

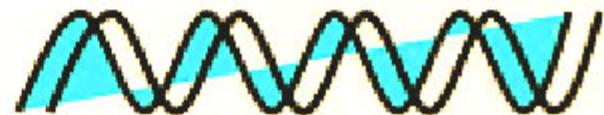
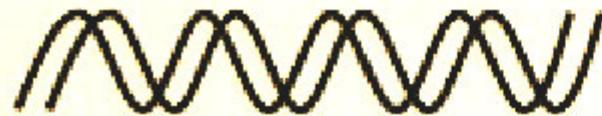


# Spine Development and Early Onset Scoliosis



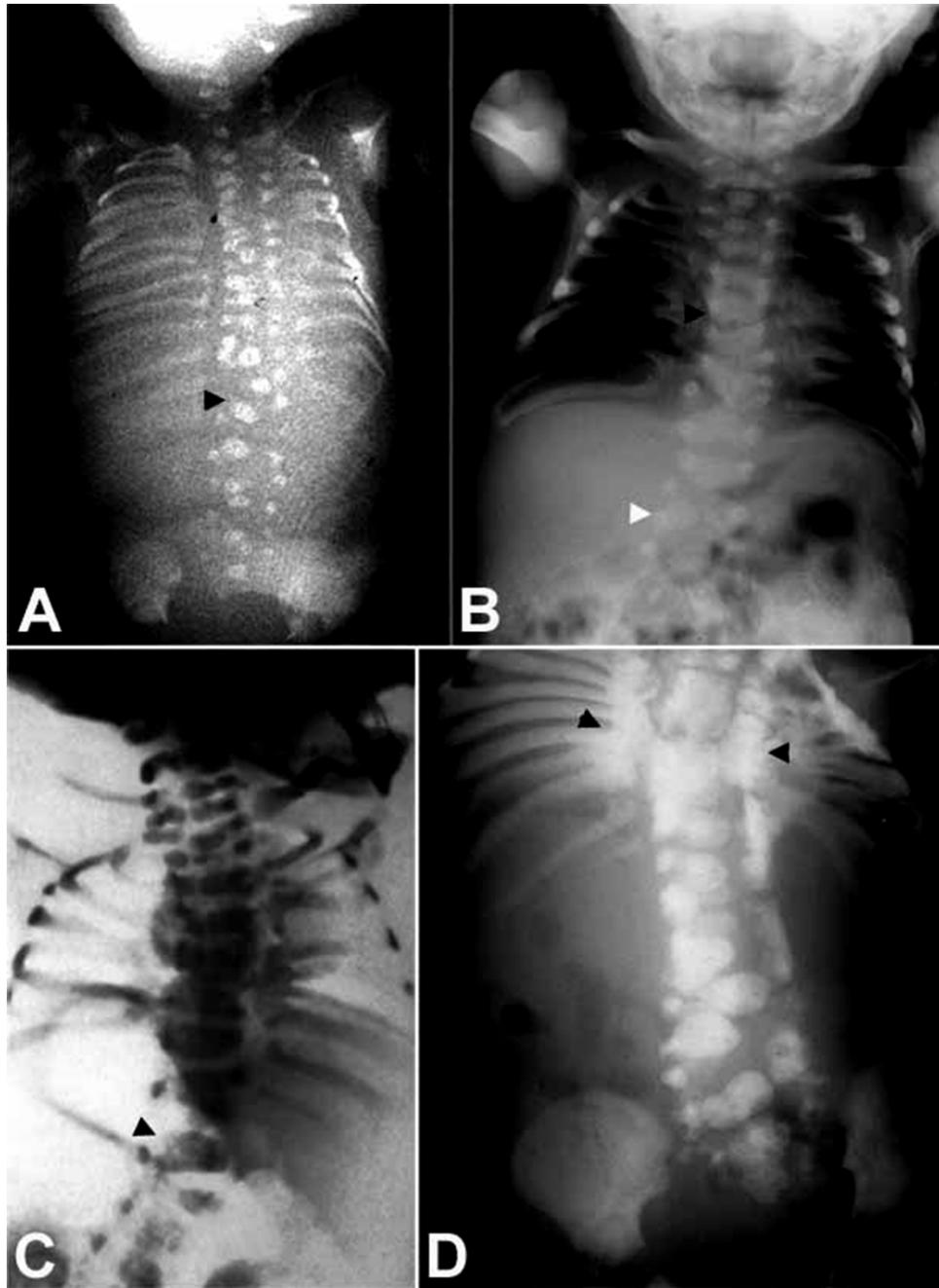
Duke Orthopaedics



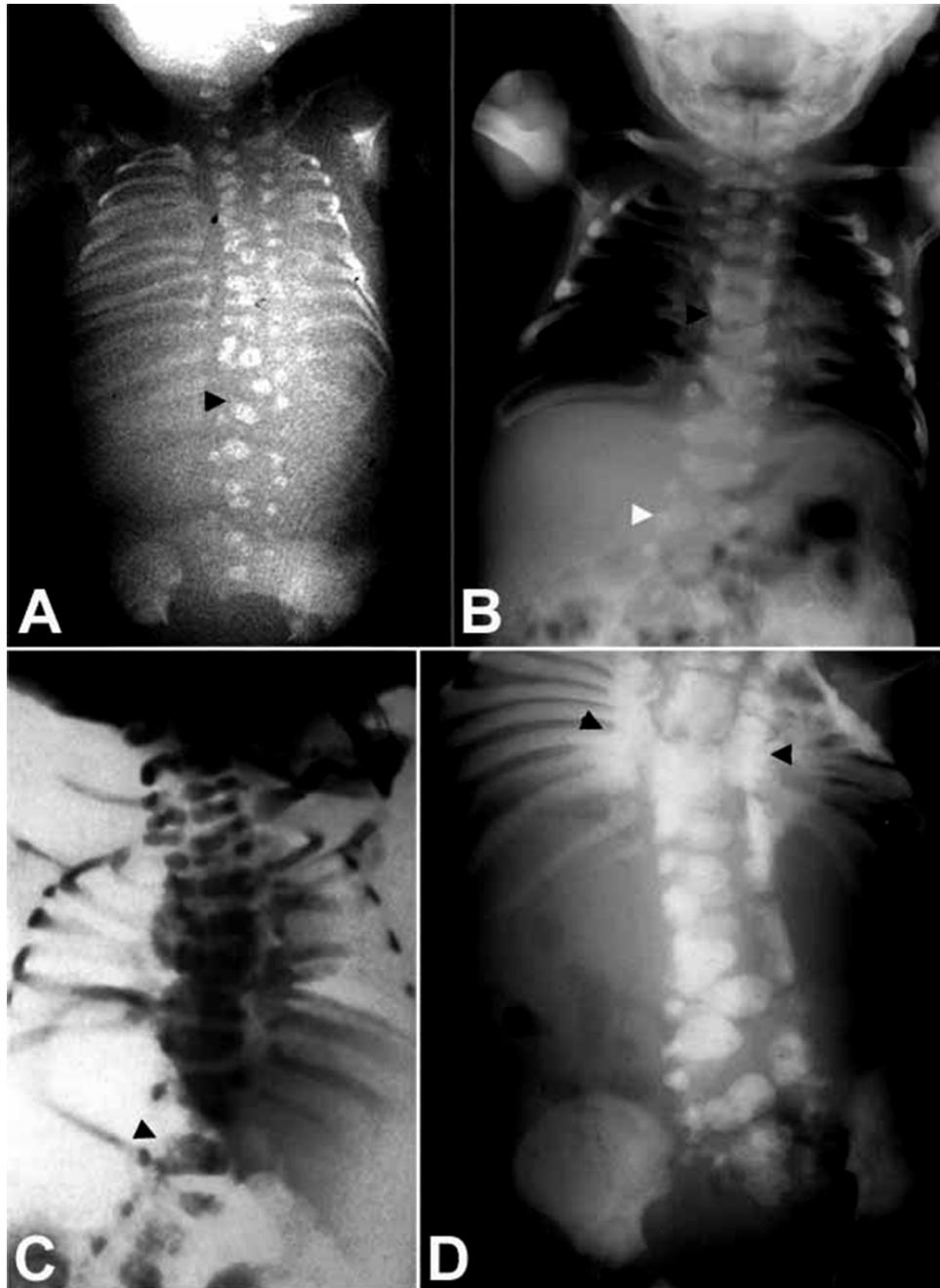


Syndromic  
Neuromuscular  
Congenital  
“idiopathic”

Syndromic  
Neuromuscular  
Congenital  
“idiopathic”

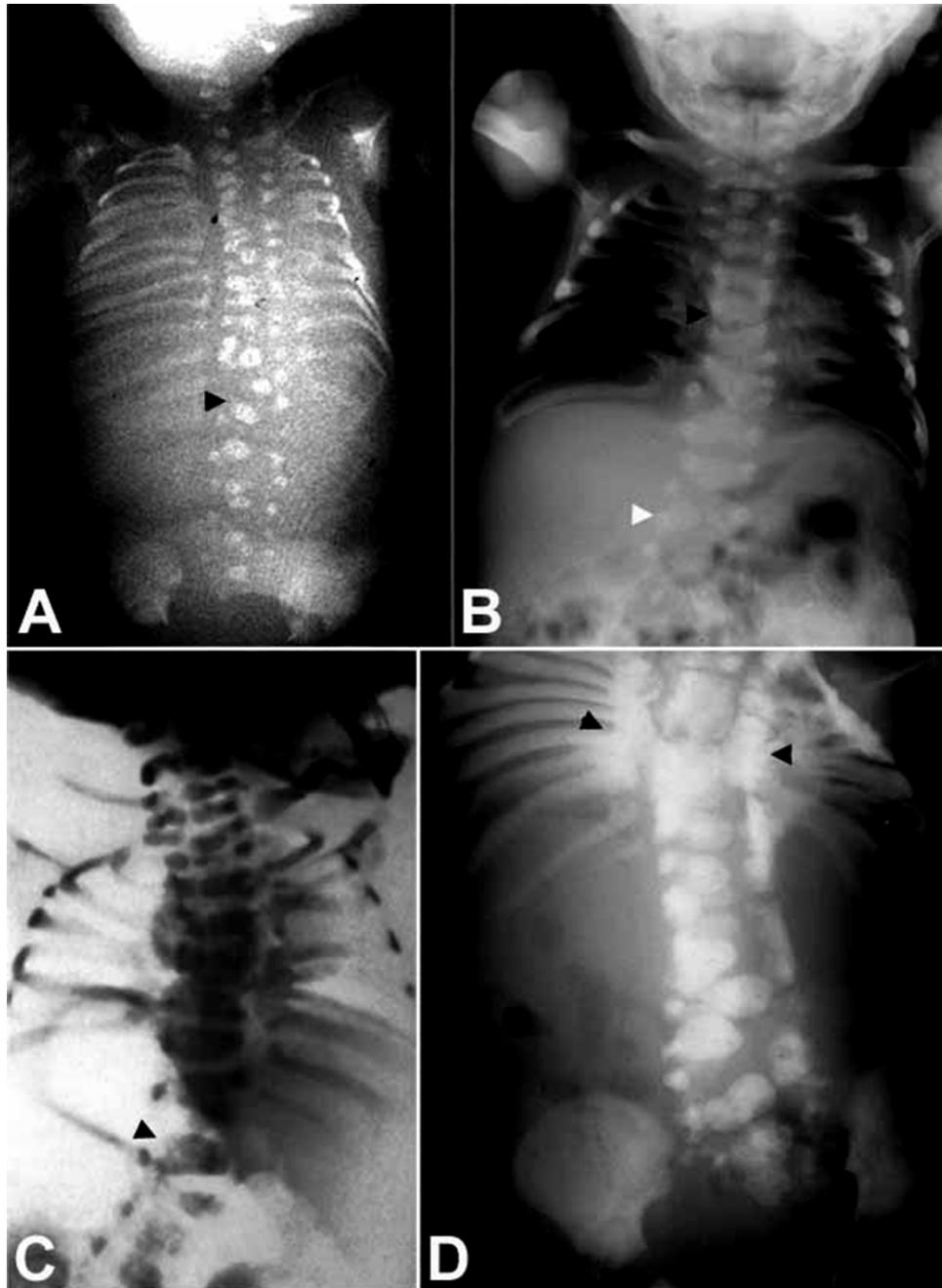


Spondylocostal  
dysplasia



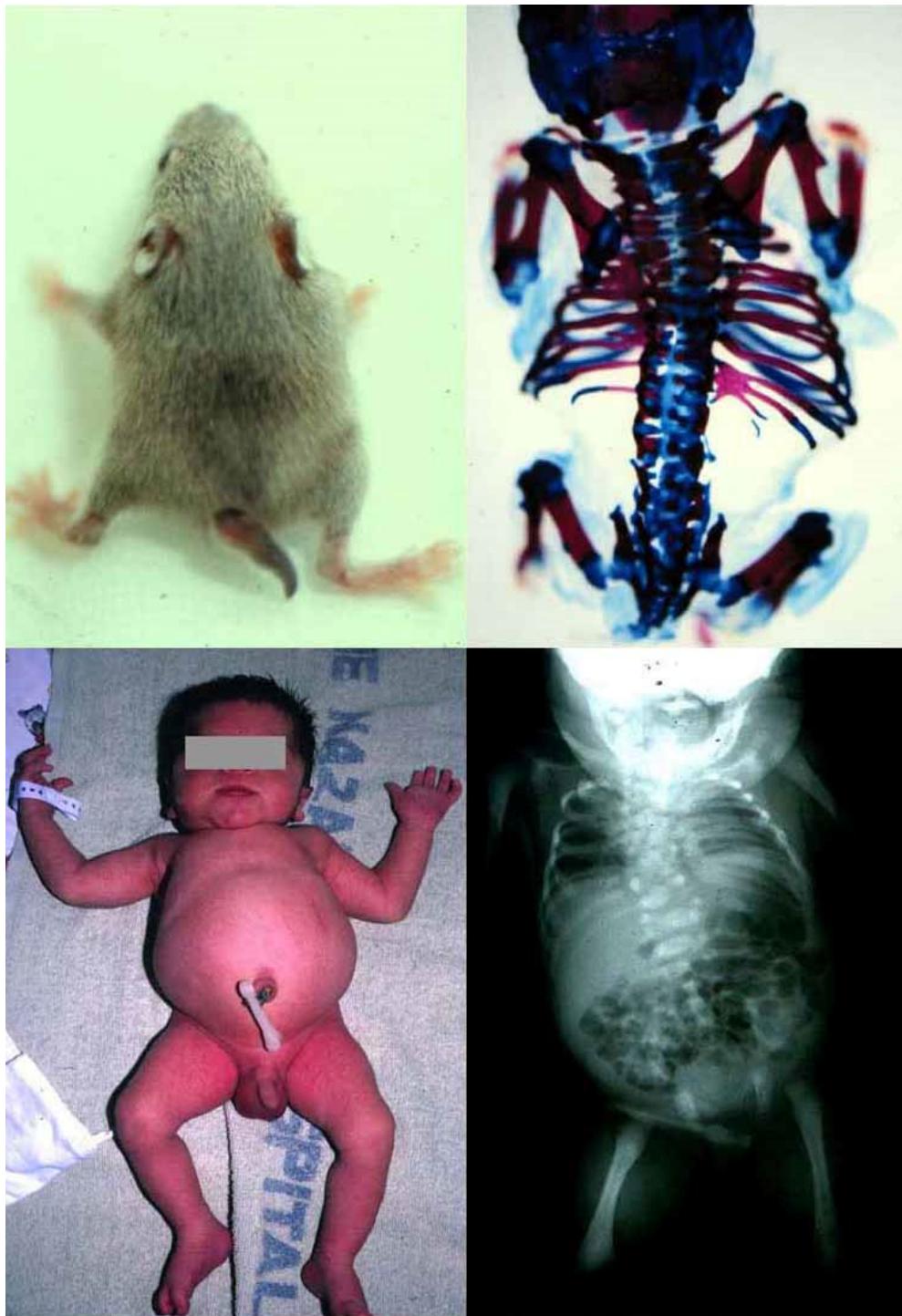
Spondylocostal  
dysplasia





# Spondylocostal dysplasia caused by a mutation in delta-like-3

Bulman MP, Kusumi K, Frayling TM, McKeown C, Garrett C, Lander ES, Krumlauf R, Hattersley AT, Ellard S, Turnpenny PD. Mutations in the human delta homologue, DLL3, cause axial skeletal defects in spondylocostal dysostosis.  
Nat Genet. 2000 Apr;24(4):438-41



## Delta-like-3 Pudgy mouse

Kusumi K, Sun ES,  
Kerrebrock AW, Bronson  
RT, Chi DC, Bulotsky MS,  
Spencer JB, Birren BW,  
Frankel WN, Lander ES.  
The mouse pudgy  
mutation disrupts Delta  
homologue Dll3 and  
initiation of early somite  
boundaries.

Nat Genet. 1998  
Jul;19(3):274-8.

## A Clock and Wavefront Model for Control of the Number of Repeated Structures during Animal Morphogenesis

J. COOKE†

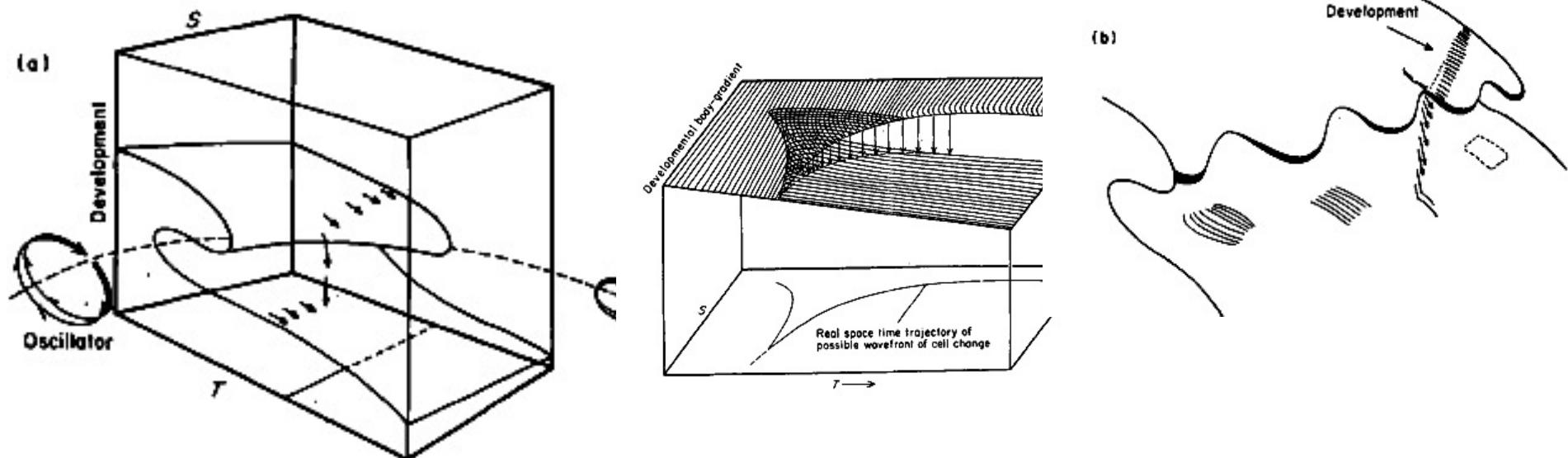
*National Institute for Medical Research,  
The Ridgeway, Mill Hill, London NW7 1AA, England*

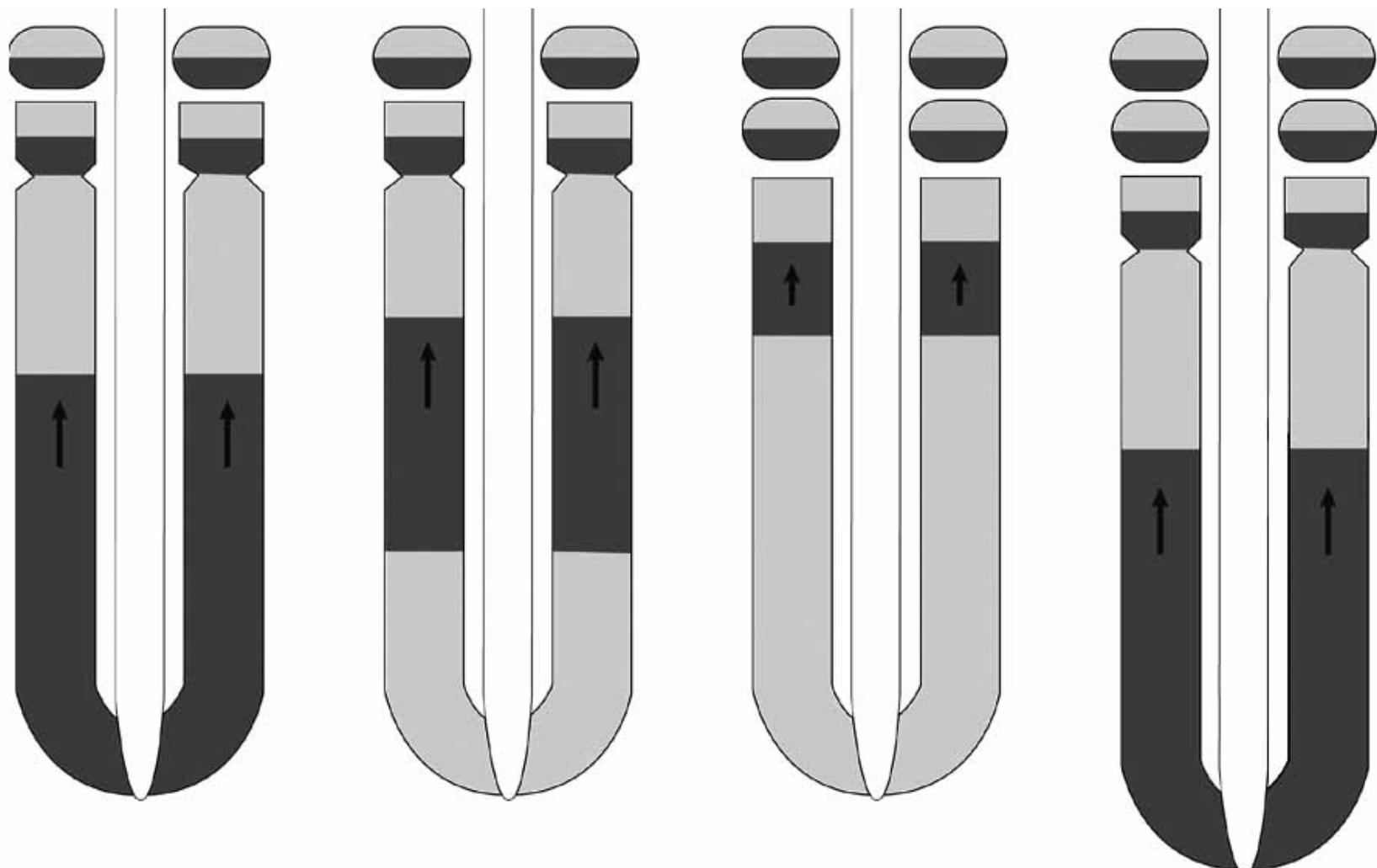
AND

E. C. ZEEMAN

*Institute of Mathematics, University of Warwick,  
Coventry, Warwick, England*

(Received 17 June 1975, and in revised form 1 October 1975)





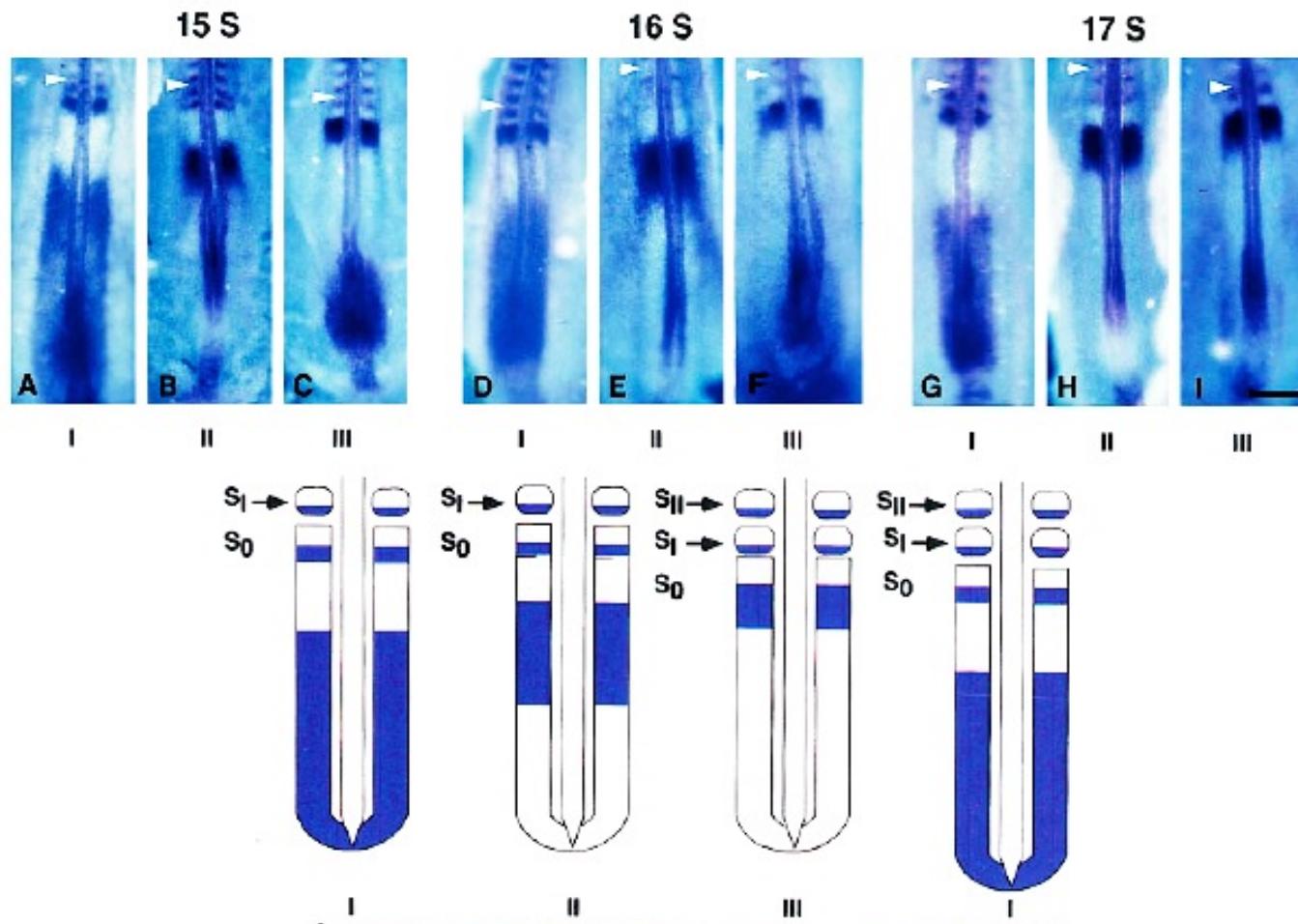
time, one cycle period

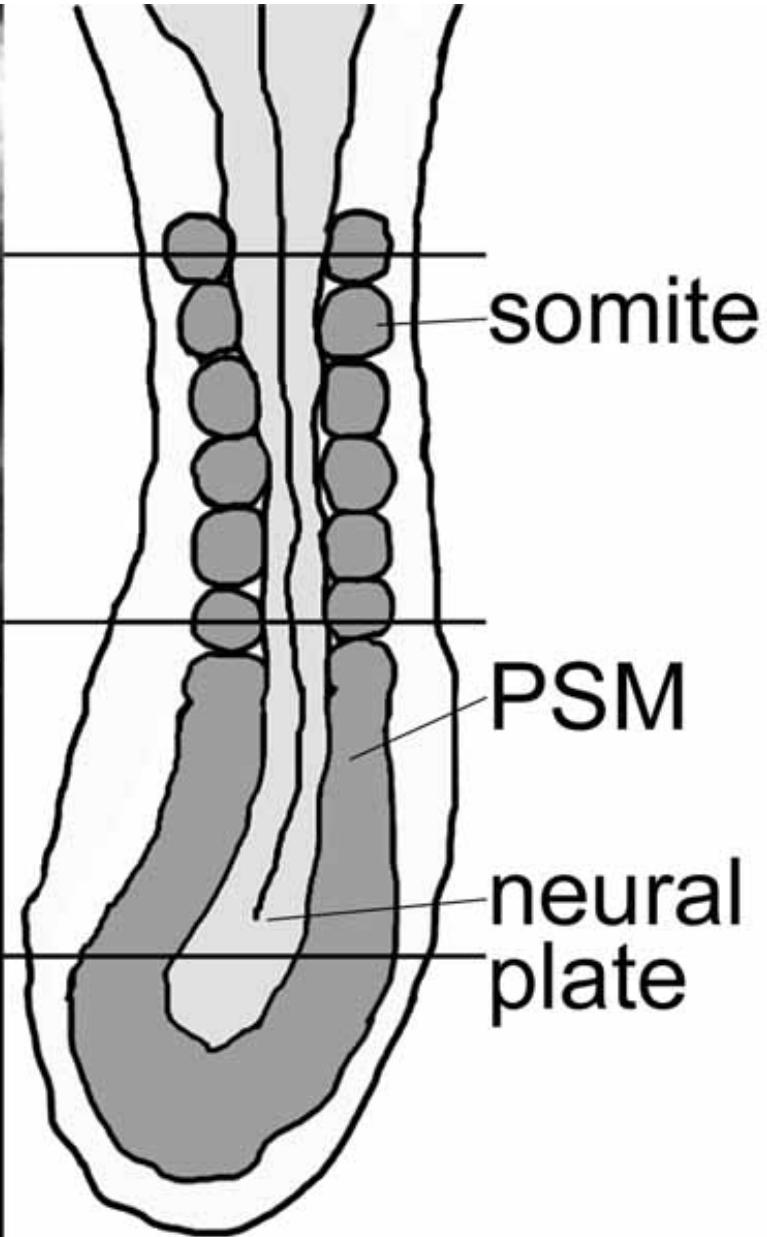
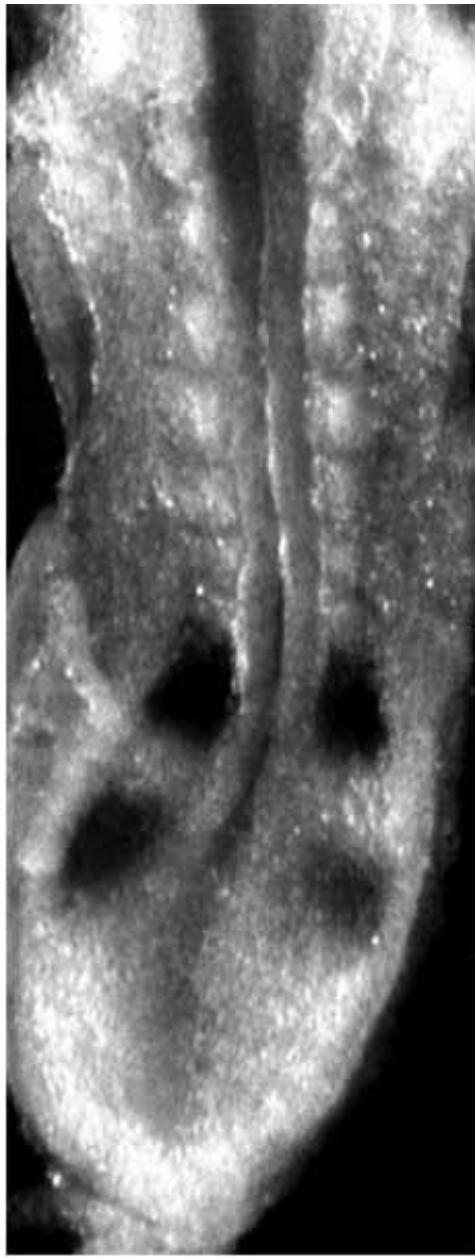


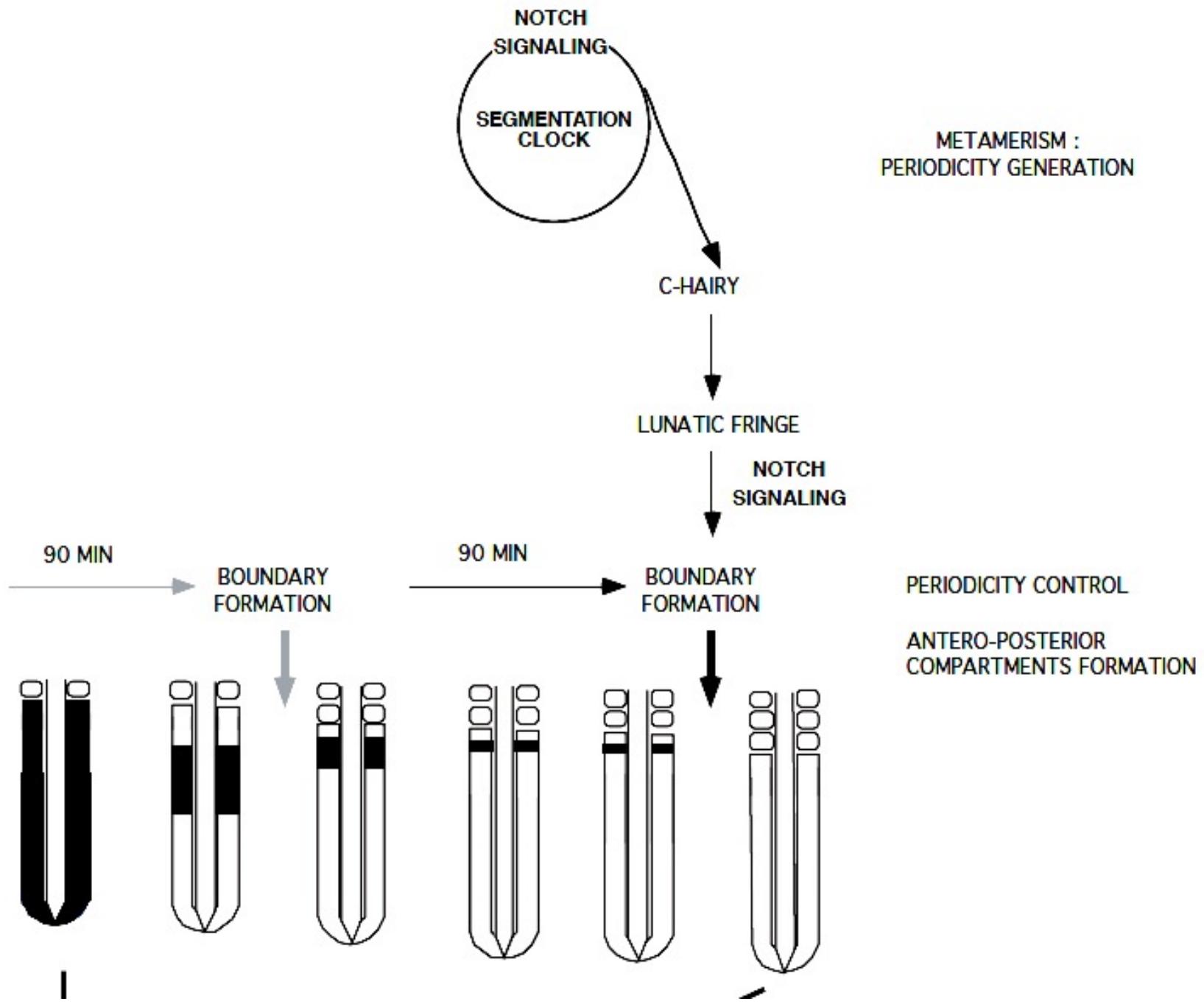
# Avian *hairy* Gene Expression Identifies a Molecular Clock Linked to Vertebrate Segmentation and Somitogenesis

Isabel Palmeirim,\* Domingos Henrique,<sup>†§</sup>  
David Ish-Horowicz,<sup>†</sup> and Olivier Pourquié<sup>‡||</sup>

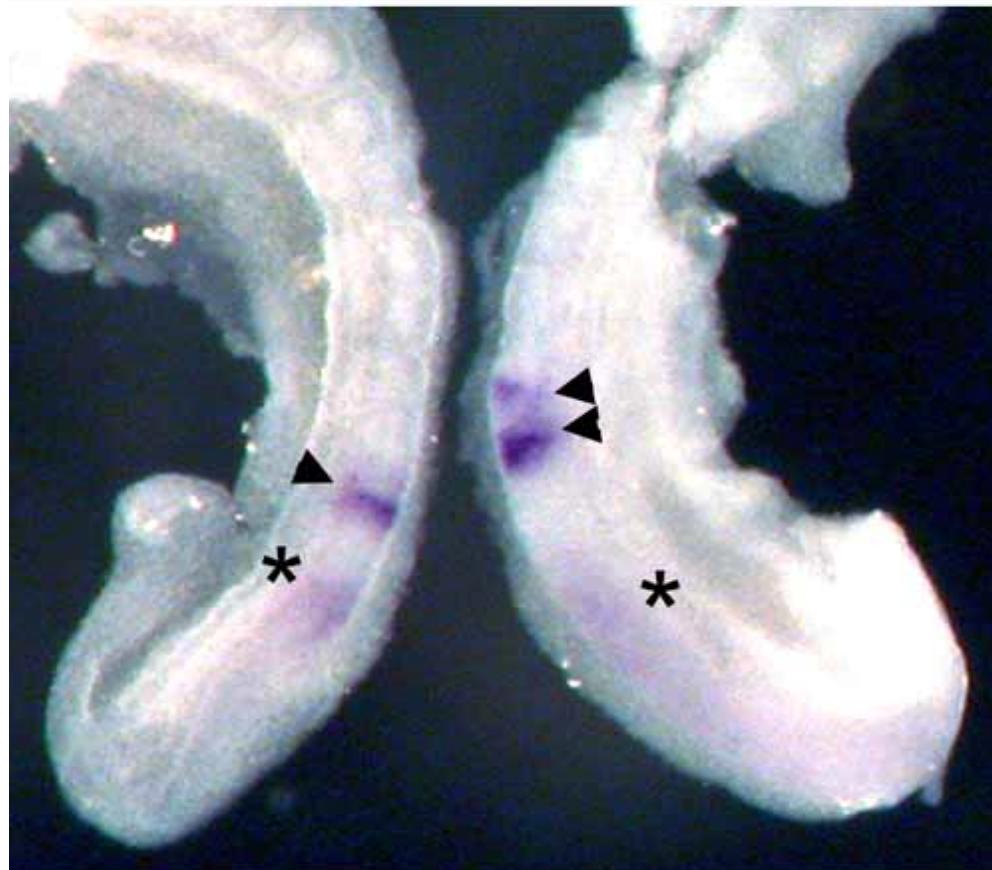
are laid down sequentially from  
during the course of development







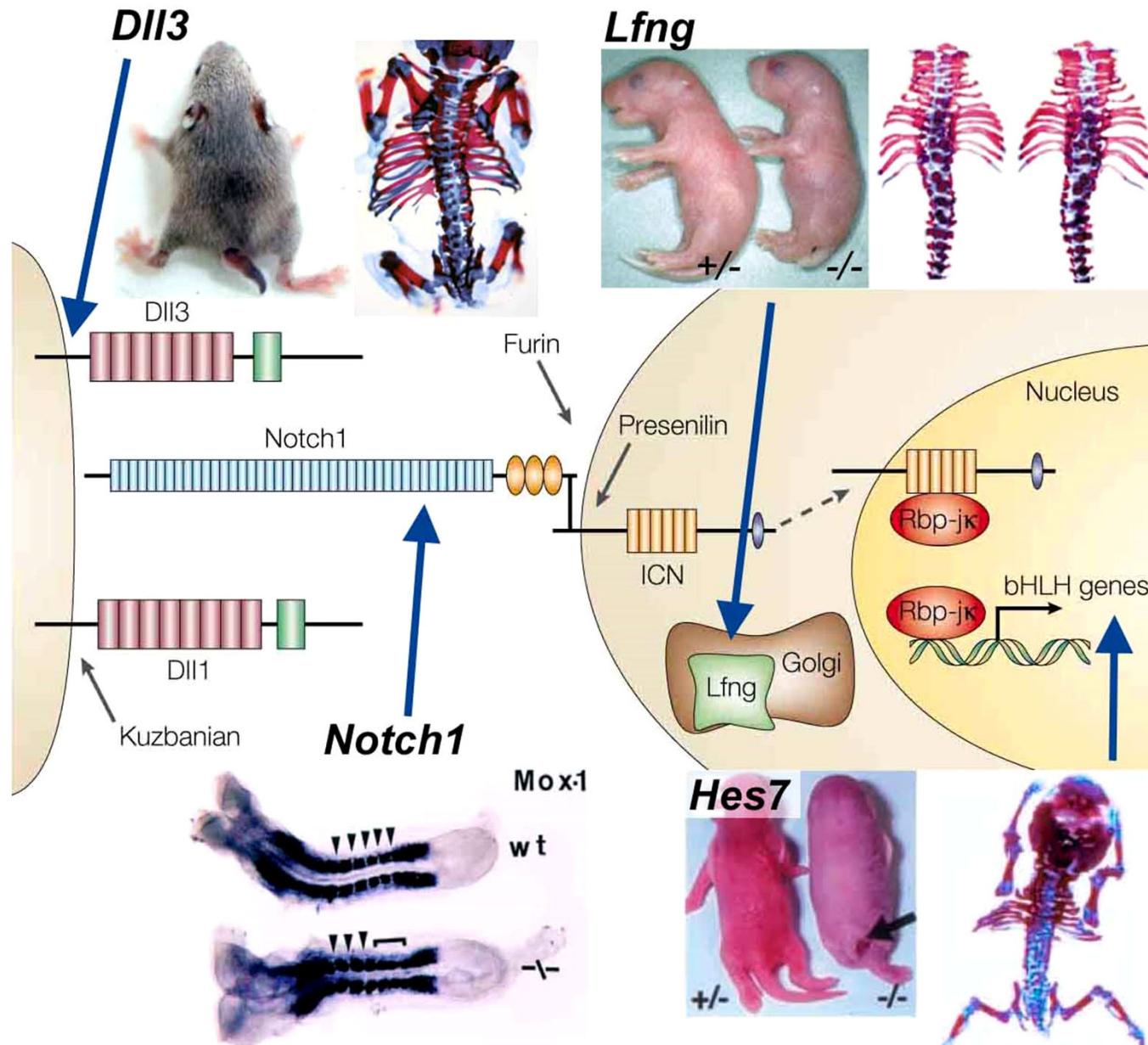
*wt*

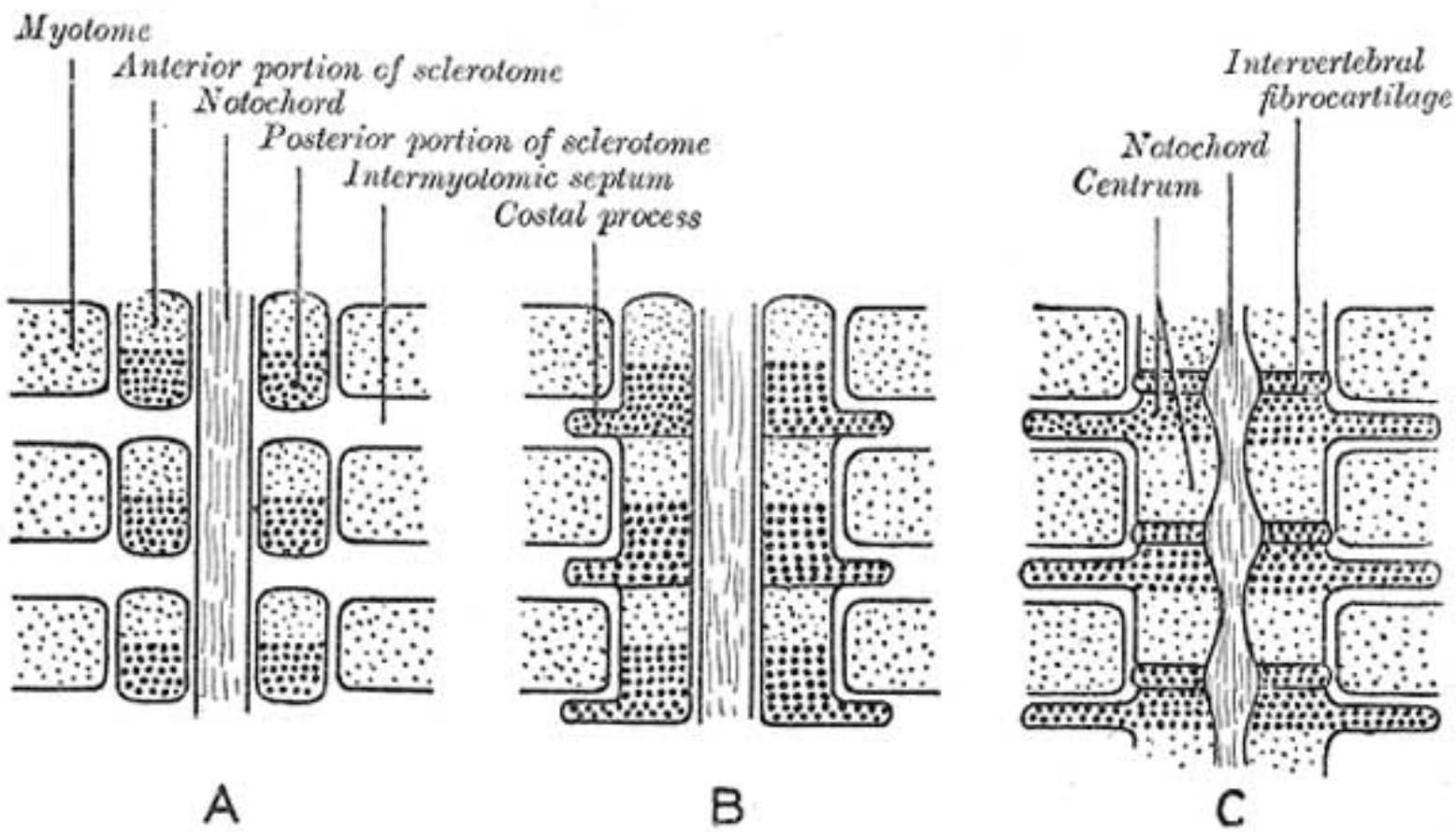
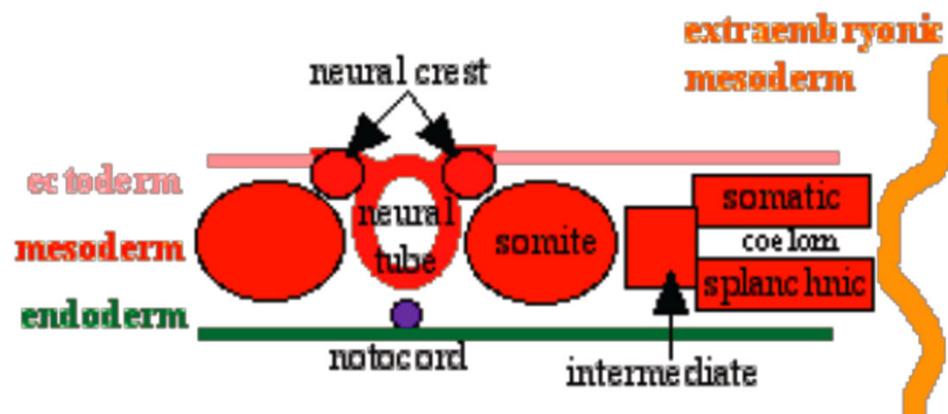


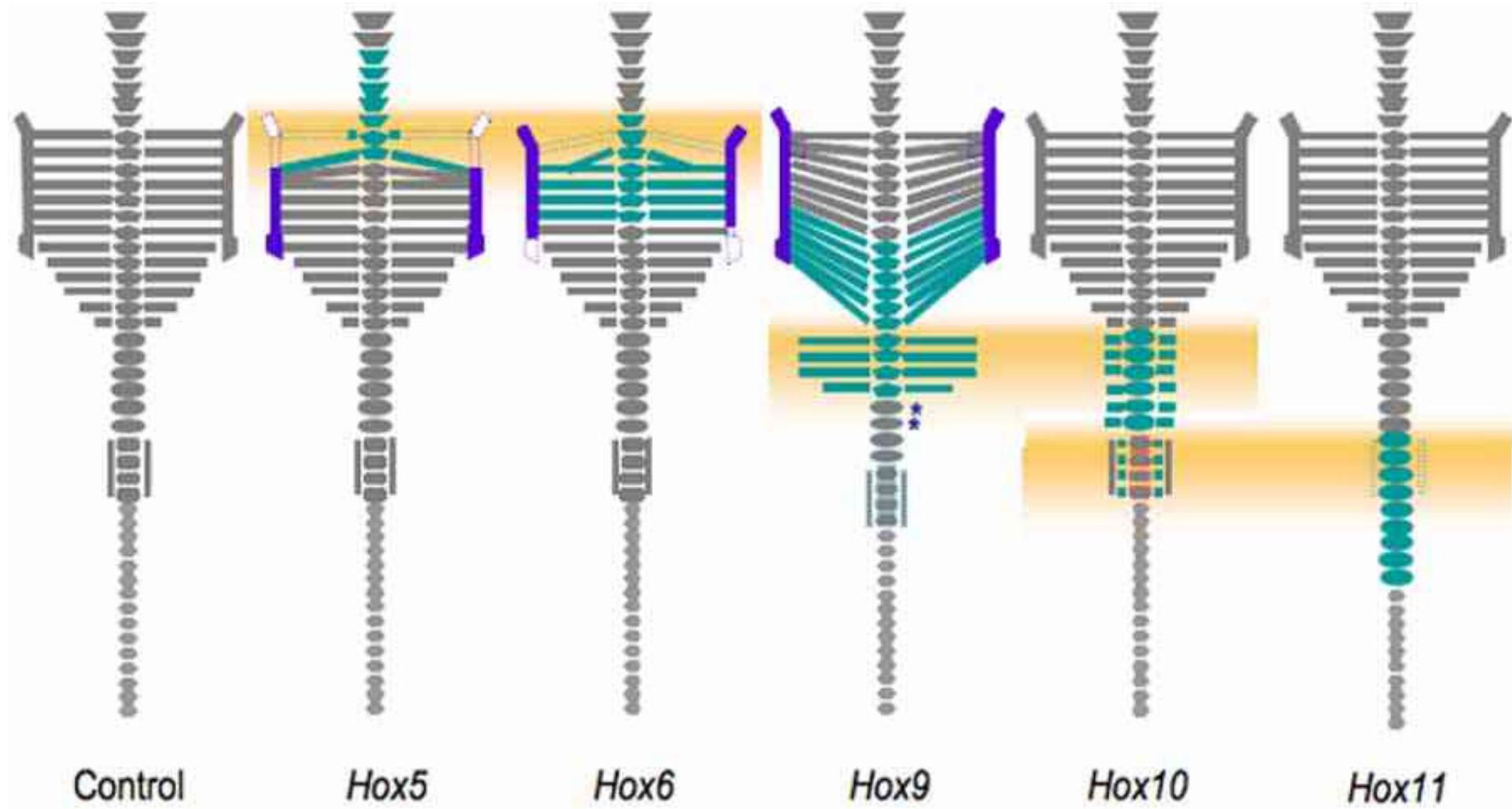
*DII3<sup>pu</sup>*



# Delta-like-3 is in the notch signaling pathway







Control

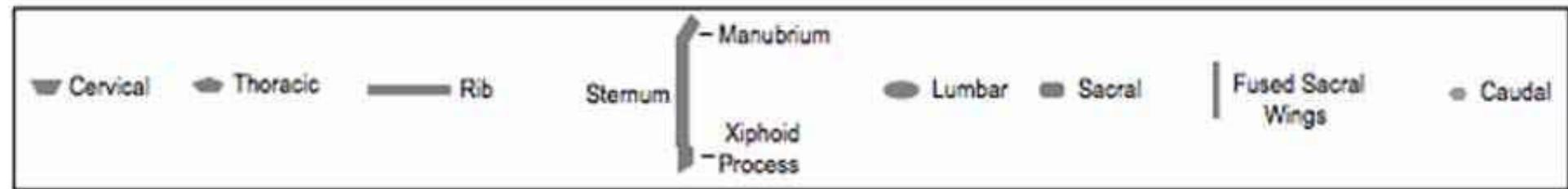
*Hox5*

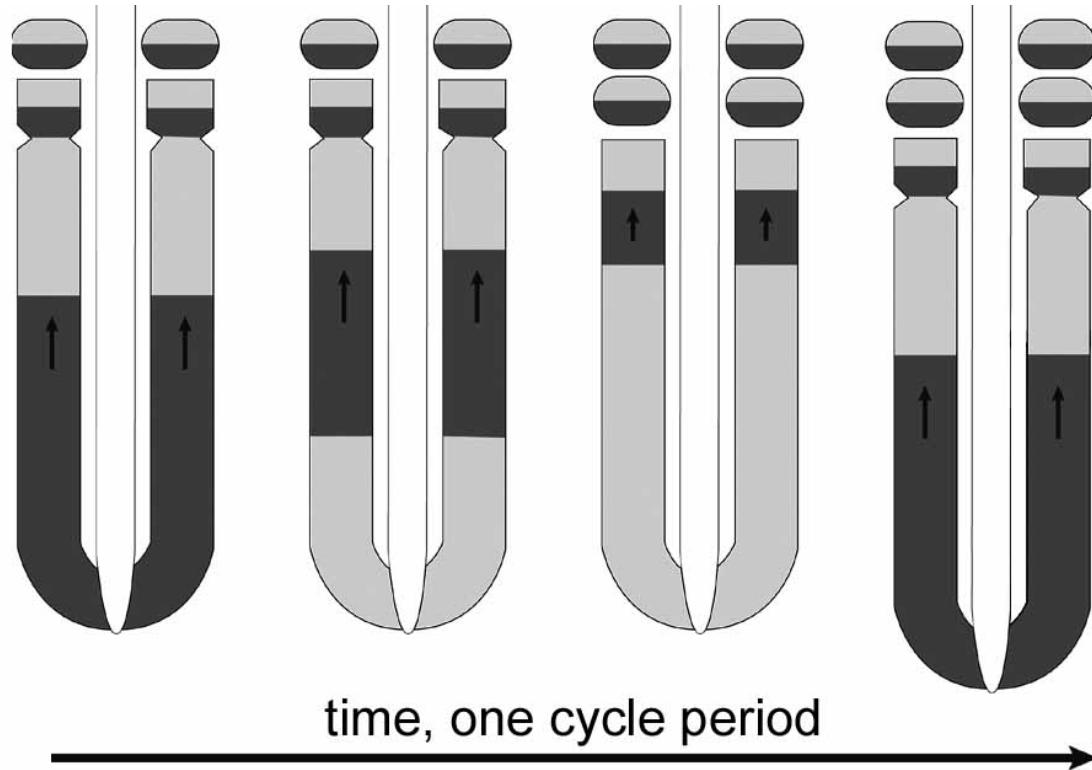
*Hox6*

*Hox9*

*Hox10*

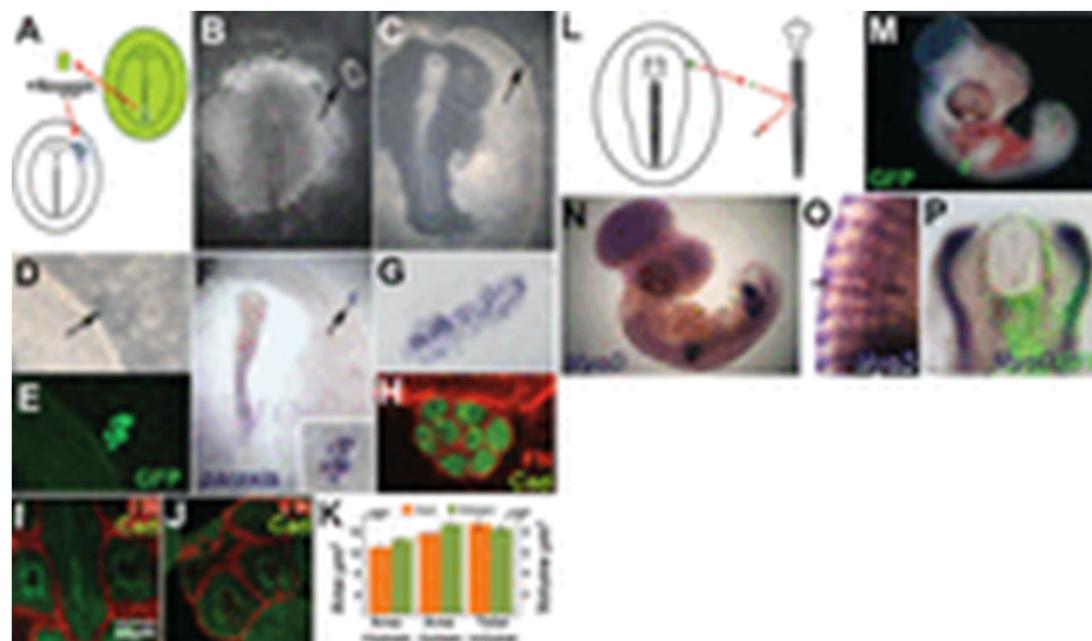
*Hox11*





- clock and wave
- Notch (Wnt) are the clock
- FGF is the wave
- This expression specifies somite development and activation of Hox genes

Dias AS1, de Almeida I, Belmonte JM,  
Glazier JA, Stern CD. Somites without a  
clock. Science. 2014 Feb  
14;343(6172):791-5.



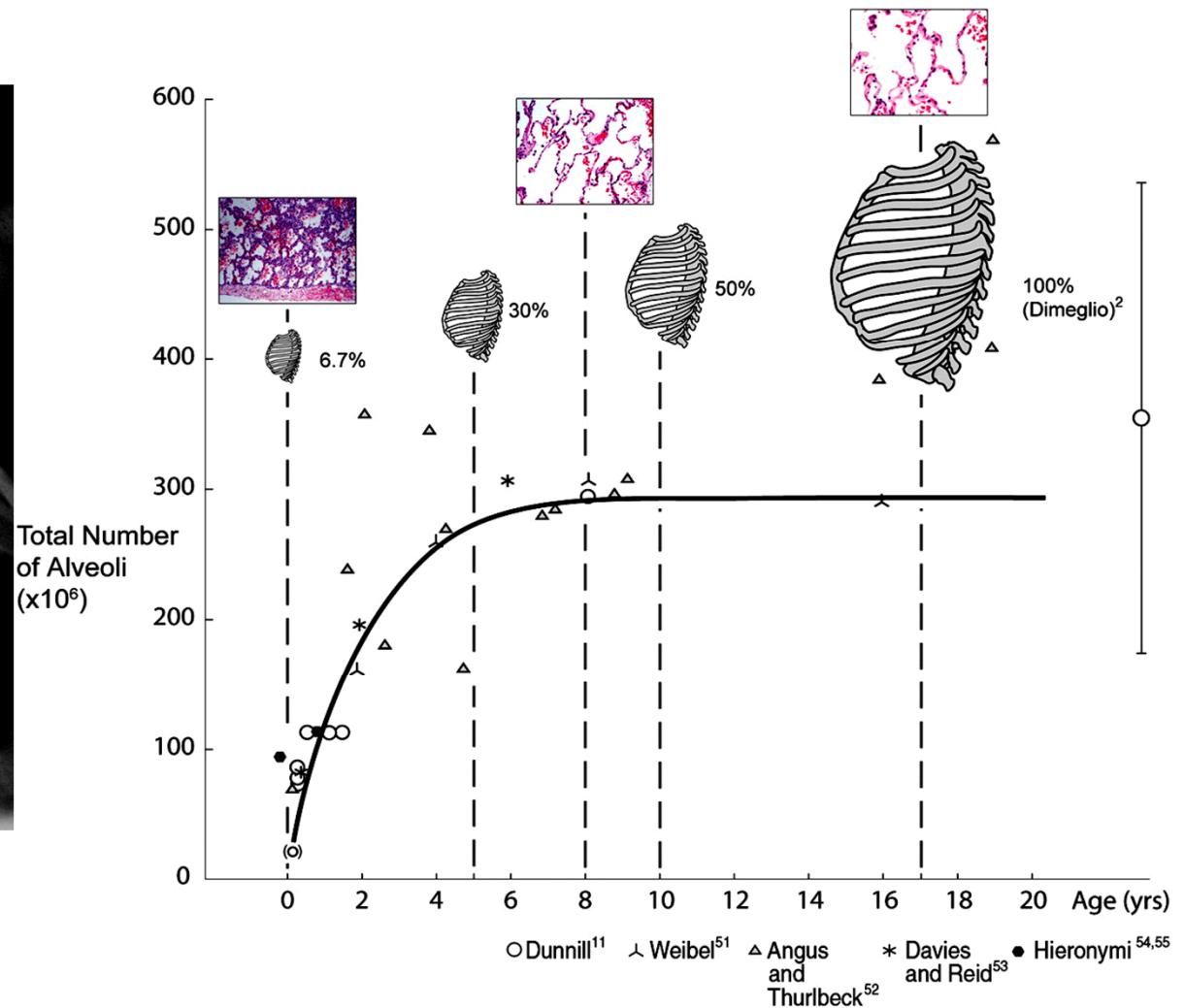
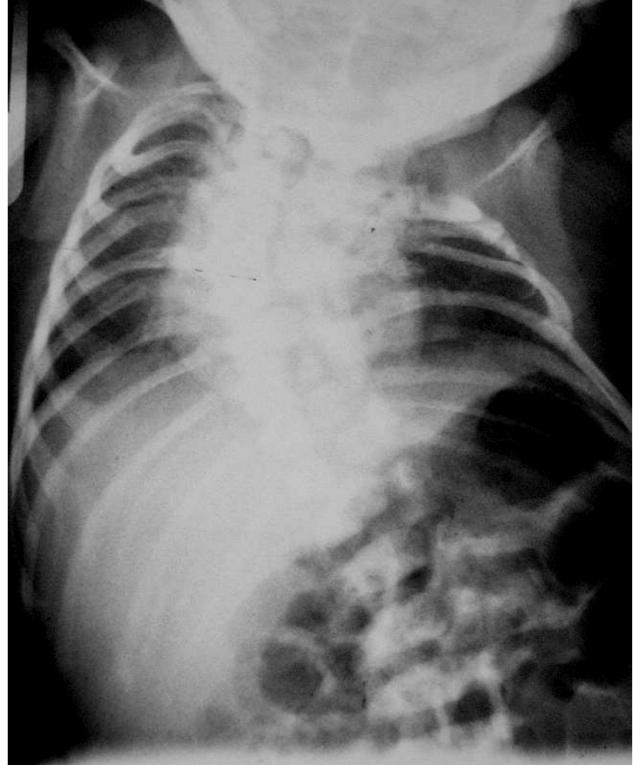


**Mouse: Curly bob**

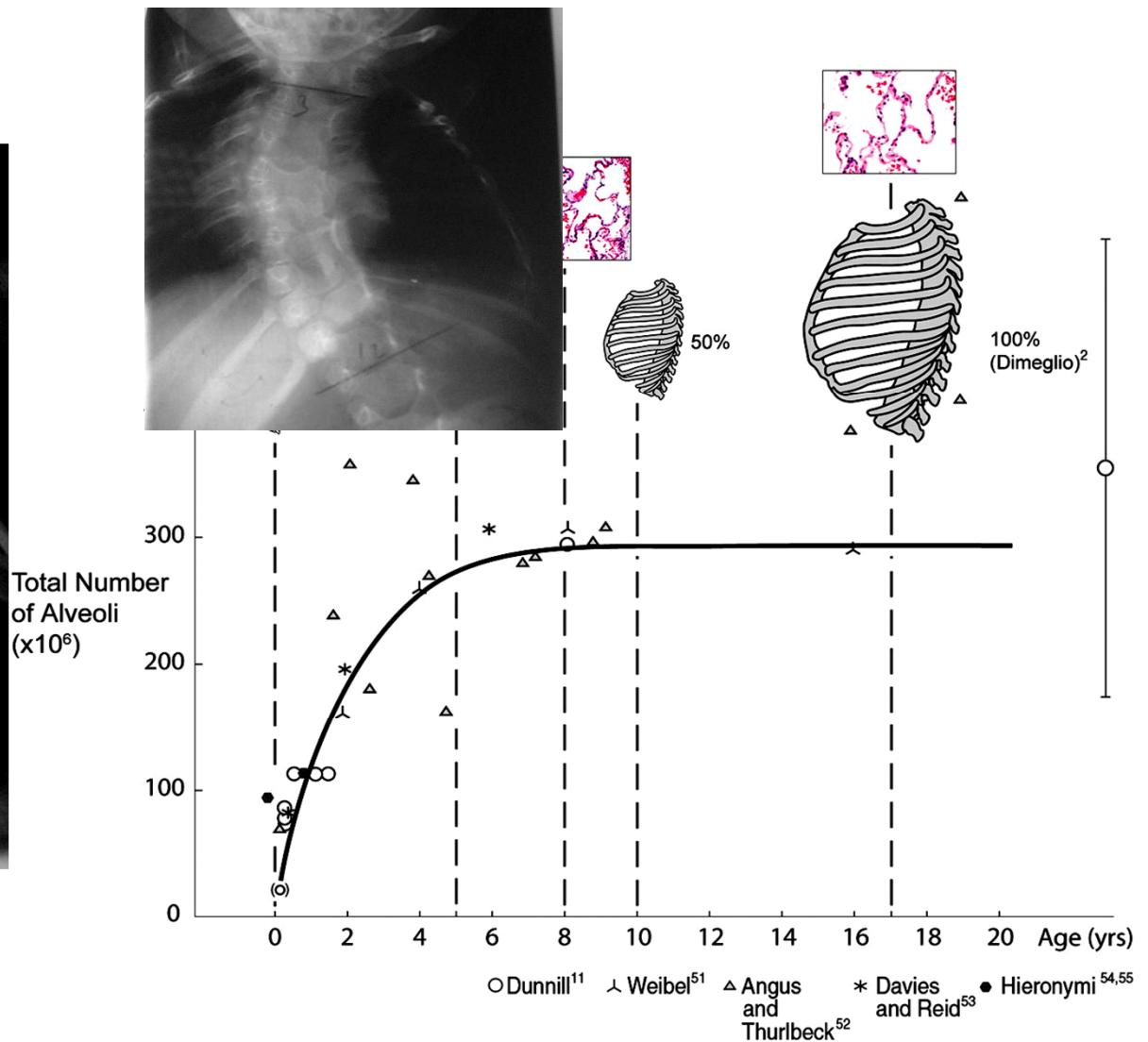


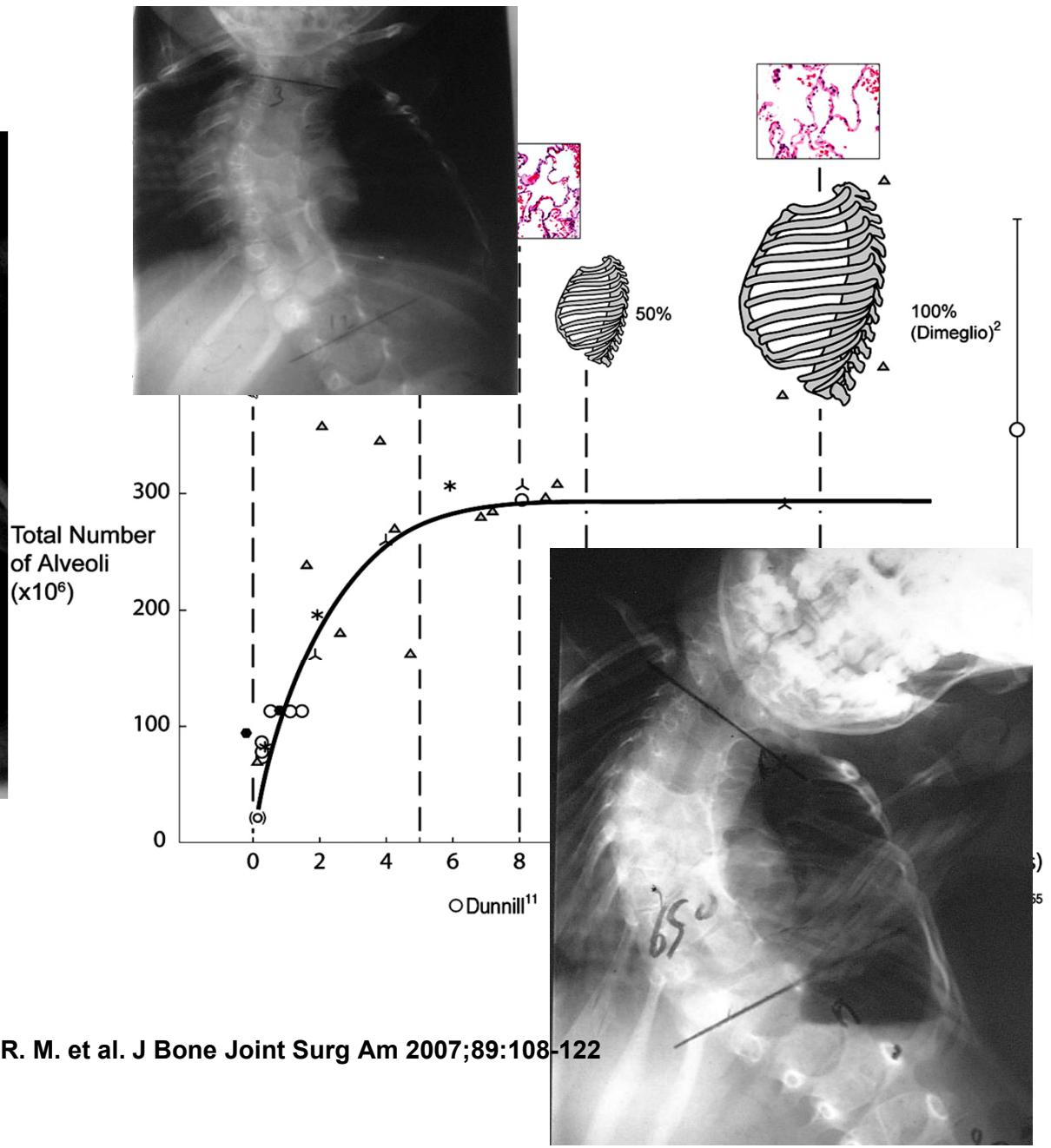
**Human: congenital scoliosis**



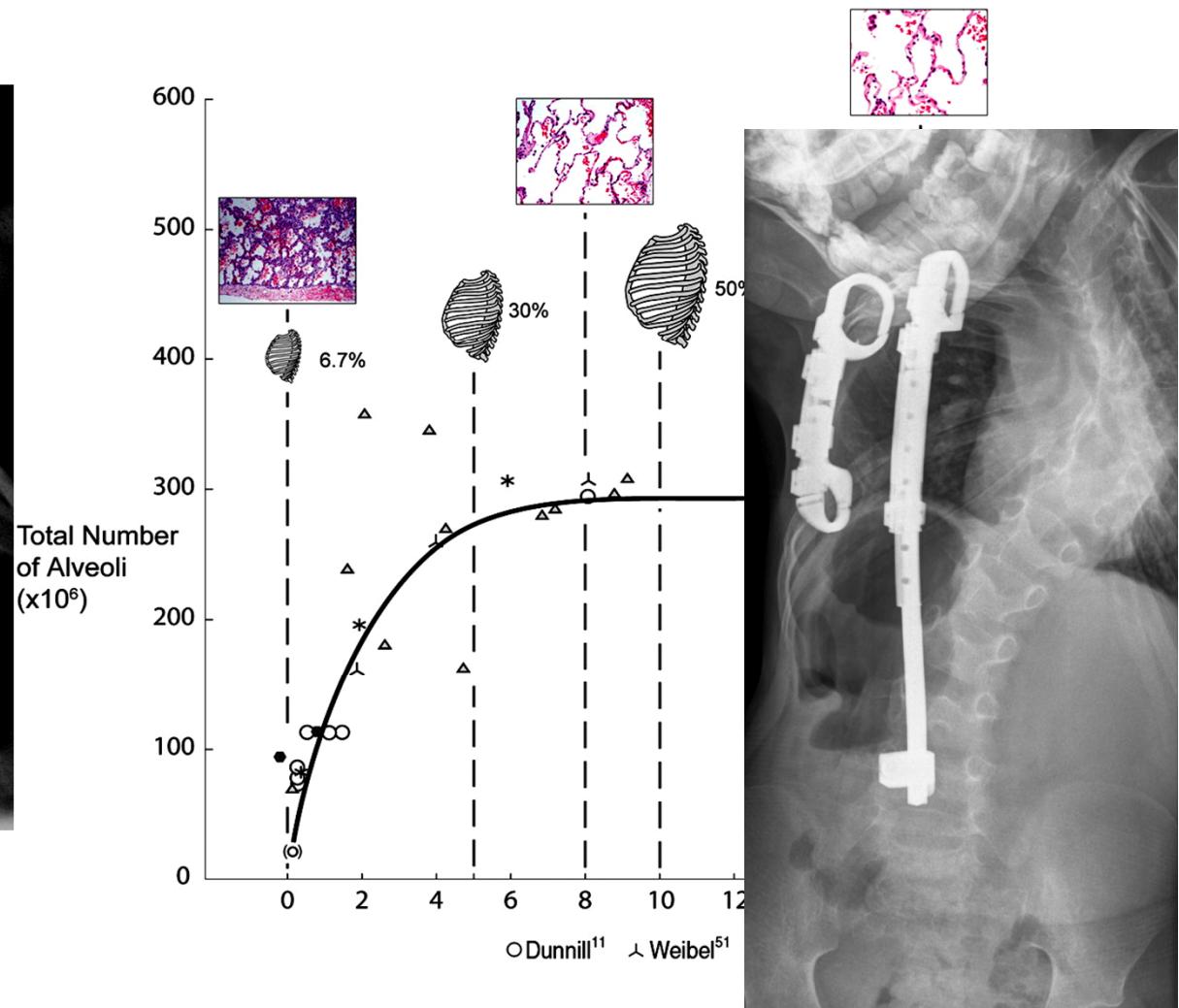


Campbell, R. M. et al. J Bone Joint Surg Am 2007;89:108-122



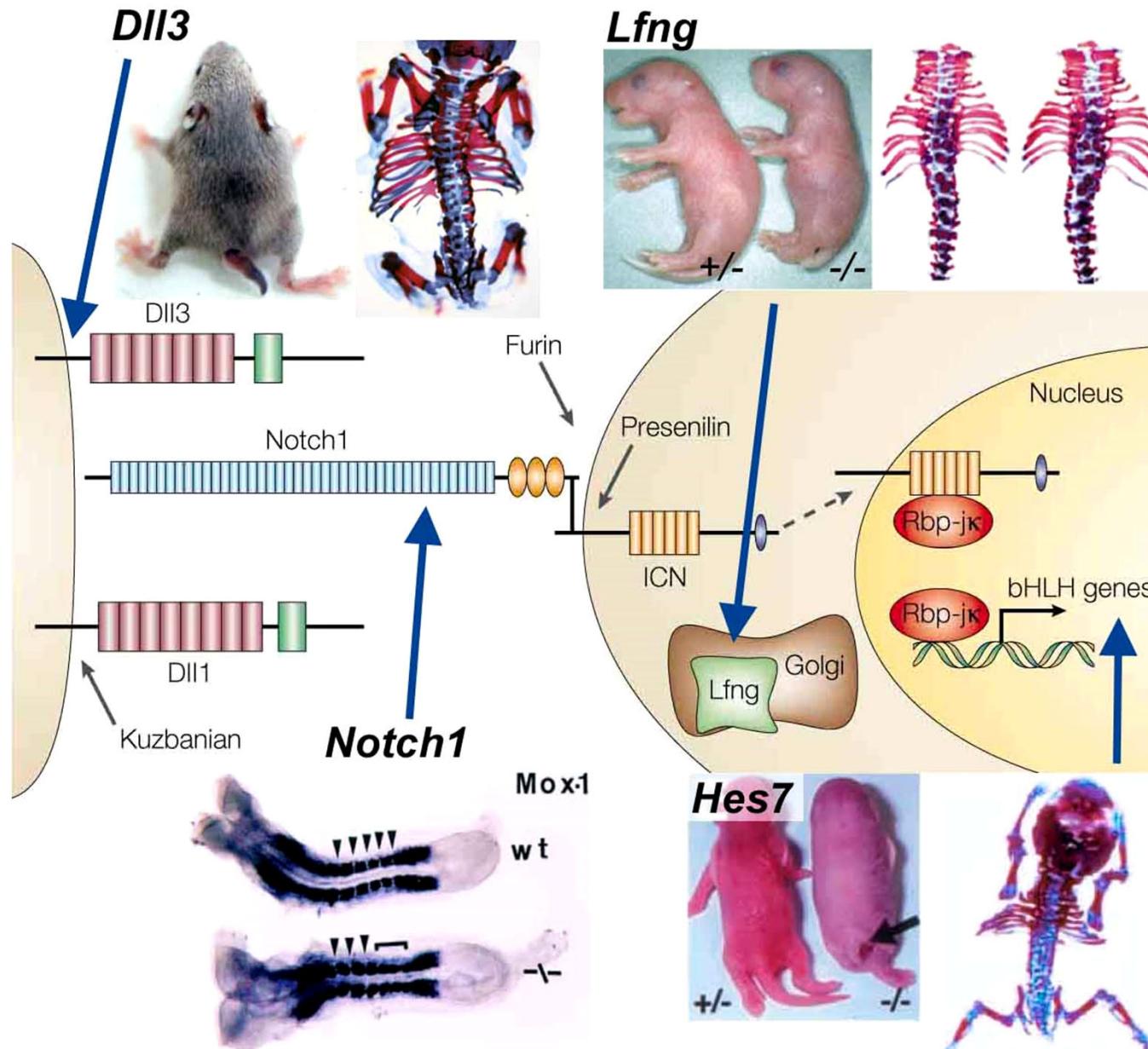


Campbell, R. M. et al. J Bone Joint Surg Am 2007;89:108-122



Campbell, R. M. et al. J Bone Joint Surg Am 2007;89:108-122

# Delta-like-3 is in the notch signaling pathway



# Unknowns – Notch in the lung

- Will the cause of scoliosis will also change alveolar development?
- Zhang S<sup>1</sup>, Loch AJ, Radtke F, Egan SE, Xu K. Jagged1 is the major regulator of Notch-dependent cell fate in proximal airways. *Dev Dyn.* 2013 Jun;242(6):678-86.
- Xu K<sup>1</sup>, Moghal N, Egan SE. Notch signaling in lung development and

*Am J Physiol Lung Cell Mol Physiol* 292: L725–L741, 2007.  
First published November 17, 2006; doi:10.1152/ajplung.00221.2006.

Mesenchymal maintenance of distal epithelial cell phenotype during late fetal lung development

Julie Deimling,<sup>1</sup> Kate Thompson,<sup>1</sup> Irene Tseu,<sup>1</sup> Jinxia Wang,<sup>1</sup>  
Richard Keijzer,<sup>1</sup> A. Keith Tanswell,<sup>1,2,3</sup> and Martin Post<sup>1,2,3,4</sup>

<sup>1</sup>Lung Biology Program, Hospital for Sick Children Research Institute; and Departments of <sup>2</sup>Paediatrics,

<sup>3</sup>Physiology, and <sup>4</sup>Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Submitted 15 June 2006; accepted in final form 10 November 2006

Oncogene (2003) 22, 1988–1997  
© 2003 Nature Publishing Group All rights reserved 0950-9232/03 \$25.00

[www.nature.com/onc](http://www.nature.com/onc)

## Constitutive activation of Notch3 inhibits terminal epithelial differentiation in lungs of transgenic mice

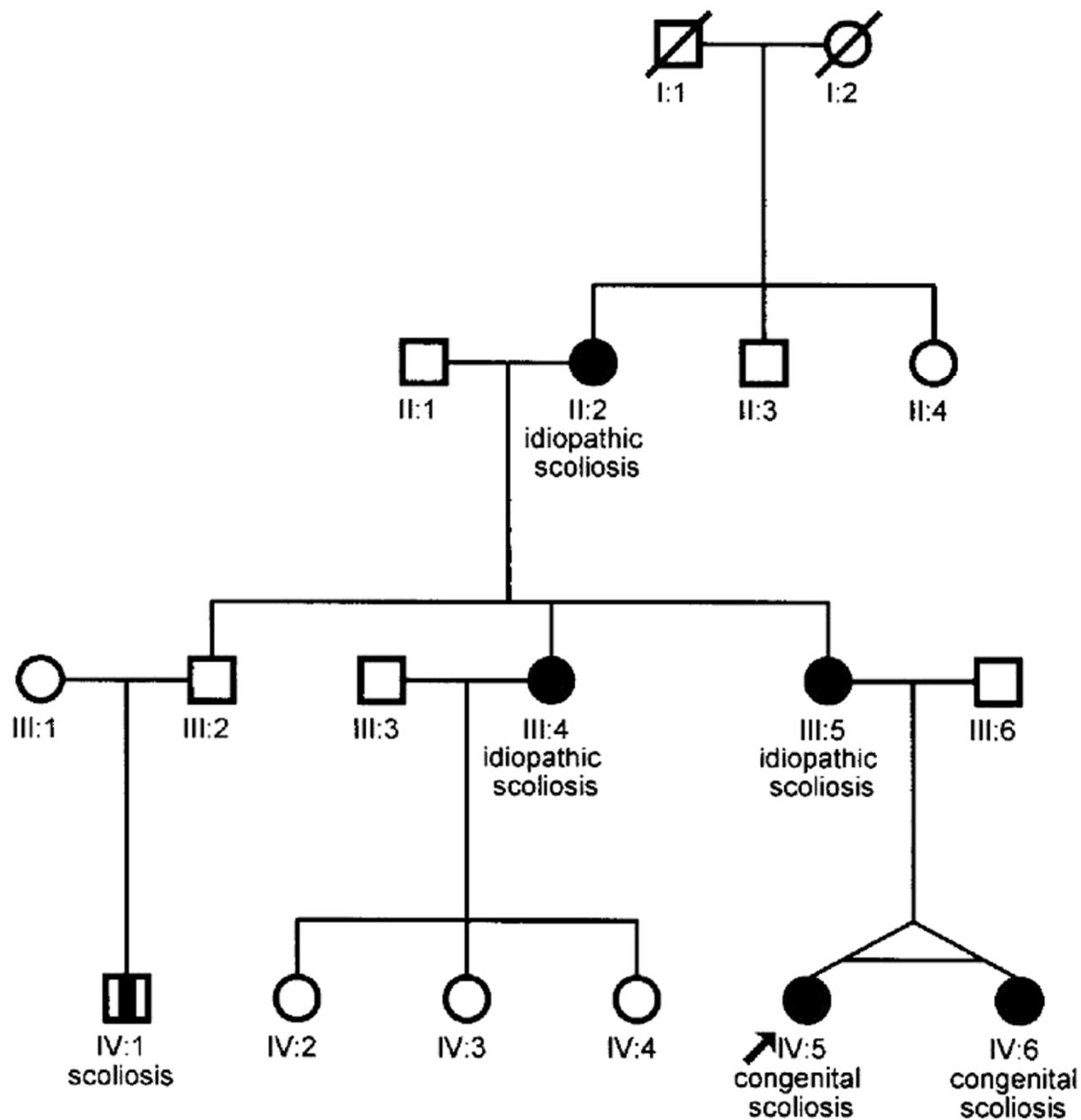
Thao P Dang<sup>\*1</sup>, Shannon Eichenberger<sup>1</sup>, Adriana Gonzalez<sup>2</sup>, Sandra Olson<sup>2</sup> and David P Carbone<sup>1</sup>

<sup>1</sup>Division of Hematology and Medical Oncology, Vanderbilt University Medical Center, Nashville, TN, USA; <sup>2</sup>Department of Pathology, Vanderbilt University Medical Center, Nashville, TN, USA



# Is familial occurrence really so rare?

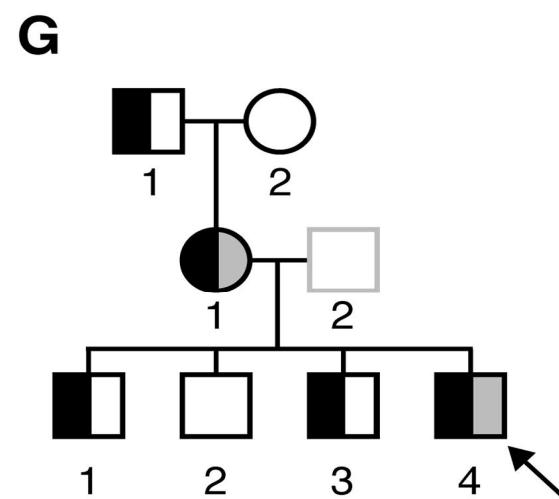
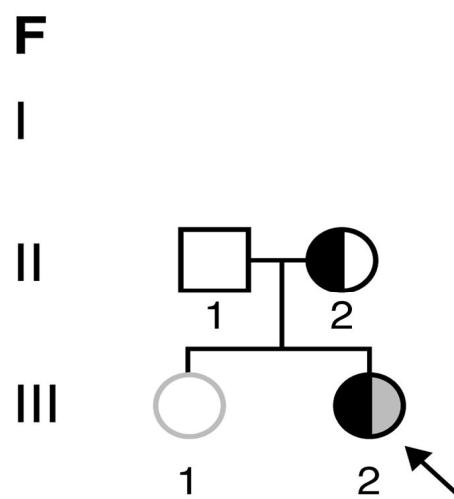
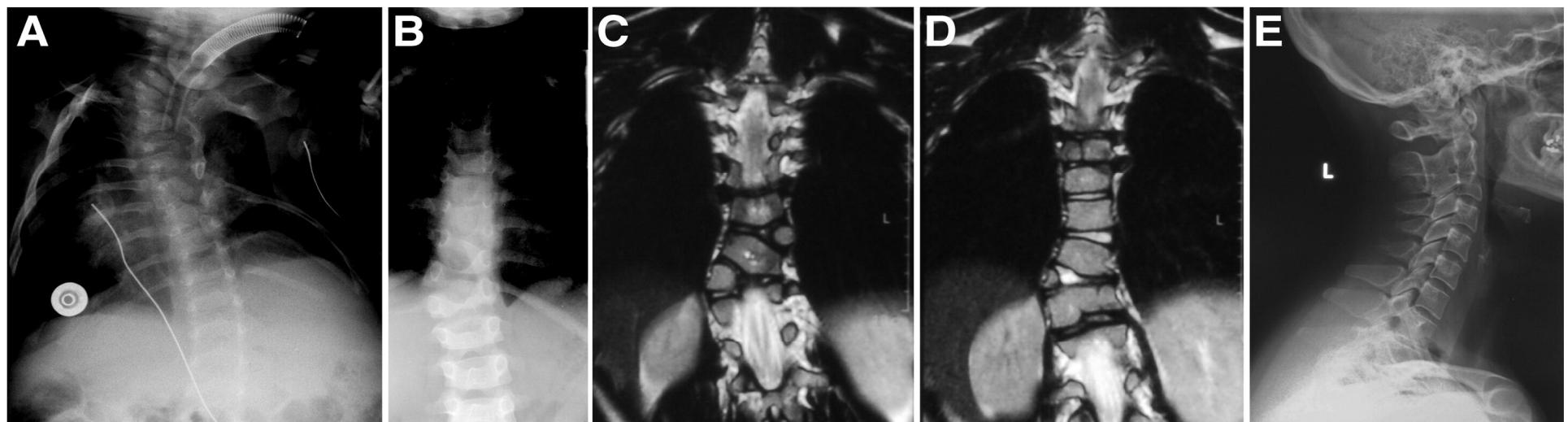
- Examined 297 probands
- 49 had at least one other family member with scoliosis (16%)
- 10 had other members with congenital scoliosis
- Rest had other members with idiopathic scoliosis



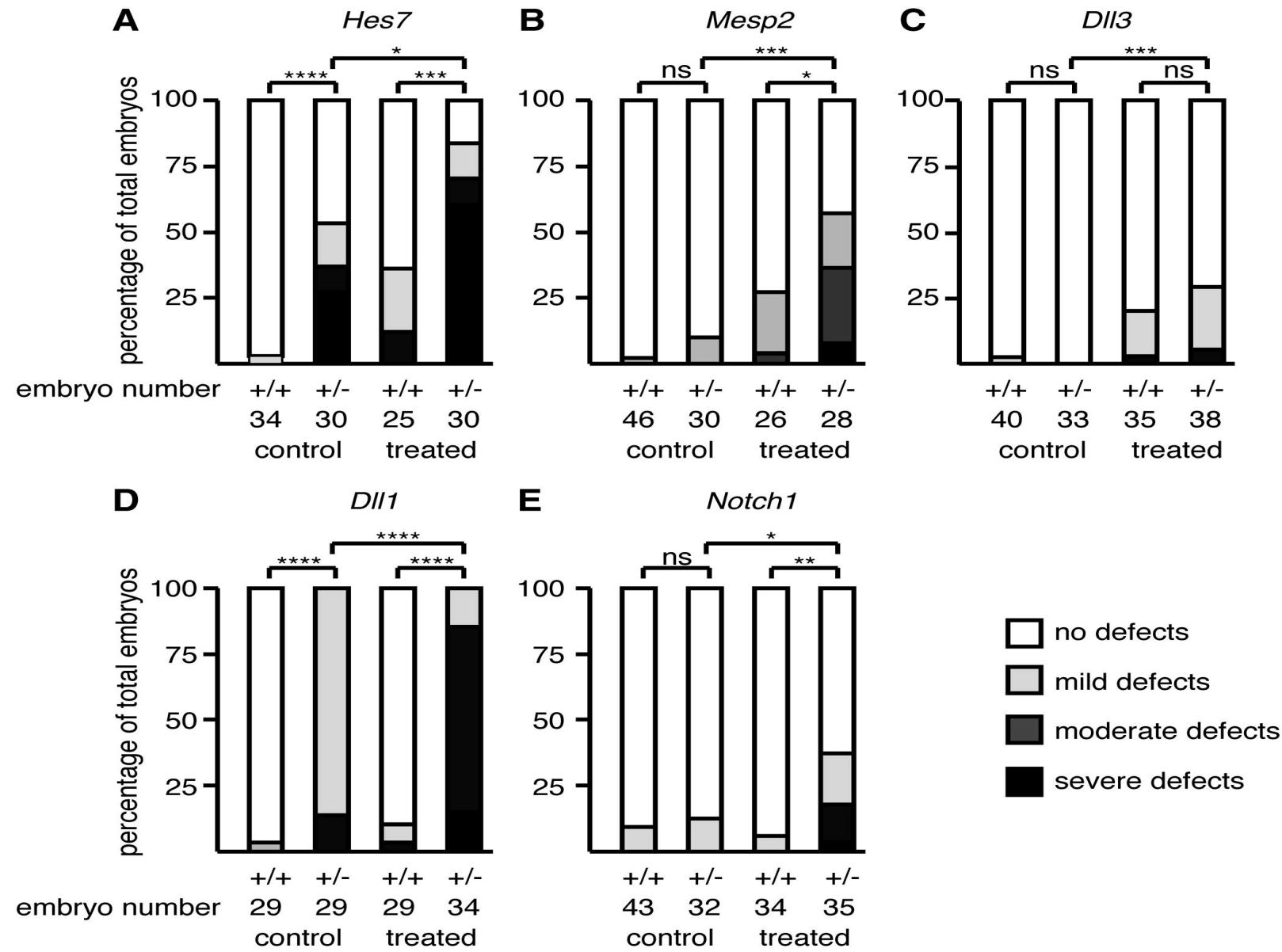
# A Mechanism for Gene-Environment Interaction in the Etiology of Congenital Scoliosis

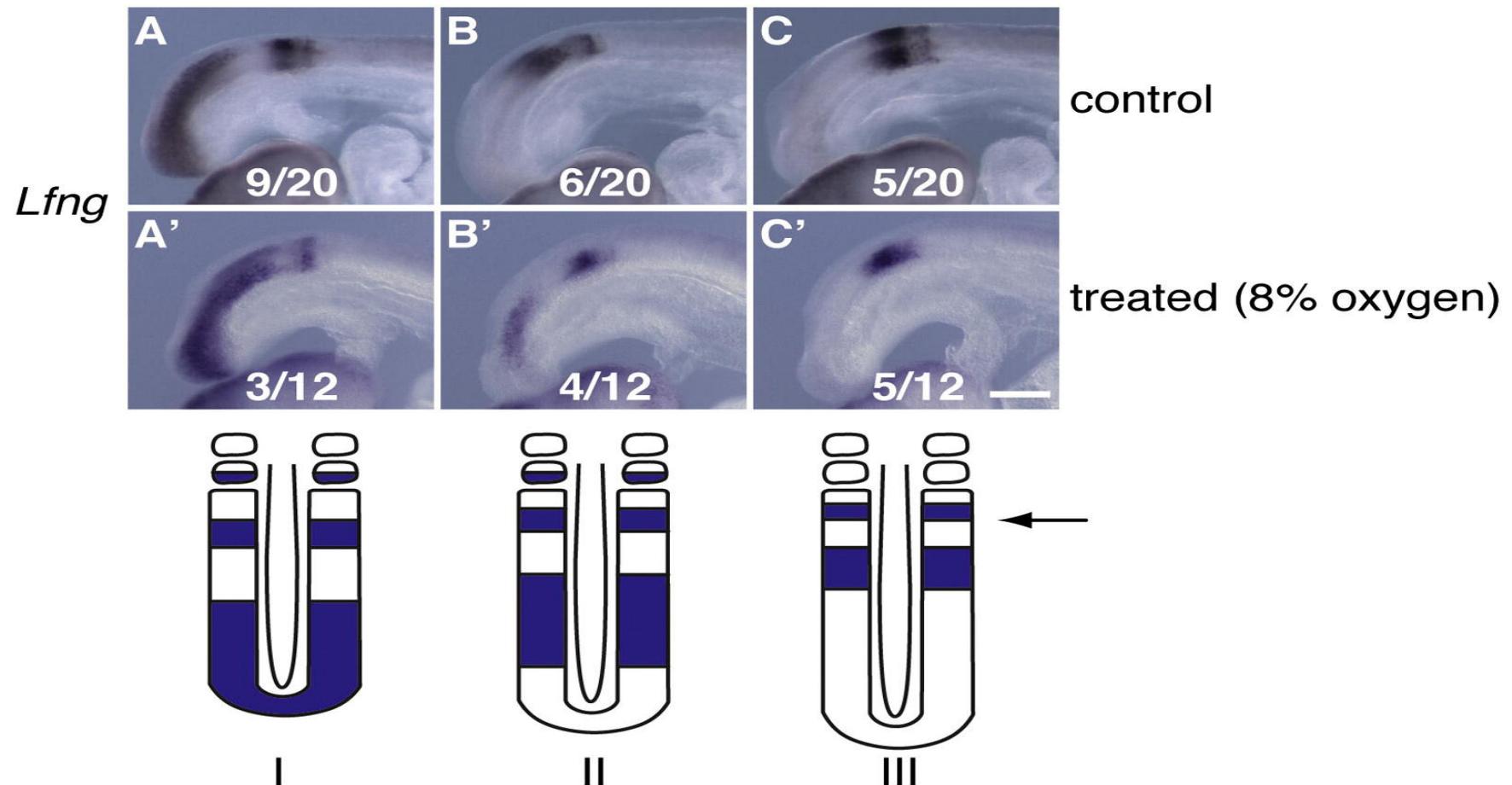
Duncan B. Sparrow,<sup>1,2,\*</sup> Gavin Chapman,<sup>1,2</sup> Allianceson J. Smith,<sup>3</sup> Muhammad Z. Mattar,<sup>1</sup> Joelene A. Major,<sup>1</sup> Victoria C. O'Reilly,<sup>1</sup> Yumiko Saga,<sup>4</sup> Elaine H. Zackai,<sup>5,7</sup> John P. Dormans,<sup>6,8</sup> Benjamin A. Alman,<sup>9,10,11</sup> Lesley McGregor,<sup>12</sup> Ryoichiro Kageyama,<sup>13</sup> Kenro Kusumi,<sup>3</sup> and Sally L. Dunwoodie<sup>1,2,\*</sup>

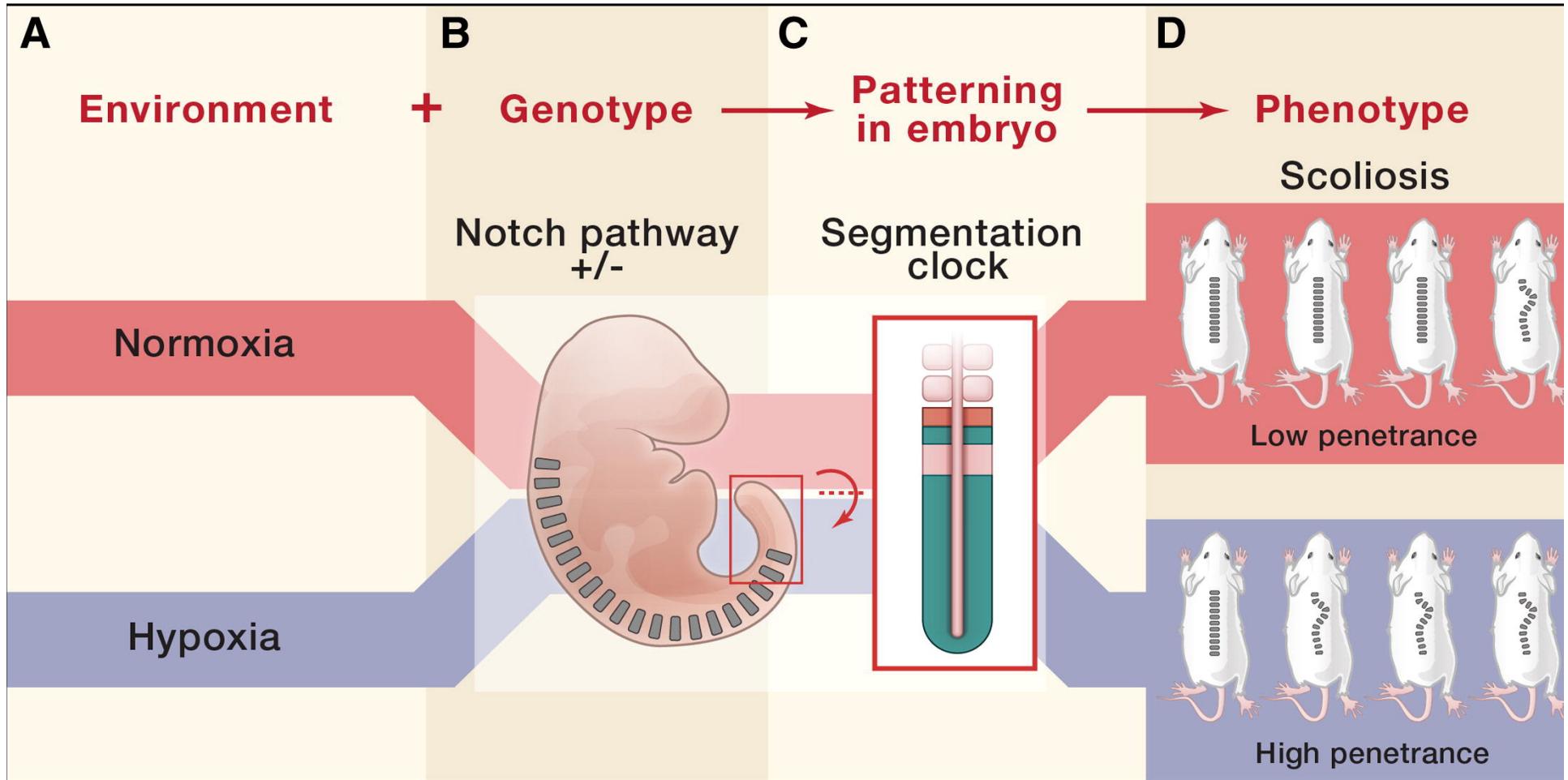
Cell, Volume 149, Issue 2, 2012, 295 - 306



- Heterozygote CS phenotype
- Heterozygote no phenotype
- not tested







# Future

Better Understanding genetics, and  
using this to predict outcome and  
best intervention

Modulation of pathways to slow  
progression

Understanding Environment

# Somite Clock

Notch, Hox, etc

Effect of clock pathways on  
development of other organs: e.g.  
lung development

Environment – Gene interactions



# Duke Orthopaedics

