Validation of Genetic Determinants of Skeletal Diseases

Dr Kasia Piróg

(Newcastle University)

EUROPEAN COMMISSION

SEVENTH FRAMEWORK PROGRAMME

What is VSYBIL?

Prof Michael Briggs

Project Coordinator

Partners

Name

Newcastle University
University of L'Aquila
University of Manchester
Alacris Theranostics
University of Pavia
Polygene
Consiglio Nazionale delle Ricerche
Institut National de la Santé et de la Recherche Médicale
Certus Technology Associates Limited
Charité - Universitaetsmedizin Berlin
GATC Biotech AG
University Medical Center Hamburg Eppendorf
Evercyte (EVCYT)
University Hospital of Cologne
PRIMM Srl
University of Freiburg
University of Antwerp
Finovatis

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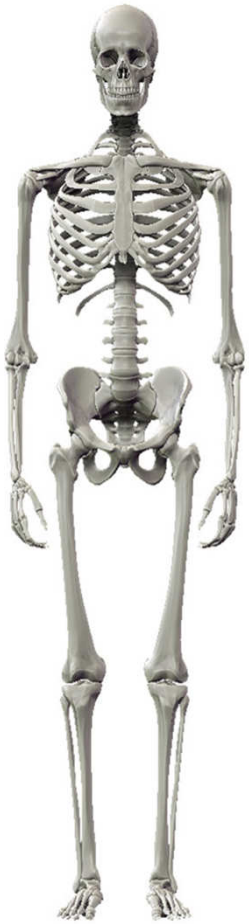
Skeletal conditions

Common

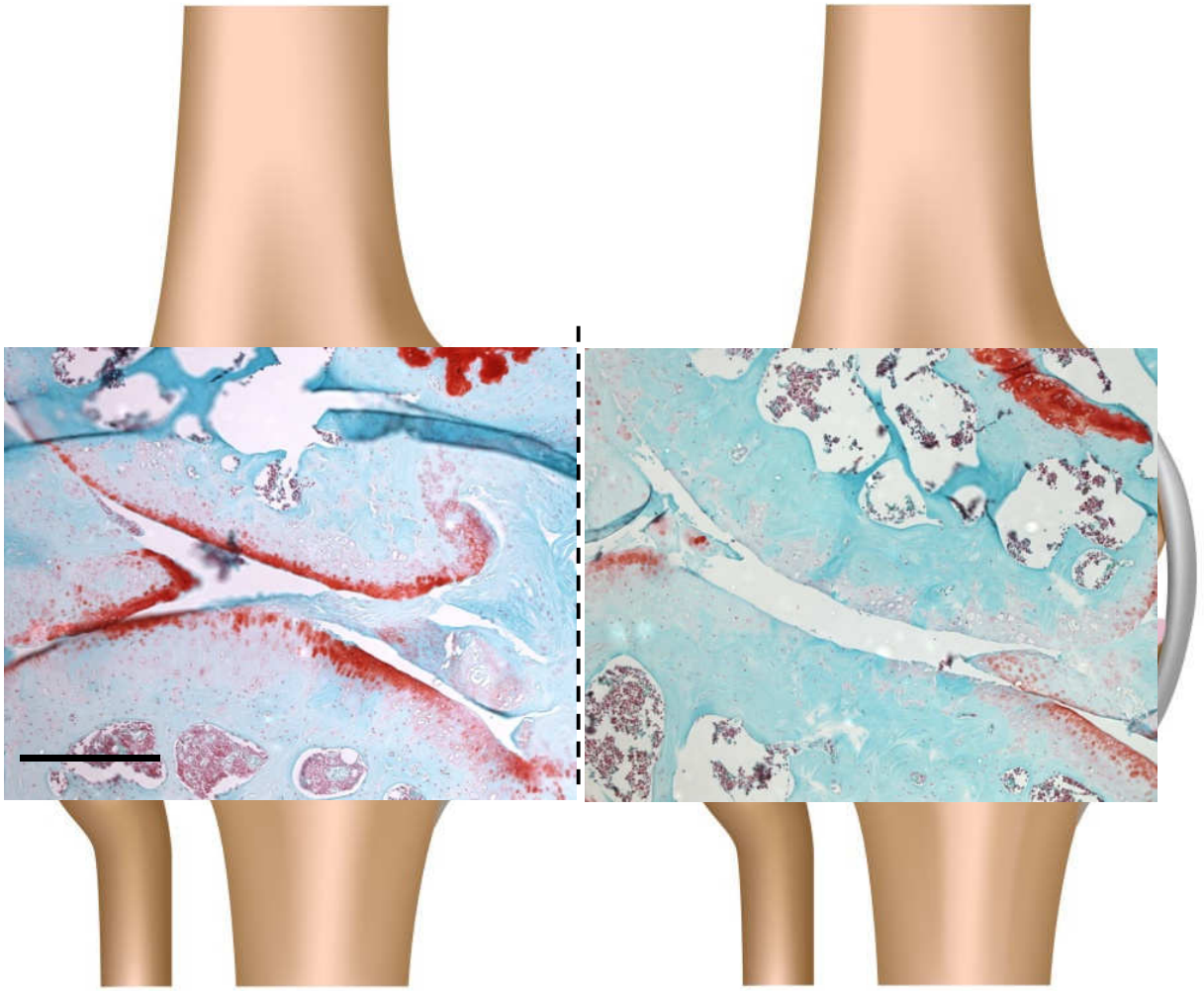
- related to ageing and/or injury
- often multifactorial
- often difficult to model
- SYBIL focuses specifically on osteoarthritis (OA) and osteoporosis (OP)
- **35-40 million people** suffer from **OA** in Europe
- the lifetime risk for OP fractures is 30-50% in women and 15-30% in men
- **OA and OP represent a major healthcare burden with the projected expansion of elderly population**



Rare

- **450** different rare skeletal conditions
- an overall incidence of **1/4000**
- extrapolates to **225,000 people** in the EU
- affect growth and development of the skeleton
- often monogenic (mutation in single gene)
- modelled in cells and in transgenic animals
- **a simple model to analyse the effects of genetic defects on disease progression**

Case study - osteoarthritis

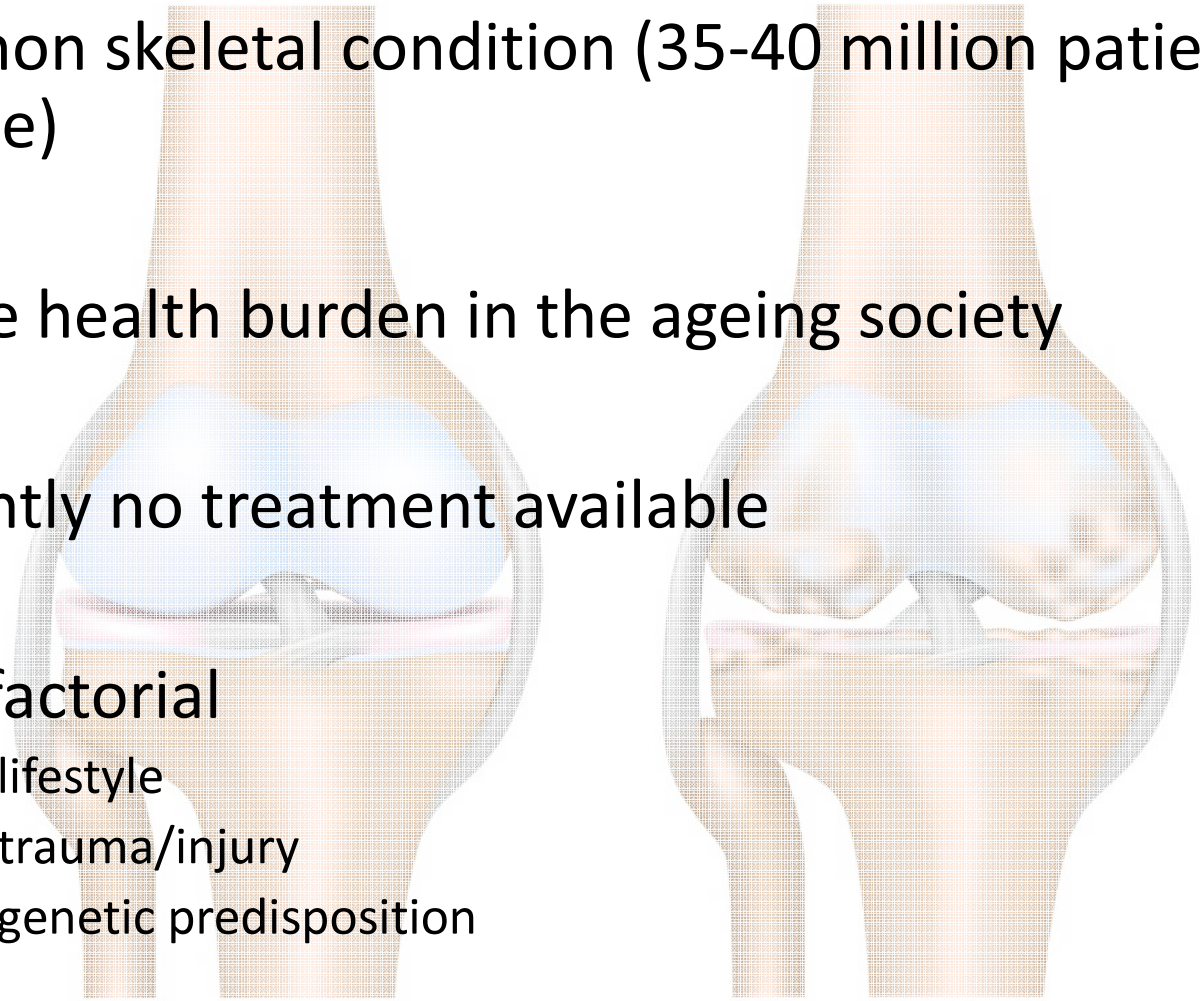


Healthy knee joint

Osteoarthritis

Case study - osteoarthritis

- common skeletal condition (35-40 million patients in Europe)
- severe health burden in the ageing society
- currently no treatment available
- multifactorial
  - lifestyle
  - trauma/injury
  - genetic predisposition
- modelled in animals often with surgical intervention



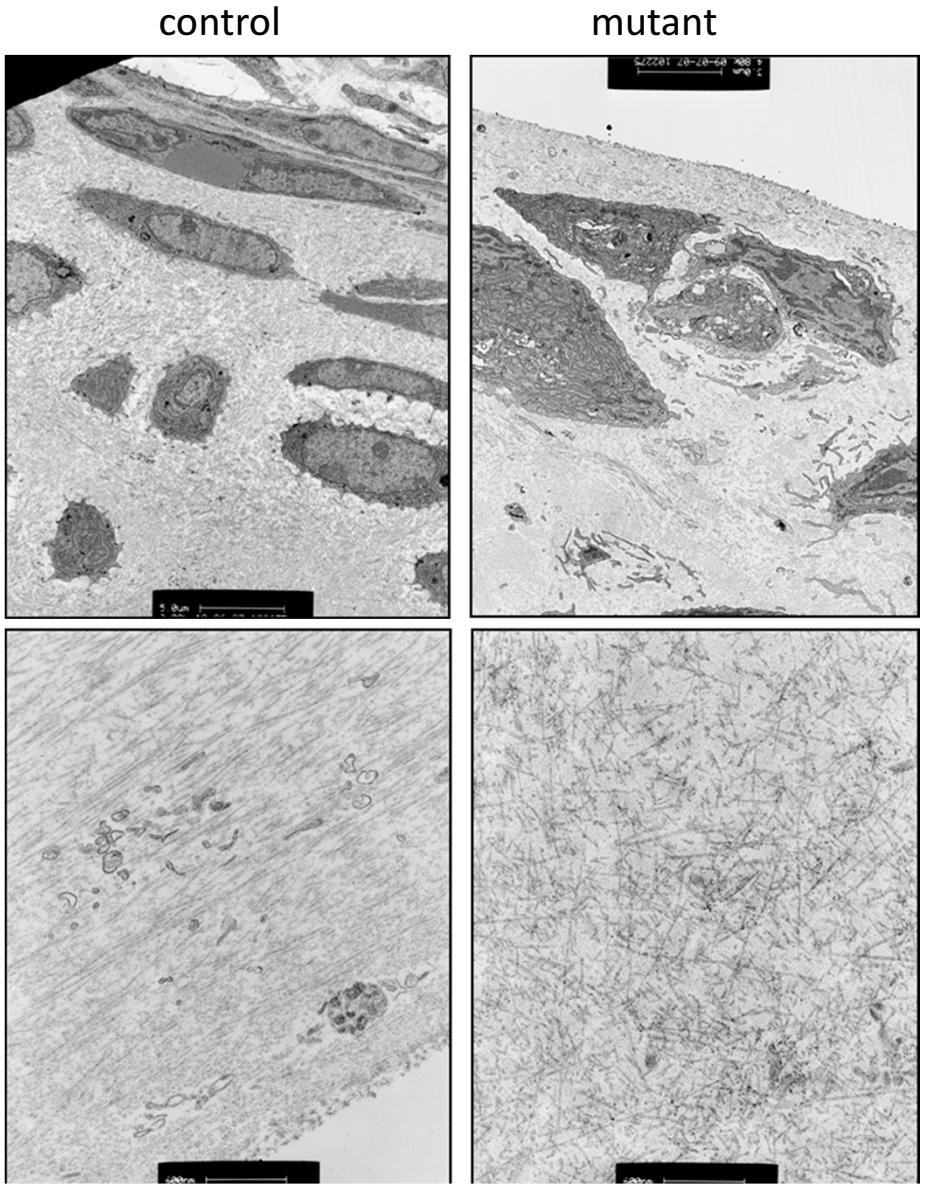
Rare skeletal conditions associated with osteoarthritis

- affect development and growth of the skeleton
- monogenic (mutation in a single gene)
- individually rare conditions but quite common as a group of disorders
- associated with musculoskeletal complications such as osteoarthritis
- easy to model in the laboratory setting

Multiple epiphyseal dysplasia

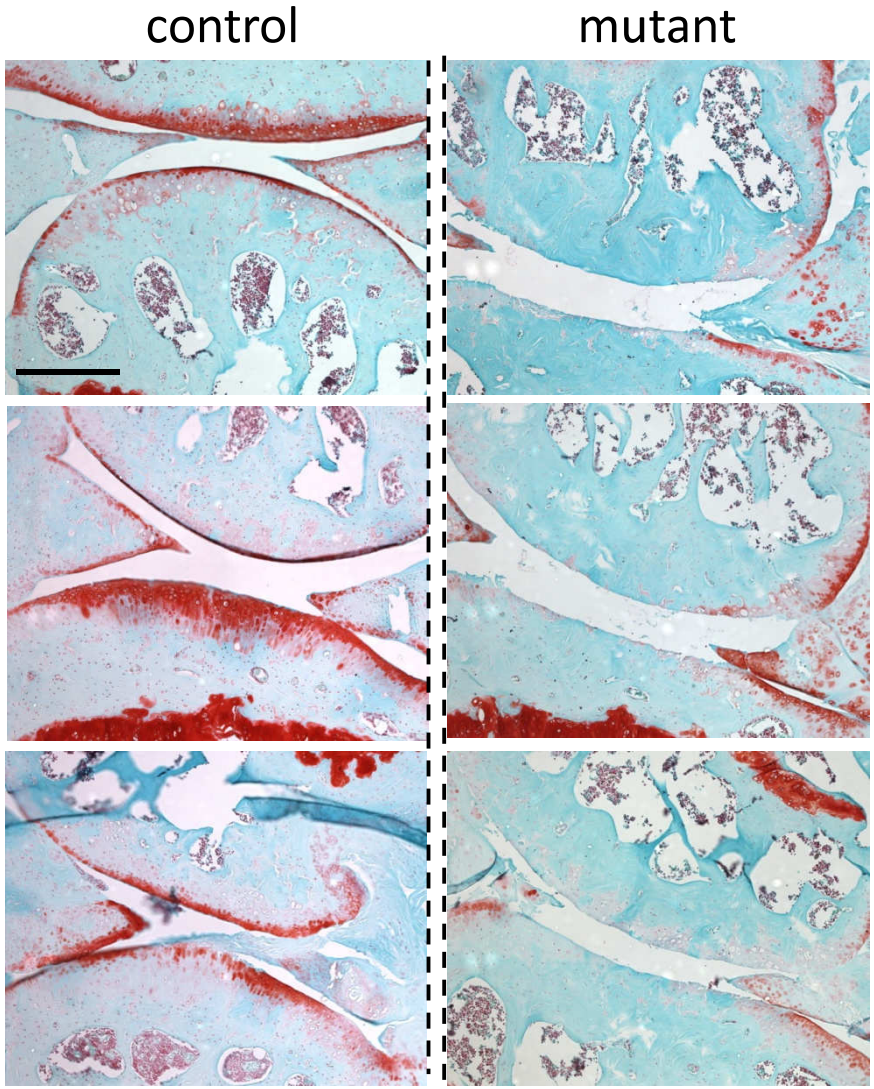
- autosomal dominant
- rare skeletal condition
- results from mutations in genes encoding structural proteins in cartilage
- short limbed dwarfism
- joint laxity
- **early onset osteoarthritis**

Mouse models allow the study of early degenerative changes



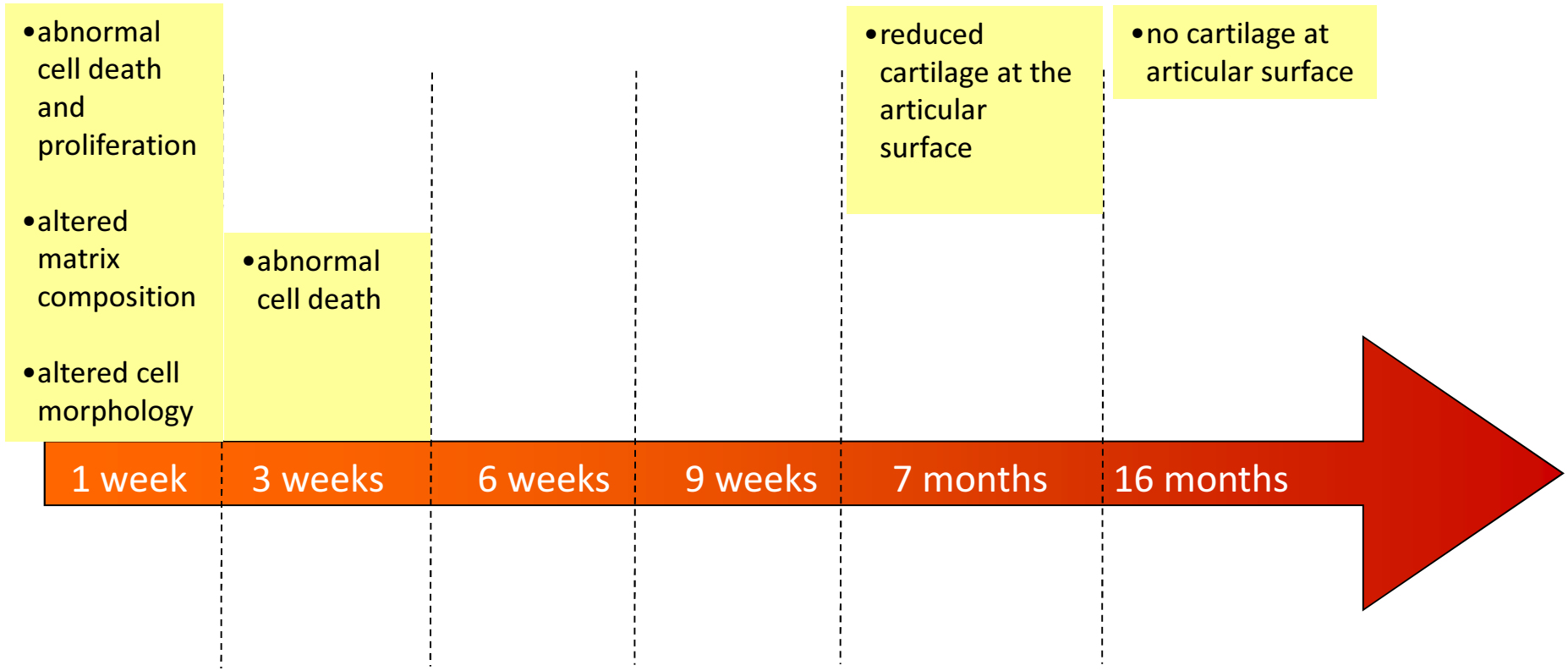
- first changes at 1 week
- abnormal cell death
- altered matrix composition
- altered cell morphology

MED mouse model develops early onset osteoarthritis



mouse	human
1 month	2.5 years
3 months	7.5 years
6 months	15 years
1 year	30 years
2 years	60 years
3 years	90 years

Mouse models allow the study of disease progression

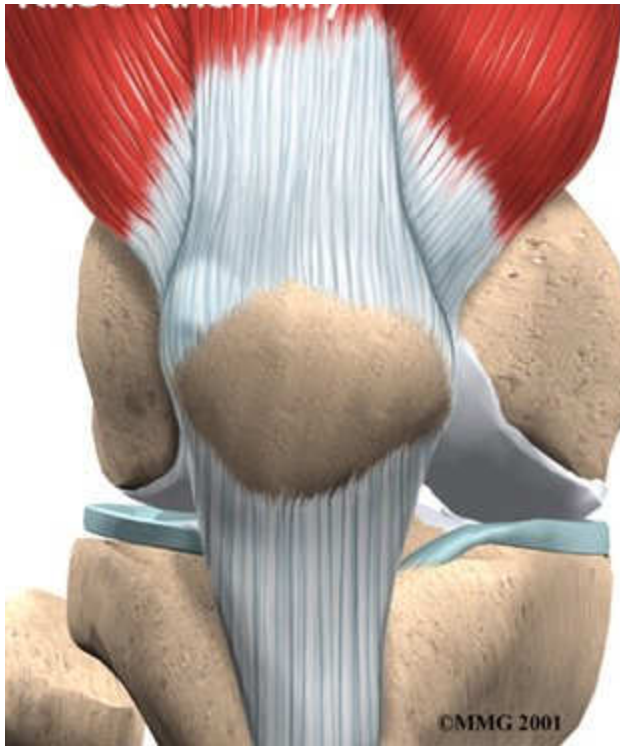


Soft tissue complications in osteoarthritis

- muscle weakness, tendon/ligament injury and joint laxity are the recognised conditions affecting the OA progression

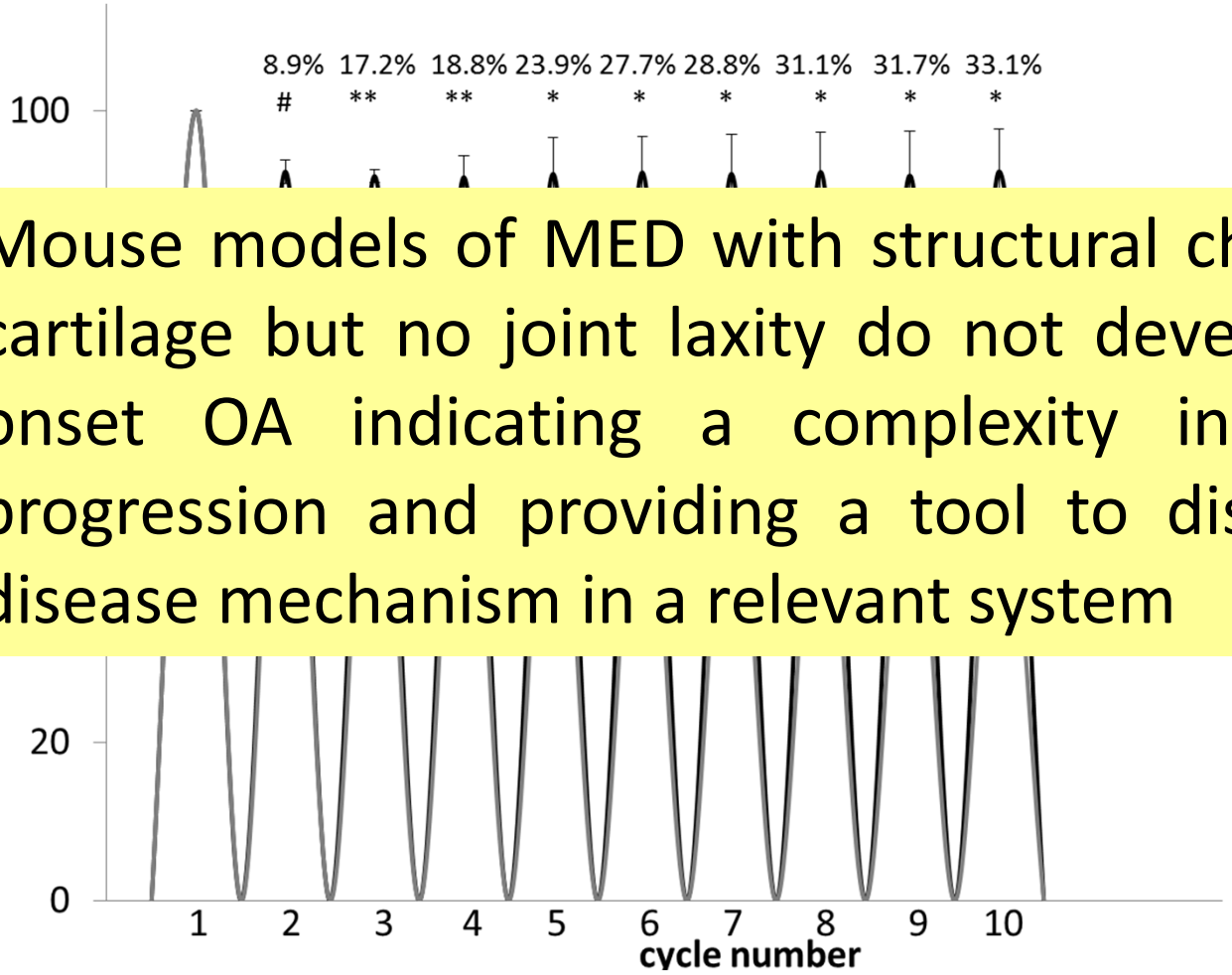
- some MED patients are diagnosed with a “neuromuscular disorder” prior to correct skeletal diagnosis

- MED patients often suffer from tendon/ligamentous laxity



Soft tissue complications in osteoarthritis

Achilles tendons of mutant mice are more lax in cyclic testing



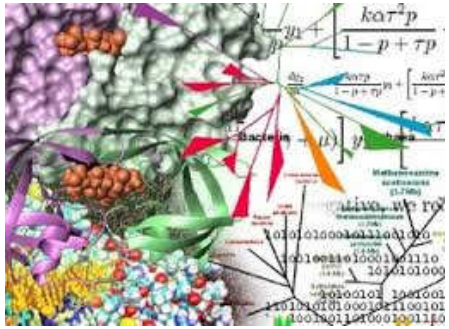
Mouse models of MED with structural changes in cartilage but no joint laxity do not develop early onset OA indicating a complexity in disease progression and providing a tool to dissect the disease mechanism in a relevant system

Piróg et al. Hum Mol Gen 2010 19(1): 52-64.

Systems biology approach

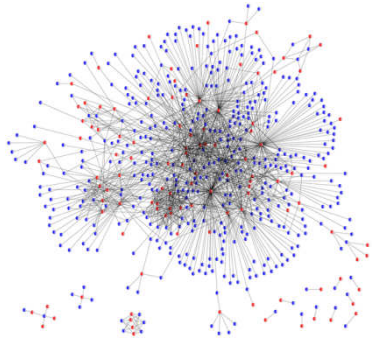
perform an experiment

molecular behaviour in bone/joint



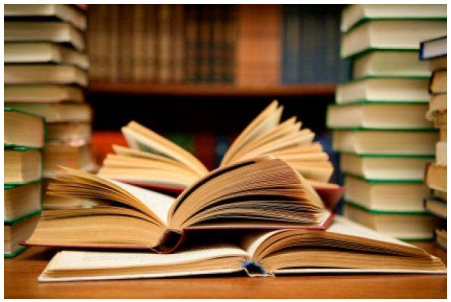
gather “omics” data

gene expression, proteomics etc.



generate a network

protein to protein or gene interactions



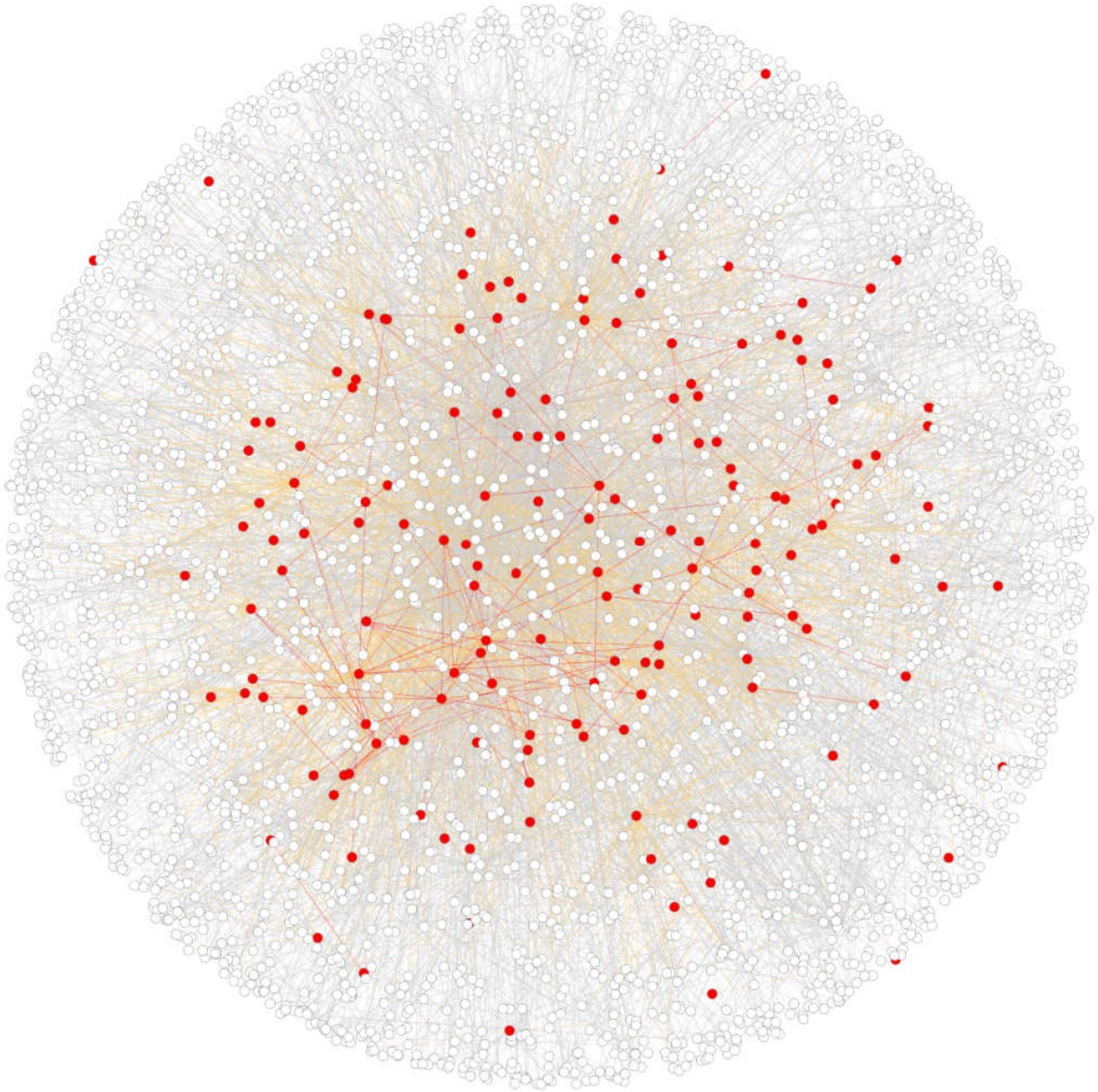
perform literature search

genes of interest, “omics” databases.

delineate mechanisms

diagnosis, treatment, predictions

Systems biology approach



What do we expect to achieve?

Functional validation of genetic determinants of skeletal conditions and ageing processes in animal and cellular models

- use animal and cellular models to study functions of genes associated with human diseases and/or ageing processes
- develop efficient, standardised and reliable tools and procedures
- identify, validate and create a portfolio of new biomarkers and therapeutic targets
- integrate and maintain the data in publically accessible web portals

For more information please visit:

http://www.sybil-fp7.eu/

https://twitter.com/SYBIL_news

http://mikebriggs1910.wordpress.com/

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