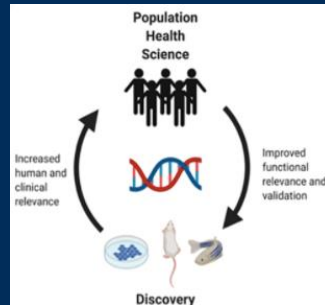


Integrating Health Research: Mechanisms to Populations





Mechanisms to Populations EBI Strand

Background: Ruth Mitchell

Integrating fundamental bioscience and population health: integrating cell biology and epidemiology

Scope for engagement in the strand

Examples outputs



Antigen-specific peptide immunotherapy

Mouse model of multiple sclerosis - Experimental autoimmune encephalomyelitis (EAE)

Tg4 (B10.PL, H-2u) - TCR specific for myelin basic protein MBP Ac1-9



David Wraith

Th1 response:

Pathogenic
IL-2
IFN- γ
Proliferative



Th1

in vivo
differentiation
→
Successive treatments
MBP Ac1-9



Tolerised

Anergic

IL-10 secreting
Suppressive

T-bet+

Protect mice from EAE
upon
adoptive transfer

IL-10

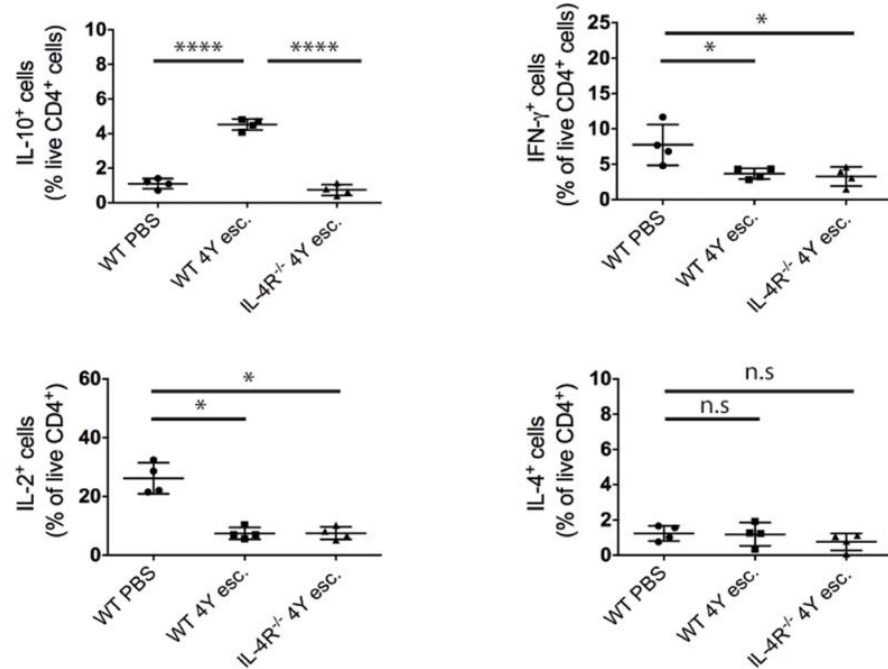


IL-4 upregulates IL-10 in Th1 cells

Tg4.IL-4R^{-/-}

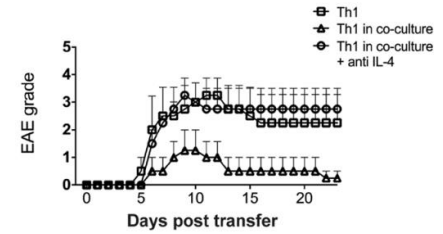
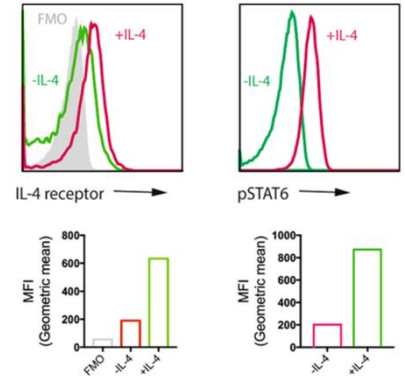
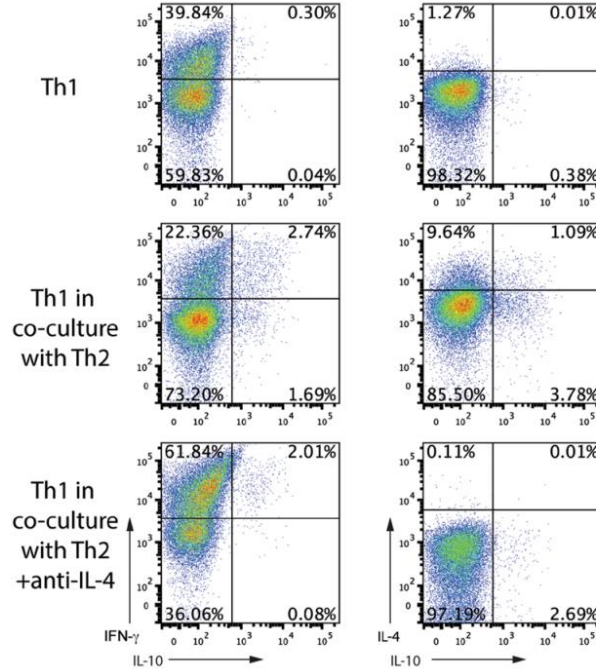
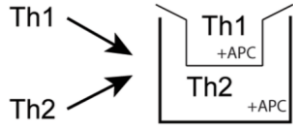
Dose escalation protocol
MBP Ac1-9

Mitchell et al,
PLOS ONE, 2017





IL-4 upregulates IL-10 in Th1 cells



Mitchell et al,
PLOS ONE, 2017



Transitioning into epidemiology



Postgraduate Discipline Hopping Fellowships



Lavinia
Paternoster



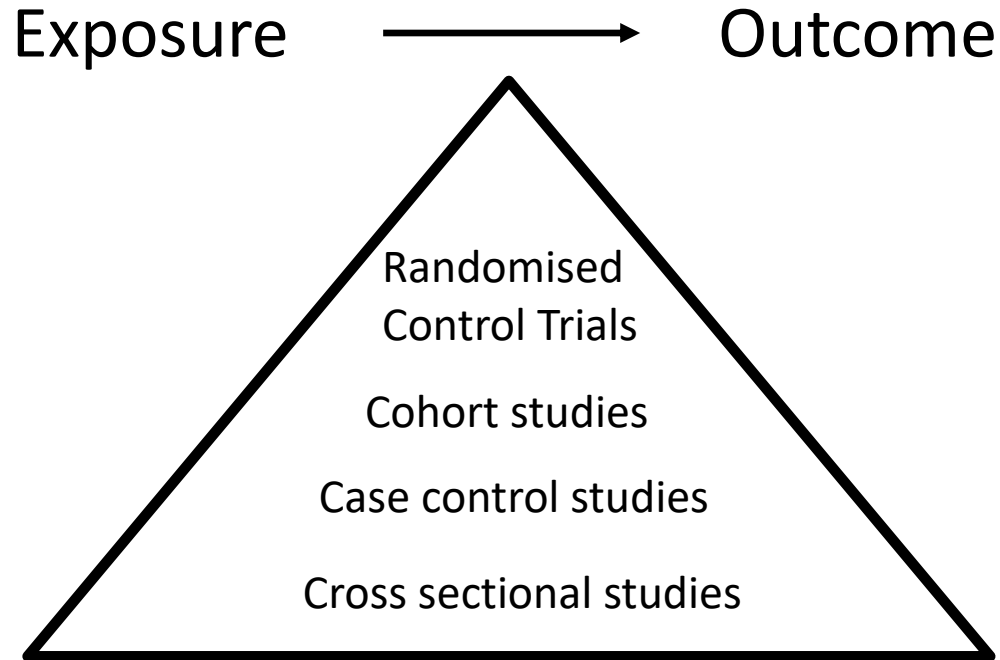
George
Davey Smith



Nic
Timpson



Epidemiology study designs





Avon Longitudinal Study of Parents and Children (ALSPAC)

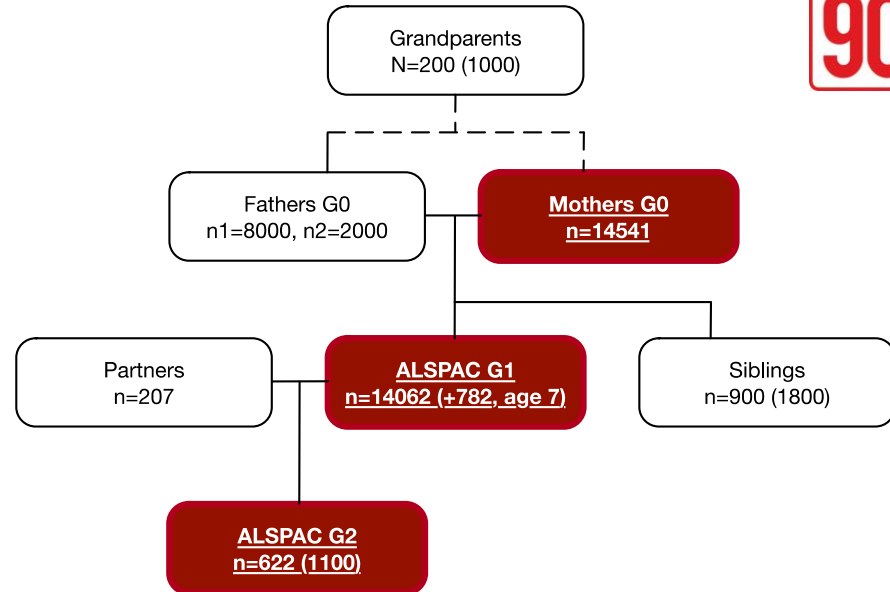


- Bristol based birth cohort study
- 1991 – 1992: 14,500 pregnant women
- Follow-up



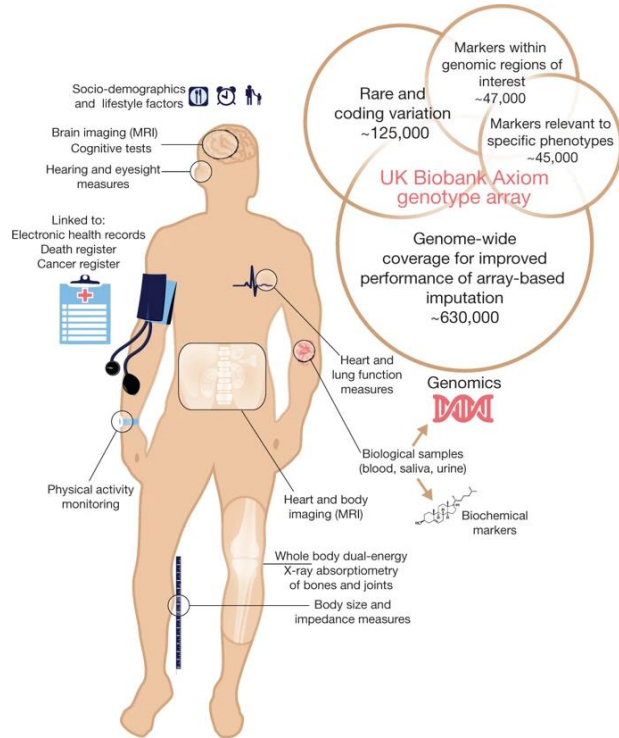
Depth of data:

- Ongoing data collection
- Multi-generational data sets
- Longitudinal data





UK Biobank



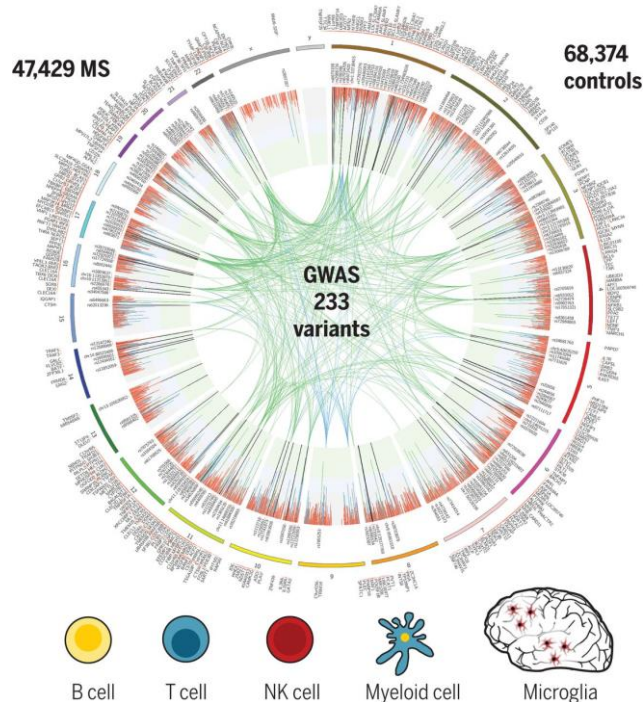
- 500,000 individuals
- Age 40 - 69 at recruitment

Biological measurements, lifestyle indicators, biomarkers in blood and urine, and imaging of the body and brain

biobank^{uk}
Improving the health of future generations



Multiple sclerosis PheWAS in UK Biobank



International Multiple Sclerosis Genetics Consortium, Science, 2019

200 associations non-HLA
genome

33 associations HLA
genome

Genetic risk
score for MS

- weighted by log odds ratios
- z-score transformed

Phenome



Multiple sclerosis PheWAS in UK Biobank

Non-HLA genetic risk score for MS → Phenome

Excluded MS cases



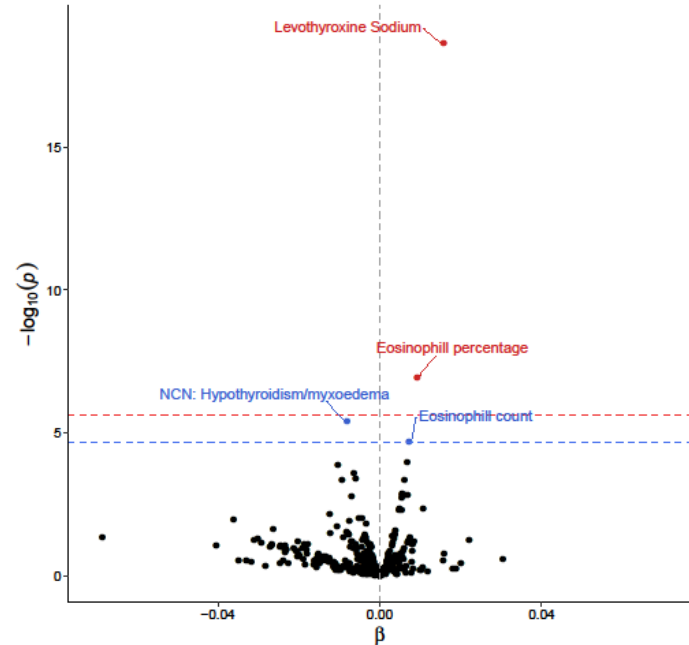
International Journal of Epidemiology, 2018, 29–35
doi: 10.1093/ije/dyx204
Advance Access Publication Date: 5 October 2017
Software Application Profile



Software Application Profile

Software Application Profile: PHESANT: a tool for performing automated phenome scans in UK Biobank

Louise AC Millard,^{1,2*} Neil M Davies,¹ Tom R Gaunt,¹ George Davey Smith¹ and Kate Tilling¹

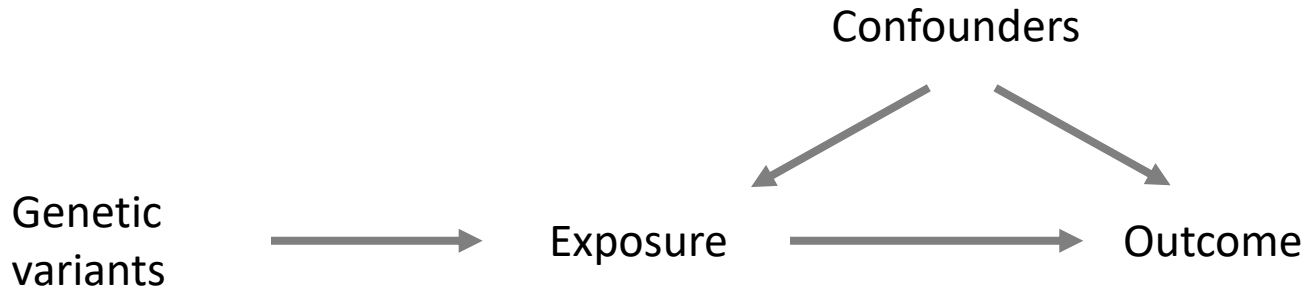




Mendelian Randomization

Two minute MR primer – George Davey Smith

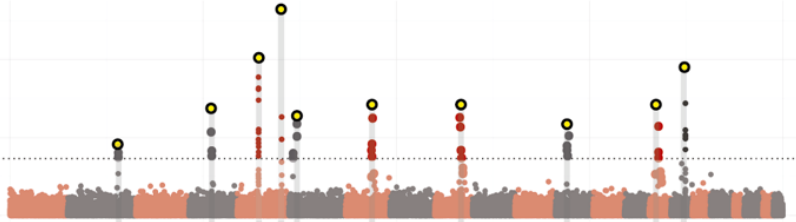
<https://www.youtube.com/watch?v=LoTgfGotaQ4>



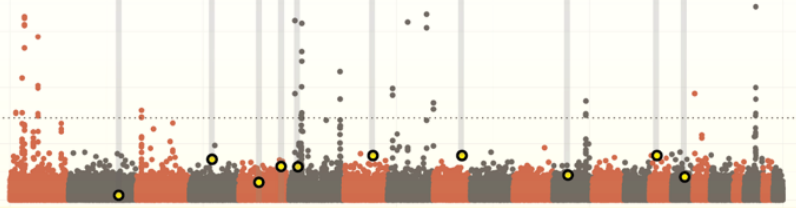


Two sample Mendelian Randomization

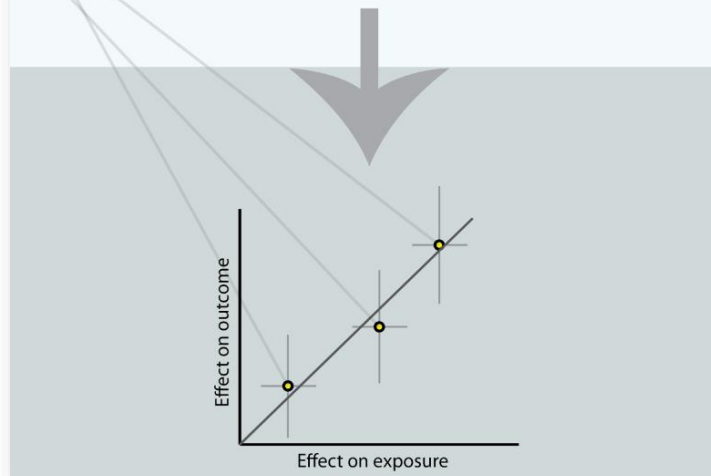
GWAS top hits used to instrument exposure



Extract selected SNPs from complete summary data of outcome GWAS



SNP	Exposure GWAS				Outcome GWAS			
	Effect	Effect allele	Other allele	Effect allele frequency	Effect	Effect allele	Other allele	Effect allele frequency
rs123456	0.132	A	G	0.28	0.022	A	G	0.26
rs234567	-0.485	G	T	0.41	-0.056	G	T	0.39
rs345678	0.203	G	C	0.11	0.046	G	C	0.12





Mendelian Randomization – MR Base

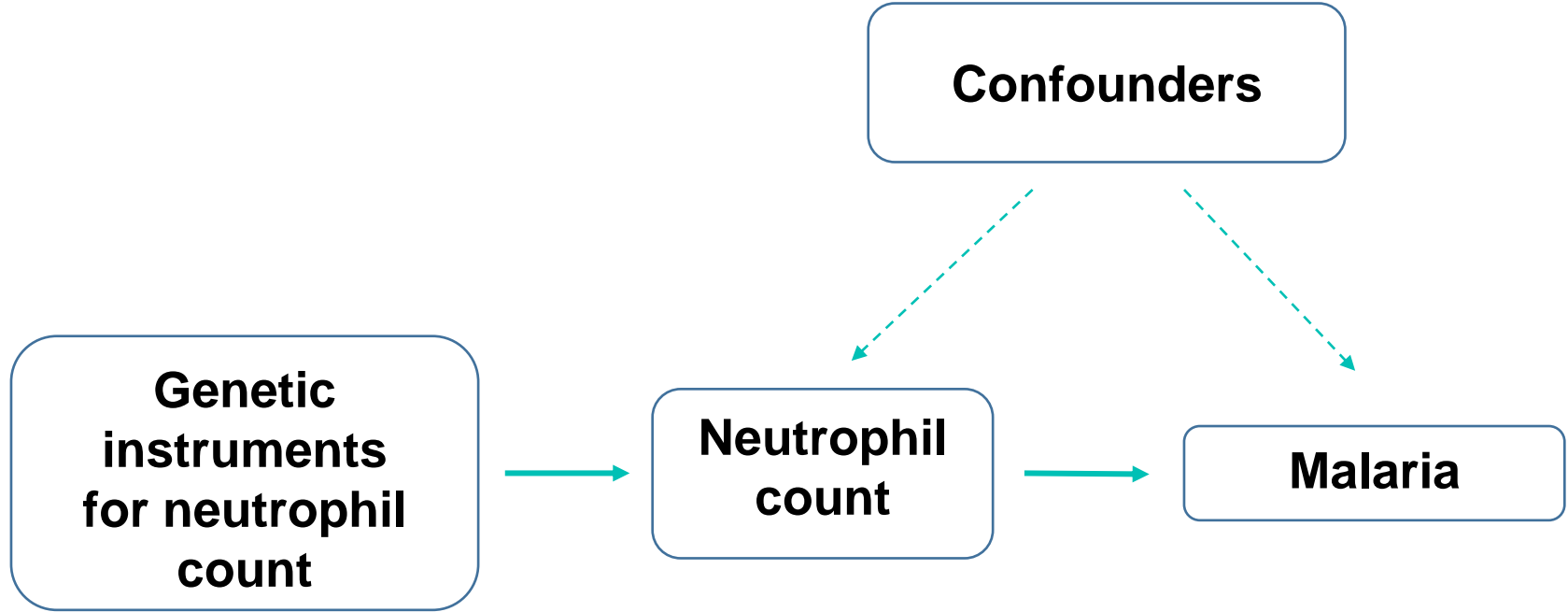
The screenshot shows the MR Base website in a browser window. The URL is www.mrbase.org/alpha/. The page features a dark sidebar on the left with navigation links: 'Welcome to MR Base', 'About', 'Acknowledgements', and 'Data access agreement'. The main content area has the MR Base logo and a description: 'A platform for Mendelian randomisation using summary data from genome-wide association studies'. Below this, a blue button prompts users to 'Review access agreement'. A 'Current status' box provides app version (1.1.7 da7d25) and last update (09 July 2016). On the right, four statistics are displayed in blue boxes: SNP-PHENOTYPE ASSOCIATIONS (3,417,657,704), TRAITS WITH INSTRUMENTS (340,164), GWAS CONSORTIA (36), and GWAS STUDIES WITH FULL SUMMARY DATA (990).

Category	Count
SNP-PHENOTYPE ASSOCIATIONS	3,417,657,704
TRAITS WITH INSTRUMENTS	340,164
GWAS CONSORTIA	36
GWAS STUDIES WITH FULL SUMMARY DATA	990

www.mrbase.org



Investigating the causal relationship of neutrophils on malaria





Exposure – Neutrophil count instruments

European population

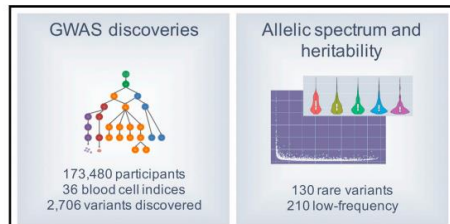
African population in UK Biobank

Cell

Resource

The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease

Graphical Abstract

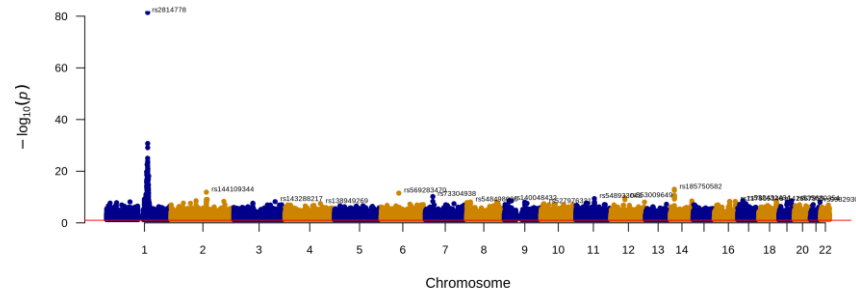


Authors

William J. Astle, Heather Elding,
Tao Jiang, ..., Willem H. Ouwehand,
Adam S. Butterworth, Nicole Soranzo

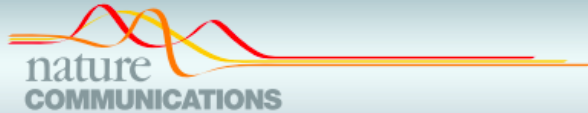
Correspondence

jd292@medschl.cam.ac.uk (J.D.),
david.roberts@ndcls.ox.ac.uk (D.J.R.),
who1000@cam.ac.uk (W.H.O.),
asb38@medschl.cam.ac.uk (A.S.B.),
ns6@sanger.ac.uk (N.S.)





Outcome – Malaria



ARTICLE

<https://doi.org/10.1038/s41467-019-13480-z>

OPEN

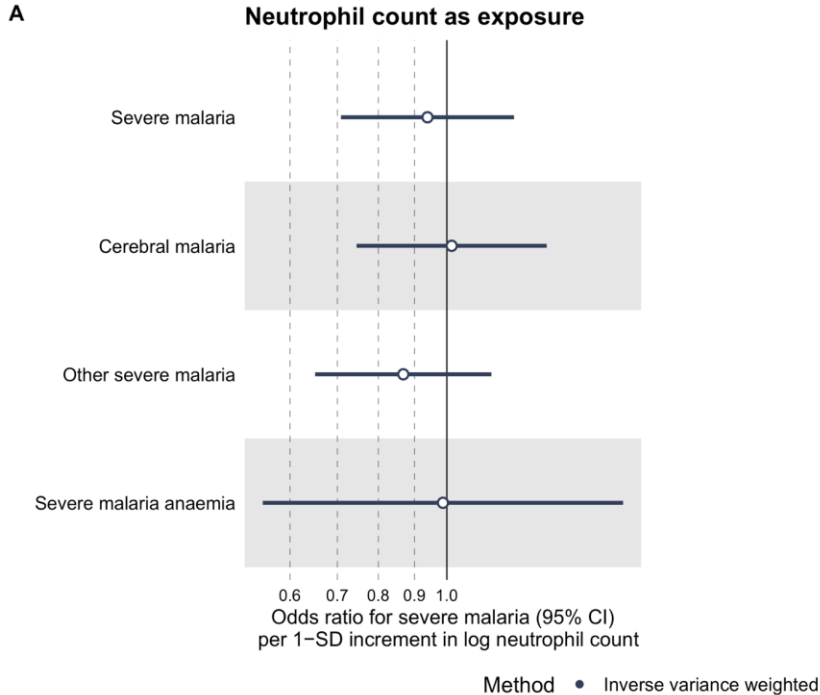
Insights into malaria susceptibility using genome-wide data on 17,000 individuals from Africa, Asia and Oceania

Malaria Genomic Epidemiology Network

17,000 severe malaria cases and population controls from 11 countries

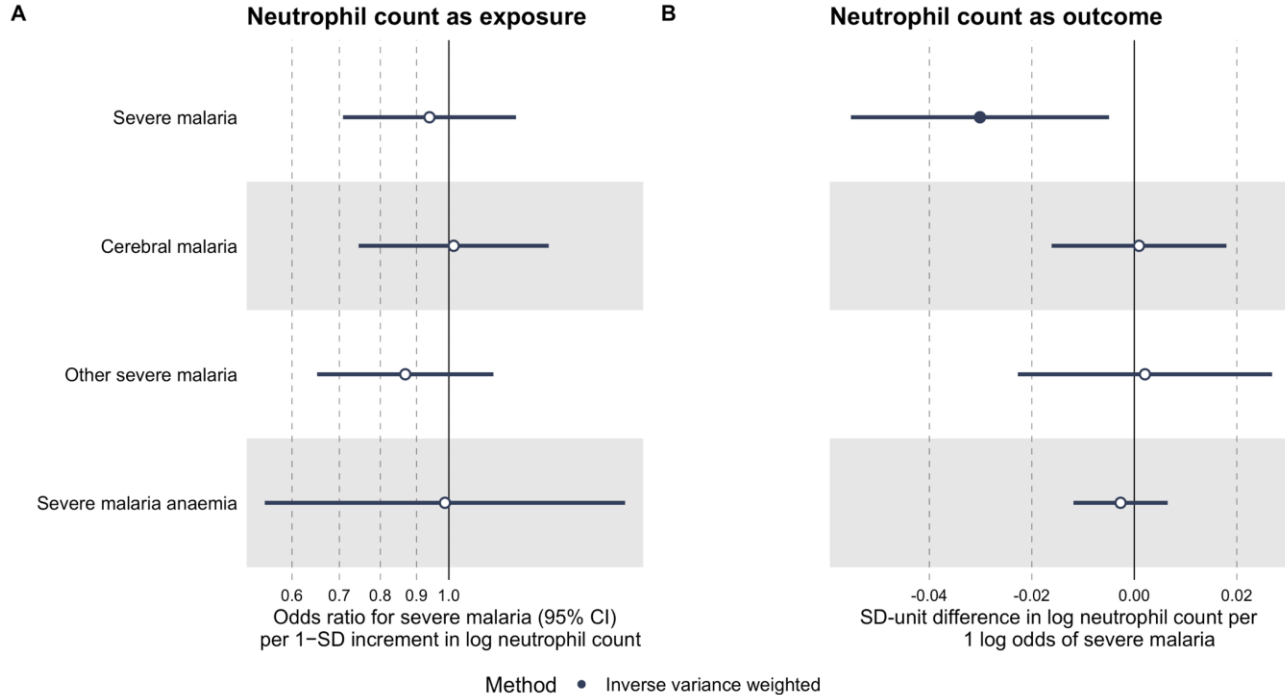


Investigating the causal relationship of neutrophils on malaria



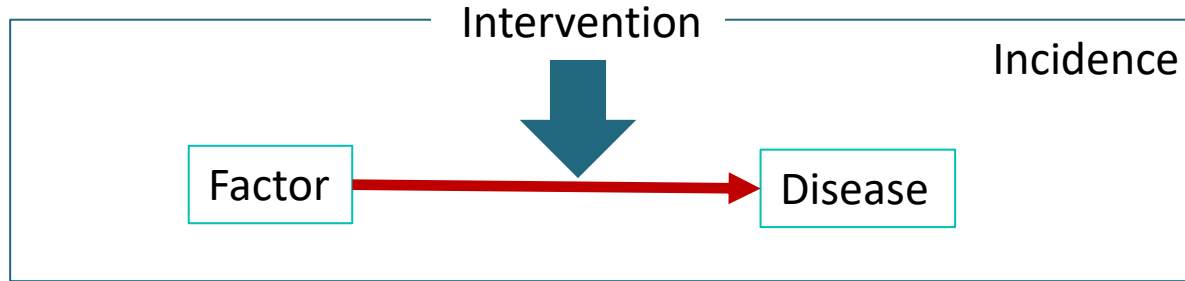


Investigating the causal relationship of neutrophils on malaria

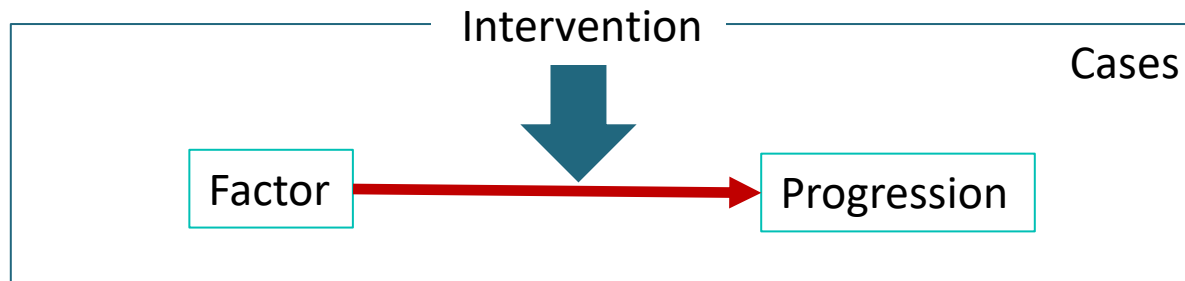




Disease progression



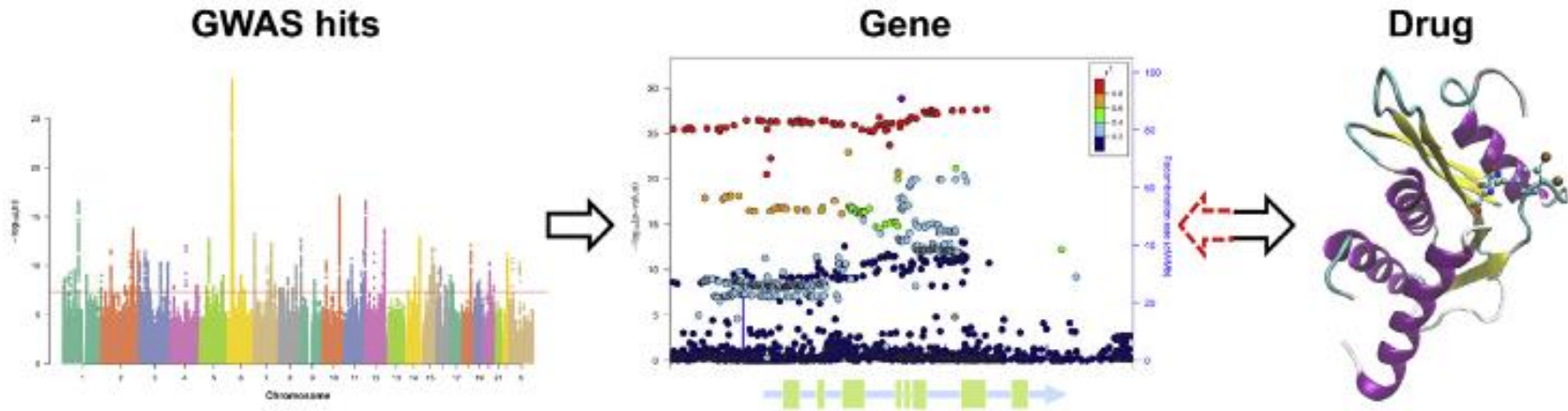
Causes &
potential mechanisms
for prevention



Effective treatment



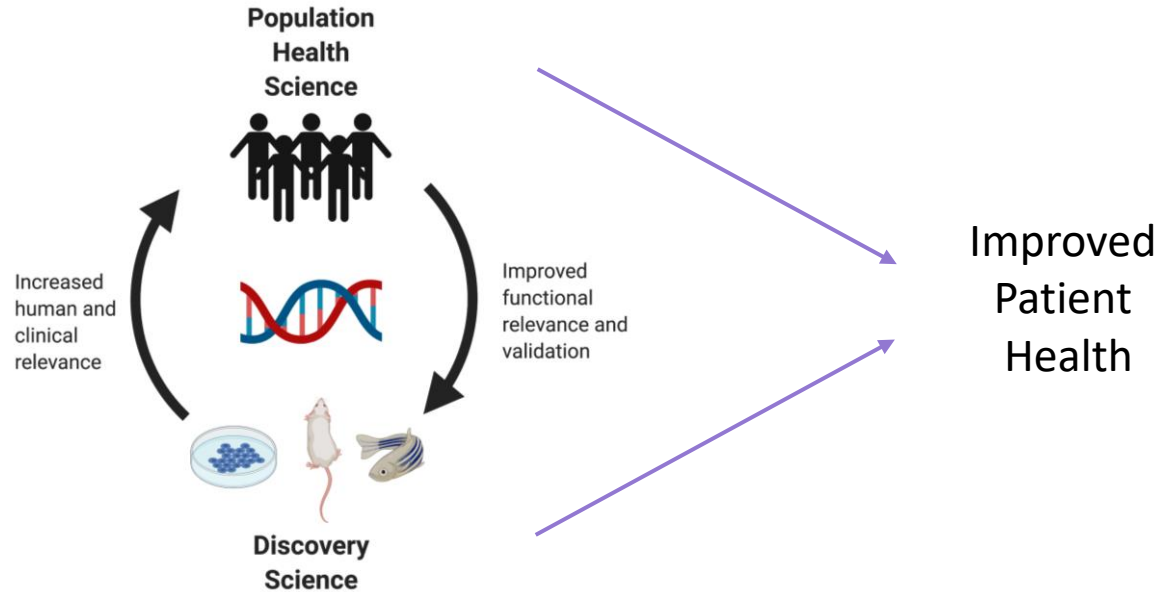
Genetic epidemiology





Cross-talk between epidemiology and laboratory science

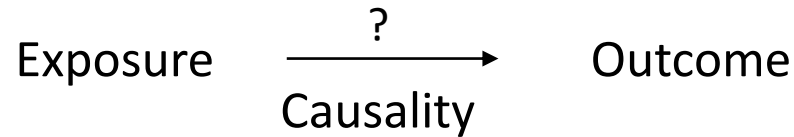
“the process of applying ideas, insights, and discoveries generated through scientific inquiry to the treatment or prevention of human disease.”





Cross-talk between epidemiology and laboratory science

Population Health Sciences



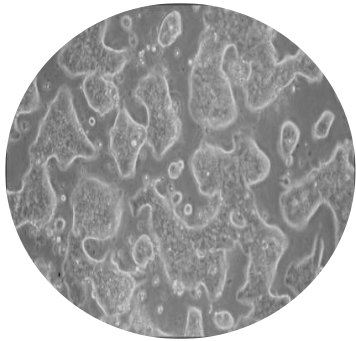
- Whole body human system
- Human population
- Inform laboratory science

Causal trait/causal gene to then take into further analysis



Cross-talk between epidemiology and laboratory science

Bioscience



- Pathways
- Proteins
- Model organisms



Disease or trait
of
interest

- Extremely difficult to instrument activity in an intracellular pathway
- Population Health Sciences limited by the data that can be collected



Genetic epidemiology – Protein GWAS



nature
International journal of science

Article | Published: 06 June 2018

Genomic atlas of the human plasma proteome

Benjamin B. Sun, Joseph C. Maranville, [...] Adam S. Butterworth

Nature **558**, 73–79 (2018) | Download Citation | 14k Accesses | 52 Citations | 409 Altmetric | Metrics >>

Abstract

Although plasma proteins have important roles in biological processes and are the direct targets of many drugs, the genetic factors that control inter-individual variation in

Download PDF

Sections | Figures | References

Abstract

Main

Genetic architecture of the plasma proteo...

Overlap of eQTLs and pQTLs

trans pQTLs identify pathways to disease

Causal evaluation of candidate proteins i...



Human Molecular Genetics, 2015, Vol. 24, No. R1 | R93-R101

doi: 10.1093/hmg/ddv263
Advance Access Publication Date: 9 July 2015
Invited Review

OXFORD

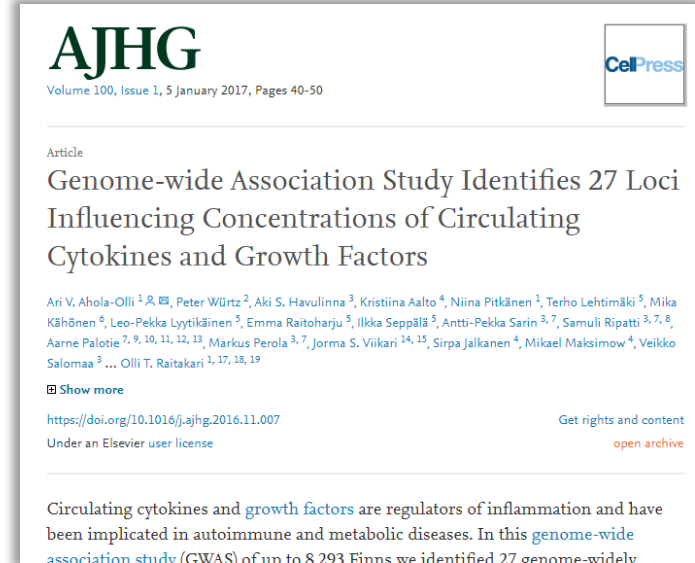
INVITED REVIEW

Genetics of human metabolism: an update

Gabi Kastanmüller^{1,4}, Johannes Raffler¹, Christian Gieger^{2,3} and Karsten Suhre^{1,5,*}

¹Institute of Bioinformatics and Systems Biology, ²Research Unit of Molecular Epidemiology and ³Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany, ⁴German Center for Diabetes Research, Neuherberg, Germany and ⁵Department of Physiology and Biophysics, Weill Cornell Medical College—Qatar, Doha, Qatar

*To whom correspondence should be addressed at: Weill Cornell Medical College—Qatar, Qatar Foundation—Education City, PO Box 24144, Doha, Qatar. Tel: +974 4402 8462; Email: karsten@uhw.de



AJHG
Volume 100, Issue 1, 5 January 2017, Pages 40-50

CellPress

Article

Genome-wide Association Study Identifies 27 Loci Influencing Concentrations of Circulating Cytokines and Growth Factors

Ari V. Ahola-Olli^{1,2,3,4,5,6}, Peter Würtz², Aki S. Havulinna³, Kristiina Aalto⁴, Niina Pitkänen¹, Terho Lehtimäki⁵, Mika Kähönen⁶, Leo-Pekka Lytykäinen³, Emma Raitoharju³, Ilkka Seppälä⁵, Antti-Pekka Sarin^{3,7,8}, Samuli Ripatti^{3,7,8}, Aarne Palotie^{7,9,10,11,12,13}, Markus Perola^{3,7}, Jorma S. Viikari^{14,15}, Sirpa Jalkanen⁴, Mikael Maksimow⁴, Veikko Salomaa³ ... Olli T. Raitakari^{1,17,18,19}

Show more

<https://doi.org/10.1016/j.ajhg.2016.11.007> Get rights and content

Under an Elsevier user license open archive

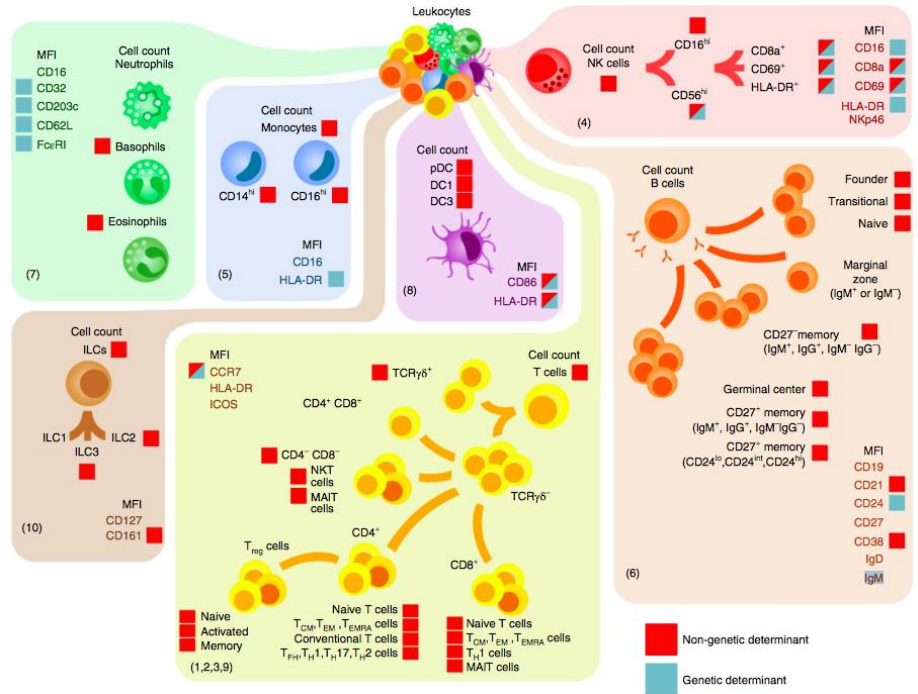
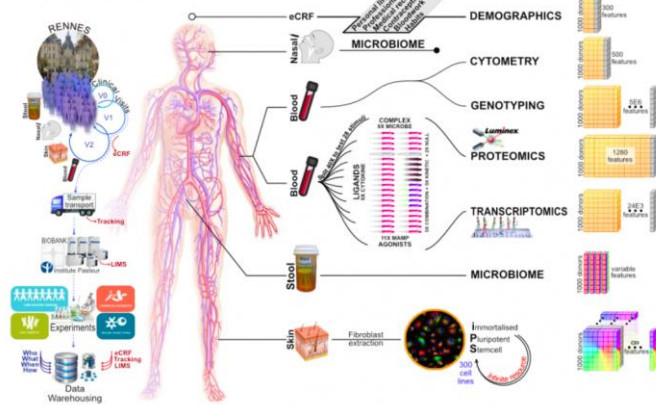
Circulating cytokines and growth factors are regulators of inflammation and have been implicated in autoimmune and metabolic diseases. In this genome-wide association study (GWAS) of up to 8,293 Finns we identified 27 genome-wide



Genetic epidemiology – Protein GWAS

The Milieu Intérieur Project

Hosted by Institute Pasteur on behalf of the Milieu Intérieur Consortium



Patin et al., *Nature Immunology*, 2018



Genetic epidemiology – ‘look up’

Gene – SNPs – search for these in published GWAS

GTEx Portal

Home Datasets Expression QTLs & Browser Sample Data Documentation

Search Gene or SNP ID... Sign In

2019-08-26
GTEx Portal V8 Release
The GTEx V8 non-protected data is now available on the GTEx Portal. Release V8 includes 17,362 RNA-Seq samples from 945 donors, representing an increase of 49% and 33% relative to V7, respectively. Release V8 includes a new quantitative trait to...

Resource Overview | Explore GTEx

Current Release (V8)
Tissue & Sample Statistics
Tissue Sampling Info (Anatomogram)
Access & Download Data
Release History
How to cite GTEx?

The Genotype-Tissue Expression (GTEx) project is an ongoing effort to build a comprehensive public resource to study tissue-specific gene expression and regulation. Samples were collected from 54 non-diseased tissue sites across nearly 1000 individuals, primarily for molecular assays including WGS, WES, and RNA-Seq. Remaining samples are available from the GTEx Biobank. The GTEx Portal provides open access to data including gene expression, QTLs, and histology images.

News and Events

- 2019-08-26 GTEx Portal V8 Release
- 2019-07-24 GTEx V8 data release
- 2019-03-07 New Histology Image Viewer
- 2017-10-18 ASHG GTEx Workshop Materials

Documentation

Browse

- By gene ID: Browse and search all data by gene
- By variant or rs ID: Browse and search all data by variant
- By Tissue: Browse and search all data by tissue
- Histology Image Viewer: Browse and search GTEx histology images

Expression

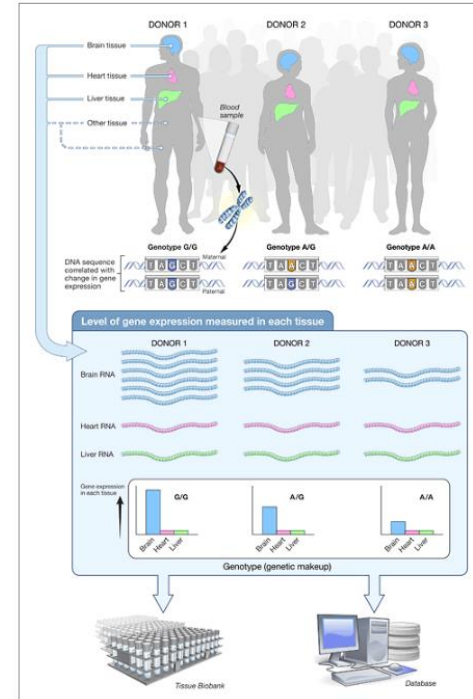
- Multi-Gene Query: Browse and search expression by gene and tissue
- Top 50 Expressed Genes: Visualize the top 50 expressed genes in each tissue
- Transcript Browser: Visualize transcript expression and isoform structures

QTL

- Locus Browser: Visualize QTLs by gene in the Locus Browser
- IGV eQTL Browser: Visualize eQTLs in the IGV Browser
- eQTL Dashboard: Batch query eQTLs by gene and tissue
- eQTL Calculator: Test your own eQTLs

eGTEx

- Data coming soon! DNA, RNA methylation, ChIP-seq and more





Genetic epidemiology – ‘look up’

- Top
- Gene Expression
- Exon Expression
- Single-Tissue eQTLs
- Single-Tissue sQTLs

Copy CSV Search: Show 10 entries

GeneCode Id	Gene Symbol	Variant Id	SNP	P-Value	NES	Tissue	Actions
ENSG00000136634.5	IL10	chr1_206771300_T_C_b38	rs1518111 dbSNP ↗	4.3e-9	0.25	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206771516_A_C_b38	rs1518110 dbSNP ↗	4.3e-9	0.25	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206773062_T_G_b38	rs1800872 dbSNP ↗	4.4e-9	0.25	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206773289_A_G_b38	rs1800871 dbSNP ↗	4.4e-9	0.25	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206771966_A_C_b38	rs3024490 dbSNP ↗	5.1e-9	0.25	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206770888_A_G_b38	rs1554286 dbSNP ↗	2.9e-8	0.24	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206782306_T_C_b38	rs6686931 dbSNP ↗	4.4e-7	0.22	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206759348_T_C_b38	rs76178457 dbSNP ↗	0.000017	-0.31	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206775294_C_T_b38	rs6703630 dbSNP ↗	0.000031	0.18	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot
ENSG00000136634.5	IL10	chr1_206753553_A_G_b38	rs74630871 dbSNP ↗	0.000043	-0.36	Whole Blood	eQTL violin plot, IGV eQTL Browser, Multi-tissue eQTL Plot

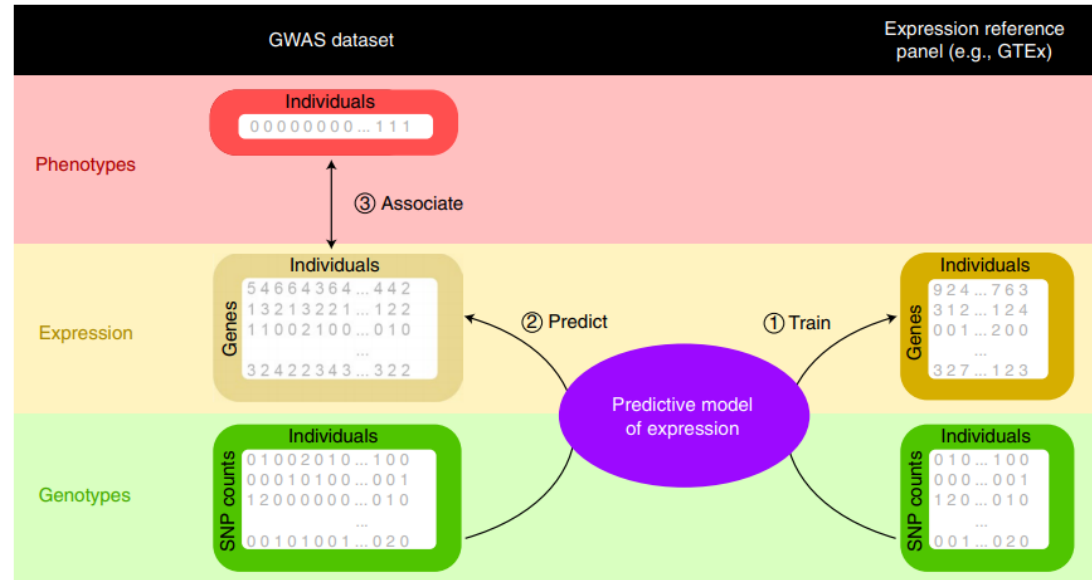
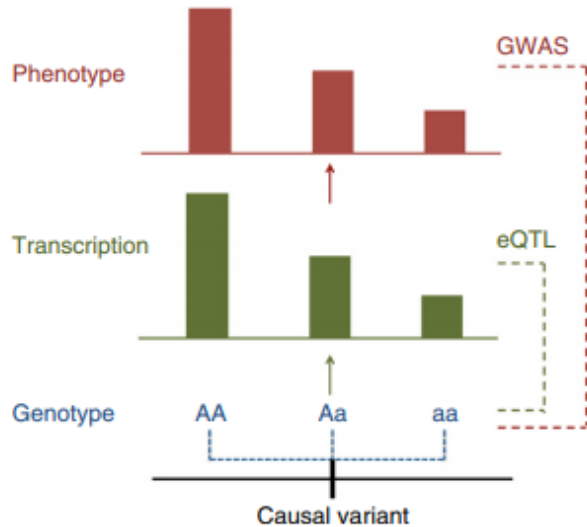
Showing 1 to 10 of 19 entries

First Previous 1 2 Next Last



Genetic epidemiology - TWAS

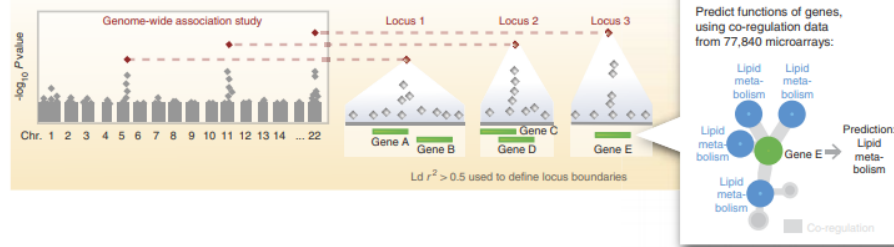
Transcriptome-wide association studies: integrates GWAS and gene expression datasets to identify gene-trait associations



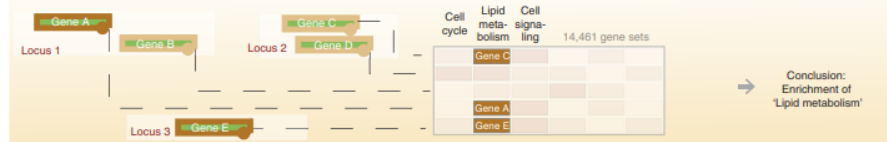


Genetic epidemiology – integrating eQTL and GWAS data

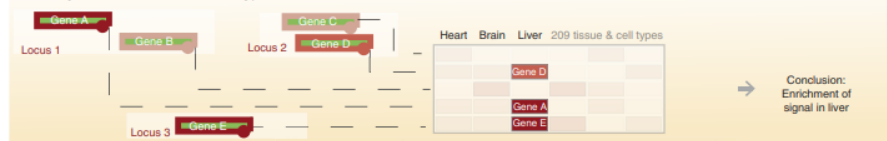
1. Identify genes in associated loci based on input SNPs



2. Identify enriched reconstituted gene sets



3. Identify enriched tissue and cell type annotations



AJHG

Volume 99, Issue 6, 1 December 2016, Pages 1245-1260

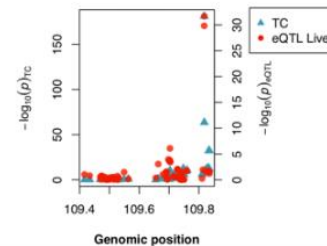


Article

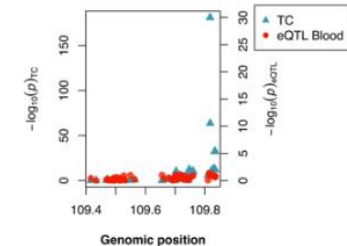
Colocalization of GWAS and eQTL Signals Detects Target Genes

Farhad Hormozdiani¹, Martijn van de Bunt^{2,3}, Ayellet V. Segrè⁴, Xiao Li⁴, Jong Wha J. Joo¹,
Michael Bilow¹, Jae Hoon Sul^{5,6}, Sriram Sankaraman^{1,8}, Bogdan Pasaniuc^{7,8}, Eleazar Eskin^{1,8}

SORT1 Expression (Liver) and Total Cholesterol

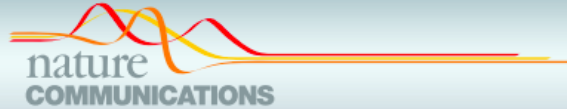


SORT1 Expression (Blood) and Total Cholesterol





Mendelian Randomization – tissue specific MR



ARTICLE

<https://doi.org/10.1038/s41467-019-13921-9>

OPEN

A transcriptome-wide Mendelian randomization study to uncover tissue-dependent regulatory mechanisms across the human phenome

Tom G. Richardson ^{1*}, Gibran Hemani ¹, Tom R. Gaunt ¹, Caroline L. Relton¹ & George Davey Smith ¹



Mendelian Randomization – tissue specific MR

An atlas of tissue-dependent Mendelian randomization associations



Input Type:

GWAS

PheWAS

Cross-tissue comparison (Gene)

Cross-tissue comparison (Variant)

Gene-centric tissue-wide evaluation:

Please select a gene:

Please select a complex trait:

Description [Table of Results](#) [Manhattan plot](#) [PheWAS plot](#) [Cross-tissue plot](#)

Summary

This web application can be used to investigate associations between genome-wide gene expression and 395 complex traits by applying Mendelian randomization and genetic colocalization¹. Analyses have been undertaken using gene expression derived from whole blood made available by the eQTLGen consortium² (n=31,684), as well as 48 different tissue types from the GTEx project³. Findings from this web application can help uncover associations yet to be detected by genome-wide association studies and also investigate tissue-specific effects between gene expression and complex traits.

Instructions

To query results from our atlas please select parameters on the left hand side of this page before clicking the 'Search Atlas' button. This will generate results in the **Tables of Results**.

There are 4 ways to query the results of our atlas depending on the **Input Type** selected:

GWAS - Genome-wide association study. Select a **complex trait** and **tissue** of interest from the drop-down menus before clicking the 'Search Atlas' button. This will evaluate all genome-wide MR associations and plot results using a manhattan plot⁴.

PheWAS - Phenome-wide association study. Type in a **gene** and select a **tissue** of interest from the drop-down menus and click the 'Search Atlas' button. This will query the findings against your target gene and all traits in our atlas. An interactive plot⁵ will be generated to display $-\log_{10}$ p-values multiplied by the corresponding direction of effect for each result. As such, positive associations reside above $-\log_{10}0$, whereas negative associations reside below. Points are grouped and coloured based on their corresponding traits subcategory.

Cross-tissue comparison (Gene) - Tissue-wide association study. Enter a **gene** and select a **complex trait** from the drop-down menus to investigate associations across all available tissue types. Results are plotted using an interactive plot⁵ as described above, except points are grouped and coloured based on tissue types.

Cross-tissue comparison (Variant) - Tissue-wide association study. Type a **genetic variant** (e.g. rs5882) and select a **complex trait** from the drop-down menus to evaluate associations across all available tissues in the atlas. If your variant is not an expression quantitative trait loci (eQTL) then a warning message will appear. As above, an interactive plot⁵ will be displayed with points coloured based on tissue types.

The **Download** button can be used to download a comma-separated value (csv) file for the results you have queried.



Mendelian Randomization protein specific MR



Proteome PheWAS browser

Click to view the list of [proteins](#) or [traits](#).

Results presented here can also be downloaded programmatically using the [EpiGraphDB API](#).

✔ or ✘: passed or failed test respectively; ⚠: warning, results might be unreliable; ? : data are missing or not applicable.

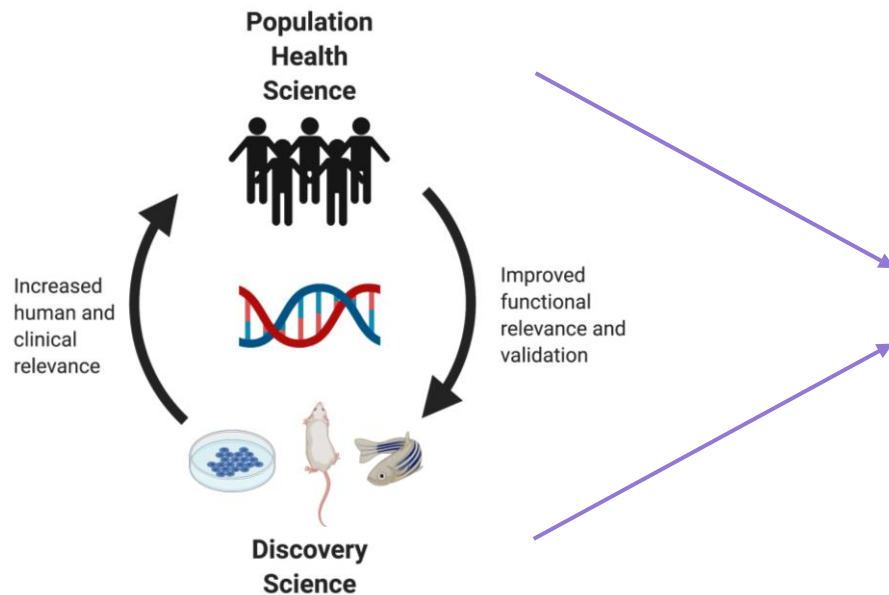
Basic summary | MR results | Single SNP MR results | SNP information | Sensitivity analysis

⌵ ALL RESULTS FILTER:

Protein	MRBase ID	Combined Instruments Tests		rsID	Individual Instrument Tests			
		Protein associates with trait	Low heterogeneity		Cis acting instrument	Correct causal direction	Instrument associates with one protein	Shared causal variant
Inflammatory bowel disease								
IL23R	294	2.213e-166	?	rs11581607	✔	?	✔	?
Crohn's disease								
IL23R	12	5.801e-149	?	rs11581607	✔	✔	✔	✔
Ulcerative colitis								
IL23R	970	4.342e-62	?	rs11581607	✔	✔	✔	✔
Non-cancer illness code self-reported: psoriasis								
IL23R	UKB-a:100	9.475e-10	?	rs11581607	✔	✔	✔	✔



Cross-talk between epidemiology and laboratory science





Scope for engagement in the strand

- Discrete piece of work
- Facilitate collaborations
- Community building events
- Potentially one-off seminars

Elizabeth Blackwell Institute for Health Research
Funding opportunities
Our research focus
↳ COVID-19 research
↳ Mental health
↳ Research strands
↳ Bioethics, Biolaw and Biosociety
↳ Medical Humanities
↳ Bristol AMR
↳ Digital Health
↳ Health Data Science
↳ Global Public Health
↳ Mechanisms to Populations
↳ Research Networks
↳ Related research

Integrating Health Research: Mechanisms to Populations

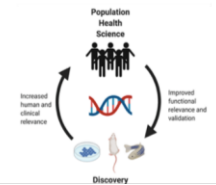
Building research capacity at the University of Bristol in the interdisciplinary space between fundamental biosciences and population health sciences.

Purpose

The aim of the 'Integrating Health Research: Mechanisms to Populations' research strand is to promote and facilitate interdisciplinary research between fundamental bio-scientists and population health scientists. The strand will bring together the ground-breaking research into disease mechanisms being carried out in the fundamental biosciences with the state-of-the-art methodologies and applied techniques in the population health sciences. The ultimate objective is to enhance the understanding of disease processes and accelerate the arrival of therapies into the clinic.

The strand will provide a formal structure for promoting and facilitating interdisciplinary research between fundamental bioscience and population health science through dedicated researcher capacity with the necessary skills in locating, accessing and analysing population health data as well as providing a space to foster collaborations. In doing so our aim is to support interdisciplinary grant applications and publications.

Fundamental bioscience is the study of the molecular processes that form the basis of life. Research in fundamental bioscience at the University of Bristol is diverse and

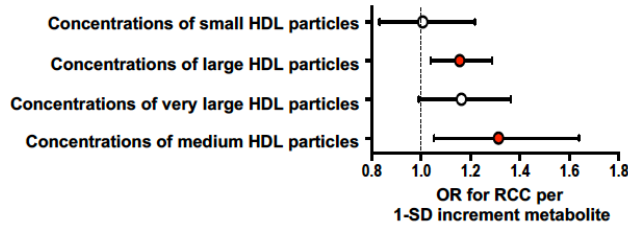




Example output: contributions to papers

HDL and Renal Cell Carcinoma

Mendelian Randomization

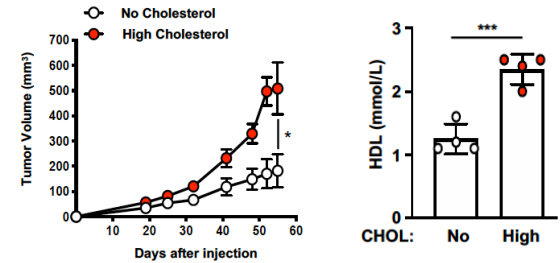


Tissue expression

Genes involved in **Cholesterol uptake**

Gene	Gene expression changes in tumor vs normal tissue	p-adj
SCARB1	16.80653	4.66E-208
LDLR	-2.39152	9.65E-14
VLDLR	1.55408	4.29E-11
CD36	2.16743	3.87E-44

Mouse models and cell biology



Accepted for publication in Cancer Discovery.

E Vincent, C Bull, C Simon, M Johansson, N Skuli



Example output: Team collaboration



Repeat clinics (December 2020; April 2021 and June 2021)

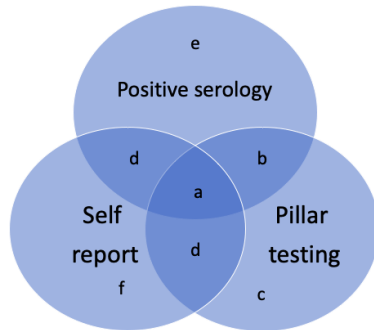
Measurable traits

BMI
General Health
Asthma

Biosamples

T cells
Antibodies
Pseudoviruses

Cases	123
Matched controls	103
Random controls	98





Example output: Grant applications

Finding new osteo-anabolic drug targets for osteoporosis

1. Population studies data gathering

Large Genomic Studies Humans

100,000s of possible polymorphisms



Gene - bone trait Association
In silico prioritisation

100s of possible polymorphisms
10s of candidate genes

2. Functional zebrafish studies

CRISPR-Cas9 + gRNA
One-cell embryo

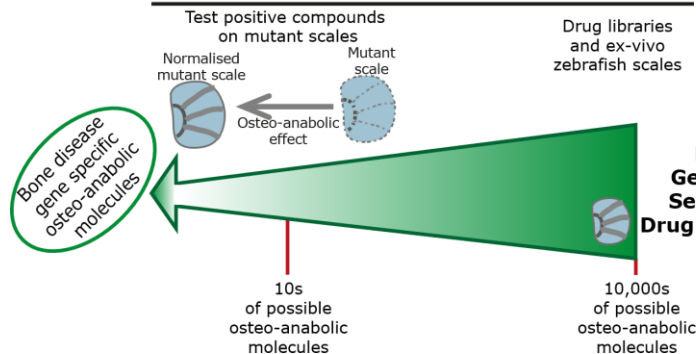
Mutant generation
Phenotyping

Mutants with osteoblast / bone mass phenotype

3.

Large Genetically Sensitised Drug Screening

Ex-vivo scale culture
Normal Scale





How can we help?

- Are in Bioscience or in population health?
- What stage of collaborating are you at?
- What engagement do people want?

Email: ebi-mechanisms-populations@bristol.ac.uk

Website: www.bristol.ac.uk/blackwell/health-research/research-strands/mechanisms-to-populations/

Acknowledgements

Emma Vincent and Chrissy Hammond



Pete Cullen & Paul Martin
Chrissy Hammond, Kate Nobes
David Wraith
Wraith lab



Lavinia Paternoster
Nic Timpson
George Davey Smith
MRC Integrative Epidemiology Unit



Elizabeth Blackwell Institute
for Health Research