PREMUTATION IN ACHONDROPLASIA

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INTRODUCTION

The genetic characteristics of achondroplasia can be summarized as follows:

1. It is a common disorder ranging in prevalence from 2.5 to 5 per 100,000; in Italy, Camera and Mastroiacovo (7) documented a prevalence of 1/28,000 live- and stillborn children; the best estimate of prevalence after correcting for under-ascertainment was 1/22,500.

2. Most cases (80-90 percent) are sporadic; in the study of Camera and Mastroiacovo 24/25 cases were sporadic.

3. The fertility of all achondroplasia couples (including couples with one or two achondroplastic spouses and those who had no children and all of those who had at least one child) is low, namely 0.96 (21).

4. The mutation rate has been variably estimated between 1.4 to 1.93 x 10^-5 per generation (21,22); Camera and Mastroiacovo calculate a mutation rate of 2 x 10^-5 per gamete per generation.

5. A paternal age effect was first alluded to by Weinberg in 1912 (34), but was first demonstrated conclusively by Penrose in 1957 (26) using Wright's method of partial correlation coefficients (35). The mean paternal age is between 36 and 39 years. Murdoch et al. (21) also used Wright's method; investigating paternal age versus incidence with maternal age being held constant gave r = +0.27. Camera and Mastroiacovo found a relative risk of 5.3 and 21.4 for the paternal age group of 30 - 39 and ≥40, respectively.

6. To date, all published monozygotic twins have been concordant and there has never been concordance in dizygotic twins. Prof. Judith G. Hall (14) has pointed out to me the possible existence of two pairs of discordant MZ twins studied at Johns Hopkins Hospital. At this conference Dr. Cheryl Reid of Camden, N.J. (27) confirmed that she had seen one of these pairs and was
going to attempt to do appropriate zygosity studies.

7. In hereditary cases, there seems to be complete (100 percent) penetrance.

8. Achondroplasia is a disorder with relatively little variability and such a characteristic phenotype as to allow diagnosis with 100 percent accuracy at birth, making this an ideal trait for studies of mutation rates.

9. Presumed homozygous achondroplasia infants born to couples consisting of two achondroplastic spouses seem to die, invariably making presumed homozygous achondroplasia lethal. This demonstrates, as in almost all other autosomal dominant traits studied in humans, that achondroplasia is not a complete, but an incomplete dominant since the presumed homozygous form of the mutant gene is not of equal severity as the heterozygous form.

10. It has been suggested on several occasions that hypochondroplasia is an allele at the achondroplasia locus which remains unmapped, but that achondroplasia/hypochondroplasia "compounds" may also be interpreted as doubly heterozygous, i.e. with the mutant alleles being at different loci.

UNUSUAL FAMILIES AND OBSERVATIONS

At the first Birth Defects Conference (1968) Opitz presented an unusual pedigree with one suspected and two proven achondroplastic individuals. The older, well-documented affected male in that family, was a first cousin of the paternal grandmother of the little achondroplastic girl studied by Opitz (23). The affected man in that family may have had an affected one-half second cousin, a stillborn baby girl whose diagnosis is less well-documented (Fig. 1). In that paper, Opitz first raised the possibility of "unstable premutation" as an explanation for the familial occurrence of achondroplasia in affected individuals related to each other through a large number of normal individuals. This suggestion was based on a prior suggestion of Charlotte Auerbach (2) involving a study of human ectrodactyly (13,20); this suggestion was rejected by Vogel (32) who explained the ectrodactyly pedigrees as an example of variable expressivity and reduced penetrance.

At the first Birth Defects Conference, W. Lenz also expressed the opinion that independent mutational events were a more likely explanation of the pedigree demonstrated by Opitz than premutation.

At the same conference, Rimoin and McKusick (30) described the remarkable case of a man with severe achondroplasia whose left second through fifth fingers and metacarpals were nonmutant. Also at that conference, Wadia (33) demonstrated affected first cousins; these were described again by Siggers in 1974 (31). In that year, Bowen (6) also described affected sisters born to normal parents, one of these sisters having delivered an affected daughter.

In 1974, in an abstract for the American Society of Human Genetics, Leroy and Van Hauwaert (18) described a family in which one-half third cousins, respectively an affected male and a female, had achondroplasia and therefore were connected to each other through six normal relatives.