



Construction of a Review About Epigenetics for Biology Teachers and Other Non-experts

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Abstract

Epigenetics, the new research field at the cutting edge of biology research, needs to be introduced in biology education. The aim of this review is to support biology teachers and other non-experts to get an overview of the field, as a review in epigenetics has hardly been written for these groups. This review was done by finding documents describing central features of epigenetics, increasing the understanding of epigenetics' contribution to perspectives in society, and to be a model for a review in a rapidly developing science field. As an example of societal perspectives, the old dispute about “nature” or “nurture” is discussed, epigenetics focusing on the role of “nurture's” influence on “nature.” Consequently, epigenetics dispels biological determinism. As this review was intended to fill a gap in the literature, a theoretical framework for the construction of the review had to be invented. This was done in an iterative process during the construction of the review. Documents were searched for in the databases of ERIC, Scopus, and Web of Science, peer-reviewed, and had been published by a well-renowned publisher. The search time frame was January 2016 to December 2019, including document types books and book chapters, plus journal articles for ERIC; documents had to be written in English and published as open access. Searches were divided into pre-defined categories based on a newly performed Delphi study. Exemplar studies, which best described each category, are discussed in the light of frontline research. As implications from epigenetics are important for a variety of areas within society, the review is a contribution to the field of sociology of science, aiming to support science education at the very front of science.

1 Introduction

The old controversial dispute about “nature” or “nurture,” the debate about which characteristics depend on genes and which depend on the environment, has a new dimension due to the novel field of epigenetics. In brief, epigenetics describes how genes, “nature,” are activated or not, and this activation/inactivation could be influenced by environmental factors, “nurture.” Focus in the debate has shifted to the increasing understanding of how

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environmental factors model our lives. This leads to us now better understanding our possibilities to influence our lives by our lifestyles; “everything is not written in stone.” In this way, new knowledge on biology contributes with novel perspectives in a long-lived controversial dispute. It could also be expressed as epigenetics dispels biological determinism, the thought that we are ruled by our genes. This is an example of an important consequence of our increased knowledge in epigenetics. The big spectrum of implications of epigenetics in society puts the review in the field of sociology of science and seeks to promote better teaching and learning.

The aim of this study is to support biology teachers and other non-experts to recognize epigenetics’ big implications for natural sciences and the social sciences by offering a broad overview of epigenetics, highlighting epigenetics as an important issue of subject matter content in biology. However, epigenetics has only to a limited extent found its place in the curricula; that is why researchers argue for their inclusion (Zuidare & Fraile, 2020). Only a small amount of studies have been published describing its role in biology education (e.g., Heyduck & Harms, 2015; Zuidare & Fraile, 2020). Epigenetics renews biology education with research frontline knowledge, one of its roles being of great importance by informing students about how life style issues might have great impact on the health through epigenetic mechanisms. However, there might be limitations in introducing new content in genetics education. Classroom studies of secondary schools report that genetics teaching often is highly traditional (Thörne, 2018). By introducing epigenetics, genetics teaching needs to be reevaluated.

A common way to get an overview of a field is to read a review over that particular field. During 2016–2019, there were approximately 8,900 published reviews concerning epigenetics (Web of Science database). However, these reviews are written by scientists for scientists, often in a quite advanced level, and in the parlance of the profession. It could be difficult for biology teachers and other non-experts to grasp the context in these reviews. A search for reviews about epigenetics for biology teachers or other non-experts gave hardly any results, highlighting the need to construct a review about epigenetics devoted to these target groups. The review has to be written with high-quality texts as a base, however, avoiding difficult specialist terms. This review fulfills both these requirements and contributes to fill a clear gap in the literature. Furthermore, the construction of the review could be a model for and applied on how to design a review of other rapidly developing science fields as well.

1.1 Epigenetics: an Overview

Epigenetics deals with a deepened knowledge of basic cellular processes (Allis et al., 2015). In brief, it concerns which genes are active and which are silent in an organism, governing a vast amount of processes, and obviously being of great importance for living organisms. Due to it being fundamental for cellular processes, our increased understanding of these aspects leads to big consequences for a range of fields. Epigenetics’ importance stretches from different fields such as medicine (e.g., Wang, 2019), psychology (e.g., Xu et al., 2020), and pedagogy (e.g., Pickersgill, 2020), to ethics (e.g., Taki & de Melo-Martin, 2021) and law (e.g., Dupras et al., 2019), although the knowledge base is not as firmly established for the last three compared to for medicine and psychology. This universal importance is why some biologists talk about a paradigm shift (Gilbert & Epel, 2009).

However, researchers also question the magnitude of epigenetics' importance. Isle (2015) discusses that epigenetics has caused controversies with overblown claims and talks about a hype. Heard and Martienssen (2014) put our eyes on that epigenetics has been increasingly "associated with the hope that we are more than just the sum of our genes" (p. 95). They agree that "the environment can certainly influence gene expression" but disagree that epigenetic marks could be transgenerational inherited, at least in human. Müller et al. (2017) point to the interdisciplinary character of epigenetics and advocate for researchers from different disciplines to cooperate to see the full potential of epigenetics and avoid misunderstandings. They give examples of how such collaboration could be designed. Deichmann (2020) discusses different interpretations of the importance of epigenetics, depending on the interpreter's purpose. The author focuses the social construction of the epigenome and points to the occurrence of self-interest, where only parts suitable for the interpreter are highlighted.

Epigenetics refers to mechanisms acting "above" the sequence of the base-pairs of DNA; thus, they do not change the base-pair order of the DNA. "Epi" comes from the Greek word "over"/"above," indicating no change in the base-pair order. The epigenetic mechanisms build different epigenetic patterns in different cells, governing the cells into different directions, being crucial during the differentiation process. Due to epigenetic mechanisms, genes are accessible or not for transcription. Genes in an "open" state are accessible and could be transcribed, while they are silenced in a "closed" state. Briefly, epigenetics is about "opening up" or "closing" genes, which is fundamental for the cellular processes in an organism.

Allis et al. (2015) provide an overview of the epigenetic mechanisms. The most studied and best understood is DNA methylation, where methyl groups are bound to, preferably, promotor regions of DNA. Generally speaking, methyl groups bound to promotor regions put the DNA in a "closed" state and inhibit an expression of genes. A second epigenetic mechanism is modifications of histones, the associated proteins around which the DNA is wound. There are many types of histone modifications, e.g., methylations, acetylations, and phosphorylations, where different variants work in opposite directions, both "opening" or "closing" the DNA. A third epigenetic mechanism is the state of the chromatin structure, the coiling, looping, and the general structure of DNA. Corresponding to histone modifications, DNA is "opened up" or "closed" because of the state of the chromatin structure. Small regulatory micro-ribonucleic acids (miRNAs) exert a fourth epigenetic mechanism. These put out formed mRNA in the translation process. Concurrently with the fast-developing knowledge of epigenetics, new epigenetic mechanisms are suggested. One of these is methylation of RNA (Nilsson et al., 2018).

Epigenetic processes take place during the development of an organism, from the fertilization of an egg and the formation of a zygote, during the fetus development until a baby is born. Epigenetic mechanisms are part of the differentiation process, which decides the fate of cells into different destinations and functions. However, epigenetic processes do not stop at birth; rather, they continue to be part of the fundamental cell processes during the rest of the life. In recent years, it has been obvious that epigenetic processes are involved in processes like learning (Collins et al., 2019; Kim & Kaang, 2017; Leighton et al., 2018), stress responses (Cao-Lei et al., 2016; Li et al., 2020; Xu et al., 2020), and during physical activity (Hall et al., 2020; Lindholm et al., 2014; Seaborne et al., 2018). Additionally, individuals suffering from different diseases and disorders present changed epigenetic patterns. Examples of such diseases are cancers (Biswas & Rao, 2017; Liu et al., 2019a; Wang, 2019), neurodegenerative diseases like Alzheimer's (Marques & Outeiro, 2013; Qazi et al., 2018; Tecalco-Cruz et al., 2020) and Parkinson's (Marques & Outeiro, 2013;

Pavlou & Outeiro, 2017), and mental illnesses (Hoffman et al., 2019; Nestler et al., 2016). Two decades ago, DNA methylation was shown to be a reversible process (Ramchandani et al., 1999). When changed epigenetic patterns showed up in diseases and disorders, the idea was launched that reversal of epigenetic patterns by epigenetic drugs could be a new therapeutic method. Research about epigenetic drugs is a new area, pictured in a review by Ganesan et al. (2019). This brief overview of epigenetics shows that it has implications for a wide range of human activities.

1.2 Aim of the Study

The aim of this study is to support biology teachers and other non-experts in getting an overview of the new field of epigenetics, and to be a model for how to design a review in a rapidly developing science field. Thus, it is not presented as a conventional review. As epigenetics has big implications not only for natural science but also for the social sciences, the intention was to cover a broad area, albeit in a human perspective. The following three guiding statements structure and elucidate the aim:

- 1) To find documents that increase the understanding of how epigenetics contribute with new knowledge and perspectives in the social sciences
- 2) To find documents that describe central features and different aspects of epigenetics to facilitate the understanding of the nature of epigenetics
- 3) To be a model for how a review in a rapidly developing science field could be designed

2 Methods

2.1 Theoretical Framework

This study was intended to provide a novel approach on how to design a review for non-experts in a rapidly developing science field. The development of the theoretical framework was an iterative process that was constructed during the process of conducting the review. The procedure had to be invented to a certain extent, and the process was chiseled during the work and is therefore cautiously described in the text.

Inspiration was obtained from the theoretical framework systematic reviews (Gough et al., 2017) and from the design of a review about teacher professional development (van Driel et al., 2012), both used when applicable. More explicit information about which methods were inspired from Gough et al. (2017) and van Driel et al. (2012), respectively, is described in the next section, Search Strategies and Criteria.

2.2 Search Strategies and Criteria

There was a need to explore new strategies and to test new ideas, as a review about epigenetics for biology teachers and other non-experts has hardly been performed before. The first prerequisite was that selected documents should be of high-quality; thus, databases of good repute were chosen for the collection of documents. The framework of systematic reviews recommends not less than three databases (Gough et al., 2017); thus, the three databases. Education Resources Information Center (ERIC), Scopus, and Web of Science,

covering different aspects of epigenetics, were chosen. ERIC is a library of education research and information; Scopus includes health, life, social, and physical sciences; and Web of Science covers science, social science, and arts and humanities. All chosen documents were peer-reviewed, but as an extra control to be selected for this review, they had to be published by a well-renowned publisher. Illustrative examples are Annual Reviews, Cold Spring Harbor Laboratory Press, Elsevier, Karger, Portland Press, Routledge, SAGE, Springer, and Wiley.

The second prerequisite was that the documents had to be written in a moderately advanced level, avoiding difficult specialist terms to match non-experts; thus, it was checked which document types were most suitable for the review. The following were tested and evaluated: books, book chapters, conference papers, conference reviews, editorials, letters, meeting abstracts, meeting summaries, notes, proceeding papers, reviews, and short surveys. These were checked for hits, including the number of hits they generated, to see if they were written in a moderately advanced level. The three databases cover different research areas, and their search engines are differently built; consequently, there was a need to explore which search strategy was optimal for each database. Summarizing the results from the tests, the document types books and book chapters crystallized to be optimal. However, for the database ERIC, the document type journal article was used, as a search on “epigenetics” for books and book chapters only revealed one document for the period of interest. In addition, as ERIC covers documents mostly from the educational field, the texts, even journal articles, are not written on a highly advanced natural science level.

The third prerequisite was that the search time should be set to a recent and short period, as epigenetics is a rapidly developing field. The 4-year time interval between January 2016 and December 2019 was found to encompass a sufficient number of documents. Further prerequisites were that only documents with open access, written in English, were collected. It was considered important that if readers wanted to dig deeper into the literature, it should be easy and convenient to find the documents.

The searches were divided into a number of pre-defined categories with different principal features and aspects of epigenetics. These were chosen based on the results from a Delphi study, performed on a group of 35 acknowledged experts answering questions about different aspects of epigenetics (Gericke & Mc Ewen, [submitted](#)). The experts came from the fields of medicine, biology, education, communication, and philosophy; however, experts from education, communication, and philosophy also had a solid base in genetics. The categories were Epigenetics and Nature of Science, Epigenetics Connecting Nature with Nurture, Epigenetics as a Dynamic Process, Epigenetic Mechanisms, Epigenetics as a Metaphor, and Epigenetic Inheritance. One difference compared to Gericke & Mc Ewen, [submitted](#) was that issues about health and diseases were treated in the category Epigenetics as a Dynamic Process — Medicine, and issues about pollution in the category Epigenetics as a Dynamic Process — Pollution, due to the many hits in Epigenetics as a Dynamic Process. Thus, altogether, this review encompasses seven different categories (Table 1).

The strategy for finding search terms was based on the framework of systematic reviews (Gough et al., 2017). Search terms used for each category are shown in Table 2. To decide on search terms besides “epigenetics,” which was used in all searches, these were found in citations and descriptions of how the 35 experts in the Delphi study by Gericke & Mc Ewen, [submitted](#) regarded epigenetics. Search terms were also found in scientific articles describing different areas of epigenetics corresponding to the seven categories. Different combinations of search terms were tested several times with the purpose of finding a balance and avoiding being too strict, which would result in too few relevant documents, or using too extensive conditions, leading to an overlay of documents, a strategy

Table 1 Numbers of documents for the seven categories before exclusion of doublets and those not fitting the aim of the study

Category	ERIC	Scopus	Web of Science	Three databases
1, Epigenetics and Nature of Science	3	2	2	7
2, Epigenetics Connecting Nature with Nurture	12	9	22	43
3, Epigenetics as a Dynamic Process — Medicine	1	9	55	65
4, Epigenetics as a Dynamic Process — Pollution	0	5	20	25
5, Epigenetic Mechanisms	2	8	61	71
6, Epigenetics as a Metaphor	0	5	6	11
7, Epigenetic Inheritance	4	2	14	20
Total	22	40	180	242

Table 2 Search strings for the seven categories

Category 1, Epigenetics and Nature of Science (epigenetic* AND ((nature of science) OR nos OR essentialis* OR determinis* OR (genetic determinis*)))
Category 2, Epigenetics Connecting Nature with Nurture (epigenetic* AND ((genotype phenotype) OR (genotype versus phenotype) OR (genotype vs phenotype) OR environment* OR surrounding* OR milieu* OR external*))
Category 3, Epigenetics as a Dynamic Process — Medicine (epigenetic* AND ((dynamic process*) OR revers* OR medicine OR disease* OR cancer* OR treatment* OR therapeut* OR drug*))
Category 4, Epigenetics as a Dynamic Process — Pollution (epigenetic* AND ((dynamic process*) OR toxin* OR toxic* OR pollut* OR chemical*))
Category 5, Epigenetic Mechanisms (epigenetic* AND (mechanism* OR (dna methyl*) OR (methyl pattern*) OR (histone modification*) OR noncoding rna* OR ncRNA*))
Category 6, Epigenetics as a Metaphor (epigenetic* AND (metaphor* OR analog* OR (waddington* landscape) OR orchestra* OR book* OR software OR (comput* software) OR layer OR (add* layer) OR (add on)))
Category 7, Epigenetics and Inheritance (epigenetic* AND (inherit* OR heridit* OR transgeneration* OR (across generation*) OR offspring*))

recommended by Gough et al. (2017). During searches in the databases, the search terms had to be found in the documents' titles or abstracts or among the keywords of the documents. The documents were then saved in the reference treatment system EndNote for further analyses.

2.3 Analysis

Searches were performed according to the above search strategies, and the criteria delivered a number of documents for each category and each database (Table 1). This table also reflects the number of documents, as compiled from the three databases.

The next step was to check for documents that were obviously not addressing the aim of this review (Gough et al., 2017). These belonged to the following groups and were therefore excluded:

- 1) Not published as open access (9 documents)
- 2) Documents about plants (7 documents), insects (2 documents), model organisms (1 document), or microbiology (1 document)
- 3) Bibliographies (1 document)
- 4) Published from an unrenowned publisher (1 document)

It was found that the discrepancies between the databases' tagging of documents as open access and if documents really turned out to be open access could be due to only parts of a book being open access, not the whole book. This resulted in nine documents being excluded. As the review has a human perspective, documents about plants, insects, model organisms, and microbiology (altogether 11 documents) were also excluded. Further, one bibliography did not fit the aim of this review. One document was excluded because it was written with an unprofessional approach and had an unrenowned publisher. Thus, altogether, 22 documents were excluded. Table 3 shows the number of hits for the seven categories in each database after excluding those documents that did not fit the aim of the study. Observe that doublets, documents found in more than one category, had not been excluded yet. The doublets explain the difference between 242 documents (Table 1) and 198 (Table 3) being larger than the 22 excluded. Figure 1 shows a flow chart of the analysis process.

By briefly reading the documents' abstracts, it became obvious that quite a lot of them covered a broad research area. Many of these documents had been selected for more than one of the categories by the search engines. Thus, to facilitate the subsequent management of the data material, doublets were set aside, and the remaining documents were compiled into one final group, containing 94 documents for further analyses.

As most of the categories could be described by quite a lot of documents, it was decided to filter out "the stronger and more convincing examples of studies" (van Driel et al., 2012, p. 131) as "exemplar studies" (p. 129) to characterize a certain category. Therefore, all abstracts of the 94 documents were carefully read, and documents best describing each of the seven categories were chosen as exemplar studies for further analyses. Thirty-two documents belonged to this group (Table 4). These were

Table 3 Numbers of documents for the seven categories after omitting those not fitting the aim of the study but before exclusion of doublets

Category	ERIC	Scopus	Web of Science	Three databases
1, Epigenetics and Nature of Science	2	1	2	5
2, Epigenetics Connecting Nature with Nurture	11	5	21	37
3, Epigenetics as a Dynamic Process — Medicine	1	6	48	55
4, Epigenetics as a Dynamic Process — Pollution	0	2	19	21
5, Epigenetic Mechanisms	2	6	50	58
6, Epigenetics as a Metaphor	0	1	6	7
7, Epigenetic Inheritance	3	1	11	15
Total	19	22	157	198

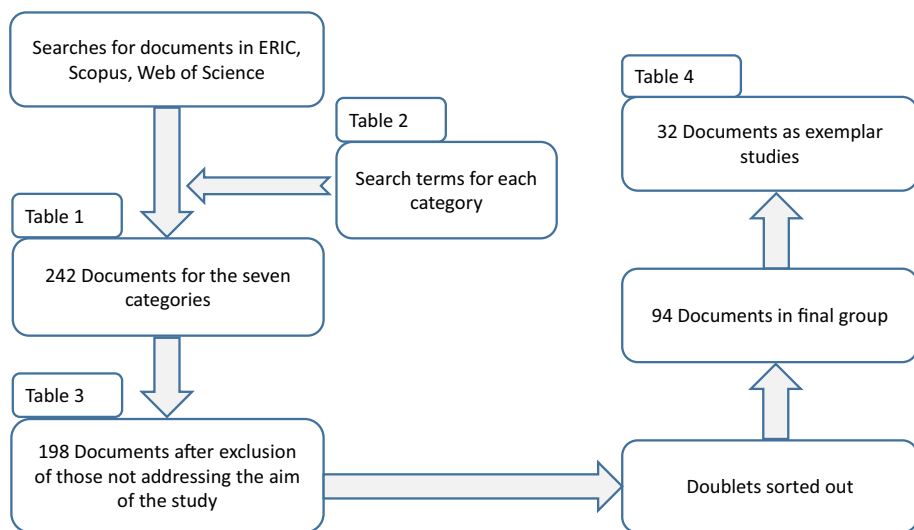


Fig. 1 Flow chart of the analysis process

cautiously read and summarized, pointing to the main perspectives of the category of interest, and are presented in the Results section. The exemplar studies are marked in the text by brackets and with an asterisk (*), e.g., [Skvortsova et al., 2019*], to distinguish these from other references. To ensure that exemplar studies characterized the seven categories, an expert in epigenetics confirmed that the choices of exemplar studies well represented the categories.

3 Results

The construction of the review of epigenetics to support biology teachers and other non-experts resulted in the development of a theoretical framework. It was constructed in an iterative process during the process of conducting the review. The procedure had to be invented to a certain extent; the process was chiseled during the work and is therefore cautiously described in the text. This theoretical framework could be used as a model for how to design a review in a rapidly developing science field.

The search encompassed 94 relevant documents; however, this group was reduced to 32 exemplar studies, emphasizing strong and convincing examples. It was done in the three trustworthy databases, ERIC, Scopus, and Web of Science, having different areas of focus, circumscribing both social science and natural science aspects of epigenetics. The document type for all documents from the ERIC was journal articles; searches in Web of Science only revealed book chapters; and the majority of the documents from Scopus were book chapters. To support readers to find these documents, only those marked as open access were chosen. Below, a handful of exemplar studies are presented for each of the seven categories, characterizing and reflecting the main

Table 4 Final group of 32 exemplar studies reached through the links or according to the descriptions of how to find them

- Ahuja, N., Sharma, A. R., & Baylin, S. B. (2016). Epigenetic therapeutics: A new weapon in the war against cancer. In C. T. Caskey (Ed.), *Annual Review of Medicine* 67 (pp. 73–89). Annual Reviews
<http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC4937439&blobtype=pdf>
- Bennett, R. L., & Licht, J. D. (2018). Targeting epigenetics in cancer. In P. A. Insel (Ed.), *Annual Review of Pharmacology and Toxicology* 58 (pp. 187–207). Annual Reviews
<http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC5800772&blobtype=pdf>
- Carroll, B. (2019). Understanding the needs of children who are known to have experienced neglect in the first years of life: The potential effects of early adversity on later self-regulation skills and school functioning. *Psychology of Education Review* 43(2), 9–19
 [University library.]
- Chen, Q. Y., DesMarais, T., & Costa, M. (2019). Metals and mechanisms of carcinogenesis. In P. A. Insel (Ed.), *Annual Review of Pharmacology and Toxicology* 59 (pp. 537–554). Annual Reviews
<http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC6348465&blobtype=pdf>
- Doherty, T. S., & Roth, T. L. (2018). Epigenetic landscapes of the adversity-exposed brain. In D. R. Grayson (Ed.), *Epigenetics and Psychiatric Disease* 157 (pp. 1–19). Elsevier
<http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC6056018&blobtype=pdf>
- Drmic, I. E., Szatmari, P., & Volkmar, F. (2017). Life course health development in autism spectrum disorders. In N. Halfon, C. B. Forrest, R. M. Lerner & E. M. Faustman (Eds.), *Handbook of Life Course Health Development* (pp. 237–274). Springer
 [Authors and document title in Google Scholar.]
- Duncan, K. W., & Campbell, J. E. (2018). Epigenetic modulators. In M. J. Waring (Ed.), *Cell II. Topics in Medicinal Chemistry* 28 (pp. 227–288). Springer
 [Authors and document title in Google Scholar.]
- Ford, N. D., Patel, S. A., & Narayan, M. V. (2017). Obesity in low- and middle-income countries: Burden, drivers, and emerging challenges. In J. E. Fielding (Ed.), *Annual Review of Public Health* 38 (pp. 145–164). Annual Reviews
<https://www.annualreviews.org/doi/abs/10.1146/annurev-publhealth-031816-044604>
- Halfon, N., & Forrest, C. B. (2017). The emerging theoretical framework of life course health development. In N. Halfon, C. B. Forrest, R. M. Lerner & E. M. Faustman (Eds.), *Handbook of Life Course Health Development* (pp. 19–43). Springer
 [Authors and document title in Google Scholar.]
- Heindel, J. J., & Blumberg, B. (2019). Environmental obesogens: Mechanisms and controversies. In P. A. Insel (Ed.), *Annual Review of Pharmacology and Toxicology* 59 (pp. 89–106). Annual Reviews
http://blumberg-lab.bio.uci.edu/reprints/heindel_blumberg-2019.pdf
- Helin, K., & Minucci, S. (2017). The role of chromatin-associated proteins in cancer. In T. Jacks & C. L. Sawyers (Eds.), *Annual Review of Cancer Biology* 1 (pp. 355–377). Annual Reviews
<https://www.annualreviews.org/doi/abs/10.1146/annurev-cancerbio-050216-034422>
- Hnisz, D., Schuijers, J., Li, C. H., & Young, R. A. (2018). Regulation and dysregulation of chromosome structure in cancer. In T. Jacks & C. L. Sawyers (Eds.), *Annual Review of Cancer Biology* 2 (pp. 21–40). Annual Reviews
<https://www.annualreviews.org/doi/abs/10.1146/annurev-cancerbio-030617-050134>
- Hong, S., & Cheng, X. D. (2016). DNA base flipping: A general mechanism for writing, reading, and erasing DNA modifications. In A. Jeltsch & R. Z. Jurkowska (Eds.), *DNA Methyltransferases—Role and Function. Advances in Experimental Medicine and Biology* 945 (pp. 321–341). Springer
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5542066/>
- Jackson, M., Marks, L., May, G. H. W., & Wilson, J. B. (2018). The genetic basis of disease. In S. Perrett (Ed.), *Understanding Biochemistry 4. Essays in Biochemistry* 62(5) (pp. 643–723). Portland Press
<https://portlandpress.com/essaysbiochem/article/62/5/643/78430/The-genetic-basis-of-disease>
- Kappil, M., Wright, R. O., & Sanders, A. P. (2016). Developmental origins of common disease: Epigenetic contributions to obesity. In A. Chakravarti & E. Green (Eds.), *Annual Review of Genomics and Human Genetics* 17 (pp. 177–192). Annual Reviews
<http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC5045029&blobtype=pdf>

Table 4 (continued)

- Ahuja, N., Sharma, A. R., & Baylin, S. B. (2016). Epigenetic therapeutics: A new weapon in the war against cancer. In C. T. Caskey (Ed.), *Annual Review of Medicine* 67 (pp. 73–89). Annual Reviews <http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC4937439&blobtype=pdf>
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- Skvortsova, K., Stirzaker, C., & Taberlay, P. (2019). The DNA methylation landscape in cancer. In M. Blewitt (Ed.), *DNA Methylation. Essays in Biochemistry* 63(6) (pp. 797–811). Portland Press <https://portlandpress.com/essaysbiochem/article/63/6/797/221497/The-DNA-methylation-landscape-in-cancer>
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Table 4 (continued)

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- Youdell, D. (2016). New biological sciences, sociology and education. *British Journal of Sociology of Education*, 37(5), 788–800 [University library.]
- Youssef, N., Budd, A., & Bielawski, J. P. (2019). Introduction to genome biology and diversity. In M. Anisimova (Ed.) *Evolutionary Genomics. Methods in Molecular Biology* 1910 (pp. 3–31). Humana Press https://link.springer.com/protocol/10.1007/978-1-4939-9074-0_1

perspectives of the category of interest. For category 3, *Epigenetics as a Dynamic Process — Medicine*, a few more documents were chosen due to the many hits for this category. Table 4 shows the final group of 32 exemplar studies reached through the links or according to the descriptions of how to find them.

3.1 Category 1: Epigenetics and Nature of Science

The search for documents in category 1, *Epigenetics and Nature of Science*, resulted in five documents (Table 3) and is best described by three exemplar studies from the ERIC database. These focus on the importance of dispelling biological determinism and highlight desirable changes in education, thanks to the new knowledge of epigenetics.

All three exemplar studies [Stetsenko, 2017*, 2018*; Youdell, 2016*] discuss the rapidly developing fields within contemporary biology research, where epigenetics is emphasized as being an important potential for change. Epigenetics is the most highlighted area, besides neuroscience, developmental systems perspectives, and activity-centered cultural–historical frameworks [Stetsenko, 2017*, 2018*]. The same author argues that epigenetics dispels biological determinism in the light of being one of the “emerging conceptual breakthroughs” [2018*, p. 44]. Further, and because of this, the author declares all individuals’ infinite potential, which could not be calculated in advance or being pre-defined in terms of having any putative inborn “endowments.”

Both Youdell [2016*] and Stetsenko [2017*, 2018*] highlight education as an especially important field where epigenetics is predicted to give new perspectives. Youdell [2016*] emphasizes the particular potential of epigenetics to speak to sociology of education (p. 788). In her review essay, entitled “New biological sciences, sociology and education,” she discusses four texts, all about different perspectives of how the new biological sciences could influence education from a sociology perspective. Stetsenko [2017*, 2018*] foresees that epigenetics would disrupt inequality in education and counteract discrimination and marginalization, by the understanding of epigenetics’ strength in explaining the environment’s, “nurture’s,” impact on the phenotype. The same author claims a correlation between educational success and access to teachers’ experiences and skills [Stetsenko 2018*, p. 44]. Thus, to facilitate educational success, the author claims that teachers ought to be supported to understand the potential of epigenetics.

3.2 Category 2: Epigenetics Connecting Nature with Nurture

Category 2, *Epigenetics Connecting Nature with Nurture*, gave rise to 37 documents (Table 3). The category is best characterized by a handful of exemplar studies, all but one from the ERIC and Scopus databases. These documents point to interactions between genes, “nature,” and the environment, “nurture,” together forming the characteristics of humans. The increased understanding of this interplay leads to an improved comprehension of consequences for human development. The exemplar studies deal with three different themes: epigenetic patterns being important for normal development, research about epigenetics and human behavior in relation to early childhood adversity, and the formation of the framework of Life Course Health Development.

Law and Holland’s [2019*] article, entitled “DNA methylation at the crossroads of gene and environment interactions,” reflects that epigenetic marks are at the center between genes and the environment during development. The authors highlight the inherited plasticity of development, a result of the epigenetic mechanisms’ influence on gene expression. Lester et al. [2016*] summarize the importance of epigenetics in explaining human behavior as providing an opportunity to revolutionize our understanding of the role of genetics and the environment (p. 29). Human behavior is seen in the light of epigenetics being the bridge between the biological and environmental factors, with special focus on embryonic and young children’s development. Carroll [2019*] and Sciaraffa et al. [2018*] argue that the developing brain of a newborn child is very susceptible, being partly formed by epigenetic processes mediating influences from the child’s environment. Early adversity could bring health problems later in life, implicating the importance of early childhood educators identifying children with adverse childhood experiences to develop protective skills [Sciaraffa et al., 2018*]. Furthermore, early adversity during a child’s first year of life is hypothesized to bring difficulties in self-regulation through epigenetic mechanisms [Carroll, 2019*]. As self-regulation is regarded as a key factor to engage successfully in a social classroom, neglected caregiving early in life might contribute to difficulties in school behavior.

Halfon and Forrest [2018*] describe the formation of the theoretical framework of Life Course Health Development in *Handbook of Life Course Health Development*. This framework is a reaction to conventional health science’s failure to explain what health means, how health develops over the lifespan, and the consideration of health as an absence of disease or its risk factors. In contrast, the Life Course Health Development framework focuses on health. It was formed using a new multidisciplinary framework, resulting from scientific breakthroughs in fields like epigenetics, neurodevelopment, and life course chronic disease epidemiology. It bridges “what have sometimes been assumed to be polar opposites: nature versus nurture, mind versus body, individual versus population, and short-term versus long-term change” (p. 20). Seven principles guide the framework, whereof one is the continuous development of health over the lifespan, shaped by prior experiences and environmental interactions. In the last chapter of *Handbook of Life Course Health Development*, Halfon et al. [2018*] advocate that a Life Course Research Agenda is launched with special attention to children and their mothers to improve lifelong health outcomes. In another chapter of the same book, Drmic et al. [2018*] recommend the use of the framework to give inspiration to novel approaches to the study of autism spectrum disorders.

3.3 Category 3: Epigenetics as a Dynamic Process — Medicine

This category gathered 55 documents (Table 3). The following exemplar studies provide an overview of epigenetics as a dynamic process in diseases and disorders, and that reversibility of epigenetic patterns is discussed as a new therapeutic method. The exemplar studies, except for two, are from the Web of Science database. After a section about the genetic and epigenetic basis of diseases, the role of epigenetics in cancers, autism spectrum disorders, stress, psychiatric disorders, and obesity is described. At the end, possible epigenetic therapeutic treatments for diseases and disorders are discussed.

A broad overview of the genetic basis of disease, also describing the role of epigenetics, is presented by Jackson et al. [2018*]. This book chapter deals with many topics, such as the variation of the human genome, chromosomal structure and chromosomal disorders, single-gene disorders, and mitochondrial disorders. It also treats complex disorders, genetic testing, and challenges in delivering genetic services. The text points to the research communities' accumulating knowledge about epigenetics' role in diseases and disorders, focusing on epigenetic modifications in cancer proliferation, as cancers are denoted as one of the most prevalent public health diseases.

Skvortsova et al. [2019*] describe the DNA methylation landscape in normal and cancer cells, reporting on the widespread changes of DNA methylation across the whole genome of the latter. These changes could be either too many DNA methylations or too few. Despite the availability of many technologies for assessing and interpreting DNA methylation events, the authors address a need for the development of new and better methods. Other approaches describing epigenetic changes in cancers come from Hnisz [2018*], who discusses regulation and dysregulation of chromosome structure, and Helin and Minucci [2017*], pointing to the role of chromatin-associated proteins.

Autism spectrum disorders is a group of complex brain-based neurodevelopmental disorders, characterized by impairment in social and communication interactions, patterns of stereotypic rigid behavior, restricted interests, and unusual sensory processing with onset in early childhood (Svendsen, 2014). However, the molecular basis underlying most of the different cases of autism spectrum disorders are not fully understood [Tremblay & Jiang, 2019*]. The authors address twin studies, showing that autism spectrum disorders are partly inherited but that there are also suggestions of epigenetic mechanisms being involved. Studies demonstrate changed DNA methylation patterns in genes coding for proteins and enzymes involved in chromatin modifications in the etiology of (the causes, origins, or reasons behind) autism spectrum disorders. Lyall et al. [2017*] state that there is a growing interest in the gene-by-environment interaction (G×E) perspective on the etiology of autism spectrum disorders, indicating that exposure to environmental factors could change DNA methylation patterns.

The relationship between epigenetics and early adversity and stress and psychiatric disorders such as depression is currently under intense investigations. Doherty and Roth [2018*] describe the link between early adversity and epigenetic regulation of genes, implicating stress response and psychiatric disorders. The authors report on DNA methylation marks due to early adversity that could be traced across the lifespan. Depression is a complex heterogeneous syndrome, resulting from an interplay of biological and external factors [Peña and Nestler, 2018*]. Earlier life experiences, particularly stress related, increase the risk for depression. There has been considerable focus on the role of epigenetics in the pathophysiology of (physiological changes due to) depression during the last decade. The authors describe the roles of the epigenetic mechanisms, DNA methylation,

histone modification, chromatin remodeling, and noncoding RNAs, in depression. In addition, these authors call for more research about the assessment of epigenetic changes in different cell types, as epigenetic changes are known to be specific in different developmental stages, tissues, and regions of the human body. Also, complex neurological diseases like Alzheimer's [Smith and Lunnon, 2018*] and Parkinson's diseases [Soldner and Jaenisch, 2017*] are reported as a result of complex physiological interactions where epigenetic mechanisms are involved.

The period just before and after birth is susceptible to life experiences, which are discussed to program for later onset of obesity [Kappil et al., 2016*]. Although the mechanisms are not fully understood, recently, researchers have begun to realize that epigenetic mechanisms might play a role in this developmental programming. Studies include the roles of parental obesity, diet, nutritional supplementation, intrauterine growth restriction, and the effects of environmental pollutants. One way to describe the link between obesity and epigenetic processes is by "obesogens," environmental chemicals, which might promote obesity by acting on different cell processes, potentially epigenetic ones [Heindel and Blumberg, 2019*].

There is one decisive difference between genetic and epigenetic changes; epigenetic changes could be reversed under certain conditions (Ramchandani et al., 1999), contrary to genetic ones, mutations, which are far more stable. This means that a changed epigenetic pattern, found in, e.g., cancers, might be reversed, potentially curing the disease. Epigenetic drugs are agents used in epigenetics therapeutics. Ahuja et al. [2016*] and Bennett and Licht [2018*] give examples of epigenetic dysregulation in cancers and summarize the development of epigenetic therapies for cancers. Duncan and Campbell [2018*] present an overview of different epigenetic modulators, the so-called readers, writers, and erasers, and review their current use in clinical investigations.

3.4 Category 4: Epigenetics as a Dynamic Process — Pollution

The search for documents in the category 4, *Epigenetics as a Dynamic Process — Pollution*, led to 21 documents (Table 3). The exemplar studies are all from the Web of Science database. The first is an overview of environmental contaminants' influence on cellular processes through epigenetic mechanisms. Thereafter, different kinds of contaminants, which might be involved in epigenetic processes, are presented, followed by documents speculating about pollutants being coupled to autism spectrum disorders and obesity.

The overview is presented by Martin and Fry [2018*], who describe the effects of environmental exposures of contaminants on DNA methylation. DNA methylation is one of the epigenetics mechanisms that is most studied in relation to environmental exposures. The overview contains studies on air pollution, tobacco smoke, and persistent organic pollutants among other contaminants. It also addresses gaps in the literature, for example, our lack of knowledge about consequences of mixtures of pollutants. Mechanisms of metal-induced cancers, focusing on the five most prevalent carcinogenic metals, arsenic, nickel, cadmium, chromium, and beryllium, is reported by Chen et al. [2019*]. The authors implicate that epigenetic mechanisms might take part in cellular processes leading to cancers, thus providing valuable insights for new therapeutic treatments.

Environmental pollutants like certain chemicals are discussed as being potential risk factors for the etiology of autism spectrum disorders [Lyll et al., 2017*]. Certain environmental chemicals, which cross the placenta and the blood–brain barriers and accumulate in the brain, could interfere with the normal neurodevelopment in the fetus. The authors focus

on air pollution and endocrine-disrupting chemicals, the two areas where most studies have been performed during the last decade. Furthermore, exposures to environmental pollutants such as tobacco, alcohol, or organic pollutants during development in utero have been shown to impact the DNA methylation of offspring [Tremblay and Jiang, 2019*].

Environmental pollutants are also discussed as being potential risk factors for obesity [Ford et al., 2017*; Heindal and Blumberg, 2019*]. As described above, Heindal and Blumberg [2019*] present the term “obesogenes,” environmental chemicals, which might promote obesity besides the more common way of looking at obesity, the imbalance between caloric intake and energy expenditure. Among the “obesogenes,” the authors highlight endocrine-disrupting chemicals, which would interfere with the normal hormonal regulation of appetite and satiety, implicating that epigenetic mechanisms might be involved. Ford et al. [2017*] report that the organochloride insecticide DDT is still used in many countries for malaria protection. Organochloride insecticides are considered as being endocrine-disrupting chemicals, effecting the development of obesity through, among others, epigenetic mechanisms.

3.5 Category 5: Epigenetic Mechanisms

Category 5, *Epigenetic Mechanisms*, resulted in the highest number of documents for all categories, 58 (Table 3). The following four exemplar studies represent this category. First, epigenetics is positioned in the genomic field; second, the freely available Ensembl Genome Browser is introduced. Thereafter, the main epigenetic mechanisms are presented plus the so-called writers, readers, and erasers. Two of the exemplar studies are from the Web of Science database and two from the Scopus database.

A broad introduction to the genome and epigenome biology fields is given by Youssef et al. [2019*]. This book chapter presents an overview of genomes in a diversity of cell types: viruses, bacteria, archaea, and eukaryotes. The genome structure and organization are described as genomic storage and processing of information. Epigenetics' role in gene expression is explicitly pronounced, exemplified by DNA methylation and histone modifications. Due to the rapid development in molecular biology research, the authors argue for a revision of the fundamental definition of the genome, pointing to a more dynamic view. Another approach to the genome and epigenome fields is given by Newman et al. [2018*], who introduce the Ensembl Genome Browser, where freely available genomic, including epigenomic, data can be accessed for different purposes within eukaryotic genetics, genomics, and molecular biology. The document contains hands-on description of how to navigate in the browser.

A comprehensive overview of the major epigenetic mechanisms is presented by Peña and Nestler [2018*]. The most and best studied mechanism is DNA methylation, where the methyl groups are attached to cytosine bases on the DNA molecule. The methyl groups are not randomly placed, but they are often clustered within or around promoters. Methylation of the DNA molecule often represses gene expression and is regarded as a relatively stable epigenetic mechanism. In contrast, epigenetic modifications of histone proteins are considered more dynamic. Histones are proteins around which the DNA molecule is wired. Depending on the particular histone modification used, genes are expressed or depressed because of how available the DNA is in the DNA-histone protein complex of interest. The third presented epigenetic mechanism is transcriptional regulation, exerted by noncoding RNAs. The understanding of the

role of noncoding RNAs as an epigenetic mechanism is just in its infancy. A fourth epigenetic mechanism is the three-dimensional organization of the chromatin, where, e.g., loop formations could make genes more or less accessible. A deeper analysis of chemical modifications of DNA bases is given by Hong et al. [2016*], who enlarge the description to the so-called writers, readers, and erasers of the modified bases, presented in a structural synopsis.

3.6 Category 6: Epigenetics as a Metaphor

Only seven documents, all from the Web of Science database, were found using metaphorical explanations for the overarching role of epigenetics (Table 3). Three of these were chosen as exemplar studies. Ahuja et al. [2016*] talk about epigenetics as “software” and express that “epigenetic modulation acts as software that regulates the packaging of DNA to guide potential for gene expression patterns” (p. 74). The authors compare with DNA, which is “the hard drive that contains the information to guide every cellular function” (p. 74). Pflueger et al. [2019*] regard epigenetics as a “regulatory layer of the genome” (p. 813). Both Ahuja et al. [2016*] and Riera et al. [2016*] use the metaphor of an “epigenetic landscape” and an “epigenomic landscape” to describe the role of epigenetics in gene expression patterns. There is also a formulation of “a new conserved layer of epigenetic regulation,” regarding the less studied methylation of the base adenine in the DNA compared to the more studied cytosine [O’Brown and Greer, 2016*].

3.7 Category 7: Epigenetic Inheritance

Fifteen documents were found for category 7, *Epigenetic Inheritance* (Table 3), of which three were selected as exemplar studies. The first two are from the Web of Science database and the third from the Scopus database. None of the 15 documents provide any proofs of epigenetic inheritance in humans.

Li and Casanueva [2016*] present an overview of the status of our knowledge about epigenetic inheritance. The important distinction between intergenerational and transgenerational inheritance is explained, which decides if epigenetic mechanisms pass through the germ line or not, being of great principle importance. Intergenerational inheritance occurs when environmental factors act directly on somatic cells in a fetus or on its germ cells, which are induced very early during fetus’ development. This means that epigenetic marks are not inherited through meiosis. On the other hand, transgenerational inheritance means inheritance through meiosis in the germ line. We could not take for granted that this has been achieved until epigenetic marks have passed on to the fourth generation (women) or the third (men), exemplified by the inheritance of epigenetic marks from a grandmother’s mother or a grandfather, respectively. The different numbers of generations for women and men depend on different sex strategies for the formation of germ cells. The authors describe studies from different animal groups, including mammals. According to these authors, there is no proof that epigenetic mechanisms are involved in transgenerational inheritance of acquired characteristics in humans.

Another molecular perspective, discussing possible participation of epigenetic mechanisms in inheritance, comes from Heindel and Blumberg [2019*]. The authors highlight two major arguments raised against the concept of epigenetic transgenerational inheritance. First, transgenerational inheritance postulates that heritable information could cross

the Weismann barrier, moving information from somatic to germ cells in the germ line. Second, the genome-wide erasing of epigenetic programmed somatic cells before these enter the germline to form germ cells is argued as being an obstacle. However, Heindel and Blumberg [2019*] report that both arguments are discussed in the light of new studies, violating the Weismann barrier, and if some information in epigenetic programmed cells could escape the genome-wide erasing before cells enter the germ line. Also, Youssef et al. [2019*] discuss the possibility of epigenetic inheritance, without referring to which of the epigenetic mechanism(s) are involved. To summarize, no epigenetic mechanism for possible transgenerational inheritance in humans is reported.

4 Discussion

The aim of this review is to offer a broad overview of epigenetics for biology teachers and other non-experts and to be a model for how to construct a review in a rapidly developing science field. To structure and elucidate this aim, three guiding statements were formulated. The first and second guiding statements are debated in the light of the exemplar studies from the seven categories. The first, *To find documents that increase the understanding of how epigenetics contribute with new knowledge and perspectives in the social sciences*, is best described by the exemplar studies found in the four categories: 1, *Epigenetics and Nature of Science*; 2, *Epigenetics Connecting Nature with Nurture*; 3, *Epigenetics as a Dynamic Process — Medicine*; and 4, *Epigenetics as a Dynamic Process — Pollution*. Correspondingly, the second, *To find documents that describe central features and different aspects of epigenetics to facilitate the understanding of the nature of epigenetics*, is best described by the exemplar studies found in the three categories: 5, *Epigenetic Mechanisms*; 6, *Epigenetics as a Metaphor*; and 7, *Epigenetic Inheritance*. The exemplar studies are discussed in the light of the frontline research of today, both possibilities and critical perspectives, when applicable. The third guiding statement, *To be a model for how a review in a rapidly developing science field could be designed*, resulted in the development of a theoretical framework for construction of reviews. It is discussed in relation to the model's search strategies, criteria, and analysis and reports experiences from the elaboration of the strategy.

4.1 The First Guiding Statement

4.1.1 Category 1: Epigenetics and Nature of Science

Three exemplar studies, well characterizing category 1, *Epigenetics and Nature of Science*, were found in the ERIC database. These focus on the importance of grasping new knowledge on biology, with the aim to implement it into the societal debate and to realize its strength for change. It is encouraging that implications of epigenetics have begun to spread in the society and that researchers with a background within the social sciences have detected its potential. The three exemplar studies focus on the old classical debate about “nature” or “nurture,” coupled with the controversial dispute about biological determinism. Also presented is the sociology education field, where epigenetics is highlighted as offering a tool to disrupt inequality and to counteract discrimination and marginalization, both heavily rejected due to epigenetic scientific molecular reasons. This tool is our understanding of epigenetics' strength, being an exploratory molecular biology model of how

the environment, “nurture,” could influence our genome, “nature.” This in turn focuses the importance of the environment’s, “nurture’s,” role in discussions about counteracting discrimination and marginalization.

The history of biological determinism and its role in the age of genomics is pictured by Graves (2015). The author examines biological determinism’s different expressions from creationism to nowadays molecular understanding of epigenetics and criticizes that biological determinist thinking has not been eliminated despite advances in biological sciences. The same thoughts have been pronounced by Jamieson and Radick (2017). They write, “Twenty-first-century biology rejects genetic determinism, yet an exaggerated view of the power of genes in the making of bodies and minds remains a problem” (p. 1261). Biologists now understand in more detail how epigenetic molecular mechanisms transmit environmental signals to the genome of the cells in our bodies. Thus, environmental signals contribute to decisions about which genes are expressed and thus what happens in our cells and consequently in our whole bodies. Environmental signals entering the body are of a great range of characters, emanating from, for example, stressful situations (Cao-Lei et al., 2016; Li et al., 2020; Xu et al., 2020), food and drink (De Fabiani et al., 2010; Landecker, 2011; Silva et al., 2019), and physical activity (Hall et al., 2020; Lindholm et al., 2014; Seaborne et al., 2018). This insight has great consequences; with the new knowledge of epigenetics, we could claim our ability to control and steer our lives to a higher degree than thought before. To summarize, research shows that we are not condemned to be ruled only by our genes, as stated by biological determinism. This is why Stetsenko [2017*, 2018*] so resolutely dispels biological determinism.

There have only been a few texts about epigenetics’ role in education, especially in the sociology of education. One of these texts is by Pickersgill (2020), who highlights the variety of dialogues emerging at the interface of epigenetics and education (p. 74) and advocates the need for reciprocal exchange between education researchers and biologists, who address educational issues (p. 72). Another text is by Bueno (2019), expressing that educational professionals should enhance their knowledge about genetics, epigenetics, and neuroscience to understand biological origins of differences in mental capabilities (p. 1), empowering them with the possibility to adopt more respectful and flexible educational practices. These two authors’ statements support the arguments in the exemplar studies, as both Stetsenko [2017*, 2018*] and Youdell [2016*] point to the strength of the epigenetic model of explanation, where environmental conditions are awarded more significance. They argue that with biological determinism dispelled, there will be more focus on all individuals’ unlimited potentials, hopefully leading to social justice and equity, counteracting discrimination and marginalization.

Contrary to the few studies of epigenetics discussed in sociology of education, there are quite a lot suggesting that epigenetic processes are part of cell processes during learning (e.g., Colciago et al., 2015; Collins et al., 2019; Kim & Kaang, 2017; Leighton et al., 2018). Of special importance for learning are two regions of the brain: the hippocampus, critical for memory consolidation (Day & Sweatt, 2010), and the cortex, important for long-term memory storage (Miller et al., 2010). It has been suggested that epigenetic mechanisms take part in both these cellular processes. There is an emerging understanding of epigenetic processes taking part in cellular processes also during stress situations and exercise. Essex et al. (2013) report correlations between DNA methylation patterns from 15-year-old children and their parents’ reports of stress during the children’s infancy and preschool periods. Rönn et al. (2013) show changed epigenetic patterns for 7,600 genes after a 6-month exercise intervention

in a group of middle-aged men. As the same epigenetic mechanisms are seen during such different situations as learning, stressful conditions, and physical exercise, we now have a new tool to understand the connections between these. In the article *Epigenetics and learning*, Mc Ewen (2015) addresses these questions in more detail. This might be of great value when discussing circumstances for learning in the context of sociology of education.

4.1.2 Categories 2, *Epigenetics Connecting Nature with Nurture*; 3, *Epigenetics as a Dynamic Process — Medicine*; 4, and *Epigenetics as a Dynamic Process — Pollution*

Many of the documents found in the database searches concerning categories 2, *Epigenetics Connecting Nature with Nurture*; 3, *Epigenetics as a Dynamic Process — Medicine*; and 4, *Epigenetics as a Dynamic Process — Pollution* raised societal aspects on health, diseases, and disorders. This shows that the new knowledge of epigenetics is practiced on vital questions for humanity. Epigenetics was introduced early on into the healthcare field to give new perspectives on how to better understand and bring solutions to different diseases and disorders. To test new knowledge and add novel aspects on old problems could be a successful way to move forward. The development of epigenetic drugs, with the aim of reversing changed epigenetic patterns found in diseases and disorders, represents an innovative idea of treatment, based on epigenetics and its role in diseases and disorders (Laufer & Singh, 2015; Teijido & Cacabelos, 2018).

Exemplar studies from category 2, *Epigenetics Connecting Nature with Nurture*, point to the novel bridge between “nature” and “nurture,” made possible by the new knowledge of epigenetics. Epigenetic mechanisms’ importance during human development could be expressed as representing the plasticity of development, placing epigenetic processes at the center between genes and the environment [Law and Holland, 2019*]. In focus is the fetus and the early childhood development, seen as an especially sensitive period during which epigenetic processes are thought to be involved in forming the individual [Carroll, 2019*; Lester et al., 2016*; Sciaraffa et al., 2018*]. Adversity conditions during this period could bring health problems later in life [Peña and Nestler, 2018*; Sciaraffa et al., 2018*]. Examples of these are stress and psychiatric disorders like depression [Doherty and Roth, 2018*]. These authors also report on changed DNA methylation marks, due to early adversity, being detected across the lifespan.

The line of arguments discussed above is supported by classical studies of one of the tragic famine periods during the Second World War, the so-called Dutch Hunger Winter, due to a German blockade of the northwest of the Netherlands between November 1944 and May 1945 (Lumey et al., 2007; Persson & Persson, 2019). Food rations were decided on a weekly basis, depending on actual circumstances, and ranged between 500 to barely 1,000 kcal per day and person, including pregnant women. The consequences for individuals who were fetuses during this period have been investigated on numerous occasions from the 1970s to today. Studies on individuals in their 50 s to 60 s show effects such as an increased risk of being stricken with coronary artery disease (Painter et al., 2006), diabetes (Lumey et al., 2011), and schizophrenia (Brown & Susser, 2008). Heijmans et al. (2008) also report on the consequences of the Dutch Hunger Winter. The authors show that DNA methylation of the *IGF2* (insulin-like growth factor) gene was less for exposed individuals compared to unexposed siblings of the same sex, *IGF2* being a key factor in human growth and development. This reveals the importance of proper conditions for a normal fetus

development, and the exemplar studies from category 2, *Epigenetics Connecting Nature with Nurture*, focus on a crucial area for the formation of an individual, well described in the research literature.

Exemplar studies from categories 3, *Epigenetics as a Dynamic Process — Medicine*, and 4, *Epigenetics as a Dynamic Process — Pollution* discuss epigenetics in relation to cancers and the potential of new therapeutic treatments, autism spectrum disorders, obesity, and the role of early adversity for stress and psychiatric disorders later in life.

The exemplar study of Skvortsova et al. [2019*] describes widespread DNA methylation changes in the genome of cancer cells compared to normal ones. This is in line with the current research showing the involvement of epigenetics in cancers. Numerous reviews of this theme have been published during the last decade. Dawson and Kouzarides (2012) present the basic principles of epigenetic pathways and highlight the suggestion that misregulation of these can cause cancers. Biswas and Rao (2017) present an overview of fundamentals of epigenetics in cancers, where the last 15 years, according to the authors, have given exceptional new information, showing the involvement of different epigenetic mechanisms in cancer proliferation. Kanwal et al. (2015) pronounce that epigenetic and genetic alterations contribute to cancer initiation and progression (p. 3). The authors describe how genetic changes are preceded by epigenetic modifications in the early phases of cancers.

The insight of epigenetic mechanisms being part of cancers has led to new ideas in pharmaceutical research, targeting anti-cancer drugs, with the aim to change epigenetic patterns in cancers. Already 20 years ago, Ramchandani et al. (1999) showed that DNA methylation is a reversible biochemical process, similar to other physiological biochemical processes. Below is an actual description of the current status of research about epigenetic drugs in cancer treatments. Ganesan et al. (2019) depict the timeline from the epigenetic drug discovery to what is needed for the implementation of epigenetic drugs into clinical treatment of today. The authors argue that until today, only a few drugs have been clinically introduced, and they call for cooperation between chemists, biologists, and clinicians to optimize the development of epigenetic drugs. Verma and Kumar (2018) report that drugs can reverse some epigenetic changes found in cancers; however, only a few epigenetic drugs work alone. Combinations of different epigenetic drugs seem to be needed in cancer treatments. These authors also report on novel epigenetic drugs directed at chromatin and associated components, due to recent advances in chromatin research. Liu et al. (2019b) discuss epigenetic drugs to treat solid cancers and state that there are both a potential and limitations. These articles provide a glimpse of the promises, but also the obstacles, using epigenetic drugs in the treatment of cancers. The exemplar studies by Ahuja et al. [2016*], Bennet and Licht [2018*], and Duncan and Campbell [2018*] bring to the forefront the question of epigenetic drugs and are thus in line with current research. Even though positive results have been confirmed, research about epigenetic drugs is in its infancy. To summarize, the above discussion shows that the exemplar studies are well in line with current research about cancers and epigenetic drugs.

Besides cancers, the etiology of other diseases and disorders is discussed in the light of epigenetics. Three exemplar studies [Drmic et al., 2018*; Lyall et al., 2017*; Trembley and Jiang, 2019*] address autism spectrum disorders in relation to the environment's influence on its etiology, thus coupling epigenetic processes to it. Lyall et al. [2017*] focus on the growing interest in the gene-by-environment interaction (G×E) perspective, highlighting environmental factors that might change the DNA methylation patterns. These environmental factors could be certain environmental chemicals, crossing the placenta and the blood–brain barriers during fetus development. According to twin studies, Trembley and Jiang [2019*] claim that autism spectrum disorders is only partly inherited, thus opening

the option for environmental factors being involved in its etiology. Drmic et al. [2018*] bring new ideas into the debate by viewing autism spectrum disorders in the interpretation of Life Course Research Agenda, focusing on health instead of disease. Put together, due to our knowledge of epigenetic processes, these authors argue for a new way of looking at autism spectrum disorders, focusing more on the environment's role.

Research supports the view that autism spectrum disorders could not be explained by genetic inheritance alone. Ronald and Hoekstra (2011) reviewed twin studies for autism spectrum disorders from 1977 to 2010. Monozygotic twins share the same genotype, age, sex, and maternal environment in the uterus as well as exposure to many shared environmental factors, while dizygotic twins differ in genotype and could have a different sex. Various studies in the review showed a considerably higher presence of the same characteristics in both individuals in a twin pair among monozygotic compared to dizygotic twins. This supports a heritable pattern. Even though monozygotic twins show a higher presence of the same characteristics in both individuals, they do not display 100% similar characteristics despite having identical genes. This indicates non-genetic factors; thus, epigenetic mechanisms have been focused on (Grayson & Guidotti, 2016; Sivanesan et al., 2017). Forsberg et al. (2018) offer an overview of the current knowledge of epigenetic changes in autism spectrum disorders and present studies describing candidate genes with different DNA methylation patterns in healthy and affected individuals. To conclude, the exemplar studies are well in line with the incipient perspective of environmental factors' influence on the etiology of autism spectrum disorders discussed in research.

Three exemplar studies [Ford et al., 2017*; Heindel and Blumberg, 2019*; Kappil et al., 2016*] address the problematic situation about the worldwide increasing public health disease obesity. These authors point to new ways of confronting this disorder by discussing if epigenetic factors might be involved, although the mechanisms are not fully understood. As highlighted before, the fetus and the early childhood during which the individual is formed are in center [Kappil et al., 2016*]. The insecticide DDT, considered as an "obesogene," has been shown to promote obesity in an animal model (Skinner et al., 2013). Furthermore, exposure to chronic stress can alter the adipose tissue metabolism, contributing to dysfunction of appetite regulation and adipocyte physiology, leading to obesity (Xiao et al., 2020). A systematic review of van Dijk et al. (2015) shows that due to technological advances in epigenome profiling, a number of studies have investigated the role of DNA methylation in obesity. Potential epigenetic markers for obesity were identified, where a number were found at birth and associated with obesity later in life. This finding may open possibilities for targeting prevention programs. The obese state is also related to metabolic changes, presenting a risk for developing diabetes through epigenetic mechanisms in metabolism regulation (Ling & Rönn, 2019; Rosen et al., 2018). To summarize, new research supports the idea from the three exemplar studies of introducing a new perspective, the involvement of epigenetic processes, on the etiology of obesity.

Two exemplar studies, Doherty and Roth [2018*] and Peña and Nestler [2018*], describe the supposed connection between early adversity, on the one hand, and stress response and psychiatric disorders later in life, on the other. Epigenetic mechanisms are thought to be part of this assumed connection. This is in line with the plasticity of the individual development discussed above in the section about "nature" and "nurture" and shows the importance of offering care and good conditions to children and their mothers, as pointed out by Halfon et al. [2018*]. In research, there is an emerging understanding of how stressful situations could have extended consequences through epigenetic processes. In a review, Cao-Lei et al. (2016) have summarized the association between the fetal environment and epigenetic change, focusing on DNA methylation. The conclusion was that there

is an incipient understanding of the critical role of epigenetics in fetal programming due to environmental factors. Li et al. (2020) report on childhood adversities, which through epigenetic processes might be an explanation for depression in adulthood. The same ideas are shared by Xu et al. (2020), who address that early life stress could induce mental illness.

The severe neuropsychiatric disorder schizophrenia is also discussed in terms of epigenetic processes being part of its etiology (Birnbaum & Weinberger, 2017). The authors point to genetic and epigenetic risk factors being present during early brain development, suggesting these being more important than risk factors occurring later during adolescence and early adulthood, when the diagnosis is often made. Another perspective comes from an animal model system, described in the classical study by Weaver et al. (2004), showing lifelong stress symptoms due to neglect of care early in life. Although not directly applicable to humans, the study shows that there are cell physiology systems reacting to stress conditions, transforming them through epigenetic mechanisms to stress symptoms, observed during the whole life. To conclude, there is an increasing understanding of the role of epigenetic processes for mental health, where conditions during the early life are significant for well-being during the rest of the life.

4.2 The Second Guiding Statement

The second guiding statement, *To find documents that describe central features and different aspects of epigenetics to facilitate the understanding of the nature of epigenetics*, is of a natural science character. As expected, almost all of the documents were found in the Web of Science database.

4.2.1 Category 5: Epigenetic Mechanisms

The large number of documents, 58, found in category 5, *Epigenetic Mechanisms* (Table 3), shows that epigenetic mechanisms are of central importance for the research field of epigenetics. The most studied mechanisms are DNA methylation, histone modifications, non-coding RNAs, and chromatin structure, described in one of the exemplar studies, Peña and Nestler [2018*]. As research about epigenetic mechanisms is in the core of the epigenetic research field and develops very rapidly, new molecular mechanisms are suggested to be added to the list. The methylation of RNA is one of these (Nilsson et al., 2018). An overview of the classical epigenetic mechanisms is found in the study by Allis et al. (2015).

4.2.2 Category 6: Epigenetics as a Metaphor

The above shows that research about epigenetic mechanisms is very dynamic and that our view of how genes are regulated develops all the time. Contrary to category 5, *Epigenetic Mechanisms*, category 6, *Epigenetics as a Metaphor*, included only a few documents (Table 3). One explanation for the low number could be that scientists use a defined professional scientific language and therefore seldom talk in metaphorical terms in scientific communication.

4.2.3 Category 7: Epigenetic Inheritance

Category 7, *Epigenetic Inheritance*, included 15 documents, most of them from the Web of Science database (Table 3). Compared to the number of documents in category 5,

Epigenetic Mechanisms, 15 documents constitute quite a small group and could be interpreted as indicating a low prioritized research field within epigenetics. However, the issue is of great principal importance. Among biologists, it has long been considered that acquired characteristics do not pass on to new generations (Landman, 1991) as postulated by Lamarck; see Por (2006) for a description of Lamarck's ideas. Yet, insights into epigenetic processes have opened up for a discussion about the possibility of acquired characteristics being inherited. A range of observations has confirmed this insight, where it appears that acquired characteristics might be inherited across generations. To exemplify this, the adult children of parents exposed to stressful events during the Holocaust were more likely diagnosed with a psychiatric disease compared to a control group (Yehuda et al., 2014). It has been proposed that these acquired characteristics might be inherited, but no epigenetic mechanism in humans responsible for the inheritance has yet been presented (Morgan et al., 2019). As expected, none of the exemplar studies of category 7, *Epigenetic Inheritance* [Heindel and Blumberg, 2019*; Li and Casanueva, 2016*; Youssef et al., 2019*], presents any epigenetic mechanism for inheritance of acquired characteristics in humans.

Nevertheless, the issue is thrilling. If inheritance of acquired characteristics proves to be true, it can have great consequences. All subject fields encompassing human physiology and behavior, e.g., medicine, psychology, and sociology, will handle new exciting perspectives. This would, for example, mean that the imprint of ancestors' environmental conditions, e.g., diseases, could be inherited across generations and be traced in the characteristics of today's humans. The scenario is gripping and also debated in social media, e.g., in the YouTube video "Epigenetic inheritance" (Mitchell, 2017). However, as discussed above, there are yet no scientific proofs of transgenerational inheritance through epigenetic mechanisms of acquired characteristics in humans. This shows the importance of mediating correct information to the citizen. Teachers are an important group to spread truthful information regarding biology. This review is an example of how trustworthy biology facts are delivered to biology teachers and other non-experts, to counteract false information flourishing in the society.

4.3 The Third Guiding Statement

To construct a model for how a review in a rapidly developing science field could be designed, new strategies had to be explored and new ideas tested. This review included elaboration and evaluation of quite a lot of unique moments, a work that is carefully described and discussed. The text emanates in the development of a theoretical framework with suggestions of how to construct a model for reviews in current advancing fields of science. In addition, problems associated with the development of the theoretical framework are discussed. It should also be mentioned that there is a scarcity of critical voices about epigenetics in the review, discussed to be due to the search terms used, based on a newly performed Delphi study with 35 epigenetics experts. A good summary of what could be interpreted as critics against unconditional adopting of epigenetics is written by Müller et al. (2017), "The biosocial genome? Interdisciplinary perspectives on environmental epigenetics, health and society."

4.3.1 Databases

Searches were performed in three databases of good repute, covering different areas of interest for this review, a procedure suggested by Gough et al. (2017). Ninety-four

documents were collected from the databases after excluding those that did not fit the aim of the study (Table 4), showing that there were an adequate number of documents for the construction of a review. The distribution of documents between the categories was uneven; however, all categories contained enough documents for the construction of the review (Table 3). There was a considerable difference in the number of documents found between the databases, noticeably being highest for the Web of Science database. It is not a problem per se that different databases deliver varying amounts of documents as long as relevant ones from the whole area of interest are selected by the databases. The databases of Web of Science, Scopus, and ERIC focus on different areas of natural science, social sciences, and education, respectively. It is logical that most documents were found in a database focusing on natural science, as this review highlights a new scientific field, epigenetics. The lower number of documents found in Scopus and ERIC databases is probably due to the time-lag for new findings to be embraced, interpreted, and implemented into the societal debate, e.g., discussed by Müller et al. (2017), and in education (Desha et al., 2009; Jamieson & Radick, 2017).

4.3.2 Search Period

The search strategy should ensure that enough relevant documents from all fields are captured during the searches. In this review, an increase of the search period from 4 years to, for example, 10 years ought to have collected more documents from Scopus and ERIC. Since implementation of new research findings in society and education is time-lagged natural science, it would not be critical if the search period for databases focusing social sciences and education extends backwards. More thoughts and reflections ought to be gathered in this way. On the contrary, to prolong the search period for a database focusing on natural science, in this review, the Web of Science database will deliver documents that are not up-to-date due to the rapid development of the scientific field. Further, this could result in an unreasonably high total number of documents, leading to difficulties in the forthcoming analysis process. The task when designing the model is to find an optimal search period, enclosing enough of the relevant documents without making it an unreasonably high total amount, according to strategies in the theoretical framework of systematic reviews (Gough et al., 2017).

4.3.3 Document Types

The choice of document types is critical in a review designed for non-experts. The documents have to be written in a moderately advanced level, summarizing the research field and its implications. During construction of the review, quite a lot of different document types from the databases were checked: books, book chapters, conference papers, conference reviews, editorials, letters, meeting abstracts, meeting summaries, notes, proceeding papers, reviews, and short surveys. These have distinct advantages and disadvantages. It might be presumed that the document type “reviews” was optimal for non-experts; however, even such summarizing documents turned out to be too complex for non-experts. The more even, less advanced, level of texts in books and book chapters turned out to be optimal. There might be some suspicion that books and book chapters do not hold enough quality. On that account, the process contained a requirement that all documents had to be peer-reviewed and published by a well-renowned publisher.

4.3.4 Open Access

The goal of writing a review is to offer readers a brief introduction to a field and to give inspiration to read the suggested documents, i.e., the exemplar studies. Subsequently, it should be easy for the readers to find the documents. Open access gives readers the possibility to read documents without purchasing the document; this is the best choice for a strategy addressing non-experts. Most of the documents in the three chosen databases are not delivered as open access; however, for this study, the chosen search criteria allowed for a sufficient amount of open access documents to be collected for the construction of this review. For constructing other reviews, search criteria have to be tested to encompass this prerequisite.

All 32 exemplar studies, except for three, could easily be found on the Internet (Table 4 provides information about the links, etc. for each exemplar study). However, three turned out to be open access in a slightly different sense, as these were open access through a university library system. In several countries, it is possible for the citizens to have the same access to documents at university libraries as university staffs, being a realistic option for many non-experts. The reason that the three documents showed up not to be open access in the general sense could be found in the databases' tagging of documents sometimes showing ambiguousness. This problem should be taken into account when constructing reviews. As the three exemplar studies were regarded as key documents for this review, they were retained as exemplar studies (marked "University library" in Table 4).

4.3.5 Search Terms

One of the moments in collecting documents for the different categories was to decide upon relevant search terms, a process following the strategy described in the framework of systematic reviews (Gough et al., 2017). In this review, search terms were found in citations and descriptions of how experts regarded epigenetics in a Delphi study (Gericke & Mc Ewen, submitted) and in scientific articles describing different areas of epigenetics corresponding to the seven chosen categories. The framework of systematic reviews recommends consultations with some experts and reading of scientific articles to find relevant search terms (Gough et al., 2017). The process of finding relevant search terms in this review is in accordance with this recommendation, albeit even more elaborated, as the search terms were based on citations and descriptions of how 35 acknowledged experts regarded epigenetics, besides finding relevant search terms in scientific articles. However, few critical studies of epigenetics were captured in the searches due to the method of choosing search terms, which relied on a newly performed Delphi study with 35 experts in epigenetics.

4.3.6 Subject Content Knowledge

To construct a review of a rapidly developing science field requires great knowledge in the particular subject. In this review, the author holds a Ph.D. with a focus on cell physiology; furthermore, she has been engaged in the study of epigenetics for at least a decade and is an Associate Professor in science education. Further, to check that the exemplar studies well represented the seven categories, an expert in epigenetics from Karolinska Institutet, Sweden, confirmed the choices of exemplar studies.

4.3.7 Relevant Documents

To address the situation of eliminating documents having no relevance for the study, e.g., if documents dealt with plants, it was necessary to use a reference documentation system; in this study, EndNote was used. Doublets, bibliographies, documents concerning other organisms besides humans, and documents only partly being open access were excluded. Other review studies will determine which documents ought to be excluded or included for that particular study. Another sorting procedure was to choose exemplar studies to represent the category of interest. This stage required great subject content knowledge of epigenetics and was confirmed by an expert in epigenetics, Karolinska Institutet, Sweden, who verified that the choices of exemplar studies well represented the categories. One idea for the construction of other reviews could be to work in teams, comprising scientists and science educators.

4.3.8 Suggestion on How to Design a Review

To summarize, this review could be a model for how to design a review for non-experts in a rapidly developing science field. The following ought to be taken into consideration: (1) choose at least three databases of good repute, covering different aspects of the field. (2) Search periods ought to be recent, aiming at an optimal length, including enough relevant documents without it being an unreasonably high number of documents leading to difficulties in the forthcoming analyses process. (3) Document types books and book chapters turned out to be optimal, but in other reviews focusing on other fields, other document types might be optimal. (4) The documents have to be peer-reviewed to guarantee the quality of the documents. (5) They should be published as open access, in the sense that they ought to be accessible to citizens. (6) The documents should be published by a well-renowned publisher. (7) It is recommended to consult experts in the research field of interest to find relevant search terms besides those found in scientific articles. (8) Great knowledge on the subject matter is required; one possibility to receive the necessary level of knowledge is to work in teams comprising scientists and science educators. (9) A reference documentation system is necessary to structure how documents will be handled. (10) The process of choosing exemplar studies to illustrate different categories is a demanding task which requires expertise knowledge on the subject.

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Declarations

Conflict of Interest The author declares no conflict of interest.

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