**GENE IMPRINTING**

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**Introduction: -**

Every creature contains two copies of genes, one inherited from each parent. As a result, each parent contributes two sets of genes during the developmental process. As a result, there are two copies of each gene. Most of the time, all copies of a gene activate, but for some genes, only one copy activates to perform the activities. Notably, the mechanism known as epigenetic silencing allows for gene deactivation or silencing. These are genes that have been imprinted. And let me tell you, these genes completely defy the Mendelian inheritance pattern. Non-mendelian inheritance is responsible for the expression of imprinted genes. Silencing of genes occurs at the pre-developmental stage of sperm and egg maturation.

***“Genomic imprinting****– In mammals, a small portion of genes is inherited solely from a single parent and is epigenetically controlled during parental germline division."*

For many years, genomic imprinting was a mystery. However, it has now gotten additional light. According to the study, a limited number of genes are mono-allelic and have parent-specific origins. That is, only one copy of a pair of genes is activated. Imprinting happens during germinal cell division, is passed on to children via fertilization (kept), and is erased during the creation of a new set of germ cells. In mammals, the entire cycle of epigenetic programming and reprogramming is highly regulated and occurs continuously in response to environmental inputs. The entire cycle involves a recognized epigenetic marker or mechanism.

Several enzymes from the same family catalyze the programming, maintenance, and reprogramming cycles. So, here we see what exactly the mechanism is

## **Molecular Mechanism of Genomic Imprinting**

Parental genomes are functionally inequivalent, indicating that even if both parents contribute the same number of chromosomes and genes, they are not functionally equivalent. Each has a unique epigenetic pattern. It is functionally distinct to its parental genome. As a result, both parents' genomes are necessary to fertilise and produce a healthy embryo. The major process underlying the functional diversification of some genes is imprinting by DNA methylation, a recognised and documented epigenetic feature of the mammalian genome. The majority of genes were inherited equally by both parents in diploid creatures (like us). However, A small fraction of genes is uniparentally expressed, meaning they can be expressed from either the maternal or paternal side. Imprinting renders a gene from a single parent dormant.

For example,

If a gene is maternally imprinted, only the parental allele activates; similarly, if a gene is paternally imprinted, only the maternal allele activates. Imprinting is classified as an epigenetic alteration in broad terms.

**Epigenetics’ –**

Changes in gene expression are studied rather than changes in gene structure. Demonstrating not just the structure of a gene, but also its differential expression, helps to the production of varied phenotypes.

Methylation, acetylation, and histone changes such as histone phosphorylation, ubiquitination, methylation, and others are well-studied epigenetic mechanisms. These are also referred to as epigenetic tags. DNA methylation is one of the most well-known and widely used epigenetic markers for the existence of genomic imprinting. Enzyme methyltransferases (DNMT) catalyse numerous methylation and demethylation activities during imprinting creation, maintenance, and removal. DNA methylation occurs atypically in the CpG-rich region of our genome, where the majority of imprinted genes are located. The methyltransferase enzyme attaches the methyl group to the C5 residue of the cytosine nitrogenous base, rendering it transcriptionally inactive.

A typical cell has two sets of chromosomes, one from the mother and one from the father. Typically, autosomal alleles from maternally and paternally inherited chromosomes are expressed at comparable quantities. This chapter is dedicated to an exception to this rule: the expression of genes regulated by genomic imprinting is dependent on the parental origin of the allele, resulting in a lack of equivalence between maternal and paternal genomes. As genetically identical alleles can exist in two expression levels within the same nucleus, genomic imprinting is a paradigm of epigenetic gene regulation. The parental allele imprints are established in the parental germline, preserved during child development, but reset before being passed on to the following generation.

In mammals, the major imprint is usually a differentially methylated area at the locus, but histone changes can also mark the parental alleles. Many imprinted genes are involved in human disease and serve key functions in development. Interestingly, genomic imprinting originated separately in humans and seed plants, and similar techniques have been used to control imprinted expression in both kingdoms.

Epigenetic imprints can either activate or silence the “imprinted” allele, and hence imprinting can be associated with either an expressed or silenced allele. The imprint is placed during male or female gametogenesis and determines the differential expression state of the alleles in post fertilization tissues.

1. Maternally expressed genes (MEGs)
2. Paternally expressed genes (PEGs)

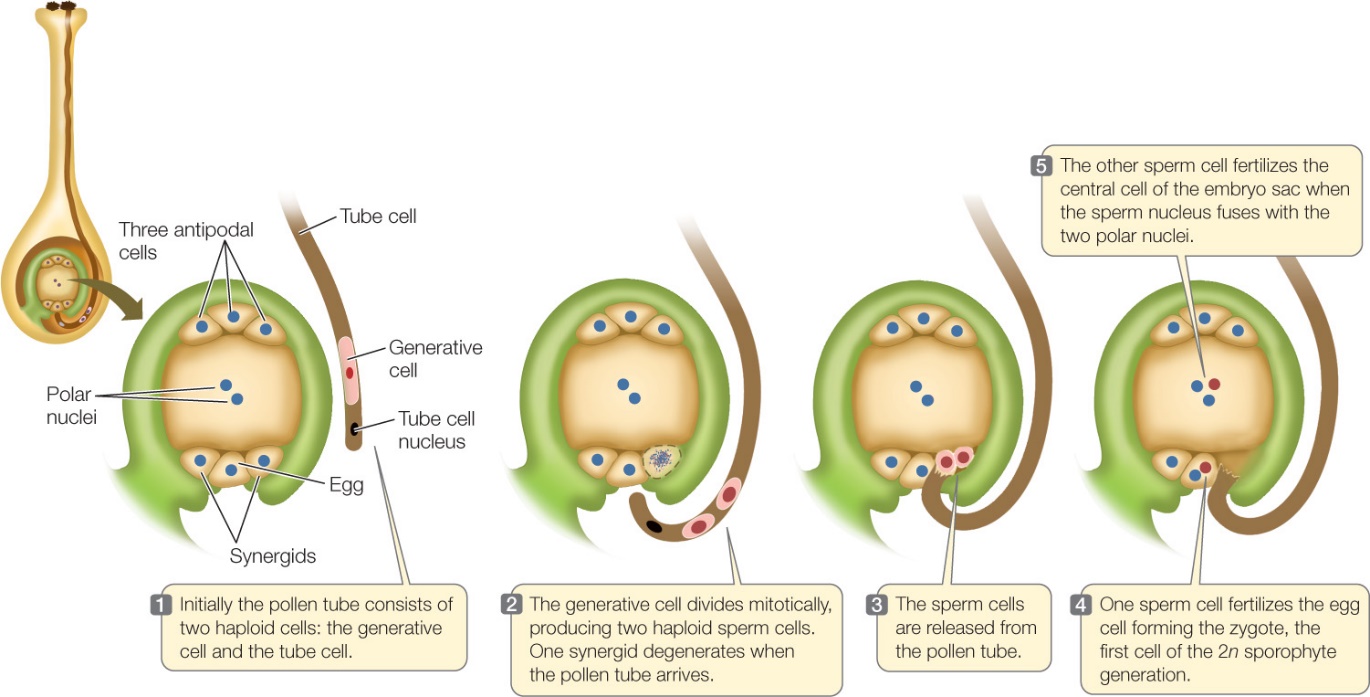
**Paternal imprinting** means that an allele inherited from the father is not expressed in offspring.

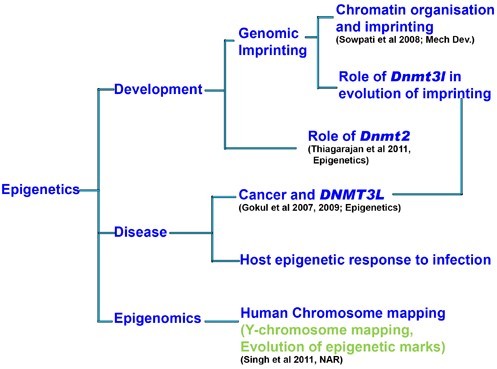
**Maternal imprinting** means that an allele inherited from the mother is not expressed in offspring.

In mammals and flowering plants, imprinting occurs in the embryo as well as in embryo nourishing tissues, the placenta and the endosperm, respectively,

* Imprinted genes control the nutrient flow from the mother to the offspring.
* Imprinting in angiosperms occurs in endosperm early embryo but not in adult tissues.

Fig: Double Fertilization





#### Evolution of genomic imprinting:

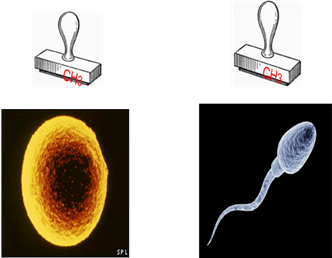
#### Parental conflict theory

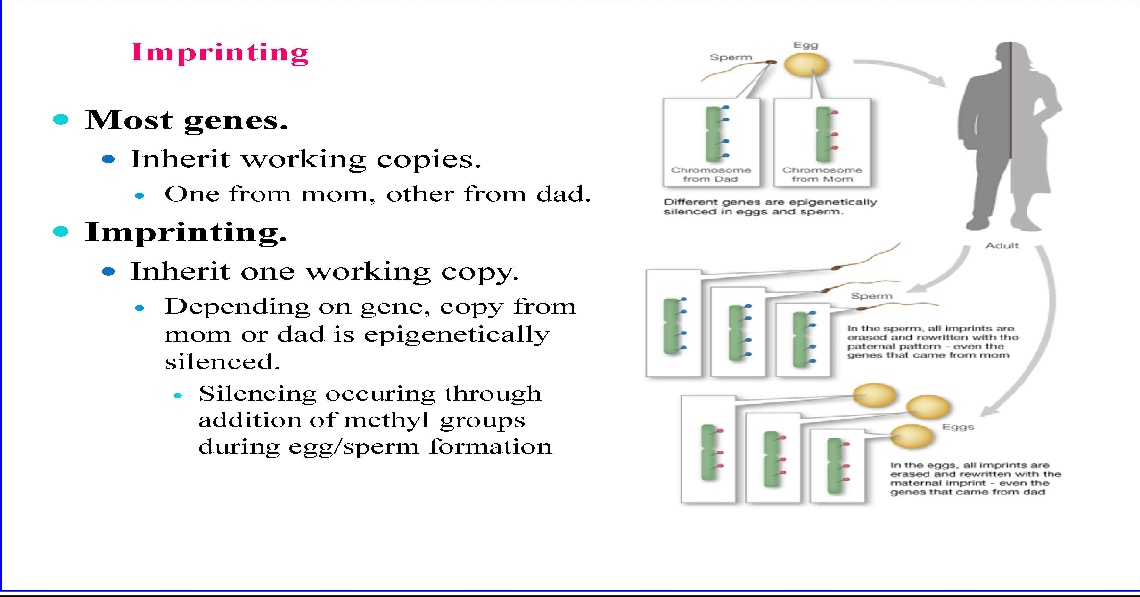
#### If genomic imprinting was solely limited to angiosperms and mammals, this would be consistent with the parental conflict theory, whereby imprinting has evolved in organisms which have a placental habit allowing conflict between males and females over the level of maternal resource allocation to the offspring.

#### The theory also suggests that genes that restrict zygote growth become paternally silenced, whereas genes promoting growth would be silent from maternal alleles.

* First report by Helen Crouse in 1960.
* The first description of the imprinting phenomenon was given by McGrath and Solter in 1984.
* The word “Imprinting” was first used to describe events in insect *Pseudococcus nipae.*
* In plants first demonstrated in maize by Kermicle (1970)
* The study of gene specific imprinting during seed development in *Arabidopsis*.
* The development of embryo and endosperm is highly coordinated.
* Crosstalk between these two is essential for synchronized development.
* Mutations in a specific class of genes disrupt such developmental synchrony and seeds eventually abort.

#### What is imprinting?

* Imprinted chromosomes are “marked”
* Imprinting differs in sperm and egg
* Imprinting turns off specific genes
* Imprinting does not change the nucleotide sequence.
* It is an inheritance process independent of the classical mendelian inheritance.
* If the allele inherited from the father is imprinted and thereby silenced then only the allele from the mother is expressed. (In the case of gene H19 or CDKN1C).
* If the allele from the mother is imprinted then only the allele from the father is expressed (e.g., in the case of gene IGF-2).



**Genome imprinting is mediated via –**

* DNA methylation
* Histone modification

#### Types of gene imprinting:

**Allelic Imprinting:** In which only alleles from a certain background are subject to parent- of origin–specific gene expression.

**For Example:** An imprinted angiosperm gene was in alleles of the maize R gene. The R gene conditions anthocyanin accumulation in the aleurone (the outer cell layer of the endosperm) of maize kernels. When an RR female (red) is mated to a rr male (colorless), all of the kernels have a fully colored aleurone. However, the reciprocal cross gives rise to kernels with mottled aleurone pigmentation, indicative of irregular anthocyanin distribution (Kermicle, 1970). This phenomenon is specific to the endosperm, and no reciprocal differences are observed in embryos or seedlings (Brink *et al*., 1970).

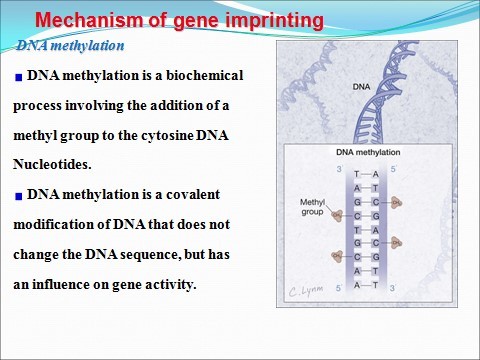
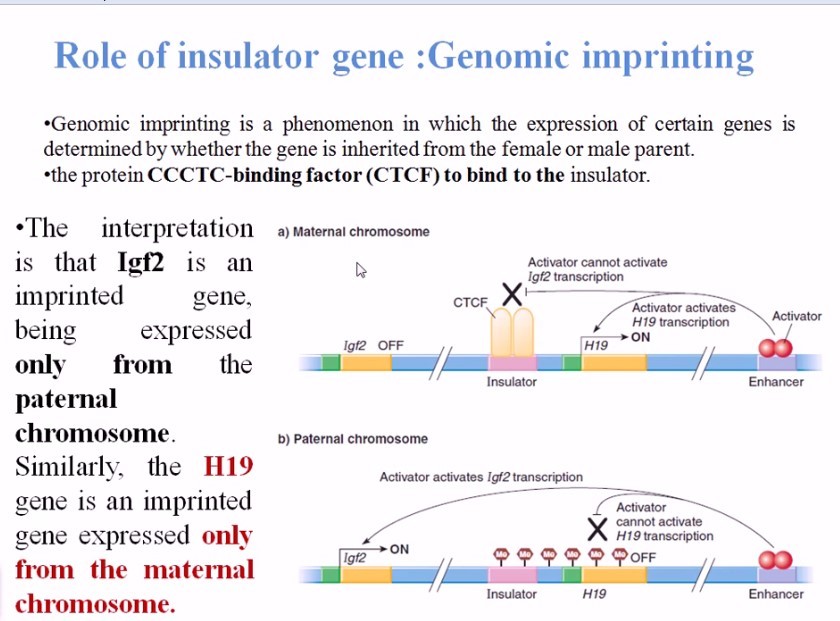
|  |  |  |  |
| --- | --- | --- | --- |
| **Sr.No** | **Genes** |  | **Reference** |
| 1 | R | Endosperm | Kermicle(1970);Ludwig et al., (1989) |
| 2 | Dzr-1 | Endosperm | Chaudhari & Messing (1994) |
| 3 | Zein | Endosperm | Lund et al., (1995a) |
| 4 | Alpha-tubulin | Endosperm | Lund et al., (1995a) |
| 5 | Locus- specific imprinted genes | Tissue-specific expression | |
| 6 | ZmFie1 | Endosperm | Danilevskaya et al., (2003)., Gutierrez Marcos et al (2006) |
| 7 | ZmFie2 | Endosperm | Hermon et al (2007); Haun and Springer (2008) |
| 8 | Nrp1 | Endosperm | Danilevskaya et al., (2003)., Gutierrez Marcos et al (2006) |
| 9 | Meg1 | Endosperm | Gutierrez-Marcos et al., (2004) |
| 10 | Mez1 | Endosperm | Gutierrez-Marcos et al., (2004) |
| 11 | Mee1 | Embryo & Endosperm | Haun et al., (2007); Haun & Springer 2008 |
| 12 | VIM5 | Endosperm | Jahnke and Scholten (2009) |
| 13 | YUC10 | Endosperm | Zhang et al (2013) |

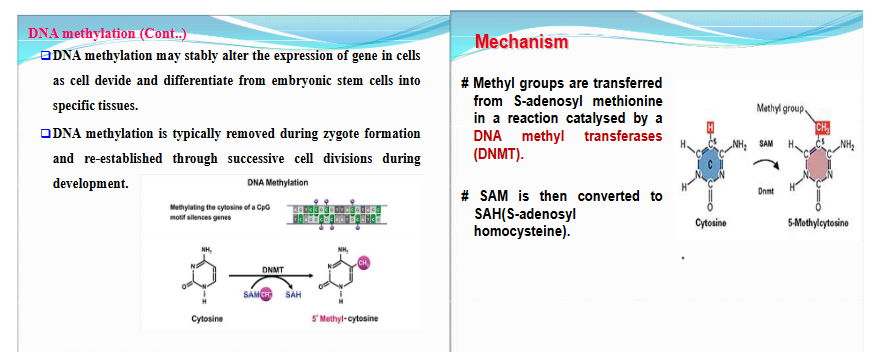
(SOURCE: Bhavani et al., 2012)

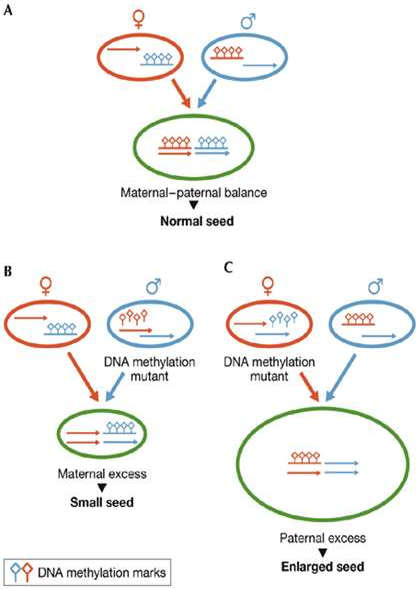
#### Locus imprinting:

#### In which all known alleles from different backgrounds are under parent- of origin control.

Example: **The Arabidopsis MEDEA (MEA) gene**

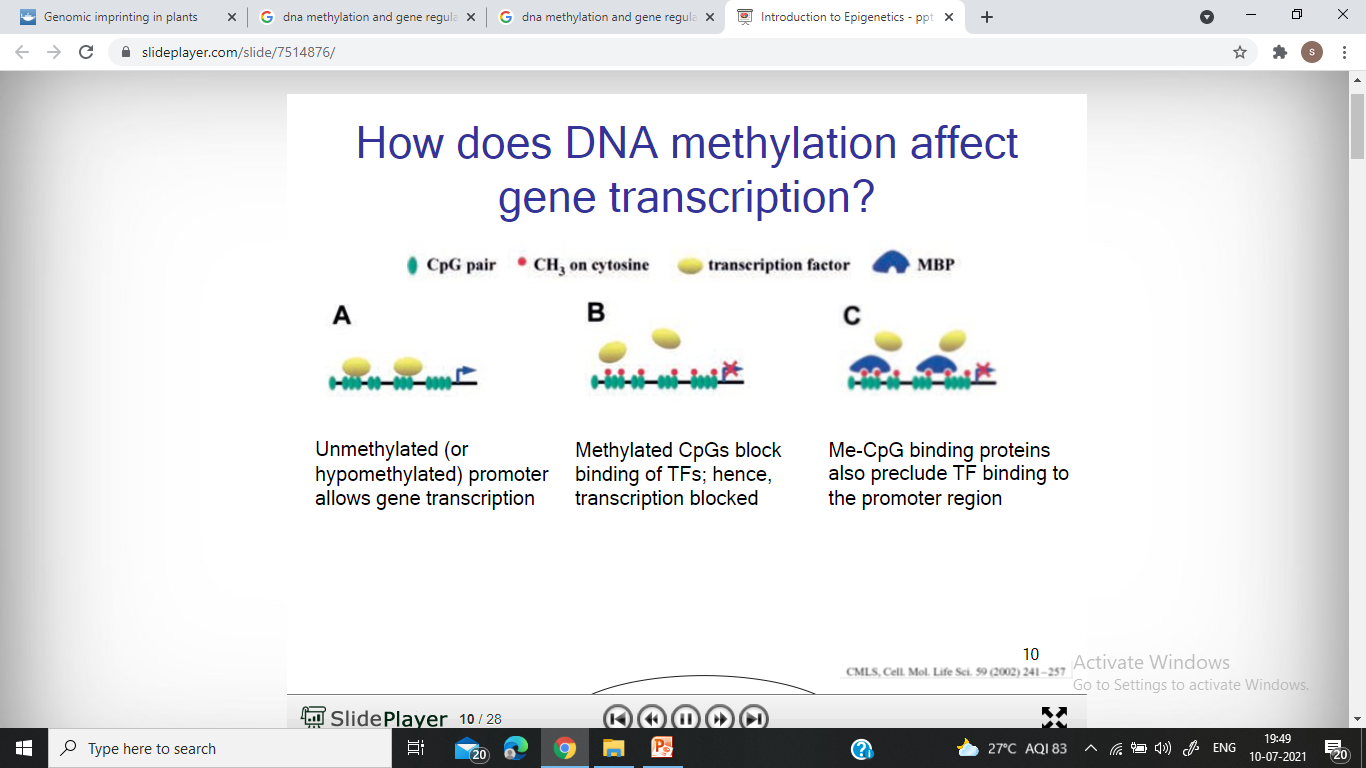






#### DNA methylation affect gene transcription by:

#### 



#### Histone modification:

#### A histone modification is a covalent post-translational modification (PTM) to histone proteins which includes-

#### Methylation

#### Phosphorylation

#### Acetylation

#### Ubiquitylation

#### Sumoylation.

#### In most species, histone H3 is primarily acetylated at lysines 9, 14, 18, 23, and 56, methylated at arginine 2 and lysines 4, 9, 27, 36, and 79, and phosphorylated at ser10, ser28, Thr3, and Thr11.

#### Histone H4 is primarily acetylated at lysines 5, 8, 12 and 16, methylated at arginine 3 and lysine 20, and phosphorylated at serine 1.

#### Imprinted genes in plants:

In flowering plants (angiosperms).

During fertilization of the egg cell, a second, separate fertilization event gives rise to the endosperm, an extra-embryonic structure that nourishes. Unlike the embryo, the endosperm is often formed from the fusion of two maternal cells with a male gamete. This results in a triploid genome. The 2:1 ratio of maternal to paternal genomes appears to be critical for seed development. It has been suggested that these imprinted genes are responsible for the triploid block effect in flowering plants that prevents hybridization between diploids and auto- tetraploids.

#### Role of genomic imprinting in seed development:

#### Seed development in flowering plants is initiated by double fertilization.

#### One haploid sperm fuse with the haploid egg to produce the diploid embryo and the second haploid sperm fuses with the diploid central to form the triploid endosperm.

#### The embryo has a maternal : paternal parental genomic ratio of 1:1 (1m:1p) whereas the ratio in the endosperm is 2m:1p.

**Gene imprinting in *Arabidopsis thaliana***

#### 4 genes in *Arabidopsis* are imprinted –

#### MEDEA (MEA), FWA and FERTILIZATION INDEPENDENT SEED 2 (FIS2) are maternally expressed and paternally silence.

#### PHERES1 (PHE1) is the only plant gene known to be paternally expressed and maternally silenced.

#### Imprinting Regulation at the Maternally Expressed *MEDEA* Locus in *Arabidopsis thaliana*

#### *MEA* encodes SET- Domain protein and controls seed development.

#### Loss of function mutations of *MEA (mea)* show a parent-of-origin maternal effect.

#### When inherited maternally (but not paternally), the mutant *MEA* allele induces endosperm and embryo over proliferation and eventually leads to seed abortion.

#### By default, *MEA* genes more likely to be transcriptional silencing due to DNA methylation (cytosine methylation) by *METHYLTRANSFERASE 1 (MET1)*.

#### A maternal-specific activator(s) releases the default silencing and activates maternal expression only in the female gametophyte.

#### In the male gametophyte, by contrast, the paternal allele would remain silent due to an absence of a maternal-specific activator(s).

#### *DEMETER (DME)* has been identified as a transcriptional activator positively regulating MEA in the central cell.

#### *DME* encodes a DNA glycosylase that specifically removes 5-methylcytosine from DNA

#### Ovules carrying mutant *dme* do not express MEA and as a result the seeds eventually abort.

#### It was thus hypothesized that *DME* removes DNA methylation at the maternal *MEA* allele in the central cell and the hypomethylated maternal *MEA* is exclusively expressed in the early endosperm while the methylated paternal *MEA* is transcriptionally silenced

#### Imprinting Regulation at the Maternally Expressed *FWA* Locus in *Arabidopsis thaliana*

#### The FWA (FLOWERING WAGENINGEN) gene was the second imprinted gene to be discovered in Arabidopsis thaliana, where it behaves as a maternally expressed imprinted gene in the endosperm.

#### FWA is presumed to affect flowering through the speculated photoperiod promotion pathway.

#### FWA also plays a role in the control of flower meristem identity.

#### FWA by default remains silenced due to DNA methylation by METHYLTRANSFERASE 1 (MET1).

#### Gain in function of FWA gene occurs due to when DME removes the methyl group from the DNA making the FWA gene transcriptionally active.

#### This eventually leads to delayed flowering phenotype.

#### Imprinting Regulation at the Paternally Expressed PHERES1 Locus in Arabidopsis thaliana

#### PHERES1 (PHE1) is third imprinted gene studies in the Arabidopsis endosperm.

#### In Arabidopsis thaliana PHERES1 gene is involved in ending of seed dormancy and regulation of transcription of MADs-box genes.

#### Whereas MEA, FIS2, and FWA are maternally expressed, paternal PHE1 expression predominates in the endosperm, while the maternal PHE1 is silent or very weakly expressed because maternally expressed MEDEA gene represses its expression in female gametophyte.

#### This protein was called 'Pheres' in memory of one of the murdered sons of the mythological 'Medea', as PHERES1 is repressed by MEDEA

#### The PHE1 locus is regulated by histone trimethylation on H3K27 residues

#### Imprinting Regulation at the Maternally Expressed FIS2 Locus in Arabidopsis thaliana

#### The fourth imprinted gene discovered in the Arabidopsis genome is the Fertilization Independent Seed 2 (FIS2) gene which is maternally expressed in the endosperm.

#### At the imprinted FIS2 locus, the maternal allele of FIS2 is also activated by DME in the central cell.

#### Conclusion:

#### The study of imprinting in plants has significantly grown over the past decade. The wide availability of mutants affecting epigenetic processes in plants has allowed the plant imprinting field to apply such mutants to genetically dissect the mechanisms controlling imprinting in plants.

#### Genetic imprinting is found to have major role in many key developmental processes and genome dosage is one of the factors contributing to the imprinting.

#### To date, the scientific community is still debating on its role in evolution and significance in the process of crop improvement.

#### Imprinted gene regulates the transfer of nutrients to the developing progeny.

#### Advanced technologies like genome-wide approaches may contribute in helping the researchers to unravel the potential mechanism of genetic imprinting and its possible benefits to crop improvement.

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