Genetica della Popolazione, Mutazione e Selezione Naturale

Population Genetics, Mutation and Natural Selection

SIMPOSIO II

SYMPOSIUM II

9 Settembre 1961

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Human Population Genetics, 1961

Introductory remarks

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The more significant developments in the field of human population genetics during the past decade can for the most part be subsumed under three headings, as follows:

1. The recognition of an increasing number of genetic traits capable of serving as analytic tools in population studies.

2. The recognition that many of these traits attain frequencies, although some only in limited areas, such that they have to be labelled genetic polymorphisms. Table 1 is an attempt to list the presently recognized human polymorphisms for which the genetic basis seems clear.

3. The emergence of at least a few clues as to the factors responsible for the maintenance of some of the plymorphisms, although it must be confessed that for the majority of the traits listed in Table 1, there is as yet no real insight into their role in populations.

As is well known from the contributions of Fisher, Wright, Dobzhansky, Lerner, Crow, Kimura, and others, genetic polymorphisms have the property of acting as stabilizing mechanisms in maintaining certain aspects of the fitness of populations. Consequently, whereas what we may term the " classical model " of the dynamics of a genetic locus in a population looked to mutation pressure as the source of the impairment of population fitness which could be traced to that locus, the " polymorphic model " views that impairment as in part a price a population pays for the maintenance of an optimum level of heterozygosity at that locus. The two models have such profoundly different practical and philosophical consequences that it is small wonder that in recent years the running discussion of their relative merits and roles has generated a degree of heat matched by few other current biological questions.

Beyond any doubt, the chief problem of human population genetics today is to determine the relative importance of these two models. Concerning the fact that both are appropriate to specific situations, there can be no doubt. What is at issue is the matter of defining their respective roles. At the very outset of any discussion of this question there arises a problem of definition. By what criteria can we assess the relative importance of the two types of systems? Certainly the simplest and most obvious criterion involves the relative contributions of the two systems to population fitness or morbidity and mortality, i. e., to population " loads ". But since only a few loci associated with marked heterozygote advantage could disproportionately influence the results of inbreeding, in the ultimate understanding towards which we are striving an equally important criterion would seem to concern the proportion of alleles and genetic loci involved in each of the two types of systems. In this connection, we must be careful not to categorize loci as either " classical " or " polymorphic ". Although there may be some loci where the various alleles all function as demanded by the classic model.

I rather doubt, the facts of mutation being as well established as they are, whether there are any entirely " polymorphic " loci or traits maintained entirely by segregational load, and attempts to place the problem in that perspective, such as the recent papers of Morton and his collaborators (Morton, 1960, 1961; Morton and Chung, 1959; Chung, Robison, and Morton, 1959), represent gross oversimplifications which culminate in the fiery destruction of straw

Tab. 1. A listing of some of the simple genetic polymorphisms recognized for man

A. Those for which the selective mechanism is partially understood
- Hemoglobinopathies
- ABO
- Rh

B. Those for which there is essentially no data concerning the selective mechanism

MNS	Gm factor
Duffy	Haptoglobins
Kell	Transferrins
Kidd	Isoniazide inactivation
Lutheran	Phenylthiocarbamide taster
P	Level of β-aminoisobutyric acid excretion
Lewis	Gluocose-6-phosphatase deficiency
Diego	
Sutter	

men of little scientific substance. Rather, as illustrated by the distribution of the hemoglobin alleles in West Africa (review in Rucknagel and Neel, 1961) it seems likely that at most and probably all loci at which there occur alleles involved in polymorphic systems, there will also occur alleles maintained by mutation pressure. In our efforts to understand the true situation, we are confronted, then, with the very laborious prospect of dissecting the human genome locus by locus.

In the remainder of this brief introductory address, I should like to comment briefly on some of the sometimes overlapping approaches to this problem, as seen by one who quite obviously feels that only the barest start has been made on unravelling the complexities of the issues.

1. *The mathematical approach.* Despite a great deal of brilliant groundwork, only a beginning has been made on the systematic exploration of the more complex population models, such as those involving loci at which there occur some alleles maintained by heterozygote advantage and some by mutation pressure, as were just referred to, or systems involving several loci, for which the interdependence of the ABO and Rh loci will serve as an example (see discussion by Kirk, 1961). My associates and I have recently been exploring some of the many possible models of what we may term " mixed " systems. One of the simplest is certainly a three-allele situation, where q_1 is homozygous lethal and maintained in frequency by mutation pressure, q_2 is homozygous lethal but maintained by a selective advantage when combined with q_3, and the combination $q_1 q_2$ is also lethal. With reasonable assumptions concerning selective advantages and mutation rates, the model yields quite low inbreeding effects. In other words, the inbreeding effect we usually associate with a rare recessive lethal tends to be obscured under

these circumstances. Quite another complication in the interpretation of inbreeding effects, arising from the " spotty " or uneven distribution in human populations of abnormal genes and the equally uneven frequency of consanguineous marriages, will be considered in another paper at this Conference by my colleagues and self. For this and other reasons, we feel that for the present, until the mathematical theory of inbreeding for a wide variety of systems is further along, extreme caution in the interpretation of inbreeding effects is indicated.

2. *The biochemical approach.* A balanced polymorphism exists because under certain circumstances the two different alleles of a heterozygote convey information of greater value to the organism than is conveyed by homozygosity for either of the two. The actual expression of this concept is best understood for the sickle cell locus. By an extension of this information-level type of concept to traits in whose etiology multiple loci are concerned, one can visualize, with Lerner (1954), traits which arise when an individual " falls below the threshold of the obligate proportion of loci needed in the heterozygous state to ensure normal development ". The recent demonstration that individuals simultaneously heterozygous at both the α and β hemoglobin loci form a hybrid hemoglobin molecule with properties different from the molecules formed by either of the two single hybrids (Atwater, et al., 1960; Itano and Robinson, 1960; Raper, et al., 1960) would appear to supply a concrete demonstration of how the information potential of hybrids can exceed that of homozygotes. With the current great interest in protein structure and its genetic control, it seems assured that the question of how often the structure of complex protein molecules is under the control of several loci, with the possibilities of " hybrid " molecules, will shortly receive a great deal of attention.

3. *The " selected trait " approach.* Reference has already been made to the many polymorphisms whose biological function is not yet understood. An important line of investigation consists in attempts to relate these polymorphisms to specific traits whose nature and whose frequency in the population suggest they might be involved in polymorphic systems. For instance, several years ago I suggested that a significant proportion of congenital malformations might be regarded as " phenodeviants " in the sense of Lerner, maintained by complex homeostatic or polymorphic systems (Neel, 1958). More recently, following a study in depth of a specific malformation whose attributes render it unusually favorable for such studies, my associates and I have pointed out that whereas children with congenital hypothyroidism who possess thyroid tissue appear in the vast majority of cases to owe their disease to simple recessive inheritance, children with congenital hypothyroidism who appear to lack thyroid tissue — the so called athyrotic cretins — fall into no such simple genetic pattern, but rather in a number of their epidemiologic aspects resemble children with congenital defects, and by inference might to some extent reflect the action of homeostatic systems (Neel, et al., 1961). The past year has witnessed two reports of a relative excess of non-tasters for phenylthiocarbamide among athyrotic cretins (Shepard and Gartler, 1960; Fraser, 1961). While the reports must be viewed with caution because of the difficulties of taste testing in children so often mentally defective as these, here may be the first concrete implication of a polymorphism with a phenodeviant.

4. *The study of mixed populations.* If balanced polymorphisms are important to human populations and if, as seems likely, long-separated subdivisions of the human species have evolved different polymorphisms, then, since hybridization should disrupt polymorphisms

Tab. 2. Mortality effects in inbreeding studies

In the main, the figures are based on stillbirths and deaths during the first 10-20 years of life, but, because of varying ages of subjects and the inclusion in some series of abortions and miscarriages, care must be exercised in comparing the results of the various series. The B/A ratios are based on two points only, namely, results of first cousin marriages as contrasted to results of non-consanguineous marriages, and so are extremely approximate.

Author	Population studied	Percent deaths in children of first cousin marriages	Percent deaths in children of control marriages	Difference	B/A ratio
CAUCASIANS					
Arner (1908)	U.S.A.	16.8 $\left(\frac{113}{672}\right)$	11.6 $\left(\frac{370}{3184}\right)$	5.2	7.2
Sutter and Tabah (1953, 1954)	Morbihan	12.2 $\left(\frac{53}{436}\right)$	5.4 $\left(\frac{86}{1594}\right)$	6.8	20.2
	Loir-et-Cher	6.9 $\left(\frac{19}{274}\right)$	3.8 $\left(\frac{40}{1103}\right)$	3.1	13.1
Böök (1957) [1]	North Sweden	25.6 $\left(\frac{30}{117}\right)$	31.6 $\left(\frac{55}{174}\right)$	—6.0	—3.0
Slatis, et al. (1958)	Chicago, U.S.A.	22.6 $\left(\frac{56}{248}\right)$	16.0 $\left(\frac{31}{194}\right)$	6.6	6.6
Freire-Maia, Freire-Maia, and Quelce-Salgado (1961)	Brazil	31.1 (280)	31.1 (2375)	0.0	—0.0
Zerbin-Rüdin (1961)	Germany	32.2 $\left(\frac{38}{118}\right)$	29.5 $\left(\frac{31}{105}\right)$	2.7	1.5
Freire-Maia (unpublished)	Brazil	28.0 (397)	29.0 (4723)	—1.0	—0.6
NEGROES					
Freire-Maia, Freire-Maia, and Quelce-Salgado (1961)	Brazil	43.8 (32)	30.6 (595)	13.2	6.9
Freire-Maia (unpublished)	Brazil	46.0 (148)	31.2 (3846)	14.8	7.6
Roberts and Tanner (unpublished)	Tanganyika	32.1 $\left(\frac{129}{402}\right)$	34.3 $\left(\frac{119}{347}\right)$	—2.2	—1.0
ORIENTALS					
Schull and Neel (this Conference)[2]	Hiroshima	10.1 $\left(\frac{76}{752}\right)$	6.4 $\left(\frac{98}{1542}\right)$	3.7	9.3
	Nagasaki	8.9 $\left(\frac{113}{1276}\right)$	7.3 $\left(\frac{170}{2342}\right)$	1.6	3.5
Japanese collaborative study (Tanaka, 1960)	Shizuoka	11.1 (752)	5.8 (2095)	5.3	14.6

[1] Based on children born 1927-1947.

[2] Figures restricted to livebirths.

but increase the apparent effects of inbreeding, a comparison of certain characteristics of hybrid populations with those of the parent types should be revealing. Formidable questions in such studies are the representativeness of individuals who enter into cross-cultural marriages, and comparability in the care and reporting of medical problems. Surprisingly little solid knowledge exists concerning the results of hybridization, and that available is conflicting. There is certainly an urgent need for the study of such populations with sampling procedures designed to take socio-economic factors into proper consideration.

5. *The consanguinity approach.* The study of consanguinity effects appears to be the best single approach to an over-all assessment of the relative roles of mutational and segregational loads. Many of the studies of the past suffer from such obvious biases that they can serve only to confuse the issues. It is not commonly realized how divergent are the results of the apparently acceptable studies. Table 2 is a summary of the results of a number of studies on mortality in the children of first cousin marriages as contrasted to the children of unrelated parents. Since the various studies cover different age intervals and also involve populations with differing age-specific death rates, they are not directly comparable. Furthermore, few studies answer the important question of whether first cousins who marry differ in their biological attributes from the control population. Be this as it may, the variability in the results to date, as summarized in Table 2, is so striking as to lead to only one conclusion, namely, the need for more work. Since the B/A ratios of Morton, Crow, and Muller (1956) derived from the first two studies have been extensively quoted in support of the argument that " classical-type " alleles are much more important than " polymorphic-type ", I have calculated B/A ratios for all the studies to date, but with many mental reservations concerning their interpretation, especially for populations where the frequency of non-genetic death is high. Incidentally, negative B/A ratios, as result from three studies, either imply an unexpectedly large compatibility load or reflect sampling errors. Similar sampling errors may enter into some of the higher positive values. Crow (1961) has recently argued that the results of consanguinity studies " make it highly improbable that more than a minute fraction of the inbreeding effect is due to alleles maintained by balanced selective forces " (p. 148). In my opinion the present data simply do not support any such sweeping conclusion.

In closing this presentation, I call your attention to an approach many have commented on in recent years but few have pursued, namely, the need for combining all these approaches in studies on the fast vanishing primitive populations of the world, where many of our present-day polymorphisms may have arisen.

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