

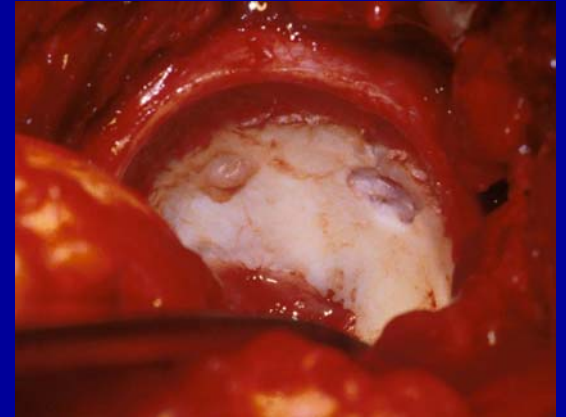
# arcOGEN, a large-scale GWAS for osteoarthritis

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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



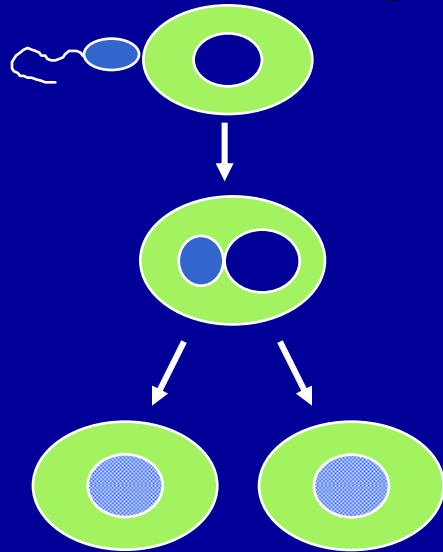
How do we know that genes influence the risk of someone getting OA?

- Epidemiological studies

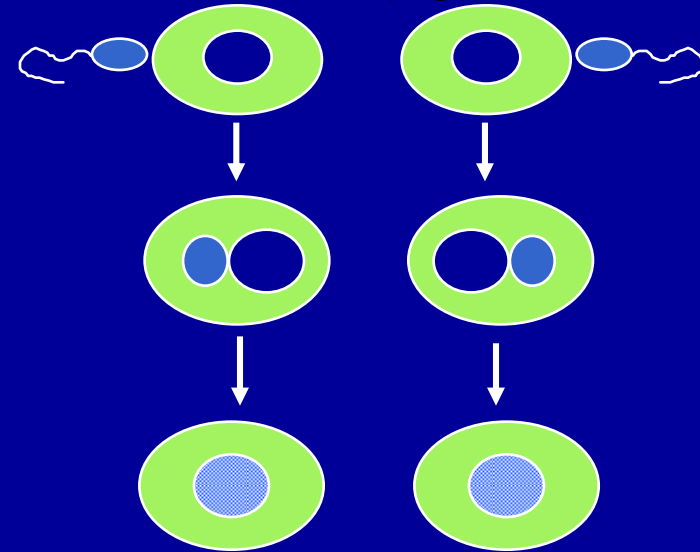
# Twin studies

1 in 89 deliveries

1/3 Monozygotic



2/3 Dizygotic



# % Concordance rates

	<u>MZ</u>	<u>DZ</u>
Cystic Fibrosis	100	25
Die on a Tuesday	14	14
Osteoarthritis	55	20

# OA is multifactorial & polygenic

Environment

Gene1

Gene 2

Gene 3

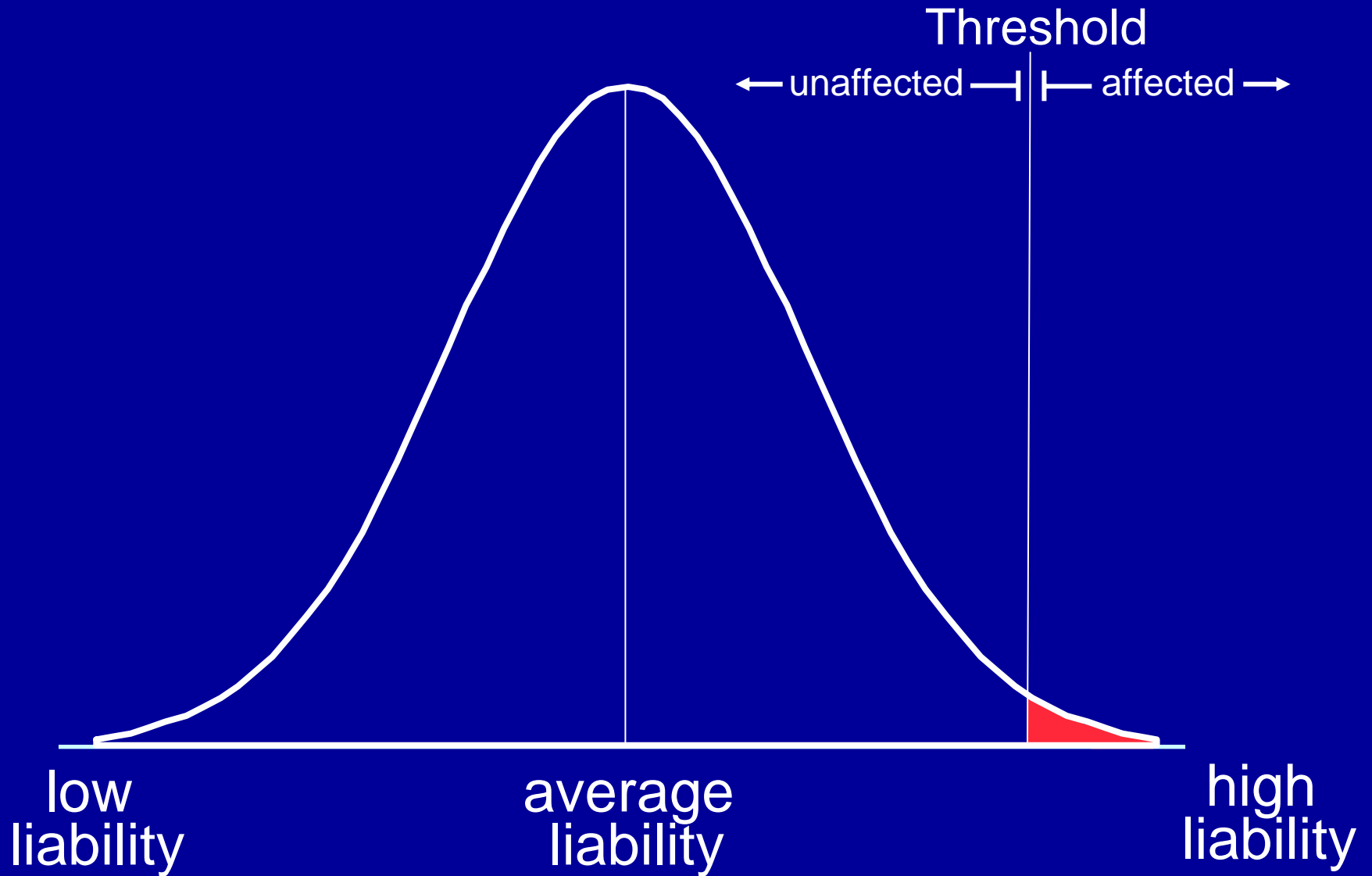
Gene 4

Etc, etc

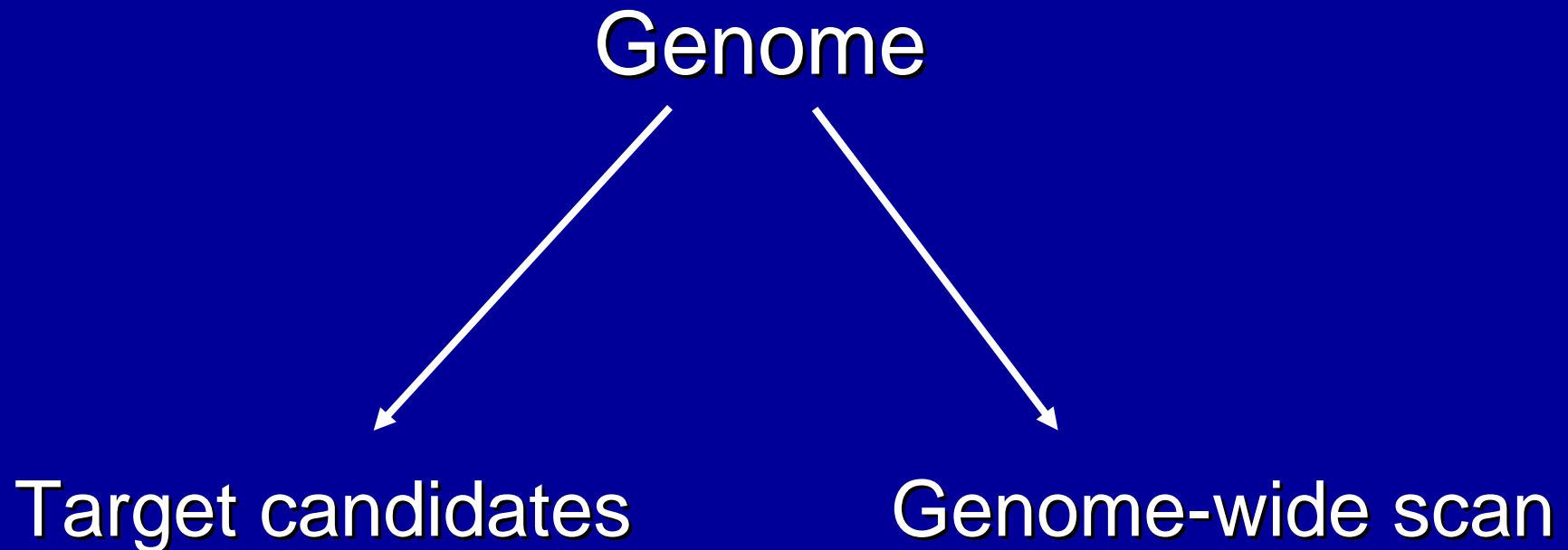
OA

A diagram illustrating the multifactorial and polygenic nature of Osteoarthritis (OA). On the left, a list of factors includes 'Environment' (in pink), 'Gene1' (in yellow), 'Gene 2' (in light blue), 'Gene 3' (in red), 'Gene 4' (in white), and 'Etc, etc' (in white). Arrows of corresponding colors point from each of these factors towards the right, where the letters 'OA' are displayed in a large yellow font. The arrows from Gene 1 and Gene 3 are curved, while the others are straight.

# Distribution of liability



# Two broad approaches to identifying susceptibility loci



# *arc*OGEN

## 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

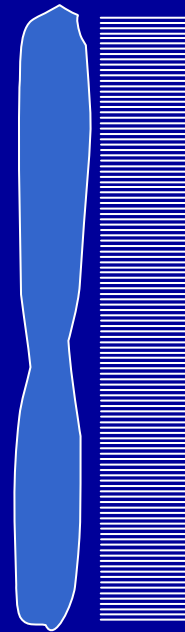
The human genome has a large number of DNA sequence differences, *polymorphisms*

The most common are single nucleotide polymorphisms, *SNPs*

T-allele TCGAGAGGCTAGGCTAGGA

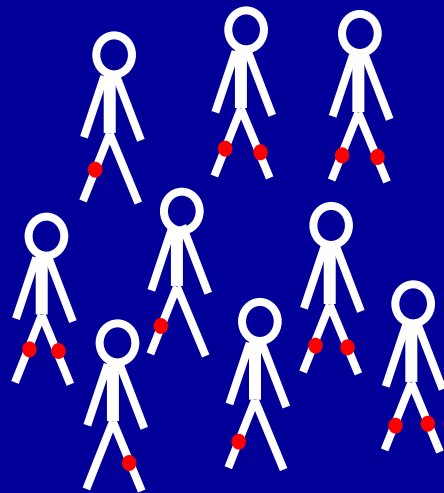
C-allele TCGAGAGGCCAGGCTAGGA

arcOGEN will study SNPs across  
the whole human genome

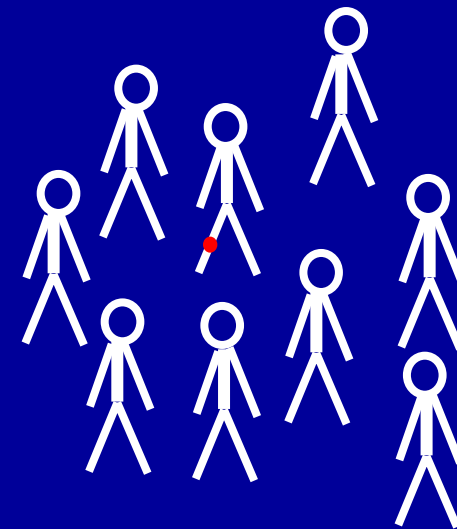


**SNPs**

# 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



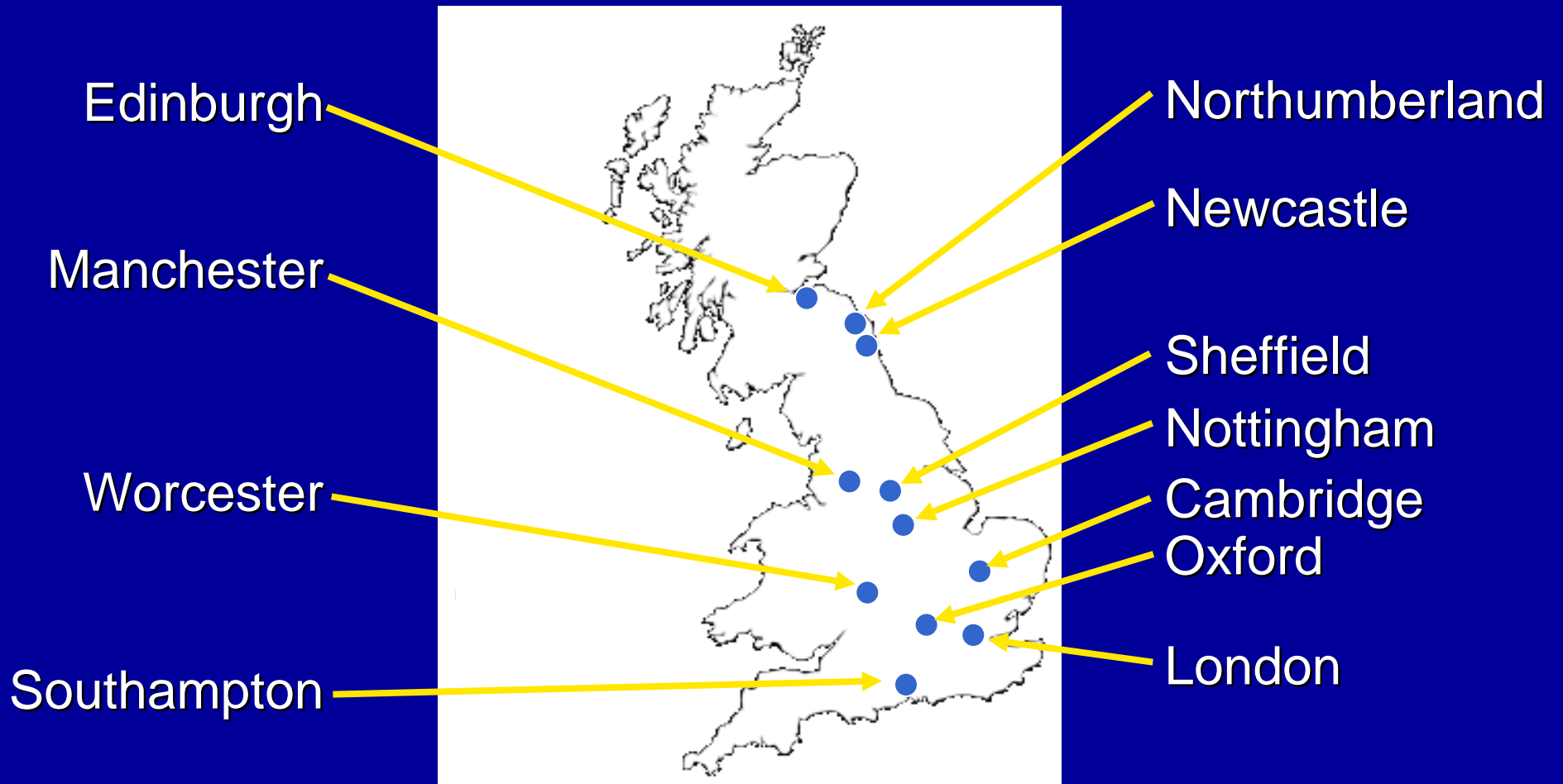
# 610-Quad

- 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

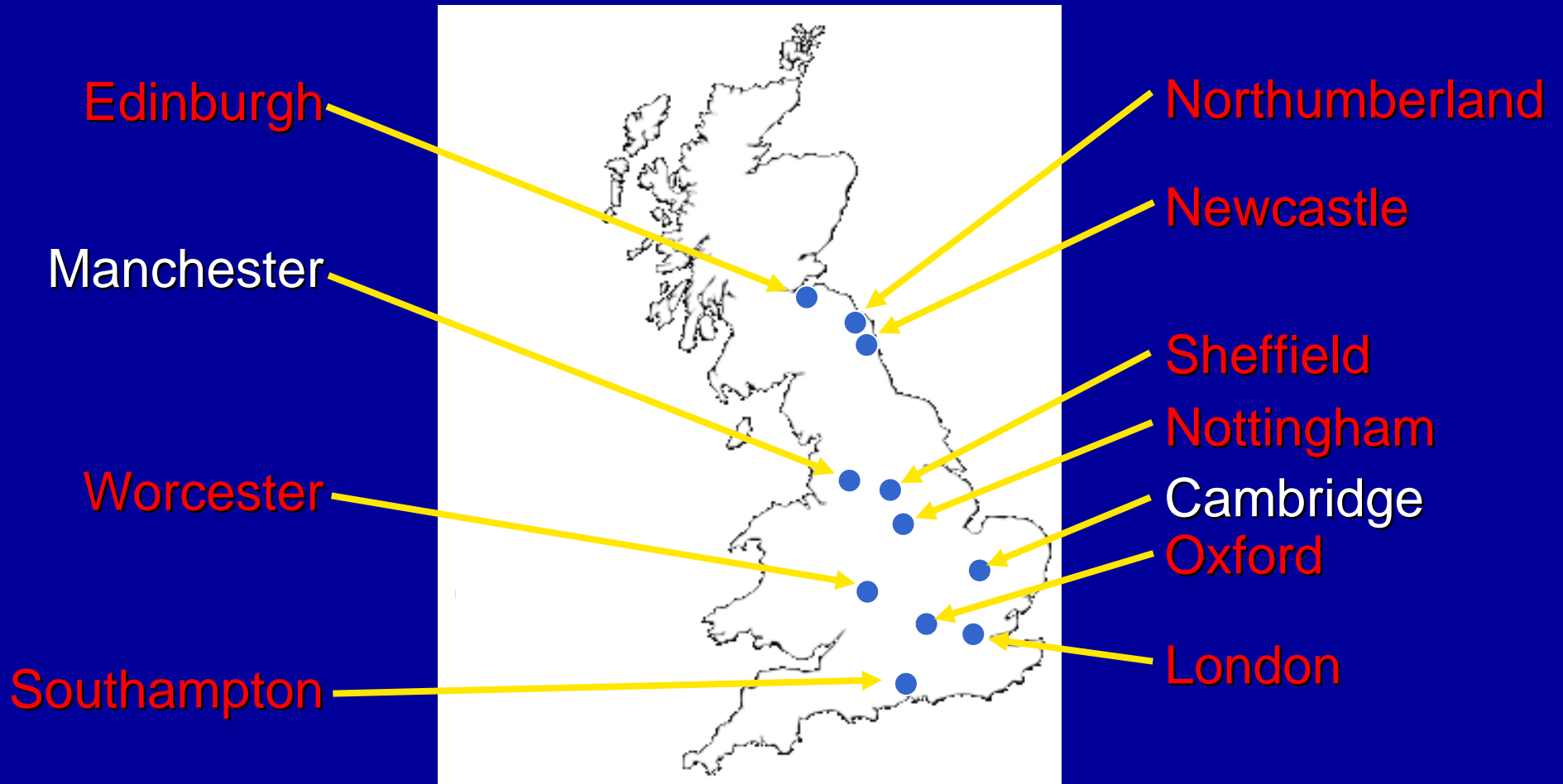
# Why the 610-Quad?

- 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!

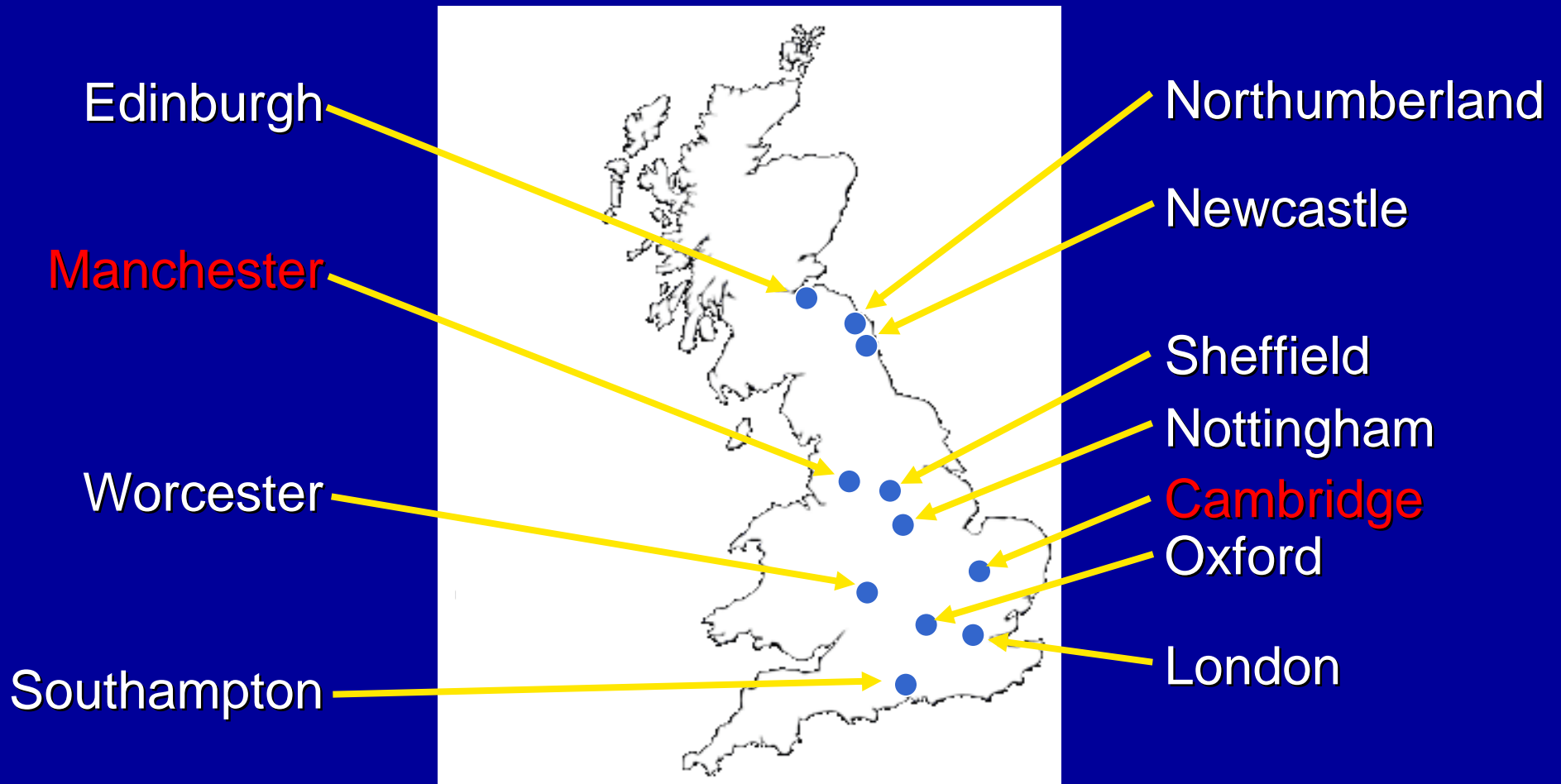
# There are 11 participating sites in arcOGEN



# 9 sites are collecting new cases



# DNA extraction, genotyping & analysis



# 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

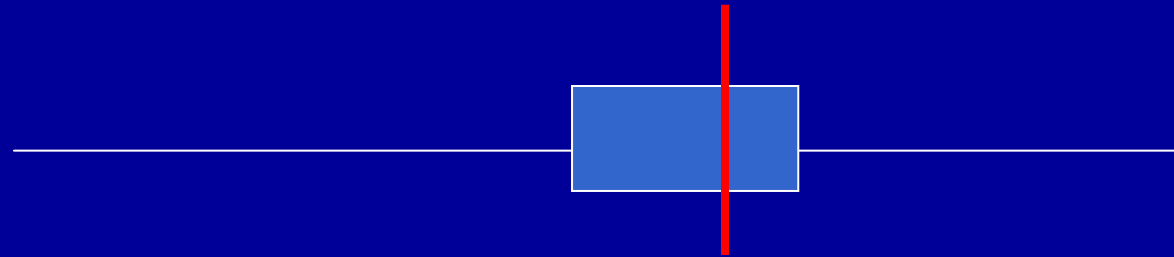
# What next

- Complete the scan, replicate hits and then search for the functional variants
- Sounds so easy!

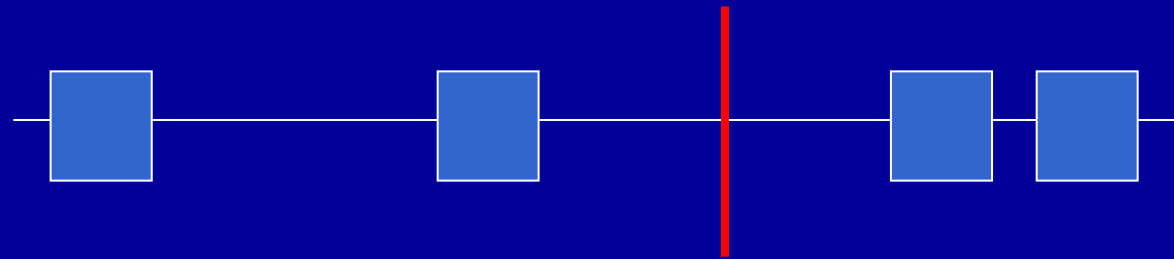
# Three scenarios

Associated SNP

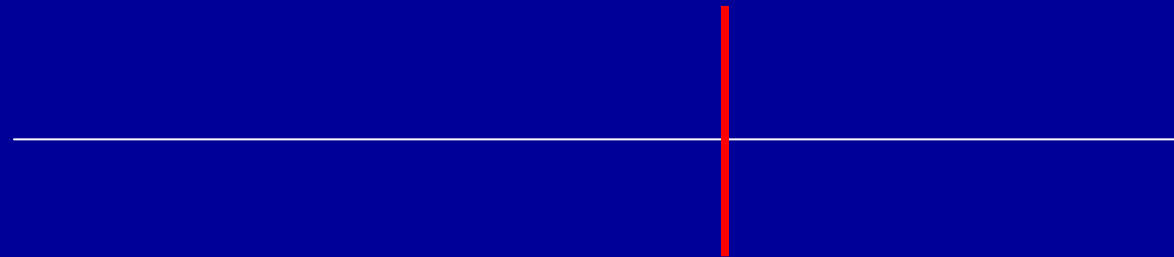
Ideal



OK



Nightmare!



# New concern

NEWS FEATURE PERSONAL GENOMES

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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