



Opinion piece

Cite this article: Haig D. 2013 Imprinted green beards: a little less than kin and more than kind. *Biol Lett* 9: 20130199.
<http://dx.doi.org/10.1098/rsbl.2013.0199>

Received: 27 February 2013

Accepted: 15 July 2013

Subject Areas:

evolution, cellular biology, plant science

Keywords:

inclusive fitness, imprinting, siRNA, green beards, relatedness

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One contribution of 12 to the Special Feature '50 Years on: the legacy of William Donald Hamilton' organized by Joan Herbers and Neil Tsutsui'.

Imprinted green beards: a little less than kin and more than kind

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RNA is complementary to the DNA sequence from which it is transcribed. Therefore, interactions between DNA and RNA provide a simple mechanism of genetic self-detection within nuclei. Imprinted RNAs could enable alleles of maternal and paternal origin to detect whether they are the same (homozygous) or different (heterozygous), and thereby provide strategic information about expected relatedness to siblings.

'The situations in which a species discriminates in its social behaviour tend to evolve and multiply in such a way that the coefficients of relationship involved in each situation become more nearly determinate'. [1, p. 24]

1. Introduction

The probabilities that factor into calculations of relatedness can be parsed into probabilities, given a genealogy and uncertainties of genealogy. Genealogy may be uncertain, for instance, because a littermate is sometimes a full-sib, sometimes a half-sib, or because a herd contains kin of different degrees, but members cannot distinguish the categories [2]. Hamilton proposed that natural selection favours reduction of genealogical uncertainty. He further proposed that natural selection favours 'discrimination of those individuals which do carry one or both of the behaviour-causing genes from those which do not' ([1], pp. 24–25). Here, he considered the possibility of genes 'recognizing' their own copies and directing benefits on the basis of this privileged information [1].

Dawkins called gene-based discrimination 'the Green-Beard Altruism Effect'. He envisaged a gene that encoded both a phenotypic label, the green beard, and the tendency to be nice to green-bearded individuals [3]. Kinship is a major cause of identity by kind but the label is independent of genealogy. Green-beard effects were considered implausible because genetic self-recognition and altruism were viewed as complex behaviours unlikely to be encoded by a single gene or tightly linked cluster of genes. Kinship seemed a much stronger basis for altruism. The situation is reversed at the genic level. It is much simpler to imagine a gene, or its products, preferentially interacting with identical genes, or their products, than to envisage a gene that recognizes half-cousins [4,5].

The interaction between labels of genic identity (green beards) and parental origin (genomic imprinting) makes possible a novel form of discrimination. I first review effects of genomic imprinting on estimates of genic relatedness, then describe the unusual evolutionary properties of imprinted green beards.

2. Parent-specific relatedness

The standard way to calculate the probability that a gene in *A* has an identical-by-descent copy in *B* is to multiply by one-half for each generation back from *A* to a common ancestor *C*, by one-half for each generation forward from *C* to *B*, and then sum these products for all distinct paths linking *A* to *B*. Ascending and descending factors of one-half arise from different sources of uncertainty. For

each step backward from offspring to parent, a randomly chosen gene in the offspring may come from either mother or father. For each step forward from parent to offspring, the offspring receives one of two alleles in the parent.

Genomic imprinting enables genes to discriminate between matrilineal and patrilineal kin [6]. The factor of one-half for the first backward step resolves into a factor of one or zero when genes have imprinted expression. In the case of sibs, an imprinted gene of maternal origin is definitely present in an offspring's mother and transmitted to littermates with probability one-half, whereas an imprinted gene of paternal origin is definitely present in the offspring's father and transmitted to littermates with probability $p/2$, where p is the chance of shared paternity. Because relatedness is lower when genes are paternally derived, imprinted genes are predicted to behave more 'selfishly' toward littermates when paternally derived and less 'selfishly' when maternally derived.

If genes carried imprints of grandparental origin, then factors of one-half for the first and second backward steps would resolve into factors of either one or zero [7]. Thus, half-cousins who share a maternal grandmother are related by one-quarter for genes of maternal grandmaternal origin but are unrelated for all other genes. As yet, there is no clear evidence for second-order imprints.

3. Imprinted green beards

Complementarity between the strands of a double helix, and between DNA and the RNA transcribed from its sequence, allow allele-specific interactions within nuclei between different copies of the same gene. A diverse fauna of small RNAs participate in a wide variety of regulatory processes. Many of these processes depend on selective interaction with complementary DNA or RNA [8]. Because complementary sequences represent each other, their interaction can be viewed as a simple form of genetic self-recognition that makes possible intranuclear green-beard effects.

24-nucleotide small-interfering RNAs (siRNAs) of *Arabidopsis* cause RNA-directed DNA methylation (RdDM) and transcriptional silencing of DNA sequences with motifs complementary to the siRNA. The template for synthesis of siRNAs is probably the sequence subject to RdDM [8]. Dosage-sensitive responses to an siRNA would allow a sequence to 'count' its copies within a nucleus. Imprinted expression of an siRNA would allow alleles of maternal origin to signal their presence to alleles of paternal origin or vice versa. A silent allele can 'hear' what the other allele has to say.

An abundant class of maternally expressed siRNAs (mesiRNAs) are expressed from madumnal (maternally derived) chromosomes of endosperm [9]. MesiRNAs target genes that delay onset of endosperm cellularization and prolong endosperm proliferation [10], consistent with theoretical predictions that maternally expressed imprinted genes should inhibit endosperm growth [11].

Consider the introduction of mesidna (a motif that encodes mesiRNA) into a previously unimprinted gene encoding a growth enhancer. Transcription of A , the established allele without mesidna, is expected to be a compromise between a lower level favoured as a madumnal allele and higher level favoured as a padumnal (paternally derived) allele. By contrast, A' , the initially rare allele with mesidna, will be transcribed at the same level as A when it is a

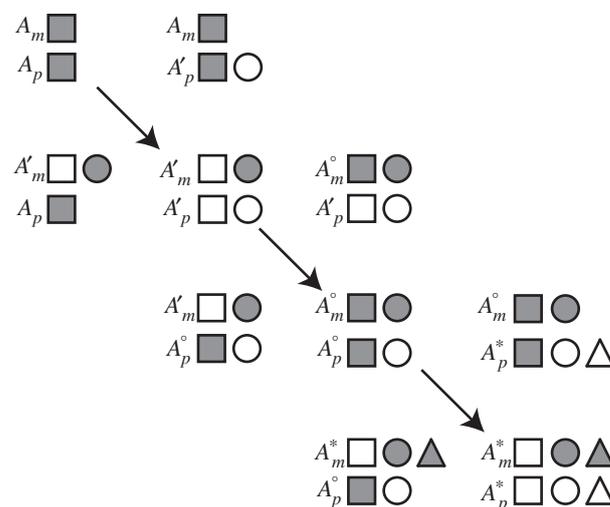


Figure 1. The mesiRNA ratchet. A population initially fixed for allele A (upper left) is successively invaded by an allele A' that also encodes a mesiRNA; an allele A° that retains the mesiRNA but is insensitive to its effects and an allele A^* that encodes a new mesiRNA (lower right). Subscripts m and p indicate madumnal and padumnal alleles. Squares represent the coding sequence of an mRNA. Circles and triangles represent coding sequences of mesiRNAs. Filled symbols are expressed. Unfilled symbols are silent. Homozygotes lie on the main diagonal. Off-diagonal elements are heterozygotes.

padumnal allele because the siRNA is not expressed, but at lower levels than A when it is a madumnal allele because the siRNA is expressed. Thus, A' behaves as a padumally expressed, madumnally silent allele when heterozygous. It will increase in frequency at the expense of A because it makes finer discriminations of relatedness.

By contrast to its behaviour in heterozygotes, A' mRNA is transcribed from neither allele in homozygotes, because both alleles are silenced by the mesiRNA. The siRNA produced by madumnal A' informs padumnal A' that the seed contains an $A'A'$ embryo rather than an AA' embryo and that the mother carries at least one copy of A' . Therefore, at least half of other embryos will receive A' from their mother (in addition to those that receive A' from their father). Thus, mesiRNA signals a doubling of 'relatedness' to self and increased 'relatedness' to littermates (r_L). If r_L more than doubles, the balance of benefits to self and costs to littermates for padumnal A' shifts in favour of production of less growth enhancer, as occurs in the presence of mesiRNA.

Whether r_L is doubled will depend on allele frequencies, the frequency of selfing and the number of fathers per brood. A complete analysis of this problem is beyond the scope of this letter, although some insight can be gained by considering effects when A' is rare. In an outbreeding population, A' will be transmitted predominantly by AA' parents, with padumnal A' expressed when mothers are AA but inhibited by mesiRNA in 50% of seeds when mothers are AA' . MesiRNA signals a doubling of r_L for single paternity of a mother's offspring and more than doubling for multiple paternity. Therefore a reduction in seed size, with concomitant increase in seed number, would appear to benefit A' . MesiRNA functions as a 'secret hand-shake' that allows padumnal A' to recognize its allelic partner as self and to reduce its own transcription for the benefit of madumnal A' in littermates.

MesiRNA could also function as an adaptive signal of self-fertilization. Selfing shifts the optimal trade-off between

seed size and number to smaller seeds for genes expressed in filial tissues [12]. If mothers sometimes self, padumnal A' will be more likely to encounter mesRNA in selfed seeds than outcrossed seeds, especially when A' is rare. Therefore, padumnal A' will promote smaller seeds on selfing and larger seeds when outcrossed.

A' produces less mRNA in homozygotes than is optimal for an unimprinted allele expressed in offspring. Therefore, near fixation of A' , rare alleles (such as A) that are expressed more than A' will be favoured by natural selection. This suggests that A and A' will be maintained at a polymorphic equilibrium.

Green-beard altruism is vulnerable to 'cheats' who flaunt the label, receive its benefits, but do not reciprocate [13]. A° , a version of A' that retains mesRNA but is insensitive to its inhibitory action, would increase in frequency at the expense of A' because madumnal A° induces padumnal A' to reduce demand, benefiting A° , but A° does not reciprocate when

madumnal and padumnal roles are reversed. Once A° eliminates A' , the population is primed for the introduction of A^* , an allele that possesses a beard of a different colour (new mesRNA) [14]. Such an iterative process (figure 1), in which successively introduced mesRNAs are only transiently effective, could explain the diversity of mesRNAs, their rapid evolutionary turnover and mild effects [9,15].

Imprinted gene clusters of mammals contain many non-coding RNAs [16]. DNA–DNA associations and RNA–DNA interactions within these clusters may be facilitated by somatic pairing of madumnal and padumnal chromosomes [17,18]. MicroRNAs processed from maternally expressed *antiPeg11* cause mRNA degradation of paternally expressed *Peg11* [19]. Mutations of madumnal *Rasgrf1* silence the padumnal copy of a neighbouring non-coding RNA [20]. Disruption of madumnal *Ube3a* upregulates padumnal *Ube3a-antisense* [21]. Such examples suggest the possibility of green-beard effects at mammalian imprinted loci.

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