Population-genetic models of sex-limited genomic imprinting

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HIGHLIGHTS

- Sex-limited genomic imprinting models were not formally equivalent to prior models.
- Stable equilibria differ depending on if the imprinting and imprinted sex are the same.
- Since alleles are inactivated in consecutive generations if these sexes are the same.

ABSTRACT

Genomic imprinting is a form of epigenetic modification involving parent-of-origin-dependent gene expression, usually the inactivation of one gene copy in some tissues, at least, for some part of the diploid life cycle. Occurring at a number of loci in mammals and flowering plants, this mode of non-Mendelian expression can be viewed more generally as parentally-specific differential gene expression. The effects of natural selection on genetic variation at imprinted loci have previously been examined in a several population-genetic models. Here we expand the existing one-locus, two-allele population-genetic models of viability selection with genomic imprinting to include sex-limited imprinting, i.e., imprinted expression occurring only in one sex, and differential viability between the sexes. We first consider models of complete inactivation of either parental allele and these models are subsequently generalized to incorporate differential expression. Stable polymorphic equilibrium was possible without heterozygote advantage as observed in some prior models of imprinting in both sexes. In contrast to these latter models, in the sex-limited case it was critical whether the paternally inherited or maternally inherited allele was inactivated. The parental origin of inactivated alleles had a different impact on how the population responded to the different selection pressures between the sexes. Under the same fitness parameters, imprinting in the other sex altered the number of possible equilibrium states and their stability. When the parental origin of imprinted alleles and the sex in which they are inactive differ, an allele cannot be inactivated in consecutive generations. The system dynamics became more complex with more equilibrium points emerging. Our results show that selection can interact with epigenetic factors to maintain genetic variation in previously unanticipated ways.

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Introduction

Parental origin of alleles is an important factor affecting the expression of many mammalian genes, especially genes involved in embryonic development. Genomic imprinting, the silencing of alleles of a particular parental origin at a specific locus, has been observed in approximately 100 human genes and is estimated to occur in no more than a few hundred genes (Kelsey and Bartolomei, 2012; Wilkins et al., 2016). Imprinted expression is often restricted to certain tissues (Babak et al., 2015; Baran et al., 2015; Prickett and Oakey, 2012) and recently it has been reported that both alleles are expressed but at different levels for many imprinted genes (Morcos et al., 2011; Wang and Clark, 2014). Hence, imprinting can be viewed more broadly as unequal expression of the maternally and paternally derived alleles in at least some tissues during some period of development.

While silencing or unequal expression of alleles may not immediately appear to have sufficient selective advantage to invade a population, genomic imprinting has become widespread in mammals and has arisen independently in many lineages. First observed as a disparity in phenotype between clonal mice (McGrath and Solter, 1984; Surani et al., 1984), genomic imprinting is now extensively studied at the molecular level and bioinformatics tools

are being developed to detect more imprinted loci (Reik and Walter, 2001; Wang and Clark, 2014). All known examples of imprinting affect male and female offspring equally, but the findings of Hager et al. (2008) suggest that sex-limited cases of genomic imprinting may yet be observed. Moreover, some hypotheses for the origin of genomic imprinting predict the existence of imprinted expression specific to one sex. Day and Bondurlansky (2004) postulated that sex-limited genomic imprinting could alleviate intralocus sexual conflict and account for some cases of phenotypic sexual dimorphism. Given the widespread differences in gene expression between males and females (Ellegren and Parsch, 2007), it would perhaps be surprising if some imprinted genes were not also differentially expressed in the two sexes. In this paper, we explore the population-genetic consequences of viability selection acting on loci subject to sex-limited imprinting.

The behavior of imprinted loci in population-genetic models has yielded non-intuitive results. For example, constant viability selection at imprinted loci often gives rise to allele-frequency dynamics that are identical to non-imprinted systems that differ in fundamental ways. One notable phenomenon is "pseudoheterosis", non-heterotic fitness values in imprinting systems that give rise to stable polymorphic equilibria because the allele-frequency dynamics are equivalent to non-imprinting systems that do exhibit heterozygote advantage (Pearce and Spencer, 1992). Similarly, fertility-selection models can show an analogy with genetic dominance (Anderson and Spencer, 1999). Imprintable alleles can invade a Mendelian locus (and become fixed) provided that imprinted individuals have a selective advantage over Mendelian heterozygotes (Pearce and Spencer, 1992). Modifier loci typically become fixed or extinct depending on whether they are compatible with this invasion of imprintable alleles (Spencer and Williams, 1997; van Cleve and Feldman, 2007). Pearce and Spencer (1992) showed that which parental allele is inactivated does not affect the equilibrium state reached under standard viability selection. Many models of genomic imprinting are formally equivalent to models without imprinting (Anderson and Spencer, 1999; Pearce and Spencer, 1992), but this finding does not apply when there is a sex difference in viability or ploidy, such as for the X chromosome. If sex-limited genomic imprinting occurs, differential viability between the sexes would be expected since males and females with the same genotype would manifest different phenotypes. Therefore, we would predict that existing results would not necessarily pertain to models of sex-limited imprinting, nor would these models be equivalent to those already known.

Models

Model 0A: Mendelian expression with differential viability of the sexes

In order to facilitate later comparisons with imprinting models, we first outline the standard one-locus two-allele Model with differential viability of the sexes (Bodmer, 1965; Kidwell et al., 1977; Mérat, 1969; Owen, 1953). In such a model, Owen (1953) showed multiple stable polymorphic equilibria were possible and Mérat (1969) generalized this Model to show that up to three polymorphic equilibria could exist with conflicting selection in either sex. Bodmer (1965) found that a stable polymorphic equilibrium occurs if both fixation equilibria are unstable and Kidwell et al. (1977) showed that polymorphic equilibrium was only possible with opposing directional selection in each sex or under heterozygote advantage for fitnesses averaged over the sexes. We assume a population of diploid, sexual organisms with discrete generations, random mating, constant viability fitness, and negligible genetic drift, mutation, and migration (Hartl and Clark, 1997).

We have two alleles, A_1 and A_2, with frequencies p_f and q_f, respectively, in females, and p_m and q_m, respectively, in males. The genotypes A_1A_1, A_1A_2 or A_2A_1, and A_2A_2 (in which the maternally derived allele is written first) have fitnesses f_{11}^*, f_{12}^*, and f_{22}^* respectively in females and m_{11}^*, m_{12}^*, and m_{22}^* respectively in males (where $*$ indicates a non-imprinted system for comparison with later models). All viabilities must be non-negative and we can assume they are no greater than one without loss of generality. As Kidwell et al. (1977) showed, we form the following recurrence equations for female and male allele frequencies, respectively:

$$p'_f = \frac{f_{11}^* p_f p_m + \frac{1}{2} f_{12}^* (p_m q_f + p_f q_m)}{f_{11}^* p_f p_m + f_{12}^* (p_m q_f + p_f q_m) + f_{22}^* q_f q_m} \tag{1}$$

$$p'_m = \frac{m_{11}^* p_f p_m + \frac{1}{2} m_{12}^* (p_m q_f + p_f q_m)}{m_{11}^* p_f p_m + m_{12}^* (p_m q_f + p_f q_m) + m_{22}^* q_f q_m} \tag{2}$$

This system has equilibrium allele frequencies when $p_f = p'_f - p_f = 0$ and $p_m = p'_m - p_m = 0$. The fixation equilibria, $(\hat{p}_f, \hat{p}_m) = (1, 1)$ and $(\hat{p}_f, \hat{p}_m) = (0, 0)$ exist for all parameter values, and are locally stable when the absolute value of the leading eigenvalue of the Jacobian matrix is less than 1 as described in the Appendix A: Eqs. (16) and (17). The equilibrium $(\hat{p}_f, \hat{p}_m) = (1, 1)$ is a locally stable if there is selection for A_1 in both sexes, i.e. (i) $0 \leq m_{12}^* < \frac{(2f_{11}^* - f_{12}^*) m_{11}^*}{f_{11}^*}$. Similarly, $(\hat{p}_f, \hat{p}_m) = (0, 0)$ is locally stable if there is selection for A_2 in both sexes, i.e. (ii) $0 \leq m_{12}^* < \frac{(2f_{22}^* - f_{12}^*) m_{22}^*}{f_{22}^*}$ (see also Kidwell et al., 1977; Mérat, 1969).

The equations $p_f = 0$ and $p_m = 0$ can be rearranged and one substituted into the other. The equilibria are then solutions to a quintic equation, which reduces to a cubic equation by factoring out the fixation equilibria (Kidwell et al., 1977). Therefore, up to 3 polymorphic equilibria may co-exist but, as noted by Kidwell et al. (1977), the cubic equation is difficult to analyze. Nevertheless, it is possible to show that, for certain viabilities, up to 2 polymorphic locally stable equilibria can exist. It can be shown that the polymorphic equilibrium is only possible without heterozygote advantage if the selective pressures are opposite in the different sexes (Bodmer, 1965; Kidwell et al., 1977; Mérat, 1969; Yanchukov, 2009). Selgrade and Ziehe (1987) have shown that this system has strong monotonicity and every initial state converges to equilibrium, precluding the existence of limit-cycle behavior.

Model 0B: complete paternal inactivation with differential viability of the sexes

We now present Pearce and Spencer's (1992) Model with differential viability of males and females, assuming that the paternally derived allele is completely inactivated in both sexes. Writing the maternal allele first, the genotypes A_1A_1 or A_1A_2, and A_2A_1 or A_2A_2 have fitness f_{11} and f_{22}, respectively, in females, and m_{11} and m_{22}, respectively, in males. As Pearce and Spencer (1992) showed, we have the following recurrence equations for female and male allele frequencies, respectively:

$$p'_f = \frac{f_{11} p_f p_m + \frac{1}{2}(f_{11} p_f q_m + f_{22} p_m q_f)}{f_{11}(p_f p_m + p_f q_m) + f_{22}(q_f p_m + q_f q_m)} \tag{3}$$

$$= \frac{f_{11} p_f p_m + \frac{1}{2}(f_{11} p_f q_m + f_{22} p_m q_f)}{f_{11} p_f + f_{22} q_f} \tag{4}$$

$$p'_m = \frac{m_{11} p_f p_m + \frac{1}{2}(m_{11} p_f q_m + m_{22} q_f p_m)}{m_{11}(p_f p_m + p_f q_m) + m_{22}(q_f p_m + q_f q_m)} \tag{5}$$

$$= \frac{m_{11} p_f p_m + \frac{1}{2}(m_{11} p_f q_m + m_{22} q_f p_m)}{m_{11} p_f + m_{22} q_f} \tag{6}$$