University Institute of Human Genetics, Oslo (Norway)

Concerning the Genetics of Mental Features

Jan Mohr

It is immediately apparent, that the difficulties encountered in studies of the genetics of the mind are formidable, for several reasons. In the first place, the traits concerned are difficult or impossible to classify or to measure with accuracy. In the second place, they may be unstable towards environmental influence; and they vary with age, or exhibit periodic changes.

It is therefore not surprising that our understanding of genetic mechanisms is limited in those conditions where analysis has been carried out merely on the basis of the mental traits.

The situation is strikingly different in the conditions where an association has been found between a mental trait and some clearly recognisable physical or biochemical trait. As we all know, in several such cases an exact genetic analysis in Mendelian terms has been found possible, for instance in the amaurotic idiocies and phenylketonuria.

Present State of the Genetics of Mental Features

Let us now consider to what extent our present knowledge approaches what may be taken as the primary goal of human genetics, namely to identify the specific genes, to describe their distribution and behaviour in the population, and to recognize their manifestations in the individual.

Consider first *oligophrenia* or mental deficiency, including feeblemindedness, imbecility and idiocy.

There seems to be a general consensus of opinion that there are two kinds of oligophrenia One of these may be said to represent the lower end of the normal distribution of intelligence, and is represented largely by the feebleminded, that is those milder degrees of oligophrenia where education in special schools is possible.

This brings us to the wider problem of hereditary influence on *intelligence*. The genetics of intelligence, as defined by intelligence tests, has been studied by biometric methods, and the results expressed by coefficients of correlation and regression.

The observed parent-child and inter-sib correlations are compatible with an almost complete genetic determination by a system of polygenes without dominance or recessivity. However, this interpretation assumes random mating. In reality, as we know, mating is highly assortative with respect to intelligence, and therefore higher correlations than those observed would be expected. The deviations suggest substantial environmental influences.

The kind of oligophrenia represented by the lower end of the distribution of intelligence,

would then be due to an unfavourable assortment of polygenes, none of which may separately be considered pathological.

The more serious grades of oligophrenia, on the other hand, that is imbecility and idiocy, are thought to include only very few cases from the lower tail of the normal distribution, and the fewer the lower the intelligence, so that in idiocy there should be practically none.

In these serious grades of defect, the majority of cases are considered to be pathological, either caused by some pathological gene or other aberration of the genetic material, or by some environmental influence during pregnancy or later, such as hemorrhage or infection.

As regards the relative importance of the underlying causes, only very tentative estimates have been possible. Penrose (1958) has estimated the etiological distribution of severe mental deficiency as follows: Dominant gene 4% (examples: acrocephaly, epiloia, neurofibromatosis), sex linked gene 0.5% (examples: microphthalmos, Gargoylism), recessive gene 40% (examples: amaurotic idiocy, cerebral diplegia, phenylketonuria), mongolism 12.5 per cent, and the rest — miscellaneous, including birth injury and infection, 43%.

Since we know today that mongolism is caused by chromosomal aberration, and because a certain percentage of the miscellaneous group may also be attributed to this etiology — for instance a proportion of the Klinefelters — more than 12.5 per cent is probably due to chromosomal aberrations, perhaps considerably more.

As to the incidence of oligophrenia, this may, according to Böök (1953) conservatively be put at around 0.5 per cent for the severe degrees, that is imbecility and idiocy, and at between 2 and 3 per cent for the milder degrees.

Passing then to the *psychoses*, the difficulties in genetic analysis appear just as serious as in oligophrenia, when based on mental features alone.

Nevertheless, genetic studies have, as is known, here given highly valuable results. For instance, the finding (Steenstedt, 1952; Kallmann, 1953) that there is no increased frequency of maniodepressive psychosis among the relatives of schizophrenic propositi and vice versa, which suggests that there is no biological relation between these two major kinds of psychosis. Further, morbid risk figures have been determined for relatives of the propositi.

The data are even suggestive as to the kind of genetic mechanism. According to Bøøk (1960), the familiar distribution of schizophrenia appears compatible with a causation by major gene differences, which express themselves regularly in homozygotes and occasionally in heterozygotes. Also in maniodepressive psychosis, major gene differences are suspected.

Concerning the incidence of psychoses, the general morbid risk may be put at around 2 per cent, of which schizophrenia contributes approximately one-half.

I shall not dwell on other mental features, such as *neurosis*, or traits of *personality* within the normal range, in spite of their great interest. A satisfactory genetic analysis would appear to be even more difficult here than in the cases considered.

Future Possibilities

Concerning the possibilities for further progress in genetic analysis, I shall consider the following five kinds of approach:

First, the direct approach through the mental feature itself. Some progress may perhaps

be made through further refinement of diagnostic procedures. But in the light of the past it seems unlikely that this would to any extent lead to reliable recognition of specific major gene differences. Up to now success has not been achieved by this approach in a single case, when the same strict requirements are maintained as, for instance, in the case of a blood group system.

Secondly, an approach through the mental feature towards a physical or biochemical correlate. The ideal situation is here exemplified by Følling's disease, where phenylketonuria is the biochemical correlate, which in this case, as is known, is a recessive trait.

In order to be really helpful for a rigorous genetic analysis, the correlate must show almost such a strict one-to-one relation with the gene as in phenylketonuria. For this reason few of the correlates that are found, will resolve the difficulties. This of course does not detract from their interest in other respects.

The *third* approach I have in mind, would be rather indirect, and probably of practical interest only in a fairly distant future. I am thinking of an approach through marker genes.

As is known, the genes are generally pleiotropic. Hitherto very little has been done in the way of a systematic search for other effects of marker genes than the ones by which they are diagnosed, although a beginning has been made by the discovery of relationships between blood groups and disease.

The sickle-cell trait is also instructive in this connection. It demonstrates how a genetic marker may make it possible to reveal an important influence by a major gene on the susceptibility to a disease, where a hereditary influence would otherwise perhaps not have been considered at all.

The number of marker systems is already now considerable, and new markers are being discovered in rapid succession. For each marker gene a systematic search should be made for associations with any of a battery of physical and mental traits or diseases.

In the long run it would appear possible that some considerable part of the variation in genetically complex traits, such as intelligence and other aspects of the mind, could be accounted for through marker systems.

The *fourth* kind of approach I shall consider, is studies of genetic linkage.

In cases in which a major gene is suspected, such as in schizophrenia and maniodepressive psychosis, it might perhaps even now be worth while collecting material for study of linkage. The demonstration of linkage between, for instance, a blood group and schizophrenia would imply confirmation of the hypothesis of a major gene influence on schizophrenia. But a positive result would require rather favourable circumstances, namely closeness of the major gene locus to that of the blood group system, and a rather strong effect of the gene.

At present the chances of a positive result in studies of linkage are still slight for any chosen trait; but they increase in step with the number of marker systems.

The *fifth* and last approach I shall mention, is the obvious one of continued studies of chromosomes. To judge from the ample results gained during the short time such studies have been going on, there should here be ground for expectations.

Conclusion

To conclude: If strict criteria are applied, very few major genes with influence on mental features have so far been diagnosed with certainty, while there is reason to think that a considerable part of the variation in question is due such major genes.

Valuable results concerning the distribution of oligophrenia and psychosis in families and populations have been obtained, including morbid risk figures for relatives of the propositi. Such results, based on the mental features alone can, however, scarcely give satisfactory information on the specific genes. A mere augmentation of numbers will not be of any help. The traditional family and population surveys will scarcely lead to the desired goal, however comprehensive. They would probably rather lead to frustration, or in some cases the advancement of a specific genetic hypothesis for which the data do not really give sufficient support.

Hitherto, recognition of the specific genes in question has in all cases been made through a physical or biochemical correlate. And this trend is likely to continue.

In the very long run perhaps some considerable part of the variation in mental features may be accounted for through genetic marker systems: by pleiotropy of marker genes, and in part through linkage relations.

In other words I think that progress in the genetics of mental features will to a large extent depend upon progress in other branches of biology. And that is a rather satisfactory conclusion for those of us who are working in such other fields.

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