arcOGEN, a large-scale GWAS for osteoarthritis

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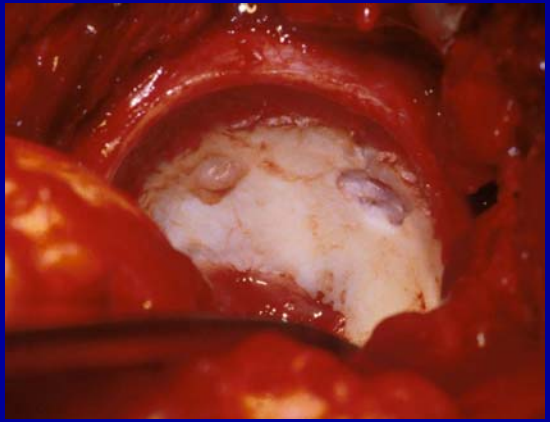
OA in the UK

- 5 million adults
- Majority aged > 60 years
- More females than males (3:1)

- Over 2 million GP appointments & 50,000 joint replacements annually



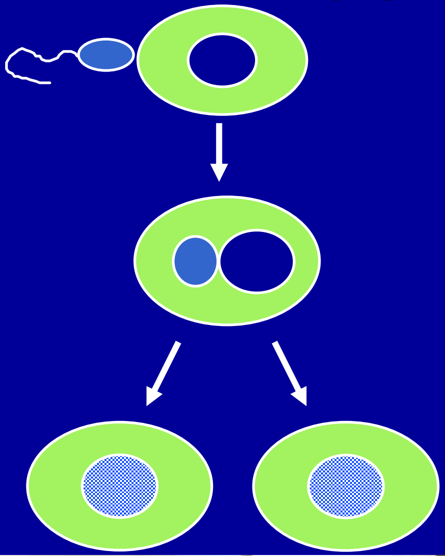
How do we know that genes influence the risk of someone getting OA?

- Epidemiological studies

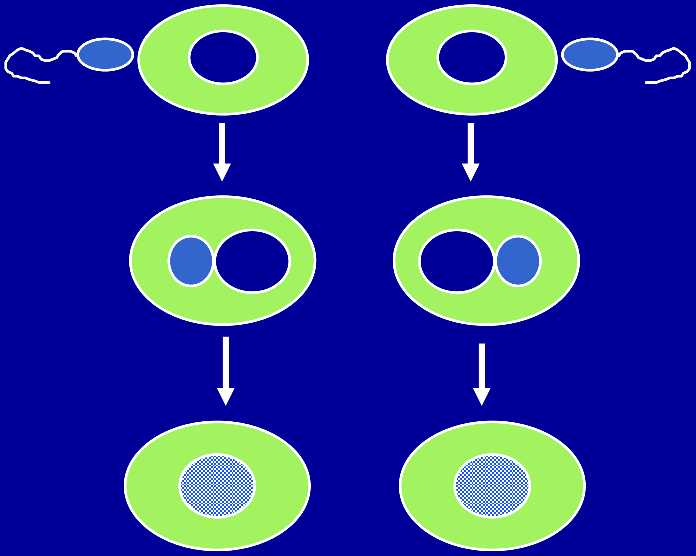
Twin studies

1 in 89 deliveries

1/3 Monozygotic



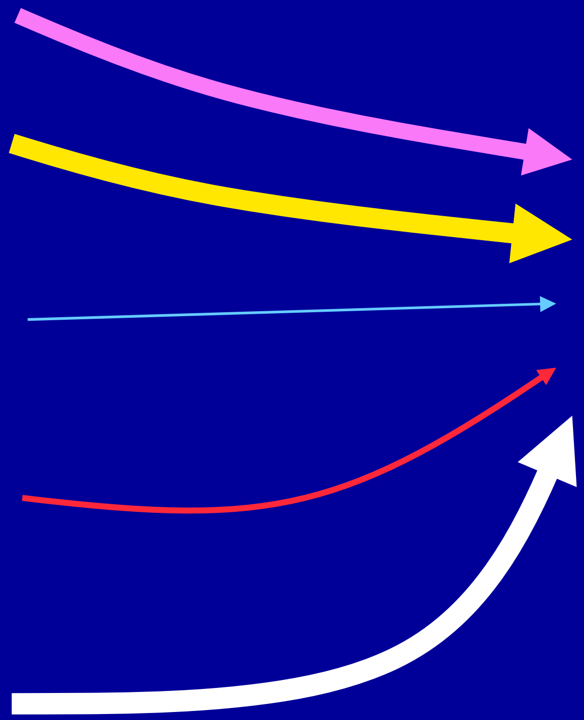
2/3 Dizygotic



% Concordance rates

	MZ	DZ
Cystic Fibrosis	100	25
Die on a Tuesday	14	14
Osteoarthritis	55	20

OA is multifactorial & polygenic



Environment

Gene1

Gene 2

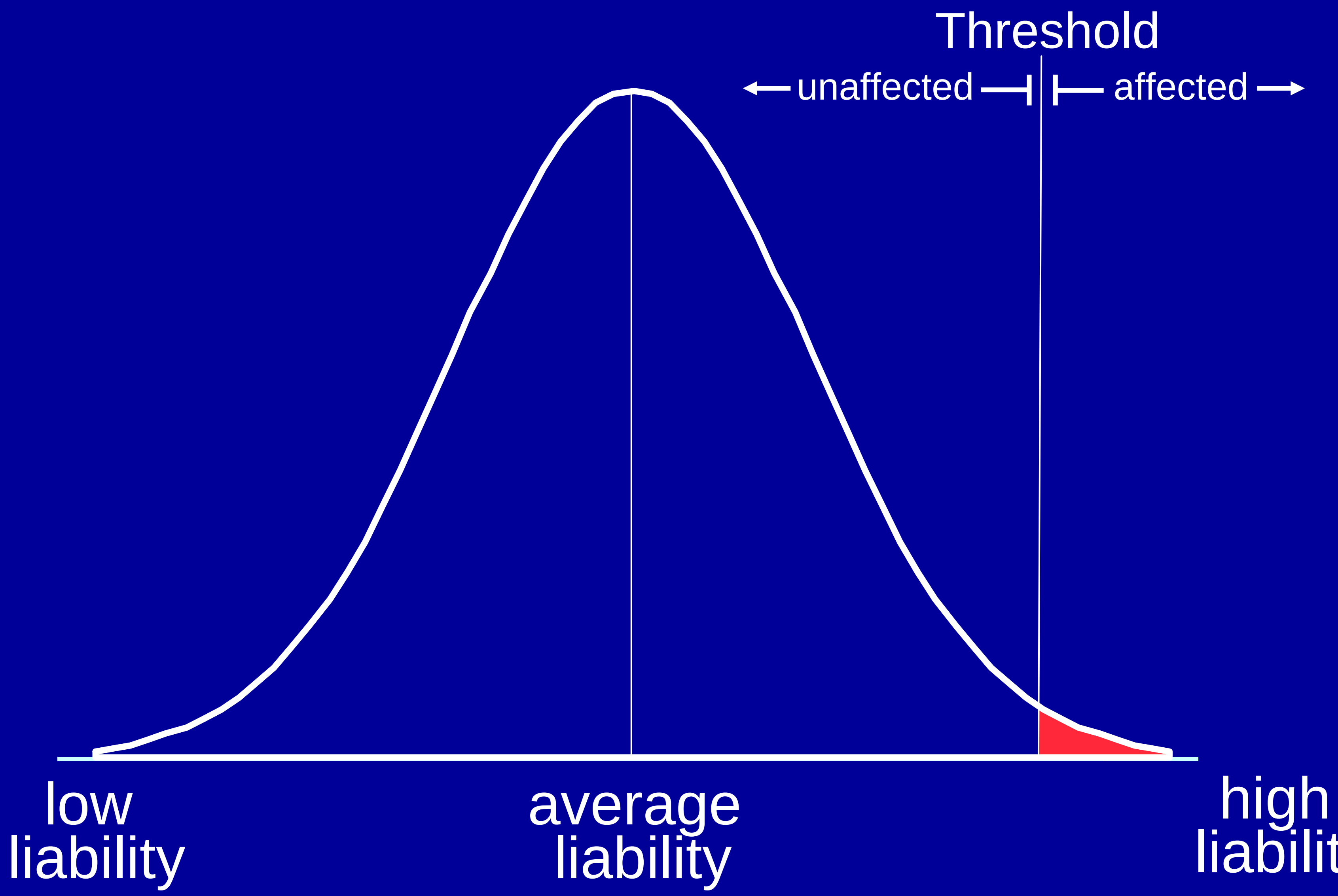
Gene 3

Gene 4

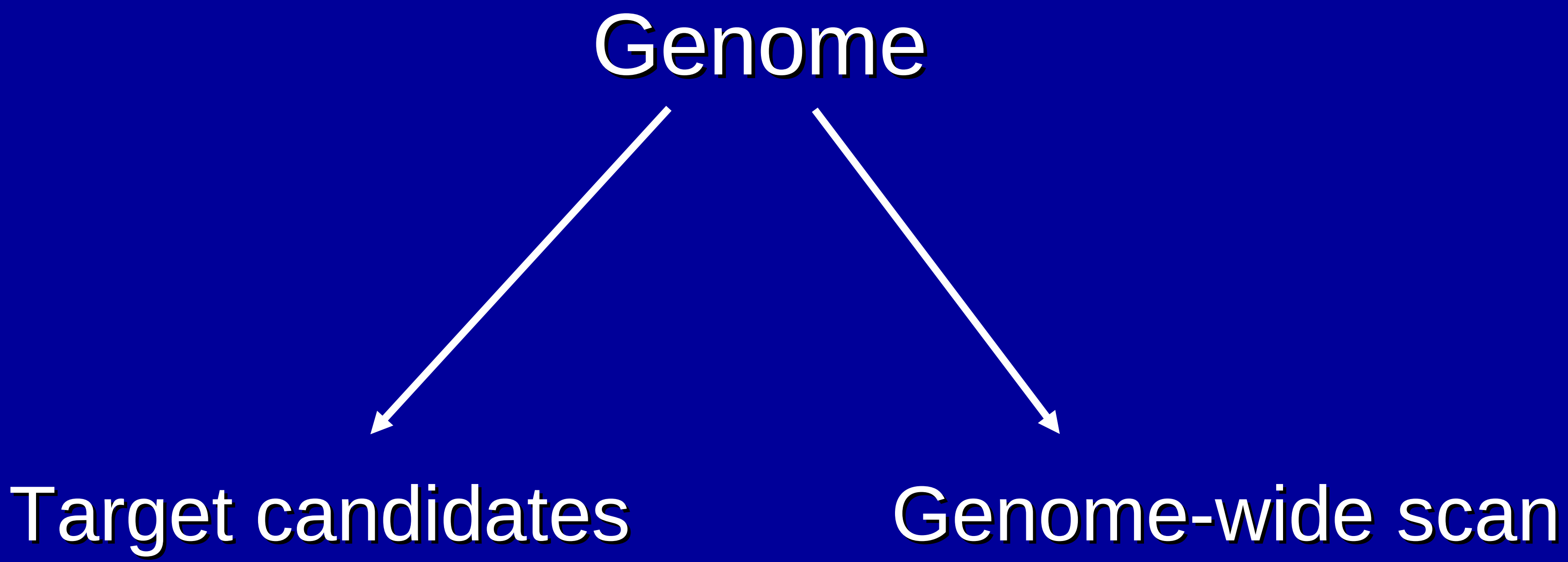
Etc, etc

OA

Distribution of liability



Two broad approaches to identifying susceptibility loci



Genome

Target candidates

Genome-wide scan

arcOGEN

arthritis research campaign
Osteoarthritis Genetics

- Largest single grant ever awarded by the *arc*
- £2.2 million

What is the aim of arcOGEN?

- To identify the DNA changes present in, or near, our genes that increase the risk of us developing OA

How will this help people?

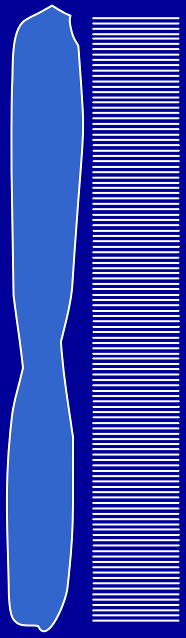
- Will lead to an understanding of the molecular basis of the disease
- Will suggest new therapies
- Will allow the development of DNA-based diagnosis and prognosis

The human genome has a large number of DNA sequence differences, *polymorphisms*

The most common are single nucleotide polymorphisms, *SNPs*

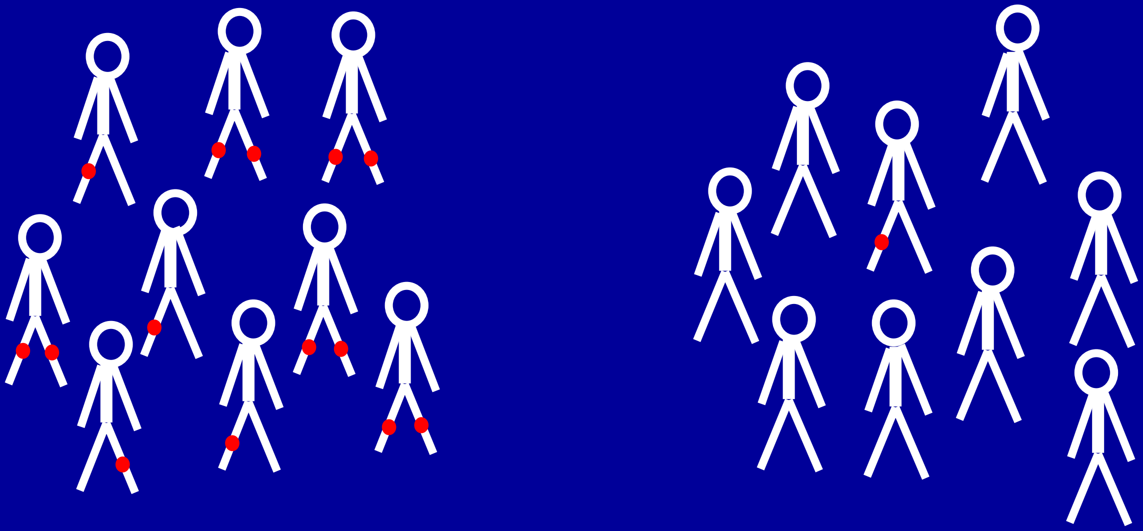
T-allele	TCGAGAGGC<u>T</u>AGGCTAGGA
C-allele	TCGAGAGGC<u>C</u>AGGCTAGGA

arcOGEN will study SNPs across the whole human genome



SNPs

In cases and in controls



Cases

Controls

SNP frequency 22% 18%

We are therefore performing a genome-wide association scan

GWAS

The arcOGEN protocol

- 8000 hip or knee OA cases
  - Joint replacement surgery
  - Males and females
  - 3200 already collected (extant cases, stage 1)
  - 4800 being collected (new cases, stage 2)

- 8000 controls

- Illumina 610-Quad Array

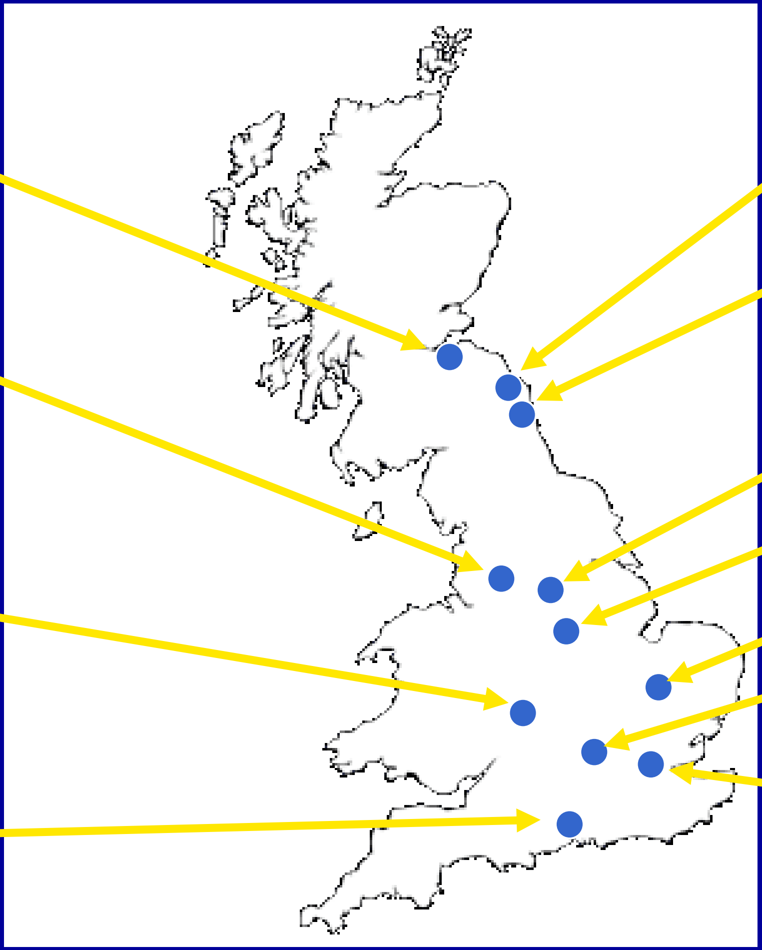
610-Quad

- 620,000 polymorphic markers
  - Covers approximately 90% of genome
- 138 mitochondrial SNPs
- Copy number variation (CNVs)
- Common polymorphisms
  - mean minor allele frequencies of 0.23

Why the 610-Quad?

- February 2007
  - Two options: Illumina and Affymetrix
  - Chose Illumina HumanHap 300 array
    - 317,000 SNPs
- October 2007
  - Funding approved
  - We could now afford the 610-Quad!

There are 11 participating sites in arcOGEN



Edinburgh

Manchester

Worcester

Southampton

Northumberland

Newcastle

Sheffield

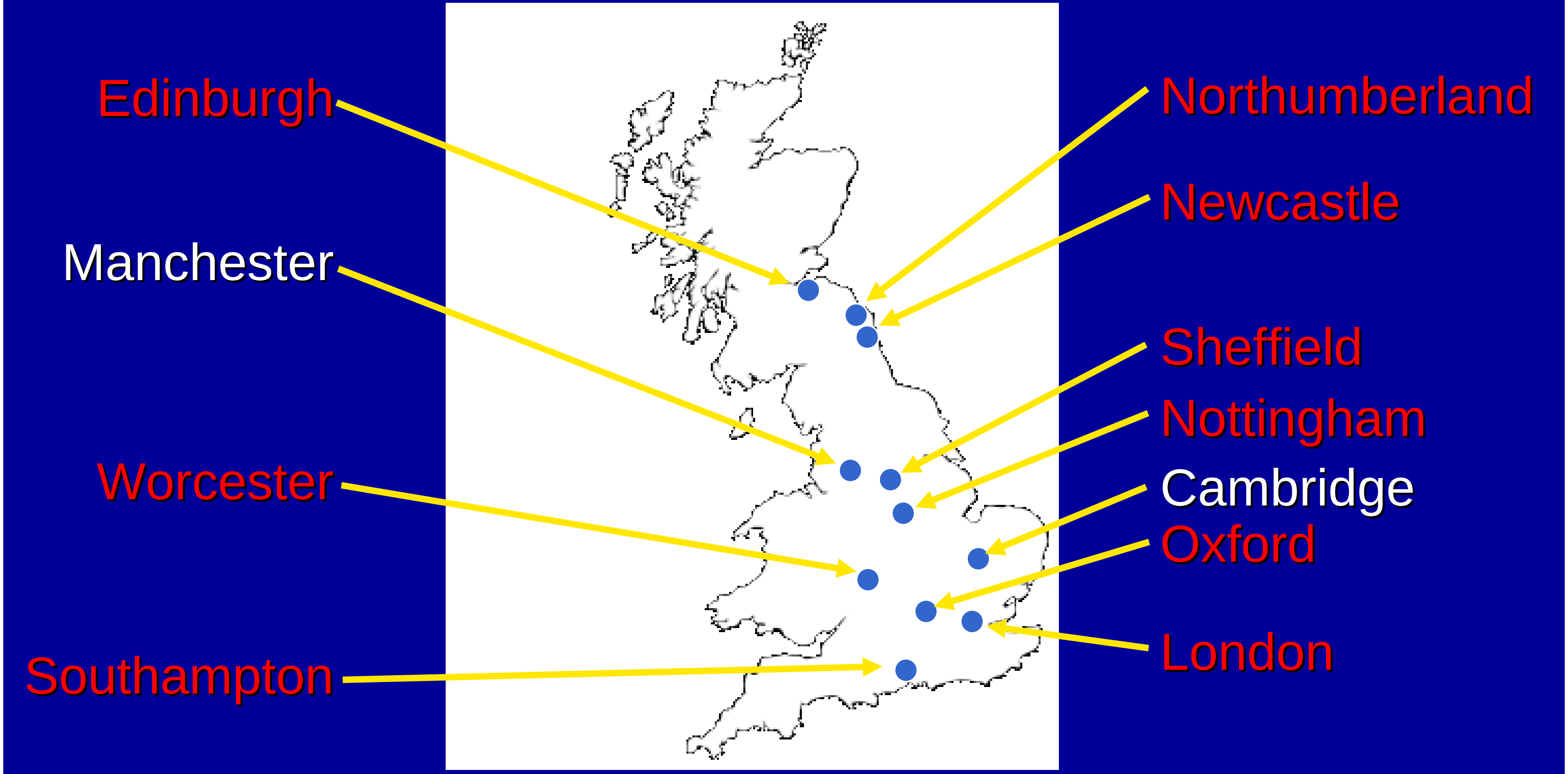
Nottingham

Cambridge

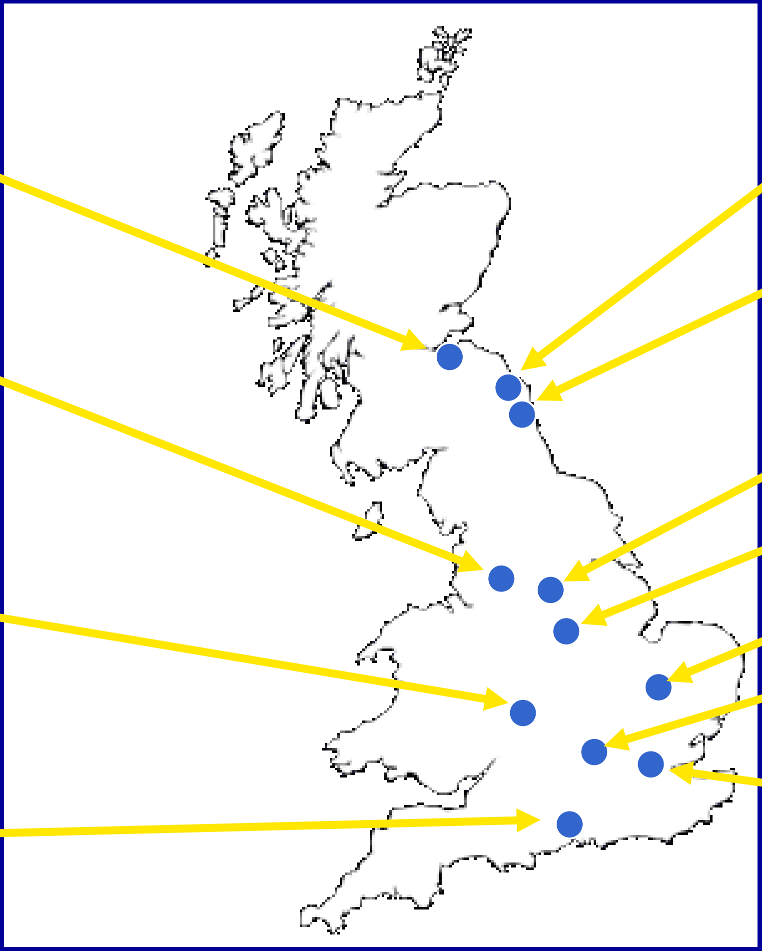
Oxford

London

9 sites are collecting new cases



DNA extraction, genotyping & analysis



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Current status

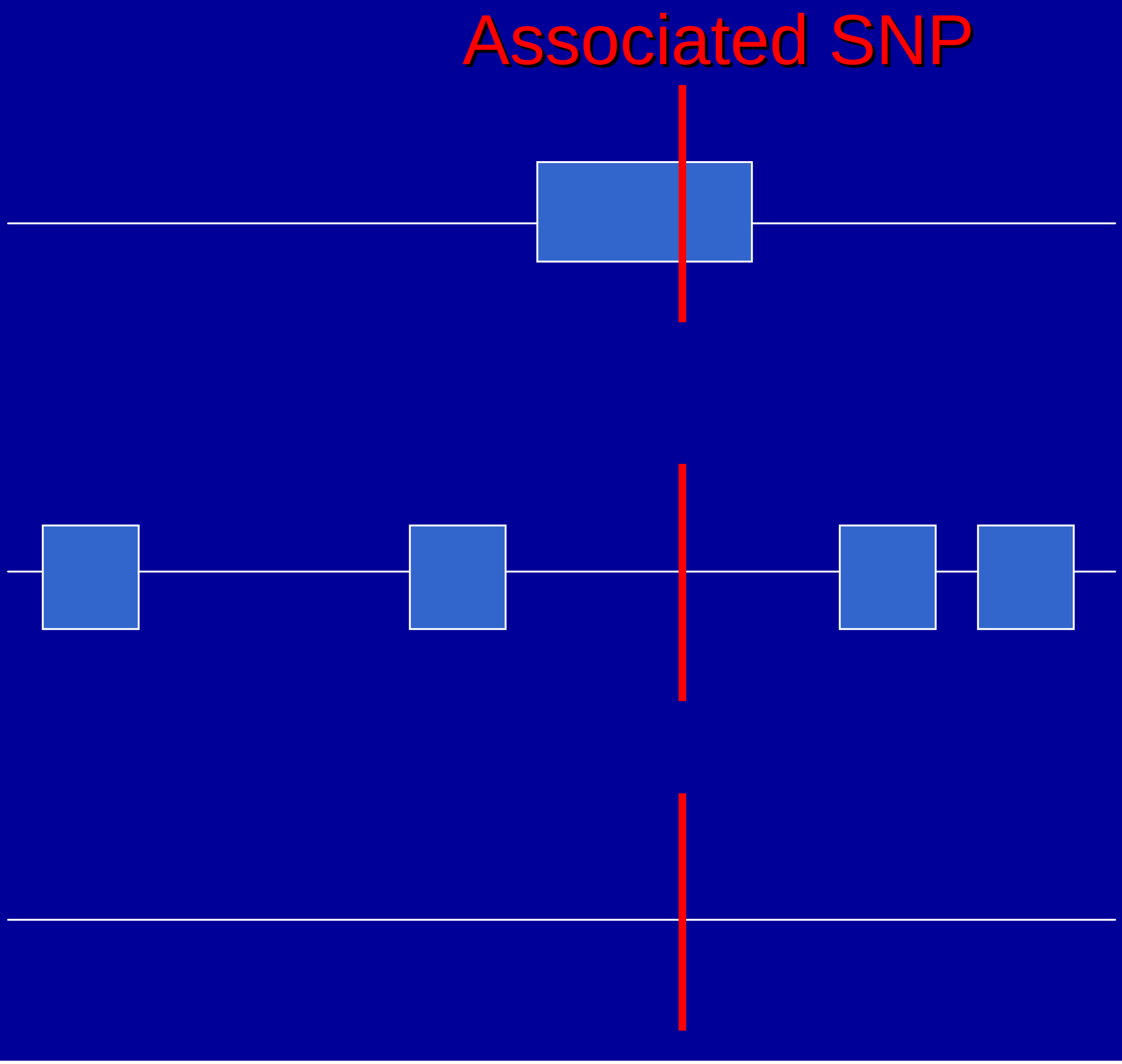
- Stage 1 genotyping complete
  - 515,00 SNPs in 3,177 cases and 4,894 controls
  - *in silico* replication on 102 independent SNPs
  - *de novo* genotyping underway on 36 SNPs in 16,700 cases & controls
- 3,851 of the 4,800 new cases so far collected

What next

- Complete the scan, replicate hits and then search for the functional variants

- Sounds so easy!

Three scenarios



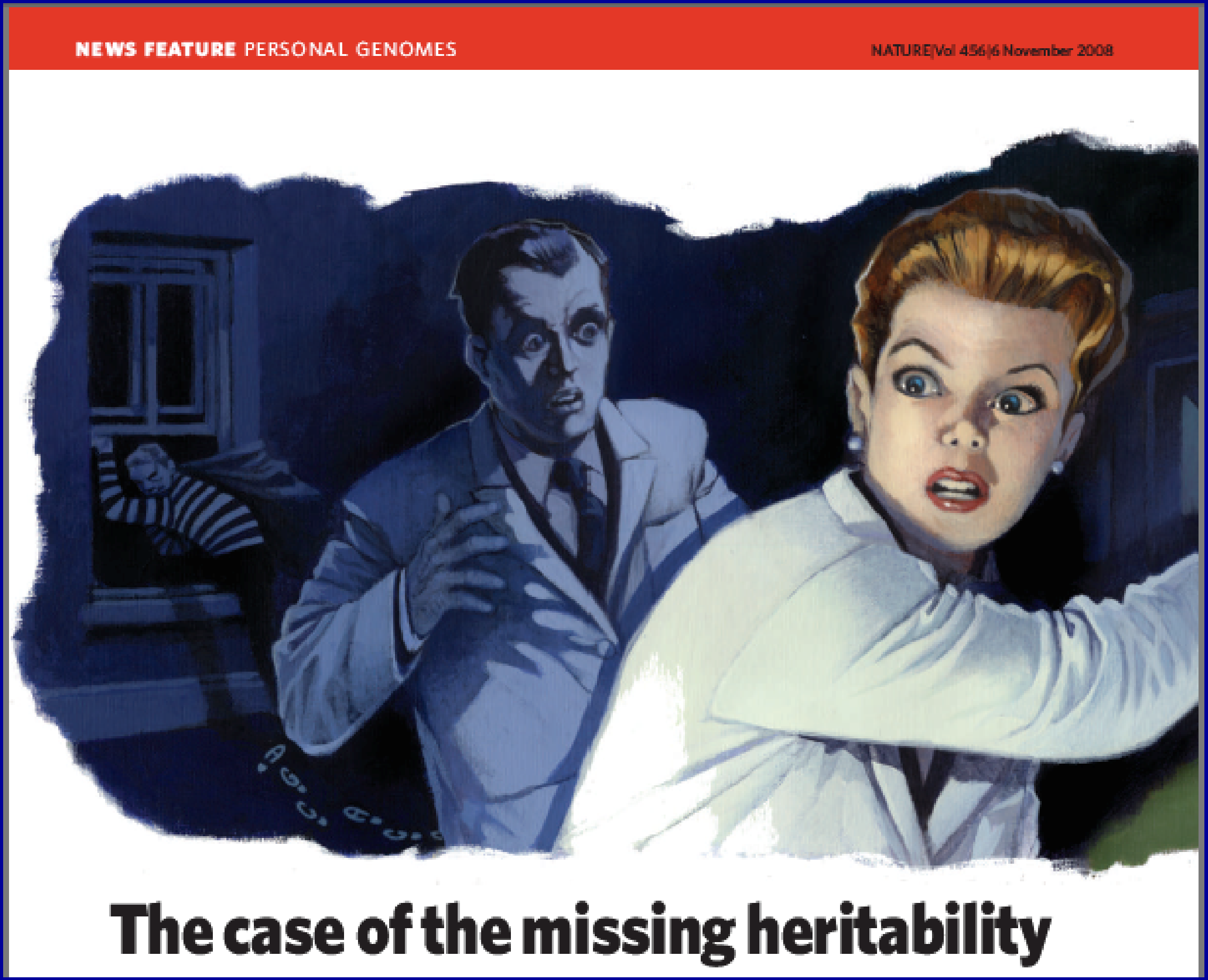
Associated SNP

Ideal

OK

Nightmare!

New concern



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NATURE|Vol 456|6 November 2008

The case of the missing heritability

Potential remedies

- Rare variants of high penetrance
  - Whole genome & candidate gene sequencing in large cohorts
- Common variants of even lower penetrance than those already studied
  - Much larger case-control cohorts
- Copy number variation (CNVs)
  - Both large and small ones

Concluding remarks

- A GWAS is just the beginning of a long, long journey……

Acknowledgements

arcOGEN consortium

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