The verification of dominant inheritance by means of pedigree investigation

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Research on the genetic basis of human characteristics, hereditary diseases and developmental disorders has recently been carried out through modern biological methods. However, even nowadays it is primarily the pedigree investigations and statistical analyses that play a role in the detection of the inheritance type.

In this study we discuss the genetic aspects of an almost everyday disease on the basis of a pedigree analysis. Our investigations show how easily one can recognise the type of inheritance if one bears in mind the significance of the hereditary factors when cases accumulate.

The diagnosis of the clinical picture

The condition of congenital *exostosis cartilaginea multiplex* was described by Stanlay in 1848. The essence of the bone disease is the bone formation developing from the epiphysis, presumably from the attached islets of cartilage. This bone formation occurs mostly at the distal end of the long shaft bones between the tenth and 25th years of life.

These bone growths may increase from the size of a pea to the size of a child's head. The afflicted patients are usually short of stature, their height being six per cent shorter than the average. Their musculature is strong. The larger the exostoses are, the more the bones lose from their original length. The smaller exostoses cause few complaints, the larger ones bring about pressure symptoms, or disorders of function.

X-rays are of great help when diagnosing the changes, because they show well that the exostoses are connected to the growth-cartilage by means of a peduncular shaft.

Surgical removal is advisable for pressure symptoms, or disorders of function, statistics suggest that malignant degeneration may occur in about seven per cent.

A review of our cases

A pedigree was prepared by means of examining and interrogating the members of the afflicted family. The usual designations were employed in the drawing: the empty circles mean female, the empty squares male individuals, while the black symbols indicate the diseased members of the family.

Four generations are represented by the pedigree, of which two generations were available and could therefore be examined, while in the case of one great-grandparent and one grandparent who were no longer living, we had to rely upon the anamnestic data confirmed and verified by the rest of the family.

The 12 afflicted patients examined by us proved to be mostly short of stature. In general, the bone growths, ranging from the size of a nut to that of a green apple, were located below and above the knees, at the elbow, on the scapulae and the ribs.

In two cases operations were required because of a bigger exostosis, the x-ray of which can be seen in the figures.

Chromosome analysis was performed in three patients selected at random. In the lymphocyte cultures of the peripheral blood, no structural or numerical aberration was found in the light-microscopic preparations after evaluating 10–15 metaphases. The karyotype of two male patients was 46,XY, that of a girl patient was 46,XX.

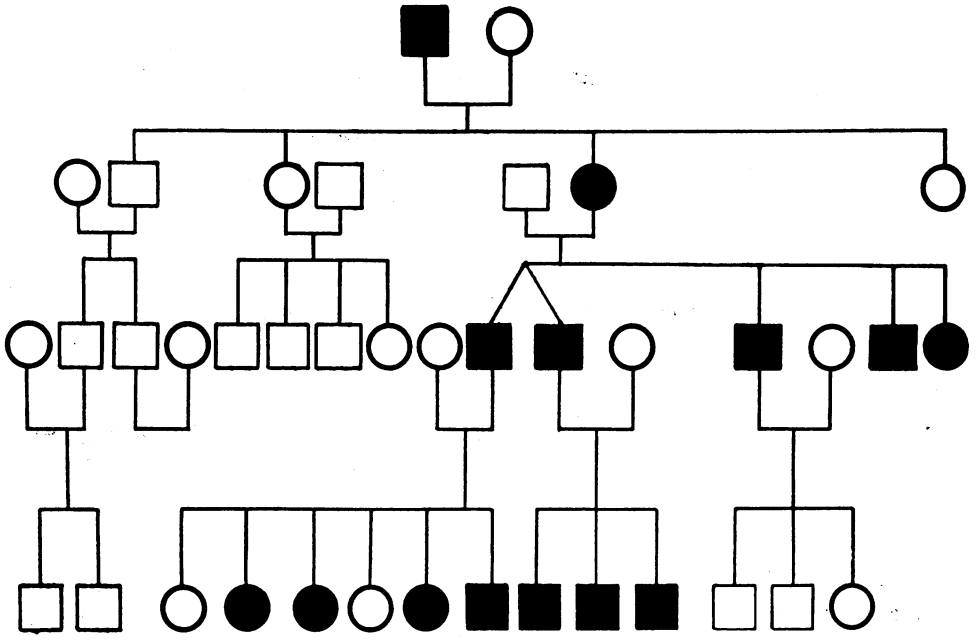
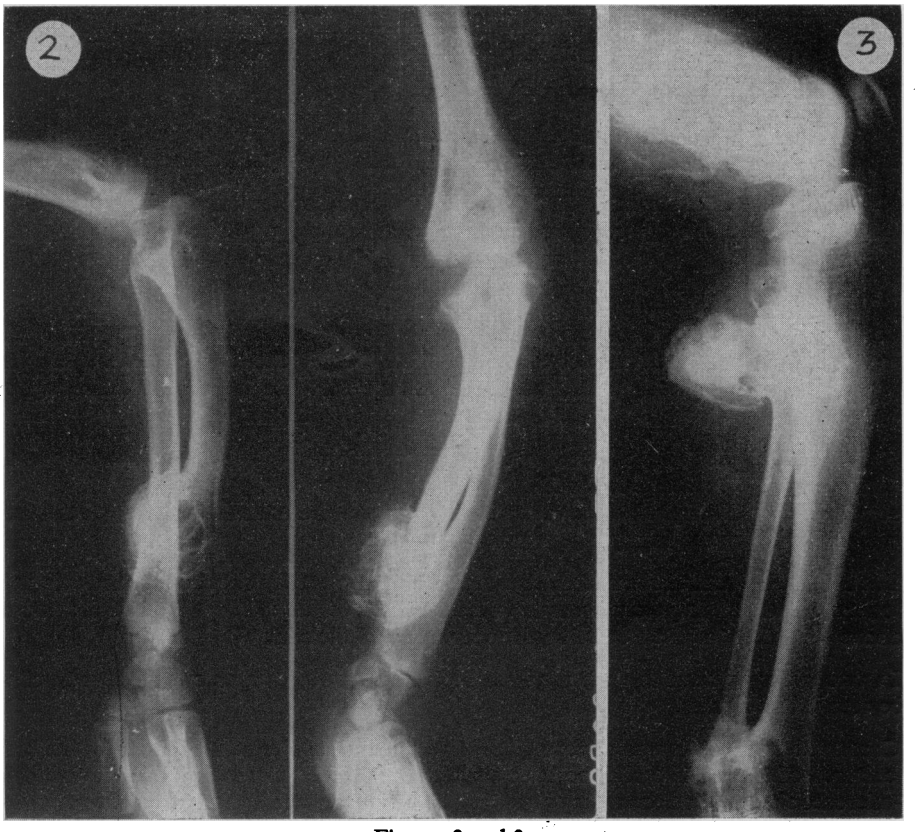


Figure 1
Pedigree of afflicted family



Figures 2 and 3
X-rays of exostoses

Discussion

Since the end of the last century numerous authors have observed that exostoses show a family accumulation, while the performed pedigree analyses give evidence of autosomal dominant inheritance.[1-8, 10-12, 15, 16, 18, 20, 21]

As is known, it is characteristic of the dominant inheritance that a definite factor—the responsible gene—is necessary and at the same time *adequate* for bringing about the disease. The disease cannot be inherited by way of healthy persons, only a characteristic carrier can transmit the pathological gene. Therefore nobody can have a dominant gene without being a carrier himself, while healthy offspring cannot be abnormal gene carriers. Each carrier has such a parent, because the gene must come from one or the other parent, except for the possibility of the gene being brought about by mutation. The marriage, of the healthy children of carriers with healthy children, can *only* result in healthy descendants. This of course refers to later descendants, too.

In the pedigree characteristic of dominant inheritance, it is noteworthy, that among the descendants originating from the marriage of carriers and healthy individuals, the carriers and healthy individuals can be found on average in equal proportions.[17, 19] There are often varying manifestations corresponding to the penetration, expressivity and specificity.

The word *penetration* is used in connection with the manifestation of the genes. If the influence of the genes always manifests itself (in the case of dominant inheritance a single dose of the pathological gene is adequate, in the case of recessive inheritance only if two pathological genes are present), in this case we can speak of complete penetration. If the effect of the gene does not always manifest itself, the penetration is partial, its degree may be expressed in numbers: e.g. the penetration can be 90, 50 or only 20 per cent.

The *expressivity* includes all the variations in the manifestation of the gene in individuals in whom the gene is present and in whom some effect of the gene is always recognisable.

The *specificity* refers to the localisation of the exostosis, to its extent, and to its other characteristics. The environment is of great significance in the manifestation of the gene's influence.

In the literature we can find the report of the pedigree of a blood-relationship marriage in which the husband was afflicted.[20] The first descendant-generation showed a 100 per cent penetration, and the following generations a strong penetration.

In general, the changes manifest themselves more weakly in women, and more strongly in men. According to Lenz [9] this may be explained by hormonal effects: in men the osseous system, in particular the acral parts, are more coarsely developed. It is also interesting to observe on the basis of the pedigree that the afflicted fathers beget more sons than daughters as compared to the healthy fathers. Our relevant knowledge is far from being complete, but it can certainly be assumed that the sex-chromosomes have something to do with the inheritance of exostosis cartilaginea multiplex. The manifestation is therefore also influenced by sex.

In the pedigree investigated by us, the characteristics of the dominant inheritance described above can be found unequivocally. The most interesting feature of our pedigree is that it includes a monozygotic pair of twin, in whom the degree of penetration proved to be aberrant, similar to the case of Birkenfeld.[2] Our cases therefore are a contribution to the known concept that the manifestation is brought about as a result of the interaction of the genetic constitution and the environmental factors.

From the viewpoint of *genetic counselling* it is essential to know that our cases are concerned with dominant inheritance. In accordance with this, the offspring of healthy families will be healthy without exception, whereas the afflicted will give birth to diseased children with a penetration of 50 per cent. The degree of manifestation of the latter cannot, of course, be predicted. In the accidentally very rare case of two exostotic heterozygotes marrying, there may be a 25 per cent chance of a seriously afflicted child being born, and approximately the same probability of a healthy infant being born. In accordance with Mendel's laws, an afflicted child will be born bearing a gene of average penetration, the chances being 50 per cent.

For the sake of eliminating the first double dominant gene-dose which would be brought

about with a 25 per cent probability, it may even be necessary to advise parents against continuing with a pregnancy.

The determination of the genetic prognosis is naturally the task of the genetic counsellors, whereas the consultation may occur in the light of other circumstances, too.[14] No chromosome anomalies can be found in the case of disorders perpetuated by major genes. This view is supported by our own investigations, too.

Summary

We call attention to the dominant inheritance of an accumulatively occurring *exostosis cartilaginea multiplex* by means of pedigree investigation and discuss the role of the genetic counselling in connection with the clinical picture.

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