

## LETTERS TO THE EDITOR

### Prevalence of fragile X syndrome

In view of the findings of Sutherland and Baker<sup>1</sup> of a non-pathological fragile site at Xq27.2 (the common fragile site FRAXD), which may be confused with the mental retardation fragile site at Xq27.3 (FRAXA), we have reanalysed our data, presented in this Journal in 1986,<sup>2</sup> which had given an overall prevalence of the fragile X mental retardation syndrome of 1 in 952 schoolchildren.

This prevalence was based on 29 positive results out of 347 children who were tested, and allowance was made for the 122 children whose parents withheld permission for the study. We reviewed the levels of fragile X expression in these 29 patients, together with results in any affected relatives, and considered that the diagnosis of the fragile X syndrome was unequivocal in 19 children. Slides of seven patients were adequate for review and we considered that the original diagnosis was firm in five of them, but that two had the common fragile site (FRAXD). We felt that further blood samples were required from three children, but in only one instance could this be obtained; in this boy the diagnosis of the fragile X syndrome was substantiated by further examination.

The two who were definitely not FRAXA were 'AW' and 'JO' from the series of Thake *et al.*<sup>3</sup> The two doubtful cases were 'SH' from the series of Bunday *et al.*<sup>4</sup> and 'MJ' from the series of Thake *et al.*<sup>3</sup> All four children had IQs over 50; two fell into the 11 to 16 age range which we had used for our most accurate prevalence figures. Two were males and two were females. We have therefore recalculated the prevalence of the fragile X syndrome by removing from our results these four children. We now amend our conclusions from the Coventry prevalence study.

Firstly, the numbers of ESN(M) children with the fragile X syndrome still exceed the numbers of ESN(S) children, as there were 17 of the former

and eight of the latter. Considering males alone there were nine ESN(M) boys and five ESN(S) boys. Secondly, the prevalence in schoolchildren aged from 11 to 16 years becomes 1 in 1039 (range 1 in 840 to 1 in 1178) and is approximately the same for both sexes. This is not very different from our previous prevalence figure of 1 in 952.

We have been interested to see whether the publicity given to the fragile X syndrome has resulted in any increase in diagnosis of the condition in the West Midlands. We considered children born in 1980 to 1984 inclusive, who will now be aged 6 to 10, and took as our base population those children in the West Midlands Regional Health Authority who were aged 0 to 5 in 1984 (Population and Vital Statistics 1984). There were 334 200 children in this age range, of whom 322 would be expected to suffer from the fragile X syndrome. As two-thirds of these would probably be only mildly mentally retarded, we would not expect complete ascertainment by 10 years. However, only 10 children (nine males and one female) with the fragile X syndrome, born in the years 1980 to 1984, are known to the two cytogenetics departments of the WMRHA! Has the incidence of the condition fallen, or is more education of hospital and community paediatricians required?

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T WEBB

SARAH BUNDEY

Department of Clinical Genetics,  
Birmingham Maternity Hospital,  
Edgbaston,  
Birmingham B15 2TG.

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### HLA markers, hormones, and disease

In 1972, Ivanyi *et al.*<sup>1</sup> reported that a genetic factor identical to or closely linked to the H-2 system in the mouse is involved in the control of sex hormone metabolism. On the basis of this finding, they made a remarkable prediction: "If the situation in histocompatibility genetics in man is analogous to that in the mouse, a great number of physiological characters and disorders may be expected to display a statistically significant association with HL-A types. On the basis of the mouse model, continuous (rather than discontinuous) variation may be expected to be found in the HL-A traits . . .".

Over the intervening years, both parts of this prediction have been confirmed. In 1973, ankylosing spondylitis and Reiter's disease were both shown to be closely associated with HLA-B27<sup>2</sup>; other conditions (multiple sclerosis, lupus erythematosus, and various categories of arthritis) have since been shown to be less closely associated with HLA markers. And in all these illnesses, continuous variation is apparent, as predicted.

In general, the mechanisms responsible for the associations of HLA with disease are not established, and workers have assumed that either (1) the HLA antigen plays no immediate role, its locus being close to disease susceptibility genes, or (2) the HLA antigen on the cell membrane interacts with other factors (for example, infectious agents) to produce disease, or (3) molecular mimicry has a role in disease development.<sup>3</sup>

It is interesting to consider another alternative suggested by the prediction of Ivanyi *et al.*<sup>1</sup> namely that HLA genes index endocrine abnormalities which form necessary (but not sufficient) conditions for the diseases. (1) All the major diseases associated with HLA-B27 (Reiter's disease, ankylosing spondylitis, acute anterior uveitis, psoriatic arthritis) occur predominantly in men. (2) All the major diseases associated with HLA-B8 (Graves' disease, coeliac disease, myasthenia gravis, Sjögren's disease, systemic lupus erythematosus) occur predominantly in women. (3) Men have higher testosterone levels than women.

Accordingly, one might wonder whether B27 indexes high testosterone levels in men and B8 indexes low testosterone levels in women. The latter point has been tested explicitly by Gerencer *et al.*,<sup>4</sup> who reported that indeed B8 does index low testosterone levels in women ( $\chi^2=5.0$ ,  $p=0.025$ ). In regard to men, one may exploit the data on their mean testosterone levels by MHC class I antigens published by Ollier *et al.*<sup>5</sup> These workers published data on 138 healthy males and 71 male patients by 12 different markers at the B locus. The mean testosterone levels of the HLA-B27 positive men ranked respectively second and third out of 12 in the two rankings. These were independent rankings so their joint significance may be assessed by the Haldane-Smith test<sup>6</sup> ( $z=1.64$ ,  $p=0.05$ , one way).

I suggest that high testosterone levels are a necessary but not sufficient condition for the expression of HLA-B27 associated disease, and low testosterone levels for the expression of HLA-B8 associated disease.

It is interesting to consider HLA markers and testosterone levels in regard to idiopathic haemochromatosis, a condition in which men outnumber women by about 20 to 1.<sup>7</sup> This disease is reportedly associated with HLA-A3 (risk ratio 8.2) and HLA-B14 (risk ratio 4.7).<sup>8</sup> These antigens are both strongly associated with high testosterone levels in the data of Ollier *et al.*<sup>5</sup> Their rankings were third out of eight, and first out of eight, and first out of 12 and second out of 12, respectively. Assuming no linkage disequilibrium between these two antigens, it is valid to test the rankings as independent. Tested against chance expectation by the Haldane-Smith test, the rankings jointly just fall short of significance at the 0.01 level (two way), so there is a strong suggestion that high androgen levels are associated with this condition too.

Thus there is substantial evidence for the hypothesis that HLA antigens operate as markers for disease by indexing hormone levels which are pathogenic.

WILLIAM H JAMES  
MRC Mammalian Development Unit,  
University College London,  
Wolfson House,  
4 Stephenson Way,  
London NW1 2HE.

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cohort are over the age of 18 years, his findings provide the best available data on the natural history of this syndrome into adulthood. The growth data on the Dutch subjects are combined with those on an additional 50 American patients (Stevens and Blackburn) in order to produce very useful height, weight, height velocity, and OFC curves. The chapter that includes detailed results from the psychological and speech studies is of particular value and the one likely to be of most relevance to parents and caregivers.

This study was initiated by the Dutch parents support group and the results brought together in this book should be available to all professionals involved in the health and educational care of children and adults with Rubinstein-Taybi syndrome. The book also serves as a model to researchers embarking on clinical studies of other syndromes with multiple anomalies/retardation in the future. Dr Hennekam is to be congratulated on his efforts, and also on the choice of such a delightful cover photograph.

HELEN E HUGHES

## BOOK REVIEWS

**Essential Medical Genetics.** 3rd ed. J M Connor, M A Ferguson-Smith. (Pp 259; £24.95.) Oxford: Blackwell Scientific Publications. 1990.

This well established and popular basic textbook now enters its third edition with this issue. The format of the book remains unchanged in that there are two sections to the text. The first 11 chapters outline and explain basic genetic principles, while the remaining 10 chapters refer to the modern day practice of medical genetics. This latter comprehensive section covers genetic counselling, prenatal diagnosis, single gene disorders, congenital malformations, and chromosomal disorders. The topics of population screening and prevention of genetic disease are also included, as are excellent contributions on immunogenetics and cancer genetics. The basic principles section deals with topics such as DNA structure and function, mitosis and meiosis, chromosomes and aberrations thereof, patterns of inheritance, gene mapping, and population genetics. Three brief appendices outline odds and probabilities, simple applications of Bayes's theorem, and coefficients of inbreeding and relationship. Dividing

**The Rubinstein-Taybi Syndrome in the Netherlands: A Clinical Genetic Survey.** R C M Hennekam. (Pp 81; Dfl 49.50.) Amsterdam: Thesis Publishers. 1990.

In 1985, Dr Raoul Hennekam embarked on a clinical study of Dutch children and adults with the Rubinstein-Taybi syndrome. The results of his endeavours are now available in the form of this short book of 11 articles or chapters, some of which have been published separately in the *American Journal of Medical Genetics*, among others. The size of the book in no way reflects the amount of work involved in producing the very comprehensive data on 45 affected subjects ranging in age from 0 to 60.5 years, and who represent an almost total ascertainment of the syndrome in the Netherlands in the late 1980s.

In a nutshell, these series of articles and extensive bibliography bring together all that is currently known about this well recognised syndrome. As just over a third of Dr Hennekam's