Exclusion of retinoic acid receptor and a cartilage matrix protein in non-syndromic CL(P) families

We read with interest the report of Vintiner et al. suggesting exclusion of linkage to RARA (17q21), 1-09 to 0-69 and 0-37 to 0-16 on X chromosome. 2 Although the authors state that all loci were rejected using the 0.99 cll (15) LOD score, we have recalculated the four loci in eight generational white families with autosomal dominant non-syndromic cleft lip with or without cleft palate (CL(P)). 2 We have also tested linkage to the same locus in ten non-syndromic CL(P) white families at these same loci, and can confirm the reported exclusions. 2 The report of linkage to RARA was tested using Southern gel and Gibson non-radioactive techniques. 2 Tight linked flanking short tandem repeat PCR markers at the RARA locus, Thra1, D1S188 (D1S7559), D1S7580, and Hox2B and CRTL were amplified and separated on 8% sequencing gels, 2 and visualised by silver staining using the GELCODE® system. 2 Linkage was tested by using MLINK and LIPED, assuming a dominant mode of inheritance for CL(P) with a penetrance of 0.32 in males and 0.24 in females and with a 0.01 allele frequency. 2 The lod scores were -2.1 at 0-37, -2.1 at 0-37, -2.1 at 0-37, and -2.1 at 0-37, respectively. 2 The summed lod scores for the four CL(P) families were -2.1 at 0-37, -2.1 at 0-37, and -2.1 at 0-37, respectively. 2 The exclusion region for the F13A1 locus and the entire region spanning from F13A1 to TCDE, which included the HLA region. 2 Our findings and those of Vintiner et al. suggest that RARA, CTL1, and F13A1 do not have a major causal role in the aetiology of CL(P) in the 18 families tested. However, as previously suggested, we can not distinguish whether RARA plays a modifying role in the aetiology of CL(P). 2

Further report of a patient with humeralrondulcer synostosis and hydronephrosis

A case of humeralrondulcer synostosis with lambloid synostosis was published recently in this journal. 3 We report on a male baby with clinical and skeletal abnormalities very similar to those previously reported. 3,4

The proband was the first child of young and healthy non-consanguineous parents. He was born at term following a normal pregnancy, because of cephalopelvic disproportion. Birth weight and length were 3490 g and 51 cm, respectively. Apart from the upper limb defects and a midline cleft palate, no other abnormality was found on physical examination. At 11 months he measured 73-5 cm (50th centile), head circumference was 47 cm (50th centile), and weight was 8300 g (10th centile). Psychomotor development has been normal. Both upper limbs were short, the left one more malfomed than the right. Both shoulders had normal range of movement. The left upper limb was shorter than the right and kept in a fixed position; there were two digits joined
X rays of the upper limbs showing (top) humeroradial synostosis and (below) humeroulnar synostosis and absent thumb ossification.

along their axis. On the right side only absence of the thumb was observed.

Radiographs obtained at 4 months showed left humeroradial-ulnar synostosis, two metacarpophalangeal bones (probable fusion of a third metacarpal bone), and the middle phalanx of the 5th finger was absent. On the right, there was humeroradial synostosis and thumb ossification was absent (figure). Lower limb radiographs disclosed no abnormality. Skull x ray failed to show craniosynostosis as reported by Edwards et al.2

An abdominal ultrasound scan showed hydrenephrosis of the left kidney, with a pyelogram suggestive of left pyeloureteral stenosis. This finding, however, could be coincidental, and should be searched for in similar cases.

This case represents an example of the possible variability of this condition, the pathogenesis of which still remains obscure.2

BOOK REVIEW

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In the excitement of the rapid developments of today, it is easy for readers of this journal to be unaware of the debt that they owe to JBS Haldane, for much of the theory on which clinical genetics is founded originated with his work. His influence, great in all fields of genetics human and non-human, was equally great in physiology and biochemistry. He wrote some 400 scientific articles, 20 books, and numerous essays, and at least 20 of his pupils were elected Fellows of the Royal Society. It was therefore fitting to commemorate the centenary of his birth, and the same idea occurred to several. Thus a one day symposium was organised at University College London on behalf of the Biometric Society, by Professor C A B Smith, and there seven of Haldane's friends and colleagues spoke on aspects of his work and ideas, essentially a personal tribute. A much more ambitious celebration, a full conference, was organised in December 1992 at the Indian Statistical Institute in Calcutta, to which Haldane retired. The proceedings of that conference form the subject of this book. Its object was to evaluate the effect of Haldane's contributions in various areas of human genetics, in the light of the more recent developments.

C R Rao, a former Director of the Research and Training School of the Indian Statistical Institute, and jointly responsible (with Mahalanobis) for attracting haldane there, gave the opening address of which a condensed version opens this book, illustrating with examples the scientific method followed and advocated by Haldane. The technical papers are then grouped in five sections.

The first, devoted to population genetics and evolution, opens with a highly provocative paper by W J Edwards, criticising several aspects of Haldane's thought and work. The very readable style of this criticism continues in Ewen's discussion of key developments in population genetics post 1955, in which flesh has been added to the Fisher-Haldane-Wright skeleton, for example, the incorporation of multilocus systems and the development of stochastic theory appropriate for the situation of infinitely many alleles that is emerging from recent molecular work.

Other noteworthy contributions in this section are those by N Takahata on the evolution of the immune system, and by T Gojobori and T Imanishi who draws together a great deal of MHC gene frequency data, and the phylogenetic trees based on them show the importance of the major racial groupings in contributing to variation at these loci.

The second part concerns the formal genetics of man, and the papers here are outstanding, though not easy reading for the mathematically fearful. C C Li reviews the several methods of segregation analysis that have been developed in the past Haldane period. They are essentially applicable for cases of complete ascertainment, which is much more attainable today with modern computerisation of records than at the time of Haldane's pioneer work in the early thirties. Li fees that the segregation models involving varying values of ascertainment probabilities are somewhat arbitrary and inadequate, largely on account of complex social factors that contribute to the completeness or incompleteness of ascertainment. To overcome these difficulties he recommends striving for complete ascertainment by establishing adequate systems of registration and reporting by health agencies. R Elston to oœxamine recent developments in the theory of segregation analysis. He describes the two well established multiparameter models available for performing likelihood based analyses (the transmission probability and the mixed model). P P Majumder's chapter, also on segregation analysis is complementary, for he concentrates on a multilocus epistatic model with or without variable age of onset, but finally provides a reminder of the value of a...