An introduction to quantitative genetics

1. What is the genetic architecture and molecular basis of phenotypic variation in natural populations?

2. Why is there phenotypic variation in natural populations?

Types of traits

Monogenic traits (rare)
- discrete binary characters
- but modified by genetic and environmental background

Polygenic traits (common)
- discrete (bristle number) or continuous (height) or binary (disease)
- binary traits with a polygenic basis are often described by a threshold model

History and origins of quantitative genetics

“Finally, that from the uninterrupted concurrence of these causes or from these laws of nature, together with much time and with an almost inconceivable diversity of influential circumstance, organic beings of all the orders have been successively formed.”

1802 in Recherches sur l’Organisation des Corps Vivans

Pangenesis

“The hypothesis of Pangenesis, as applied to the several great classes of facts just discussed, no doubt is extremely complex, but so are the facts. The chief assumption is that all of the units of the body, besides having the universally admitted power of growing by self-division, throw off minute gemmules which are dispersed through the system. Nor can this assumption be considered as too bold, for we know from the cases of graft hybridization that formative matter of some kind is present in the tissues of plants, which is capable of combining with that included in another individual, and of reproducing every unit of the whole organism. But we have further to assume that the gemmules grow, multiply, and aggregate themselves into buds and the sexual elements; their development depending on their union with other nascent cells or units. They are also believed to be capable of transmission in a dormant state, like seeds in the ground, to successive generations.”

1869 in The Variation of Animals and Plants Under Domestication

1869 Hereditary Genius: An Inquiry into its Laws and Consequences.

"The Twins have a special claim upon our attention; it is, that their history affords means of distinguishing between the effects of tendencies received at birth, and of those that were imposed by the special circumstances of their after lives; in other words, between the effects of nature and nurture."


"The famous Galtonian law of regression and its corollaries elaborated by Pearson pretended to have established the laws of "ancestral influences" in mathematical terms. Now, by the pure-line explanation of the well known action of selection in poly genotypic populations, theso laws of correlation have been put in their right place: such interesting products of mathematical genius may be social statistics in optics forms, but they have nothing at all to do with genetics or general biology. "Their premises are inadequate for insight into the nature of heredity."

Heritability – the proportion of phenotypic variation that is attributable to genotypic variation

- Phenotype (P) = Genotype (G) + Environment (E)
- Var(P) = Var(G) + Var(E) + Cov(G,E)
- Broad-sense Heritability ($H^2$) = Var(G) / Var(P)
- Broad-sense heritability includes additive, dominance, epistatic variation along with maternal and paternal effects.
- Genetic (G) = Additive (A) + Dominance (D) + Interactions (I)
- Var(G) = Var(A) + Var(D) + Var(I)
- Narrow-sense heritability ($h^2$) = Var(A) / Var(P)

Estimating Heritability

Analysis of variance or regression (correlation)

$H^2 = r / b$
- $r$ = the correlation coefficient or Cov(X,Y) / Var(Y)
- $b$ = the coefficient of reanalysis or the probability that at a random locus, the alleles there will be identical by descent.

What is the heritability if the correlation between brothers is 50%? What if the correlation is >50%?

Heritability from Twins

For comparison of monozygotic (MZ) and dizygotic (DZ) twins:

$\tau_A = A + C$
$\tau_D = 0.5 * A + C$
$A = 2(\tau_M - \tau_D)$
$C = \tau_D - \tau_A$
$E = 1 - \tau_M$

Where the components of variance are A for additive, C for common environment and E for unique environment.

What explains heritable variation in natural populations?

- Mutation and genetic drift
- Mutation-selection balance
What explains heritable variation in natural populations?

Mutation and genetic drift
Lynch and Hu (1986)

10Nṁ < Var(.tm) < 4Nṁ

N = effective population size

V(m) = the new variance from mutation added to the population every generation

Mutation-selection balance

Figure 4. Expected equilibrium level of broad-sense heritability for a neutral character as a function of the effective population size (N) under the assumption that \( V_m = 10^{-6}, 10^{-7}, \) or \( 10^{-8}. \)

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Mutation-selection balance

Mutation increases Var(G)
Selection decreases Var(G)
S = selection differential and R = selection response
Var(G) = \( \text{Var}(4Nv(m)Var) \) for mutations of small effect
Var(G) = \( \text{Var}(4Nv(m) \text{Var}) \) for mutations of large effect

Var(m) = variance in the fitness function

Estimating the mutation rate for monogenic traits

“\( \mu \) be the proportion of haemophilic males in the population, and \( f \) their effective fertility, that is to say their chance, compared with a normal male, of producing offspring, the ratio of the haemophilic males to nonhaemophilic males being given as 1:2 \( \mu \). Hence we have only to consider the frequency of haemophilia in males to arrive at the approximate mutation rate.”


AA = 1, Aa = \( \alpha \), aa = \( \alpha \), \( \alpha = \) mutation rate from A to a, then

The equilibrium frequency: \( q = \alpha / (2\mu) \)

If \( \mu Aa \equiv 2\mu, q = u/\alpha \)

Estimating the mutation rate for polygenic traits


Cross Scheme

15/101 lines carried a recessive lethal

Using the Popper rate of lethal mutation \( = 0.0062 \)

per second chromosome

Viability index \( (v) \)

\( v = 100 \times \left( \frac{v}{n} \right) \)

\( \frac{v}{n} = \text{total} \times \left( \frac{O}{n} - \frac{O}{n} \right) \)

Control viabilities

*Table 1*:

<table>
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<tr>
<th>Line No.</th>
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<th>Total viability index</th>
<th>Avg. viability index</th>
<th>Variability</th>
<th>Vg</th>
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*Table 1* (continued):

Average viability index: 0.81
Mutation accumulation causes a decline in viability

Figure 2.—Distribution patterns of viability indices in generations 10, 30, and 25 (25°C).

Figure 5.—Distribution patterns of viability indices in generations 15 and 25 (25°C).

Estimating mutational parameters

Assuming a linear increase in the number of mutation over time and interactions between mutations are not large the rate of polygenic mutation for viability is

\[ P \Sigma v = \tau \]

\[ (1 + \tau^2) p = \sigma_G^2 \]

\( a = \) average effect size
\( v = \) viability index
\( \sigma_G = \) among line genetic variance
\( \sigma_a = \) variance in effect size
\( p = \) average number of mutations

difference in viabilities per generations = 0.126
increase in variance per generation = 0.113

A high mutation rate for small effects

The characteristics of polygenic mutations affecting viability

<table>
<thead>
<tr>
<th>trait</th>
<th>Estimate</th>
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<tr>
<td>Number of mutations/generation (p)</td>
<td>0.0015 &lt; p</td>
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<tr>
<td>Average effect of single mutations (d)</td>
<td>( d &lt; 0.007 )</td>
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<tr>
<td>Range of ( \sigma_G )</td>
<td>( 0 &lt; \sigma_G &lt; 0.15 )</td>
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</tbody>
</table>

* Serial chromosome test.

Conclusion:
1. Mutation rate is very high, 20x that of lethals supported by frequency of mutation-free lines
2. Mutations are predominantly of small effect