

Epigenetics

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ABSTRACT

Ever wondered how traits are inherited without changing DNA? Enter epigenetics, a fascinating branch of genetics. This article breaks down what epigenetics is and how it differs from traditional genetics. We focus on three key players: DNA methylation, where adding a methyl group influences gene behaviour; histone modification, where changes in packaging proteins lead to variation; and RNA-directed DNA methylation, a guided mechanism for molecular adjustments. By unravelling these mechanisms, we uncover the hidden world shaping our genes. This exploration unveils the intricate relationship between genes and their environment, showcasing the profound impact of epigenetics on our understanding of inheritance and biological complexity.

INTRODUCTION

Not all changes result from Darwinian selection of random variations created by the shuffling of genes and rare chance mutation. Researchers are increasingly focusing on exploring the characteristics of various heritable variations, and there is a growing awareness regarding the significance of non-DNA sequence heritable variations that is EPIGENETIC VARIATION.

What is Epigenetics?

The term **Epigenetics** was coined by **C.H.WADDINGTON** in 1942. The **Greek prefix epi-**("upon," "on," "over," "near," "at," "before," and "after,") is the traditional genetic basis for inheritance (Nathan M. *et al.*, 2017; Zahida Akhter *et al.*,2021). Epigenetics can be defined as "A stable heritable phenotype

resulting from changes in a chromosome, without alteration in the DNA sequence".

In Figure 1 which represents a normal black mouse Vs an agouti yellow mouse, because of agouti mutation in a normal black mouse, the mouse turns to yellow, much



Fig 1. Black normal mouse vs Agouti mouse

fatter, and has a short life span. Researchers started working on normal black mouse, where they fed different food for some time, without causing any changes in DNA sequence. After a certain period, they got agouti mouse from normal mouse. Both the agouti mouse and the typical black mouse had the same DNA sequence, but their phenotypic appearance differed. What caused this change ...? It is because of Epigenetics.

So, let's look at how epistatic variation differs from genetic variation to obtain a better understanding of epigenetic variation.

Difference between epigenetics and genetic variations:

Property	Epigenetic variations	Genetic variation
Variation type	No change in DNA sequence, but change in DNA methylation chromatin structure	Change in DNA sequence
Origin usually	Random due to imperfection of DNA methylation patterns or non-directed environmental effect	Usually, random
Unit of variation	The activity of the gene	DNA bases sequence
heritability	varies	100%
Frequency of forward & background variation	Very wide range up to 100 % locus	More limited range in forward <10-4 per locus, in background extremely low

Now that we have seen the difference let's focus on what is the cause of these epigenetic variations:

Mechanisms under epigenetic variations

- DNA Methylation
- Histone Modification
- RNA-directed DNA methylation

1. DNA Methylation

DNA methylation is an important **heritable** epigenetic modification (Xiaoguo Zheng *et al.*,2016). It is catalyzed by DNA Methyltransferases, which transfer an activated methyl group from **S-adenosyl methionine(SAM)** to the 5' position of cytosine. It predominantly occurs at **CpG** dinucleotide sequences (Lingyon Kong *et al.*,2020). Cytosine methylation is a repressive chromatin mark.

Transcription is required for a gene to be expressed. Transcription requires RNA polymerase, certain transcription factors & certain activators bound to DNA. When DNA is methylated, it prevents RNA polymerase or transcription factors from attaching to it, preventing gene expression.DNA Methylation alters the affinity of DNA binding proteins (transcriptional machinery) to DNA (or) recruiting proteins involved in gene expression.

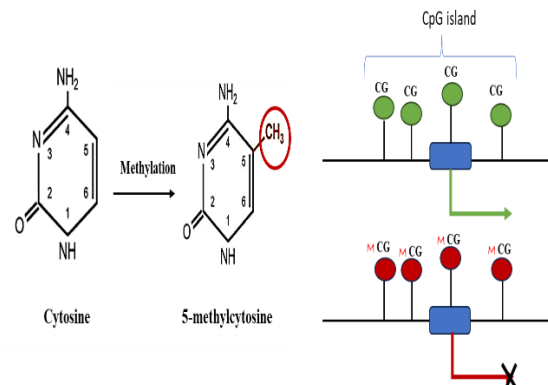


Fig: 2. represents methylation of cytosine nitrogen base b) methylation of CpG(cytosine phosphate guanine) islands .

2. Histone modification:

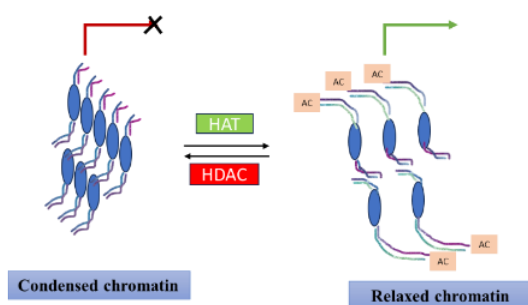


Fig. 3. Binding of acetyl & deacetyl group to tail region of histone, which in turn leads to activation & inactivation of chromatin respectively

It refers to the modification made in the **N-terminal tail of histones** which involves the addition or removal of acetyl, methyl, and phosphate groups, it leads to both activation & repression of gene expression. Histones are wrapped by DNA in nucleosome, when acetyl group binds to the tail region of the histone, it will unwrap the DNA, making it accessible for transcription, and allowing the gene to be expressed. If some other deacetyl groups bind the tail region, it will make the wrapped DNA compact, thereby preventing the expression of the gene. Histone Modification depends on the type of group that is binding it, binding of an acetyl group reduces the positive charge of histone protein. As a result interaction between DNA & bound histones is weakened which in turn unwarap compact DNA . Hence DNA is more freely available for transcription (Lingyon Kong *et al.*,2020;Saurabh Saraswat *et al.*,2017). On the other hand, binding of methyl group may lead to either activation (or) inactivation of the gene. Methyl group alters the hydrophobicity of DNA resulting in altered DNA histone interaction.

3. RNA- directed DNA Methylation (RdDM):

An epigenetic mechanism was first discovered in plants (Wassenegger *et al*, 1994). Several noncoding RNAs (small non-coding RNAs as well as long noncoding RNAs) modify the sequence, structure, and expression of

mRNAs. In this process dsRNAs are processed to 21-24 nucleotide small interfering RNAs (siRNAs) and direct the addition of DNA methylation to specific DNA sequences, This in turn associated with transcriptional repression of the genetic sequences targeted.

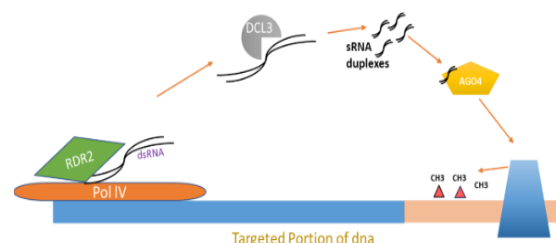


Fig. 4. Pol IV: RNA polymerase 4 attaches to the targetted DNA that has to be methylated and uses DNA as a template to create ssRNA.b) Then there's RDR2, which stands for RNA-dependent RNA. Polymerase 2 synthesizes RNA that is complementary to ssRNA. As a result, dsRNA is created. c) **DCL3: Dicer –Like3(Cuts RNAs) & breaks into smaller fragments called smaller RNA .d) Smaller RNA binds to **AGO4**: Argonaute 4, which helps in the transport of smaller RNA. E) They recruit DNA Methylation Machines and bond to the targeted area of DNA during their transportation. f) Then methylate the targeted DNA. (Adela Pribylova *et al.*,2019; Huiming Zhang *et al.*,2018)**

CONCLUSION

As we finish exploring epigenetics, we've learned how it's like a secret code influencing our genes. We compared it to regular genetics and talked about three key players: DNA methylation, histone changes, and RNA's role. Remember, epigenetics is like a hidden world shaping how our genes work. I encourage you to keep exploring this fascinating topic.

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