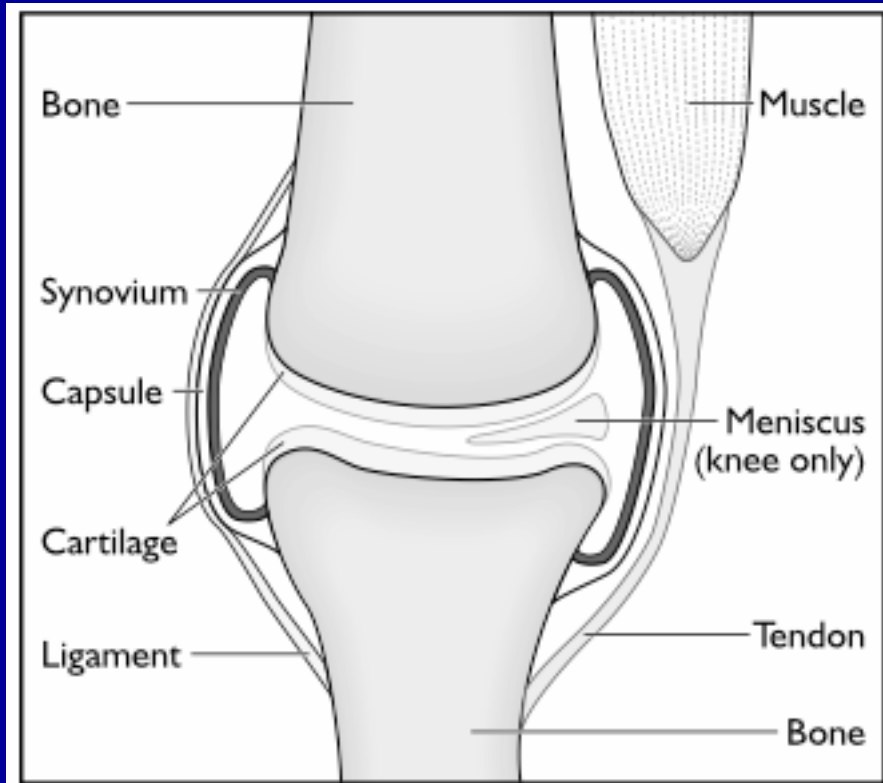


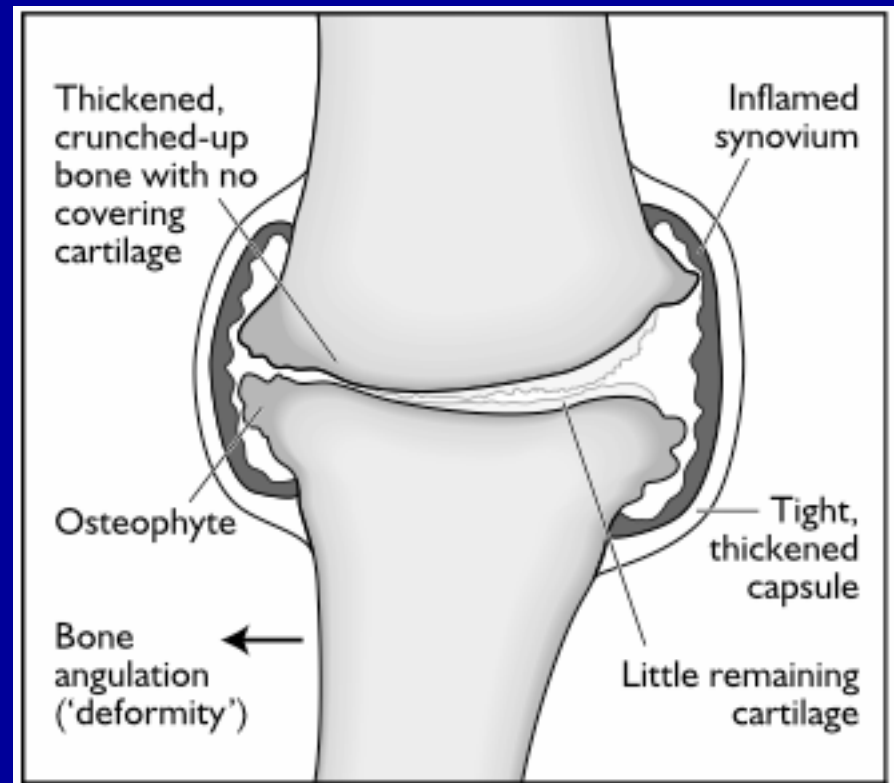
Osteoarthritis - is it all in the genes?

Dr John Loughlin
University of Oxford

The OA joint



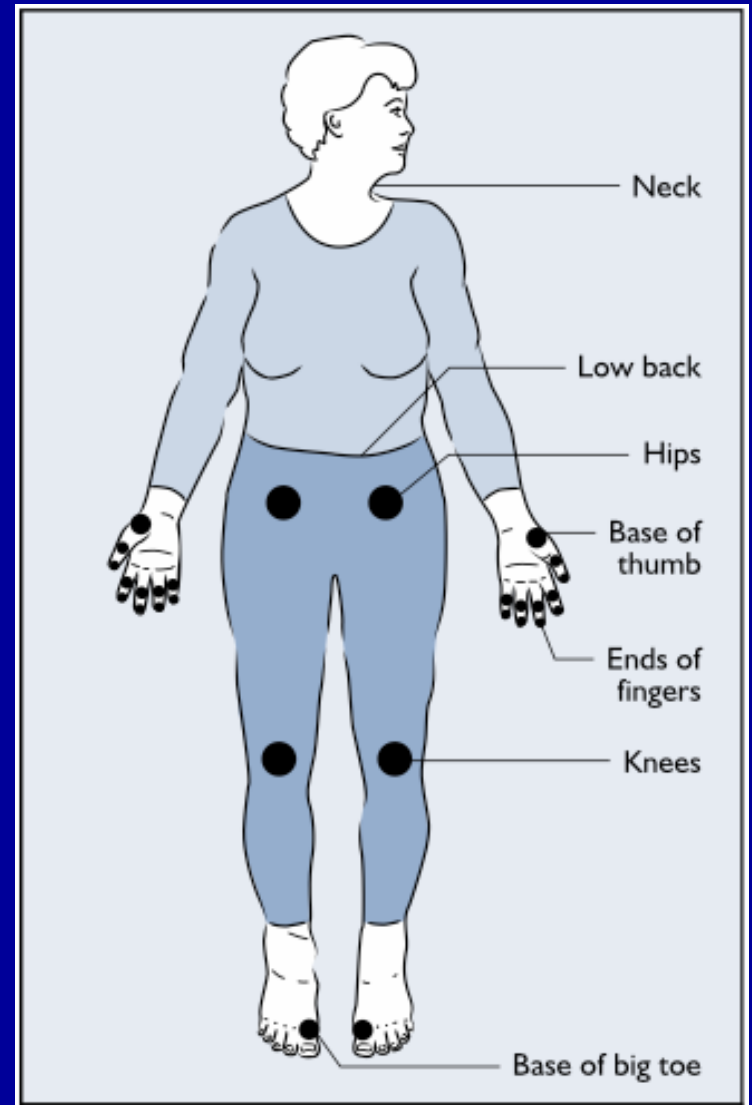
A healthy joint



An OA joint



An OA hip



Principal sites for OA

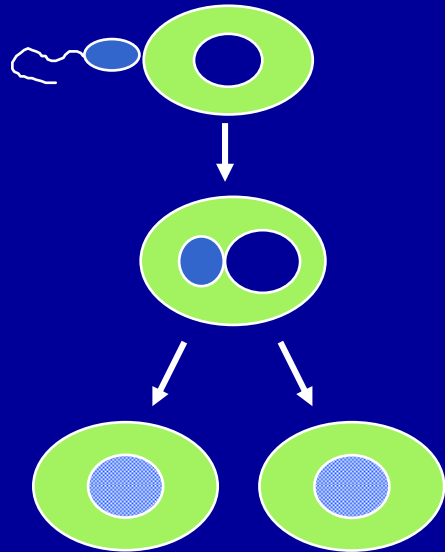
OA prevalence in the UK

- 5 million adults
- Majority aged > 60 years
- More females than males (3:1)
- Over 2 million GP appointments each year

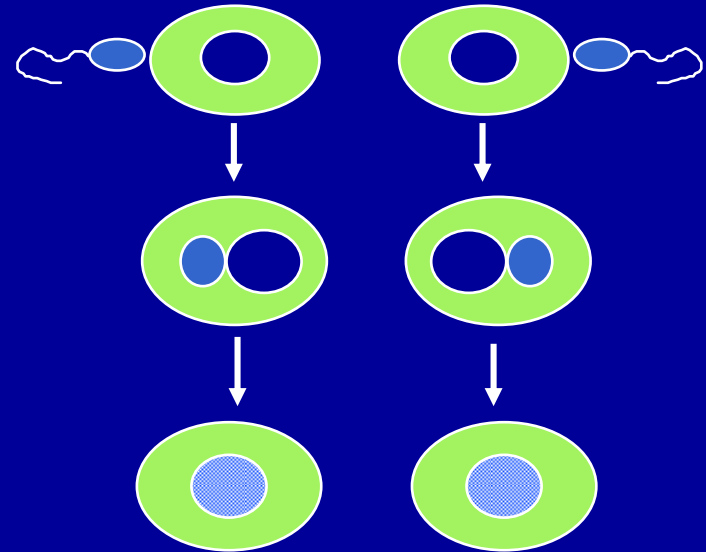
Twin studies

1 in 89 deliveries

1/3 Identical



2/3 non-identical



% Concordance rates

| | <u>Identical</u> | <u>Non-identical</u> |
|------------------|------------------|----------------------|
| Cystic Fibrosis | 100 | 25 |
| Die on a Tuesday | 14 | 14 |
| Osteoarthritis | 55 | 20 |

100%
Environmental



Struck by lightning

Infection

Weight

Hair Colour

Cancer

← Osteoarthritis

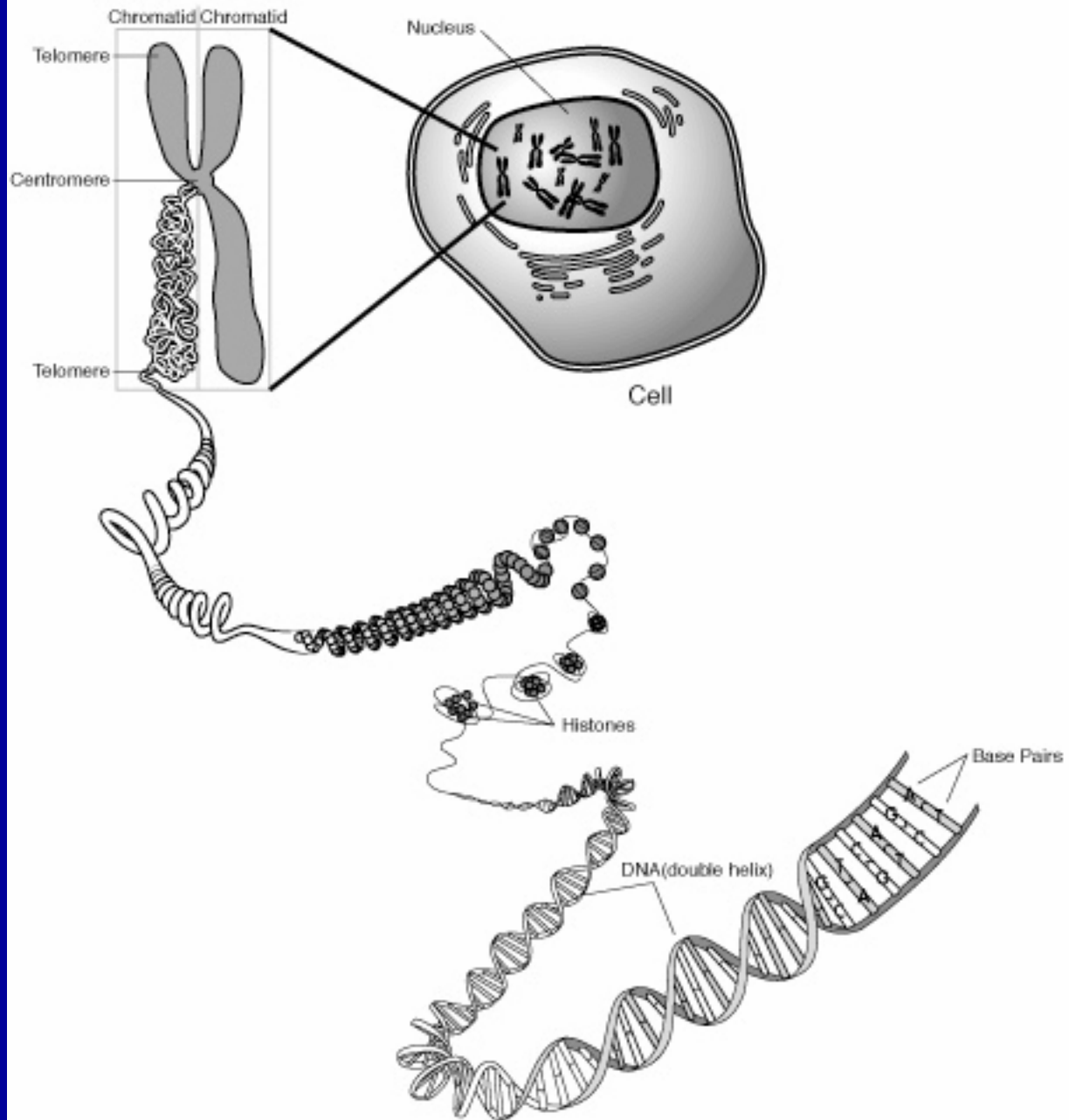
Diabetes

Height

Sex, cystic fibrosis

100%
Genetic

Chromosome



DNA sequence

.....TTTTCAGGTTGGTATCCCCACCGCATT.....

Makes protein

.....TTTTCAGGTTGGTATCCCCACCGCATT.....



TTT-TCA-GGT-TGG-TAT-CCC-CAC-CGC-ATT
phe-ser-gly-trp-tyr-pro-his-arg-ile

A new “mutation”

.....TTTTCAGGTTGGTATCCCCACCGCATT.....

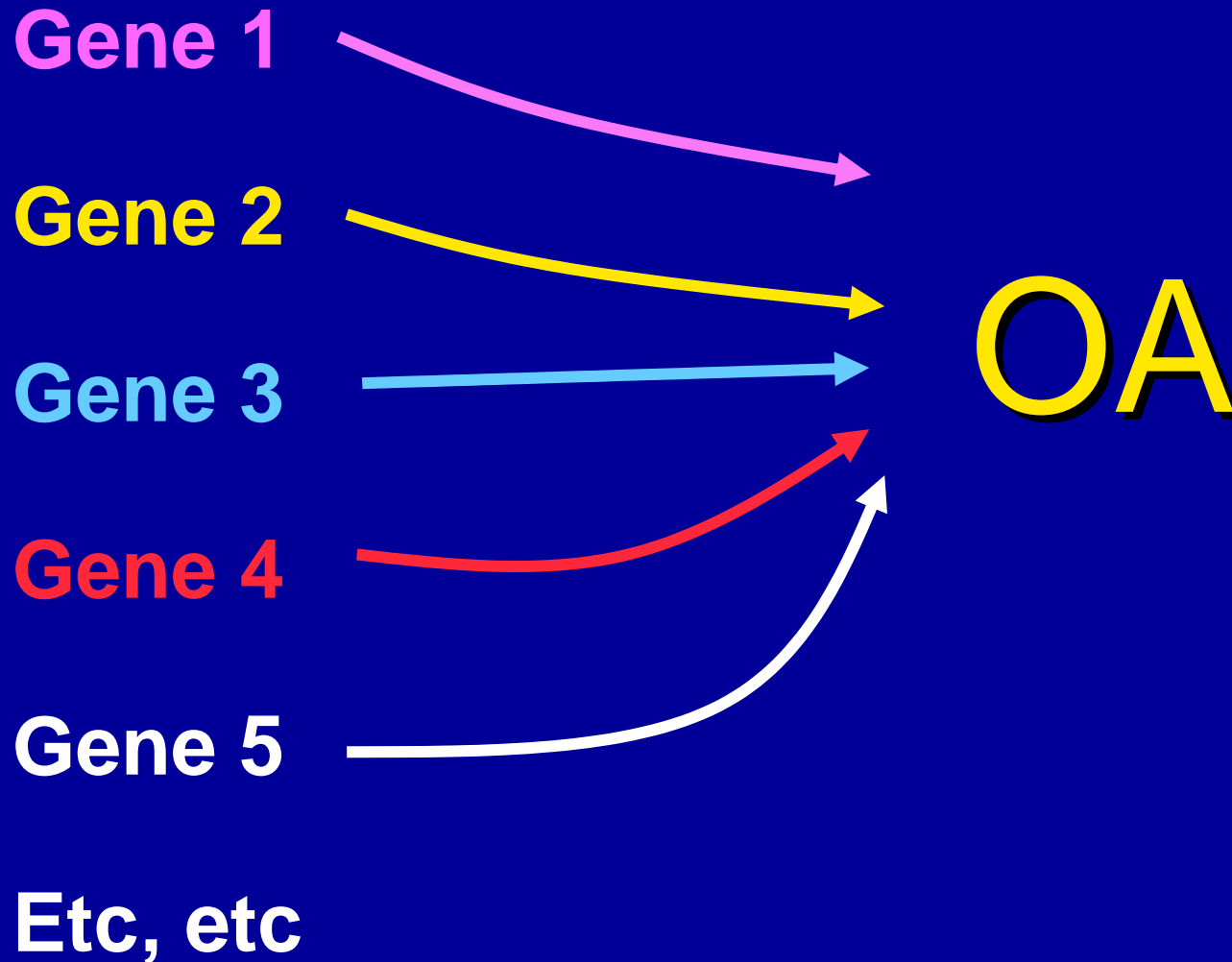


TTT-TCA-GGT-TGG-TAT-CCC-CAC-CGC-ATT
phe-ser-gly-trp-tyr-pro-his-arg-ile



TTT-TCA-GGT-TGG-CAT-CCC-CAC-CGC-ATT
phe-ser-gly-trp-his-pro-his-arg-ile

OA is polygenic

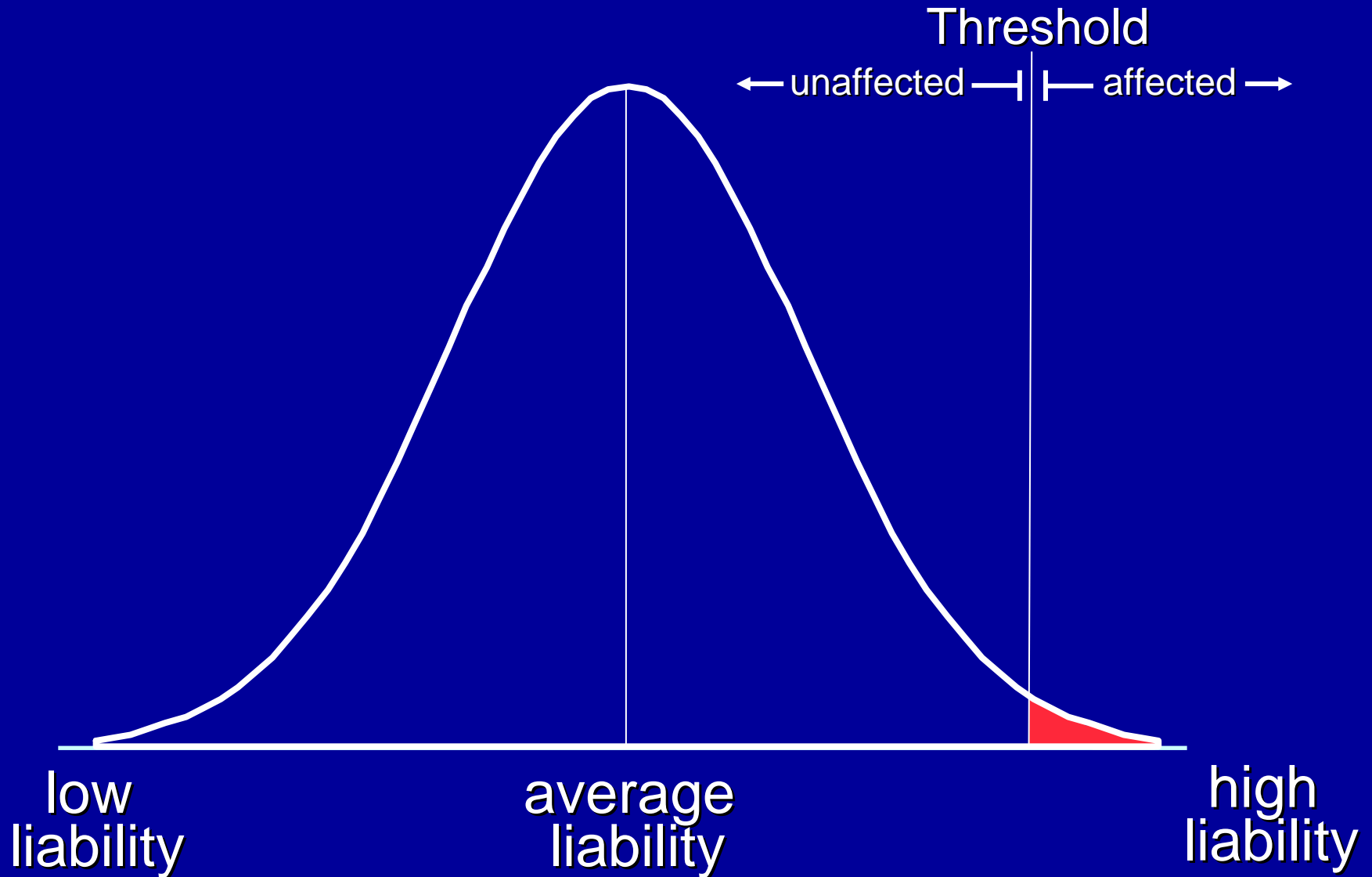


Osteoarthritis genetic susceptibility

- The disease manifests once a certain threshold of susceptibility has been surpassed

Threshold Model of Susceptibility

Distribution of liability

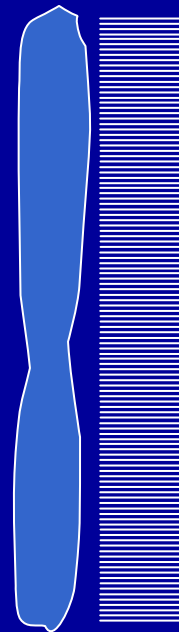
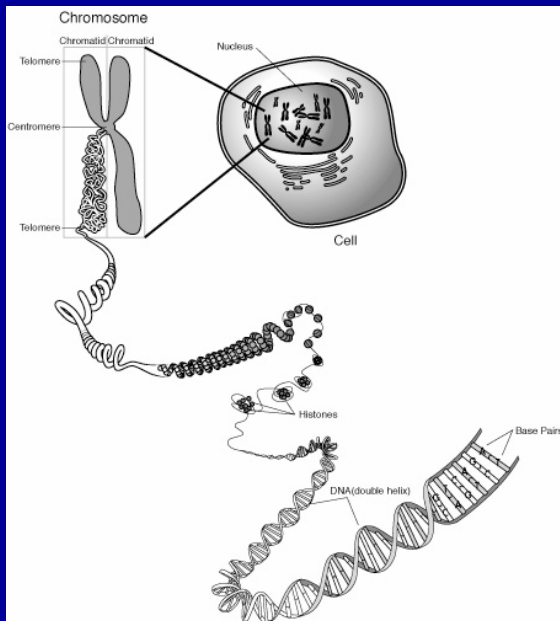


Crossing the threshold

- A combination of the genes one has inherited and the exposure one has had to environmental risk factors

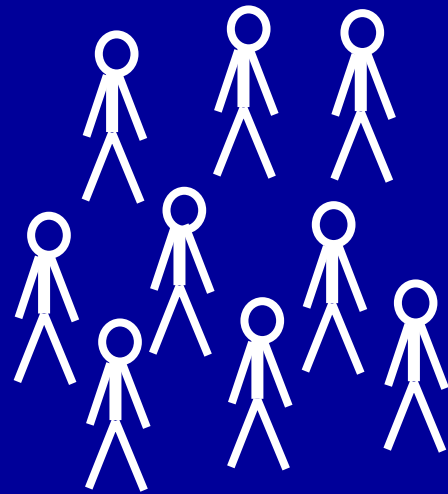
Finding OA genes

Investigate all of the DNA polymorphisms

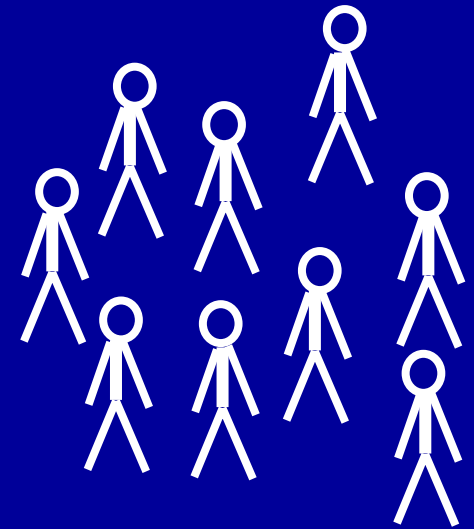


polymorphisms

Case-control Association Analysis



1000 Cases



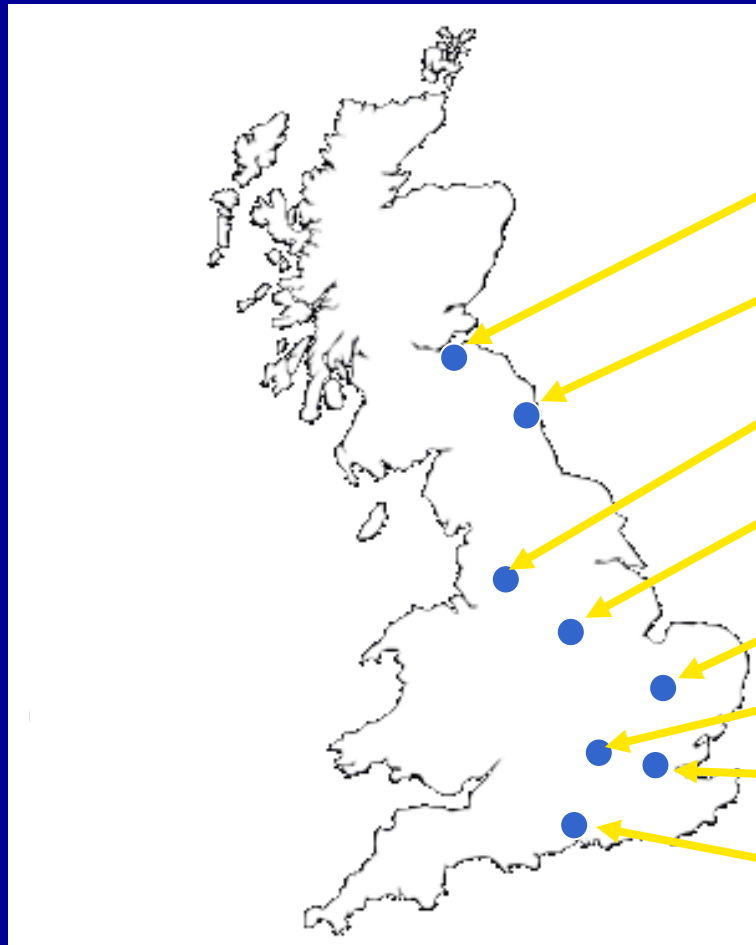
1000 Controls

Frequency of
polymorphism

11%

7%

The arcOGEN Consortium



Edinburgh

Newcastle

Manchester

Nottingham

Cambridge

Oxford

London

Southampton

The research plan

- 8000 OA cases & 6000 controls
- 500,000 polymorphisms
- 4 billion bits of data
- Open access of data for all

Potential utility of the genes we will identify

- Diagnosis and prognosis
- Genetic biomarkers for selection of patients for clinical trials
- New treatment development
 - Insights into mechanisms and pathways



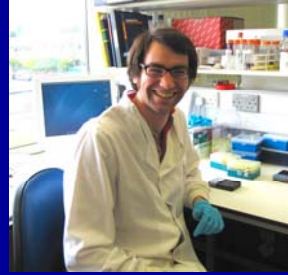
Lorraine
Southam



Sarah
Snelling



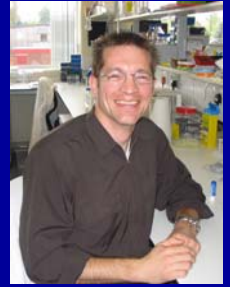
Kay
Chapman



James
Wilkins



Inken
Lorenzen



Rainer
Egli

