lesions or both, and mental retardation or seizures or both. Rushton and Shaywitz\textsuperscript{1} discuss a family in which the mother and maternal grandfather of a proband with tuberous sclerosis appear to be non-manifesting obligate heterozygotes for the tuberous sclerosis gene. These authors propose segregation of a second unlinked autosomal dominant modifying gene to explain the apparent non-expression of the tuberous sclerosis gene, but they fail to consider that they have insufficient information to conclude that these two relatives do not manifest the gene.

In addition to physical examination and Wood’s lamp examination of the skin, examination of the retina by indirect ophthalmoscopy, CT scan of the brain, ultrasound examination of the kidneys or an excretory urogram or both, and skeletal survey should be diagnostic screening tests that are completed on each subject at risk for carrying the tuberous sclerosis gene. Only when all the clinical and laboratory parameters of gene expression have been investigated can a subject be judged to be a non-manifesting heterozygote by pedigree analysis.

Would Rushton and Shaywitz\textsuperscript{1} invoke this second gene hypothesis even if their patients were fully evaluated, since we so readily accept ‘non-penetrance’ of other variably expressed autosomal dominant genes?

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\textbf{Reference}

This letter was shown to Drs Rushton and Shaywitz who reply as follows:

\textbf{SIR,}

When our investigation on the inheritance of tuberous sclerosis was begun, we were aware of recent studies which had shown the value of neuroradiological techniques for the detection of intracranial calcifications in persons who were otherwise asymptomatic.\textsuperscript{1,2} The obligate heterozygotes in the pedigree which we presented were older adults who did not wish to have more children. We decided that it was ethically unjustifiable to subject these normal persons to the expense and radiation exposure required for computerised axial tomography of the brain.

The most important test of our hypothesis of a second modifying gene in this disorder will be to examine the future progeny of the young sister of our index case. When she approaches reproductive age, she will be offered full diagnostic evaluation for tuberous sclerosis, including CAT scan. This information can then be used for genetic counselling purposes.

Tuberous sclerosis is certainly an autosomal dominant disorder with variable penetrance. The fact that we usually attribute this phenomenon to ‘variable penetrance’ implies our lack of knowledge regarding modulation of expression of human dominant gene action. Pedigree analyses in the future will hopefully provide further understanding of this intriguing syndrome.

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\textbf{References}

\textbf{Congenital hypothyroidism and Klinefelter’s syndrome}

\textbf{SIR,}

The paper by Campbell and Price (\textit{JMG}, December 1979) overlooks the recognised association of autoimmune thyroiditis with abnormal chromosomal states such as Down’s syndrome\textsuperscript{1} and Turner’s syndrome.\textsuperscript{2}

The case histories in the paper do not preclude an acquired autoimmune thyroiditis as a cause of the hypothyroidism with onset in infancy or early childhood. Hashimoto’s disease may be present in young patients with lower antibody titres, and therefore low titres do not exclude the diagnosis.\textsuperscript{3} Case 4 with presentation at the age of 7 years and a bone age of 2.5 years is not ‘congenital hypothyroidism’. Consequently, there must be considerable doubt about the validity of the authors’ concept of the association between congenital hypothyroidism and Klinefelter’s syndrome.

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