

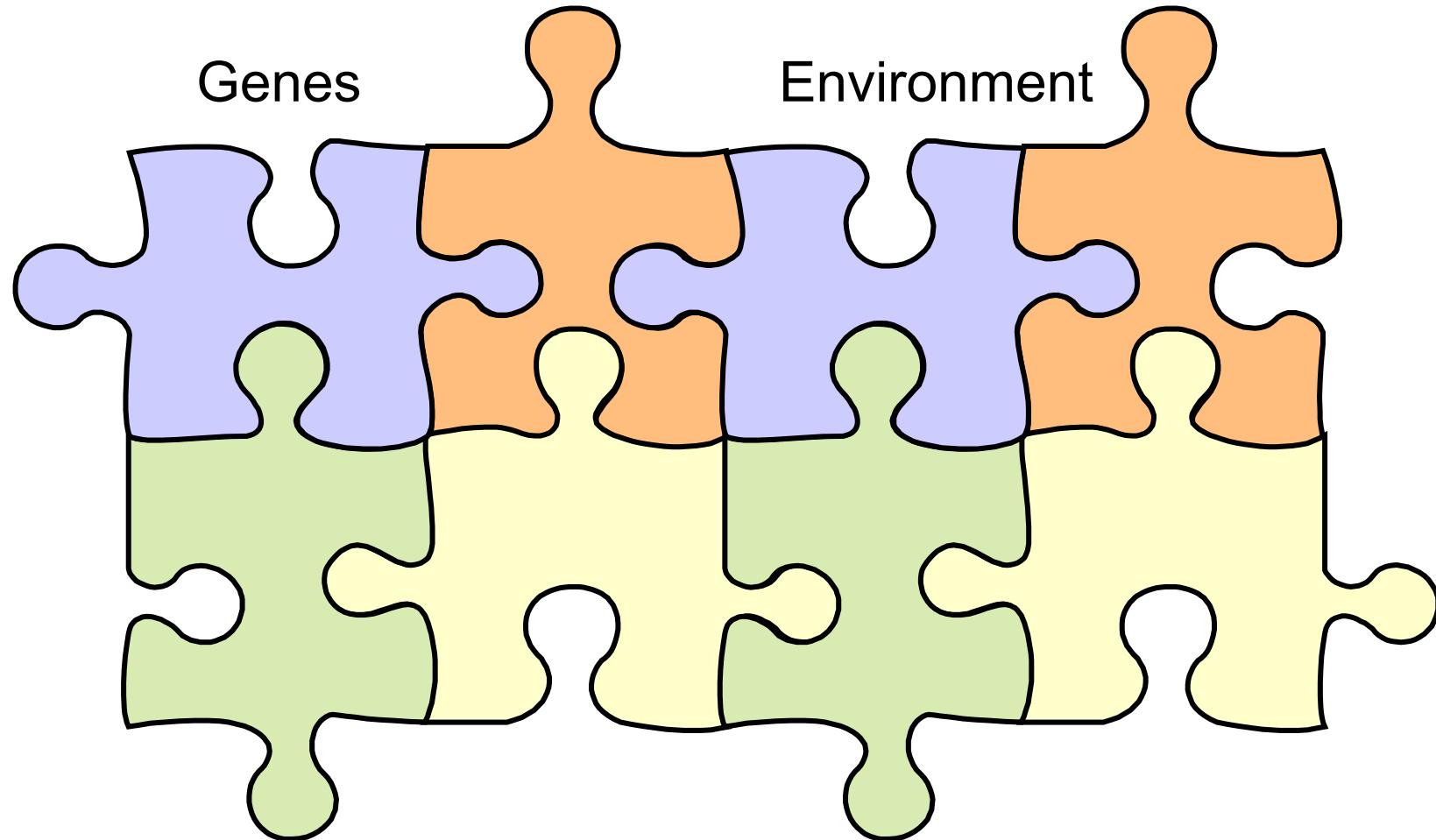
# Introduction to complex trait genetics

Eleftheria Zeggini

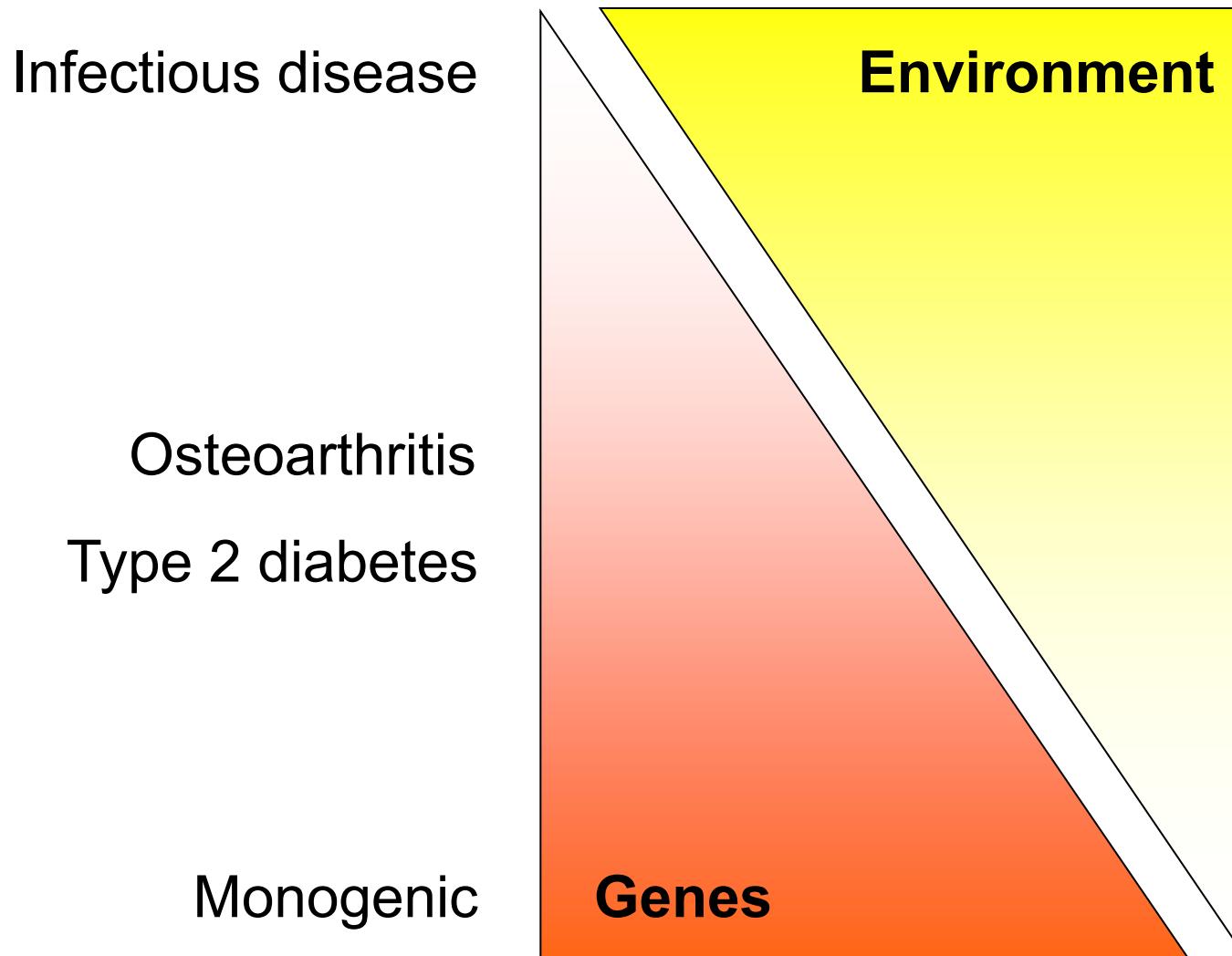
Institute of Translational Genomics

[eleftheria.zeggini@helmholtz-muenchen.de](mailto:eleftheria.zeggini@helmholtz-muenchen.de)

# Complex diseases



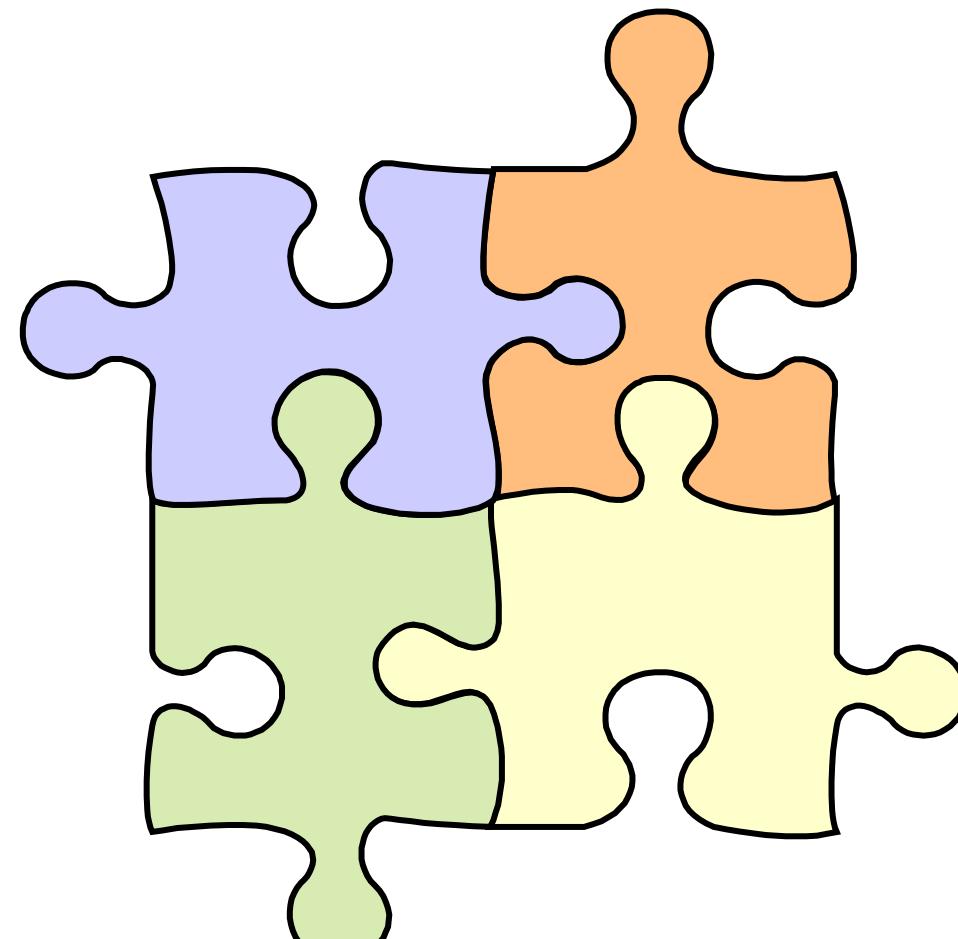
# Genes vs environment



# Genetic architecture of complex traits

Common variants

Rare variants



Small effect size

Large effect size

## Large sample collections



Large sample collections



Understanding of patterns of human genome sequence  
variation



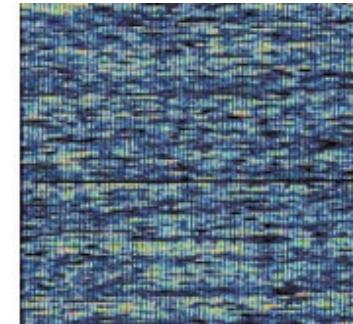
**1000 Genomes**  
A Deep Catalog of Human Genetic Variation

## Large sample collections



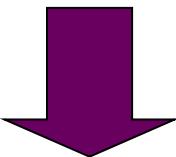
Understanding of patterns of human genome sequence variation

High-throughput technologies for genotyping



# Principles

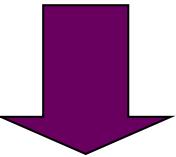
Case-control pairs (or population cohorts)



Type for 200k-2.5M SNPs

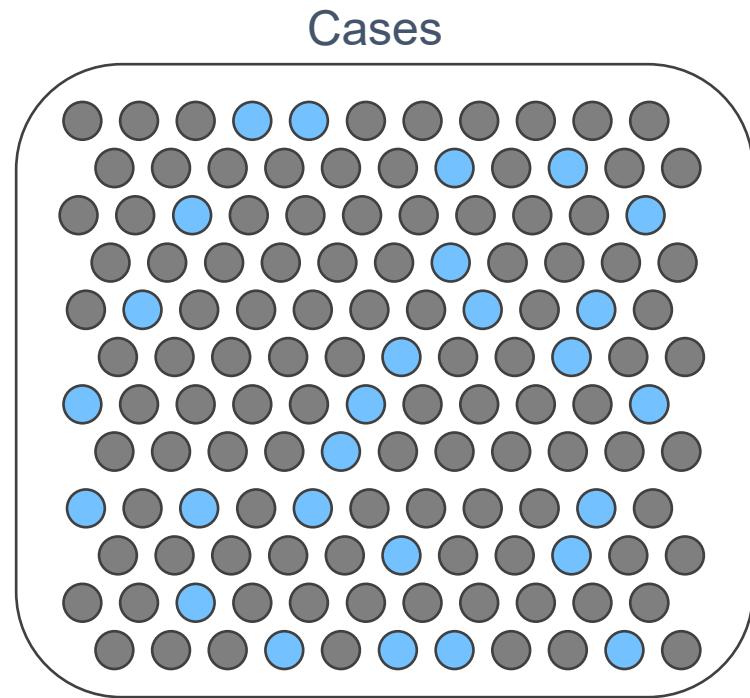


Obtain information about strength of association  
genome wide  
(within limits of sample size, allele frequency etc)

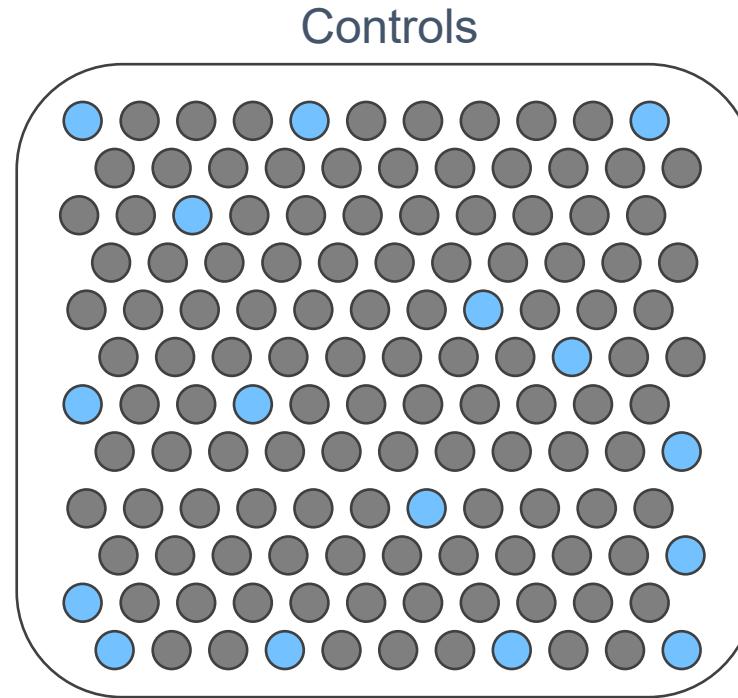


Follow-up what looks interesting

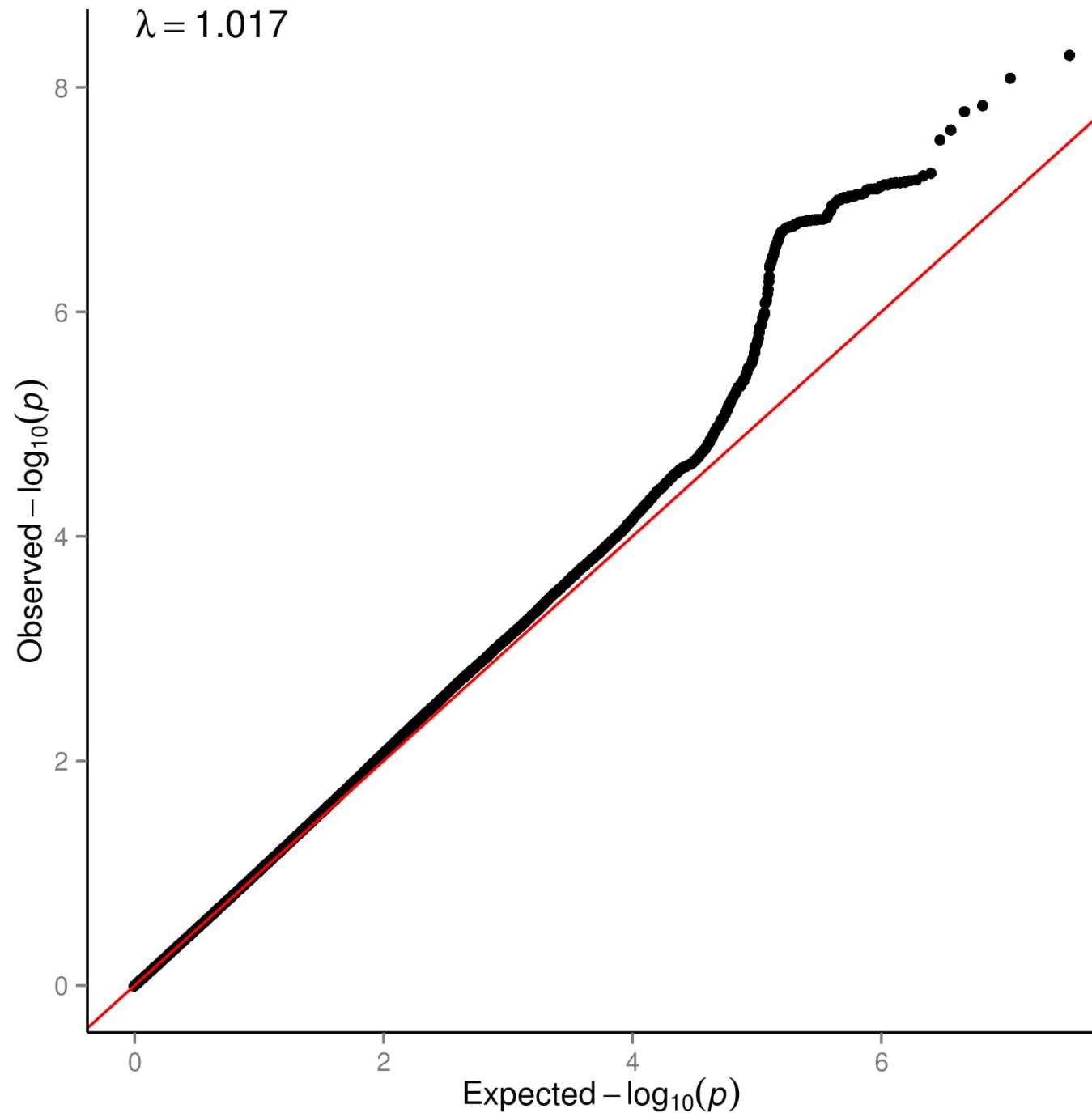
# Association between genetic variants and disease

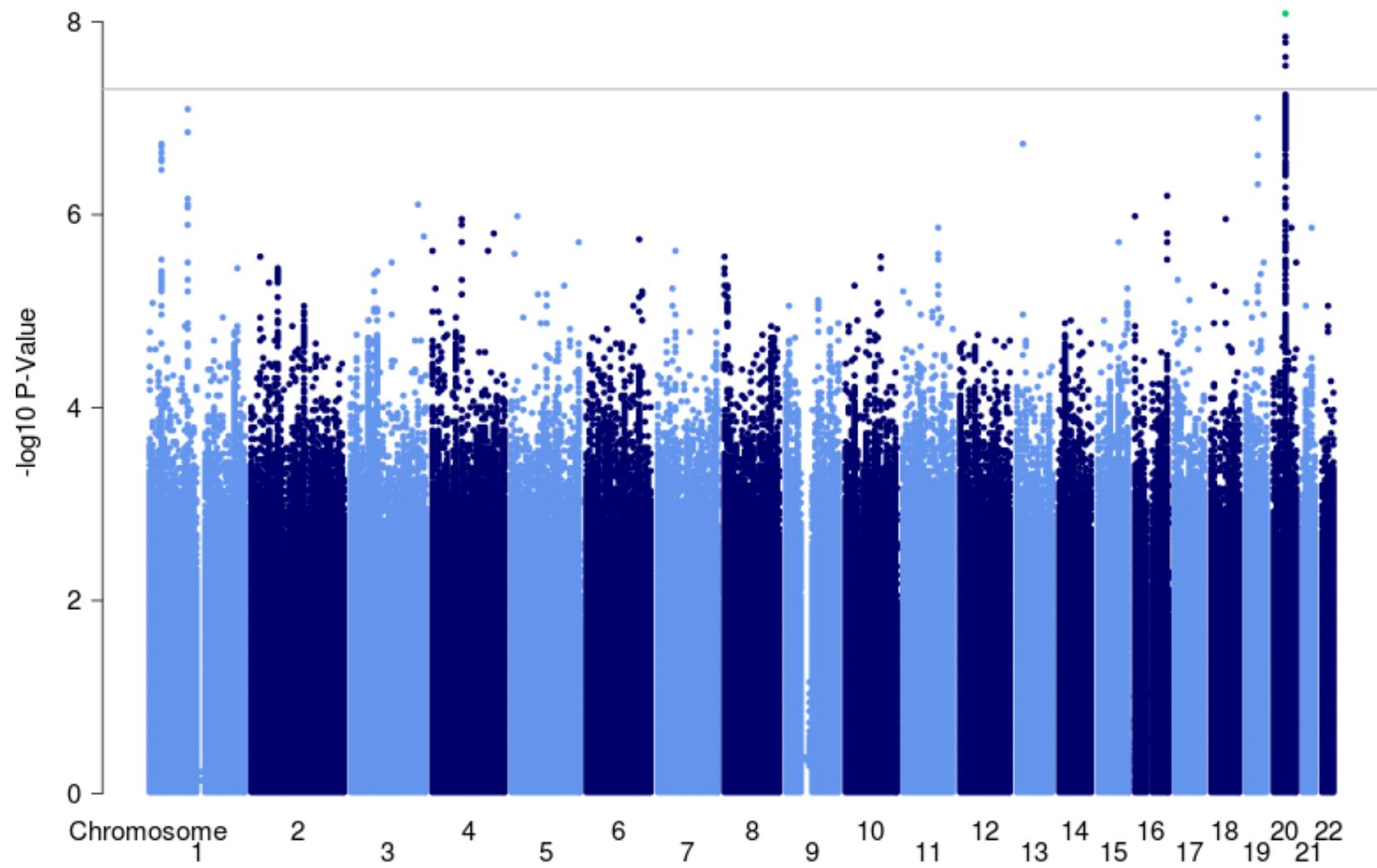


25%



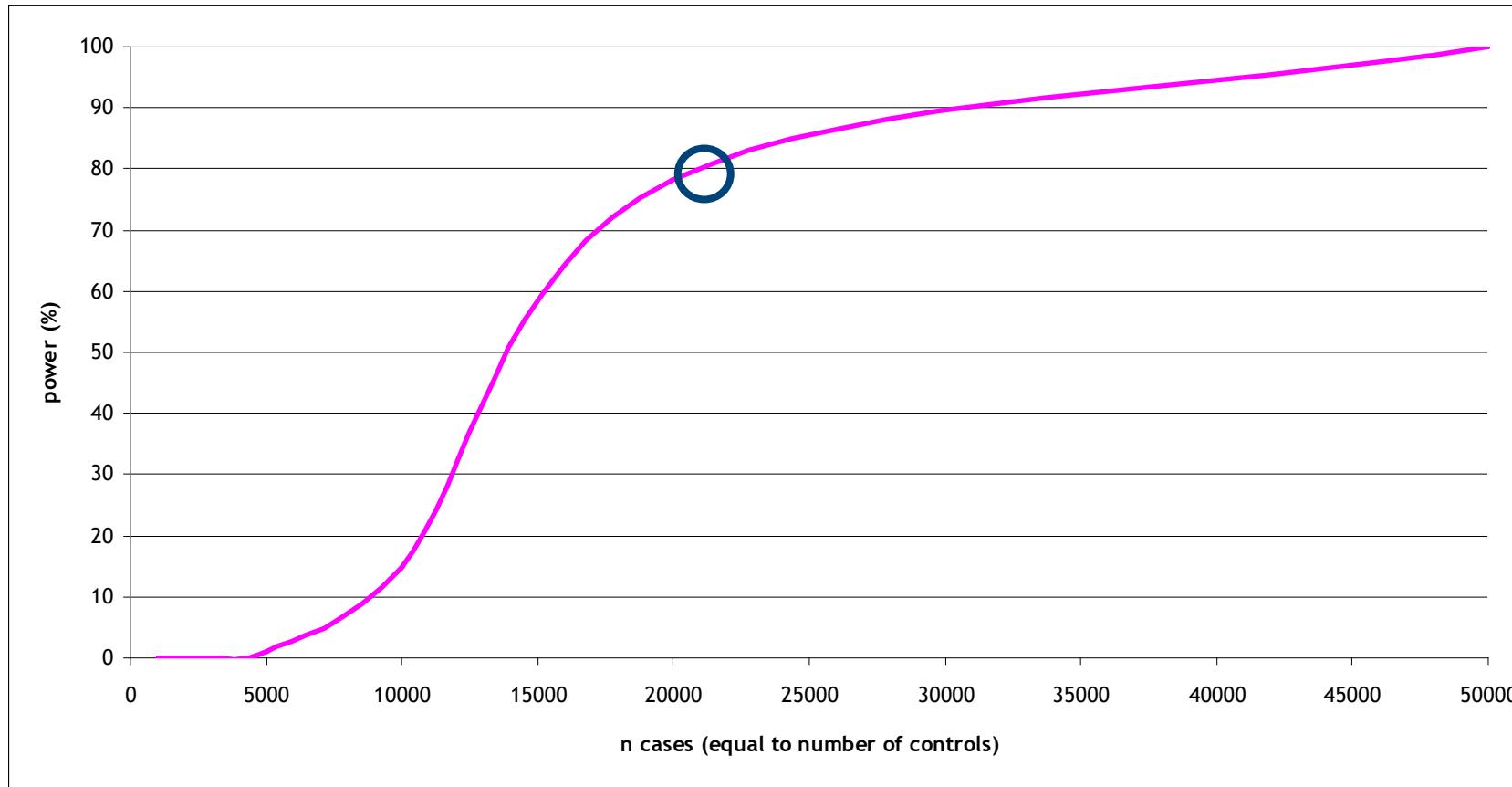
15%



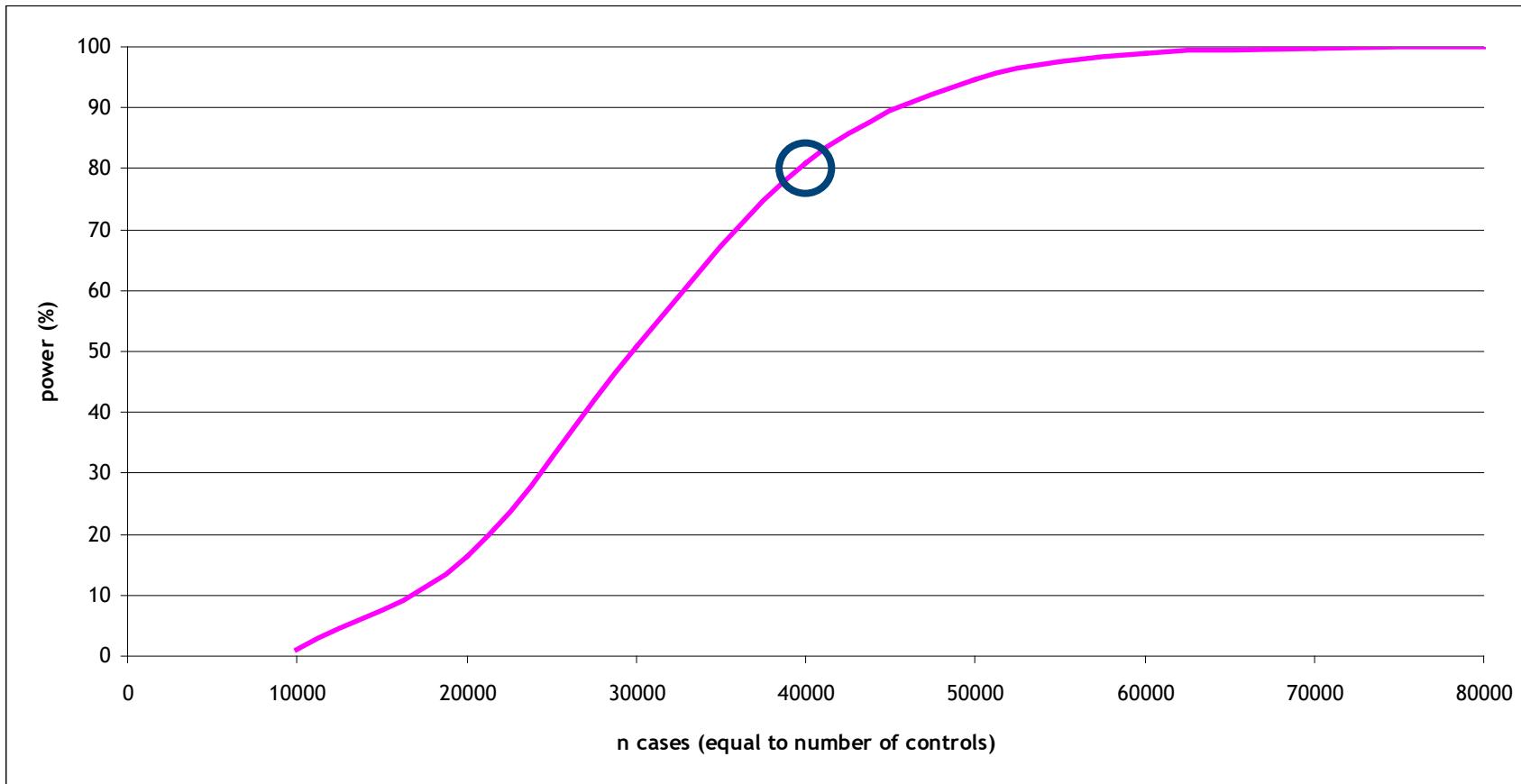


# Sample size matters

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 is characterised by cartilage degeneration in the joints leading to pain and loss of function



20% of people over the age of 40 years

50% of people over the age of 70 years

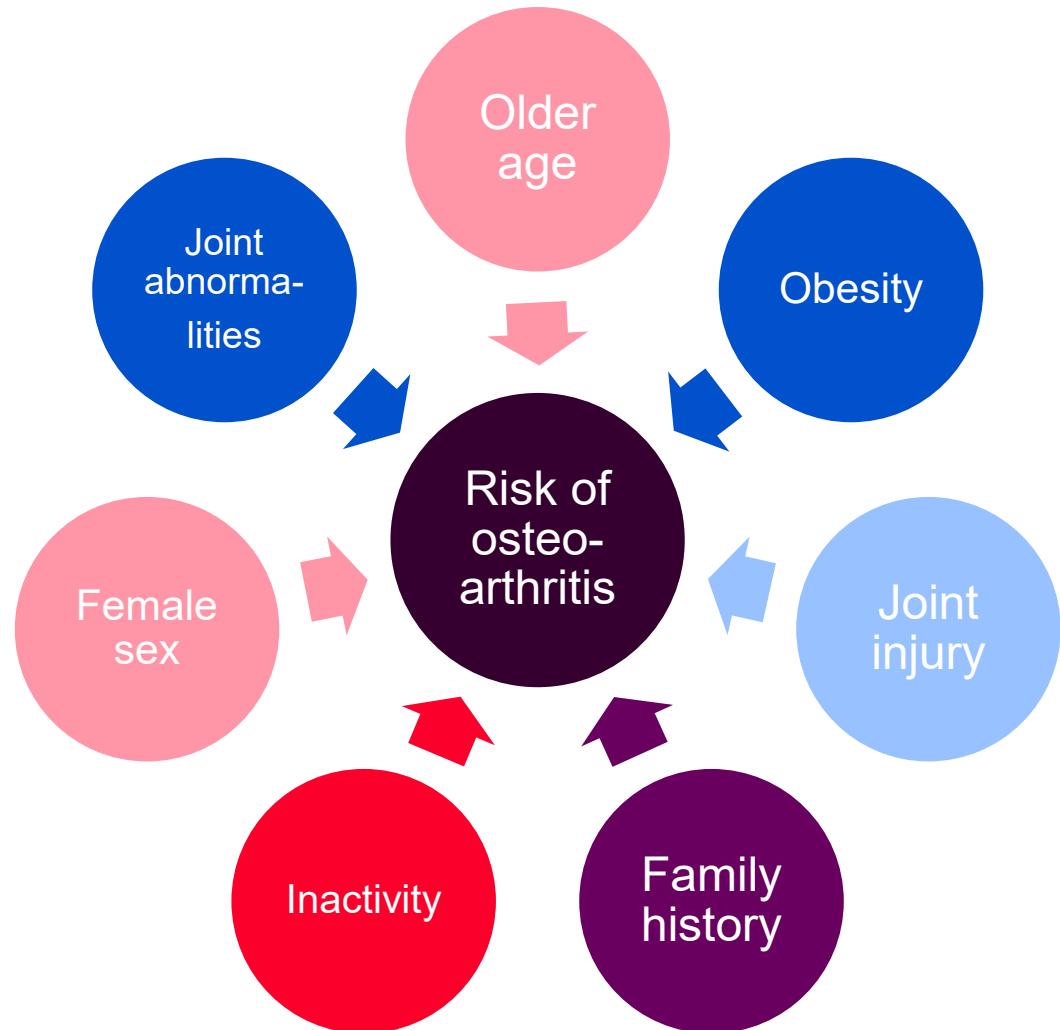
>60 million people in Europe suffer from knee or hip osteoarthritis

# The burden of osteoarthritis



- No curative therapy: analgesics, total joint replacement
- 1.76 million joint replacement surgeries annually in the EU
- Clear need to understand mechanisms of disease to develop disease-modifying treatments

# Osteoarthritis risk



# Heritability of osteoarthritis

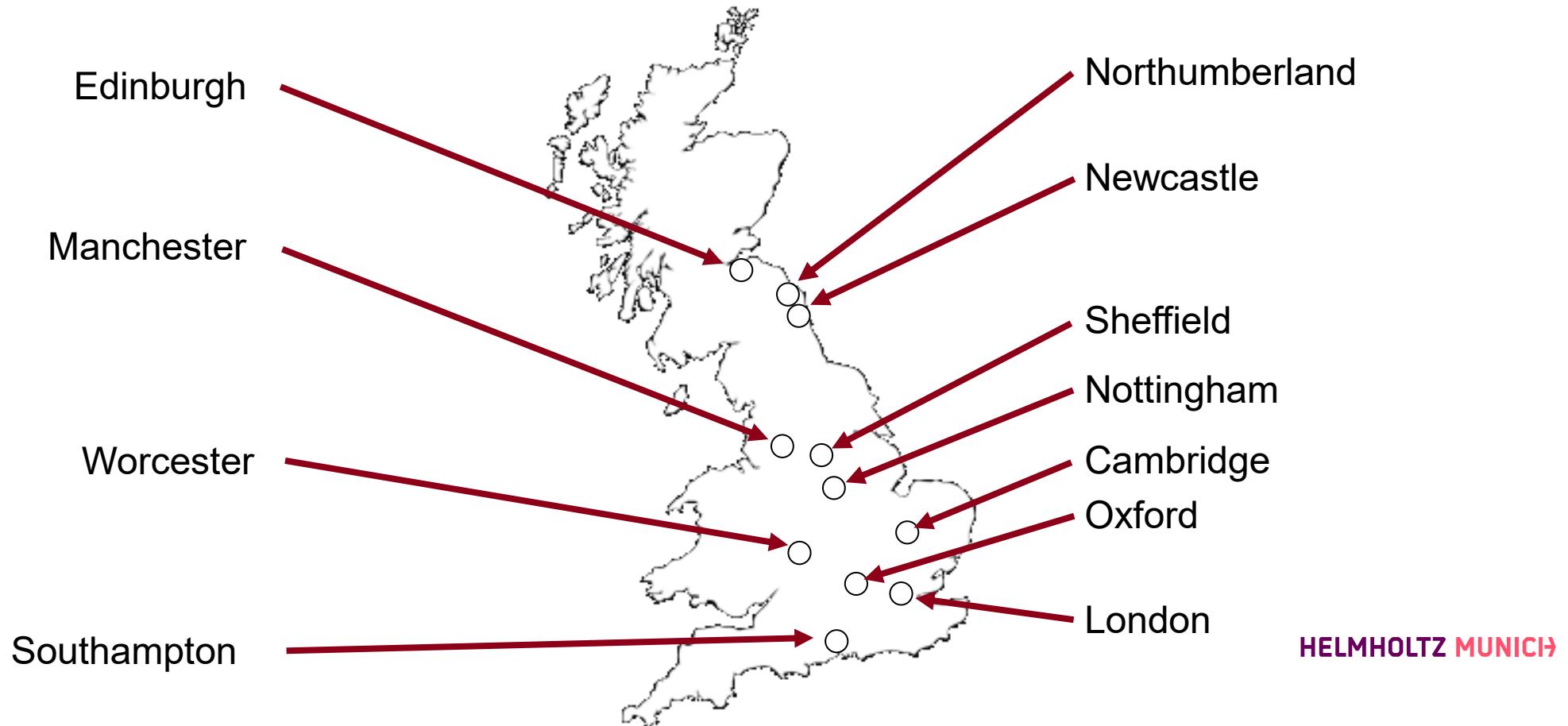


~50%: half of the variation in susceptibility to osteoarthritis in the population is due to genetic factors

# arcOGEN Consortium -arc Osteoarthritis Genetics

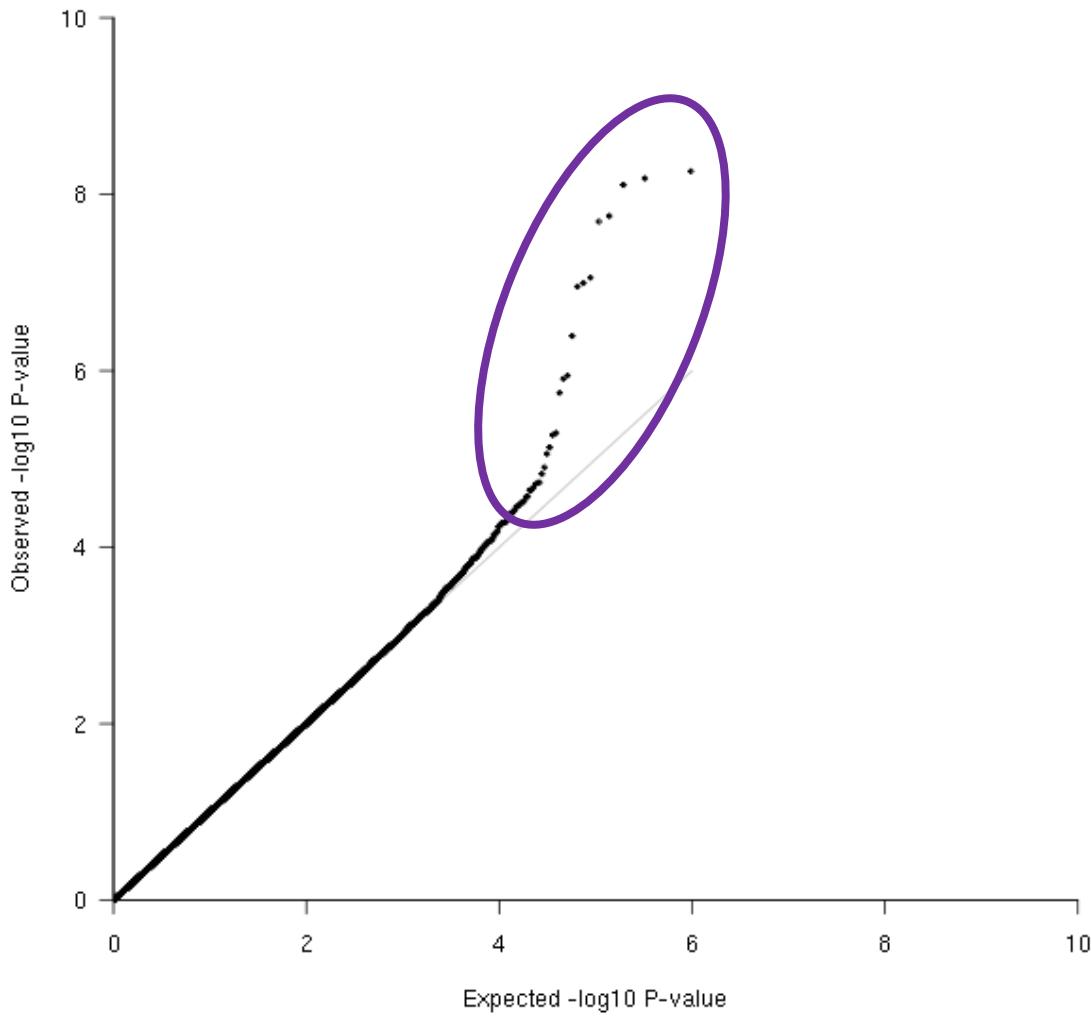


Arthritis  
Research UK 11 participating sites:



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# 7,410 cases v. 11,009 controls



# Replication Replication Replication

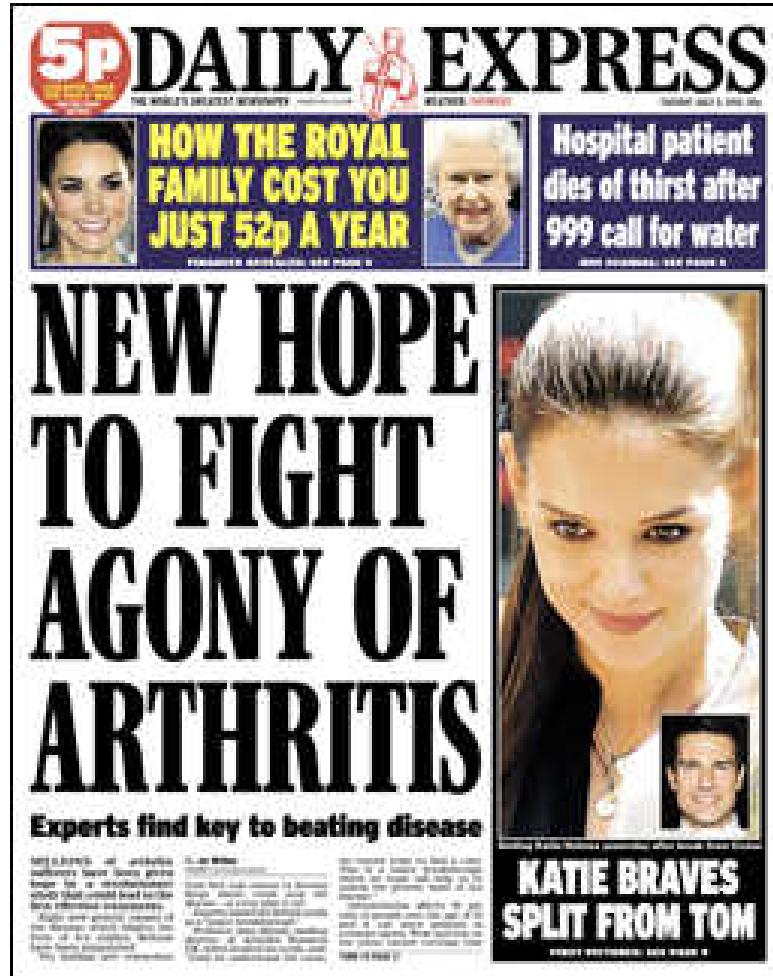


**Combined analysis**

14,883 cases and 55,775 controls

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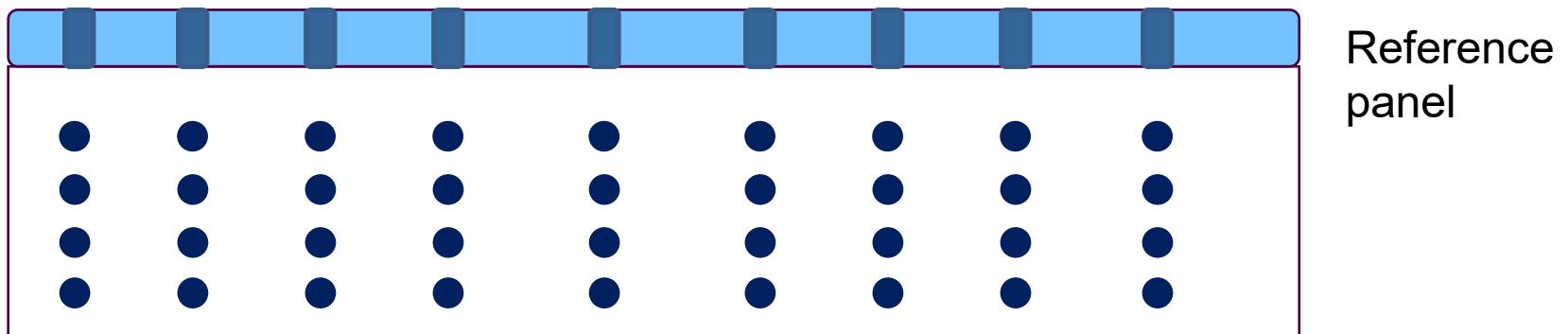
# arcOGEN finds 9 new OA risk variants



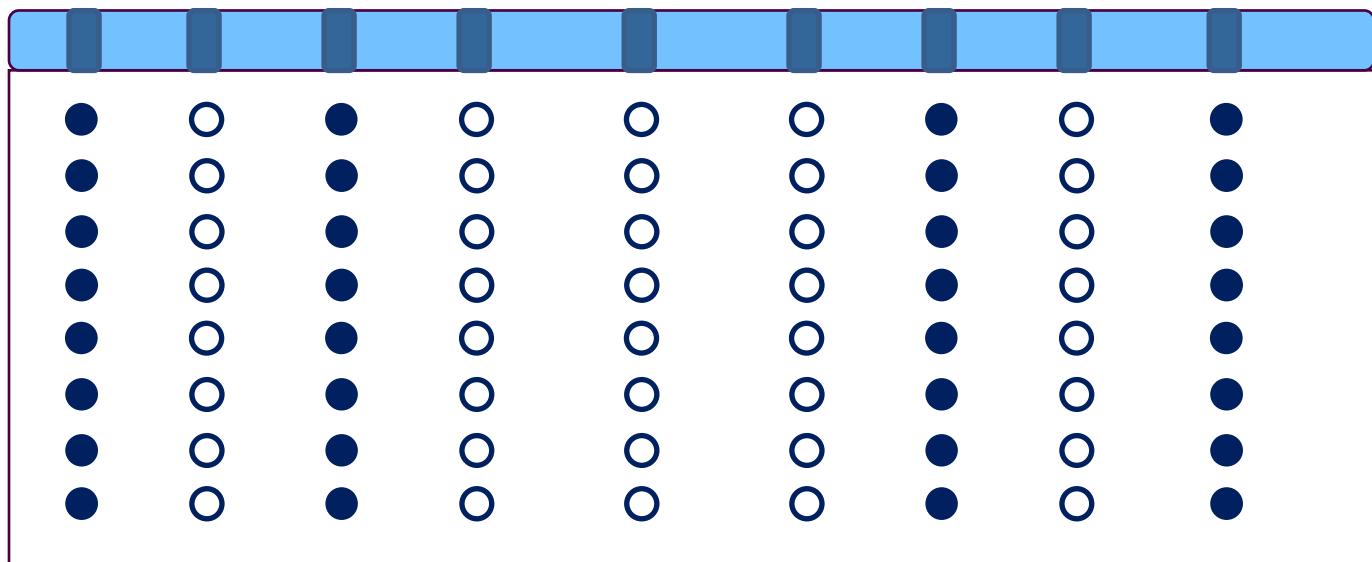
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# Imputation

# Imputation -principles



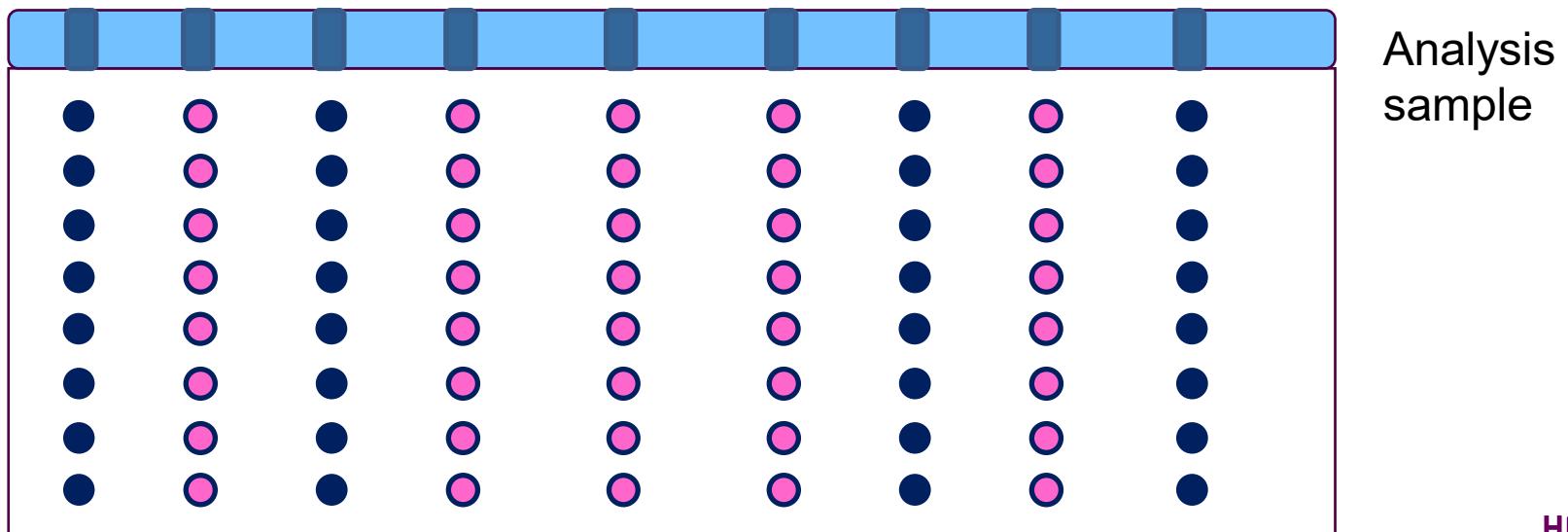
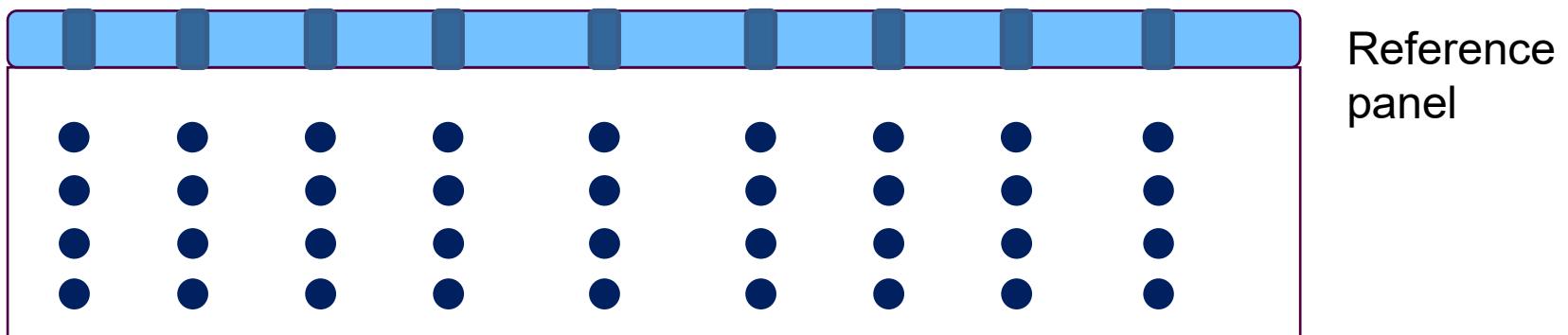
Reference  
panel



Analysis  
sample

chromosomal position

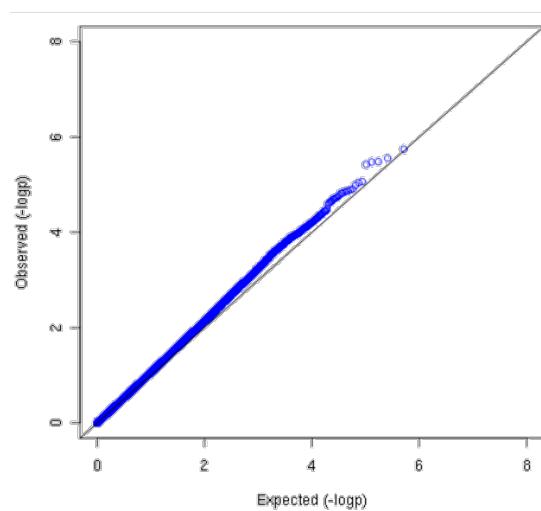
# Imputation -principles



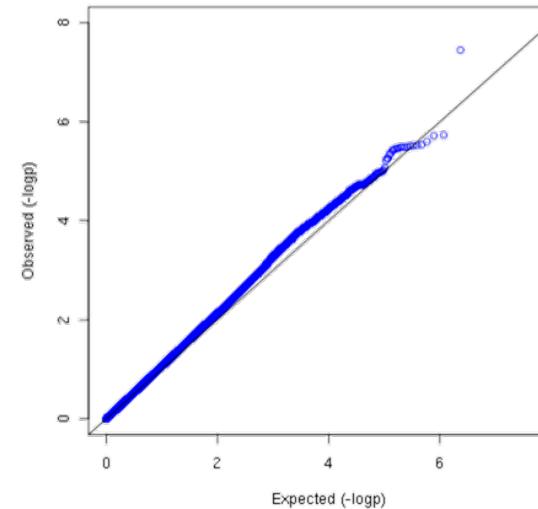
chromosomal position

3,177 cases  
4,854 controls

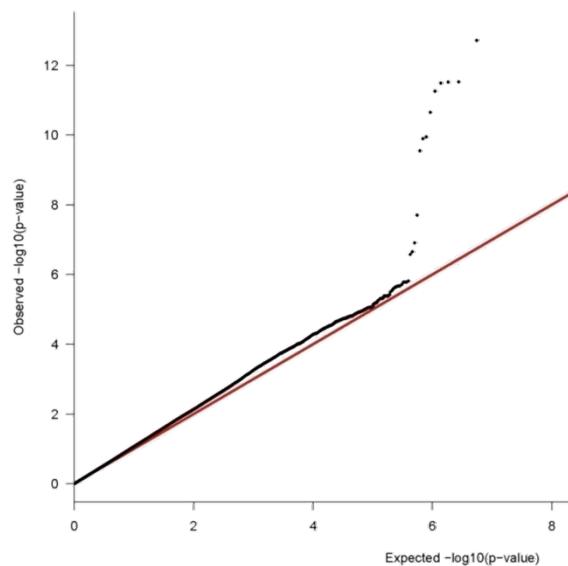
Directly typed SNPs (Illumina 610k)



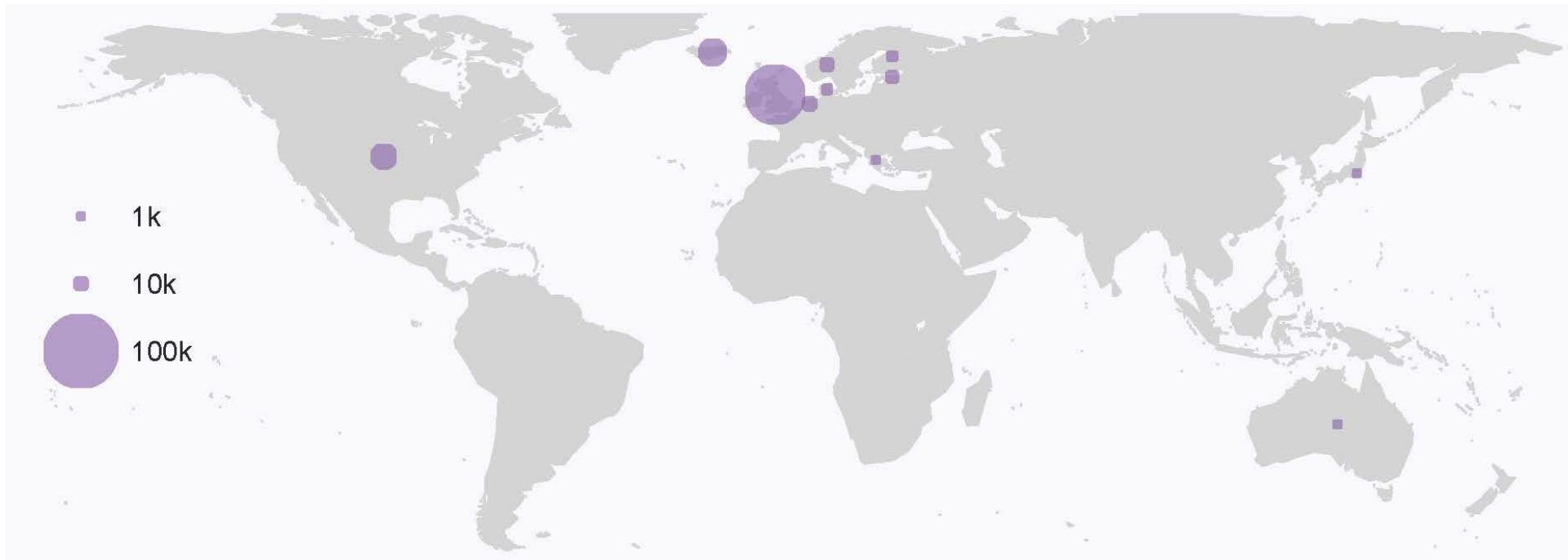
Imputed SNPs: HapMap



Imputed SNPs: 1000 genomes



# GO -Genetics of Osteoarthritis



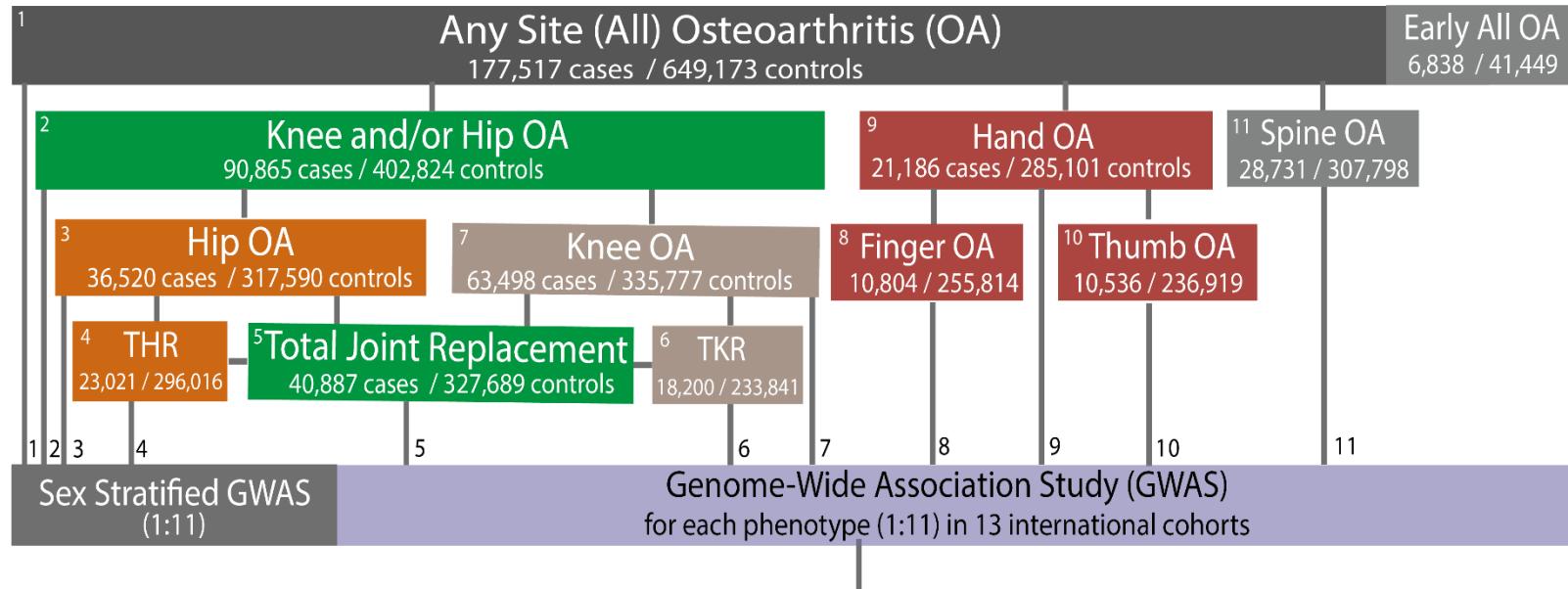
180,000 cases, 1M controls



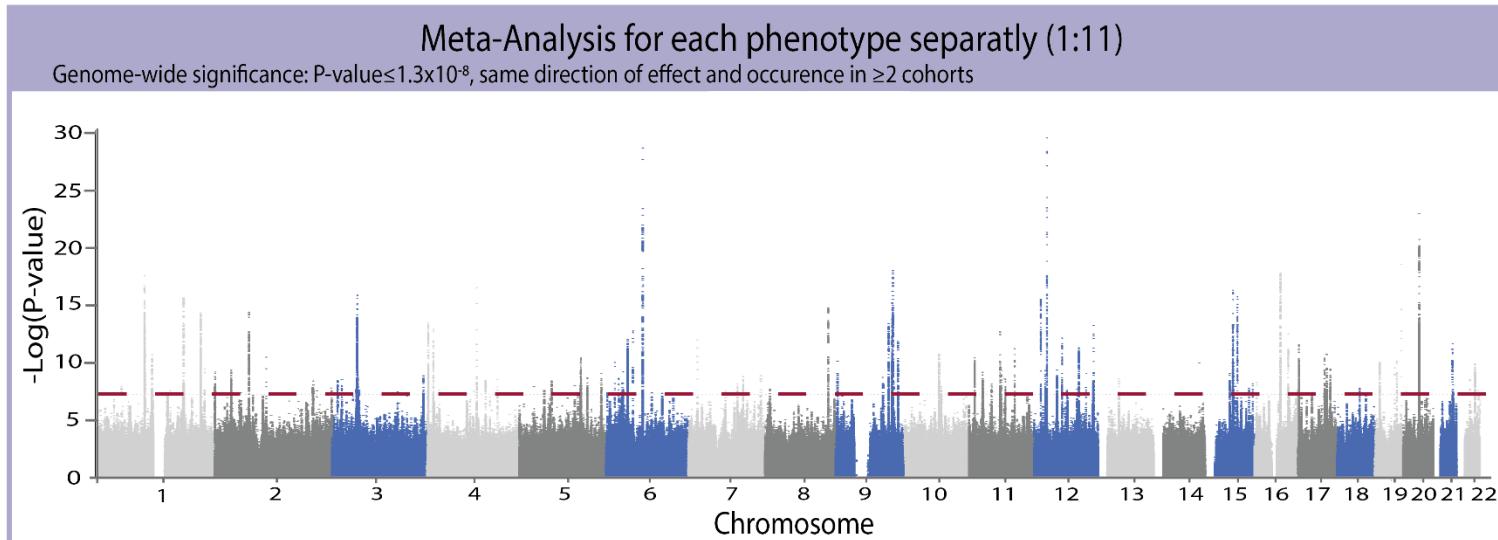
<https://www.genetics-osteoarthritis.com>

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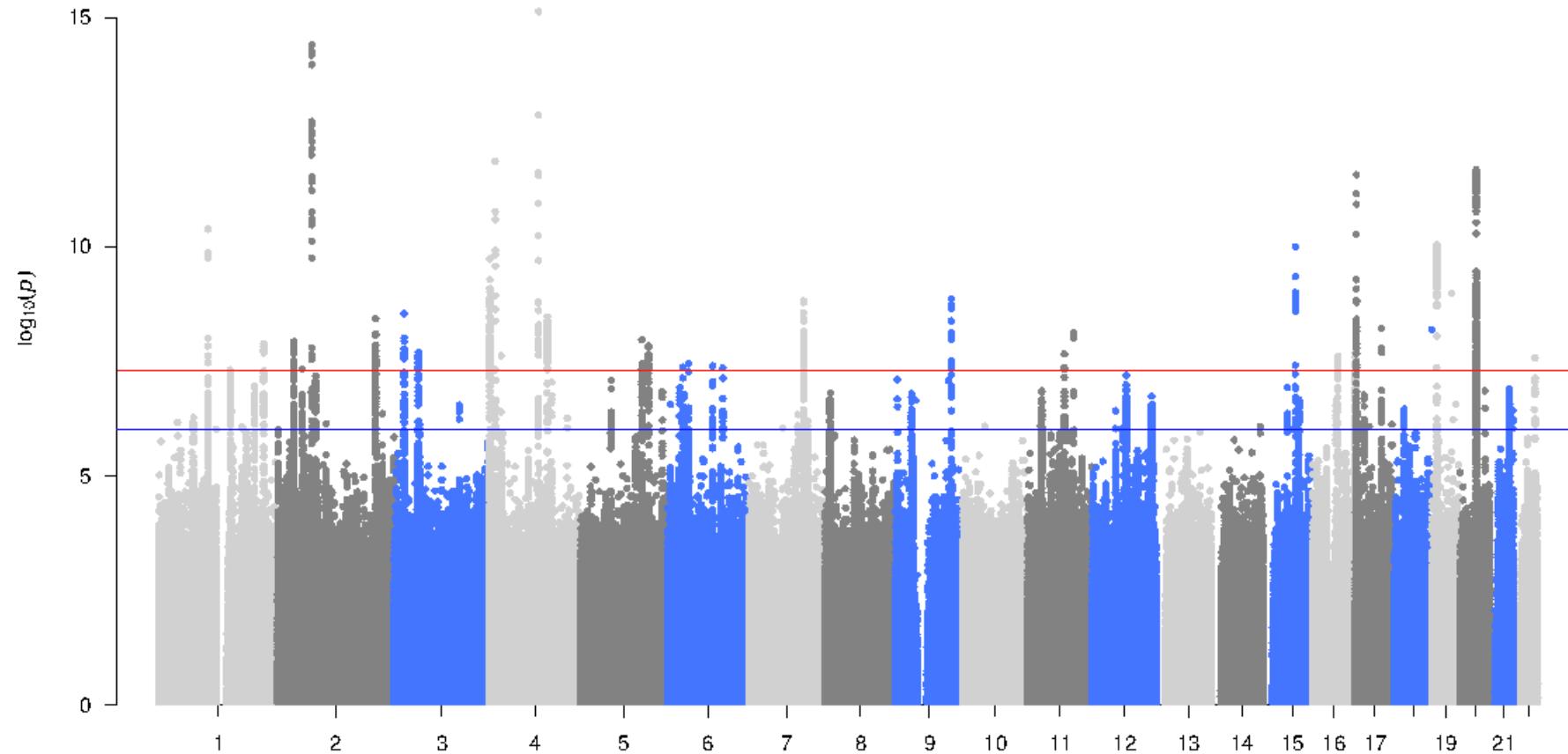
A

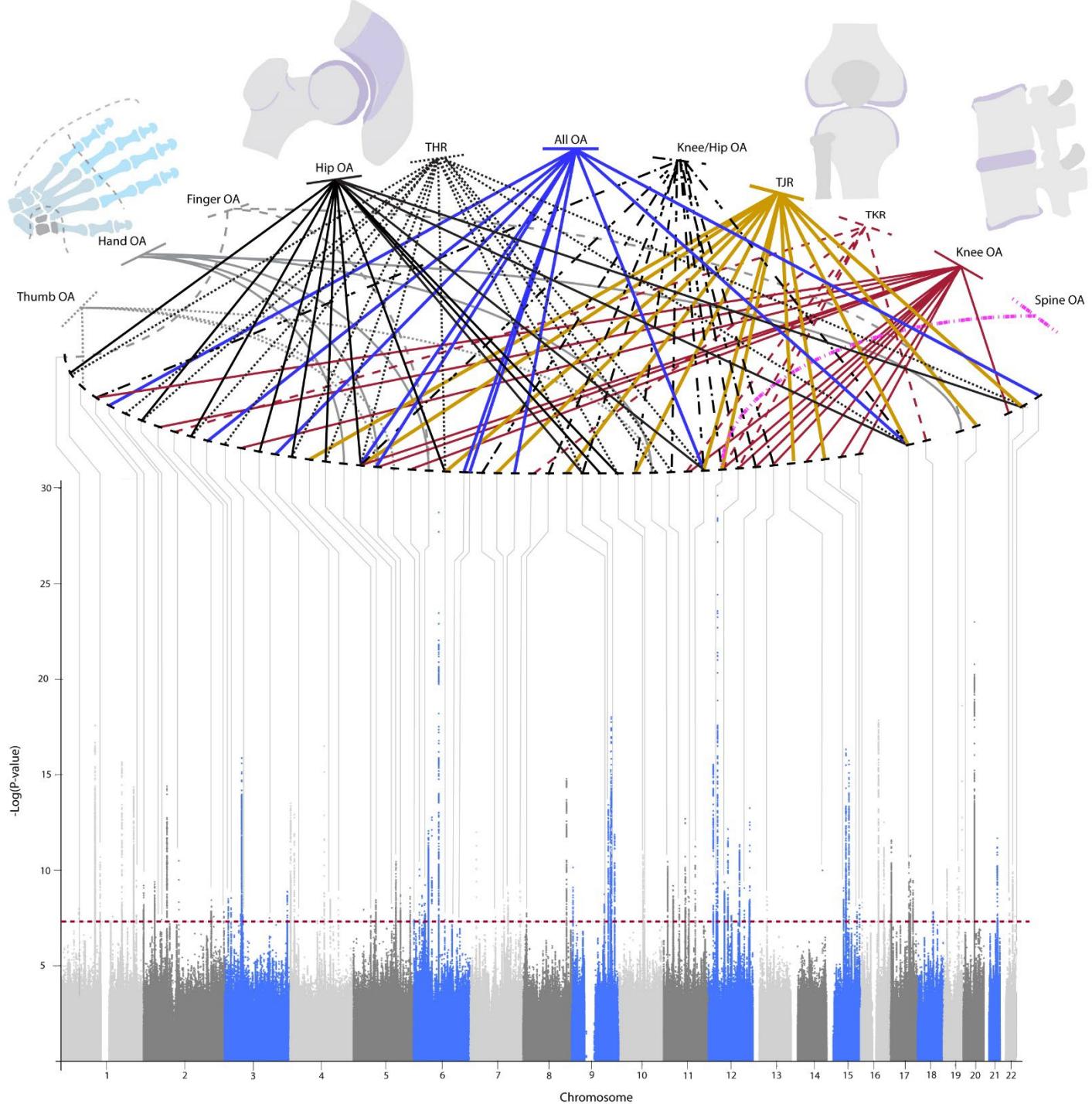


B



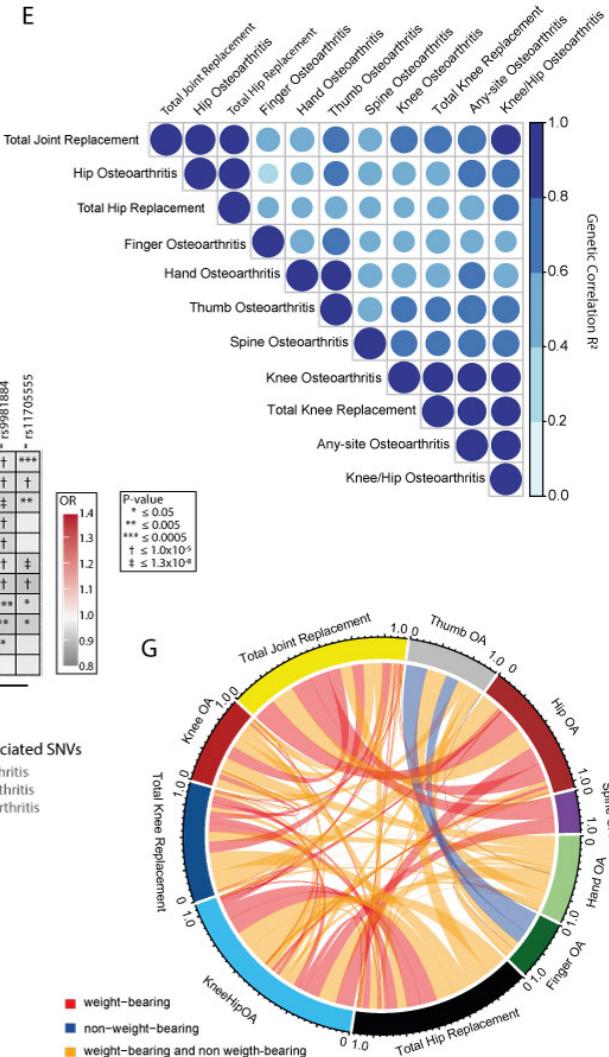
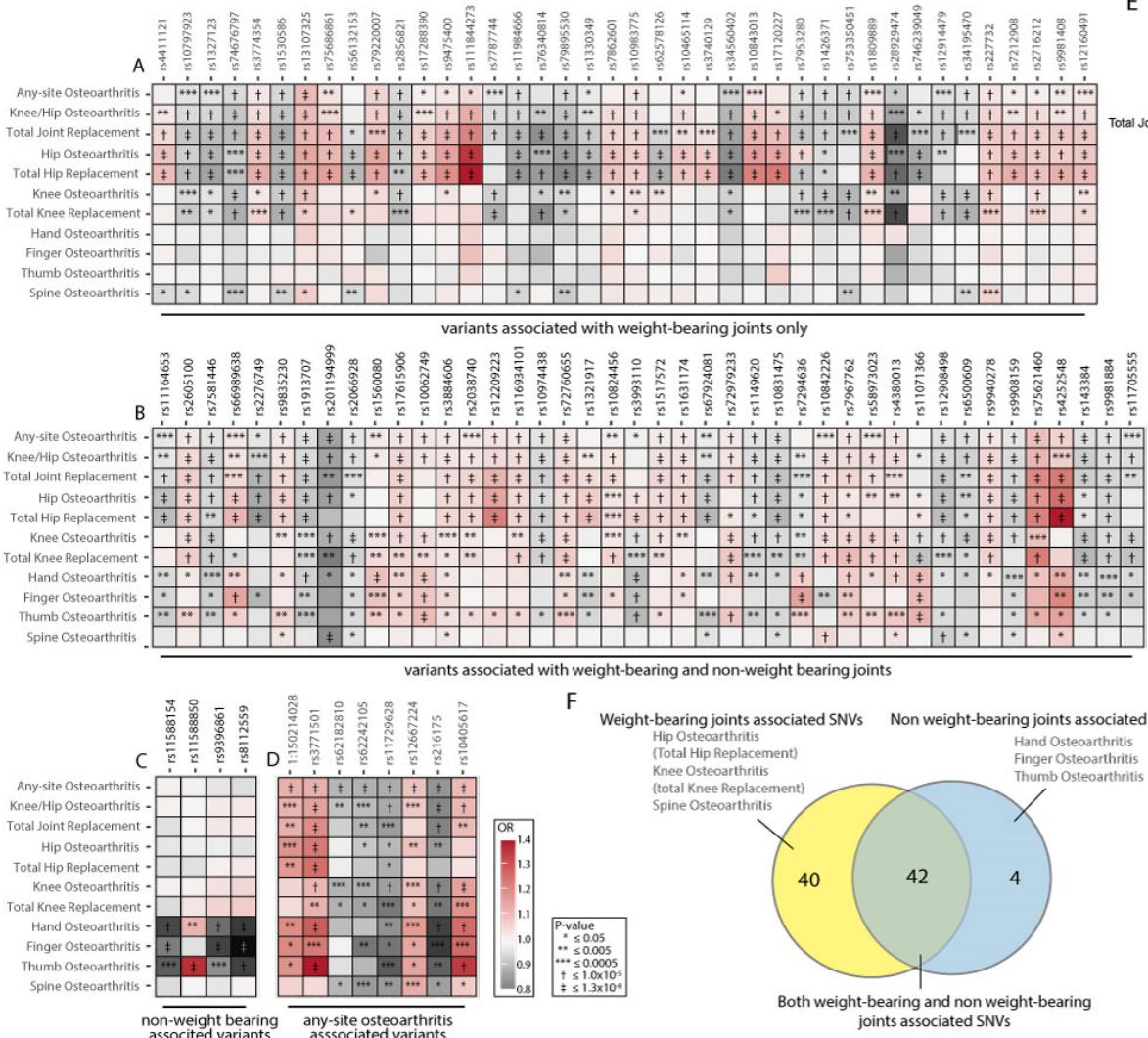
over **150** signals





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# Similarities and differences of signals across phenotypes



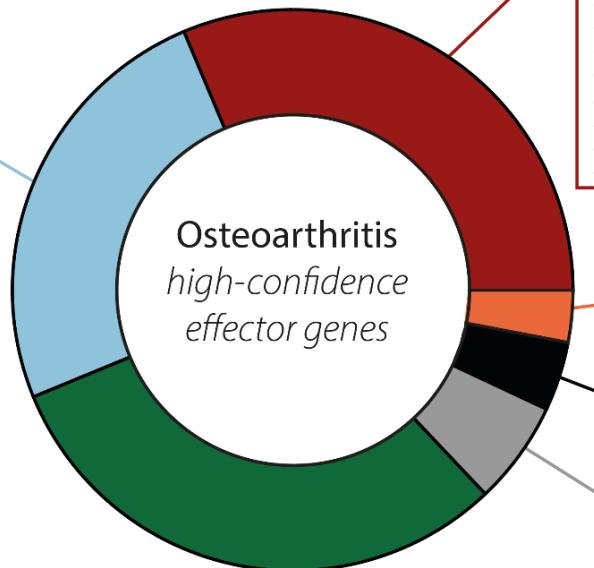
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A

### Joint Degeneration

<i>ALDH1A2</i> (rs11071366)	<i>MAP2K1</i> (rs12908498)
<i>BHLHA9</i> (rs216175)	<i>MAP2K6</i> (rs2716212)
<i>C2orf40</i> (rs66989638)	<i>MGP</i> (rs7294636)
<i>CHST3</i> (rs3740129)	<i>NR3C1</i> (rs10062749)
<i>CLIC5</i> (rs17288390)	<i>PFKM</i> (rs7967762)
<i>COL11A1</i> (rs11164653)	<i>PRKAR1A</i> (rs2716212)
<i>COL27A1</i> (rs1330349)	<i>PTCH1</i> (rs76340814)
<i>COL27A1</i> (rs72760655)	<i>RUNX2</i> (rs17288390)
<i>COL2A1</i> (rs7967762)	<i>SERPINF1</i> (rs216175)
<i>CREBBP</i> (rs6500609)	<i>SH3PXD2B</i> (rs3884606)
<i>CTSK</i> (1:150214028)	<i>SMARCA4</i> (rs10405617)
<i>CUX1</i> (rs116934101)	<i>SNAP47</i> (rs11588850)
<i>CYP19A1</i> (rs4380013)	<i>TACC3</i> (rs1530586)
<i>ERF</i> (rs75621460)	<i>TBX4</i> (rs7212908)
<i>ERG</i> (rs9981408)	<i>TGFA</i> (rs3771501)
<i>FBN2</i> (rs17615906)	<i>TGFB1</i> (rs75621460)
<i>FGF18</i> (rs3884606)	<i>TLR4</i> (rs10983775)
<i>GDF5</i> (rs143384)	<i>TNC</i> (rs1330349)
<i>HFE</i> (rs79220007)	<i>TNFSF11</i> (rs58973023)
<i>IDUA</i> (rs1530586)	<i>TRIOBP</i> (rs12160491)
<i>IGF1R</i> (rs12914479)	<i>TSEN15</i> (rs1327123)
<i>IL11</i> (rs4252548)	<i>VDR</i> (rs7967762)
<i>ILF3</i> (rs10405617)	<i>WNT1</i> (rs7967762)
<i>LTBP1</i> (rs7581446)	<i>WNT10B</i> (rs7967762)
<i>LTBP3</i> (rs67924081)	<i>WWP2</i> (rs34195470)

### Osteoarthritis high-confidence effector genes



### Skeletal Development

<i>ALDH1A2</i> (rs11071366)	<i>FGFR3</i> (rs1530586)	<i>MYO6</i> (rs12209223)	<i>SMO</i> (rs143083812)
<i>APOE</i> (rs8112559)	<i>FTO</i> (rs9940278)	<i>NOG</i> (rs227732)	<i>SNAP47</i> (rs11588850)
<i>BHLHA9</i> (rs216175)	<i>GDF5</i> (rs143384)	<i>NOG</i> (rs908159)	<i>TACC3</i> (rs1530586)
<i>C2orf40</i> (rs66989638)	<i>HFE</i> (rs79220007)	<i>NOS3</i> (rs7787744)	<i>TBX4</i> (rs7212908)
<i>CHST3</i> (rs3740129)	<i>CHST3</i> (rs3740129)	<i>PIK3R1</i> (rs56132153)	<i>TEAD1</i> (rs3993110)
<i>CLIC5</i> (rs17288390)	<i>COL11A1</i> (rs11164653)	<i>PIK3R1</i> (rs1530586)	<i>TGFA</i> (rs3771501)
<i>COL2A1</i> (rs7967762)	<i>COL27A1</i> (rs1330349)	<i>PTCH1</i> (rs76340814)	<i>TGFB1</i> (rs75621460)
<i>CREBBP</i> (rs6500609)	<i>COL27A1</i> (rs72760655)	<i>PTHLH</i> (rs10843013)	<i>TLR4</i> (rs10983775)
<i>CTSK</i> (1:150214028)	<i>COL2A1</i> (rs7967762)	<i>RNF144B</i> (rs9396861)	<i>TSEN15</i> (rs1327123)
<i>CUX1</i> (rs116934101)	<i>CTSK</i> (1:150214028)	<i>RPGRIP1L</i> (rs9940278)	<i>TWIST1</i> (rs111844273)
<i>CYP19A1</i> (rs4380013)	<i>CUX1</i> (rs116934101)	<i>RUNX2</i> (rs10465114)	<i>VDR</i> (rs7967762)
<i>ERF</i> (rs75621460)	<i>CYP19A1</i> (rs4380013)	<i>SH3PXD2B</i> (rs3884606)	<i>VGLL4</i> (rs2276749)
<i>ERG</i> (rs9981408)	<i>ERF</i> (rs75621460)	<i>SERPINF1</i> (rs216175)	<i>WNT1</i> (rs7967762)
<i>FBN2</i> (rs17615906)	<i>ERG</i> (rs9981408)	<i>SH3PXD2B</i> (rs3884606)	<i>WWP2</i> (rs34195470)
<i>FGF18</i> (rs3884606)	<i>FBN2</i> (rs17615906)	<i>SMAD3</i> (rs12908498)	
<i>GDF5</i> (rs143384)	<i>FGF18</i> (rs3884606)	<i>SMAD3</i> (rs12908498)	
<i>HFE</i> (rs79220007)	<i>FTO</i> (rs9940278)	<i>SMARCA4</i> (rs10405617)	
<i>IDUA</i> (rs1530586)	<i>GDF5</i> (rs143384)	<i>SMARCA4</i> (rs10405617)	
<i>IGF1R</i> (rs12914479)	<i>HFE</i> (rs79220007)	<i>SP1</i> (rs1149620)	
<i>IL11</i> (rs4252548)	<i>IDUA</i> (rs1530586)	<i>TGFB1</i> (rs75621460)	
<i>ILF3</i> (rs10405617)	<i>IGF1R</i> (rs12914479)	<i>WNT10B</i> (rs7967762)	
<i>LTBP1</i> (rs7581446)	<i>KCNJ6</i> (rs9981408)		
<i>LTBP3</i> (rs67924081)	<i>LCRTR2</i> (rs9475400)		

### Neuronal Function & Development

<i>ALDH1A2</i> (rs11071366)	<i>CYP19A1</i> (rs4380013)	<i>IDUA</i> (rs1530586)	<i>NOG</i> (rs9908159)	<i>SERPINF1</i> (rs216175)	<i>TLR4</i> (rs10983775)
<i>APOE</i> (rs8112559)	<i>ENHO</i> (rs10453201)	<i>IGF1R</i> (rs12914479)	<i>NOS3</i> (rs7787744)	<i>SF3B4</i> (1:150214028)	<i>TNC</i> (rs1330349)
<i>BHLHA9</i> (rs216175)	<i>ERF</i> (rs75621460)	<i>KCNJ6</i> (rs9981408)	<i>NR3C1</i> (rs10062749)	<i>SH3PXD2B</i> (rs3884606)	<i>TRIOBP</i> (rs12160491)
<i>C2orf40</i> (rs66989638)	<i>FBN2</i> (rs17615906)	<i>LMX1B</i> (rs10465114)	<i>PFKM</i> (rs7967762)	<i>SMAD3</i> (rs12908498)	<i>TSEN15</i> (rs1327123)
<i>CHRM2</i> (rs571734653)	<i>FGFR3</i> (rs1530586)	<i>LMX1B</i> (rs62578126)	<i>PIK3R1</i> (rs56132153)	<i>SMARCA4</i> (rs10405617)	<i>TSKU</i> (rs1149620)
<i>CHST3</i> (rs3740129)	<i>FTO</i> (rs9940278)	<i>MAP2K1</i> (rs12908498)	<i>PRKAR1A</i> (rs2716212)	<i>SMO</i> (rs143083812)	<i>TWIST1</i> (rs111844273)
<i>CLIC5</i> (rs17288390)	<i>GDF5</i> (rs143384)	<i>MEGF8</i> (rs75621460)	<i>PTCH1</i> (rs76340814)	<i>SNAP47</i> (rs11588850)	<i>USP8</i> (rs4380013)
<i>COL2A1</i> (rs7967762)	<i>HCRTR2</i> (rs9475400)	<i>MTMR2</i> (rs10831475)	<i>PTH1RH</i> (rs10843013)	<i>SPTBN4</i> (rs75621460)	<i>VDR</i> (rs7967762)
<i>CREBBP</i> (rs6500609)	<i>HFE</i> (rs79220007)	<i>MYO6</i> (rs12209223)	<i>RPGRIP1L</i> (rs9940278)	<i>TEAD1</i> (rs3993110)	<i>WNT1</i> (rs7967762)
<i>CTSK</i> (1:150214028)	<i>HMOX2</i> (rs6500609)	<i>NOG</i> (rs227732)	<i>RUNX2</i> (rs17288390)	<i>TGFB1</i> (rs75621460)	<i>WNT10B</i> (rs7967762)
<i>CUX1</i> (rs116934101)	<i>IARS2</i> (rs2605100)				

### Adipogenesis

<i>FTO</i> (rs9940278)	<i>RPGRIP1L</i> (rs9940278)	<i>WNT10B</i> (rs7967762)
<i>PIK3R1</i> (rs56132153)	<i>WNT1</i> (rs7967762)	<i>ENHO</i> (rs10453201)

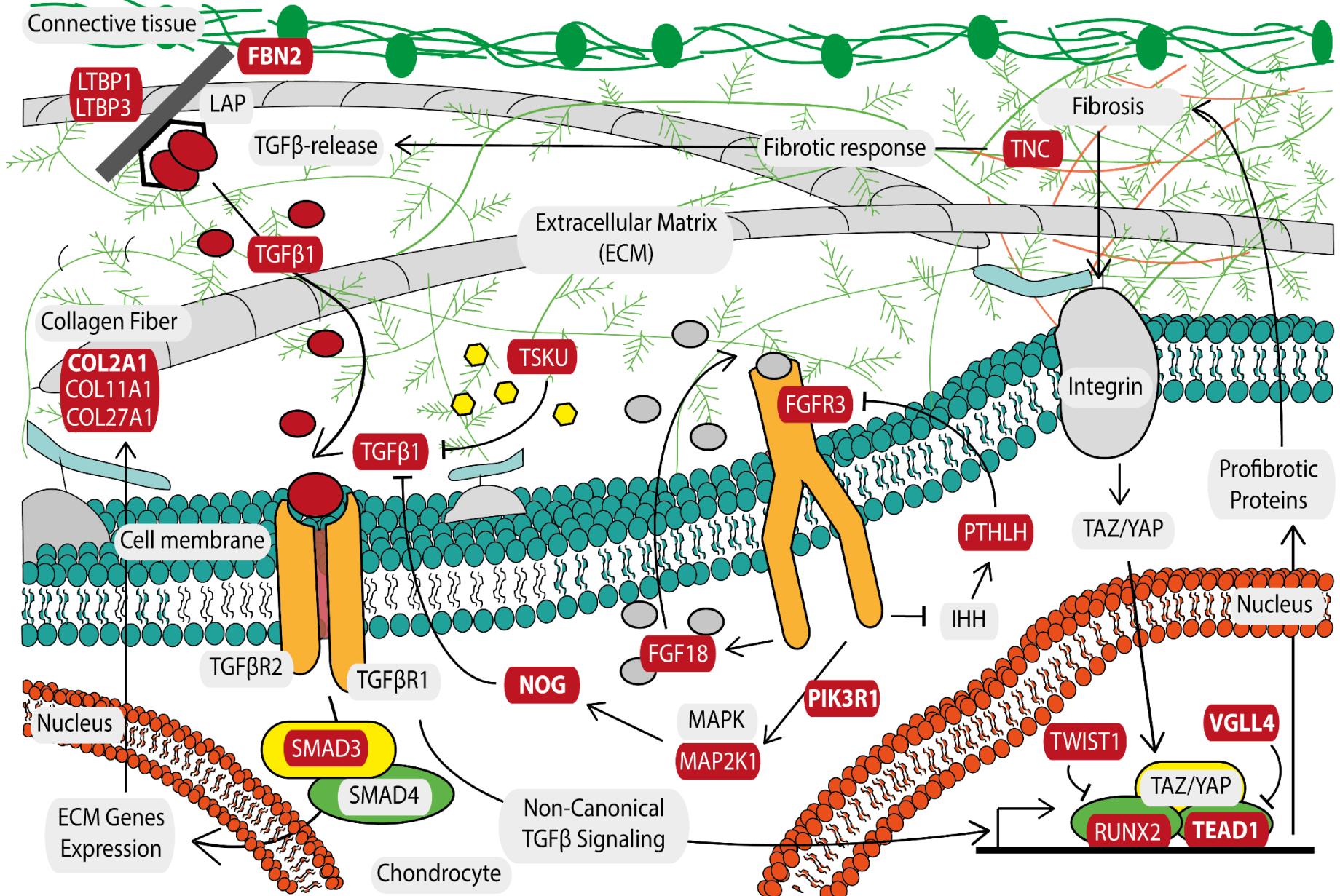
### Muscle Function

<i>CHRM2</i> (rs571734653)	<i>HMOX2</i> (rs6500609)	<i>SPTBN4</i> (rs75621460)
<i>ENHO</i> (rs10453201)	<i>KCNJ6</i> (rs9981408)	<i>TLR4</i> (rs10983775)
<i>HCRTR2</i> (rs9475400)	<i>PFKM</i> (rs7967762)	

### Immune Response & Inflammation

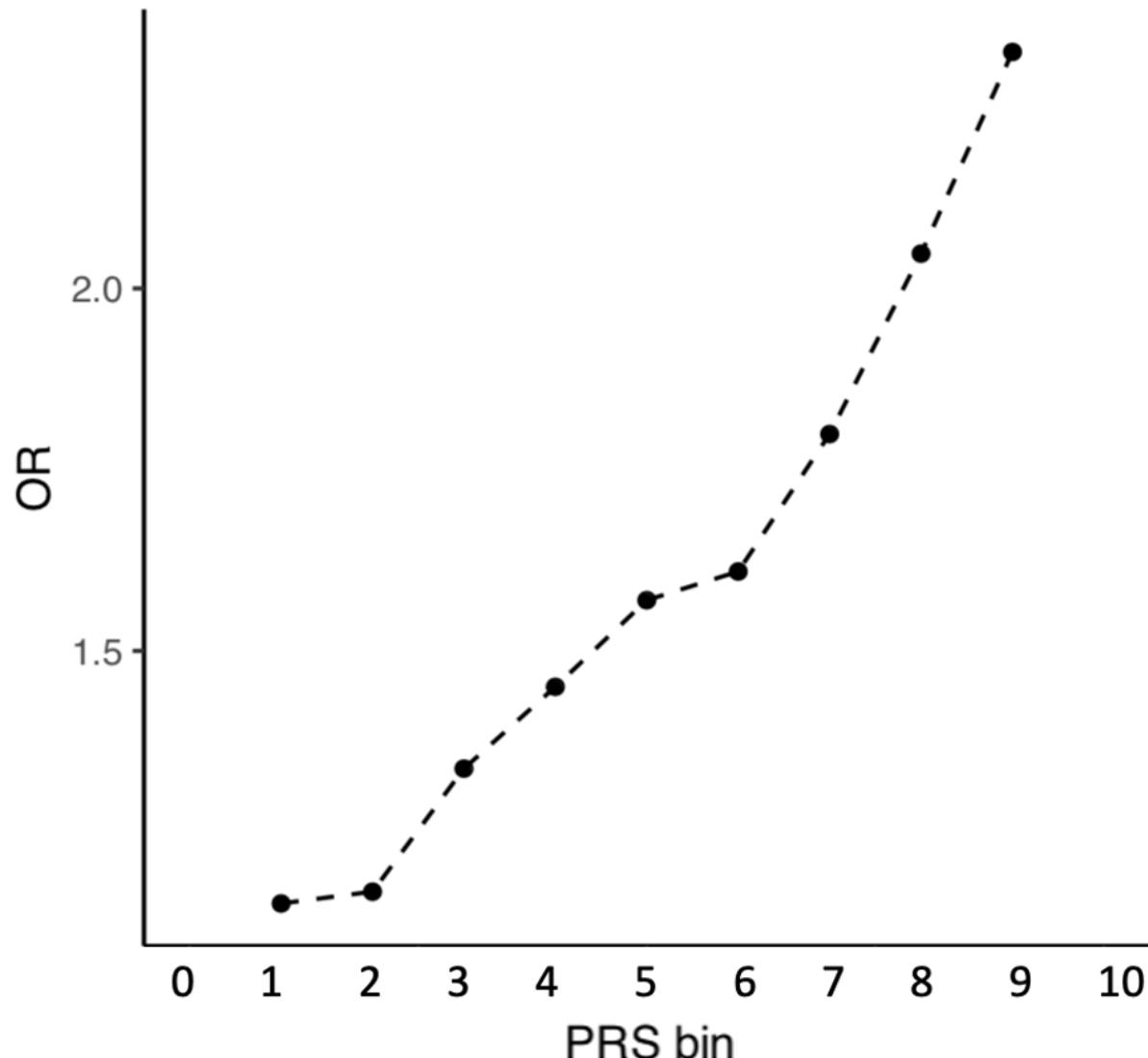
<i>APOE</i> (rs8112559)	<i>MAP2K6</i> (rs2716212)	<i>TLR4</i> (rs10983775)
<i>ERG</i> (rs9981408)	<i>NR3C1</i> (rs10062749)	<i>TNC</i> (rs1330349)
<i>IL11</i> (rs4252548)	<i>PIK3R1</i> (rs56132153)	<i>TNFSF11</i> (rs58973023)
<i>ILF3</i> (rs10405617)	<i>TGFB1</i> (rs75621460)	<i>VDR</i> (rs7967762)

B



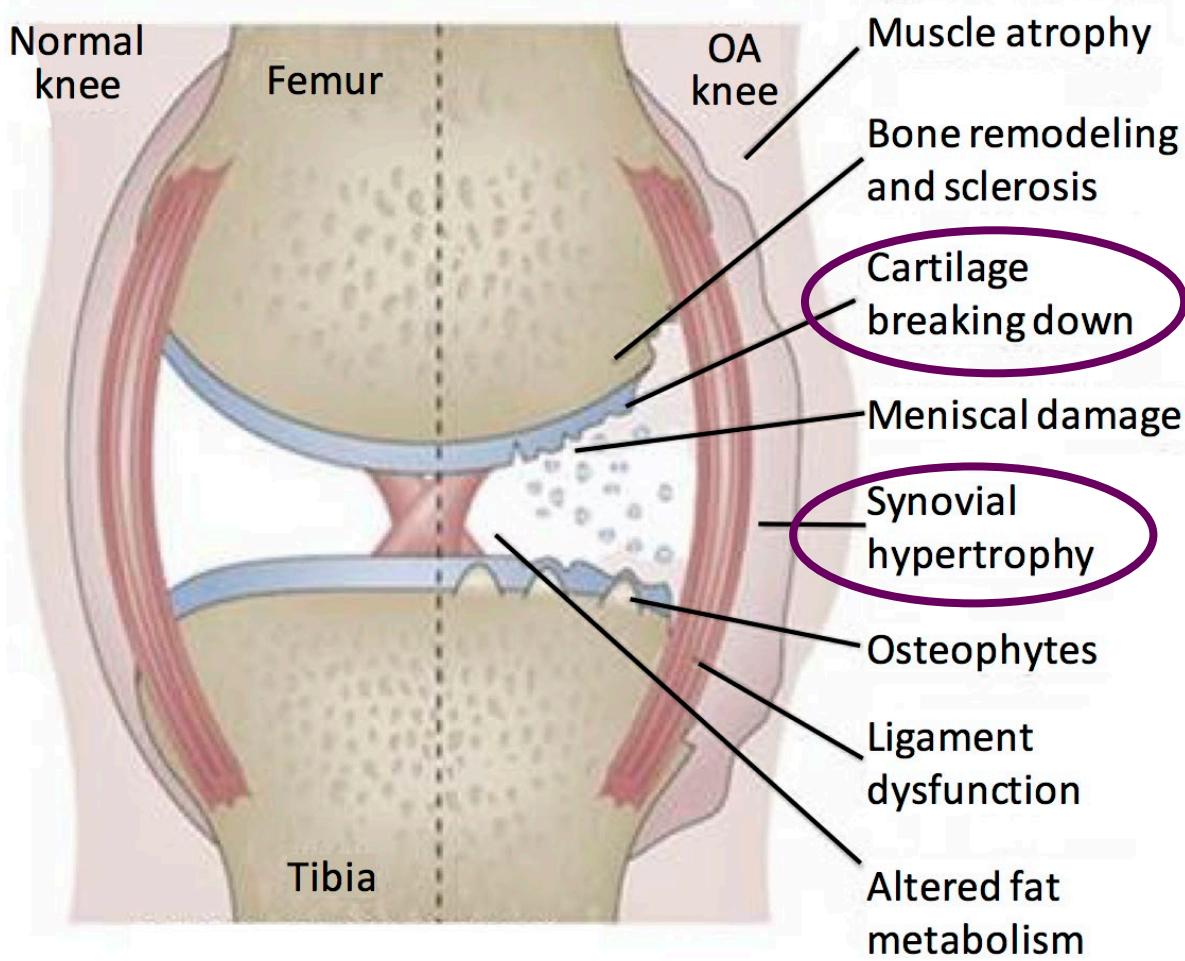
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# Total hip replacement polygenic risk score



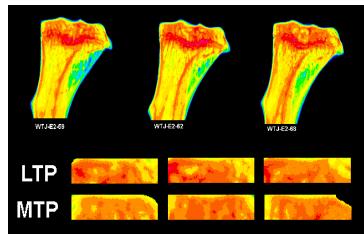
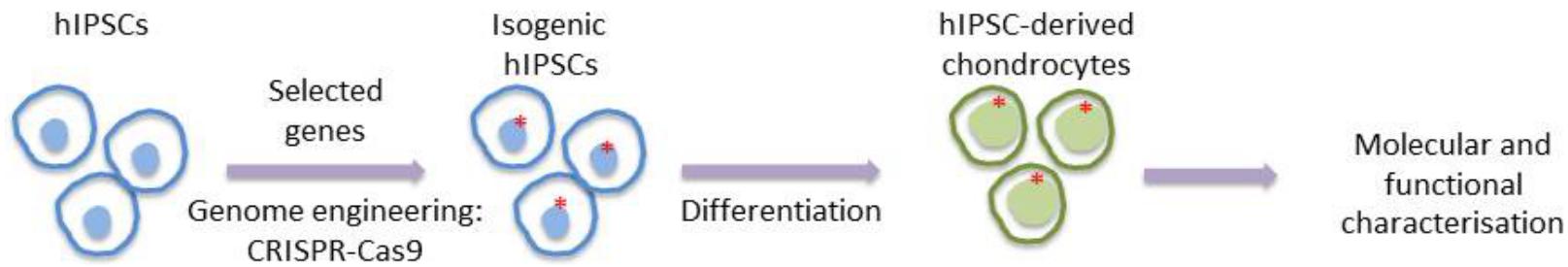
# Drug target identification

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>	Smoothened 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



The underlying molecular mechanisms of osteoarthritis pathogenesis and progression remain incompletely characterised

# Pathway to understanding mechanism of action



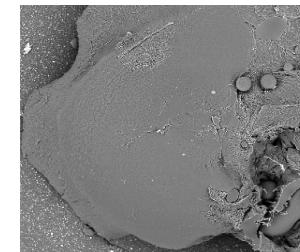
*Matn4*: low bone volume



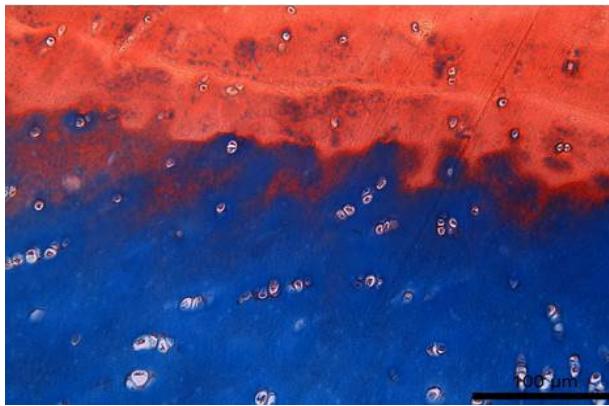
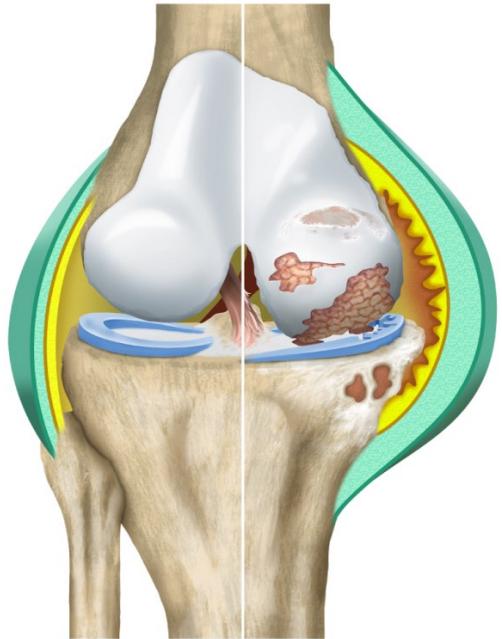
## Origins of Bone and Cartilage Disease

An international collaboration identifying genetic causes of bone and cartilage disease

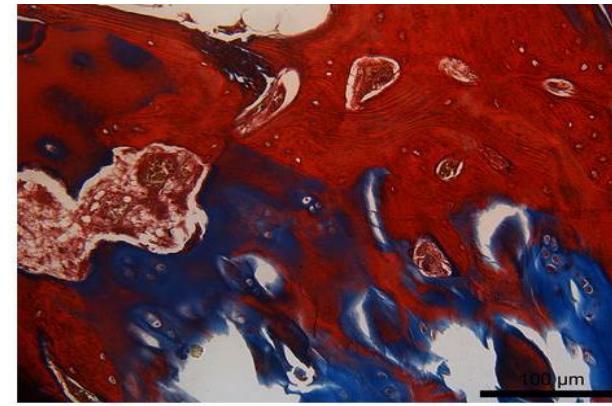
Rapid-throughput phenotyping of knockout mice



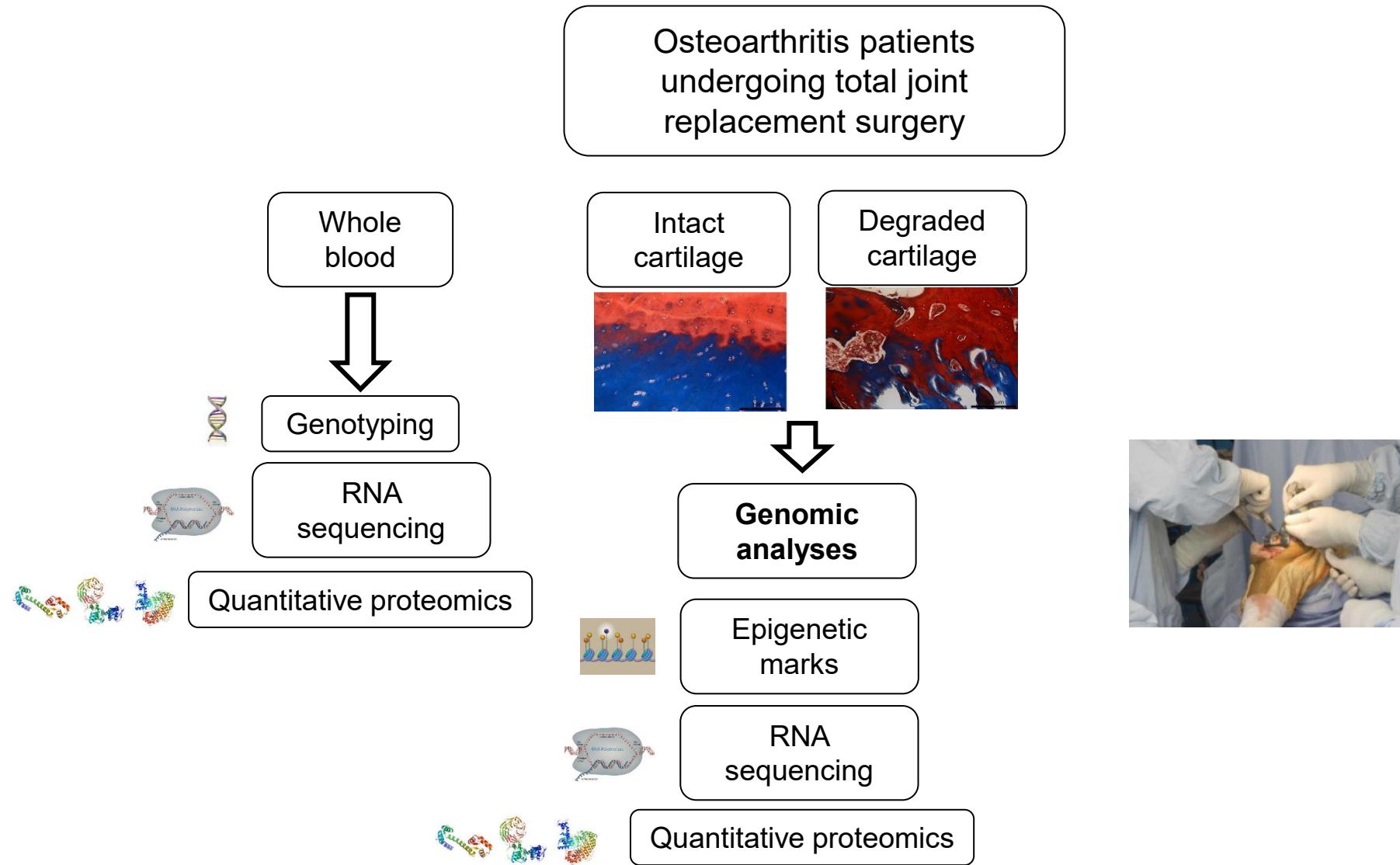
*Sqrdl*: high cartilage damage



Intact cartilage

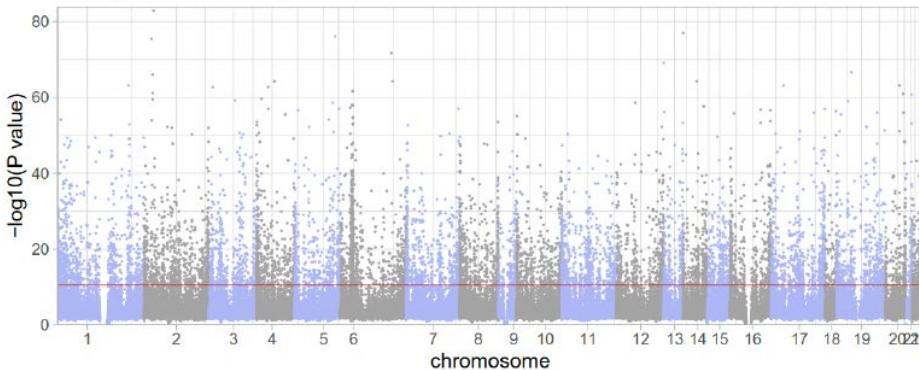


Degraded cartilage

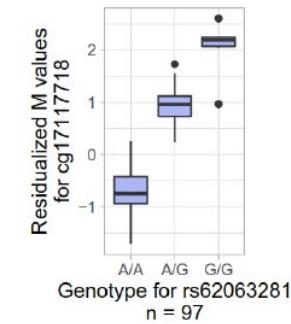


# Molecular QTL maps

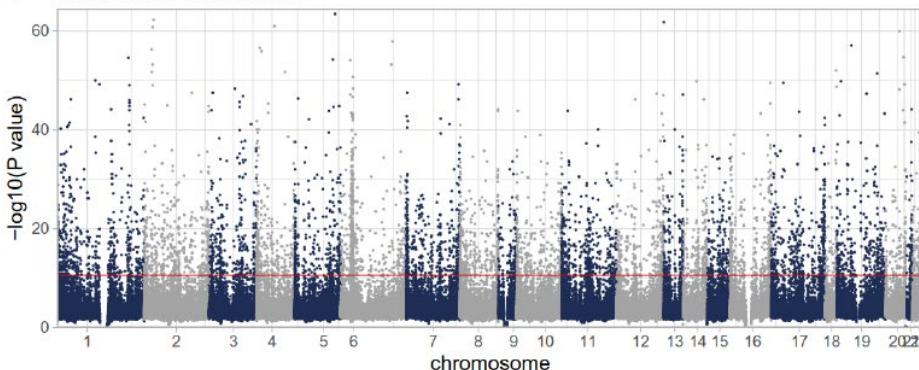
**A** Low-grade OA cartilage



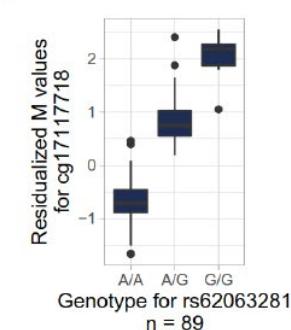
**B**



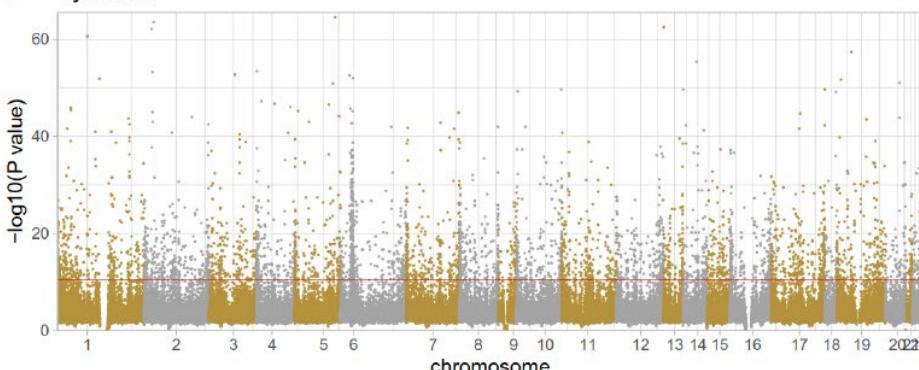
**C** High-grade OA cartilage



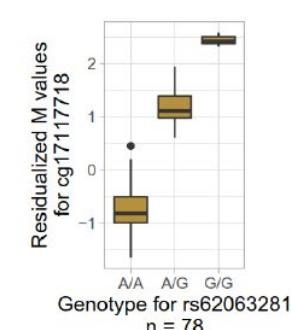
**D**



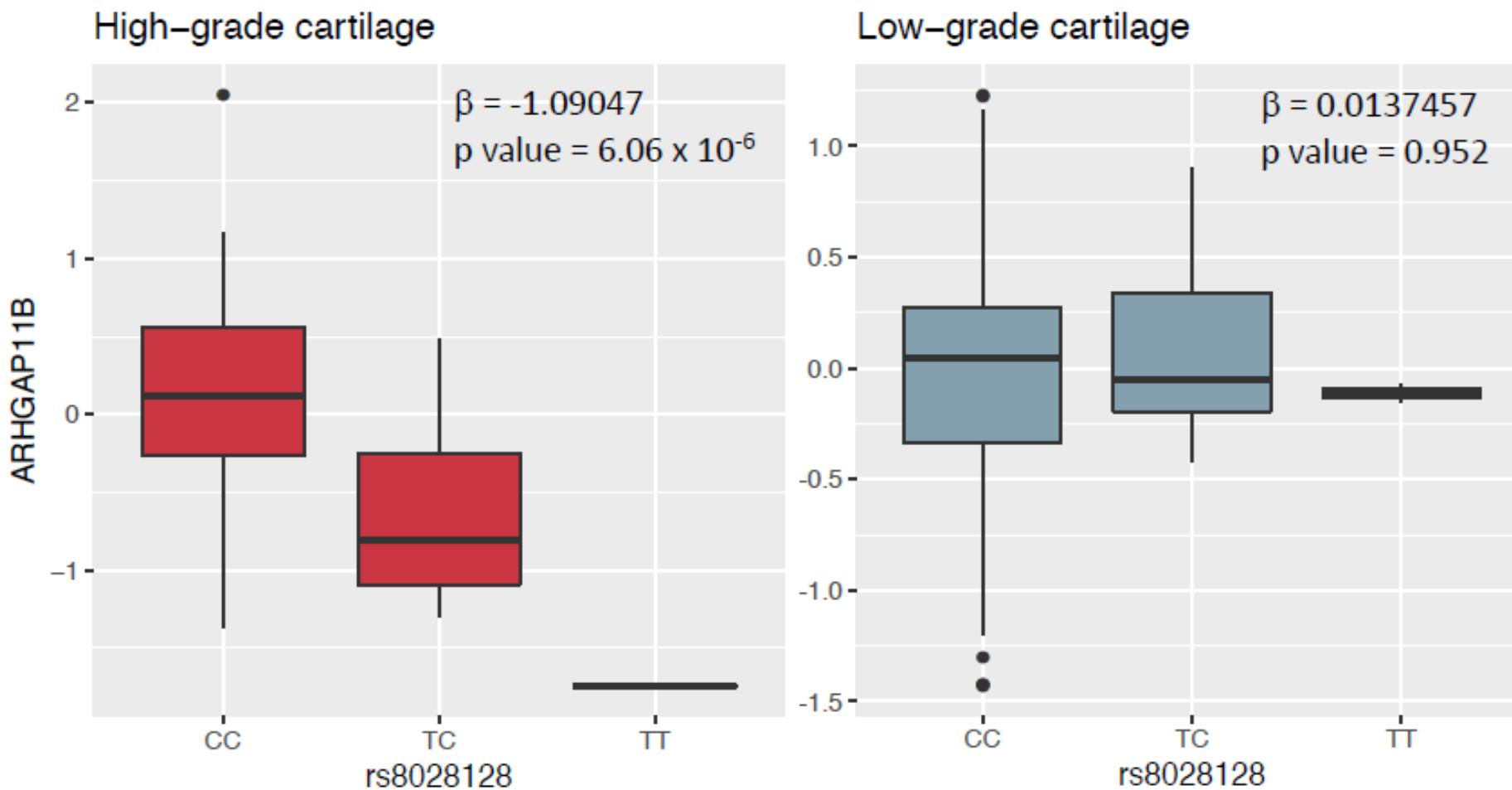
**E** Synovium



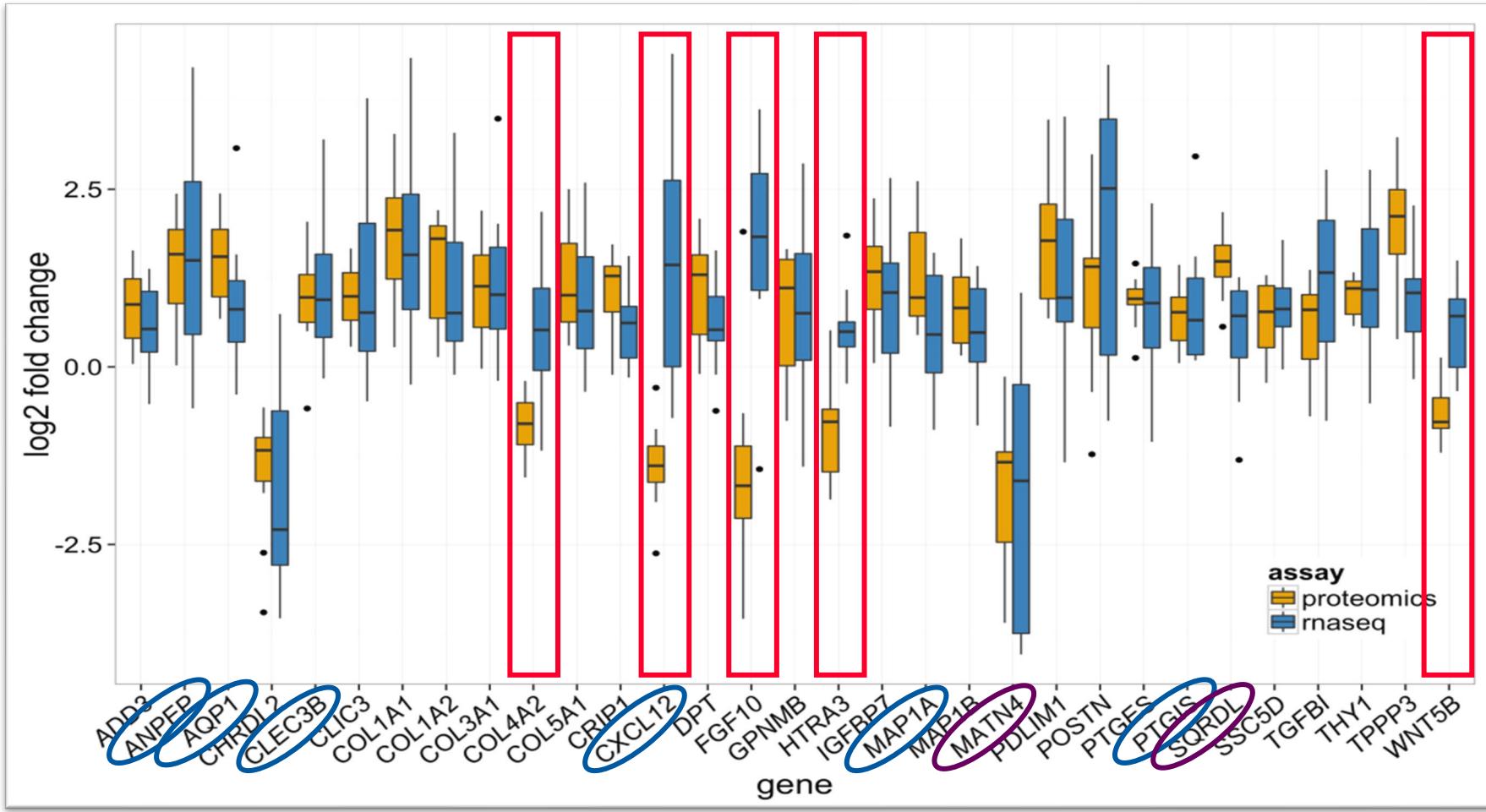
**F**



# Differential molecular QTLs

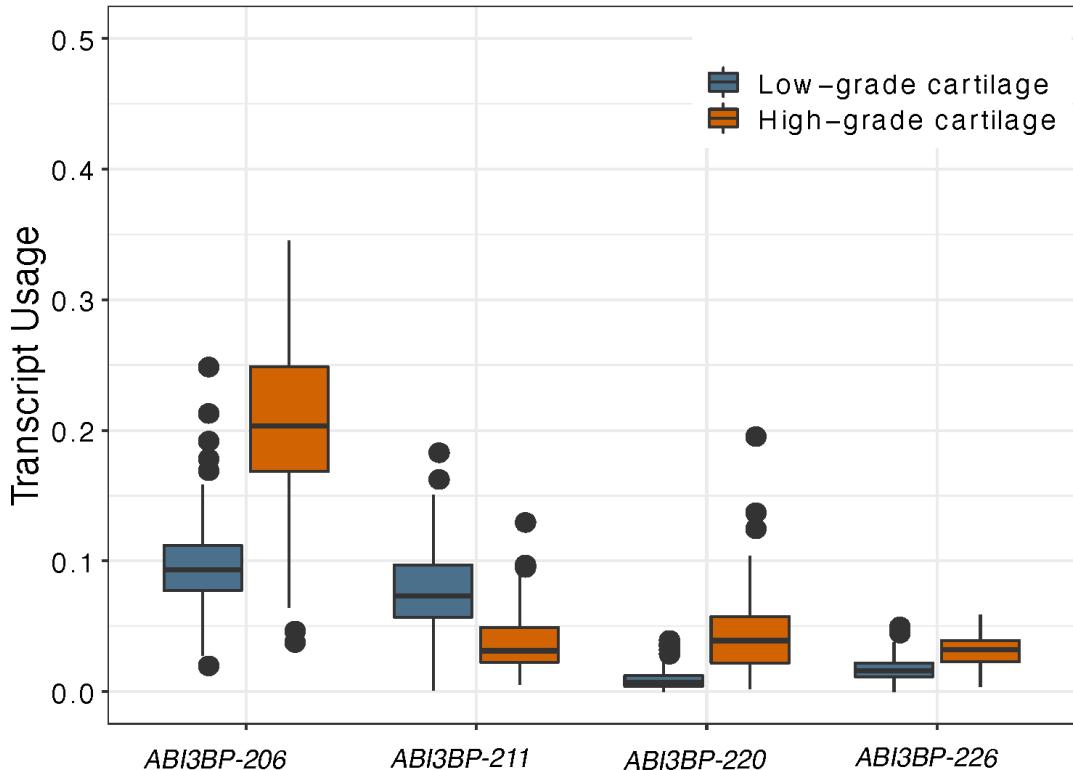


# Differentially expressed in multiple omics levels

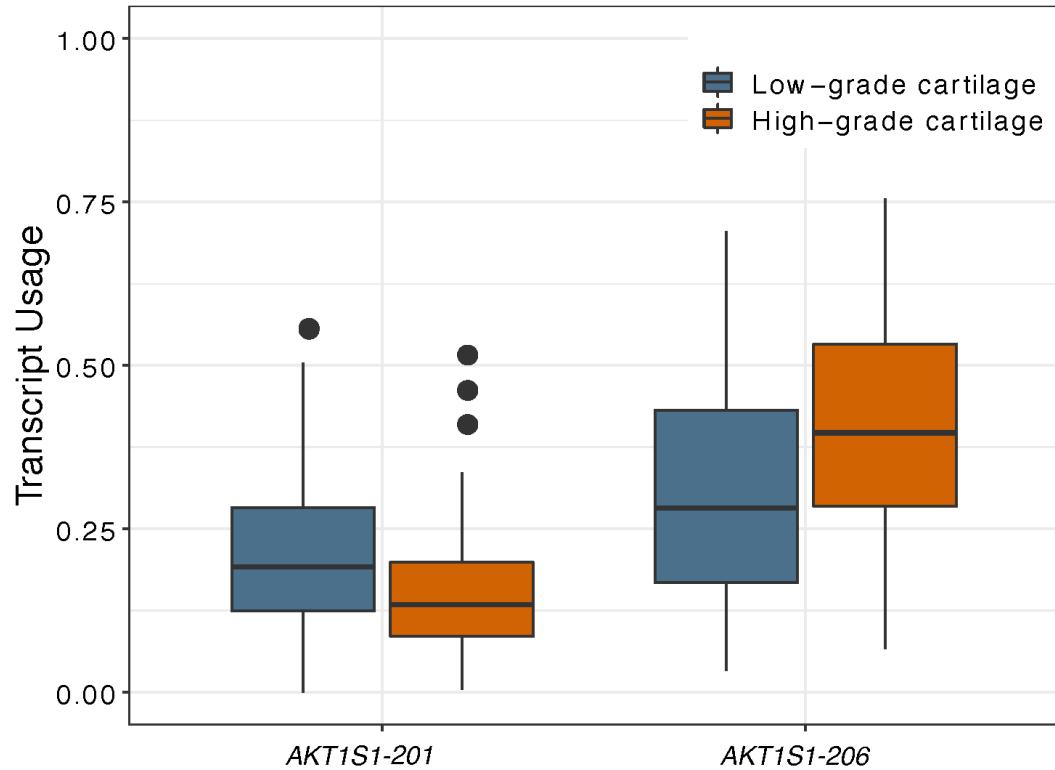


# Differential transcript usage

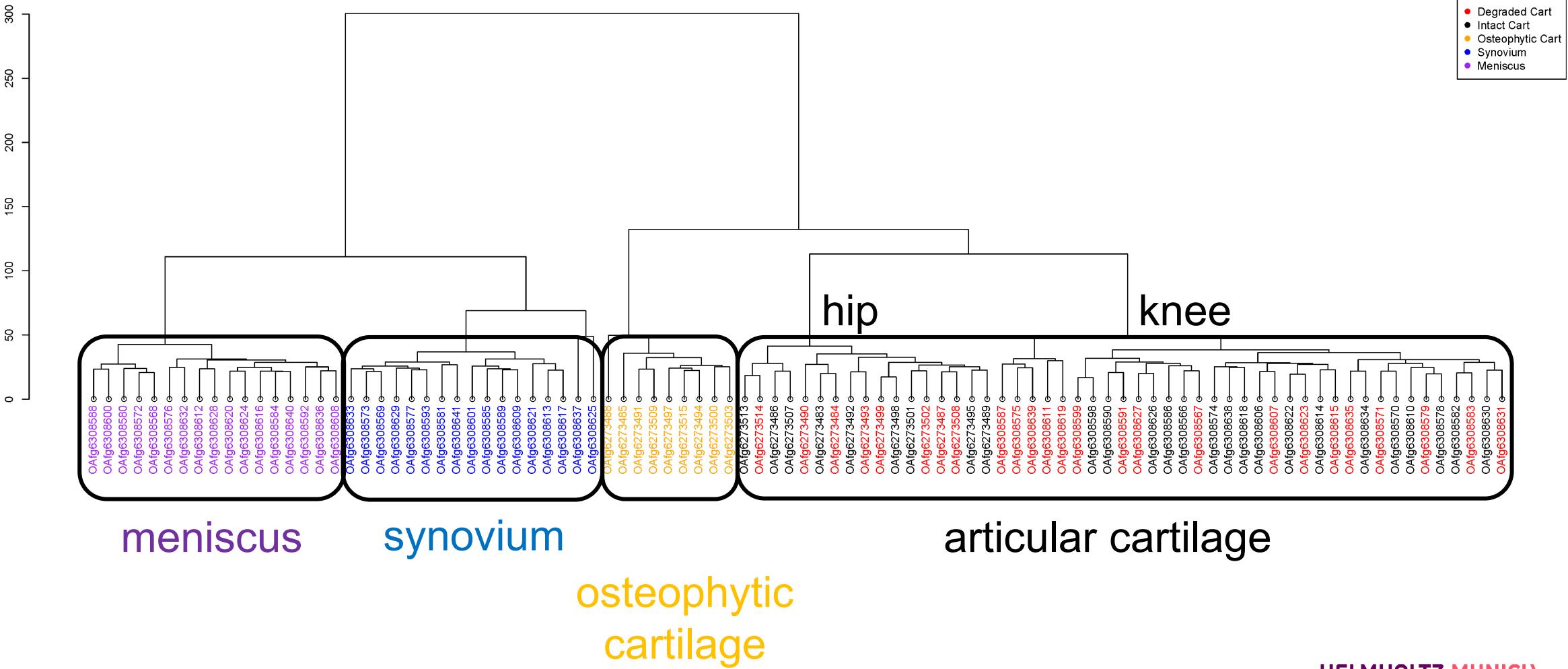
***ABI3BP***



***AKT1S1***



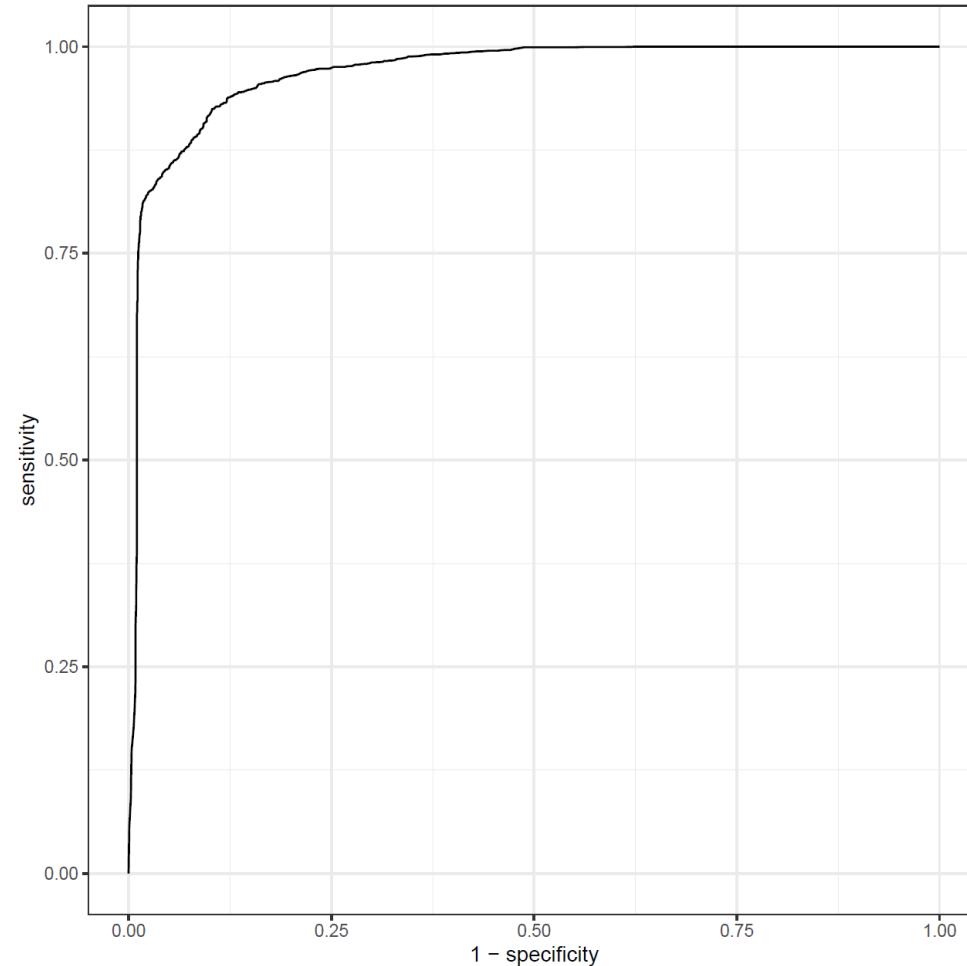
# Omics clustering by tissue



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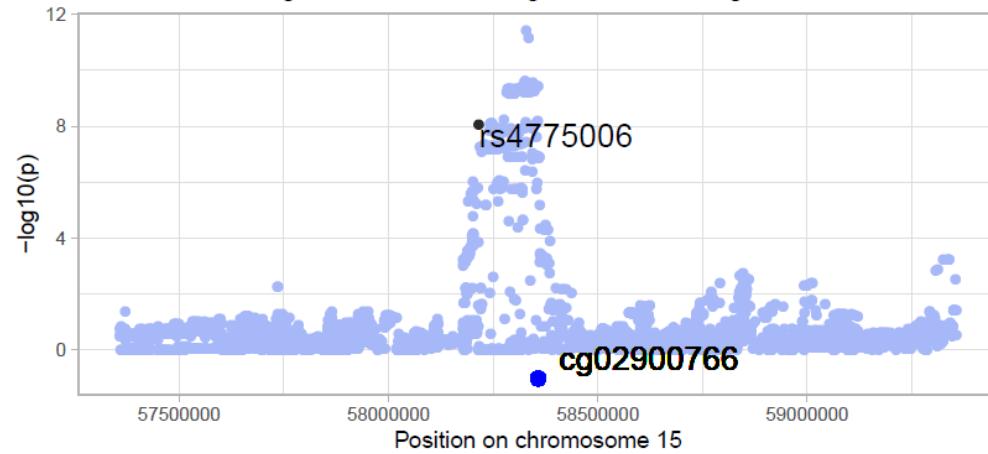
# Methylation-based classifier distinguishes between low-grade and high-grade cartilage

- Train and test random forest-based classifier in our patient cohort
  - High accuracy: 90.69% (SD: 4.71)
- Validate classifier in independent data set
  - In 17 knee osteoarthritis patients:
    - Accuracy: 82% (95% CI 0.65-0.93)
  - In 14 hip osteoarthritis patients:
    - Accuracy: 64% (95% CI 0.44-0.81)

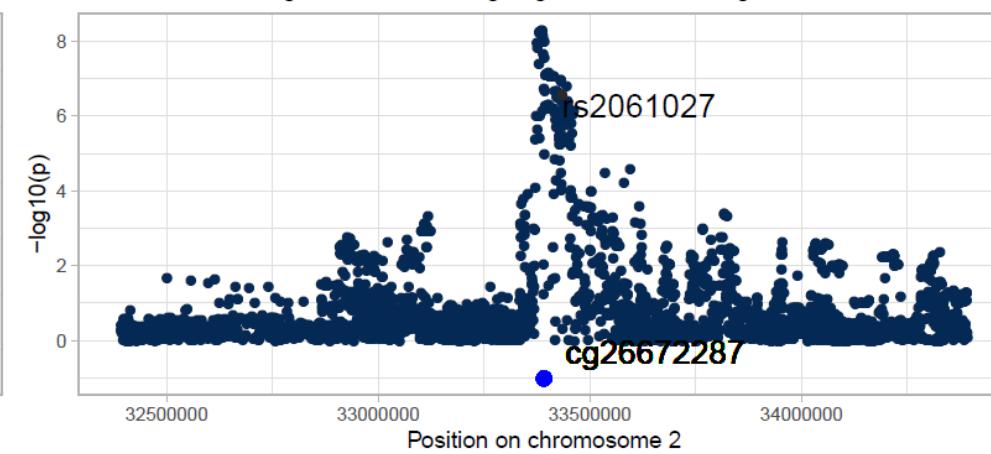


# Resolution of GWAS signals

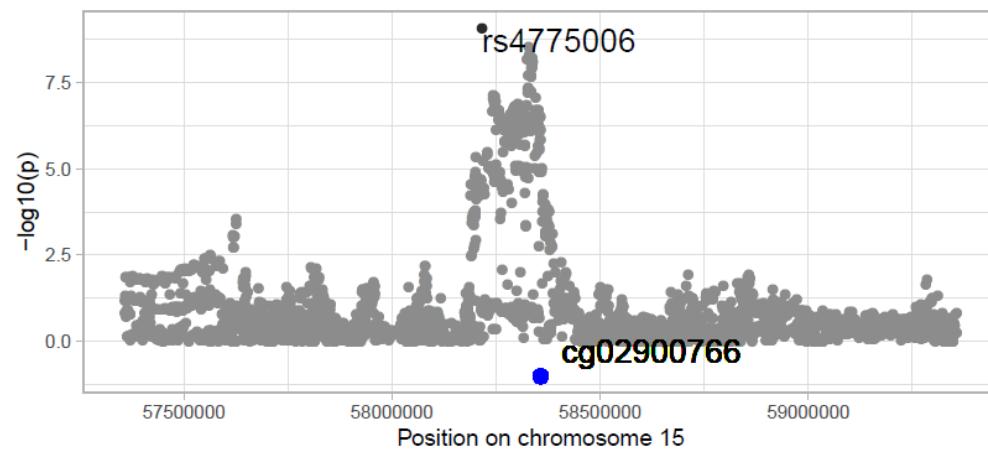
A cis-mQTLs for cg02900766 in Low-grade OA cartilage



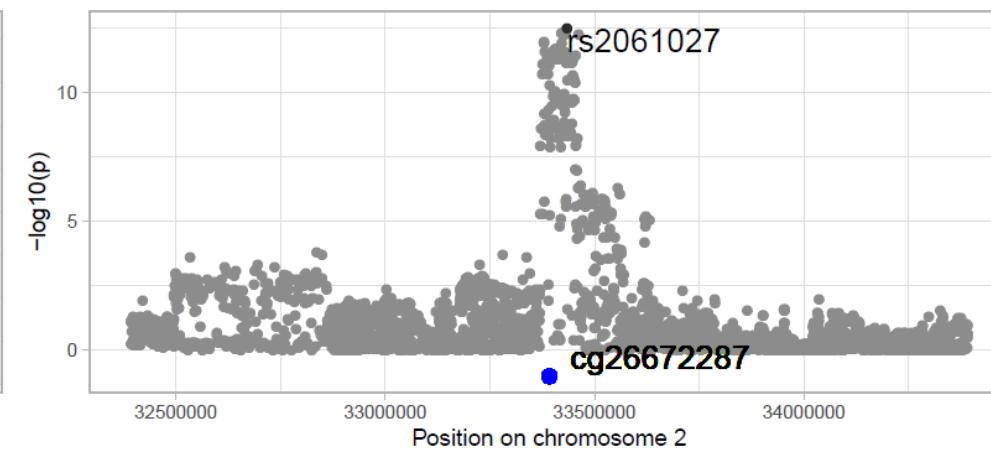
B cis-mQTLs for cg26672287 in High-grade OA cartilage



GWAS for KneeOA

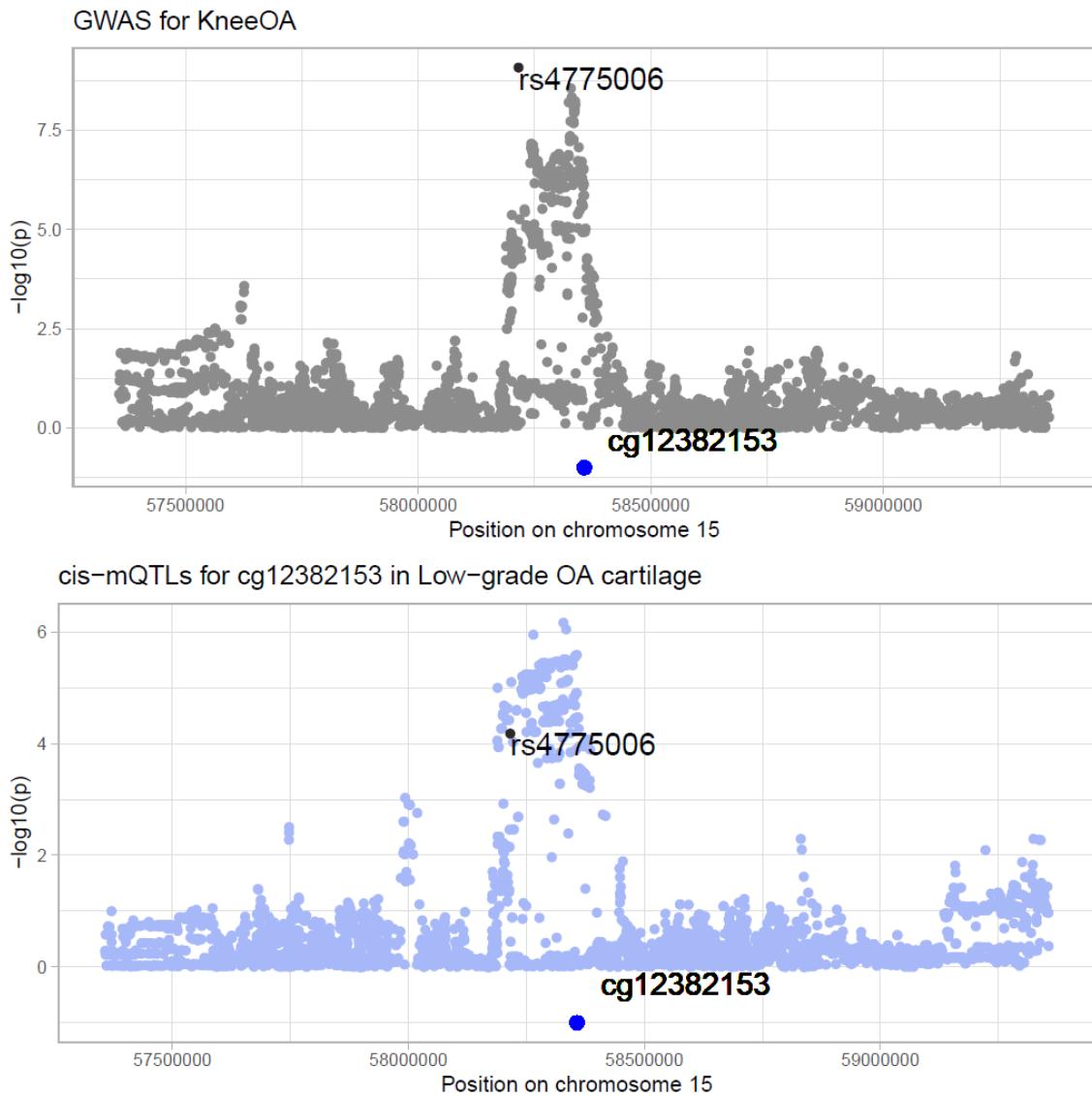


GWAS for allOA

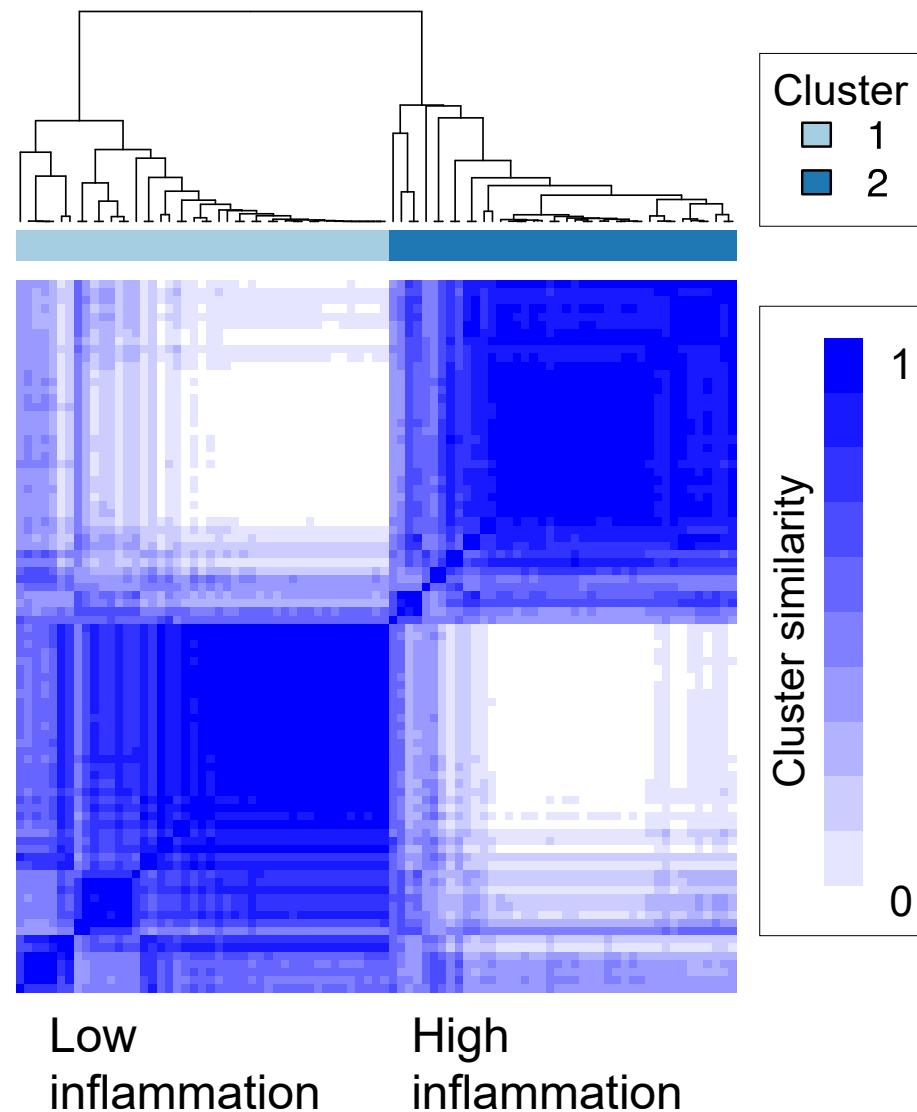


# Resolution of GWAS signals

- **Colocalising GWAS signals for knee osteoarthritis** (lead variant rs4775006) with low-grade cartilage mQTL signals for cg12382153 annotated to a distant gene (*ALDH1A2*, 30 kb away from rs4775006)
- **eQTL effect** of rs4775006 on *ALDH1A2* ( $p = 0.0031$ ) in low-grade cartilage
- *ALDH1A2* is **significantly upregulated** in high-grade compared to low-grade cartilage (FDR = 0.0017, logFC = 0.38)



# Patient stratification based on transcriptional profiles



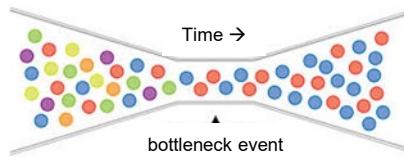
Between-cluster DE		
Gene	logFC	FDR
MMP13	-2.22	$2.2 \times 10^{-13}$
MMP2	-1.78	$4.7 \times 10^{-13}$
APOD	1.29	$3.5 \times 10^{-14}$
CYTL1	1.57	$4.7 \times 10^{-12}$
MMP1	-1.54	$1.1 \times 10^{-11}$
IL6	-2.46	$1.7 \times 10^{-10}$
C15orf48	-1.72	$8.3 \times 10^{-11}$

# Special populations

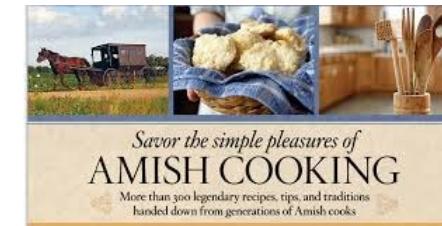
# Population isolates

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

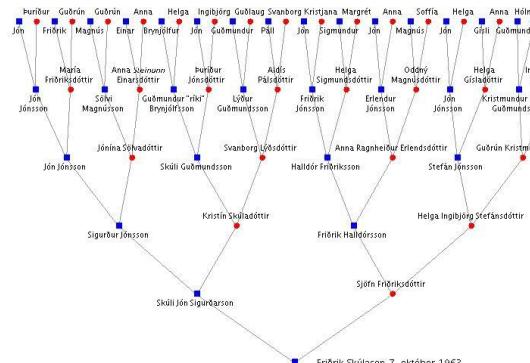
- Some rare variation is lost, and rare variants may have increased in frequency



- linkage disequilibrium tends to be extended



- homogeneous environment



# Findings in isolated populations and their wider relevance

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FOCUS ON GENOMES OF ICELANDERS

BRIEF COMMUNICATIONS

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

Jeroen R Huyghe<sup>1</sup>, Anne U Jackson<sup>1</sup>, Marie P Fogarty<sup>2</sup>, Martin L Buchkovich<sup>3</sup>, Alena Stančáková<sup>3</sup>, Heather M Stringham<sup>1</sup>, Xueling Sim<sup>1</sup>, Lingyao Yang<sup>1</sup>, Christian Fuchsberger<sup>1</sup>, Henna Cederberg<sup>4</sup>, Peter S Chines<sup>4</sup>, Tanya M Teslovich<sup>1</sup>, Jane M Romm<sup>5</sup>, Hua Ling<sup>5</sup>, Ivy McMullen<sup>5</sup>, Roxann Ingessoll<sup>5</sup>, Elizabeth W Pugh<sup>5</sup>, Kimberly F Doheny<sup>6</sup>, Benjamin M Neale<sup>6-8</sup>, Mark J Daly<sup>6-8</sup>, Johanna Kuusisto<sup>3</sup>, Laura J Scott<sup>1</sup>, Hyun Min Kang<sup>1</sup>, Francis S Collins<sup>1</sup>, Gonçalo R Abecasis<sup>1</sup>, Richard M Watanabe<sup>9,10</sup>, Michael Boehnke<sup>1,11</sup>, Markku Laakso<sup>3,11</sup> & Karen L Mohlke<sup>2,11</sup>

Cell

Resource

## Genetic Variants Regulating Immune Cell Levels in Health and Disease

Valeria Orrù<sup>1,12</sup>, Mariella Steri<sup>1,12</sup>, Gabriella Sole<sup>1</sup>, Carlo Sidore<sup>1,2,22</sup>, Francesca Virdis<sup>1</sup>, Mariano Deli<sup>1</sup>, Sandra Lai<sup>1</sup>, Magdalena Zoledziewska<sup>1</sup>, Fabio Businero<sup>1</sup>, Antonella Mulas<sup>1,3</sup>, Matteo Floris<sup>1</sup>, Wieslawa I. Mienteni<sup>1</sup>, Silvana A.M. Urru<sup>1</sup>, Stefania Olla<sup>1</sup>, Michele Marongiu<sup>1</sup>, Maria G. Piras<sup>1</sup>, Monia Lobina<sup>1,3</sup>, Andrea Maschio<sup>1</sup>, Maristella Pitzalis<sup>1</sup>, Maria F. Urru<sup>1</sup>, Marco Marcelli<sup>4</sup>, Roberto Cusano<sup>1,4</sup>, Francesca Deidda<sup>1,4</sup>, Valentina Serra<sup>1,3</sup>, Manuela Oppo<sup>1</sup>, Rosella Pilu<sup>1,4</sup>, Frederic Reiner<sup>1</sup>, Riccardo Berutti<sup>1,4</sup>, Luca Preddoli<sup>1,5</sup>, Ilenia Zara<sup>4</sup>, Eleonora Porcu<sup>1,3</sup>, Alan Kwong<sup>1</sup>, Christine Brennan<sup>11</sup>, Brendan Tarrer<sup>11</sup>, Robert Lyons<sup>11</sup>, Hyun M. Kang<sup>1</sup>, Sergio Uzzau<sup>3,6</sup>, Rossano Atzeni<sup>4</sup>, Maria Valentini<sup>1</sup>, Davide Finelli<sup>1</sup>, Lidia Looni<sup>1</sup>, Gianluca Rotta<sup>5</sup>, Silvia Naitza<sup>1</sup>, Andrea Angius<sup>1,4</sup>, Mauro Congia<sup>9</sup>, Michael B. Whalen<sup>1</sup>, Chris M. Jones<sup>1</sup>, David Schlessinger<sup>10</sup>, Gonçalo R. Abecasis<sup>1</sup>, Edoardo Fiorillo<sup>1,12,\*</sup>, Serenella Sanna<sup>1,12</sup> and Francesco Cuccia<sup>1,3,22</sup>

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

Elaine T. Lim<sup>1,2,3,4</sup>, Peter Würts<sup>5,6,7</sup>, Aki S. Havulinna<sup>8</sup>, Priti Palta<sup>8,9</sup>, Taru Tukiainen<sup>1,2,3</sup>, Karola Rehnström<sup>9</sup>, Tönu Esko<sup>1,2,3,9,10</sup>, Reedik Mägi<sup>9</sup>, Michael Inouye<sup>11</sup>, Tuuli Lappalainen<sup>12,13</sup>, Yingleong Chan<sup>2,4,10</sup>, Rany M. Salem<sup>11</sup>, Monkof Lek<sup>1,2,3</sup>, Jason Flannick<sup>2,3</sup>, Xueling Sim<sup>14</sup>, Alisa Manning<sup>15</sup>, Claes Ladenbärg<sup>15</sup>, Suzannah Bumpstead<sup>9</sup>, Eija Hämäläinen<sup>16</sup>, Kristina Aalto<sup>16</sup>, Mikael Maksimow<sup>19</sup>, Marko Salmi<sup>17</sup>, Stefan Blankenberg<sup>16,17</sup>, Diego Ardissono<sup>19</sup>, Sveti Shah<sup>20</sup>, Benjamin Horne<sup>21</sup>, Ruth McPherson<sup>22</sup>, Gerald K. Hovingh<sup>24</sup>, Muredach P. Reilly<sup>25</sup>, Hugh Watkins<sup>26</sup>, Anuj Goed<sup>26</sup>, Martin Farall<sup>26</sup>, Domenico Girelli<sup>27</sup>, Alex P. Reiner<sup>28</sup>, Nathan P. O’Donnell<sup>29</sup>, Sekar Kathiresan<sup>30</sup>, Stacey Gabriel<sup>2</sup>, Jeffrey C. Barrett<sup>2</sup>, Terhi Lehtimäki<sup>31</sup>, Markku Laakso<sup>32</sup>, Leif Groop<sup>33,34</sup>, Jaakko Kaprio<sup>35</sup>, Markus Perola<sup>3</sup>, Mark I. McCarthy<sup>35,37</sup>, Michael Boehnke<sup>14</sup>, David M. Altshuler<sup>38</sup>, Cecilia M. Lindgren<sup>1,2,38</sup>, Joel N. Hirschhorn<sup>2,10</sup>, Andrei Metspalu<sup>39</sup>, Nelson B. Freimer<sup>39</sup>, Tanja Zeller<sup>18,19</sup>, Sirpa Jalkanen<sup>17</sup>, Seppo Koskinen<sup>40</sup>, Olli Teronen<sup>41,42</sup>, Richard Durbin<sup>40</sup>, Daniel G. MacArthur<sup>1,2,3</sup>, Veikko Salomaa<sup>8</sup>, Samuli Ripatti<sup>4,6,33,43</sup>, Mark J. Daly<sup>1,2,3\*</sup>, Aarno Palotie<sup>1,2,3,44</sup>, for the Sequencing Initiative Suomi (SiSu) Project

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

Carlo Sidore<sup>1-3,19</sup>, Fabio Businero<sup>1,2,4,19</sup>, Andrea Maschio<sup>1,2,4,19</sup>, Eleonora Porcu<sup>1-3,19</sup>, Silvia Naitza<sup>1,19</sup>, Magdalena Zoledziewska<sup>1</sup>, Antonella Mulas<sup>1,3</sup>, Giorgia Pitsilis<sup>1</sup>, Mariella Steri<sup>1</sup>, Fabrice Daniell<sup>1</sup>, Alan Kwong<sup>1</sup>, Vicente Diego Ortega del Vecchio<sup>2</sup>, Charleston W K Chang<sup>1</sup>, Jennifer Bragg-Gresham<sup>2</sup>, Christian Jadhao<sup>1,3</sup>, Rosanna Atzeni<sup>4</sup>, Brendan Tarrer<sup>1</sup>, Robert Lyons<sup>11</sup>, Sergio Uzzau<sup>5</sup>, Nicholas J Timpton<sup>1</sup>, Daniela Tonello<sup>12</sup>, Paolo Gasparini<sup>1,14</sup>, Giovanni Matera<sup>15</sup>, George Dedousis<sup>16</sup>, Eleftheria Zeggini<sup>10</sup>, Nicole Soranzo<sup>16,17</sup>, Chris Jones<sup>1</sup>, Robert Lyons<sup>1</sup>, Andrea Angius<sup>1</sup>, Hyun M. Kang<sup>1</sup>, John Novembre<sup>18</sup>, Serenella Sanna<sup>1,20</sup>, David Schlessinger<sup>1,20</sup>, Francesco Cuccia<sup>1,22</sup> & Gonçalo R Abecasis<sup>1,20</sup>

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 relatives<sup>8</sup> to investigate whether any of the genes located in the regions showing common variant association with Alzheimer’s

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

Toni I. Pollin,<sup>1</sup> Coleen M. Damcott,<sup>1</sup> Haiqing Shen,<sup>1</sup> Sandra H. Ott,<sup>1</sup> John Shelton,<sup>1</sup> Richard B. Horenstein,<sup>1</sup> Wendy Post,<sup>2</sup> John C. McLenithan,<sup>1,3</sup> Lawrence F. Bielak,<sup>2</sup> Patricia A. Peyser,<sup>4</sup> Braxton D. Mitchell,<sup>5</sup> Michael Miller,<sup>1</sup> Jeffrey R. O’Connell,<sup>1</sup> Alan R. Shuldiner,<sup>1,3</sup>

LETTERS

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

Julus Gudmundsson<sup>1,23</sup>, Patrick Salem<sup>1,23</sup>, Daniel F. Gudbjartsson<sup>1</sup>, Gisli Masson<sup>1</sup>, Bjarni A. Agnarson<sup>2,3</sup>, Kristrún R. Benediktsdóttir<sup>1,23</sup>, Asgeir Sigurdsson<sup>1</sup>, Olafur Th Magnusson<sup>1</sup>, Sigríður A. Guðjónsson<sup>1</sup>, Ólafur Þ. Helgason<sup>1</sup>, Hrafnhildur Thorgrimson<sup>1,24</sup>, Áslaug Jonasdóttir<sup>1</sup>, Asgeir Sigurdsson<sup>1</sup>, Hrein Stefansson<sup>1</sup>, Thomas Werger<sup>5</sup>, Thorunn Rafnar<sup>1</sup>, Lambertus A. Kiemeney<sup>6,7</sup>, Babar Parvez<sup>2</sup>, Raufia Muhammed<sup>8</sup>, Dan M Roden<sup>9</sup>, Dawood Darbar<sup>8</sup>, Gudmar Thorleifsson<sup>1</sup>, G Bragi Walters<sup>1</sup>, Augustine Kong<sup>1</sup>, Unnur Thorsteinsdóttir<sup>1,4</sup>, David O’Amar<sup>1,8</sup> & Kari Stefansson<sup>1,4</sup>

LETTER

doi:10.1038/nature13425

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

Ida Moltke<sup>1,2,a</sup>, Niels Grarup<sup>3,b</sup>, Marit E. Jorgensen<sup>4</sup>, Peter Bjerregaard<sup>5</sup>, Jonas T. Treebak<sup>6</sup>, Matteo Fumagalli<sup>7</sup>, Thorfinn S. Kornelius<sup>8</sup>, Marianne A. Andersen<sup>9</sup>, Thomas S. Nielsen<sup>9</sup>, Nikolaj T. Krarup<sup>9</sup>, Anette P. Gjesing<sup>9</sup>, Julieen R. Zierath<sup>6,9</sup>, Allan Linneberg<sup>10</sup>, Xueli Wu<sup>11</sup>, Guangjiang Sun<sup>11</sup>, Xin Jin<sup>11</sup>, Jumana Al-Aama<sup>11,12</sup>, Jun Wang<sup>11,12,13,14</sup>, Knut Borch-Johnsen<sup>15</sup>, Oluf Pedersen<sup>3</sup>, Rasmus Nielsen<sup>7,16</sup>, Anders Albrechtsen<sup>3</sup> & Torben Hansen<sup>3,17</sup>

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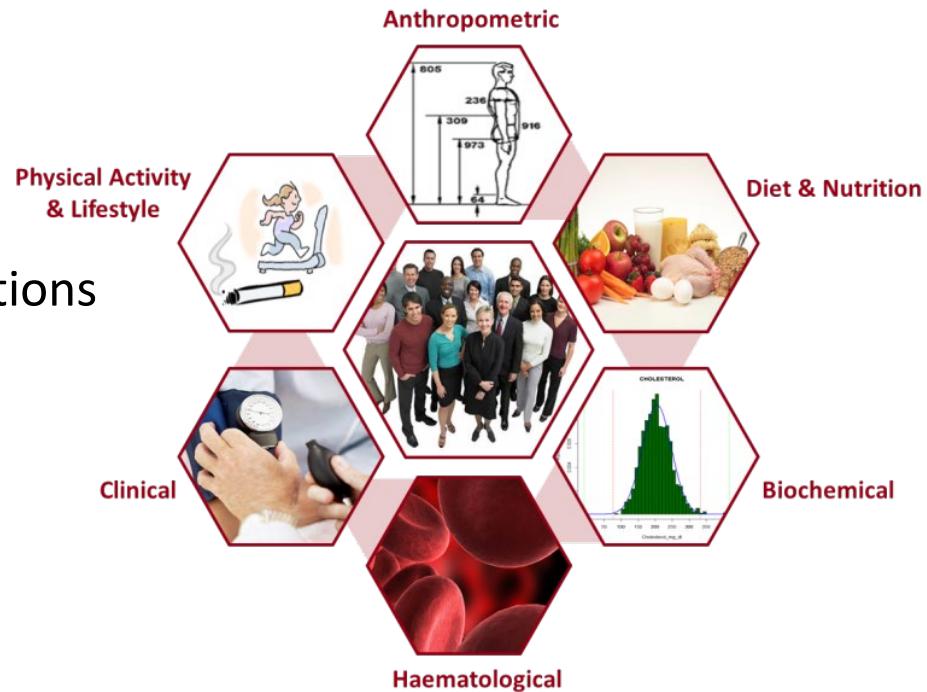
# HELIC: Hellenic isolated cohorts



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



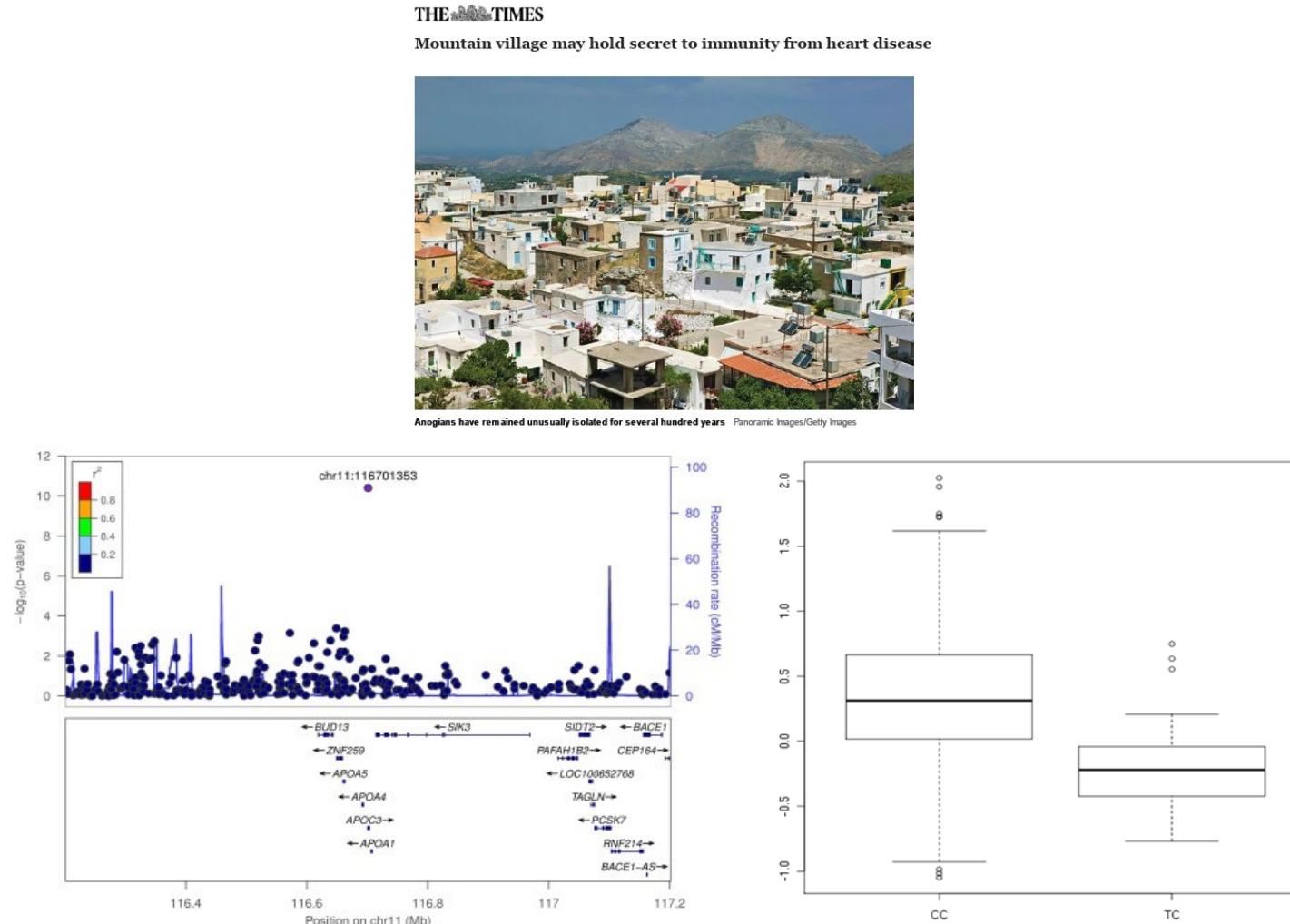
- Deeply phenotyped
- High fat content diet
- High rates of longevity
- Low rates of metabolic disease complications
- Ability to recontact individuals



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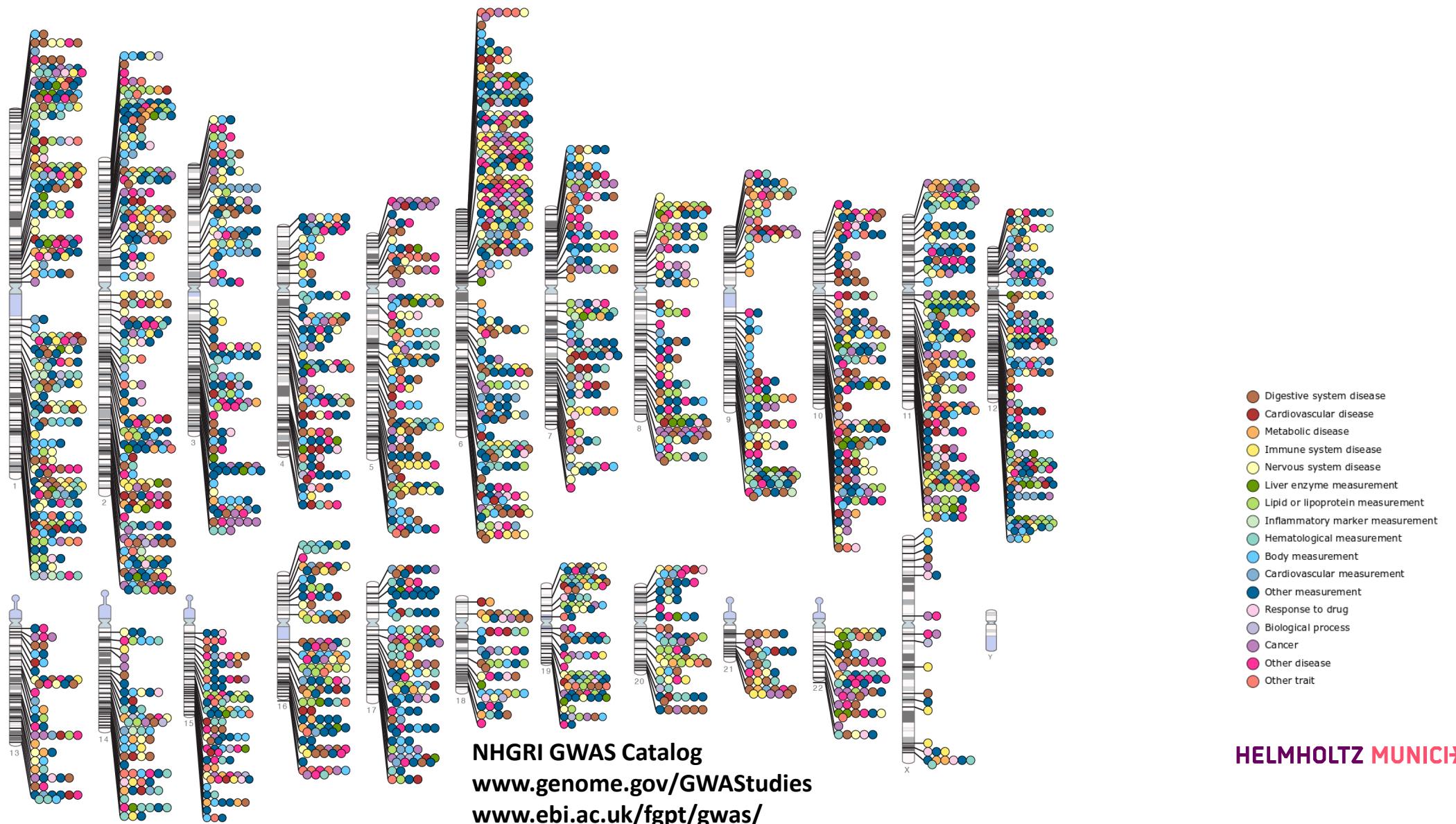
[www.helic.org](http://www.helic.org)

# R19X APOC3 cardioprotective variant

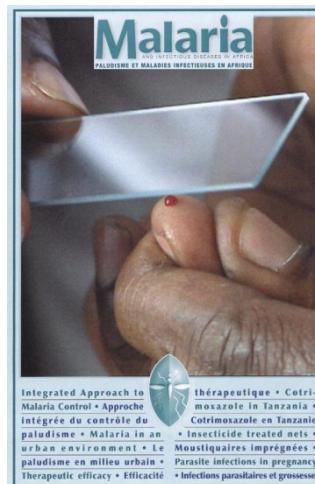


- Mylopotamos villages (n=1256, MAF 2%, p=10<sup>-11</sup>)
- Detection of this effect would have required 67,000 Europeans (MAF 0.05%)

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



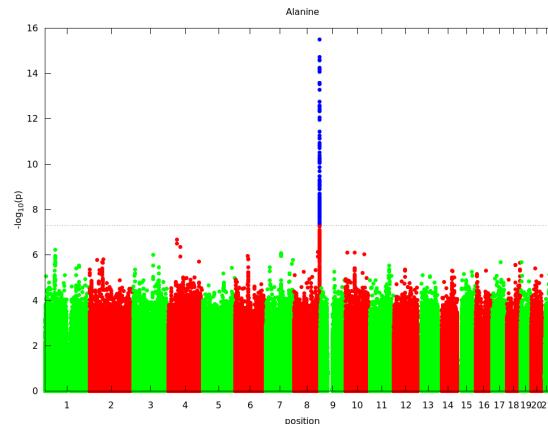
# Burden of disease in Africa



# 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

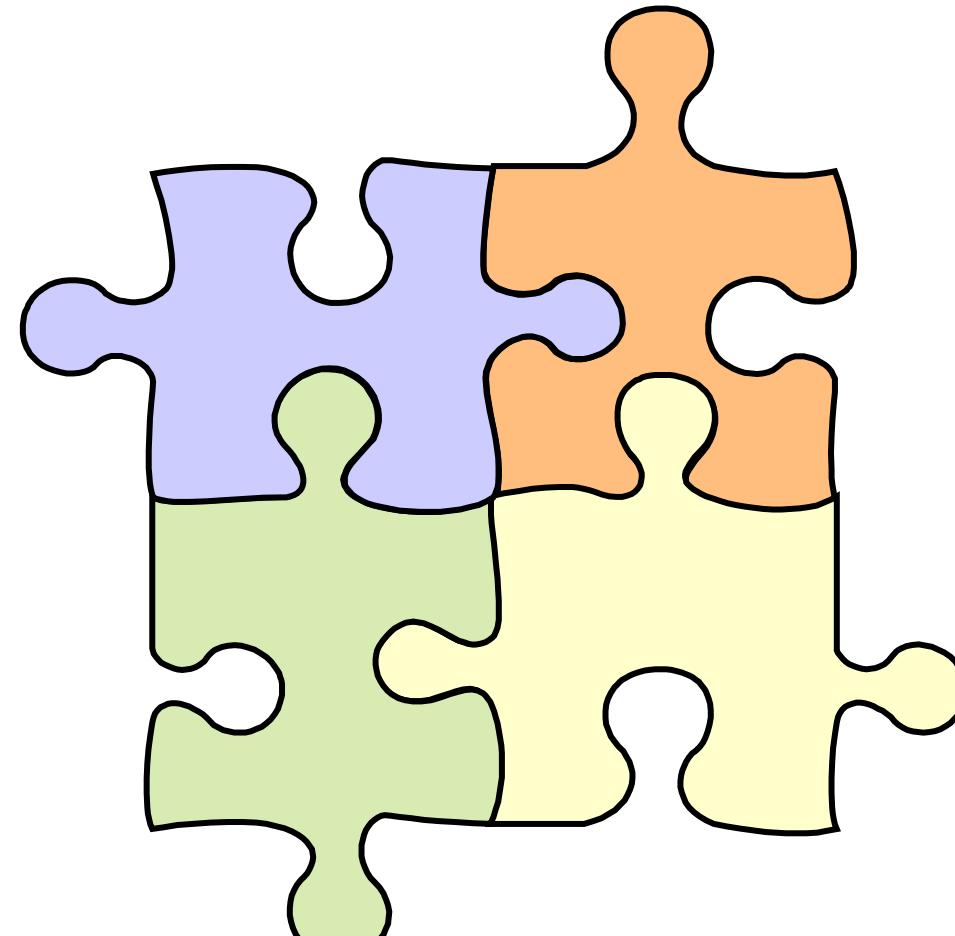


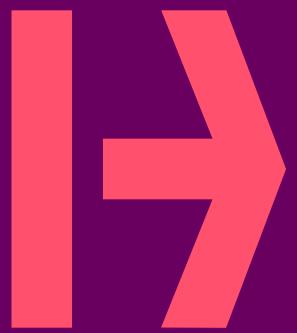
Liver enzymes- ALT  
GPT gene- produces enzyme  
Monomorphic in Europeans  
Ugandan frequency: 26%

# Genetic architecture of complex traits

Common variants

Rare variants





Thank you.