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Letter to the Editor

scat$^+$ Is a Selfish Gene Analogous to *Medea* of Tribolium castaneum

Peters and Barker (1993) elegantly demonstrate a curious means of inheritance of murine severe combined anemia and thrombocytopenia (Scat). Originally classified as a recessive autosomal disease with alleles *scat* (recessive) and *scat*$^+$ (dominant), it was found that if both mother and offspring are *scat* homozygous, then the progeny are unaffected. Only when the mother is heterozygous and the offspring *scat* homozygous are the disease symptoms witnessed. An interesting precedent for such a condition results from the action of a selfish gene, *Medea*, in populations of flour beetles (Tribolium castaneum).

Medea of T. castaneum is a maternal effect lethal (Beeman et al., 1992) that produces a disease that in its genetics is directly analogous to Scat. *Medea* is a nuclear gene with alleles *M* and *m*. As with Scat, the *mm* offspring of *Mm* mothers die while the heterozygous offspring survive and the offspring of *mm* mothers never show high early mortality. Similarly, the *M* gene in the offspring need not be maternally derived to permit survival of embryos in mothers containing *M*.

The spread of both *M* and *scat*$^+$ becomes transparent when they are considered as selfish genes (cf. Bull et al., 1992). Originally, all mice would have been *scat* homozygous. *scat* may well be an amorph. That is, it is not necessarily a gene that produces a required product. The same is true for the *m* allele of *Medea*. This amorphy is consistent with the viability of *scat* homozygotes developing in mothers that are also *scat* homozygotes. Consider now a mutant gene that when in a mother injects "toxin" into the fetus. Let us assume that in linkage disequilibrium with this gene is another mutant gene that when in the fetus can neutralize the toxin. This toxin–anti-toxin gene complex is *scat*$^+$.

A mother that is heterozygous for the mutant gene complex will, at the point of invasion of the gene into the population, produce equal proportions of heterozygotes and *scat* homozygotes. Owing to the action of the *scat*$^+$ toxin, the *scat/scat* embryos die. However, owing to the possession of the *scat*$^+$ anti-toxin, the *scat*$^+$*/scat* embryos survive. This differential mortality has the effect of increasing the frequency of the *scat*$^+$ gene. This could be due to the reduction in the frequency of *scat* genes due to their differential removal (this effect is most significant in small populations) and/or because $^+$/scat offspring receive more resources and/or less competitive interference than they would otherwise.

scat$^+$, like *Medea*, may spread until it is at fixation. When every individual is homozygous *scat*$^+$, no disease will be witnessed as every embryo will have the anti-toxin. Mothers may, however, be producing something (*scat*$^+$ toxin) that will be imported into the embryo but once there will be neutralized (by *scat*$^+$ anti-toxin). Redundancy of this variety is one of the fingerprints of selfish genes.

How reasonable is it to suppose that a toxin and anti-toxin may come into linkage disequilibrium? It does appear unlikely that two such genes should appear side by side. However, the very same invasion condition is necessary for other analogous selfish genetic elements, and the required linkage disequilibrium has been demonstrated in several instances (e.g., autosomal meiotic drive genes [Lyttle, 1991]). Autosomal meiotic drive genes are usually linked to the centromere (Lyttle, 1991). This is probably because the domain around the centromere has a low rate of recombination, and hence the probability that the toxin and anti-toxin genes would come into linkage disequilibrium is higher than in chromosomal domains with free recombination. It is thus significant that *scat* is very close to the centromere on chromosome 8.

The above models describe two loci, but strictly speaking this is not a requirement. If a single gene could provide both toxin and anti-toxin, then it is sufficient to invade as described above. Under this circumstance, however, linkage to the centromere may be incidental. Whether both Scat and Medea involve one or two genes at the same segregating locus could be revealed by very detailed linkage mapping.

Medea and Scat, though genetically identical, are phenomenologically slightly different. Whereas Scat progresses in phases with bouts of remission followed by bouts of disease, the effect of *Medea* is less plastic. One might conjecture that this difference may be accountable to another major difference in the two systems, namely that in mammals mother and fetus are in continual placental contact for much of early development, whereas there is no mother/offspring resource transfer in beetles, and hence the toxin must be placed in the egg prior to embryonic development.

Medea is at fixation within populations of T. castaneum, and its existence was first described because of the emergent hybrid inviability. It would be interesting to know whether *scat*$^+$ can also act as a hybrid inviability factor. Were it to do so, this would increase the roll call of analogous selfish genetic elements that are thought to be important in postzygotic isolation of species (see, e.g., Breewer and Werren, 1990; Pomiankowski and Hurst, 1993). As with postzygotic isolation, it is often assumed that disease is an unfortunate side consequence of things going wrong. This view needs some correction. Scat, like beetle embryonic mortality and like many forms of postzygotyic isolation, is no accident but the consequence of the action of gene complexes whose spread is dependent upon their deleterious effects. Some disease may be the deliberate action of a conspiracy of genes.

Laurence D. Hurst
Department of Genetics
University of Cambridge
Cambridge CB2 3JE
England

References

Beeman, R. W., Friesen, K. S., and Denell, R. E. (1992). Science *256*, 89–92.

Breeuwer, J. A. J., and Werren, J. H. (1990). Nature *346*, 558–560.

Bull, J. J., Molineux, I. J., and Werren, J. H. (1992). Science *256*, 65.

Lyttle, T. W. (1991). Annu. Rev. Genet. *25*, 511–557.

Peters, L. L., and Barker, J. E. (1993). Cell *74*, 135–142.

Pomiankowski, A., and Hurst, L. D. (1993). Genetics *133*, 425–432.