Review article

The role of epigenetics in human evolution

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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 downplayed 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.,

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**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.

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[65x711]
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.

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 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 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 (Slootkin 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 microbial 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 genome 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 genome 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 FKBPs5 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, it is 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.

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