Transposon dynamics and the epigenetic switch hypothesis

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Abstract

The recent explosion of interest in epigenetics is often portrayed as the dawning of a scientific revolution that promises to transform biomedical science along with developmental and evolutionary biology. Much of this enthusiasm surrounds what we call the epigenetic switch hypothesis, which regards certain examples of epigenetic inheritance as an adaptive organismal response to environmental change. This interpretation overlooks an alternative explanation in terms of coevolutionary dynamics between parasitic transposons and the host genome. This raises a question about whether epigenetic enthusiasts tend to overlook transposon dynamics more generally. To address this question, we surveyed a large sample of scientific publications on the topics of epigenetics and transposons over the past 50 years. We found that enthusiasm for epigenetics is often inversely related to interest in transposon dynamics across the four disciplines we examined. Most surprising was a declining interest in transposons within biomedical science and cellular/molecular biology over the past two decades. Also interesting was a delayed and relatively muted enthusiasm for epigenetics within evolutionary biology. An analysis of scientific abstracts from the past 25 years further reveals systematic differences among disciplines in their uses of "epigenetic," especially with respect to heritability commitments and functional interpretations. Taken together, these results paint an interesting picture of the rise of epigenetics and the possible neglect of transposon dynamics, especially among biomedical scientists.

1. Introduction

It is widely maintained that biology is undergoing an epigenetic revolution. According to this narrative the gene is being dethroned from its privileged explanatory and investigation-guiding roles. In its place, scientists are focusing on various epigenetic factors –equally significant to genes in their casual and information-bearing functions, or so it is argued– that have long been neglected in the study of development and evolution.

The study of human disease is one of the fields that epigenetics is expected to transform. Biomedical interest in epigenetics traces back to the discovery that widespread loss of DNA methylation is associated with cancer [1]. At the time, it was a significant discovery that cancer could be triggered not only by mutation in gene sequence, but also by the removal of methylation

marks. During the 2000s, biomedical work on epigenetics explored the tendency for cells to acquire an elevated vulnerability to stress [2]. This phenomenon was associated with alterations to DNA methylation triggered by environmental factors, such as a reduction in quality of diet [3], that are potentially transmitted to offspring in utero [4]. More recently, we have seen the rise of large-scale research consortia such as ENCODE, which aimed to identify all functional elements in the human genome by focusing in particular on "regions of transcription, transcription factor association, chromatin structure and histone modification" ([5], p. 57). Their most controversial and widely publicized result stated that over 80% of the human genome has some "biochemical function." From a gene-centric perspective this would be surprising, since protein coding regions comprise a mere 4% of the human genome [6]. Detractors objected that ENCODE's finding relied on an overly permissive definition of "function," also that ENCODE used unjustifiably weak criteria for identifying genetic candidates as functional, and further that their framework could not explain differences among species' genome sizes [7-10]. In defense of ENCODE, some authors interpret their controversial statement as an estimate of the proportion of genomic regions that are of potential biomedical interest [11]. Generally speaking, we see that epigenetics has motivated considerable research within the biomedical sciences, challenging conventional notions of biological function, and expanding the range of entities thought to be functionally relevant to human disease.

It is tempting to follow authors like Jablonka and Lamb [12] who claim that epigenetics involves paradigm shift in biology, or Bonduriansky and Day [13] who suggest that epigenetics constitutes a "new understanding of evolution and development." This a seductive picture, especially to philosophers. Conceptual change in science is an established field of philosophical research. The study of gene concepts has been one of the most fecund topics within the philosophy of biology. This work reveals that scientific conceptions of the gene and genetic disease are in an ongoing historical dialogue with technological advances in biology [14-16]. To many philosophers, it would be unsurprising if further technological developments led to additional modifications to scientific conceptions of heredity. We have seen that gene concepts are fluid, the thinking goes. Why shouldn't gene centrism itself be up for grabs?

Some authors challenge the suggestion that there is an epigenetic revolution afoot. It is possible to distinguish three general objections. The first takes issue with the claim that epigenetic insights qualify as revolutionary. Godfrey-Smith [17] notes that over the course of its

historical development molecular biology has become gradually less doctrinaire. Theoretical principles that were central to this discipline in its early stages (e.g. “one-gene one-enzyme”) have become less important as molecular details are filled in. Epigenetic phenomena might have posed a serious challenge to the principles on which molecular biology was founded. However, in Godfrey-Smith’s view, these phenomena are less threatening now that principles have been supplanted with mechanistic details.

A second objection focuses on the various meanings of “epigenetic” [18-20].. Some instances of epigenetic regulation merely involve the (gene mediated) influence of an environmental factor on some phenotype. Gene centrists have always allowed that environmental factors influence gene expression. Such examples of “epigenetic” phenomena are therefore not unorthodox. At the same time, the term epigenetic sometimes refers to the open-ended transmission of a phenotypic change that involves no change in gene sequence. This phenomenon is thought to be rare in eukaryotes [21] and would indeed call for a radical shift in biological thinking if it were common. Conflating familiar epigenetic effects with more controversial or rare phenomena potentially gives a distorted impression of what the study of epigenetics is about.

A third objection concerns the functional interpretation of certain epigenetic phenomena. Epigenetic revolutionaries point to examples of phenotypic mutation that are induced by some environmental change, appear to be adaptive for the organism, involve no change in DNA sequence, but are transmitted in sexual lineages across generations. Such examples are interpreted as evidence for a switch-like mechanism that rapidly adapts the phenotype to environmental change. Such mechanisms are allegedly less visible from a research program focused on genes. Also, if adaptive epigenetic inheritance is common, this challenges the neo-Darwinian idea that adaption typically involves random genetic variation and selection.

Our first aim in this paper is to explore an alternative explanation of epigenetic inheritance that views it not as an adaptive epigenetic switch, but rather as the byproduct of transposon dynamics. This explanation has long been available but is rarely considered, raising the question of whether transposon dynamics generally tend to be neglected in discussions about epigenetics. Our second aim is to address this question using a quantitative analysis of papers sampled from the Web of Science. We examined the popularity of “epigenetics” versus

"transposons" across different disciplines over the past five decades. Finally, we performed a qualitative analysis comparing different conceptions of epigenetics across disciplines over the past 25 years. This allowed us to compare the views of epigenetics researchers across disciplines on the topics of heritability and function.

2. Epigenetic switches and the significance of transposons

One of the most widely discussed examples of epigenetic inheritance involves the transmission of coat colouration in lab mice. The agouti gene is expressed in mouse hair follicles and normally produces a dark brown coat. However, in some mice there is a change in the expression of this gene, producing sometimes a yellow coat or on other occasions a mixed colour. All strains share the identical agouti gene with no variation in nucleotide sequence. Differences in coat colour are instead produced by variation in methylation patterns upstream of the pigment gene. An interesting feature of this example is that colour pattern is maternally inherited for up to three generations, indicating that parents transmit methylation patterns to their offspring.

The agouti gene has become a model system for epigenetics. For instance, a study by Dolinoy et al. [22] exposed female mice to a toxic chemical (BPA) and noticed a colour change in offspring. Again, this was caused not by a DNA mutation but rather a change in methylation. Moreover, this effect was counteracted if female mice were fed a methyl-doner enriched diet.

Such examples have been interpreted as evidence of an epigenetic inheritance mechanism, or switch, that rapidly adapts organisms to their environment. In discussing the agouti mouse, Jablonka and Lamb propose that,

> because it provides an additional source of variation, evolution can occur through the epigenetic dimension of heredity even if nothing is happening in the genetic dimension. But it means more than this. Epigenetic variations are generated at a higher rate than genetic ones, especially in changed environmental conditions, and several epigenetic variations may occur at the same time. Furthermore, they may not be blind to function, because changes in epigenetic marks probably occur preferentially on genes that are induced to be active by new conditions ([12], p.144-5).

Likewise, Bonduriasnky and Day claim that the agouti mouse example "shows how such epigenetic traits could contribute to adaptive evolution" ([13], p. 58). There are three basic

components to this interpretation. First, the proposal that phenotypic changes are induced by the environment. Second, those changes involve a modification to methylation or some other epigenetic mark, but no change in gene sequence. Finally, there is often a suggestion that epigenetic changes are biased toward adaptive phenotypic responses. The conjunction of these three properties is what we mean by "epigenetic switch."

Others have raised doubts about the existence of epigenetic switches because the relevant effects persist for no more than three generations. To be of evolutionary interest, it is argued, an epi-mutation would have to persist for much longer. A recent review by Sánchez-Tójar et al. [21] found little evidence for such trans-generational epigenetic effects. However, this remains a topic for further research.

Perhaps a more philosophically interesting objection concerns the fact that the agouti mutation involves the suppression of a transposable element, located upstream of the agouti gene. Jablonka and Lamb mention in passing that "there was a small extra bit of DNA (originating from a transposon) in the regulatory region of a coat color gene" (2005 p. 142); however they overlook the theoretical significance of this point. As we will explain in the next few paragraphs, the fact that epigenetic mutations are often transacted by TEs [22], suggests an alternative to the epigenetic switch hypothesis.

Transposable elements (TEs) are mobile strands of DNA capable of jumping into new chromosomal locations. The act of transposition (jumping) often involves the creation of additional TE copies. Hence, individual TEs can replicate multiple times per generation in a process akin to meiotic drive. It is well known that TE insertion can interfere with protein synthesis or cause various sorts of harmful mutation. Organisms have thus evolved a variety of mechanisms for deactivating, suppressing, or removing TEs from the genome. These mechanisms, in turn, impose a selection pressure on TEs to evolve ways to overcome the host organism's defenses. Over millions of years these coevolutionary dynamics have given rise to eukaryotic genomes replete with TEs (e.g. between 40-60% of the nuclear DNA in humans descends from TEs), most of which are temporarily silenced or permanently deactivated [23].

There are several reasons why TEs can appear to have organism-beneficial functions when they are in fact deleterious. One way for a TE lineage to potentially avoid deactivation or deletion is by inserting copies very close to a protein-coding gene [24]. These are "safe haven"

sites because the host cannot easily methylate TEs at these locations without altering the expression of its own genes. It is therefore no surprise that many TEs preferentially insert close to protein coding genes [25].

It is easy to mistake these stealthy TEs for organism-beneficial insertions [10]. Genomics researchers identify the strands of DNA located adjacent to genes as "regulatory regions" because they contain transcription factor binding sites. The occurrence of transposons within regulatory regions has led some genomics researchers to implicate them in gene regulation, disregarding the possibility that the TEs might simply be hiding in a safe location. This interpretation is further encouraged by the fact that TEs contain their own binding sites which are normally used to harness the host's replication machinery for their own benefit. Hence, TEs are especially effective mimics of genuine regulatory regions.

Another deceptive feature of TEs is that they are activated by stress. When an organism is exposed to chemical, thermal, or other forms of stress there is sometimes a burst of TE activity [25]. Barbara McClintock [26] interpreted TE bursts as evidence for a switch-like mechanism that facilitates rapid phenotypic adaptation by elevating mutation rate. Once again, however, the situation looks different from the perspective of TE-host coevolution. Organisms employ various strategies to protect genes from TE insertion. Some suppression strategies occur at the level of the DNA strand, where methyl groups are inserted on top of transposon binding sites to prevent them from being recognized by the host's transcription factors and replicated. In fact, it is now thought that DNA methylation originated as a system for TE suppression, with gene regulation a secondary (exapted) function [27]. Important for our argument is that suppression mechanisms are themselves compromised by stress. Just as a parasite can get the upper hand on a patient with a compromised immune system, so can TEs flourish in a genome with weakened suppression. Thus, what appears to be switch-like behaviour in response to environmental change might in fact be a breakdown in TE suppression machinery.

These considerations cast new light on the agouti mouse. Recall that variability in coat colour is caused by variable methylation patterns surrounding a TE insertion upstream of the pigment gene. It is quite plausible that different colour morphs represent different levels of TE suppression, with more heavily methylated strains being a step ahead in the coevolutionary arms race. Were this TE to be removed or degrade, the site would presumably cease to become hyper-

methylated and the yellow phenotype would disappear. Moreover, if this example is typical, and epigenetic effects typically involve an effort to suppress TEs, then it is unlikely that epigenetic mutations will have adaptive effects. It is essentially "up to the transposon" where it wants to insert. Selection acting among TE lineages (within the organism) will favor transposons that avoid detection and deletion. This might involve "stealthy" insertions close to genes, or in other cases the avoidance of genic regions altogether, but there is no reason to expect an insertion preference for regions that will benefit the host.

David Haig argues that it is often in the evolutionary interest of both the organism and the transposon for TE insertions to be silenced in somatic tissues (as opposed to the germline) [28]. This allows the host organism to survive and reproduce, passing along its complement of TEs to the next generation. Evolutionary interests conflict more directly in the germ line. If a TE insertion kills the host, then the TE will be removed from the population. This imposes a downward selection pressure moderating the rate of TE replication. However, it has long been recognized that in sexual species it is difficult for selection to entirely purge the genome of determinantal TEs [29]. Eukaryotic organisms are stuck with these genetic parasites and, again, there is no reason to expect that TEs will preferentially insert into regions that are likely to benefit the host. Nor does the methylation of those insertions occur with some directed beneficial effect on the organism, other than to mitigate the negative effects of a TE insertion on normal host function. These considerations cast doubt on the idea that epigenetic responses to environmental change will tend to be adaptive, at least, not insofar as they are associated with the suppression of TEs.

If epigenetic differences are typically driven by responses to TE insertion, this also has implications for the persistence of epi-mutations. Organisms are engaged in a constant effort to detect and suppress TEs. Eventually, active TE insertions will degrade and no longer attract methylation. Hence, any TE mediated switch will have a limited life span because processes within the organism are actively degrading it.

What about the suggestion that epigenetic switches respond to specific environmental cues? From a coevolutionary perspective, not just any environmental factor can become "hooked up" to the epigenetic machinery. If the loss of methylation is typically caused by a breakdown in TE suppression, then only harmful environmental factors will induce this type of epigenetic

change. Relatedly, after the stressful conditions have subsided, the TE suppression machinery ought to resume its job of methylating TE insertions. Hence, unless the organism is exposed to a continual regime of stress, persisting over many generations, one would expect TE-based epigenetic mutations to be short lived.

The topic of TE-host dynamics is a fascinating area of research that would take us beyond the objectives of this paper to describe in detail. Hopefully, we have said enough to at least raise questions about the ways that examples of epigenetic inheritance are interpreted by some epigenetics enthusiasts. At the very least, one might expect that considerations about TE dynamics would be raised as an alternative explanation for examples such as the agouti mouse. Instead of being viewed as an epigenetic switch, the environmental induction and epigenetic transmission of the coloured phenotype might simply be the byproduct of TE suppression. Why has this alternative been largely ignored by authors working on epigenetic inheritance?

It has been suggested that the fields of molecular biology and genomics are simply out of touch with recent trends in evolutionary biology [31]. This could be due to insufficient evolutionary training in those fields. Another potentially relevant factor is the prevalence of adaptationist thinking within molecular biology and genomics. A number of authors have recently noted that neutralist (non-adaptive) hypotheses receive undue attention in these disciplines [7-9, 32-33]. Another, non-exclusive possibility concerns the influence of large research consortia like ENCODE and the economic incentives driving these projects. Garnering large sums of public funding sometimes involves interpreting results in ways that sound exciting, revolutionary, or relevant to human disease. Describing examples like the agouti mouse as an epigenetic switch sounds more exciting than the alternative possibility, that this phenomenon is the fleeting, stress-induced byproduct of a genetic parasite.

We have suggested that information about TE/organism coevolution recommends an explanation of certain epigenetic phenomena that rivals the epigenetic switch hypothesis. This raises the question of whether, given the ballooning popularity of epigenetics research, those coevolutionary dynamics are generally being overlooked or downplayed? This question can be explored by comparing the relative popularity of epigenetic versus transposon research over time and across disciplines. We expect that researchers working in the field of evolution, who are familiar with genome-level coevolutionary dynamics, are less enthusiastic about epigenetics

compared to researchers working in proximal biological sciences, where evolutionary thinking is less common. Likewise, if the attraction to epigenetics is influenced in part by large research consortia like ENCODE, then one might expect epigenetics to be more popular in biomedical biology and genomics compared to other disciplines.

A related set of questions concerns the ways that different disciplines conceptualize epigenetics. It is possible that researchers in biomedical fields rarely embrace the epigenetic switch hypothesis and use "epigenetic" to refer to different phenomena than researchers working in other disciplines, for instance. The remainder of this paper describes two bibliometric studies attempting to shed light on these questions.

3. Methods

3.1 Topics and Disciplines

Our methods were inspired by Haig's [19] survey of scientific articles published between 1950 and 2010, which showed a dramatic increase in the proportion of scientific papers with "epigenetics" in the title. Using digital tools and databases associated with the Web of Science we undertook two bibliometric analyses of scientific articles.[1] This database allows users to search papers according to terms appearing in specific sections (e.g. title, keywords or associated metadata). We first selected all papers in Web of Science published between 1970 and 2019 with "DNA" in their Topic[2] and organized them into five-year intervals. To give some idea, between 1970 and 1974 there were roughly 10,000 papers on DNA. By 2015-2019, there were over 315,000 papers on this Topic. We then selected the subset of DNA papers that also have "epigenetics" in their Topic. The procedure was then repeated for "transposon." Considering that Web of Science is a comprehensive database, our analyses likely included most scientific papers published on a given topic. This enabled us to compare scientific interest in "epigenetics" and "transposon" as proportions of the total scientific interest in "DNA" over time. Although the absolute number of papers on any topic tends to increase with the growing number of scientific articles published each year, the proportion of papers on a Topic can either rise or fall depending on its popularity. Hence, our measure provides an estimate of the *proportional* interest in epigenetics and transposons.

[1] Analyses were performed in June, 2020.
[2] "Topic" searches include the paper title, abstract, author keywords, and Keywords Plus.

Journals in the Web of Science are coded according to subject, known as the Web of Science Categories, and all papers appearing within a given journal are assigned to its corresponding Category or Categories. For the search of "epigenetics" within "DNA" there are hundreds of Categories ranging from "Genetics & Heredity" to "Logic" to "Theatre." However, most papers fall into a small number of Categories. We focused our analysis on what we identify as four "Disciplines": Biomedicine, Proximal biology, Evolution, and General Biology. Biomedicine was a conjunction of five Web of Science Categories: Medicine General Internal, Medicine Research Experimental, Oncology, Pharmacology, and Immunology. These were chosen partly because they were highly represented and also because they fall under the general theme of biomedical research. We lumped them into a single variable primarily to simplify the analysis. However, we performed a consistency check, comparing each Category within the Biomedical Discipline to check for anomalies in their relative proportions.

Likewise, Proximal Biology was a conjunction of four Web of Science Categories: Cell Biology, Developmental Biology, Genetics Heredity, and Biochemistry Molecular Biology. Again, these Categories were highly represented under the Topic of DNA and they struck us as thematically similar. We applied the same rationale and consistency check to these Categories.

General Biology and Evolution were stand-alone categories provided by Web of Science. We included General Biology in our analysis with the expectation that it would provide a baseline for comparing other Disciplines. Evolution was included because of its relevance to our focal questions.

3.2 Quantitative Analyses

We conducted two quantitative analyses to determine relative scientific interest in epigenetics and transposons across disciplines. The first analysis tracked the proportion of "epigenetic" papers within the general Topic "DNA" for each of the four Disciplines across all five-year intervals. Our second quantitative analysis did the same for "transposon." This provided a gauge of relative scientific interest in these two Topics among our four Disciplines over the past 50 years.

3.3 Epigenetic Commitments

It is widely recognized that the term "epigenetic" is ambiguous and it is rarely possible to glean a definition of this term from a research paper. However, it is usually possible to discern certain logical commitments based on what authors say about epigenetic phenomena. A

distinction that we find useful identifies two dimensions along which such commitments vary. The first dimension is an author's heritability commitment. In classifying some modification to DNA as "epigenetic" you might simply be referring to a basic mark (e.g. a methylation pattern or histone modification) that is conspicuously associated with DNA. Minimally, there need be no commitment to whether that mark is inherited by daughter cells or for how long. A stronger commitment maintains that epigenetic marks are transmitted mitotically when cells divide, but remains agnostic about transmission by meiosis. A third level of commitment proposes limited meiotic cell division, such as when an epigenetic mark is transmitted to offspring but no further. Finally, the strongest commitment proposes open-ended meiotic transmission. These definitions are summarized and operationally defined in Table 1.

Table 1. Four conceptions of "epigenetic" that vary in the strength of their heritability commitments.

Inheritance	Commitment	Operational definition
Basic mark	The presence/absence of some mark is associated with DNA (e.g. methylation, histone modification), but its heritability is unspecified.	Applied to abstracts describing differences in epigenetic factors over time or comparing epigenetic similarities/differences among cells, but which made no explicit mention of whether those factors are heritable.
Mitotic	Some mark associated with DNA is transmitted by mitotic cell division.	Applied to abstracts explicitly mentioning mitotic transmission and/or described the persistence throughout division in a somatic cell lineage.
Limited Meiotic	Some mark associated with DNA persists through meiotic cell division and/or is transmitted over a limited number of sexual generations.	Applied to abstracts explicitly mentioning epigenetic transmission from parent to offspring up to the F2 generation.
Open-ended	Some mark associated with DNA persists indefinitely through meiotic cell division and/or is transmitted over a large number of sexual generations.	Applied to abstracts that explicitly proposed a multi-generational epigenetic influence (e.g. "transmitted over many generations") or that equated the heritability of epigenetic marks with genes.

The second dimension concerns an author's functional interpretation of epigenetic marks. None of the heritability commitments just outlined imply that an epigenetic mark is functional. We think it crucial not to conflate heritability commitments with functional interpretations because they have different epistemic criteria. Advances in sequencing technology have greatly simplified our ability to detect epigenetic marks and their various degrees of heritability. As the ENCODE controversy reminds us, assessing function is much more difficult and often contentious. A related concern is that if function is conflated with inheritance, researchers might gravitate towards a particular functional interpretation without demanding adequate evidence. Deans and Maggert [30] note that this is in fact a common mistake: "It's not that histone modification and DNA methylation are not correlated with gene expression differences—they are—but the possibility that they may be responsive rather than causal has not been disproved". The list of functional roles that we analyzed are outlined in Table 2.

Table 2: Four functional roles commonly associated with epigenetic marks.

Functional role	Explanation	Operational Definition
Disease related	Some epigenetic mark associated with a disease (e.g. tumor growth) is thought to influence its promotion or suppression.	Applied to abstracts implicating an epigenetic mark in some disease unless they explicitly proposed that the mark is involved in normal gene expression or phenotypic development.
Transposon suppression	Some epigenetic mark is thought to normally function in the suppression of TE activity.	Applied to abstracts that explicitly assigned this functional role to epigenetic marks, but not to those which proposed that TE activity is part of an epigenetic mechanism for adaptive phenotypic plasticity.
Regulation	Some epigenetic mark is thought to normally function in the regulation of a gene and/or trait.	Applied to abstracts proposing that an epigenetic mark "regulates" gene expression or trait development.
Phenotypic adaptation	Some epigenetic mark is thought to regulate genes in ways that adapt the organism to its environment, either by adaptively modifying the phenotype to environmental changes and/or by stabilizing a beneficial phenotype.	Applied to abstracts explicitly proposing that epigenetic marks preserving adaptive phenotypes or suggested that they function in adaptive phenotypic plasticity.

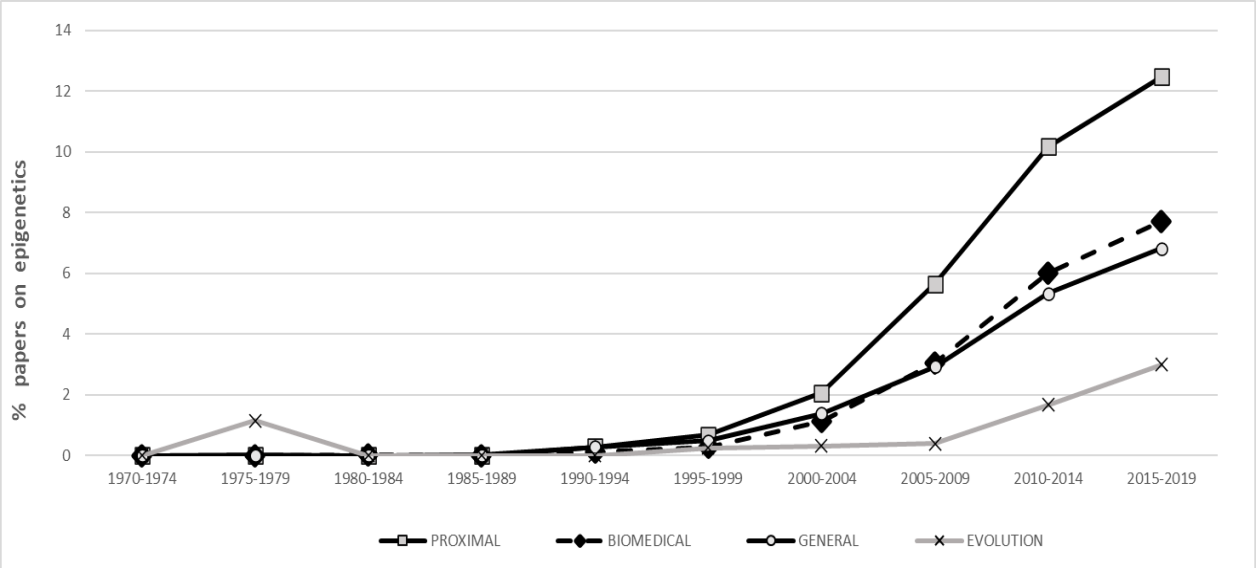
3.4 Qualitative Analyses

To compare heritability commitments and functional interpretations across Disciplines over time, we focused on the top 25 most cited papers under the Topic of "epigenetics" within "DNA" for each five-year interval from 1995 and 2019. The reason for not going further back is that one of the Web of Science Categories (Evolution) had fewer than 25 papers per five-year period prior to 1995 and would have biased our comparisons. Each title and abstract was carefully examined and classified according to the operational definitions outlined in Tables 1 and 2.

4. Results

Our results concur with the trend reported by Haig [19], there is a sharp rise in the proportion epigenetics papers beginning in the mid-1990s (Fig. 1). In the most recent interval (2015-2019) a whopping 19% of all 316, 191 papers on the Topic of DNA had "epigenetics" in the title, keywords, or abstract. However, Disciplines varied over time in their enthusiasm for epigenetics. Proximal Biology was an early adopter, with Biomedicine and General Biology showing a more delayed response. By contrast, the delayed and relatively small amount of enthusiasm coming from Evolution is striking. This Discipline only began warming to epigenetics after 2005 and its contribution to the pool of papers on epigenetics remains low.

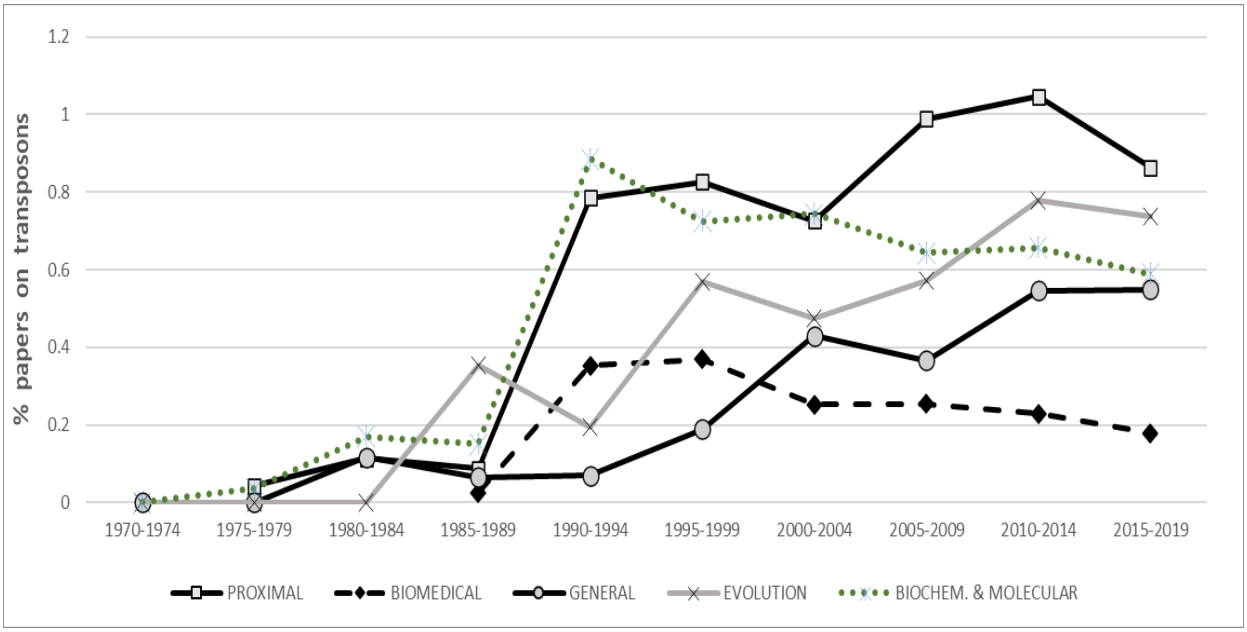
Figure 1. Percentages of papers in Web of Science on the general Topic of DNA mentioning "epigenetics" in the title, abstract or keywords viewed in five-year intervals across four biological Disciplines.



Turning to the popularity of transposons, overall enthusiasm for this topic is much lower compared to epigenetics, never exceeding 2% of the total papers on DNA. Across all disciplines there was a spike in transposon research beginning in the early to mid-1980s. Evolution and General Biology exhibit steady increases in the proportions of papers on transposons. By contrast, Biomedicine initially showed interest in transposons in the late 1980s and early 1990s, but this tapers in the late 1990s and starts declining in the early 2000s.

The pattern exhibited by Proximal Biology is more complicated. Interest in transposons picks up in the late 1980s, flattens during the 1990s, and it picks up again in the early 2000s. Only in the last five-years has interest in transposons started to decline in Proximal Biology. Our consistency check (see methods) revealed a difference among Categories that comprise this Discipline. Within Cell Biology, Developmental Biology, and Genetics Heredity the proportional interest in transposons begins to decline only in the last five years. However, in the field of Biochemistry and Molecular Biology the decline begins much earlier and follows a pattern similar to Biomedicine (see the two dotted lines in Figure 2).

Figure 2. Percentages of papers in Web of Science on the general Topic of DNA mentioning "transposons" in the title, abstract or keywords viewed in five-year intervals across four biological Disciplines (plus one subdiscipline/Category).



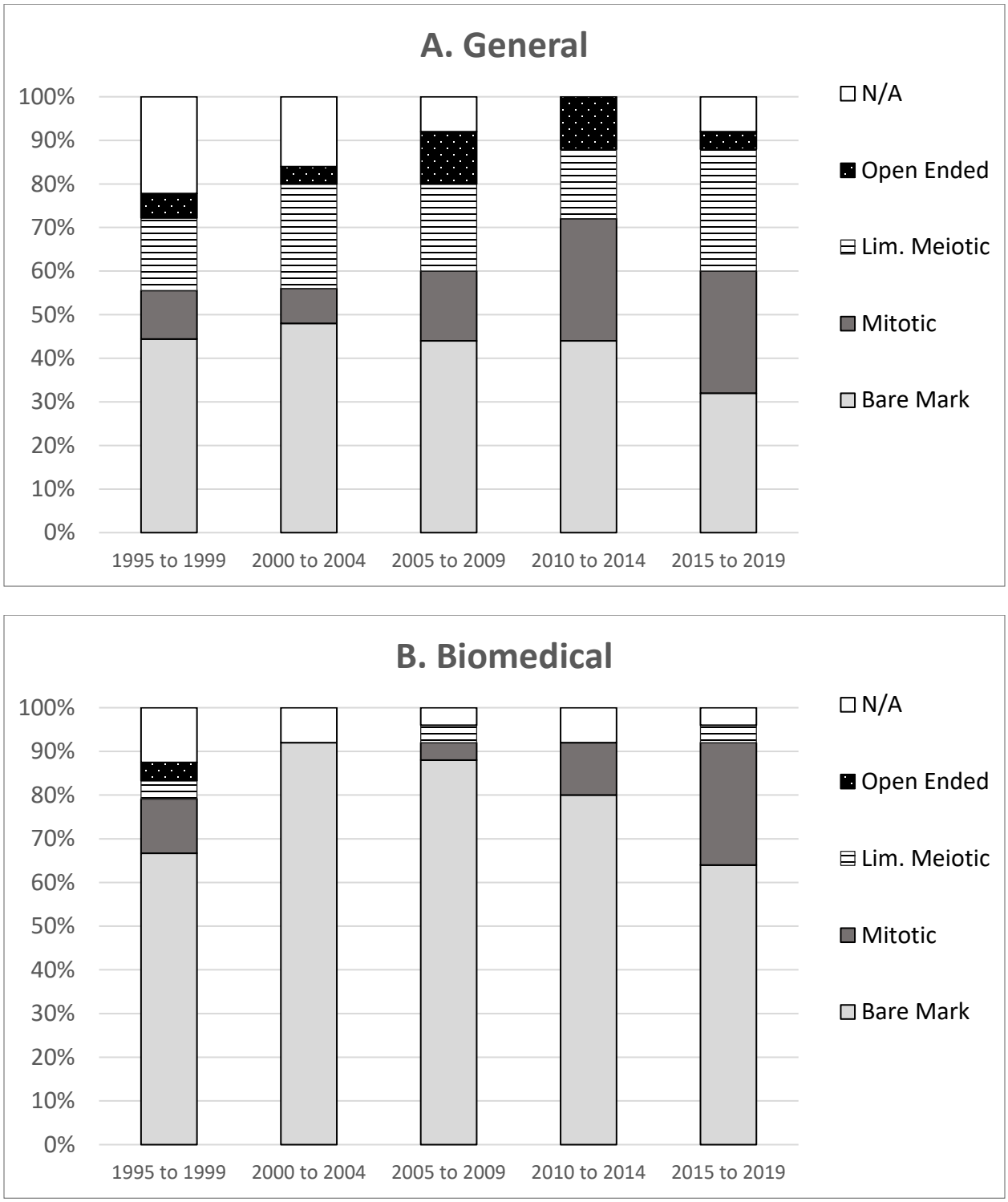
Turning to our qualitative analysis of heritability commitments, in analyzing these data we were interested in whether a particular commitment is dominant in a given Discipline and

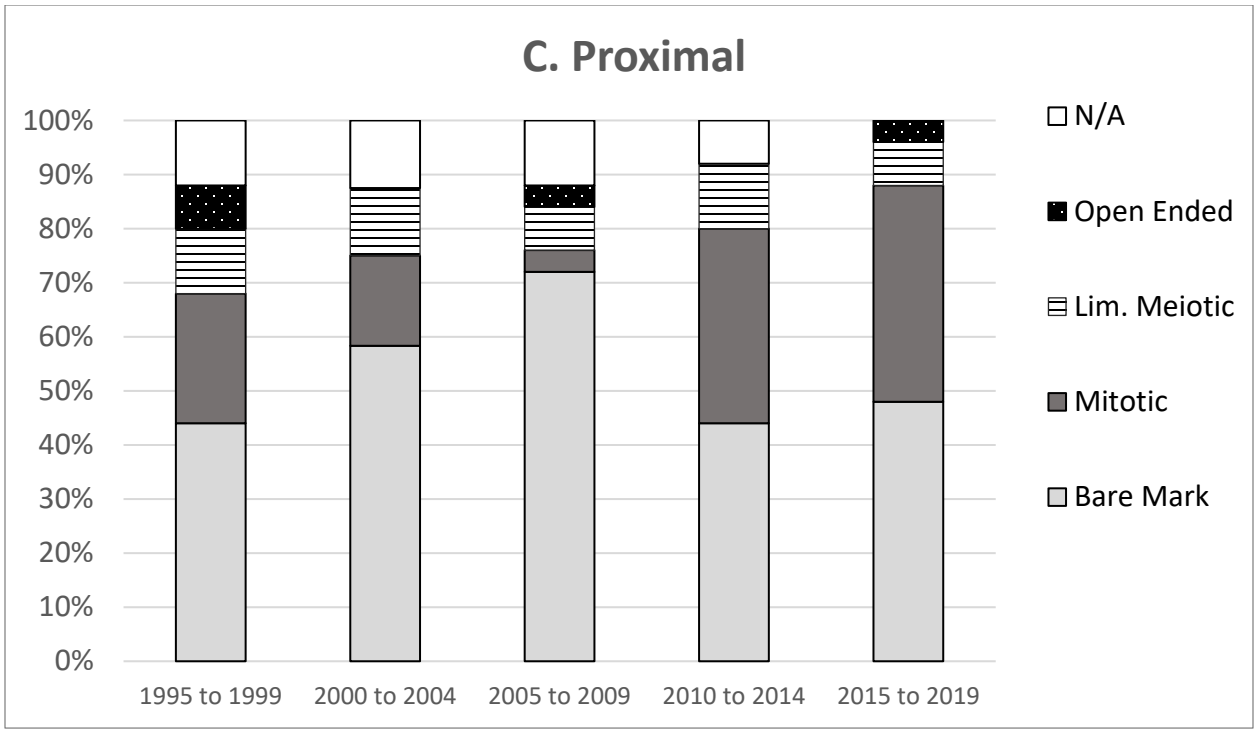
whether it changes over the 25-year period. These questions can be addressed by comparing percentages of commitments and functional interpretations, without any fancy statistics. General Biology exhibits a broad mixture of heritability commitments, as one might expect if this Discipline is regarded as a baseline. The commitment to bare marks (Fig. 3A, light grey bar) comprised a large and stable percentage (32-42%) of the abstracts over the entire period. There appears to be a slightly growing trend in authors' commitments to mitotic inheritance (Fig. 3A dark grey bar), from 8-10% in the 1990s to 25-28% in the most recent decade. Commitments to limited meiotic inheritance (Fig. 3A striped bar) remained stable, between 20-30% with a slight dip (7%) between 2010-2014. The least common commitment is to open ended inheritance (Fig 3A black spotted bar), which remained between 5-10%.

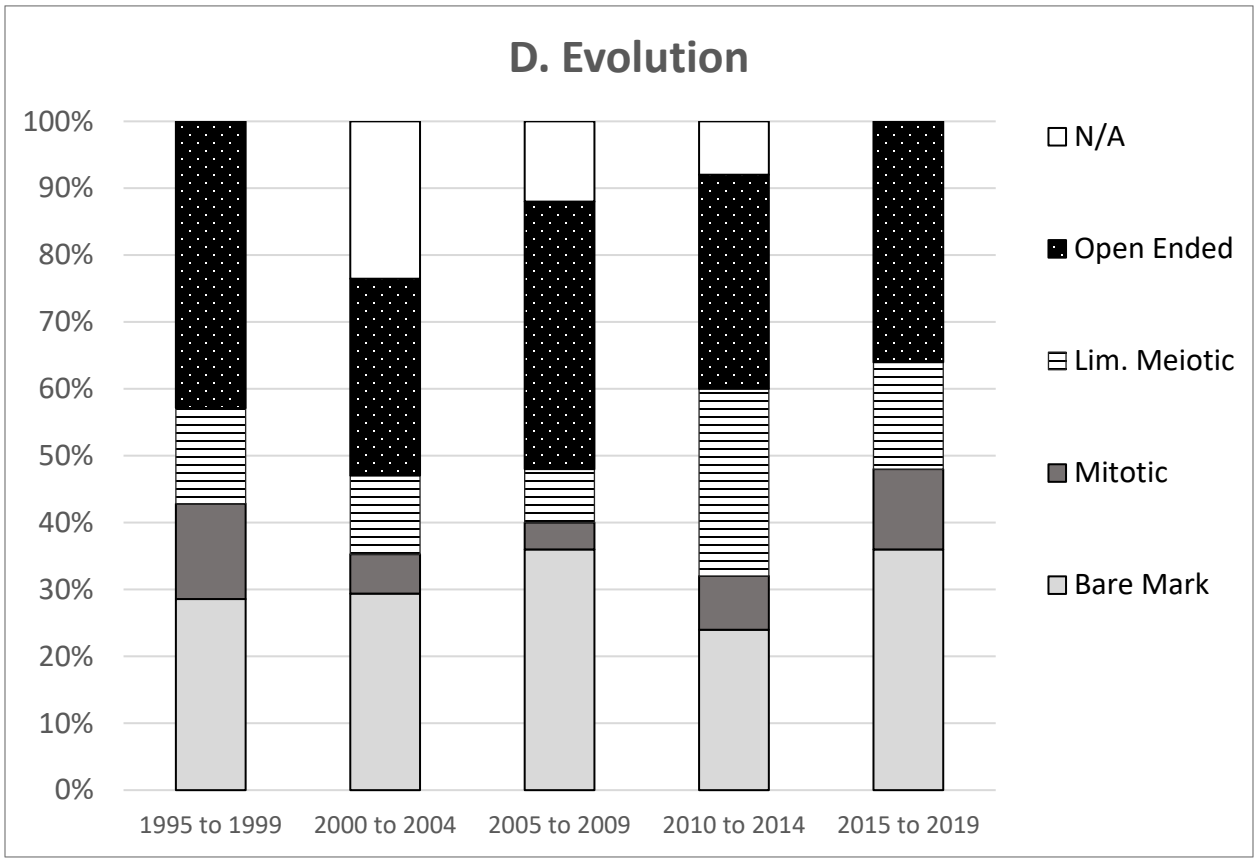
Biomedicine (Fig. 3B) exhibits a simpler pattern, with a dominant commitment to bare marks (>60%) over the entire period, and a slight growth in commitment to mitotic inheritance over the last decade. The majority of abstracts in Proximal Biology (Fig. 3C) were likewise committed to bare marks, ranging (42% to 72%). However, in the two most recent intervals, commitment to mitotic inheritance has been roughly equal to bare marks (32-39%) in Proximal Biology. In both Biomedicine and Proximal Biology the commitment to limited meiotic inheritance is quite low (consistently < 10%), with almost no commitment to open ended inheritance.

This is in sharp contrast to Evolution where open ended inheritance is the most popular commitment, ranging from 42% of the abstracts in the early 1990s to around 33% in the most recent decade. The next most common commitment in Evolution is to bare marks (consistently 25-35%). There was a slight increase in commitment to limited meiotic inheritance in recent years, but very little commitment to mitotic inheritance in Evolution abstracts.

Figure 3. Frequencies of heritability commitments reflected in abstracts of 25 most highly cited articles in Web of Science on "DNA/epigenetics" per five-year interval in (A) General Biology, (B) Biomedical, (C) Proximal Biology, (D) Evolution.

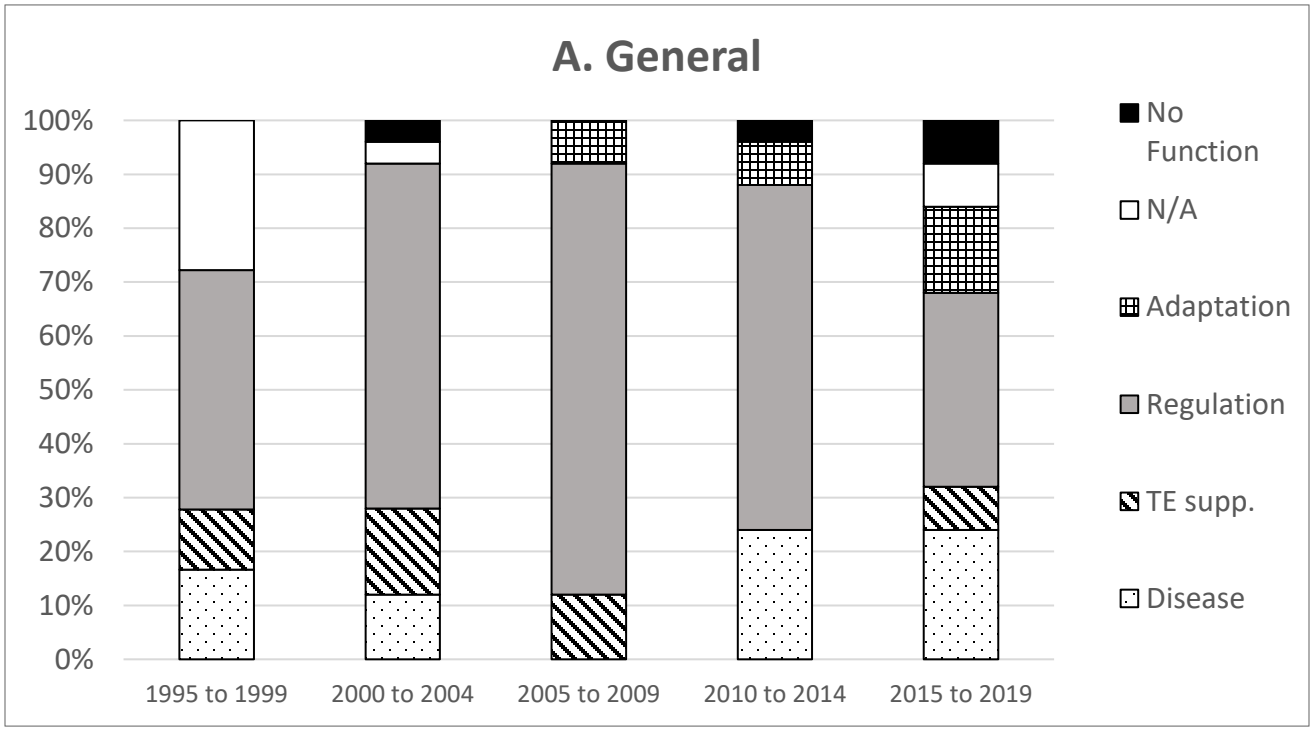


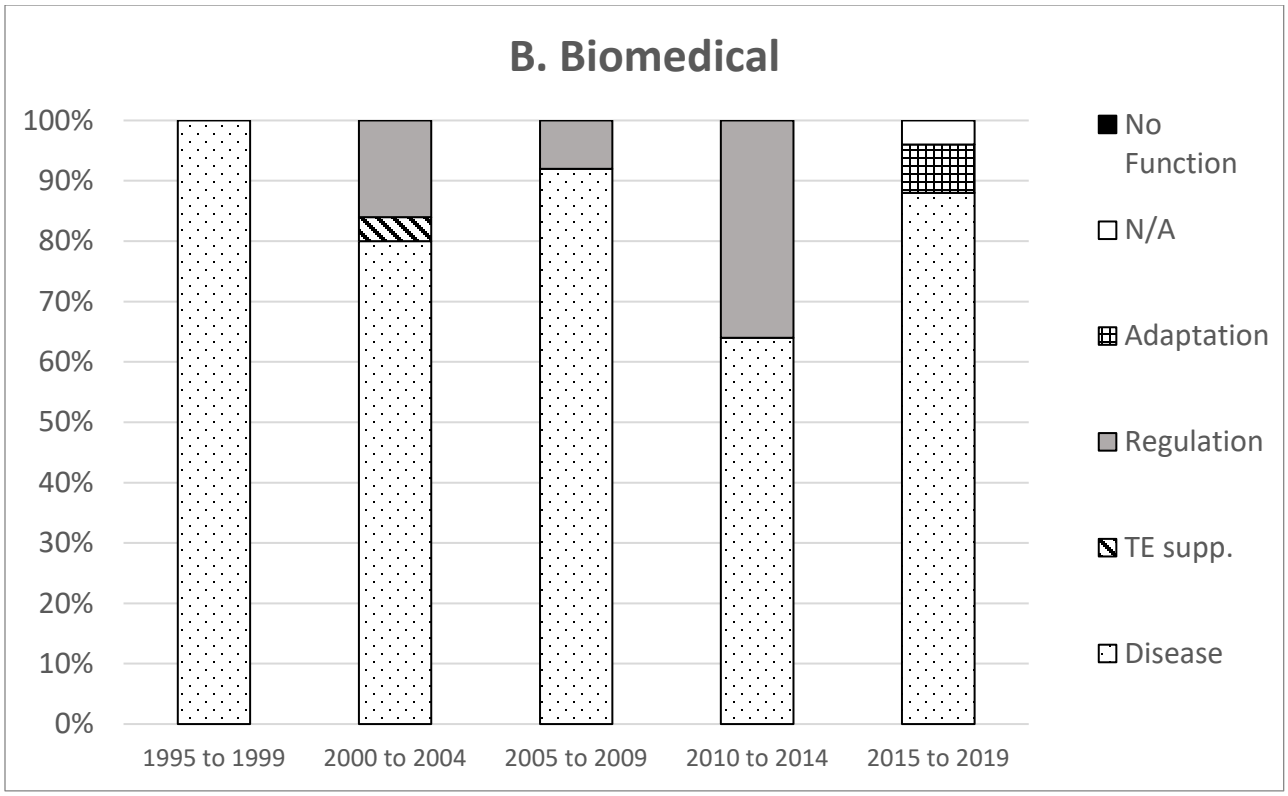

C. Proximal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1995 to 1999
2000 to 2004
2005 to 2009
2010 to 2014
2015 to 2019
N/A
Open Ended
Lim. Meiotic
Mitotic
Bare Mark

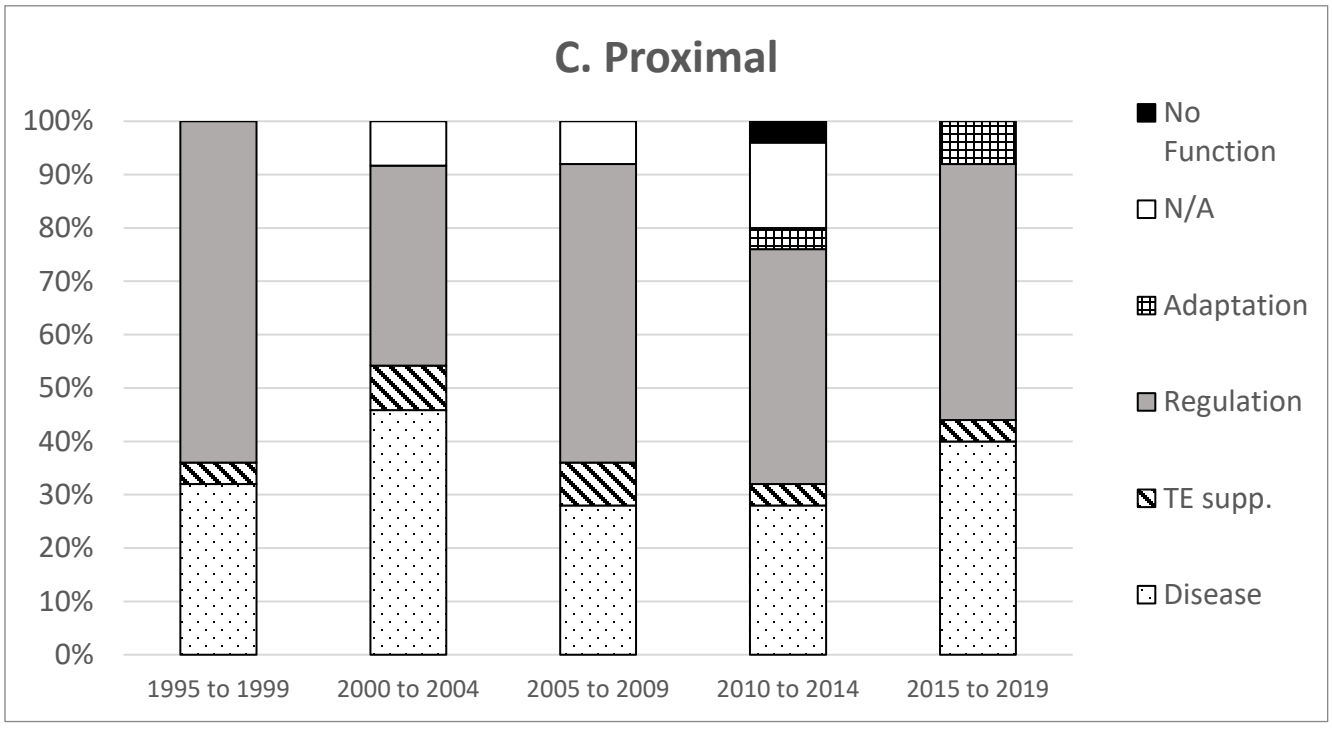

D. Evolution
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1995 to 1999
2000 to 2004
2005 to 2009
2010 to 2014
2015 to 2019
N/A
Open Ended
Lim. Meiotic
Mitotic
Bare Mark

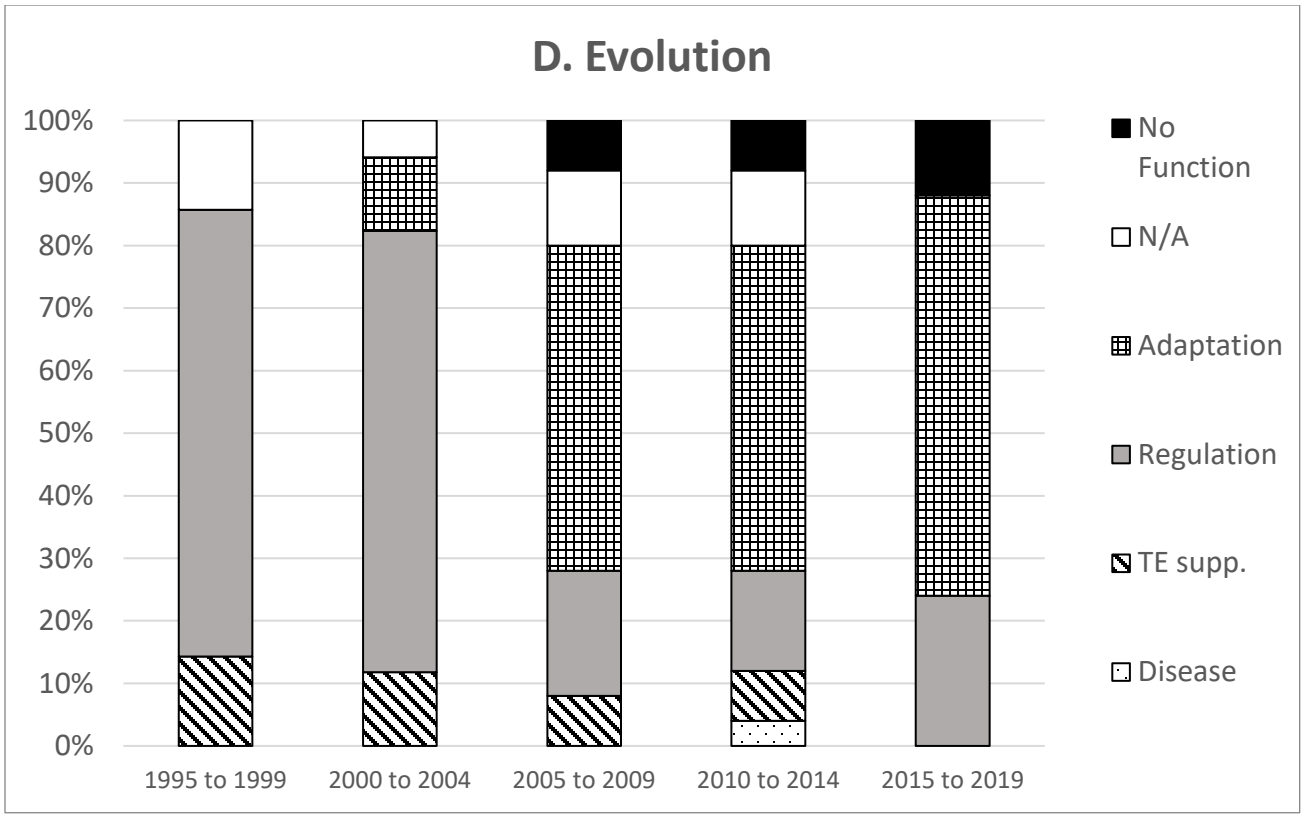
Turning to functional interpretations, within General Biology regulation is the dominant functional interpretation (Fig. 4A, solid grey). However, this interpretation seems to have peaked in the early 2000s when it accounted for 80% of the abstracts and falling to 35% in the most recent period. In Biomedicine, it is perhaps no surprise that the most common functional interpretation is relevant to disease (Fig. 4A, dotted bar), which accounted for >80% of the abstracts in all but one period (2010-2014) when functional interest in regulation briefly spiked (37%). This was in contrast to Proximal Biology, where regulation (38- 61%) was followed by disease (24 -36%) as the two most popular functional interpretations. Interestingly, there is a low (2-7%) but persistent interest in TE suppression among Proximal Biology papers over the entire period (Fig. 4C, dotted bar). Evolution again contrasts with other Disciplines. Here we see a shift from a majority interest in regulation (roughly 70% from 1995-2004) to a majority interest in adaptation (growing 52% in 2005-9 to 86% in 2015-19). This is a sharp and dramatic swing in functional interpretation found only in Evolution.

Figure 4. Frequencies of functional interpretations associated with epigenetic marks as reflected in abstracts of 25 most highly cited articles in Web of Science on “DNA/epigenetics” per five-year interval in (A) General Biology, (B) Biomedical, (C) Proximal Biology, (D) Evolution.




B. Biomedical
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1995 to 1999
2000 to 2004
2005 to 2009
2010 to 2014
2015 to 2019
No Function
N/A
Adaptation
Regulation
TE supp.
Disease


C. Proximal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1995 to 1999
2000 to 2004
2005 to 2009
2010 to 2014
2015 to 2019
No Function
N/A
Adaptation
Regulation
TE supp.
Disease



5. Discussion

Our two analyses were motivated by the question of whether transposon dynamics are generally neglected by epigenetic enthusiasts, as seems to have been the case with some proponents of the epigenetic switch hypothesis. TE coevolutionary dynamics have been largely understood since the mid-1980s. Hence, when it comes to examples like the agouti mouse, where phenotypic effects are caused by methylation of a known TE insertion, one might expect researchers to entertain TE dynamics as a viable alternative to the epigenetic switch. Yet this is somewhat rare.

It has been suggested that the disciplines of molecular biology and genomics are out of touch with advances in evolutionary theory [8,9,31]. If this is correct, then one would expect less enthusiasm for epigenetics in Evolution compared to Proximal Biology or Biomedicine. Figure 1 supports this prediction, exhibiting a delayed and comparatively muted enthusiasm for epigenetics in Evolution compared to other Disciplines. Likewise, Figure 2. exhibits declining interest in transposons in Biomedicine and in Molecular Biology, though not in the other Categories comprising Proximal Biology. This was most surprising. It is difficult to understand why, as TEs have become increasingly recognized as major constituents of eukaryotic genomes,

and given their known mutagenic effects, the biomedical sciences have become gradually *less* interested in TEs. At the very least, one would expect interest in both epigenetics and transposons to have increased in Biomedicine, as we see in most other Disciplines.

What explains the relatively small and delayed interest in epigenetics within Evolution compared to other Disciplines? An epigenetic revolutionary might take this to suggest that Evolution is a conservative discipline, clinging to the "dogma" of gene centrism. Alternatively, greater familiarity in this discipline with transposon dynamics and genome evolution suggest that its practitioners are perhaps less enamored by functional interpretations that ignore these factors. Likewise, the relatively small influence of Big Biology on Evolution compared to Biomedicine and Proximal Biology might also explain the differential enthusiasm for epigenetics across these disciplines. For better or worse, evolutionary thinkers have been slow to jump on the epigenetic bandwagon. Perhaps questionnaire methods could resolve the finer gained question of why exactly this is the case.

It should be kept in mind that Evolution papers on epigenetics embraced a different set of heritability commitments and functional interpretations compared to similar papers in Proximal Biology, Biomedicine, and to some extent General Biology. Putting these findings together, although the topic of epigenetics is relatively unpopular in evolutionary circles, those thinkers who do embrace epigenetics are more extreme in both their heritability commitments and functional interpretations. Also noteworthy is the sea change in functional interpretations that occurred in the mid-2000s, away from basic gene regulation and toward adaptive responses to environmental changes. This coincides with the publication of Jablonka and Lamb's influential book [12] and could reflect its impact on evolutionary thinking.

It is noteworthy that Biomedicine and Proximal Biology largely overlap in their heritability commitments and are quite similar in their functional interpretations. Despite the general concern that epigenetics research is fraught with ambiguity [20, 30], our analysis suggests that practitioners in at least these Disciplines mean roughly the same thing by "epigenetic." This was in contrast to General Biology, where there is much more diversity in heritability commitments and functional interpretations, and of course to Evolution.

In sum, our results support the suspicion that enthusiasm for epigenetics has not only overshadowed interest in transposons, but that in some fields where enthusiasm for epigenetics is

most prevalent (Biomedicine, Biochemistry and Molecular Biology) interest in TE dynamics is even declining. We suspect that this trend could lead researchers in these disciplines to uncritically embrace certain functional interpretations, such as the epigenetic switch hypothesis, without due consideration of alternative explanations. Hopefully, our findings will inspire further interest in transposon dynamics, especially among researchers drawn to the idea of an epigenetic revolution.

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