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Genetics of Osteoporosis and Osteoarthritis

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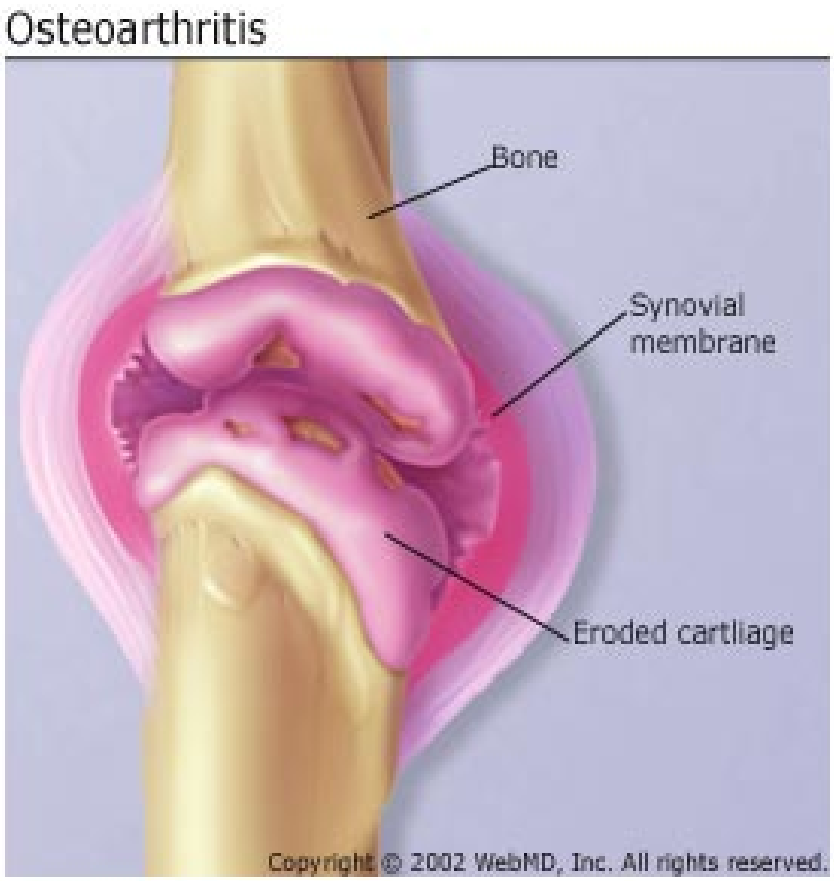
Outline

1. Introduction and risk factors for osteoarthritis (OA) and osteoporosis
2. Sex differences
3. Genetics of OA and osteoporosis
   - What have we learned and where are we going?

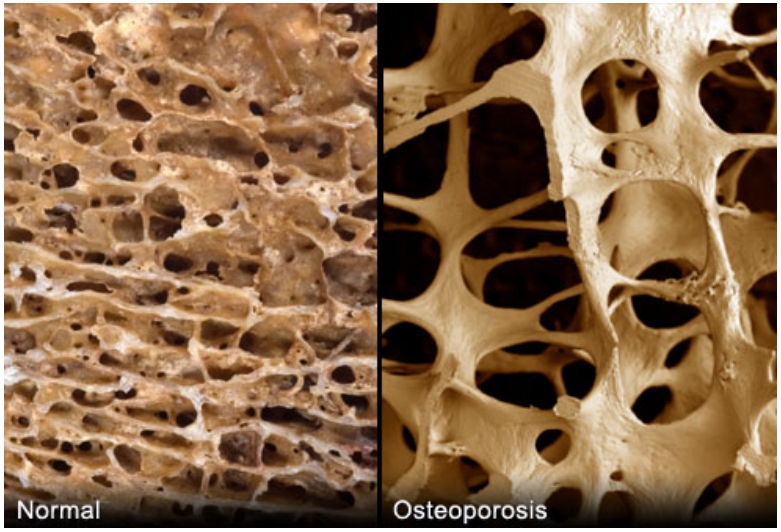
Osteoarthritis (OA)

- Most common form of arthritis
- Nearly 1 in 2 people will experience painful knee OA and 1 in 4 painful hip OA during their lifetime
- Most common in weight bearing joints
- Often leads to disability
- Few treatment options available



Osteoporosis

- Characterized by porous bone, leading to fracture
- Due to low peak bone mass or rapid bone loss following menopause
- 75% of hip fractures in women
- Nearly 1 in 2 women and 1 in 4 men age 50+ will have an osteoporosis-related fracture later in life (wrist, hip, spine)
- Prevalence higher in thin, white women



http://www.webmd.com/osteoporosis/ss/slideshow-osteoporosis-overview

Risk Factors for OA and Osteoporosis

Osteoarthritis

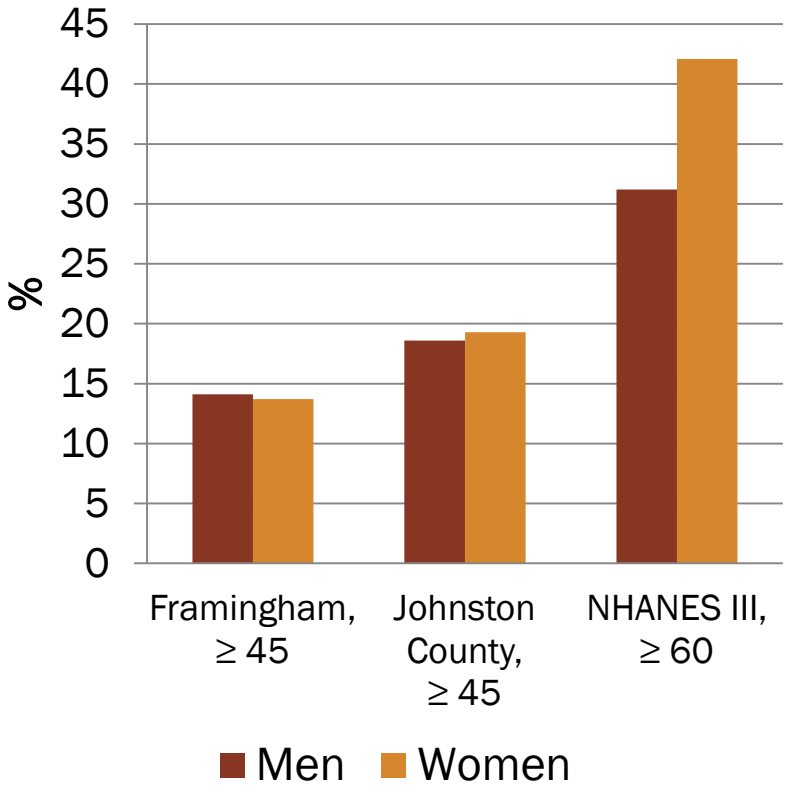
- Women
- High BMI
- Prior joint injury
- Bone density (higher)

Osteoporosis

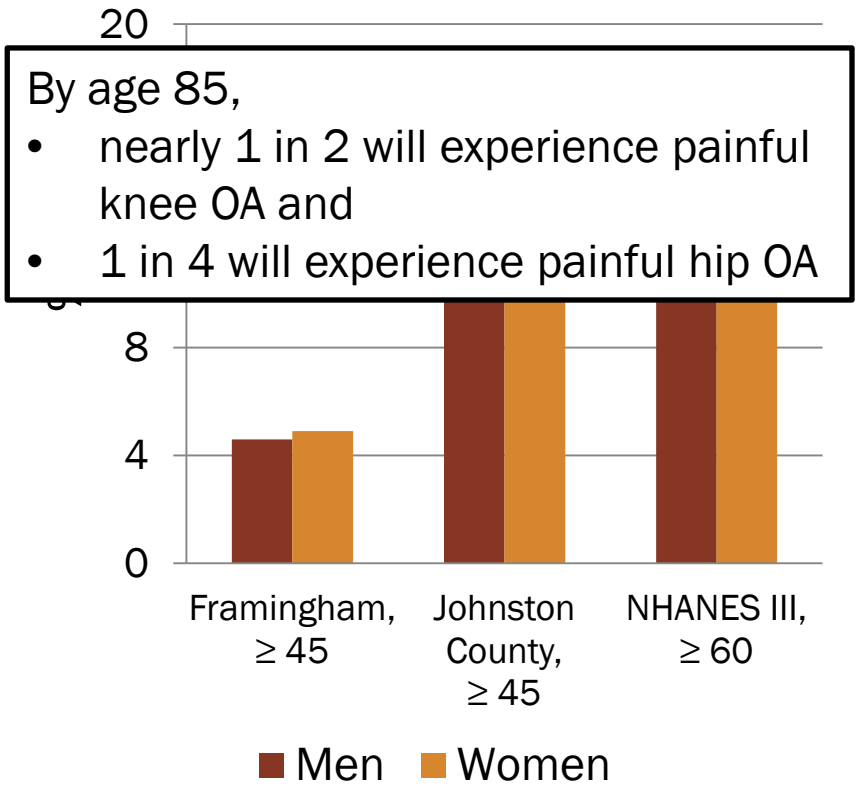
- Women
- Low BMI
- Physical inactivity
- Smoking
- Low estrogen levels
- Calcium and vitamin D intake
- Some medications (e.g., corticosteroids)

Prevalence of knee OA by sex

Radiographic OA



Symptomatic OA



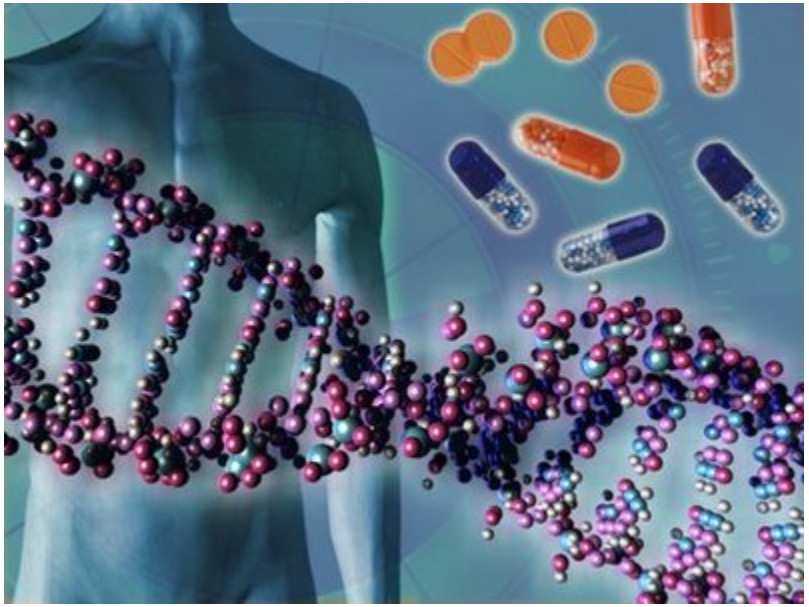
Source: Lawrence et al., Arthr & Rheum 58:26, 2008

Why are bone and joint disorders more common in women?

- Sex differences in risk factors
- Hip geometry?
- Interplay between risk factors and genetics?

Why study genetics of bone and joint disorders?

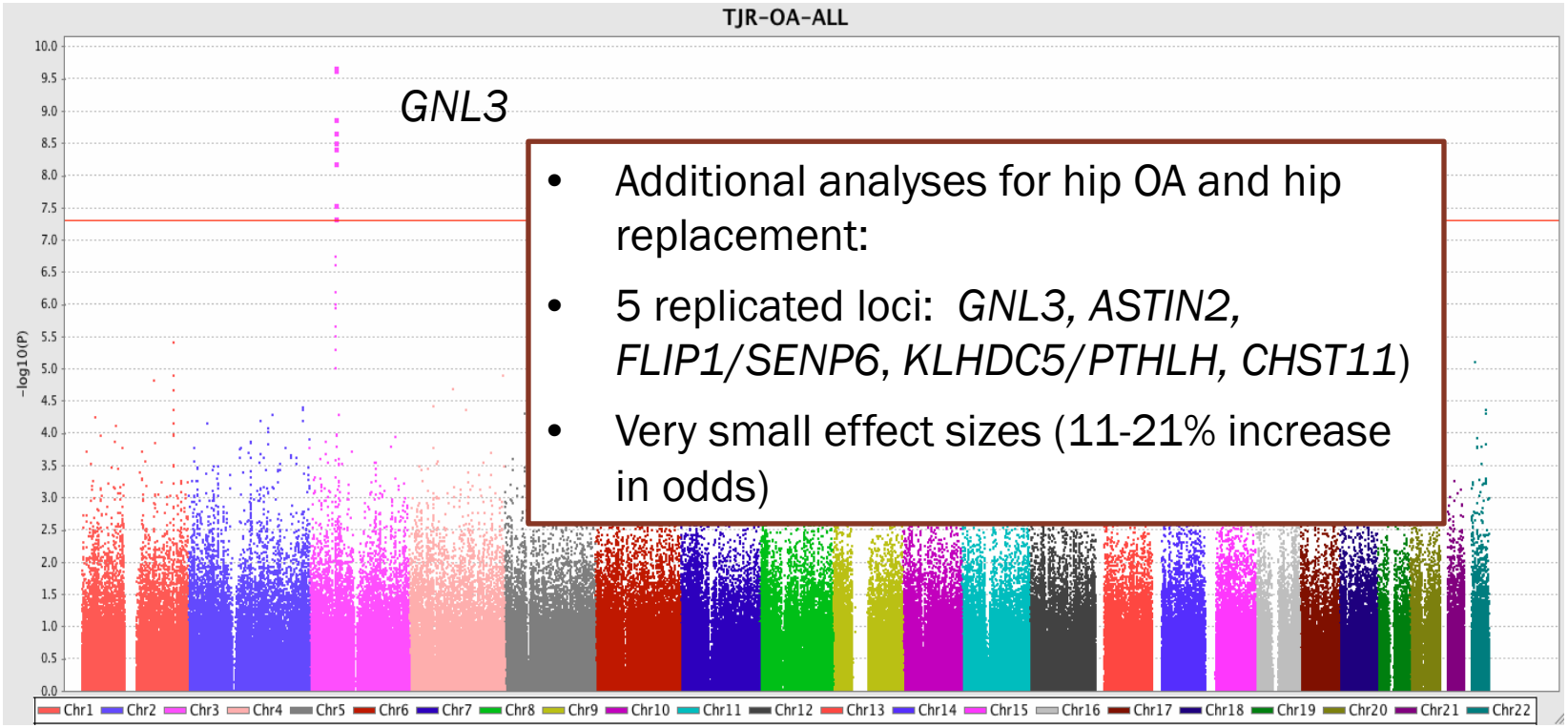
- Root ‘causes’ of osteoporosis and OA are not clear.
- Identifying genes associated with bone and joint disorders may provide new insights about disease pathways and ultimately new therapeutic targets



Genetics of OA and osteoporosis

- Heritability/familial aggregation
  - Heritability of radiographic OA at hip and knee: 40-60%
  - Heritability of bone mineral density: 50-60%
- Identifying susceptibility genes
  - Candidate gene studies (early approaches)
  - Genome-wide approaches (more recent approaches)

Genome-wide association study of OA (total joint replacement)

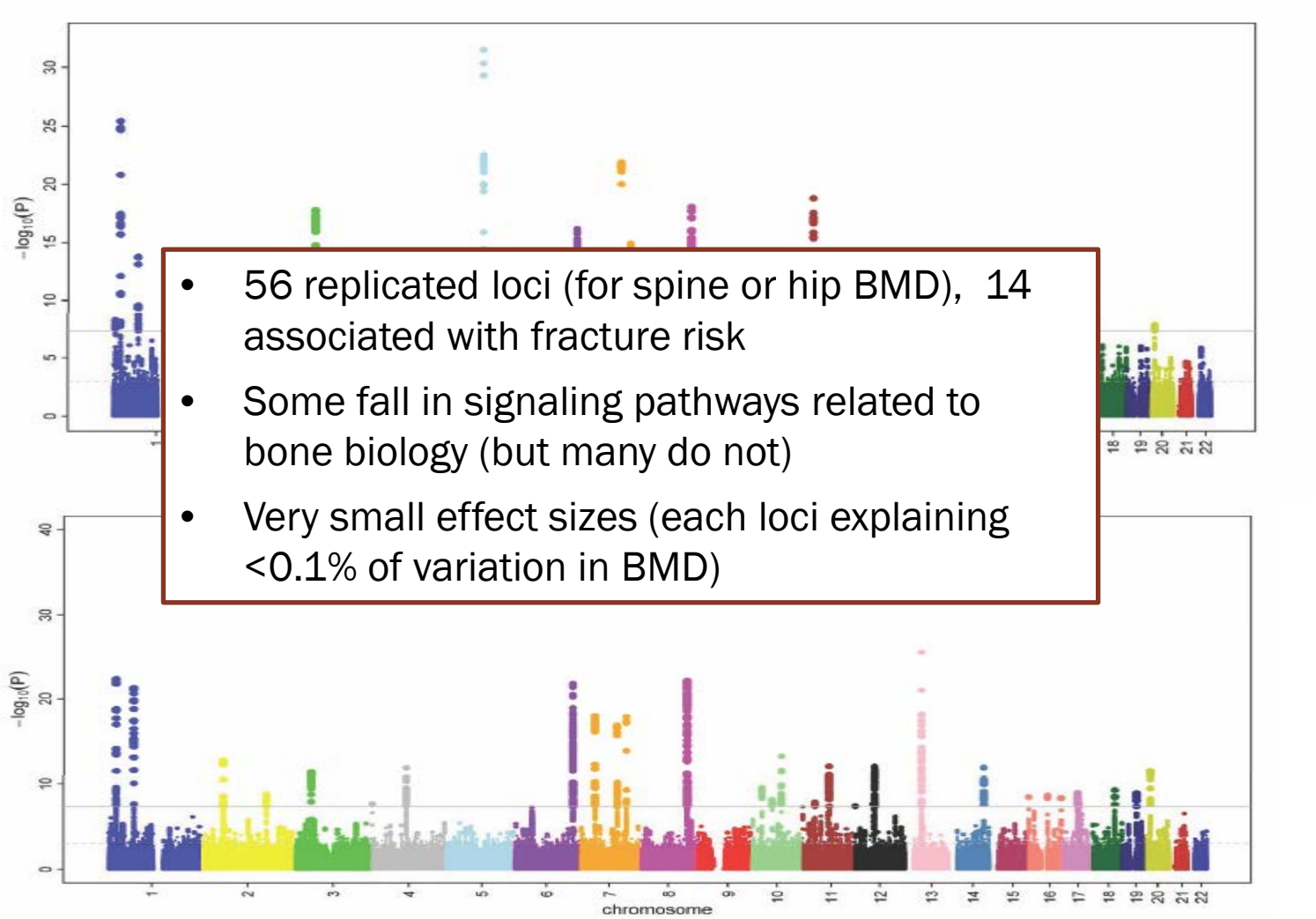


- Additional analyses for hip OA and hip replacement:
- 5 replicated loci: *GNL3, ASTIN2, FLIP1/SENP6, KLHDC5/PTHLH, CHST11*)
- Very small effect sizes (11-21% increase in odds)

- 7,410 cases (with replication in an additional 7,473 cases)

Source: arcOGEN Consortium, Lancet 380:815, 2012

Genome-wide association study of BMD



- 56 replicated loci (for spine or hip BMD), 14 associated with fracture risk
- Some fall in signaling pathways related to bone biology (but many do not)
- Very small effect sizes (each loci explaining <0.1% of variation in BMD)

- ~33,000 subjects (with replication in ~51,000 subjects)

Source: Estrada et al., Nat Genet 44:491, 2012

Can genetics inform us about gender differences in bone/joint diseases?

- Sex-specific genetic effects?
- To what extent do susceptibility genes act via their effects of hormonal/nutritional pathways?
- Impact of genetics on:
  - Genetic susceptibility to pain
  - Disease progression
  - Fracture risk (e.g., balance)

Where might genetics take us in understanding/treating bone/joint diseases?

- Will genetics be useful for disease prediction? (almost certainly not)
- Lead to targeted treatments based on underlying molecular defects?
  - Development of new drugs?
  - Patient-specific interventions depending on the underlying defect?

Conclusions

- Osteoarthritis and osteoporosis are common disorders, with enormous public health impact.
- Environmental risk factors identified, but both disorders show strong evidence for familial aggregation and genetic susceptibility.
- Some genes identified but all have very small effects and not useful for prediction.
- Identifying new genes may inform us about the biology and ‘root’ causes of the disease, possibly suggesting new therapies and personalized approaches to treatment and prevention.