

Introduction to complex trait genetics

Eleftheria Zeggini

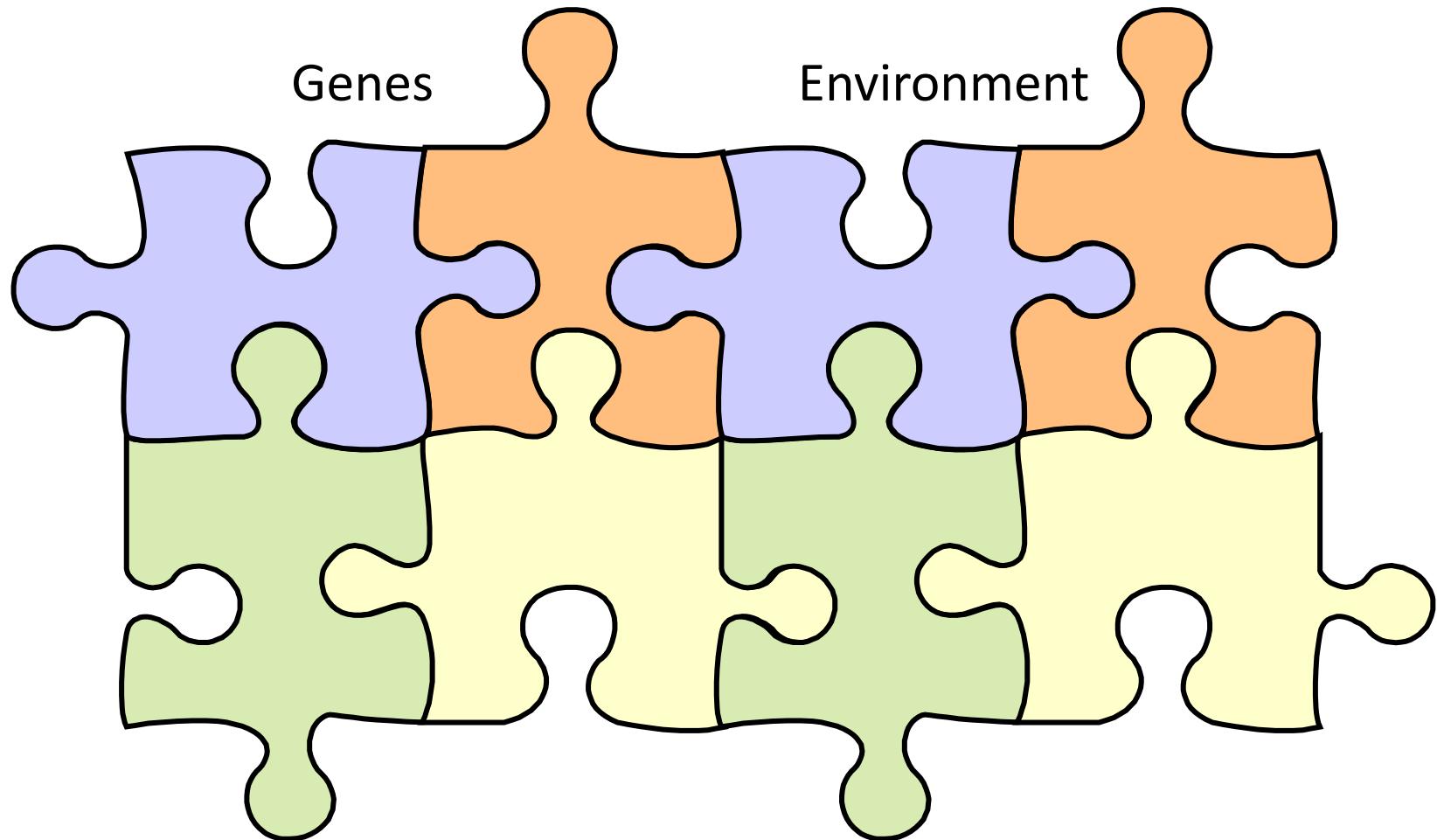
Human Genetics

Wellcome Trust Sanger Institute

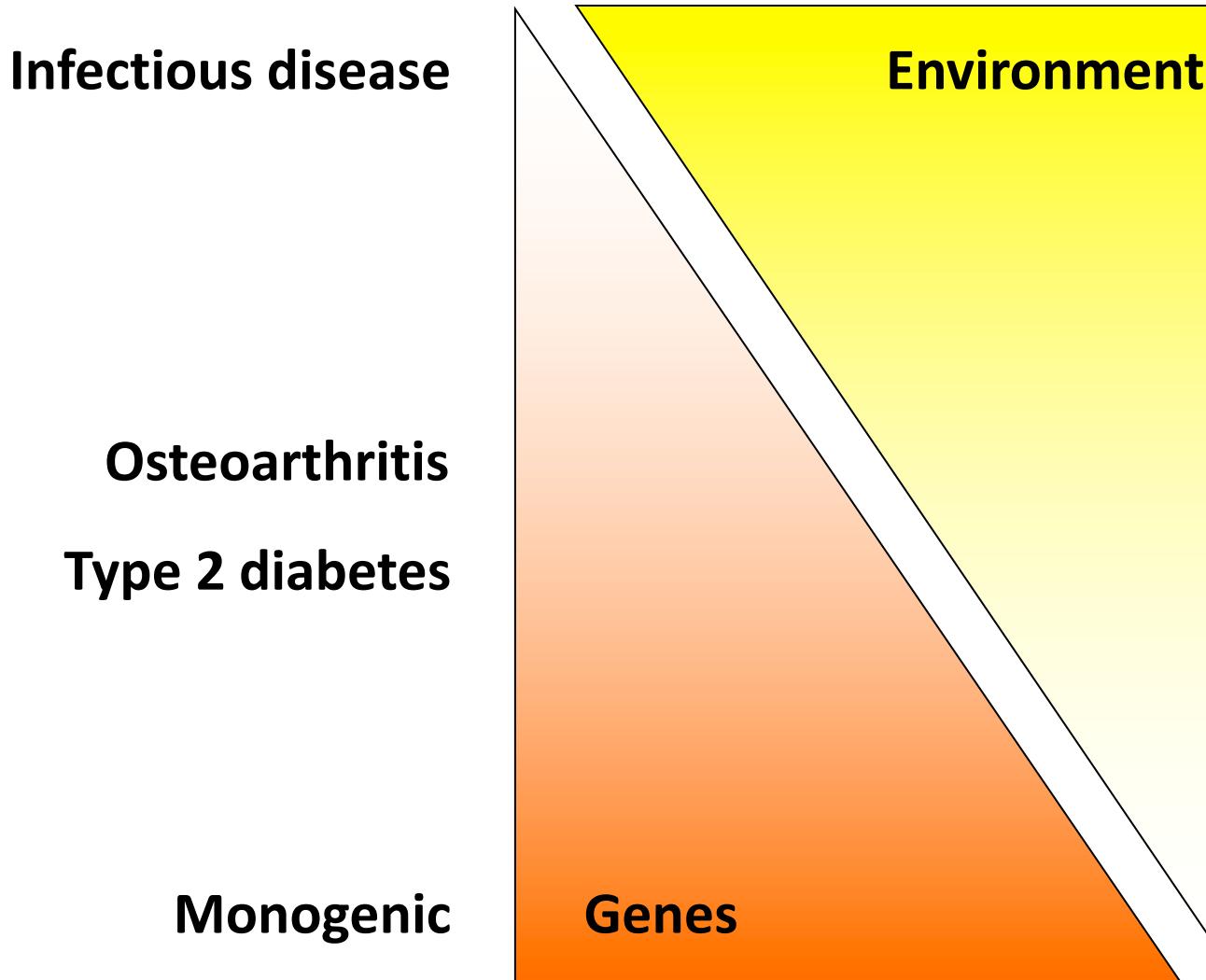
eleftheria@sanger.ac.uk



Complex diseases



Genes vs environment

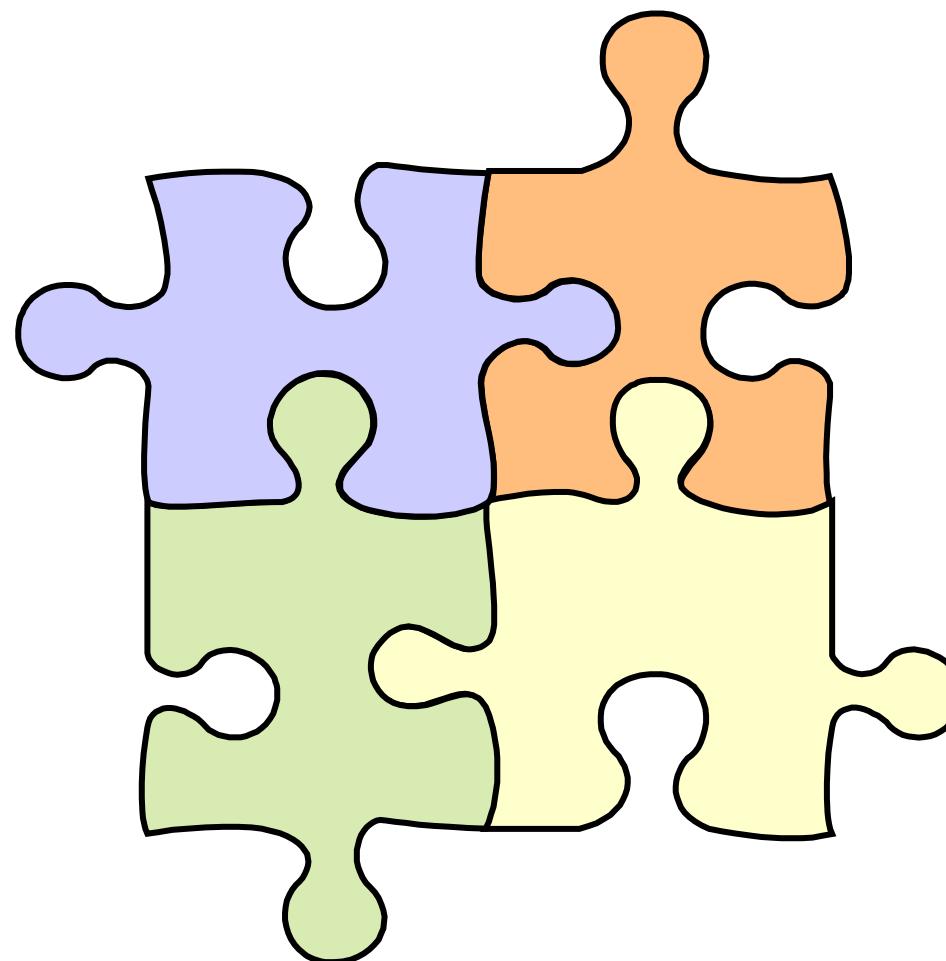


Genetic architecture of complex traits

Common variants



Rare variants



Small effect size



Large effect size

Large sample collections



THE MILLION WOMEN STUDY
A confidential national study of women's health



biobank^{uk}
Improving the health of future generations
www.danubienetwerk.de

Large sample collections



Understanding of patterns of human genome sequence variation



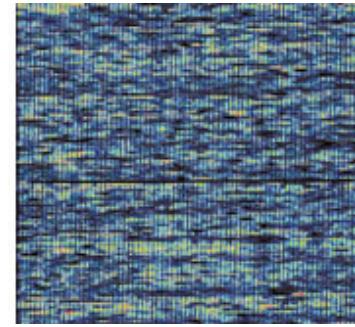
1000 Genomes
A Deep Catalog of Human Genetic Variation

Large sample collections



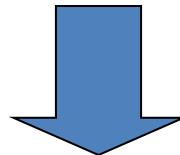
Understanding of patterns of human genome sequence variation

High-throughput technologies for genotyping

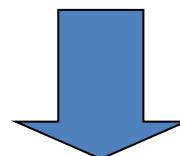


Principles

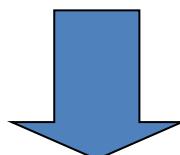
Case-control pairs (or population cohorts)



Type for 500k-2.5M SNPs

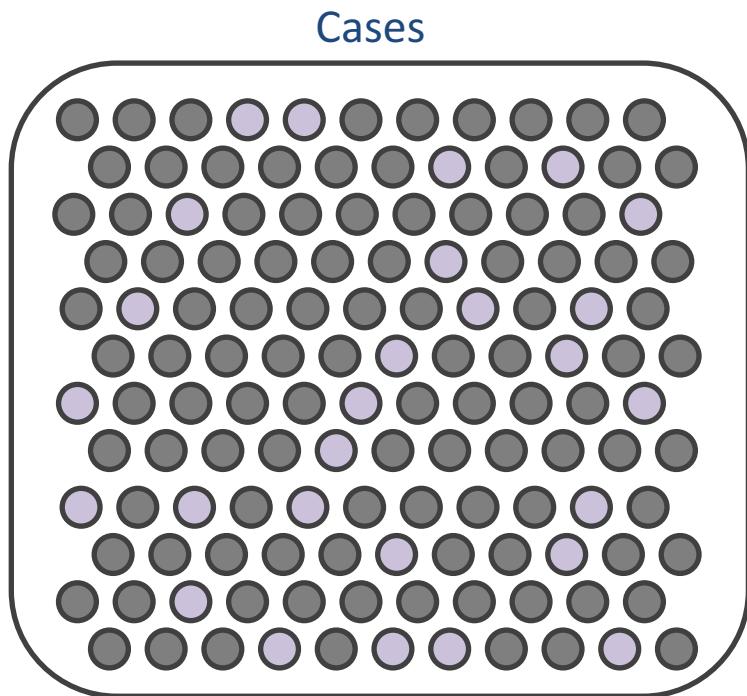


Obtain information about strength of association
genome wide
(within limits of sample size, allele frequency, LD etc)

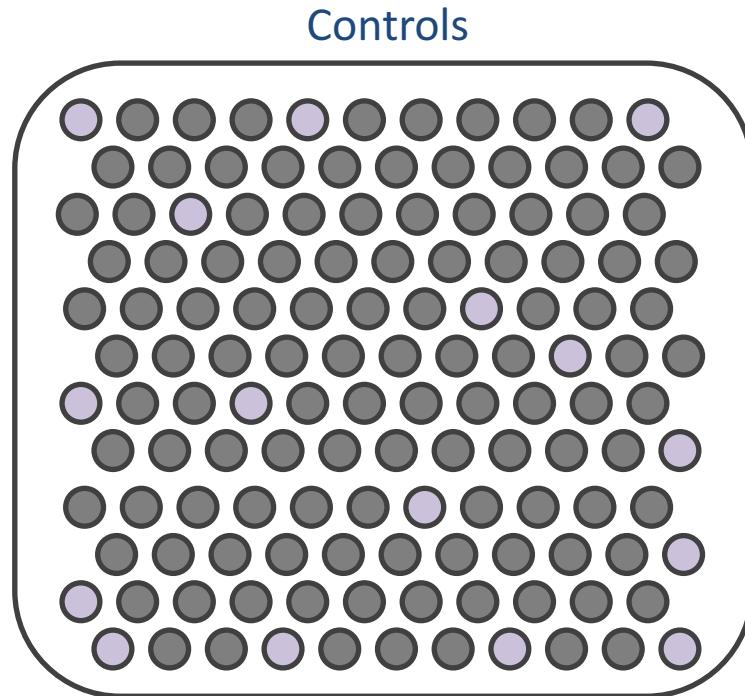


Follow-up what looks interesting

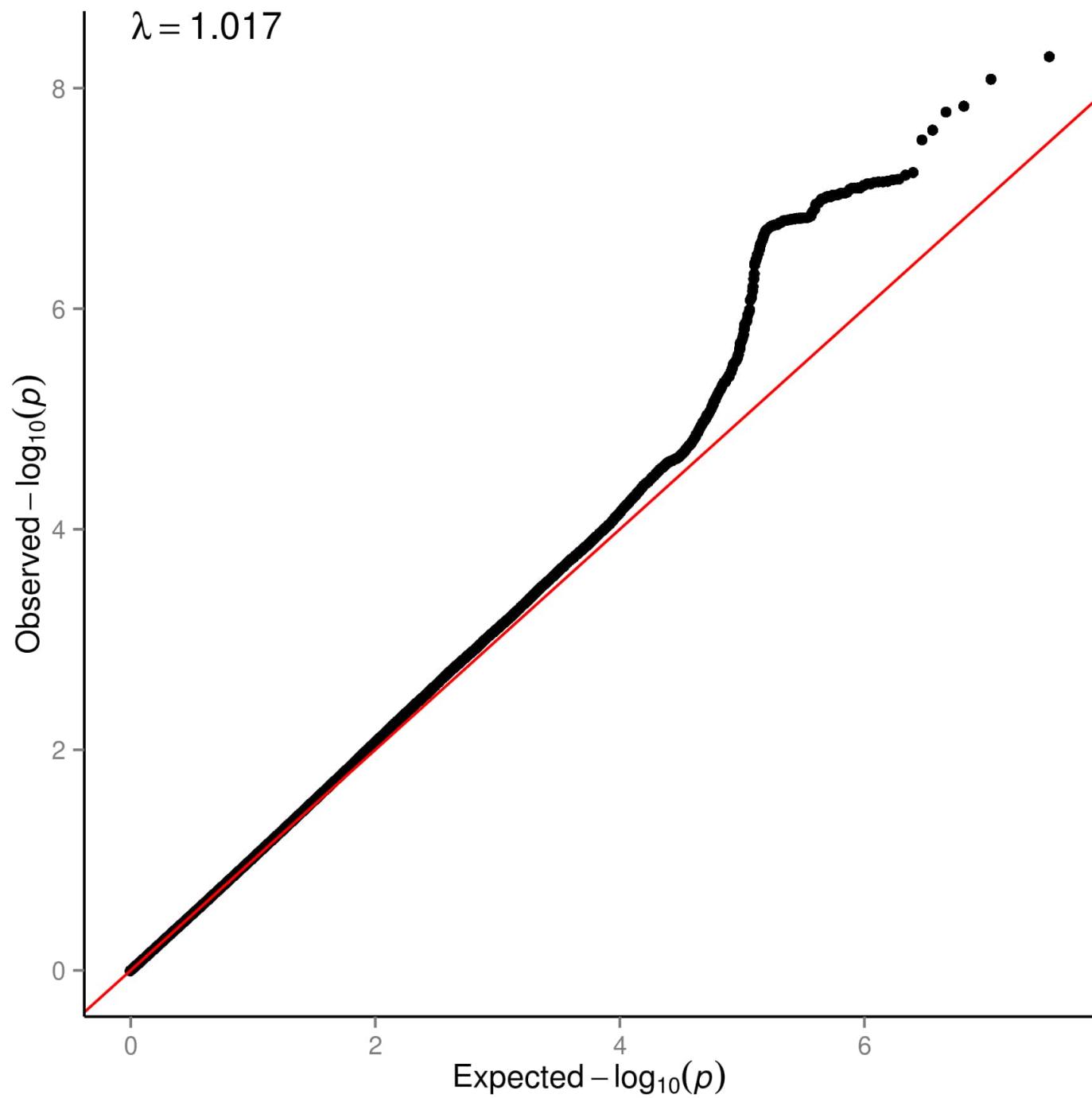
Association between genetic variants and disease

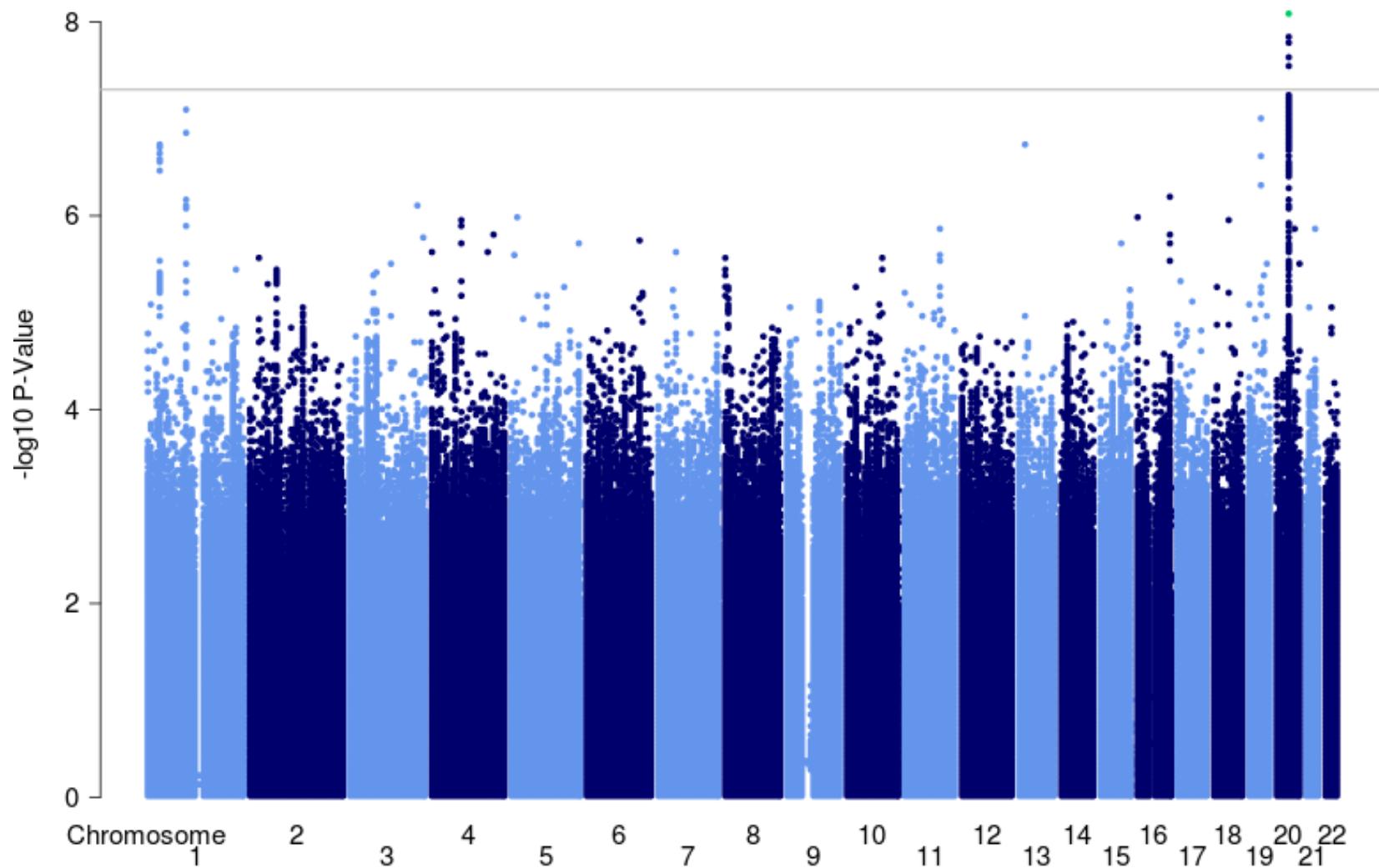


25%



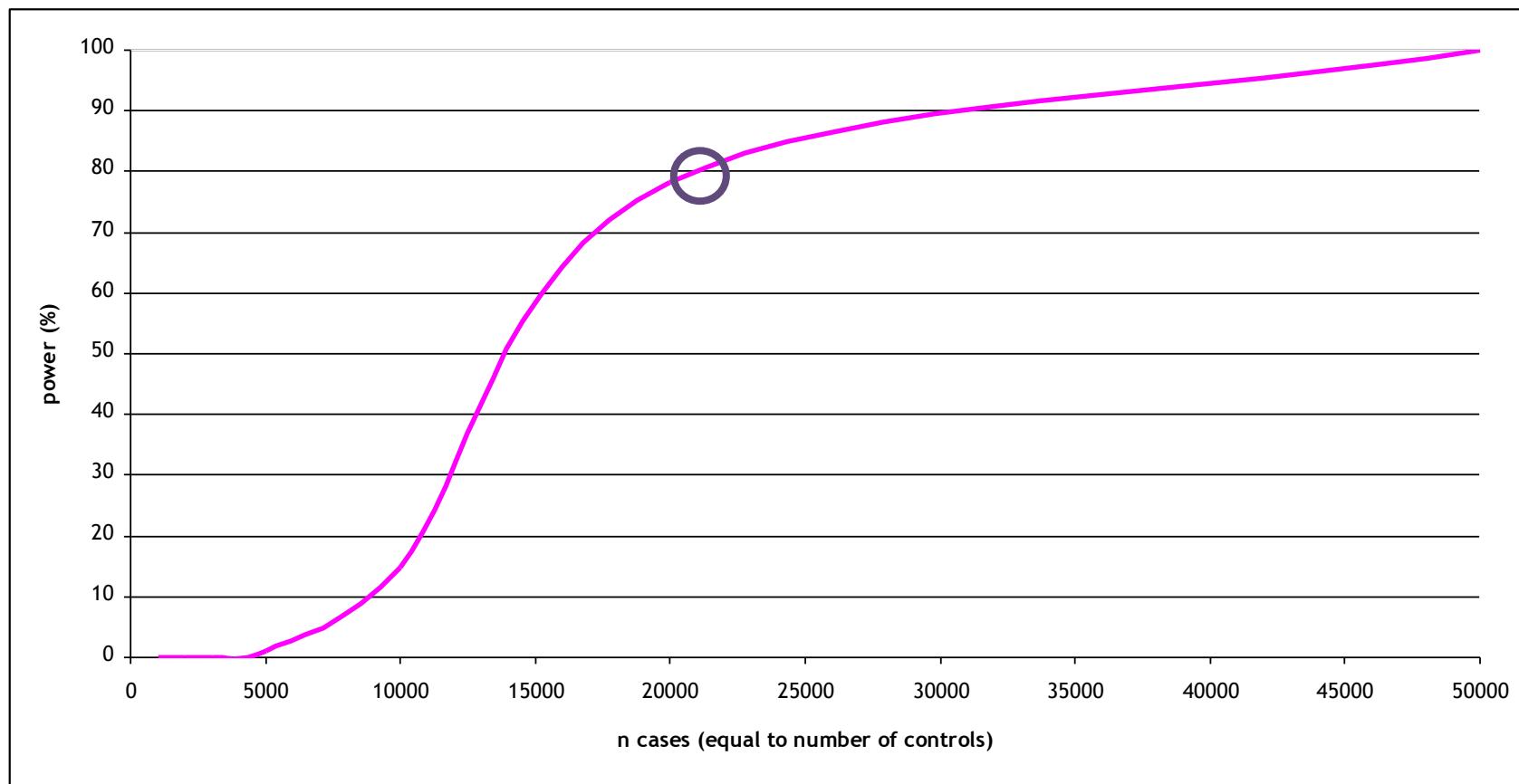
15%



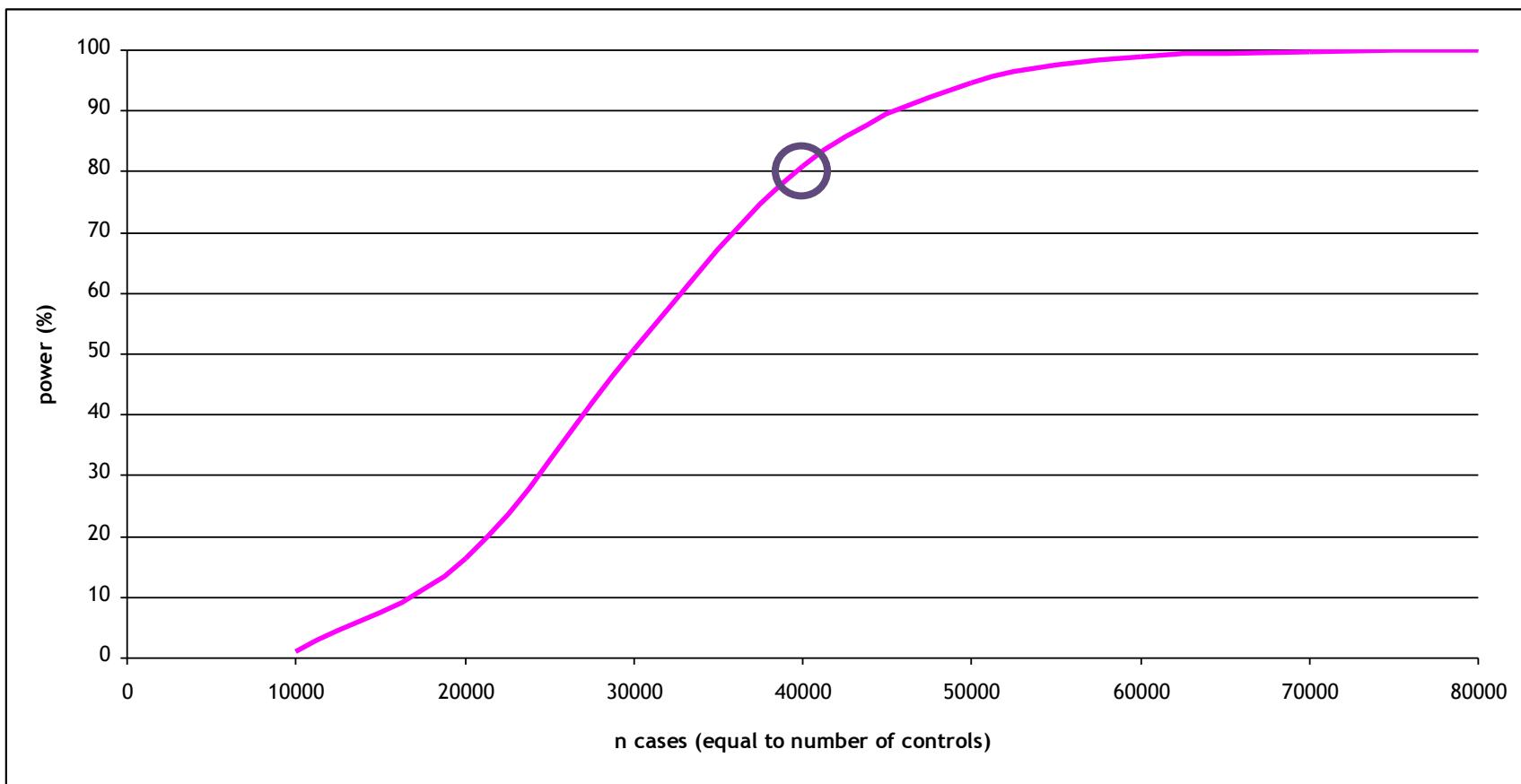


Sample size matters

Power to detect association ($p=5\times 10^{-8}$) at a variant with risk allele frequency 0.30 and allelic OR 1.10



Power to detect association ($p=5\times 10^{-8}$) at a variant with risk allele frequency 0.005 and allelic OR 1.50



Osteoarthritis

Osteoarthritis (OA) is characterised by cartilage degeneration in the joints leading to pain and loss of function



50% of people over the age of 70 years

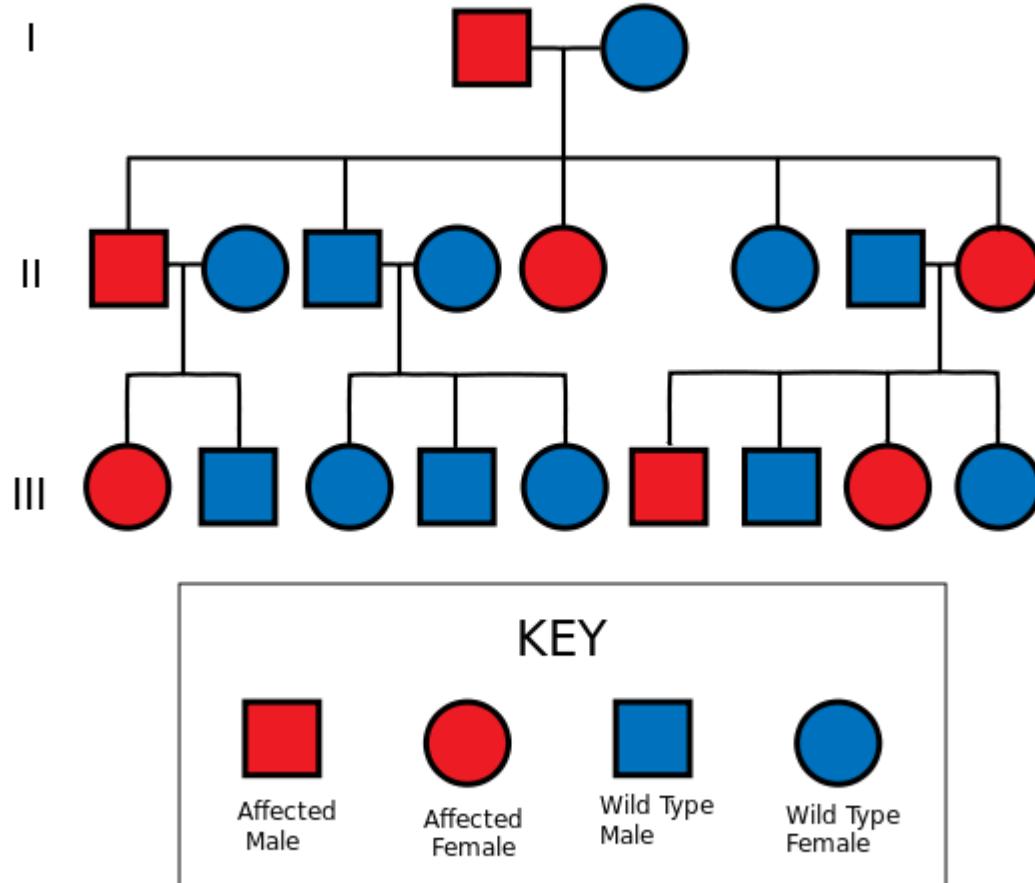
No curative therapy: analgesics, total joint replacement

Heritability of OA

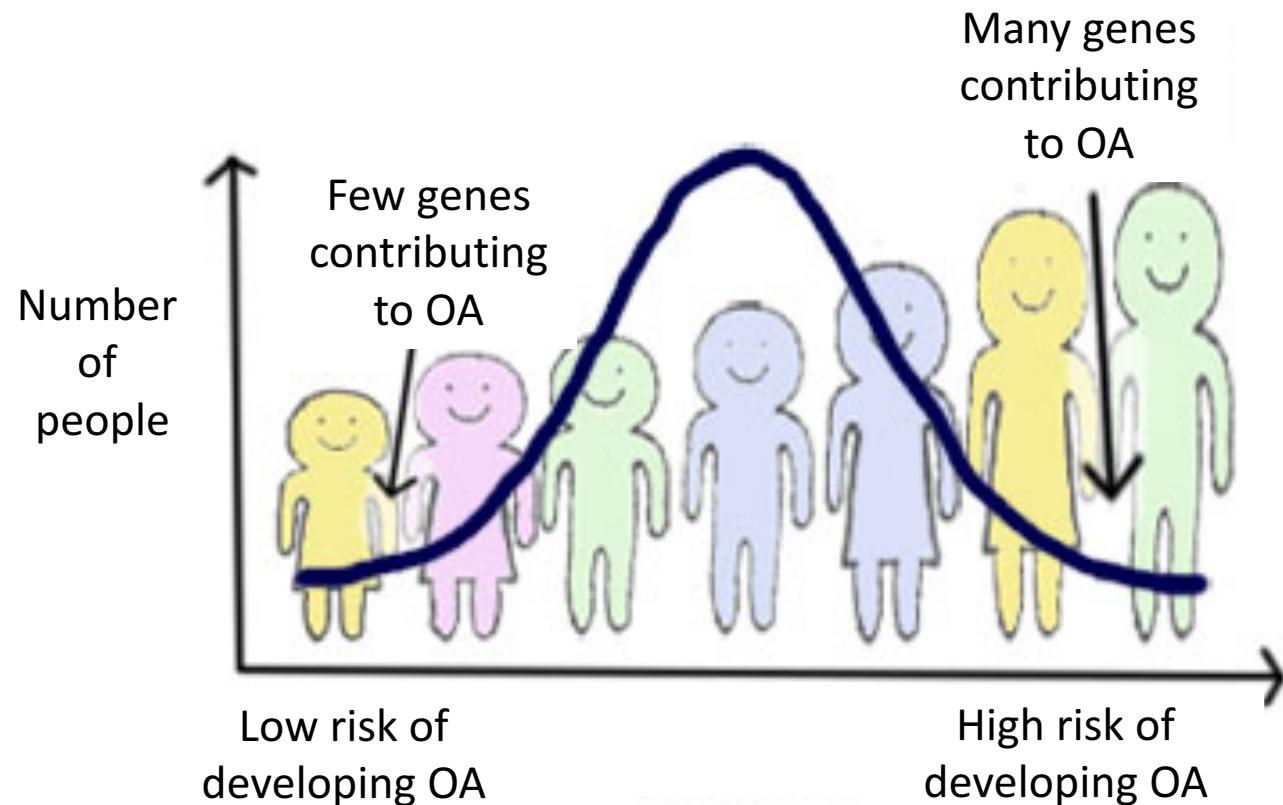


~50%: half of the variation in susceptibility to OA in the population is due to genetic factors

OA is not a single gene disorder



OA is a complex or polygenic disease



arcOGEN Consortium

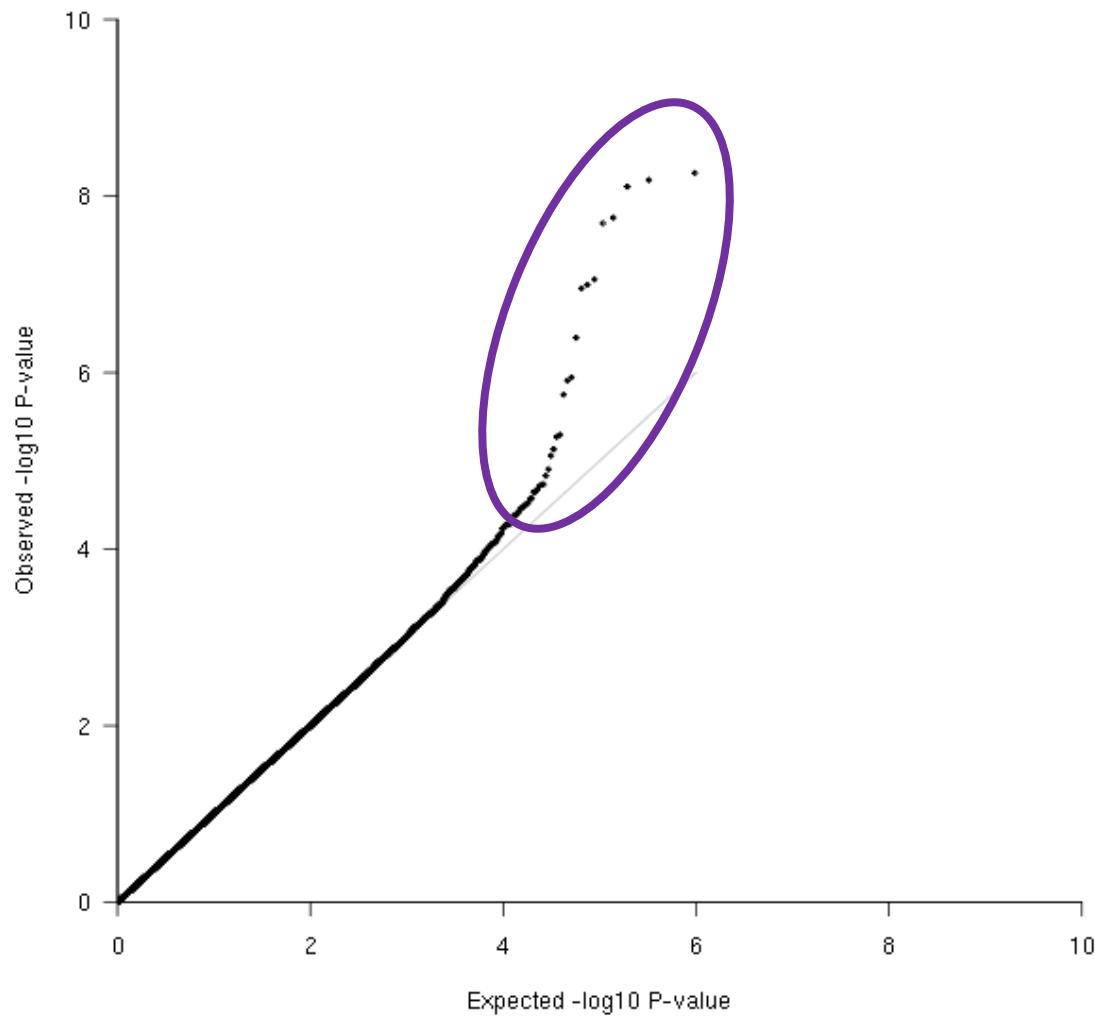
arc Osteoarthritis Genetics



11 participating sites:



7,410 OA cases v. 11,009 controls



Replication Replication Replication



Combined analysis

14,883 cases and 55,775 controls

arcOGEN finds 9 new OA risk variants



Replicating signals

SNP	Chr	Nearest gene(s)	Effect Allele Freq (controls)	OR [95% CIs]	P
rs6976	3	<i>GLT8D1</i>	0.37	1.12 [1.08-1.16]	7.24E-11
rs4836732	9	<i>ASTN2</i>	0.47	1.20 [1.13-1.27]	6.11E-10
rs9350591	6	<i>FILIP1, SENP6</i>	0.11	1.18 [1.12-1.25]	2.42E-09
rs10492367	12	<i>KLHDC5, PTHLH</i>	0.19	1.14 [1.09-1.20]	1.48E-08
rs835487	12	<i>CHST11</i>	0.34	1.13 [1.09-1.18]	1.64E-08
rs11842874	13	<i>MCF2L</i>	0.07	1.17 [1.11-1.23]	2.07E-08
rs12107036	3	<i>TP63</i>	0.48	1.21 [1.13-1.29]	6.71E-08
rs8044769	16	<i>FTO</i>	0.50	1.11 [1.07-1.15]	6.85E-08
rs10948172	6	<i>SUPT3H</i>	0.29	1.14 [1.09-1.20]	7.92E-08



Potentially interesting targets



- Carbohydrate sulfotransferase 11 gene, *CHST11*, affects cartilage proteoglycan
 - Nutraceutical compounds like chondroitin sulfate have been studied with contradictory results
-
- Parathyroid hormone-like hormone gene, *PTHLH*, is the basis for parathyroid hormone-based treatments for osteoporosis
 - These compounds may also be effective in osteoarthritis

Fat mass and obesity-associated gene



<http://www.nairaland.com/965900/what-obesity>

the guardian

News | Sport | Comment | Culture | Business | Money | Life & style |

News > Science

Obesity is not just gluttony - it may be in your genes

- Half of population carry a copy of 'problem' version
- Scientists insist diet and exercise still important

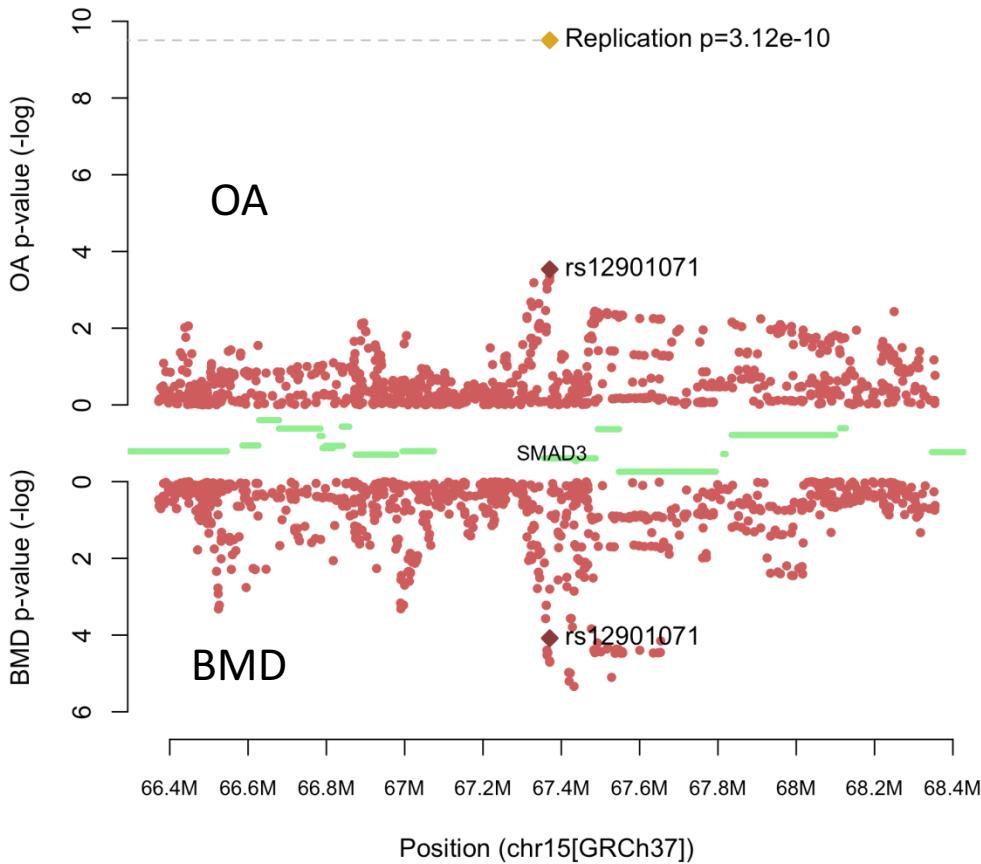
James Randerson, science correspondent
The Guardian, Friday 13 April 2007

Scientists have discovered the first clear genetic link to obesity that is carried by significant numbers of people, according to a study yesterday. One copy of the gene leads to a 1.2kg (2.6lb) weight increase while those with two copies are on average 3kg heavier.

The scientists say it will open up new avenues of research into who is susceptible to obesity and how best to prevent the condition that is the second largest cause of death in the UK.

FTO exerts its effect on OA through obesity

Shared genetic determinants of linked diseases



- High bone mineral density is correlated with increased risk of OA
- Risk of osteoporosis is inversely correlated with risk of OA
- Examined genetic overlap between OA and BMD to identify pleiotropic loci
- Replication in 23,425 OA cases and 236,814 controls

SMAD3 plays a role in bone remodeling and cartilage maintenance

Bigger sample size

Harnessing the power of large biomedical resources



National Joint Registry
www.njrcentre.org.uk

Working for patients, driving forward quality

Accessing registry records and patient recruitment

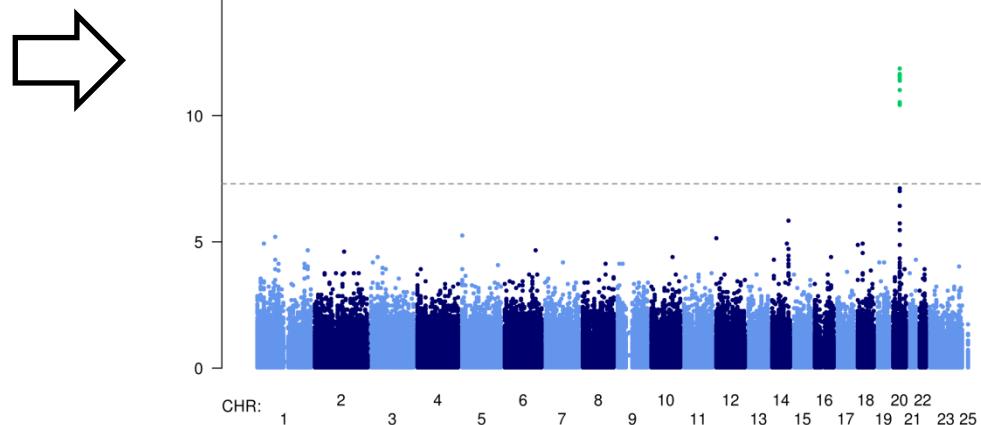
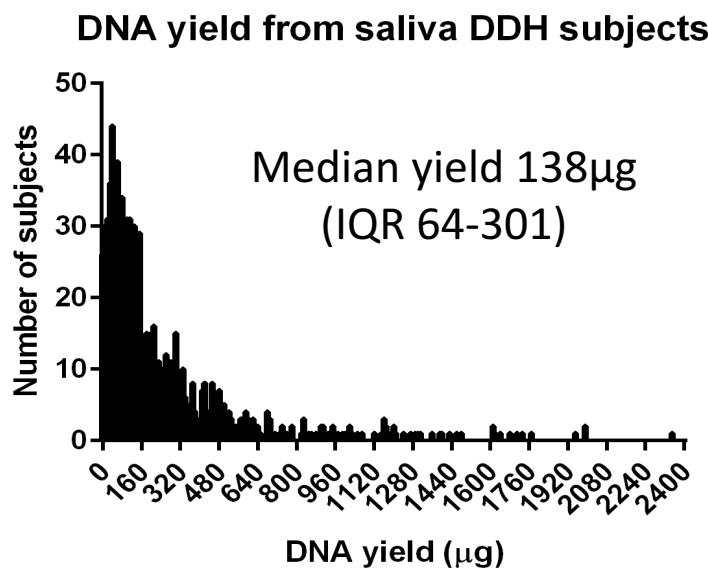
Developmental dysplasia of the hip -National Joint Registry

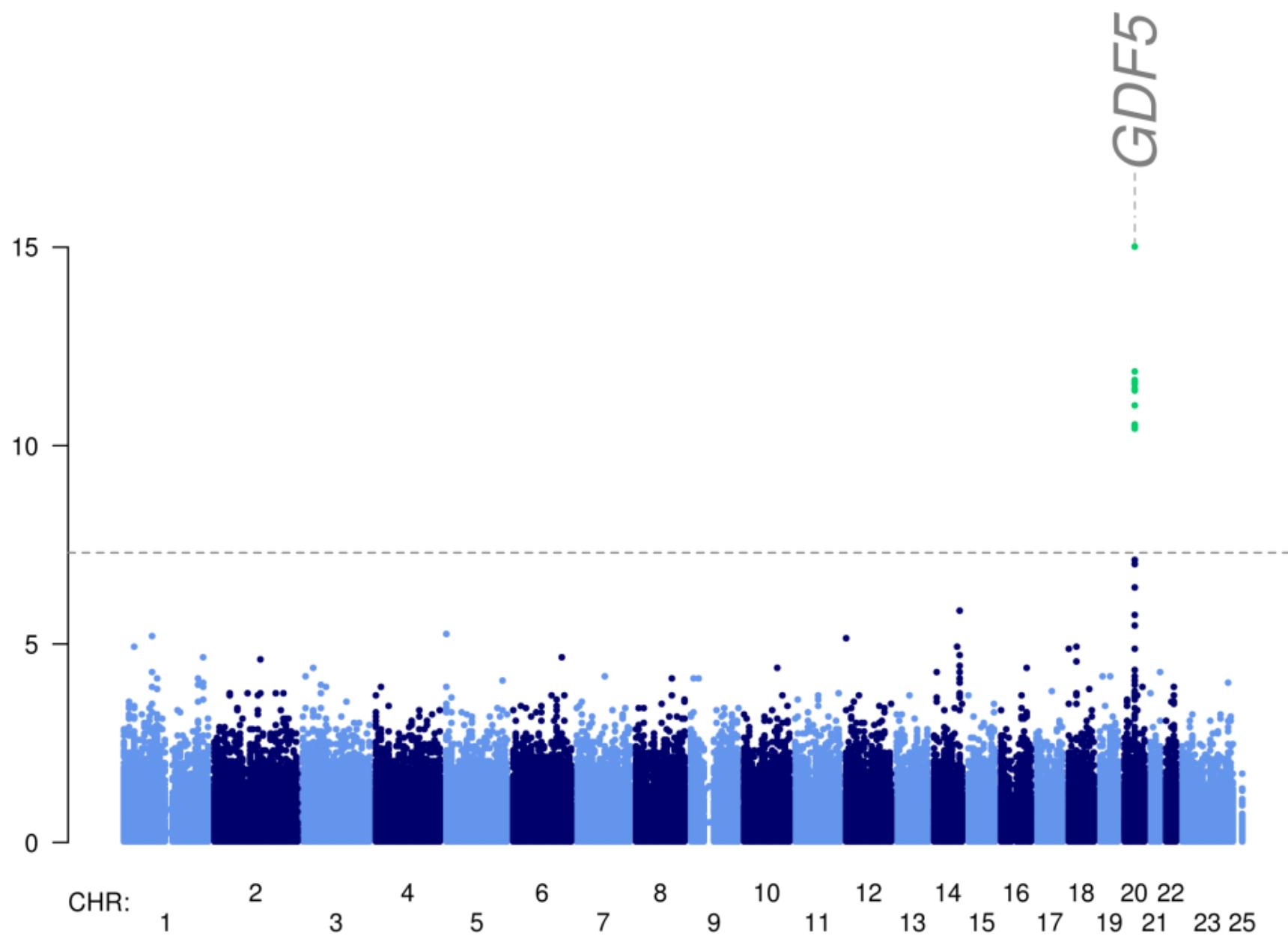
1,091 postal DNA kits to pre-screened consenting participants

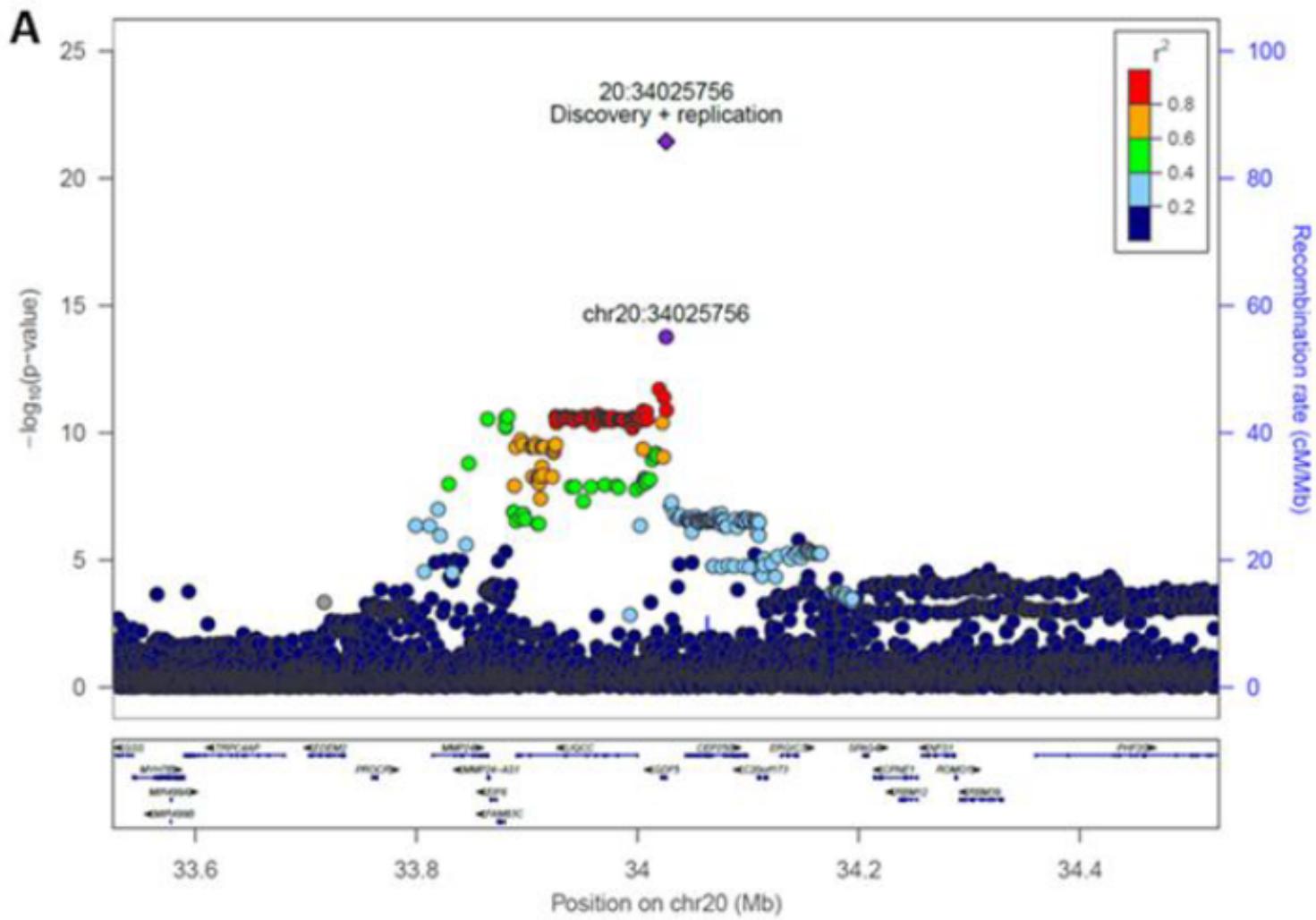


907 returns

Electronic radiographs obtained through Image Exchange Portal







- GDF5 is essential for normal bone and joint development
- The lead variant is located in the *GDF5* promoter and modulates gene expression

ARGONAUT: Accelerating the discovery of genomics in osteoarthritis through national clinical audit data

25k
unicompartmental
knee replacement

25k
total knee
replacement



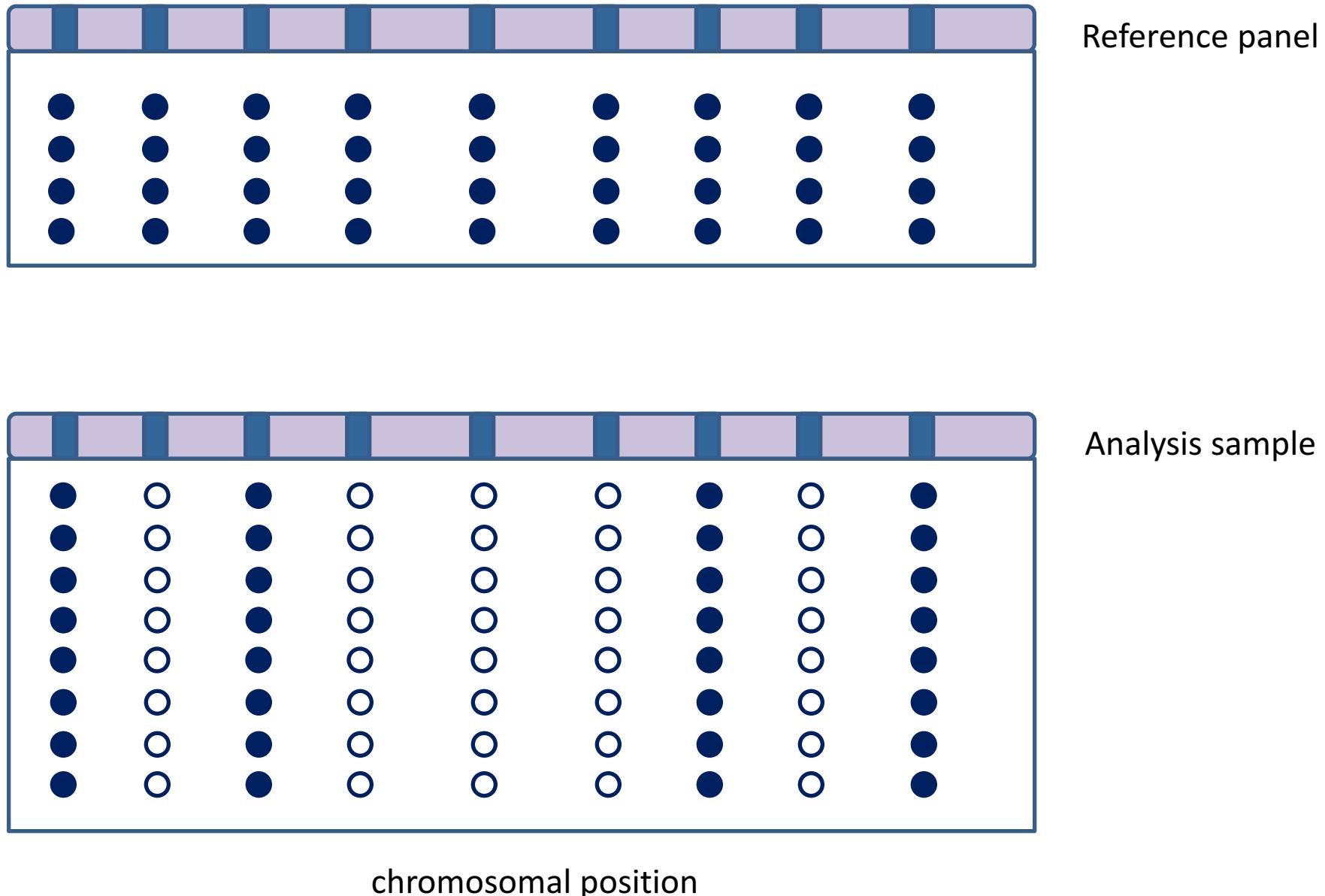
- Compartmental involvement
- Pre-operative scores
- Post-operative scores
- Complications



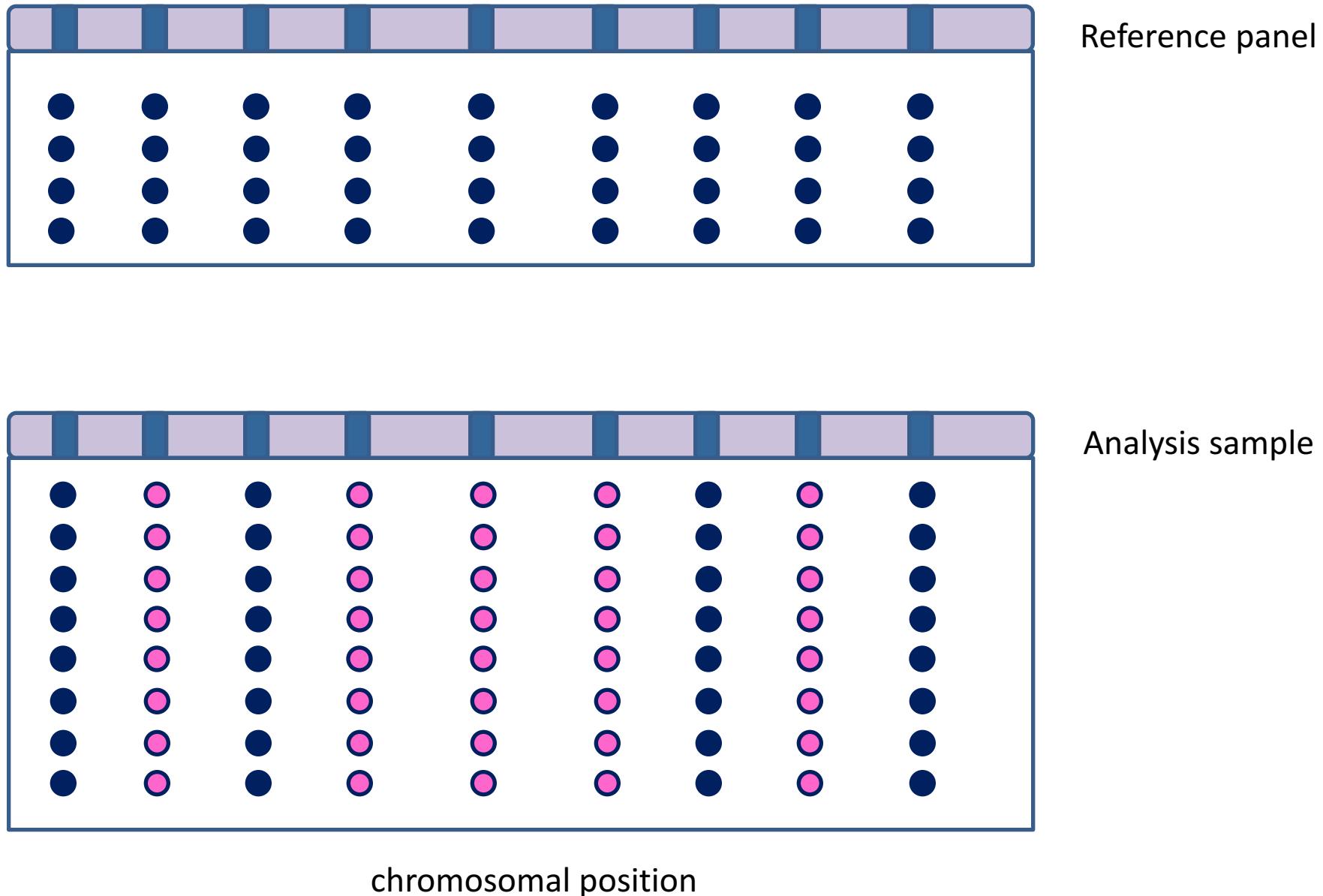


Imputation

Imputation -principles



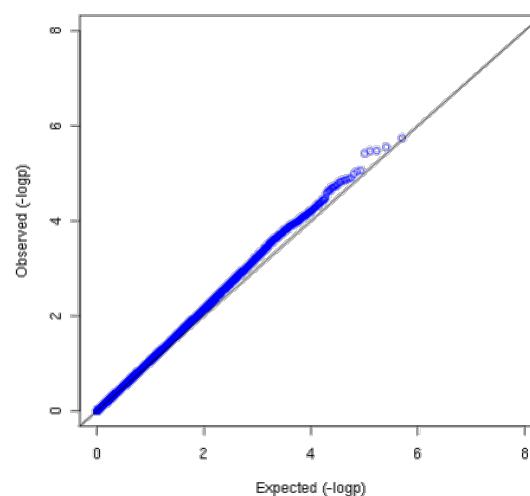
Imputation -principles



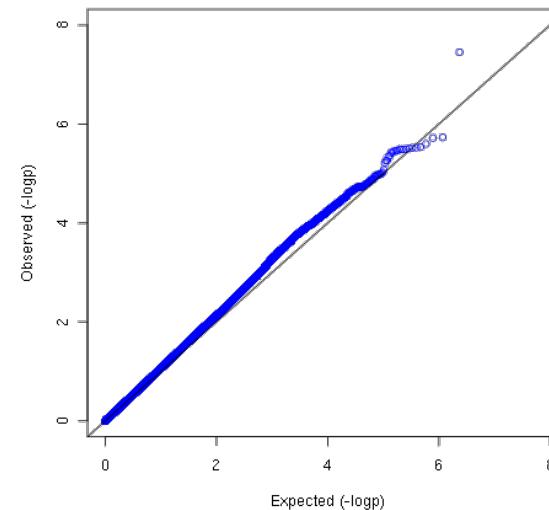
3,177 OA cases

4,854 controls

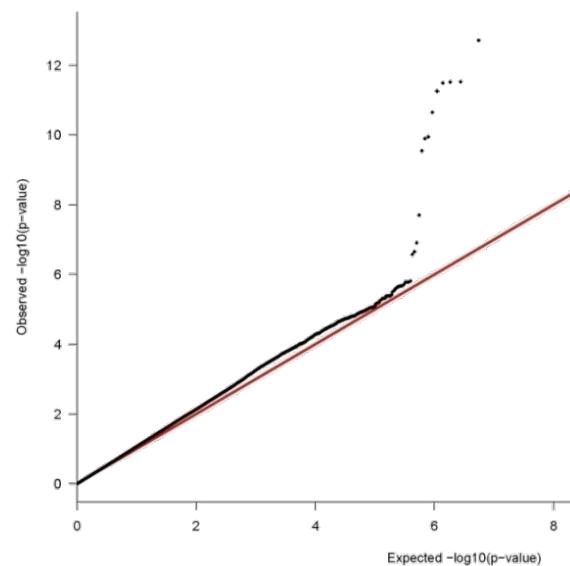
Directly typed SNPs (Illumina 610k)



Imputed SNPs: HapMap



Imputed SNPs: 1000 genomes

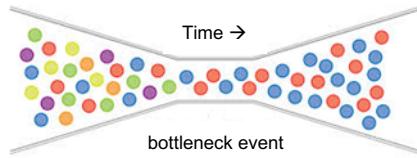


Special populations

Population isolates

The study of rare variants can be empowered by focusing on isolated populations

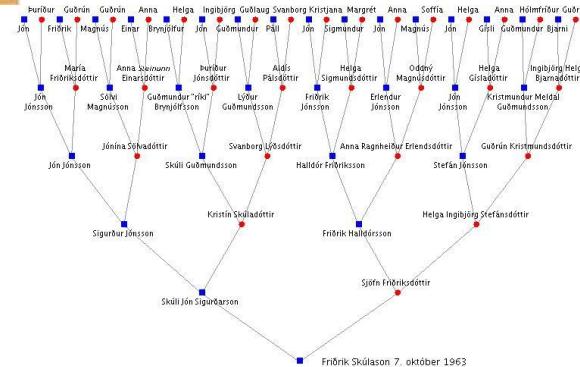
- Some rare variation is lost, and rare variants may have increased in frequency



- linkage disequilibrium tends to be extended



- homogeneous environment



- better knowledge of population history

Findings in isolated populations and their wider relevance

LETTERS

LETTERS

FOCUS ON GENOMES OF ICELANDERS

BRIEF COMMUNICATIONS

nature
genetics

Exome array analysis identifies new loci and low-frequency variants influencing insulin processing and secretion

Jeroen R Huyghe¹, Anne U Jackson¹, Marie P Fogarty², Martin L Buchkovich², Alena Stančáková³, Heimir M Stringham⁴, Xueling Sim¹, Lingyao Yang¹, Christian Fuchsberger¹, Hanna Cederberg⁵, Peter S Chines⁶, Tanya M Teslovich¹, Jane M Romm³, Hua Ling⁵, Ivy McMullen⁷, Roxann Ingersoll⁸, Elizabeth W Pugh⁵, Kimberly F Doheny⁵, Benjamin M Neal^{6–8}, Mark J Daly^{6–8}, Johanna Kuusisto⁹, Laura J Scott¹, Hyun Min Kang¹, Francis S Collins⁴, Gonçalo R Abecasis¹, Richard M Watanabe^{9,10}, Michael Boehnke^{1,11}, Markku Laakso^{3,11} & Karen L Mihlike^{3,11}

Cell

Resource

Genetic Variants Regulating Immune Cell Levels in Health and Disease

Valeria Orrù^{1,12}, Maristella Steri^{1,12}, Gabriella Sole¹, Carlo Sidore¹, Francesca Virdis¹, Mariano Dei¹, Sandra Lai¹, Magdalena Zoledziewska¹, Fabio Busonero¹, Antonella Mulas^{1,2}, Matteo Floris⁴, Wieslawa I. Mertzen¹, Silvana A.M. Urru⁴, Stefania Olla¹, Michele Marongiu¹, Maria G. Piras¹, Monia Lobina^{1,3}, Andrea Maschio^{1,2}, Maristella Pitzalis¹, Maria F. Urru¹, Marco Marcelli¹, Roberto Cusano^{1,4}, Francesca Deidda^{1,4}, Valentina Serra^{1,3}, Manuela Oppo¹, Rosella Pltu^{1,4}, Frederic Reiner⁴, Riccardo Berutti^{3,4}, Luca Pireddu^{4,5}, Ilenia Zara⁴, Eleonora Porcu^{1,3}, Alan Kong^{1,6}, Gianluca Rotta¹, Brendan Turner¹, Robert Lyons^{1,11}, Hyun M. Kang¹, Sergio Uzzau^{1,6}, Rossano Atzeni⁴, Marco Vallolini¹, Davide Firini¹, Lydia Leon¹, Gianluca Rotta¹, Silvia Naltsa¹, Andrea Angius^{1,4}, Mauro Congia⁹, Michael B. Whalen¹, Chris M. Jones¹, David Schlessinger¹⁰, Gonçalo R. Abecasis¹, Edoardo Fiorillo^{1,12}, Serena Sanna^{1,12} and Francesco Cucca^{1,3,12}

OPEN ACCESS Freely available online

PLOS GENETICS

Distribution and Medical Impact of Loss-of-Function Variants in the Finnish Founder Population

Elaine T. Lim^{1,2,3,4}, Peter Würz^{2,6,7}, Aki S. Havulinna⁸, Päivi Palta^{3,5}, Taru Tuukainen^{1,2,3}, Karola Rehnström⁵, Tönu Esko^{2,3,9,10}, Reedik Mägi⁹, Michael Inouye¹¹, Tuuli Lappalainen^{12,13}, Yingling Chan^{2,10}, Rany M. Salem^{2,10}, Monkol Lek^{1,2,3}, Jason Flannick^{2,3}, Xueling Sim¹⁴, Alisa Manning², Claes Ladenbäck^{15,16}, Suzannah Bumpstead⁸, Elja Hämäläinen^{5,6}, Kristina Aalto¹⁶, Mikael Maksimow⁹, Marko Salmi¹⁷, Steven Blankenberg^{18,19}, Diego Arildsson²⁰, Svatí Shah²¹, Benjamin Horne²², Ruth McPherson²³, Gerald K. Hovingh²⁴, Muredach P. Reilly²⁵, Hugh Watkins²⁶, Anuj Goel²⁶, Martin Faralló²⁶, Domenico Giardina²⁷, Alex P. Reiner²⁸, Nathan O. Stitzel²⁹, Sekar Kathiresan³⁰, Stacey Gabriel², Jeffrey C. Barrett³¹, Terho Lehtimäki³¹, Markku Laakso³², Leif Groop^{31,32}, Jaakko Kaprio^{33,34}, Markus Perola³, Mark I. McCarthy^{35,36,37}, Michael Boehnke¹⁴, David M. Altshuler^{2,3}, Cecilia M. Lindgren^{1,2,38}, Joel N. Hirschhorn^{3,10}, Olaf Raitakari^{41,42}, Richard Durbin³⁹, Daniel G. MacArthur^{1,2,3}, Kaitiina Salomaa⁶, Daniela Ripatti^{5,6,8,33,43}, Mark J. Daly^{1,2,3,9}, Aarno Palotie^{1,2,5,44*} for the Sequencing Initiative Suomi (SiSu) Project

ARTICLES

ARTICLES

A rare variant in *MYH6* is associated with high risk of sick sinus syndrome

Hilma Holm^{1,9}, Daniel F Gudbjartsson^{1,9}, Patrick Sulem¹, Gisli Masson¹, Hafdis Th Helgadottir¹, Carlo Zanon¹, Olafur Th Magnusson¹, Agnar Helgason¹, Jóna Saemundsdóttir¹, Arnaldur Glyfason¹, Hrafnhildur Stefansdóttir², Solveig Grettarsdóttir¹, Stefan E Matthiasson³, Guðmundur Thorgerðsson^{2,4}, Áslaug Jónasdóttir¹, Asgeir Sigurdsson¹, Hreinn Stefansson¹, Thomas Werge⁵, Thorunn Rafnar¹, Lambertus A Kiemeney^{6,7}, Babar Parvez⁸, Raafia Muhammad⁸, Dan M Roden⁸, Dawood Darbar⁹, Guðmar Thorleifsson¹, G Bragi Wálters¹, Augustine Kong¹, Unnur Thorsteinsdóttir^{1,4}, David O Arnar^{2,4} & Kari Stefansson^{1,4}

nature
genetics

ARTICLES

Genome sequencing elucidates Sardinian genetic architecture and augments association analyses for lipid and blood inflammatory markers

Carlo Sidore^{1–3,19}, Fabio Busonero^{1,2,4,19}, Andreia Masicpol^{1,2,4,19}, Eleonora Porcu^{1–3,19}, Silvia Naltsa^{1,19}, Magdalena Zoledziewska¹, Antonella Mulas^{1,2}, Giorgia Saccoccia¹, Maristella Steri¹, Fabrice Damjou¹, Alena Stančáková³, Yves-Alain D'Ortega y Vaca¹, Christopher W. Chitwood¹, Barbara Bore-Gresham², Maristella Pitzalis¹, Ramiah Nagaraja³, Brendon Turner⁴, Christine Brennan⁵, Sergio Uzzau¹, Christian Fuchsberger¹, Rossano Atzeni⁶, Frederic Reiner⁴, Riccardo Berutti^{3,9}, Jie Huang¹⁰, Nicholas J Timpton¹¹, Daniela Tonello¹², Paolo Gasparini^{13,14}, Giovanni Matherba¹⁵, George Dedousis¹⁶, Eleftheria Zeggini¹⁰, Nicole Soranzo^{16,17}, Chris Jones¹⁸, Robert Lyons¹⁴, Andrea Angius^{1,2}, Hyun M. Kang¹, John November¹⁸, Serena Sanna^{1,20}, David Schlessinger²⁰, Francesco Cucca^{1,3,20} & Gonçalo R Abecasis^{1,20}

nature
genetics

nature
genetics

FOCUS ON GENOMES OF ICELANDERS

nature
genetics

Loss-of-function variants in *ABCA7* confer risk of Alzheimer's disease

We used our imputation of the whole-genome sequences of 2,636 Icelanders into 104,220 long-range phased individuals and their close relatives⁸ to investigate whether any of the genes located in the regions showing common variant association at Alzheimer's disease (excluding the *MHC*) also harbored rare variants conferring

A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin¹, Coleen M. Damcott¹, Haiqing Shen¹, Sandra H. Ott¹, John Shelton¹, Richard B. Horenstein¹, Wendy Post², John C. McLennihan^{1,3}, Lawrence F. Bielak⁴, Patricia A. Peyer⁴, Braxton D. Mitchell¹, Michael Miller¹, Jeffrey R. O'Connell³, Alan R. Shuldiner^{1,3}

LETTERS

nature
genetics

A study based on whole-genome sequencing yields a rare variant at 8q24 associated with prostate cancer

Julius Godmundsson^{1,22}, Patrick Sulem^{1,22}, Daniel F Gudbjartsson¹, Gisli Masson¹, Birnir Aagnarsson^{2,3}, Kristrún R Benediktsson^{1,23}, Asgeir Sigurdsson¹, Olafur Th Magnusson¹, Steingrímur A Gudjonsson¹, Stefán B Óskarsson¹, Guðmundur Thorgerðsson¹, Hafdis Th Helgadottir¹, Sigrúnur S. Sverrisdóttir¹, Adalbjörn Þorsteinsson¹, Stefán Óskarsson¹, Guðrún Þorleifsson¹, Þorunn Rafnar¹, Lamberta A Kiemeney^{6,7}, Laurydur Þorláksson¹, Chi-Fai Ng¹⁰, Peter K F Chui¹¹, Inge M van Oort¹², Sita H Vermeulen^{13,12}, Jenny L Donovan¹⁴, Freddy C Hamdy¹⁵, Chi-Fai Ng¹⁰, Peter K F Chui¹⁴, Kin-Mang Lau¹², Maggie C Y Ng¹², Jeffrey R Gulech¹⁶, Augustine Kong¹, William J Catalano¹⁷, Jose I Mayordomo¹⁸, Guðmundur V Einarsdóttir¹⁹, Rosa B Barkardottir^{2,20}, Eirikur Jonsson²⁰, David Mates¹, David F Neufeld¹, Lamberti A Kiemeney¹², Úlfur Þorsteinsdóttir^{1,21}, Thorunn Rafnar¹ & Kari Stefansson¹

LETTER

doi:10.1371/journal.pgen.13425

A common Greenlandic *TBC1D4* variant confers muscle insulin resistance and type 2 diabetes

Ida Moltke^{1,2,8}, Niels Grarup^{7,8}, Marit E. Jorgensen⁹, Peter Bjergregaard⁵, Jonas T. Treebak⁶, Matteo Fumagalli⁷, Thorfinn S. Korneliusson⁸, Marianne A. Andersen⁸, Thomas S. Nielsen⁸, Nikolaj T. Krarup¹, Anette P. Gjesing¹, Juleen R. Zierath^{6,9}, Allan Linneberg¹⁰, Xueli Wu¹¹, Guangqiang Sun¹¹, Xin Jin¹¹, Junuma Al-Aama^{11,12}, Jun Wang^{11,12,13,14}, Knut Borch-Johnsen¹⁵, Oluf Pedersen³, Rasmus Nielsen^{7,16}, Anders Albrechtsen³ & Torben Hansen^{3,17}

HELIC: Hellenic isolated cohorts



- HELIC-MANOLIS (Minoan Isolates)
- Mylopotamos villages, Crete, Greece
- Geographically isolated
- Ancient Dorian dialect
- N~4,500 of which 1,800 collected



- Deeply phenotyped
- High fat content diet
- High rates of longevity
- Low rates of metabolic disease complications
- Ability to recontact individuals





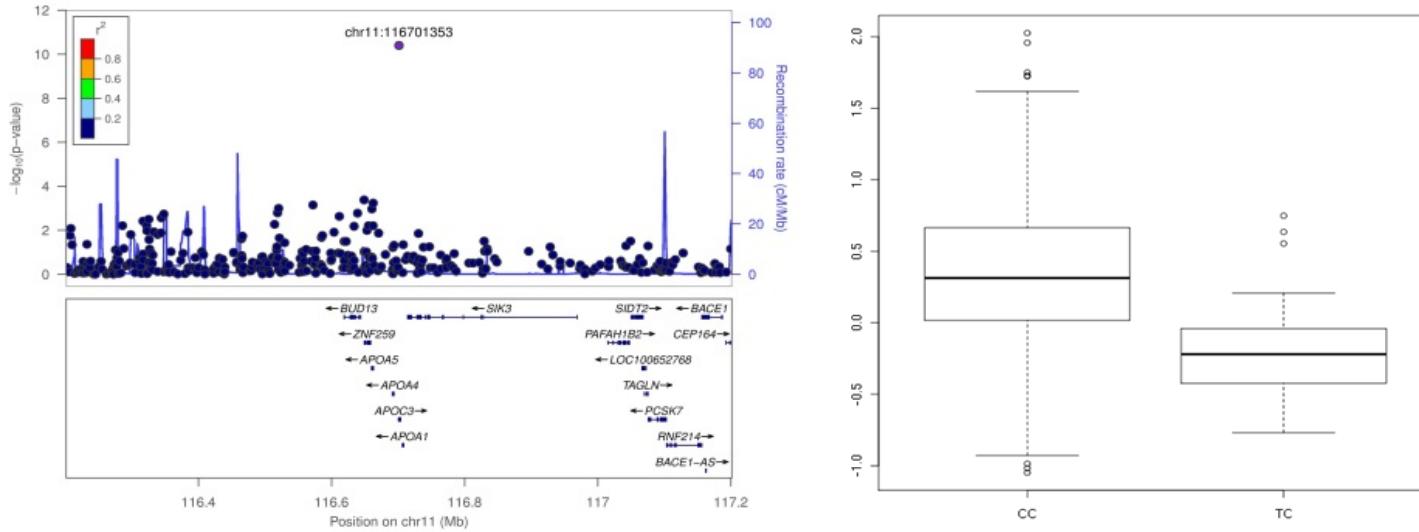
R19X APOC3 cardioprotective variant

THE TIMES

Mountain village may hold secret to immunity from heart disease

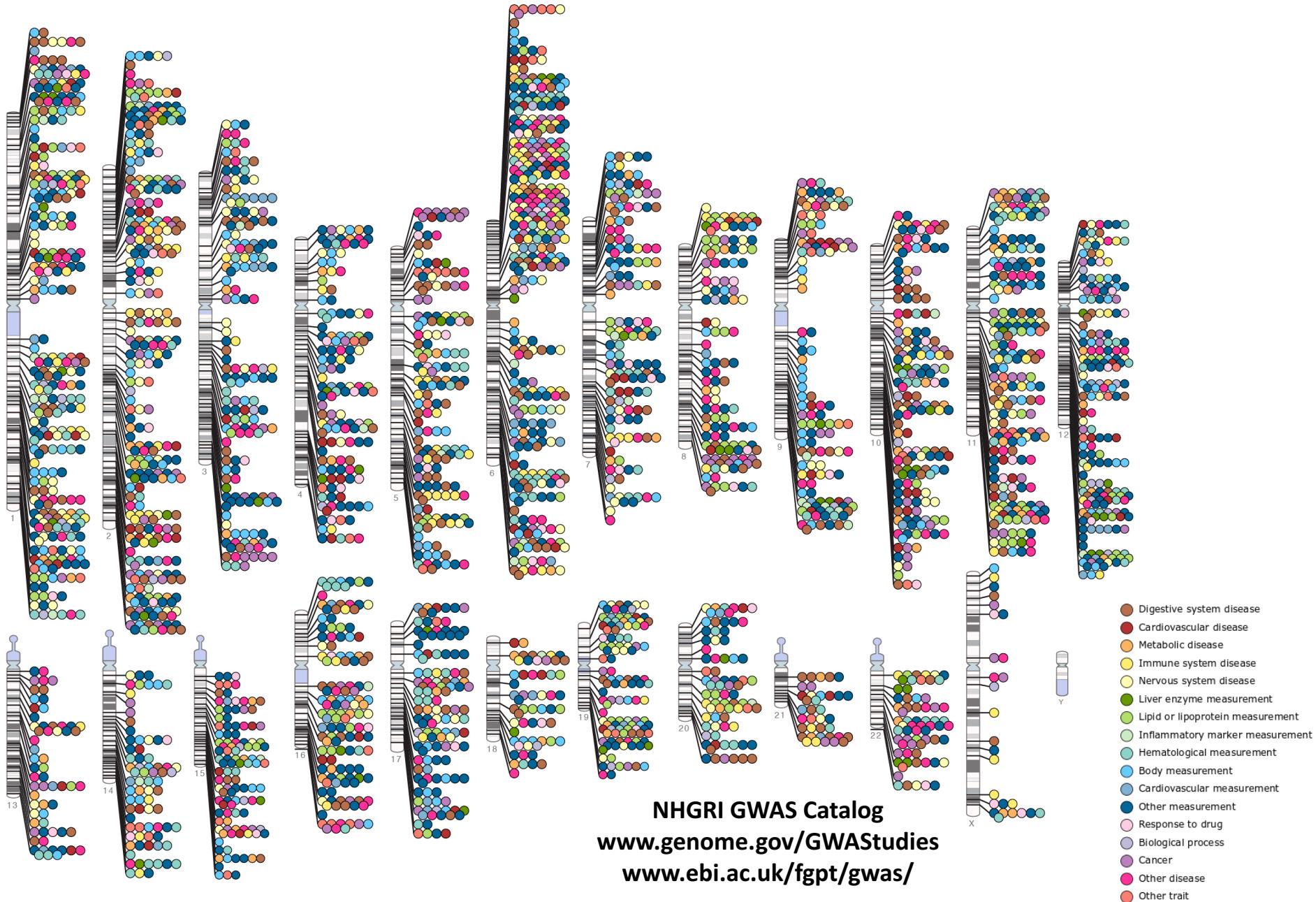


Anogians have remained unusually isolated for several hundred years Panoramic Images/Getty Images

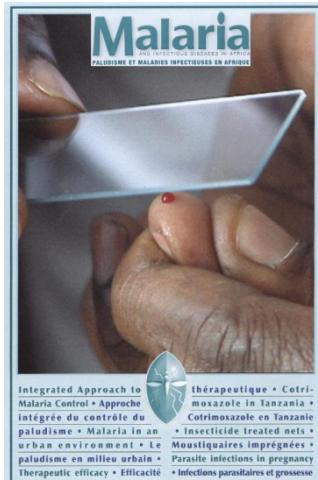


- Mylopotamos villages (n=1256, MAF 2%, p=10⁻¹¹)
- Detection of this effect would have required 67,000 Europeans (MAF 0.05%)

Published GWAS at $p \leq 5 \times 10^{-8}$ for 17 trait categories

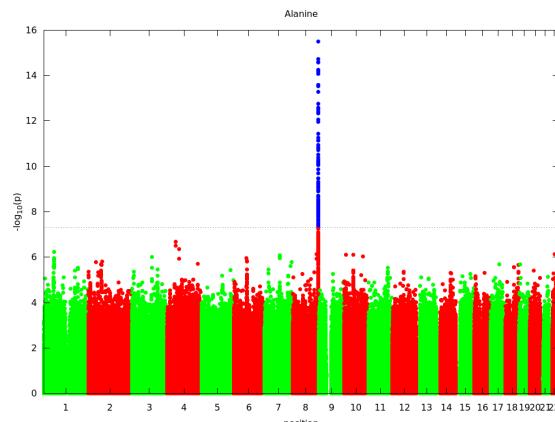


Burden of disease in Africa



Large-scale GWAS in a Ugandan cohort

- ~7000 individuals from the General Population Cohort
 - 2000 with whole genome sequence 4x
 - 5000 with Omni 2.5M genotypes
 - 50 phenotypic traits: hematological, anthropometric, blood pressure, metabolic, liver function and infectious disease traits



Liver enzymes- ALT

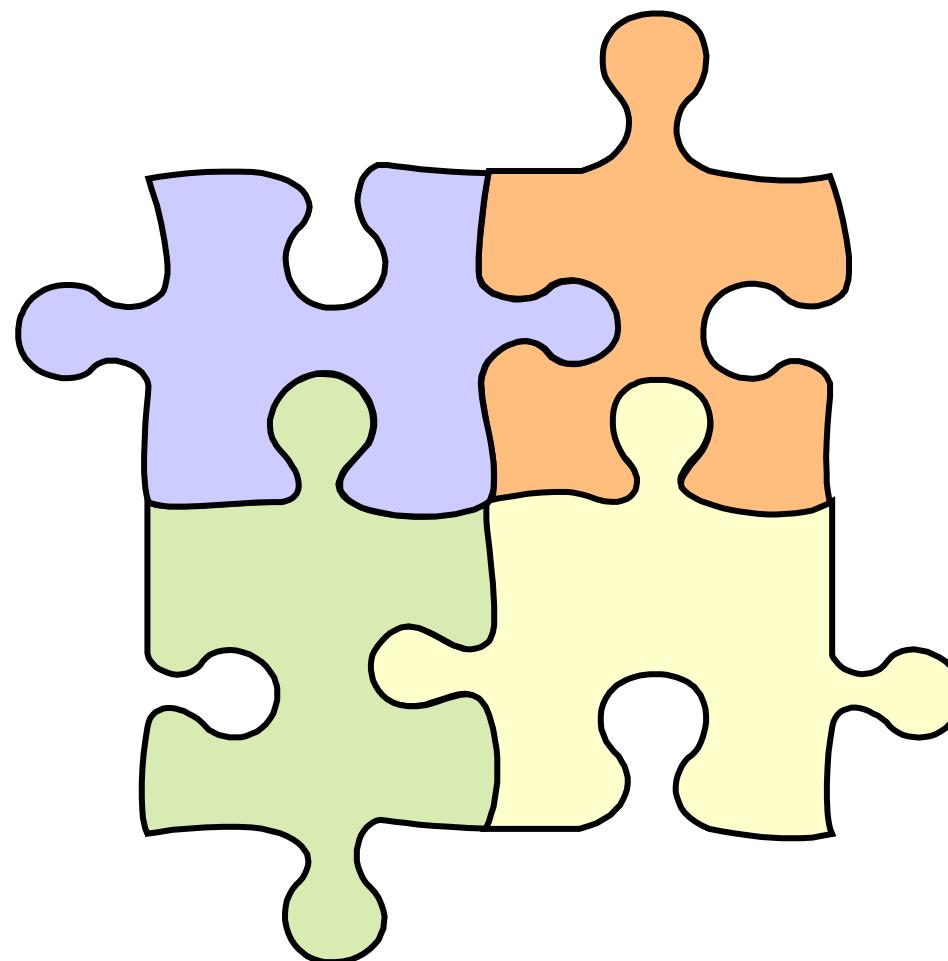
GPT gene- produces enzyme
Monomorphic in Europeans
Ugandan frequency: 26%

Genetic architecture of complex traits

Common variants



Rare variants



Small effect size



Large effect size

