Epigenetics Communications

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Being against reductionism regarding epigenetics

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In a recent correspondence letter to *Clinical Epigenetics* titled "Why epigenetics is (not) a biosocial science and why that matters," Chiapperino and Paneni (2022) argue that the way epigenetics research is currently being conducted impedes the fulfillment of the field's promise as a *biosocial science* [1]. This is because, they say, "the tools, techniques, and ways of doing science inaugurated with genomics… got repurposed for multi-omics and big data analytics," but these "were neither meant to nor fit well with the purpose of disentangling complex interactions and looping effects among biological and environmental factors" (p.144). According to the authors, "(e)lucidating these complex biosocial loops is the challenge epigenetics… should be concerned with" (p.145). They thus call for less reductionism and more holistic methods in epigenetics research.

In this commentary, I outline reasons for questioning the framing of Chiapperino and Paneni's invitation. To be clear, I am generally sympathetic to their call for caution against a merely biomedical translation of emerging knowledge in epigenetics. I have time and again expressed similar concerns [2–4]. However, my approach to being against reductionism regarding epigenetics is not based solely on conceptualizing epigenetics *as different from* genetics. Perhaps I should say, it is not anymore. I have come to observe that, in addition to the differences, there are also important similarities and blurred lines between the fields, and the latter raise considerable epistemological, ethical, and policy issues [5–7]. Framing the problem of reductionism regarding epigenetics as a question of whether epigenetics is accomplished (or not) *as a biosocial science* has serious limitations and may be misleading. It may lead us to overlook various types of simplistic assumptions regarding epigenetics (*and* genomics); some of which are, in my opinion, too rarely acknowledged. Below, I briefly discuss five such assumptions.

Assumption 1: Genetics is not a biosocial science

Conceptualizing epigenetics as a biosocial science *in contrast to genetics* appears to implicitly condemn genetics to the realm of "non-biosocial" sciences. However, there are reasons to believe this may not be the most appropriate thing to do. First, it is wrong to believe that our genes cannot be modified by their social and physical environments. In fact, our genomes are constantly exposed to and disrupted by ionic radiations, oxidative stress, mutagens, and viruses, all of which can affect the linear sequence of our DNA and therefore gene expression. DNA repair mechanisms exist, and while they are very active, they are not always successful. Repeated exposure to stressors coupled with imperfect repair may end up causing permanent mutations that affect gene expression in the long term — not unlike epigenetic modifications [8]. Second, social factors may affect the prevalence of certain genes within families, communities, and populations. Historical events, migrations, niche construction behaviors, or mating patterns, for instance, are but a few social phenomena that may influence the human genome, its diversity, and the distribution of genetic variants, over the course of time [9]. Third, social scientists have long observed that social

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groups develop and are reinforced by the sharing of different types of biological traits. Such "biosocial groups" may be based on shared genetic traits but also on phenotypic traits (such as a specific disease status), and the feeling of belonging to such groups may in turn encourage individuals in adopting or reinforcing behaviors that are associated with these groups [10], a phenomenon sometimes referred to as "biosociality" [11]. Taken together, these examples suggest that genetics may be more "biosocial" than is often assumed, and that conceptualizing epigenetics as the biosocial science *par excellence* may be an oversimplification. If it is the case, the relevant and more challenging question becomes as follows: How is the biosocial aspect of epigenetics different from that of genetics?

Assumption 2: Epigenetics is a biosocial science

In addition to questioning the assumption that epigenetics is biosocial *in contrast to* other research fields in biology, it is worth questioning the biosocial aspect of epigenetics *in and of itself*. For instance, we may ask: What exactly about epigenetics is biosocial? Are all epigenetic mechanisms or biological properties of these mechanisms biosocial? And what makes such properties biosocial, or not? There are no simple answers to these questions [12]. First, many epigenetic traits are almost entirely determined by widely shared components of the human genome, which leave very little room for social factors to weigh in. This is the case, for example, in the biological processes through which our cells and tissues differentiate and acquire their specific functions during embryogenesis and fetal development, i.e., through "obligatory" epigenetic modifications [13]. These highly conserved and necessary biological processes occur in large part through DNA (de)methylation programs. Thus, they are epigenetic processes, but it is hard to see how they could qualify as "biosocial" processes. Second, thinking of epigenetics as a biosocial science downplays the variety of external factors that may affect epigenetic mechanisms, such as physical rather than social environments (e.g., chemicals found in the environment and pharmaceutical products) or lifestyle (e.g., tobacco or alcohol consumption); all of which are, at least to some extent, influenced by social and relational contingencies but may also be associated with individual behavior and decision-making [12, 14]. The question then becomes: How comprehensively representative of reality is it to conceive epigenetics *as a whole* as a biosocial science?

Assumption 3: Epigenetics is a homogenous scientific field

The question of whether epigenetics is a biosocial science begs another relevant yet challenging question: What is epigenetics? Based on the results of our recent survey of epigenetic researchers, there is currently no consensus on what the appropriate definition and scope of the field should be [15]. Specifically, we found that, while most researchers agree that DNA methylation and histone modifications fall within the scope of epigenetics, there is disagreement on whether other biological mechanisms commonly referred to as "epigenetic," such as RNA interference and the regulation of transcription factors, should be treated as such. Dissensus regarding the scope of the field is not a problem per se, but it does create important challenges, for instance, when trying to determine whether existing policies would or should apply to epigenetic information — for example, in assessing and addressing the risk of "epigenetic discrimination" [4, 6, 16]. Perhaps more importantly, our survey showed that researchers working in epigenetics are spread across a large variety of subfields, such as disease epigenetics, functional epigenetics, developmental epigenetics, methods in epigenetics, environmental epigenetics, and epigenetic inheritance [15], to name only a few. I find it important to highlight that there are various relevant, yet different and complementary scientific endeavors within the broad field of epigenetics. Better understanding of the interactions between social factors and human biology and "biosocial loops" is not the focal point of many subfields or initiatives. For instance, the goal of the International Human Epigenome Consortium (IHEC) has been, from its inception, to promote epigenetic data sharing for a better understanding of the reference human epigenomes for various cell types. This is an enormous task and ambitious endeavor, which is inevitably accompanied by challenges and limitations. One limitation is that by focusing on mapping "control" epigenetic variants, it does not provide information about their status when affected by various exposures or diseases. Yet, it is a very valuable objective from a methodological standpoint because it can provide more solid grounds for comparative analyses of epigenetic variations in different circumstances. In addition, I find it important to highlight that, based on my experience, not all researchers we might see as epigenetic researchers identify as such. Some of them appear to find the term "epigenetic" too broad or too narrow to appropriately characterize the work that they do. To summarize, there is not such a thing as a homogenous epigenetics field giving itself biosocial objectives, and this is probably a good thing.

Assumption 4: Epigenetics and genomics are fundamentally distinct

The first reaction one naturally has after hearing about epigenetics for the first time is usually being amazed by the way it differs from genetics [17]. Indeed, epigenetic mechanisms are often presented and analyzed in comparison to genetics in scientific and public discourses.

However, there are some features of epigenetic mechanisms that much resemble those of genetics. As explained above, although some epigenetic variants may be relatively plastic and sometimes reversible, others are very stable over time and can hardly be affected by environmental or social exposures. Some epigenetic variants may even be considered innate rather than acquired. Just as it is the case for genetic variants, these epigenetic variants will most likely persist in their original status throughout the life course of the carrier, from birth to death. But the distinction between genetics and epigenetics is also controversial for another reason. One of the most often used definitions of modern epigenetics is the following: "the study of changes in gene function that are mitotically and/or meiotically heritable and that *do not entail a change in DNA sequence* (our emphasis)" [18]. While it is obvious that histone modifications or RNA interference do not entail a change in DNA sequence, it is much less clear regarding DNA methylation. Thinking twice over the matter, with Lappé and Landecker (2015), one can appreciate that the italicized portion of the definition depends very much on the perspective that we decide to adopt [19]. Why do we take for granted that DNA methylation does not result in a changed DNA sequence? What if we had initially conceptualized DNA methylation as the transformation of a cytosine (C) into a *methylcytosine* (M) rather than merely into a *methylated cytosine* (meC)? Would this make us see DNA methylation as changing the DNA sequence? If this conundrum is seriously considered, we are left with two options: to redefine epigenetics, or to reconceptualize DNA methylation as a genetic change. In any case, these questions appear to blur the line significantly between genetic and epigenetic changes, and they encourage us to be very cautious when conceptualizing the two fields as fundamentally distinct.

Assumption 5: Epigenetics' biosocial aspect makes it socially desirable

In addition to the conceptual challenges that have been presented thus far, there is also a need for caution regarding the assumption that the biosocial aspect of epigenetics will necessarily generate socially desirable outcomes. As discussed previously, there is a need to question the seemingly natural appeal of epigenetics for social scientists and public health advocacy. I agree with Chiapperino and Paneni that the focus of epigenetics research may well be "skewed in favor of an understanding of biomarkers as mere targets for molecular and… pharmacological intervention" (p.146). At the same time, I wonder whether epigenetic marks should be praised as promising targets of preventive interventions at the social level. The main reasons for my concern have been fleshed out in a previous publication [2]. To summarize, I wonder why we came to assume that knowledge of the molecular effects of social phenomena will result in a greater recognition of — and action at the policy level to prevent — inequities created and exacerbated by the social determinants of health. In fact, why do we even assume that it is necessary? The main challenge faced by public health may be more (bio)political than scientific, and it is unclear what added value knowledge of the *molecular* causal relationship between the social environments, health risks, and diseases will represent. One reason for concern is that gaining such knowledge may play out in favor of more biomedical interventions aimed at fixing the biological effects of morally questionable social inequalities while leaving the latter unaddressed. Another reason for concern lies in the risk of increased stigmatization and discrimination that could result from emphasizing correlations between socio-cultural factors and biological differences between individuals and groups [20, 21]. Finally, the goal of correlating complex social and environmental phenomena with biological marks seems inevitably prey to reductionism. There are practical and ethical reasons to be skeptical about the feasibility and desirability of investigating these links further at the molecular level. These reasons include, for instance, the fact that a large diversity of social stimuli can affect the same epigenetic variants, and that one specific social stimulus can affect multiple epigenetic variants, thus making it very challenging to correlate, accurately and precisely, scales that are largely incommensurable. At minimum, it may not always be relevant or useful to do so.

Conclusion

The threat of reductionism regarding epigenetics, genomics, and other fields is real and multi-faceted. As pointed out in this commentary, it may result from the overly broad characterization of a field or from the assumption of ill-justified dichotomies between seemingly different fields. This may lead us to believe, with Chiapperino and Paneni, that epigenetics research requires a distinct set of methodological tools. However, it is not clear what this would mean in practice. What is the problem with the so-called omics methods, and what can we hope for in terms of more "precise and accurate measurements of the environment" in epigenetics? How exactly can "the repertoire of tools and interventions of epigenetics… be expanded to complexify its grasp of biosocial processes of health differentiation" (p.146)? While being in favor of a greater recognition of complexity in epigenetics may look good on paper, specifying and operationalizing that posture in the daily conduct of research can be very challenging, and it may not sufficiently account for the many similarities and blurred lines that exist between genetics and epigenetics.

There might be sociohistorical reasons for our reductionist reflexes. Modern epigenetics is still a burgeoning field. Yet, it has been welcomed with open arms by those rightly displeased with decades of genetic reductionism and the persisting belief that knowledge of the human DNA "blueprint" will solve the mysteries of our biological identities and vulnerabilities altogether. Thus, epigenetics has been mobilized most vigorously, in the scholarly literature as well as in public discourses, for its differences from and in contrast to genetics. In this commentary, I have attempted to provide reasons against such a polarization of the fields. Instead, epigenetics may be better represented, as Meloni (2016) suggests, as a "boundary object" [22], i.e., a study object the nature and significance of which can be appreciated by people of various perspectives and from different epistemological standpoints. Hence, it has the potential to promote dialogue and greater reflexivity in biology and the social sciences. It is by encouraging and facilitating such dialogue that we will be most successful in addressing the issues of determinism, essentialism, and exceptionalism [23], biases that have been traditionally associated with genetics but which may also impede nuanced understandings and representations of epigenetics.

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