SUMMER RESEARCH PROJECT

POPULATION GENETIC ANALYSIS OF SEX LIMITED GENOMIC IMPRINTING

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Parental origin dependent gene expression has been found in many forms. Transgenic and cloned mammals showed the first clear monogenic parental origin effects, some genes were found to only express the allele of a specific parental origin (McGrath and Solter, 1984; Surani, Barton and Norris, 1984). Now at least 80 known mammalian genes have this 'genomic imprinting' that supresses the expression of the maternal or paternal allele which can be distinguished by differential methylation in the gametes (Reik and Walter, 2001). Pearce and Spencer (1992) found models of genomic imprinting could be formally equivalent to existing non-imprinting models and that imprinting introduced 'pseudoheterosis', stable polymorphic equilibrium without heterozygote advantage. In light of this novel population-genetic behaviour and hypotheses for the origin genomic imprinting involving sexual conflict (Day and Bonduriansky, 2004), models of genomic imprinting where imprinting is sex-limited could yield results with interesting implications to populations.

We extended the standard autosomal one-locus two-allele viability selection model (Hartl and Clark, 1997) in a similar manner for the sex-limited case as Pearce and Spencer (1992) had done for imprinting in both sexes. Due to distinct gene expression patterns, differential viability between the sexes was assumed and the allele frequencies of each sex independent variables. Recurrence equations were developed to model the frequency of each allele in each sex in a given generation as a function of the allele frequencies of the previous generation.

The main focus of this project was to determine the equilibrium states and the parameter values for which they are stable. This makes it possible to predict the long-term behaviour of the system and determine whether stable polymorphic equilibrium is possible. Equilibrium allele frequencies were found where the difference between the allele frequencies is zero. The equilibrium was defined to exist if for some parameter values, the allele frequency in both sexes lies within the interval 0-1 inclusive. The equilibrium was defined as locally stable if the absolute value of the eigenvalues of the Jacobian Matrix evaluated at the equilibrium is less than 1.

Several autosomal models of sex-limited imprinting were constructed and found to be formally equivalent in some cases. The models each represented a different form of gene expression in males and incomplete dominance in females. First we modeled complete maternal and paternal inactivation, which are cases of the more general monoallelic expression model. The monoallelic model can be modified for partial imprinting, in which probability of imprinting and parental origin of the inactivated allele can vary. The partial imprinting model was generalised to allow imprinted and homozygous individuals to have distinct phenotypes. The partial imprinting model was altered to construct a model in which only one allele has a probability of imprinting in males and competes with a mendelian allele. A model of differential gene expression, where each male genotype has a distinct phenotype due to imprinting, is formally equivalent to all of the above models. Further analysis considered similar behaviour at an X-chromosomal locus, independence of parameters and imprinting occurring in both sexes with differential viability.

As expected, the fixation equilibria (where one allele becomes extinct) were equilibrium states independent of all parameters in every model. A fixation equilibrium was locally stable if and only if there was sufficient selection for the appropriate allele and homozygotes of the allele are viable in both sexes. In these models, the state of the polymorphic equilibrium is dependent on the stability of the fixation equilibria. The polymorphic equilibrium was locally stable if and only if both fixation equilibria were unstable. The polymorphic equilibrium only otherwise can only exist if it is unstable when both fixation equilibria are locally stable.

Equilibrium states are important to determine whether sex-limited imprinting would be detectable today had it ever existed at low levels in an ancestral population. Since most populations have been evolving for some time, they are likely to have approached equilibrium. In order to conserve genetic variation, the polymorphic equilibrium

must be locally stable or the locus will become fixed. Population-genetic selection models predict far less genetic variation than observed in natural populations.

As found by Pearce and Spencer (1992), genomic imprinting without sex-limiting can predict stable polymorphic equilibrium without heterozygote advantage, so called 'pseudoheterosis'. Heterozygote advantage is an important but rare case in population genetics in which natural selection can preserve genetic variation. Pseudoheterosis can also occur in loci with sex-limited genomic imprinting and shows the importance in epigenetic effects as mechanisms for maintenance of genetic variation. Genomic imprinting may be selectively advantageous to control traits under sex-specific selection and increase selectively neutral variation.

The sex-limited case of genomic imprinting has some differences from imprinting in both sexes. Pearce and Spencer (1992) found that a model of maternal inactivation without differential viability between the sexes produced the same recurrence equation as a general model for paternal inactivation. In other words, if imprinting occurred in both sexes, the parental origin of the inactive allele did not affect the system. However, I found that models of maternal and paternal inactivation have distinct behaviours in the sex-limited case, a finding that is probably the most important from this study. This difference leads to the use of a generalized monoallelic expression model as the basis of sex-limited partial imprinting models.

Partial Imprinting models are particularly useful to determine whether the probability of imprinting increases could be selectively advantageous. If a partially imprinted allele competes at a locus with a mendelian allele we can test whether an imprinted allele could enter a population at a locus fixed for a mendelian allele. In order to enter the population it must be possible that, for some parameter values, the equilibrium for extinction of the imprinted allele could be unstable. The relevant model showed that a sex-limited imprinted allele could invade a population if it were introduced at low levels by mutation or migration and not eradicated by genetic drift.

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