# New Insights Revealed by Genetic Studies and the Future of Treating Bone Health Related Issues

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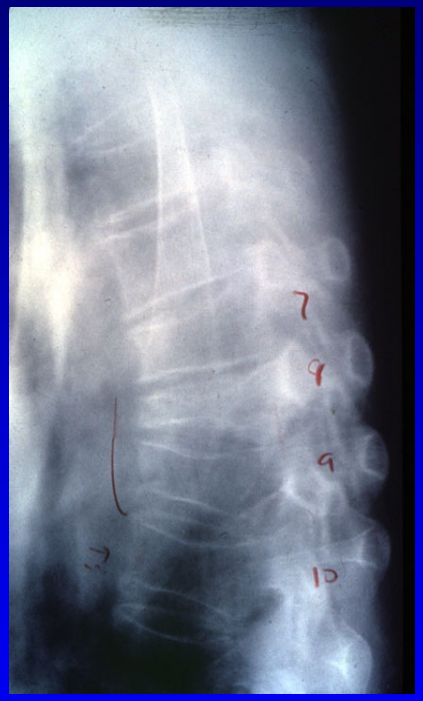
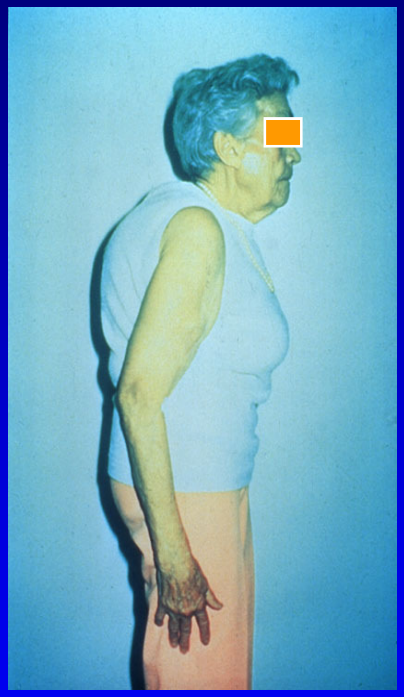
# Genetics of Bone

- 20-70% of the variation in bone properties are estimated to be inherited
- During the past 15 years there have been a number of major efforts to identify genes underlying bone traits
- While it was originally thought (hoped) that a few major effect genes would underlie various bone traits; current results indicate dozens, perhaps hundreds of genes may be involved.

# Osteoporosis





# The Osteoporosis Epidemic

- 30-40% increase in population over 50 years of age by 2020
- If nothing changes 50% of population over 50 years will have osteoporosis and or low bone mass
  - Osteoporotic fractures annually exceed the combined numbers of heart attacks, strokes and breast cancer
  - ~50% of women who suffer an osteoporotic hip fracture will die within 1 year.
- Increase in health care costs predicted to be as high as $200 billion

# Genetic Dissection of Bone Traits

- Candidate gene studies (CGS)
- Genome wide association studies (GWAS)
- Gene expression profiling (GEP)

Dr. H.-W. Deng

- Single gene trait segregating in families
  - Dr. Y. Ueki (*SH3BP2*, Cherubism)
  - Dr. M.L. Johnson (*LRP5*, HBM)

# Genes Identified/Confirmed from Genome Studies

| Gene | Signaling Pathway | Study Design |
|---|---|---|
| *LRP5* | Wnt/β-catenin | Human family linkage<br>GWAS, CGS<br>Mouse genetics |
| *SOST* | Wnt/β-catenin | Human family linkage<br>GWAS |
| *sFRP4* | Wnt/β-catenin | GWAS, CGS<br>Mouse genomics and genetics |
| *ALOX 12/15* | Arachidonic acid metabolism | Mouse genomics and genetics<br>GWAS, CGS |
| *BMP2* | BMP signaling | GWAS, CGS<br>Mouse genomics and genetics |
| *VDR* | Transcriptional regulation | CGS, GWAS |
| *ESR1/ESR2* | Transcriptional regulation | CGS, GWAS |
| *STAT1* | Transcriptional regulation | GEP, CGS<br>Mouse genetics |
| *Col1A1* | Extracellular matrix | CGS<br>GWAS |

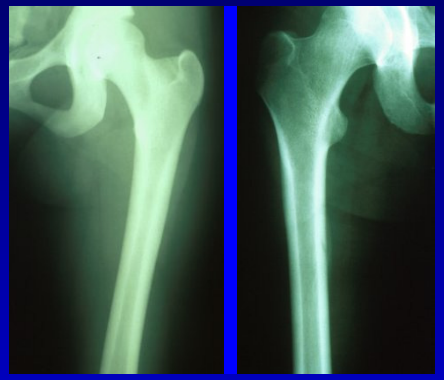
GWAS: genome-wide association study; CGS: candidate gene study; GEP: gene expression profiling

*Johnson, et al. Genome Med. 2009 Sep 7;1(9):84*

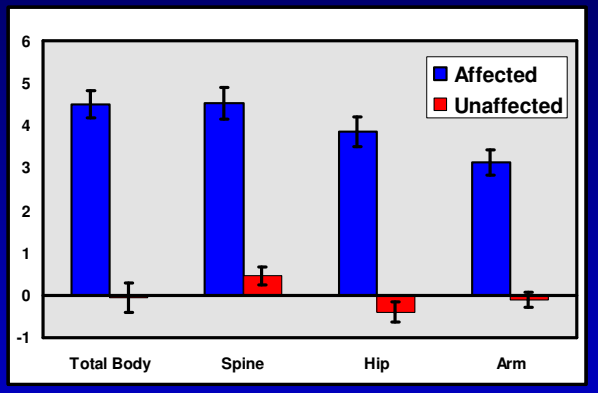
# Impact of Bone Gene Identifications

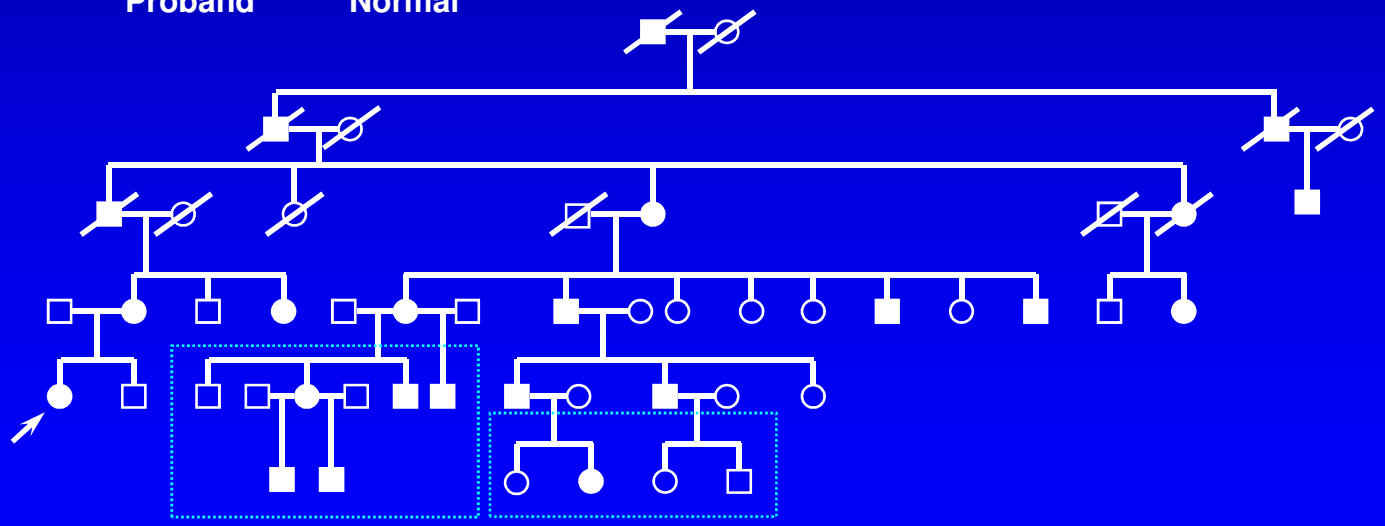
- Revealed new pathways important in bone biology (ex: Wnt/β-catenin signaling)
- Generated new targets for drug development for treating diseases of bone
- Placed us on the threshold of personalized bone treatments/therapies

# High Bone Mass Kindred

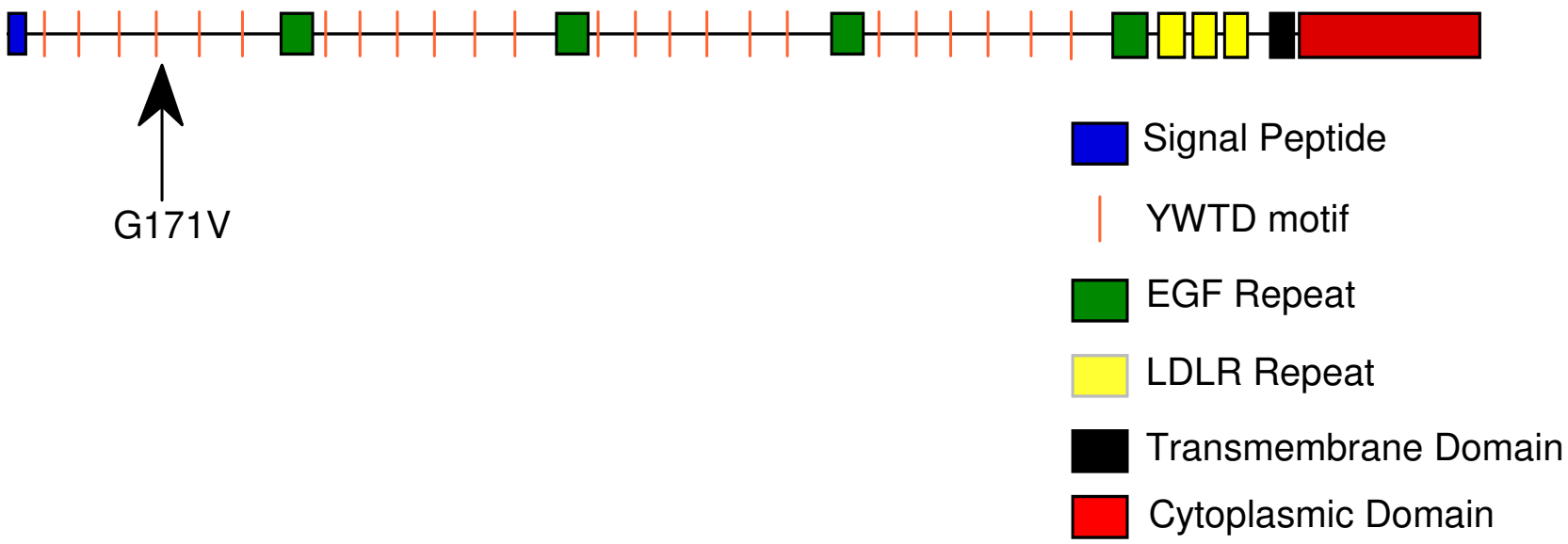


Proband Normal



# Structure of LRP5 and HBM Mutation




**Little et. AJHG 70:11-19, 2002**

# Sclerosteosis/Van Buchem Diseases

- Sclerosteosis: mutation in the *SOST* gene
- Van Buchem: large deletion of the promoter region of the *SOST* gene
- *SOST* gene encodes the protein sclerostin

# LRP5 and Sclerostin

- LRP5 is a co-receptor (along with frizzled) for the Wnt proteins and this binding activates Wnt/β-catenin signaling pathway.
- Sclerostin binds LRP5 and prevents Wnt proteins from binding, thereby inhibiting the Wnt/β-catenin signaling pathway.

# Wnt/β-catenin Signaling Pathway as a Drug Target

- Sclerostin antibody (Amgen)
- Diphenylsulfonyl sulfonamides (target sFRPs) (developed by Wyeth)
- GSK-3β inhibitors (several groups)
- Sclerostin Inhibitors (OsteoGeneX Inc., KC)

# New Biology Revealed by Studying the Role of Wnt/β-catenin Signaling in Bone

- Better understanding of how bone responds to mechanical loading (exercise) and the role of various bone cells in the bone regulation process – Dr. L. Bonewald, Dr. S. Dallas, Dr. M.L. Johnson (UMKC)
- Means to identify other factors produced by bone cells that regulate bone formation and new assays for monitoring bone formation – Dr. J. Gorski (UMKC)
- New targets for therapy – Dr. D Ellies (OsteoGeneX, Inc.)
- New paradigm for treating bone diseases such as osteoporosis; i.e. perhaps we can develop agents that will enhance the skeleton's ability to respond to mechanical load and thereby use the natural mechanisms intrinsic in bone to treat diseases such as osteoporosis

# Future of Bone Scaffolds and Bone Tissue Engineering

- Creating better scaffolds
  - Ultimately we want to achieve scaffolds that are indistinguishable from bone
- Bone tissue engineering
  - Growing new bone from an individual's MSCs (personalized therapy).

# Future of Bone Scaffolds and Bone Tissue Engineering

- These efforts need to incorporate a full understanding of basic bone biology; including an understanding of the pathways that regulate normal bone formation.
- Genetic studies have revealed a number of important pathways and potential targets for treating bone diseases and likewise revealed biology needed to support scaffold and bone tissue engineering development.

# Personalized Therapy for Treating Bone Diseases

The identification of genes underlying various bone traits and understanding how these contribute to both variation in the general population and basic bone biology will be key steps towards developing therapeutic approaches that are customized on an individual by individual basis.

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