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Segmental morphogenesis of somites, homeotic transformations and associated congenital malformations: facts and speculation

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To the Editor,

It was interesting to read an article recently published in this journal [Analytical view of the simultaneous occurrence of sacralisation and congenital anomalies. *Eur J Anat,* 16 (2): 127-133 (2012)]. The author should be congratulated on presenting a bird's eye review of certain aspects of homeobox genetics that relates to vertebral segmentation. However, the conclusions promulgated by the author attract some discussion. An abundant pertinent literature has already addressed and discussed these issues with succinct observational and experimental data. The following observations are put forward after reviewing some relevant publications. Citing all of these materials is out of the scope of this letter:

1. There are several important published studies that have reported, as well as debated, the relationships between spine segmentation patterns and other somatic anomalies (Bardeen, 1904; Galis 1999; Erken et al., 2002; Galis and Metz, 2003; Durston et al., 2011; Tague, 2011; Varela-Lasheras et al., 2011; Ten Broek et al., 2012).

2. The segmentation anomaly (sacralisation only) presented by the author is too narrow in its scope to merit such discussion related to the genetics of cranio-caudal segmental dysgenesis and its deleterious consequences on other organ systems. Lumbosacral transitional variational anomalies have been included under the LSTV umbrella (Tini et al., 1977; Castellvi et al., 1984), which gives us a wider scope of understanding the pattern of segmental anomalies at the lumbosacral region with their clinical implications. Homeotic transformations of the vertebral segmental patterning in the embryonic period is not only confined to the sacrum, but are related to the 'boundaries' of the cervico-thoracic, thoracolumbar and lumbo-sacral (pre-sacral) segments (Galis et al., 2006; Aulehla and Pourquie, 2010; Ten Broek et al., 2012). Strong correlations have been demonstrated between the 'strength' of associated systemic malformations on the 'length' of disturbance of vertebral patterning. This means that the more the levels/locations of abnormal homeotic transformations involving multiple transition zones along the spine, the more organ systems are affected (Steigenga et al., 2006; Ten Broek et al., 2012). Thus, a lot of potential segmental anomalies due to defective expression of the Hox genes at very early stages of embryogenesis have been related to severe multi-system malformations that are, in fact, mostly incompatible with life (Yuksel et al., 2005; Hershkovitz 2008; Ten Broek et al., 2012). Given the prevalent rates of lumbo-sacral segmental dysgenesis in the population, the clinical overtones drawn by

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the author in relation to sacralisation vis-à-vis projected systemic disorders likely to be found in these people seems an oversimplification (Bornstein and Peterson, 1966).

3. On the same grounds, it appears to be self-contradictory when, on the one hand the article acknowledges that "it is generally accepted that a specific combination of Hox genes expressed at a particular somitic level determines the axial identity of the resulting structures," and "however, an association between Hox somitic expression and mutant phenotypes is not always easy to establish", and on the same breath the article conjectures correlation between a vast array of varied and non-specific range of somatic anomalies with a narrow width of anatomical malformations like sacralisation. Homeotic transformations of the vertebral patterning are, indeed, much localized systems of events involving co-expressions and interactions between multiple factors (Wellik and Capecchi 2003; Cordes et al., 2004), a phenomenon that has been experimentally well verified (Carapuco et al., 2005). Homeotic transformations (or aberrancies), on the other hand, may not always imply a change in the total number of vertebrae (Varela-Lasheras et al., 2011). Thus, looking for a wide array of pleiotropic outcomes relying on a single parameter of a skeletal anomaly could be insufficient to make such an association, much the same way as the classification of sacralisation in this article is too narrow and deficient in its purpose (Pionnier and Depraz, 1956).

Vertebral segmentation anomalies at one region have very often been correlated with pathology at another region of the spine (Erken et al., 2002; Hershkovitz, 2008). To a large extent, clinical effects of sacralisation may be explained by obvious local effects on the lower back and the pelvis (Tague, 2009; Mahato, 2010a). Detailed published material is available on the spectrum of clinical effects of the skeletal condition described. (Luoma et al., 2004; Bron et al., 2007).

4. The hypoplastic and diversely structured cornual structures discussed in the text, and the incomplete fusion of the first sacral vertebral body with the remaining sacral corpus (representing post-ossification disc remnants) (shown in the article as Fig. 2), are extremely common observations in osseous sacral samples (Kumar et al., 1992; Mahato, 2010b). One needs to justify and substantiate statistically the correlation of these common variations drawn with a possibility of detecting suggested organ-system malformations by the author (Brewin et al., 2009).

The article states that "the hypothesis regarding the genetic view of sacralisation and associated anomalies is the most important conclusion in this study. This hypothesis, if established by clinicians as advised, will not only revolutionise the entire medical world, but also provide a new dimension to the diagnosis and treatment of sacralisation and associated anomalies-related diseases". Also, inferring that "Sacralisation is always accompanied by anomalies (misshapen knee joints, fore and hind limbs, modified parathyroid, thymus, involvement of ultimobranchial body, the absence of teeth, a cleft secondary palate, supernumerary digits), either in part or in full, depending on mutation of Hox11 and Pax1/Pax9 genes to varying degrees in human embryos" seems premature and unsatisfactorily derived from the context of the contents discussed in the manuscript. Therefore, one probably needs to tread cautiously when claiming "the simultaneous occurrence of sacralisation and congenital anomalies" as something being as novel and interrelated, as has been reported in the article.

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REPLY TO EDITOR LETTER

Dear Sir/Madam,

Thanks for providing an opportunity to see the critical comments on my paper entitled **Analytic view of simultaneous occurrence of sacralisation and congenital anomalies.** It is a matter of great pride, privilege and pleasure that my paper could attract the kind attention, time and knowledge of the learned reader. Therefore I sincerely appreciate the time, efforts and knowledge that have led to this critical examination of my article.

But I regret that it has been read partially by picking a few extracts, and not in its totality. The reading is sometimes biased and its intention is seldom to improve the argument.

I appreciate the critic's efforts to correct the negative aspects in my paper. I can agree with this learned reader that the hypothesis has been derived from limited evidence. However, it cannot be denied that it is innovative not only to connect the results of experiments on mice to human beings, but also to provide a revolutionary diagnostic tool to medical science.

Scientific research is always based on concepts and philosophy derived from data, however scanty it is. If Lord Thomson had not conceptualized the first atomic structure, Rutherford would not have followed, nor would Neils Bohr. Here it is pertinent to mention that I am not comparing myself with such renowned scientists, but sometimes "nothing is impossible." The study is fundamental and includes a lot of relevant works by scientists in the field of genetics who have been duly acknowledged through references.

The learned reader deserves appreciation, but not for belittling the substance of my paper. For the information of this honourable reader, a project is being designed to validate the hypothesis. Shortly the outcome may be published. Scientific research is always probabilistic, but seldom deterministic.

Thanks and regards.

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