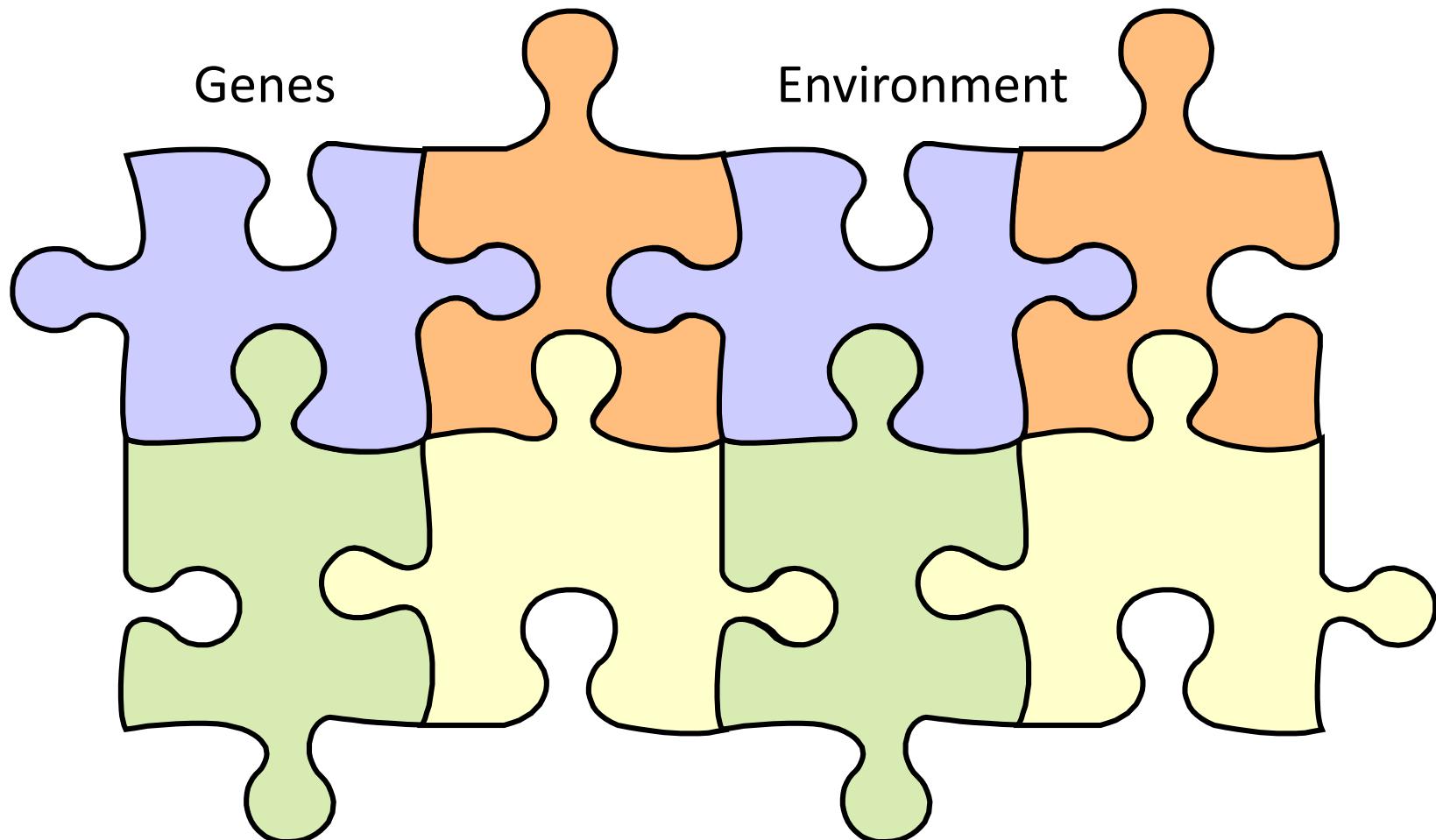


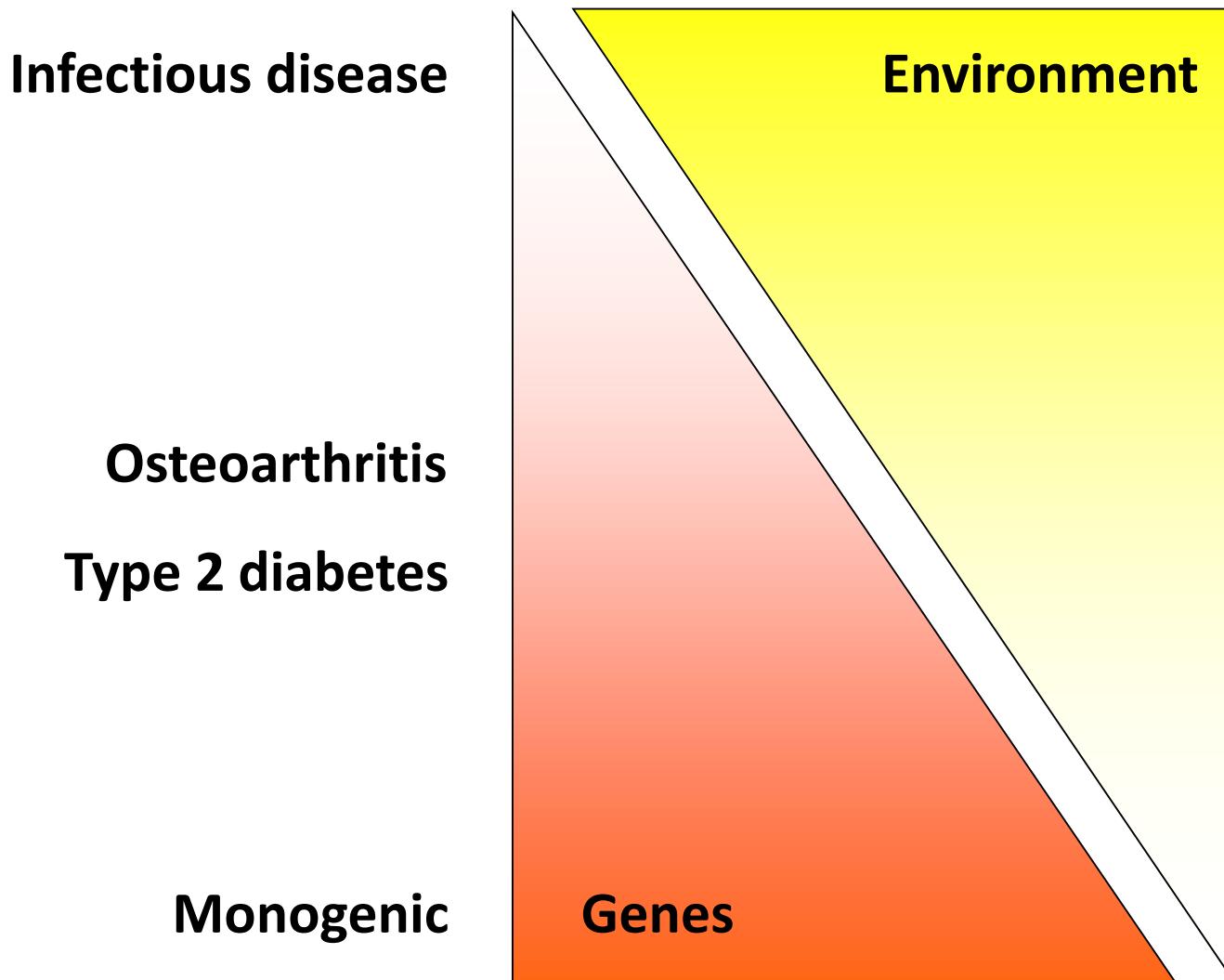
# Introduction to complex trait genetics

Eleftheria Zeggini  
Institute of Translational Genomics  
[eleftheria.zeggini@helmholtz-munich.de](mailto:eleftheria.zeggini@helmholtz-munich.de)

# Complex diseases



# Genes vs environment

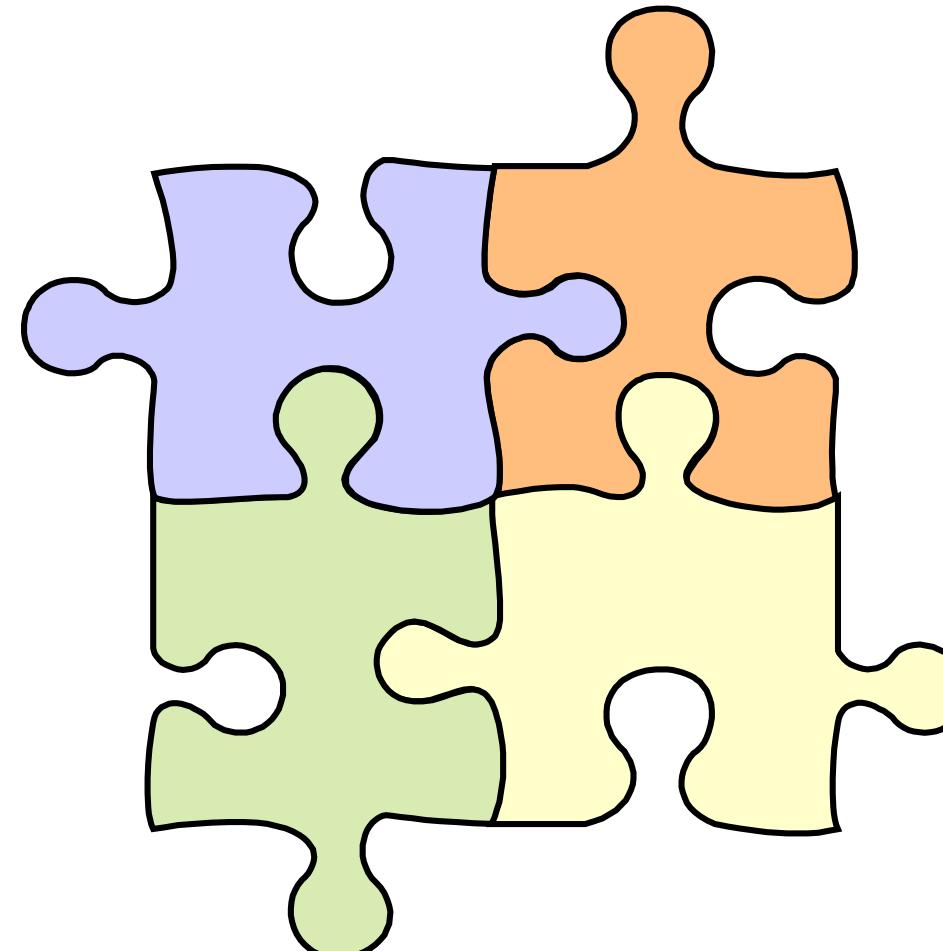


# Genetic architecture of complex traits

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

Large sample collections



Understanding of patterns of human genome sequence variation



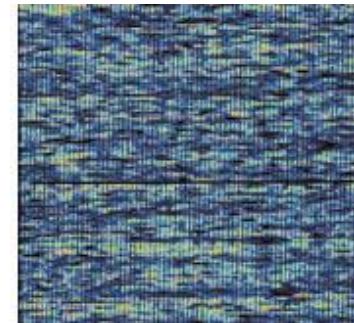
**1000 Genomes**  
A Deep Catalog of Human Genetic Variation

## Large sample collections



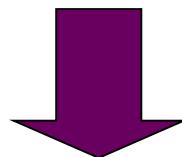
Understanding of patterns of human genome sequence variation

High-throughput technologies for genotyping

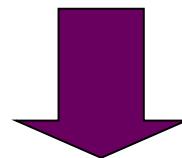


# Principles

Case-control pairs (or population cohorts)

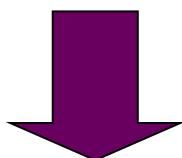


Type for 500k-2.5M SNPs



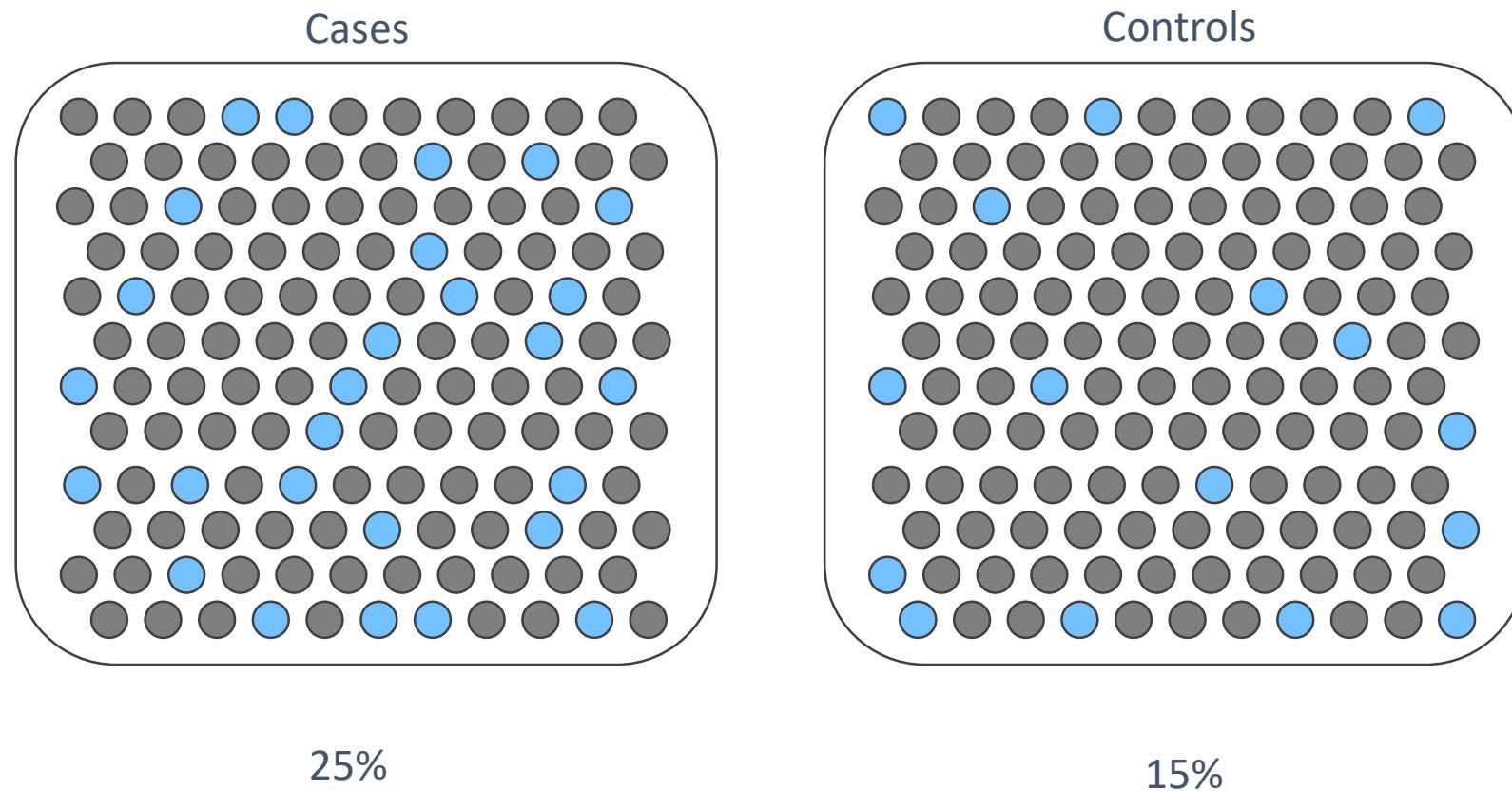
Obtain information about strength of association  
genome wide

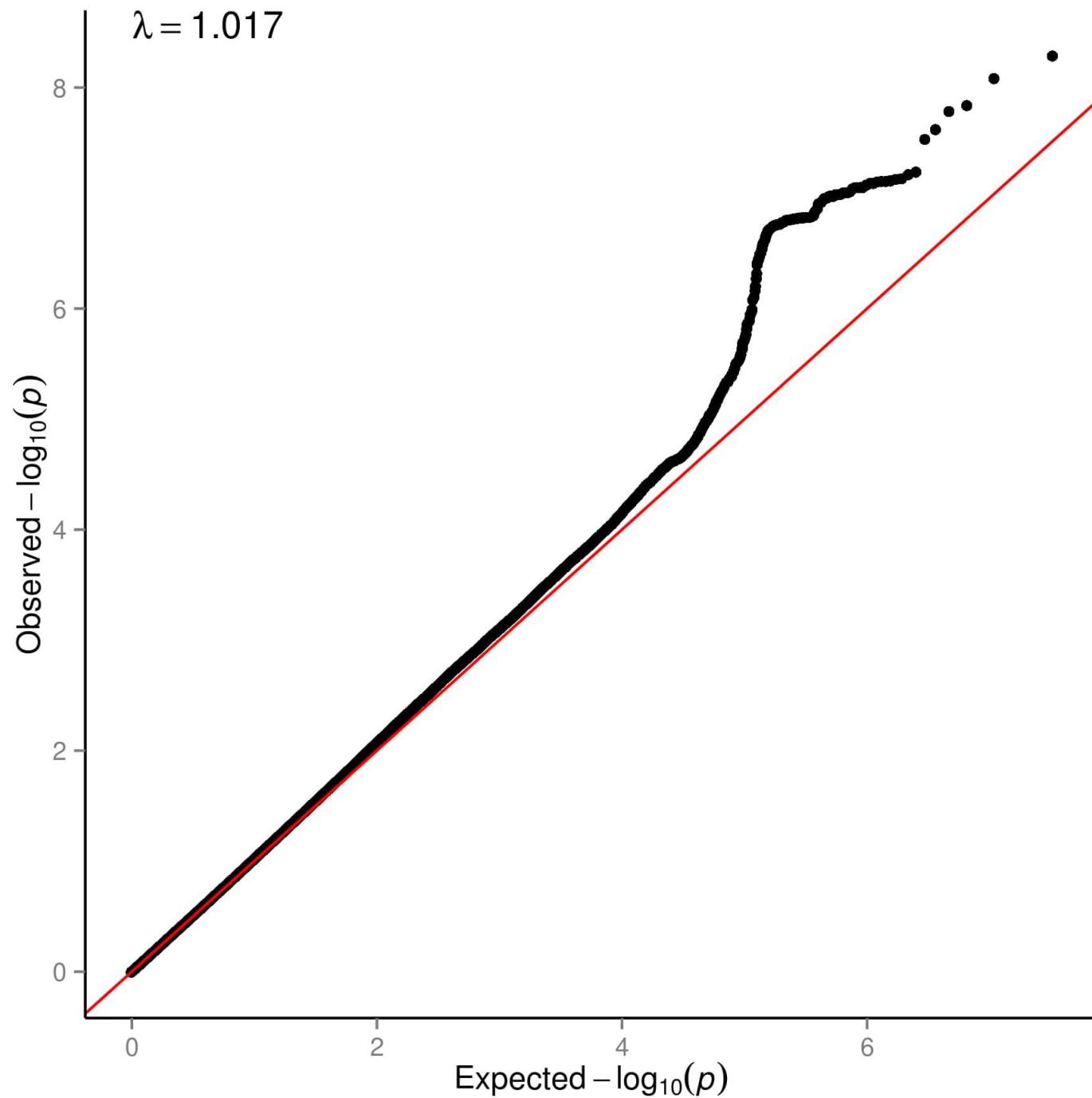
(within limits of sample size, allele frequency, LD etc)

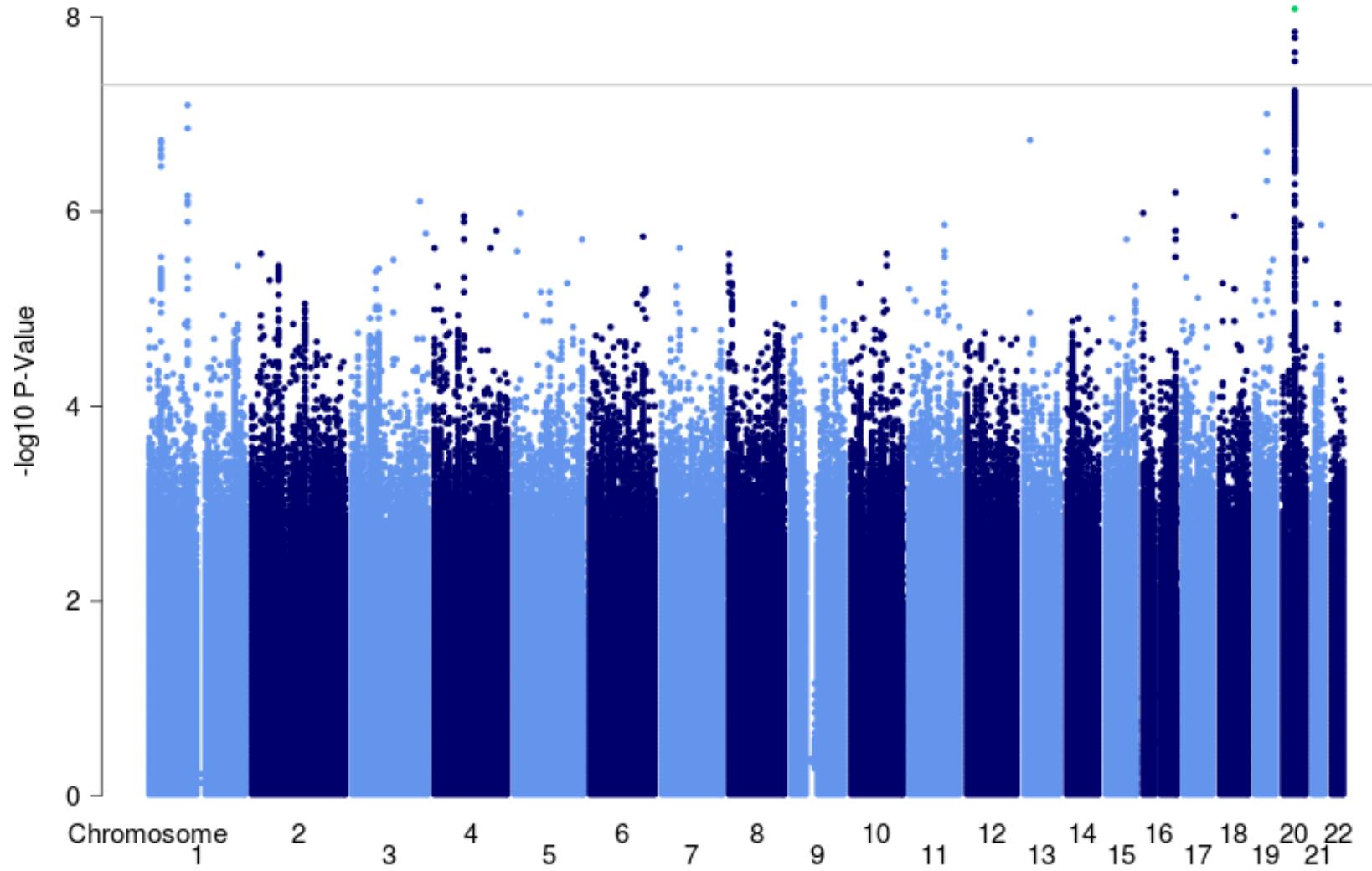


Follow-up what looks interesting

# Association between genetic variants and disease

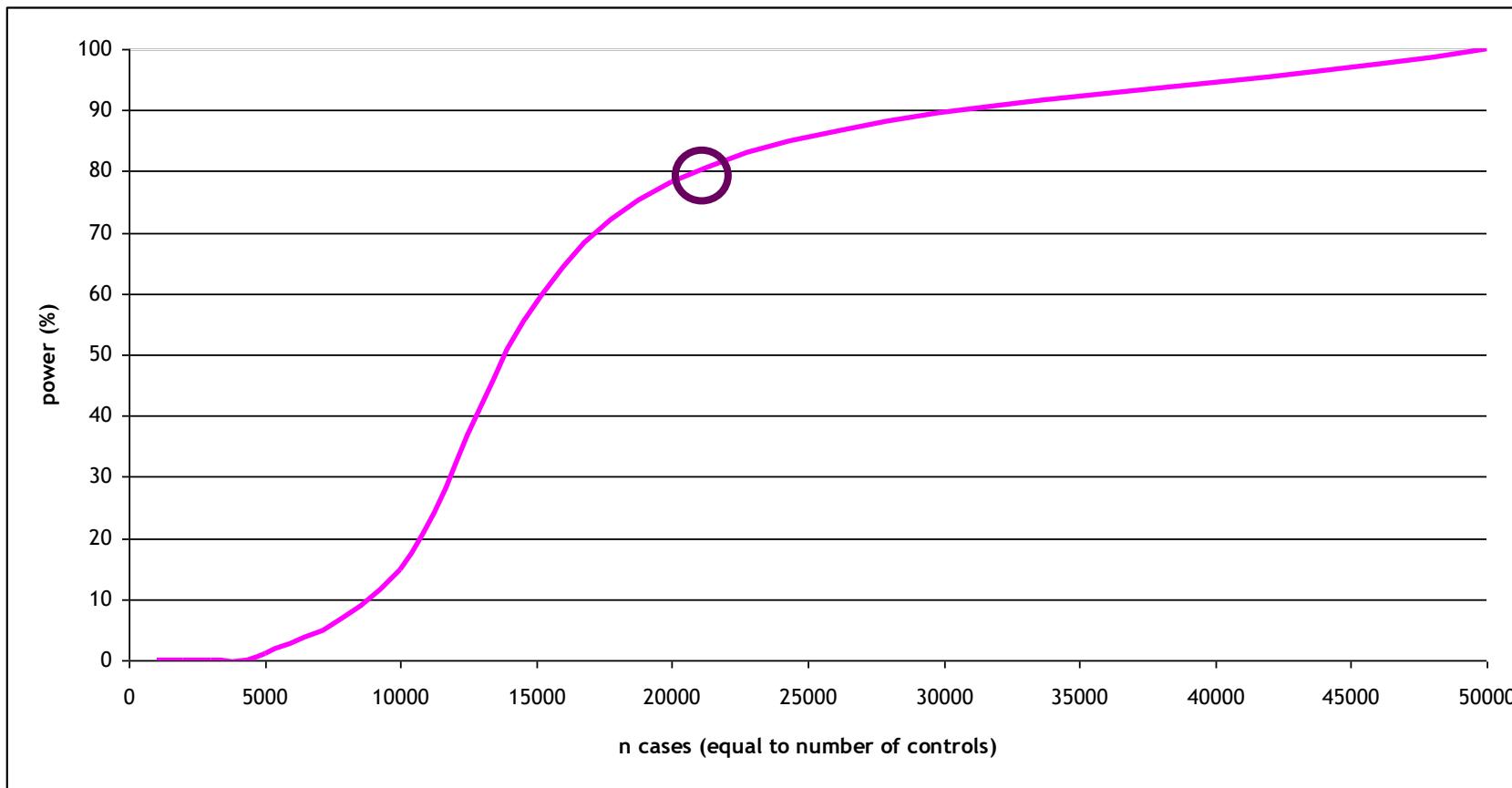




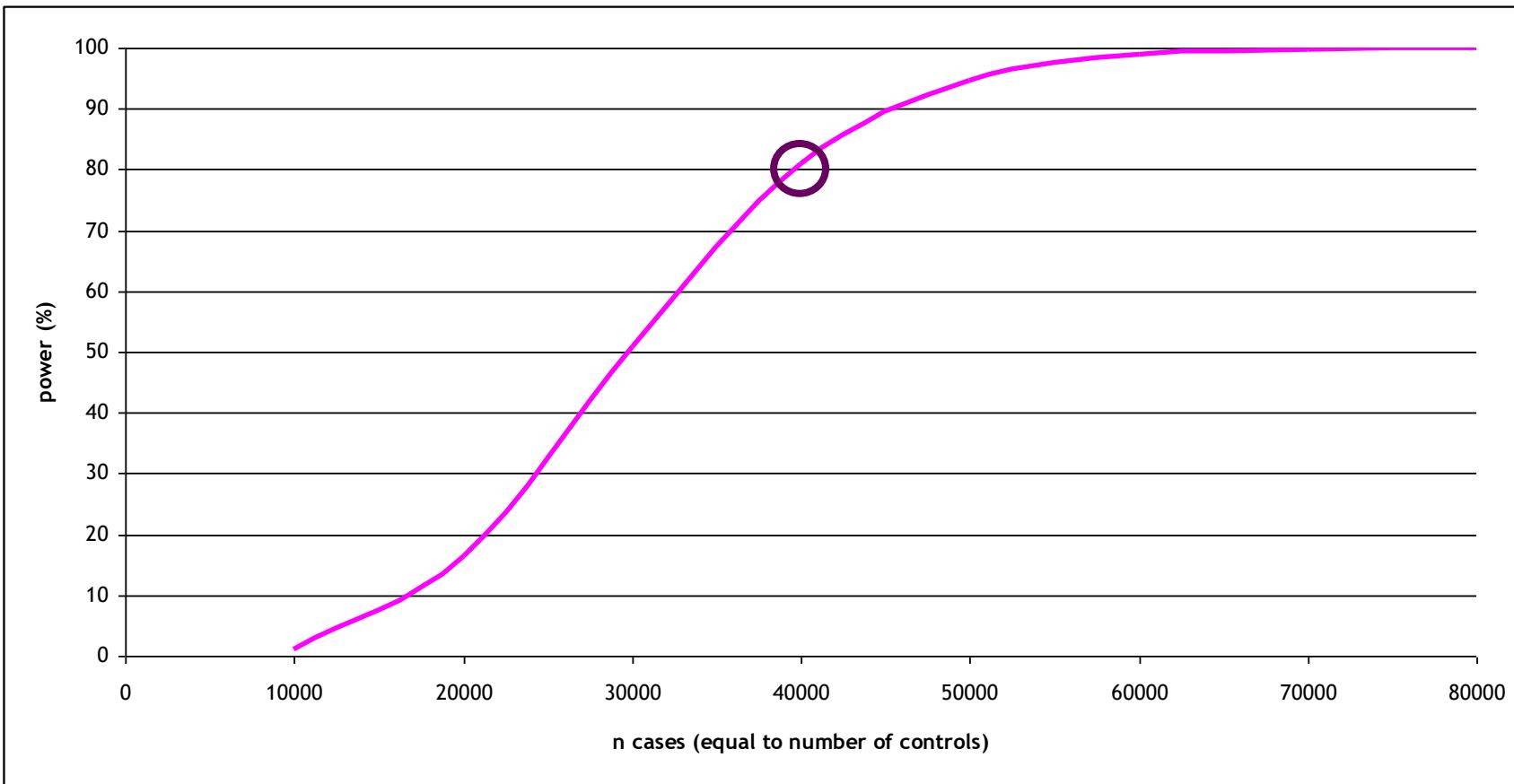


# Sample size matters

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



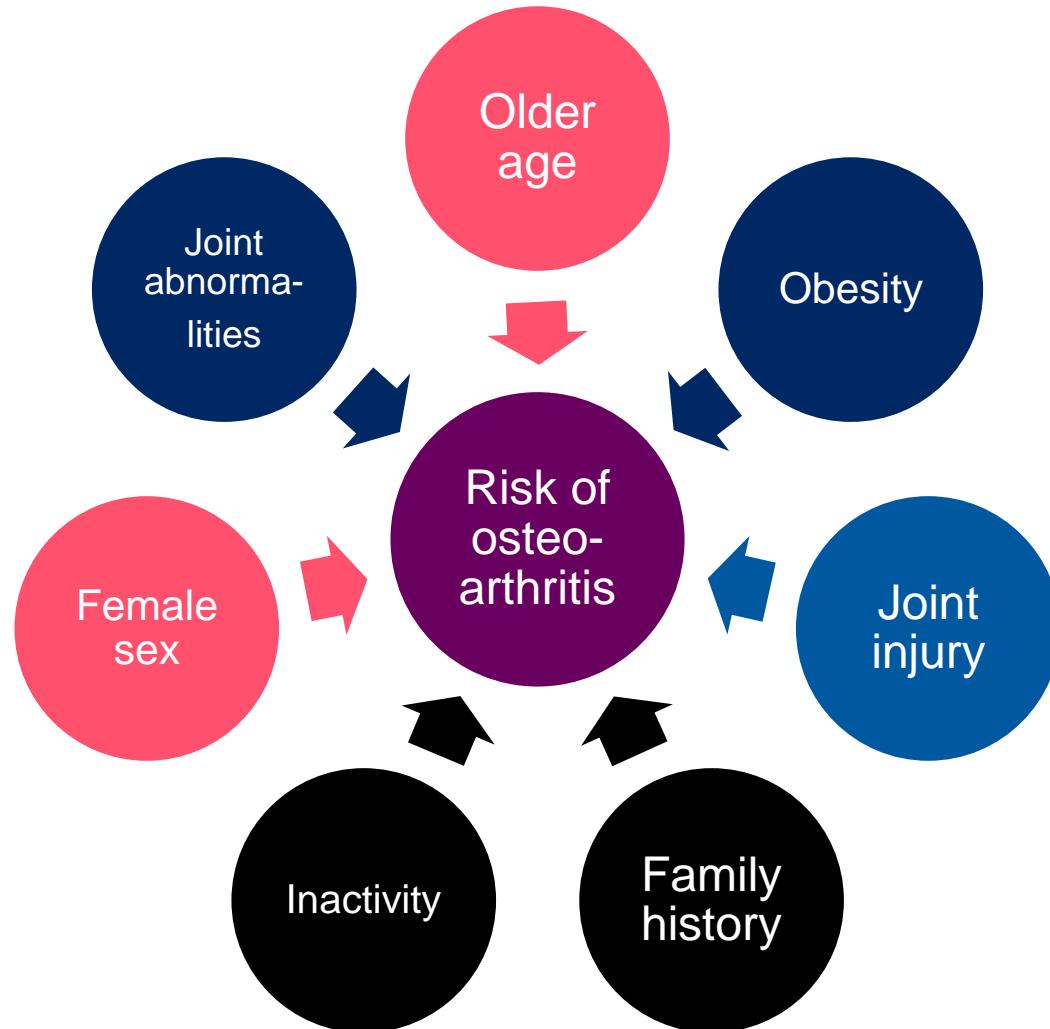
# Osteoarthritis

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

# Osteoarthritis risk

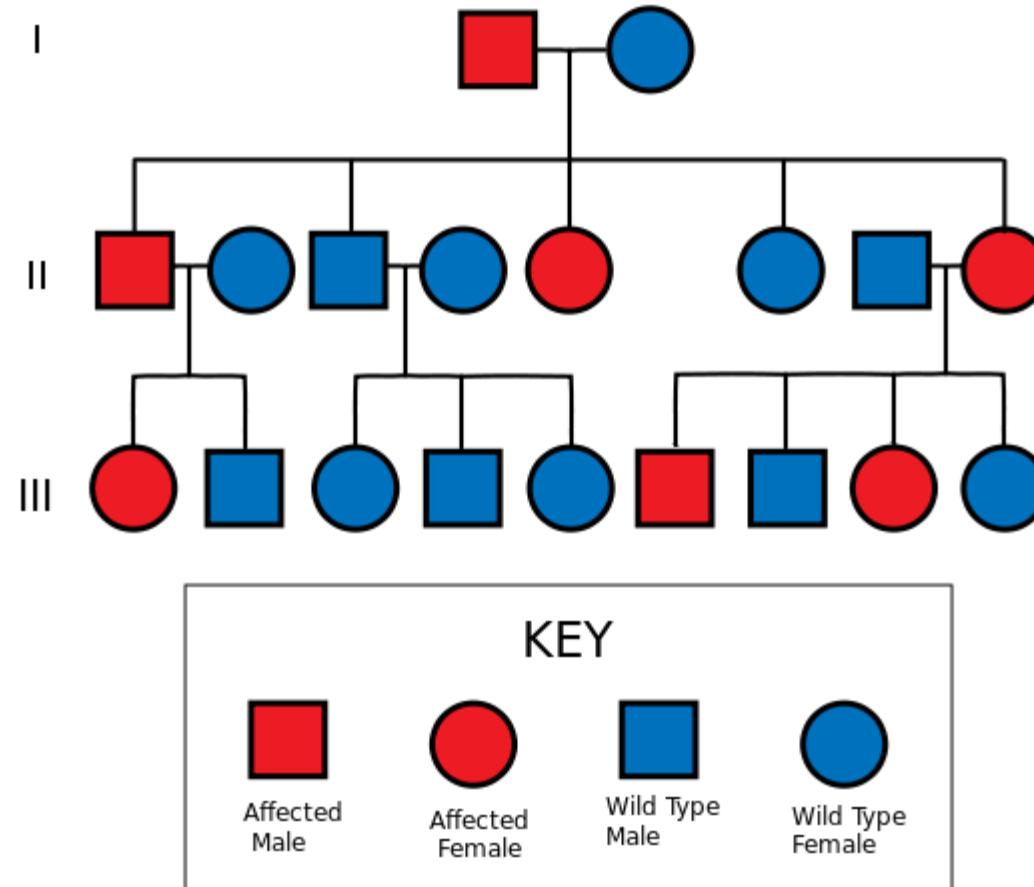


# Heritability of OA

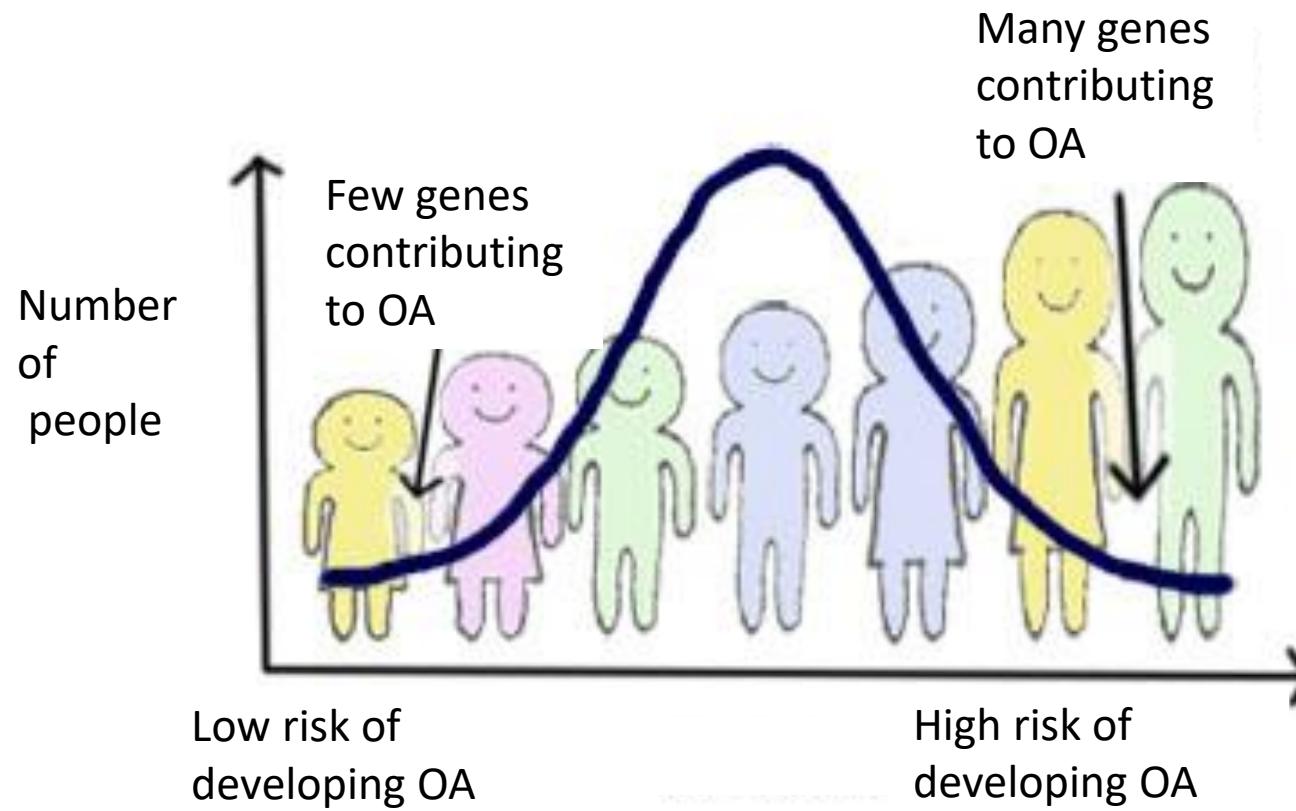


~50%: half of the variation in susceptibility to OA in the population is due to genetic factors

# OA is not a single gene disorder



# OA is a complex or polygenic disease



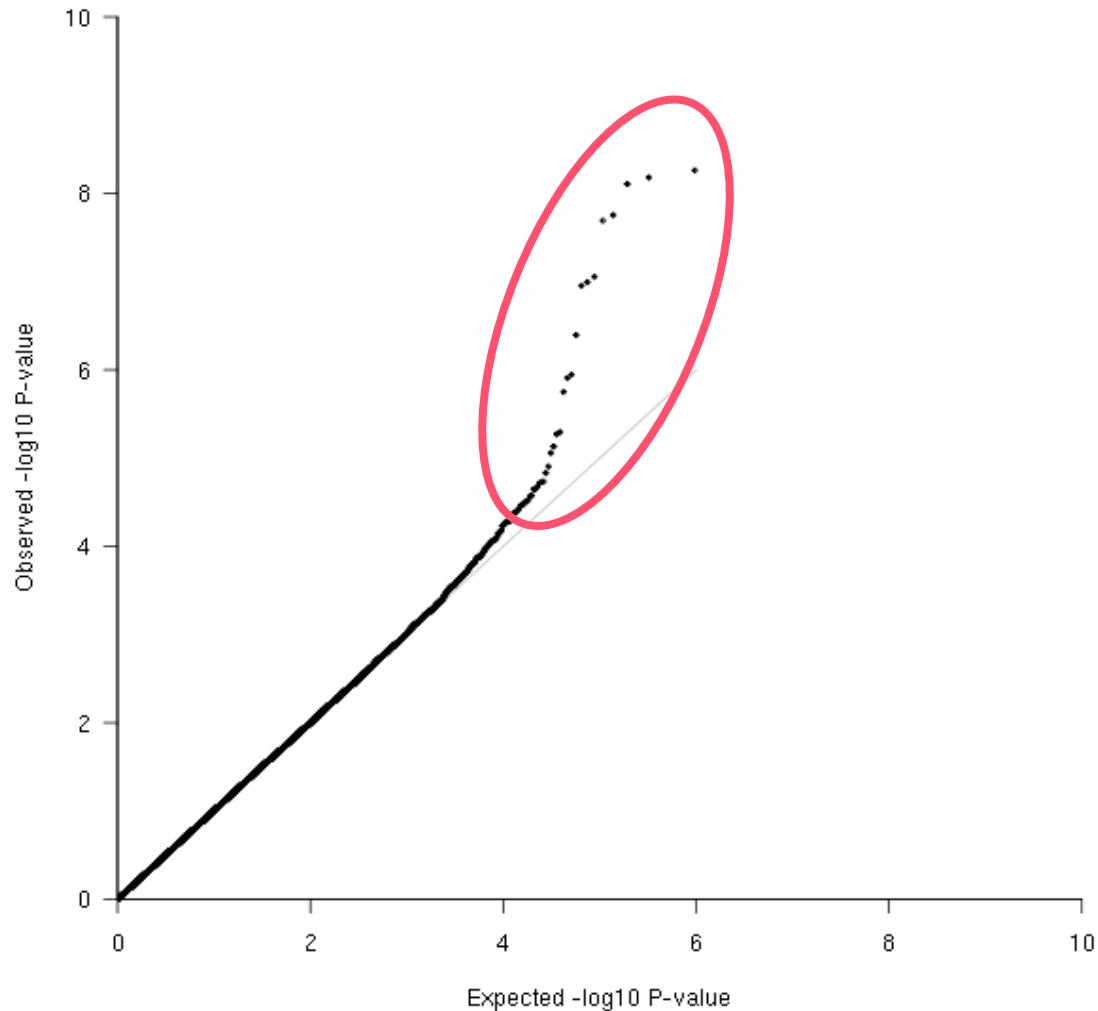
# arcOGEN Consortium

## arc Osteoarthritis Genetics

11 participating sites:



# 7,410 OA cases v. 11,009 controls



# Replication Replication Replication

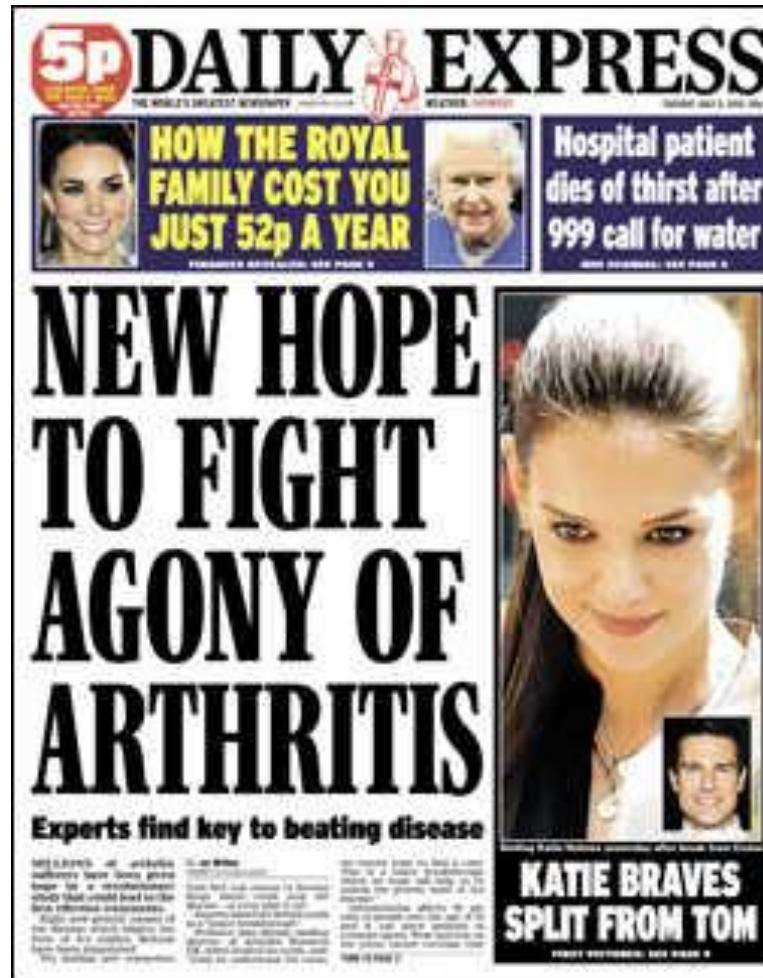


**Combined analysis**

14,883 cases and 55,775 controls

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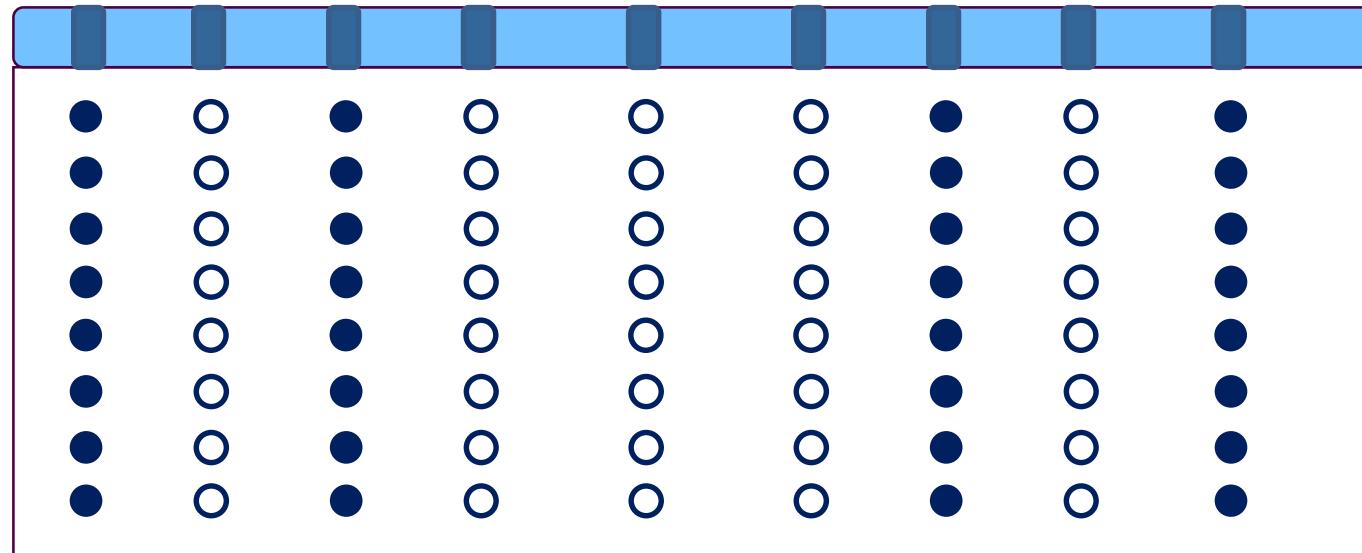
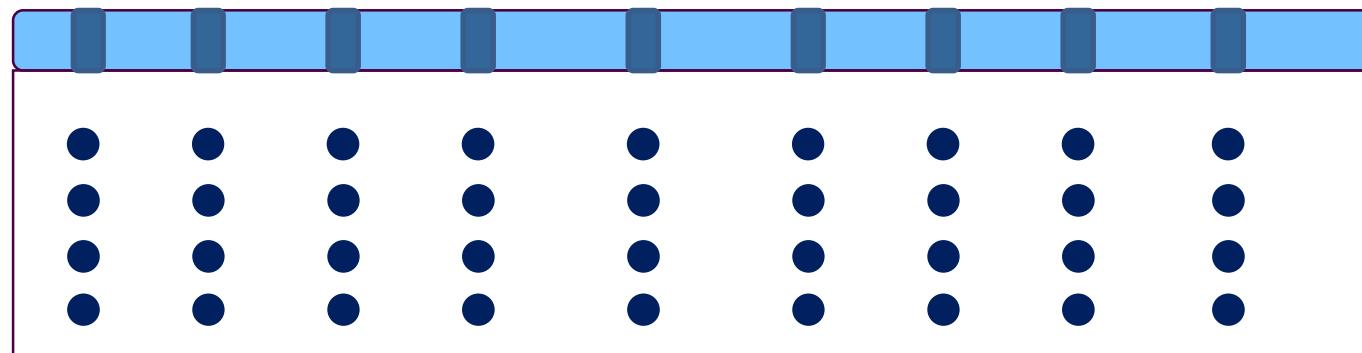
# arcOGEN finds 9 new OA risk variants



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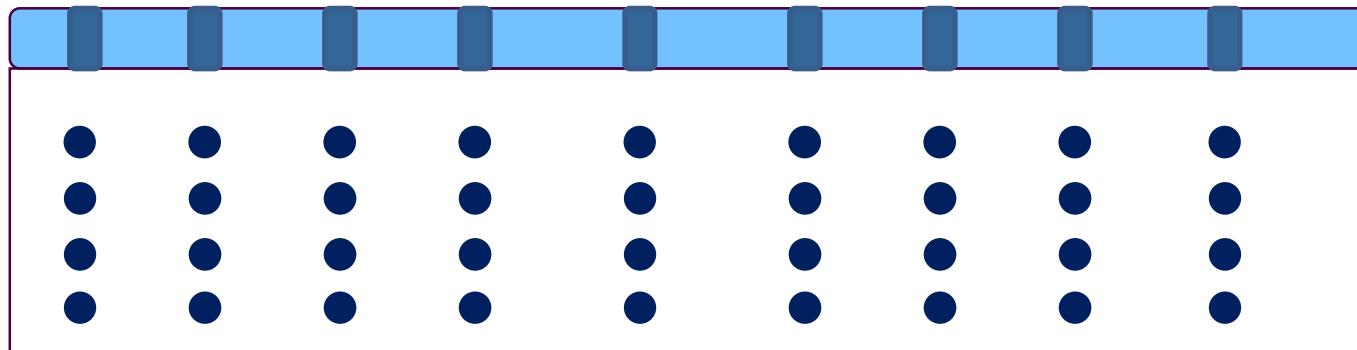
# Imputation

# Imputation -principles

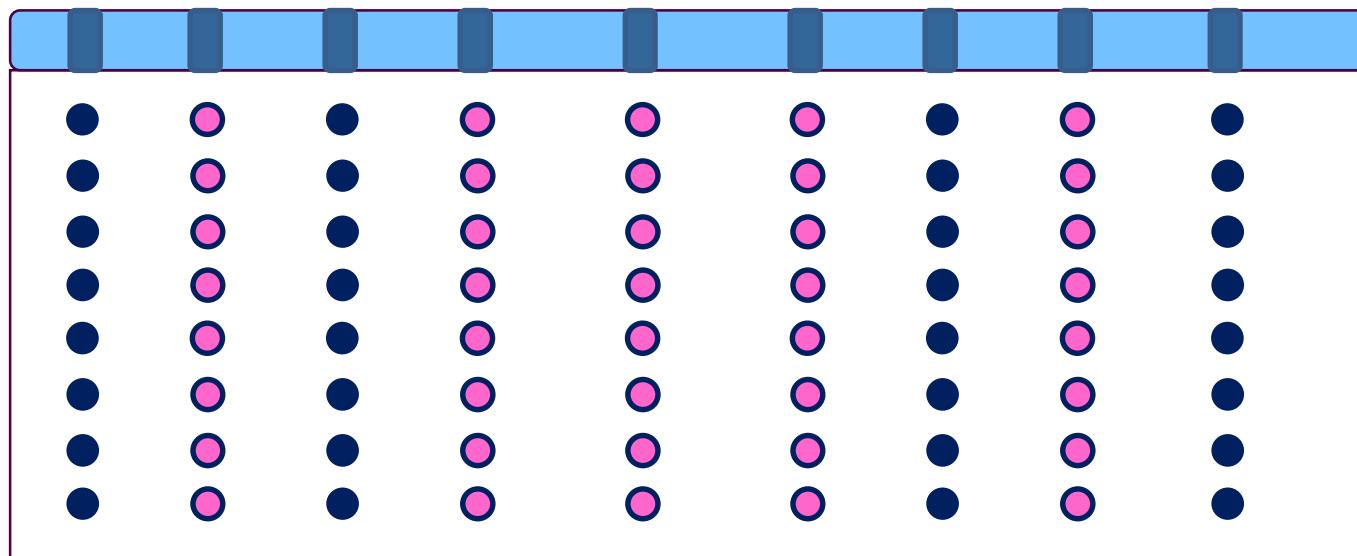


chromosomal position

# Imputation -principles



Reference panel

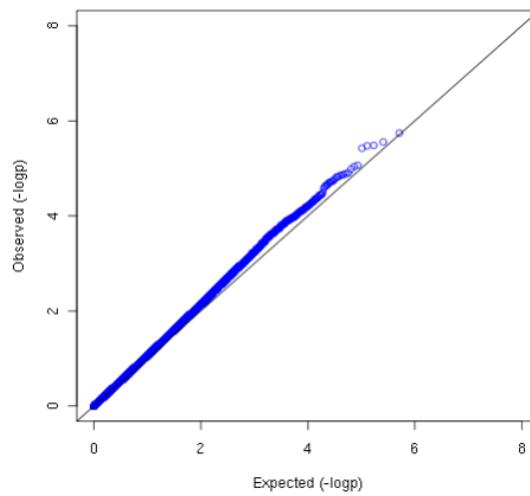


Analysis sample

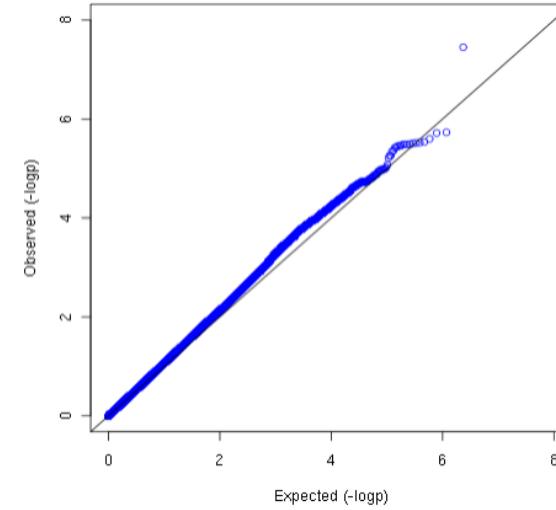
chromosomal position

3,177 OA cases  
4,854 controls

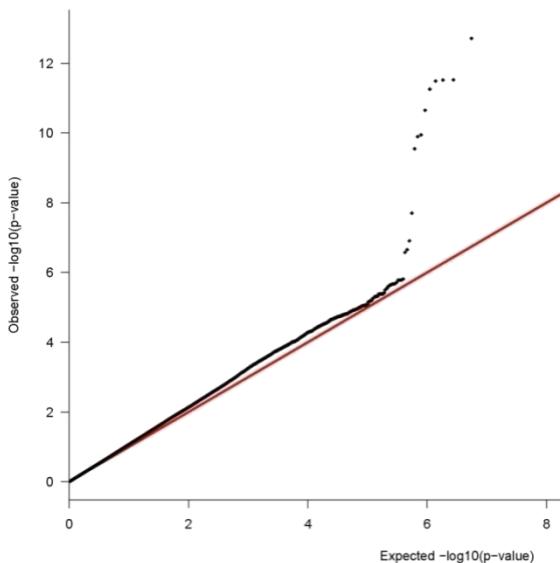
Directly typed SNPs (Illumina 610k)



Imputed SNPs: HapMap



Imputed SNPs: 1000 genomes



Harnessing the power of large biomedical resources





National Joint Registry

[www.njrcentre.org.uk](http://www.njrcentre.org.uk)

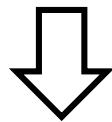
Working for patients, driving forward quality

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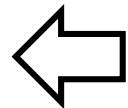
# Accessing registry records and patient recruitment

Developmental dysplasia of the hip -National Joint Registry

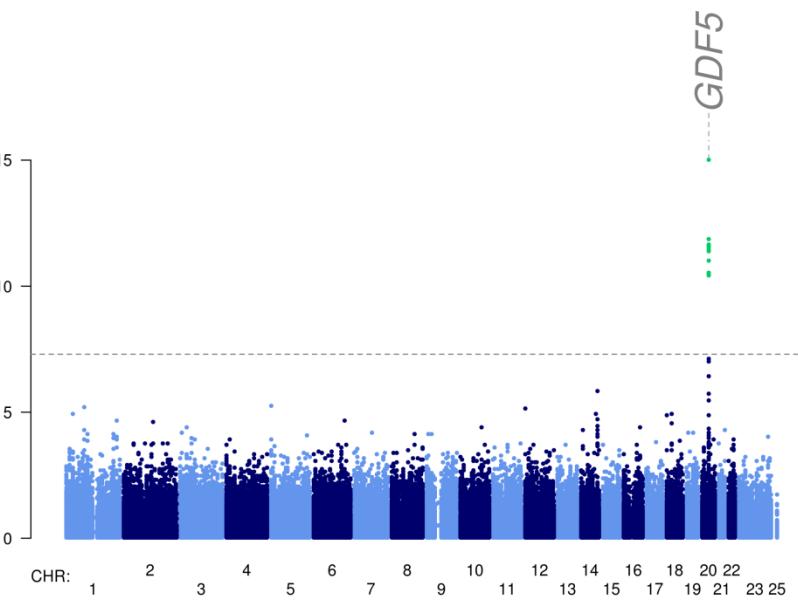
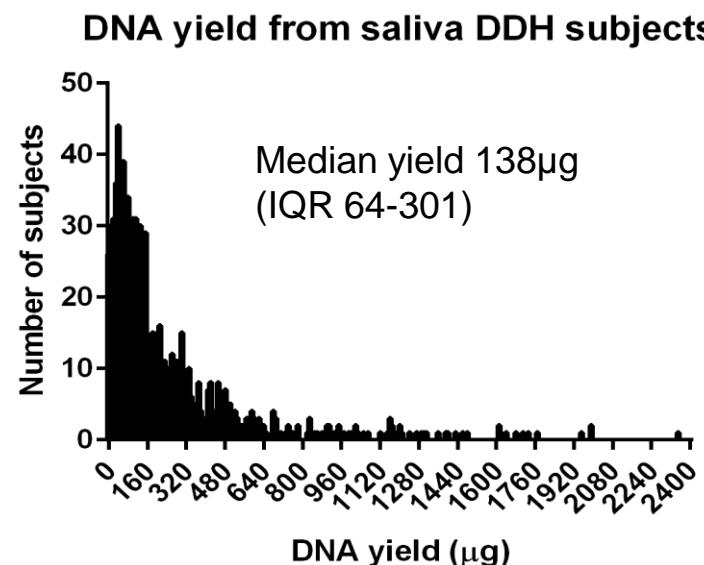
1,091 postal DNA kits to pre-screened consenting participants



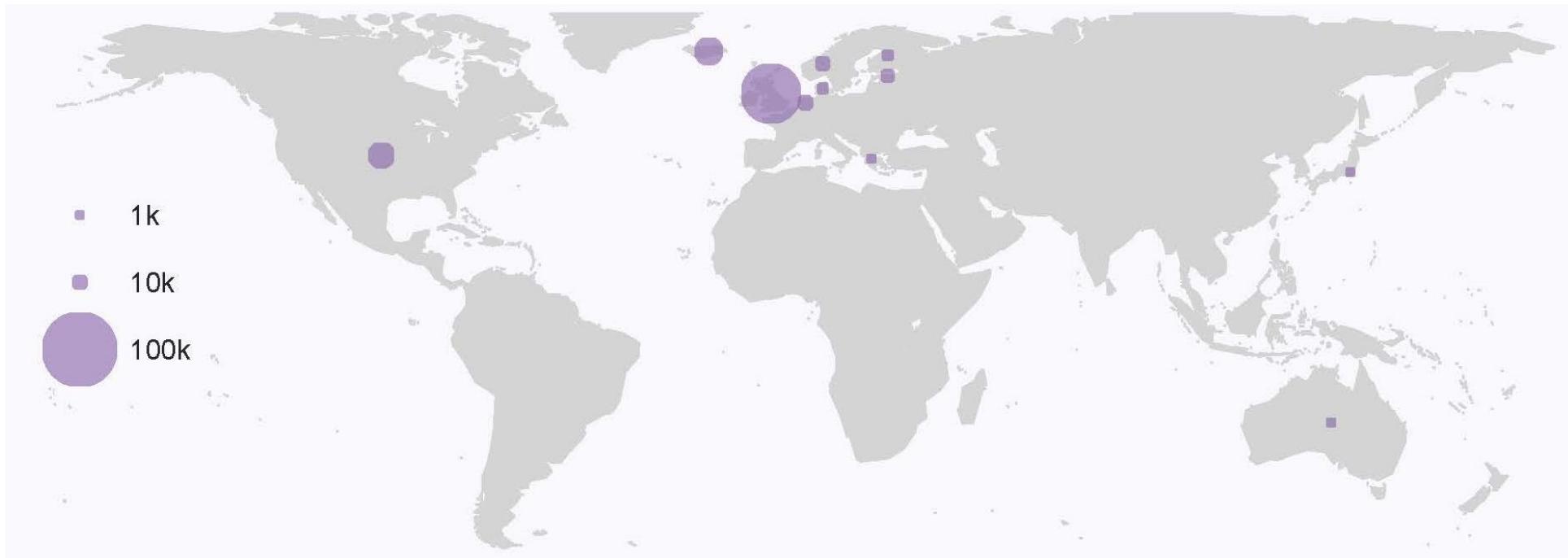
907 returns



Electronic radiographs obtained through Image Exchange Portal



# GO Genetics of Osteoarthritis

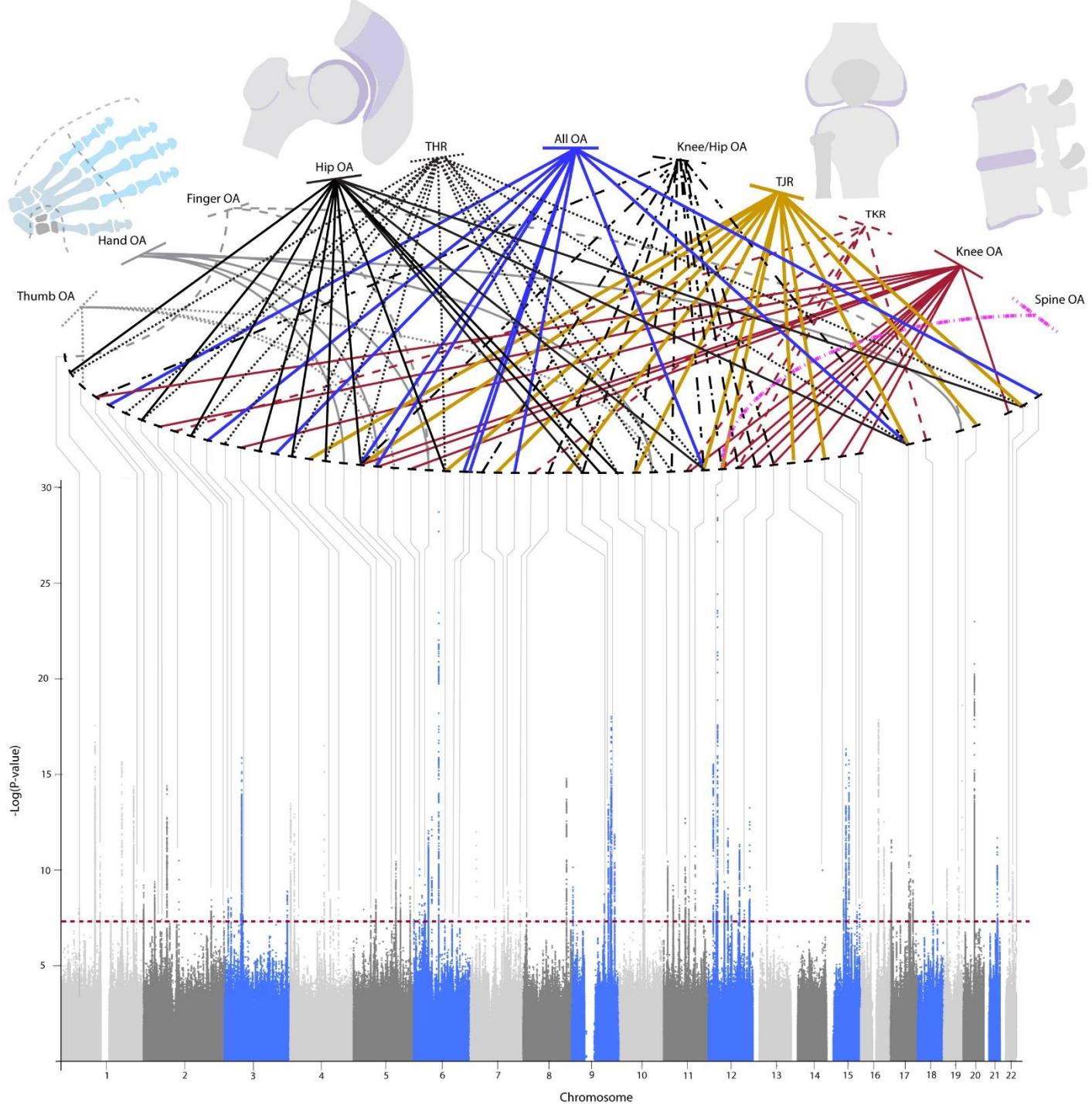


180,000 cases, 1M controls



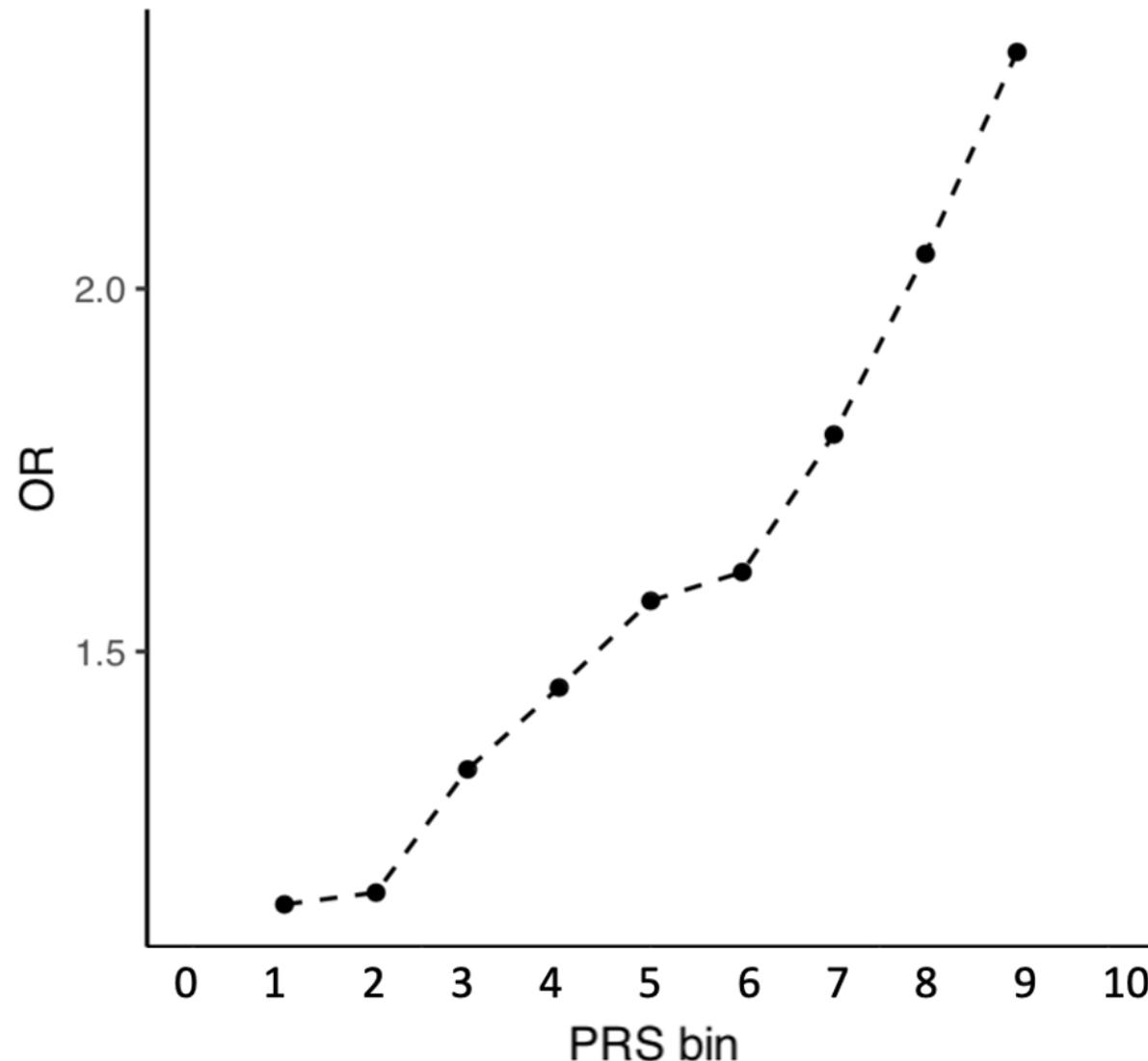
<https://www.genetics-osteoarthritis.com>

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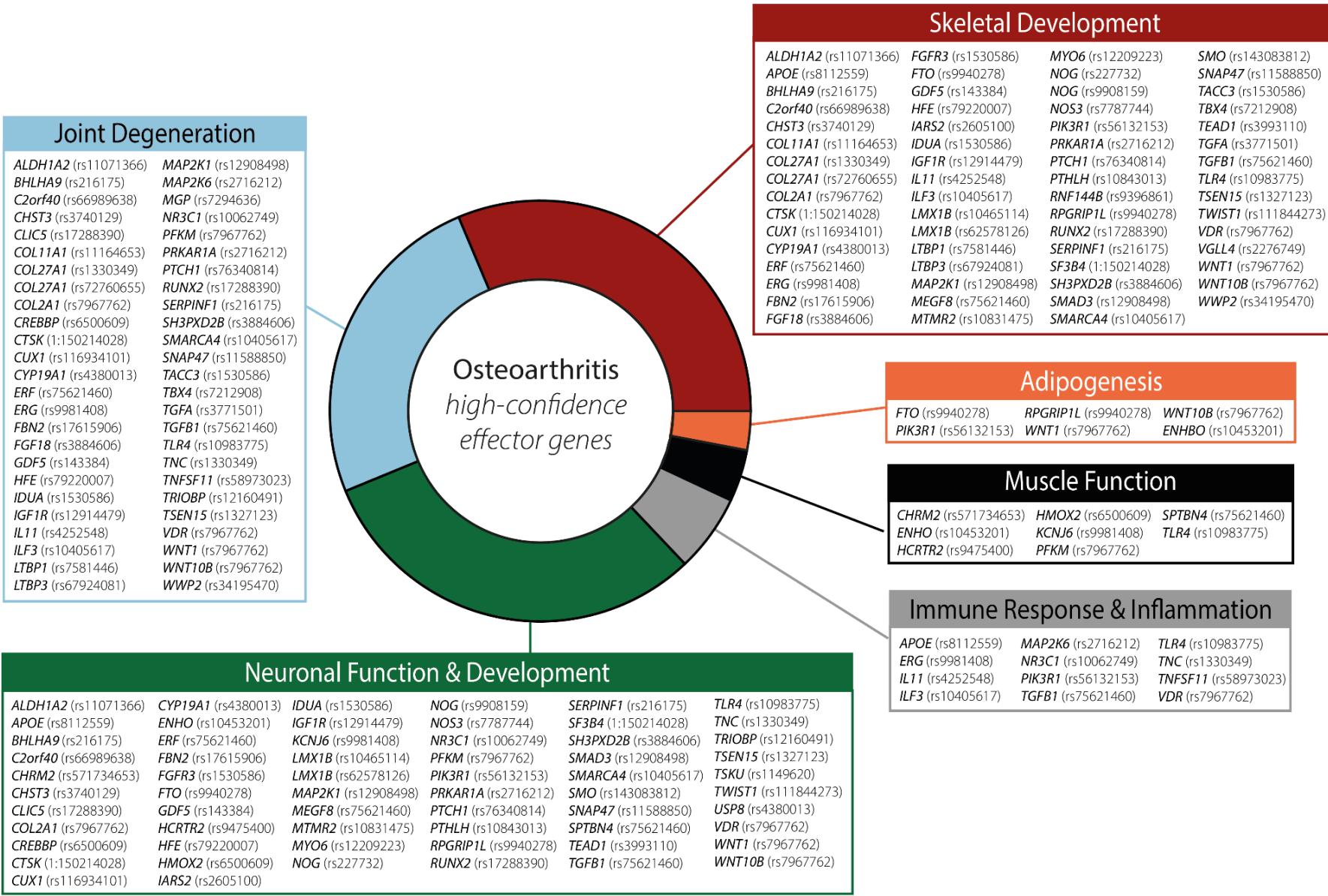


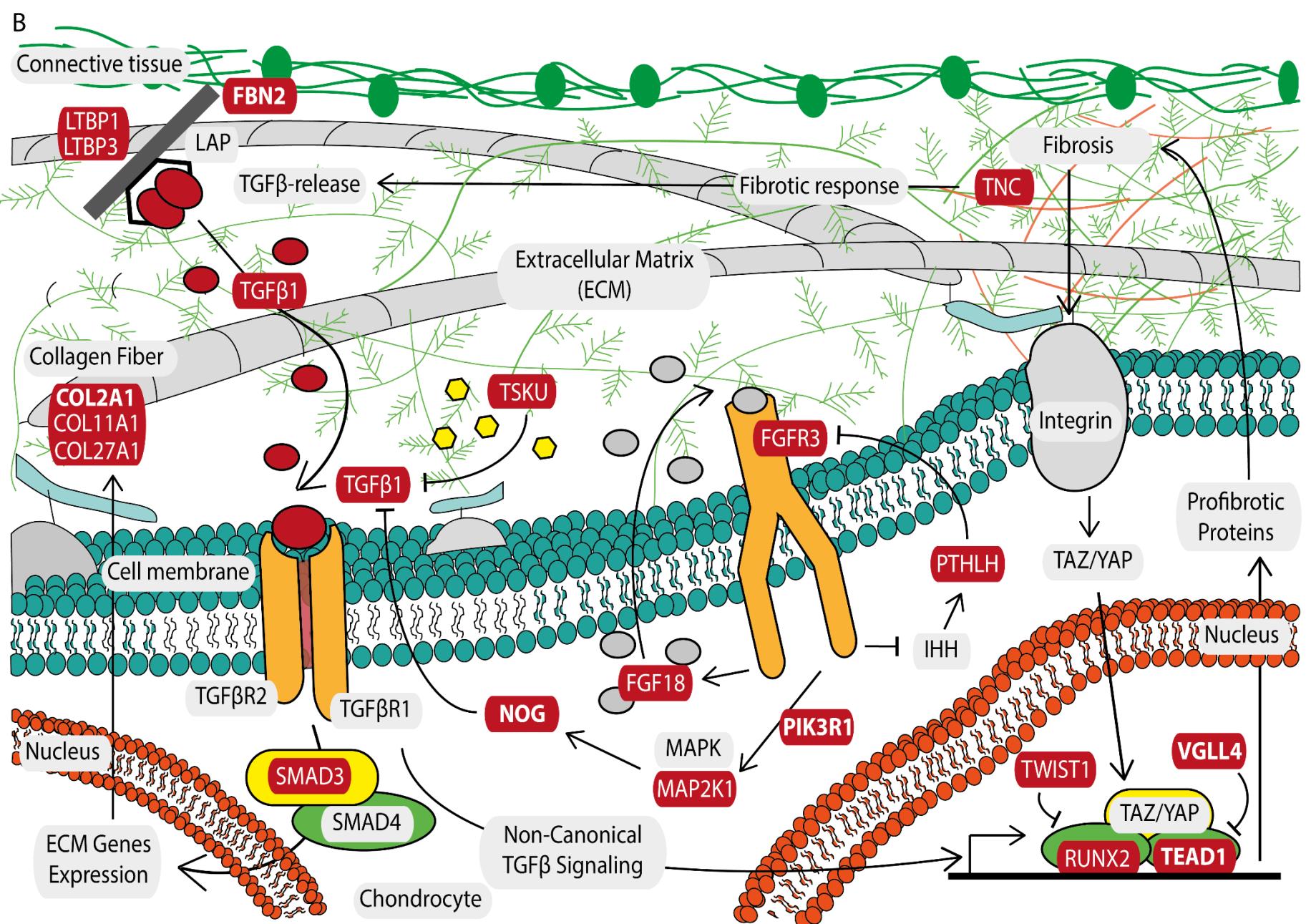
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# Total hip replacement polygenic risk score



A





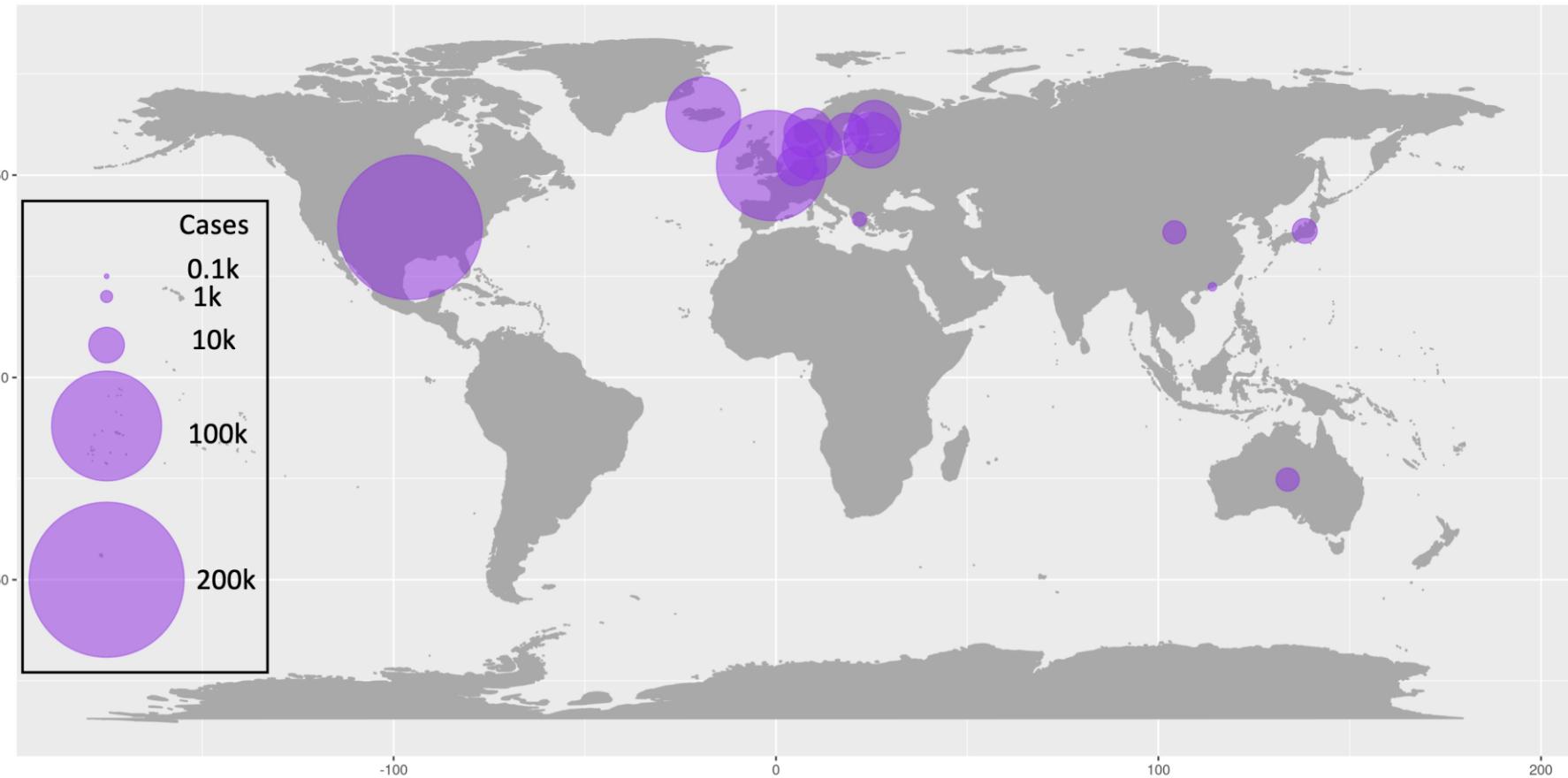
# Drug target identification

Gene	Encoded protein	Drug name	Drugbank Id	Molecule type	Development phase	Molecular mechanism of action	Mechanism of action	Current clinical indication(s)
<i>NR3C1</i>	Glucocorticoid receptor	Prednisolone	DB00860	Small molecule	Approved	Agonist	Anti-inflammatory, immunosuppressive, anti-neoplastic, vasoconstrictive	Multiple indications involving inflammation and immunity, investigational in osteoarthritis
<i>CTSK</i>	Cathepsin K	MIV-711	DB15599	Small molecule	Investigational	Antagonist	Osteoclast inhibitor	Investigational in osteoarthritis
<i>VDR</i>	Vitamin D receptor	Calcitriol	DB00136	Small molecule	Approved	Agonist	Calcium metabolism	Vitamin D deficiency, chronic kidney disease, hyperparathyroidism (secondary), investigational in osteoarthritis
<i>EGLN2</i>	Egl nine homolog 2	Ascorbic acid	DB00126	Small molecule	Approved	Agonist	Co-factor in collagen synthesis, carbohydrate and lipid metabolism. Antioxidant.	Vitamin C deficiency, investigational in osteoarthritis
<i>FGF18</i>	Fibroblast growth factor 18	Sprifermin	DB12616	Recombinant protein	Investigational	Agonist	Cell morphogenesis, chondrogenesis, cartilage thickening in OA	Osteoporosis, cancer bone metastasis, investigational in osteoarthritis
<i>TNFSF11</i>	Tumor necrosis factor ligand superfamily member 11	Denosumab	DB06643	Monoclonal antibody	Approved, investigational	Antagonist	Inhibits osteoclast formation, function and survival	Osteoporosis, bone metastasis, investigational in osteoarthritis
<i>PTHLH</i>	Parathyroid hormone like hormone	Teriparatide	DB06285	Protein	Approved, investigational	Agonist	Calcium and phosphate metabolism	Osteoporosis, investigational in osteoarthritis
<i>ALDH1A2</i>	Retinal dehydrogenase 2	Tretinoin	DB00755	Small molecule	Approved	Agonist	Cell reproduction, proliferation, differentiation	Acne, skin keratinisation disorders
<i>APH1A</i>	APH1A gamma secretase subunit	E-2012	DB5171	Small molecule	Investigational	Antagonist	Inhibits beta-amyloid production through inhibition of gamma secretase activity	Investigational in Alzheimer's disease
<i>CDK7</i>	Cyclin-dependent kinase 7	Seliciclib	DB06195	Small molecule	Investigational	Antagonist	CDK inhibitor	Investigational for multiple cancers, viral infection and chronic inflammatory disorders
<i>CHST3</i>	Carbohydrate sulfotransferase 3	Thalidomide	DB01041	Small molecule	Approved, withdrawn for hypnotic indications	Agonist	Modulates cytokine release, catalyses sulfation of chondroitin	Immunosuppressive, anti-angiogenic
<i>CYP19A1</i>	Cytochrome P450 19A1	Aminoglutethimide	DB00357	Small molecule	Approved	Antagonist	Aromatase inhibitor (1 of several in class), blocks conversion of androgens to oestrogens	Breast cancer, prostate cancer
<i>IGF1R</i>	Insulin-like growth factor 1 receptor	Mecasermin	DB01277	Protein	Approved	Agonist	Mediates effects of growth hormone through cell surface receptor tyrosine kinases, anabolic	Growth failure in children due to IGF1 deficiency
<i>JAK2</i>	Janus kinase 2	Metreleptin	DB09046	Recombinant protein	Approved	Agonist	Fat metabolism	Lipodystrophy
<i>MAP2K1</i>	Mitogen-activated protein kinase kinase 1	Fostamatinib	DB12010	Small molecule	Approved, investigational	Antagonist	Tyrosine kinase inhibitor, role in osteoclast activation and endochondral ossification through SOX9	Rheumatoid arthritis, immune thrombocytopenic purpura
<i>MAP2K6</i>	Dual specificity mitogen-activated protein kinase kinase 6	Fostamatinib	DB12010	Small molecule	Approved, investigational	Antagonist	Tyrosine kinase inhibitor, role in osteoclast activation and endochondral ossification through SOX9	Rheumatoid arthritis, immune thrombocytopenic purpura
<i>NFKB1</i>	Nuclear factor kappa beta p105 subunit	Thalidomide	DB01041	Small molecule	Approved, withdrawn for hypnotic indications	Agonist	Modulates cytokine release, catalyses sulfation of chondroitin	Immunosuppressive, anti-angiogenic
<i>NISCH</i>	Nischarin	Tizanidine	DB00697	Small molecule	Approved	Agonist	Alpha-2 adrenergic receptor agonist	Muscle spasm
<i>NOS3</i>	Nitric oxide synthetase	Citrulline	DB00155	Small molecule	Approved		Non-essential amino acid	Nutritional supplement
<i>PAK1</i>	Serine/threonine protein Kinase 1	Fostamatinib	DB12010	Small molecule	Approved, investigational	Antagonist	Tyrosine kinase inhibitor, role in osteoclast activation and endochondral ossification through SOX9	Rheumatoid arthritis, immune thrombocytopenic purpura
<i>PPARD</i>	Peroxisome proliferator-activated receptor delta	Treprostinil	DB00374	Small molecule	Approved	Agonist	Synthetic prostacyclin analogue (1 of several in class), vasodilatation, anti-platelet	Pulmonary artery hypertension
<i>PPARG</i>	Peroxisome proliferator-activated receptor gamma	Rosiglitazone	DB00412	Small molecule	Approved, investigational	Agonist	Thiazolidinedione, selective ligand of PPAR $\gamma$	Diabetes mellitus, increases insulin sensitivity
<i>PRKCD</i>	Protein kinase C delta type	Ingenol mebutate	DB05013	Small molecule	Approved	Agonist	Neutrophil-mediated inflammation	Actinic keratosis
<i>S1PR2</i>	Sphingosine-1-phosphate receptor 2	Fingolimod	DB08868	Small molecule	Approved, investigational	Antagonist	Sphingosine 1-phosphate-induced cell proliferation, survival, and transcriptional activation	Multiple sclerosis
<i>SMO</i>	Smoothed frizzled family receptor	Vismodegib	DB08828	Small molecule	Approved, investigational	Antagonist	Frizzled family G-protein-coupled receptor in hedgehog signalling	Basal-cell carcinoma
<i>TGFB1</i>	Transforming growth factor beta 1	Terazocin	DB1162	Small molecule	Approved	Agonist	Multifunctional peptide: cell growth, proliferation and differentiation	Benign prostatic hyperplasia, hypertension

# GO 2.0

## Sample size

Cases	Controls	Ancestry	%
<b>489,952</b>	<b>1,472,094</b>	All	
2,422	18,894	S Asian	1.09
10,408	128,633	E Asian	7.09
25,698	34,718	African	3.08
441,288	1,271,822	European	87
8,128	9,759	Hispanic	0.91
2,131	8,268	Mixed	0.05

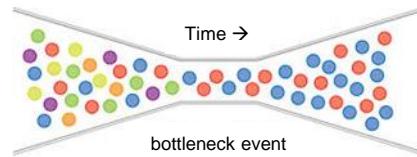


# Special populations

# Population isolates

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

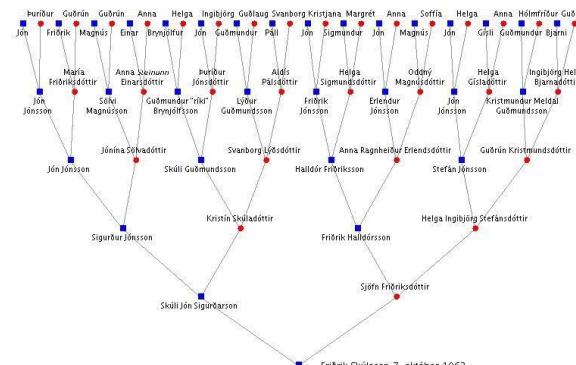
- Some rare variation is lost, and rare variants may have increased in frequency



- linkage disequilibrium tends to be extended



- homogeneous environment



- better knowledge of population history



# 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



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[www.helic.org](http://www.helic.org)

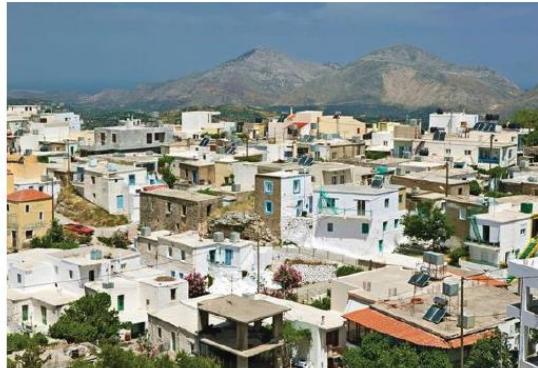


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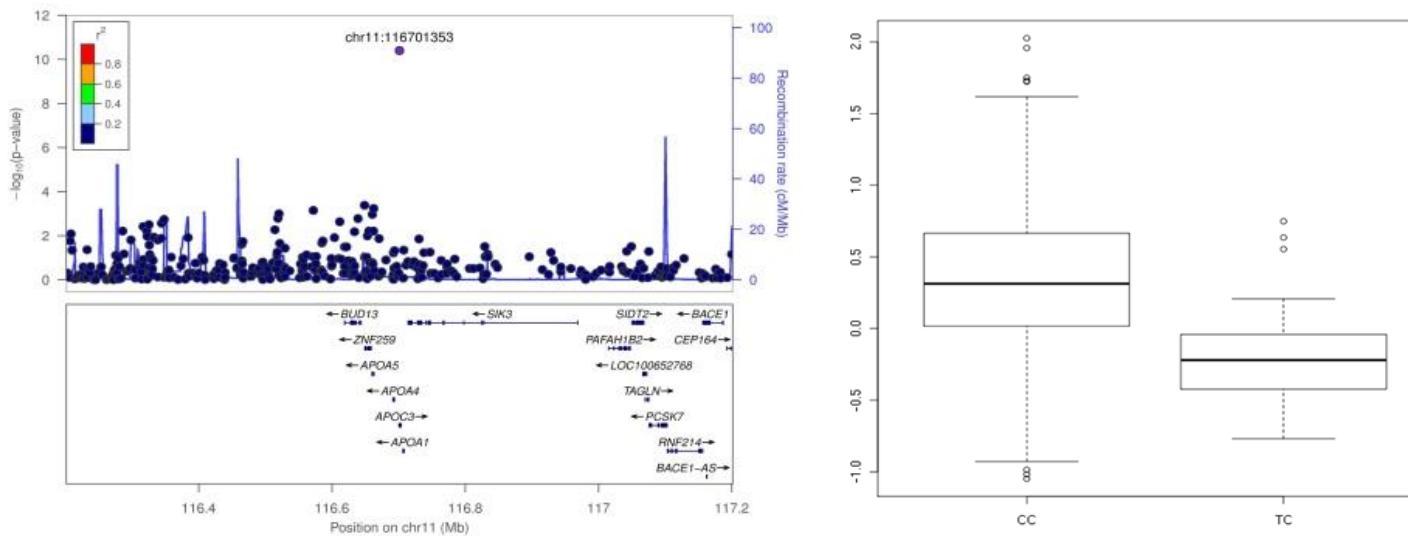
# R19X APOC3 cardioprotective variant

THE TIMES

Mountain village may hold secret to immunity from heart disease



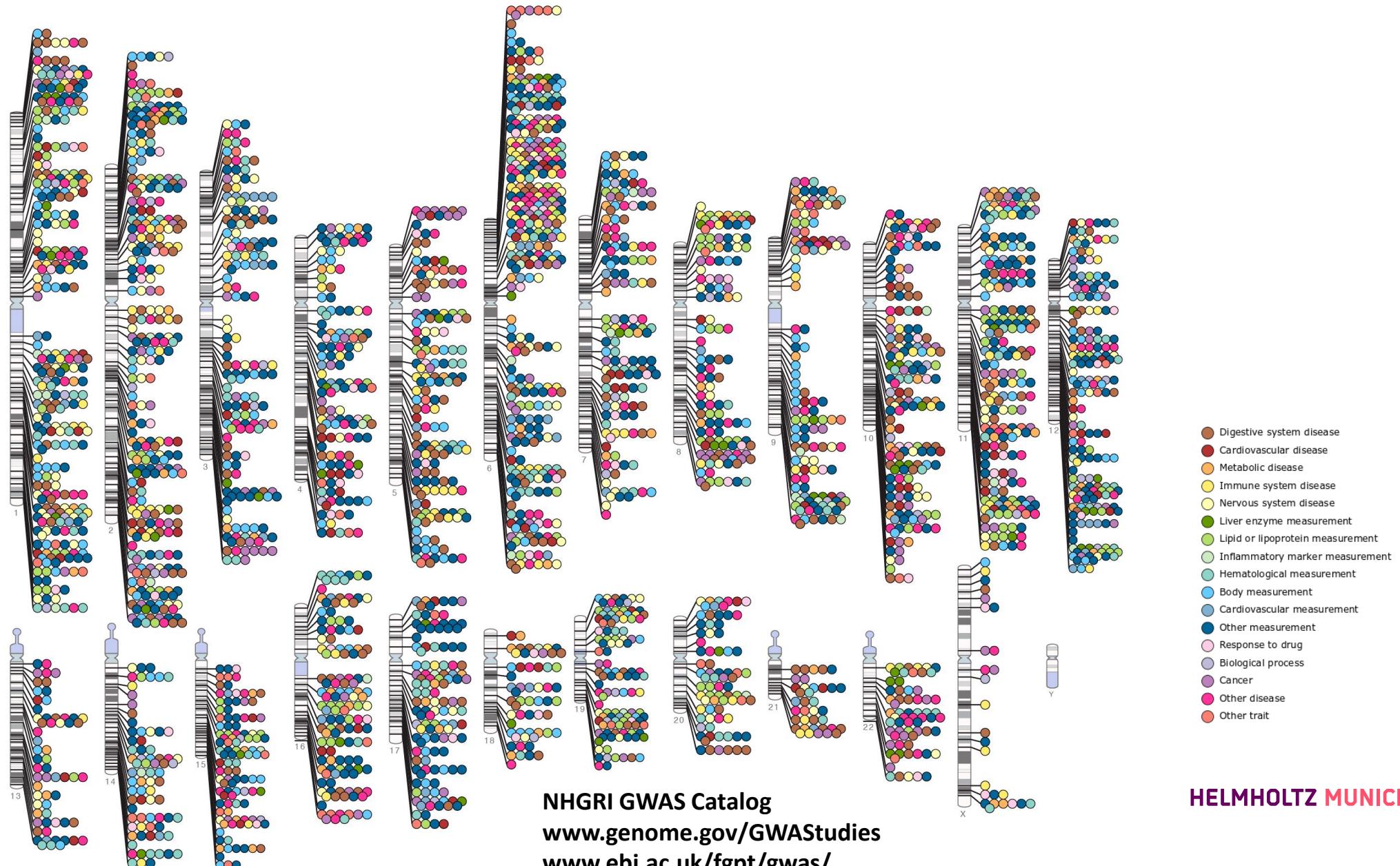
Anogians have remained unusually isolated for several hundred years Panoramic Images/Getty Images



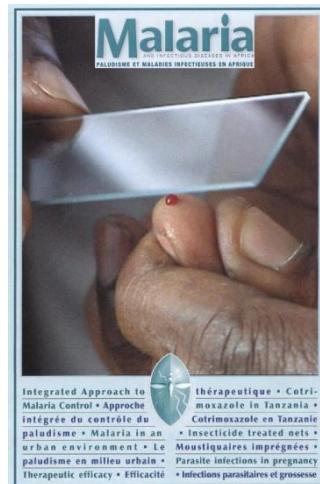
- Mylopotamos villages (n=1256, MAF 2%, p=10<sup>-11</sup>)
- Detection of this effect would have required 67,000 Europeans (MAF 0.05%)

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



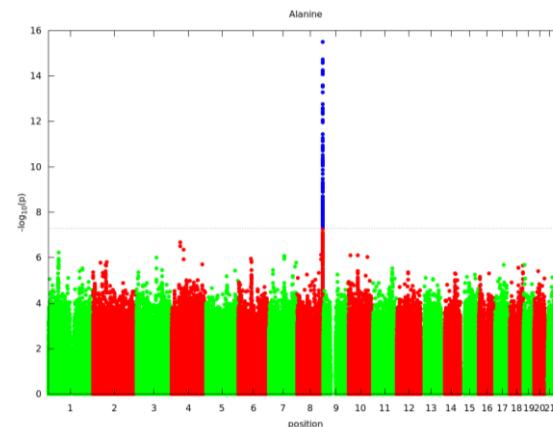
# Burden of disease in Africa



# 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

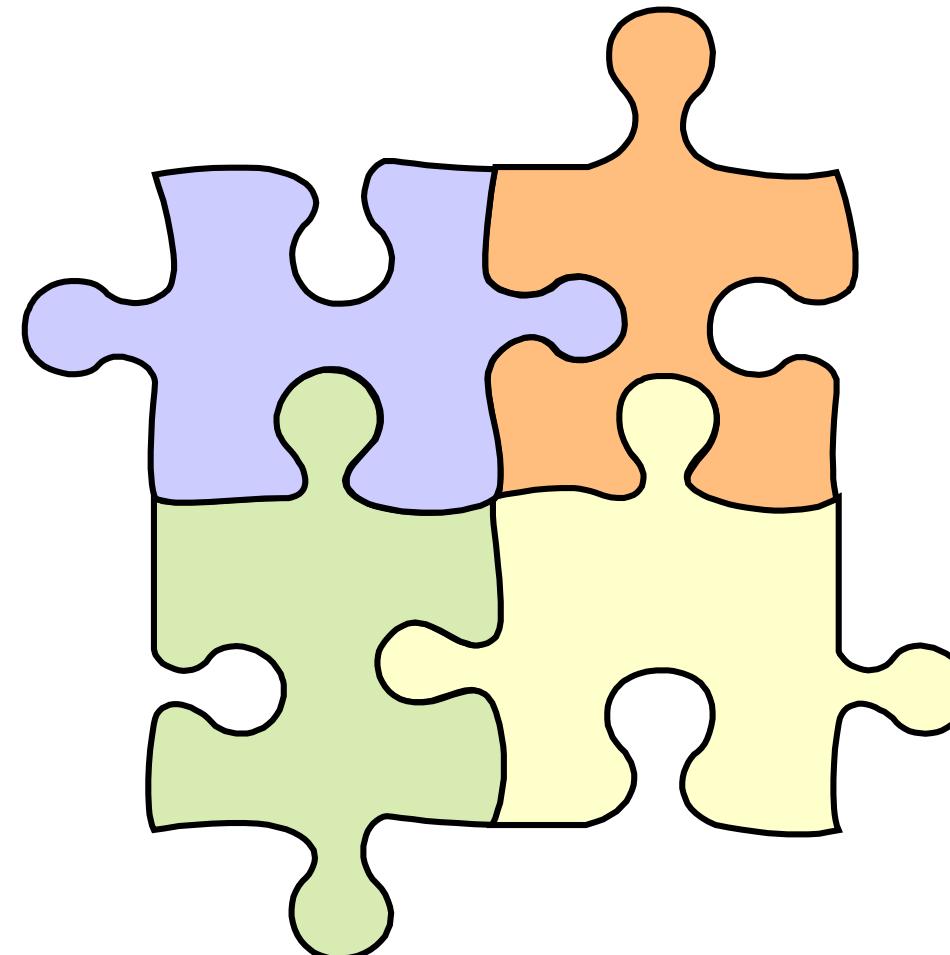
GPT gene- produces enzyme  
Monomorphic in Europeans  
Ugandan frequency: 26%

# Genetic architecture of complex traits

Common variants



Rare variants



Small effect size



Large effect size