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Overdominance and Evolution:
Beauty in the Eye of the Gene-Holder

Natural selection, usually conceived of as directional selection, diversifies species and causes speciation, yet reduces variance within populations. Overdominance, also known as balancing selection or the heterozygote advantage, is selection that favors heterozygosity within species, maintaining allelic diversity. This form of selection is thought to be rare (Freeman & Herron, 2007), and isolating the effects of heterozygosity at a single locus across a population is often difficult. Overdominance has phenotypic and genotypic effects, which are often the result of pleitrophy (Lie et. al. 2008).

The most studied and cited case of overdominace is that of the sickle-cell anemia locus in African populations where malaria outbreaks occur frequently. This case-study provides insight about the utility of overdominance in both masking harmful alleles and improving fitness. It also suggests a positive relationship between health, immunity and heterozygosity (Bunn, 2013), a relationship that has been supported by studies of parasite-host relationships (Kerstes & Wegner, 2011), geographical pressures (Loiseau, 2009; Oliver, 2008), and the major histocompatibility complex of vertebrates (Huchard et al., 2010; Lenz, 2011; Lie et al., 2008).

Sickle Cell Anemia and Malaria

The human locus 6q23 has two common alleles: A and S. SS individuals express the sickle cell genotype while AA individuals have normal red blood cells. AS individuals express the dominant A allele and have healthily functioning erythrocytes, but the masked allele S has been found to increase resistance to severe malaria, *Plasmodium falciparum,* in African populations where malaria infections are common (Bunn, 2013).

Several mechanisms and explanations for overdominance have been suggested, including the sickling of S in AS genotypes (Luzzatto, 1970) and the miRNAs that accompany the AS genotype (LaMonte, 2012). In the first mechanism, AS genotype cells sickle in presence of *Plasmodium falciparum* parasites due to an oxygen deficit induced by the single S allele (Luzzatto, 1970). The body, accustomed to healthily-shaped erythrocytes, recognizes the deformed sickle-cells and organs like the liver "sludge" out the infected cells, discarding the damaged erythrocytes as well as the parasites; the healthy

erythrocytes persist while infected cells are eliminated by the body's regulatory mechanisms; the disease is stopped while oxygen levels are sufficient to support the uninfected body. The second mechanism relies on the observation that microRNAs (miRNAs) occur more frequently in AS and SS individuals than in AA individuals (LaMonte, 2012). These miRNAs translocate into the parasites, possibly suppressing parasitic translation or triggering degradation of parasitic mRNA. The parasite dies, leaving healthy dominant-phenotype erythrocytes with AS genotypes. These two mechanisms are not mutually exclusive, and may act together to form a clear heterozygote advantage. This suggests that overdominance may be more clearly identifiable in this case because the effects of heterozygosity are multifold.

Effects of overdominance at the 6q23 locus are factors in a dynamic immune response, however, and other genetic mechanisms for malaria resistance have been suggested, indicating pleiotrophy. Genome-wide association reveals that certain alleles at human chromosome loci lq32 and 16q22.2 also increase resistance to malaria. The former inhibits parasitic growth, disrupting parasitic development by disturbing calcium cation equilibrium in erythrocyte host cells, while the latter varies the MARVEL3 protein, which creates tight junctions in endothelial cells, altering the barrier functions and inflammatory responses of endothelial tissues, and changing parasite-host contact and interaction (Timmann, 2012). This suggests that overdominance may be difficult to study because of pleitrophy, which means that other forms of inheritance and selection can act on the same phenotypes. In other cases, heterozygosity may aid in resistance, but other mechanisms may appear in homozygous individuals that decrease the relative advantage of the heterozygote's advantage.

Thus, although the AS locus is plausibly the best example of overdominance, it is nonetheless imperfect. Overdominance may be uncommon because the same selective pressure may also favor other genes that influence selection (Timmann, 2012). The multiplicity of effects of the AS allelic combination perhaps illustrates how overdominance might become the main form of selection in certain regions, as it boosts immune response, increasing host fitness (Luzzatto, 1970) while simultaneously decreasing parasitic reproduction and parasitic success (LaMonte, 2012).

While some parasite-host interactions show strong overdominance, others suggest that overdominance is possible only in limited circumstances. Chinook salmon have high levels of heterozygosity at the major histocompatibility complex (MHC) class I (Evans, 2009) and songbirds with more heterozygosity have increased fitness, both of which increase resistance to parasites (MacDougall-Shackleton, 2005). Overdominance may be a short-term, possibly frequency-dependent selective pressure most common in the MHC, since it is perhaps strongest in conditions, such as the malaria example, where there are two different pressures. In conditions, such as the bacterial infections of Chinook salmon, where there are dozens of selective parasites (Evans, 2009), heterozygote advantage is less identifiable, since two-allele inheritance and diversity is probably not enough to confer resistance to a multiplicity of parasites.

High levels of heterozygosity in *Oncorhynchus tshawytscha,* Chinook salmon, at the MHC class I when bacterial infections are widespread suggests a positive relationship between polymorphic genotypes and fitness (Evans, 2009). This may be because of widespread variation in the species of bacteria that infect the salmon while different alleles confer resistance to different strains. Whereas in the malaria example, the A allele is subject to malaria (an inter-species pressure) and S is selected on by sickle cell (an intra-organism defect), it is possible that many overdominance incidents have multiple parasitic selections (inter-species pressures), which would be consistent with the high polymorphism at MHC loci (Evans, 2009).

Overdominance may also be favored in songbird populations in which MHC heterozygotes have higher fitness due to parasites (MacDougall-Shackleton, 2005). However, these same populations have strong assortative mating and inbreeding, rarely breeding with the other genotypes. Perhaps this is a case in which heterozygotes only recently gained a selective advantage and outbreeding favoring prezygotic mechanisms have not yet evolved.

Saccharomyces cervisiae, a common yeast, has been found to display heterozygote advantage in clinical environments along with high levels of MHC polymorphism, such that there were 161 unique multilocus genotypes in a genotyping sample of 170 yeast cells (Muller, 2009). Yeast cells that result from

outcrossing, also called hybrids, may have more vigor. Additionally, heterothallism is strongly favored over homothallism, indicating a selective advantage to outbreeding and increased heterozygosity (Muller, 2009). Again, the effects of overdominance are overshadowed by the presence of inbreeding, since inbreeding reduces fitness in general.

Tribolium casteneum, the red flour beetle, was also suspected to display overdominance in its MHC, particularly conferring resistance to the parasite *Nosema whitei* (Kerstes, 2011). However, inbreeding increased development time and early mortality of *Nosema whitei*, but did not conclusively increase overall mortality. Perhaps the parasite inbreeds enough naturally that most deleterious alleles have been purged. However, as with the songbirds and yeast, even if the red flour beetle conclusively favored heterozygosity at resistance loci, the negative effect of high levels of inbreeding cannot necessarily be distinguished from the positive effect of heterozygosity (Kerstes, 2011; Muller, 2009; MacDougall-Shackleton, 2005). Nonetheless, unexplained levels of heterozygosity at MHC loci in Chinook salmon, songbirds, and yeast all suggest a long-term selective advantage for heterozygotes.

The Heterozygote Advantage and Geographical Pressures

Geographical pressures also influence overdominance. *Passer domesticus,* or the house sparrow, has large variation at MHC regions (Loiseau, 2009). Moreover, when two populations of sparrows are relatively close to one another, there is more diversity within the populations than between them. This is consistent with overdominance in response to different parasitic species (Evans, 2009), indicating that having multiple habitats has similar effects to having multiple parasites. In both multi-geographic and multi-parasitic cases, homozygosity allows parasites to attach onto organisms and transfer within a population easily. Since parasites are less likely to transfer between populations, populations can be very similar to each other, even if it is selectively advantageous for individuals in a population to be heterozygous.

Scottish water vole populations demonstrate local adaptation of the MHC through heterozygote advantage (Oliver, 2009). In specific ABS sites of water vole MHC, 43%-57% of alleles differed from the most common forms, an extremely high number for mutation-selection balance. However, the

populations also face population depression and shrinking habitats, having low diversity overall. Thus, the allelic diversity should continue to decrease due to inbreeding and genetic drift. Therefore, increased heterozygosity against these strong selective forces suggests that heterozygosity may sometimes be a strong evolutionary force for maintaining diversity.

The heterozygous advantage is perhaps more likely to evolve in populations that are exposed to stressful and variant abiotic conditions, as has been found with the sparrow and the vole. This supports the idea that heterozygous forms may provide additional protection against changing environments, allowing quicker adjustment to environmental changes (Freeman & Herron, 2007).

MHC, Overdominance, and Sexual Selection in Primates

Trends in MHC heterozygosity and MHC-dependent selection extend to primates (Lenz, 2011). If these trends were evolutionarily advantageous in the long-run, one might predict that sexual selection at the MHC complex might arise.

Computational analyses of antigen producing genes for *Plasmodium falciparum* (malaria), Hepatitis B Virus, HIV, and *Myanobacterium tuberculosis* in humans mirror the trends found in malaria (Lenz, 2011). The antigen-binding proteins encoded at these respective loci displayed higher-than-predicted levels of heterozygosity and polymorphism, suggesting that all four of these loci on the MHC may evolutionarily favor overdominance due to strong selective forces. Although no evident MHC loci in wild baboons predict sexual preference(Huchard, 2010), mating preferences in humans often align with MHC allelic diversity (Lie, 2008).

In wild baboons, *Papio ursinus*, no sexual selective tendency could be found for heterozygote genotypes on a particular MHC region (Huchard, 2010). This, however does not mean that there is not one; it simply indicates that there is not a preference at the particular locus analyzed. Additionally, *Papio ursinus* have sex-biased dispersal and group living, which might also influence sexual selection (Huchard, 2010). Also, perhaps the analyzed loci were relatively new in predicting fitness and being heterozygous at that locus has not always been advantageous. If that were the case, sexual selection may not have had time to evolve mechanisms that predict fitness.

There has, however, been evidence of disassortitive human mating in respect to the MHC, wherein females select for facial symmetry that correlates with genetic diversity at the MHC regions (Lie, 2008). Males, however, do not display particularity to MHC diversity. Both of these observations are consistent with human (and generally mammalian) sexual dimorphism, wherein males should be less choosy than females (Freeman and Herron, 2007). Females, therefore, ought to evolve choosiness for honest indicators of good genes. Since evolution is generally a long-term process, choosiness should only evolve for long-term trends, indicating that historically, symmetry has related to MHC heterozygosity. Perhaps this is why a preference based on immuno-compatibility, enhanced by visual cues, has evolved in humans. If both studies about primates are true, humans may have evolved female MHC-based selection since the speciation of a common ancestor with wild baboons.

Conclusion

The complexity of overdominance cannot be overlooked: geographic, inter-species, and intra-species consequences of genotypes all influence whether heterozygosity is favored over homozygosity. Overdominance is perhaps the result of strong and opposed selective forces (such as sickle cell anemia and malaria), but also involves population dispersal, social dynamics, and sexual selection (Huchard, 2010).

The heterozygote advantage compensates for genetic drift and maintains allelic diversity by favoring polymorphic forms of a trait. This results in deleterious alleles, such as the sickle-cell alleles, appearing in unexpectedly high frequencies, most often masked in their heterozygous form (Bunn, 2013). Additionally, strong selection for allelic diversity within a population could result in more similarity between individuals in different populations than individuals from the same population (Loiseau, 2009).

Overdominance often results from the interaction of exterior pressures and serves a key function in the coevolution of hosts and parasites, as hosts with heterozygous alleles tend to have higher resistance and parasites with heterozygous alleles tend to have higher success (Evans, 2009; Muller, 2009). The heterozygotes of both groups may have greater success because of their adaptability to other parasites

and hosts, as well as to the evolving interaction between each other. Similarly, heterozygosity is directly related to immunity and health, particularly in vertebrates and possibly yeast.

Overdominance may occur as a result of frequent adaptation in diploid species (Sellis et al., 2011), meaning that heterozygotes may have greater fitness in presence of selective pressures. This suggests that populations with higher than predicted heterozygosity may reveal historical overdominance rather than the favoring of heterozygotes by current selection pressures. Whether or not sexual selection is attuned to heterozygotes may provide more information on which traits favor overdominance historically, beyond current, observable pressures (Lie, 2008). The evolutionary significance of overdominant traits increases the difficulties in pinpointing and supporting the concept, perhaps because they are rare currently, even if not historically (Sellis et al., 2011). Moreover, pure overdominance may not exist, even at the MHC, due to pleimorphic resistance and unstudied or extinct diseases (Penn et al., 2002).

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