Genetics of Osteoporosis and Osteoarthritis

Braxton D. Mitchell, PhD
Professor of Medicine
University of Maryland
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

By age 85, • nearly 1 in 2 will experience painful knee OA and • 1 in 4 will experience painful hip 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)

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

- 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)

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.