

Intragenomic politics

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Abstract. The mammalian genome contains multiple genetic factions with distinct interests in the outcomes of interactions among kin. In the context of an offspring's relations with its mother, these factions are proposed to align into two 'parties', one favoring increased demand by offspring and the other favoring reduced demand. A possible

alignment has inhibitors of demand located on the X chromosome and enhancers of demand located on autosomes, because X-linked loci are maternally derived two-thirds of the time by contrast to autosomal loci which are maternally derived half of the time.

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Family conflicts

The traditional view of the evolutionary process has been that natural selection acts to promote the survival and reproduction of individuals. From this view, all genes in the genome have a common interest in promoting individual fitness: what is good for one gene is good for all genes of the individual. This view must be modified in organisms that exhibit social interactions among relatives, including the maternal-fetal relationship in viviparous organisms.

Relatives are individuals that share some, but not all, of their genes. Consider a transaction between related individuals in which one individual takes some resource that has a value to himself (in terms of fitness) V_s but that would have had a value to the other individual V_o . Hamilton (1963) argued that natural selection would favor the individual taking the resource provided that

$$\frac{V_s}{V_o} > r \quad (1)$$

In this inequality, the coefficient of relatedness r represents the probability that the second individual carries a copy, by

recent common descent, of the gene in the first individual that is responsible for taking the resource. Intra-genomic conflict over whether to take the resource arises if different agents (genes) within the first individual have different coefficients to the second individual. Specifically, there is an internal conflict if agent 1 and agent 2 have coefficients of relatedness r_1 and r_2 , where

$$r_1 > \frac{V_s}{V_o} > r_2 \text{ or } r_2 > \frac{V_s}{V_o} > r_1 \quad (2)$$

One agent would gain a net benefit from taking the resource whereas the other would obtain a net loss.

Haig and Westoby (1989) recognized that such an internal conflict exists within offspring between genes of maternal and paternal origin over how much resource to take from a mother. This conflict is paradigmatic for a broader range of conflicts that arise in any situation in which individuals predictably interact with other individuals to whom they are differentially related through the male and female line (Haig, 1997, 2000a). The theory is not restricted in its application to the special case of mother-offspring interactions.

Theoretical analyses of these conflicts have been largely restricted to pairwise interactions between maternally derived and paternally derived autosomal genes. However, more than two conflicting interests may exist within an individual. The purpose of this paper is to begin to explore how multiple genetic interests will interact within an individual. For this purpose, I will consider a very simple version of the

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paradigmatic conflict over transfer of resources from mother to offspring. The model considers multiple factors with independent effects on an offspring's level of demand. Thus, the model does not consider complex interactions among factors. The qualitative conclusions of this model should also apply in more complex models.

Genomic factions

Consider a set of agents (present in the genome of an offspring) that produce factors influencing the level of demand Z that the offspring imposes on its mother, i.e. $Z = \Phi(A_1, \dots, A_n)$ where A_i is the amount of factor i produced by agent i . The offspring's reproductive value U is assumed to be an increasing function of Z whereas the mother's residual reproductive value V is assumed to be a decreasing function of Z . Agent i shares fully in U but obtains an expected share r_i of V , where r_i is the expected proportion of the mother's future offspring with identical-by-descent copies of agent i . A_i also contributes to a cost C that is subtracted from U . Thus, $C = \psi(A_1, \dots, A_n)$ represents costs to offspring that are determined by the amount of factor i produced (A_i), independent of the factor's effect on the level of demand (Z). Such costs can be considered to be the negative pleiotropic effects of producing factor i and are assumed to be an increasing function of A_i . Thus, a measure of agent i 's fitness is given by

$$W_i = (U - C) + r_i V$$

$$\frac{\partial U}{\partial Z} > 0, \frac{\partial V}{\partial Z} < 0, \frac{\partial C}{\partial A_i} > 0, A_i \geq 0 \quad (3)$$

The inclusive fitness effect of a change in production of factor i for agent i is

$$\frac{\partial W_i}{\partial A_i} = \frac{\partial U}{\partial Z} + r_i \frac{\partial V}{\partial Z} \frac{\partial Z}{\partial A_i} - \frac{\partial C}{\partial A_i} \quad (4)$$

Factor i will be said to be acting as a demand enhancer if $\partial Z / \partial A_i > 0$ and to be acting as a demand inhibitor if $\partial Z / \partial A_i < 0$.

Suppose that the system comes to an evolutionary equilibrium at which no agent can benefit from a change in the production of its own factor. There are two possibilities. First, agent i could be silent at equilibrium. Zero production of factor i at equilibrium ($\hat{A}_i = 0$) requires that $\partial W_i / \partial A_i < 0$. Second, agent i could produce an amount of factor i that corresponds to a local maximum of W_i with respect to A_i . The first-order condition for non-zero production of factor i at equilibrium ($\hat{A}_i > 0$) is that $\partial W_i / \partial A_i = 0$. This implies

$$\frac{\partial U}{\partial Z} + r_i \frac{\partial V}{\partial Z} = \frac{\partial C}{\partial A_i} \bigg/ \frac{\partial Z}{\partial A_i} \quad (5)$$

Let r_c be the ratio at equilibrium of the marginal benefit to the offspring of a change in demand and the marginal cost to its mother of the same change:

$$r_c = - \frac{\partial U}{\partial Z} \bigg/ \frac{\partial V}{\partial Z} \quad (6)$$

Substituting (6) into (5) gives

$$(r_i - r_c) \frac{\partial V}{\partial Z} = \frac{\partial C / \partial A_i}{\partial Z / \partial A_i} \quad (7)$$

Therefore, if factor i is produced at equilibrium, $(r_i - r_c)$ and $\partial Z / \partial A_i$ must have opposite signs because $\partial V / \partial Z < 0$ and $\partial C / \partial A_i > 0$. I will call r_c the *fulcrum* and refer to a set of agents with the same value of r_i as a *faction*. Equation (7) means that the greater the difference between r_i and the fulcrum, the greater the costs that the members of a faction would be prepared to incur to shift demand. If $r_i < r_c$, then $\partial Z / \partial A_i > 0$. Factor i must function as a demand enhancer. If, on the other hand, $r_i > r_c$, then $\partial Z / \partial A_i < 0$. Factor i must function as a demand inhibitor. These conclusions can be summarized as two general principles:

Factional unity: It is evolutionarily unstable for members of a faction to produce a costly demand enhancer together with a costly demand inhibitor. At evolutionary equilibrium, a faction should produce demand enhancers or demand inhibitors, but not both.

Factional alliances: If demand enhancers and demand inhibitors are both produced at evolutionary equilibrium, the factions producing demand enhancers (the Enhancer Party) should all have lower r_i than the factions producing demand inhibitors (the Inhibitor Party). Party membership will be determined by whether r_i falls above or below the fulcrum.

For simplicity, the model has been framed in terms of different genetic agents influencing the level of a one-dimensional 'demand,' where demand refers to an offspring's activities that enhance the offspring's reproductive value at cost to its mother's residual reproductive value. In real organisms, demand may have multiple dimensions (demand for amino acids, for calcium, for oxygen, etc.) that would be under partially independent genetic control. Each of these dimensions could be considered a different 'political issue,' with the possibility that r_c (and factional alliances) could shift for different issues. The question of multiple dimensions of demand requires formal analysis, but lies outside the scope of the present paper.

Special case 1: within faction

Agent i and agent j belong to the same faction if $r_i = r_j$. From (6), a necessary condition for an evolutionary equilibrium at which A_i and A_j are both positive is

$$\frac{\partial C}{\partial A_i} \bigg/ \frac{\partial Z}{\partial A_i} = \frac{\partial C}{\partial A_j} \bigg/ \frac{\partial Z}{\partial A_j} \quad (8)$$

This is a statement about the equalization of marginal costs at equilibrium. At such an equilibrium, the level of demand Z will be equally sensitive to small changes in A_i and A_j when these changes are measured in common units of cost. If it were otherwise, there would be an evolutionary incentive to redistribute production from the less cost-effective factor to the more cost-effective factor. This process would continue until marginal costs were equal or until there was zero production of the less cost-effective factor.

Factional efficiency: At evolutionary equilibrium, the production of demand enhancers (or demand inhibitors) will be

distributed among the members of a faction to equalize marginal costs for all factors influencing demand. Less efficient factors will be silenced.

The principle of factional efficiency may lead to the level of demand being determined by a small number of agents (one might call these the spokesgenes of their faction). The marginal cost of production of a demand enhancer includes negative pleiotropic effects that are unrelated to demand. At the equilibrium described by equation (5), higher levels of demand would be favored if marginal costs could be reduced. Assume that the effects of increased production of enhancers on demand are subject to diminishing marginal returns and consider a mutation that reduces the negative pleiotropic effects for one demand enhancer, thus increasing its efficiency relative to other enhancers. The effect of this mutation would be to favor a new evolutionary equilibrium at which there was increased production of the more efficient enhancer and decreased production of all other enhancers because of equalization of marginal costs. Iteration of this process would lead to the effective level of demand being determined by a small number of relatively 'pure' demand enhancers.

An example of a pure demand enhancer whose effects may be a product of this evolutionary process is insulin-like growth factor 2 (Igf2). Knockouts of the expressed copy of this imprinted gene result in newborn mice that are 60% normal size but otherwise well-proportioned (DeChiara et al., 1991). Thus, zero production of Igf2 has minimal pleiotropic effects. By contrast, overexpression of human IGF2 in Beckwith-Wiedemann syndrome results in multiple anomalies, in addition to increased size (Weksberg et al., 1993). This asymmetry in the effects of under- and over-production is explainable in terms of the scenario outlined above. The current high level of production of IGF2 is seen as the outcome of a process of evolutionary escalation in which the reduction of pleiotropic costs has allowed ever higher production. However, there has not been a similar evolutionary history of reducing pleiotropic costs of production well above the current level. (As an aside, the evolution of spokesgenes may partially explain the relative rarity of imprinted genes in the mammalian genome.)

Special case 2: shared product

Suppose that two agents from different factions contribute amounts A_i and A_j to the production of a common factor, $A_i + A_j = A$. Then

$$\frac{\partial W_i}{\partial A_i} = \frac{\partial U}{\partial Z} + r_i \frac{\partial V}{\partial Z} \frac{\partial Z}{\partial A} - \frac{\partial C}{\partial A} \quad (9)$$

$$\frac{\partial W_j}{\partial A_j} = \frac{\partial U}{\partial Z} + r_j \frac{\partial V}{\partial Z} \frac{\partial Z}{\partial A} - \frac{\partial C}{\partial A} \quad (10)$$

If A functions as demand enhancer and $r_i > r_j$, then $\partial W_i / \partial A_i < \partial W_j / \partial A_j$, because $\partial Z / \partial A > 0$ and $\partial V / \partial Z < 0$. That is, the agent with the lesser interest in the mother's residual reproductive value always gains a greater increase (or suffers a smaller decrease) in inclusive fitness from a marginal increase in the production of a demand enhancer. Therefore, an evolutionary equilibrium must have the form $A_i = 0$ ($\partial W_i / \partial A_i <$

0) and $A_j > 0$ ($\partial W_j / \partial A_j = 0$). Conversely, if A functions as a demand inhibitor, then $\partial W_i / \partial A_i > \partial W_j / \partial A_j$, because $\partial Z / \partial A < 0$. In this case, an evolutionary equilibrium must have the form $A_i > 0$ ($\partial W_i / \partial A_i = 0$) and $A_j = 0$ ($\partial W_j / \partial A_j < 0$).

Loudest-voice-prevails principle: Members of different factions are not expected to contribute a common product to a single pool. A demand enhancer should be produced solely by the agent with the smallest value of r_i . A demand inhibitor should be produced solely by the agent with the largest value of r_i .

Haig (1996, 1997) has used this principle to explain the silencing of maternally derived (henceforth madumnal) alleles for demand enhancers and paternally derived (henceforth padumnal) alleles for demand inhibitors at loci subject to genomic imprinting. The madumnal/padumnal terminology for genes derived from mothers/fathers is used because ambiguities can arise in discussions of the evolution of genomic imprinting when maternal and paternal can be used to refer *either* to genes present in mothers and fathers *or* to genes derived from mothers and fathers present in offspring.

Factional splits

Sex chromosomes

r_A , the expected share of V for an allele at an autosomal locus of an offspring, is an average of the allele's expected shares of V when maternally derived (r_M) and when paternally derived (r_P); namely, $r_A = (r_M + r_P)/2$. On average, an offspring's madumnal alleles would be present in half of its mother's other offspring, but padumnal alleles would be present in less than half, because a mother's offspring sometimes have multiple fathers. That is, $r_P < r_M = 1/2$. Suppose that all loci were initially autosomal and unimprinted and thus belonged to a single faction (r_A). Now consider the political ramifications of the origin of a dominant male-determining allele Y . Such an allele would always be paternally derived ($r_Y = r_P$). By contrast, its alternative allele X would be maternally derived two-thirds of the time ($r_X = [2r_M + r_P]/3$).

There is no reason why X or Y should have directly influenced demand, but their new role in sex determination would have altered the effective values of r_i for alleles at linked loci producing demand enhancers. At such loci, alleles that cause higher production would become positively associated with Y ($r_i < r_A$), whereas alleles that cause lower production would become positively associated with X ($r_i > r_A$). Moreover, the epistatic interaction between the sex-determining locus and demand-enhancing loci would favor suppression of recombination to preserve the selectively-favored combinations. Within the non-recombining region, $r_i = r_X$ for all X -linked alleles, and $r_i = r_P$ for all Y -linked alleles. If the r_A faction was a member of the Enhancer Party because of mother-offspring conflict, then the Y -linked faction would also be a member of this party ($r_Y < r_A < r_c$; see Hurst, 1994). The X -linked faction would join the Enhancer Party if $r_A < r_X < r_c$ or would join the Inhibitor Party if $r_A < r_c < r_X$.

The above arguments were framed in terms of the origins of X - and Y -linked factions. Each offspring would initially

Table 1. The appropriate value of r_i ('relatedness' to mother's other offspring) for genes with different patterns of expression and different chromosomal locations

	Unimprinted	Female-limited expression	Male-limited expression	Maternally expressed	Paternally expressed
Autosomal	$\frac{r_M + r_P}{2}$	$\frac{r_M + r_P}{2}$	$\frac{r_M + r_P}{2}$	r_M	r_P
X-linked	$\frac{2r_M + r_P}{3}$	$\frac{r_M + r_P}{2}$	r_M	r_M	r_P
Y-linked	r_P	–	r_P	–	r_P

have possessed two alleles at each sex-linked locus and the derivation of $r_X = (2r_M + r_P)/3$ should be understood in this context. With the degeneration of the Y-linked allele and the evolution of dosage compensation, the single maternally derived X-linked allele in males may have more 'power' to influence outcomes than either X-linked allele in females. I remain uncertain as to what should be the appropriate value of r_X under these circumstances, but, whatever the resolution of this question, r_X will be a maternal-biased average of r_M and r_P , whereas r_A will be an unbiased average, such that $r_M < r_X < r_A < r_P$. It is the ordering of factional interests, not the precise value of r_X , that will be relevant to subsequent arguments.

This section presupposes that the expression of X-linked agents is not sex-limited. An X-linked agent with female-limited expression would give equal weight to matrilineal and patrilineal expectations, and would thus belong to the 'autosomal' r_A faction. An X-linked agent with male-limited expression would be subject to selection only on its effects when maternally derived, and would thus belong to the r_M faction (Haig, 2000b).

Genomic imprinting

An agent at an imprinted locus belongs to the r_M faction when maternally derived but to the r_P faction when paternally derived, where $r_P < r_A < r_X < r_M$. Genomic imprinting thus creates the potential for at least four factions within an offspring. In order of increasing weight given to effects on its mother's residual reproductive value, these are: the r_P (paternally expressed imprinted) faction (including the Y-linked block); the r_A (unimprinted autosomal) faction; the r_X (unimprinted X-linked) faction; and the r_M (maternally expressed imprinted) faction. The loudest-voice-prevails principle predicts that demand enhancers will be silenced when maternally derived and demand inhibitors will be silenced when paternally derived (Wilkins and Haig, 2001). The r_P and r_M factions, if these factions exist, will be members respectively of the Enhancer and the Inhibitor Parties, but the party allegiances of the r_A and r_X factions will depend on the precise value of r_c . A summary of the factional allegiances of different kinds of genetic agents is provided in Table 1.

The origin of imprinting is predicted to cause a major increase in the level of expression of the active allele at evolutionary equilibrium. Consider an unimprinted autosomal demand enhancer. The maternal and paternal alleles each

produce an amount A_U such that the total level of expression is $2A_U$. At evolutionary equilibrium, $2A_U$ will be a compromise between a higher level of expression favored when the allele is paternally derived (A_P) and a lower level favored when the allele is maternally derived (A_M). That is, $A_M < 2A_U < A_P$. Suppose that imprinting evolves when a mother shuts down the expression of the alleles she transmits to her offspring. The initial effect will be to reduce total expression in her offspring to A_U . However, the locus is now subject to natural selection solely on its level of expression when paternally derived. At evolutionary equilibrium, the paternal allele is predicted to be expressed at level A_P , more than the combined level of expression from both alleles prior to imprinting (Haig, 1997). This is the pattern observed at the *IMPACT* locus (see Fig. 6 of Okamura et al., 2005): there is much higher expression of *IMPACT* mRNA in species in which the gene is imprinted (mouse, rat, rabbit) than in species in which the gene is unimprinted (pig, human, macaque).

Does the X chromosome inhibit demand?

The selective forces acting on the X chromosome differ from those acting on autosomes in many respects, and there has been a recent spate of papers comparing the functions of X-linked and autosomal genes (Ko et al., 1998; Saifi and Chandra, 1999; Wang et al., 2001; Graves et al., 2002; Lercher et al., 2003; Khil et al., 2004; Vallender and Lahn, 2004). My intention is not to review this literature but to focus on the specific prediction that the X chromosome should express a bias toward inhibiting the demands that offspring impose on their mothers. This can be called the hypothesis of X-linked Inhibitory Bias (XLIB).

The prediction that demand inhibitors will be preferentially located on the X chromosome arises from a fundamental asymmetry in the inheritance of X-linked and autosomal genes. An average autosomal gene has spent half its ancestry in female bodies and half in male bodies, and has thus been maternally and paternally inherited with equal frequency. By contrast, an average X-linked gene has spent two-thirds of its ancestry in female bodies and one-third in male bodies, and has thus been maternally inherited two-thirds of the time and paternally inherited one-third of the time. This asymmetry in the evolutionary histories of autosomal and X-linked loci leads to two predictions about the differential selective forces

acting on X-linked genes. First, the effects of X-linked genes should show a bias favoring females over males (sexual antagonism). Second, the effects of X-linked genes should show a bias favoring maternal over paternal interests (parental antagonism). The XLIB hypothesis invokes the latter asymmetry to predict that enhancers of demand will be preferentially located on autosomes whereas inhibitors of demand will be preferentially located on the X chromosome. Below, I review evidence that tests predictions of XLIB. The evidence is suggestive rather than compelling, but rapid progress in genomics and developmental biology should soon provide ample data for a definitive test.

Evidence from X chromosome aneuploids

Burgoyne et al. (1995) have summarized evidence that the presence of two X chromosomes, rather than one, inhibits early embryonic growth in mice. For example, XO fetuses are heavier than XX fetuses at 10.5 days post conception (dpc). Burgoyne et al. (1995) suggested that the most plausible explanation is that activity of two X chromosomes prior to X chromosome inactivation is suboptimal for development. This is consistent with the hypothesis that the effects of X-linked genes on growth are principally inhibitory. Ishikawa et al. (2003) have found that XO and XY placentas are heavier than XX placentas, suggesting that an extra dose of X-linked genes is also inhibitory for placental development in mice.

Evidence from X-linked placentally expressed genes

The placenta is the principal organ that mediates an offspring's demands on its mother during pregnancy. XLIB predicts that enhancers of placental demand will be preferentially located on autosomes whereas inhibitors of placental demand will be preferentially located on the X chromosome. This prediction is strengthened for mice because the paternal X chromosome is inactivated in trophoblast (Takagi and Sasaki, 1975; Moore et al., 2005). Thus, genes expressed in trophoblast will be subject to selection solely on their effects on matrilineal inclusive fitness.

There have been conflicting reports as to whether genes expressed in the placenta are underrepresented or overrepresented on the X chromosome. Ko et al. (1998) mapped the genomic location of 155 novel cDNAs expressed in the ectoplacental cone of 7.5-dpc mouse embryos. Contrary to the authors' own expectations, only two of these cDNAs were X-linked, a significant under-representation. By contrast, Hemberger (2002) reported that 13 out of 153 genes expressed in trophoblast mapped to the X chromosome. Khil et al. (2004) similarly found that genes preferentially expressed in the mouse placenta were overrepresented on the X chromosome. Ko et al. (1998) studied an earlier stage of placental development (ectoplacental cone) than did the other authors, and it is possible that this explains the discrepancy in conclusions. Such screens provide suggestive evidence that natural selection may act differently on X-linked and autosomal loci expressed in the placenta, but do not reveal whether X-linked loci inhibit or enhance demand.

Direct tests of XLIB will come from analysis of the functions of X-linked genes expressed in placental tissues. The

available data are limited and currently do not provide strong evidence for, or against, XLIB. A major constraint on interpretation is our limited understanding of the role of different cell types within the placenta and the consequences, for placental demand, of small changes in the relative development of different cell types. A second constraint is the interpretation of undergrowth in mutant animals, which may result from developmental disruption or decreased demand during gestation. The following discussion highlights interesting candidate genes involved in placental function, but the interpretation of mutant phenotypes with respect to XLIB requires further developmental data in order to evaluate the relationship between gene expression and demand.

Esx1 is an X-linked homeobox gene expressed in the mouse placenta (Li et al., 1997). Female mice with an inactivated paternal allele of *Esx1* appear normal, consistent with paternal X chromosome inactivation in extraembryonic tissues, but male and female mice with an inactivated maternal allele are 20% smaller than normal at five days postpartum (Li and Behringer, 1998). At first sight, this suggests that wild-type ESX1 functions as a demand enhancer, rather than as a demand inhibitor. However, the reduced weight of pups with a mutated maternal allele may be misleading. As fetuses, these pups are normal-sized with enlarged placentas at 13.5 days post copulation, with growth retardation developing late in gestation (Li and Behringer, 1998). Thus, it is possible that wild-type ESX1 does function as an inhibitor of early placental growth, with growth retardation developing late in gestation as a secondary effect of developmental disturbances due to complete loss of ESX1 function. Consistent with this interpretation, mouse interspecific hybrids with hyperplastic placentas show reduced expression of *Esx1* (Zechner et al., 2002). *Esx1* is a member of a gene family that includes other X-linked genes expressed in trophoblast. Two other members of this family, *Pem* (*Rhox5*) and *Gpbox* (*Rhox9*), have been knocked-out without discernable phenotype (Pitman et al., 1998; Takasaki et al., 2001).

PLAC1 is an X-linked gene with trophoblast-specific expression. In the mouse placenta, it is expressed in ectoplacental cone, trophoblast giant cells, and labyrinthine trophoblast (Cocchia et al., 2000). In the human placenta, *PLAC1* mRNA is strongly upregulated as villous cytotrophoblasts undergo differentiation into syncytiotrophoblasts (Massabba et al., 2005).

Inactivating mutations of the X-linked *CHM* gene cause photoreceptor cell degeneration in humans. Both sexes transmit *CHM* mutations to offspring in humans, but *Chm* mutations are associated with embryonic lethality in mice because of defects in placental development (van den Hurk et al., 1997; Shi et al., 2004). The placentas of mutant mice have increased trophoblast giant cells but reduced spongiotrophoblast, associated with embryonic growth retardation. This placental phenotype resembles that of mice with an inactivated maternal copy of *Mash2* (*Ascl2*) (Guillemot et al., 1995; Shi et al., 2004). An interpretation in terms of effects on demand remains unclear.

Cited1 is an X-linked gene expressed in mouse trophoblast. Inactivation of *Cited1* results in an enlarged and ir-

regular spongiotrophoblast with a reduced labyrinthine layer in the placenta. Mutant mice are growth restricted and most die shortly after birth (Rodriguez et al., 2004).

Evidence from X-autosome interactions

The existence of a similar phenotype from inactivating mutations of *Chm*, an X-linked gene, and of *Mash2 (Ascl2)*, a madumally expressed autosomal gene (see above), is consistent with the factional alliances proposed in this paper. A number of other examples from the literature suggest similar comparisons that are broadly compatible with XLIB.

Loss-of-function mutations of *Gpc3* (glypican-3) result in Simpson-Golabi-Behmal syndrome (SGBS) in humans (Li et al., 2001) and fetal overgrowth in mice (Cano-Gauci et al., 1999; Chiao et al., 2002). Overgrowth in SGBS, an X-linked disorder, has many phenotypic resemblances to overgrowth in Beckwith-Wiedemann syndrome (BWS), a disorder of imprinted autosomal loci, suggesting that SGBS and BWS may involve disruptions in a common pathway (Hughes-Benzie et al., 1992). BWS can be caused by mutations in the active madumal allele of *CDKN1C*, an imprinted locus encoding a cyclin-dependent kinase inhibitor (Hatada et al., 1996), or by reactivation of the silent madumal allele of *IGF2* (Weksberg et al., 1993). Thus, similar phenotypes can be caused by inactivation of two putative demand inhibitors, one X-linked (*GPC3*) and the other autosomal but padumally silent (*CDKN1C*), or by the overexpression of a madumally silent demand enhancer (*IGF2*). This pattern is consistent with the predicted factional alliances of my model.

Another potential interaction between an imprinted autosomal locus and an X-linked locus comes from Prader-Willi syndrome (PWS). HBII-52 is a padumally-silent small nucleolar RNA (from the PWS region on chromosome 15) that is suspected of influencing RNA editing of transcripts of *HTR2C*, an X-linked serotonin receptor (Cavaillé et al., 2000). My model predicts that the modifications to *HTR2C* transcripts that are caused by HBII-52 will act to decrease demand relative to transcripts that are unmodified by HBII-52. This prediction remains to be tested. An interpretation of the phenotype of Prader-Willi syndrome in terms of postnatal behavioral demands of offspring on mothers has been attempted by Haig and Wharton (2003).

Reciprocal crosses between two species of deer mice, *Peromyscus maniculatus* and *P. polionotus*, exhibit marked difference in placental size and birth weight. When *P. maniculatus* is the mother, F1 hybrids and their placentas are smaller than is typical of either parental species, whereas hybrid mice and placentas are larger than either species when *P. polionotus* is the mother (Dawson, 1965; Rogers and Dawson, 1970; Vrana et al., 1998). The combination of an imprinted (padumally expressed) autosomal allele from one species and an X-linked allele from the other makes a major contribution to the difference in placental weight between the reciprocal crosses (Vrana et al., 2000).

If the existence of an interaction between an imprinted autosomal gene and an X-linked gene were the only available information, one would be unable to distinguish between two interpretations: (1) the autosomal locus encodes a demand

enhancer and the X-linked locus a demand inhibitor, with alleles from *P. polionotus* having 'weaker' effects than alleles from *P. maniculatus*, or (2) the reverse, the autosomal locus encodes an inhibitor and the X-linked locus an enhancer, with 'weaker' alleles coming from *P. maniculatus*. However, information about mating systems of the two species supports the first interpretation. *P. polionotus* is a 'monogamous' mouse whereas *P. maniculatus* has a polyandrous mating system (Vrana et al., 1998; Haig, 1999). Therefore, the value of rP will be lower for *P. maniculatus* than for *P. polionotus*. As a result, *P. maniculatus* is predicted to have the 'stronger' alleles, with its padumal genome making greater demands on mothers than the corresponding genome of *P. polionotus*, and its madumal genome predicted to be more assertive in resisting padumal demands. Thus, interspecific hybrids between *P. maniculatus* and *P. polionotus* provide evidence of an association of demand inhibitors with the X chromosome.

Interspecific F1 hybrids in the genus *Mus* show a similar contrast between placental hypoplasia in one direction of the cross and placental hyperplasia in the other, with genetic evidence for large effects of the X chromosome (Zechner et al., 1996, 2002; Hemberger et al., 1999). However, not enough is known about mating systems in these species to interpret these X-linked effects as inhibitory.

Conclusions

There are two major conclusions I wish to draw from the models of this paper. The first concerns the complexities of multiple genetic interests within an individual. I have argued that such multipartite conflicts among *factions* have a tendency to simplify into a bilateral conflict between two parties, one favoring more of some 'quantity' (e.g. 'demand') and the other favoring less. The second conclusion concerns relations between X-linked and autosomal genes. These genes will belong to different factions, with X-linked genes showing bias in favor of matrilineal over patrilineal interests. It is possible that they will also belong to different parties in which case X-linked genes are predicted to inhibit the demands offspring make on their mothers. Further research into the developmental effects of X-linked, placentally expressed genes may benefit from considering the role these play in demand during gestation.

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