

# Different yet similar: evolution of imprinting in flowering plants and mammals

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## Abstract

Genomic imprinting refers to a form of epigenetic gene regulation whereby alleles are differentially expressed in a parent-of-origin-dependent manner. Imprinting evolved independently in flowering plants and in therian mammals in association with the elaboration of viviparity and a placental habit. Despite the striking differences in plant and animal reproduction, genomic imprinting shares multiple characteristics between them. In both groups, imprinted expression is controlled, at least in part, by DNA methylation and chromatin modifications in *cis*-regulatory regions, and many maternally and paternally expressed genes display complementary dosage-dependent effects during embryogenesis. This suggests that genomic imprinting evolved in response to similar selective pressures in flowering plants and mammals. Nevertheless, there are important differences between plant and animal imprinting. In particular, genomic imprinting has been shown to be more flexible and evolutionarily labile in plants. In mammals, imprinted genes are organized mainly in highly conserved clusters, whereas in plants they occur in isolation throughout the genome and are affected by local gene duplications. There is a large degree of intra- and inter-specific variation in imprinted gene expression in plants. These differences likely reflect the distinct life cycles and the different evolutionary dynamics that shape plant and animal genomes.

## Introduction

Genomic imprinting is a mechanism that leads to the differential expression of alleles depending on whether they are maternally or paternally inherited. Thus, mutations in imprinted genes show a non-Mendelian inheritance pattern. Unlike other parent-of-origin effects, which can be caused by cytoplasmic contributions of the egg or sperm to zygotic development, genomic imprinting is characterized by *de novo* differential expression from the parental alleles after fertilization [1]. Imprinting is initiated by the distinct epigenetic marking ("imprint") of specific DNA sequences in the parental germ lines of mammals and in the gametophytes of plants. This mark is stably inherited after fertilization and eventually results in the unequal expression of the two parental alleles.

The first imprinted gene was discovered in maize (*Zea*

*mays*). Through a series of elegant genetic experiments, Kermicle [2] determined that *R*, a gene conferring anthocyanin pigmentation to seeds, is fully expressed only when inherited from the mother. Subsequently, plant geneticists observed that the relative dosage of maternal and paternal chromosomes plays an important role in seed development, indicating that parental genomes are not equivalent [3–5]. In mammals, the non-equivalence of maternal and paternal genomes was demonstrated by nuclear transplantation experiments showing that mouse embryos with either two paternal or two maternal genomes are inviable [6,7]. Imprinting in mice was later shown to be restricted to specific loci [8], the first of which (*Igf2*, *Igf2r*, and *H19*) were molecularly identified in 1991 [9–11]. Here, we discuss how imprinting may have evolved in these distinct lineages but refer to other reviews that compare and contrast the molecular mechanisms of genomic imprinting in seed plants and mammals (for example, [1,12–15]).

### Why did genomic imprinting evolve?

Today, hundreds of genes have been reported to be imprinted in plants and animals [1,15,16]. Nevertheless, the evolution of genomic imprinting has puzzled evolutionary biologists and has been a source of heated disputes for over two decades. Imprinting poses a fitness cost because it exposes recessive mutations, yet the imprinting status of many genes is conserved over millions of years. So why did genomic imprinting evolve? Addressing this question should take into consideration the diversity of imprinting mechanisms in flowering plants and mammals.

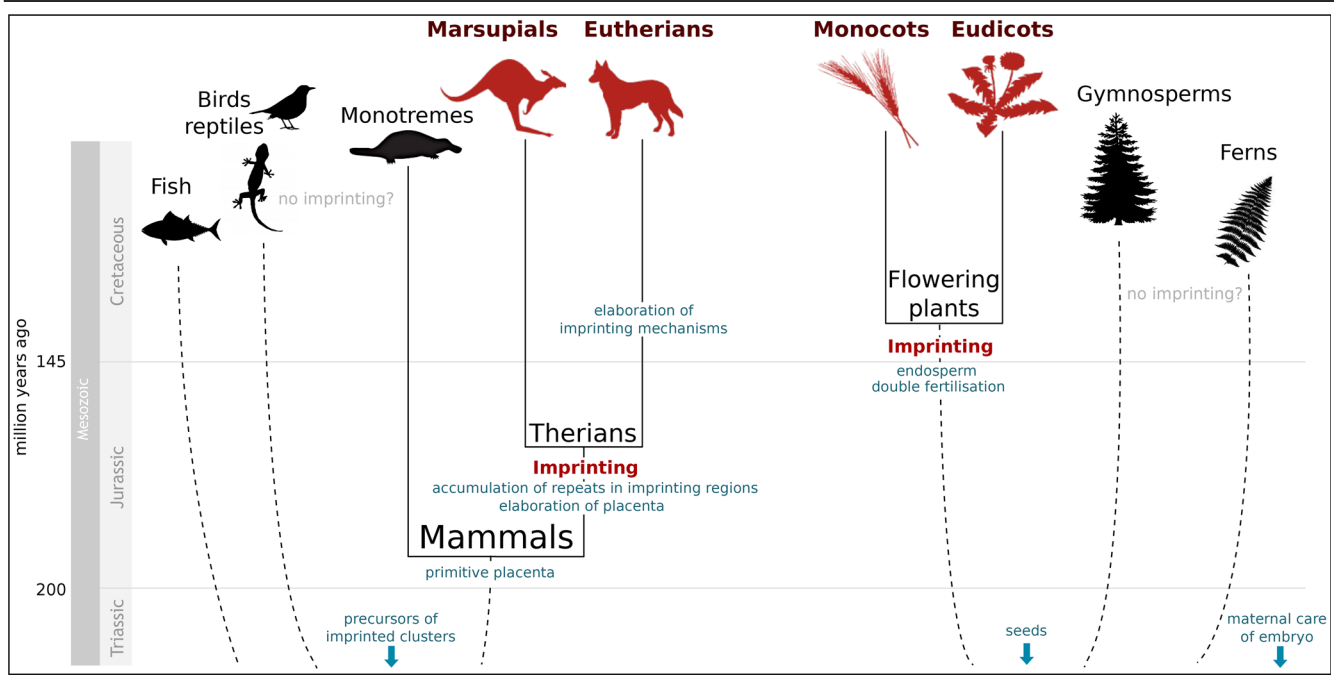
The term “imprinting” was coined to describe the selective marking and elimination of all paternal chromosomes in sciarid insects [17]. Here, however, we consider only genomic imprinting that affects individual genes or gene clusters rather than entire chromosomes or genomes. In animals, genomic imprinting of individual genes has been identified in eutherian and marsupial mammals but not in monotremes or in non-mammalian vertebrates, such as birds [18,19]. This suggests that the evolution of genomic imprinting was associated with the elaboration of viviparity in the common ancestor of all therian mammals, which lived in the Jurassic period, 160 to 200 million years ago [20,21] (Figure 1). In plants, genomic imprinting has been identified in the endosperm and embryo—the two products of double

fertilization—of monocots and eudicots (reviewed in [1,15]) but has not been reported in non-flowering plants, likely due to a lack of experimental investigation. These findings suggest that imprinting evolved in association with the evolution of the endosperm (an embryo-nourishing tissue) in the Early Cretaceous, 100 to 145 million years ago [22] (Figure 1).

### Imprinting and the placental habit

Clearly, the evolution of genomic imprinting was linked to the evolution of the placental habit in therian mammals and in flowering plants. In these groups, the embryo is embedded and nourished by a placenta or an endosperm, sexually derived structures that share the same set of genes as the embryo. The mammalian placenta is derived post-fertilization from the trophoblast and other extra-embryonic tissues [23]. The endosperm originates from double fertilization, where twin male gametes fuse with two female gametes that usually carry one and two copies of the same genome (1n egg and 2n central cell), giving rise to the 2n embryo and 3n endosperm, respectively (although there are variations to this theme [24,25]). The elaborated viviparity and the placental habit of mammals and flowering plants allow both maternal and paternal genes to play an active role during embryogenesis (for example, in nutrient acquisition from the mother). Accordingly, the endosperm and the trophoblast/placenta appear to be the primary sites of imprinting [1,15,26].

Figure 1. Timescale for the evolution of imprinting in animals and plants



Despite the clear association between genomic imprinting and viviparity, not all viviparous groups evolved imprinting. Although this point is often overlooked, viviparity is widespread among many animal groups, including scorpions, seahorses, sharks, lizards, snakes, and amphibians [27]. To our knowledge, it remains to be tested whether imprinting is present in any of these groups. All land plants have an intimate maternal-offspring relationship, with multicellular sporophytic embryos being nurtured and protected by the maternal plant for an extended period of time [28]. However, there is currently no report of imprinting in any plant group outside the angiosperms. This, however, may be due simply to a sampling bias. Nevertheless, the widespread presence of parthenogenesis (development of an embryo in the absence of fertilization) in many of these taxa suggests that imprinting may indeed be absent; this is because one consequence of genomic imprinting is the failure of parthenogenetic progeny to properly develop due to the non-equivalence of maternal and paternal genomes. Parthenogenetic mice can be obtained only through the genetic engineering of imprinted genes [29,30]. Interestingly, although apomixis (asexual reproduction through seeds) is common among flowering plants, most apomicts require fertilization of the central cell for the development of functional endosperm [31]. Nevertheless, parthenogenetic embryo development (and rare cases of autonomous endosperm development) in apomicts suggests that a bypass of genomic imprinting requirements is relatively common in plants.

### **The kinship and maternal-offspring coadaptation theories**

The evolution of imprinting in association with the placental habit strongly suggests that imprinting evolved as a regulator of maternal-offspring interactions. Many different theories have been put forward to explain the evolution of imprinting [32–35]. Although it is unlikely that any one theory can explain all cases of imprinting, two theories have gained the most popularity because they provide a general explanation for imprinting that is supported by empirical evidence: the kinship (or parental conflict) theory [36–38] and the maternal-offspring coadaptation theory [39].

The kinship theory of genomic imprinting suggests that maternal and paternal alleles of a gene have conflicting interests. This conflict arises because, in viviparous polyandrous (multiple paternity) species, paternally derived genes benefit from maximizing resource allocation at the expense of embryos from other fathers. Conversely, maternally derived genes benefit from promoting equitable growth of all embryos because all progeny are equally related to their mother. The kinship

theory predicts that this conflict can result in the evolution of mechanisms that cause growth-promoting genes to be active when inherited paternally but silenced when inherited maternally. The kinship theory was later expanded to include not only parental effects on embryo growth but all other kin interactions that involve asymmetries of genetic relatedness [38]. More recent reinterpretations of the kinship theory propose that imprinting evolved as a consequence of an asymmetry generated by differences in relatedness and demography between maternally and paternally derived alleles [40,41].

Since it was proposed 25 years ago, the kinship theory has been by far the most popular theory to explain the evolution of genomic imprinting. It is supported by the dosage-dependent and opposing roles of reciprocally imprinted genes, such as *Igf2* and *Igf2r*, during mouse fetal growth [9,10] or *MEDEA* and *PHERES1* during plant seed development [42,43]. Yet the large number of alternative theories and the recurring misinterpretations of the kinship theory have made it controversial. One criticism that is often raised is that the kinship theory fails to predict the direction of imprinting in some loci. Two often cited examples are *Ascl2/Mash2* and *Meg1*, imprinted genes that encode positive regulators of trophoblast development in mice and endosperm development in maize, respectively [44,45]. A naïve interpretation of the kinship theory would predict that these genes would be paternally expressed (because they promote growth), but they are maternally expressed. However, these apparent contradictions of the kinship theory can be explained if one considers the diverse roles of genes during the early and late stages of embryogenesis [32,46].

Another criticism raised against the kinship theory is the apparent predominance of maternally expressed genes (MEGs) over paternally expressed genes (PEGs) found in both mice and plants [15,16]. The maternal-offspring coadaptation theory provides an explanation for the overabundance of MEGs [39]. It proposes that, in species with extended maternal care, the offspring have higher fitness if they have a higher resemblance to their mother. Therefore, the expression of maternal alleles is favored because it facilitates the coadaptation of maternal and offspring traits. However, the maternal-offspring coadaptation theory is challenged by the occurrence of many PEGs, including an apparent dominance of PEGs in the placenta of reciprocal hybrids of horse and donkey [47]. Furthermore, the coadaptation theory is expected to lead to loss of genetic variation at imprinted loci (and consequently a loss of imprinting) [32,39]. This prediction is somehow hard to reconcile with the conservation of imprinted gene expression across millions of years.

### Evolutionary origins of imprinted genes

In mice, imprinted genes are usually found in large clusters that are regulated by imprinting control regions [48,49]. Synteny analyses show that some of these clusters are also present in bird, amphibian, and fish genomes [50,51]. This means that these clusters existed long before they became imprinted. Interestingly, in chicken, these gene clusters are located predominantly in chromosomes that possess distinct chromatin properties [52]. This raises the intriguing possibility that this distinct chromatin environment might have facilitated the evolution of imprinted gene expression in early mammals [50]. Other genes became imprinted at different stages during eutherian evolution [53,54]. Plants do not have similar imprinted gene clusters. Although some predicted plant imprinted genes form microclusters [55], these lack the size and complexity of imprinted clusters in mammals. Many of the predicted plant microclusters consist of paralogous genes, suggesting that local gene duplications may play an important role in the evolution of imprinting in plant genomes [56].

Although the mechanisms differ, part of the molecular machinery leading to imprinted gene expression, including the central role played by cytosine methyltransferases, is also used by the cell to silence foreign DNA (such as retroviruses and transposable elements). This led to the suggestion that genomic imprinting evolved as a by-product of the genome's defense against foreign DNA [57–60]. Indeed, there was a significant expansion of certain types of repeat elements in the imprinted clusters of therians, compared with the same (unimprinted) clusters of monotremes [61]. This suggests that transposon insertion may have been a driving force for the origin of imprinted expression in therian mammals and lends support to the host defense hypothesis. It is important to distinguish the host defense hypothesis from adaptive theories, such as the kinship and coadaptation theories, the former is a model to explain the origin of mechanisms leading to imprinted gene expression, whereas the latter models analyze how selective pressures could drive the propagation and fixation of imprinted gene expression.

### Evolutionary dynamics of imprinted genes

Since conflicts can drive fast evolution, it has been proposed based on the kinship theory that imprinted genes should evolve faster than other genes. This was confirmed by the discovery of signatures of positive selection in *Igf2r* in rodents [62], *KLF14* in humans [63], and *MEDEA* in *Arabidopsis* [64–66]. However, explicit modeling of antagonistic evolution of imprinted loci predicts that imprinted loci should reach a stable equilibrium [67]. Evidence from empirical studies supports this conclusion: some early studies found no evidence of

positive selection on imprinted genes [68], and a more recent study found that the majority of mammalian imprinted genes are not subject to positive selection [69]. When comparing mice and human imprinted genes, MEGs were found to be subject to reduced selective pressure, but a strong shift to purifying selection was found for PEGs of rodents, suggesting that MEGs and PEGs are under different evolutionary pressures [70]. Interestingly, genes that are imprinted exclusively in the placenta (as opposed to genes that are imprinted in both embryo and extraembryonic tissues) are often not conserved between mice and humans [71]. This may be a reflection of the stronger intra-litter competition that occurs during mice pregnancies, which, according to the kinship theory, would lead to an increased pressure to maintain imprinting. The mechanisms that regulate imprinting in these genes appear to be different (more dependent on histone modifications and less so on DNA methylation) than the mechanisms that regulate imprinting ubiquitously in placental, embryonic, and adult tissues, where differential DNA methylation plays a central role [72].

Around 30% to 40% of the genes imprinted in mice show conservation of imprinting in humans [73]. Fewer genes have conserved imprinting between eutherians and marsupials [27], and only two show a conservation of the associated differentially methylated regions [74,75]. This suggests that imprinting has evolved independently at individual loci in marsupials and eutherians since the two lineages separated over 160 million years ago. The increased number of imprinted genes and elaboration of imprinting mechanisms in eutherians may have been caused by their longer placental gestations.

In plants, imprinted genes are more labile. Recently, the use of allele-specific RNA sequencing greatly increased the number of imprinted candidate genes in *Arabidopsis*, maize, and rice (reviewed in [76]). However, there is rather limited overlap between independent studies, and it is difficult to separate inherent biological variation from technical biases: RNA sequencing has been shown to create a very large number of false positives, as high as 10 times the true number of imprinted genes in the mouse brain [77]. In addition, homology comparisons across distantly related plant species are confounded by a complex history of gene and genome duplications [78]. Nevertheless, a few homologous genes are predicted to be imprinted in both eudicots and monocots, and the *E(z)*-like homologs *MEDEA* and *Mez1* have been directly confirmed to be imprinted in the endosperm of *Arabidopsis* and maize, respectively [64,79,80]. This suggests that imprinted expression of at least some plant genes may have been conserved for more than 100 million years (alternatively, imprinted expression evolved multiple

times at these genes). Interestingly, two paralogous maize genes (*FIE1* and *FIE2*) show imprinted gene expression, although the expression and DNA methylation dynamics of the two genes are dissimilar [81,82]. This suggests that imprinted gene expression can be maintained and modified after allo-tetraploidization or gene duplication events.

Although only a limited number of tissues have been analyzed, imprinted gene expression in mammals is thought to occur primarily during embryogenesis, but some genes are also mono-allelically expressed in other tissues, such as the brain. There is a high degree of spatial and temporal variation in imprinted expression, with some imprinted genes being monoallelically expressed in some cell types but biallelically expressed in others [83,84]. In plants, imprinted gene expression occurs primarily in the endosperm. Although some genes are also imprinted in the embryo [85,86], imprinted gene expression has not been found in adult *Arabidopsis* tissues [86,87].

Variation in imprinted gene expression in plants also occurs at the intra-specific level. Allelic variation for imprinting was first identified in maize [2], and recent estimates suggest that 10% to 20% of imprinted plant genes show allelic variation (some alleles are imprinted and others are biallelically expressed) [88,89]. In mammals, imprinting at any given gene appears to be much more stable across lineages (some earlier reports of allelic variation at the human insulin-like growth factor 2 receptor (*IGF2R*) and serotonin-2A loci [90,91] were probably due to technical issues [92,93]). Nevertheless, the effects of individual imprinted loci in mice have been shown to depend on interactions between pairs of alleles [94] and to be influenced by the genetic background [95].

## Outlook

The study of genetic imprinting has been extremely valuable to understand the epigenetic mechanisms that regulate gene expression in plants and animals [1,14,15,48,96]. Yet many questions remain regarding the molecular mechanisms that cause imprinted expression and of how variation in *cis* and *trans* can modulate genomic imprinting. High-throughput cell sorting and sequencing technologies now allow an increasingly detailed profiling of genomes and epigenomes. These have revealed large differences in gene expression and imprinting between cell types. There is also evidence for a large difference in the *cis*-regulatory control of allelic expression [97] and even for widespread stochastic monoallelic expression in mammals [98]. A detailed profiling of allelic expression in different species and cell types will allow us to better understand the diversity and evolution of imprinting mechanisms. This will continue

to offer us valuable insights into the mechanisms that regulate gene expression in animals and plants.


## Abbreviations

MEG, maternally expressed gene; PEG, paternally expressed gene.

## Disclosures

The authors declare that they have no disclosures.

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