Editorial: Genetic associations of glaucoma

Haemophilia and retinitis pigmentosa each result from the presence, in homozygous or heterozygous form, of a single specific pathogenic gene. A second gene may be linked on the same chromosome with a pathogenic gene, and the manifestation of this second gene—for example, a particular blood group—will accompany the disease in any one family. But because of crossing over of genes in sexual reproduction different alleles will be linked with the pathogenic gene in other families, so that the disease in question will not invariably be associated with the manifestation of the same gene (in this example the same blood group). In the population as a whole there will be no statistical association between the disease and the manifestation of any one allele.

There are many diseases which are common in particular families but which cannot be explained by classical Mendelian patterns. This is because the inheritance of them is polygenic. A number of genes must be present to overstep the threshold needed for the development of the full-blown disease.

Miller has emphasised that in the 2 main forms of primary glaucoma each has a familial incidence, and almost invariably only one type occurs in a particular family. Both appear to be polygenic in inheritance, but in each case—in some families at least—one gene has a preponderant effect. A pharmacogenetic system which influences the incidence of chronic simple glaucoma expresses itself primarily in variations in response of intraocular pressure to topically applied dexamethasone. In closed-angle glaucoma the depth of the anterior chamber has a marked effect. This hereditary anatomical feature is mainly determined by one genetic system. Alsbirk has shown that in Greenland Eskimos there is a high incidence of shallow anterior chambers, and closed-angle glaucoma is relatively common. There are sufficient clues, however, in the pedigrees of patients with glaucoma to indicate that other genes are involved apart from the one principally responsible, and it is a fruitful pursuit to try to identify them.

Apart from specific pathogenic genes most of the recognisable genes in man concern blood groups (and factors). If such a gene is involved in the aetiology of a disease, there should be a statistical association in the population as a whole between the blood group and the disease. Blood groups vary in frequency between different populations. Part of this variation is the result of random processes (genetic drift), but much, and perhaps most of it, is due to natural selection related to the differing environments, physical and microbiological, in which the populations live.

The world distribution of a number of other genetically determined characters has been studied. An example is the hereditary presence (or absence), in the saliva of the individual's ABO blood group antigen, which is referred to as ABH secretion (or nonsecretion). Another is the ability (or inability) to taste certain thyroid-inhibiting derivatives of thiourea, such as phenylthiocarbamide. Individuals are usually called PTC tasters (or nontasters). Some of these genetically determined characters are associated with specific diseases. However, it is important to realise that in order to establish the statistical association of a disease with other genetically determined characters large numbers of observations must be made. When the disease is uncommon this involves combining data, by established statistical methods, from a number of different research centres.

The statistical associations of glaucoma have attracted attention because it has been claimed that this disease (usually of unspecified type) tends to be associated with goitre (again mostly of unspecified type), and 2 of the firmly attested associations of disease with genetic polymorphisms concern goitre and PTC tasting. Sufferers from nontoxic goitre include an excess of nontasters, and sufferers from toxic goitre an excess of tasters.

Several searches have been made for associations between PTC tasting and glaucoma. The overall results show a raised incidence of nontasters among patients with primary chronic simple glaucoma and of tasters among patients with closed-angle glaucoma. A small number of cases of congenital glaucoma show a large excess of tasters. Moreover Becker et al. found low levels of protein-bound iodine in cases of chronic simple glaucoma as compared with those with closed-angle glaucoma.

These results are surprisingly consistent but so far unexplained, though some of the series are small, and further independent data are needed. Several studies have also been made on the ABO blood groups of small numbers of patients who suffer from glaucoma. The overall results show a greater relative frequency of A than of B and O. A single study of only 100 mixed cases of glaucoma shows a marked deficiency of ABH secretors.

This brief summary of the associations of glau-
coma and genetic polymorphisms indicates the probability that one or more of the commonly studied human polymorphisms contribute to the polygenic aetiology of the glaucomas. Clearly confirmatory studies should be done using the 3 polymorphisms already investigated, but other associations should also be sought. The careful work reported in this issue by David and Jenkins is welcome. They sought associations with 13 polymorphisms in a series of 100 patients with primary chronic simple glaucoma. The results from such a small group, although inconclusive, will form a firm base for future investigations and should encourage others to collect and publish further data.

References

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