No mutations in the serotonin related *TPH1* and *HTR1B* genes in patients with monogenic sclerosing bone disorders

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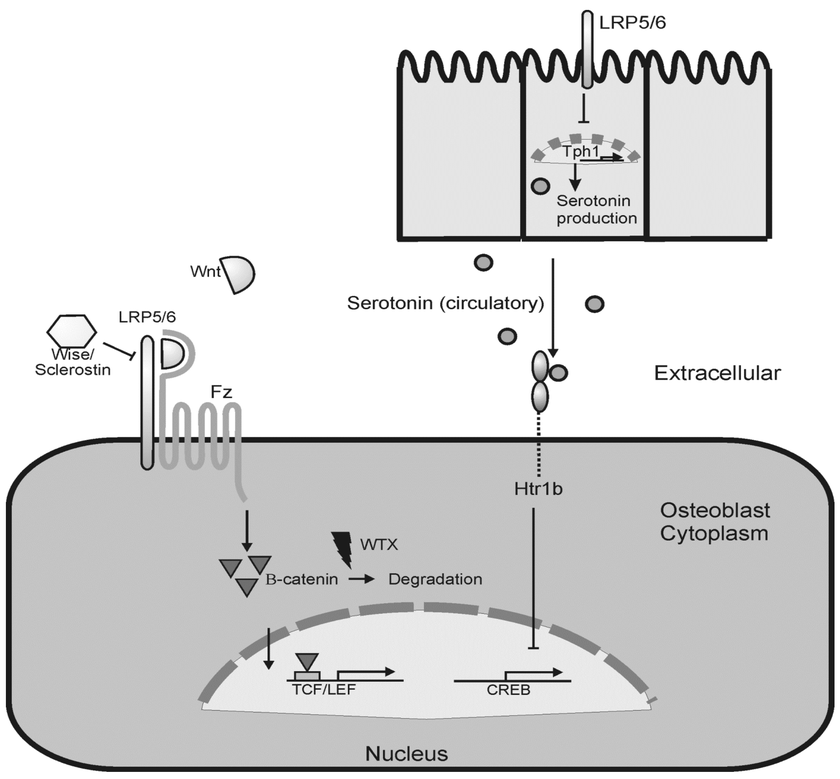
Introduction

Craniotubular hyperostosis:

- Group of rare monogenic sclerosing bone disorders
- ↑ bone mass: skull and tubular bones mainly affected
- Autosomal dominant disorders
  → Mutations in the first β-propeller domain of LRP5
- Autosomal recessive disorders
  → Mutations in *SOST* or *LRP4*

LRP5 → regulates bone formation

- Direct effect: canonical Wnt signaling together with *LRP4* and *SOST*
- Indirect effect: regulating serotonin synthesis in the gut



Perdu and Van Hul, 2010, Crit Rev Eukaryot Gene Expr

Serotonin dependent regulation of bone mass:

- **TPH1:** tryptophan hydroxylase 1
  - Rate limiting enzyme for the serotonin synthesis
  - *Lrp5*$^{-/-}$ mouse
    - ↓ bone mass and bone formation
    - ↑ *tph1* expression
  - *Tph1*$^{-/-}$ mouse:
    - ↑ bone mass and bone formation
    - ↓ serotonin level
- **HTR1B:** 5-hydroxytryptamine receptor 1B
  - Serotonin receptor on the osteoblast
  - *Htr1b*$^{-/-}$ mouse:
    - ↑ bone mass and bone formation
    - ↓ serotonin level

Material & Methods

Patients:

- 53 patients diagnosed with some form of craniotubular hyperostosis
- No mutations in the known causative genes: *LRP5*, *LRP4* and *SOST*

Methods:

- Direct sequencing of all coding exons and intron/exon boundaries of *HTR1B* and *TPH1*
  - *HTR1B:* 4 amplicons
  - *TPH1:* 11 amplicons

Results

TPH1:

- 5 variants found in our patient cohort:
  - 4 known polymorphisms
  - 1 unknown heterozygous variation: **IVS1 -36C>T**
    - French woman with sclerosteosis
    - Prediction programs (Spliceport and Netgene2)
      → no effect on splicing

HTR1B:

- 9 known polymorphisms reported in the patient cohort
  - 4 coding SNPs → 2 rare non-synonymous SNPs (heterozygous)
    - rs130060
    - rs150030508

    → Both SNPs are found in a Columbian boy diagnosed with sclerosteosis

    → Compound heterozygous

- **Sclerosteosis**
  - Autosomal recessive disorder
  - ↑ bone mass of the skull and tubular bones
  - Syndactyly
- **Rs130060 (p.Phe124Cys/-)**
  - Prediction programs: benign (Polyphen, polyphen2, mutPred, Sift)
  - Previously reported homozygous and heterozygous
    → not likely to be disease causing
- **Rs150030508 (p.Ile225Thr/-)**
  - Prediction programs: possibly damaging (Polyphen, polyphen2, mutPred, Sift)
  - Sclerosteosis → autosomal recessive
  - *Htr1b*$^{-/-}$ & *htr1b*$^{+/-}$ mice → ↑ bone mass, no syndactyly
    → not likely to be the disease causing variant

Discusion & Conslusion

A few years ago, Yadav *and colleagues* suggested that **LRP5** regulates bone formation not only via the **canonical Wnt signaling** but also via the regulation of the **serotonin** production in the gut *(Yadav et al, 2008, Cell).* In order to increase the knowledge on the involvement of serotonin in the regulation of bone formation, we screened two key proteins, **TPH1 and HTR1B**, for mutations in the coding regions of the genes in patients diagnosed with several forms of sclerosing bone disorders. Unfortunately, we were not able to identify disease causing mutations in these genes. Therefore, we could not increase the insights of the role of serotonin in the regulation of bone formation by osteoblasts.

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