Tuberous sclerosis: possible modification of phenotypic expression by an unlinked dominant gene¹

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SUMMARY A unique pedigree is presented which shows tuberous sclerosis in three generations of a family, in which two heterozygotes for the mutant gene were found to be clinically asymptomatic. A genetic model is proposed to explain these findings based upon the segregation of a second unlinked autosomal dominant gene modifying the expression of the gene for tuberous sclerosis.

Tuberous sclerosis is an autosomal dominant disorder characterised by mental retardation, epilepsy, and adenoma sebaceum. Associated lesions include retinal phakomata, shagreen patches, white naevi, subungual fibromata, and benign visceral tumours. Affected persons may exhibit milder forms of the disease, such as skin or eye lesions alone without retardation or epilepsy (Donegani *et al.*, 1972). The disease may rarely be diagnosed at necropsy in a patient who appeared to be clinically unaffected (Lagos and Gomez, 1967; Tsukada and Pickren, 1967).

The inheritance of tuberous sclerosis has been studied in several large series of patients. About 80% of cases appear to be sporadic mutations, arising in families with no other affected relatives. These cases are identical to those which are familial. Extensive pedigree analysis has shown an autosomal dominant inheritance pattern with variable expressivity in affected family members. No instances of a 'skip' generation have been noted, that is, one in which a heterozygote did not have any symptoms of the disease (Borberg, 1951; Dickerson, 1951; Marshall *et al.*, 1959; Nevin and Pearce, 1968; Zaremba, 1968; Bunday and Evans, 1969; Singer, 1971; François, 1975; Ponsot and Lyon, 1977).

The purpose of this paper is to report the pedigree of a patient with tuberous sclerosis; this appears to show heterozygotes with the mutant gene, but without clinical symptoms. A genetic model is proposed to explain these findings based on a second unlinked autosomal dominant gene modifying the expression of the tuberous sclerosis gene.

Case report

The proband (IV.5, Fig. 1) was a 5-year-old boy who presented at age 4 months with *grand mal* seizures, which were controlled with phenobarbitone and phenytoin. At 2 years, he was mentally retarded and had adenoma sebaceum, intracerebral calcifications, and a phakoma in the left eye. The diagnosis of tuberous sclerosis was made. At age 4½ years, he developed headaches, increasing lethargy, and blurred vision. A CAT scan showed a vascular mass in the left cerebral hemisphere adjacent to the third ventricle which, at operation, was found to be a giant cell astrocytoma.

Complete physical examination (including skin examination by Wood's lamp) was performed on the patient's sister, aged 9 years (IV.4), mother (III.32), father (III.9), and maternal grandfather (II.12). No signs or symptoms of tuberous sclerosis were found.

A maternal great-uncle (II.11) had died at age 40 after operation for bilateral brain tumours and seizures since childhood. Skin lesions were not described at necropsy, but he probably had tuberous sclerosis. A maternal uncle (III.36) had the disease with adenoma sebaceum, mental retardation, and seizures since childhood. Other family members have none of the signs of tuberous sclerosis.

Discussion

Tuberous sclerosis is an inherited disease characterised by variable phenotypic expressivity. Patients may have adenoma sebaceum alone or in combination with epilepsy, mental retardation, shagreen patches, white naevi, retinal phakomata, or visceral

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Fig. 1 Pedigree of a family affected with tuberous sclerosis. The propositus is IV.5.

tumours (Lagos and Gomez, 1967). This variability has been attributed by different authors to the action of environmental factors and postulated modifier genes (Gunther and Penrose, 1935; Cuendet, 1961; Nevin and Pearce, 1968; Bunday and Evans, 1969; François, 1975).

Gunther and Penrose (1935) postulated that a gene A existed which modified the expression of the tuberous sclerosis gene E. In their model, the genotype EeAA was normal, EeAa was mildly affected, and Eeaa was severely affected. The theoretical frequencies of cases affected in these varying degrees corresponded fairly well to the number observed in a collected series of pedigrees, but in no cases were phenotypically normal heterozygotes of genotype EeAA documented.

Several pedigrees have been published in older reports which appear to show the inheritance of tuberous sclerosis from an unaffected heterozygote (Gunther and Penrose, 1935; Vaas, 1940). These findings may, however, be the result of incomplete examination (Cuendet, 1961). More recent large series have failed to document any such 'skip' generations (Borberg, 1951; Dickerson, 1951; Lagos and Gomez, 1967; Nevin and Pearce, 1968; Zaremba, 1968; Bunday and Evans, 1969; François, 1975; Ponsot and Lyon, 1977).

The pedigree in this report has shown two apparent heterozygotes for tuberous sclerosis who were clinically asymptomatic but who produced affected progeny. This has provided a unique opportunity to examine the segregation and expressivity of the

tuberous sclerosis gene in several generations of one family. A genetic model to explain the findings in this family involves the modification of expression of the dominant tuberous sclerosis gene E by another postulated unlinked dominant gene B. The presence of B is required for the phenotypic expression of E. Fig. 2 presents the pedigree of this family with presumptive genotypes assigned to each individual. The maternal great-uncle (II.11) had tuberous sclerosis and genotype EeBb. The maternal grandfather (II.12) is a heterozygote for the disease but is clinically normal; his genotype, therefore, must be Eebb. The mother of the index case (III.32) is also a normal heterozygote Eebb, but her brother (III.36) has tuberous sclerosis and genotype EeBb. The propositus (IV.5) has the disease (genotype EeBb), while his sister is normal (genotype ee/bbb). The affected individuals in this family had severe symptoms, and it is possible that other genes exist which could modify the clinical spectrum of the disease.

The great majority of the cases of tuberous sclerosis appear to be the result of new mutations. Thus, most affected patients have clinically normal parents. The cases in this report indicate that normal parents can, in fact, be carriers of this genetic disease and would have a 50% probability of transmitting this dominant gene to each of their progeny. Detailed investigation of the pedigree of each family with an affected individual must, therefore, be completed for knowledgeable genetic counselling and family planning.

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Fig. 2 Partial pedigree of the family affected with tuberous sclerosis. Presumptive genotype is assigned to each individual. E, tuberous sclerosis gene; B, dominant modifier gene. Other symbols are the same as Fig. 1.

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