A DEFINITION AND STANDARD NOMENCLATURE FOR " POLYGENIC LOCI "

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Summary

Studies of qualitative and quantitative or continuous genetic variation are, in part, historically and methodologically separate. But the traditional distinction between major genes and polygenes has unfortunately caused some confusion in discussions of the location of polygenes and the nature of the loci which contribute to quantitative variation. Consequently, this paper proposes that the term " polygenic locus " replace the term " polygene " when reference is made to the effects of individual loci. A polygenic locus is defined as a genetic locus composed of one or more closely linked genes at which allelic substitutions contribute to the variance in a specified quantitative character. A standard nomenclature is described.

1. Introduction

A CHARACTER shows quantitative or continuous variation when the phenotype is affected by a number of factors, each of which makes a contribution which is small relative to other sources of variation. When these factors include allelic variation at one or more genetic loci, the other sources of variation, which may be environmental, genetic, or both, make it difficult to classify individual genotypes. Thus, segregation at individual loci cannot be studied directly. On the other hand, a character shows qualitative, discontinuous, or Mendelian variation when genetic variation at one or a very small number of loci makes large individual contributions to phenotypic variance relative to other genetic and environmental factors. In such a situation, variation in the character allows individuals to be classified into distinct phenotypic classes with the result that the segregation of individual alleles can be easily detected.

One of the primary differences between genetic studies of quantitative variation and of classical Mendelian differences is in the way the data are handled statistically. The ability to classify the phenotypes of discontinuous characters into discrete groups and make counts of the number of individuals in each group leads to statistical analyses using the χ^2 test of goodness of fit. The continuous distributions observed in quantitative characters, however, lead to analyses which compare the variances between and within classes and, thus, to a biometrical approach.

Although studies of major gene and minor gene differences are to some extent separated historically and methodologically, the genes responsible for continuous and for discontinuous variation are generally considered to differ only in the relative magnitude of their phenotypic effects. Genes of small effect, or polygenes (Mather, 1941), show both segregation and linkage (Mather, 1949), and otherwise appear to be inherited in the classical Mendelian fashion. Thus, in spite of the fact that little is known about the precise ways in which individual genes affect quantitative variables (but,

see Spickett, 1963; Mohler and Swedberg, 1964; Milkman, 1970*a*), the distinction between polygenes and major genes is usually considered to be empirical, rather than qualitative.

Some, however, believe that at least a proportion of the genetic factors contributing to the variance in a quantitative character fall into qualitatively distinct classes. For instance, Mather (1949; see also Mather and Jinks, 1971) points out that at least some of the genetic variation of quantitative characters is associated with the heterochromatic regions of the genome. In discussing this association, Mather and Jinks (1971) draw a functional distinction between major genes and polygenes, in which major genes have a specific role in development, while polygenes, being non-specific and interchangeable within a polygenic system, play a less precise role in development. " Duplication or deficiency for a small number of polygenes is not likely to be unconditionally deleterious as the small effects of the change could be balanced by other members of the polygenic system " (Mather and Jinks, 1971, p. 29).

One difficulty is that such a statement appears to associate with a *locus* a level of importance in development which is proportional to the phenotypic effects of known alleles at that locus. Allelic differences of small effect at a locus otherwise known through " major mutants " could, therefore, lead to the classification of the same locus into two different categories. On experimental grounds, there is as yet no compelling evidence that different types of loci are involved in any specific instance, except perhaps in so far as some effects upon continuous variables are associated with heterochromatin. In addition, the level at which the character is studied (Spickett, 1963; Spickett *et al.*, 1967) or the genetic background on which segregation is investigated (Spickett and Thoday, 1966; Thompson, 1973) may determine to a large extent whether or not allelic substitution produces discrete phenotypic classes or overlapping distributions. Indeed, the degree to which the allelic differences appear to involve specificity may sometimes, or even usually, be the result of an inability to observe gene effects sufficiently closely related to the biochemical level at which they act, rather than a result of functional differences among loci.

Others, including Rendel (*e.g.* 1968) and Pandey (1972), have also suggested that at least some polygenes may be functionally distinct from major genes. For example, Pandey (1972) suggests that major genes are structural gene loci, while polygenes have any of a variety of regulatory functions. Clearly, we have much to learn in this area.

What, then, is the precise nature of the effects which polygenic variation has upon the development of the phenotype? Such a question can be properly answered only when it is possible to isolate and manipulate individual components from a polygenic system. Thoday (1961) has described a technique for isolating individual factors in a polygenic complex, and Spickett (1963) used lines containing factors isolated by this technique to describe specific effects of individual loci affecting sternopleural chaeta number in *Drosophila melanogaster*. Other techniques are also available for the location or isolation of factors affecting quantitative characters in a variety of species (Wehrhahn and Allard, 1965; Law, 1966, 1967; Milkman, 1970*a*).

Polygene isolation techniques depend upon controlling, as far as possible, genetic and non-genetic sources of phenotypic variation, while studying the

effects that small chromosome segments have upon the quantitative character. They often involve time-consuming breeding programmes which concentrate upon specific chromosome segments and attempt to discover segregation at individual loci or closely linked loci making up " effective factors " as Mather (1949) called them. Even though the resolution of these techniques only allows one to locate those components which have comparatively large phenotypic effects, the loci studied in this way have often accounted for a major proportion of the variance under investigation (see for example, Spickett and Thoday, 1966).

Thus, we have seen that (1) polygenes are genes of small effect which contribute to the variance of a quantitative character, (2) little is known about the ways in which polygenes produce their phenotypic effects, and (3) in order to study polygene function, one must be able to isolate and manipulate individual factors. Practical and conceptual problems arise, however, as soon as individual factors are abstracted from a polygenic system. The first of these problems is that it is technically very difficult to know whether one is dealing with a single genetic locus or a complex, in the sense of tightly linked genes of similar effect. This will be discussed below, though in practice it is not as important as the second problem, which is the fundamental confusion between the " major gene " and " polygene " categories that results from the traditional separation of the studies of qualitative and quantitative genetic differences. The second problem is basically one of definition.

There are major difficulties with any definition which gives the impression that polygenes and major genes are necessarily different kinds of genes. One such difficulty is made clear by the fact that when it has proved possible to locate some components of a polygenic system, the question immediately arises whether a " located polygene " is still a " polygene " (if we may use the word in the singular for the moment). For example, consider the work of Spickett, Shire and Stewart (1967) on mouse strain differences in the production of steroids by the adrenal glands. If adrenal activity is measured by the *in vitro* synthesis of corticosteroids from the precursor progesterone and expressed as mμg corticosteroid per gram of body weight, the distribution of phenotypes is found to be continuous, and the parental strains have similar distributions. If activity is expressed in terms of a more specific measure, steroid per unit adrenal weight, the distribution is still continuous, but the overlap between strains is smaller than with the cruder metric, which did not take into consideration variation in relative adrenal weight. If measurement of steroid production is made with respect to the zona glomerulosa and fasciculata, the adrenal zones which produce the steroids, the overlap between strains is even less. Finally, if the activity of a particular steroid is considered, *e.g.* corticosterone per unit weight of the zona glomerulosa and fasciculata, the character is defined in such specific terms that the genetic differences between strains become distinct and the character can be handled in the classical Mendelian manner. Thus, this process has abstracted, from a complex, one of the components distinguishing the parental strains and has associated it with a Mendelian segregation. This segregating unit, however, must still be part of the polygenic system which gave rise to the distribution of phenotypes from which the investigation began.

At the initial descriptive level of the character, the segregation of genetic

differences is polygenic, while at the final, more specific level, segregation is not polygenic. Clearly there is a problem. Assertions that polygenes do not exist, except as an unfortunate shorthand (Lerner, 1972) or that all characters are affected by a large number of genes and are, therefore, polygenic (Rieger *et al.*, 1968) are by themselves unhelpful, for they dismiss the problem without trying to resolve it. In a given investigation, the question is not " how many genes affect the character ", but " how many alleles are segregating " in the material being studied. It is a problem of first defining the phenotype which is to be studied, then of attempting to control and isolate individual variables, and, when possible, describing the relationships among component morphogenetic processes.

2. Definition

Terminology is one possible source of confusion in the distinction between major genes and polygenes. To speak of " a " polygene or " located " polygene (Spickett and Thoday, 1966) is really self-contradictory, since polygene is a term which describes the *system* of genes affecting a particular character. A solution to this difficulty is to introduce a term which focuses attention upon the individual loci involved in the production of the phenotype, rather than upon the system of genes as a whole. Thus, we propose the term " polygenic locus " be used to describe any individual locus which is included in the system of genes responsible for the genetic component of variation in a quantitative character. Such variation is due to the segregation of particular alleles, and it must, therefore, be noted that there may also be other alleles at a " polygenic locus " whose effects are large enough to produce qualitative differences. Even though the more clumsy " polygenic-variation locus " might be a more nearly correct description, the simpler term has been chosen. It retains a logical link with the work already published in this area, and it underlines the importance of the individual genetic factors which contribute to the variance in a quantitative trait. Indeed, this term may have occasionally been used in such contexts, though not to our knowledge defined formally.

A *polygenic locus* is a genetic locus composed of one or more closely linked genes at which allelic substitutions contribute to the variance in a specified quantitative character.

A polygenic locus may be either a simple or a complex genetic locus in the conventional sense, that is, either a single gene or a closely linked block of functionally related genes, which have been located to a general chromosome region by the techniques of Thoday (1961) and others. The resolution of these techniques is usually such that it is difficult to establish allelism among polygenic loci or between a polygenic locus and a major gene locus, although allelism tests are possible in some systems (Milkman, 1970*b*). Indeed, testing allelism is often difficult enough when dealing with alleles having discrete phenotypic effects. For this reason, the term " isoallele " (Stern and Schaeffer, 1943) cannot properly be applied to most polygenic loci, since the use of this term implies that allelism between the mutants in question has been firmly established. Certainly isoallelic variation may be involved in quantitative variation, and indeed may even be a major contributor to such variation. But one must not confound the theoretical possibilities with the technically testable hypotheses. The point

is simply that isoallelism between a polygenic locus and a locus known through major mutants may be very difficult to establish, and until it is established the use of the term is misleading.

The inability to establish allelism is not really a great handicap, however, for in most instances polygenes are located in order to study their developmental effects and interactions more precisely. The emphasis, then, is upon manipulation of the loci within a defined experimental situation and upon naming the loci so that they can be discussed unambiguously within the context of the experiment. Emphasis is not usually upon precise chromosome location or upon separation of component loci, both of which may be difficult or impossible (see McMillan and Robertson, 1974).

In the same way it is very important to specify the character which is being studied and to discuss polygene action in relation to that character. Sternopleural chaeta number is a quantitative character. If one is interested in the ways in which individual loci contribute to changes in chaeta number under selection, it is not a valid objection to the conclusions, that at a more basic phenotypic level one can identify particular developmental effects, such as increase in cell number or bristle distribution (Spickett, 1963), which can be associated with single gene differences. Indeed, at some level of gene action, any distinction between major gene effects and polygene effects must disappear. However, if one objects that a polygenic locus, at which segregation of individual alleles can be studied, is no longer a polygene in the classical sense, one is left with the unfortunate paradox that it is not possible to learn how quantitative characters are determined. This is clearly an unproductive approach. But the problem can be resolved easily by remembering that a polygenic locus still contributes to the overall variance in the character as it was originally defined.

3. Standard nomenclature for polygenic loci

If polygenic loci are to be discussed unambiguously, they must be assigned convenient symbols. One criterion for a useful nomenclature is that the symbol assigned to each locus be concise and distinctive. Problems arise, however, when loci having phenotypically similar effects are distributed throughout the genome. This is true not only of polygenes but also of several classes of major gene mutations, such as the Minutes, lethals, female steriles, and male steriles in *Drosophila melanogaster.*

We have, therefore, followed the conventions adopted for naming lethals and other such loci in *Drosophila* (Lindsley and Grell, 1967) and propose to represent each located polygene by a symbol composed of the letters *PL* (*i.e.* polygenic locus or P-locus), followed by the chromosome number in parentheses, and then by a distinguishing designation such as a phenotype abbreviation or initial. Such notation could easily be modified to conform with the standard nomenclature used in other organisms.

There are two particular problems which must be overcome in naming polygenic loci. One of these has been discussed above. This is that allelism between two independently obtained polygenic loci is often technically quite difficult to establish. The nomenclature which we discuss will, therefore, make no direct provision for denoting alleles, although this could be done with appropriate superscripts as is now done for major gene mutations. The second problem is in a sense related to the first. This is that in order

for allelic substitution to contribute to the variance in a quantitative trait, at least two alleles must be segregating in the original population. Polygenes, however, are experimentally located and isolated from more or less homozygous selection lines, the location being done by comparison with a particular inbred assay chromosome. Thus, it must always be remembered that, although a given polygenic locus in, for example, a high bristle number selection line may produce an increase in bristle number, the original stock also carried an allele which caused a relative decrease in bristle number. The effect of a specific allele should usually be clear from the context of the discussion and should be included in the description of the polygenic locus when it is named, but unless ambiguities begin to occur, we shall exclude notations of the direction of phenotypic effect. This is justified in view of the fact that in practice most polygenic loci will probably be named and studied in the context of a specific set of experiments.

Consider, for example, the locus associated with a difference in sternopleural chaeta number, which was shown by Thoday, Gibson and Spickett (1964) to be located at about 30·2 cM on the third chromosome. This locus might be symbolised *PL(3)sp*^{T1}. Most major mutants have a variety of pleiotropic effects. It is customary, however, to name a locus by one of its most obvious or useful phenotypic effects. The polygenic locus in this example was first identified through its effect upon sternopleural chaetae number. The designation after the chromosome number, therefore, includes the abbreviation *sp*, which makes the locus readily identifiable as a sternopleural chaeta number modifier. The superscript *T1* shows that it is one in a series of chaetae loci described by Thoday and his colleagues. Alternatively, the various loci could simply be distinguished by a sequence of numbers, *e.g. PL(3)sp1*, *PL(3)sp2*, and so on.

Spickett (1963) showed, however, that at this locus the allele which increased chaeta number produced its effect by increasing cell number and, thus, influenced chaeta number only indirectly. In most instances the precise developmental effects of polygenic loci are not yet known. When such additional information becomes available, however, it would be appropriate to include it in the phenotypic description of the mutant, but would not usually warrant the confusion which a change in the symbol might cause.

The phenotypic description of a polygenic locus should also include details of the standard chromosome against which the gene was located. As noted above, location techniques usually work by comparing the variance in a selected chromosome or recombinant region with the variance in a multiply marked chromosome which is arbitrarily taken as a standard. This means that these methods can only detect loci at which alleles in the chromosome being tested and the standard marked chromosome differ. If, for example, the selected line has two linked factors which increase chaeta number (+ +), but the assay stock is homozygous for a chromosome which carries a plus allele at the first locus and a minus allele at the second (+ −), only the right-hand locus can be detected in tests of recombinants between the lines (Thoday, 1973). Recombination assays using a different standard might reveal different loci. Thus, the standard stock should always be specified in the description of a new locus.

With the exception of the assignment to chromosome, it is necessary to avoid including in the symbol specific information such as genetic location.

In this way such information can be revised when necessary without changing the symbol. It is also probably not advisable to use the designations " suppressor " and " enhancer ", since an allele which acts as a suppressor of one phenotype may also act as an enhancer of another (cf. Thompson and Thoday, 1972) and thus lead to confusion in the discussions of polygene action.

Although a major mutant which has pleiotropic effects upon a quantitative character is in one sense a polygenic locus, the major phenotypic effect should take precedence when naming the mutant allele.

The polygenic loci described by Thoday and his colleagues are listed in table 1. These have been assigned standard symbols according to the

TABLE 1

Summary of standardised symbols assigned to polygenic loci described in Drosophila melanogaster *by Thoday and his colleagues*

Symbol	Location	Synonym	References
$PL(1)sp^{S1}$	1-2.4	—	Spickett and Thoday, 1966
$PL(1)sp^{S2}$	1-51.5	—	Spickett and Thoday, 1966
$PL(2)sp^{G1}$	2-27.5	—	Gibson and Thoday, 1962
$PL(2)sp^{S3}$	2-41.1	II	Spickett and Thoday, 1966
$PL(2)sp^{G2}$	2-47.5	—	Gibson and Thoday, 1962
$PL(3)w^{S}$	3-13	III*w*	Spickett, 1963
$PL(3)sp^{T1}$	3-30.2	3*a*	Thoday *et al.*, 1964
$PL(3)sp^{T2}$	3-32.6	3*b*	Thoday *et al.*, 1964
$PL(3)sp^{W1}$	3-49	*a*	Wolstenholme and Thoday, 1963
$PL(3)sp^{W2}$	3-51	*b*	Wolstenholme and Thoday, 1963

sp = sternopleural chaetae; *w* = weight.

guidelines discussed above. The list includes only those loci for which progeny testing was used to increase the homogeneity of the genetic background and to verify the classification of the individual recombinant chromosomes, for we believe that this is a vital step in the location process. Synonyms and references to the original descriptions are also given.

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