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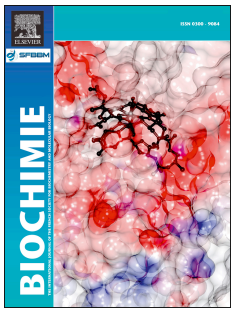

Primers on nutrigenetics and nutri(epi)genomics: origins and development of precision nutrition

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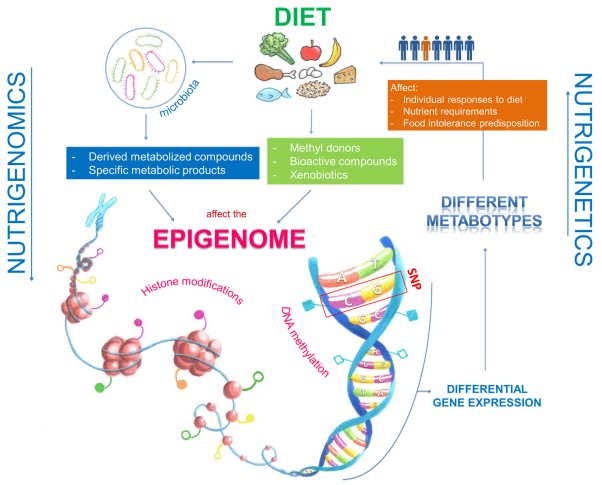
Abstract

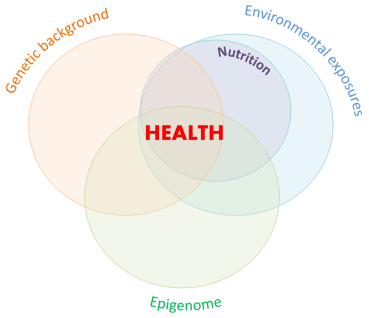
Understanding the relationship between genotype and phenotype is a central goal not just for genetics but also for medicine and biological sciences. Despite outstanding technological progresses, genetics alone is not able to completely explain phenotypes, in particular for complex diseases. Given the existence of a "missing heritability", growing attention has been given to non-mendelian mechanisms of inheritance and to the role of the environment. The study of interaction between gene and environment represents a challenging but also a promising field with high potential for health prevention, and epigenetics has been suggested as one of the best candidate to mediate environmental effects on the genome.

Among environmental factors able to interact with both genome and epigenome, nutrition is one of the most impacting. Not just our genome influences the responsiveness to food and nutrients, but vice versa, nutrition can also modify gene expression through epigenetic mechanisms. In this complex picture, nutrigenetics and nutrigenomics represent appealing disciplines aimed to define new prospectives of personalized nutrition. This review introduces to the study of gene-environment interactions and describes how nutrigenetics and nutrigenomics modulate health, promoting or affecting healthiness through life-style, thus playing a pivotal role in modulating the effect of genetic predispositions.

Keywords: nutrigenetics, nutrigenomics, epigenetics, gene-environment interaction, personalized nutrition.



Nutrition is as a major environmental factor able to affect health



Nutrigenetics and nutrigenomics represent the future of personalized nutrition

Review article

Primers on nutrigenetics and nutri(epi)genomics: origins and development of precision nutrition

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Abstract

Understanding the relationship between genotype and phenotype is a central goal not just for genetics but also for medicine and biological sciences. Despite outstanding technological progresses, genetics alone is not able to completely explain phenotypes, in particular for complex diseases. Given the existence of a "missing heritability", growing attention has been given to non-mendelian mechanisms of inheritance and to the role of the environment. The study of interaction between gene and environment represents a challenging but also a promising field with high potential for health prevention, and epigenetics has been suggested as one of the best candidate to mediate environmental effects on the genome.

Among environmental factors able to interact with both genome and epigenome, nutrition is one of the most impacting. Not just our genome influences the responsiveness to food and nutrients, but vice versa, nutrition can also modify gene expression through epigenetic mechanisms. In this complex picture, nutrigenetics and nutrigenomics represent appealing disciplines aimed to define new prospectives of personalized nutrition. This review introduces to the study of gene-environment interactions and describes how nutrigenetics and nutrigenomics modulate health, promoting or affecting healthiness through life-style, thus playing a pivotal role in modulating the effect of genetic predispositions.

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Abbreviations

5caC	5-carboxylcytosine
5fC	5-formylcytosine
5hmC	hydroxymethylcytosine
AKU	alkaptonuria
ASM	alleles specific DNA methylation
BMI	body mass index
CGIs	CpG islands
CNP	copy number polymorphisms
CNV	copy number variant
DNMT	DNA methyl transferases
DOHaD	developmental origin of health and disease
DTC	direct-to-consumer
eQTL	expression quantitative trait locus
GxE	gene-environment interactions
HDAC	histone deacetylase
Insdel	insertion/deletion
LCT	lactase
LD	linkage disequilibrium
LEARn	latent early life associated regulation
LINE	long interspersed nuclear elements
LTR	long terminal repeat
MTHFD1	5,10-methylenetetrahydrofolate dehydrogenase 1
MTHFR	methylenetetrahydrofolate reductase
PAR	predictive adaptive response
PEMT	phosphatidylethanolamine-N-methyltransferase
PGCs	primordial germ cells
PKU	phenylketonuria
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
SINEs	short interspersed nuclear elements
SNP	single nucleotide polymorphism
TET	Ten-Eleven Translocation
WHO	World Health Organization

1. Gene-environment interactions: from genetics to epigenetics

1.1 Healthy or Unhealthy Phenotype: is it nature or nurture?

As early as 350 BC, trying to understand the origin of human behavior, philosophers such as Plato and Aristotle epistemologically gave raised to the Nature vs Nurture debate. About 2000 years after, we are nowadays almost sure that nor nature or nurture can exist in a manner that can be considered independently quantifiable [1]. To paraphrase Richard Lewontin [2], "There are no genetic factors that can be studied independently of the environment, and there are no environmental factors that function independently of the genome".

After the advent of the Human Genome Project [3], genome scientists, medical geneticists, and science policy leaders worked to establish the value of genomic science by defining the fields of public health genomics and precision medicine. These fields gave rise to a new post-genomic combination of methods and disciplines who made a shift from a "nature versus nurture" dichotomy to a more systemic vision of the gene-environment interactions, promising to lead to more accurate and consistent explanations for diseases and a future based on personalized prevention and treatment. Nevertheless, despite the consensus about the presence of gene-environment interactions and their influence on health and disease, researchers struggled to define, analyze and quantify the environmental effects on the genome.

The concepts explained in this first section introduce strengthens and weakness of genetic and epigenetic approaches to study gene-environment interactions. These notions are propaedeutic to clearly comprehend origins and development of nutrigenetics and nutrigenomics, their limits and pitfalls, and the importance of the integration between genetic and epigenetic information in precision nutrition.

1.2 Genetic determinants of health.

Inheritable information given by the primary sequence of DNA plays a key role in determining variations in the susceptibility and severity of disease. The human genome includes about 3×10^9 base pairs of DNA, and the amount of genetic variation in humans is such that no two subjects (except for identical twins), have ever been genetically identical. The amount of genetic variation between any two humans is about 0.1 percent. This signifies that about one base pair out of every 1000 is different between any two individuals [4]. In both plant and animal genomes, the predominant forms of sequence variations is represented by single nucleotide polymorphisms (SNPs), which distinguished from rare variations by having a frequency of the least abundant allele of 1% or more [5]. Copy number variants (CNVs) or copy number

polymorphisms (CNPs), including duplications, deletions, insertions and complex multi-site variants, are again other source of variation in the genome [6]. Genetic variants can differ between ethnicities, are inherited from ancestors and can take place through the entire genome. Whether functional role of various non-synonymous variants (comprising nonsense, missense, frameshift and other types of variations) occurring in the coding region has been hypothesized, it is still matter of debate how genetic variants taking place in the non-coding genome can actually have an impact [7]. That question is particularly challenging considering that genetic variants in the non-coding genome are the most abundant in general, and also that most of the single-nucleotide variants significantly associated with an increased risk of complex diseases have been mapped to non-coding regions [7].

However, understanding the connection between genotype and phenotype is one of the main goals which several projects are contributing to achieve. First of all, the reference human genome sequence provided the basis for the study of human genetics; then the public catalogue of variant sites (dbSNP 129) archived approximately 11 million SNPs and 3 million short insertions and deletions (insdels) identified in the genome; again, the International HapMap Project indexed both allele frequencies and the correlation patterns between nearby variants (i.e. the linkage disequilibrium), across several populations for 3.5 million SNPs [3,8,9]. This knowledge leds to the genome-wide association studies (GWAS), which analyze numerous hundred thousand of variant sites, combining them with the information about linkage disequilibrium structure and permitting to test the majority of common variants (those with 5% minor allele frequency) for their association with disease. The 1000 Genomes Project (describing the genomes of 1092 individuals from 14 population) clarified the properties and distribution of common and rare variations, providing insights into the processes that shape genetic diversity, and strongly increased the knowledge about disease biology [10,11]. As a result, GWAS and other genetic studies identified the association of more than 15000 SNPs with numerous pathologies or traits [12]. They have impressively extended our knowledge about how germline genetic variations impact disease susceptibility and outcome [13,14], and also about how somatic changes in DNA sequence severely impair gene expression, leading to the genesis and advancement of disease [15].

However, these increased knowledge of genotypic information were rarely flanked with downstream functional studies, that are still needed to identify causal variants that contribute to human phenotypes. Expression quantitative trait locus (eQTL) assays were performed to ascertain associations between genotypes and gene expression variations, but in most eQTLs the causal variant was unidentified, and even when the expected causal variant could be reliably identified, the involved regulatory mechanism was largely challenging to be recognized [16,17]. Furthermore, whether genetic influence is clearly established for monogenic traits, the landscape becomes more and more intricate for complex polygenic characters.

1.3 Limits and pitfalls of the genetic approach.

For more than a century, individual differences in human traits have been studied; nevertheless the causes of variation in human traits, complex traits in particular, still remain controversial [18–23]. Actually, in the last years, research has definitely established that GWAS findings alone, besides large investments and scientific efforts, does not tent to identify causal loci of complex diseases and predict individual disease risk [13]. This has been hypothesized to be due, among other factors, to the fact that GWAS avoid to consider CNV and, above all, environmental factors in the analysis. Large-scale GWAS demonstrates that many genetic variants contribute to the complex traits variation, but the effect sizes for these traits are typically small. Furthermore, the sum of the variance explained by the noticed variants is much smaller than the reported heritability of the trait. This surprising and interesting concept has been referred as 'missing heritability'[24,25]

These observations contrast with the common disease–common variant hypothesis [13], which advocated that common variants distributed in all populations determine phenotypic variation or disease risk and that these variants all together are responsible for an additive or multiplicative effect on trait variation or disease risk. On these behalf, several explanations have been suggested to clarify the architecture of complex traits and diseases: (A) the hypothesis that a large number of common variants exerting a small-effect account for disease risk and quantitative trait variation; (B) the hypothesis that a large number of rare variants having a large-effect motivates the observed associations; or (C) the theory that a combination of genotypic, epigenetic, and environmental interactions can explain the observed relations [13]. This complex scenery leads some researchers to focus on the importance of non-additive variation models in genetics [26,27]. Beside, considering that the nature of complex diseases is multi-factorial, many researchers have supported the idea that major factors contributing to the missing heritability are the interactions among genetic loci, so-called epistatic interactions. Indeed, multifaceted interactions between environmental factors and genetic variants, both potentially associated to disease risk, have been suggest to be taken into account.

For all these reasons, while numerous studies in the last decades centered their attention to the identification of different genetic variants that could explain a certain phenotype, nowadays concepts such as epistasis, gene-gene interaction and gene-environment interactions represent the research focus that could provide further information about the genetic determinants of a certain phenotype [24]. Moreover, this landscape highlights opportunities to consider epigenetics as a functional modifier of the genome and a major contributing factor for disease etiology [28]. If heritability is classically described as the ratio of the genetic to the total phenotypic variance, in a population [29], the more contemporary concept of 'broad

sense heritability' denotes the genetic effect including non-additive components, such as gene-gene interactions, gene-environment interactions (G×E), and epigenetics [13].

1.4 The epigenome

Beginning over 70 years ago, the field of epigenetics massively grew to elucidate mechanisms through which various cellular phenotypes originate from a single genotype throughout the intricate process of developmental morphogenesis termed epigenesis. The word ''epigenetics'' was firstly coined by Conrad Waddington (1905–1975) in 1940s. He used it to define "the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being" [30]. After some debates, a consensus definition was delineated and epigenetics was defined as "stably heritable phenotypes resulting from changes in a chromosome without changes in gene sequence" [31]. Epigenetic mechanisms of gene regulation, which collectively make up the epigenome, mainly encompass enzymatic methylation of cytosine bases (DNA methylation), post-translational modification of tail domains of histone proteins (histone modifications) and chromatin remodeling. These modifications arise all over the developmental stages or ensue to environmental factors exposure, providing both variability and rapid adaptability, that allow organisms to respond to external stimuli both in the short and in the long term.

The relevance of epigenetics in the development is connected to the ability of a single-cell zygote with a fixed genomic sequence to give rise to an organism with hundreds of cell types thanks to its ability to control subset of genes expressed in each cell type. Specifically, extensive removal and reestablishment of lineage-specific epigenetic signatures, through a process designated as epigenetic reprogramming, are at the basis of cellular differentiation[32]. Conservation and inheritance of these epigenetic marks during cell division is fundamental to preserve a committed cell lineage and cellular phenotype in descendant cells, and establish a memory of transcriptional status. In detail, epigenetic marks are reprogrammed in a global scale, concomitantly with restoration of developmental potency, at two points in the life cycle: firstly on fertilization in the zygote, and secondly in primordial germ cells (PGCs), that are the direct precursors of sperm or oocyte. A distinctive set of mechanisms regulates epigenome erasure and re-establishment [32–34]. In this picture, 'epigenetic' marks describe the developmental potency of the zygote and promote differentiation towards a specific cell fate in future cell generations.

Methylation of the fifth carbon of the cytosine base in DNA and post-translational histone tail modifications are probably the best-studied epigenetic modifications in mammals [35]. DNA methylation is the covalent addition of a methyl group at the 5-carbon of a cytosine ring, resulting in 5-methylcytosine (5mC), likewise informally defined as the "fifth base" of DNA. This reaction is catalyzed by DNA methyltransferases (DNMTs) enzymes [36]. There are three main DNMTs: DNMT1 copies methylation

marks from the parental strand of DNA to the newly synthesized strand during the process of DNA replication (thus it is defined as the maintenance DNMT, which allows transmission of DNA methylation patterns from cell to cell), while DNMT3A and DNMT3B establish a *de novo* DNA methylation [36,37]. DNA methylation is the most chemically stable epigenetic modification and it is unambiguously stably transmitted during cell division. As a consequence of its biologic interest, it is the most well characterized epigenetic mark and the most extensively measured in epidemiologic research.

In mammals, DNA methylation occurs primarily on cytosines within a CpG dinucleotide, of whom approximately 70–80% are methylated [38]. Besides, stretches of CpG-rich sequences with low levels of DNA methylation, also called CpG islands (CGIs), exist [11,39]. CpG islands are defined as sequences with a G+C content above 60% and a ratio of CpG to GpC of at least 0.6 [40]. They frequently are highly enriched at gene promoters (about 60% of all mammalian gene promoters are CpG-rich). Unmethylated CpG islands are usually open regions of DNA with low nucleosome occupancy (euchromatin), promoting relaxed chromatin structure that facilitates accessibility to the transcription start site of RNA polymerase II and other components of the basal transcription machinery [41,42]. On the other hand, DNA methylation is frequently related to gene repression [43,44]. Many targets of *de novo* DNA methylation are promoters of stem cell- and germline-specific genes during differentiation, repetitive DNA sequences, such as those within the chromosomes centromeric and pericentromeric regions or in the endogenous transposable elements (i.e. long interspersed nuclear elements (LINEs), short interspersed nuclear elements (SINEs) and long terminal repeat (LTR)-containing endogenous retroviruses) [43,45]. Moreover, DNA methylation recruits methyl-CpG-binding proteins which interacts with proteins that can play a role in the repression of genes with CpG islands (i.e. Methyl CpG binding protein 1, MeCP1) or, on the other hand, can add silencing modifications to neighboring histones (i.e. MeCP2) [46]. This harmonization between DNA methylation and silencing histone marks determines the compaction of chromatin and gene repression. However, DNA methylation is also found within the bodies of genes, where higher levels of intragenic methylation correlate with higher levels of gene expression. Thus, the functional significance of gene body methylation is less clear, and regulation of alternative transcription initiation sites or regulation of splicing are two potential role hypothesized to explain this phenomenon [47–50].

Despite it was originally retained that DNA methylation was a stabile mark which once established was then maintained throughout the life course of the organism (because of its thermodynamic stability and the initial incertitude of a biochemical mechanism that could directly remove the methyl group from 5mC), it is now clear that DNA methylation can be dynamically regulated [49]. Recent discoveries showed that, together with DNMTs-mediated methylation processes, passive or enzymatically-directed DNA demethylation also occur. Several DNA demethylases such as Ten-Eleven Translocation (TET) proteins, Methyl Binding Domain protein, DNA repair endonucleases XPG and a G/T mismatch repair DNA glycosylase

has been identified. They do not act by directly removing the methyl group, but through a multistep process linked either to DNA repair mechanisms or through further modification of 5mC such as 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC). TET proteins can oxidize 5mC to 5hmC but also to 5fC and/or 5caC, which are subsequently excised by thymine DNA glycosylase, or deaminated by activation-induced deaminase, whose deamination product (5-hydroxymethyluracil), activates base-excision repair pathway leading to demethylation [51–56]. Among these other DNA modifications, 5hmC acquired growing importance, specifically in certain cell types, not just as an intermediate of demethylation processes, but as an epigenetic mark itself. High levels of 5hmC are found in embryonic stem cells, in multipotent adult stem cells and progenitor cells. During differentiation, levels decrease in most of cells, except that in Purkinje neurons and other neural subtypes, where high levels can be still measured [57]. Like 5mC, 5hmC is not uniformly distributed though the genome. 5hmC are enriched within gene bodies and at transcription start sites and promoters associated with gene expression, supporting the premise that 5hmC is associated with gene activation [58–60]. Interestingly, DNA hydroxymethylation has been demonstrated to be affected in response to environmental stress through redox system alterations and, in particular, TET proteins activation [61,62]. Which are the connections between 5mC, 5hmC and gene expression regulation is still to be completely elucidated.

Together with DNA modifications, epigenetic gene regulation also includes modifications in histones that make up the nucleosomes. Nucleosomes are the basic unit of chromatin in eukaryotic organisms, composed by the DNA wrapped around a core of eight histone proteins (H2A, H2B, H3 and H4), essential to reduce its size. Beside this fundamental function, it is now clear that histones are not only important for DNA packaging, but also exert pivotal roles in gene expression regulation, in conjunction with DNA methylation [63]. Histone proteins contain a globular domain and an amino tail domain. The amino tail domains protrude out of the nucleosomes and are rich in positively charged amino acids, that interact with the negatively charged DNA. These tails are subject to a large number of post-translational modifications, among which the most frequent are acetylation, methylation, ubiquitination, sumoylation, and phosphorylation, raising up to thousands of potential combinations of modifications within a single nucleosome [64]. Thus, whereas DNA can primarily be methylated, histones are capable of carrying a wide array of post-translational modifications, with different role in gene expression regulation processes [65,66]. They are dynamic, and several enzymes involved in their modulations have been identified [67]. Recurrently, specific histone variants are found at definite locations within the chromatin or are used to demarcate heterochromatic and euchromatic regions. Histone modifications can directly influence interactions between histone and DNA or between different histones, or they can be targeted by protein effectors also called histone-binding domains. To define proteins that deposit, remove and recognize histones post-translational modifications, respectively, the terms ‘writer’, ‘eraser’ and ‘reader’ were coined

[68,69]. They can act in cooperation, and it is the peculiar arrangement of histone modifications at a specific site that habitually defines which protein complexes are recruited to activate or repress transcription, catalyze further histone modifications or recruit other histone-modifying proteins [70], regulating various DNA-dependent processes, including DNA replication, transcription and repair. The collection of the "post translational modifications of specific amino acid residues within the histones that leads to the binding of effector proteins that, in turn, bring about specific cellular processes" is defined as histone code [71,72]. While mechanisms of transmission of DNA methylation has been recognized, it is still debated how histone modifications are transmitted during cell replication [73,74]. Furthermore, more recent evidence suggests that local and three-dimensional chromatin architecture provide additional levels of gene regulation in pluripotent stem cells. Local chromatin architecture defines the position and density of nucleosomes as well as the presence of histone variants [75,76]. However, its roles in cellular reprogramming has not been completely elucidated yet. Ongoing projects are producing cell-specific reference data sets that offer a basis for defining the complex interaction between epigenomic processes and the transcriptome: ENCODE (Encyclopedia of DNA Elements) project and the International Human Epigenome Consortium [77] intended to classify the regulatory elements in human cells and to investigate the epigenomic signatures of cell cultures; the Roadmap Epigenomics Project (from US National Institutes of Health) extends the ENCODE project and is devoted to clarify in what way epigenetics contribute to human biology and disease [78,79]. Providing reference epigenomes for numerous human tissues and cell-types, research provided the basis to understand how epigenomic are linked to the corresponding genetic information. The final goal would be to clarify the complete landscape of epigenomic elements which controls gene expression in the human body [80].

1.5 Interaction between genetics and epigenetics

Epigenetic mechanisms may be considered complementary to genetic functions in the regulation of gene expression and can be saw as the way by which a specific cell or tissue interprets the genome information [81]. At the same time, primary DNA sequence is a strong determinant of the epigenetic state. This can be evidently inferred by noting that the distribution of epigenetic marks across the genome is, at least in part, determined by CpG density and G:C content in the sequence [82,83]. Additionally, proximity to repetitive elements such as Alu and LINE, nuclear architecture and binding sequences for transacting proteins represent further genetic influences. Furthermore, some evidences suggested that genetic polymorphisms can affect epigenetic state [34]. In fact, mutations in genes encoding epigenetic modifiers (such as DNMTs, chromatin remodeling proteins or histone modifying enzymes) can contribute to epigenetic changes, and have been well documented in several diseases [34]. Aberrant epigenetic modifications can directly modulate regulation of target genes or can interact with specific genetic variants

predisposing to them [34]. Furthermore, studies that investigated both genetic variations and DNA methylation demonstrated that alleles specific DNA methylation, related to polymorphic nucleotides situated nearby the DNA methylation site, can extensively occur through the genome [84].

Given the complexity of the genome and the notable intricacy of epigenetic changes, that take account of dozens of different post-translational histone modifications and more than 50 million sites of potential DNA methylation in a diploid human genome, it appears that no two human cells would have identical epigenomes, which, additionally, change over time in response to developmental and pathological progressions, as well as consequentially to environmental exposures and random drift [34].

1.6 Epigenetics as a bridge between the environment and the genome

In accordance with the World Health Organization (WHO), more than 13 million deceases per annum are caused by environmental issues and so far as 24% of disease is due to exposures which could be prevented [85]. A conspicuous amount of lifestyle and environmental factors have been revealed to affect numerous diseases; however, not all of them have been characterized as genotoxic agents, able to promote DNA sequence mutation [86]. Thus, genome-environment interactions have been discussed extensively, and the role of epigenetics has been progressively more acknowledged as a mechanism of interface between them [87]. Indeed, multiple differences in gene expression have been recognized in numerous tissues already from newborn identical twins (presumably reflecting intrauterine epigenetic differences), suggesting that not just differences in the genome, but also different exposure to environment, can affect the epigenome [88]. Considering that several epigenetic events have been identified as tissue-specific and reversible, epigenetics is particularly compelling to explain differential susceptibilities in the exposed population and why exposures affect precise organs.

Since a lot of epigenetic modifications can be modulated by both external and internal factors and can change gene expressions, epigenetics is considered a key mechanism through which genomes interact with environmental exposures, providing a novel approach in the exploration of etiological factors in numerous environment related pathologies [89]. As these epigenetic marks are potentially cumulative and could take place over time, to identify the cause-effect associations among epigenetic changes, environmental factors and diseases represents a big goal. However, even if mechanisms of action of some of these agents remains to be completely elucidated, some others has been well characterized [34,89,90].

The epigenome appears more susceptible to environmental factors during periods of extensive epigenetic reprogramming in early life, particularly during the prenatal, neonatal and pubertal periods, when the epigenome is being established and environmental insults may interfere with processes that

regulates its reprogramming. However, somatic changes to epigenetic marks might also ensue from environmental exposures in adults, as it has been observed in aging and numerous disease processes (i.e. cancer, neurodegenerative and metabolic diseases among others) [34,89,90].

Furthermore, numerous environmental factors, from nutrition to toxicants, have been shown to induce an epigenetic transgenerational inheritance [91], which is described as the germline transmission of epigenetic information between generations without direct exposure [92]. Several different model of epigenetic inheritance of disease and phenotypic variation has been proposed to be linked to environmental exposure. Drake and Lui [93–95] outline three possible mechanisms that could be responsible of multigenerational observations: a) persistent environmental exposures (i.e. generation after generation) during early development; b) a single "maternal environment" exposure that can yet induce a multigenerational phenotype; and c) epigenetic effects which can be transmitted across the germline. Transgenerational epigenetic inheritance induced by environmental agents has been mainly studied performing exposure to environmental insult during pregnancy, which can affect a mother (F0 generation), the developing fetus (F1 generation) but also the fetus germ cells which will go on to form the F2 generation. Nutrition, [96] temperature [97], stress [91], and toxicants [91] can all induce epigenetic transgenerational inheritance of phenotypic variation [98]. This evidence has been demonstrated in plants, fish, insects, pigs, rodents, and humans [91]. The altered transgenerational phenotypes have been observed for generations in mammals [91], and for hundreds of generations in plants [99]. The capacity of environment to modify phenotype and phenotypic variation through epigenetic mechanism is suggested to be important for evolution. Environmentally induced epigenetic inheritance can bring a population closer to an increased fitness in a faster way than genetic changes; then, genetic variations may ultimately follow (if the new environment is stable), likewise the genetic fixation of initially induced phenotypes occurs. Furthermore, the selection can act upon randomly induced metastable epialleles, thus contributing to adaptation in a similar way than genetics [100].

Indeed, environmental epigenetics and epigenetic transgenerational inheritance represent the molecular mechanism able to support the neo-Lamarckian theory, which assert that environmental factors directly alter phenotypes. Although aspects of the original Lamarckian evolution theory, such as having "directed" phenotypes within a generation, were not accurate [101–103], the notion that environment can impact phenotype is reinforced by environmental and transgenerational epigenetic studies. These findings do not contrast the Darwinian theories, but rather overlap with them, suggesting that a new integrated theory should be hypothesized. Specifically, the well-established aspect of Darwinian evolution is the ability of environment through natural selection to act on phenotypic variation, with genetic mutations and variation considered the main molecular mechanism involved in generating the phenotypic variation. Nevertheless, being the environment able to impact epigenetic programming through generations,

environmentally induced epigenetic changes can be considered as another source of phenotypic variation. Guerrero-Bosagna and colleagues reports an example of how developmental effects of environmental exposures can influence adult characters in mammals also potentially having evolutionary consequences [104]. They demonstrated that a high consumption of isoflavones can alter both epigenetic and morphometric characters or sexual maturation, which are characters that might play relevant roles from an evolutionary perspective. All in all, the unified evolutionary theory sustains that both environmental epigenetics (impacting on phenotypic variation) and the capacity of environment to intercede in natural selection will be equally important for evolution [105]. Another relevant aspect is the ability of epigenetic processes to endorse genetic mutations [106], in particular CG to TG transitions [107]; thus, environmental epigenetics might not merely provide increased phenotypic variation, but could drive genetic change and directly increase genotypic variation likewise.

Being both genetic and environment pivotal phenotypic determinants, genetic X epigenetic X environmental interactions has to be taken into account [108], in order to carefully define intricate biological interactions and, as ultimate goal, ascertain susceptible subpopulations. Beyond implication of evolutionary prospectives, it is intuitive that epigenetics has considerable potential for identifying new biomarkers to predict which exposures would increase the risk in exposed subjects and which individuals are particularly vulnerable to develop disease.

1.7 The role of environment as a strong determinant of health

There has been a growing awareness of environmental effects on human health, and that neither purely environmental factors, nor purely genetic factors can entirely explain the observed estimates of disease incidence and progression. Furthermore, the balance between genetic and epigenetic contributions in the development of pathologies appears to change during life. While, for instance, the majority of childhood tumors are connected to an inherited genetic or epigenetic (for example, imprinted) problem, this equilibrium shifts in favor of acquired epigenetic and genetic burden in tumors in adult or elderly age [109]. Many epidemiologic studies investigated the effects of exposure to chemical, social or physical factors in relation to several pathologies, such as cardiovascular disease, diabetes and cancer among others. These kind of studies are starting to incorporate gene-environment interactions and epigenetic modifications to better investigate the multidisciplinary nature of individual, in order to have a better estimate of the complexity of exposure biology and the small effects that are easily disturbed [110].

Numerous environmental factors have been suggested to be able to influence the epigenome, resulting in long-term changes in gene expression and metabolism: air pollution, tobacco smoke, oxidative stress, organic chemicals, endocrine disruptors, metals and, last but not least, nutrient intake and social

environments [34,109]. The totality of our exposures from conception onward has been defined by Christopher Wild with the new coined term “exposome”. Exposures come from our external environment and lifestyle, but are also the outcome of our internal biological processes and metabolism; given this more complete view of the exposome, the concept was redefined by Miller and Jones as “the cumulative measure of environmental influences and associated biological responses throughout the lifespan.” Current scientific opinion sustains that the study of the exposome could be helpful to clarify the interaction between genetic and environmental factors that contribute to disease, with the potential to revolutionize biomedical science, especially in term of prevention of late onset chronic disease that represent the main burden in the modern society [111].

Several different models have been hypothesized to explain the role of epigenetics on the late onset disease. Barker hypothesized that adult diseases are consequences of fetal adverse conditions due to the fetus adaptation to a certain environment to which it was exposed in early life[112]. Adaptive responses, which can be either in the form of metabolic changes or sensitivity of the target organs to hormones, will not induce immediate consequences in the newborn but could lead to physiologic and metabolic disturbances in later life. Gluckman and Hanson suggested that fetal exposure to adverse conditions makes immediate changes which are reversible, except in the case that stress conditions persist [113]; in that case fetus undergoes to irreversible changes that will persist throughout life, influencing (positively or negatively) the adulthood [114]. They coined term predictive adaptive response (PAR) for the phenomenon. Another hypothesis is represented by the DOHaD (Developmental origin of health and disease) model, which postulate that not merely embryonic development but also the period of development during infancy is responsible for late life risk of diseases. Another theory, which represents the evolution of the previously listed, is the LEARn (Latent early life associated regulation) model. This concept sustains that environmental agents such as nutrition, metal exposure, head trauma and lifestyle are “hits” that are related to the cause and progression of common late onset diseases. LEARn is based on the idea that latent epigenetic changes induced in early life do not result in any disease symptom immediately, but create a perturbation in the genome. It is just later in life, after a latency period (which finish when a second triggering agent manifest), that the epigenetic perturbation will result in manifested consequences. Genes that respond late in relation to early life responses are called LEARned genes, while others which don’t are called unLEARNed. The responses to the early life environmental triggers after the latency period is defined as LEARning [115].

2. Nutrigenetics

2.1. Introduction to Nutrigenetics

The notion that interactions between genetics and nutrition are responsible for the final phenotype was recognized by Archibald E. Garrod in 1902, when he published in The Lancet a milestone paper in which he depicted his observations of people with black urine or black bone disease, also known as alkaptonuria (AKU) [116]. AKU is a rare disorder of autosomal inheritance. It is caused by a mutation in the homogentisate 1,2 dioxygenase gene, resulting in the accumulation of homogentisic acid. It was one of the first disorders found to conform with the principles of Mendelian recessive inheritance in humans, and was primarily described as an example of genetic disruption of food metabolism. The increasing in biochemical knowledge gradually started to support fruitful nutritional intervention for handling some of these metabolic pathologies. In 1934, Asbjørn Følling discovered that another defective metabolism of a dietary amino acid (phenylalanine) could induce severe mental deficiency in subjects affected by a metabolic defect called phenylketonuria (PKU). Later, in 1953, Horst Bickel demonstrated that nutritional treatment can be effective in treating this condition, helping to prevent devastating consequences just starting a specific nutritional treatment few days after birth. The same happened with other untreatable inherited diseases (maple syrup urine disease, biotinidase deficiency and others), for which early nutritional intervention resulted to be effective [117].

In 1960, Dr JA Roper explained the links between genetics and nutrition with a paper entitled ‘Genetic determination of nutritional requirements’ [118]. There was quite slight progress in understanding interactions between genotypes and nutrition in humans until the Human Genome Project was completed; few time later, ‘nutrigenomics’, i.e. the study of the gene-nutrients interactions, was predicted would be the future of nutrition [119,120]. Nutritional genomics (or nutrigenomics) has been described as the branch of science investigating all types of interactions between nutrition and the genome by high-throughput genomic tools [121]. Nutritional genetics (or nutrigenetics) is described as a sub-set of nutrigenomics, which aims to understand how genomic variants interact with dietary factors and which implications derive from such interactions (Figure 1 A).

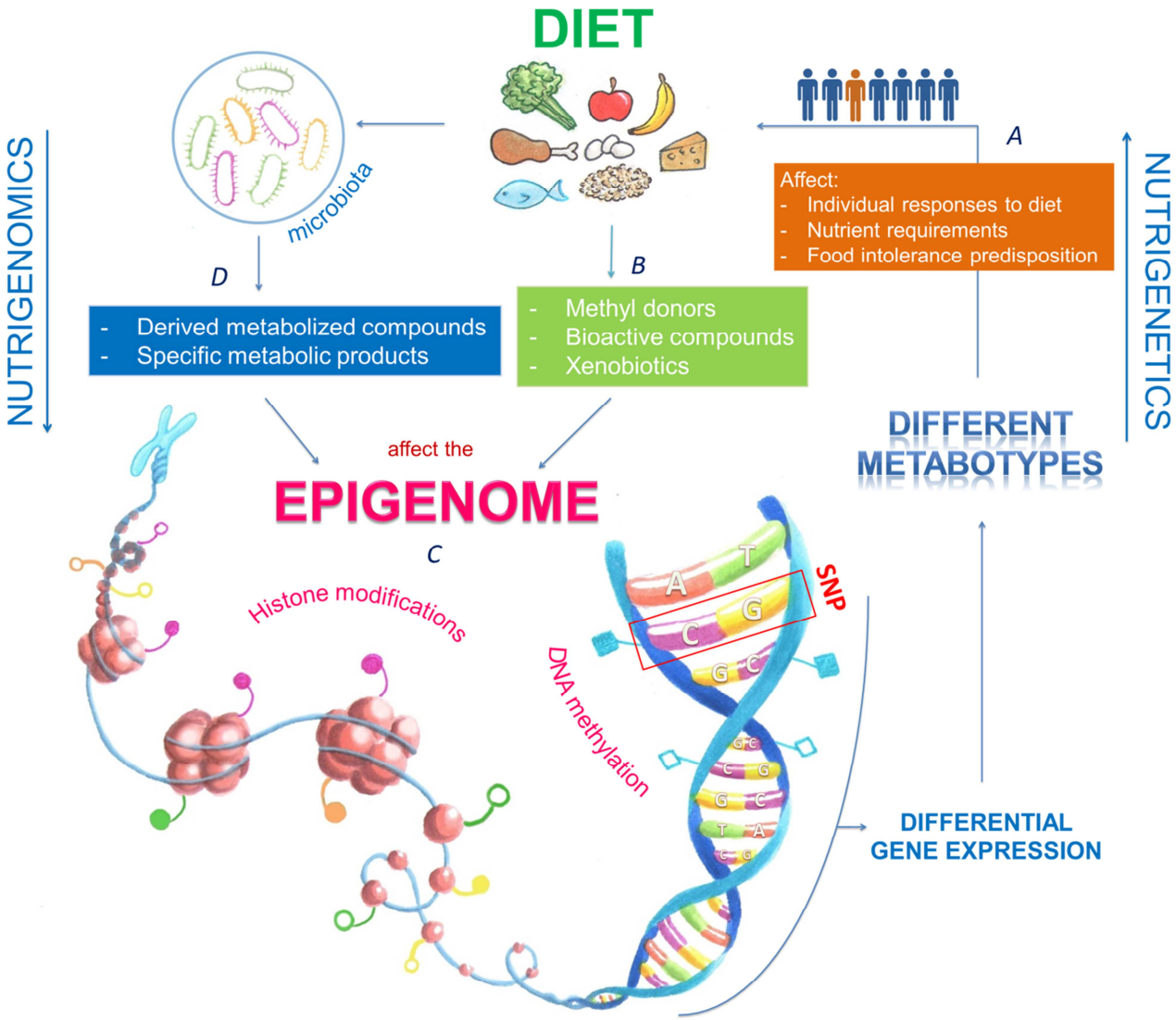

Figure 1. Graphical representation of interactions between diet and the genome. *(A) Nutrigenetics:* genetic polymorphisms can induce differential gene expression. As a result, different metabotypes, which show different responses to diet, different nutrient requirement and potential food intolerance, exist. Of note, the location of the SNPs can also affect epigenetic modifications. *(B-C-D) Nutrigenomics*: methyl donors availability, bioactivity of dietary compound and xenobiotics (B) can affect the one-carbon cycle and other pathways thus, consequentially, affect DNA methylation and histone modifications (C). Not just parental molecules (B) but also derived compounds and metabolic products of microbial activity (D) can affect these pathways (C).

2.2 The role of genetic variants in nutrition

Nutrigenetics examines inherited differences in nutrient metabolism and investigates how to use individual genetic information to tailor better nutrition plans [117]. Several different types of genomic structural variation emerged from the investigation of human genome [122]. SNP, inverted gene sequences, gene deletion, segmental duplication and CNV has been almost all associated to some nutritional-related phenotype or showed to be able to modify individual's response to diet.

While the 'simple' Mendelian genetics is responsible for inborn errors of metabolism such as alkaptonuria or phenylketonuria, multifactorial diseases, such as diet-related diseases and obesity, are seldom due to single genetic variants. For example, at least ninety-seven variants resulted to be associated with body fatness , and together these explain <3 % of the variance in BMI [123,124]. Numerous pathways affecting the central nervous system (i.e. satiety regulations or food intake) or metabolic features, such as lipid metabolism and adipogenesis, are regulated by the involved genes. Additionally, genetic variants involved in various cell biology, cell signaling and in RNA binding processing has been related with adiposity risk as well [123]. This is just an example intended to underline the complexity of nutrigenetics, which aim to study complex polygenic traits, related to numerous different physiological pathways.

Genetic variants able to modulate the effects of certain dietary factors or to affect food preferences can be investigated through different experimental approaches. The candidate gene approach is based on the selection of a gene because of its putative function or for other specific knowledges about it. In dependence on the number of SNPs in the gene and their potential functional effects, assessments can be conducted using single SNPs or combinations of them, such as haplotypes. More recently, genome-wide approach started to be applied in modern studies. This method is based on the identification of previously unknown genetic variants which can modify response to diet scanning the entire genome. Whether a candidate gene approach is preferential if few genetic variance (selected *a priori* following a certain hypothesis) want to be tested with a high power, GWAS has the advantage to be hypothesis-free and can be useful for exploratory analysis, testing large number of variants at the same time. At the same time, very large populations are required for GWA studies to have a good power. Other strategies, such as meta-analysis of GWAS or calculation of genetic risk score, can be helpful to increase the analyzed population or take into account different genetic model, respectively.

Recognizing relevant diet-gene interactions will not only be useful for individual personalized dietary advices, but will improve public health recommendations (supported by scientific evidences connecting specific dietary compounds to different health outcomes) and scientific research as well. In fact, studying people responses to a nutrient assuming that they are all metabolically similar, often results in the identification responders and non-responders to the intervention, and this observed variation in the

outcome is frequently attributed to weaknesses in the scientific design of the study, making obtained results difficult to publish ad difficult to use to improve human health. Thus, the usage in study projecting of modern genetic methods, through which is possible to predict who are the responders, could strongly help to improve results and optimize resources [117].

2.3 Genetic determinants of responsiveness to dietary interventions.

Diet represents a key modifiable risk factor for human health. However, benefits we currently gain are significantly reduced comparing to the full potential of its protective effects. Several reasons can be at the basis of this phenomenon, including individual variability in response to certain nutritional regimen. Taking into account that genetic variants can create metabolic inefficiencies, it is reasonable to hypostesize that such SNPs can influence dietary requirements. Thus, it is almost evident that taking into account individual responses is essential to gain the full benefit of dietary regimes [125].

There are considerable evidences that inter-individual variation in response to dietary interventions can influence beneficial effect that certain individuals or population subgroups can obtain, more than others, from a diet, in dependence on their genotype, phenotype, and environment [126]. Despite that, dietary reference values, which are designed for the general population assuming a unique Gaussian distribution, are not optimized for genetic subgroups, which may significantly differ for noteworthy metabolic aspects (such as for example the activity of metabolic enzyme requiring micronutrients as cofactors and/or micronutrient transport proteins) because of their genetics [126]. Considering that the "one-size-fits-all" approach applied in nutrition until now resulted to be unsuccessful, the identification of genetic variants, that recognize responsive and non-responsive individuals for specific dietetic intervention, represents one of the most challenging and potentially useful goal of nutrition research. If the issue is relatively easy for monogenic characters (such as the genetic determinant of lactose intolerance), the landscape becomes more intricate for complex polygenic traits, such as predisposition to hypertension or diabetes. Despite consistent efforts, it is still to be cleared how to modulate disease development through consumption of a complex diet based on different genotypes [125].

2.4 Nutrigenetic tests for personalized nutrition

Precision nutrition can occur at three levels: (1) conventional nutrition, following general guidelines for population groups by age, gender and social determinants; (2) individualized nutrition, that take into account also phenotypic information about current nutritional status of the subject (such as, among others, biochemical and metabolic analysis, anthropometry and physical activity), and (3) genotype-directed

nutrition, taking into consideration rare or common gene variation which determine different responses to certain nutritional plans [127]. The use of genotypic information in tailoring personalized dietary advice has been a major objective since the beginning of the modern nutrigenomics era [128]. Several beneficial effects of providing personalized nutritional advices, such as supporting disease prevention, reducing health care costs and improving motivation to change, has been observed [129,130]. Besides, recent randomized control trials showed that genotype-based personalized dietary advices were better understood and increased the adherence to the nutritional plan than general dietary advice[130,131]. This result is not irrelevant, considering that compliance and diet adherence has been identified as one of the most effective parameters in nutritional intervention success [132].

Relevant findings concerning this aspect come from the EU-funded Food4Me project[133]. It is a multi-center study aimed to investigate if fully internet delivered personalized nutrition advice (according to individual phenotype and genotype) could affect people's lifestyle. Promising data from the Food4Me European randomized controlled trial involving 683 participants shows greater body weight and weight circumference reductions in risk carriers than in non-risk carriers of the fat mass and obesity-associated (*FTO*) gene, when participants were informed to be carriers of the *FTO* risk allele [134]. Further investigations from the Food4Me study showed that adherence to specific healthy regimens, such as the Mediterranean diet, can have beneficial effects on anthropometric parameters overcoming an adverse genetic load [135]. Nevertheless, San-Cristobal and colleagues demonstrated that a higher genetic risk score (calculated by several genetic variants related to metabolic risk features) may reduce benefits on total cholesterol levels and influences the levels of plasma carotenoids, indeed suggesting that gene × nutrient interactions might contribute to the implementation of practical accurate nutrigenetic advice. However, despite promising evidences, no univocal demonstration that including phenotypic plus genotypic information can improve the effectiveness of the personalized nutritional advice can be inferred from this big study [136,137].

All in all, nutrigenetics is still involved in an extensive discussion about personal genetics, which started in 2001 with the presentation of Sciona Ltd. (in the United Kingdom), and persisted with the subsequent launch of popular companies such as 23andMe, Navigenics and deCode in the following years [138]. The principal query, indeed, concerns the clinical utility of nutritional genetic tests: can the evidences coming from nutrigenetic studies be translated into helpful dietary recommendation which would not be accessible without the use of genetic information? There is emerging consensus on the idea that each subject's health is established by interactions between his or her fixed genotype and nutrition (among other environmental exposures), in addition to the effects of stochastic events, as hypothesized in the ''health pendulum'' theory. Nevertheless, current knowledge in this area is fragmentary, and a limited number of diet–gene–health associations have been tested for causality in intervention studies on humans

[128]. Filling these gaps will require larger, even better-designed randomized controlled trials. At the same time, it is also true that most of nutritional recommendation come from observational and epidemiological studies. Thus, it is debated why the level of evidence for genetically influenced nutritional advice are not evaluated according to the same standards used for traditional nutritional recommendations [138]. Gorman and collaborators also discuss risks and benefits of precautionary principle, thus ignoring nutrigenetics. For certain nutrigenetic evidences, such as those regarding methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism, folic acid, and homocysteine, it is to choose that chronically high homocysteine is potentially less dangerous than increasing daily folic acid intake, in individuals who don't benefit of the standard recommended intake because carriers of the TT genotype. Whether ignore new scientific evidences can sometimes be synonymous of applying the precautionary approach, it is probably not always the case of nutrigenetics. Wildavsky [139] claims that in the case of lack of knowledge, small-risk taking, followed by stepwise evaluation, is a safer course than avoiding risk. Cautious estimation of the balance between benefits and risks, together with a step by steps approach able to progressively increase the benefits and diminish the risks, would be probably the best way to approach nutrigenetics. This means that more and more research on this promising field is required. The inconsistent results produced by the candidate-gene association studies are actually not associated to the research quality in general, but rather to the complexity of nutritional effects in the long term. Technological improvements and the increasing usage of genotype analysis in randomized control trials suggest a promising increase of knowledge in this field in the next years.

Thus, it is clear that nutrigenetics is not a science with easy answers and it doesn't rely on a standard dietary recommendation to each genotype. Nutritional factors interactions with the genome are very complex and need competent nutrition professionals who can guide patients successfully through this complex landscape [117]. Furthermore, from a dietetic point of view, there is often not just one simply solution for a specific problem. On the contrary many solutions can be designed by dieticians, physician and nutritionist, depending by other characteristics of each analyzed subject beyond its genetics. In fact, personalized nutrition is based, per definition, on the knowledge and integration of the genetic background with biological and cultural variations, such as food preferences, intolerances and allergies. This means that the genetic profile alone is usually not sufficient to provide a personalized dietetic plan, while it has to be integrated by expert professionals with patient anamnesis, anthropometry, food preferences and life-style. For this reason, another open debate is currently centered on the legitimacy of direct-to-consumer (DTC) tests [140], which, in a certain way, bypasses this multifaceted approach, avoiding the mediation of professionals able to provide a correct interpretation and usage of genetic data.

Concluding, to understand what can be legitimately used, a deep knowledge of the topic is essential. In addition, personalized nutrition needs to be kept in its proper context, that not overlaps with clinical

genetics, disease treatment, or disease prediction. In fact, nutrigenetics uses genetic information in a different way than classical genetics; it does not estimate disease risk based on association studies but provides exact information based on specific interactions between gene and diet, to identify subgroups which could maximize the benefit of different nutritional interventions.

3. Nutrigenomics

3.1 Introduction to Nutrigenomics

Nutrition research has gone through a relevant shift in the past decade, from focusing on physiology and epidemiology to biochemistry, genetics and molecular biology. Micronutrients and macronutrients have been clearly recognized as powerful dietary signals able to affect metabolic programming of cells, with a central role in the control of body homeostasis [141]. These evidences make the scientific community to realize that it is not possible to really understand the impact of nutrition on health and disease without a deep knowledge of molecular effects of nutrients. Nutrigenomics, which also includes the study of genes that influence different predisposition to nutrition-related impairment (hence nutrigenetics), attempts to study in a broad way the genome-wide influences of nutrition, with the major goal to apply this knowledge to prevent diet-related diseases.

3.2 Nutritional factors that can influence the epigenome and the mechanisms involved

In some ways, nutrigenomics can resemble to pharmacogenomics[142]. However, an important difference between these two disciplines is that pharmacogenomics concerns with the effects on the genome of drugs, which are pure compounds, given in exact doses, while nutrigenomics has to take into account the complexity and variability of nutrition. This concept is just a tip to have an idea of the complexity of this research field.

The study of gene expression patterns, protein expression and production of metabolites in response to certain nutrients have been the main object of nutrigenomic studies at the beginning of this new science. From the point of view of nutrigenomics, nutrients are dietary signals which are perceived by the cellular sensor systems, and which are able to affect gene and protein expression and, consequently, metabolite production [143].

Recently, among the wide spectrum of activities for which many nutrients are known in their role on prevention and mitigation of various diseases, epigenetic effects acquired an emerging importance. This specific research area, which describes effects of nutrients on human health through epigenetic modifications, has been referred as nutritional epigenomics, or “nutriepigenomics” [144] (Figure 1 B-C).

Whether several studies demonstrated that numerous nutrients and bioactive compounds influence different pathways through which epigenetics affects gene expression, there are still relatively few information about the precise mechanisms through which nutrients modulate epigenetics. Different ways through which what we eat can influence the expression of our gene through epigenetics have been suggested. These multiple mechanisms are mutually compatible and may operate together in time, enriching the complexity of this regulative pathway [144,145]. They can be clustered in three main groups: 1) food provides substrates necessary for proper methylation of DNA and histones, cofactors that modulate enzymatic activity of DNA methyltransferases and can regulate activity of the enzymes involved in the one-carbon cycle; 2) bioactive molecules contained in food can directly or indirectly interact with the epigenome, as well as 3) toxicant contained in food also can (Figure 1 B).

Most of the understanding concerning the ability of nutritional factors to modulate gene expression by epigenetic mechanisms refers to the one-carbon metabolism, a complex network of interrelated biochemical reactions in which methyl donor nutrients provide one-carbon units to different biochemical and molecular reactions. This step is essential for several molecular pathways including DNA synthesis, purine synthesis, methylation of DNA, RNA, protein, phospholipids and small molecules [146]. Nutrients are processed through the folate cycle and the methionine cycle, serving as methyl sources for the universal methyl donor, S-adenosylmethionine (SAM). A methyl group from SAM can be enzymatically transferred to other molecules (i.e. specific cytosines in the DNA), thus generating S-adenosylhomocysteine (SAH) (which acts as an inhibitor of methyltransferases themselves) as an end product. For this reason, nutrients affecting one of the two main metabolites of the one-carbon metabolism (i.e. SAM or SAH) can potentially alter the methylation of DNA and histones. DNA methylation can be affected by four different type of nutrients: 1) dietary methyl donor nutrients (methionine, choline, betaine, serine); 2) B vitamins (B12, B6, B2, B9) as coenzymes of one-carbon metabolism (with folate acting as acceptor or donor of methyl groups), 3) micronutrients which can affect one-carbon metabolism (zinc, retinoic acid, selenium) and 4) bioactive food compounds that can modulate DNA methyltransferases' activity [81].

Not just specific nutrients play a role in nutrigenomics, but also bioactive molecules, such as secondary plant metabolites, can modulate gene expression. Epigallocatechin-3-gallate, genistein, equol, myricetin, but also butyrate, sulforaphane and curcumin have been showed to be epigenetically active [144,147], not just regulating DNMTs functions, but also acting as chromatin remodelers through modulation of histone deacetylases (HDAC).

Interestingly, it must be noticed that epigenetic mechanisms are strongly associated to cellular oxidative stress homeostasis [148], and, finally, they are not just involved in nuclear gene expression regulation, but also strictly involved in mitochondrial functions regulation too [149]. These observations further increase the number of potential indirect effects exerted by nutrigenomics on health.

Another aspect to consider is that molecules contained in the food we eat can affect and be affected by the gut microbiome. The production of metabolites acting as allosteric regulators and critical cofactors of epigenetic processes, is one of the major mechanisms linking gut microbiota and control of gene expression. Indeed, the gut microbiota produce numerous low weight bioactive molecules which can play a role in epigenetic processes, i.e. folate, butyrate, biotin, and acetate. In addition, the absorption and excretion of minerals such as zinc, selenium, iodine, cobalt (indeed, cofactors of enzymes participating in epigenetic processes) is influenced by the microbiota, which can also metabolize bioactive compounds contained in food (i.e. ellagic acid and ellagitannins are metabolized in urolithins) influencing their bioavailability [150,151] (Figure 1 D).

Moreover not just natural food components but also several classes of pesticides (including persistent organic pollutants, arsenic, endocrine disruptors, several herbicides and insecticides) have been shown to modify epigenetic marks [152–154]. Numerous investigations studied the effects of environmental exposures on epigenetic markers, identifying many toxicants able to modify epigenetic states (in particular in terms of DNA methylation and histone modifications) similarly to what happens in some pathological conditions [152,155–157]. Additional investigations are necessary to clarify if epigenetics can act as a causal link between exposure to pesticide and health outcomes, or rather be a sensitive early biomarker of exposure.

3.3 Susceptible period of exposure, epigenetic reprogramming and transgenerational effects in nutrigenomics

The mechanisms previously described provide convincing evidence that epigenetic marks serve as a memory of exposure to environmental factors and, among others, inadequate or inappropriate nutritional factors. These environmental stimuli can have different impact depending on the period of life of the exposed organisms. Considering the epigenetic plasticity of growing and developing tissue, exposures during early life represent a critical period [158–160]. Not just pre-natal and intrauterine periods, but also post-natal early life and periods of epigenetic remodelling characterized by rapid physiological changes (such as puberty and aging) represent susceptible period of exposure[147,161].

Several examples of late onset disease have been found to take their origins in early life period, or at least to be influenced by episodes occurring in the first stages of life. Furthermore, in addition to prenatal and postnatal nutritional effects, which can result in stable changes and predispose individuals to disease later in life (which is referred as “early life programming”), transgenerational mechanisms must be considered. Transgenerational epigenetic inheritance can result from several different environmental exposures, even though little is known about the mechanism undergone to the maintenance of the

epigenetic marks suggested to be involved in this phenomenon. It has been established that factors like maternal diabetes, behavioral programming (maternal care), nutritional interventions (carbohydrate-rich or fat-rich diet or caloric restriction), glucocorticoids and exercise, endocrine disruptors, stress during gestation and lactation may all cause imprinting in the following generations [144].

One of the most cited and studied example that clearly shows the role of nutrigenomics is the Agouti mouse, where coat color variation and healthy/unhealthy phenotype is established early in development according to maternal diet [162,163]. Another example is represented by protein malnutrition in pregnant mice which resulted to determine significant gene expression changes, miRNA changes, and different DNA methylation patterns in brains of the offspring [164]. Studies on humans that corroborate transgenerational inheritance also exists. One of the first example is the "the Dutch famine study", which showed that starvation in one generation affects the risk for glucose intolerance and metabolic disorders in its offspring [165]. Another pivotal study has been conducted on the Överkalix population, where overeating by paternal grandfather or father induced increased risk for cardiovascular diseases or diabetes in grandsons, while a reduced food availability during father adolescence exerted an opposite effect in the offspring [166].

Despite better controlled studies in humans are needed, a hypothesis which could powerfully impact our lives is emerging: what do we eat, is not just important for us, but may affect future generations' health as well. Moreover, given that thousands of nutrients and other compounds are contained in food, but only few of these have been tested for transgenerational epigenetic effects, further research in this field is essential in order to promote public health and set sensible public policy.

3.4 Interactions between nutrigenetics and nutrigenomics

Even if based on different scientific approach, nutrigenetics and nutrigenomics cannot be considered separately. In fact, if it is true that certain dietary molecules can potentially modify cellular homeostasis, it is also true that the alteration of the homeostatic mechanisms especially occurs in individuals with susceptible genotypes [143]. Indeed, not only nutrients, but also the genetic make-up can surely impact one-carbon metabolism (Figure 1 A). Among different combinations of nutrients and genes, folate and the MTHFR 677 C to T SNP represents a peculiar example of nutrient x gene interactions affecting DNA methylation. In particular, carriers of the MTHFR 677TT genotype display a reduced availability of 5-methyl tetrahydrofolate and a consequent higher folate requirement for the regulation of plasma homocysteine concentrations. Interestingly, researchers showed that not all MTHFR 677TT carriers had impaired global DNA methylation levels, but just those who were deficient for folate, suggesting that MTHFR C677TT SNP affects genomic DNA methylation status through an interaction with folate status [167].

Similar conditions can occur for other metabolites of the one-carbon cycle, such as for choline, a methyl donor necessary for the conversion of homocysteine to methionine [168]. Excluding diet, the only other source of choline is the de novo biosynthesis of phosphatidylcholine (can be converted to choline) catalyzed by phosphatidylethanolamine-N-methyltransferase (PEMT) in liver. Considering that the consume of foods containing choline are often discouraged because rich in fat and cholesterol (e.g. eggs and liver), it has been measured that only a small percent of the population achieves the recommended adequate intake for choline, in particular man, post-menopausal women and the 44% of pre-menopausal women. The risk of choline deficiency is reduced in young woman because PEMT is estrogen-inducible; however, it is interesting that those women that are more prone to choline deficiency (even at youngest age) have a SNP in PEMT (rs12325817); similarly women with the rs2236225 SNP in the gene MTHFD1 (5,10-methylenetetrahydrofolate dehydrogenase 1) are 15 times more predisposed to develop signs of choline deficiency in case of low-choline diet respect to wild types [169]. This example shows how dietetic intake of choline can be particularly important for a certain subpopulation (pre-menopausal women carriers of the susceptible gene alleles), not just simply counteracting a specific metabolic deficiency, but also protecting from impairment of epigenetic regulation processes.

Another different interesting example of interaction between genetic and epigenetics is represented by the lactase persistence. To date, inter-individual differences in lactase expression in human adults have been ascribed merely to DNA sequence variation upstream of lactase (LCT) gene. Specifically, the rs4988235 SNP (C/T-13910) has been related to the phenotypes of lactase persistence and non-persistence in European populations [170]. Nevertheless, it is interesting to notice that in non-Europeans, this SNP does not fully explain lactase persistence, with certain African individuals exhibiting lactase in the absence of LCT-associated variants. Furthermore, the molecular mechanism able to explain the age-dependent changes of LCT expression (that varies from very high levels in infancy to significant downregulation in most of adults) is also unclear. Considering that DNA sequence is steady, more dynamic regulatory systems must be dragged in the temporal variation of lactase non-persistence. Interestingly, recent studies showed that lactase non-persistence derives from accumulation of transcriptionally suppressive epigenetic changes on the SNP C-13910 carriers, while T-13910 carriers escape from epigenetic inactivation facilitating lactase persistence [171].

3.5 Personalized epigenomics

Improvement in personalized epigenetics for the therapy and management of several specific pathologies is quickly conducting to an important increase of the tools accessible to clinicians in preventing and controlling diseases that have an epigenetic base in their etiology and pathogenesis. An case in point is

represented by chronic pain management, for which an important role of epigenetics has been highlighted. In this case, assessing the epigenomic marks in subjects suffering from chronic pain could have substantial utility in the selection of adequate analgesics which can give relief to patients affected by chronic pain [172]. Several genes which are under epigenetic control can also affect the onset of obesity and related metabolic diseases (for instance diabetes) [173]. Dietary factors are well known to produce epigenetic changes, with a certain inter-individual variability of the effects. Concerning obesity, both the quality and the quantity of diet have been demonstrated to modulate the epigenetic signature of individuals inducing epigenetic irregularities that could be managed by personalized therapy [174]. Thus, taking into account personalized epigenetic approaches would represent a great improvement in the efficacy of obesity management. Furthermore, personalized epigenetics can be useful also in prevention, considering that environmental factors have central roles in the development of obesity, and epigenetic modifications can be reversible through changes in environmental factors (life-style in particular) that lead to such a disorder [174].

Even if this prospective is quite far from immediate practical application, interesting evidences about therapeutic applications of epigenetically active nutrients are available[147]. In fact, as epigenetic modifications are reversible and tissue-specific, a regulation of these processes through diet or specific nutrients could also help diseases prevention and health maintenance. Some of the natural products which showed positive outcomes on particular human diseases are also being studied in clinical trials. Surrogate endpoints associated with metabolic syndrome resulted to be improved by genistein indirectly reducing the risk of developing diabetes and cardiovascular disease [175]; similarly, a reduction of type II diabetes onset has been observed in pre-diabetic individuals supplemented with curcumin [176]. Genistein, curcumin, epigallocatechin-3-gallate and resveratrol are some of the phytochemicals that have been demonstrated to trigger the anti-inflammatory machinery and improve some of the symptoms associated with metabolic syndrome [177]. These are just few examples of potential epigenetically active nutrients and their beneficial effect that has been hypothesized to be exerted through epigenetic processes[147].

Furthermore, nutrigenomics strongly improves current knowledge in nutrition providing, through the usage of metabolomic and epigenetic approaches, novel biomarkers of food intake and dietary patterns which will lead to more objective and robust measures of dietary exposure [121]. For all these reasons, it is clear that application of nutrigenomics research can offer considerable potential to improve public health [178].

4. Conclusions

Nutrition is one of the most important life-long environmental factors able to impact human wellbeing. Among the mechanisms involved, *genome x nutrient* interactions have been definitely demonstrated to play an important role in health maintenance and disease prevention. The disciplines of nutrigenetics and nutrigenomics aim to address how genetics and epigenetics can explain individual dietary susceptibility and to understand how human variability in preferences, requirements and responses to diet can be implemented in a personalized nutrition. Despite a growing interest of the scientific community for these topics, the body of research is still to be enlarged to make the actual knowledge able to provide personalized advices tailored by nutrigenetics and nutrigenomics [179]. Given the high potential of these disciplines, research on nutrigenetics and nutrigenomics should be promoted and divulged to a wide-reaching audience [180,181], in order to make both professionals and the general population aware of the profound effects of nutrition on our health.

Author contributions

L.B. wrote the article, R.G. supervised, revised and proofread the paper. All the authors approved the final version of the manuscript.

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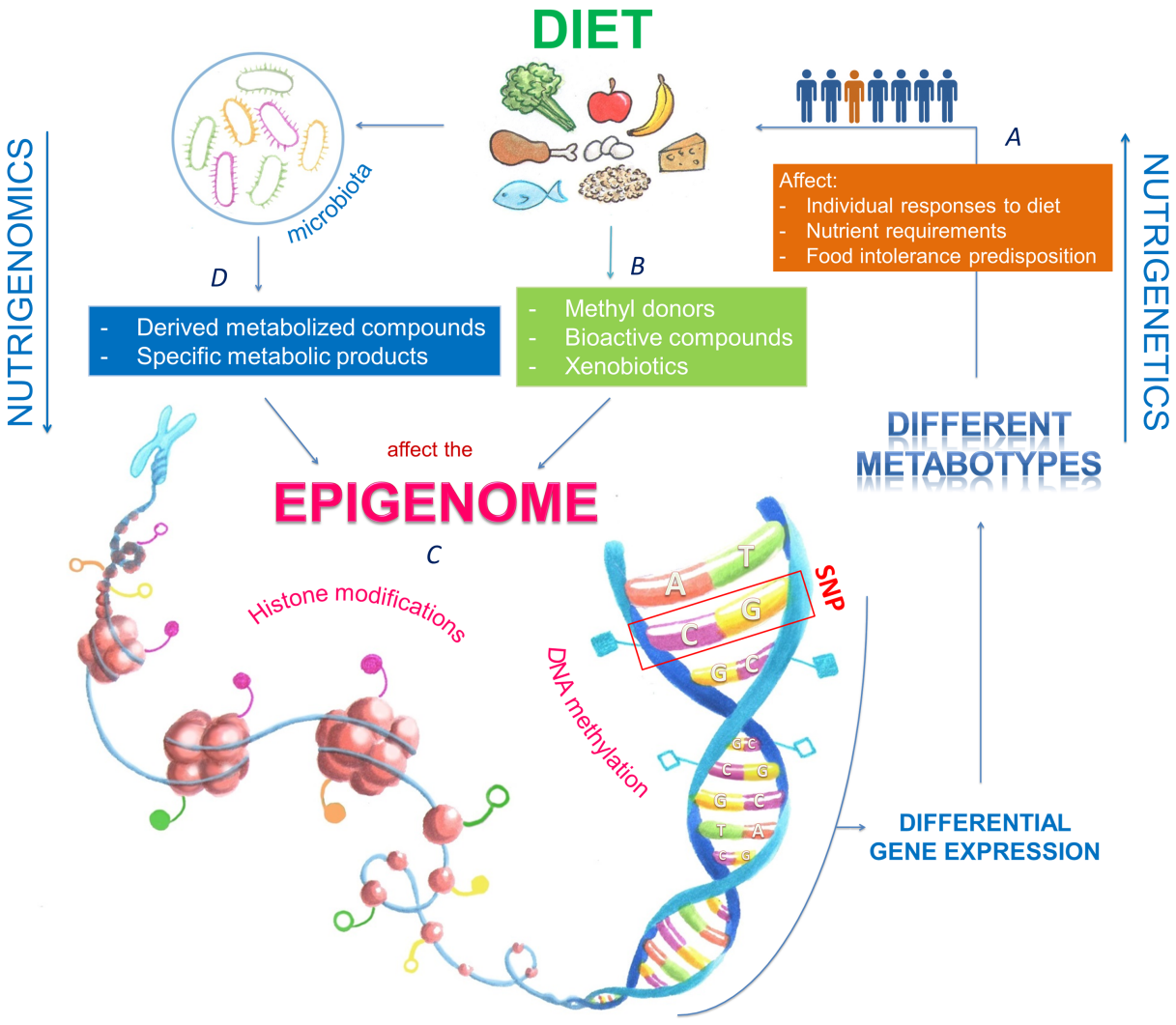
DIET
microbiota
A
Affect:
- Individual responses to diet
- Nutrient requirements
- Food intolerance predisposition
NUTRIGENOMICS
NUTRIGENETICS
D
B
- Derived metabolized compounds
- Specific metabolic products
- Methyl donors
- Bioactive compounds
- Xenobiotics
affect the
EPIGENOME
C
DIFFERENT METABOTYPES
Histone modifications
DNA methylation
SNP
DIFFERENTIAL GENE EXPRESSION

- Nutrition is a major environmental factor able to interact with the genome
- Polymorphic variants affect individual predisposition to food intolerance and nutrient requirements
- Nutrition affects gene expression, also via epigenetic mechanisms
- Food contains methyl donors, bioactive molecules and xenobiotics which can affect the epigenome
- Further studies on nutrigenetics and nutrigenomics would lead to personalized nutrition

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