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Tyrosinase positive albinism with familial 46,XY,t(2;4)(q31.2;q31.22) balanced translocation

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Abstract

A subject with clinical and biochemical tyrosinase positive oculocutaneous albinism (OCA) also had a balanced translocation, 46,XY,t(2;4)(q31.2;q31.22). This observation provides evidence for a possible gene locus in the q31 region of chromosome 2 or 4.

Albinism is a heterogeneous group of inherited, congenital, generalised hypomelanotic conditions which particularly affect the biosynthetic pathways that produce pigment in eyes, skin, and hair. Classification of the several forms of albinism is according to clinical manifestations and tyrosinase activity as measured by a standardised hair bulb test.[1 2] By these criteria, the majority of patients can usually be assigned to a particular form of albinism, autosomal recessive tyrosinase negative and tyrosinase positive oculocutaneous albinism (OCA) being the most common types. However, several other less common types of albinism may prove difficult to define both biochemically and clinically.[1] Ascertainment of the genes for all forms of albinism should resolve the issue of heterogeneity and enable a more accurate diagnostic approach. Recently, mutations within the tyrosinase gene on chromosome 11 responsible for the most severe autosomal recessive tyrosinase deficient OCA, type IA, have been characterised.[3]

A patient with clinical albinism and a familial balanced translocation is presented here. The nature of the defect in this subject may provide important information in the ascertainment of a putative tyrosinase positive albinism gene.

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Case report

A male patient, the first born of non-consanguineous parents, presented at the age of 3½ years, after family reports that a paternal nephew, who had been investigated for moderate intellectual handicap, carried a balanced translocation which was present in seven other physically and intellectually normal family members (fig 1). He had no neonatal problems and developmental milestones were normal with the exception of some mild speech and language difficulties.

The proband was of normal physique with height (98·5 cm) and weight (15·1 kg) within the 10th to 25th centiles. Rapid horizontal nystagmus, blue translucent irides, photophobia, and albinoid retinae were evident. The skin was pale, with no freckling, minimal capacity to tan, and was reported to burn

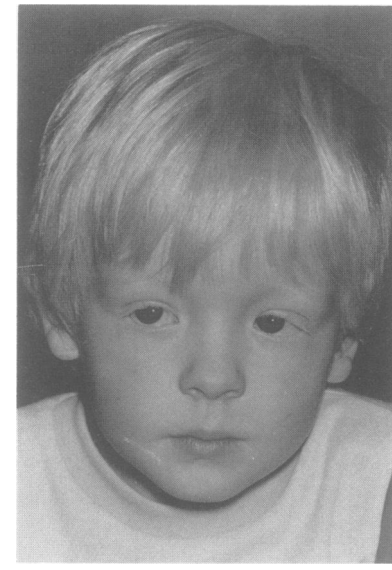

Figure 1 The proband showing sandy colour of hair and fair skin. The irides were translucent with photophobia and the retinae albinoid.

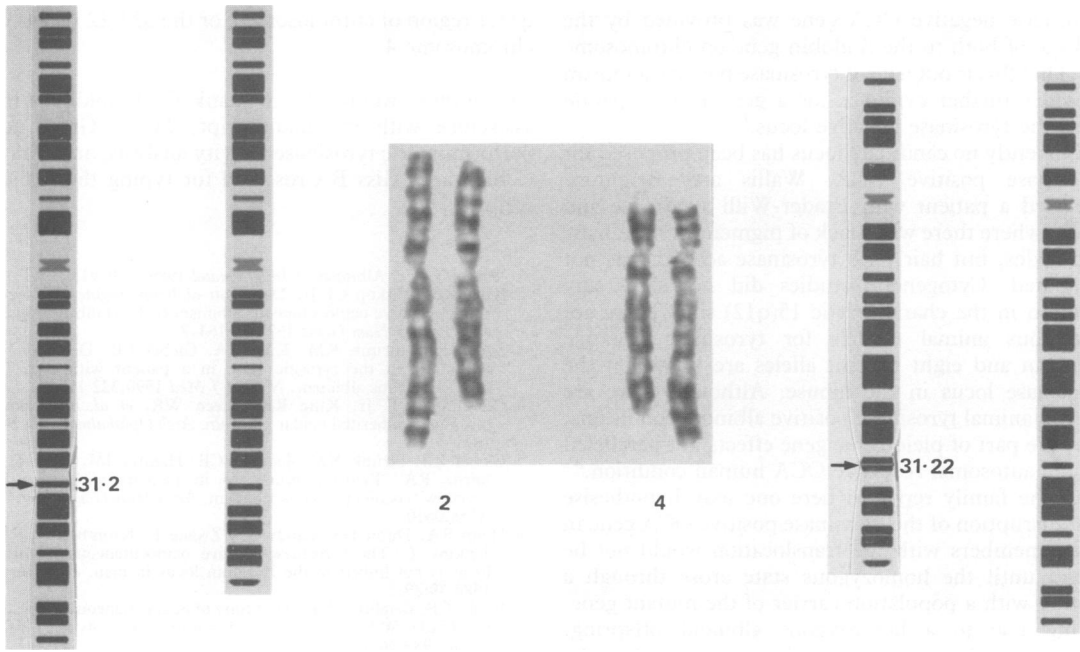

Figure 2 Ideogram and chromosome pairs 2 and 4 from a representative karyotype. The breakpoints are identified by arrows. The abnormal homologue is on the left.

easily in sunlight. Scalp hair, eyebrows, and lashes were a sandy colour which was said to have been much paler, almost white in earlier years. Audiometry was normal in both ears. Ophthalmological examination confirmed the above findings; visual acuity was assessed as 6/60 and 6/36 and bilateral astigmatism was present. Examination of the maternal fundus and skin was normal.

Cytogenetic studies using cell synchronisation and Giemsa-trypsin banding confirmed the presence of a translocation. The karyotype, as defined by analysis of extended chromosomes, was 46,XY,t(2;4)(q31.2;q31.22) (fig 2).

Hair specimens were sampled for root bulb tyrosinase activity. The results were obtained using the method of King and Witkop.[2] Sample 1: 1·43 pmol/120 min/hair (slightly pigmented brown hair). Sample 2: 0 pmol/120 min/hair (slightly pigmented brown hair). Sample 3: 0·73 pmol/120 min/hair (white hairs).

The blonde reference interval was 0·18–3·94 pmol/120 min/hair, and supported by a control group. These results therefore support hair root bulb tyrosinase positivity.

Discussion

Clinically the type of albinism shown by our patient and supported by the hair bulb test is that of tyrosinase positive oculocutaneous albinism (OCA). It is in this type of OCA and ocular albinism (OA), where the patient has moderate to considerable amounts of pigment in the integument, or sometimes the eyes, that difficulty in diagnosis arises most frequently.[4] Autosomal recessive tyrosinase positive OCA is the most common form of albinism.[1] Caucasian tyrosinase positive albinos are lightly pigmented and may be difficult to differentiate clinically from tyrosinase negative platinum OCA and yellow mutant OCA. Yellow mutant albinos are very pale in early life, resembling tyrosinase negative albinos, but by 2 to 3 years of age the hair may be bright yellow or yellow-red (sandy) in colour and a light skin tan is possible. Such colour changes were described in the patient reported here, but this diagnosis was excluded by the level of tyrosine activity. The amount of hair pigment was less than that usually seen in autosomal recessive OA.[1]

Recently the human tyrosinase gene has been sequenced on the long arm of chromosome 11 and mutations identified in tyrosinase negative type IA and IB OCA.[5] Tyrosinase positive OCA is autosomal recessive and non-allelic with tyrosinase negative OCA as indicated by clinical and current molecular observations. Four matings of tyrosinase negative and tyrosinase positive couples, as summarised by Witkop,[1] have produced unaffected offspring. Earlier evidence of linkage of the tyrosinase gene locus to the

tyrosinase negative OCA gene was provided by the linkage of both to the β globin gene on chromosome 11. That this is not true of tyrosinase positive albinism provides further evidence for a gene locus separate from the tyrosinase negative locus.[6]

Currently no candidate locus has been proposed for tyrosinase positive OCA. Wallis and Beighton[7] reported a patient with Prader-Willi syndrome and OCA, where there was a lack of pigment in skin, hair, and irides, but hair bulb tyrosinase activity was not estimated. Cytogenetic studies did not show any deletion in the characteristic 15(q12) site. There are numerous animal models for tyrosinase negative albinism and eight mutant alleles are known at the tyrosinase locus in the mouse. Although there are several animal tyrosinase positive albinoid conditions, they are part of pleiotropic gene effects not paralleled by the autosomal recessive OCA human condition.[8]

In the family reported here one may hypothesise that disruption of the tyrosinase positive OCA gene in those members with the translocation would not be found until the homozygous state arose through a mating with a population carrier of the mutant gene, giving rise to a homozygous albinoid offspring. Therefore, this report provides evidence that the tyrosinase positive OCA gene locus may reside in the q31.1 region of chromosome 2 or the q31.22 region of chromosome 4.

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