

Re: Article: Whew! Your DNA Isn't Your Destiny

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- *From:* "whitesickle@xxxxxxx" <whitesickle@xxxxxxx>
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RAGLAND:

Hello Robert. I agree with some of Keim's statements but not with others or let me just say "we don't know enough yet". In the past I've written about the importance of epigenetics and I believe even quoted an epigeneticist who stated before we can unravel or separate the human DNA genome we must be able to unravel the epigenetics of people. I came across these definition and short article on epigenetics:

Covers a broad range of effects, and several are discussed in this special issue. But how did epigenetic regulation arise? For RNA-mediated silencing and DNA methylation there is evidence that they have evolved as part of a host defense mechanism against viruses and parasitic DNA. The substrate – double-stranded RNA (dsRNA) – for both posttranscriptional gene silencing (PTGS) [or RNA interference (RNAi)] and transcriptional gene silencing (TGS) seen in plants is a common intermediate in the life cycle of many viruses and transposons. [Guy Riddihough and Elizabeth Pennisi, "The Evolution of Epigenetics" *Science* 293 (5532): Aug. 20, 2001]

Epigenetics

8/1/03. By RT

Changes to DNA and its associated proteins can alter gene expression without altering the DNA sequence.

DNA does not exist as naked molecules in the cell: it is associated with proteins called histones to form a complex substance known as chromatin.

Chemical modifications to the DNA or the histones alter the structure of the chromatin without changing the nucleotide sequence of the DNA. Such modifications are described as epigenetic.

Changes to the structure of the chromatin have a profound influence on gene expression: if the chromatin is condensed, the factors involved in gene expression cannot get to the DNA, and the genes will be switched off. Conversely, if the chromatin is 'open', the genes can be switched on if required.

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While many heritable disorders in humans are caused by DNA sequence changes (mutations) that abolish gene expression, a number of human diseases are caused by inappropriate gene silencing, brought about by epigenetic modifications. Indeed, most cancers involve the epigenetic silencing of genes that normally control cell proliferation. The major forms of epigenetic modification occurring in human tumours are DNA methylation and histone deacetylation.

DNA methylation is a chemical modification of the DNA molecule itself; it is carried out by an enzyme called DNA methyltransferase. Methylation can directly switch off gene expression by preventing transcription factors binding to promoters.

However, a more general effect is the attraction of methyl-binding domain (MBD) proteins. These are associated with further enzymes called histone deacetylases (HDACs), which function to chemically modify histones and change chromatin structure. Chromatin containing acetylated histones is open and accessible to transcription factors, and the genes are potentially active. Histone deacetylation causes the condensation of chromatin, making it inaccessible to transcription factors and the genes are therefore silenced (see Figure).

Since epigenetic modification plays such an important role in cancer, novel therapeutic strategies are being developed that are based on the reversal of DNA methylation and the inhibition of histone deacetylation. These are being combined with new technologies to rapidly screen the genome for DNA methylation and histone acetylation patterns.

However, diseases can also be caused by inappropriate gene activation. One example is Burkitt's lymphoma, which is caused by the overactivity of a gene called MYC. In this case, the gene is normally found in repressed chromatin and is expressed at a low level. Its function is to promote cell proliferation.

Certain abnormal chromosome rearrangements occurring in lymphocytes move this gene into a region of open and active chromatin, causing the production of large amounts of the protein. The result is the uncontrolled proliferation of lymphocytes, resulting in lymphoma.

RAGLAND:

Everybody has an epigenetic genome. Not just identical twins. I don't believe socioeconomic status in general has an impact on the epigenome as Szyf states. Social classes have existed for thousands of years. Being wealthy and pampered obviously increases your chances of reproduction and survival than if you are a worker building a pyramid. Several major diseases have important epigenetic factors and many people die from them in part. One could consider this natural selection in the sense of differential reproduction and survival and access to available resources.

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However, many of the modern diseases struck with much less frequency in the past due to the harsher environment. At least in the affluent and middle class Western industrialized countries and perhaps elsewhere. Life expectancies in the industrialized West have increased compared to our evolutionary past. A 70 year old man who has a wife or more than one and has fathered several children and been in a career position which afforded him advantageous differential reproduction and survival and access to resources could hardly be considered a failure by Darwinian standards. Even a middle class or lower class man who didn't have as much access to resources but scored good on the differential survival and reproduction card would come out looking good although belonging to different socioeconomic classes.

Although I don't see the origination of the epigenetic code as part of the DNA nucleotide sequence or code I don't see it as purely environmental either but a part of Darwinian selection and evolution. As stated above, "Covers a broad range of effects, and several are discussed in this special issue. But how did epigenetic regulation arise? For RNA-mediated silencing and DNA methylation there is evidence that they have evolved as part of a host defense mechanism against viruses and parasitic DNA. The substrate – double-stranded RNA (dsRNA) – for both posttranscriptional gene silencing (PTGS) [or RNA interference (RNAi)] and transcriptional gene silencing (TGS) seen in plants is a common intermediate in the life cycle of many viruses and transposons. [Guy Riddihough and Elizabeth Pennisi, "The Evolution of Epigenetics" Science 293 (5532): Aug. 20, 2001]

Something is far less than perfect with our epigenetic system today. The major forms of epigenetic modification occurring in human tumours are DNA methylation and histone deacetylation. How did this come about? Is there an extensive record in our evolutionary history of these human tumours caused primarily by DNA methylation and histone deacetylation? I mean symptoms which suggest that.

Is it possible that just as our DNA has not really evolved much in ten thousand years and has created problems for us moderns neither has our epigenetic system been able to keep pace. Maybe our evolutionary DNA nucleotide sequence and epigenome in our early evolutionary environment never intended us to live that long. Just long enough for some of us to survive and reproduce and the rest die. Nobody can dispute natural selection doesn't work strongly today as it did in our evolutionary past. There are way too many people on earth. One can argue a massive nuclear conflict or a natural or manmade plague sweeping the globe would be a form of natural selection. It may be but with the technology as high as it is today and accelerating it will be a more intense natural selection. The conventional definition of natural selection would be canceled out since the magnitude of those dying would certainly include those capable of successful differential reproduction and survival as well as those not.

But back to my point about how our epigenome has failed. It may not be

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merely natural selection but that the way our epigenome evolved never "intended" us to live as long as we do. This puts the craze of living immortally into perspective. Just as our DNA nucleotide sequence will need to be changed so will our epigenome.

Sincerely,
Michael Ragland
P.S. Spare me the list of Octogenerians

Figure

Epigenetic modifications that abolish gene expression. Top panel – open chromatin is characterized by non-methylated DNA and histones with acetylated tails. This allows the assembly of transcription factors and transcription by RNA polymerase. Middle panel – DNA methyltransferase activity results in the methylation of DNA. This may directly block binding by transcription factors and prevent transcription. It may also recruit methyl-binding domain proteins that have associated histone deacetylases. Bottom panel – DNA methylation and histone deacetylation result in the condensation of chromatin into a compact state that is inaccessible by transcription factors.

• **References:**

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