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Associative overdominance caused by linked detrimental mutations*

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SUMMARY

Associative overdominance due to linked detrimental mutations was investigated using the method of moment equations based on diffusion models. The expectation of the apparent selective value at the marker (neutral) locus has been evaluated. Assume two linked loci, at one of which the steady flux equilibrium is reached under constant mutational input of deleterious mutations (with rate v) having disadvantages hs in heterozygote and s in homozygotes. At another locus, the neutral alleles are segregating with frequencies near 0·5. Let N_e be the effective size of the population and c be the recombination fraction between the two loci. Then the coefficient of associative overdominance at the neutral locus can be obtained by taking the expectation with respect to chromosome frequencies at steady flux equilibrium. It becomes approximately

$$s' \approx \frac{L_I - L_0}{2N_e(c+hs)+c/2hs},$$

where $(L_I - L_0)$ is the inbreeding depression caused by deleterious mutations under complete inbreeding, and $N_e hs \gg 1$ and $hs \gg v$ are assumed. More generally, if the inbreeding depression of a chromosome segment with a length of recombination fraction C is $(L_I - L_0)$ then s' at the neutral marker at the edge of the segment is

$$s' \approx \frac{L_I - L_0}{2N_e C} \log \frac{C+hs}{hs},$$

where hs is the average heterozygote disadvantage of detrimentals.

The significance of the associative overdominance is discussed in relation to actual observations. It is proposed that the most of the observed heterozygote superiority including inversion chromosomes of *Drosophila*, isozyme alleles in *Avena* and ABO blood group genes in man could be explained by the associated detrimentals.

1. INTRODUCTION

In previous reports (Ohta & Kimura, 1970, 1971*b*; Ohta, 1971) we have shown that both in experimental and natural populations the behaviour of neutral alleles is significantly influenced by linked overdominant loci. Namely, apparent

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overdominance appears at the neutral locus. Such associative overdominance is caused by linkage disequilibrium between the marker (neutral) and overdominant loci due to random genetic drift in finite populations.

Actually, associative overdominance will be created not only by overdominant alleles but also by deleterious alleles that are linked to neutral alleles. Considering the ubiquity of lethal and detrimental mutants, it is desirable to investigate the apparent selective force created by linked detrimental mutations. Because of short persistence of detrimentals, it is possible that non-random association of neutral alleles with detrimentals is more pronounced than with overdominant alleles. Also, in contrast to overdominant alleles, we now have fairly precise knowledge of the nature of detrimental mutations (cf. Crow, 1968).

The purpose of the present paper is to investigate the nature of associative overdominance at a neutral locus caused by linked detrimental mutations in finite populations. Also, the bearing of such associative overdominance on the investigation of polymorphism will be discussed.

2. BASIC THEORY

In order to evaluate the effect of many detrimental loci on a neutral locus, I shall investigate a model of two loci, neutral and selected. The apparent selection coefficients at the neutral locus may then be obtained by taking the expectation with respect to the selected loci that may exist at various recombination distances from the neutral locus. Let us consider a random mating diploid population of effective size N_e and two linked loci with recombination fraction c between them. We assume that at one of the loci, two neutral alleles A_1 and A_2 are segregating with respective frequencies y and $1-y$, and at the other locus, steady flux of detrimental mutations occurs with very low frequencies, equilibrium being reached under mutational input, selective elimination and random drift. To simplify the treatment, we assume that the relative change of y (frequency of the neutral allele) is negligible in comparison with rapid elimination of deleterious mutants. This assumption is realistic because each detrimentals survive a dozen or two generations before extinction, while neutral alleles which happen to reach intermediate frequencies will take an order of $2N_e$ generations until extinction or loss (Kimura & Ohta, 1969*a*, *b*). Hence we tentatively assume that y is constant.

Let x_1 be the frequency of the detrimental mutant in A_1-carrying chromosomes and let x_2 be that in the A_2-carrying ones. Further, let v be the mutation rate for detrimentals per locus. Our main problem is to evaluate the expected values, $E(x_1^2)$, $E(x_1x_2)$ and $E(x_2^2)$, since the apparent selective advantage of A_1A_2 over A_1A_1 or A_2A_2 can be expressed using these quantities. Namely, if we denote the fitnesses of these three genotypes by $W_{A_1A_1}$, $W_{A_1A_2}$ and $W_{A_2A_2}$ we have

$$\left.\begin{aligned} W_{A_1A_1} &= 1-2hsx_1-s(1-2h)x_1^2, \\ W_{A_1A_2} &= 1-hs(x_1+x_2)-s(1-2h)x_1x_2, \\ W_{A_2A_2} &= 1-2hsx_2-s(1-2h)x_2^2, \end{aligned}\right\} \tag{1}$$

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where hs and s are respectively the selection coefficients against the detrimental mutant in hetero- and homozygous conditions.

Clearly, $E(x_1) = E(x_2)$, and hence the apparent heterozygote advantages are

$$\left.\begin{aligned} E(W_{A_1A_2} - W_{A_1A_1}) &= s(1-2h)\,E(x_1^2 - x_1x_2), \\ E(W_{A_1A_2} - W_{A_2A_2}) &= s(1-2h)\,E(x_2^2 - x_1x_2). \end{aligned}\right\} \tag{2}$$

In order to derive the second moments of x_1 and x_2, we make use of the method developed by Ohta & Kimura (1969, 1971*a*). Let f be an arbitrary (continuous) function of x_1 and x_2. Then, under steady flux of mutations, we have

$$E\{L(f)\} = -\Delta_{mut}E(f), \tag{3}$$

where L is the differential operator of the Kolmogorov backward equation involved and $\Delta_{mut}E(f)$ represents the mutational input with respect to $E(f)$.

Although, in general, f in the above equation must vanish at the boundaries $x = 0$ and 1 (cf. Ohta & Kimura, 1971*a*), we need not worry about its behaviour at $x = 1$ in the present case since $x_1 \ll 1$, $x_2 \ll 1$. By way of illustration, and also for their use in subsequent development, let us obtain the first and second moments of the frequency (x) of deleterious mutant in panmictic populations. For a single variable x, the equation corresponding to (3) is

$$E\left\{\tfrac{1}{2}V_{\delta x}\frac{d^2f}{dx^2} + M_{\delta x}\frac{df}{dx}\right\} = -\Delta_{mut}E(f),$$

where

$$V_{\delta x} = x(1-x)/(2N_e) \quad \text{and} \quad M_{\delta x} = -x(1-x)\,[sh(1-2x) + sx].$$

Noting that x is practically restricted to a small range near 0, and assuming that the mutants have appreciable dominance in fitness so that $M_{\delta x}$ can be approximated by $-shx$, the equation may be sipmlified.

$$E\left\{\frac{x(1-x)}{4N_e}\frac{d^2f}{dx^2} - shx\frac{df}{dx}\right\} = -\Delta_{mut}E(f). \tag{4}$$

Letting $f = x$, we get

$$E(x) = \frac{v}{sh},$$

since $\Delta_{mut}E(x) = v$.

Next, let $f = x^2$, we get

$$E(x^2) = \frac{\hat{x}(1+4N_ev)}{4N_esh+1},$$

since $\Delta_{mut}E(x^2) = 2\hat{x}v$ where $\hat{x} = v/(sh)$. This agrees essentially with Nei (1968), whose formula is $E(x^2) = \hat{x}(1+4N_ev)/(4N_esh)$ in our notation. Actually, his formula can be obtained by neglecting $-x^2/4N_e$ in the left-hand side of equation (4).

Let us now consider the neutral and detrimental loci simultaneously. Our basic equation (3), then, contains two variables x_1 and x_2, and it can be expressed as follows;

$$\begin{aligned} E\Bigg[\frac{x_1(1-x_1)}{4N_ey}\frac{\partial^2 f}{\partial x_1^2} + \{(1-y)\,c(x_2-x_1) - shx_1\}\frac{\partial f}{\partial x_1} \\ + \frac{x_2(1-x_2)}{4N_e(1-y)}\frac{\partial^2 f}{\partial x_2^2} + \{yc(x_1-x_2) - shx_2\}\frac{\partial f}{\partial x_2}\Bigg] = -\Delta_{mut}E(f), \end{aligned} \tag{5}$$

where c is the recombination fraction between the two loci.

Now let $f = x_1$, then

$$E\{(1-y)c(x_2-x_1)-shx_1\} = -v.$$

Let $f = x_2$, then

$$E\{yc(x_1-x_2)-shx_2\} = -v.$$

Thus, we obtain $\hat{x}_1 = \hat{x}_2 = v/sh$, where $\hat{x}_1 = E(x_1)$ and $\hat{x}_2 = E(x_2)$. To obtain the second moments, we let successively $f = x_1^2$, $f = x_1x_2$ and $f = x_2^2$. First by letting $f = x_1^2$, we have,

$$E[\{1+4N_eysh+4N_ey(1-y)c\}x_1^2-4N_ey(1-y)cx_1x_2] = 2N_ey\Delta_{mut}E(x_1^2)+\hat{x}_1.$$

Next, letting $f = x_1x_2$, we have

$$E[(c+2sh)x_1x_2-ycx_1^2-(1-y)cx_2^2] = \Delta_{mut}E(x_1x_2).$$

Finally, letting $f = x_2^2$,

$$E[\{1+4N_e(1-y)sh+4N_ey(1-y)c\}x_2^2-4N_ey(1-y)cx_1x_2] = 2N_e(1-y)\Delta_{mut}E(x_2^2)+\hat{x}_2.$$

It can be shown that Δ_{mut} terms are given by

$$\Delta_{mut}E(x_1^2) = 2\hat{x}_1v, \quad \Delta_{mut}E(x_1x_2) = \hat{x}_1v+\hat{x}_2v = 2\hat{x}_1v \quad \text{and} \quad \Delta_{mut}E(x_2^2) = 2\hat{x}_2v.$$

Then, by solving the above simultaneous equations, we obtain the following formulae for the second moments,

$$E(x_1x_2) \equiv \widehat{x_1x_2} = \frac{\hat{x}_1[2vA(A+B)+yc(4N_eyv+1)(A+B)+(1-y)c(4N_e(1-y)v+1)A]}{(c+2sh)A(A+B)-4N_ey(1-y)c^2(A+By)}.$$

$$E(x_1^2) \equiv \widehat{x_1^2} = [4N_ey(1-y)c\widehat{x_1x_2}+\hat{x}_1(4N_eyv+1)]/A, \tag{6}$$

and

$$E(x_2^2) \equiv \widehat{x_2^2} = [4N_ey(1-y)c\widehat{x_1x_2}+\hat{x}_1(4N_e(1-y)v+1)]/(A+B),$$

where $A = 4N_ey(1-y)c+4N_eysh+1$ and $B = 4N_e(1-2y)sh$.

The magnitudes of associative overdominance, in terms of selection coefficients are

$$\left.\begin{aligned} s_1' &= E\{W_{A_1A_2}-W_{A_1A_1}\} = s(1-2h)\{E(x_1^2)-E(x_1x_2)\}, \\ s_2' &= E\{W_{A_1A_2}-W_{A_2A_2}\} = s(1-2h)\{E(x_2^2)-E(x_1x_2)\}. \end{aligned}\right\} \tag{7}$$

When the frequency of neutral allele is 0·5 ($y = 0{\cdot}5$), the above formulae are much simplified and we have

$$s_1' = s_2' = s(1-2h)\frac{2(hs-v)\hat{x}_1}{(c+2hs)\{1+2N_ehs(1+c/(c+2hs))\}}. \tag{8}$$

Table 1 lists values of s_1' (coefficient of associative overdominance) for various combinations of values of y, N_e and c. Note that the value of s_1', although dependent on y, changes relatively little as long as y takes an intermediate value.

When $hs \gg v$, the formula (8) giving apparent selection coefficient for A_1A_2 is simplified, and it becomes approximately,

$$s' \approx \frac{1-2h}{2h}\frac{L_0}{2N_e(c+hs)+1+c/2hs} = \frac{L_I-L_0}{2N_e(c+hs)+1+c/2hs}, \tag{9}$$

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where $L_0 = 2v$ is the mutation load under random mating and $L_I = L_0/2h$ is the inbred load such that $(L_I - L_0)$ represents an inbreeding depression caused by complete inbreeding. Note that hs is roughly the same for lethals and mildly detrimental mutants so that we may treat the numerator and the denominator of (9)

Table 1. *Associative overdominance expected by one linked deleterious locus at which steady flux equilibrium is reached by constant mutational input of detrimentals with the rate* 10^{-5}

(Selection coefficients against deleterious mutant are; $hs = 0{\cdot}01$ and $s(1-2h) = 0{\cdot}1$. First column under letter y gives the frequency of the neutral marker (A_1). Associative overdominance (s_1') is $E(W_{A_1A_2} - W_{A_1A_1})$. The value of s_2' ($= E(W_{A_1A_2} - W_{A_2A_2})$) is obtained by replacing y with $1-y$.)

	s_1' ($\times 10^{+6}$)			
y	$N_e = 10^3$, $c = 0{\cdot}01$	$N_e = 10^3$, $c = 0{\cdot}05$	$N_e = 2\times10^3$, $c = 0{\cdot}01$	$N_e = 2\times10^3$ $c = 0{\cdot}05$
0·1	10·93	3·91	5·83	2·02
0·2	5·79	1·99	3·00	1·02
0·3	3·94	1·34	2·02	0·68
0·4	2·99	1·01	1·53	0·51
0·5	2·41	0·81	1·23	0·41
0·6	2·02	0·68	1·02	0·34
0·7	1·74	0·58	0·88	0·29
0·8	1·54	0·51	0·77	0·26
0·9	1·39	0·46	0·69	0·23

as being practically independent. The formula shows that when h is small, as in lethal genes, s' is large relative to the load. Also when $c \gg hs$, s' becomes roughly

$$s' \approx \frac{L_I - L_0}{(2N_e + 1/2hs)c}. \tag{10}$$

If, $N_e hs \gg 1$,

$$s' \approx (L_I - L_0)/(2N_e c). \tag{10a}$$

If, in addition, $h \ll 1$,

$$s' \approx L_I/(2N_e c) \tag{10b}$$

since in this case $L_0 \ll L_I$.

An interesting generalization emerges if we compare the above formula with a corresponding one for associative overdominance due to linked overdominant loci. According to Ohta & Kimura (1970) and Ohta (1971), when overdominance is symmetric with heterozygote advantage s and the frequency of the neutral marker near $\frac{1}{2}$, the magnitude of apparent overdominance s' becomes approximately,

$$s' \approx \frac{s}{4N_e c} = \frac{L_I - L_0}{2N_e c}, \tag{11}$$

where L_I is the inbred load due to overdominant alleles. Comparison of the two formulae (10b) and (11) shows that the magnitude of associative overdominance is approximately given by $(L_I - L_0)/(2N_e c)$ irrespective of whether the load is mutational or segregational. It is remarkable that the same formula holds for

entirely different selective forces. It is also worth while to mention that even detrimentals on different chromosomes will contribute to associative overdominance, since the value of $1/(N_e c)$ may not always be very small for them.

3. DISCUSSION

We have obtained a simple relationship between the degree of associative overdominance (s') and inbreeding load (L_I). Now, let us consider the bearing of this result on observational facts.

We shall first estimate the expected associative overdominance in an extreme case of an inversion where recombination is almost completely suppressed ($c \approx 0$). Temin *et al.* (1969) reported that the homozygous loads on viability at F (inbreeding coefficient) $= 1$ is about 0·4 for the second or third chromosome of *Drosophila melanogaster*. In the following, homozygous load or inbreeding depression means those at $F = 1$ and we assume that the necessary parameters like N_e or homozygous load are about the same for *D. pseudoobscura* and *melanogaster*. Nei (1968) estimated the value of $N_e hs$ to be 17·63 with respect to lethal bearing third chromosome of *D. pseudoobscura* based on theoretical study on the frequency distribution of lethals in finite populations. The effective number N_e here should correspond to that of the local population. If the inversion is of same size as that used by Temin *et al.* (1969), s' becomes, using formula (9) and assuming $L_0 \ll L_I$,

$$s' \approx \frac{L_I}{2N_e hs} = \frac{0{\cdot}4}{35{\cdot}3} = 1{\cdot}1\,\%.$$

This must be a minimum estimate, since the total homozygous load should contain not only pre-adult viability but also other components of fitness such as fertility. In fact, Latter & Robertson (1962) found the homozygous load on competitive ability to be about 2·0 per genome. More recently, Sved & Ayala (1970) reported that the homozygous load found in their competition experiments amounted to 1·0 per second chromosome of *D. pseudoobscura*, after excluding lethal chromosomes. By adding lethal load, which amount to about 0·25 (Temin *et al.* 1969), the total homozygous load becomes 1·25 per second chromosome in *Drosophila*. If we assume that this is solely due to detrimental and lethal mutations, and that the inversion is of large size and effectively suppresses the recombination of the whole chromosome, s' becomes approximately

$$s' \approx \frac{1{\cdot}25}{35{\cdot}3} = 3{\cdot}5\,\%.$$

However, if the load is due to true overdominance, s' can become larger. Using the results by Ohta & Kimura (1971*b*) and assuming $N_e c \approx 1$, we get

$$s' \approx \frac{L_I}{2N_e c + 0{\cdot}5} \approx 50\,\%.$$

The relative importance of mutational and segregational loads is not known at present. Experimental results on the heterozygote advantage of inversion chromosomes (for example, see Wright & Dobzhansky, 1946) give impression that

homozygous depression is mainly due to overdominant loci. However, following consideration will show that this is not necessarily the case.

Usually, a competition experiment starts with two types of homologous chromosomes carrying different inversions. Often these chromosomes are sampled from laboratory lines established for individual markers. Unless individual lines were derived from many individuals at the start and kept as a large population, these lines are more or less inbred. In such cases, we may assume that the two lines have different alleles at other loci that are concerned with competitive ability. Then, $x_1 = 1$ and $x_2 = 0$ or $x_1 = 0$ and $x_2 = 1$ in formula (2). Therefore, inversion heterozygote will enjoy selective advantage over homozygote, as easily seen by noting $x_1^2 = 1$ or $x_2^2 = 1$ whereas $x_1 x_2 = 0$. The observed heterozygote advantage of $30 \sim 40\,\%$ (Wright & Dobzhansky, 1946) can be explained by assuming that the two experimental lines used for competition are differentiated with respect to about one-third of the total homozygous load. It is likely that this large homozygous load (1·25 per chromosome) is mainly mutational, since the expressed load (L_0) of natural populations can be much smaller than the inbreeding depression if the load is mutational whereas the expressed load is almost equal to the inbreeding depression if the load is segregational. Of course the intrinsic overdominance may still exist even if they represent only a minor fraction of homozygous load. At any rate, the above estimate of 3·5 % associative overdominance of inversion polymorphisms seems sufficient to account for most of the observational facts.

Also, by this simple mechanism of differential association of detrimentals in each chromosome by linkage, it should be possible to explain the apparent overdominance observed in some predominantly self-fertilizing plants such as *Avena barbata* studied by Marshall & Allard (1970). These authors estimated the degree of heterozygote advantage of several isozyme marker alleles in two populations, and they obtained values of around 0·5 in one population but 0·2 in the other. They also estimated the amount of outcrossing in the two populations and found that it is much lower in the population showing higher heterozygote advantage (around 0·5). Our formula (9) indicates negative correlation between s' and $N_e c$ and therefore their result can easily be explained by the association of the marker (isozyme) alleles and detrimentals. The main reason for this is that the effective recombination frequency is proportional to the amount of outcrossing. Thus it is likely that overdominance they observed is spurious and merely reflects linkage disequilibrium between the marker and detrimentals. Such overdominance is probably ineffective as a mechanism for actively maintaining isozyme polymorphisms in these predominantly self-fertilizing plants. Also, inbreeding depression in predominantly self-fertilizing plants should be mainly mutational. It is difficult to imagine the existence of a very strong intrinsic overdominance at individual locus, which is required for a polymorphism due to overdominant alleles to be stable in self-fertilizing organisms (cf. Kimura & Ohta, 1971).

Let us consider more generally the bearing of associative overdominance on the studies of experimental and natural populations. In experimental populations, marked associative overdominance may occur in the initial stage of the competition

experiment as explained above for the case of inversions. Usually, after the chromosome lines carrying each marker alleles are mixed for competition, linkage disequilibrium between the marker and detrimental loci will be broken through recombination, and therefore the associative overdominance will diminish rapidly in a few generations. Unless the marker locus is tightly linked to the detrimentals as in the case of inversion, it becomes practically negligible if the size of experimental populations is large. Asymmetric associative overdominance will appear at the initial stage when the detrimentals are fixed unevenly among marker lines. As the associative overdominance diminishes, the marker alleles will approach some intermediate frequencies. The process of change might mimic the frequency dependent selection since the seemingly strong selection for the less frequent allele appears only in the initial stage of the experiment. In fact, when the marker lines are strongly inbred, the experimental result is repeatable, giving a similar outcome of marker frequencies. Then it looks as if the measured fitness really represent those of the marker alleles themselves. An important point to note here is that although the experimental outcome is repeatable if the same inbred stocks are used, the equilibrium frequencies may differ completely from the corresponding frequencies in natural populations.

The associative overdominance may play an important role also in natural populations even without special mechanism such as inversion or selfing. Let us assume, as before, that the homozygous load per one chromosome with the length of 100 centimorgans is 1·25 as in *Drosophila*, and that this is due to 10^4 evenly distributed loci with equal effect. Then, using formula (9), the magnitude of associative overdominance at the neutral marker locus located in the middle of the chromosome becomes approximately

$$s' \approx \sum_{i=1}^{5000} \frac{2 \times 1{\cdot}25 \times 10^{-4}}{35 + 2N_e \times i \times 10^{-4}} = 4{\cdot}2 \times 10^{-3}$$

by assuming $N_e = 10^3$. This value of N_e corresponds to $N_e hs \approx 20$ when hs is about 2% as estimated for lethals (Crow & Temin, 1964) and detrimentals (Crow, 1968). So it is consistent with Nei's estimate of $N_e hs \approx 17{\cdot}5$. Moreover, detrimentals on different chromosomes will also contribute significantly to associative overdominance. With another chromosome of the same inbreeding depression, the associative overdominance will be increased approximately by

$$\frac{1{\cdot}25}{2N_e \times 0{\cdot}5} = 1{\cdot}25 \times 10^{-3}.$$

Thus, not only detrimentals on the same chromosome but also those on different chromosomes will have significant effects.

We must note that the effective population size appropriate here is that of the local population and is much smaller than the effective size of the total species. This is because the selective force involved is much larger than the migration rate and therefore the effective population number for detrimentals is determined by the local size of the population (cf. Nei, 1968). According to Dr Maruyama (1971, personal communication), this conclusion is corroborated by his extensive mathe-

matical analysis on the stepping-stone model of finite size. On the other hand, the effective population number appropriate to describe the behaviour of the neutral mutant is that of the whole species, much larger than that of the local size. The effective size of local population is also appropriate when we consider the effect of recombination. In other words, the variance of linkage disequilibrium is determined by the local population size, since the effect of recombination predominates the effect of migration. However, when we consider linkage disequilibrium between nucleotide sites within a cistron as treated by Ohta & Kimura (1971*a*), the population size of the whole species must be taken into account, since the recombination fraction is very small and the effect of migration may predominate.

Generally, if the homozygous load per chromosome segment with a length of recombination fraction C is L_I and the average heterozygote disadvantage of deleterious mutant is hs, the value of s' at the marker locus which is located at the edge of the segment becomes approximately

$$s' \approx \frac{L_I}{2N_e C} \log \frac{C+hs}{hs}. \tag{12}$$

It is assumed that the homozygous load is evenly distributed and that $h \ll 1$.

Although s' can become larger for the case of inversion chromosome or self-fertilizing plants, even 0·4% of associative overdominance as estimated above might have some influence as a stabilizing factor of segregating alleles. Much more important is the possibility that it can account for most of the experimental observations concerning heterozygote superiority. In some local populations, the effective population size might be quite small. Therefore strong associative overdominance will appear in such cases. Even the overdominance in ABO blood-group genes in human populations reported by Chung, Matsunaga & Morton (1960) and many others may be due to associated detrimentals in local populations. In primitive human societies, the local effective population size must generally be very small due to restricted matrimonial migration.

It is possible that the associative overdominance is ineffective as a mechanism for the maintenance of genetic variabilities, except for some special cases such as inversion chromosome and semi-isolated local populations. Its real importance lies in the fact that it is probably responsible for most of the observed superiority of heterozygotes.

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