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Demography, kinship, and the evolving theory of genomic imprinting

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Genomic imprinting is the differential expression of an allele based on the parent of origin. Recent transcriptome-wide evaluations of the number of imprinted genes reveal complex patterns of imprinted expression among developmental stages and cell types. Such data demand a comprehensive evolutionary framework in which to understand the effect of natural selection on imprinted gene expression. We present such a framework for how asymmetries in demographic parameters and fitness effects can lead to the evolution of genomic imprinting and place recent theoretical advances in this framework. This represents a modern interpretation of the kinship theory, is well suited to studying populations with complex social interactions, and provides predictions which can be tested with forthcoming transcriptomic data. To understand the intricate phenotypic patterns that are emerging from the recent deluge of data, future investigations of genomic imprinting will require integrating evolutionary theory, transcriptomic data, developmental and functional genetics, and natural history.

Patterns of imprinted gene expression

Genomic imprinting is the phenomenon where the pattern of allelic expression depends on the parental origin of the allele [1]. In the simplest case of imprinting, an allele inherited from one parent is epigenetically silenced, whereas the alternative allele is expressed. In more complex cases, the pattern of silencing varies between cell types and isoforms (e.g. the *GRB10* and *Gnas* loci [2,3]). This differential expression depends on epigenetic differences (e.g. DNA methylation and histone modifications) that are established separately in the male and female germ lines and are propagated through development [4]. Genomic imprinting is both best documented and best understood in angiosperms and eutherian mammals [5]; however, preliminary evidence for imprinted expression in other taxa is accumulating [6–8].

The first imprinted genes identified in mammals were the insulin-like growth factor type 2 (*Igf2*) and the insulin-like growth factor type 2 receptor (*Igf2r*) in mice [9,10], which are only expressed when paternally and maternally derived, respectively. Both of these genes are associated with prenatal growth: *Igf2* is a growth enhancer and *Igf2r* is a growth suppressor. Many imprinted genes were subsequently shown to influence prenatal growth, and early molecular and theoretical research focused primarily on describing and understanding these growth effects (e.g. [11–15]).

More recently it has become clear that imprinted genes significantly affect aspects of the phenotype other than growth. In particular, loci influencing cognitive and behavioral phenotypes are often imprinted [16,17]. Individual imprinted genes have been connected to behaviors including maternal care [18,19], reactivity to novel environments [3], social dominance [20], and memory consolidation [21]. The use of RNA sequencing technology (RNA-seq) now allows for a comprehensive identification of imprinted transcripts [22–26]. For example, by reciprocally crossing two inbred mouse strains and sequencing the transcriptomes of offspring from each cross direction and both parents, Gregg *et al.* [24,25] obtained expression levels of maternally and paternally derived alleles in different regions of the brain. These studies found evidence for more than 800 imprinted genes and showed that imprinted expression varies according to sex, developmental stage, and brain region. Although such studies are currently restricted to controlled crosses between inbred strains of model systems, the falling price of next-generation sequencing will soon make it possible to obtain similar data from non-model species

To predict and interpret the patterns of imprinted gene expression we require a general framework in which one can consider the effect of selection on alleles that affect social interactions and other complex phenotypes [16]. The framework begins with the idea (from Haig [27]) that relatedness differences between maternally and paternally derived alleles at a locus (i.e. relatedness asymmetries) make it likely that the inclusive finess of maternally and paternally derived alleles will differ. Therefore, genomic imprinting could be favored as mechanism for increasing expected inclusive fitness conditional on knowledge of parent of origin. Building on this basic insight, we present a synthetic theoretical framework for considering the relationship between imprinted gene expression and social interactions within specific demographic models. We argue that numerous demographic factors (including sex-ratio skew and sex-specific migration in addition to the nature of the mating system) that generate asymmetric relatedness favor the evolution of genomic imprinting. This framework incorporates the recent contributions of several authors [28–33] and provides a flexible and general methodology

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Table 1. Predicted imprinting status under alternative demographic parameters

Demographic factor	Origin of expressed allele		Scale of fitness interactions	Some potential taxa for future investigation	Refs
	Helping behaviors[a]	Harming behaviors[b]			
Sex difference in juvenile dispersal[c]	The more sedentary sex	The more migratory sex	Non-sibling neighbors	Female dispersal: *Saccopteryx bilineata*, greater sac-winged bat Male dispersal: *Nyctalus noctula*, noctule bat	[62,63]
Female defense or harem polygyny	Paternally derived	Maternally derived	Paternal siblings	*Marmota flaviventris*, yellow-bellied marmot; *Ips grandicollis,* bark beetle; *Equus caballus,* horse	[64–66]
Female multiple mating	Maternally derived	Paternally derived	Maternal siblings	*Crocuta crocuta*, spotted hyena; *Peromyscus maniculatus*, deer mouse	[64,67]
Sex difference in fertility variance[d]	Sex with greater fertility variance	Sex with lesser fertility variance	Non-sibling neighbors	Females with greater variance[e]: *Apteryx mantelli,* brown kiwi Males with greater variance: *Oxyura jamaicensis,* ruddy duck	[68]

[a]Helping behaviors include alloparental care, resource sharing, restrained resource acquisition or reproductive output.

[b]Harming behaviors include resource hoarding, non-cooperation, and shading.

[c]Cooperative breeding is often associated with sex-biased dispersal, providing an excellent opportunity for further investigation.

[d]This creates a different effective number of mothers and fathers per deme.

[e]Greater investment in parental care is taken here as a proxy for lower fertility variance.

that can be applied to many fitness interactions, including food sharing, territory defense, and maternal, paternal, and alloparental care, among others (Table 1). In such a framework, alleles that increase the fitness of the neighbors of a focal individual are likely to be expressed from the parental copy of an allele that is more likely to be shared through common decent with those neighbors than the alternative copy, which is repressed.

Conceptual framework

Numerous theories have been proposed to explain the evolutionary origins of imprinted gene expression (Box 1). Generally, the evolution of genomic imprinting requires differential selection on expression of maternally and paternally derived alleles. This differential selection often arises from fitness interactions between individuals with different degrees of relatedness at maternally and paternally derived alleles [34] (however, note in Box 1 that in some cases this differential selection might not depend on classic relatedness asymmetries). Several sociodemographic factors, including the type of mating system and sex differences in survival and the rate or timing of migration, can generate differential relatedness [28–32,35,36]. We present below a synthetic framework that considers the evolution of imprinting in demographically structured populations (Box 2) that can be tested against transcriptome data.

The effect of natural selection on allele frequency depends not only on the effect of an allele on the fitness of an individual, but also on how the fitness of that individual is affected by copies of that allele in other members of the population [33]. The consequences of selection depend in part on the probability that two interacting individuals share identical alleles (relatedness) [33,37,38]. When the relatedness of two individuals that engage in fitness interactions differs at maternally and paternally derived alleles, selection can favor the evolution of imprinted expression [27] (Box 2). These fitness interactions encompass a broad

Box 1. Theories for the evolution of genomic imprinting

The initial description of genomic imprinting attracted numerous evolutionary theories ([69] for review). Traditionally, any theory based on an explanation other than an intragenomic conflict over maternal resources was viewed as being in conflict with the kinship theory [12,13,70]. In fact, many of these alternative proposals fall within the broader definition of the kinship theory described here. For example, it has been argued that genomic imprinting can evolve at loci that are under sexually antagonistic selection [59,71]. In the simplest case of this model, a locus is under selection in one sex, but neutral in the other. In this case, genes contributed by the sex under selection at that locus are expressed in that sex, whereas genes contributed by the other sex are silenced. This theory could explain maternal and paternal silencing of genes in a sex-specific manner. Another theory argues that genomic imprinting evolves in genes under selection for maternal–fetal coevolution [72]. Silencing of genes contributed by the father facilitates the coadaptation of mother–offspring traits during pregnancy. A different theory argues that genomic imprinting evolves in genes under selection for parental resemblance [73].

In each of these models, imprinted gene expression is a consequence of an asymmetry in the way that natural selection acts on maternally and paternally inherited alleles. These asymmetries do not result from conflict over resource transfer across the placenta, but each asymmetry relies on differences in patterns of relatedness between maternally and paternally inherited alleles. For example, in the models of sexually antagonistic selection, the expressed allele is the one that is more closely related to the parent in which the locus was under stronger selection.

Models that do not fit within this broader definition of the kinship theory include those that focus on advantages of monoallelic expression (e.g. [59,74]), where that advantage does not depend on which allele is silenced. Such considerations contribute to a quantitative description of the selection for imprinting, but to the extent that there are strong patterns in the direction of imprinting (e.g. maternal silencing of growth enhancers and paternal silencing of growth suppressors), these models cannot provide a complete explanation by themselves.

Box 2. How to make an imprinting model

Here, we present a kin-selection model following the 'direct fitness' method [75–78] that determines the fate of a mutation with differential effects on fitness interactions via maternally and paternally inherited alleles. Due to its mathematical tractability, the direct fitness method has become the most common approach for modeling kin selection.

Consider N_f and N_m diploid females and males that live in a population of D demes connected by migration of juveniles. We consider a locus that influences a helping behavior, where helping increases juvenile survival. The resident allele codes for a level x of helping and the mutant allele for levels $x + \delta_M$ and $x + \delta_P$ of helping when maternally and paternally derived, respectively. After dispersal, adults compete for reproductive spots. We define W_{uvij} as the number of offspring of sex v left by parent j of sex u in deme i that survive and reproduce in the next generation. To study the evolution of helping, we calculate the expected change in frequency of the mutant allele in adults after one generation (Δp). Following standard analyses of evolution in class structured populations [79], we write Δp as the expected number of male and female offspring produced by each mother and father parent weighted by the expected frequency of the mutant allele in each parent, the reproductive value of the sex of the offspring (1/2), and the probably that the mutant allele is transmitted from parent to offspring (1/2) [28,31,78]:

$$\Delta p = \frac{1}{4}\frac{1}{D}\sum_{i=1}^{D}\left(\sum_{j=1}^{N_f}\left(\frac{W_{ffij}}{N_f}+\frac{W_{fmij}}{N_m}\right)p_{fij} + \sum_{j=1}^{N_m}\left(\frac{W_{mfij}}{N_f}+\frac{W_{mmij}}{N_m}\right)p_{mij}\right) - p \quad \text{(I)}$$

Within each deme, the fitness of an individual depends on its level of helping, x_0, the average level of helping in its deme, x_1, and the average level of helping in the whole population, x_2, that is $W_{uv} = W_{uv}(x_0,x_1,x_2)$. The levels of helping x_0, x_1, and x_2 can be written in terms of the mutant deviations δ_M and δ_P and mutant allele frequencies in the focal individual, focal deme, and other demes. We can then write a first-order Taylor-series expansion of Δp as

$$\Delta p = p(1-p)\sum_{u,v\in\{f,m\}}\sum_{i\in\{0,1,2\}}\frac{\partial W_{uv}}{\partial x_i}\left(R_{vM,ux_i}\delta_M + R_{vP,ux_i}\delta_P\right) + O(\delta^2) \quad \text{(II)}$$

where $O(\delta^2)$ represents terms less than or equal in magnitude to δ_M and δ_P that can be mathematically neglected. The terms R_{vM,ux_i} and R_{vP,ux_i} are functions of probabilities of genetic identity and can be used to calculate relatedness coefficients [31,77,78]. For example, R_{fM,mx_1} is the probability that a maternally derived allele in a female is identical to another allele taken from a random male in the deme. Relatedness coefficients are generally ratios of probabilities of genetic identity [38,77,80,81]. For example, if we assume (as in [28]) that there is no sex-specific effect of helping, the relatedness of an individual via its maternally derived allele to another random individual in the deme is $r_M = R_{M,x_1}/R_{x_0}$, where R_{x_0} is the probability of genetic identity with self [28]. The fitness derivatives $\delta W_{uv}/\delta x_i$ can be thought of as the cost or benefit of the mutant helping level on the expected number of offspring of sex v produced by a parent of sex u.

We can separate the terms in equation (II) with δ_M from those with δ_P:

$$\Delta p = p(1-p)(S_M\delta_M + S_P\delta_P) + O(\delta^2) \quad \text{(III)}$$

where

$$S_Z = \sum_{u,v\in\{f,m\}}\sum_{i\in\{0,1,2\}}\frac{\partial W_{uv}}{\partial x_i}R_{vZ,ux_i} \quad \text{(IV)}$$

is a 'selection gradient' that measures the strength of selection on expression of the maternally (Z = M) or paternally derived (Z = P) allele. The selection gradients S_M and S_P are functions of the number of males and females, N_f and N_m, and the level of helping determined by the resident allele, x. By formulating a specific socio-demographic model, the selection gradients become a function of sex-specific migration and survival rates among other demographic parameters (see [28,29,31] for examples of sex-specific migration and survival). When there is no difference between selection gradients, $S_M = S_P$ and genomic imprinting is not favored by natural selection [27,31,51,52]. Assuming that there are some sex differences in demographic factors, selection on maternally and paternally inherited alleles differs, $S_M \neq S_P$, and the evolution of imprinting is favored. If the mutant considered cannot separate its expression by parent of origin, $\delta_M = \delta_P = \delta$ (gene cannot be imprinted), then it will increase in frequency provided that $S_M + S_P \geq 0$. A mutant that can separate its expression by parent of origin, that is $\delta_M \neq \delta_P$ (gene can be imprinted), will increase in frequency when $S_M \geq 0$ or $S_P \geq 0$. Expression levels from maternally and paternally derived alleles evolve towards their optima: x^*_M, when $S_M = 0$, and x^*_P, when $S_P = 0$. Given that a particular convergence condition holds (see 'convergence stability' in [31,51]), the allele with the higher optimal level of expression evolves to be expressed at that level and the other allele becomes silenced [27,31,51,52]; for example, expression from the maternally derived allele and silencing of the paternally derived allele occurs when $x^*_M > x^*_P$ and vice versa for $x^*_M < x^*_P$.

range of phenomena, including any situation in which the fitness of one individual is affected by the genotype of one or more other individuals. Examples of fitness interactions include competition (direct or indirect) for limited resources or breeding sites [39–41], mating [42], and other social interactions such as grooming, food sharing, dominance displays, alarm calls and territory defense, as well as the accumulation of maternally and paternally derived resources [12,35].

Many demographic factors (e.g. the sex ratio, migration rates, survival rates, or variances in reproductive success) can generate relatedness asymmetries that allow the evolution of genomic imprinting [28–31,36,43]. Because both fitness interactions and relatedness asymmetries are common [28,44,45], the potential explanatory power of theories based on a framework of asymmetries in relatedness conditional on parental origin is broad. Whereas early research in the kinship theory focused on conflict over the sequestration of maternal resources during early development in plants and mammals [12–14], our framework applies to traits expressed in most species throughout various stages of development. For example, consider a plant species with extensive pollen dispersal and limited seed dispersal. Here, seedlings in a neighborhood will be more likely to share maternally derived genes than paternally derived genes. This differential relatedness, coupled with the many mechanisms by which neighboring plants influence each others' fitness (such as branchiness, which can reduce the shading of neighbors and is modulated in response to kin [46]), presents an opportunity for selection to favor imprinted expression of alleles involved in plant growth morphology. In this example we expect alleles that increase shading to be silenced when maternally derived, and expressed when paternally derived, because such expression would decrease the fitness of neighbors.

To generate and evaluate models for the evolution of genomic imprinting based on asymmetric relatedness, one requires a good characterization of fitness interactions that are biologically relevant and a knowledge of in what kind of groups such interactions occur: in other words, which traits

in which individuals influence the fitness of which neighbors [28–31,36]. These interactions can differ among different traits and developmental stages. For example, early in life (prenatally or directly after birth) offspring could interact primarily with their maternal siblings; thus, the most appropriate fitness interaction group would be the brood or the nest. Later in life, individuals of all ages can interact randomly with all members of the population in which they were born, and in which case the most appropriate fitness interaction group is the natal deme (Box 2).

Once the relevant fitness interaction group has been identified, it is possible to determine the difference in relatedness between neighbors at maternally and paternally derived loci. Differential relatedness at maternally and paternally derived alleles can be conceptualized by comparing the probability of two maternally derived alleles coalescing back in time with that of the coalescence of two paternally derived alleles (Figure 1). The probability that alleles chosen from different individuals and derived from parents of the same sex coalesce in the preceding generation depends on the reciprocal of twice the effective number of parents of that sex in the group. Alleles derived from the sex with the lower effective number of reproducing individuals are more likely to be identical by descent than alleles inherited from the other sex [28–31]. The effective number of mothers and fathers depends on the sex ratio at birth, sex differences in survival, the mating system, and factors affecting mate choice [47].

In addition, sex differences in migration can generate relatedness asymmetries – because migration precludes coalescence within a deme, two individuals are more closely related at alleles derived from the more sedentary sex [28,29,31,36]. However, the influence of sex differences in dispersal on the evolution of imprinting requires special care because local competition between kin can diminish the benefits of kin cooperation [39–41,48]. For populations in which there is a sex bias in reproductive success and dispersal [31,49,50], the effect of kin competition is complex and might not prevent the evolution of cooperation [49,50] or genomic imprinting of genes for cooperation [28,29]. The effect of kin competition due to limited migration can even result in imprinting of genes with survival effects even without social interactions, provided that survival is sex-specific [31]. An exciting example of the relation between genomic imprinting and local competition is the observation that under many demographic parameters the optimal sex ratio differs for maternally and paternally derived alleles, setting the stage for imprinting of alleles involved in sex determination [32].

In Box 2 we describe how allele frequency change over time is affected by expression from maternally and paternally derived alleles. Using the equations developed in Box 2, the potential for selection to favor imprinting can be conceptualized by finding the optimal expression levels of maternally and paternally derived alleles. A difference between optima results in an intragenomic conflict that is resolved evolutionarily by the silencing of the allele with the lower optimal level of expression, and by expression of the alternative allele at its optimal level [27,31,51,52].

From the above framework, we can generate concrete predictions about the imprinting status of specific genes based on the fitness effects of those genes and the demography, ecology, and life history of the species in question (Table 1). In the next section we provide some examples of such predictions and suggest how they can be tested.

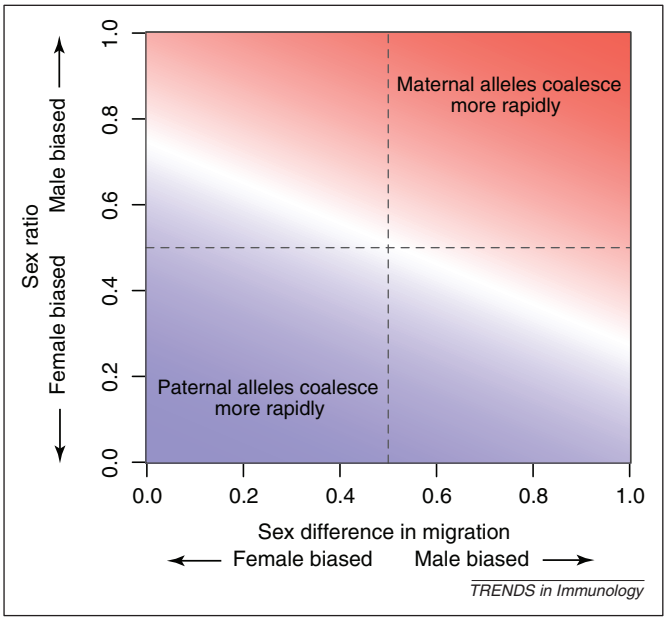

Figure 1. Sex ratio and sex differences in migration can generate different relatedness at maternally and paternally derived alleles. In one of an infinite number of demes, an allele can coalesce within that deme before migration, or it can be lost to the greater metapopulation. By color, we display the log of the probability that a paternally derived allele coalesces before migration divided by the probability that a maternally derived allele coalesces before migration. As colors become more blue, maternally derived alleles coalesce before paternally derived alleles. As colors become more red, maternally derived alleles coalesce before paternally derived alleles. Note that at an equal sex and migration ratio the ratio of coalescence probabilities equals one. Each deme consists of 100 individuals with a sex-averaged migration rate of $m = 0.1$. We vary the sex ratio (N_m / N_f, y axis), and the migration ratio [m_m / (m_f + m_m), x axis].

Merging theory and empirical studies

It is straightforward to construct a plausible-sounding evolutionary argument about why a particular gene in a given species should be imprinted. However, plausibility does not constitute strong evidence for any particular model. We therefore develop here genomic and comparative approaches to understanding the selective forces that favor the imprinting of genes influencing specific fitness interactions. These approaches require an integration of explicit evolutionary models with a detailed understanding of natural history and studies in molecular and functional genetics. Specifically, such comparative studies begin with a knowledge of the relevant demographic parameters (e.g. the scale of interaction, sex differences in migration, survival, reproductive success) in the taxa of interest. By incorporating these demographic details into explicit evolutionary models, hypotheses can be generated that detail how the imprinting status of classes of genes depends on demographic details. Our generic prediction is that when relatedness differs at maternally and paternally derived alleles, silencing of the more closely related allele is expected when it decreases the fitness of its neighbors. Such predictions can be tested by surveying the transcriptome (by using a method such as RNA-seq) to determine the extent of parent-of-origin specific gene

expression in diverse taxa and incorporating knowledge of the phenotypic effects of imprinted genes from functional genetic studies.

Hypotheses derived from the framework above can be tested by examining patterns of expression within a single species. For example, consider a species in which individuals interact with their nest mates when very young and with individuals from neighboring nests when they are older juveniles. Then, adult females disperse broadly to new populations and mate with multiple males who remain in their natal population. In this hypothetical species, nest mates are more closely related at maternally than paternally derived alleles, whereas neighboring juveniles are more closely related at paternally than maternally derived alleles. In this species, we predict that alleles which increase the fertility or survival of nest-mates (e.g. transcripts expressed while in the nest) at the expense of individual fertility or survival are likely to be expressed when maternally inherited, and suppressed when paternally inherited. This class of predictions has already received much attention in the specific case when maternal half-siblings compete for maternal resources before birth. The prediction that alleles that demand maternal resources will be silenced when maternally derived has received much support [e.g. 53].

However, once individuals leave the nest and begin interacting with neighbors, we expect a reversal in this pattern. To test this hypothesis in a species of interest, one would characterize allele-specific expression at developmental stages corresponding to the time in the nest and at a later point some time after fledgeling. Next, imprinted genes would be classified by their effects on individual fertility or survival and the fertility or survival of other group members. Such classification would make use of previous studies on the functions of these genes. One could then test whether the expression patterns of imprinted genes that reduce individual fertility or survival, and increase fertility or survival of group members, meet theoretical expectations. Current high-throughput methods used to discover imprinted expression make use of reciprocal crosses between inbred lab strains [22–26] and are useful for testing specific predictions in a few model systems. However, it seems likely that this type of data will soon be accessible for non-model systems.

This approach would provide some evidence for or against the hypothesis that mating systems and sex differences in migration favor the imprinting of genes which influence the fitness of others. A more convincing test of such hypotheses would utilize an interspecific or comparative approach that leverages natural variation in sex differences in migration rates. Imprinted genes would be identified in multiple species that differ in their migration patterns, with the expectation that 'cooperative' genes will be expressed when paternally inherited in systems in which males are more sedentary than females, but that this pattern would be reversed when females migrate less than males. A more mature version of this comparative approach would incorporate additional demographic parameters predicted to influence relatedness differentially by parent of origin and would correlate these parameters with the imprinting status of cooperative genes. Finally, additional models focusing on genes with different phenotypic effects (e.g. begging behavior or prenatal growth) could be used to generate new predictions for the imprinting status of these genes based on the same demographic variables as the cooperative genes. Using transcriptomic data to test the predicted imprinting status of genes with diverse phenotypic effects in a suite of species with significant variation in demographic parameters would provide a powerful test of the ability of this framework to explain the evolution of genomic imprinting.

As with all broad tests of evolutionary hypotheses, it is important to consider the potentially confounding effects of common descent. For example, an ancestral species with female-biased dispersal might evolve paternal expression at some loci associated with a cooperative behavior. Descendants of this species would be expected to follow this pattern unless changes in dispersal rates or other demographic parameters exert a sufficiently strong selection pressure to reverse the pattern. Several statistical methods have been developed to correct for this phylogenetic non-independence [54–56] and could be used when performing comparative analyses of genomic imprinting. In addition, phylogenetic methods can be used to reconstruct ancestral states [56], and this would allow one to determine in which ancestral species imprinting of a particular gene evolved. Furthermore, mechanistic considerations could influence the likelihood that imprinted expression is lost or reversed at a particular locus, and these considerations could act differently at maternally and paternally expressed loci [57,58]. Such considerations can be included in a detailed phylogenetic analysis using likelihood or Bayesian methods.

One or more of several scenarios could explain specific cases where the above framework fails. The first is that alternative theories (Box 1) could better explain the imprinting status of these genes. Second, the model might omit ecological or demographic details important for studying the evolution of traits in the species in question. Third, even positively selected alleles can be lost from a population as a result of genetic drift when such alleles are at low frequency; in consequence a locus at which imprinting is selectively advantageous might not be imprinted until positively selected alleles achieve a sufficiently high frequency to allow them to escape genetic drift. Alternatively, loci that are predicted to be imprinted, but are known to be biallelically expressed, could resist the evolution of imprinting due to some cost of monallelic expression. Such a cost might be due to the exposure of recessive deleterious mutations [59,60] or to some pleiotropic cost of imprinted expression [61]. It is possible to include these costs in models such as those presented in Box 2, and doing so would allow one to determine whether the costs are large enough to explain biallelic expression when imprinting might otherwise be predicted.

Concluding remarks

As a result of revolutions in sequencing technology, researchers will soon be able to collect genome-wide data on gene expression in many non-model species with unique ecological and demographic features. Such data will hopefully motivate the generation of demographically detailed

models as described above that predict which genes in these species might be imprinted. Comparing these predictions to genome-wide data for multiple species with variation in demography would provide a novel and comprehensive picture of the evolution of genomic imprinting; in those places where the models accurately describe the data, our understanding of the relevant evolutionary and demographic processes would be confirmed, whereas mismatches between the models and data would point to new avenues for theoretical research.

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