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REVIEW

Gene interactions in the evolution of genomic imprinting

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Numerous evolutionary theories have been developed to explain the epigenetic phenomenon of genomic imprinting. Here, we explore a subset of theories wherein non-additive genetic interactions can favour imprinting. In the simplest genic interaction— the case of underdominance—imprinting can be favoured to hide effectively low-fitness heterozygous genotypes; however, as there is no asymmetry between maternally and paternally inherited alleles in this model, other means of enforcing monoallelic expression may be more plausible evolutionary outcomes than genomic imprinting. By contrast, more successful interaction models of imprinting rely on an asymmetry between the maternally and paternally inherited alleles at a locus that favours the silencing of one allele as a means of coordinating the expression of high-fitness allelic combinations. For example, with interactions between autosomal loci, imprinting functionally preserves high-fitness genotypes that were favoured by selection in the previous generation. In this scenario, once a focal locus becomes imprinted, selection at interacting loci favours a matching imprint. Uniparental transmission generates similar asymmetries for sex chromosomes and cytoplasmic factors interacting with autosomal loci, with selection favouring the expression of either maternal or paternally derived autosomal alleles depending on the pattern of transmission of the uniparentally inherited factor. In a final class of models, asymmetries arise when genes expressed in offspring interact with genes expressed in one of its parents. Under such a scenario, a locus evolves to have imprinted expression in offspring to coordinate the interaction with its parent's genome. We illustrate these models and explore key links and differences using a unified framework.
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INTRODUCTION

The expression of alleles at an imprinted locus depends on its parental origin. There has been a diversity of ideas put forth to explain this striking pattern of gene expression, with each theory providing a mechanism that can potentially generate selection favouring or disfavouring parent-of-origin-dependent expression (see Patten *et al.*, 2014). Because imprinting alters gene expression levels (Reik and Walter, 2001), many theories for the evolution of imprinting evaluate the selective consequences of tuning expression of the gene copies inherited from one parent or another for dosage-sensitive phenotypes, especially those related to demands for maternal resources (Haig, 2002). Here, we examine an alternative set of recently proposed 'interaction' models in which genomic imprinting is favoured because it acts to coordinate the interaction between some set of genetic factors.

We focus on the conceptual links between these interaction models to understand why various phenomena could influence the evolution of imprinting, and briefly explore the relevant empirical data for each scenario. We aim not to play advocate or critic for any particular theory, but rather to present a more fully developed and conceptually unified interaction theory of genomic imprinting, to examine its consistency with current knowledge, and to suggest future research directions that can best discriminate between competing models for specific cases of the evolution of imprinting.

MODIFICATION OF DOMINANCE

We begin with the simplest interaction model of the evolution of imprinting—a single-locus model where imprinting acts as a modifier of dominance. Imprinting can modify dominance effects (Sapienza, 1989; Spencer and Williams, 1997; Van Cleve and Feldman, 2007) by effectively enforcing haploid expression, thereby removing the physiological basis for dominance that arises from interactions between alleles at a locus (i.e., with only one allele being expressed, the second allele is irrelevant and therefore cannot interact with the expressed allele). On this basis, imprinted expression can be favoured at underdominant loci and loci where a deleterious allele shows some degree of dominance over the beneficial allele. With underdominance, imprinting effectively removes the heterozygous phenotypic class in which both alternative alleles are expressed, and when a deleterious allele shows some degree of dominance over the beneficial allele, complete imprinting restores additive fitness by silencing beneficial and deleterious alleles with equal frequency and thereby increasing the average fitness of heterozygotes. Below, we consider the underdominance model to illustrate how the presence of dominance can favour imprinting.

We consider a single biallelic locus, A, with alleles, A_1 and A_2, at frequencies p and $q = 1 - p$. We assume that the three diploid genotypes (here we do not distinguish between maternally and paternally derived copies at the locus) A_1A_1, A_1A_2 and A_2A_2, occur at frequencies p^2, $2pq$ and q^2, respectively. For simplicity, we consider a case where there is symmetric underdominance in which the three

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genotypes, respectively, have fitnesses $w_{11} = 1$, $w_{12} = 1-s$ and $w_{22} = 1$ in the absence of imprinting, where s is positive.

We include imprinting by assuming that imprinting dampens the expression of an imprinted parental allele by amount, i, which is bounded by 0 and 1. Therefore, in this underdominance model ($w_{12} < w_{11}$ and $w_{12} < w_{22}$), the three genotypic finesses are: $w_{11} = 1$, $w_{12} = 1 - s(1-i)$ and $w_{22} = 1$, that is, imprinting increases heterozygous fitness by a proportion i because the imprinting converts the heterozygote fitness into the fitness of a homozygote. The strength of selection on an imprinting modifier in this case would be $2pqs$, reflecting the fact that the selective advantage of imprinting is proportional to the frequency of heterozygotes ($2pq$). We do not examine the evolution of the imprinted locus, and refer readers to Spencer and Williams (1997) for a treatment of this two-locus problem.

Note that, in this model, imprinting is a form of dominance modification, and parent-of-origin-dependent expression simply serves as a mechanism by which to achieve monoallelic expression. Therefore, the model does not predict which parental copy should be silenced. However, if one parental copy evolves to be silenced, selection would presumably maintain the expression of the alternative parental copy to retain gene expression. Hence, once one form of imprinting evolves at a locus, selection would disfavour the alternative form of imprinting, as it would yield null expression.

This underdominance model (as well as the case of a dominant deleterious allele) shows that imprinting can evolve as a mechanism of dominance modification; however, this model leaves numerous questions unanswered. First, it does not explain why underdominant loci would have segregating variation given that this sort of variation should be largely eliminated by selection. This same argument applies to the case of a dominant deleterious allele (above) where selection is expected to remove efficiently such dominant deleterious alleles. Second, the model does not answer why imprinting evolves rather than another form of dominance modification. That is, because it is the silencing of a gene copy that is adaptive, not parent-of-origin-dependent expression of alleles, an allele causing random monoallelic expression would have the same selective advantage as an imprinting allele (Gimelbrant et al., 2007; Kreuger and Morison, 2008). However, neither challenge negates the potential for imprinting to evolve as a mechanism of monoallelic expression. Imprinting could be a more reliable or less noisy way to achieve monoallelic expression than alternative mechanisms (because it ensures that exactly one allelic copy will be expressed), and the theory of imprinting should not have the burden of explaining the existence of certain types of genetic variation. We therefore present this underdominant model as a simple but imperfect theory, and as an opening framework for the more complex models, below.

GENE INTERACTION MODELS FAVOURING PARENT-OF-ORIGIN-DEPENDENT EXPRESSION
Above we explored how imprinting can be selected to modify the interaction between alleles at the same locus. Here, we examine scenarios where imprinting modifies the interaction between loci, focussing on cases where such interactions are expected to favour parent-of-origin-dependent expression rather than monoallelic expression.

We begin with two scenarios in which fitness is determined by the interaction between loci within the same genome—one where both loci are autosomal and another where one of the two loci is sex linked (see Figures 1 and 2 for a visual presentation of these models). We then consider the case of an autosomal locus
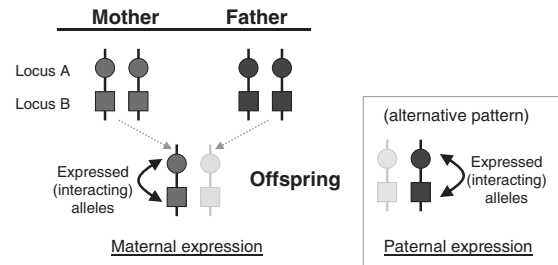

Figure 1 Imprinting coordinates interactions between autosomal loci. In this scenario, there are two loci, A (indicated by filled circles) and B (indicated by filled squares), each with two alleles indicated by the fill colour (red versus blue). Epistatic selection favours 'matching' alleles, meaning that higher fitness is associated with the matching of colours at the two loci. Because of past epistatic selection, positively interacting alleles will tend to be coinherited, indicated here by the same coloured alleles appearing on each haplotype (illustrated by the alleles linked by a vertical line). The offspring inherits a coadapted haplotype from its mother and father. By silencing one haplotype the offspring is able to express a pair of coadapted alleles that were inherited together. This 'coordinated' expression of coadapted alleles can be achieved by maternal expression of the two loci, as illustrated in the main part of the figure (with the silenced paternal haplotype appearing faded), or by paternal expression of the two loci, as illustrated as the alternative pattern in the inset box (with the silenced maternal haplotype appearing faded). A full color version of this figure is available at the Heredity journal online.
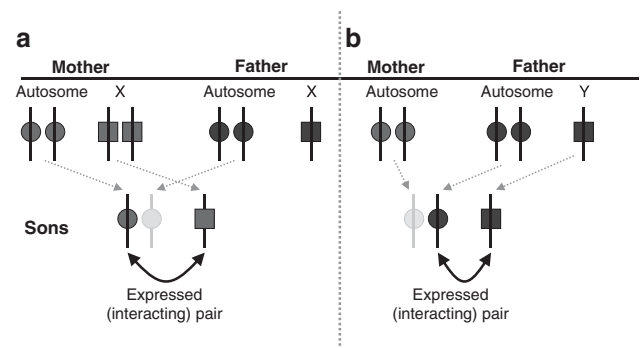

Figure 2 Sex-chromosome inheritance in heterogametic males introduces an asymmetry into sex-chromosome–autosome interactions that can favour imprinting. In both scenarios illustrated there are two loci, one autosomal locus (indicated by filled circles) and one sex-linked locus (indicated by filled squares), each with two alleles indicated by the fill colour (red versus blue). Epistatic selection favours 'matching' alleles, meaning that higher fitness is associated with the matching of colours at the two loci. Epistatic selection would be expected to build an association between positively interacting alleles, indicated in each example by the fact that the parental individuals have the same coloured alleles at both loci. (**a**) In the case of the X chromosome, the interaction in males is between the maternally inherited X chromosome and an autosomal locus. Consequently, maternal expression (indicated here by the paternal haplotype appearing faded) allows the coadapted alleles that were inherited together (from the mother) to be coexpressed. (**b**) In the case of the Y chromosome, the interaction in males is between the paternally inherited Y chromosome and an autosomal locus. Paternal expression of the autosomal locus; therefore, allows males to express the autosomal copy that was coinherited with the Y, and hence has evolved some degree of coadaptation with the autosomal locus. A full color version of this figure is available at the Heredity journal online.

interacting with a cytoplasmic factor. Finally, we consider the case where the interaction is between loci expressed in a mother and her offspring.

Epistasis and co-adapted gene expression

Gene interaction networks appear to be enriched for imprinted loci. For example, the Zac-1-regulated imprinted gene network (Varrault et al., 2006; Lui et al., 2008) contains a set of coregulated imprinted genes that have an important role in embryonic growth. Similar results appear in the human 'interactome', where imprinted genes are highly connected through the protein interaction network (Sandhu, 2010). Imprinted domains often contain non-coding RNAs, providing opportunities for interactions through RNA-mediated regulatory processes (Royo and Cavaille, 2008), which are responsible for the striking callipyge phenomenon in sheep (Davis et al., 2005). Finally, data on interactions between genomic regions appear to be enriched for interactions involving imprinted chromosomal regions (Zhao et al., 2006). The presence of these sorts of interactions could potentially be important for the evolution of genomic imprinting because the presence of imprinting alters the pattern of allelic variation available to be involved in the interaction.

Autosomal loci

To examine the general consequences for interaction effects in the evolution of genomic imprinting, we can examine a two-locus system (cf Wolf, 2013), which has the same basic structure that we will examine for subsequence models. As in the single-locus case, locus A has two alleles, A_1 and A_2, in frequencies p and q, respectively. At a second locus, alleles B_1 and B_2 have frequencies x and y, respectively. The four possible two-locus haplotypes (A_1B_1, A_1B_2, A_2B_1 and A_2B_2) have frequencies (denoted h_1, h_2, h_3 and h_4, respectively):

$$
\begin{aligned}
h_1 &= F(A_1B_1) = px + D, \\
h_2 &= F(A_1B_2) = py - D, \\
h_3 &= F(A_2B_1) = qx - D, \\
h_4 &= F(A_2B_2) = qy + D,
\end{aligned}
\tag{1}
$$

where D is a measure of covariance between alleles at different loci (i.e., linkage or gametic disequilibrium).

In this model, we distinguish between reciprocal heterozygotes because we wish to understand the consequences of parent-of-origin-dependent expression (i.e., we explore the evolution of imprinting as a mechanism for creating parent of origin dependence). Thus, we consider ordered genotypes with the paternal contribution written first. Assuming a random union of gametes, the frequencies of the 16 possible two-locus combinations of ordered genotypes are simply the products of the appropriate haplotype frequencies, for example, $F(A_1B_1/A_2B_2) = h_1h_4$ (see Hedrick, 2000).

We assume that the loci interact to affect fitness such that selection favours one pattern of combination and disfavours another (i.e., 'additive-by-additive' epistasis, see Cheverud and Routman, 1996). To reflect this pattern, we assign the same subscripts to those alleles that work best together. We focus on this form of epistasis because it does not contain any dominance effect, and therefore these models are not influenced by selection on dominance modification, discussed above. This model further assumes that dosage does not influence fitness, a break from many other theories (see above).

In the additive-by-additive model, individual fitness is simply the average fitness of all of the two-locus allelic combinations comprising the diplod two-locus genotype (see Wolf, 2013), where haplotype fitness is described as follows. Beginning with a baseline fitness of 1, allelic combinations at the two loci with matching subscripts (A_1B_1 or A_2B_2) increase fitness by s, and mismatched subscripts (A_1B_2 or A_2B_1) decrease fitness by s. This match versus mismatch is a key feature of the additive-by-additive model. Such a pattern could reflect selection

favouring matching binding domains of interacting proteins, genome sequences, or RNA–target combinations.

Genomic imprinting of either locus alters fitness by changing the expression pattern within a two-locus genotype. The degree of silencing at loci A and B are i_A and i_B, respectively. Positive values of i_A or i_B indicate the degree of silencing of the paternally inherited allele (i.e., the degree to which there is maternal expression), with a value of $+1$ indicating complete silencing of the paternally inherited allele. Likewise, negative values of i_A or i_B indicate the degree of silencing of the maternally inherited allele, with a value of -1 indicating complete paternal expression of the locus. To illustrate the fitness model, we consider a case where one locus is heterozygous, such as $A_1A_1B_1B_2$. In the absence of imprinting, fitness is determined by the average of the fitness effect of the A_1B_1 interaction $(1+s)$ and of the A_1B_2 interaction $(1-s)$, making the expected fitness (the unweighted average of these fitness values) 1. However, imprinting of the B locus determines whether the paternally inherited B_1 or maternally inherited B_2 allele is expressed, making fitness $1+i_Bs$. In this case, expression of the paternally inherited B_1 allele increases fitness because it has a positive interaction with the A_1 alleles present at the A locus. We present the expected fitness of all 16 two-locus genotypes in Table 1, and an illustration of this case in Figure 1.

With this model, we examine conditions favouring alternative forms of imprinting at the two loci. We do not explicitly examine the dynamics of the imprinting modifier locus here, but the conditions that favour the evolution of imprinting at the loci are essentially equivalent to the conditions that favour an imprinting modifier allele (Wolf, 2013). Therefore, we examine the pattern and strength of selection on the imprinting status of loci A and B, i_A and i_B, respectively. This is simply the partial derivative of mean fitness with respect to either i_A or i_B.

The effects of the imprinting status of locus A and locus B on individual fitness have the values sDi_B and sDi_A, respectively (i.e., these are the linear/additive effect that a change in imprinting status at a locus has on expected fitness). We use these simple expressions as proxies for the strength of selection favouring imprinting as they indicate how a change in the imprinting status in an individual would affect the fitness of that individual, and hence indicate the strength of selection on imprinting (cf Equations (3) and (4) in Wolf, 2013). These expressions indicate that selection, therefore, depends both on the presence of linkage disequilibrium (LD) between loci (D) and on the imprinting status at the alternate locus (i_B and i_A, respectively). This association is expected because selection builds LD between loci by favouring beneficial combinations of alleles (the coupling combinations, A_1B_1 or A_2B_2), while disfavouring negatively interacting

Table 1 Expected fitness of the two-locus combinations of ordered genotypes for the autosomal interaction model

	B locus genotype			
	B_1B_1	B_1B_2	B_2B_1	B_2B_2
A locus genotype				
A_1A_1	$1+s$	$1+i_Bs$	$1-i_Bs$	$1-s$
A_1A_2	$1+i_As$	$1+i_Ai_Bs$	$1-i_Ai_Bs$	$1-i_As$
A_2A_1	$1-i_As$	$1-i_Ai_Bs$	$1+i_Ai_Bs$	$1+i_As$
A_2A_2	$1-s$	$1-i_Bs$	$1+i_Bs$	$1+s$

The fitness of each of the sixteen two-locus genotypes is defined in terms of the strength of selection (s) and the imprinting status of the A locus (defined by i_A) and B locus (defined by i_B). All fitness values are defined as deviations from an expected fitness of 1 (cf Wolf, 2013).

combinations (the repulsion combinations A_1B_2 or A_2B_1). To see this, consider a simple case beginning in linkage equilibrium, with free recombination between loci and relatively weak selection. Under these conditions, the change in the LD across generations (ΔD) is simply $pqxys$, illustrating that the presence of selection and allelic variation at the two loci will build LD with the same sign as the pattern of selection (Crow and Kimura, 1970). More complex scenarios (e.g., linkage) complicate this expression but do not change the qualitative conclusion that selection generates beneficial allelic combinations.

This simple model demonstrates that selection can favour imprinting at each locus, but only if the other locus is already imprinted. Specifically, selection favours a pattern of imprinting at a locus that matches the pattern present at the other locus. Thus, if either locus is imprinted, we predict the two loci to coevolve such that interacting loci will have matching imprinting patterns. This occurs because cotransmitted alleles are likely beneficial combinations because they have been favoured by selection in the previous generation, and imprinting essentially reinforces the influence of LD on mean fitness by allowing individuals to express the potentially coadapted haplotype that they inherited from one parent. In this additive-by-additive model, selection does not favour one pattern of expression *per se* (i.e., selection does not favour paternal or maternal expression); rather, it favours a matching pattern of expression at the two loci.

The scenario above requires one locus to be imprinted for selection to favour imprinting at an interacting locus; however, this requirement can be circumvented if an imprinting modifier locus can simultaneously control the imprinting status of both interacting loci. Because imprinting of multiple genes is often regulated by the same elements, which are known as imprinting control regions (see Bartolomei, 2009), this scenario is highly plausible. With a single locus controlling imprinting at both loci, it can be shown that the strength of selection favouring an imprinting modifier is sDi_Ai_B. Thus, if the locus led to coordinated imprinting at the pair of loci (i_A and i_B are of the same sign), then the evolution of LD between loci would immediately favour imprinting.

A challenge to the epistatic model is the fact that imprinting will only be favoured at a given locus if the locus it interacts with is already imprinted (or if their imprinting evolves in synchrony under the influence of a shared transregulator). Therefore, something outside of the immediate scope of this theory is required for additive-by-additive epitasis to favour the evolution of imprinting; however, this theory suggests a cascading effect in imprinted expression can spread through a gene network. This theory predicts that interacting genes will tend to show similar patterns of imprinting. This hypothesis has not yet been rigorously examined; however, we point out one suggestive example. The Zac-1-regulated imprinted gene network contains mostly paternally expressed genes (7 of the 10 genes that have only a single form of imprinting), but the degree of enrichment is not significant (Lui *et al.*, 2008). A systematic survey of imprinting status in interactions would be crucial in evaluating the empirical evidence for this model.

If the maintenance of beneficial allelic combinations favours the evolution of imprinting as highlighted in this model, we may further predict that, to enhance coadaptation, selection should favour mechanisms that reduce recombination between interacting loci. A likely mechanism to reducing the recombination rate between loci is for them to evolve to become physically linked. As coadaptation evolves, it can favour the evolution of imprinting, and therefore we would expect selection to favour physical linkage between coadapted, jointly imprinted, loci. If such a process were responsible for physical linkage (or clustering) of imprinted genes, we would expect that the interacting loci would be expressed from the same parental haplotype. If epistatic selection were responsible for the pattern of linkage, we would also expect to see functional variation at the loci, with a pattern in which coadapted variants are coinherited (i.e., are in LD). However, while variation must be present for epistatic selection to favour the origination of imprinting and physical linkage, it is possible that such variation could be lost without the subsequent loss of imprinting at the loci (although epistatic selection would no longer directly favour either).

Imprinted genes are generally clustered in mammalian (Verona *et al.*, 2003; Morison *et al.*, 2005; Williamson *et al.*, 2012) and plant genomes (Zhang *et al.*, 2011) and the clustering in mammals appears to be a conserved feature in vertebrate evolution (Dunzinger *et al.*, 2005), which could either reflect selection favouring such linkage, or could be a phenomenon that has facilitated the evolution of imprinting at linked genes. Although the presence of physical linkage between sets of imprinted genes supports the basic tenets of this model, this support is tentative because many linkage groups include oppositely imprinted genes (Morison *et al.*, 2005), an observation not predicted by the epistatic model. We also note that, in addition to structural rearrangements, selection can maintain genetic combinations by modifying the recombination rate; however, contrary to predictions of the epistatic model, imprinted regions are recombination hotspots (Sandovici *et al.*, 2006), perhaps because of their sequence and epigenetic features.

Finally, we note that, in this epistatic model, selection favours the expression of the pair of alleles inherited from one parent (either the mother or father), but is indifferent with regard to which parent is silenced. Therefore, as in the dominance model, selection could favour random monoallelic expression if it operated on parental haplotypes, not single genes. Thus, because imprinting achieves coordination in the expression of alleles with the same parental origin at different loci, which could be difficult to achieve mechanistically through a random silencing process, it appears to be more likely outcome.

Sex chromosomes

We now consider an interaction model like that above, but where one locus is sex-linked (see Figure 2). Because the inheritance of sex-linked alleles is asymmetrical with regard to parent-of-origin, it seems likely that such an asymmetry could favour specific patterns of parent-of-origin-dependent expression. Similar logic underlies the model for evolution of imprinting on the X chromosome derived by Iwasa and Pomiankowski (2001), but their model is an extension of the conflict theory (Haig, 2000) that considers evolution of imprinting on the X chromosome, while we consider how interactions between sex chromosomes and the autosomes drives evolution of imprinting on autosomes.

We start by examining the case where the B locus is X-linked and the A locus is autosomal (see Figure 2a for an illustration of this scenario). We again designate the frequencies of two-locus combinations as above (Equation (1)). While females contain a pair of two-locus haplotypes, males have a two-locus haplotype inherited from their mothers, but only an autosomal allele inherited from their fathers. Assuming that allele frequencies are the same in both sexes, genotypes in females have frequencies determined by the products of the haplotype frequencies (following Equation (10)), while males have genotype frequencies that are the product of a haplotype frequency (again, given by Equation (1)) and the frequency of an autosomal allele. For example, females with the genotype $A_1A_1B_1B_1$ have the frequency h_1^2, while males with the analogous genotype $A_1A_1B_1Y$ have the frequency h_1x.

We assume that the pattern of fitness in females matches that given above for the autosomal model. In males, we assume that fitness shows the same basic pattern as the autosomal model, except that the X-chromosome locus (B) is haploid and so we assume the fitness of hemizygotes and homozygotes at the B locus are equivalent (e.g., the fitness of $A_1A_1B_1Y$ males is the same as that of $A_1A_1B_1B_1$ females). Like the autosomal model, selection generates LD, although the expression for changes in LD is more complex because of the different genotypic structure of males and females (not shown).

Because females are diploid for both the sex chromosome and autosome, the pattern of expression and therefore the pattern of selection will match that expected for the autosomal model above. In males, selection to change the imprinting status of the A locus has a value independent of imprinting status at the B locus, $2Ds$. This result demonstrates a key observation–selection for imprinting at the A (autosomal) locus in males is the same as the pattern expected if the B (X-linked) locus showed maternal expression. This occurs because the X chromosome in males is functionally equivalent to a maternally expressed locus, except the maternal expression is achieved by the fact that individuals are hemizygous for a maternally inherited allele. Therefore, unlike the autosomal model, this sex-linked model does not require the pre-existence of imprinting at one locus to favour imprinting at another locus. In addition, unlike the models above, here the type of parental imprinting is not arbitrary.

Although selection can favour maternal expression of the autosomal locus in males, whether imprinting will evolve depends, to some degree, on the pattern of selection in females. Consider the autosomal locus A, there is initially no direct benefit to imprinting in females, and so imprinting could evolve to be sex-dependent (e.g., Hager et al., 2008) or selectively neutral in females. However, if the autosomal locus evolves to be imprinted because of selection in males, then this can set the stage for the evolution of X-chromosome imprinting in females under the conditions seen in the autosomal model above (where selection favours a matching pattern of imprinting for the pair of interacting loci in females, and so if the autosomal locus evolves maternal expression, the X-chromosome locus would follow its lead). Despite the presence of X inactivation, there is evidence for multiple imprinted genes on the X chromosome (Davies et al., 2005; Raefski and O'Neill, 2005), which could potentially be candidates for such a process.

We can also consider the case of an interaction between a Y-chromosome locus and an autosome (see Figure 2b for an illustration of this scenario). In this case, females obviously have no role because they have no Y chromosome, while in males we essentially have the analogous situation as the X–autosome interaction model (i.e., an interaction between a uniparentally inherited locus and an autosome). Indeed, we expect selection to build an association between the autosomal locus and the Y-linked locus in males and for their male offspring to inherit these coadapted combinations from their fathers. As a result, selection favours paternal expression on the autosome for the same reason it favours maternal expression in the case of the X–autosome interaction. However, in the Y–autosome interaction case, imprinting of the autosomal locus has no functional role in females because females never have a Y chromosome. Therefore, imprinting is neutral in females and could potentially evolve to be male-specific.

Cytonuclear interactions

We now examine how interactions between nuclear and cytoplasmic loci (hereafter, cytonuclear epistasis) can favor the evolution of imprinting (Figure 3). There are ample opportunities for cytonuclear
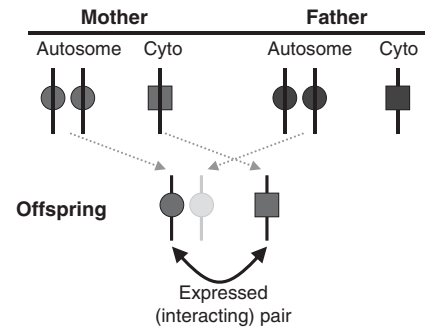

Figure 3 Maternally inherited cytoplasmic factors introduce an asymmetry into gene interactions that can favour maternal expression. An autosomal/nuclear locus (indicated by filled circles) and a cytoplasmic locus (indicated by filled squares) each have two alleles, indicated by the fill colour (red versus blue). Epistatic selection favours 'matching' combinations of cytoplasmic and autosomal alleles, meaning that higher fitness is associated with the matching of colours at the two loci. Epistatic selection would be expected to build an association between positively interacting cytonuclear allelic combinations, indicated by the fact that the parental individuals have the same coloured alleles at both loci. Because the interaction occurs between a maternally inherited factor and a biparentally inherited (autosomal) factor, maternal expression of that biparentally inherited factor (indicated here by the paternal autosomal haplotype appearing faded) allows individuals to express the copy inherited along with the maternally inherited factor (with which it will show some degree of coadaptation). A full color version of this figure is available at the Heredity journal online.

epistasis because most (if not all) protein complexes in chloroplasts and mitochondria that are composed from multiple subunits contain proteins produced by both the nuclear and organelle genomes (Rodermel et al., 1988) and the nuclear genome encodes most of the genes needed for mitochondrial and chloroplast development, function and maintenance (Rand et al., 2004). For example, mitochondrial ribosomal proteins are products of both nuclear and mitochondrial genes (Blier et al., 2001). These intimate connections between the nuclear and organelle genomes result in coordination of protein synthesis in the nucleus and organelles (Blier et al., 2001), and may have a major role in shaping patterns of genomic architecture (Wade and Goodnight, 2006; Brandvain et al., 2007; Brandvain and Wade, 2009).

Here we examine a case where cytonuclear epistasis favours cytonuclear coadaptation—that is, the build up of associations between alleles in the nuclear and cytoplasmic genomes (following Wolf, 2009). Such cytonuclear linkage disequilibrium has been observed in many studies, and can be strong and potentially important in some systems (Cruzan and Arnold, 1999; Brandvain et al., 2007; Dowling et al., 2007; Brandvain and Wade, 2009). We assume that the A locus is autosomal, and that the B locus is cytoplasmic and maternally inherited (Figure 3). Fitness follows the same basic assumptions used above, where the A_1 autosomal allele yields high fitness when paired with the B_1 cytoplasmic allele and low fitness when paired with the B_2 cytoplasmic allele (resulting in fitness deviations of $+s$ and $-s$ in the two scenarios). Although selection acts in both sexes, only selection in females is relevant because it generates heritable cytonuclear associations, in contrast to males where the cytoplasm and therefore cytonuclear allelic combinations are not transmitted to offspring.

For proper accounting, we use the expressions in Equation (1) to represent the frequencies of cytonuclear combinations inherited from the mother, where the parameter D measures cytonuclear linkage disequilibrium (cf Clark, 1984; Asmussen et al., 1987). Fathers

contribute only an allele at the nuclear locus, and so the combinations of the eight possible cytonuclear genotype combinations are simply the products of the frequencies of the maternal gamete (Equation (1)) times the frequencies of the paternal gamete types (which are simply p and q) (cf Clark, 1984).

This cytonuclear model is analogous to the Y-autosome model described above, because the Y, like a cytoplasmic factor, shows uniparental inheritance (cf Figures 2b and 3). However, unlike the Y, both sexes have the cytoplasmic factor. Because the cytoplasmic factor reach a dead end in males (Gemmell et al., 2004; but see Wade and Brandvain, 2009), this difference may seem irrelevant from an evolutionary perspective; however, it is meaningful as any pattern of selection in females that might favour cytonuclear coadaptation or imprinting will have the same fitness consequences in males as it has in females (assuming, as we do throughout the manuscript that loci have identical direct fitness effects in both sexes). That is, while the inheritance of the cytonuclear combinations is asymmetrical, the expected fitness in males is the same as in females. Therefore, while selection in females builds cytonuclear LD, selection in either sex can influence the evolution of imprinting at the nuclear locus. This result contrasts with the Y-chromosome model where only selection in males favours imprinting at the autosomal locus.

In the cytonuclear model, selection on the imprinting status of the nuclear (A) locus is $2Ds$, which matches that seen in males for the X-chromosome case. This resemblance is owing to the fact that, in both cases, the interaction is between an autosomal locus and a maternally inherited factor (the cytoplasm or the male X). However, unlike the case of the X–autosome interaction, imprinting in this case is directly favoured in both sexes.

In this cytonuclear model, the strength of selection for imprinting depends on the strength of selection favouring cytonuclear coadaptation and the degree of cytonuclear disequilibrium. Although the amount of linkage disequilibrium is likely to be a result of selection on cytonuclear combinations, other processes, such as admixture between differentiated subpopulations (Asmussen et al., 1989; Orive and Barton, 2002), or other non-random systems of mating can generate cytonuclear linkage disequilibrium (Wade and Goodnight, 2006).

Whether the conditions for cytonuclear interactions to drive imprinting exist remains an empirical problem. However, this model provides an unambiguous testable hypothesis. It makes the strong prediction that imprinted loci interacting with the cytoplasmically inherited factors will show maternal expression.

Maternal–offspring interactions

Interactions between parents and offspring are a major determinant of offspring fitness in many taxa. These interactions can start soon after fertilization, where histocompatibility factors can determine whether the embryo is successfully implanted in a mammalian mother (and potentially in other internally brooding systems), and can continue to be important well into life. To understand how interactions between parents and their offspring can favour the evolution of genomic imprinting, we briefly examine two cases, one where selection favors the coadaptation of complementary maternal and offspring traits, which interact to affect offspring fitness (Wolf and Hager, 2006), and a second in which we assume that the interactions are 'negative', with mothers selectively aborting (or showing selective implantation) offspring as a function of their genotype (Wolf and Hager, 2009). We note that we do not directly explore the role of conflict in the evolution of imprinted loci (described by the conflict theory, ; Haig, 1993; Wilkins and Haig, 2003), or how conflict could shape the

evolution of interactions between parents and offspring, (see Haig, 1996, 1997, 2002) and that this work in no way dispels the success of the conflict theory of genomic imprinting.

Interaction and coadaptation

Selection can favour the coadaptation of traits or loci expressed in mothers and their offspring (see Wolf and Brodie III, 1998; Kölliker et al., 2005; Wolf and Hager, 2006). In mammals, there are opportunities for coadaptation before birth through the placenta, a tissue in which imprinted expression is common (Geordiades et al., 2001; Wagschal and Feil, 2006). Here we explore two analogous models following Wolf and Hager (2006): a two-locus model analogous to those explored above, where a locus expressed in mothers interacts with a locus expressed in her offspring, and a single-locus model, where the same locus is expressed in mothers and their offspring. In both scenarios, we assume that selection acts on offspring, which follows the typical logic of maternal effects models (Cheverud, 1984).

In the two-locus scenario (Figure 4a), fitness and inheritance show the same patterns as in the autosomal model, except that the A locus is expressed in the mother and the B locus in the offspring. As in the autosomal model, selection builds LD, albeit only to half as much the level of disequilibrium generated in the autosomal model because one locus appears in the mothers and the other in her offspring, and so disequilibrium evolves by indirect selection on relatives (Wolf, 2000). Selection does not favour a change in the imprinting status of the A locus expressed by mothers. However, selection on the imprinting status of the B locus expressed in offspring equals Ds. Thus, despite the fact that the model is analogous in many ways to the autosomal model, it does not require the locus expressed in the mothers to be imprinted (as opposed to the autosomal model, where selection favours imprinting at one locus only if the other locus is already imprinted). Furthermore, selection only favours maternal expression in this case (i.e., favours a positive value of i, so individuals express the maternally inherited allele at the B locus). Thus, this outcome is analogous to the cytonuclear model or to the pattern of selection in males for the X–autosome model.

To generate a single-locus model, like that of Wolf and Hager (2006), we replace the B locus in offspring with the A locus (Figure 4b). Here, fitness increases by s when offspring and maternal alleles match and decreases by s when maternal and offspring alleles mismatch. Fitness of each combination is calculated as in the two-locus models, above (see Wolf and Hager, 2006). We assume that mother–offspring genotype combinations occur in the frequencies expected under random mating, resulting in missing combinations (e.g., A_1A_1 mothers cannot have A_2A_2 offspring) (Wade, 1998). We assume that genotype frequencies are approximately the same in parents and offspring (i.e., weak selection). We can therefore ignore the complications imposed by different allele frequencies in mothers and their offspring. Under these conditions, selection for a change in the imprinting status of the A locus is $2pqs$. This differs from the other scenarios in that it does not require linkage disequilibrium for the simple reason that an association between maternal and offspring genotypes is enforced by transmission. The model simply requires that the locus be pleiotropic such that it has both a direct and a maternal effect, with the direct effect of an individual's genotype depending on the maternal effect of its mother's genotype and vice versa. Selection does not favour imprinting of the locus when expressed in mothers (i.e., imprinting of the maternal effect) because both alleles in the maternal genotype are symmetrically related to their offspring (whereas only the maternally inherited allele in
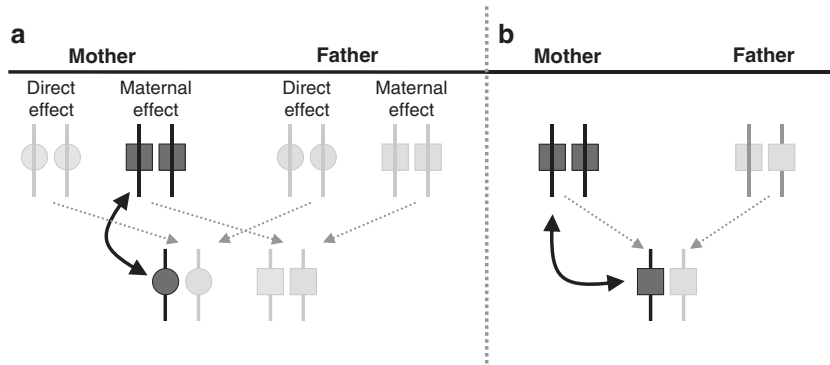
Figure 4 Imprinting with maternal expression can coordinate interactions between mothers and their offspring. (**a**) In the two-locus scenario, one locus is expressed in offspring and has a direct effect (indicated by filled circles) and a second locus is expressed in mothers and has a maternal effect (indicated by filled squares). Both loci have two alleles as indicated by the fill colour (red versus blue). Epistatic selection favours 'matching' combinations of alleles expressed in offspring and their mothers (indicated by a matching of colours at the maternal effect locus in mothers and direct effect locus in their offspring). Because of past epistatic selection, positively interacting alleles will be associated (in linkage disequilibrium) and so the direct effect allele inherited from the mother will tend to be coadapted with the maternal effect alleles in her genome. Therefore, selection favours the expression of the maternally inherited direct effect allele (such that the paternally inherited copy is silenced and appears faded) because it is coadapted to the maternal effect (the interacting alleles are indicated by the bold double-ended arrow). (**b**) In the single-locus scenario, a locus is expressed in the offspring and has a direct effect and is also expressed in mothers and has a maternal effect. The locus has two alleles as indicated by the fill colour (red versus blue). Because the copy inherited from the mother will be correlated with the alleles in the maternal genotype, and hence the maternal effect, selection favours maternal expression of the locus in offspring (where the fading of the paternally inherited copy indicates silencing). Such a pattern of expression enhances the 'match' between the direct effect allele expressed by offspring and the maternal effect alleles expressed by mothers (the interacting alleles are indicated by the bold double-ended arrow). A full color version of this figure is available at the *Heredity* journal online.

offspring is correlated to the mother's genotype). However, selection does not directly disfavour imprinting in mothers and so if a gene evolves to be imprinted because of selection on its direct effect (or for some other reason), it may also show an imprinted maternal effect.

This model predicts that direct effect loci that interact with maternal effect loci will be expressed from the maternally derived copy. This expectation is supported for many loci, where many genes expressed in placental (Wagschal and Feil, 2006) and early seed development show maternal expression (Baroux *et al.*, 2002) (but see the conflict theory for an alternative interpretation of these observations, e.g., Haig, 2000; Wilkins and Haig, 2003). We caution that when considering a careful empirical evaluation of this model, the specificity of the assumptions about the nature of the maternal–offspring interaction at a locus—it requires a matching system at the genetic level—must be taken into account. For example, under some models of maternal zygotic epistasis, heterozygous offspring of heterozygous mothers may have high fitness (e.g., Wolf and Brodie III, 1998; Wolf, 2000); however, that scenario does not favour imprinting because it would silence high-fitness heterozygous genotypes. What is clear from the analytical approach is that the imprinted status of the paternally expressed genes that affect maternal care, *Peg1* and *Peg3* (Lefebvre *et al.*, 1998), do not support a coadaptive model, contrary to previous claims (Curley *et al.*, 2004; Keverne, 2013).

Interaction and compatibility

We now examine a model of maternal–zygotic epistasis where the interaction between maternal and offspring genomes results in genetic incompatibility, where the maternal genotype selectively aborts offspring based on their genotype at the same locus. Following Wolf and Hager (2009), we consider cases where selective abortion is increased by genetic similarity (their 'incompatibility scenario') and where selective abortion is decreased by genetic similarity (their 'compatibility scenario'). Following the single-locus model examined above for the maternal–offspring coadaptation scenario, we focus on the *A*

locus and assume that parent–offspring genotype combinations conform to Hardy–Weinberg expectations.

In the incompatibility scenario, we assume that maternal genotypes have an increased probability of selectively aborting genotypes that are genetically similar to themselves. This selective abortion will increase heterozygosity at specific loci in their offspring (e.g., major histocompatibility complex; Knapp *et al.*, 1996), and could therefore be adaptive. The probability of aborting is increased by sharing and reduced by non-sharing of alleles, with the selection parameter s representing the change in the probability of survival. The model for fitness is analogous to that used in the other models above, except that sharing alleles leads to lower fitness, rather than higher fitness. For example, homozygous offsprings that have mothers that are homozygous for the same allele have fitness of $1 - s$. Homozygous offspring of homozygous mothers that do not share alleles cannot occur. Homozygous offspring of heterozygous mothers have a fitness value of 1 because they share one maternal allele but do not share the other. These values are changed by imprinting because imprinting is essentially a means of 'cloaking' an allele so the mother's incompatibility system cannot 'see' it. For the homozygous offspring that have mothers that are homozygous for the same allele, imprinting has no effect because they still have matching allele, regardless of what allele is expressed. However, in heterozygous offspring of homozygous mothers, the silencing of a copy in the offspring affects fitness, with it increasing fitness if an incompatible allele is silenced and decreasing fitness if a compatible allele is silenced (see Wolf and Hager, 2009). In this scenario, the pattern of selection on the imprinting status of the locus has the value $-pqs$, meaning that selection favours the silencing of the maternal copy (i.e., paternal expression). This pattern of expression hides the maternally inherited copy and thereby reduces the genetic similarity of mothers and their offspring at the locus. Of course, such a scenario could lead to conflict over silencing given that the 'exposed' copy inherited from the father could lead to spontaneous abortion, an outcome presumably disfavoured from the father's perspective in some systems (e.g., where there is multiple paternity).

The solution presented here (and by Wolf and Hager, 2009) assumes that selection maximizes offspring fitness, which implies that there is no difference between the expected fitness through the maternal and paternal lineages (i.e., that the interests of both parents coincide). However, under a scenario, such as with multiple mating, a male may lose fitness if his offspring are aborted to the gain of competing males. Thus, although such conflict is not considered here, certain scenarios could generate conflict between males and females over imprinting, which could have important implications for expected patterns across systems.

We can also consider the opposite scenario in which mothers preferentially abort offspring that are genetically dissimilar to themselves. This pattern could result from a maternal immune response, where genetically dissimilar offsprings are more likely to be recognized as foreign and aborted by their mothers (Clark et al., 1999). This scenario is therefore the mirror image of the incompatibility scenario, and therefore the pattern of selection on the imprinting status of the locus has the value pqs, meaning that selection favours the silencing of the paternal copy (i.e., paternal expression). Analogous to the incompatibility scenario, this pattern of expression hides the paternally inherited allele from the mothers immune system and thereby enhances the genetic similarity of mothers and their offspring at the locus. Because fitness variation introduced through this pattern of selective abortion is within maternal families, it is not expected to generate conflict between parents over the pattern of imprinting.

The maternal–zygotic interaction/compatibility models therefore make the simple prediction that those loci in which genetic similarity could result in spontaneous abortion or other forms of incompatibility should show paternal expression, while those in which genetic dissimilarity could result in spontaneous abortion should show maternal expression.

Data support the assumption that spontaneous abortion can be a function of allele sharing at histocompatibility loci (Hedrick, 1988; Knapp et al., 1996). Studies have suggested that some histocompatibility loci are imprinted in the placenta, such as major histocompatibility complex class I antigens in rats (Kanbour-Shakir et al., 1990), but other studies have not found evidence for imprinting of histocompatibility loci in the placenta, such as in the mouse (Drezen et al., 1994) or horse (Donaldson et al., 1994). The question of whether histocompatibility loci show patterns of imprinting that are consistent with the expectation of this model therefore remains an open problem. Most importantly, expression data are required for the critical period in development when selective abortion occurs since the model is only relevant for that critical window of developmental time. Therefore, any evidence in support of or refuting the predictions of this model is only relevant if it applies to the specific period of gene expression when the assumed pattern of selection could be operating. If correct, this model would suggest that loss of imprinting defects could be a potential contributor to spontaneous abortion.

CONCLUSIONS

The collection of scenarios explored above document the rich ways in which simple genetic interactions can favour the evolution of genomic imprinting as a mechanism of generating adaptive multiallelic expression patterns. These scenarios differ from most alternative models of genomic imprinting that, by and large, investigate imprinting as a strategy used to modulate gene dosage (e.g., the kinship theory, Haig, 2002). As a result of this difference, the two sets of models make fundamentally different assumptions about both the

importance of dosage in the evolution of imprinting as well as the nature of standing genetic variation (see Haig, 2014).

By their very nature, all interaction models require polymorphism at loci that interact to influence fitness. This variation is required to generate selection on imprinting status in the models examined here, where selection on imprinting arises when the fitness effect of an interaction depends on the specific combination of alleles involved. In contrast, the kinship theory (and other dosage centred models of imprinting) does not require standing variation. Models focused on gene dosage simply assume that there was genetic variation in the pattern of imprinting at some stage of its evolution, allowing imprinting to evolve from a non-imprinted state. However, although the interaction models examined here require the presence of variation for selection to favour imprinting, the lack of variation does not necessarily imply that such a process is not responsible for the presence of imprinting owing to past selection. Once evolved, it is possible that imprinting is maintained because it becomes 'locked in' by genomic adaptations (perhaps in response to monoallelic expression), or it may be simply a relic that reflects the lingering influence of past selection.

Furthermore, while the kinship theory generally makes broad predictions about the pattern of expression on traits mediating interactions between kin (Haig, 2004), the interaction models each make predictions that are specific to particular scenarios. The relative importance of the alternative interaction models explored above remains an open question—each is built on a set of biologically plausible assumptions, but we are largely lacking specific tests aimed at differentiating these from competing hypotheses in explaining imprinting at specific genes. Thus, the importance of interaction effects in explaining the presence of imprinting at specific genes remains an open question. Finally, we emphasize that the scenarios we have explored are each hypotheses that are not designed to replace other theories, but rather, are complementary and are aimed at exploring the space in which imprinting could potentially be adaptive.

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