Epigenetics Communications

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Will epigenetics ever be a biosocial science? A reply to Chiapperino and Paneni

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Abstract

The recent correspondence article by Chiapperino and Paneni in *Clinical Epigenetics* correctly points to the inability of epigenetics to incorporate fine-grained mapping data of the individual's surrounding milieu. The authors underline similar shortcomings of genomics. I argue that the tight link between DNA sequence and epigenetic marks is likely to reproduce those shortcomings in epigenetic studies. Moreover, biosocial epigenetics, if ever fully accomplished, would inevitably unmask genetics-based phenomena. The latter would be highly controversial from the viewpoint of dominant identity politics and social constructivism.

Keywords Epigenetics, Genetics, Disease, Biosocial sciences

Background

The recent correspondence article by Chiapperino and Paneni in *Clinical Epigenetics* touches many important issues in contemporary epigenetics research [1]. The authors and the journal deserve praise for contributing to the public debate about the epistemology of science. Moreover, their appreciation of the daylight between epigenomics and fine-grained mapping of the individual's surrounding milieu is correct and reflects previous concerns [2]. As admitted by the authors, that problem is a formidable one to solve even by the best interdisciplinary research and technological advances. The question though is whether the alignment between epigenetics and fine-grained social profiling is a goal worth pursuing, given the emerging characteristics of epigenetics. The latter are core concepts in the current debate, that are often clouded by a degree of confusion about what epigenetics is and can do for us. A very short history of epigenetics is a necessary premise. The reader is referred to excellent historical narrations for details and depth [3, 4]. It is widely accepted that the concept of epigenetics is rooted in Waddington's definition of epigenesis formulated in the 1940s [5]. That original concept is problematic per se, as it is a description of molecular development that is bound to create some dissonance with the wide scientific community's intuition of modern epigenetics. Epigenetics has later remained a little understood discipline until it was revived by the advent of genomic imprinting, which lent DNA methylation as a mechanism to explain that clearly non-genetic phenomenon [6]. The next breakthrough was the appreciation that epigenetic marks can be modified by exogenous factors [7]. Consequently, epigenetics became a promising tool to identify markers or molecular mechanisms for a range of non-communicable diseases, particularly in the light of the missing heritability problem that genetics has faced [8]. The result is the widely adopted concept of epigenetics: a DNA sequence-independent, highly exogenous factor-sensitive phenomenon regulating gene expression. That general definition of epigenetics can be easily dismantled and survives only for historical reasons. I argue that this is an example of a historical origin-justified concept akin to cultural or religious ideas rooted in ancient traditions that are usually impermeable to competing reason or empirical evidence.

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It is truly surprising that such a non-scientific posture shapes one of the central ideas in modern biology and medicine. Here are the weaknesses of that definition. First, although some or all cases of genomic imprinting may well be independent from DNA sequence, the phenomenon of methylation QTL first documented by Tycko's group accounts for the vast majority of DNA methylation variation in humans [9–11]. Accordingly, a comprehensive survey of human tissues concluded that ~ 2-fold more methylation QTL than expression QTL colocalize with GWAS-identified SNP [12]. Curiously, a clear example of dependence of DNA methylation on sequence context has long been documented but is rarely stated: mammalian CpG islands are generally unmethylated as a result of their peculiar sequence [13]. The genetics' grip on epigenetics is further strengthened by the fact that Mendelian Randomization is the best available tool to assess the causality between any DNA methylation profile and phenotype [14, 15]. One prediction based on the tight link between DNA methylation and genetics is that individual differentially methylated CpG would exert comparatively small effects, akin to the genetics' missing heritability problem: that prediction seems to be correct [16]. Independence from "changes in DNA sequence" is often stated as the main difference between epigenetics and genetics, which shows signs of further confusion: genetics deals with sequence variation in populations rather than sequence changes, except for the relatively minor topic of mutations. Second, the idea that the epigenome is an open book for the environment to erase, change or add information has been questioned. Perhaps the clearest example is the famous *The New Yorker* article that proposed epigenetics as the underlying mechanism for phenotypic divergence between homozygotic twins; particularly noteworthy are the subsequent reactions by prominent epigeneticists[1]. This goes without saying that another very enthusiastically held idea, i.e., the existence of epigenetic transgenerational inheritance in humans, is highly controversial [17, 18]. In conclusion, epigenetics describes a highly sequence-dependent and comparatively weakly exogenous factor-sensitive mode of transcription regulation, akin to the activity of transcription factors or DNA-binding long non-coding RNAs. Incidentally, further confusion has been created by including the latter and micro-RNAs in the definition of epigenetics. It can be argued that epigenetics should be rebaptized *paragenetics* to better describe its essence. One wonders whether we would be witnessing the current enthusiasm for epigenetics had methylation QTL been documented 40 years ago rather than in 2008. Not to mention that if the higher affinity of DNA methyltransferases for RNA relative to DNA had been appreciated then, textbooks would describe those enzymes as RNA-binding proteins that modify the DNA's chemistry [19].

In conclusion, reducing the daylight between epigenetics and fine-grained mapping of the social milieu is a noble and useful enterprise. The central concern is that given its significant dependence on DNA sequence, epigenetics will reproduce the shortcomings of genomics that Chiapperino and Paneni have pointed out. Those hurdles will eventually be overcome only by prior correct understanding of the essence of epigenetics, however changing and dynamic that can be. The devils of genetics when applied to social sciences and economics are obvious, but hidden ones may lurk in epigenetics. For example, the quest for "pure" DNA methylation profiles exclusively written by an adverse milieu—whether politically or economically adverse or else - to explain how social circumstances create and maintain disadvantaged groups is bound to discover genetics-related phenomena. Those data would be highly controversial if misaligned with dominant views of identity politics or social constructivism. It feels like a remote territory from pipettes and tubes: should scientists walk that far?

Acknowledgements
I thank Dr. Gertrud Lund for critically reading the manuscript.

Author's contributions
SZ performed all necessary work to produce this article. The author read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 26 April 2023 Accepted: 5 May 2023
Published online: 17 May 2023

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