The Dutch Winter of Hunger

- After World War II, the winter of 1944-45 became known as the 'Hunger Winter' in the Netherlands after German blockades cut off food supplies to the area.
- Genetic studies have identified epigenetic imprinting in the DNA of children whose mother's were exposed to the famine during their pregnancy. These genetic imprints make the children and their offspring more susceptible to obesity, diabetes and cardiovascular disease during later life.
- One of these imprints is a reduction in the normal amount of DNA methylation of the IGF2 gene.
- To improve their health you need to methylate the IGF2 gene (Gene 1).

Heijmans,B.T.,Tobi,E.W.,Stein,A.D.etal.(2008)PersistentEpigeneticdifferences associated with prenatal exposure to famine in humans, Proceedings of the National Academy of Sciences, 105 (44), 17046–17049

Fragile X Syndrome (FXS)

- Fragile X syndrome (FXS) is the most common form of inherited intellectual disability.
- It is an inherited genetic condition that causes a range of developmental problems including learning disabilities.
- Affects both males and females, but males are more severely affected.
- Symptoms include delays in talking, anxiety, hyperactive behavior, and sometimes seizures. Physical features might include large ears, a long face, a prominent jaw and forehead, and flat feet.
- FXS can result from a genetic imprinted increase of methylation of the FMR1 gene.
- To improve their health you need to acetylate the FMR1 gene (Gene 2).

Coffee, B., Keith, K., Albizua, I., Malone, T., Mowrey, J., Sherman, S. L., & Warren, S. T. (2009). Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. The American Journal of Human Genetics, 85(4), 503–514.

Lactose Tolerance

- Epigenetic imprinting plays a key role in the dietary adaptations individuals carry in their DNA, making them more suited to the diet of their parents.
- An example is lactose tolerance, also called lactase persistent. Epigenetic imprinting on the LCT gene allows some populations to maintain lactase persistence throughout their adult lives while other populations lose the ability to digest lactose after childhood.
- Genetic studies have identified genetic imprinting of the LCT gene as being responsible for the lifelong lactose tolerance.
- To maintain their lactose tolerance you need to acetylate the LCT gene. (Gene 4)

Ingram, C. J. E., Mulcare, C. A., Itan, Y. et al. (2009) Lactose digestion and the evolutionary genetics of lactase persistence, Human Genetics,124 (6), 579–591.

Persistence of Foetal Haemoglobin (POFH)

- Sickle Cell Anemia, a genetic disorder and preventative adaptation against malaria, affects red blood cells and their ability to uptake oxygen. It can also result in very painful and/or life threatening conditions.
- With advances in anti-Malaria treatments and mosquito control, malaria concerns are decreasing within some populations.
- Genetic studies have revealed a genetic imprinting in the DNA of these populations that produces Persistence of Foetal Hemoglobin (POFH), a condition where an individual never undergoes a switch to adult hemoglobin, and thus avoids expression of Sickle Cell Anemia.
- To improve their health you need to methylate the BCL11A gene (Gene 6).

Sankaran, V. G., Xu, J. and Orkin, S. H. (2010) Advances in the under-standing of haemoglobin switching, British Journal of Haematology,149 (2), 181–194

The Oromo of Ethiopia

- The Oromo people migrated to the northern Ethiopian highlands from the southern Ethiopian lowlands during the early 1500's.
- Genetic studies have identified genetic imprinting in the Oromo DNA that appears to show epigenetic imprinting acting as a catalyst for the introduction of variation in gene expression, resulting in a wide range of phenotypes for protection from the new viral threats that they were exposed to upon arriving in the region
- One of these genetic phenotypes involves the APOBEC3G gene which codes for a protein which targets virus RNA by producing multiple mutations that make the virus less dangerous.
- To protect them from new viruses, you need to acetylate the APOBEC3G gene. (Gene 3)

Alkorta-Aranburu, G., Beall, C. M., Witonsky, D. B. et al. (2012) The gen-etic architecture of adaptations to high altitude in Ethiopia, PLoSGenetics, 8 (12), e1003110.

Post Traumatic Stress Disorder

- Genetic imprinting can result from traumatizing experiences that put individuals under extreme mind and body stress. Survivors acquires DNA methylations from this time in their lives that are then passed on to following generations.
- An example of this is the accumulation of epigenetic imprinting in the descendants of Holocaust survivors that result in a marked increase of PTSD, depression and obesity, all resulting from methylation of the FKBP5 gene.
- To improve their health you need to acetylate the FKBP5 gene (Gene 5).

Yehuda, R., Daskalakis, N. P., Bierer, L. M. et al. (2015) Holocaustexposure induced intergenerational effects on FKBP5 methylation,Biological Psychiatry, 80, 652–656.

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Role of Epigenetics in Developmental Biology and Transgenerational Inheritance

Michael K. Skinner*

Center for Reproductive Biology, School of Biological Sciences, Washington State University, Pullman, WA

Abstract

The molecular mechanisms involved in developmental biology and cellular differentiation have traditionally been considered to be primarily genetic. Environmental factors that influence early life critical windows of development generally do not have the capacity to modify genome sequence, nor promote permanent genetic modifications. Epigenetics provides a molecular mechanism for environment to influence development, program cellular differentiation, and alter the genetic regulation of development. The current review discusses how epigenetics can cooperate with genetics to regulate development and allow for greater plasticity in response to environmental influences. This impacts area such as cellular differentiation, tissue development, environmental induced disease etiology, epigenetic transgenerational inheritance, and the general systems biology of organisms and evolution.

Keywords

epigenetics; development; environment; transgenerational; systems biology; differentiation; disease etiology

Current Paradigm for The Molecular Control of Developmental Biology

Traditionally genetic mechanisms and processes have been thought to provide the primary control for cellular differentiation and developmental biology. This involves the regulation of genome activity through a series of genetic factors such as a cascade of critical transcription factors, regulation of gene expression to promote a programming of transcriptional events essential for cellular differentiation and eventual development of the tissue and organism. Abnormal development associated with events such as disease development have also been thought to be regulated primarily from genetic mutations. The role of genetics in the regulation of developmental biology is well established and many studies support the actions of numerous genes and genetic processes. As with any area of biology, genetics is a critical element of the normal and abnormal development of a cell, tissue or organism. However, there are several observations that suggest genetics alone is not sufficient to regulate the entire phenomena of development or systems biology.

*Correspondence to: Michael K. Skinner, Center for Reproductive Biology, School of Biological Sciences, Washington State University, Pullman, WA 99164-4236. skinner@wsu.edu.

Abnormal development and critical windows of exposure have demonstrated environmental factors can promote adult onset disease, which is associated with early alterations in normal development of a cell or tissue. These environmental factors include nutrition, environmental compounds, and stress. These factors generally do not have the ability to directly promote DNA sequence mutations nor permanently alter genetic processes. This fetal basis of adult onset disease clearly involves an abnormal developmental process, but is difficult to explain on the basis of genetic processes alone. Environmental factors can also promote alterations in normal development to induce developmental mutations and defects, but again most factors have not been shown to alter DNA sequence. On a population level, many evolutionary processes appear to be influenced by environmental factors to promote rapid alterations in development and adaptations, which are also difficult to explain with genetic mechanisms alone.

An additional molecular mechanism that can complement genetics to influence developmental biology is epigenetics. The ability of environment to influence development can also be facilitated by epigenetic processes. The paradigm that genetics is the primary factor to regulate developmental biology is limited and ignores the plasticity to respond rapidly to environment, nor does it explain abnormal development and disease etiology in the absence of genetic alterations. Epigenetics provides an additional molecular mechanism to complement genetics in the regulation of development. Therefore, the paradigm shift is that layers of molecular control and cascades of both epigenetic and genetic factors or processes are involved in regulating developmental biology, Figure 1. This provides a more robust and thorough control of development that integrates these two critical molecular processes.

Epigenetics

Epigenetics is defined as molecular factors and processes around DNA that regulate genome activity, independent of DNA sequence, and that are mitotically or meiotically stable (Skinner et al., 2010). The term heritable has been used, but is defined as generational inheritance by definition so does not include all elements of epigenetics. Therefore, mitotically stable is more precise and clarifies that as the cell undergoes mitosis the epigenome is replicated. An environmentally induced stable alteration in the epigenome can permanently alter the regulation of genome activity during cell differentiation and development processes.

The origin of the use of the term epigenetics was by Conrad Waddington in the 1940s while he was studying environment—gene interactions to promote phenotypes (Van Speybroeck, 2002; Waddington, 1940, 1956). The first molecular epigenetic factor identified was DNA methylation (Holliday and Pugh, 1975) in the 1970s which was subsequently shown to influence processes such as X chromosome inactivation and gene expression (Chen and Riggs, 2005). In the late 1980s imprinted genes were identified and shown to be regulated by DNA methylation as well (Chen and Riggs, 2005). In the 1990s histone modifications and chromatin structure were identified and shown to regulate promoter activity and gene expression (Turner, 1998). In 2000, small noncoding RNAs were found to have epigenetic activity and regulate gene expression (Berdasco and Esteller, 2010). Around 2005 the first

genome wide mapping of the epigenome appeared (Pokholok et al., 2005). Therefore, the molecular characterization of epigenetics is relatively new and additional epigenetic marks are likely to be identified in the future (e.g., hydroxy-methylcytosine) (Kriaucionis and Heintz, 2009).

The functions of the various epigenetic marks and factors are distinct. The DNA methylation has a role in early development to help establish early cell lineages (e.g., stem cells) and can regulate the activity of promoters and general genome regions (e.g., repeat elements) (Kazazian, 2004). Many DNA methylation events are distal to promoters, but can influence gene expression (Illingworth and Bird, 2009). Histone modifications are primarily localized in the promoter and gene regions and fine tune the regulation of specific genes (Turner, 1998). These histone modifications are not generally involved in establishing the absence or presence of expression of a specific gene, but the subsequent expression and responsiveness to transcriptional control (Turner, 1998). The chromatin structure can modulate gene expression at a distance through looping, nuclear matrix association and nucleosome positioning (Biddie, 2011). The noncoding sRNAs can act at a distance to regulate gene expression through promoter modulation and can influence other epigenetic factors (Wan and Bartolomei, 2008). The combination of all these elements creates the epigenome and a complex regulation of genome-wide activity. All these factors are critical and play distinct roles in the process. In regards to development, the DNA methylation is thought to have the initial programming role followed by chromatin structure and histone modifications to fine tune the regulation of gene expression at the various stages of differentiation and development.

An important aspect of epigenetics, first clarified by Arthur Riggs (Russo et al., 1996), is that the epigenetic marks are mitotically and meiotically stable. The initial reference was to heritable, but the term heritable is most commonly defined as generational transmission (i.e., inheritance). Therefore, a more accurate term is “mitotically stable” and implies as a cell divides or proliferates the epigenetic marks constituting the epigenome are replicated. If an epigenetic mark or change was not mitotically stable, then the mark would only be relevant in the individual cell and would not be important outside that cell's function. When an epigenetic mark is mitotically stable, then all cells that come from that initial cell will have the same epigenome. Therefore, early in life an environmental signal could modify a cell's epigenetic marks that then would be mitotically stable and appear later in development in the tissue the cells reside. Therefore, the epigenome is programmed and maintained in a cell population as it further differentiates and is associated with the development of any tissue or organism. As the epigenome regulates gene expression, the environmental or developmental shifts in the epigenome can become a critical element affecting the developmental process. The process of mitotic stability for DNA methylation is understood, but how histone modifications and chromatin structure are replicated and transmitted through cellular division is not as well understood. For example, during DNA replication associated with mitosis, the parental DNA strand has a methylated nucleotide and as the new strand of DNA is synthesized the associated methyltrasferase methylates the hemimethylated DNA to replicate the original parental strand epigenetic mark. Further research is needed to elucidate how the complete epigenome is replicated and mitotically stable. This aspect of epigenetics is critical and allows for a dramatic influence on development and biology.

As the epigenetic marks that make up the epigenome are mitotically stable, an alteration in the epigenome early during cell differentiation or development is transmitted through that cells lineage to later stages of development of the tissue or organism. Therefore, environmental factors that can alter the epigenome promotes an abnormal programming that permanently alters the cell, tissue or organism development and function. This environmental epigenetics will have a critical impact on the developmental process and functions of cells or tissues later in life after the environmental exposure is removed. Environmental factors can include nutritional factors, environmental compounds or stress (Jirtle and Skinner, 2007; Skinner et al., 2010). Any external factor that can modulate normal development and the epigenome can be considered an environmental insult that impacts genome activity without altering DNA sequence. The mitotic stability of the epigenome suggests an environmental insult, even after its removal, will have a lasting effect on cell differentiation and development to promote alterations in physiology later in life. This provides a molecular mechanism for the fetal basis of adult onset disease or the developmental basis of disease (Barker et al., 2009; Bruce and Hanson, 2010). In addition, this provides a mechanism for environmental toxicology not previously considered, and explains how an early life exposure can promote a later life physiological effect. Environmental epigenetics will be a critical concept to consider in developmental biology, as well as most areas of biology (Jirtle and Skinner, 2007; Skinner et al., 2010).

Integration of Epigenetics and Genetics in Developmental Biology

Genetics has a central role in biology and in the control of development. Observations for the past several decades have identified many specific genes and genetic processes involved in the development of most cells, tissues and organisms. Epigenetics is an additional molecular process that can influence development and provides a mechanism for the environment and early life events to regulate cell differentiation and development. Therefore, epigenetics and genetics compensate and cooperate to control and regulate most biological processes, including developmental biology. They should not be viewed as conflicting or opposing processes, but when integrated provide a more robust molecular control of developmental biology.

A cascade of genetic and transcriptional events allows a cell or tissue to develop from a stem cell or basal state to a more mature or adult stage of development. This requires many steps and each step needs to be carefully controlled to allow the next step to proceed, Figure 1. As there is a cascade of genetics steps, there is also a cascade of epigenetic steps to cooperate with genetics to promote the developmental pathway. The epigenetic processes can respond to environmental factors to then integrate with the genetic processes to lead to a developmental step. The cascade of epigenetic and genetic steps during development is critical to promote the normal development process, Figure 1. Early in development there are critical windows of development that are more responsive to environmental factors to modify development. Later in development, the adult or at a more mature stage, the developmental process has been programmed and is less responsive to environmental factors to alter development. In the event an early critical window was influenced through an alteration in the cascade of epigenetic events, the final stage of development can be modified from the normal developmental state, Figure 1. This is generally reflected in the genome

activity or transcriptome of the differentiated cells or tissue. The result of this cascade of epigenetic and genetic processes and the final influence on cell and tissue genome activity is the differentiation and development of the cell, tissue and organism. Abnormal development and alterations in the normal cascade of events through these mechanisms are likely to be a significant element of disease etiology. The overall process and integration of epigenetics and genetics leading to these developmental processes provides the systems biology of the tissue or organism, Figure 1.

Epigenetic Transgenerational Inheritance

The inheritance of environmentally induced phenotypes is the origin of the concept of epigenetics (Waddington, 1940; 1956). In the event these environmental factors modify the epigenome of the germ line and this becomes permanently programmed (imprinted) then the altered epigenome and phenotype become transgenerational and appear in subsequent progeny and generations in the absence of any further environmental exposures (Anway et al., 2005; Daxinger and Whitelaw, 2010; Jirtle and Skinner, 2007; Skinner et al., 2010). The mechanism involves the actions of an environmental factor at a critical time of gonadal sex determination in the mammalian fetus when the germ line cell fate is determined and the primordial germ cell differentiates into a male or female germ lineage (Skinner et al., 2010). During this critical period of development of the germ line an erasure of DNA methylation occurs and then upon gonadal sex determination the germ line DNA is remethylated in a male or female specific manner (Durcova-Hills et al., 2006). The actions of an environmental factor such as an endocrine disruptor (Anway et al., 2005; Anway et al., 2006b; Anway and Skinner, 2008) can modify this germ line methylation and promote a permanently altered epigenome (Anway et al., 2005; Guerrero-Bosagna C et al., 2010) in the germ line (e.g., sperm) that gets transmitted to subsequent generations transgenerationally (Anway et al., 2005; Anway et al., 2006a,b; Anway and Skinner, 2008; Guerrero-Bosagna C et al., 2010). Therefore, the basic mechanism of epigenetic trans-generational inheritance involves the actions of an environmental factor (e.g., chemical or nutrition) during germ line remethylation at gonadal sex determination to permanently alter the germ line epigenome (Anway et al., 2005; Guerrero-Bosagna C et al., 2010; Skinner et al., 2010) to then transmit this altered germ line epigenome to subsequent generations (Anway et al., 2005; Anway et al., 2006a,b; Anway and Skinner, 2008; Guerrero-Bosagna C et al., 2010; Skinner et al., 2010). As the embryonic stem cell epigenome is altered due to this germ line transmission, all cell populations and tissues will have an altered epigenome and corresponding transcriptome (Anway et al., 2008; Skinner et al., 2010). The germ line generated by the next generation will also have this altered epigenome and transmit it to the subsequent generation (Guerrero-Bosagna C et al., 2010; Skinner et al., 2010). Exposure to the endocrine disruptors at other times of development do not appear to have the capacity to permanently alter the germ line epigenome (Anway et al., 2005; Anway and Skinner, 2008; Skinner et al., 2010). Of course, the vast majority of exposures will alter the somatic cells at critical periods of development to modify later cellular development and potential adult onset disease, Figure 1, but this does not have the capacity to become transgenerational as the germ line is not involved (Skinner et al., 2010). Epigenetic transgenerational inheritance through a permanently altered epigenome of the germ line has the capacity to have a

dramatic influence on developmental biology, as well as other areas of biology such as evolution.

In the event the base-line epigenome is altered, then the cascade of epigenetic and genetic steps during development will be altered and a modified differentiated or developmental state achieved, Figure 1. Therefore, epigenetic transgenerational inheritance has a dramatic effect on the developmental biology of all cells and tissues derived from the germ line transmitting this modified baseline epigenome. Although not all cell types or tissues will develop a disease state, those tissues that have a sufficiently altered transcriptome will have a greater susceptibility to develop disease (Skinner et al., 2010). As all development and differentiation processes involve a cascade of epigenetic and genetic steps, alteration of the baseline epigenome, similar to alteration in the genetic baseline, will have the capacity to promote abnormal development which may lead to disease later in life. For this reason, environmentally induced epigenetic transgenerational inheritance through the germ line will have a significant impact on developmental biology. This mechanism and consideration of the cascade of integrated epigenetic and genetic events during development, Figure 1, will be an important factor in disease etiology not previously considered (Skinner et al., 2010).

In addition to the effects of epigenetic transgenerational inheritance on developmental biology and disease etiology, this phenomena will impact nearly all areas of biology, including evolutionary biology (Crews et al., 2007). If the base-line epigenome is modified, similar to the base-line effects of genetics, then the biological system will respond by altering the phenotype, physiology, and general biology of the organism. In considering the molecular mechanisms that promote an adaptation event and natural selection to allow an evolutionary event, an integration of epigenetics and genetics will be equally as important. The current paradigm of DNA mutational events promoting evolution is accurate, but the inclusion of epigenetics allows for a much higher degree of variability in the biological system to facilitate an adaptation event. In addition, the inclusion of epigenetics allows for a mechanism to have environment influence evolutionary processes. Therefore, epigenetic transgenerational inheritance is a novel process to consider in evolutionary biology not previously considered. This does not alter the basic Darwinian evolutionary paradigm, but simply provides a neo-Lamarckian component and more diverse molecular mechanism to be involved. Future research into the integration of epigenetics and genetics will likely reveal more powerful mechanistic considerations to be applied to all areas of biology, including evolutionary biology (Skinner et al., 2010).

Conclusions

Epigenetics will have a critical role in developmental biology and differentiation due to its function in regulating genome activity and the mitotic stability of the epigenetic marks to be replicated as cells proliferate. Therefore, epigenetic marks and alterations in the epigenome have the capacity to be maintained within a cell type or population for the life span of the organism. As an integration and cascade of epigenetic and genetic processes are required throughout development, Figure 1, modification of an epigenetic state has the capacity to create a new phenotype, and if abnormal a disease state. In contrast to genetics, epigenetics can be modified readily by environmental factors, such that epigenetics provides a molecular

mechanism for the environment to alter genome activity and developmental biology. Future considerations of the molecular processes involved in developmental biology, as well as other areas of biology, requires a consideration of epigenetic processes.

The germ line creates through developmental biology nearly all species. Genetic modifications in DNA sequence have the capacity to dramatically alter the development of a species. As epigenetics is intimately integrated with genetics, alterations in the germ line epigenome also has the capacity to dramatically alter the development of a species. Therefore, epigenetic transgenerational inheritance induced by environmental factors will have a critical role in the biology, disease etiology and general development of most, if not all, species. A change in the base-line epigenome in the germ line through its integration with genetic processes and the cascade of events required in a developmental system, Figure 1, will have the capacity to alter phenotype (Waddington, 1940, 1956) and biological processes such as evolution (Crews et al., 2007). The complementary and integrated roles of epigenetics and genetics is what allows these new developmental events to occur and create new phenotypes.

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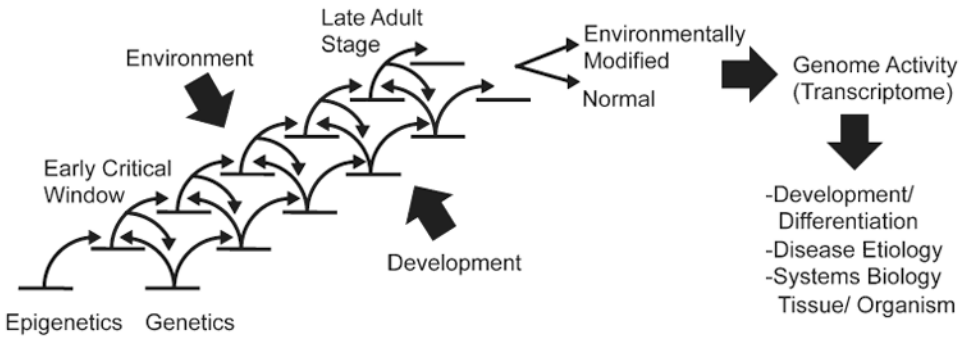

Figure 1.
Epigenetic and genetic cascade of events involved in development.

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Review article

The role of epigenetics in human evolution

Alexander Osborne*

University of Glasgow, 5 Rosemount Square, Kilwinning KA13 6LZ, UK

***Corresponding author:** Alexander Osborne, Email: alexander103050@hotmail.co.uk

Supervisor: Christopher Finlay, University of Glasgow, Glasgow G12 8QQ, UK

This review aims to highlight the key areas in which changes to the epigenome have played an important role in the evolution and development of our species. Firstly, there will be a brief introduction into the topic of epigenetics to outline the current understanding of the subject and inform the reader of the basic mechanisms and functions of the epigenome. This will lead on to more focussed detail on the role played by epigenetic changes in the rapid evolution of our species and emergence from our ancestor species, as well as the Human Accelerated Regions that played a role in this. The discussion highlights how epigenetics has helped and hindered our species' development via changes to the epigenome in more modern times, discussing case examples of documented instances where it is shown that epigenetics has played a role in the evolution of humanity.

Key words: epigenetics, evolution, human, methylation, HARs, modification

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Introduction

Human evolution is often thought of as something abstract and distant, something that played a role in the development of our long forgotten ancestors but does not affect the modern state of our species. Even when we consider genetic conditions that once provided an evolutionary advantage to populations of early humans but have now become deleterious, it is often thought that modern medical care compensates and, in large part, negates their symptoms. These include conditions such as Sickle Cell Anaemia and Diabetes Mellitus Type 1; many of the individuals that carry these conditions live full and healthy lives thanks to modern medicine. So we consider these conditions via the lens of disease and not as relics of our evolutionary history. At one time Sickle Cell Anaemia provided an important defence against Malaria (Wiesenfeld, 1967) and there is evidence that Diabetes Mellitus Type 1 developed in early Europeans as an adaptation to the colder climate (Moalem et al., 2005). As technology has advanced and compensated for the evolutionary drivers of these traits, they are no longer as advantageous to the individuals who carry them as they once were. However, evolution is an ongoing process, one that modern humans are not exempt from, despite the fact that the advancement of science has down played the role of selection. Humans are not above the effects of evolution and recent research into epigenetics serves as a reminder of that fact.

Epigenetics is a mechanism of gene control that can promote or repress the expression of genes without altering the genetic coding of an organism (Feinberg, 2008). In other words epigenetics represents a system by which the gene expression of an individual can be altered without altering their genome's sequence. Our current understanding has identified some of the controlling epigenetic processes that regulate gene expression, referred to as epigenetic 'marks'. For example, methylation of DNA, alteration of the histone molecules that hold together DNA super structures via methylation or acetylation and various RNA and Dicer protein dependent processes that inhibit gene expression. In combination, the sum total of all these epigenetic marks in an individual is known as the epigenome. This review will mainly focus on studies that involve the methylation of DNA as this is the

most widely studied epigenetic mechanism, but other aspects of the epigenome will be touched upon. Methylation of DNA is already known to be very important; for example extreme cases of demethylation, representing a loss of gene expression control, are associated with oncogenesis (Feinberg and Tycko, 2004). This review will, however, not focus on the influence that changes to the epigenome can have on an individual's health, instead it will discuss the role this mechanism of gene expression control has played in the evolution of our species, both the emergence of the human species and the effects it has had more recently.

Before we can fully grasp the effects epigenetics has had on our species a firmer understanding of what epigenetics is and the way in which it can alter gene expression is needed. Gene control is a fascinating area of genetics and this is particularly interesting to those with a fascination for human evolution. Epigenetic influence over gene expression possibly originated as a defence against Transposons, parasitic DNA that jumps around in the genome and can disrupt genes by inserting into the middle of them (Slotkin and Martienssen, 2007). A possible mechanism of defence can be achieved via methylation of DNA, as illustrated in Fig. 1. Silencing these transposable elements and preventing or limiting damage to an organism's genome provides an important advantage to those first species to develop this mechanism. Eventually this process evolved into a method of promoting and repressing host genes (Feinberg, 2008) that could not only be acquired throughout the lifetime of an individual, but also passed onto its offspring (Jones, 2012). This mechanism of gene silencing may have also allowed for the development of multicellular organisms by allowing a single genome to tailor its expressed genes in each individual cell within the larger organism (Badyaev, 2014).

While epigenetics is a relatively new understanding of the systems involved in gene control and expression it also represents something very important, a fundamental revaluation of the theory of evolution. Acquired traits, while not alterations of the genome, can be inherited (Jones, 2012). This review will examine the implications this has for the concept of human evolution and highlight interesting examples and case studies in which these effects are notable.

Method of inheritance

The study of epigenetics has revealed an interesting facet of this method of gene expression control. The methylation of DNA and other epigenetic marks do not alter the genes that they influence at a sequence level but nonetheless alter the expression of these genes. Furthermore these marks can be acquired throughout the lifetime of the individual and, if carried in their gametes, these marks are inheritable. In this section, the focus will be on the ways in which these marks can be inherited.

The semi-conserved nature of mitosis results in two sets of daughter chromatids, one in each set carrying the Epigenetic marks from the original chromosome (Feinberg, 2008), as illustrated in Fig. 2. This allows the transfer of epigenetic marks from mother cells to daughter cells in somatic tissue. This explains how these marks can be maintained in an individual, but not how they are spread to the next generation of offspring.

These marks can also be conserved in their daughter chromatid during meiosis, resulting in all gametes carrying the epigenetic marks of the individual of origin. However, many of these marks are removed during the process of gamete formation. It is now understood that some genes are protected from this process of demethylation, resulting in the marks being maintained in their gametes' epigenome (Giuliani et al.,

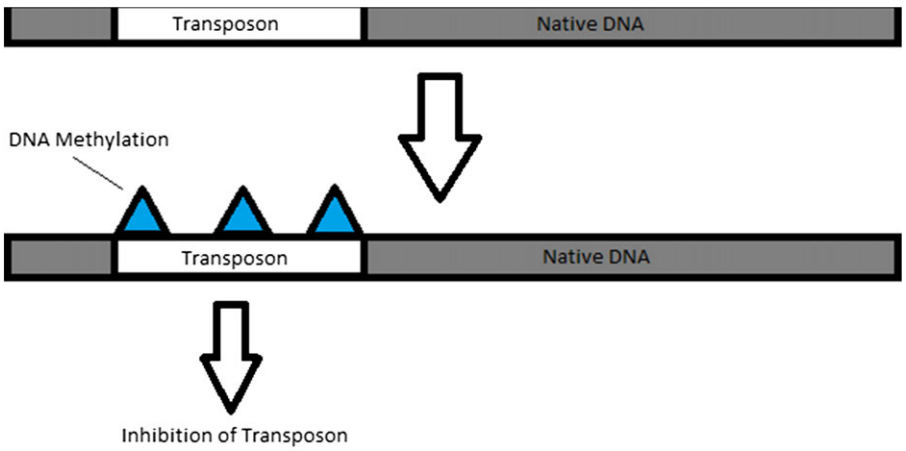

Figure 1. Methylation as a defence against Transposons. The figure illustrates how methylation can help an organism defend itself from Transposons. Over time the DNA coding vital proteins for the Transposon will become methylated and cease to be expressed, therefore trapping the Transposon in its current position in the host's genome. This prevents the Transposon from 'jumping' and possibly disrupting the expression of vital genes elsewhere in the host's genome.

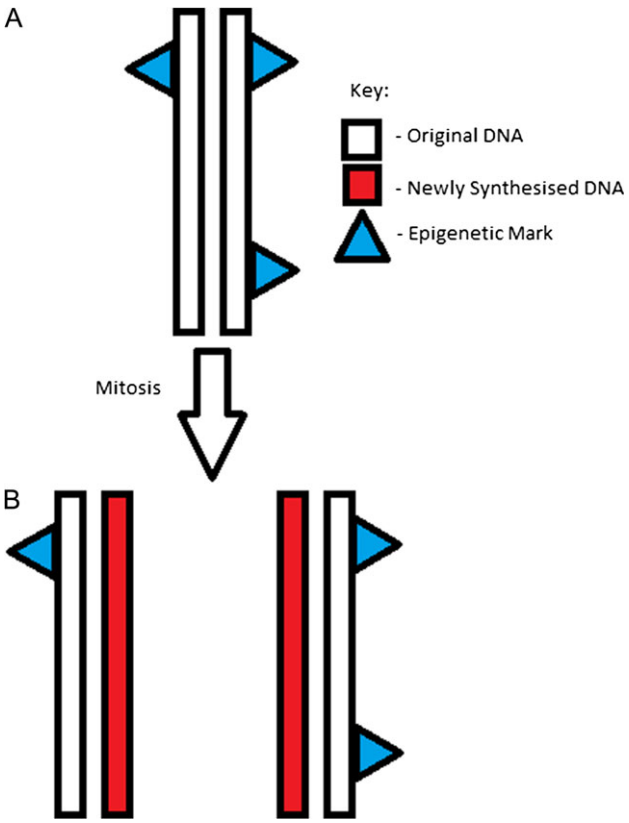

Figure 2. Preservation of epigenetic marks during mitosis. The figure demonstrates how epigenetic marks can be maintained in an individual cell's epigenome during mitosis. As can be seen in (**A**) the original chromosome contains epigenetic marks on both chromatids, and in (**B**) both daughter chromosomes contain some of the epigenetic marks of the mother chromosome due to the semi-conserved nature of mitosis.

2015). The overall mechanics of the process do leave some unanswered questions but histone modification is known to be key to identifying areas of the offspring's genome for methylation after fertilization of the gametes (Samson et al., 2014).

Methylation marks can be inherited from either the maternal (Giuliani et al., 2015) or paternal gamete (Soubry, 2015). Through the father, the offspring can inherit a wide array of methylation marks, with the majority of these marks in some way affecting the digestive systems of the child (Soubry, 2015). In this way, the father's own diet can influence the development and adaptation of his child to be better suited to the dietary conditions he lived in. Far more influence is exerted by the maternal parent's epigenome concerning dietary conditions. The mother has twice as much influence on her offspring's epigenome, firstly by her own epigenetic adaptations, acquired by her in the periconceptional period of her life (Giuliani et al., 2015), and secondly, during the pregnancy itself (Heijmans et al., 2008). The comparably increased influence of the mother's epigenome is further highlighted in cases of famine. If the affected parent is the mother the effects of deleterious epigenetic marks are more heavily expressed in the offspring's phenotype, especially if famine occurs during the early stages of pregnancy (Tobi et al., 2009). For an example of this deleterious nature of hypomethylation one can look at the Dutch Winter of Hunger, a well-documented example of famine in the modern world that occurred from 1944 to 1945 due to a blockage preventing the movement of fuel and food in the Netherlands. This starvation resulted in the hypomethylation of the *IGF-2* gene, the gene responsible for the formation of insulin-like growth factor 2. This protein is essential in the growth and development of a foetus and so the genes' methylation and subsequent silencing led to an increase in metabolic disease in infants (Heijmans et al., 2008). The ability of parental malnutrition to affect the epigenome of the offspring in an overtly negative and harmful way will be examined more closely later in the review.

Not all inheritable epigenetic marks inherited the digestive systems of the offspring, with many affecting the offspring's immunological capabilities. This was very useful and advantageous for nomadic peoples and a case study of this can be seen in the comparison of the Oromo peoples and the Amhara peoples of Ethiopia (Alkorta-Aranburu et al., 2012). In this case it appears that epigenetic marks actual favour immunological variation within the newly arrived population. This will be examined in more depth as part of the Case studies section later in the review. Another case of inherited epigenetic marks that affect an individual's adaptation to the environment is the strong influence that an individual's epigenome exerts on the homoeostatic system (Gluckman, Hanson, and Spencer, 2005). An individual's adaptation to their environment is strongly influenced by their parents' own acquired traits and as generations pass by, each generation will accumulate more and more epigenetic marks that influence their generations' homoeostatic systems. This will eventually result in a population that is genetically similar to the original settlers but will be more adapted to their surrounding environment. This process will produce a homoeostatic phenotype that better compensates for their native climate in a shorter timespan than if the population's phenotype had changed under a combination of genetic mutation and evolutionary pressure alone.

Influences on the development of the human species

To understand the impact epigenetics has had on our development into modern humans we have to compare the areas of gene methylation seen in our species and our closest living relatives. Many of the regions in the human genome that are methylated are not genes that are unique to humans, with the biggest differences in methylation occurring in regions of DNA involved with Transcription Factors (or TFs) and gene control (Hernando-Herraez et al., 2015). This is because TFs have a wide-reaching influence on the expressed phenotype of

an individual due to these factors functioning as a form of gene expression regulation, therefore promoting or suppressing other genes in the genome. Even small differences in the epigenome surrounding TFs can result in widely varying phenotypes between individuals of the same species due to their wide-reaching influences (Heyn et al., 2013). So it can only be assumed just how important these phenotypic changes are in the variation that separates us from our ancestor species.

Of note are the epigenetic changes that are known to have occurred in Human Accelerated Regions (or HARs) (Hubisz and Pollard, 2014). HARs are regions of DNA that have undergone rapid changes since the emergence of the human species far and above the normal rate of mutation. These regions stand out due to the extremely accelerated rate of mutations they have undergone and are widely understood to be responsible for the speedy divergence of humans from other species (Hubisz and Pollard, 2014). The exact nature of the role played by epigenetic changes in HARs is not clear but the importance of their role is undoubtable, with epigenetic changes possibly predating sequential changes in DNA (Badyaev, 2014). A suggested theory is that these marks actually promoted the occurrence of mutations in the genes that are responsible for our species existence.

Studying the epigenomes of our related species sheds light on the relatively large divergence that has occurred since our emergence from our distant cousins, a divergence of such stature that it cannot be solely explained by nucleotide changes (Hernando-Herraez et al., 2015). It has even been speculated that epigenetic changes could be more impactful on the Darwinian evolution of a species than genomic mutations (Badyaev, 2014) and this area of research only adds more weight to these claims.

Influences on evolution of modern humans

Modern humans have survived and thrived in a wide array of environments for thousands of years, from the Arctic tundra to Saharan deserts. The key to this success has always been the uniquely human ability to adapt quickly and epigenetics has played a role in this capacity to adapt. While cultural adaptations to environments, such as changes in clothing or ritualistic behaviour, are the most visual signs of this adaptability, no less important are the more subtle genetic and epigenetic changes that a population undergoes as they live in an area for generations. For example a population that has lived in an arid environment will carry many genetic mutations that make them more suitable to a dry climate. If a catastrophic climate shift occurs and their ancestral lands suddenly become cold and damp they can adapt to wear thicker clothing (Cavalli-Sforza and Feldman, 1983) to protect against the cold and may even take on new customs and rituals around hygienic behaviour to protect against new diseases that have taken root in the region (Wiesenfeld, 1967). This population will however still carry many of the genetic mutations that made them suited to their old environment until selection pressure allows new mutations to compensate for these genetic relics.

An important idea is the way in which to consider each different type of adaptation in comparison to one another. Cultural adaptation is a catch all term that encompasses all artificial adaptations an individual can pick up to become more comfortable in an environment (Cavalli-Sforza and Feldman, 1983). Clothing and the development of new customs are all useful tools in the face of environmental challenges but these represent short-term adaptations that do not affect the species' expressed phenotypes. In comparison genetic changes, such as the prevalence of Sickle Cell Anaemia in regions prone to malaria outbreaks, represent much longer term adaptations. These changes take longer to gain and cannot as easily be shaken off once their usefulness has run its course, such as an individual simply changing their attire to suit the weather (Laland, Odling-Smee, and Myles, 2010).

What do epigenetic changes represent in this model then? Firstly they exemplify medium-term adaptations, falling between cultural changes and genetic evolution in the time it takes an individual to acquire them (Giuliani et al., 2015). In this model of understanding human adaptation epigenetic changes also serve as a time-keeping mechanism, helping to mitigate the negative effects of genetic relics acquired by ancestor populations under different evolutionary pressures (Badyaev, 2014). By silencing older genes that once served a vital purpose epigenetics also helps to prevent the build-up of complexity in an organism, silencing older, less frequently transcribed genes (Badyaev, 2014), much in the same way that DNA methylation combats the damage caused by transposons (Slotkin and Martienssen, 2007).

A good way to examine this model of adaptation is to consider the way each of these changes would affect a hypothetical population that has suddenly become exposed to a harsh, cold climate. Very quickly, this population will adapt, first by increasing their protection against the elements by wearing thicker clothes. While this is an effective method of staying warm their bodies have not yet adapted to the cold, and so, their genes controlling homoeostasis will still function in the same way as they had in a warmer climate, something that might be considerably wasteful and possibly deleterious. Where once their perspiration would help keep the heat from damaging their bodies it now wastes water. At this stage, after a considerable number of generations, epigenetic changes will begin to take affect under selective pressure. DNA methylations and histone modifications will accumulate, fine tuning their homoeostatic gene expression to the colder environment. This results in the silencing of genes that were better suited to the hotter climate and promotes the expression of other genes that confer an advantage in this colder one. Finally, after even more generations new alleles will take hold in the populations that represent novel genes. These novel genes will encode new proteins that in some way will provide a selective advantage that is near permanent in expression, if not in providing an advantage.

In the short- to long-term adaptation model discussed above, the longer the period of time taken to acquire and adapt the more significant the changes will be to an individual's physiology and expressed phenotype. Another point highlighted by this model is that the longer an adaptation takes to be acquired the less likely it is to ever be lost. After all, it is much easier to take a jacket off than to spontaneously lose a gene responsible for increasing metabolic activity. Epigenetics comes in yet again at this point as not only does it silence older genes that are no longer required, under the influence of selective pressure, it also introduces more plasticity into the expression of genes (Giuliani et al., 2015) by allowing individuals that carry the same, or incredibly similar genome, to have altered gene expression. Through this mechanism epigenetics allows the variability of phenotypes that are required for adaptation and selection (Tobi et al., 2009).

Case studies

An interesting examination of epigenetics that provides an example of its role in human evolution is a study into the different epigenetic markers between the Oromo and Amhara peoples of the Ethiopian highlands, which revealed something surprising: researchers expected to find that individuals of the Oromo peoples, who are migrants to the highlands, would have an increase in epigenetic marks around genes associated with oxygen uptake or red blood cell production. These are adaptations that the Amhara peoples already had, allowing them to live successfully in their elevated homeland. Instead many of the epigenetic markers the researchers found in the Oromo population were around genes associated with the immune system (Alkorta-Aranburu et al., 2012). More interesting was that these marks were not uniform throughout the population and instead varied widely from person to person (Alkorta-Aranburu et al., 2012). This appears to show epigenetic marks acting as a catalyst for the introduction of variation in gene expression, resulting in a wide range of phenotypes and responses to combat the new microbiological threats that the migrating population were exposed to upon arriving in the region.

Here, these epigenetic marks are compensating for the lack of immunological adaptation the Oromo peoples have for this new climate compared to the native Amhara people, mitigating the damage done to the Oromo populations in the interim before a genetic mutation could occur that provides stronger protection.

As discussed earlier epigenetics plays a key role in the dietary adaptation individuals carry, producing an individual who carries epigenetic marks that make them more suited to the diet of their parents. Lactose tolerance is one of the ways this epigenetic digestive adaptation manifests (Ingram et al., 2009). Phenotypes of 'patchy' lactose tolerance have been witnessed in populations lacking the lactose tolerance mutation. With the increasing availability of dairy products worldwide, the epigenetic modification that produces a weaker tolerance to lactose can only be expected to increase, at least until the lactose tolerance mutation proliferates into the global gene pool.

Various genetic conditions affect red blood cells and their ability to uptake oxygen. These include Sickle Cell Anaemia and Thalassaemia, both of which only occur once the switch to adult haemoglobin is complete in an individual (Sripichai et al., 2009). In the case of Sickle Cell Anaemia it is known that the condition confers a resistance to Malaria. With anti-Malaria treatments becoming more and more efficient and mosquito culling beginning to keep infection rates under control it has become a condition that now mostly serves to burden fledgling health services around the world. As the selective pressure on these populations has changed, the epigenome of these populations has also reacted. Two different studies have discovered epigenetic markers that can produce Persistence of Foetal Haemoglobin (or POFH) (Sripichai et al., 2009; Sankaran, Xu, and Orkin, 2010). POFH is a condition where an individual never undergoes the switch to adult haemoglobin, and thus avoids expressing the Sickle Cell Anaemia and Thalassaemia mutations. While they still carry these mutations these individuals do not express the deleterious phenotypes due to epigenetic markers that inhibit the associated genes. This is illustrated in Fig. 3.

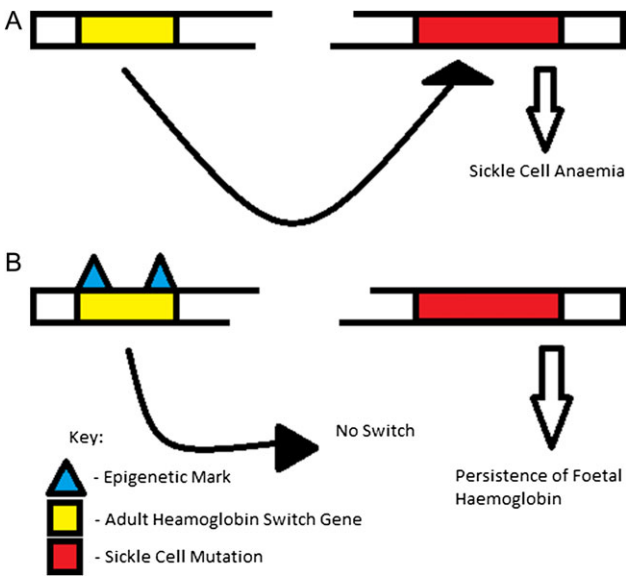

Figure 3. Epigenetic prevention of Sickle Cell Anaemia.
the figure shows how epigenetic marks can prevent the expression of the Sickle Cell Mutation. (**A**) shows what occurs in an individual who carries the mutations but does not have any epigenetic marks silencing the Adult Haemoglobin Switch Gene. These individuals will eventually develop Sickle Cell Anaemia. In (**B**) the Adult Haemoglobin Switch Gene is silenced by epigenetic marks, and as such the Sickle Cell Anaemia gene is never expressed as the individual maintains production of Foetal Haemoglobin.

Vulnerabilities of epigenetics

Throughout this review changes to the epigenome of an individual have been discussed in an overly positive light. Such changes can be a mechanism that provides a quicker form of adaptation than genetic mutations (Giuliani et al., 2015). It can also act as a time-keeping mechanism in older and now deleterious genes (Badyaev, 2014). Lastly it can be an influential response to Darwinian pressures on an individual or population (Alkorta-Aranburu et al., 2012). As with any process of adaptation, there does exist a negative side and, like genetic mutations, epigenetic marks are often damaging to an individual's health. For example, there is a known link between hyper-demethylation and oncogenesis (Feinberg and Tycko, 2004), but this review will consider the negative aspects of epigenome changes in terms of its impact on human evolution.

Epigenetics can act as a time-keeping mechanism by silencing genes that have outlived their purpose. However it is worth noting that this function of epigenetic marks has limits, as in many cases the gene in question is not entirely silenced (Badyaev, 2014), but instead is expressed at a lower rate. From a Darwinian perspective this is an undesirable consequence as the individual will survive but their offspring will instead now possess a trait that reduces their adaptability. In this way many traits that lower the overall fitness of the species may accumulate.

The role epigenetics plays in digestive adaptation also comes as a double-edged sword. This has been demonstrated by the research into numerous cases of famine, including modern examples such as the Dutch Winter of Hunger (Tobi et al., 2009; Giuliani et al., 2015; Soubry, 2015). The research shows that parental exposure to famine resulted in the accumulation of negative traits in the offspring due to dysregulation of methylation marks, including a pertinacity towards diabetes and obesity and increased rates of cardiovascular disease (Heijmans et al., 2008).

Finally, and perhaps the most chilling aspect of the epigenome is the ability for individuals who have survived traumatizing experiences that put their mind and body under extreme stress to acquire, and then pass on, the resulting epigenetic marks and traits from this time in their lives. The most poignant example of this is the accumulation of epigenetic marks in the descendants of Holocaust survivors that result in a marked increase of PTSD, depression and obesity, all resulting from differential methylation of the *FKBP5* gene (Yehuda et al., 2015). While these effects are less severe than genetic mutations the effects of epigenome changes, by virtue of being less powerful in their effect on phenotype, allow for the accumulation of traits that, if they were expressed at the sequence level, would not be carried on to the next generation.

Conclusion

Throughout this review the different effects the epigenome exerts on the evolution of our species has been discussed. Its positive ability to act as a response to selective pressures and as a way of mitigating deleterious mutations can be advantageous. However its significant control over gene expression can also lead to harmful consequences, e.g. as an avenue for oncogenesis or as a mechanism for accumulating traits that lower fitness and adaptability. The most important thing to understand about the epigenome is that it is not always about positive or negative influences on our species' development, but rather that it has given our genome plasticity (Giuliani et al., 2015). By encouraging the variations and adaptability of our species, epigenetic mechanisms for controlling gene expression have ensured that humanity could survive and thrive in any number of environments. Epigenetics is a significant part of the reason our species has become so adaptable, a trait that is often thought to distinguish us from what we often think of as lesser-evolved and developed animals that we inhabit this earth with. Indeed, it can be argued that epigenetics is responsible for, and provided our species with, the tools that truly made us unique in our ability to conquer any habitat and adapt to almost any climate. The study of epigenetics has also made the evolution of our species less abstract and distant; we can now better understand the effects of different traits at a generational level and better observe the driving factors behind changes to our species. More importantly, this provides the evidence that humanity is not above or untouched by the effects of selective pressure. Finally, a deeper understanding of epigenetics has altered how we think of evolution, constituting a fundamental re-understanding of the topic and how this mechanism allows us to acquire traits in a lifetime, and pass these traits on to our offspring. Of course, survival of the fittest remains the golden rule of evolution but by delving ever deeper into the epigenome we understand that the traits that govern fitness, and therefore an individual's fitness, are more fluid and malleable than when thought of purely through the lens of genetic mutation and inherited traits.

The most important lesson learned from studying the epigenome of our species is that it has provided an understanding of the factors that have separated us from our closest living relations within the animal kingdom that cannot be explained by genetic mutations alone.

Outlook

The central theorem that has driven this review is understanding epigenetics from the perspective of it serving a role in allowing for medium-term adaptation. To further this hypothesis, and support the evidence provided in this review, deeper research must be conducted on the emergence of epigenetic marks in populations facing changing selective pressure. The work done in studying and comparing the epigenome of the native and newly migrated populations in the Ethiopian highlands is a strong example of the way in which this research can be conducted (Alkorta-Aranburu et al., 2012). Moreover, an ideal area that might shed even more insight into the role

epigenetics plays in the evolution of humans is a comparison of the populations of the Upper and Lower Nile. These areas historically faced similar threats in the form of Malaria but development along the Lower Nile, backed up by investment in prevention by the Egyptian Government, has in recent decades lowered the transition rates by mosquitos of Malaria drastically. Furthermore, both these areas have had significant levels of Sickle Cell Anaemia (El-Hazmi, Al-Hazmi and Warsy, 2011). Both these factors in combination make this region ideal for research into emerging epigenomic changes in the face of changing selective pressure. It could be predicted that epigenetic marks that silence the effects of Sickle Cell Anaemia (Sripichai et al., 2009), as discussed earlier, would become more prevalent in these areas but that cannot be known for certain, as was the case with the predicted epigenome changes in the Ethiopian highlands (Alkorta-Aranburu et al., 2012).

Author biography

As a genetics graduate from the University of Glasgow my interests began to focus on the field of epigenetics quite late in my academic career. However, after delving into epigenetics and the sheer number of questions and theories raised by the topic that turn genetics on its head, epigenetics has captivated me. I hope to one day either conduct research into the influence of epigenetics on human evolution or become a journalist focused on the subject.

Acknowledgements

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