Genetic heterogeneity in tuberous sclerosis: phenotypic correlations

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Abstract

There is increasing evidence for genetic heterogeneity in tuberous sclerosis (TSC) on the basis of linkage analysis in affected kindreds. We have performed a detailed assessment of an affected South African family in which there is no evidence of linkage to chromosome 9 markers. The affected persons have atypical clinical features, namely prominent nuchal skin tags, a confetti pattern of hypopigmentation of the skin of the lower legs, and absence of ungual fibromata. Further investigation of these unusual phenotypic features is warranted in order to determine whether these lesions are con-

sistently present in families in whom the gene for TSC is not on 9q34. We conclude that confetti depigmentation and nuchal skin tags may be clinical pointers to an alternative locus for TSC.

Tuberous sclerosis (TSC) is inherited as an autosomal dominant trait and is characterised by multisystem hamartosis. The areas of predilection are the skin, central nervous system, kidneys, and heart, while other organs are less frequently affected.¹ Certain skin lesions are pathognomonic of TSC (adenoma sebaceum, periungual fibromata, shagreen patches, fibrous facial plaques). Other skin changes may be suggestive (ash leaf macules) or compatible with the diagnosis of TSC in the appropriate clinical setting (café au lait macules, poliosis, guttate hypopigmentation, fibromas, fibrous skin tags).

Linkage analysis initially showed a locus for TSC on 9q.² In particular, Sampson *et al*³ reported positive linkage in seven out of eight families studied (lod score 6.1) with the Abelson oncogene (9q34). Subsequent investigations have indicated greater heterogeneity on the basis of linkage data with a probable second locus on 11q.⁴ We have now undertaken

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Figure 1 A pedigree of the affected family.

Figure 2 Multiple acrochordons (skin tags) at the base of the neck of (a) patient III-19 and (b) patient III-22.

Figure 3 Guttate hypopigmentation on the legs of (a) patient III-19 and (b) patient III-22.

further clinical evaluation of the eighth family in the series of Sampson *et al.*,³ which showed no linkage to 9q. Phenotypic differences which we document in this article may correlate with the linkage data and provide clinical indicators for the recognition of genetic heterogeneity.

Case reports

Four affected persons in two generations of a rural

South African family of mixed ancestry were studied (fig 1). Details of the phenotype of each person, as well as a description of one affected member (II-3), now dead, are shown in the table. The significant skin lesions, illustrated in figs 2 to 4 are the numerous skin tags at the base of the neck of II-3 III-19, III-21, and III-22, as well as the whorled pattern of confetti-like depigmentation on the limbs of the two young men. Periungual fibromata were absent in all affected subjects.

Figure 4 A whorled pattern of confetti depigmentation and a café au lait macule on the leg of patient III·19.

Histological examination was undertaken on skin lesions from III·19 and III·21, using standard fixation and haematoxylin and eosin stains. The ash leaf spot and shagreen patch biopsied from III·21 showed the characteristic histological changes, as did the adenoma sebaceum and café au lait macule of III·19. Sections of skin from the whorls of confetti depigmentation on the leg of III·19 showed reduction in pigment in the basal melanocyte layer. The skin tag excised from the neck of III·19 contained papillomatous lesions lined by unremarkable epidermis. The soft tissue core was mildly oedematous with slight prominence of vascularity. Delicate collagen fibrils produced a glial appearance, suggestive of adenoma sebaceum.

Indirect ophthalmoscopy showed an infratemporal phakoma in the fundus of III·19. III·21 and IV·9 had an identical pattern of unilateral patchy atrophy of the retina, while III·22 had diffuse bilateral retinal atrophy.

Limited skeletal surveys were undertaken on all affected subjects. Radiographs of the skull of the adults showed calcification typical of TSC. Sclerotic areas were evident on the third right metatarsal of

Phenotypic features of the four affected family members and description of patient II·3, now dead.

	II·3	III·19	III·21	III·22	IV·9
Skin					
Adenoma sebaceum	Centrofocal	Centrofocal	Centrofocal	Centrofocal	Centrofocal
Shagreen patch	Low back	—	Small, low back	2, low back	—
Ash leaf macules	—	3, legs	Multiple, arms, legs, back	Multiple	Multiple
Periungual fibromata	—	—	—	—	—
Café au lait macules	—	Multiple	—	—	—
Acrochordons	Multiple, base neck*	Multiple, base neck*	4, base neck	Multiple, base neck*	—
Confetti depigmentation	Arms, legs*	Legs*	—	Legs*	—
Whorled depigmentation	—	Legs	—	—	—
Renal					
Symptoms	Unknown	—	—	—	—
Angiomyolipomata	Unknown	Bilateral	—	Right interpolar	—
Cysts	Unknown	—	—	—	—
CNS					
Epilepsy	Grand mal	—	—	Petit mal	—
Mental retardation	—	—	—	Severe	—
CT scan	Unknown	SCP	SCP	SCP	SCP
Dentition					
Pitting	Unknown	Slight	—	Slight	—
Ophthalmological					
Astrocytoma	Unknown	Right intratemporal	—	—	—
Retinal atrophy	Unknown	—	Patchy, right eye	Diffuse, bilateral	Patchy, right eye
Other	—	Right traumatic retinal detachment	—	—	—
Skeletal					
Skull	Unknown	Calcification	Calcification	Calcification	Calcification
Hands	—	Mild cortical thickening middle phalanges	—	—	—
Feet	—	Sclerotic area L 1st metatarsal	—	—	Sclerotic area
Pelvis	—	—	—	—	—

*Denotes unusual features.

SPC=subependymal paraventricular calcification.

IV·9 and cortical thickening of the first left metatarsal and the middle phalanges of both hands of III·19.

Ultrasonic scan of the kidneys undertaken in III·19 and III·22 showed hyperechoic masses consistent with the angiomyolipomata of TSC. No renal cysts were identified. CT scan of the skull showed multiple foci of subependymal and paraventricular calcification in all affected subjects.

Discussion

Many of the features in this family were entirely typical of TSC, but the affected subjects were unusual by virtue of multiple nuchal skin tags and guttate depigmentation of the skin of the legs.

Acrochordons, or skin tags, are not uncommon in the general population. They may be multiple and small on the neck and axillae, or larger, solitary, pedunculated growths on the lower trunk. Multiple tags are often associated with obesity; histologically identical tags¹ are also a consistent feature of Gardner's and Cowden's syndromes.

The histological examination of small skin tags shows papillomatosis, hyperkeratosis, and irregular acanthosis with occasional horn cysts. The larger lesions have less marked epidermal changes; the connective tissue stalk is composed of loose collagen fibres and may contain dilated capillaries filled with erythrocytes.

Multiple skin tags have been reported in TSC.⁵ A study of 29 affected persons⁵ described nuchal acrochordons in 'a few' of these subjects. In a study of 103 affected persons,⁶ 19 adult patients (18·4%) had soft fibrous tags on the neck, axillae, and eyelids. The histological changes noted in these lesions were of an angiofibromatous appearance with increased cellularity, resembling the facial lesions of the patients studied. Of the 25 persons studied in an earlier survey of TSC in the Western Cape region of South Africa,⁷ where the family reported reside, no mention is made of skin tags.

The nuchal distribution of numerous acrochordons in three family members in this study was notable. A fourth subject (III·21) had only four fibrous tags; she described spontaneous regression of several other such lesions.

The histological changes were those of adenoma sebaceum, as was the case in the previous report⁵ and quite unlike the simple acrochordon unassociated with genetic disorders. It is of interest that in his monograph on TSC, Gomez¹ describes the skin tags of TSC as histologically indistinct from those in the general population or those associated with Cowden's

or Gardner's syndromes. They do differ, however, from the cutaneous neurofibromas of neurofibromatosis. Further studies are warranted to elucidate fully the histology of the tags of TSC.

Guttate or speckled hypopigmentation is occasionally seen in normal adults. Butterworth⁸ reported a single case of this white 'freckling', suggesting that this may be a feature of TSC. A comprehensive survey of 23 affected persons recorded three with a confetti-like hypopigmentation of the legs.⁹ No affected persons showed these pigmentary changes in either the early study of 103 patients⁶ nor in the earlier South African study.⁷

More striking than the morphology of the confetti-like lesions was the whorled patterning of this pigmentary loss (fig 4) reminiscent of the lesions of hypomelanosis of Ito. To the best of our knowledge this streaked patterning of hypopigmentation has not previously been described in TSC.

In conclusion, two unusual clinical features of TSC have been observed in a family in whom the gene for TSC is not linked to 9q34. Further linkage analysis is under way in search of an alternative locus for TSC. We submit that detailed documentation of clinical stigmata in affected families may yield important pointers in the recognition of genetic heterogeneity.

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