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...
the same father and a healthy, unrelated young mother. Genetic counselling was requested at the beginning of the pregnancy and a thorough echo-
graphic survey was proposed. Echographic measure-
ments of the femur remained normal until the sixth
month when the curve began to decrease. Femoral
length was 47 mm at the 32nd week (5th centile for
gestational age). Fetal x ray showed short femur and
humerus, frontal bossing, and metaphyseal flaring
of the long bones, suggesting the diagnosis of
achondroplasia. When the child was born, the
diagnosis was confirmed (fig 2). Birth length was 42
cm and weight 2680 g. Fig 3 shows an x ray of the
pelvis at six months of age showing the typical aspect
of the iliac wings.

Parental heights are: I.1 1·63 m, I.2 1·66 m, and
I.3 1·64 m.

Discussion

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 phenom-
ena. 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 attrac-
tive 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 auto-
somal dominant conditions such as pseudoachon-
droplasia or tuberous sclerosis8 occur in sibs of
normal parents.

Opitz,1 in his review, suggested that an unstable
premutation with reduced penetrance or pheno-
 trance 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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