Genomic conflict and genomic imprinting

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The green-bearded placenta

a placenta  a green beard  a green-bearded placenta

an idea of Haig 1996
Summary: Genomic conflict and genomic imprinting

- genomic conflict
  - clarifying terminology
  - transposable elements
  - cytoplasmic genetic elements
  - cytoplasmic male sterility
- genomic imprinting
  - the kinship hypothesis
  - imprinting of growth factors in mouse
  - double fertilisation in plants
- the green-bearded placenta
Genomic conflict

• genomic conflict is genetic conflict within an organism
  • genomic conflict can occur within an individual’s genome, as well as between the different genomes within an individual
  • many organisms are composed of different genomes and genetic elements

transposable elements
supernumerary chromosomes  e.g. B chromosomes

conflict arises at reproduction for primarily two reasons
• because not all genes are transmitted in the same way or according to the same (strict) rules
  • e.g. some cytoplasmic organelles, symbionts and sex chromosomes are transmitted by only one sex
• because not all of the offspring inherit the same set of alleles
  • so alleles that can bias fair transmission have an evolutionary advantage
Genomic conflict

- genes that cause such genomic conflict are called selfish genetic elements (also selfish DNA, ultra-selfish genes, genetic parasites)
- selfish genetic elements are harmful to the individual carrying them
  - they act via, for example, the disruption of gene function, meiotic drive, sex-ratio distortion, or male sterility
- so there is scope for conflicts between the genetic and individual levels of selection
  - recall the example of the c-haplotype in mice
- this should lead to the evolution of (generally) nuclear restorer and suppressor genes
  - defence mechanisms that counteract the action of the selfish genetic elements
- these kinds of conflicts may not be visible under normal conditions
  - but they may appear when genetically divergent populations are crossed, since this often leads to a mismatch between attack and defence adaptations

Transposable elements

- transposable elements (TEs) usually occur in multiple copies in the genome
  - TEs make up ~35% of the mammalian genome
- two main types of TEs
  - retro-elements or -transposons
  - DNA elements
- TEs can replicate within the host genome
  - this increases the probability that they are successfully transmitted to the offspring

Fig. 7.1. Replicative transposition is shown for the two classes of transposable elements (a) retroelements and (b) DNA elements. In each, a transposon encodes proteins needed for transposition including reverse transcriptase. This converts retrotransposon RNA back into DNA, which can then be inserted into a new location in the host chromosome. DNA elements also encode proteins involved in transposition. The molecular basis of transposition is less well understood. It is thought that excision of elements DNA during DNA replication is followed by insertion elsewhere. The double-strand gap left by excision is filled by sister chromatid repair.

from Pomiankowski in Keller 1999
Transposable elements

• TEs are considered selfish genetic elements, because they can lower the fitness of their host
• TE insertion is probably one of the major causes of spontaneous mutation in natural populations
  • they cause >50% of mutations in *Drosophila*
  • this also means that many mutations are not point mutations!
• if transposition occurs into a coding or regulatory gene sequence, this will often disrupt the normal function of the gene

Transposable elements

• several traits of TEs suggest they evolved strategies to reduce harm to their host
  • transposition usually does not occur in somatic cells, as this could harm the host (and thus the TEs), but does not increase TE transmission
  • some TEs (group I introns) can self-splice out of RNAs or proteins, leading to normal mRNA and protein function
  • the *P* element of *Drosophila* codes for two proteins, a transposase and an inhibition factor; the inhibition factor is maternally expressed (also in the egg), so the TE only transposes when a *P*-carrying male crosses with a female without any (or only few) *P* elements
  • because TEs are sensitive to the cellular environment in which they reside, some may actually have become ‘domesticated’ and are now involved in regulatory functions

*Figure 6.4* Association of HEGs with self-splicing introns or introns. A. The *α* element of yeast mitochondria consists of a HEG inserted into a self-splicing group I intron, which in turn is inserted in the host LSU ribosomal gene. The endonuclease recognizes a sequence in the host gene, and inversion and HEG home as a unit. B. The VDE element of yeast nuclei consists of an endonuclease domain inserted into a self-splicing intron domain, which in turn is inserted into the host *VMAI* gene. Again, the 2 domains home as a unit. In both cases, self-splicing preserves the function of the host gene.

from Burt & Trivers 2006
Transposable elements

- DNA methylation is involved in the silencing of transposable elements (Kakutani et al. 2005)
  - in plants, mutations that disrupt DNA methylation can lead to aberrant phenotypes
  - in Arabidopsis thaliana the ddm1 mutation (decrease in DNA methylation) leads to uncontrolled release of many transposable elements, because it causes the genome to be insufficiently methylated
  - interestingly, these aberrant phenotypes persist over multiple generations, even when the mutant plants are back-crossed into a wild-type background where methylation is again normal
  - this is because the transposition of these TEs leads to actual mutations that are stably inherited to the offspring

Cytoplasmic genetic elements

- cytoplasmic genetic elements (CGEs) do not segregate as precisely as nuclear genes (no equivalent to fair mitosis or fair meiosis!)
- in an asexual host cell lineage, competitively superior CGEs can spread, but in the whole population they likely cannot, since they probably harm their asexual hosts
- but if the host cells are sexual, the cells containing different CGEs can fuse, leading to competition between CGE genotypes within the fused cells
- CGEs that are successful in this competition may thus spread in the population, even if they harm the host cells carrying them

from Stearns & Hoekstra 2005
Cytoplasmic genetic elements

- for sexual host cells, a powerful solution to this type of genomic conflict is to impose uniparental inheritance of CGEs
- uniparental inheritance often occurs via the female function
  - maybe it is the female function, because, due to anisogamy, the egg contributes many more cytoplasmic genetic elements to the zygote compared to the sperm
  - however, the sperm mitochondria sometimes enter the zygote and thus can make small contribution to the zygote
  - but during spermatogenesis these sperm mitochondria are sometimes actively labelled with ubiquitin for subsequent degradation in the zygote
- interestingly, uniparental inheritance of CGEs also occurs in isogamous species
  - and there it is usually linked to the mating type of the zygote
- uniparental inheritance effectively prevents (or at least strongly reduces) this type of genomic conflict

but uniparental inheritance leads to a new type of genomic conflict, because under uniparental inheritance males are an evolutionary dead end for the CGEs
- CGEs that are able to bias the investment of resources towards the female function can have a transmission advantage
- nuclear restorer genes are expected to appear to counteract these biases, and sex chromosomes may partly have this function

from Werren et al 2008
Cytoplasmic male sterility

- about 5% of angiosperms are gynodioecious
  - this means that populations consist of hermaphrodites and females (which can simply be thought of as male-sterile hermaphrodites)
- male sterility is usually caused by mitochondrial mutations
  - mitochondria with male-sterility mutations are expected to have a higher fitness
  - we expect a trade-off between resource allocation to the male and female sexual function, so male-sterile plants that make fewer (or no) pollen will make more and/or better seeds
- cytoplasmic male sterility is an important tool in crop plants
  - male-sterile plants generally have a higher yield (we mainly eat seeds, not pollen)
  - male-sterile plants are easier to cross with a high-yield paternal genotype, because the own pollen does not interfere in fertilisation
  - for the same reason male-sterile plants are easier to hybridise with distant strains (used, for example, in the sugar beet *Beta vulgaris*)

the interaction between male-sterility mutations and nuclear restorer genes was shown in *Plantago coronopus*
Cytoplasmic male sterility

- crossing different strains, so that offspring vary in the number of restorer alleles
- the number of restorer alleles correlates with the sex ratio in the population
- the investment into both male and female function changes with the sex ratio

Figure 2. Relationship between the (inferred) number of restorer alleles and the sex ratio (H fraction) among the progeny of MS × H (filled circles) and H × H (open circles) crosses.

Genomic conflict
Genomic imprinting

- Genomic imprinting is parent-of-origin-specific gene expression
  - i.e. the expression of an allele depends on whether it was inherited from the father or the mother
- Occurs in ~100 mammalian genes
  - Most of these genes are in some way linked to resource uptake and growth of the embryos
- Genomic imprinting is not restricted to mammals, but it also occurs in some invertebrates and plants
  - It can occur whenever there is post-zygotic investment

Genomic imprinting

- Haig (2004) proposed the kinship theory of genomic imprinting
  - “… parent-specific gene expression evolves at a locus because a gene’s level of expression in one individual has fitness effects on other individuals who have different probabilities of carrying the maternal and paternal alleles …”
- What is required is conflict over the level of post-zygotic investment between so-called asymmetric kin
  - E.g. mother vs. offspring
    - An offspring is (almost) certain that its maternally derived allele is present in the mother (unless there has been a mutation or a mix-up) and it is (almost) certain that its paternally derived allele is absent in the mother (assuming outcrossing)
  - E.g. offspring vs. offspring
    - In females that have mated multiply, the offspring are less related in their paternally inherited alleles than their maternally inherited alleles
Genomic imprinting

• in mammals genomic imprinting occurs primarily in genes involved in mother-foetus interaction and lactation
  • but some effects also occur after weaning
• the father can gain fitness benefits by switching on an allele that induces its offspring to ask for more resources from the mother than she wants to give (unless there is strict life-long monogamy)
  • the mother’s future reproduction is not important to the father, if he is unlikely to be the father of future offspring (this is similar to male manipulation in other sexual conflict scenarios)
• the mother should try to silence such alleles (e.g. by changing the state of methylation via an epigenetic modification)
• this leads to the evolution of genomic imprinting
  • alleles at ‘demand’ loci are only expressed when inherited via the father
  • alleles at ‘defence’ loci are only expressed when inherited via the mother

Genomic imprinting

• imprinting of growth factors in mouse
  • the insulin-like growth factor 2 (Igf2) is expressed in the foetus and promotes the acquisition of resources from the mother across the placenta
    • ➔ the paternal allele of Igf2 is expressed, but the maternal allele is inactive
  • the insulin-like growth factor 2 receptor (Igf2r) appears to inhibit the action of Igf2
    • ➔ the maternal allele of Igf2r is expressed, but the paternal allele is inactive
• the effect was tested experimentally
  • mice with both Igf2 alleles inactivated attain only 60% of the normal birth weight
  • mice with both Igf2r alleles inactivated attain a 30% higher than normal birth weight
Genomic imprinting

• genomic imprinting might potentially help to explain the absence of the evolution of parthenogenesis among mammals
  • parthenogenetically produced zygotes would presumably lack effects of the (usually) paternally expressed demand genes, while suffering from a double effect of the (usually) maternally expressed defence genes

Genomic imprinting

• most of the well-understood examples of genomic imprinting come from placental mammals
• but more generally, genomic imprinting is expected to evolve whenever there is asymmetric kin and post-zygotic investment
  • how might this work in the sex-role reversed seahorses?
  • could this explain sperm-dependent parthenogenesis in many asexual planarians?
Genomic imprinting

- a brief reminder about fertilisation and seed set in plants
- the maternally-dominated 3N endosperm tissue is responsible for the provisioning of the growing embryo and seed
- so plants may also show genomic imprinting

<table>
<thead>
<tr>
<th>Genomic imprinting</th>
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<tbody>
<tr>
<td>Male gametophyte</td>
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<td>Female gametophyte</td>
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<td>Double fertilisation</td>
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The green-bearded placenta

- imagine an allele that has three effects
  - it signals its presence in an individual (feature)
  - it permits to detect its presence in others (perception)
  - it helps any carriers of such alleles (response)
- such an allele could spread through a population, even if it harms the individuals that carry it
- the term green-beard gene was coined by Dawkins (1976), but the mechanism was conceived by Hamilton (1964)
The green-bearded placenta

- green-beard genes may be involved in mother-foetus interactions in placental mammals (Haig 1996)
  - in a heterozygous mother only 50% of the offspring inherit a given allele
  - if an embryo could signal to the placenta that it has inherited the allele, the maternal allele could respond by increasing provisioning to that embryo
  - this could occur at a fitness cost to the other embryos (and thus also to the mother)
  - ➔ gestational drive

The green-bearded placenta

- cadherins are involved in establishing cell-cell contacts and they have all the necessary green-beard properties
  - cadherins have homophilic interactions (feature and perception)
  - cadherins lead to good cell-cell contact and are involved in gene activation (response)

- if cadherin genes were involved in gestational drive, then the evolution of suppressors is expected
- this should leading to (rapid) antagonistic coevolution
The green-bearded placenta

- a recent study provides preliminary evidence for this hypothesis
- the authors tested for positive selection (using the $d_N/d_S$ ratio approach) on the evolution of cadherin genes
  - by comparing these genes in a range of different mammals
- E-, P- and VE-cadherin, which are all involved in maternal-foetal interactions, showed at least some signs of positive selection
- H-cadherin, which is not expressed in the placenta, did not show any signs of positive selection

The genetic code is redundant

- some mutations are silent (synonymous) whereas other mutations change the amino acid (non-synonymous)

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Summers & Crespi 2005
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Literature

- Mandatory Reading
- Suggested Reading
- Books