

Is NOTCH- Sonic Hedgehog signalling pathway the missing link between Hajdu-Cheney Syndrome and syringomyelia?

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Background:

- Hajdu-Cheney syndrome (HCS) is a rare autosomal dominant condition characterized by osteoporosis, acro-osteolysis, short stature and specific craniofacial features
- HCS is caused by mutations in the NOTCH2 gene which codes for a single-pass transmembrane protein that plays a critical role in skeletal development and bone remodelling.
- Syringomyelia has been reported in 5 of 75 reported cases of HCS worldwide. The mechanism for this association is unknown and has not been explored.

Case:

- 17 year old white Caucasian male who had the typical dysmorphic features of the condition, osteoporosis and multiple wedge fractures of the thoracolumbar vertebrae, as well as metatarsals and metacarpals, and had a pathogenic NOTCH2 mutation.
- He also developed a thoracic and cervical syrinx necessitating foramen magnum widening, though there was no Arnold Chiari malformation or platybasia.

Method:

- A literature search was undertaken to examine the relationship between NOTCH mutations and its effects on bone and the nervous system.

Results:

- NOTCH mutations are associated with over-activity of RANKL system and resultant osteoclast mediated osteoporosis.
- NOTCH signalling also plays a crucial role in enabling neural progenitors to attain sufficiently high levels of sonic hedgehog (SHH) pathway activity which in turn is needed to direct the fates of the ventral-most cells in the developing nervous system which ultimately forms the spinal cord.

Conclusion:

- Its already been known that genetic mutations causing either gain or loss-of-function of the NOTCH signalling pathway are associated with diverse skeletal disorders, confirming that NOTCH is critical for skeletal development and subsequent osteoporosis.
- Although HCS affects a limited number of individuals, by discovering a potential mechanism of NOTCH –SHH pathway leading to maldevelopment of neural progenitor cells causing subsequent syringomyelia one can be more vigilant about the future development of more severe & potentially life threatening condition.

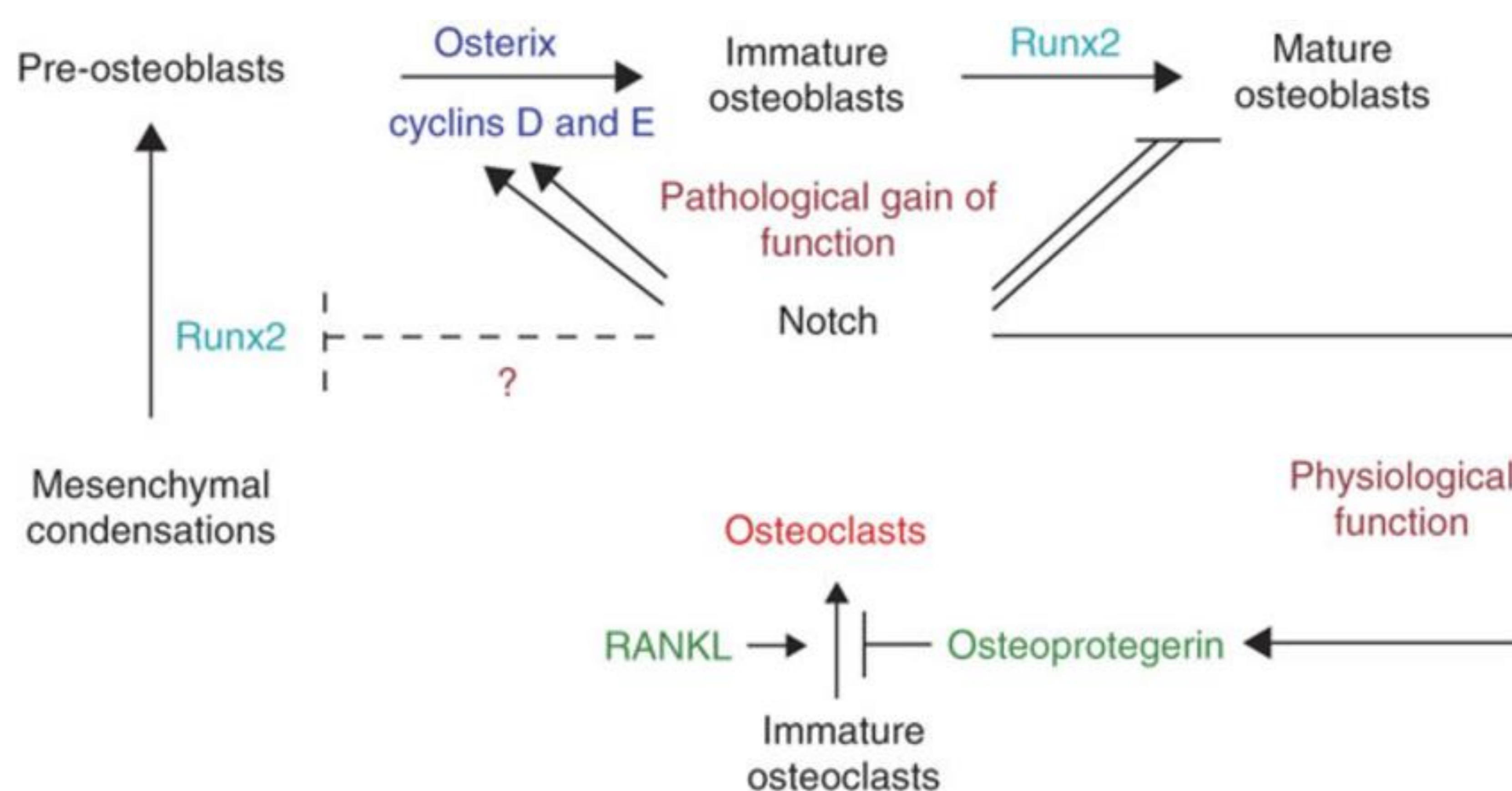


Fig-1. Notch gene role in development of osteoporosis secondary to over activation of RANKL system

Reference:

Regan J, Long F. Notch Signaling and Bone Remodeling. *Current osteoporosis reports*. 2013;11(2):126-129.

Notch signaling: simplicity in design, versatility in function Emma R. Andersson, Rickard Sandberg, Urban Lendahl *Development* 2011 138: 3593-3612;

Conflict of interest: – none stated

