

Gestational drive and the green-bearded placenta

(meiotic drive/parent–offspring conflict/intragenomic conflict/cell adhesion)

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ABSTRACT A “green beard” refers to a gene, or group of genes, that is able to recognize itself in other individuals and direct benefits to these individuals. Green-beard effects have been dismissed as implausible by authors who have implicitly assumed sophisticated mechanisms of perception and complex behavioral responses. However, many simple mechanisms for genes to “recognize” themselves exist at the maternal–fetal interface of viviparous organisms. Homophilic cell adhesion molecules, for example, are able to interact with copies of themselves on other cells. Thus, the necessary components of a green-beard effect—feature, recognition, and response—can be different aspects of the phenotype of a single gene. Other green-beard effects could involve coalitions of genes at closely linked loci. In fact, any form of epistasis between a locus expressed in a mother and a closely linked locus expressed in the fetus has the property of “self-recognition.” Green-beard effects have many formal similarities to systems of meiotic drive and, like them, can be a source of intragenomic conflict.

In a previous paper, I discussed (1) genetic conflicts in human pregnancy. Two sources of conflict were emphasized: conflict between genes expressed in the mother and genes expressed in the fetus and conflict between the maternal and paternal genomes of the fetus. Brief mention was made of a conflict that could arise if genes in the mother were able to favor offspring that carried their replicas, at the expense of offspring without replicas. This would create a conflict, within the mother’s genome, between the agents of nepotism and other genes that were not systematically favored. I called this hypothetical mechanism gestational drive to emphasize its conceptual similarity to meiotic drive. The present article explores the relationship between parent–offspring conflict and meiotic drive, argues that systems of genetic self-recognition are plausible at the maternal–fetal interface, and briefly discusses the implications for human disease.

Parent–Offspring Conflict and Meiotic Drive

Suppose that a mother has limited resources available for reproduction and produces offspring one at a time. The less she invests in each offspring, the more offspring she produces, but the lower the probability of survival for each individual offspring. The amount of investment per offspring that maximizes maternal fitness can be represented by m^* , the quantity that optimizes the trade-off between offspring number and offspring quality (2). Consider a single Dd female in a population of dd individuals. If meiosis is fair, each of this female’s offspring has an equal chance of being Dd or dd . All other mothers produce an unbroken sequence of dd offspring, each of whom receives m^* (by assumption). Therefore, if D causes offspring to receive $m^* + \delta$, the Dd mother will leave fewer

surviving offspring than a dd mother, even though the offspring who receive the extra amount have enhanced survival.

Does the lower “fitness” of the Dd mother ensure that D will be eliminated by selection? The answer depends, in part, on whether D increases the amount of resources received by each of the mother’s offspring, or only the 50% with a Dd genotype. The D allele would be at a selective disadvantage if it were expressed in the mother and caused all of her offspring to receive $m^* + \delta$, because any departure from m^* reduces the number of surviving offspring (by definition of m^*), of which number 50% would be Dd . However, if D were expressed in offspring and caused Dd offspring (but not their siblings) to receive $m^* + \delta$, more than 50% of the survivors would be Dd because they individually received a greater share of maternal care than each of their dd siblings. Thus, D could increase in frequency when rare, provided that the “more than 50%” of the smaller number of surviving offspring of a Dd mother was greater than the 50% of the larger number of surviving offspring of a dd mother. This informal analysis shows that the unbeatable level of provisioning for genes expressed in a mother (m^*) can be subverted by genes expressed in offspring that take a little bit extra ($m^* + \delta$). Therefore, genes expressed in offspring will be selected to extract more resources from parents than genes expressed in parents will be selected to supply (3).

The analysis also clarifies the conceptual similarity between models of meiotic drive and models of parent–offspring conflict. In the former, genetic agents are able to invade a population because they distort the process of meiosis to gain access to more than 50% of successful gametes. In the latter, genes that cause increased offspring demands are able to invade a population because they distort the process of parental care to gain more than their fair share of resources. This underlying similarity has been obscured because models of meiotic drive usually emphasize parameter values for which the segregation distorter does not go to fixation, whereas models of parent–offspring conflict are usually constructed in a manner that ensures the population is monomorphic at equilibrium. The pragmatic reason for this difference is that segregation distortion cannot be observed in a DD homozygote, whereas parent–offspring conflict will still be expressed in a population in which all parents and all offspring are DD . The crucial methodological difference is that models of meiotic drive assume a small number of alleles of fixed effect whereas most models of parent–offspring conflict use calculus to find evolutionarily stable strategies and thus implicitly assume an infinite set of alleles.

Green Beards

Hamilton (4) recognized that the impartiality of parental genes toward offspring depended on a gene’s lack of information about which offspring inherited which genes. He speculated about “something like a supergene affecting (a) some percep-

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Abbreviations: NK, natural killer; IL, interleukin; NIMH, noninherited maternal haplotype.

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tible feature of the organism, (b) the perception of that feature, and (c) the social response consequent upon what was perceived." He continued that "If some sort of attraction between likes for purposes of co-operation can occur the limits of evolution of altruism . . . would be very greatly extended, although it should still never happen that one individual would value another more highly than itself, fitness for fitness. And if an individual can be attracted toward likes when it has positive effects—benefits—to dispense, it can presumably be attracted the other way, toward unlikes, when it has negative effects to dispense (i.e., when circumstances arise which demand combat, suggest robbery, and so on)."

Dawkins (5) commented "It is theoretically possible that a gene could arise which conferred an externally visible 'label,' say a pale skin, or green beard, or anything conspicuous, and also a tendency to be specially nice to bearers of that conspicuous label. It is possible, but not particularly likely. Green beardedness is just as likely to be linked to a tendency to develop ingrowing toenails or any other trait, and a fondness for green beards is just as likely to go together with an inability to smell freesias. It is not very probable that one and the same gene would produce both the right label and the right sort of altruism." Since then, social interactions that depend on the direct perception of genetic identity have been known as green-beard effects, but they have usually been considered little more than a theoretical curiosity because of the requirement for close linkage of genes that determine Hamilton's triad of feature, perception, and response. Queller (6), however, showed that green-beard effects need not require implausible recognition mechanisms, and in this paper, I will argue that responses based on genetic self-recognition are quite likely in organisms with intimate placental interfaces between maternal and offspring tissues.

Hamilton's discussion (4) did not address an important complication of the idea that altruism could be contingent on the direct perception of genetic identity. If a parent discriminates between the members of a brood on the basis of some segregating feature, such discrimination will benefit some of the parent's genes at the expense of others. If the total number of surviving offspring is decreased, the nepotistic haplotype gains an advantage, not only at the expense of alternative haplotypes, but also at the expense of other genes that segregate independently of the haplotype (7–9). Thus, discussions of the inclusive fitnesses of individuals can be misleading, because an individual's fitness is ill-defined in the context of intragenomic conflict.

Ridley and Grafen (8) contrasted green-beard effects that operate between relatives with those that operate between nonrelatives. If costs and benefits are borne solely by green-bearded individuals, a green beard can spread only if it increases the combined fitness of the interactants. Therefore, an unlinked modifier that suppressed both the receipt and donation of benefits would be eliminated by selection because the modifier would occur with equal frequency in potential donors and recipients (and would thus lose more than it gained by the suppression). This argument does not apply to modifiers that suppress donation but not receipt. However, for interactions among relatives, costs could be imposed on relatives without green beards for lesser benefits gained by relatives with green beards. In this case, Ridley and Grafen (8) noted that the green-beard effect would be analogous to a system of meiotic drive and, like meiotic drive, would be expected to be suppressed by modifiers elsewhere in the genome that segregate independently of the costs and benefits.

Genes expressed in offspring are widely thought to favor their own offspring, whereas genes expressed in parents are thought to provision offspring impartially. But it is the information available to the gene that is the logically crucial element, not where the gene is expressed. A gene can invade a population if it enables its possessors to obtain a distorted

share of maternal care, whether the gene is expressed in a heterozygous mother or in her offspring. In this manner, "parent-offspring conflict" can be expressed within the mother's genome, between the genes for a green beard and genes with a different pattern of segregation. Further complexities would arise if a mother were heterozygous for multiple independent green beards.

Cell Adhesion

During the early stages of human placentation, placental cells (trophoblast) invade the mother's spiral arteries and transform these vessels into large-bore low-resistance channels bringing blood to the placenta. The walls of the spiral arteries are surrounded by maternal cells that are similar to natural killer (NK) cells of the immune system. These cells may function to limit the extent of placental invasion, and thus restrict the offspring's access to maternal resources. An evolutionary conflict is expected between maternal and fetal genes, with fetal genes favoring a greater depth of invasion by trophoblast (1). Genetic self-recognition at the maternal-fetal interface would enable genes for green beards in maternal NK cells to give green-bearded embryos greater access to maternal resources in preference to their clean-shaven sibs. Whether favoritism is observed would depend on whether or not the relevant genes had spread to fixation. All embryos would be treated equally if a green beard were fixed in a population, in which case its effects would give the appearance of maternal-fetal cooperation.

Some homophilic cell adhesion molecules combine all the requirements for a green-beard effect within a single molecule—their extracellular domains recognize copies of themselves on other cells while their cytoplasmic domains are able to initiate actions within the cell. An allelic variant of such a molecule, with higher affinity for cells expressing the same variant, would constitute a self-recognition device if it were expressed by cells on both sides of the maternal-fetal interface, and would constitute a green beard if self-recognition initiated actions that favored the fetus. A variety of self-adhesive molecules are expressed in the pregnant uterus: P-cadherin is abundantly expressed on placental cells and the maternal decidua of mice (10) whereas a related molecule, E-cadherin, is expressed on the corresponding cells of humans (11); neural cell adhesion molecule (NCAM/CD56) exhibits homophilic binding (12) and is strongly expressed on human trophoblasts found within the lumens of maternal spiral arteries (13) and on maternal NK cells that surround these arteries (14); and a homophilic adhesion molecule (trophinin) has recently been implicated in the initial adhesion of macaque blastocysts to the endometrium (15).

Cell adhesion molecules need not be homophilic to satisfy the requirements of a green beard, provided that receptor and counterreceptor are sufficiently closely linked. For example, CD2 and CD58 (LFA-3) are cell-surface receptors of the human immune system that are each other's principal ligand. Their genes are located within 250 kb on human 1p13 and may have been derived from a recent gene duplication (16). One could imagine an interaction between a variant CD2 (expressed on maternal NK cells) and a variant CD58 (expressed on trophoblast) that benefited embryos who inherited a maternal haplotype with both variants or that harmed embryos without this haplotype. In this scenario, the interaction of CD2 and CD58 would sometimes activate and sometimes inhibit NK cells, depending on the precise allelic identity of receptor and counterreceptor. The two loci would be analogous to the Distorter and Responder loci of a system of meiotic drive. CD2 is expressed on many uterine NK cells (17) but expression of CD58 on trophoblast has not been reported.

Enzyme–Substrate, Ligand–Receptor, and Other Interactions

Green beards have often been dismissed as implausible for the kinds of interactions of traditional concern to ethologists, but the intimacy of maternal–fetal relations allows natural selection to act on simple forms of recognition. In fact, any epistatic interaction between the products of closely linked loci, where one locus is expressed in maternal cells and the other in placental cells, is a potential device for genetic self-recognition because an offspring's treatment by its mother depends on which genes it inherits. Thus, linkage disequilibrium (generated by transgenerational epistasis) provides genes with better information about the location of their replicas than is provided by relatedness alone. The possibility of epistasis between loci expressed in different individuals is, of course, not limited to maternal–fetal relations.

A casual inspection of the human genome reveals many pairs of linked loci that are potential candidates for transgenerational epistasis: including ligands and their receptors, enzymes and their substrates, and growth factors and their binding proteins. I will use three pairs of linked functionally related loci from the human genome to illustrate the kinds of interaction that could constitute a system of gestational drive. These are the genes for renin and angiotensinogen, transferrin and the transferrin receptor, interleukin 1 (IL-1) and the IL-1 receptors. My purpose is not to argue that these particular loci do, in fact, constitute agents of internal conflict. Rather, it is to indicate the mundane nature of the biochemical interactions that can fulfill the requirements for a green-beard effect during pregnancy. If experience is any guide, natural selection is remarkably effective at finding clever tricks for short-term genetic advantage.

The genes for renin and angiotensinogen are located on distal 1q (18). Renin cleaves angiotensinogen to release angiotensin, which raises blood pressure. Other things being equal, a fetus benefits from higher maternal blood pressure because this increases the flow of maternal blood through the intervillous space of the placenta (1). Therefore, if a variant angiotensinogen were preferentially cleaved by a variant renin and their respective genes occurred on the same haplotype, the haplotype could benefit from gestational drive. In this scenario, the driving haplotype would produce angiotensinogen in maternal cells and renin in placental cells, with both products released into the maternal circulation. The blood pressure of a heterozygous mother would then rise higher in those pregnancies in which the fetus inherited the driving haplotype and produced the variant renin.

Similarly, a fetus obtains all of its iron from its mother, who may become iron-depleted during pregnancy. Iron circulates in the mother's blood complexed to transferrin, which binds to transferrin receptors on trophoblast (19, 20). These cell-surface receptors internalize the complex and release the iron. If a maternal haplotype carried a gene for a maternally expressed transferrin with a preferential affinity for its linked receptor expressed on trophoblast, iron would be preferentially transferred to offspring who inherited the haplotype. Such a system could be interpreted as maternal beneficence to offspring with the haplotype or maternal neglect of their sibs, depending on what level of iron transfer one adopted as a baseline. Transferrin and its receptor are linked on human chromosome 3q, but the linkage is not close (21) and a system of gestational drive seems unlikely.

The structurally related genes for IL-1 α , IL-1 β , and the IL-1 receptor antagonist are tightly linked at 2q14 (22, 23) whereas the IL-1 type 1 receptor has been mapped to 2q12 (24) and the IL-1 type 2 “decoy” receptor to 2q12–q22 (25). IL-1 α and IL-1 β are major promoters of inflammatory responses via the type 1 receptor, whereas IL-1 receptor antagonist and the type 2 receptor can inhibit these responses. The close linkage of

ligands, receptors, antagonists, and decoys in the human genome—but not in mice (26)—is rich with possibilities for epistasis during the invasive phase of human placentation between genes expressed in decidua and genes expressed in trophoblast.

Green Beards and Intragenomic Conflict

Few formal models specifically address gestational drive, but models of meiotic drive provide some guidance; the principal added complication being the presence of a paternal genome. Meiotic drive involves an interaction between the two alleles at a locus in a diploid spermatocyte or oocyte, whereas gestational drive involves interactions between two maternal alleles and one or more paternal alleles. The dynamics of gestational drive will, therefore, depend on the pattern of paternity, whether monandrous or polyandrous.

Wade and Beeman (27) presented a one-locus model in which a maternally expressed gene caused the death of offspring without the gene, for the benefit of siblings with the gene. Their model predicted fixation of the gene or a balanced polymorphism, depending on the severity of homozygous effects on maternal fitness. Wilson and Dugatkin (28) explored a haploid model in which a gene caused altruism to be withheld from siblings that did not carry the gene. Although this model was ostensibly about interactions among sibs, it can be interpreted as a model of relations between a gene in a diploid mother and the maternal alleles in her offspring. That is, the maternal gene causes resources to be preferentially distributed to offspring who inherit the gene. Feldman and Eshel (29) developed a two-locus model in which a gene *B* caused parents to redistribute resources from offspring without a gene *a* to offspring with *a*. For some parameter values, an *aB* haplotype could invade a population fixed for *Ab*, even though neither *a* nor *B* could invade on its own.

An informal argument suggests significant differences between green-beard effects that confer benefits on offspring with a particular haplotype and those that withhold benefits from offspring without a haplotype. Suppose that a maternal haplotype confers a benefit (*B*) on an offspring with the haplotype at a cost (*C*) to future offspring. The maternal haplotype benefits on average if $B > 2C$ because future offspring have a 50% chance of inheriting the haplotype. By contrast, if the maternal haplotype imposed the same cost on an offspring without the haplotype for the benefit of future offspring, the haplotype would benefit for any $B > 0$ because the cost is borne by an individual who does not inherit the haplotype. For example, a gene that caused heterozygous mothers to abort embryos without the gene could be maintained in a population if, as seems reasonable, there were some reproductive compensation for early pregnancy losses.

Once (and if) a gestational green beard reaches fixation, it no longer distorts the distribution of benefits among offspring. If the green beard functioned by conferring extra benefits on green-bearded offspring, each offspring would receive more resources than the maternal optimum, and the standard theory of parent–offspring conflict would apply—genes expressed in mothers (but not in offspring) would be selected to reduce the amount received by offspring, even if the maternally expressed genes are alleles at the green-beard locus itself. If gestational drive functioned by withholding resources from offspring without green beards, it is possible that each offspring would receive the maternal optimum at fixation (but this would depend on the outcome of parent–offspring conflict at other loci).

Genetic self-recognition allows benefits within segregating families to be preferentially distributed to green-bearded members. This creates an intragenomic conflict because different parts of the genomes of green-bearded donors have different probabilities of being present in green-bearded ben-

efficiaries. A gene's representation in green-bearded sibs will depend on the closeness of its linkage to the green beard and whether linkage is in coupling or repulsion. As a corollary, genetic modifiers of green-beard effects will be subject to different selective forces depending on the closeness and phase of their linkage to the green beard. Modifiers that benefit from gestational drive will be selected to enhance drive, whereas modifiers at other chromosomal locations will evolve to suppress drive: that is, suppressors will be favored at unlinked and weakly linked loci, whereas enhancers will be favored in coupling, and suppressors in repulsion, at loci closely linked to the agents of drive (30).

Modifiers of gestational drive could take many forms. If a homophilic adhesion molecule on NK cells triggered a cytolytic attack against trophoblasts that expressed a different version of the molecule, genetic modifiers could act to deflect or suppress the cytolytic response at any stage between cell-surface recognition and unleashing the attack, with the action of natural selection at modifier loci depending on their linkage to the green-beard locus. The operation of a two-locus green beard depends on linkage disequilibrium. Therefore, genetic modifiers, or chromosomal rearrangements, that influence the frequency of recombination between the loci will be subject to natural selection because of their effects on gestational drive. Thomson and Feldman (31) and Haig and Grafen (32) examined this three-locus problem in the context of meiotic drive. In general terms, modifiers that benefit from epistasis at the green-beard loci (i.e., those that are linked in coupling) will be selected to reduce recombination, whereas modifiers at other locations will be selected to increase recombination. If gestational drive is a major problem for viviparous organisms, one might expect higher recombination in females than in males; but other hypotheses would undoubtedly make the same prediction.

A difficult problem posed by the paternal genome has not yet been addressed. The maternal genes of an offspring will generally favor a level of maternal investment that is intermediate between a higher level favored by the offspring's paternal genes and a lower level favored by genes in the mother (33). Intuitively, an offspring's maternal genes will side with the offspring's paternal genes if investment is less than this intermediate level and will side with the mother's genes if investment is greater. Therefore, one might expect the genes for a green beard to side sometimes with the mother and sometimes with the offspring's paternal genes. This is because a genetic agent expressed in mothers that confers benefits on offspring who inherit the agent is subject to similar selective forces to a maternal gene expressed in offspring. The interplay of forces is complex, and formal genetic models are required.

Implications for Disease

If a system of gestational drive goes to fixation, all individuals will have green beards and all will be treated equally. Balanced polymorphisms however are of potential medical significance because gestational drive would then be associated with fitness differences within the population. At a stable polymorphic equilibrium, gestational drive must be balanced by countervailing fitness costs to (at least some) individuals with green beards. For example, the benefits that a driving haplotype (*D*) gains from preferential treatment of its bearers by heterozygous mothers (*Dd*) could be balanced by viability costs to individuals that receive the haplotype in double dose (*DD*). Although polymorphism is maintained by fitness costs to *DD* homozygotes, this is not a simple example of heterozygote advantage because there are winners (*D*) and losers (*d*) within the genome of *Dd* heterozygotes. A *D* haplotype could be maintained at appreciable frequencies by segregation distortion or gestational drive even if *dd* is the most fit genotype (as measured by fertility and viability).

Gestational drive may also be associated with fitness costs for the *dd* offspring of *Dd* mothers, even though *dd* offspring of *dd* mothers are perfectly healthy. The variable phenotype of the *dd* genotype would conventionally be interpreted as incomplete penetrance of "predisposing" *d* alleles and the *D* haplotype would be interpreted as "protective" because it does not occur in affected individuals. In such cases, geneticists risk "blaming the victim" when the true culprit is the noninherited maternal haplotype (NIMH). Negative fitness effects of NIMHs should not be surprising because natural selection is indifferent to the effects of a haplotype on individuals without the haplotype, unless these effects have consequences for individuals with the haplotype. Effects of NIMHs at the major histocompatibility complex have been reported for some autoimmune diseases (34, 35). For example, one study found HLA-DR6 was underrepresented among sufferers of rheumatoid arthritis but overrepresented among their NIMHs (34).

Thus, evidence of gestational drive may sometimes have been overlooked because disease is caused by genes that are absent in affected individuals and because the results of *in vitro* experiments will often seem inconsistent unless attention is paid to allelic variation within the population. The paucity of reports of gestational drive, however, is unlikely to be explained solely by the theoretical blinkers of previous research. Gestational drive requires maternal haplotypes to have information about which offspring inherit which genes, a requirement that is most easily satisfied by a maternal gene that engages in homophilic interactions with itself in offspring. Otherwise, gestational drive requires long-range linkage disequilibrium between epistatic loci, and long-range disequilibria are usually degraded rapidly by recombination. Therefore, gestational drive is most likely to occur in regions of the genome where recombination is suppressed, such as the extended haplotypes of the major histocompatibility complex or within segregating inversions (if these occur at appreciable frequency in the human population).

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