



Review Article

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Epigenetics and its essence in understanding human growth, development and disease

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Abstract

Epigenetics is a scientific discipline encompassing the genetic and non-genetic related perspectives of heritable phenotypic modifications of whose aetiologies include behavioural, anthropogenic, environmental, metabolic and spatiotemporal variables. Behavioral epigenetics examines how epigenetics shapes animal and human behaviour to explicate how nurture moulds nature; nature prefers to biological heredity and nurture prefers to occurrences in the environment **and** hereditary during the lifespan of all individuals. Behavioural epigenetics features how experiences and the environment produce individual disparities in behaviour, cognition, personality, and mental health influence gene expression. Epigenetic gene regulation relates to modification of DNA sequence and histones as well as DNA methylation. These epigenetic alterations effect the growth of neurons in the developing brain and functional modification of neurons in the developed brain, with resultant significant alterations in neuron morphology. Epigenetic changes occur in the developing fetus and throughout the lifespan of an individual, with alterations in individual traits and transgenerational inheritance. Epigenetics is associated with heritable changes in gene actions and these are not due to DNA sequence alterations. Epigenetics may be termed sustained, long-run changes in the transcription veracity of a heritable or non-heritable cell. DNA methylation and histone alteration are mechanisms which modify gene expression without changing the underlying DNA sequence. Gene expression is driven by repressor protein actions which bind to DNA silencer regions. DNA methylation turns a gene "off" culminating in genetic information impairment to be read from DNA, but extricating the methyl tag can turn "on" the gene. Histone alteration defines the packaging of DNA into the chromosomes; and these changes influence gene expression. This review provides the latitude to examine the extant information in the universal characterizations of epigenetic formulations, such as ageing, susceptibility to pollutant and irritant exposure.

Keywords: diabetes, obesity, SARS-CoV-2/COVID-19, epigenesis, genome.

I INTRODUCTION

Epigenetics is concerned with the way the environment and certain variables can manipulate the trajectory of gene expression. Although, epigenetic modifications do not result in the alteration of the sequence of the genetic code of an individual, they may be pertinent actors with implications in human growth and development. Epigenetics encompasses the interaction of behaviours and environment culminating in changes which influence gene activity. In contradistinction to genetic modifications. Epigenetic modifications are reversible; and do not provoke alterations in the DNA sequence but are capable of interference in reading the DNA sequence. DNA methylation depicts the covalent superimposed methyl group to cytosine in CpG dinucleotides. DNA methylation presents as a veritable epigenetic modification; and it governs gene expression by changing chromosome structure, DNA conformation and stability as well as the functional trajectory between DNA and protein. DNA methylation regulates gene expression via the conscription of proteins associated with gene expression or by the inhibition of the binding of transcription factor(s) to DNA. Whereas genetic alterations do modify protein formation, it is clear that epigenetic alterations impact on gene expression to have genes "turned on" and "turned off", as appropriate. Thus, genes are not always in functional mode. The resultant impact of environmental and anthropogenic presentations, such as diet and physical activity are liable to induce epigenetic modifications in behaviours and gene-environment interactions [1-4]. DNA methylation constitutes a select epigenetic process applied by cells for the control of gene expression. within the genome. Alterations in gene activity and epigenetic errors can result in varying genetic, metabolic and degenerative disorders which may disparately or in comorbid presentations influence inter alia health, gene activity or expression, protein production and functionality. This entry exemplifies the reading and understanding of epigenetics in relation to inter alia beneficial developmental theories within the human race [3].

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Evaluating Epigenetics

Epigenetics has been recruited into the evaluation of organism-environment or gene-environment interactions with particular reference to the application of genetic information within the lifespan of a person and transgenerational inheritance. Epigenetics is engulfed in the genetic and non-genetic spheres correlated to heritable phenotypic modifications, DNA methylation and regulation of gene expression. These changes are attached to genes, and do not lead to the alteration of the building blocks of the DNA [1-3]. In the genome that constitutes the complete set of cellular DNA, the epigenome regulates gene expression. The genome is established on fertilization, with the code being the same all through the lifespan, other than mutations which result in distinct cells. Epigenetics can influence the timing and magnitude of gene expression, as well as the concomitant phenotype. These epigenetic and external factors can institute slight variations to DNA via metal ion addition, acetyl or methyl group extrication from or addition to DNA or histones which control DNA wrapping and packing. Methyl group attachment ostensibly diminish transcription or suppresses acetyl group attachment to histones turns genes on. These biological genome modifications to the genome are referred to as 'epigenetic factors', as taking place supra to the genome. In essence, cellular DNA provides the code for functional protein production, while the epigenetic factors are switches which "on" and "off" genes [1, 2] as differentiation progresses during growth and development of an embryo with enduring impact on phenotypic presentations. The regulation correlates to specificity and uniqueness of protein production by cells appropriate to its functionality, such that proteins which promote muscle growth and development are not produced in hepatic cells. There are differences or variations in epigenetic modifications between persons, tissues, and disparate cells within the same tissue. Epigenetic modifications can be sustained from one cell to the other during cell division. The environment, such as diet [1-3], pollutant or irritant exposure or vulnerability can impact the epigenome; and in certain instances be inherited within generations or gene-environment interactions [4]. Mechanisms which enact such changes are DNA methylation and histone modification; and as may be implicated or evident in coronavirus infection [5-7]. The principal epigenetic processes involve DNA methylation, histone alterations and non-coding RNA. These mechanisms are established in patterned regulation of tissue-specific gene expression, cell differentiation and imprinting of the genome.

Behavioural aspects or psychobiology of epigenetics

Epigenetics is modifying the universally established linear conception of genome functionality by explicating how environmental and psychological variables regulate genome activity in the absence of alterations in the sequence of DNA. Epigenetic processes which mediate between environmental and psychological factors contribute to conventional and aberrant behavioral development [8].

Experiences during growth and development are capable of imposing in depth and sustained impacts on physical and mental disposition during the lifespan of an individual. The epigenome is dynamically associated with DNA as a layer of information that is distinct from one individual to another; it undergoes changes within diverse ambients and spatiotemporal exposures and influences. The epigenome may be regarded as a "missing moiety" of the aetiologic quagmire in explicating or elucidating initiation, development and progression of psychological or mental disorders correlate to environmental exposures and impacts, in convergence with the genome. Studies are evolving to elucidate the associated mechanisms in the initiation, sustenance, and heritability of epigenetic formulations as inextricably related to learning, memory, emotions and social behaviour in individuals within and without populations. Psychologic or behavioural epigenetics features a paradigmatic modality to understand how gene expression correlates to experiences and the environment with resultant individual

disparities in psychobiological dispositions. Current developments tend to reveal epigenetic perspectives [3] of mental health, issues, challenges and opportunities [9, 10] of epigenetic paradigms in psychology to unravel how nurture shapes nature and vice versa wherein it is controverted that genes are not destined features [8]. The incontrovertible evidence for genetic impacts on psychological traits enacts that humans are inextricably entrapped to their biology by not having any iota or modicum of control of their psyche and behaviour. As a mechanism for the regulation of gene expression, epigenetics has ostensibly enacted the departure from genetic determinism to transcend innate predispositions and modify human existence. The pertinence of the interrelatedness between genes and behaviour must be elucidated regarding the effect of the epigenetic mechanisms following birth and not merely prenatally as conventionally presented. Behavioral epigenetics depicts behavior has durable impacts in the regulation of genome functionality.

Expressing DNA methylation and histones in epigenetic essence

Thus, a universally acknowledged form of epigenetic change is DNA methylation that involves the attachment of the methyl group of one carbon and three hydrogen atoms to DNA building blocks. The occurrence of methyl groups in a gene, results in the gene being turned off or suppressed, leading to non-production of protein. A significant epigenetic feature realizable in the genome of higher eukaryotes is DNA methylation in the C-5 position of the cytosine ring. Depending on the DNA methylation locus, it may function as a suppressive or activation site for gene expression. Thus, DNA methylation is a prime control programme in gene expression modulation within numerous organisms. Gene silencing results from methylation due to DNA methyltransferases which transfer a methyl group from S-adenosyl-L-methionine to the cytosine carbon 5 position [11]. As developmental stages progress, DNA methylation presentation in the genome vary due to regulated compliance between de novo DNA methylation and demethylation. Consequently, a unique DNA formation that drives tissue-specific gene expression is inculcated and acquired by differentiated cells. Inasmuch as, DNA methylation ostensibly poses as a stable epigenetic mark, it is perspicuously fragile, with an intricate complexity in the interaction of epigenome, genome and other pertinent environmental factors during life progression antecedent to delivery/birth. The characteristic of DNA methylation in an individual dynamically varies due to environmental factors during germ cell production, embryogenesis and post-delivery exposure. During development phases, the dissipation of balances in DNA methylation may culminate in imprinting health aberrations, with nonspecified loci to increased susceptibility to diverse disorders. The epigenome uniquely drives lifetime experiences *ab initio in utero* and present future opportunities in the improvisation of clinical applications [12].

Histones are structural proteins present in the cell nucleus. DNA encloses histones with resultant configuration of their forms. Histone modification is due to either the introduction or excision of methyl or acethyl groups, each made up of two carbon, three hydrogen and one oxygen atoms. These chemical groups determine the wrapped fortification of DNA on histones that impacts gene suppression or not. DNA methylation may either inhibit binding of the transcription machinery or formulate a platform appropriate for transcription, as evident in a crosstalk with histone modifiers [12]. Definable errors in the epigenetic process due to modification of the inappropriate gene or neglect to attach a chemical group to a specific gene or histone may culminate in aberrant gene functionality or outright nonfunctionality. Invariably, histone modification is an additional frequent aetiology of epigenetic alteration. Alteration in gene activity, in addition to that engendered via epigenetic errors, constitutes a common aetiology of genetic disorders, with tumors, metabolic and degenerative diseases implicated in epigenetic untoward presentations. Exploration

to explicate and elucidate the interrelatedness between the genome and the chemical moieties which contribute to its modification are being intensified, especially, to unravel the impacts of epigenetic changes and aberrations in ageing, gene functionality, protein production, environment and health [13].

Epigenetics constitutes the reversible heritable mechanisms which result in the absence of any modification of the underlying DNA sequence. Even though, chromosomes in the human genome convey genetic information, the epigenome has the task for the functional utilization and stabilization of that veritable or vital information that correlates the genotype with the phenotype [1-3]. These epigenetic alterations may occur spontaneously or governed by extraneous or innate forces.

The functional and biological essence of epigenetics and ageing

The rate of ageing is invariably governed by evolutionarily conserved genetic pathways, environmental factors and biological mechanisms. Ageing in epigenetics relates to the functional and biological importance of the epigenetic changes which accumulate as ageing progresses, and are critical in tumorigenesis. Paradigmatic instances are extant due to the global dissipation of DNA methylation in ageing and cancer as well as via the promoter hypermethylation of genes with dual functionality in tumor suppression and progeria, such as the Werner syndrome (WRN) and lamin A/C genes [14]. Also sirtuins, a family of NAD-dependent deacetylases act on Lys16 of histone H4 as a link between cellular transformation and life span.

Ageing involves intricately complex multifactorial biological, chemical and physical processes, gene-environment interactions [4] or disparately by genes or environment exhibited by all biota. Spatiotemporally, it is depicted by premature, gradual or accelerated decline in structural- functional perspectives. Organismal aging is significant in human health in correlation to vulnerability and susceptibility to diverse diseases, such as diabetes, metabolic and other endocrine disorders as well as cancer, cardiovascular and neurodegenerative debilities [15]. Conversely, cellular or replicative senescence is a specialized and potential endogenous anticancer mechanism whereby there is irreversible growth obliteration due to response of potential oncogenic stimuli [16]. It is a potential driver in tissue remodelling in embryonic development and in the aftermath of tissue derangement that necessitates proliferation arrest [17]. Cellular senescence shares several similarities as ageing but with contrasting characteristics. Ageing and diabetes result in identical organ and system perturbations which are supported concurrently by molecular processes and cellular senescence. Cellular senescence is basically an ageing mechanism implicated in numerous ageing-related diseases, and is significantly involved in the aetiology of tissue degradation, Senescent cells aggregation occurs during the ageing process: It is not clear how senescence contributes to diabetes pathogenesis [18].

Epigenetic change depicts a critical underlying mechanism in perspicuous impaired cellular activities during ageing and age-related diseases. Patterns of DNA methylation are determined by the de novo DNA methyltransferases DNMTs being DNMT3A and DNMT3B, which are eventually sustained by DNMY1 [11]. Ageing and age-associated aberrations involve unique alterations in 5-methylcytosine concentration with usual characterization of genome-wide hypomethylation and promoter-defined hypermethylation. These modifications in the epigenetic domain reflect potential disease biomarkers and contribute to age-linked disorders. Certain diseases, such as a hereditary type of sensory neuropathy with concomitant dementia are incontrovertibly due to methylomic modifications. Epigenetic information and alterations are reversible since they are determined by enzymes; and thus, epigenetics is a potential target for therapeutic interventions in

contrast to genetic alterations which are irreversible in humans. Drugs which are target-specific for DNMTs included 5-azacytidine for rejuvenation [11]. The repercussions of epigenetic alterations in ageing are modifications of locus access to the genetic material with resultant untoward gene expression, reactivation of transposable elements as well as genomic instability [19]. A transposable element (TE, transposon, or jumping gene) is a DNA nucleic acid sequence in DNA capable of changing its position within a genome, and intermittently creating or reversing mutations and modifying the genetic identity and genome size of the cell. Transposition frequently occurs in the duplication of the same genetic material [20].

These epigenetic progressive alterations to epigenetic information run concurrently with ageing in both dividing and nondividing cells as epigenetic changes have expansive influence in the ageing process, with occurrence at diverse levels, including decreased bulk levels of core histones, modified arrangements of histone posttranslational changes and methylation of DNA, canonical histone substitution with histone variants, and modified noncoding RNA expression in both organismal chronological ageing and replicative or cellular senescence [19]. Certain varieties of epigenetic information may influence the lifespan of the offspring in a transgenerational way [19]. It is suggested that lifespan is more epigenetically predetermined than genetically predetermined. Also, that diet and other environmental factors influence lifespan through epigenetic information alterations; and epigenetic enzyme inhibitors may drive the life span of model organisms. Epigenetics studies tend to postulate that it is not nature versus nurture rather nature plus nurture, enforcing the obliteration of genetic determinism. Irrespective of the epigenome stance, it ostensibly does not translate across generations in essence. Researchers are exploiting the sphere of the epigenome in order to explicate the manner in which lifestyle factors including alcohol, obesity and smoking dictate cancer risk.

Epigenetic clocks are proximate veritable ageing mechanisms than other biomarkers

Epigenetic clocks incorporate a set of CpG loci employing DNA methylation levels to determine the age of an individual. These clocks represent extremely accurate molecular correlate of chronological age in humans. Epigenetic clocks depend on algorithms in calculating biological age, basically on the read-out of the magnitude in which various loci traversing the genome of an individual are bound by methyl groups. An instance of epigenetic alteration. DNA hypomethylation, the decrement in universal DNA methylation is probably due to methyl- deficiency from diverse environmental factors which have been postulated as a molecular marker in cancer and other biological processes [21]. The determination of the 5-mC concentration or global methylation in debilitated or environmentally affected cells may provide the latitude for veritable data for disease detection and analysis. The detection of DNA demethylation intermediate, 5-fC in diverse cells and tissues is applicable as a marker for indication of active DNA demethylation. Direct 5-fC excision by thymine DNA glycosylase, TDG for subsequent base excision repair, BER processing that reverts altered cytosine to its unaltered form. Differentially methylated regions, DMRs are DNA spheres which present critically different methylation status among numerous samples. Genome-wide methylation profiling is frequently conducted for the identification of DMRs among treated and untreated samples to unravel active areas which are associated with regulation of gene transcription due to inter alia DMRs specificity to cells, tissues and individuals. DMRs are feasible as biomarkers or potential targets for epigenetic therapy [21].

Epigenetic clocks encompass a set of CpG sites with determined DNA methylation concentrations correlate to individual age [22]. The clocks are recognisably esteemed accurate molecular correlate with chronological age in humans and other vertebrates, and quantification potential in rates of biological ageing as well as longevity

tests and rejuvenating interventions. These unravel issues and opportunities to elucidate clock mechanisms and biochemical utility which necessitate exploiting or exploring nonhuman models, epigenomic marks, population studies, drivers and regulators of age-associated modifications in single-cell, tissue- and disease- specific models, as well as ethical issues in forensic age determination and prediction of chronological ageing trajectory in a person [22]. Research suggested evidence, particularly, epigenetics for genome-wide DNA methylation changes in ageing and age-related disorders [23]. Epigenetic clocks which determine alterations in a limited number of specific CpG loci can predict chronological age accurately in an expansive range of species; and credible biomarkers for mortality prediction in humans. The impacts of ageing across the methylome in an expansive array of human and mice tissues exhibited age-related hyper- or hypo-methylation alterations. There is the tendency for the DNA methylation age-related changes to be enriched and deficient in specific genomic contexts, with certain similarities among tissues and species necessitating further research [23]. The indefatigable proof that the age-related changes in DNA methylation contribute to ageing emanates from anti-ageing interventions, such as caloric restriction [4, 24], dwarfism and rapamycin application in mice [24]. The anti-ageing interventions retard the epigenetic clocks with reversal and/or obliteration of reasonable age-related modifications in DNA methylation. Genome-wide maps [25] of DNA methylation can be generated to track biological ageing, that is distinct from chronological ageing. The initial epigenetic clocks were determined regarding blood which depicted significant relationships with blood pressure and lipid concentrations, which are other variables of blood ageing. However, the epigenetic ageing signature differs in disparate tissues [26], and thus, these observations cannot be extrapolated to the kidney, for instance. It will be interesting to configure tissue-specific epigenetic clocks which may correlate with other ageing indicators. These may expose robust divergence regarding the aetiology, expanse, mechanisms, consequences, and genes disrupted in the pathological process for the development of novel diagnostic tools and clinical applications. These technologies may generate expansive data concerning the modification of genetic material in the present and in the future.

Epigenetics is observed to be divergent to genetics but they are both inextricably-linked, with incessant research to elucidate the relationship per Jonathan Mill [27]. The environmental role in shaping the genome may have been exaggerated because cells have the self-preservation to self-insulate from environmental assault per Adrian Bird [27]. Transgenerational epigenetic inheritance prevails in the mention of epigenetics in terms of the nuances and complexities of human health and disorders. The accumulated marks in somatic cells provide expansive information regarding these spheres of influence and mechanisms as modeled for the environment or lifestyle. Epigenetics has been defined as chromatin alterations with inclusion of RNA alterations. Besides DNA methylation, DNA can undergo hydroxymethylation, while modification can also be exerted on proteins in the chromatin complex. It has been postulated that the ageing process is reversible. Despite the lifestyle, the internal clock causes certain individuals to age rapidly and die early. Also, it is suggested via epigenome study that the biological scars of traumatic experiences are passed on to their children [27], thus suggesting that DNA is not merely the mode of biological inheritance in organisms, and that acquired traits are inheritable, however, researchers are more interested in its potential to determine disease risk. As the full complement of genes are received in conception without modification until death, the information is conceivably transmitted through "epigenetic marks" as chemical tags on genes which dial gene output up or down. The transgenerational epigenetic inheritance phenomenon does not provide compelling evidence by any realisable physiological phenomenon for it to function, excepting in rare genetic disorders, definable genetic marks are

deleted from the genetic material of the ovum and sperm of humans in fertilization following nuclei fusion. The nascent epigenetic configurations are determined in every generation. It has been well-nigh impossible to estrange the genetic, epigenetic and environmental spheres to traits inherited. Neuroepigenetics depicted critical impact in the spheres of learned behaviour, addiction, cognition neurotoxicology and psychopathology with tendency towards fascinating indictments rather than established or veritable findings [28] or consequences [29].

Epigenetics and the complex interplay of aberrations and gene-environment interactions

Numerous human diseases are connected with complex gene regulations and functions. These are integrated in environmental signals for cell modulation in the functional output of the genome. Diabetes is inextricably-linked with premature ageing. There is palpable variation in the progression rate of ageing in humans. A simplistic biological paradigm is well-nigh impossible to determine both the clinicopathological and theoretical modalities in gene-environment interaction processes [3, 4]. The potential epigenetic, gerontological and clinicopathological correlates and implications are to configure the population at risk for developing premature ageing and senescence within diabetic and obese individuals [30, 31] for early development of therapeutic regimen in order to stem pecuniary burden and aberrant sequelae.

The extant understanding of the relationships between genetics, epigenetics, and environment in diabetes and evidence for the role of epigenetic factors in metabolism regulation, and diabetes with its risks and complications depict how the complex interactions between genes and environment or gene-environment interactions [3, 4] may partly be mediated via epigenetic alterations and how information regarding nutritional and other environmental stimuli are transmitted to the next generation. There is convergence in knowledge lacunae, research, recommendations and expansive interest in the epigenome, defined broadly as modifications to chromatin morphological functionality which exclude the modification of DNA sequence. Epigenetic control is crucial to both normal homeostasis and the disease state or process. Since diabetes risk complications are inextricably-linked to both genetic and environmental influences, numerous studies have perspicuously addressed the intersection of diabetes and epigenetics or epigenomics. Multiple layers of epigenetic regulation, such as direct methylation of cytosine or adenine residues, covalent changes to histone proteins, higher-order chromatin morphology, and noncoding RNA are observable [32]. These have severally been indicted in cellular mechanisms pertinent to diabetes; with sustained erstwhile inextricably-linked associations between epigenetics, diabetes, obesity, and a litany of metabolic aberrations. For instance, the agouti Ay mouse is an inbred strain that demonstrates profound obesity due to epigenomic changes of a gene that affects food consumption [33]. Incontrovertibly, obesity observed in Prader-Willi syndrome results due to impaired imprinting, a specialized epigenomic alteration [34]. Depending on the experimental paradigm, data have demonstrated that epigenome alterations by manipulating defined chromatin-modifying enzymes are associated with metabolic repercussions, with resultant obesity or mitigating obesity and hyperglycemia [35]. A vast majority of extant data inextricably relate epigenetic processes [36-38] in the risk of inherited or acquired diabetes and obesity [39, 40], as in the infamy of human experiments documented regarding the Dutch Hunger Winter, for instance [36], in conjunction with inordinate rodent research. It is purposeful to enact data relating epigenomics to diabetes and metabolism in advances for therapeutic intervention.

In another spectrum, SARS-CoV-2, the pathological aetiological agent of COVID-19 [41-46], an increasingly transmissible and pathogenic viral infection relies on the age and health status of an individual to exert

its severity and untoward consequences. It provides ample latitude to comparatively analyze viral host epigenome regulation. Epigenetic changes may be conceivably involved in the initiation of coronavirus complications necessitating epigenetic drugs to stem viral outbreak as well as configure pre- and post-exposure prophylaxis per COVID-19 [47]

Progress in procedures for DNA Methylation Analyses

Methylation analysis involves the investigation of chromosomal features of DNA or histone changes by methyl groups. The lysine residue in histone tails and the cytosine (C) base in the DNA can be subjected to methylation. The epigenetic field portrays an expansive array of methodologies in the determination of the status of DNA methylation. These are categorized into (i) the discovery of unknown epigenetic modifications; and (ii) DNA methylation assessment within defined regulatory genes and/or regions. [48]. These tools are selected based on feasibility and cost-benefit analysis. These epigenetic technologies involve nascent strategies with latitude to single-cell level, elevated-throughput genomic and epigenomic profiling with augmented high resolution having beneficial progress in epigenetics [49].

Notwithstanding the rewarding outcome of genome-wide association studies (GWAS) in the identification of loci connected to ubiquitous disorders, a vast majority of the aetiologies have not been explicated. Progress in genomic technologies has provided the latitude to commence large-scale research in human disease-related epigenetic disparity, specifically in DNA methylation [50]. These Epigenome-Wide Association Studies, EWAS provide ample and novel challenges and opportunities [51] which are not available in GWAS. Integrating EWAS and GWAS is a potential to analyse and elucidate the functionalities of complex GWAS haplotypes. Explicating and unravelling the genetic and non-genetic determinants of human complex disorders constitute a prime challenge in biomedical studies which exposed an excess of 800 single nucleotide polymorphism, SNP relationships for over 150 disorders and multiple traits. Despite the lacunae in the knowledge of complete genetic basis for human complex disorder, resequencing of exomes, and whole genomes make provision for the identification of the unelucidated causal genetic disparities. Interests persist to explore the influence of non-genetic and epigenetic factors in intricately complex disease aetiology.

Asthma is a ubiquitous chronic respiratory airway disorder elicited by environmental factors, and ostensibly via interaction with human genome culminating in epigenetic alterations. EWAS principally examined DNA methylation and its relationship with disease or traits thereof, exposure variables or gene expression [52]. A method that is precise, specific and efficient for the detection of the exact DNA methylation levels is pertinent for the elucidation of the prime functionalities of DNA methylation in biological processes or mechanisms with the objectives to augment research and development of novel optimum diagnostic and therapeutic trends and targets.

Implications of opposing dominance in epigenesis vs epigenetics

The application of the terminologies epigenesis and epigenetics has remarkably increased concurrently with confusing and conflating disparate issues prevailing in contextual biological and philosophical literature. Due to the extant confusion encompassing these two terms, it has become pertinent to explicate the disparities within their conceptual and historical evolutionary perspectives. The term "epigenesis" evolved from primordial embryological studies [53]. In contradistinction to Aristotelian natural philosophy, it was determined that epigenesis received fluctuating prominence since the 17th century, with its entry into neo-classical embryology and relevance in divergence to the preformationist stance. Whereas

preformation relates that the germ cells of any organism contains preformed minute adults which unfold during the developmental process. epigenesis propounds that the embryo is formed in progressive consecutive exchanges within an amorphous zygote. Both stances tend to explicate developmental organization, religious and metaphysical polemics within the context of embryonic matter exclusively as active or passive. The proponents of these two norms perspicuously underlie the application of gene-centric metaphors in 20th century molecular revolution.

On that score, development constitutes the central biological mechanism, and postulations about its modalities have influenced biological reasoning. Regarding "epigenesis vs preformation", epigenesis states that any developing organism arises from an unformed material and, over time, the gradual emergence of form during the development process. Conversely, preformation postulates that development starts with an entity as either in a preformed, predelineated, predetermined [54], preestablished or predefined manner. The debate of "epigenesis or preformation" is partly metaphysical about what is in existence regarding whether it is form or also the unformed that culminates in the formed. In part, it is epistemological whether it is determined and established by observation or inference. Polemics in these inextricably-linked questions have persisted since eternity but genetic determinists currently rely on the already "formed" via genetic inheritance, whereas others depend on the efficacy of environmental plasticity. There are major development theories from Aristotle on generation to current systems-theoretic and stem cell-based perspectives. Indubitably, "epigenesis vs preformation" does not represent the exclusive enduring theoretical divergence on development. However, this is an inclusive trajectory to inculcate patterns of transformation and consistency in arguments in biological development. Nature or nurture, epigenesis or preformation, genetic determinism or developmental free will, or whether a certain version of convergence are plausible remain the issues for determination. The terms of the never-ending discourse, and the undergirding hypothesis incessantly sustain arguments on the temporal beginning of life, with resultant in-depth implications for bioethics and policy. Recently, molecular biology has rapidly evolved to involve epigenetic research for the evaluation of organism-environment interactions [3] which are liable to present chronic resultant impacts. These sort of responses are likely to emanate from stress in early life stage, the usage of genetic information within the life span of an individual and transgenerational inheritance. Elucidation of epigenetic mechanisms potentiates the evaluation of multigenerational and heritable impacts due to environmental stressors, such as contaminants [55] and pollutants, as are driven by epigenetic modifiers for the identification of prime heritable marks with concomitant results at the levels of the organism and population.

DISCUSSION

Epigenetics is defined as the molecular DNA changes which regulate gene activity and are independent of DNA sequence, and are stable mitotically. Epigenetics studies have attained exponential growth recently, in progressive trajectories with remarkable resultant impacts. These demand stringent methodologies and superior technologies to promote epigenetics to apical molecular biology [3]. The prime epigenetic regulations include DNA methylation, histone modifications, and non-coding RNAs (ncRNAs) [49].

Genes are susceptible to diverse fluctuations. The stem cell epigenome simulates a fragile balance of chromatin (de-) modification mechanism. A model [56] demonstrated that modifications in DNA methylation were due to dynamics of histone alterations. This model may create a mechanistic explanation in the origin of tissue, age and cancer-specific DNA methylation profiles. DNA methylation is a critical ingredient in epigenetic change that is inextricably-linked in gene expression regulation. A key DNA

methylation pathway diminishes the potential of transcription factors to bind to gene promoter regions [57]. Although several investigations have been conducted to measure genome-wide DNA methylation levels at high resolution, the significance of these varied DNA methylation levels on transcription/factor binding potentials has not been clearly explicated.

An introduction of a computational model of stem cell populations whereby each cell has an artificial genome, depicted that transcription of the genes encoded by the genome was influenced by DNA methylation, histone alteration and a cis-regulatory network [56]. Model dynamics were investigated using molecular crosstalk between the disparate mechanisms. The epigenetic states of the genes were vulnerable to disparate magnitudes of variations. It was exhibited that the timescales of these fluctuations or temporal variations are determinants if the condition or form connected with a defined gene will hold sway or not during cell replication. The model suggests that modifications in DNA methylation states are effected via the dynamics of histone modification. It is suggested that the model demonstrates a mechanistic explication of the profiles pertaining to the origin of tissue, age and cancer-specific DNA methylation [56]. Genetic aetiologies in human diseases are exposed in accelerated dimension.. An increasing subclass of disease-causing mutations correlates to modifications in the epigenome or in the ubiquity and activity of proteins involved in chromatin structure regulation [58].

Epigenetics is accorded cognizance in tissue development and in the development and progression of several ubiquitous disorders. Although, certain risk factors have been established by population-based epigenetic epidemiologic research in epigenetic functionality in ubiquitous diseases, the relatively nascent scientific field embraces unique challenges, issues and opportunities; but these present potential resolutions [59]. In an organism, epigenetic marks are modifiable by environmental factors during the lifespan of an individual. Changes in the epigenetic code may be either beneficial or associated with adverse disorders, such as cancer and neuropsychiatric aberrations [60]. Evidence indicates that some epigenetic marks are inherited, and can remould developmental and cellular characteristics transgenerationally. This portends expansive implications for understanding biological functionalities and disease etiologies with potentials for newfangled trajectories in diagnosis and treatment of human diseases, such as the perturbative impacts of traumatic stress, drug or toxicant exposure and susceptibility to brain functionalities as well as the adaptive importance of epigenetic inheritance and cost-benefit of acquired epigenetic marks which subsist transgenerationally.

CONCLUSION

This article argues that epigenetic changes mediate environmental influences in gene expression, and modulate disease risk inextricably-linked with genetic spatiotemporal variations and transmissibility. Analytical epigenetic paradigm presents sustainable objectives and advancements for identifying, explicating and elucidating mechanisms wherein genetic and environmental influences are combinatorial contributory factors to disease risks and sequelae. The unravelling of spatiotemporal disparities in epigenetic profiling is of pertinence for the research in ageing, the variables associated with diverse diseases, such as cancer, respiratory diseases, SARS-CoV-2/COVID-19, diabetes, obesity, as well as other metabolic and endocrine disorders. Thus, this article reviews epigenetic mechanisms on DNA methylation; genetic and environmental as they influence ageing, cellular senescence and certain confounding diseases, philosophical development theories, and epigenetic psychology as they relate to humans. A conspectus of methodological analysis for epigenetic profiling is considered for cost-benefit of tools and techniques as well as advancement in disease treatment. Summarily, epigenetics is the study of the ways and means whereby human behaviour and

environment induce changes which govern the functionality of genes. Epigenetics translates to "around or surrounding genetics", as advert to naturally controlled processes which govern gene expression. Epigenetics is the mechanism in which genes are designate by cells disparately for either usage or storage. Epigenetics is the study of how the environment affects the genome of an individual during development, and the development of the descendants in the absence of alteration of the DNA sequence.

Conflicts of interest

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