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# Imprinting and its disorders in evolutionary perspective

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**Bacground.** Genomic imprinting is one of the best-studied epigenetic phenomena involving all the main epigenetic processes. Recent investigations led to a huge expansion of knowledge in this field and changed some established paradigms regarding imprinting establishment and maintenance. Evolutionary theories are intended to explain origins of imprinting and its evolutionary survival under the influence of selection pressure. The three main evolutionary theories based on selective asymmetry between maternally and paternally inherited alleles are kinship, sexual antagonism and maternal-offspring coadaptation theories. Though no one of them can explain all the aspects of imprinting, they are not mutually exclusive and multiple mechanisms may be at work at any given locus. Further evidences for imprinting importance come from investigations of human imprinting disorders. Eight of them have been described so far and multilocus imprinting defects have been recently discovered pointing to derangements in some common imprinting establishment / maintenance mechanisms.

**Conclusions.** Investigations of imprinting mechanisms, evolutionary origins and derangements led to some crucial discoveries in epigenetic processes shaping both health and disease, and a huge expansion of knowledge in imprinting is anticipated in the future, especially with wider application of advanced genetic technologies.

**Key words:** genomic imprinting, evolution, imprinting disorders

## INTRODUCTION

**Epigenetics** involves heritable but potentially reversible changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence (1). **Genomic imprinting** is a normal epigenetic process that results in diploid cells expressing a small subset of genes (no more than one to two percent of mammalian genes) from only their maternal- or paternal-inherited chromosome (1). Discovered just 30 years ago, genomic imprinting has become a general model for investigations in epigenetics which has given and is still giving a wealth of insights into human epigenetics.

As a phenomenon producing non-equivalence of maternal and paternal genomes, genomic imprinting was first discovered by Barton et al. (1984) in Cambridge, UK and McGrath and Solter (1984) in the USA. These researchers showed that parthenogenetic (PG) and androgenetic (AG) embryos (having two maternal or paternal genome copies, respectively) ended in early embryonic lethality and never developed to term. There were also major opposing differences between the phenotypes

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of the AG and PG embryos: AG embryos showed reduced fetal growth and excessive extraembryonic growth while PG embryos showed more advanced fetal development with relatively poor extraembryonic growth (2). However, parental effects on gene expression were demonstrated even earlier in insects and plants. Actually, the term "imprint" was first coined to describe epigenetic parental effects in fungus gnats of the genus *Sciara* in 1960 (2). In 1918 and 1919, two independent studies demonstrated parent-specific effects at the maize *R* locus, which controls anthocyanin pigment expression in the aleurone endosperm (2). In 1991, three imprinted genes in mice were characterized: insulin-like growth factor 2 receptor (*Igf2r*), its ligand, insulin-like growth factor 2 (*Igf2*), and *H19* (2). To date, about 80 genes have been shown to be imprinted in humans and 271 imprinted genes have been catalogued in humans, mice, cows, marsupials, sheeps and some other species (see http://igc.otago.ac.nz, as of 20th of August 2014), and many more are predicted to be revealed (1, 2).

## EPIGENETIC MACHINERY AND DEVELOPMENTAL PROCESSES

DNA methylation was the first discovered and best-studied epigenetic modification. In mammals, DNA methylation occurs almost exclusively in CpG dinucleotides and converts cytosine residues to 5-methyl-cytosine. The large majority of both inter- and intragenic CpG dinucleotides in the genome are methylated sparing only 1% to 2% of the genome, mostly the so-called CpG islands, short CG-rich stretches found preferentially at gene promoter regions (3). DNA methylation has a silencing effect on genes when present at CpG dense promoter sequences by direct restriction of transcription factors binding and indirectly, via recruitment of methyl-CpG binding domain proteins which effect alterations of chromatin conformation and histone modifications (3). Of note is the fact that the large majority of silent genes do not have a methylated CpG island at their promoter, indicating that other means of epigenetic control must exist (3). The symmetry of the CpG sequence means that both strands of DNA have a CpG dinucleotide and typically both DNA strands share the same methylation pattern, maintained through cell division by DNA methyl-transferase 1 (DNMT1). DNA methylation pattern is relatively stable in differentiated cells, however, dramatic changes occur during mammalian development. Global epigenetic reprogramming occurs in gametogenesis and later in early embryonic cells (3) involving reciprocal rounds of demethylation and *de novo* methylation. Male and female gametogeneses follow different paths ending up with gametes with distinct epigenomes.

Histones are the main protein component of chromatin in almost all cells except from spermatozoa, where the majority of histones are replaced by protamines. A huge range of histone tail modifications are associated with gene silencing or expression, the most commonly encountered in gene-active state being monomethylation at H3K9 and H3K27, trimethylation of H3K4, and acetylation at H3K9 and H3K14. Repressive modifications include dimethylation of H3K4 and trimethylation of H3K9 and H3K27 (3). Control of these modifications is exerted by a wide variety of histone methyltransferase, histone demethylase, histone acetylase, and histone deacetylases (3). Non-histone proteins exerting epigenetic control over gene expression are the Polycomb and Trithorax group proteins among others, which promote transcriptional repression and activation, respectively. Higher-order chromatin remodelling, including looping of and nuclear compartmentalisation, also plays a role in gene expression regulation. Finally, non-coding RNAs were recently shown to constitute the majority of mammalian transcriptome and their role in gene expression regulation now comes to a forefront of investigations in epigenetics (1). All described epigenetic processes comprise an actively interacting system of gene activity control.

## MECHANISMS OF GENOMIC IMPRINTING

Genomic imprinting is one of the best-studied epigenetic phenomena involving all the main epigenetic processes (2, 3, 4). More than 80% of known imprinted genes are clustered into 16 genomic regions that contain two or more genes and are situated near differentially-methylated regions (DMRs) which may serve as imprinting control regions (ICR). Differential methylation was thus identified as a heritable epigenetic feature that distinguishes maternal and paternal alleles. Major clusters of imprinted genes have been identified at 7q21.3, 7q32.2, 11p15, 15q11.2, 19q13.4, and 20q13.32 (3).

It was long believed that the primary imprint involves the classic epigenetic mark – DNA methylation. However, recent investigations and especially new high-throughput sequencing technologies allowing precise genome-wide mapping of histone and DNA modifications and transcription factors in relation to gene activity are now leading to a huge expansion of epigenetic correlative data and sometimes changing established paradigms. Compounding evidence shows that transcriptional activity of ncRNAs and histone modifications are critically important in genomic imprinting acquisition (1, 4). At first, unexpected findings were provided by the *Dnmt3L* knock-out mouse model. *Dnmt3L* deficient females produce abnormal DNA methylation imprints in their oocytes, however, some of their embryos showed a normal DNA methylation pattern at the *Snrpn* and *Peg3* DMRs. Therefore, some other mechanisms of DNA methylation establishment at DMRs must exist. Also, no evidence of allelic DNA methylation differences were found in two new placenta-specific imprinted mice loci, *Ano1* and *Gab1*. Of DMR so far described, 16 acquire methylation in oocytes (maternal DMRs) and only 3 in spermatozoa (paternal DMRs) (4). Maternal DMRs are unusual in that they are mostly intragenic and associated with transcription start sites of coding transcripts and non-coding RNAs. Meanwhile, paternal DMRs (*H19*, *Dlk1-Gtl2* and *Rasgrf1*) are all intergenic. During DNA methylation establishment in oogenesis, maternal DMRs are placed into active transcription units due to upstream oocyte-specific transcription start sites. One paternal DMR, *Rasgrf1*, depends on a quite distinct mechanism and involves small RNAs of the Piwi-interacting RNA class (PiRNAs) (4). In support of these observations also came investigations showing an open chromatin structure (DNase I hypersensitive sites) at the repressed *Igf2* promoter and providing hints to transcriptional activity (1). Also of note is observation that not all imprinted sites are completely "silent" – some of them show low-grade expression (5). Therefore, DNA methylation acquisition at imprinted loci should be regarded as a general process in the context of DNA demethylation – *de novo* methylation processes during gametogenesis and allele-specific differences mostly arise as a result of methylation-preventing mechanisms in gametes of unmethylated DMR status (mostly paternal DMRs) (1, 4).

## EVOLUTIONARY ORIGINS OF GENOMIC IMPRINTING

Genomic imprinting arose in mammalian evolution 160 to 200 million years ago in the common ancestor of all therian mammals which lived in the Jurrasic period (6) in association with the development of viviparity and placentation. It also evolved independently in plants in the Early Cretaceous period, 100 to 145 million years ago, in association with endosperm development (6). As mentioned earlier, the majority of imprinted genes are found in clusters and regulated by a common imprinting control region (ICR). Interestingly, synteny analyses of such gene clusters showed their presence in some other species, including birds and fish genomes (species where imprinting has not been found so far) (6). As silencing of an imprinted allele involves DNA methylation, non-coding RNAs and histone modifications, mechanisms implicated also in protection of the genome from foreign DNA such as retroviruses and transposable elements, this led to a suggestion that genomic imprinting could arise as a by-product of genome defence mechanisms (3, 5). DMRs themselves are highly enriched with repeats which may be remnants of transposons (2). Comparative analyses of marsupials provided the first direct evidence that an imprinted gene, PEG10, was derived from a retrotransposon insertion with further evolution of an imprinted region and DMR in mammals (7). Once established, genomic imprinting appears to spread to encompass neighbouring genes within the region and eventually leads to the complex reciprocal imprinted mechanisms occurring within a syntenic region (7). Increase in the number of genes recruited by ICRs and elaboration of imprinting control mechanisms occured in eutherian evolution (6). Many of these imprinted genes are members of a network of coregulated genes comprising a hub for other imprinted genes. Thus, it is important when considering the evolutionary significance of genomic imprinting to focus on the ICRs, and not the genes themselves which are remarkably stable (2). If one locus evolves to become imprinted, it leads to selection for its interacting partners to match its pattern of imprinting (possibly due to gene-dosage effects and epistasis). This process may help explain why imprinted genes tend to be found in clusters (8).

Regardless of the mechanism of imprinting evolution, it still rises questions of what selective

pressures could drive its propagation and fixation, on the one hand, and why it affects only a small subset in the genomes of some species (mammals and plants) and is not observed in other species at all (as in birds and fishes), on the other hand. Multiple theories were suggested as an explanation, however, no one of them can fully explain all the aspects of genomic imprinting evolution.

Monoallelic expression exposes genes to deleterious recessive mutations, both in the parental germline and in a somatic cell lineage and diploidy can mask these detrimental changes, at least at the organismal level. Therefore, diploidy is generally the norm in the somatic tissues of vertebrates and plants (9). However, according to a recent genome survey, 5–10% of autosomal genes – or well over 1 000 in the human genome – may be randomly expressed from only one allele at any given time (2, 5). The prevalence of monoallelic expression implies that it may serve some sort of evolutionary purpose. It is generally agreed that hemizygosity increases the evolvability of a particular locus, and hence the adaptability of the overall population. Because diploidy may mask both deleterious and beneficial mutations, functional haploidy may quickly eliminate undesirable recessive traits while simultaneously promoting beneficial mutations (2).

However, these plain advantages of hemizygosity cannot substantiate parental-specific aspects of imprinting. The three main evolutionary theories based on selective assymetry between maternally and paternally inherited alleles are kinship, sexual antagonism and maternal-offspring coadaptation theories. According to the kinship theory, multiple matings (multiple paternity) create unequal relatedness of fetuses and later individuals to their interactions with the mother and, on a bigger-scale, with individuals in a given population. All offspring of one mother have the same mother but different fathers (6, 10). Because resources must be carefully allocated between the mother, offspring, and siblings, it has been proposed that competition for resources imposes selective pressure on paternal and maternal genes. Therefore, maternally-derived genes favour resource-sparing for mother's future pregnancies while paternally-derived genes benefit from maximal resource exploitation during gestation, lactation, and later behavioural interactions among siblings (6, 5, 10). Indeed, some imprinted gene loci fit neatly into predictions of the kinship theory (for example, *Igf2* is paternally expressed and has a positive effect on growth in juveniles, and *H19* is maternally expressed and encodes an RNA that inhibits *Igf2*). Fascinating experiments with chimeric mouse brains are also consistent with the kinship theory: maternally expressed loci are particularly active in the cortex, which affects language (in humans), social reciprocity, planning and behavioural inhibition, and paternally expressed loci are found in the limbic system, which controls more basic drives such as hunger, fear, and aggression (5). A gene that apparently contradicts these predictions is Mash2, which is required for normal placental development in mice. One might expect this gene to be paternally expressed, yet it is maternally expressed (5). A further reinforcement for the kinship theory actually comes from the earliest experiments leading to imprinting discovery described above, where androgenetic embryos showed reduced fetal growth and excessive growth of extraembryonic tissues (which provide nourishment for the growing fetus) while parthenogenetic embryos showed the opposite pattern.

The sexual antagonism theory relies on sex-specific selection pressures (10, 11). In such a case, with time paternally-derived genes will become enriched for alleles of male benefit and maternally-derived ones for alleles of female benefit. Under the sexual antagonism theory, genomic imprinting is most likely to evolve in phenotypes under the strongest sexually antagonistic or sex-specific selection, such as primary or secondary sexual traits, and empirical studies suggest that sex-specific selection and intralocus sexual conflict are indeed widespread (5). However, sexual antagonism creates a situation where the fittest alleles derive only from the same-sex parent and can cause a maladaptation in the opposite sex. Thus, imprinting is sometimes predicted to evolve when selection is much more stronger in one sex (5, 10). In mammal populations females are typically the most demographically important sex; imprinting could elevate population fitness by allowing increasing and assymetric levels of adaptation only in females (5). In a population with a dominance of offspring-producing females and a smaller number of resources-exploiting males, capable to fertilize females equally effectively, sexually antagonistic females promoting imprinting pattern would result in a bigger progeny.

Concerted evolution of both placentation and imprinting suggests that imprinting is involved in mother-offspring interactions (5, 10). The maternal-

offspringcoadaptation theory is based on a phenomenon called epistasis (a phenomenon when interactions of certain genotypes result in a more (or less) than the sum of the interacting parts). Whenever interactions between traits affect fitness, genetic correlations are expected to evolve (11). If better fitness is expected with "matching" genotypes between the mother and the offspring, genetic covariance is favoured with silencing of paternal alleles. Conversely, if higher fitness interactions are achieved with "mismatching" genotypes, silencing of maternal alleles evolves (11). In viviparous species (where two genomes must coexist) with prolonged maternal care the offspring have higher fitness if they have a higher resemblance to their mother (6). Thefore, maternal-offspring coadaptation theory provides an explanation for the overabundance of maternal DMRs. Another co-adaptation hypothesis proposes that nuclear genes derived from the mother should tend to be more co-adapted with maternally inherited mitochondrial genes because the maternal and cytoplasmic genes underwent selection together in the previous generation (5). The kinship and coadaptation theories both derive fitness variation from social interactions. Not surprisingly, both theories predict imprinted expression in the organs of social interaction (for example, brain, endosperm, placenta) (11).

A relatively unexplored question is whether parents and offspring are ever in conflict over the imprinting status of the offspring (5). Parents might sometimes benefit from silencing of genes which increase allocation of resources in order to hinder offspring taking more than is optimal for the parent to give (5). According to an analogy to cancer, cancerous cells could be viewed as an example of a highly prolific "microevolution" leading to profuse propagation of cancer cells, but eventual demise of its host; similarly, the more "parasitic" offspring can diminish maternal fecundity and eventually the number of progeny on a population level. A longitudinal study of children born following pregnancies involving pre-eclampsia and pregnancy-induced hypertension suggests that these disorders might ultimately result from foetal attempts to extract more nutriment from the mother, since hypertension in the first trimester appears to benefit the child (5).

All these imprinting hypotheses are not mutually exclusive: different mechanisms may lead to the establishment of imprinting at different loci, and multiple mechanisms may be at work at any given locus afterwards (5). Also, whereas some genes are expected to evolve their imprinting status because of direct selection pressure, other genes may follow as a means of coevolutionary response to match the expression pattern to their interacting partners (8) (for example, due to gene-dosage effects). As a result, some genes even in the same imprinted locus will show phenotypic effects consistent with the predictions of a given evolutionary theory whilst other genes may not, having simply evolved imprinting to follow the lead of their interacting partners (8).

Other suggested hypotheses did not withstand more precise scrutiny. The 'ovarian time bomb' hypothesis suggests that mothers use imprinting to prevent development of their unfertilised eggs (i. e. parthenogenesis). The hypothesis might partially explain imprinting in mammals, in which parthenogenesis is absent and presumably costly, but not in other taxa (such as angiosperms) (5).

## IMPRINTING DISORDERS – FURTHER EVIDENCE FOR IMPRINTING IMPORTANCE

In humans, the physiological importance of genomic imprinting can be demonstrated by the imprinting disorders caused by disruptions or epimutations of imprinted genes (2, 12). Also, derangements of imprinting during the brain development were suggested to play a role in the etiology of psychiatric disorders, including autism and schizophrenia. These disorders have been hypothesised to be extreme, maladaptive manifestations of behavioural syndromes that are favoured by fathers and mothers, respectively (5). Cancer epigenetic alterations also involve multiple imprinting defects, however, their discussion goes beyond the scope of this publication.

Eight imprinting disorders (IDs) are currently known to occur in humans and multilocus imprinting defects were recently discovered (12, 13, 14). For nearly all known IDs, the same complex genetic and epigenetic alterations affecting imprinted genes / gene clusters and their expression / regulation have been reported (2, 12, 13). They include genomic mutations (uniparental disomy (UPD), chromosomal imbalances, and point mutations in imprinted genes or ICR) and true epigenetic defects (abnormal DNA methylation without DNA sequence or genomic alterations) (2, 12, 13). The incidence of different classes of mutations and epimutations varies across various IDs, suggesting

variable importance of different mutational mechanisms at different loci.

Despite marked clinical heterogenity, some common clinical features are inherent to the majority of IDs (12):

- Pre- and / or postnatal growth retardation / overgrowth;
- Hypo- or hyperglycemia;
- Failure to thrive in the newborn and early childhood period;
- Neurological abnormalities in childhood and adulthood.

Also,

- Asymmetry of body, head and / or limbs can be observed;
- Most cases are sporadic (due to epimutations, chromosomal imbalancies or uniparental disomy);
- Discordant monozygotic twins occur;
- Genotype–phenotype correlations are difficult to delineate.

Two classical human imprinting disorders, Prader-Willi syndrome (PWS) and Angelman syndrome (AS), are linked to the imprinted gene cluster at 15q11-13. PWS often presents with infantile hypotonia and poor suckling. Later, hyperphagia and obesity, hypogonadism, sleep abnormalities and mild mental disability with a distinctive behavioural pattern develop. Phenotypically, PWS is characterized by small hands and feet, narrow bifrontal diameter, almond-shaped eyes and down-turned mouth corners (12, 13). It can be caused by paternal deletion at 15q11-13, maternal uniparental disomy or, rarely, an imprinting defect. AS patients exhibit severe intellectual disability with absence of speech, aquired microcephaly, characteristic gait due to ataxia, seizures and a unique behavioural pattern with generally happy demeanor (2, 13). In AS, about 70% of patients have *de novo* deletions affecting the maternal chromosome. Further AS specific (epi)mutations include *UBE3A1* mutations, imprinting defects and paternal UPD. Transient neonatal diabetes mellitus (TNDM), in addition to hyperglycemia, is characterized by IUGR and abdominal wall defects. TNDM is associated with an overexpression of the imprinted locus *PLAGL1/ZAC* at 6q24. As with the other IDs, three (epi)genetic causes of TNDM have been identified: UPD(6)pat, paternal duplications of 6q24, and aberrant methylation at the *PLAGL1/ZAC* locus. Silver–Russell syndrome (SRS) is a congenital disorder mainly characterized by pre- and postnatal growth retardation. The children are relatively macrocephalic and their face is triangular-shaped with a broad forehead and a pointed, small chin, cafe-aut-lait spots can be observed. In many cases, asymmetry of limbs and body is present. Growth failure is often accompanied by severe failure to thrive, and feeding difficulties are reported. For those children without catch-up growth by the age of two, growth hormone therapy is encouraged. The genetic basis of SRS is very heterogeneous. In approximately 10% of SRS patients a maternal uniparental disomy for chromosome 7 (UPD(7)mat) can be found. The majority of SRS patients (about 40%) show a hypomethylation of the ICR1 in the imprinted region 11p15; in single cases maternal duplications of the whole chromosomal region in 11p15 have been reported. Beckwith–Wiedemann syndrome (BWS) is characterized by three main features of exomphalos, macroglossia, and (neonatal) macrosomia. Additional features include neonatal hypoglycemia, hemihypertrophy, organomegaly, earlobe creases, polyhydramnios, hemangioma, and cardiomyopathy. In 5 to 7% of children, embryonal tumors (most commonly Wilms' tumor) are diagnosed. The genetics of BWS is complex, but in the majority of cases an altered expression or mutations of several closely linked genes is observed in 11p15. Nearly 50% of patients carry a hypomethylation at this locus. UPD(11p15)pat is the second important alteration, while ICR1 hypermethylation is rare. Most BWS cases are sporadic but familial inheritance is observed in 15% of all cases. In BWS families without aberrant 11p15 methylation, *CDKN1C* point mutations are frequently found. UPD(14)mat and UPD(14)pat syndromes were first described in 1991 (12, 13). The UPD(14)mat phenotype is characterized by prenatal and postnatal growth retardation, muscular hypotonia, feeding difficulties, small hands and feet, recurrent otitis media, joint laxity, motor delay, truncal obesity, and early onset of puberty. The facial gestalt comprises a prominent forehead, a bulbous nasal tip and a short philtrum. UPD(14)pat is associated with a severe clinical course with polyhydramnios, a typical small, bell-shaped thorax, abdominal wall defects, and severe developmental delay. The majority of patients die *in utero* or in the first months of life. Finally, multilocus imprinting defects were described in some patients, pointing to a possible involvement of imprinting establishment and / or maintenance machinery elements common to all or most of the imprinted loci (12, 13, 14).

## CONCLUSIONS

Investigations of imprinting mechanisms, evolutionary origins and derrangements led to some crucial discoveries in epigenetic processes shaping both health and disease. However, at present we have captured only a fraction of the whole wealth of knowledge in this field. Therefore, a huge expansion of knowledge in imprinting is anticipated in the future, especially with wider application of advanced genetic technologies.

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## GENOMO ĮSPAUDAS IR JO SUTRIKIMAI EVOLIUCIJOS PERSPEKTYVOJE

*Santrauka*

**Įvadas**. Imprintingas (genomo įspaudas) – tai vienas iš išsamiausiai ištirtų epigenetikos fenomenų, apimantis visus pagrindinius epigenetinius procesus. Pastarųjų metų tyrimai šioje srityje leido sukaupti daug žinių, o taip pat pakeitė tam tikras nusistovėjusias paradigmas, apibūdinančias genomo įspaudo atsiradimo ir palaikymo mechanizmus ląstelėse. Evoliucinių teorijų tikslai – paaiškinti genomo įspaudo atsiradimą ir išlikimą evoliucijos eigoje veikiant natūraliajai aplinkai. Trys pagrindinės selektyvia asimetrija tarp motininio ir tėvinio alelių paremtos evoliucinės teorijos – tai giminystės, lytinio antagonizmo ir motinos bei palikuonio koadaptacijos teorijos. Nors nė viena iš šių teorijų negali paaiškinti visų genomo įspaudo aspektų, jos neprieštarauja viena kitai, o tam tikrame genetiniame lokuse gali veikti ne vienas, o keli mechanizmai. Genomo įspaudo svarbą įrodo ne tik evoliuciniai, bet ir žmogaus imprintingo ligų tyrimai. Iki šiol aprašytos aštuonios imprintingo ligos, o neseniai atskleisti daugybiniai imprintingo sutrikimai, kurių priežastis – bendrų imprintingo atsiradimo ir palaikymo ląstelėje mechanizmų pažeidimai.

**Išvados.** Genomo įspaudo mechanizmų, evoliucinės kilmės ir sutrikimų tyrimai leido atskleisti normalius ir patologinius epigenetinius procesus; vis plačiau taikant pažangiausias genetinių tyrimų technologijas dar daugiau žinių šioje srityje tikimasi sukaupti ateityje.

**Raktažodžiai:** genomo įspaudas, evoliucija, įspaudo sutrikimai