Osteoarthritis - is it all in the genes?

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The OA joint

A healthy joint

An OA joint

- Bone
- Muscle
- Synovium
- Capsule
- Meniscus (knee only)
- Cartilage
- Ligament
- Tendon
- Bone
- Thickened, crunched-up bone with no covering cartilage
- Inflamed synovium
- Osteophyte
- Bone angulation ('deformity')
- Tight, thickened capsule
- Little remaining cartilage
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
<table>
<thead>
<tr>
<th>Condition</th>
<th>Identical</th>
<th>Non-identical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Die on a Tuesday</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>55</td>
<td>20</td>
</tr>
</tbody>
</table>
DNA sequence

......TTTTTCAGGTTTGGGTATCCCCACCCGCATT......
Makes protein

......TTTTTCAGGTTGGTATCCCCCACCAGCATT......

↓

TTT-TCA-GGT-TGG-TAT-CCC-CAC-CGC-ATT
phe-ser-gly-trp-tyr-pro-his-arg-ile
A new “mutation”

......TTTTTCAGGTTGGTATCCCCCACCAGCATT......

↓

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

Gene 1 → OA
Gene 2 → OA
Gene 3 → OA
Gene 4 → OA
Gene 5 → OA
Etc, etc
The disease manifests once a certain threshold of susceptibility has been surpassed.
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
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