Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3906–3908, August 1978
Genetics

Effect of inbreeding on IQ and mental retardation

(consanguinity/dominance/segregation analysis)

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Communicated by Sewall Wright, June 5, 1978

ABSTRACT **Both decline of IQ and increase of mental retardation are consistent with rare recessive alleles at about 325 loci. There is no suggestion of a discrepancy that might be due to polygenic dominance or confounding of consanguinity with unfavorable environment. These data indicate that the risk for mental retardation in matings of normal parents increases from 0.012 with random mating to 0.062 for first-cousin parentage but that dominance deviations are a negligible cause of family resemblance of IQ. Implications for gene frequencies, mutation rates, and radiation response are detailed.**

A number of studies indicate that IQ declines and the frequency of mental retardation increases with inbreeding. In principle, polygenes, rare recessives, or cultural factors could account for these results. Here I develop a theory for rare recessives and then test it on the available data. This leads to inferences about the role of dominance deviations in family resemblance for IQ and about risks for mental retardation in offspring of consanguineous marriages.

Theory

Suppose that cultural confounding has been eliminated by careful selection of controls or by stratification and covariance analysis, and that dominance deviations for polygenes are negligible. There is a long tradition of resistance to the second assumption, rooted in controversy between biometricians and mendelists at the beginning of the century. The mendelists won by showing that correlations of relatives could be predicted from the mendelian laws with any distribution of dominance. However, neither then nor subsequently was evidence presented that dominance deviations are important in nearly panmictic populations. In fact, critics of early quantitative genetics were quick to point out that dominance is confounded with environment common to sibs in most data sets, and that even experimental geneticists rarely randomize the environment within families. In recent years, this criticism has led to models that include both genetic and cultural inheritance (1).

Several arguments have been raised against the traditional emphasis on dominance deviations. (*i*) Detrimental genes have been shown to approach additivity as the degree of homozygous impairment increases (2, 3). (*ii*) Even quantitative effects of major genes often approximate additivity—for example, alleles distinguished by electrophoresis typically have additive effects on enzyme activity (4). (*iii*) On mathematical grounds, small effects are expected to be nearly additive (MacLaurin's theorem). (*iv*) Interaction effects (including directional dominance) that may be detectable in crosses of inbred lines are usually small within a randomly mating population at stable gene frequencies (5). Neglect of dominance deviations for polygenes is therefore a plausible hypothesis that can be tested by observations on inbreeding effects or family resemblance.

To predict these phenomena for rare recessive genes, we require six parameters (Table 1; Fig. 1). If q_i is the frequency of recessive alleles at the ith contributing locus ($i = 1, \ldots, k$), if the probability that the homozygote be affected is $s_i = s$, and if heterozygous effects are negligible, then the panmictic load is

$$A = s \sum_{i=1}^{k} q_i^2$$

and the inbred load (6) is

$$B = s \sum_{i=1}^{k} q_i(1 - q_i)$$
$$\doteq skQ.$$

This simple theory of genetic loads is all that we require to predict the effect of rare, independent, completely recessive genes on the frequency of mental retardation, because the probability of nonaffection given inbreeding coefficient F (7) is

$$S = e^{-(A+BF)}.$$

Wright (8) showed that, if genes and environment are additive, with no confounding of inbreeding and environment, then the regression of a quantitative trait on the inbreeding coefficient is

$$b = m_1 - m_0$$

in which m_t is the mean at inbreeding F_t. Under complete recessivity, this reduces to (9)

$$-b = T\sum q_i(1 - q_i)$$
$$\doteq TkQ.$$

The genetic variance is composed of parts due to additive effects, dominance, and epistasis. For completely recessive genes, the relative dominance variance (see equation 4.1.11 of ref. 10) is

$$D = T^2\sum[q_i(1 - q_i)]^2/\sigma^2$$

which reduces as $q_i \to 0$ to

$$D \doteq T^2A/\sigma^2s.$$

To estimate Q and k we use two classical results of genetic load theory (6),

$$Q \leq A/B, \text{ and}$$
$$k \geq B^2/A.$$

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Table 1. Six parameters that predict inbreeding effects and dominance deviations

Parameter	Definition
Q	Mean gene frequency per contributory locus
T	Mean displacement between homozygotes at contributory loci
k	Number of contributory loci
s	Penetrance in homozygotes
A	Frequency of specific defect due to homozygosity for rare recessive genes in a randomly mating population (the panmictic load)
σ^2	Phenotypic variance

Inbreeding effect on IQ

Four studies estimated the regression of IQ on the inbreeding coefficient after allowance for environmental effects (Table 2). Slatis and Hoene (11) took their control from married sibs, giving preference to a sister of the wife. Data were collected by interview, supplemented by Otis IQ ratings from school records. In the small sample of 159 children, there was only 1 with mental retardation (IQ = 57).

Neel *et al.* (12) studied a sample of school children in central Hirado. Consanguineous marriage was associated with high socioeconomic status, the effect of which was removed as well as possible by covariance analysis. They noted: "In Japan the pressure to remain in school for nine years is strong. Because of the absence of special school facilities on Hirado and because of a policy of maintaining peer groups, children of subnormal intelligence are simply carried along. As a result, 16 children in attendance at the two middle schools were unable to follow the instructions for the Tanaka–Binet test. Of the 1458 children for whom tests were available, six had IQs less than 50. We would judge that the 16 unable to take the test probably also had IQs less than 50." This suggests no bias against the much more numerous retardates with IQs greater than 50.

Kudo *et al.* (13) used the Tanaka–Binet test on a large sample of school children in Shizuoka, stratified by school to control socioeconomic variation. They remarked that "only a few children did not come on the appointed day."

Schull and Neel (14) examined 2111 of a preselected group of 2285 children in Hiroshima. Mental retardation was not the assigned reason for any of the 174 omissions. Consanguineous marriage was associated in this urban sample with low socioeconomic status, which was controlled as well as possible by covariance analysis.

These four studies are in remarkably good agreement ($\chi^2_3 = 0.68$). With weighting by the reciprocal of the variance of the regression coefficient, the mean (±SD) is $b = -44.0 \pm 12.3$. Because of the care taken by the various investigators, it is unlikely that this estimate is appreciably affected by confounding with environmental factors or exclusion of mentally retarded children; in populations in which consanguineous marriage is associated with higher socioeconomic status, these biases are in opposite directions.

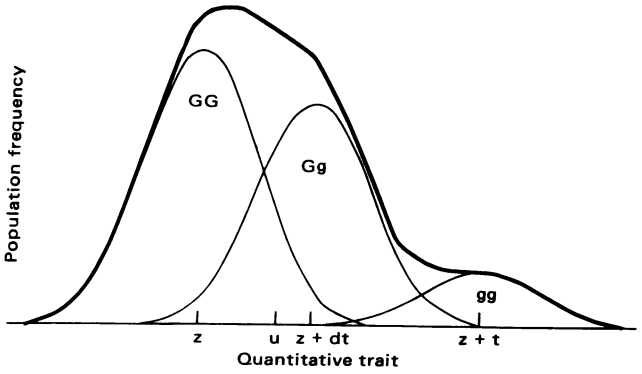

FIG. 1. The mixed model of a major locus and continuous heritable variation.

Table 2. Regression of IQ on inbreeding coefficient F

Source	Population	Regression coefficient	Weight $\times 10^4$
Slatis and Hoene (11)	U.S.	−41.6	9.9
Neel *et al.* (12)	Japan	−42.3	18.0
Kudo *et al.* (13)	Japan	−39.1	30.5
Schull and Neel (14)	Japan	−73.0	7.1

Inbreeding effect on mental retardation

Morton (6) showed how to estimate the inbred load B from probands or random samples. These methods are applied to four bodies of data in Table 3. The studies in England, Israel, and Hawaii were on probands with mental retardation (IQ < 70). The Swedish study was based on all registered marriages of first cousins in three northern Swedish parishes, each with a control family from the nearest house or farm.

Estimates of the inbred load are in close agreement ($\chi^2_3 = 0.22$). Weighted by the reciprocal of the variance, the mean (±SD) is $B = 0.792 \pm 0.069$. One implication of this fact is that risks for mental retardation (including nonrecessives) in matings of normal parents are, to a close approximation, $0.0124 + 0.792F$ (15) or 0.0124 for random mating and 0.0619 for first-cousin marriages. A recent claim of lower risk is flawed by selection bias against families with rare, recessive diseases and diagnostic exclusion of cases not proven (by unstated criteria) to be recessive (16).

Segregation analysis

The Colchester survey of 1280 cases of mental defect was submitted to complex segregation analysis, which includes random environment, environment common to sibs, polygenes, and a major locus (9). Because random mating was assumed, the recessive gene frequency estimated as 0.048 corresponds to

$$A + B\alpha = (0.048)^2$$

in which $\alpha = 406 \times 10^{-6}$ is the mean inbreeding coefficient (17). Therefore, $A = 0.002$ (15). Because the incidence of mental retardation from normal parents under random mating is 0.0124, only about one-sixth of mental retardation in matings of normal parents under panmixia is due to rare, recessive genes. From segregation analysis the mean displacement of homozygotes was estimated to be $T = 3.5\ \sigma$, in which $\sigma = 15$ is the phenotypic standard deviation of IQ. At these values, nearly all homozygotes are retarded ($s \rightarrow 1$).

Table 3. Inbred load B for mental retardation

Source	Population	Load	Weight
Penrose (22)	England	0.893	14.4
Böök (23)	Sweden	0.716	8.2
Costeff *et al.* (24)	Israel	0.790	178.5
Morton *et al.* (25)	Hawaii	0.740	8.2

Dominance deviations and numbers of loci

We are now ready to make predictions under the assumption that inbreeding effects on IQ and mental retardation are entirely due to rare recessive genes. The estimate of the relative dominance variance is

$$D = T^2A/\sigma^2s \doteq (3.5)^2(0.002) = 0.0245.$$

Heterozygous effects with dominance d would multiply this by $(1 - 2d)^2$ (equation 4.1.11 in ref. 10). Therefore, the contribution of rare recessives to dominance deviations is clearly negligible. The additive effects in proportion $2q$ are even smaller. From the increase in mental retardation with inbreeding, the mean recessive gene frequency is

$$Q \leq A/B = (0.002)/(0.792) = 0.0025$$

and the number of contributing loci is

$$k \geq B^2/A = 0.792^2/0.002 = 314.$$

This may be compared with the estimate of k from the depression of IQ with inbreeding

$$k \geq -b/TQ = 44/(3.5)(15)(0.0025)$$
$$\geq 335.$$

We could hardly ask for better agreement, which supports the assumption that the decline of IQ with inbreeding is due entirely to rare, recessive genes.

Mutational load

The evidence is also consistent with the mutation load hypothesis (7), according to which the rare, recessive genes revealed by inbreeding are maintained by recurrent mutation. On this hypothesis the mean mutation rate per contributing locus is $u = zQ$, in which z, the reciprocal of the harmonic mean persistence, is estimated to be about 0.01 (18). Therefore $u = 2 \times 10^{-5}$ per contributory locus per generation, in good agreement with other evidence. The corresponding gametic estimate is $u = 0.01$ $B = 0.008$ per gamete per generation. Therefore in a random group of 100 individuals there is expected to be 1.6 new mutants which if homozygous could cause mental retardation. Distributed over a protein with 500 codons, this corresponds to $(2 \times 10^{-5})/(500) = 4 \times 10^{-8}$ per codon per generation. If there are 10,000 structural loci at which sublethal mutation can occur, this is equivalent to 0.2 per gamete per generation. Finally, if the induced mutation rate to detrimental marker phenotypes is 2.6×10^{-7} per locus per acute rad (19), the doubling dose for acute radiation should be $(2 \times 10^{-5})/(2.6 \times 10^{-7}) = 77$ rad (0.77 Gg). The estimates could easily be in error by a factor of 2 or even 4, but they illustrate the variety of falsifiable predictions generated by a simple model.

Discussion

Although the evidence indicates that dominance deviations are negligible for IQ, they permit substantial additive variability if there is polymorphism at the contributory loci. For 325 loci and a polymorphic gene frequency of 0.5, the relative additive variance (heritability) is $325t^2/8 = 41t^2$, in which t is the displacement between homozygotes in units of the phenotypic standard deviation. For t as small as 0.1, the heritability would be 0.41; it would be greater if polygenes also occur at other loci that do not produce mental retardation. A recent estimate of heritability from correlations of relatives and their environmental indices was 0.69 in children and 0.30 in adults, with no evidence for dominance deviations (20).

These results suggest that IQ has not been subject to intense or prolonged directional selection. It is widely believed, on scanty evidence, that selection in the recent past has been stabilizing, with the greatest fitness near the mean (21). Although group selection might have been directional, there is no reason to suppose that intrapopulational selection ever conferred the greatest fitness on individuals with extremely high IQ, either during the historical period when brilliance was rewarded by celibacy or in the prehistory when reproductive fitness may have been little related to what we now measure as IQ. The persistence of much additive heritability is no more surprising for IQ than for height or finger-ridge count.

Although such speculations are of some interest, they share with the rest of evolutionary biology the difficulty of not being readily tested. Of more moment is the fact that simultaneous estimation of inbreeding effects on the mean of a quantitative trait and on the frequency of extreme deviants, here illustrated for IQ and mental retardation, can give unique information about the causes of inbreeding depression and its implications for family resemblance.

Population Genetics Laboratory paper no. 181. This work was supported by grant GM 17173 from the U.S. National Institutes of Health.

1. Rao, D. C., Morton, N. E. & Yee, S. (1976) *Am. J. Hum. Genet.* **28**, 228–242.
2. Morton, N. E., Miki, C. & Yee, S. (1968) *Am. J. Hum. Genet.* **20**, 411–419.
3. Crow, J. F. (1977) *Genetics*, in press.
4. Harris, H. (1975) *The Principles of Human Biochemical Genetics* (Elsevier, New York), pp. 138–140.
5. Wright, S. (1952) *Genetics* **37**, 313–321.
6. Morton, N. E. (1960) *Am. J. Hum. Genet.* **12**, 348–364.
7. Morton, N. E., Crow, J. F. & Muller, H. J. (1956) *Proc. Natl. Acad. Sci. USA* **42**, 855–863.
8. Wright, S. (1951) *Ann. Eugen.* **15**, 323–354.
9. Morton, N. E. & MacLean, C. J. (1974) *Am. J. Hum. Genet.* **26**, 489–503.
10. Crow. J. F. & Kimura, M. (1970) *An Introduction to Population Genetics Theory* (Harper & Row, New York).
11. Slatis, H. M. & Hoene, R. E. (1961) *Am. J. Hum. Genet.* **13**, 28–31.
12. Neel, J. V., Schull, W. J., Yamamoto, M., Uchida, S., Yanase, T. & Fujiki, N. (1970) *Am. J. Hum. Genet.* **22**, 263–286.
13. Kudo, A., Ito, K. & Tanaka, K. (1972) *Jpn. J. Human Genet.* **17**, 231–248.
14. Schull, W. J. & Neel, J. V. (1965) *The Effects of Inbreeding on Japanese Children* (Harper & Row, New York).
15. Morton, N. E., Rao, D. C., MacLean, C. J., Bart, R. C., Lang-Brown, H. & Lew, R. (1977) *J. Med. Genet.* **14**, 1–9.
16. Fraser, F. C. & Biddle, C. J. (1976) *Am. J. Hum. Genet.* **28**, 522–526.
17. Bell, J. (1940) *Ann. Eugen.* **10**, 370–391.
18. Dewey, W. J., Barrai, I., Morton, N. E. & Mi, M. P. (1965) *Am. J. Hum. Genet.* **17**, 237–256.
19. Abrahamson, S., Bender, M. A., Conger, A. D. & Wolff, S. (1973) *Nature* **245**, 460–462.
20. Rao, D. C. & Morton, N. E. (1978) in *Genetic Epidemiology* (Academic Press, New York), pp. 145–172.
21. Penrose, L. S. (1955) *Proc. R. Soc. B.* **144**, 203–213.
22. Penrose, L. S. (1938) *J. Ment. Sci.* **84**, 693–707.
23. Böök, J. A. (1957) *Ann. Hum. Genet. (Lond.)* **21**, 191.
24. Costeff, H., Cohen, B. E., Weller, L. & Rahman, D. (1977) *Am. J. Hum. Genet.* **29**, 339–349.
25. Morton, N. E., Matsuura, J., Bart, R. & Lew, R. (1978) *Clin. Genet.*, in press.