Excision 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.1 excluding linkage to RARA (17q21), FGF4 (16p24-25), and CITED1 (5q33) loci in eight multigeneration white families with autosomal dominant non-syndromic cleft lip with or without cleft palate (CL(P)). These candidate genes were chosen on the basis of their map location in the two associated syndromes which include CL(P), proximity to loci known to cause syndromes which include CL(P), and from previously published reports in the literature.2,3

We have also tested linkage to the same loci in ten non-syndromic CL(P) white families at these same loci, and can confirm the reported exclusion. The PtRPL1 in RARA was tested using Southern gel and Genius non-radioactive techniques.2 Tightly linked flanking short tandem repeat PCR markers at the RARA locus, Thr1, M6118 (D17S575), D17S800, and Hox2B and CRTL1 were amplified and separated on 8% sequencing gels,2 and visualised by silver staining using the GELCODE® system.7 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. The lod scores at F13A1, -9.57, -9.72, -8.87, and -2.49 for RARA, Thr1, D17S579, D17S800, and Hox2B, with lod scores of 2.1 at 0.9 also excluded this gene. We have previously reported exclusion of the F13A1 locus and the lod score of -2.1 at 0.9 also excluded this gene. We have previously reported exclusion of the F13A1 locus and the lod score of 2.1 at 0.9 also excluded this gene. We have previously reported exclusion of the F13A1 locus and the lod score of 2.1 at 0.9 also excluded this gene.

Further report of a patient with hemimandibular synostosis and hydrencephaly

A case of hemimandibular synostosis with lambdoid synostosis was published recently in this journal.1,2 We report on a male baby with clinical and skeletal abnormalities very similar to those previously reported.1,3,4

The proband was the first child of young and healthy non-consanguineous parents. He was born at term following a normal delivery because of cephalopelvic disproportion. Birth weight and length were 3490 g and 51 cm, respectively. Apart from the upper limb defects and a midline calvarial haemangioma, 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 markedly 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
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 J B S 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 Ewens, 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 which 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 post 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 agrees 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 ooeaximces 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 multifactor epistatic model with or without variable age of onset, but finally provides a reminder of the value of a

X rays of the upper limbs showing (top) humeroradioulnar synostosis and (below) humeroradial synostosis and absent thumb ossification.
