Congenital Deformities of Upper Ex. – Molecular Control

Mark Chong

SpR Northern Deanery Hand Term

Congenital Deformity

- Fact 1: Most reviews on congenital deformities are impenetrable.

- Quote from Bamshad et al…
- *'Comparison of homologous genes TX-12k is advantages because modifiers of developmental programs conserved among closely related species can be identified by regulatory findings of LDH-B1Z locus, whereas the identification of modifiers between taxa is more likely to represent alteration of shared developmental program rather than evolutionary convergence….'*

Deformities of Upper Limbs

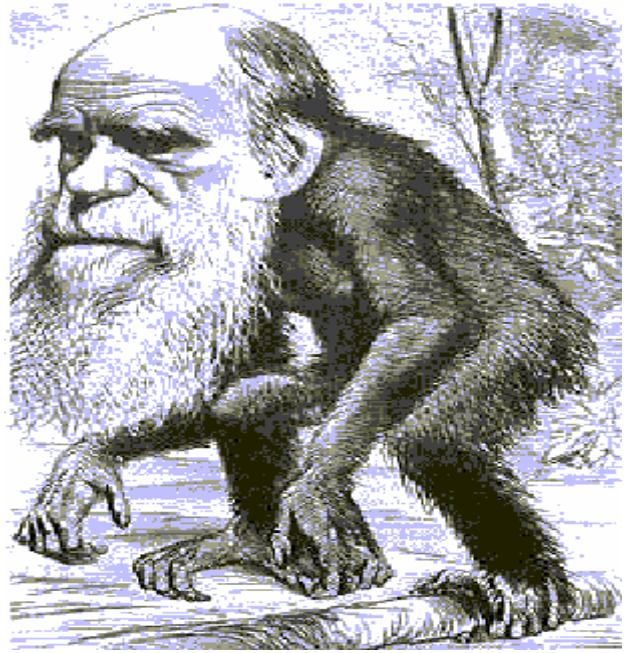
- 2nd commonest congenital defect after cardiac abnormalities
- 1 in 600 live births
- Classified according to morphological appearance. (Swanson – J Hand Surg 1976)

Swanson Classification for Congenital Hand Deformities

- Formation
- Differentiation
- Overgrowth
- Hypoplasia
- Constriction Band
- Generalised Skeletal Abnormalities

Theory of Evolution

- Roots can be traced back to Darwin's scientific theory of evolution – process of natural selection

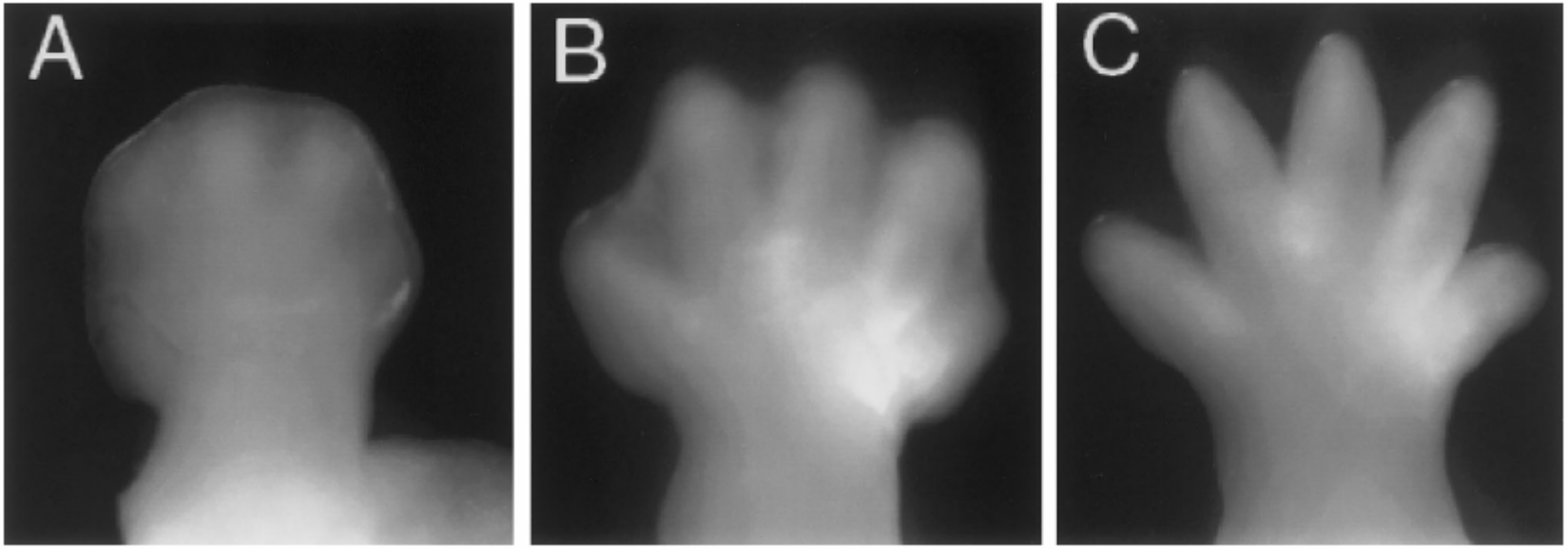


Modern Times Theory – Molecular Level

- 3 main proteins and 2 genes:
- Transcription Factors, Receptors and Ligands
- HOX and T-Box
- Understanding these interactions enable scientist to discover early diagnosis and/or therapeutic control

Normal Development

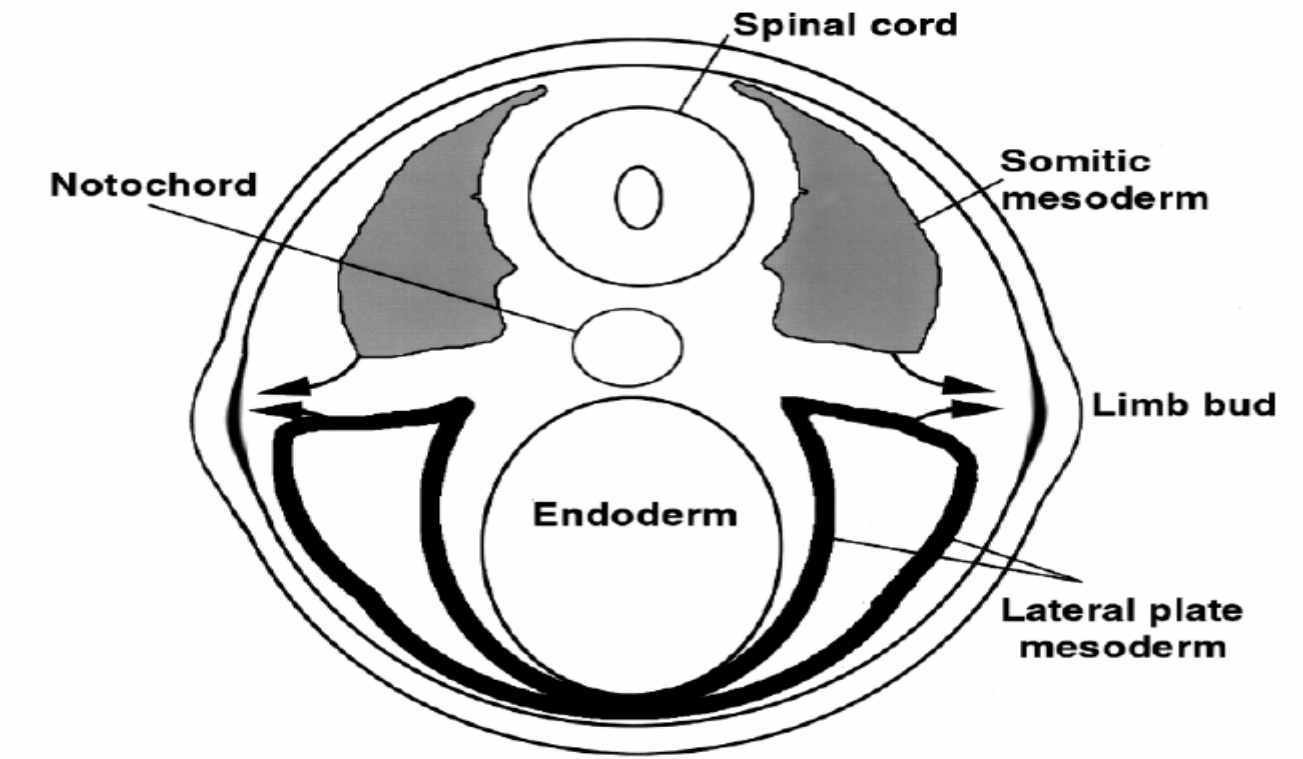
- Limb bud starts on day 28 – ends at 8th week
- Starts from somites 8 – 10th level.
- Coordinated by proteins and genes.



Mesodermal layers

2 mesodermal layers

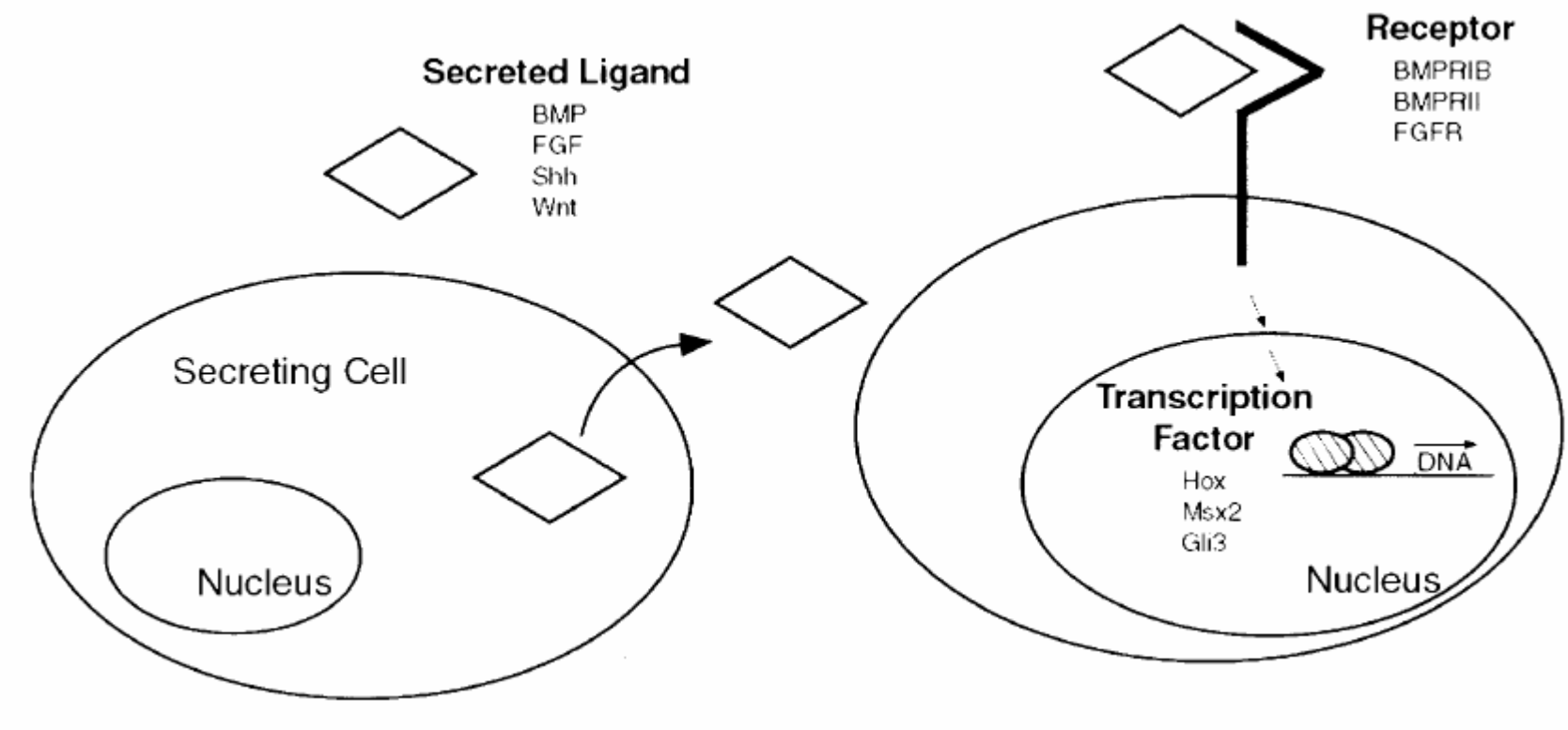
- *Somites* – transformed to muscles
- *Lateral plate* – Bones and joints



3 important proteins

- *Transcription Factors, Ligands and Receptors*
- *Ligands* – Proteins that signal neighboring cells to differentiate or populate. (BMP, FGF, Shh)
- *Receptors* – Proteins on cell membrane that binds to ligands. Ligands binding to receptors cause signal transduction leading to change in cellular behaviour.
- *T – factors* – Transmit signal from activated receptor to the cell nucleus. Binds to DNA and express new gene.

Ligands, Receptors and T-Factors



Limb Bud Development

- Limb Formation is a continuation process
- 3 spatial axes – Proximodistal (PD), Anteroposterior (AP), Dorsoventral (DV)
- All axes are governed by proteins with feedback loops to coordinate normal development of limb
- Studies derived mainly from mouse and chicken limbs

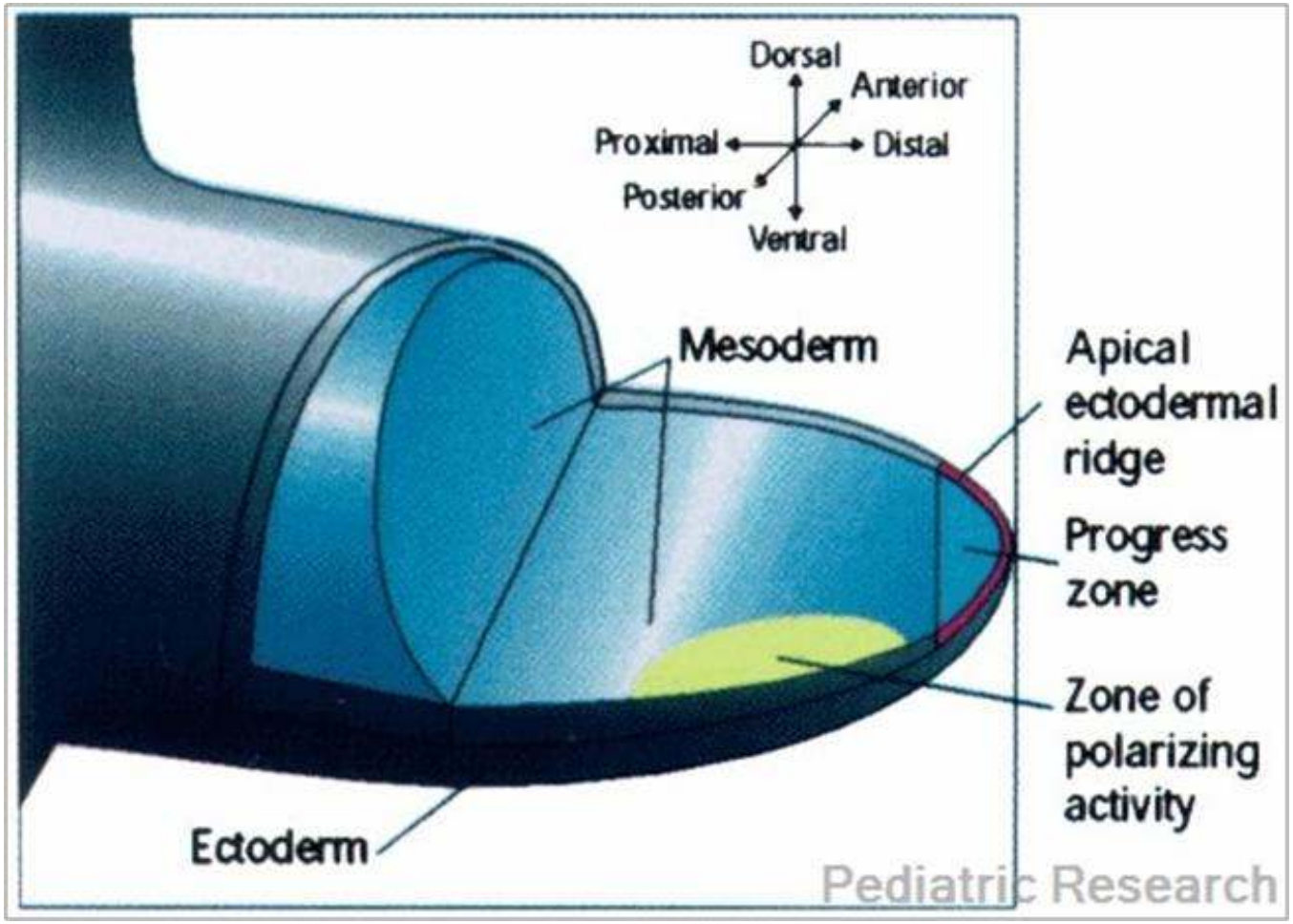
PD axis

- Controlled at the *Apical Ectodermal Ridge* (AER). This is a ridge of ectoderm forms between the meeting point of ventral and dorsal layers of ectoderm.
- When AER is surgically removed, PD growth ceases.
- If AER is implanted at remote site, extra limb bud forms
- AER acts by secreting *FGF* proteins

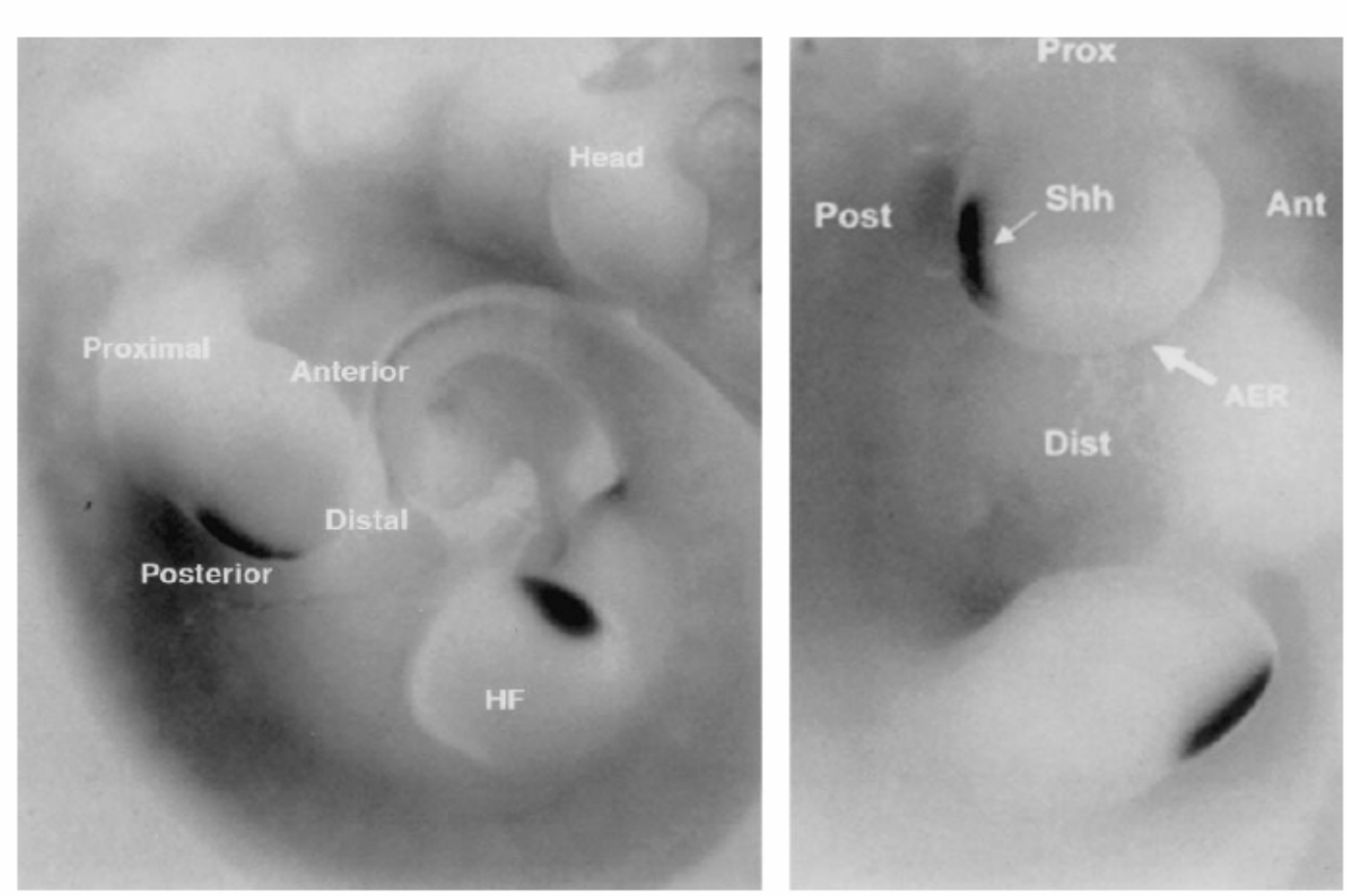
AP axis / Radial Ulna Axis

- Determined early within lateral plate before limb bud formation
- Group of cells from ulna tissue secretes protein that act on AP structures
- Located in *zone of polarization activity* (ZPA). (posterior part of the limb bud)
- Transplantation of ZPA causes *mirror hand*.
- Primary growth factor is called *Sonic Hedgehog (Shh).*
- Shh induces *FGF-4* in the AER via positive feedback loop.
- PD and AP axes are not mutually exclusive.

Schematic diagram of a limb bud



Real life Mouse Limb



- Note the position of *Shh* posteriorly and the AER at the rim of limb bud

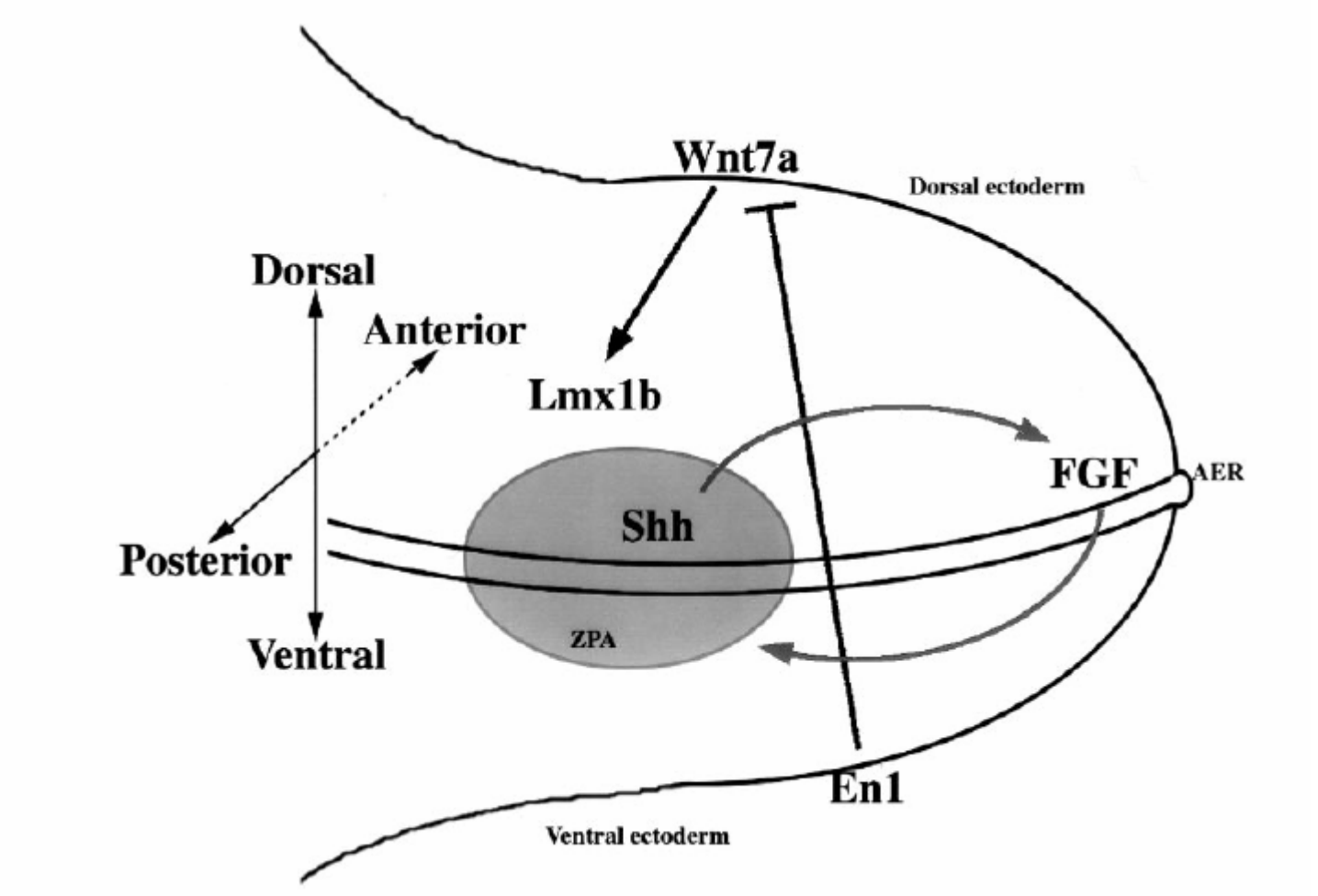
DV axis

- Less well understood
- Dorsal ectoderm secretes wingless-type mouse mammary tumour virus integration site family member 7a (*Wnt-7a*)
- Mice lacking Wnt has biventral limbs
- *Wnt-7a* induces t-factor called *Lmx1* that governs dorsal growth. Lack of *Lmx1* – nail patella syndrome

DV axis

- Reciprocally, the ventral ectoderm secretes *engrailed-1 (En1)*
- Mice lacking these has bi-dorsal limb
- Important to realise that axes are not independent of each other.
- *Shh* is thought to be the link between DV and the other axes. Hence single gene defect on *Shh* can lead to complex abnormalities

DV axis diagram



- What Happens when the complex system goes wrong?

Nail Patella Syndrome due to lack of Lmx-1

Family of T-factors

- Primary axes formation is only one facet of limb development
- Mutation in *HOX* genes also causes limb deformities. – synpolydactyly.

Syndactyly

- Mutation of *Msx-2* transcription factor

Apert's Syndrome

- Caused by mutation in FGF *receptors*

Polydactyly

- Influenced by *BMP (ligands)* and *Gli-3 (T factors)* expressions. BMP-7 & Gli-3 has suppressive role in digit formation. Hence lack of BMP-7 gives rise to extra digits.

Brachydactyly

- Mutation in GDF-5 (member of BMP family)

Holt-Oram Syndrome

- Mutation in T box – 5 gene. Associated with radial deficiency.

Conclusion

- Need to know the basics of limb bud development cascade
- Recognise the 3 axes and that they are not mutually exclusive.
- Potential therapeutic uses. Eg. BMP used in treating non-union. GDF-5 used in tendon regeneration.

Thank You

Fact 2: Chimps have 90% gene makeup of a hip surgeon…is that true?

Just take a look at your knuckles….

References

- Green Operative Hand Surgery 5th Edition http://www.greenshandsurgery.com/
- Aaron Daluiski et al. The Molecular Control of Upper Extremity Development: Implications for congenital Hand anomalies. J Hand Surg.
- Swanson AB. A classifications of limb malformations. I Hand Surg 1976; 1:8-22
- Eric Mooney, et al. Hand, Upper Extremity Embryology. http://emedicine.medscape.com/article/1287982-overview
- Gallant G and Bora William. Congenital Deformities of the Upper Extremity. Journal of American Academy of Orthopaedic Surgeons. 1996:4:162-171 http://www.former-surgery.northwestern.edu/plasticreading/Documents/curriculum/Hartigan/Handouts/004%20-%20Congenital%20Hand%202.pdf