SUPPLEMENTARY MATERIAL

Table i. Observed effects of reduced or absent movement on skeletal development. Altered mechanical stimuli affect multiple components of bone and joint development

Synovial joint formation	
Joint contractures, hip dysplasia*	Aronsson et al, 1994,[1] Pena and Shokeir, 1976[2]
Reduction/absence of synovial cavity; fusion of rudiments	Drachman and Sokoloff, 1966,[3] Fell and Canti, 1934,[4] Hamburger and Waugh, 1940,[5] Hosseini and Hogg, 1991,[6] Lelkes, 1958,[7] Mitrovic, 1982,[8] Murray and Drachman, 1969,[9] Ruano-Gil et al, 1978,[10] Kahn et al, 2009,[11] Mikic et al, 2000,[12] Nowlan et al, 2010,[13] Osborne et al, 2002,[14] Persson, 1983,[15] Roddy et al, 2011,[16] Roddy et al, 2011,[17] Rot-Nikcevic et al, 2006[18]
Hypermobility: Enlarged synovial cavities, expanded articular surface, enlarged patellae†	Ruano-Gil et al, 1985,[19] Pitsillides, 2006[20]
Absence of inter-articular ligaments, chondrogenous layer and menisci	Drachman and Sokoloff, 1966,[3] Hamburger and Waugh, 1940,[5] Hosseini and Hogg, 1991,[6] Mikic et al, 2000,[12] Roddy et al, 2011,[16] Roddy et al, 2011,[17] Ruano-Gil et al, 1978[10]
Disorganisation of differentiated tissues; altered expression patterns of Fgf2, Bmp2, Pthrp	(Nowlan et al, 2010,[13] Roddy et al, 2011[17]
Endochondral ossification	
Thin, hypomineralised bones*	Rodriguez et al, 1988,[21] Rodriguez et al, 1988[22]
Lower bone mass, reduced mechanical strength	Gomez et al, 2007,[23] Sharir et al, 2011[24]
Misshapen condyles, reduced chondrocyte proliferation at condyle sites	Drachman and Sokoloff, 1966,[3] Germiller and Goldstein, 1997,[25] Nowlan et al, 2010,[13] Nowlan et al, 2008,[26] Nowlan et al, 2008,[27] Roddy et al, 2011[16], Roddy et al, 2011,[17] Rot-Nikcevic et al, 2006[18]
Regressed tuberosities, reduced chondrocyte proliferation at humeral tuberosity	Blitz et al, 2009[28]
Reduced radial & longitudinal growth, reduced chondrocyte proliferation at the growth plate	Drachman and Sokoloff, 1966,[3] Gomez et al, 2007,[23] Hall and Herring, 1999,[29] Hosseini and Hogg, 1991,[6] Nowlan et al, 2008,[26] Nowlan et al, 2008,[27] Osborne et al, 2002,[14] Rot-Nikcevic et al, 2006,[18] Lamb et al,[30] 2003, Hogg and Hosseini, 1992[31]
Hypermobility: Increased length, increased chondrocyte proliferation†	Heywood et al, 2005[32]
Reduced bone collar and ossification, altered expression of ColX (down) and Ihh (up)	Nowlan et al, 2010,[13] Nowlan et al, 2008,[26] Nowlan et al, 2008[27]

* Effects were observed in human infants; all other effects were observed in animal models, namely mouse and chick
† Effects were induced by hyper-, rather than hypo-, mobility

References

1. **Aronsson DD, Goldberg MJ, Kling TF Jr, Roy DR.** Developmental dysplasia of the hip. *Pediatrics* 1994;94:201–208.
2. **Pena SD, Shokeir MH.** Syndrome of camptodactyly, multiple ankyloses, facial anomalies and pulmonary hypoplasia--further delineation and evidence for autosomal recessive inheritance. *Birth Defects Orig Artic Ser* 1976;12:201–208.
3. **Drachman DB, Sokoloff L.** The role of movement in embryonic joint development. *Developmental Biology* 1966;14:401–420.
4. **Fell HB, Canti, RG.** Experiments on the development in vitro of the avian knee joint. *Proc R Soc B* 1934;116:316–351.
5. **Hamburger V, Waugh M.** The primary development of the skeleton in nerveless and poorly innervated limb transplants of chick embryos. *Physiological Zoology* 1940;13:367–380.
6. **Hosseini A, Hogg DA.** The effects of paralysis on skeletal development in the chick embryo. I. General effects. *J Anat* 1991;177:159–168.
7. **Lelkes G.** Experiments in vitro on the role of movement in the development of joints. *J Embryol Exp Morphol* 1958;6:183–186.
8. **Mitrovic D.** Development of the articular cavity in paralyzed chick embryos and in chick embryo limb buds cultured on chorioallantoic membranes. *Acta Anat (Basel)* 1982;113:313–324.
9. **Murray PD, Drachman DB.** The role of movement in the development of joints and related structures: the head and neck in the chick embryo. *J Embryol Exp Morphol* 1969;22:349–371.
10. **Ruano-Gil D, Nardi-Vilardaga J, Tejedo-Mateu A.** Influence of extrinsic factors on the development of the articular system. *Acta Anat (Basel)* 1978;101:36–44.
11. **Kahn J, Shwartz Y, Blitz E, et al.** Muscle contraction is necessary to maintain joint progenitor cell fate. *Dev Cell* 2009;16:734–743.
12. **Mikic B, Wong M, Chiquet M, Hunziker EB.** Mechanical modulation of tenascin-C and collagen-XII expression during avian synovial joint formation. *J Orthop Res* 2000;18:406–415.
13. **Nowlan NC, Bourdon C, Dumas G, et al.** Developing bones are differentially affected by compromised skeletal muscle formation. *Bone* 2010;46:1275–1285.
14. **Osborne AC, Lamb KJ, Lewthwaite JC, Dowthwaite GP, Pitsillides AA.** Short-term rigid and flaccid paralyses diminish growth of embryonic chick limbs and abrogate joint cavity formation but differentially preserve pre-cavitated joints. *J Musculoskelet Neuronal Interact* 2002;2:448–456.
15. **Persson M.** The role of movements in the development of sutural and diarthrodial joints tested by long-term paralysis of chick embryos. *J Anat* 1983;137 (Pt 3):591–599.
16. **Roddy KA, Prendergast PJ, Murphy P.** Mechanical influences on morphogenesis of the knee joint revealed through morphological, molecular and computational analysis of immobilised embryos. *PLoS One* 2011;6:17526.
17. **Roddy KA, Kelly GM, van Es MH, Murphy P, Prendergast PJ.** Dynamic patterns of mechanical stimulation co-localise with growth and cell proliferation during morphogenesis in the avian embryonic knee joint. *J Biomech* 2011;44:143–149.
18. **Rot-Nikcevic I, Reddy T, Downing KJ, et al.** Myf5-/- :MyoD-/- amyogenic fetuses reveal the importance of early contraction and static loading by striated muscle in mouse skeletogenesis. *Dev Genes Evol* 2006;216:1–9.
19. **Ruano-Gil D, Nardi-Vilardaga J, Teixidor-Johé A.** Embryonal hypermobility and articular development. *Acta Anat (Basel)* 1985;123:90–92.
20. **Pitsillides AA.** Early effects of embryonic movement: 'a shot out of the dark'. *J Anat* 2006;208:417–431.
21. **Rodríguez JI, Garcia-Alix A, Palacios J, Paniagua R.** Changes in the long bones due to fetal immobility caused by neuromuscular disease. A radiographic and histological study. *J Bone Joint Surg [Am]* 1988;70:-A:1052–1060.
22. **Rodríguez JI, Palacios J, García-Alix A, Pastor I, Paniagua R.** Effects of immobilization on fetal bone development. A morphometric study in newborns with congenital neuromuscular diseases with intrauterine onset. *Calcif Tissue Int* 1988;43:335–339.
23. **Gomez C, David V, Peet NM, et al.** Absence of mechanical loading in utero influences bone mass and architecture but not innervation in Myod-Myf5-deficient mice. *J Anat* 2007;210:259–271.
24. **Sharir A, Stern T, Rot C, Shahar R, Zelzer E.** Muscle force regulates bone shaping for optimal load-bearing capacity during embryogenesis. *Development* 2011;138:3247–3259.
25. **Germiller JA, Goldstein SA.** Structure and Function of Embryonic Growth Plate in the Absence of Functioning Skeletal Muscle. *J Orthop Res* 1997;15:362–370.
26. **Nowlan NC, Prendergast PJ, Murphy P.** Identification of mechanosensitive genes during embryonic bone formation. *PLoS Comput Biol* 2008;4:1000250.

27. Nowlan NC, Murphy P, Prendergast PJ. A dynamic pattern of mechanical stimulation promotes ossification in avian embryonic long bones. *J Biomech* 2008;41:249–258.

28. Blitz E, Viukov S, Sharir A, et al. Bone ridge patterning during musculoskeletal assembly is mediated through SCX regulation of Bmp4 at the tendon-skeletal junction. *Dev Cell* 2009;17:861–873.

29. Hall BK, Herring S. Altered skeletal growth of paralyzed chick. *J Morph* 1999;206:45–56.

30. Lamb KJ, Lewthwaite JC, Lin JP, et al. Diverse range of fixed positional deformities and bone growth restraint provoked by flaccid paralysis in embryonic chicks. *Int J Exp Pathol* 2003;84:191–199.

31. Hogg DA, Hosseini A. The effects of paralysis on skeletal development in the chick embryo. *Comp Biochem Physiol Comp Physiol* 1992;103:25–28.

32. Heywood JL, McEntee GM, Stickland NC. In ovo neuromuscular stimulation alters the skeletal muscle phenotype of the chick. *J Muscle Res Cell Motil* 2005;26:49–56.