Genetic screening of *WNT5B* in three populations with extreme bone mineral density values

Hendrickx Gretl[1], Boudin Eveline[1], Nielsen Torben Leo[2], Andersen Marianne[2], Brixen Kim[2], Van Hul Wim[1]

[1]*Department of Medical Genetics, University of Antwerp, Belgium*
[2]*Department of Endocrinology, Odense University Hospital, Denmark*

Introduction

- **Osteoporosis**
  - Common and multifactorial bone disorder
  - Reduced bone mineral density (BMD) and a deteriorated micro-architecture of bone tissue
    - ➢ Increased fracture risk
  - Heritability of BMD: 50-85%

- **WNT5B**
  - Part of the WNT signaling pathway, an important pathway in bone homeostasis (Figure 1)
  - Genome-wide association studies (GWAS) revealed associations with BMD at the level of the femoral neck and the lumbar spine with genome-wide significance ($p < 5 \times 10^{-8}$) [1]
    - ➢ Interesting target for thorough genetic analysis in three cohorts characterized by extreme BMD values

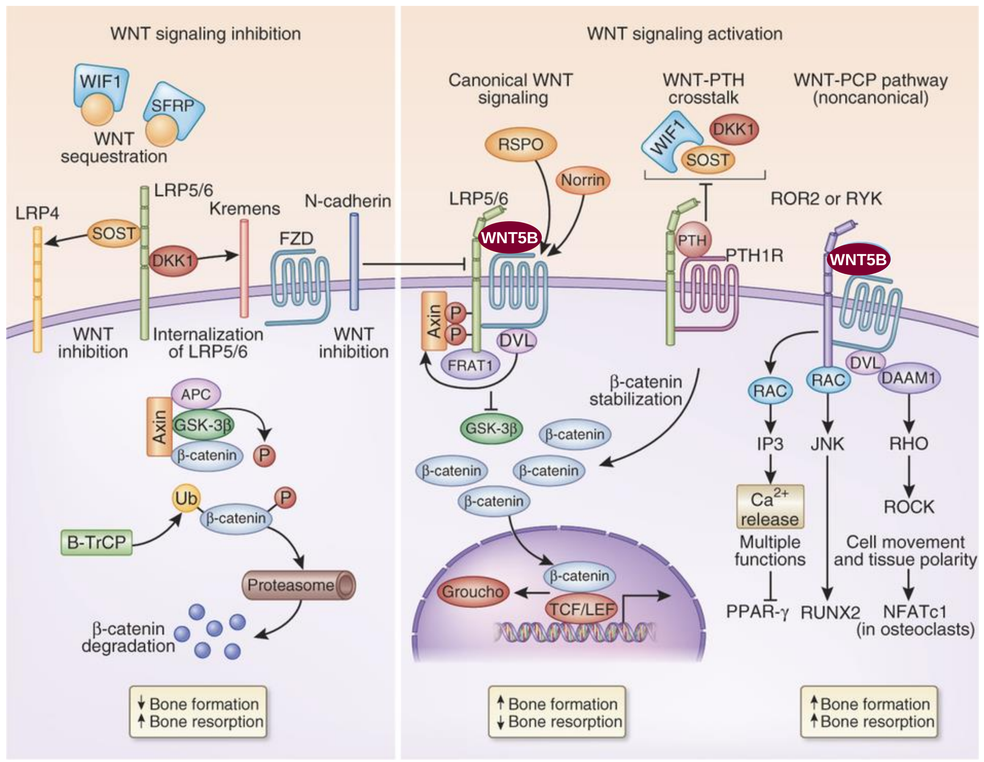
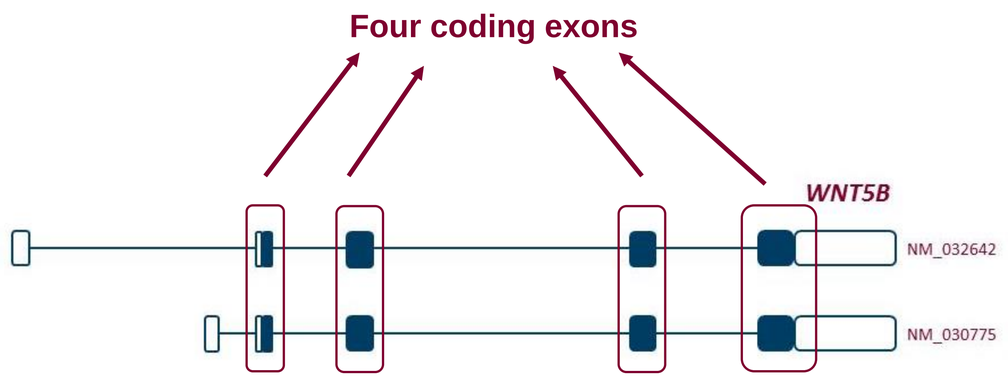


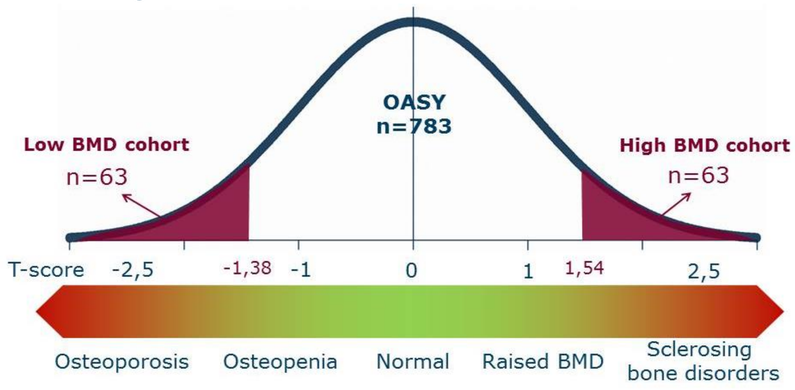
Figure 1 The role of WNT signaling in bone homeostasis [2]

Materials & Methods

- **Mutation screening**
  - Subjects: 43 patients with monogenic sclerosing bone dysplasias (Van Buchem disease, sclerosteosis, endosteal hyperostosis…)
    - Negative for mutations in *SOST*, *LRP5* and *LRP4*
  - Sanger sequencing: coding exons and intron-exon boundaries
    - ➢ Disease causing mutations in *WNT5B* ?



- **Re-sequencing**
  - Subjects: low and high BMD cohort of healthy men selected from the young Odense Androgen Study cohort (OASY)
  - Sanger sequencing: coding exons and intron-exon boundaries
  - Statistical analysis: Chi-Square test
    - ➢ Interesting rare or common variation in *WNT5B* ?



Results

- **Mutation screening**
  - No disease causing mutations found in the patient population
    - ➢ No important role of *WNT5B* in the pathogenesis of the sclerosing bone dysplasias present in our patient population

- **Re-sequencing**
  - No coding variation detected
  - Non-coding variations
    - No significant ($p < 0,05$) difference in genotype frequencies between the lower and higher BMD cohort
    - ➢ No important role of common and rare variation in *WNT5B* in the determination of BMD values in the low and high BMD cohort

Conclusion

- Despite the results from GWAS in the past, we were not able to replicate or further verify an important role for *WNT5B* in the genetic determination of BMD

[1] Estrada et al., Nat Genet (2012)
[2] Baron and Kneissel, Nat Med (2013)