Achondroplasia in sibs of normal parents

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SUMMARY  A new case of recurrent achondroplasia in sibs of normal parents is reported. Two sisters and a half sister were affected. Various mechanisms can be postulated to account for unexpected recurrence of achondroplasia in the same sibship. Germinal mosaicism and unstable premutation are discussed here.

Achondroplasia is the commonest type of short limbed dwarfism. Dominant inheritance is clearly established and sporadic cases are the result of new mutations. Three families with more than one affected sib and normal parents have been previously reported. In the present report, a normal father had three achondroplastic daughters from two different mothers.

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The family pedigree is shown in fig 1. Case 1 (II.1) was born in 1975 to a healthy, unrelated 17 year old mother and 30 year old father. Birth length was 47.5 cm and birth weight 3030 g. Achondroplasia with rhizomelic shortening of the limbs and macrocephaly was suspected at birth and x ray films of the skeleton confirmed the diagnosis. When examined for the second time, the girl was 12 years old and 116 cm tall. Psychomotor development was normal. Clinical and radiological features were typical of achondroplasia. A normal boy was born in 1977.

Case 2 (II.3), born in 1981, is the sister of case 1. The diagnosis of achondroplasia was immediately evident. At five years of age, she was 85 cm tall.

Both parents were examined. Clinical and radiological examination was normal with no stigmata of achondroplasia.

Case 3 (II.4) is the half sister of cases 1 and 2, with...
Familial recurrence of achondroplasia has been described previously and, to our knowledge, 12 pedigrees have been reported. Eleven of them are summarised in a review by Opitz1 and one has been published by Fitzsimmons.2 In the light of the frequency of the disorder, the incidence of which is estimated between 1/26 000 and 1/35 000, familial cases are uncommon. In nine families, two more or less distant relatives were affected, the relationship varying from first cousins to second cousins once removed. In two families, one of the affected probands had similarly affected children. In the last three pedigrees several subjects were affected in the same sibship. Bowen3 reported two affected sisters with normal parents, one of whom had an affected child. Opitz1 reported a family where normal parents had an achondroplastic son and daughter. The case of Fryns et al4 with three affected sisters resembles the present report. Several explanations have been proposed to account for these phenomena. First, the hypothesis of two different mutational events is supported by Reiser et al.5 This hypothesis cannot be excluded when distantly related subjects are affected, but is unlikely when achondroplasia occurs in three sibs.

Regarding the first case involving sibs, Fryns et al4 suggested germinal mosaicism. This theory is attractive but one could expect such recurrences for other fully penetrant mutations. Recently, Allanson6 reported two sisters with Apert’s syndrome born to normal parents. Hall et al7 suggested that this mechanism should be considered when other autosomal dominant conditions such as pseudoachondroplasia or tuberous sclerosis8 occur in sibs of normal parents.

Opitz,1 in his review, suggested that an unstable premutation with reduced penetrance or phenocopy would be the best way of explaining both phenomena.

Apart from the theoretical aspect, the two hypo-
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theses have very different implications in genetic counselling. If the cause is germinal mosaicism, genetic counselling is reassuring for all the healthy members of the family except for the father of the three affected girls. If the hypothesis of an unstable premutation with reduced phenotrance is accepted, then all the family members are concerned. In the present family, the risk for the healthy brother (II.2) of having an achondroplastic child is negligible on the first hypothesis and very high on the second one.

References


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