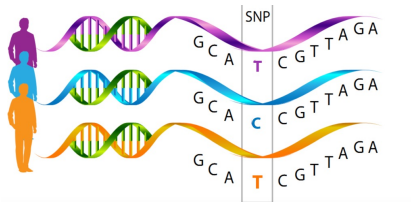
Evaluating drug targets through human loss-of-function genetic variation

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
- **Conclusion at the time – would require sample sizes that are 1000x bigger**

eQTLs as instruments for MR analysis





cis-eQTLs as proxies for drug exposure.

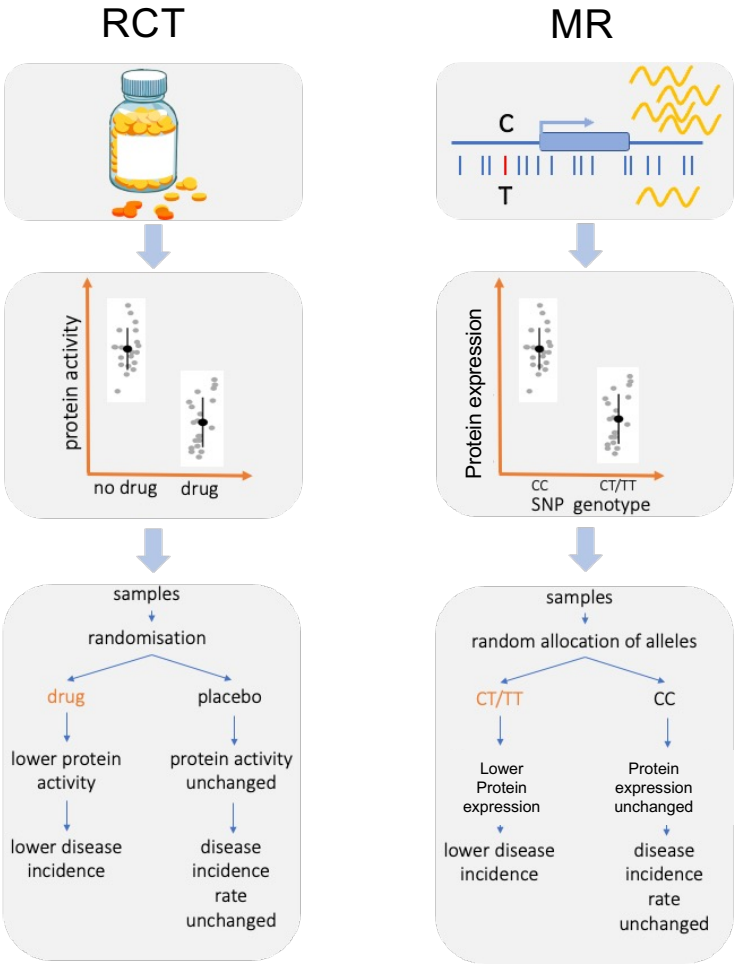
PROS:

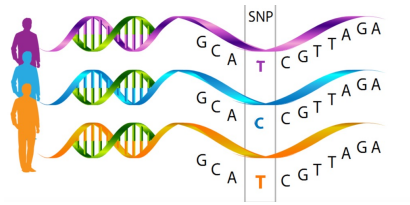
- eQTL variants are more common - more power
- eQTLs available for different tissues
- Reflect long-term exposure

CONS:

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

pQTLs as instruments for MR analysis





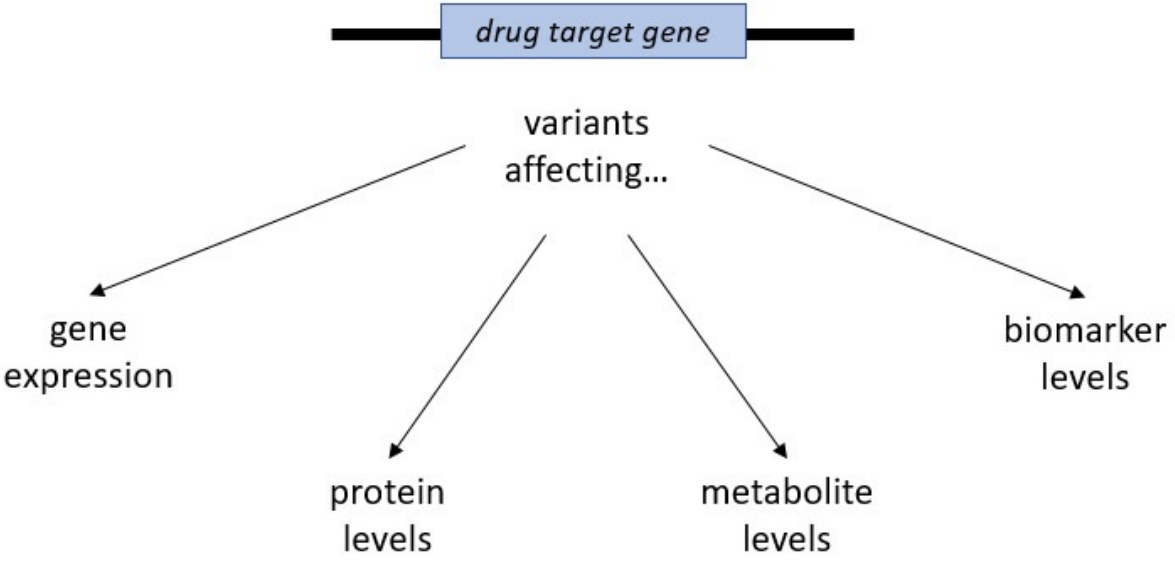
pQTLs as proxies for drug exposure.

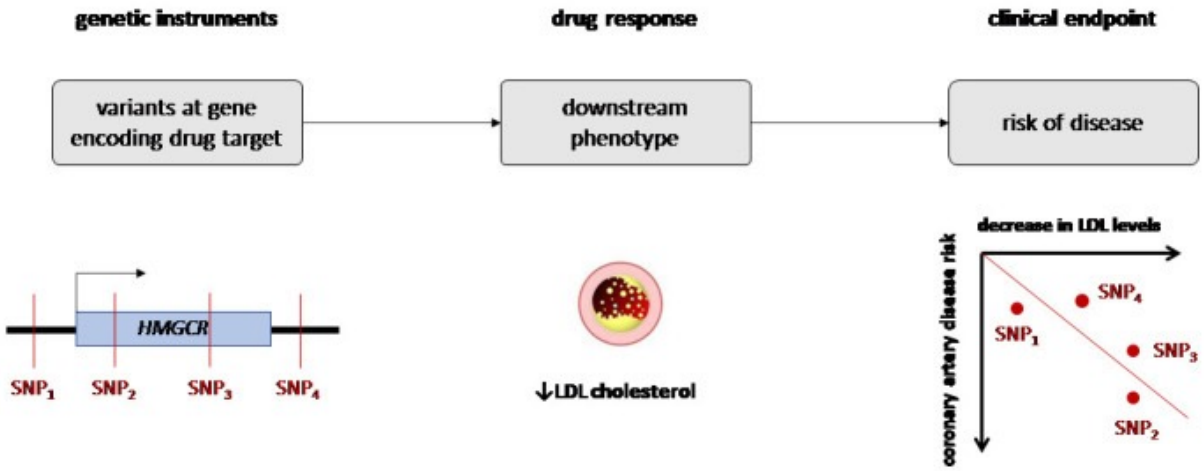
PROS:

- Closer phenotype to drug effects

CONS:

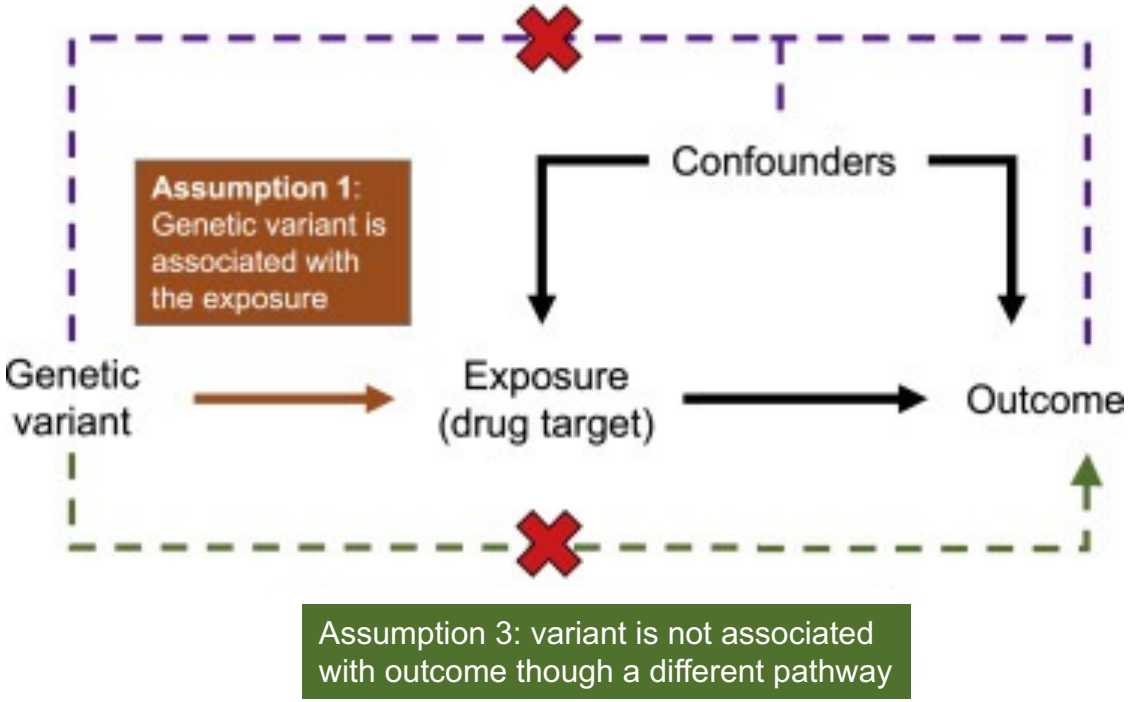
- Difficult to measure outside of blood





Gill et al Wellcome Open Research 2021

Assumptions of drug target MR



Burgess et al Am J Hum Genet 2023

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. Important to test association with confounders.

3: Effect of genetic variant on outcome is via effect on drug target. Important to check associations with other relevant phenotypes.

- 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

Box 1. Step-by-step guide for conducting Mendelian randomization (MR) analyses of drug target perturbation.

1. Determine the drug targets of interest
2. Identify the gene(s) encoding the relevant protein(s)
3. Choose data source for identifying instruments
4. Select genetic variants as instruments based on:
    a. Strength of associations with downstream effects of drug target perturbation
    b. Linkage disequilibrium structure
    c. Distance from gene(s) encoding the drug target
5. Validate genetic variants for use as instruments by confirming that they recapitulate known on-target drug effects
6. Estimate effects of drug target perturbation on outcome(s) of interest using MR
    a. Use appropriate method to account for linkage disequilibrium structure between variants
    b. Scale estimates appropriately
    c. Interpret MR as representing effects of lifelong drug target perturbation
7. Investigate potential adverse effects and repurposing opportunity using phenome-wide association study
8. Triangulate using other interventional, observational and experimental data

Gill et al Wellcome Open Research 2021

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Example: Darapladib

Published: 01 July 2014

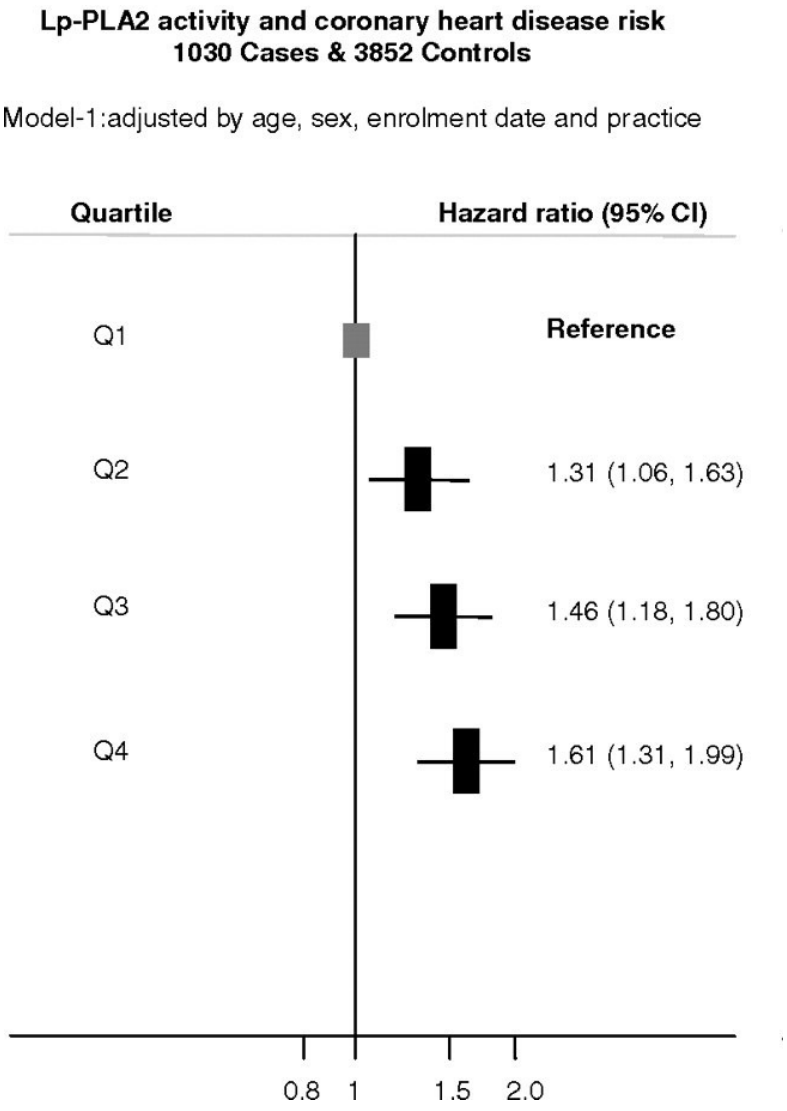
GSK's darapladib failures dim hopes for anti-inflammatory heart drugs

Asher Mullard

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

No reduction in the risk of cardiovascular death, heart attack or stroke in the STABILITY trial, in over 15,000 patients with chronic coronary heart disease

Example: Darapladib



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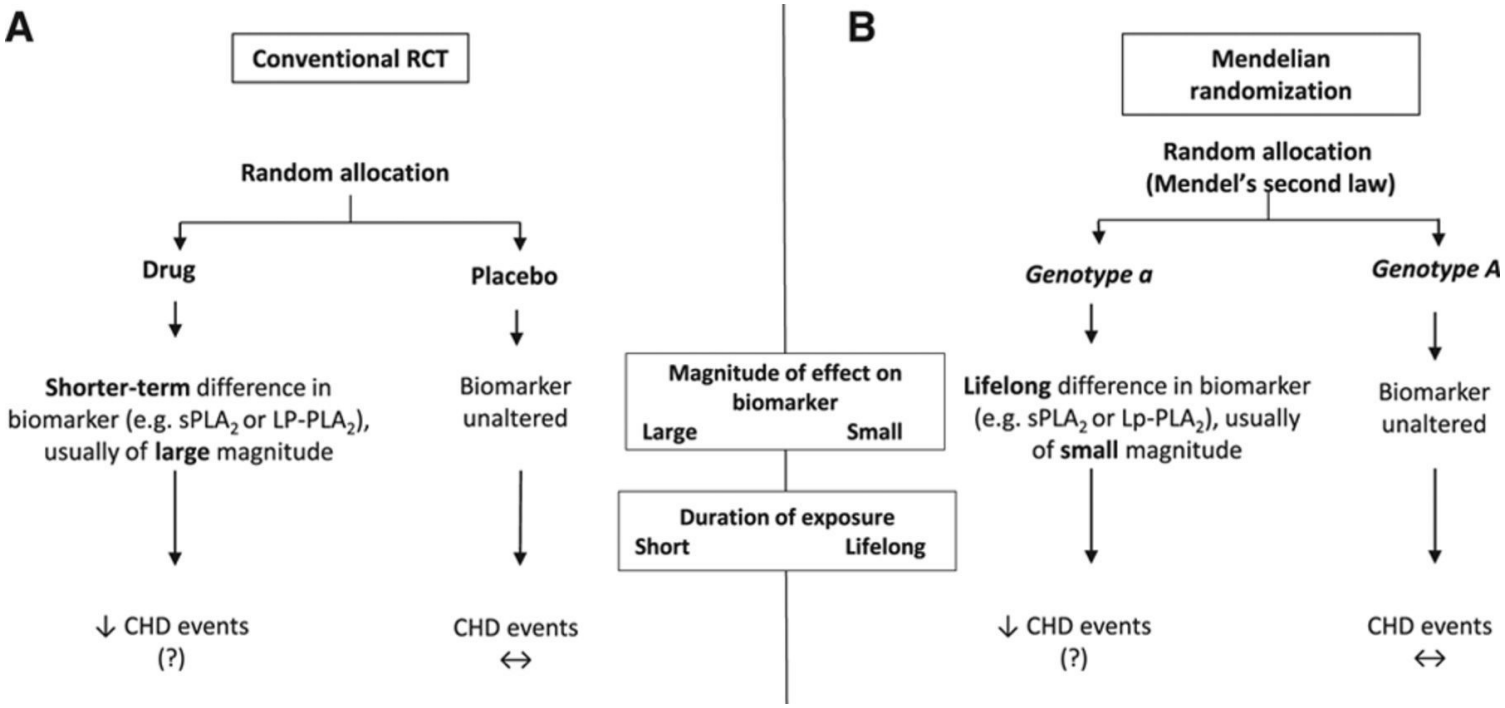
***PLA2G7* Genotype, Lipoprotein-Associated Phospholipase A_2 Activity, and Coronary Heart Disease Risk in 10 494 Cases and 15 624 Controls of European Ancestry**

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

MR to Test Causality of Lp-PLA2



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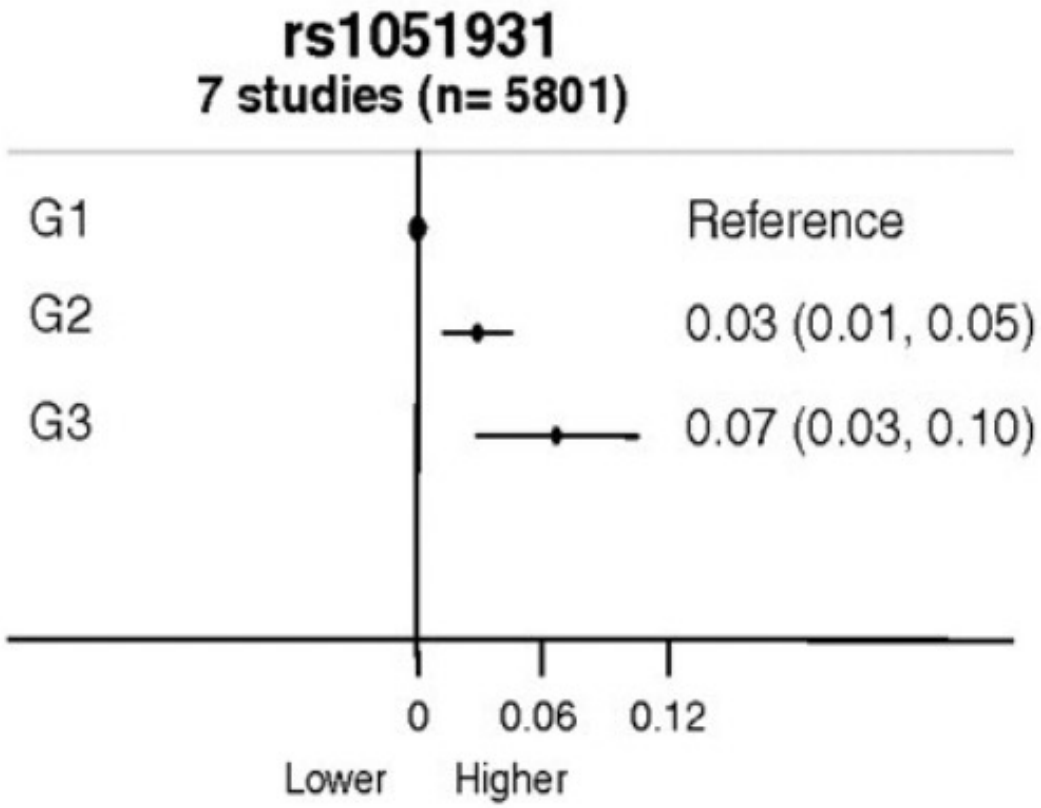

Mean difference (95%C) in log-LpPLA2 activity by PLA2G7 variants
G1: Homozygous common-allele;
G2: Heterozygous;
G3: Homozygous rare-allele

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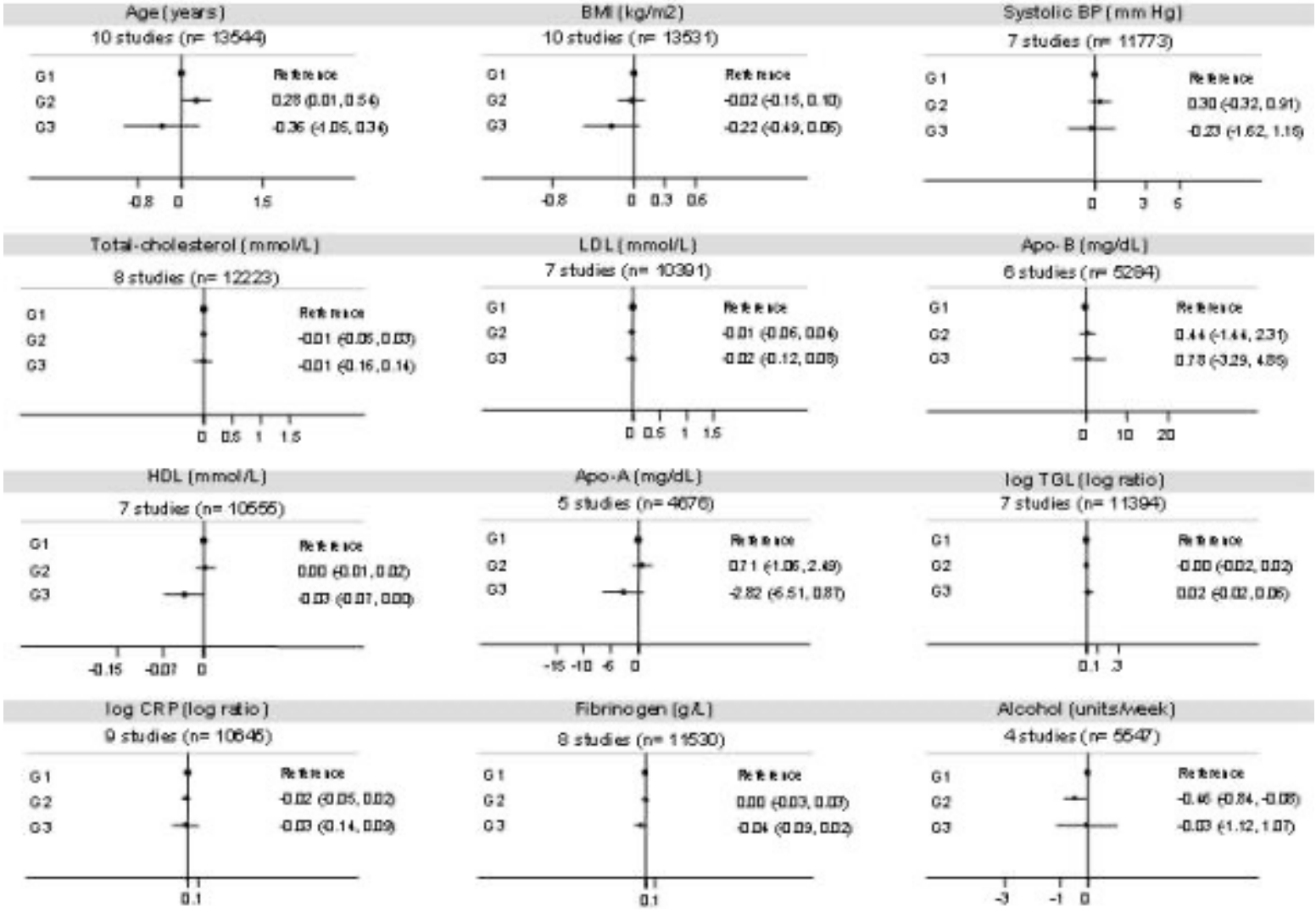
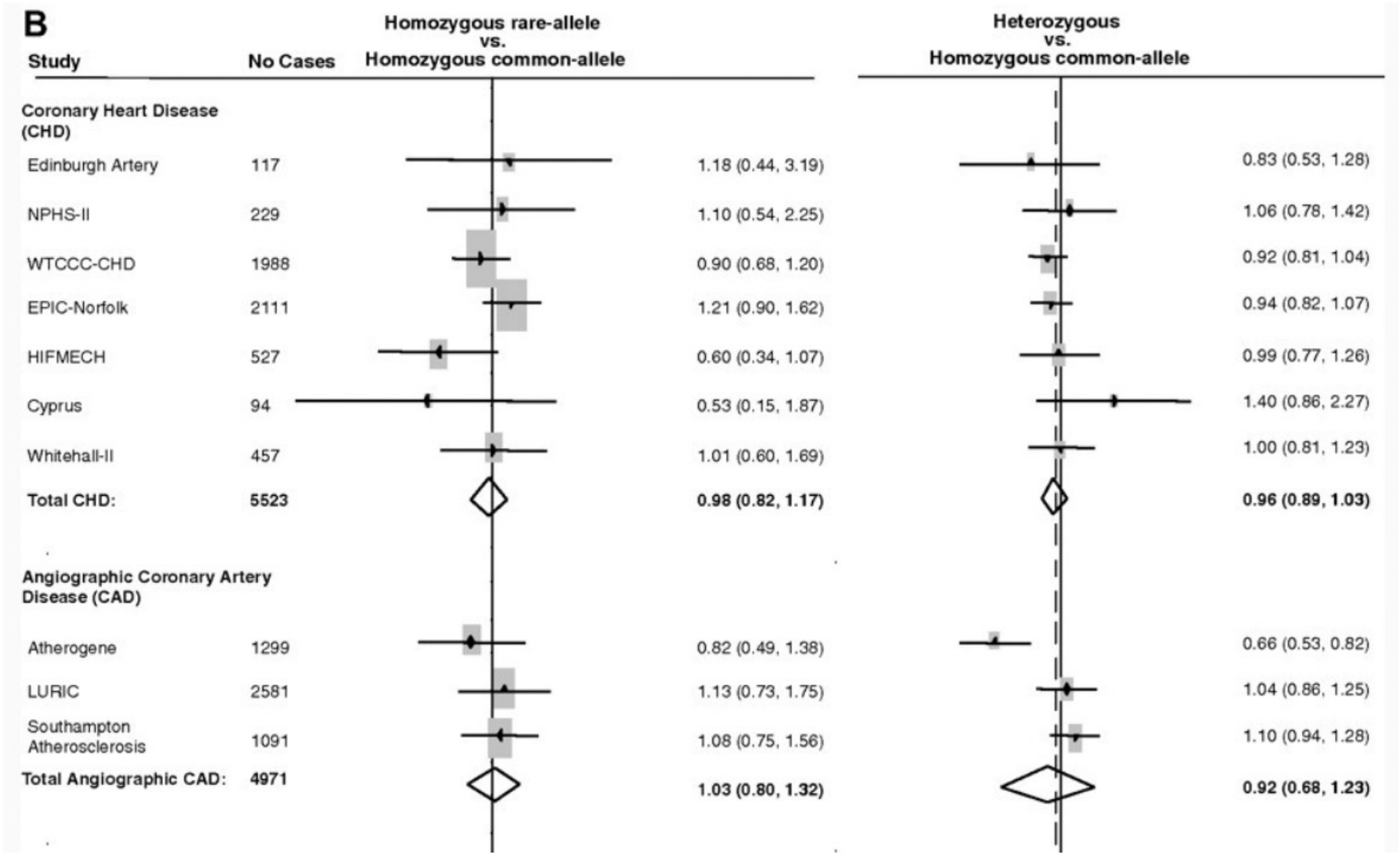
Originally published 17 May 2010 | https://doi.org/10.1161/CIRCULATIONAHA.109.923383 | Circulation. 2010;121:2284–2293

Mean difference (95%CI) in cardiovascular traits by rs1051931 genotype

[G1: Homozygous common-allele; G2: Heterozygous; G3: Homozygous rare-allele]



MR instrument not associated with other risk factors



No association of *PLA2G7* variant with risk of CHD

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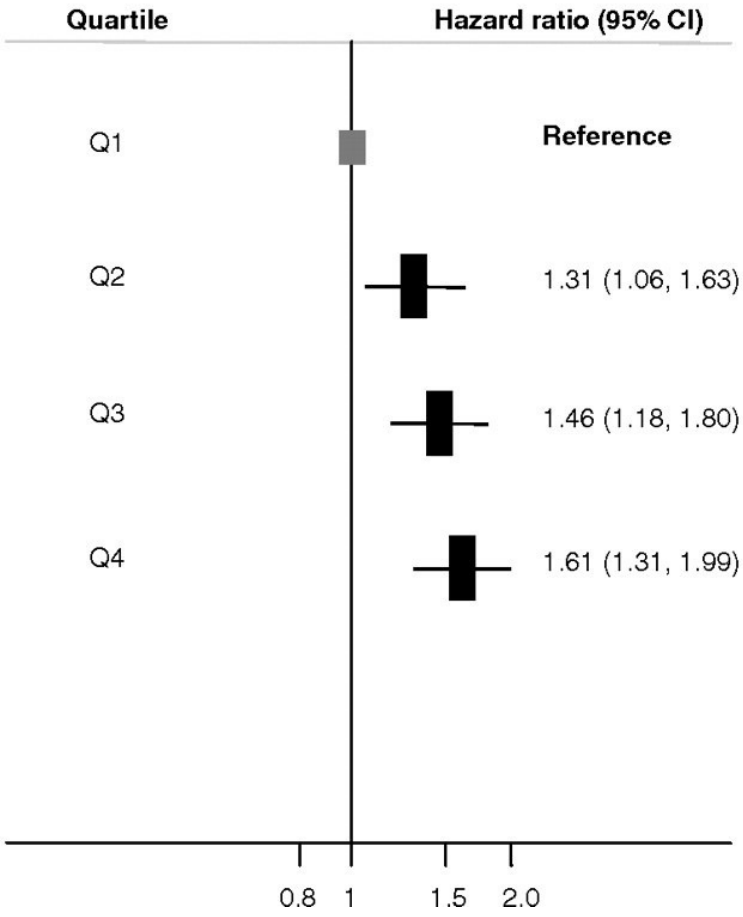
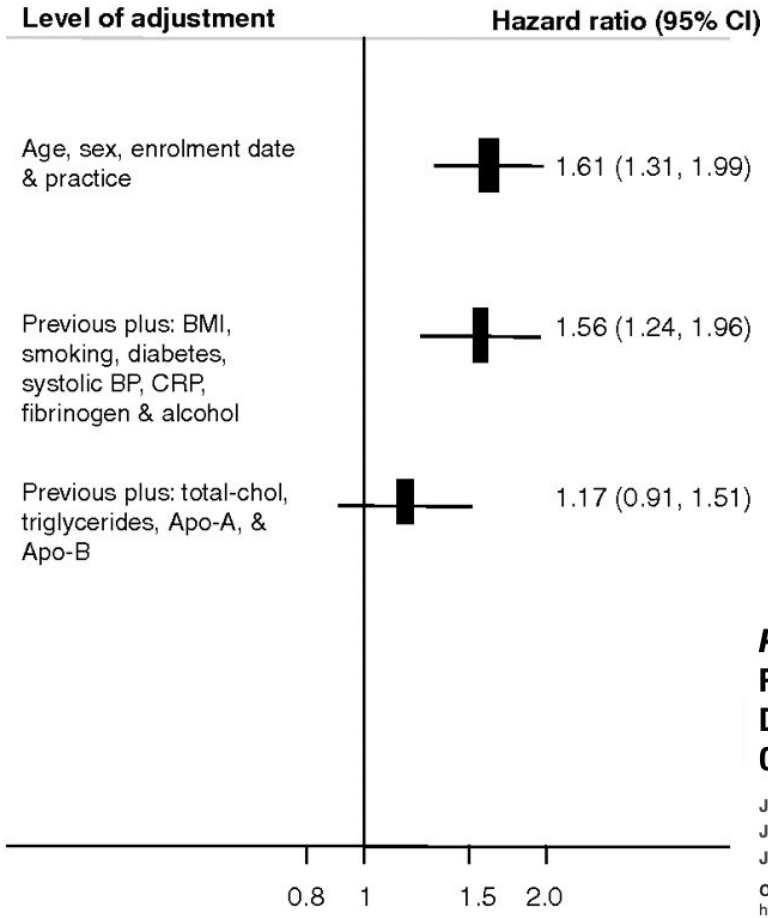
Lp-PLA2 activity and coronary heart disease risk
1030 Cases & 3852 Controls

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



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nature

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nature > letters > article

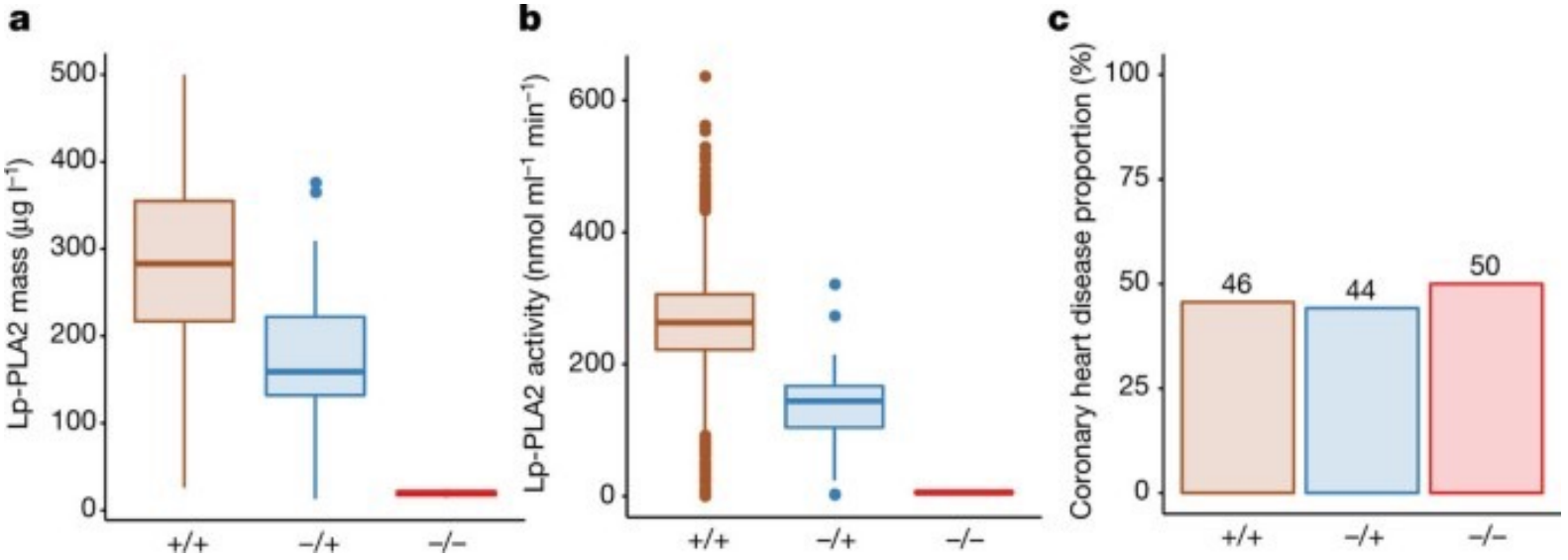
Letter | Published: 13 April 2017

Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity

Danish Saleheen ✉, Pradeep Natarajan, Irina M. Armean, Wei Zhao, Asif Rasheed, Sumeet A. Khetarpal, Hong-Hee Won, Konrad J. Karczewski, Anne H. O'Donnell-Luria, Kaitlin E. Samocha, Benjamin Weisburd, Namrata Gupta, Mozzam Zaidi, Maria Samuel, Atif Imran, Shahid Abbas, Faisal Majeed, Madiha Ishaq, Saba Akhtar, Kevin Trindade, Megan Mucksavage, Nadeem Qamar, Khan Shah Zaman, Zia Yaqoob, ... Sekar Kathiresan ✉ + Show authors

10,503 adult participants in the Pakistan Risk of Myocardial Infarction Study (PROMIS)

Coming to the same conclusion around Lp-PLA2 inhibition and CAD risk using *PLA2G7* rare pLOF in an independent study



Despite substantial reductions of Lp-PLA2 activity, *PLA2G7* c.663 + 1G>A heterozygotes and homozygotes have similar coronary heart disease risk when compared with non-carriers ($P = 0.87$).

Genetic data can help prioritise/de-prioritise drug candidates

The University Of Queensland
AUSTRALIA

nature

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nature > articles > article

Article | Open access | Published: 17 June 2026

Analysis of 173,303 exomes and genomes in the Pakistan Genome Resource

Christopher Koch, Shareef Khalid, Maleeha Zaman Khan, Shruthi Bandyadka, Brian Doyon, Daniel P. Denning, Muhammad Jahanzaib, Muhammad Rehan Mian, Wafa Gul, Muhammad Bilal Liaqat, Aneeqa Bano, Marium Dahar, Namra Saqib, Lubna Kamani, Nazish Butt, Anjum Jalal, Riffat Sultana, Shahid Abbas, Musfireh Siddiqeh, Muhammad Haroon, Asadullah Khan, Khalid Parvez Babar, Aflak Rasheed, Javed Iqbal, Regeneron Genetics Center, ... Danish Saleheen + Show authors

Nature's Human Knockout Experiment: What 173,000 Pakistanis Are Teaching Us About the Human Genome

Veera Rajagopal
MBBS, MD, PhD | Building Genetics-Driven Drug Discovery in India

June 22, 2026

Natural Human Knockouts

In populations where mating is largely random, human knockouts are extremely rare (refer back to Gnomad paper)

For a gene-inactivating variant at 0.1% frequency, you'd expect one homozygous individual in every million people.

In populations where consanguineous marriage has been practiced for centuries the odds of observing a human knockout for the same 0.1% variant rise to roughly 1 in 16,000, a 63-fold enrichment.

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June 22, 2026

Natural Human Knockouts

Nearly 1/3rd of human genes tolerate complete loss of function.
Genes depleted for knockouts in PGR are enriched for genes essential for cell survival, known Mendelian disease genes, and genes broadly expressed across human tissues.
Tissue-specific genes are much safer therapeutic targets than broadly expressed genes.

Caveats:
The sample size of PGR is small, hence not saturated for human knockouts.
Survivorship bias - absence of a gene knockout here doesn't mean biological impossibility. It means incompatibility with being a 'healthy' adult volunteer.

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Natural Human Knockouts

PRDM9

encodes a protein that controls where chromosomes break and recombine during sperm and egg formation.

Deleting the gene has caused infertility in every animal.

PGR now has 4 human PRDM9 knockouts: three women, one man. All fertile, with 2 to 7 children each.

A 14-year biological fact, overturned by four families in Pakistan.

Nature's Human Knockout Experiment: What 173,000 Pakistanis Are Teaching Us About the Human Genome

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June 22, 2026

Natural Human Knockouts

RXFP1

- encodes the receptor for a pregnancy hormone called relaxin
- Animal studies suggested a critical role in cardiovascular adaptation and connective tissue remodelling
- But relaxin-targeted drugs failed in late-stage trials.
- PGR found 16 RXFP1 knockouts, expanded to 26 via recall-by-genotype
- None had consistent cardiovascular or reproductive deficits,

Nature's Human Knockout Experiment: What 173,000 Pakistanis Are Teaching Us About the Human Genome

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Testing drug safety

- RCTs are costly and high risk
  - Small sample size
  - Short follow-up time (shorter exposure)
  - 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

Drug safety

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Original Investigation

May 9, 2017

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

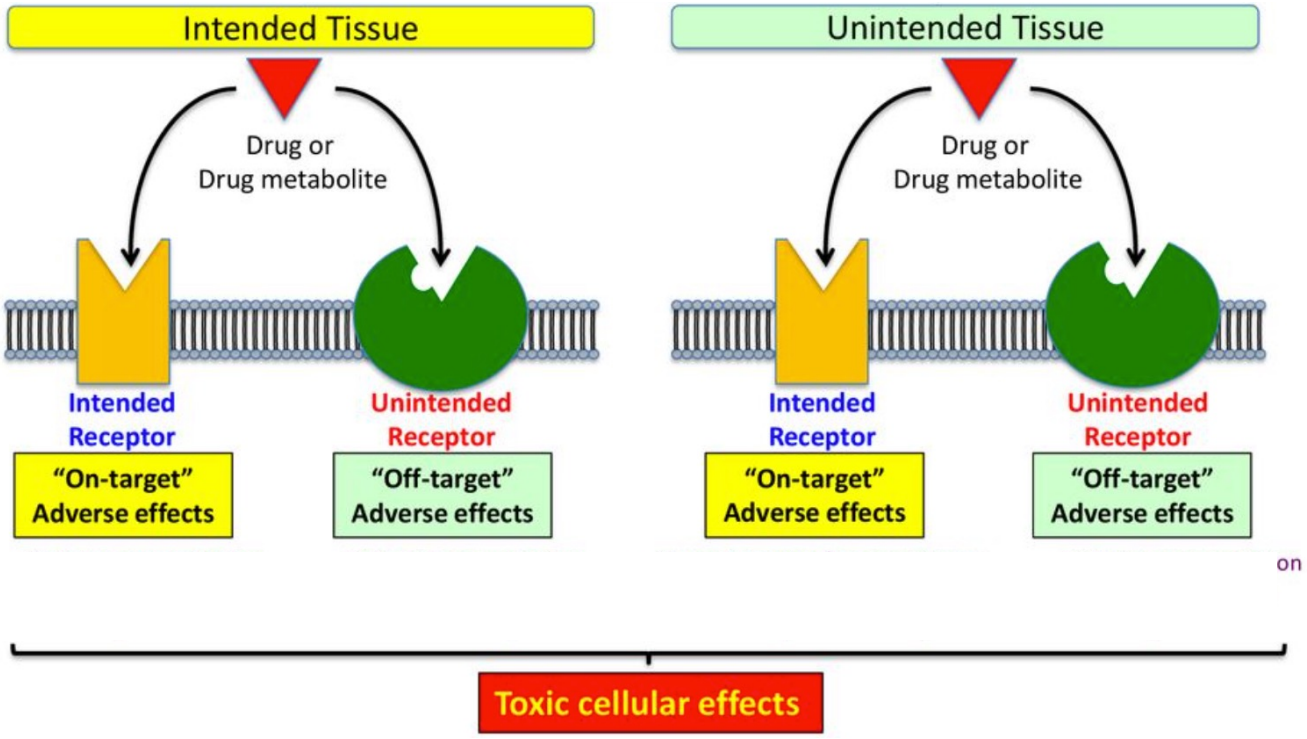
Nicholas S. Downing, MD[1]; Nilay D. Shah, PhD[2]; Jenerius A. Aminawung, MD, MPH[3]; et al

» 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



MR can only be used if we know what the on- and off-target genes/proteins are

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

MR to assess drug safety – phenome-wide MR

Natural Human Knockouts

LRRK2

- well-established Parkinson's disease risk gene.
- Activating mutations in LRRK2 are among the most common risk factors for Parkinson’s.
- RRK2 is a therapeutic target with many companies exploring ways to switch off this gene in the brain to treat Parkinson’s
- Animal knockouts warned of kidney damage.
- PGR has two LRRK2 knockouts, both with kidney disease, confirming animal studies.

Nature's Human Knockout Experiment: What 173,000 Pakistanis Are Teaching Us About the Human Genome

Veera Rajagopal
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June 22, 2026

Reducing risk of failure through human genetics

1. Identification of a drug target whose modulation in humans would be beneficial for disease treatment – drug target MR

2. Identify unknown adverse effects of the drug target - phenome-wide MR.

3. Repositioning of approved drugs reduces risk of failure due to safety concerns – are GWAS hits in genes that are targets of approved drugs?

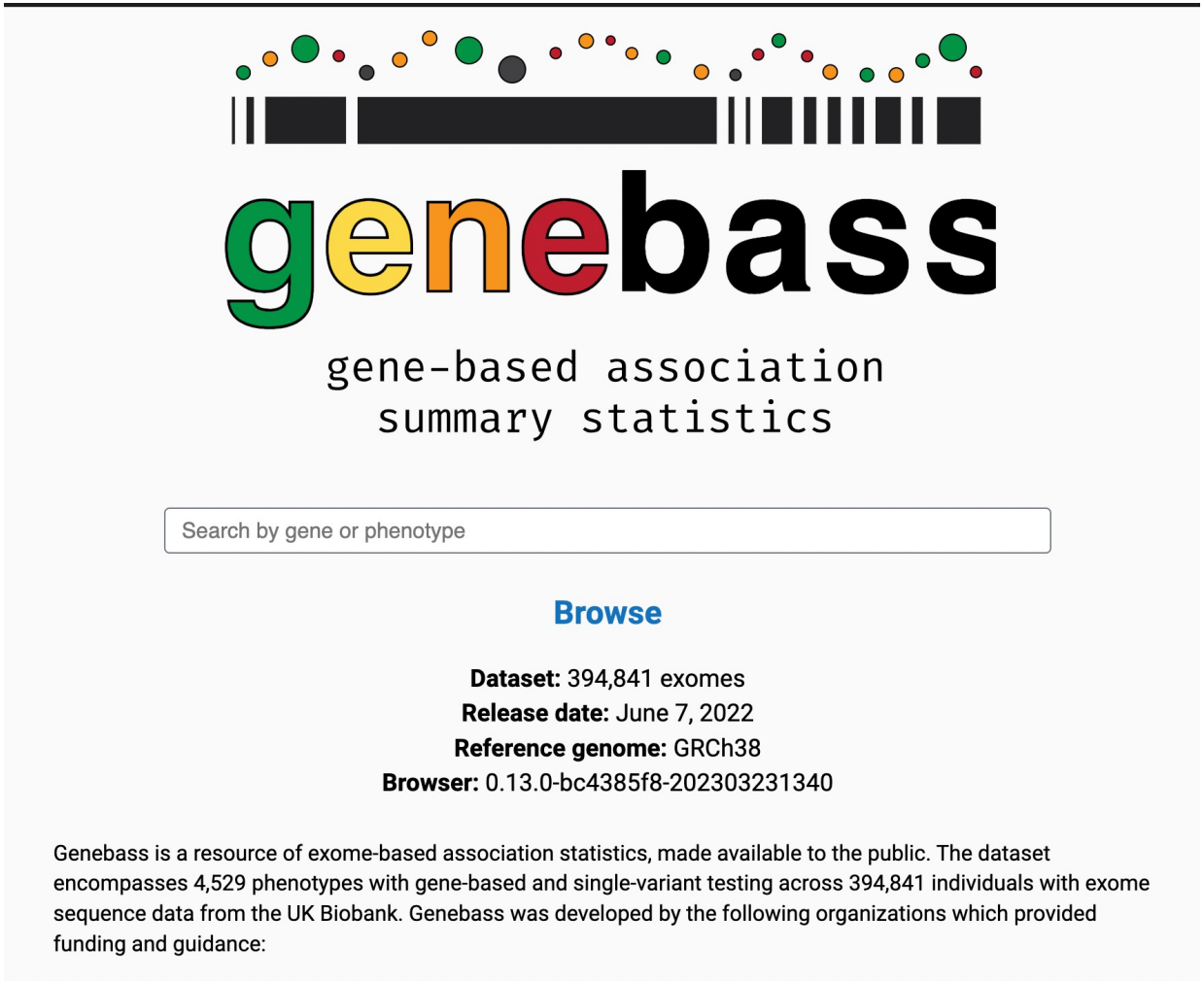
MR for drug target validation and safety

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

- Only possible due to large, publicly available GWAS and sequencing studies for 1000s of human traits
  - Drug target validation - Test for intended effect through intended target
  - Drug target safety - Test for unintended effects through intended target

Resources and methods for MR

pLOF Gene-based burden test - Genebass



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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

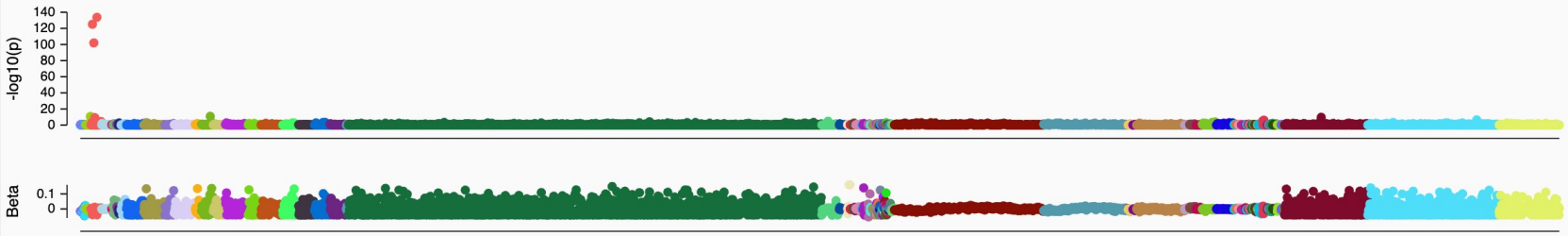
-Log$_{10}$P cutoffs
0 — 134

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	

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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

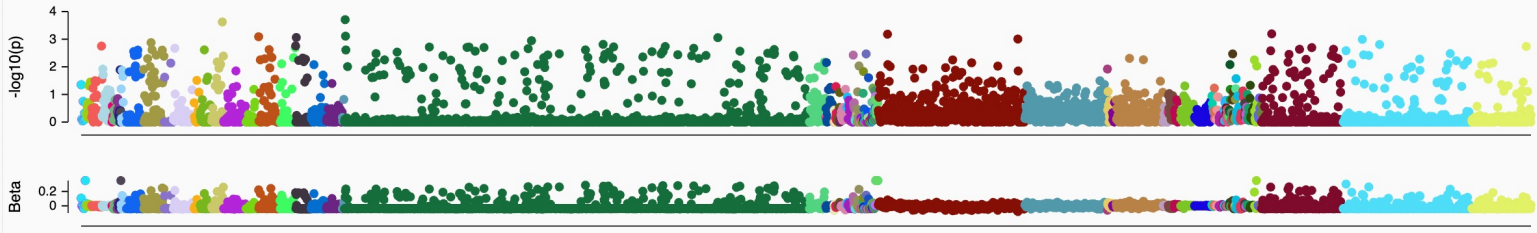
-Log10P cutoffs
0.00 — 4.00

Beta cutoffs
-0.079 — 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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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

Originally published 15 Jun 2022 | https://doi.org/10.1161/JAHA.122.025361 | Journal of the American Heart Association. 2022;11:e025361

Other version(s) of this article

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genetically proxied inhibition of the *HMGCR* gene mimicking long-term statin treatment associated with higher risk of cataract

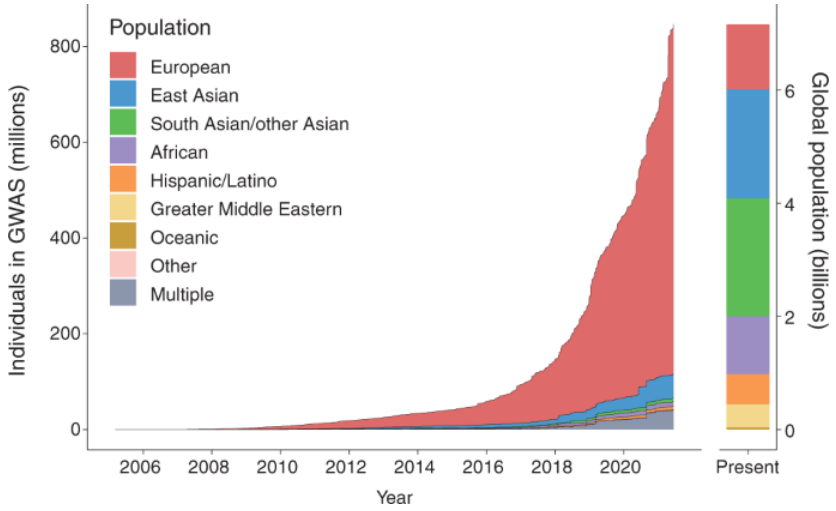
Ancestry-specific considerations

Comparing effects in different ancestral groups

- SNPs in ALDH2 allow powerful analyses to investigate effect of alcohol consumption in East Asians. No genetic variants in Europeans that explain a similar proportion of variance in distribution of alcohol consumption.

- Need matched ancestry LD reference when doing MR analyses

- Need more GWAS data in non-European population



Fatumo et al Nature Medicine 2021

Summary-based MR analysis (SMR)