LINKAGE IN HUMAN GENETICS*

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IT has been known since the early years of this century that the chance of inheriting one characteristic is not always independent of the chance of inheriting another one from the same parent. This was a fundamental discovery and gave rise to the concept of inheritance of blocks of genes later found to correspond to segments of the microscopically visible chromosomes in the cell nucleus. It was shown that, in both animals and plants, the genes were arranged in a linear order on the chromosome, that order being, in the main, constant for any species, and sometimes showing remarkable similarities even from one species to another. The position of a gene on a chromosome is called its locus.

Chromosome Maps

Maps showing the relative positions of genes on the chromosomes have been made for several animals and plants and, in the study of the fundamental genetics of these organisms, such maps have been of value in numerous and often unexpected ways.

With their help, it has become possible in *Drosophila* in a few cases to pinpoint a specific gene as being in a specific band of a chromosome as seen under the microscope. Unfortunately the technique of making good preparations of human chromosomes, so that they can be seen clearly under the microscope, is not yet very satisfactory but we do know that the chromosomes are of differing lengths and staining properties and that there are two of every type of chromosome. Every gene on one chromosome has a corresponding but often not identical gene on its partner chromosome and all such gene variants or alleles at the same locus are thought usually to resemble one another in the biochemical processes which they control and therefore to resemble one another in the type of visible product or " phenotype " of the individual.

There is little doubt that when a number of such gene loci have been charted on linkage maps in man, these maps will prove to be just as useful as research tools as they have been in other organisms.

Linkage of the A.B.O. Locus and that for the Nail-Patella Syndrome

The pedigree in Figure 1 illustrates the linkage recently demonstrated between the ABO locus and that for the nail-patella syndrome. In the large sibship, eleven

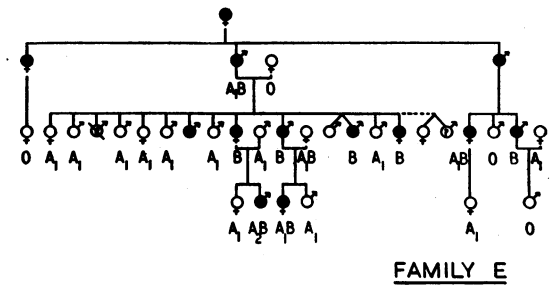


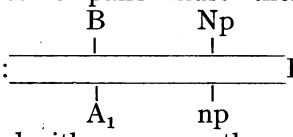
Figure 1.—Pedigree of nail-patella syndrome showing ABO phenotypes, to illustrate the linkage between the ABO and nail-patella loci.

individuals were blood-grouped and it is seen that all those who have inherited the A_1 gene from the father are normal, whereas those who have inherited the B gene have also inherited the defective nails, small patellæ, and dislocated elbows characteristic of the nail-patella syndrome.

It appears then that the father had, on one of his forty-six chromosomes, a B blood group gene at one locus and a nail-patella gene at a neighbouring locus. On the partner chromosome, he must have had an A_1 gene at the ABO locus: and, because the nail-patella gene (Np) is so rare, we can be sure

* A paper read at a Members' Meeting of the Eugenics Society on March 21st, 1956.

that he must have had a normal gene (np) opposite the nail-patella gene. One of his chromosome pairs must therefore be as follows:



Each child has inherited either one or the other chromosome unchanged.

Figure 2 shows a similar pedigree except that, in this family, the nail-patella gene appears to be usually on the same chromosome as the O gene. The syndrome has, in

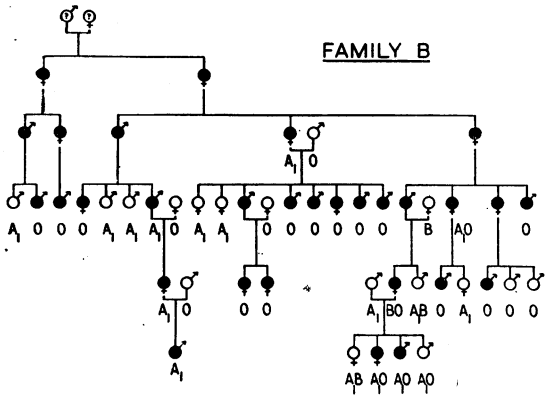


Figure 2.—Pedigree of nail-patella syndrome. The ABO groups are given and in the case of the A_1O and BO genotypes, the presence of the inferred O gene has been recorded for the sake of clarity in five individuals.

fact, nothing to do with the A, B or O genes except that the gene causing the syndrome happens to be carried on the same chromosome. This is, therefore, an entirely different situation from the *association* between blood group A and carcinoma of the stomach, for example (Aird, Bentall & Roberts 1953).

Returning to linkage, Figure 2 also demonstrates crossing-over. The last child in the youngest generation has inherited the O gene but not the nail-patella gene from his affected parent. During the meiotic division therefore of one of the cells in the mother's ovary, the two members of this particular chromosome pair must have interchanged segments and the point of interchange must have occurred somewhere between the ABO locus and the nail-patella locus. From simple mechanical considerations it is easy to see that on the whole, the nearer the loci are together, the less frequently will the point of interchange lie between them. Hence, the frequency of recombination of the genes gives a rough measure of their distance apart.

In the family shown in Figure 1 there was probably no crossing-over, but in several others there has been a varying amount, which raises the question of homogeneity. Are all these families carrying an abnormal gene at the same locus or is there another locus not near the ABO locus controlling a similar—in fact, indistinguishable—syndrome?

Figure 3 shows the counts of recombinants in the different families as estimated by an iteration method of Dr. C. A. B. Smith's. The estimated recombination fraction

Counts of recombinants by family

FAMILY	RECOMBINANTS	NON-RECOMBINANTS	TOTAL	OBSERVED REC. FRACT. %
A	1.0	12.9	13.9	7
B	2.2	23.5	25.7	8
C	4.6	11.9	16.5	28
D	2.2	13.6	15.8	14
E	0.14	23.3	23.4	0.6
G+	2.2	21.0	23.2	9
H	2.0	6.9	8.9	23
TOTAL	14.4	113.1	127.5	11.3 ± 3.0

Figure 3.—Counts of recombinants respecting the ABO and nail-patella linkage. No evidence of heterogeneity between families (see text). + Family G from Jameson *et al.* (1956).

(which would be the same as the cross-over frequency but for multiple crossing-over) ranges from practically zero in family E up to 28 per cent in the smaller family C. The heterogeneity χ^2 appropriate to this iteration method demonstrates that the variations could well be due to chance ($\chi^2=10{\cdot}3$ for 6 d.f., $\cdot 1 < P < \cdot 2$) so these linkage data show us that we have no need at present to question the singularity of the nail-patella locus.

As another illustration of the sort of way

in which linkage information may contribute to our knowledge of genetical processes, we can consider the way in which the degree of severity is controlled in the nail-patella syndrome.

When the nail defect in over 100 cases was scored according to the number of nails affected and the severity in each, there was a striking similarity between sibs (correlation coefficient of 0·46 on forty-three sib pairs) but no correlation between the severity in the parent and that in the child (correlation 0·03 ± 0·13 on fifty-seven pairs). In other words, the severity in the child was apparently independent of whether or not the affected parent was severely or mildly affected. Similar results were found as regards patellar size as measured on X-rays.

Modifying Genes at same Locus: A Hypothesis

Professor Penrose pointed out that these findings could be explained on the assumption that the degree of severity in any individual depended mainly on a modifying gene at the same locus as the main gene. Such a gene would be indistinguishable from normal in the absence of the main gene. Figure 4 shows the situation diagrammatically. All the modifiers, np_1, np_2 and np_3, have been depicted as different from one another and we do not in fact know how many alternative variants there are. On the allelic modifier hypothesis, an affected individual, in handing on the main gene to an affected child, would be automatically excluded from transmitting the modifying allele and there would therefore be no correlation expected between parent and child in the degree of severity of the syndrome. Similarly, since the normal parent would carry two of these modifying genes each affected child would receive one or the other, and the expected correlation between affected sibs can be shown to be 0·5, as was observed.

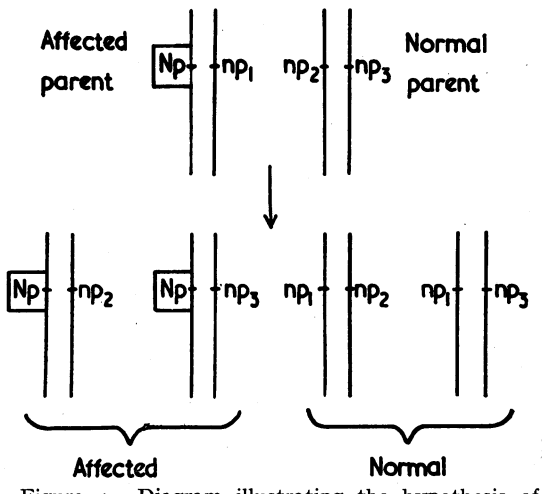


Figure 4.—Diagram illustrating the hypothesis of allelism of main gene (Np) and modifying genes (np_1: np_2: np_3) in the nail-patella syndrome.

This hypothesis of modifying genes at the main locus could theoretically be tested using our knowledge that the main nail-patella locus is closely linked with the ABO locus. We should, in fact, be able to observe linkage between the modifiers and the ABO locus. So far the data on such a rare condition are quite insufficient but Figure 5, showing some actual observations, gives an idea of the sort of family one would expect if the hypothesis were true.

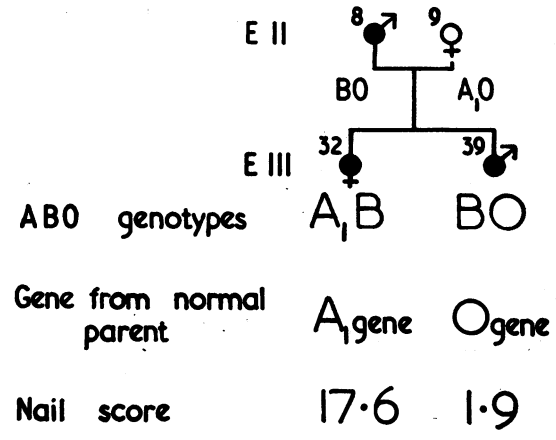


Figure 5.—Example of use of linkage to test allelism of main and modifying genes in the nail-patella syndrome.

In this family, it appears that the normal parent has two different modifying genes. One of them has been transmitted to one affected child (intensifying the nail defect) and the other has been transmitted to the

other child (alleviating the severity of the syndrome). At the same time each child has received a different blood group gene from the normal parent, as would be expected on the hypothesis of linkage between the modifier locus and the ABO locus. It will take a long time before we can accumulate sufficient data like these to strengthen or discountenance the allelic modifier hypothesis, but this is the sort of unexpected way in which linkage information could be useful.

It has often been claimed that there might in the future be opportunities to use linkage more directly in the field of medicine, and it is actually possible that some pathological gene with late manifestation could be traced through a family and prediction could be made with the help of a normal "visible" gene carried very close to it on the same chromosome. It is however unlikely that circumstances would permit such a use except on very rare occasions.

Other Linkages

As regards other linkages there are not many that one can accept with any great confidence. Of course all the sex-linked genes are necessarily on the same chromosome, the X-chromosome. In the case of hæmophilia and colour blindness we know that the loci are close to each other on the X-chromosome, with an approximately ten per cent recombination frequency as estimated by Haldane and Smith (1947). The locus

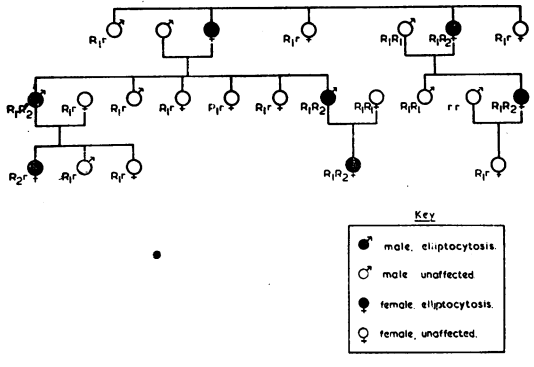


Figure 6.—Pedigree showing linkage between the loci for elliptocytosis and for the Rhesus complex. (After Goodall, Hendry, Lawler and Stephens, 1953).

for pseudo-hypertrophic muscular dystrophy of young boys is probably slightly further away from the colour blindness locus but whether it is on the same side of it as the hæmophilia locus or on the opposite side is not known. Walton, Race and Philip (1955) have recently been responsible for our information on this linkage distance.

To return to the other (autosomal) chromosomes, Figure 6 illustrates the linkage between the elliptocytosis locus and the Rhesus, or Rh, blood group locus. Elliptocytosis produces elliptical red cells instead of round ones and in this particular family, the gene is coupled with the R_2 or cDE gene complex. This linkage, which was demonstrated by Dr. Lawler and her various collaborators, has a very high level of significance.

Next, Mohr (1954) has shown convincingly that the Lutheran locus is definitely linked with some locus that has an influence on the Lewis blood groups and further work should soon define this locus more precisely. Some other linkages have been described but these are on less firm ground at the moment.

Looking now to the future, the most valuable contribution to speed up the slow rate of discovery of new linkages would be the indentification of new "marker" loci such as further blood group loci at which gene differences are common in the normal population. At present there are several blood group loci available and one could also use the locus controlling ability to taste phenylthiourea, or PTC, and probably the recently described locus controlling the serum proteins as found by Smithies (1955) in Canada. In many foreign countries one also has the loci of the abnormal hæmoglobins, but, so far, no hæmoglobin variants have been found which occur commonly in this country. We need to discover more normal or near-normal characters of this type.

An average human chromosome probably bears along its length a few thousand genes, so it is clear that the very few linkages so far established are only the prelude to the enormous mass of work which has still to be undertaken.

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