Coevolution of the Major Histocompatibility Complex and the t-Complex in the Mouse. II. Modification of Response to Sharing of Histocompatibility Antigens

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ABSTRACT

Selective pressures imposed by high complementarity associations between the major histocompatibility complex (MHC) and the t-complex on a locus that modifies the expression of prezygotic and postzygotic incompatibility are investigated through the analysis of a quantitative model. Sharing of MHC antigens between mates or between mother and offspring elicits weak inhibition of conception or gestation. In the presence of high complementarity associations between the MHC and the t-complex, weak incompatibility depresses the mean fitness of the population. Nevertheless, natural selection favors the enhancement of the expression of incompatibility if the number of antigens associated with the + haplotype exceeds the number associated with the t haplotype by a sufficient margin. Under absolute linkage between the modifier locus and the t-complex, the number associated with the + haplotype need only be greater than the number associated with the t haplotype. In the absence of linkage, a twofold difference is sufficient to ensure the initial increase of modifier alleles that intensify the expression of incompatibility.

GROUPS defined with respect to complementarity among t-complex haplotypes in the mouse show a strong congruence with groups defined with respect to antigens of the major histocompatibility complex (MHC), a phenomenon which suggests that noncomplementing t haplotypes have a common origin (Hammerberg and Klein 1975; Levinson and McDevitt 1976). In fact, direct sequence comparisons within the t-complex region indicate that all known t haplotypes share a single ancestor (Silver et al. 1987). The restriction fragment patterns of MHC regions derived from different t haplotypes exhibit great similarity; in contrast, the MHC regions derived from different + haplotypes (wild-type) are as distinct from one another as they are from those derived from t haplotypes (Shin et al. 1982; Silver 1982). Interspecific comparisons of MHC regions associated with t haplotypes indicate that the restriction of t haplotypes to particular MHC antigens antedated the divergence between Mus musculus and Mus domesticus over one million years ago (Nizetic, Figueroa, and Klein 1984; Figueroa et al. 1985). Natural populations in any single locality generally harbor only one t specific MHC antigen and several common + specific antigens (Naudeau et al. 1981; Sturm, Figueroa and Klein 1982).

I analyzed a quantitative model designed to explore the effect of prezygotic and postzygotic incompatibility on the generation and maintenance of associations between the MHC and the t-complex (Uyenoyama 1989). Incompatibility is represented in the model by a weak inhibition of conception or gestation of offspring derived from sperm bearing MHC antigens in common with the mother. Recombination suppression in +/t individuals [see Silver (1985) for a review of the genetic structure of t haplotypes] permits the existence of high complementarity equilibria, which are characterized by the occurrence of certain antigens with only the t haplotype and the occurrence of the complementary set of antigens with only the + haplotype. In conjunction with rare recombination events, the expression of incompatibility can modify the relative numbers of antigens associated with each t complex haplotype by actively promoting or excluding recombinant haplotypes. My analysis indicates that the high complementarity configuration that is stable over evolutionary time under the expression of incompatibility involves a single antigen associated with the t haplotype and no more than three to five antigens associated with the + haplotype in any one population.

The purpose of the present study is to investigate the effects of high complementarity associations between the MHC and the t-complex on the evolution of incompatibility. I have proposed that the primary evolutionary function of incompatibility systems in plants and animals is to serve as a eugenic mechanism that provides a means for parents to assess offspring quality at a stage that is sufficiently early to permit investment of resources in offspring with better prospects (Uyenoyama 1988a, b, c, d). This hypothesis requires the maintenance of associations between loci that encode the antigens that elicit the incompatibility...
response and loci that influence offspring viability or fertility. Heterozygosity at antigen loci reflects general genomic heterozygosity and, in the presence of such associations, can serve as a prospective indicator of the expression of deleterious recessive alleles at correlated loci. By virtue of its close association with the t-complex, the MHC represents a prime candidate for an indicator locus of this kind. The analysis to be described addresses whether the highly specific associations observed between the MHC and the t-complex can generate selective pressures that direct the evolution of the expression of incompatibility.

A preliminary investigation of this issue indicates that intensification of the expression of incompatibility by a separate modifier locus evolves if the magnitude of the association between the antigen locus and the locus influencing viability exceeds a threshold that depends upon the level of inbreeding, the frequency of deleterious alleles at the viability locus, and the number of antigens maintained in the population (UYENOYAMA 1989). Although the construction of this model was inspired by the associations observed between the MHC and the t-complex, it did not incorporate segregation distortion, an essential feature that maintains genetic variation within the t-complex.

To address the evolution of incompatibility systems, I develop a quantitative model of a modifier of incompatibility that evolves in response to high-complementarity associations between the MHC and the t-complex. Segregation distortion at the t-complex affects transmission at both the MHC and the modifier locus, with which it may show linkage. Incompatibility appears in the model as a weak inhibition of conception or gestation of zygotes that share more than one antigen with the mother. As in the preceding study in this series (UYENOYAMA 1989), incompatibility is distinguished from viability selection by complete reproductive compensation through the replacement of zygotes terminated by incompatibility. My conclusions regarding the adaptive significance of incompatibility are based on an analysis of the fate of a rare modifier allele that causes a small change in the level of expression of incompatibility.

MODEL CONSTRUCTION

Characterization of the resident population: “Resident” refers to the population prior to the introduction of variation at the locus that modifies the expression of incompatibility. In this population, two haplotypes, the wild-type (+) and the recessive lethal (t), segregate at the t-complex. Segregation distortion favoring the t-haplotype occurs in males, with a proportion \( k (k > 1/2) \) of the viable sperm produced by +/t males bearing the t-allele. Lethal expression of the t-allele occurs in both sexes.

An arbitrary number of antigens segregate at a locus residing on the chromosome that bears the t-complex. A rearrangement of gene order on t-haplotypes completely suppresses recombination between the antigen locus and the t-complex in +/t individuals of both sexes. The absence of recombination permits the existence of high complementarity equilibria, which are characterized by the complete association of the + haplotype with a subset of the antigens (class A) and the t-haplotype with the complementary set of antigens (class B). The number of antigens that belong to class A is \( a \), and the number that belong to class B is \( b (a, b \geq 1) \).

Specification of the joint frequencies of antigen and t-complex genotypes at the high-complementarity equilibria is given in UYENOYAMA (1989).

Maternal expression of incompatibility reduces the rate at which sperm that share antigens with the mother generate offspring that complete gestation. Prior to the introduction at the new modifier allele, sperm that share antigens with the mother produce offspring at the rate \( g_1 \) (1 \( \geq g_1 \geq 0 \)) relative to compatible sperm. As in the preceding study (UYENOYAMA 1989), offspring eliminated by incompatibility through the prevention of conception or through termination are assumed to be replaced; consequently, incompatibility causes no reduction in brood size.

Introduction of a new modifier allele: A distinct locus modifies the intensity with which incompatibility is expressed. Initially the modifier locus is monomorphic, with genotype \( B_1/B_1 \) determining the gestation rate \( g_1 \). The analysis to be described begins with the introduction in low frequency of a new modifier allele \( B_2 \) that alters the gestation rate of incompatible sperm. Females bearing genotypes \( B_1/B_2 \) and \( B_3/B_2 \) express incompatibility at the rates \( g_2 \) and \( g_3 \). The intensification of the expression of incompatibility by allele \( B_2 \) is represented by setting \( g_2 \) and \( g_3 \) less than \( g_1 \), denoting a reduction in the gestation rate of incompatible sperm.

The introduction of the new modifier allele \( B_2 \) generates four haplotype classes, distinguished by the identities of the alleles held at the t-complex and the modifier locus: \( +B_1 \) (haplotype 1), \( +B_2 \) (haplotype 2), \( tB_1 \) (haplotype 3), and \( tB_2 \) (haplotype 4). Up to terms of the first order in the frequency of \( B_2 \), two common genotypes and three rare genotypes arise upon the introduction of \( B_2 \). The frequencies of the two common genotypes are denoted \( u_{11} (+B_1/+B_2) \) and \( u_{13} (+B_1/tB_1) \), in which \( u \) and \( v \) \((u = 1 - u)\) denote the frequencies of the genotypes at the t-complex (+/+ and +/t), and the subscripts the constituent haplotypes. Expressions for \( u \) and \( v \) are obtained from (10), (11), and (12) in UYENOYAMA (1989). These variables subsume variables of the form \( u_{11}/u_{12} \) and \( u_{13}/u_{14} \), in which the second set of subscripts denote the antigens carried. The frequencies of the three rare genotypes are denoted \( u_{12} (+B_1/+B_2) \), \( u_{14} (+B_1/tB_2) \), and \( u_{23} (+B_2/...
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As is the case with the common genotype, these variables represent sums over all possible antigen genotypes. Two subgroups within the genotype represented by \( u_{12}(Hom) \) must be distinguished: \( u_{12}(Hom) \) denotes the frequency of \(+B_1/+B_2\) individuals that are homozygous at the antigen locus, and \( u_{12}(Het) + B_1/+B_2\) individuals that are heterozygous at the antigen locus. Because the set of \( t\)-specific and \(+\)-specific antigens are disjoint, all \(+/t\) individuals are heterozygous at the antigen locus. The remaining possible genotypes, all of which involve two rare haplotypes (for example, \(+B_2/tB_2\)), occur in frequencies considered negligible in the first-order analysis presented in the next section.

Within sperm, the four haplotypes occur with frequencies \( x_1 (+B_1), x_2 (+B_2), x_3 (tB_1), \) and \( x_4 (tB_2) \), which sum to unity. Ignoring terms of the order of the frequencies of the rare haplotypes, the common haplotypes (\(+B_1\) and \( tB_1 \)) occur with frequencies

\[
\begin{align*}
x_1 &= 1 - ku \quad (1a) \\
x_3 &= 1 - x_1. \quad (1b)
\end{align*}
\]

The extent to which segregation distortion within the \( t\)-complex affects the transmission ratio at the modifier locus depends on the rate of recombination \( r \). If \( 1/2 \geq r \geq 0 \) between the \( t\)-complex and the modifier locus, the frequencies of haplotypes carrying \( B_2 \) are given by

\[
\begin{align*}
x_2 &= [u_{12}(Hom) + u_{12}(Het)]/2 \\
&\quad + (1 - k)(ru_{14} + (1 - r)v_{23}) \quad (2a) \\
x_4 &= k[(1 - r)v_{14} + rv_{23}] \quad (2b)
\end{align*}
\]

Symmetries in the frequencies among antigens within class A and within class B permit reduction of the linearized recursions describing changes in the rare genotypes to four variables: \( u_{12}(Hom), u_{12}(Het), v_{14}, \) and \( v_{23} \). The object of the analysis presented in the next section is to determine the conditions under which the rare modifier allele \( B_2 \) invades the resident population. The additional assumptions of weak incompatibility in the resident population (\( g_1 \) near 1) and weak selection at the modifier locus (\( g_2 \) near \( g_1 \)) are incorporated by considering terms of the order \((1 - g_1)^2, (g_1 - g_2)^3, (1 - g_1)(g_1 - g_2)\), or smaller to be negligible.

RESULTS

Absolute linkage: In the absence of recombination \((r = 0)\), the recursion for \( v_{14} \) depends only on itself (see APPENDIX 2), providing a sufficient condition for the initial increase of the modifier allele \( B_2 \):

\[
(g_1 - g_2)(a - b) > 0. \quad (3)
\]

Condition (3) indicates that modifiers that intensify the expression of incompatibility \((g_1 > g_2)\) increase when rare if the number of antigens associated with the \(+\)- haplotype exceeds the number associated with the \( t\)-haplotype \((a > b)\). This result reflects the effectiveness of \(+/t\) mothers with genotype \( B_1/B_1 \) relative to those with genotype \( B_1/B_2 \) to inhibit fertilization by the \( t\)-haplotype. Incompatibility expressed by \(+/t\) mothers inhibits fertilization of one out of \( a \) \(+\)-haplotypes and one out of \( b \) \( t\)-haplotypes; consequently, the haplotype with which fewer antigens are associated suffers greater exclusion. For \( a \) greater than \( b \), the case that applies to the house mouse, enhanced maternal discrimination against \( t\)-bearing sperm increases offspring production.

Rates of recombination large relative to the intensity of selection: To explore the effects of incomplete linkage, I assume that the rate of recombination between the modifier locus and the antigen locus is large relative to the difference between the levels of incompatibility expressed by the common \((B_1/B_1)\) and rare \((B_1/B_2)\) genotypes. This assumption entails that quantities of the form \((g_1 - g_2)/r\) are of the same order as \((g_1 - g_2)\). For recombination rates satisfying this requirement, the condition for the initial increase of modifier allele \( B_2 \) is independent of the actual value of \( r \):

\[
(g_1 - g_2)[a(2k + 1) - b[2ku(2 - 1/a) + 2k + 1]] > 0, \quad (4)
\]

in which \( u \) denotes the frequency of \(+/+\) individuals in the resident population.

Intensification of expression of incompatibility \((g_1 > g_2)\) is favored if the number of antigens association with the \( t\)-haplotype \((b)\) is sufficiently small relative to the number of antigens associated with the \(+\)-haplotype \((a)\). For large values of \( a \), for which the term involving \( 1/a \) is small, the initial increase condition depends primarily on the ratio of the numbers of class A and class B antigens \((a/b)\). The approximate threshold ratio \((R_A)\), obtained by ignoring the \( 1/a \) term in (4), is

\[
R_A = 1 + 4ku/(2k + 1). \quad (5)
\]

Figure 1 compares the approximate ratio \((R_A)\) to the actual ratios determined by setting \( a \) equal to 3 and to 5. The approximation, which assumes arbitrarily large \( a \), improves as \( a \) increases, but agrees well with the actual ratio even for \( a \) as low as 3. Discrepancies between the approximate and actual values are small relative to the ratio itself: for segregation distortion rates appropriate for the \( t\)-complex \((k > 0.9)\), a twofold difference between the numbers of antigens associated with the \(+\)-haplotype and the \( t\)-haplotype is sufficient to favor the intensification of incompatibility.
A PARTITIONING OF THE COMPONENTS OF SELECTION

By construction, the novel allele at the modifier locus itself imparts no advantage or disadvantage in fertility or viability; the selective forces that promote its invasion or exclusion derive from associations between the modifier and the t-complex. In order to elucidate the nature and effects of such associations that arise under incomplete linkage, I develop an alternative representation of the results based on an extension of the covariance method of Li (1967, 1976 Chapter 2) and Price (1970, 1972). In addition to establishing a basis for comparison of structural features of related models (Uyenoyama 1988a, b, c, d), this approach provides an equivalent expression for initial increase condition (4) in terms of two-locus measures of association.

**Measures of association**

Three measures of association between two loci emerge from the analysis. Identity disequilibrium (Cockerham and Weir 1968) denotes the difference between the probability of two-locus identity and the product of the probabilities of one-locus identity at each locus separately. I express the analogue of this measure of association in terms of genotypic frequencies as the difference between the frequency of double heterozygotes and the product of the frequencies of heterozygotes at each locus:

\[ \eta* = v_{14} + v_{23} - (u_{12} + v_{14} + v_{23}) \]

(6)

(compare (15) in Cockerham and Weir 1968; and Weir and Cockerham 1969). Variables \( v_{14} \) and \( v_{23} \) represent the two linkage configurations for double heterozygotes, \( v \) the frequency of heterozygotes at the t-complex, and \( (u_{12} + v_{14} + v_{23}) \) the frequency of heterozygotes at the modifier locus. Near the fixation of \( B_1 \) (the initial state of the population), positive \( \eta* \) indicates that the ratio of the frequencies of \(+/t\) to \(+/+\) among \( B_1/B_2 \) individuals is greater than that among \( B_1/B_1 \) individuals:

\[ (v_{14} + v_{23})/u_{12} > v/u \]

(7)

(from (6)), which implies that the new allele \( B_2 \) is associated with the \( t \)-haplotype.

The difference between the frequencies of the two linkage configurations of double heterozygotes estimates \( D_w \), a measure of within-individual disequilibrium:

\[ D_w = v_{14} - v_{23} \]

(Cockerham and Weir 1977). Under random union of gametes and Mendelian segregation, within-individual disequilibrium among newly formed zygotes is identical to gametic phase disequilibrium; however, in the model under study, segregation distortion, unequal gametic frequencies transmitted by the sexes, and the expression of incompatibility preclude this reduction. Positive \( D_w \) represents an excess of the \( tB_2 \) haplotype over the \( +B_2 \) haplotype among double heterozygotes, which implies that the new allele is associated with the \( t \)-haplotype among double heterozygotes.

For convenience, I introduce a third measure of association, gametic phase disequilibrium among sperm (\( D_s \)), which is completely determined by \( \eta* \) and \( D_w \):

\[ D_s = x_{14} - x_{23} \]

(8)

\[ = k[\eta* + D_w(1 - 2r)[u + 2v(1 - k)]]/2. \]

(9)

Positive \( D_s \) indicates that the new allele \( B_2 \) is associated with the \( t \)-haplotype among sperm.
Components of selection

Covariance between fitness and additive genotypic value: Through its association with the t-complex, the modifier locus influences the number of viable offspring produced. Let \( M_R \) denote a random variable that represents the size of broods censused subsequent to viability selection. The value of this random variable depends on the genotype of the mother at the modifier locus and any associations between the modifier locus and the t-complex. While the level of expression of incompatibility does not, by assumption, affect brood size at the end of gestation, it influences the number of offspring that survive to reproductive age by reducing the rate of formation of t/t offspring. To mothers of genotype \( B_1/B_1, B_1/B_2, \) and \( B_2/B_2 \) associate additive genotypic values \( 2\alpha_1, (\alpha_1 + \alpha_2), \) and \( 2\alpha_2. \) The average effect of substitution \( (\alpha_1 - \alpha_2) \) expresses the extent to which variation in offspring production \( (M_R) \) can be attributed to variation in genotype at the modifier locus (see APPENDIX 1).

One measure of fitness of a given genotype at the modifier locus is the relative rate of increase of individuals carrying that genotype. For example, the rate of increase of genotype \( B_1/B_2 \) is

\[
W_{12} = Wf_{12}/f_{12},
\]

in which \( f_{12} = (u_{12} + v_{14} + v_{23}) \) represents the frequency of \( B_1/B_2 \) in the present generation, \( f_{12} \) the frequency in the next generation, and \( W(W = T) \) the normalizer that ensures that the genotypic frequencies in the next generation sum to unity. Fitnesses \( W_{11} \) and \( W_{22} \), associated with genotypes \( B_1/B_1 \) and \( B_2/B_2 \), are defined in a similar way using \( f_{11} \) and \( f_{22}. \)

The covariance between fitness and additive genotypic value with respect to offspring production resolves into covariances between the maternal character of offspring production \( (M_R) \) and the additive genotypic value of offspring:

\[
\text{Cov}(AW) = E(M_R R_a) - E(M_a) E(M_R) = \text{Cov}(M_R R_a) + E(M_R) [E(R_a) - E(M_a)], \tag{11a}
\]

\[
= \text{Cov}(M_R R_a)/\text{Var}(M_a), \tag{11b}
\]

in which \( E \) denotes expectation, \( \text{Cov} \) covariance, \( R_a \) the additive genotypic value of viable offspring, and \( M_a \) the additive genotypic value of the mother (UYENOYAMA 1988a, b, c, d). The average number of offspring produced is equal to the mean fitness \( (E(M_R) = T) \).

Parent-offspring relatedness is defined in studies of kin selection and sex ratio modification as a modified regression coefficient (UYENOYAMA 1984):

\[
b_{M-R} = \text{Cov}(M_R R_a)/\text{Cov}(M_R M_a) = \text{Cov}(M_R R_a)/\text{Var}(M_a), \tag{12}
\]

in which the last equality follows from the independence of the additive and nonadditive components of variation. Parent-offspring relatedness is a measure of similarity between the genotypic distributions of parents and their offspring (see APPENDIX 1).

The second summand in (11b) represents the difference between the average genotypic values among offspring and among parents. UYENOYAMA (1988a, b, c, d) described this component as a measure of gametic selection:

\[
GS = E(M_R)[E(R_a) - E(M_a)]. \tag{13}
\]

This component expresses the effect of incompatibility on the transmission of the modifier alleles through sperm; it derives from associations between the modifier and antigen loci, which depend in turn on the rates of recombination and segregation distortion.

Positive covariance between fitness and additive genotypic value with respect to offspring production indicates that natural selection favors the modifier allele that enhances offspring production. The condition for initial increase obtained from the stability analysis (4) is equivalent to

\[
(\alpha_1 - \alpha_2)[b_{M-R} + GS/\text{Var}(M_a)] < 0 \tag{14}
\]

(compare (24) in UYENOYAMA 1988d). Condition (14) indicates that the new modifier allele increases when rare if it enhances offspring production \( (\alpha_1 - \alpha_2 < 0) \) and natural selection favors offspring production \( (\text{Cov}(AW) > 0) \), or if both conditions are reversed.

Effect of associations on the components of selection: The assumptions of weak incompatibility \( (g_1 \text{ near } 1) \) and weak selection \( (g_2 \text{ near } g_2) \) permit much simplification in the expressions for the selection components near the fixation of \( B_1 \) (see APPENDIX 1). The average effect of substitution reduces to

\[
(\alpha_1 - \alpha_2)(u_{12} + v_{14} + v_{23}) = x_3[\eta^* + (g_1 - g_2)x_1(1 - a/b)/a], \tag{15}
\]

in which \( x_1 \) and \( x_3 \) are obtained from (1). Equation 15 reflects a linearization with respect to the frequency of genotypes bearing the new modifier allele \( B_2, \) incorporating the same level of approximation used in the first-order stability analysis.

Parent-offspring relatedness reduces to

\[
b_{M-R} = 1/2 - ux_3[D_v + D_a(1 - 2r)x_3/2]/[2(1 + x_1)(\alpha_1 - \alpha_2)(u_{12} + v_{14} + v_{23})], \tag{16}
\]

in which \( u \) and \( v \) are obtained from (10). Equation 16 indicates that associations between the modifier locus and the t-complex cause parent-offspring relatedness to depart from 1/2, the value expected under neutrality. This effect arises even in the absence of linkage \( (r = 1/2) \).

These associations generate gametic selection as
at the appropriate genotypic vector

transmission through sperm of alleles at the modifier

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Equation 19 indicates that the average effect of sub-

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or, equivalently, these expressions into (14) indicates that the new

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deletious haplotypes within the t-complex.

Wild-type mother (+/+) generate fully viable off-

spring, although a fraction may carry the t-haplotype.

Mothers of genotype +/t risk producing inviable off-

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gens than the number associated with the +-haplotype

(b < a).

In the absence of recombination between the mod-

ifier of incompatibility and the t-complex (r = 0), this

condition (a > b) ensures that modifier alleles that

enhance the expression of incompatibility are favored

(see (3)). Invasion of the population by such alleles

occurs through the increase of double heterozygotes that

carry the introduced modifier allele and the t-

haplotype in repulsion phase (tB1/+B2).

For rates of recombination large relative to the

difference in the levels of expression associated with

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production (α1 - α2 < 0). Condition (18b) indicates

that negative η*, representing the association of a new

modifier causing greater expression of incompatibility

with the t-haplotype in the population as a whole as

well as among double heterozygotes (Dw from (19)), is

sufficient to ensure the invasion of the introduced

modifier allele.

DISCUSSION

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the +-haplotype. Condition (4), which is independent

of the recombination rate, provides the threshold

ratio of antigens. Figure 1 indicates that a twofold

difference in the number of antigens associated with

the +-haplotype and the t-haplotype is sufficient to
ensure the invasion of a rare modifier allele that intensifies the expression of incompatibility.

Components of selection: In the present study, the restatement of the condition for initial increase in terms of the components of selection (14) reveals that the evolution of incompatibility depends upon two factors: the effect of the modifier on offspring production \((a_1 - a_2)\) and the transmission of the modifier allele (relatedness and gametic selection). Unlike an earlier study (UyenoYama 1988d), disequilibria between the modifier locus and the t-complex cause differential exclusion of sperm bearing the two modifier alleles. Consequently, gametic selection arises, which reflects differences between the frequencies of the new modifier allele before and after transmission; further, parent-offspring relatedness with respect to the modifier locus departs from its neutral value of \(1/2\). If the analogue of identity disequilibrium \(\eta^*\) is positive, indicating that the new modifier allele is associated with the t-haplotype among two-locus genotypes within the population as a whole, then in the absence of linkage \((r = 1/2)\) gametic selection (16) disfavors the modifier allele that intensifies the expression of incompatibility, but parent-offspring relatedness \((15)\) exceeds \(1/2\). Negative \(\eta^*\), indicating an association between the new modifier allele and the t-haplotype, generates gametic selection favoring increased expression of incompatibility but depresses parent-offspring relatedness in the absence of linkage.

Comparison to natural populations: Surveys of natural populations indicate that this condition is satisfied and, in general, exceeded by a considerable margin. In any particular locality, t-haplotypes generally occur with only one antigenic haplotype (Sturm, Figueroa and Klein 1982). Nadeau et al. (1981) detected between one and four common antigens (not including the antigens known to be associated with the t-haplotype) within thirteen populations from western Europe and Egypt. The high frequencies (up to 60%) of blanks, which failed to react with the available sera, and the small sample sizes (median = 13 mice) suggest that more antigens did in fact occur with the t-haplotype in each population. The analysis described in preceding sections indicates that the conditions prevalent in natural populations favor the intensification of the expression of incompatibility by modifier loci situated virtually anywhere in the genome.

Incompatibility generates associations between the modifier locus and the t-complex even in the absence of linkage

Differential exclusion of t-complex haplotypes: The conditions favoring the enhancement of the expression of incompatibility are independent of the recombination rate, provided that the rate is large relative to the change in the level of incompatibility caused by the introduced novel allele. This finding does not imply that the selective pressures imposed on the modifier locus are independent of its associations with the MHC and the t-complex. For greater numbers of antigens associated with the + haplotype than the t-haplotype \((a > b)\), increased expression of incompatibility in +/+ mothers promotes the production of offspring derived from sperm bearing the + haplotype. Differential exclusion of sperm on the basis of the associated MHC antigens places the resident and introduced modifier alleles in different distributions of t-complex genotypes, and generates associations between the modifier locus and the t-complex with each round of offspring production.

Absence of linkage: Under free recombination between the modifier locus and the t-complex \((r = 1/2)\), a necessary condition for the initial increase of the more active modifier is that enhanced incompatibility increase offspring production \(\left(\left(a_1 - a_2\right) < 0, \text{ see (15)}\right)\). Further, the invasion of the new allele requires its transmission through those offspring. Negative genotypic linkage disequilibrium \((D_a)\), which occurs for \(a > b\) and \(g_1 > g_2\) (see (19)), implies that the modifier allele that generates greater incompatibility becomes associated with the + haplotype in double heterozygotes. If the analog of identity disequilibrium \((\eta^*, \text{ see (6)})\) is also negative, which implies that the more active modifier is associated with the + haplotype in the general population as well, then condition \((18b)\) ensures the invasion of modifier alleles that intensify the expression of incompatibility. Increased expression of incompatibility may evolve even if the more active modifier allele is associated with the t-haplotype in the population as a whole \((\eta^* positive)\), provided that this association is sufficiently weak relative to the negative association among double heterozygotes \((D_a)\).

The association of the more active modifier allele with the t-haplotype promotes transmission through +/+ mothers, which express no inhibition against t-haplotypes, but exposes the modifier allele to elimination in t/t offspring. Although the expression of incompatibility in +/+ mothers reduces the transmission of t-haplotypes through sperm to a greater extent than + haplotypes, transmission of the t-haplotype through eggs is unimpaired. In spite of the advantage of segregation distortion favoring the t-haplotype and the modifier allele with which it is associated in sperm, the disadvantage of recessive lethality discourages the initial increase of new modifier alleles that are associated with the t-haplotype.

Proximate and ultimate effects of incompatibility on offspring viability

Dependence of the mean fitness on incompatibility: In the absence of associations between the MHC and the t-complex, evolution within each complex
proceeds entirely independently of the other complex (compare LEACH, MAYO and MORRIS 1986). In contrast, high complementarity associations between the MHC and the t-complex present a supergene to the forces of evolution, which are generated through the expression of incompatibility in conjunction with viability selection. High complementarity associations cause the depression of the mean fitness of the population under the expression of weak incompatibility relative to the absence of incompatibility (UYENOYAMA 1989). The depression of mean fitness reflects an increase in the frequency of the t-haplotype maintained under the expression of incompatibility. Incompatibility favors the t-haplotype through two effects: +/+ mothers express inhibition against sperm bearing either of the two + haplotype antigens they bear, but not against antigens associated with the t-haplotype; further, +/t mothers shelter the recessive lethal by reducing the formation of t/t offspring.

Modification of the expression of incompatibility: Were the increase of the mean fitness of the population the primary evolutionary pressure to which modifiers of incompatibility respond, the finding that weak incompatibility depresses mean fitness would imply that the enhancement of incompatibility is uniformly disfavored. The analysis described in preceding sections demonstrates that it is the proximal effects of incompatibility on the production of viable offspring and on the transmission of the new modifier allele, rather than its ultimate effect on mean fitness, that directs the evolution of incompatibility. In the absence of linkage between the modifier locus and the t-complex, a necessary condition for the enhancement of incompatibility is that it cause the production of greater numbers of viable offspring. The modifier locus, which by construction does not directly influence viability or fertility, affects offspring production only through its association with the t-complex. Increased expression of incompatibility in turn transforms the selective regime that governs evolution within the t-complex, resulting ultimately in the depression of mean fitness through its effects on the transmission of the t-haplotype and on the sheltering of its lethal expression.

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APPENDIX I

Partitioning of variation

Average effect of substitution: The average effect of substitution is obtained by minimizing the dominance variance. Let \( f_{11}, f_{12}, \) and \( f_{22} \) denote the frequencies of genotypes \( B_1B_1, B_1B_2, \) and \( B_2B_2; c_1, c_2, \) and \( c \) the trait values associated with these genotypes; and \( \epsilon \) the average trait value. The dominance variance represents the mean squared deviation between the additive genotypic value associated with each genotype and its trait value centered relative to the mean:

\[
f_{11}((c_1 - \epsilon)^2 + f_{12}((c_2 - \epsilon)^2 - (\epsilon + \epsilon_2)^2 - f_{22}((c_3 - \epsilon)^2 - 2\epsilon_2)^2, \quad (A1.1)
\]

in which \( 2\epsilon_1, (\epsilon_1 + \epsilon_2), \) and \( 2\epsilon_2 \) denote the additive genotypic values of the three genotypes. Minimization of (A1.1) with respect to the \( \epsilon \) produces

\[
(\epsilon_1 - \epsilon_2) = \frac{2f_{22}(c_3 - \epsilon) + f_{12}(c_2 - \epsilon)}{(4f_{22} - f_{12})}. \quad (A1.2)
\]

in which \( f_1 = f_{11} + f_{12}/2 \) and \( f_2 = 1 - f_1. \) Expressions for \( \epsilon_1 \) and \( \epsilon_2 \) can be obtained from (A1.2) using

\[
f_1\epsilon_1 + f_2\epsilon_2 = 0. \quad (A1.3)
\]

Components of selection: In the case under study, the trait value corresponds to the number of viable offspring produced (the random variable \( M_R \)), with \( \epsilon = T. \) The relative number of viable offspring produced by \( +/- \) individuals carrying either the common or the rare genotype at the modifier locus is 1, reflecting the complete recessivity of the \( \epsilon \)-haplotype. Up to first-order terms in the frequencies of the rare genotypes, the relative number of viable offspring produced by \( +/- \) mothers among residents (\( B_1/B_1 \)) is \( V(g_1)/N_4(g_1) \), in which

\[
V(g_1) = x_1[1 + (g_1 - 1)/a] + x_2[1 + (g_1 - 1)/b]/2, \quad (A1.4)
\]

and \( N_4(g_1) \) represents the average rate at which sperm received by these mothers generate offspring that complete gestation [see (11) in UYENOYAMA (1989)]. Among heterozygotes at the modifier locus (\( B_1/B_2 \)), the relative number of viable offspring produced is \( V(g_2)/N_4(g_2) \), in which \( V(g_2) \) and \( N_4(g_2) \) are defined in a similar way to \( V(g_1) \) and \( N_4(g_1) \), but with \( g_2 \) substituted for \( g_1 \). These values, together with (A1.2), determine the average effect of substitution (15).

Parent-offspring relatedness: Relatedness between parents and their offspring (12) depends on products involving maternal trait values of the form \( (c_i - \epsilon) \) and the average additive genotypic value within broods. For example, resident \( +/- \) mothers (\( +B_1/+B_2 \)) that are homozygous at the antigen locus have maternal trait value \( (1 - T) \) and the average additive genotypic value among their offspring is

\[
2\epsilon_1 + (\epsilon_1 + \epsilon_2)g_1[1 + (g_1 - 1)/a] + x_1/N_4(g_1), \quad (A1.5)
\]

in which \( N_4(g_1) \) represents the average rate at which offspring derived from sperm received by these mothers complete gestation (UYENOYAMA 1989). For resident \( +/- \) mothers that are heterozygous at the antigen locus, the maternal trait value is \( (1 - T) \) and the average offspring additive genotypic value is given by (A1.5) with \( N_4(g_1) \) replacing \( N_4(g_1). \) The corresponding quantities for resident \( +/- \) mothers (\( +B_1/B_1 \)) are \( V(g_1)/N_4(g_1) \) for the maternal trait value and the average offspring additive genotypic value is

\[
2\epsilon_1 + (\epsilon_1 + \epsilon_2)g_1[1 + (g_1 - 1)/a] + x_1[1 + (g_1 - 1)/b]/2]/V(g_1). \quad (A1.6)
\]

Analogous quantities corresponding to the other genotypes are used in the calculation of \( \text{Cov}(M_4, R) \).

Gametic selection: The difference between the average additive genotypic value among offspring and the additive genotypic value of the mother is averaged across broods to obtain \( \text{E}(R_m) - \text{E}(M_m) \). For example, the additive genotypic value of resident mothers is \( 2\epsilon_1 \) and the average additive genotypic value among their offspring is of the form (A1.5) for \( +/- \) mothers and (A1.6) for \( +/- \) mothers.

APPENDIX 2

Evaluation of the covariance criterion

The elements of the genotypic distribution at which the covariance criterion is evaluated are obtained from the linearized stability matrix, and does not require knowledge of the dominant eigenvalue (UYENOYAMA 1988b). For example, the linearized recursion for the variable \( v_{14} \) is given by

\[
Tv_{14} = [v_{14}(1 - \tau) + v_{24}] - [1/2 + k[u(Hom)/N_4(g_1) + u(Het)/N_4(g_1)]
\]

\[
+ x_1[[1 + (g_1 - 1)/a]/N_4(g_1)
\]

\[
- [1 + (g_1 - 1)/b]/N_4(g_1)], \quad (A3.1)
\]

in which \( u(Hom) \) and \( u(Het) \) denote the frequencies of antigen homozygotes and antigen heterozygotes in the resident population; and the \( N_4(g_1) \) the average rates at which sperm generate offspring that complete gestation (see (7) in UYENOYAMA 1989). An expression for the mean fitness \( T \) is given by

\[
T = 1/2 + k[u(Hom)/N_4(g_1) + u(Het)/N_4(g_1)] \quad (A3.2)
\]

Replacement of \( v_{14} \) by \( v_{14} \) in (A3.1), using (A3.2), produces

\[
Tv_{14} = (v_{14} + v_{24})(g_1 - g_2)x_1x_2(1 - a/b)/4a, \quad (A3.3)
\]

from which (19) follows under the assumption of weak selection ((\( g_1 - g_2 \)) small).