The Detection of Major Genes Under Additive Continuous Variation

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THE EFFECT ϵ of a gene on a character being analyzed may be called *microphenic* if small relative to σ, the phenotypic standard deviation ($\epsilon < \sigma$), and *megaphenic* if large ($\epsilon > \sigma$). Variation due to microphenic and environmental effects will be called *continuous.* We shall avoid the term *polygene,* which in defiance of molecular biology implies a class of genes without any megaphenic effects. A *major gene* has a megaphenic effect on the given phenotype, causing variation which is in principle discontinuous and for which, therefore, segregation analysis is peculiarly appropriate (Morton, 1965). We suppose that every gene has only one primary specificity, which is unique unless made redundant by duplication, but its megaphenic and microphenic effects are multiple, the discoverable number being limited only by the patience and technique of the investigator. Therefore genes with megaphenic effects on a trait whose variation is nearly neutral with respect to fitness are not, on the average, subject to more intense selection or at different frequencies than genes with microphenic effects on the same phenotype.

We shall make one important assumption: Dominance is restricted to major genes, so that continuous variation may be treated as additive. On this assumption, two properties of continuous variation will be derived, the response to inbreeding (B) and the segregation frequency (p) for high-risk families, defined operationally by segregation analysis under any of several models which assume that, among families capable of having affected children, some families are particularly at risk (Morton, 1965). If the observed estimates of these parameters significantly exceed the values predicted for continuous variation, major genes are considered to be demonstrated. By this definition, affection dependent on multiple homozygosis with high penetrance is attributed to major genes, which in high-risk families give large values of p, while affection dependent on multiple homozygosis with low penetrance (phenodeviants) is treated as continuous.

The distinction between megaphenic and microphenic effects has become important in human genetics. On the one hand, various diseases of obscure

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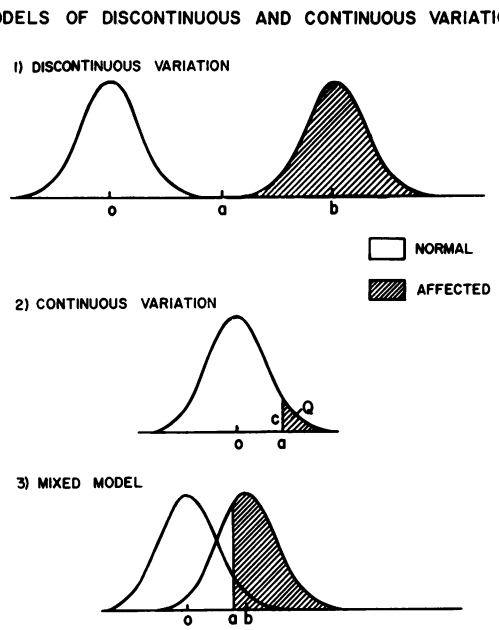

FIG. 1. Models of discontinuous and continuous variation.

etiology are attributed to the extreme deviations in a continuous distribution (Edwards, 1960; Falconer, 1965): Might it be possible, however, to isolate major genes causing a proportion of these defects? On the other hand, inbreeding effects have been attributed to rare recessive genes maintained by mutation (Morton, 1965; Crow and Kimura, 1965): Might a continuous model be more valid? This paper is concerned with methods to discriminate major genes under continuous variation, illustrated by limb-girdle muscular dystrophy, deaf-mutism, severe mental defect, malformations, and early fetal death.

THE THEORY OF ADDITIVE CONTINUOUS VARIATION

Penrose (1957) wrote: "The hypothesis of many genes, acting separately or together to produce a threshold, is extremely plausible but unattractive because it lacks precision." Recent developments in the theory of additive continuous variation have made this hypothesis more attractive.

With Falconer (1965), let *liability* denote a continuous phenotypic scale underlying affection, such that individuals with liability greater than a are affected and those with smaller liability are normal. Then a will be called the *threshold* for affection. Three situations are of interest (Fig. 1). In case 1, major genes with complete penetrance create a distribution with mean $b > a$ which does not overlap the distribution of normal genotypes. In case 2, no major gene may be discerned, but the extreme of a unimodal distribution is affected. Contributory genetic factors may be large in number, but each is of small effect. Case 3 is a mixed model, with major genes of incomplete penetrance creating a high-risk distribution that broadly overlaps the dis-

tribution of low-risk genotypes. Without loss of generality we may assume that low-risk genotypes have mean liability 0 and proportion w, and we wish to test the hypothesis that $w = 1$. We suppose that both distributions are Gaussian (normal) in form and have the same variance. With the liability measured in normal deviates (t), the distribution of low-risk genotypes is

$$e^{-t^2/2}/\sqrt{2\pi}$$

and the distribution of high-risk genotypes is

$$e^{-(t-b)^2/2}/\sqrt{2\pi}$$

In the low-risk population the frequency of affection is

$$Q = \frac{1}{\sqrt{2\pi}} \int_a^\infty e^{-t^2/2} dt \tag{1}$$

which for large a may be expanded into the series

$$Q = \frac{e^{-a^2/2}}{\sqrt{2\pi}} \left\{ \frac{1}{a} + \ldots + (-1)^k \frac{1 \cdot 3 \ldots (2k-1)}{a^{2k+1}} + \ldots \right\} \tag{2}$$

(Abramowitz and Stegun, 1965, p. 932).

The theory of quantitative variation uses two more parameters. The *heritability*, h^2, is defined as the ratio of the additive genetic to the total phenotypic variance. The coefficient of relationship, R, between two individuals i and j is

$$R = \frac{\Sigma(1/2)^{n_i + n_j}(1 + F_A)}{\sqrt{(1 + F_i)(1 + F_j)}} \tag{3}$$

where F_i, F_j, F_A are the inbreeding coefficients of i, j, and a common ancestor A who is n_i generations removed from i and n_j generations from j, and the summation is over all acyclic paths through A. In man the inbreeding coefficients are usually negligible, and we may therefore take

$$R = \Sigma(1/2)^{n_i + n_j} \tag{4}$$

or ½ for sibs and parent-child pairs, ¼ for half-sibs and uncle-niece pairs, ⅛ for cousins, etc. Falconer (1960) gives an elementary treatment of these concepts.

Two theorems involving these parameters have been applied to attributes in man. Falconer (1965) showed that if Q_o, Q_r are the frequencies in the population and in relatives of probands, respectively, and if all genetic variation is additive and the relevant environment is random among families, and if the distribution of liability among relatives is to a sufficiently close approximation normal and with the same variance as in the general population,

$$h^2 = Q_o(t_o - t_r)/Rc \qquad 0 \leq h^2 \leq 1 \tag{5}$$

where t_o, t_r are the normal deviates corresponding to Q_o and Q_r, respectively, and c is the ordinate at t_o. Edwards (1960) gave the approximation

$$Q_r \simeq Q_o^d \tag{6}$$

where $d = \ln(1 + e^{-8z/\pi})/\ln 2$

and $z = \tanh^{-1} Rh^2 = \frac{1}{2} \ln \left[\frac{1 + Rh^2}{1 - Rh^2} \right] \quad 0 < Rh^2 < 1$

However, it is not necessary to use this crude estimate of Q_r, since Falconer's theorem provides the inverse solution

$$t_r = t_o - cRh^2/Q_o \tag{7}$$

The value of Q_r corresponding to t_r is the predicted risk in relatives on the microphenic hypothesis.

We need one other result from quantitative genetics (Wright, 1951, p. 343). If the contributions of genes and environmental factors are additive, the effect of an inbreeding coefficient F is to change the variance from σ^2 to $\sigma^2 (1 + h^2 F)$, which is equivalent to changing the threshold a to

$$a/\sqrt{1 + h^2F} \tag{8}$$

To apply these results, we commonly have to make two kinds of calculations: (1) given Q_o and Rh^2, compute Q_r by Edwards's and Falconer's theorems and (2) given Q_o and Q_r, compute t_o, c, t_r, and Rh^2. Since Q, a, and c are parameters used by the above theory, which is sometimes designated *quasi-continuous*, the program for the CDC 3100 computer which performs these calculations is called QUAC.

The computational methods were suggested by Dr. N. Yasuda (Abramowitz and Stegun, 1965, pp. 932–3).

COMPARISON OF THE THEOREMS OF EDWARDS AND FALCONER

Edwards (1960) remarked of his theorem that "the approximation becomes progressively less exact as the distance of the dichotomies from the centre increases." Figure 2 compares his approximation with the result of Falconer for $Rh^2 = .05, .30, .50$, and .80. Edwards's theorem overestimates Q_r by about 5% for $Rh^2 = .05$, and the relative error increases with Rh^2. For $Rh^2 = .5$ and $Q_o < .16$, Edwards provided the inequality $Q_r > \sqrt{Q_o}$, which is true but gives only a rough approximation to Q_r. We shall use Falconer's more exact solution in the remainder of this paper.

SEGREGATION ANALYSIS

Risks in relatives are best estimated by maximum likelihood segregation analysis (Morton, 1959). Many special cases and refinements have been considered (Barrai *et al.*, 1965), only the most important of which will be given here.

In sibships including at least one proband the distribution of r affected among s sibs under incomplete selection is

$$P(r) = \binom{s}{r} p^r (1 - p)^{s-r} [1 - (1 - \pi)^r] / \{1 - (1 - p\pi)^s\} \tag{9}$$

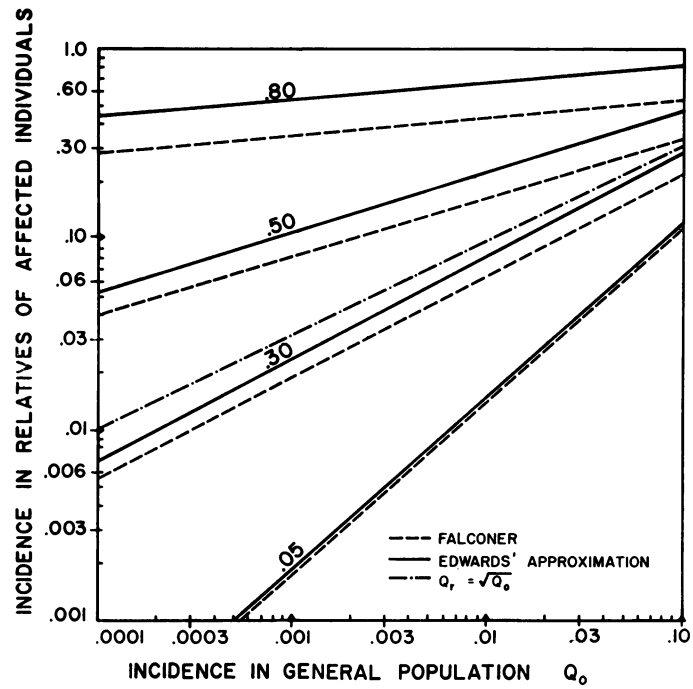

FIG. 2. Graph of incidence in relatives (Q_r) and in general population (Q_o) for Rh^2 = .05, .30, .50, and .80.

where p is the segregation frequency and π is the ascertainment probability. Under complete selection the parameter p may be estimated more efficiently from

$$P(r=0) = H + (1-H)(1-p)^s$$
$$P(r,r>0) = (1-H)\binom{s}{r}p^r(1-p)^{s-r} \qquad (10)$$

where H is the frequency of families that cannot segregate the trait in question (Morton, 1959). With H estimated from the data, p under both models has the same significance: It is an unbiased estimate of Q_r for $R = \frac{1}{2}$, the frequency of affection among sibs of affected individuals when proper allowance is made for the mode of ascertainment.

The above two equations assume that the risk in families able to segregate is uniform. More generally, there may be a group of high-risk families. For example, under incomplete selection a proportion x of cases in the population may be sporadic, with an unknown recurrence risk in sibs not much greater than Q_o. If p is now the segregation frequency for high-risk cases,

$$Q_r \simeq xQ_o + (1-x)p \qquad (11)$$

Under complete selection, a proportion w of families may have low-risk m and the remainder have high-risk p. Then $x = wm/[wm + (1-w)p]$ and

$$Q_r = \frac{wm^2 + (1-w)p^2}{wm + (1-w)p} \qquad (12)$$

Given Q_o for the general population and Q_r for sibs from segregation analysis, the theorem of Falconer permits estimation of h^2. If this significantly exceeds 1, either major genes or an important interfamily environmental variation is indicated. Estimation of Q_r for other values of R will give an additional test of the theory of continuous variation. However, a more powerful test may be provided by prediction of the segregation frequency in high-risk families. Under incomplete selection, these are defined by the condition $r > 1$ with distribution

$$P(r,r>1) = \binom{s}{r} p^r (1-p)^{s-r}[1-(1-\pi)^r]/ \{1-(1-p\pi)^s - sp\pi(1-p)^{s-1}\} \quad (13)$$

Under complete selection, the distribution for all r is

$$P(r) = \binom{s}{r}\{wm^r(1-m)^{s-r} + (1-w)p^r(1-p)^{s-r}\} \quad (14)$$

where w is the frequency of low-risk families. In either case, p estimates the risk in high-risk families (which will be an underestimate for incomplete selection unless the contribution of low-risk families to the multiplex group with $r > 1$ is negligible).

To compare p with its predicted value p^* under continuous variation, we note that the regression of relatives on an individual's phenotype goes from Rh^2 to $nRh^2/[1+(n-1)Rh^2]$ when n individuals are observed (Falconer, 1960, p. 234). Since $r > 1$ is the condition for a multiplex family, we may take $n = 2$ and $R = \frac{1}{2}$ to obtain

$$Rh^2 = h^2/\{1 + h^2/2\} \quad (15)$$

as the value to be used in applying Edwards's and Falconer's theorems to high-risk families. In so doing, we are making the greatest effort to admit a model of continuous variation, since a sibship with $r > 1$ affected members and $s - r$ normals has on the average a lower mean liability than a family chosen because both of two preassigned sibs are affected. By this simplification, we avoid the problem of the symmetrically dichotomized multivariate normal hypersurface to which Edwards (1960) referred.

INBREEDING EFFECTS

Morton (1960) derived the result

$$1 - Q = e^{-(A + BF)} \simeq 1 - A - BF \quad (16)$$

for nonaffection under inbreeding coefficient F, where A is called the panmictic load and B the inbred load. Under additive continuous variation, the predicted value of $A + BF$ corresponds to the area beyond a normal deviate $t/\sqrt{1 + h^2F}$ (8). For small F, we may use Maclaurin's series and write the deviate as

$$t + (\partial/\partial F)_o F = t(1 - h^2F/2)$$

Taking $dQ/dF \simeq B$ and retaining only the first term in (2), we find

$$B \simeq Ah^2(t^2 + 1)/2 \quad (17)$$

where t is the normal deviate corresponding to A. On this additivity assumption, the predicted value of B may be compared with observation as a test of continuous variation.

APPLICATIONS

The following five examples will illustrate the application of the method, the computations being shown in some detail in the first example. An asterisk denotes a quantity predicted from the model of additive continuous variation. The symbols used have the following meanings:

Q_o = frequency of affection in the population
t_0 = corresponding normal deviate
c = corresponding ordinate
Q_r = frequency in sibs of affected persons
t_r = corresponding normal deviate
p = frequency in high-risk sibships
h^2 = heritability
R = coefficient of relationship
B = inbred load
A = panmictic load
A' = panmictic load for high-risk cases

To test the goodness of fit of predictions from a continuous model, we need the error variances. For the prevalence Q_o, the variance is usually small (Barrai *et al.*, 1965) and sometimes unknown. The variance of Q_r from all data is generally negligible by comparison with its value for high-risk families. We shall therefore treat Q_o and Q_r as constant, and hence the derived quantities c, t, h^2, and A, which give the predicted values p^* and B^*. If p and B are estimates from the data, with standard errors σ_p and σ_B, then $(p - p^*)/\sigma_p$ and $(B - B^*)/\sigma_B$ are normal deviates testing the goodness of fit of the predictions under additive continuous variation (Table 1). Falconer (1965) gives formulae for the standard error of h^2, which are useful when two or more values are to be compared or combined.

1. *Limb-Girdle Muscular Dystrophy* (Morton and Chung, 1959)

The incidence at birth of individuals who will develop limb-girdle muscular dystrophy is $Q_o = 65 \times 10^{-6}$, from which $c = 2.64 \times 10^{-4}$, $t_o = 3.826$. Of this incidence, the proportion $1 - x = .587$ is estimated from the probability distribution underlying (11) to be due to rare recessive genes and the remainder to be sporadic, with the same risk in sibs as for the general population. Thus from (11), $Q_r = .413Q_o + .587(.25) = .147$, and the corresponding normal deviate is $t_r = 1.049$, as may be verified from appendix A of Falconer (1965). In high-risk families, the frequency at birth of individuals who will develop the disease is $p = .278 \pm .030$, which is strongly suggestive of simple recessive inheritance. With $R = \frac{1}{2}$ for sibs, heritability is estimated by Falconer's theorem (5) as

$$h^2 = 65(3.826 - 1.049)2/264 = 1.37$$

TABLE 1. TESTS OF MICROPHENIC PREDICTIONS

Trait	Risks: General population Q_o	Risks: Sibs of affected Q_r	Risks: High-risk sibships ι	Loads: A	Loads: B	Heritability h^2	Microphenic predictions: p^*	Microphenic predictions: B^*	Standard errors: σ_p	Standard errors: σ_B	Normal deviates: $p-p^*$ / σ_p	Normal deviates: $B-B^*$ / σ_B
limb-girdle muscular dystrophy	.000065	.147	.278	.000060	.0081	>1	<.131	.00047	.030	.0027	4.90	2.83
deaf-mutism	.000310	.184	.258	.000280	.080	>1	<.165	.00181	.024	.012	3.88	6.52
severe mental defect	.003088	.024	.176	.003044	.192	.50	.064	.00650	.037	.066	3.03	2.81
malformations	.0238	.060	.128	.0218	.443	.36	.104	.02003	.043	.186	0.56	2.27
fetal deaths	.0779	.121	.171	.0754	.437	.27	.164	.03084	.023	.222	0.30	1.83

This is impossibly high. At the maximal value of $Rh^2 = \frac{1}{2}$, Falconer's theorem (7) gives

$$t_r = 3.826 - (264)(.5)/65 = 1.795$$

The corresponding value of Q_r^* is .036, which is far less than Q_r. Continuing the analysis with $h^2 = 1$, we obtain $Rh^2 = 1/(1.5) = \frac{2}{3}$ for multiplex families (15), which by (7) gives $t = 3.826 - (264)(\frac{2}{3})/65 = 1.118$, and $p^* = .131$. This is significantly smaller than the observed value, with a normal deviate of

$$(.278 - .131)/.030 = 4.9 \qquad P < 10^{-6}$$

The loads by (16) were found to be $A = 60 \times 10^{-6}$ and $B = .0081 \pm .0027$. The normal deviate corresponding to A is 3.846, and so by (17) the expected value of B on the assumption of additivity is only

$$B^* = 60(3.846^2 + 1)(.5)10^{-6} = .00047 \qquad P < .003$$

These multiple inconsistencies with the microphenic hypothesis confirm the evidence for major recessive genes as the cause of familial aggregations and inbreeding effects for limb-girdle muscular dystrophy. Morton and Chung (1959) went on to estimate the number of loci (two), the mean gene frequency per locus (.0041), and the mean mutation rate per locus (3.1×10^{-5}).

2. Deaf-mutism (Chung *et al.*, 1959)

Excluding recognized acquired cases, the frequency at birth of deaf-mutes in Northern Ireland (Stevenson and Cheeseman, 1956) is $Q_o = 310 \times 10^{-6}$, and the inbreeding effects and the segregation frequencies from normal parents are as given in Table 1.

As in the previous case, the estimate of h^2 is 1.37, which is impossibly large, and so we continue with $h^2 = 1$. The value of p far exceeds its predicted value for microphenic effects ($P < 10^{-10}$), and the dominance deviation in B is presumptive evidence for major genes.

3. Severe Mental Defect (Dewey *et al.*, 1965)

Excluding mongols, hydrocephalics, and cases due to known trauma, neoplasm, or infection, the frequency at birth of severe mental defect from normal parents is $Q_o = 3088 \times 10^{-6}$, and the inbreeding effects and segregation frequencies are as given in Table 1.

By (5), the estimate of h^2 is .50, which gives $Rh^2 = .40$ for multiplex families (15). Under additive continuous variation (7), p significantly exceeds its expected value ($P < .0013$), and by (17), the inbreeding effect is too great for this model ($P < .0025$).

The inbreeding evidence against additive continuous variation is actually stronger than this. The frequency of high-risk cases in a randomly mating population is only $A' = .000324$, and all of the inbreeding effect apparently is due to this high-risk group. The corresponding normal deviate is $t = 3.41$, and so $B^* = .00164$ ($P < .002$).

4. Malformations (Mi *et al.*, 1965)

Excluding polydactyly, prehelicine fistula, and auricular appendage, the frequency of defined malformations among surviving children from normal parents is $Q_o = .0238$ in a northeastern Brazilian population. The maximum likelihood estimates by (14) are $p' = .11375$, $m = .01594$, and $w = .92476$, where $p = p' + m - p'm = .128$. The proportion of low-risk cases is $x = .605$, and the segregation frequencies and inbreeding effects are as given in Table 1.

The estimate of h^2 is .36, which gives $Rh^2 = .31$ for multiplex families. Since Q_o is relatively high, p^* is too large to be significantly different from the observed value. However, the inbreeding effect is significantly greater than expected for additive continuous variation ($P < .012$).

Again the evidence is stronger when high-risk cases are considered separately, since low-risk cases do not appear to increase with inbreeding. For high-risk cases, $A' = .0073$ and $B^* = .0156$ ($P < .011$).

5. Early Fetal Deaths (Krieger, 1966)

The same northeastern Brazilian population gives $p' = .1352$, $m = .0415$, and $w = .7193$ for early fetal deaths (less than six months gestation). Therefore, $p = .171$ and the frequency of low-risk cases is $x = .383$. The segregation frequencies and inbreeding effects are as given in Table 1.

The estimate of h^2 is .27, and $Rh^2 = .24$ for multiplex families. The estimate of p is not significantly greater than its expected value, but the inbreeding effect significantly exceeds the prediction for additive factors ($P < .034$). When high-risk cases are considered separately, $B^* = .0338$ ($P < .035$).

DISCUSSION

A generation ago, it was common for geneticists to fit monohybrid and dihybrid models to traits like skin color, weight, egg production, and extensibility of the thumbs. Such excesses of Mendelian zeal were bound to provoke an equal and opposite reaction, and it has become fashionable in recent years to attribute diseases of unknown etiology to the extreme deviations in a continuous distribution. This hypothesis is hard to disprove, and may in some cases be true, but the supporting evidence is entirely negative. That no major gene producing pyloric stenosis has yet been demonstrated does not establish the nonexistence of a major gene with this effect, nor does it justify relaxation of effort to identify major genes. One is reminded of serum cholinesterase, which shows a normal distribution of activity, yet more precise biochemical techniques have isolated two major loci responsible for much of the variation (Harris *et al.*, 1963). As more powerful methods are used to detect major genes, less of normal variation will be assumed continuous.

Sex-influenced incidence is equally consistent with continuous variation or a major genetic determinant with sex-modified penetrance (Fig. 3). Only segregation and inbreeding analysis can distinguish these two possibilities. It is unfortunate that data claimed to support continuous variation have not been published in sufficient detail to permit segregation analysis.

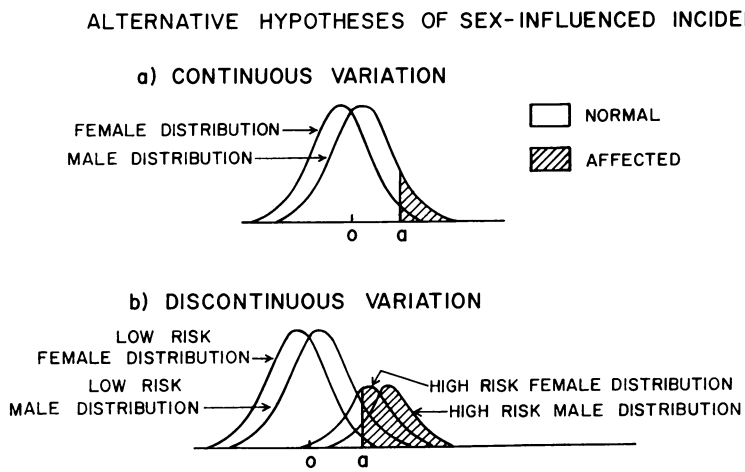

FIG. 3. Alternative hypotheses of sex-influenced incidence.

The assumption that microphenic effects are additive is not contradicted by any evidence and is required to give precision to the continuity hypothesis. Without this restriction, it seems impossible to argue convincingly for or against major genes except in the extreme case of patent discontinuity. This has been clearly recognized by Newcombe (1964) and Falconer (1965).

The discrimination of major genes is favored by a low population incidence Q_0, a large inbreeding effect, and a high segregation frequency undisturbed by incomplete penetrance or selective mortality before the age of examination. Limb-girdle muscular dystrophy, deaf-mutism, and severe mental defect meet these conditions. Malformations as defined are less satisfactory because of the relatively high incidence Q_0 and the reduced segregation frequency, due in large part to mortality before the age of examination. Fetal deaths are least suitable because of the high population incidence, coupled with incomplete ascertainment of early deaths.

The methods of this paper are quite general. Thus affection may be defined on a quantitative, graded, or discrete variable, such as "at least two standard deviates below the mean," "reaction ++ or greater," or "with a count of N or more." Also truncation may be low ("less than y"), high ("greater than Y") or double ("less than y *or* greater than Y"), all of these being mappable as $t > a$ on the liability scale.

SUMMARY

Some consequences of additive continuous variation for recurrence risks and inbreeding effects are derived, using the concept of high-risk families defined operationally by segregation analysis. Limb-girdle muscular dystrophy, deaf-mutism, severe mental defect, malformations, and fetal deaths all give evidence of segregation of major genes, the evidence being strongest with a low population incidence, a large inbreeding effect, and a high recurrence risk. When these favorable conditions are lacking, it may be impossible to detect major genes. This does not constitute proof that the distribution of liability

is continuous or all relevant genes of small additive effect, these auxiliary hypotheses serving merely to provide a defined alternative to major genes and to predict recurrence risks in relatives for traits of unknown etiology.

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