Lifestyle Genomics: Addressing the Multifactorial Nature of Personalized Health

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On behalf of Karger Publishers, we would like to welcome you to *Lifestyle Genomics* – a new journal dedicated to the dissemination of research investigating the interactions between lifestyle factors and genes, and how these interactions influence health and disease outcomes (Fig. 1). The goal of this Editorial is to formally introduce *Lifestyle Genomics* to the research community. Our hope is that when authors look to publish their research in the area of lifestyle-gene interactions, they will no longer ask the question “What is the journal *Lifestyle Genomics* all about?”, but will rather recognize it as *the* optimal journal to publish their findings. This Editorial will provide readers with an overview of lifestyle-gene interactions, and how this highly topical area will improve our understanding of ethnic-specific disease risks, unravel how lifestyle factors influence cell and tissue function, and identify factors that shape both the epigenome and microbiome. Select examples will highlight the role of dietary factors, physical activity, and sleep as important lifestyle factors that influence health outcomes. Ultimately, we anticipate that the research published in *Lifestyle Genomics* will be used to directly support the development and refinement of personalized health strategies to minimize disease risk.

Why Was *Lifestyle Genomics* Created?

The *Journal of Nutrigenetics and Nutrigenomics* was launched in 2007 with the goal to become the leading journal for the dissemination of diet-gene interactions, as well as the official journal for the International Society of Nutrigenetics/Nutrigenomics (ISNN). However, it is now widely appreciated that numerous lifestyle factors (in addition to diet) also interact with genes

to affect health and disease outcomes. Consequently, it was felt that the *Journal of Nutrigenetics and Nutrigenomics* needed to broaden its scope to reflect the rapidly growing area of lifestyle-gene interactions. This prompted the *Journal of Nutrigenetics and Nutrigenomics* to be renamed to *Lifestyle Genomics* in 2018.

Overview of Lifestyle-Gene Interactions

The sequencing of the human genome is arguably one of the most significant and impactful achievements in modern biological sciences. The outcome following this landmark milestone was that researchers and physicians now held an unprecedented quantity of genomic information with which to make transformative advances in biology and healthcare [1]. The completion of the Human Genome Project prompted the development of new technologies and analytical tools that revolutionized how basic research is conducted, and provided the impetus for equally impressive milestones, e.g., the CRISPR/Cas9 method for genome editing. Importantly, the computational and mathematical approaches to deal with these enormous amounts of data have led to the formation of multi-disciplinary teams of computer scientists, statisticians, and engineers along with biologists and biochemists to answer complex research questions. Consequently, the scientific community now finds itself holding the requisite tools and technologies, as well as the computational know-how, to study the many facets of human genetic variation.

The Human Genome Project provided the scientific community with the blueprint to better understand the links be-

Fig. 1. Lifestyle factors influence disease risk. Lifestyle factors including diet, exercise, smoking, and medication, amongst others, can modify the gut microbiome (or can be modified by the microbiome) or can act directly to regulate gene, protein, and metabolite function in a cell- and tissue-specific manner. These interactions can influence a wide range of health outcomes.

tween genes and human health. This led to establishing international consortiums, such as the HapMap Project [2] and the 1000 Genomes Project [3], to create publicly available catalogues of human variation and genotype data that are readily accessible to researchers. The data collected and curated by these consortiums continue to play a key role in the search for disease-causing single nucleotide variants (SNPs). Although common chronic diseases, such as atherosclerosis, cancers, and neurodegenerative disorders, are not caused by single genetic variants, it is clear that individual SNPs can influence disease risk. For example, individuals carrying the risk allele for a SNP (rs9939609) in the fat-mass and obesity-associated gene (*FTO*) weigh approximately 3 kg more than individuals with no copies of the risk allele [4]. While this association has been replicated in numerous independent studies and shown to have the greatest impact on body weight, this SNP does not explain obesity. Nevertheless, knowledge of SNPs that influence health outcomes will help to advance our understanding of human variability (e.g., ethnic-specific disease risk) and provide an opportunity to personalize therapies. As such, the multitude of SNPs catalogued in the human genome has laid the foundation for the fields of personalized/precision medicine and nutrition.

It is recognized that a diet-gene interaction, while incredibly important for understanding different responses to foods, is only one example of a gene-environment interaction that can influence human health. Equally important is the rapidly growing area of exercise genomics, i.e., the study of exercise-gene interactions. It has long been recognized that physical activity can improve dyslipidaemia, glucose tolerance, hypertension, and obesity. Furthermore, the response to exercise is highly variable among individuals [5]. A recent study by Guest et al. [6] eloquently demonstrated that a person's response to caffeine, which is widely used as an ergogenic aid to improve performance, is associated with a SNP in the *CYP1A2* gene. These authors reported that some athletes who carry a specific allele

in *CYP1A2* and who consume caffeine to improve their performance may, in fact, be doing the exact opposite. Equally important is the growing appreciation that chronotype, which describes preferred timing of sleep and wake and corresponds to the circadian rhythm, is a heritable trait [7]. Three genome-wide association studies (GWAS) have identified numerous SNPs in circadian clock genes that associate with chronotype and may provide additional insights to better understand the relationships between sleep patterns and chronic diseases. Additional factors such as smoking, alcohol consumption, and xenobiotics are also critically important to consider.

Genetic investigations in the general population, as well as defined subsets of the population, are essential for improving our knowledge of why people respond differently to the same lifestyle factor and how this can influence disease risk. However, lifestyle factors are also known to influence gene expression in a cell- and tissue-specific manner, both directly and via epigenetic mechanisms. Altered gene expression can influence protein abundance and function, which consequently influences metabolite levels. Studies that employ 'OMIC technologies, either singly or in an integrative manner, will generate new insights to better understand how lifestyle factors regulate cell and tissue function. Ultimately, these lines of investigation, amongst others, will help to determine causality from correlation in regard to the relationships between lifestyle factors and health outcomes. The following subsections provide brief overviews of these areas of research and their relevance to *Lifestyle Genomics*.

The Genetic Basis for Ethnicity-Specific Disease Risk

The determinants of disease are as diverse as the diseases themselves. Methodological advances in dietary assessment, such as semi-quantitative food frequency questionnaires (FFQs) [8] and metabolomic technologies [9, 10], enable the

relationships between diet and disease outcomes to be investigated in large nutritional epidemiological studies. These methodologies are widely used by the research community to uncover lifestyle factors associated with disease risks. The relationship between trans fats and cardiovascular disease risk [11], and the association between added sugars and cardiometabolic disease [12], are two examples that have been replicated in numerous studies [13, 14]. The consequences of these important discoveries have ramifications not only on the research community, but also on health policy and the food industry. For example, trans fats have recently been cut from the global food supply chain and many countries are now meeting the World Health Organization's (WHO) recommendations of <1% total energy intake from trans fats [15]. A reduction of added sugars in foods may be the next major policy to have widespread impacts. However, of the many nutrients in the human diet that have been associated with disease, few have survived the rigours of meta-analyses. Nutrients historically associated with disease risks, such as saturated fat [13, 16] and sodium [17, 18], are being revisited and reevaluated because of discrepant findings due to population and study heterogeneity.

Heterogeneity can stem from differences in study design (observational vs. intervention, outcomes of interest, metrics assessed, research infrastructure, and data collected) and study populations (e.g., geographic distribution, socioeconomic status, age, and ethnicity). When conducting a meta-analysis, differences between studies are often accounted for with subgroup analyses (e.g., stratifying by primary vs. secondary outcome) or standardized mean differences of related outcomes (e.g., BMI and body weight). However, differences in populations are more difficult to address, as this depends on the demographic details provided in published articles. Unfortunately, sufficient information is not usually available for detailed population stratification. For example, a meta-analysis reporting on the association between a plant-based diet and plasma lipids undertook a subgroup analysis between North America and South America [19]. While this enabled the influence of shared continental habits on effect sizes to be approximated, these geographic regions have very high degrees of ethnic and cultural diversity that need to be considered [20]. This represents a significant obstacle given that the genetic profiles and lifestyle habits of different ethnic groups have a major influence on disease risk [21, 22]. For example, an ethnically diverse prospective birth cohort of ~4,000 mother-infant pairs reported that consuming a plant-based diet during pregnancy was associated with a lower birth weight [23]. However, upon closer inspection, a plant-based diet was associated with reduced birth weight for infants born to white European mothers, while the opposite was seen for infants born to South Asian mothers. While this finding remains unexplained to date, differences in cooking habits and residual confounding between ethnic groups have been proposed. It is also necessary to consider underlying genetic differences related to the digestion, absorption, metabolism, and storage of nutrients when trying to elucidate ethnic-specific associations between nutrients and health outcomes.

Inherent variation between ethnic groups allows us to use data from GWAS to impute a participant's ethnicity and confirm their self-reported ethnicity [24]. Although the influence for the majority of these genetic variants is subtle, significant differences in nutrient absorption and metabolism between ethnic groups have been reported, as shown with the following two examples:

1. *Vitamin D Receptor (VDR)*. A multi-ethnic US study identified significant differences in the frequency of a SNP in the *VDR* gene (rs731236) between white European, Hispanic, African, Japanese, and Chinese ethnic groups [25]. Another small multi-ethnic study of 72 healthy American children also reported differences in the prevalence of another SNP in the *VDR* gene (rs10735810) between ethnic groups (33% of white Europeans were homozygous for the major allele, while 66% were for African-Americans) [26]. Interestingly, this study in children reported significant associations between this *VDR* SNP and bone mineral density and calcium absorption. Briefly, major homozygotes were found to absorb more calcium and had greater bone density than minor homozygotes. In light of reports suggesting there are no significant differences in calcium intake between young white Europeans and African-Americans in the US [27], it is possible that: (i) higher frequencies of favourable alleles partly explain the increased calcium absorption and bone density observed in African-Americans and reduced risk osteoporosis in later life, and (ii) white European should be more strongly encouraged to consume calcium in childhood and into adolescence.

2. *Fatty Acid Desaturases (FADS)*. Numerous studies have reproducibly shown significant differences in the frequency of SNPs in the *FADS1/FADS2* genes between African, Asian, and white European populations [28, 29]. These genetic variants associate with differences in the abundance [28, 30] and metabolism [31] of polyunsaturated fatty acids (PUFAs). Fish oils, a source of n-3 PUFAs, are associated with numerous outcomes, including type 2 diabetes (T2D). However, a high degree of heterogeneity between studies has created considerable uncertainty in the field [32–34]. Analyses in population subgroups may help to explain heterogeneous findings. For example, following the analysis of 24 observational studies (24,509 T2D cases; $n = 545,275$ participants), no association between T2D risk and total fish, n-3 PUFA, or alpha-linolenic acid was observed [35]. However, stratification by ethnicity demonstrated that total fish and n-3 PUFA associated with a reduced risk of T2D in Asian populations, while predominantly white European populations showed an increased risk of T2D. Although no studies have compared the glycaemic response to n-3 PUFA supplements in different ethnic groups, it is reasonable to hypothesize that genetic differences in *FADS1/FADS2* genes may contribute to this ethnic-specific response.

The two aforementioned examples highlight the need to better understand: (i) the genetic basis underlying ethnic-specific differences in disease risk, (ii) the different responses to common lifestyle interventions observed in different subsets of the general population, and (iii) how personalized lifestyle rec-

ommendations may need to be tailored in an ethnic-specific manner. Additional genes of interest include stearoyl-CoA desaturase (*SCD*), flavin monooxygenase (*FMO*), insulin-induced gene 2 (*INSIG-2*), fat-mass and obesity-associated gene (*FTO*), melanocortin 4 receptor (*MC4R*), and proprotein convertase subtilisin/kexin type 1 (*PCSK-1*) [36–38], amongst many others. The frequency of variants in all of these genes has been shown to vary between ethnic groups. While differences in frequency do not necessarily infer a different genetic effect, it nevertheless can have widespread implications for public health policies that make general recommendations to multi-ethnic populations. Although the need to investigate lifestyle-gene associations in ethnically diverse populations is often acknowledged in the Limitations section of a peer-reviewed article, these types of studies should be conducted more routinely. Indeed, the impact of this type of research will not only improve our basic understanding regarding the genetics of chronic diseases, but will also play a central role in the development and application of personalized lifestyle strategies to improve health and well-being in distinct subsets of the population.

Integrating 'OMIC Technologies to Elucidate the Impact of Lifestyle Interventions

Researchers routinely incorporate 'OMIC technologies into their research programs, as reflected by the explosion of the use of these terms in peer-reviewed research since the mid-1990s. The increase in the use of 'OMIC technologies owes much to the advancements in technology and bioinformatics methodologies. The term "OMIC" is used to informally refer to investigations that implement global analytical technologies, such as transcriptomics, proteomics, and metabolomics. Transcriptomics refers to the global analysis of gene expression, proteomics to the large-scale study of protein abundance, and metabolomics to the systematic analysis of metabolites (i.e., low-molecular-weight biochemical molecules including sugars, amino acids, organic acids, nucleotides, and lipids). Additionally, several other 'OMIC technologies are rapidly gaining traction in the scientific literature, including epigenomics to study changes in DNA methylation patterns and histone modifications, metagenomics to analyze microbial populations, and small regulatory RNA transcriptomics to investigate RNA interference. The overall aim of these 'OMIC studies is to comprehensively characterize different pools of biological information from a biofluid, cell, tissue, or organ to obtain a deeper understanding of the structure, regulation, and function of a physiological process.

Lifestyle factors play an important role in determining a person's health status; however, any particular lifestyle factor can affect people differently. Recent studies using 'OMIC technologies have shown the heterogeneity that exists in response to various lifestyle factors [39–41]. In light of this, study participants are often classified as "responders" (anticipated outcome), "non-responders" (no response to the intervention), or "adverse re-

sponders" (a detrimental and often unexpected outcome). These different responses are, in part, related to genetic variability in the population studied [42]. It is therefore essential for studies to integrate different 'OMIC tools to better understand the impact of lifestyle factors on a given phenotype. Moreover, 'OMIC technologies can be used for the discovery of new therapeutic targets and biomarkers to either predict disease risk or monitor response to lifestyle interventions [43, 44]. For example, the integrative Personal Omics Profile (iPOP) study was a longitudinal study conducted in ~100 individuals that monitored genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from each individual during a 14-month period [45]. The results of the iPOP study revealed extensive molecular changes during different health states [45]. Similarly, an integrative 'OMIC analysis used transcriptomics, peptidomics, and fatty acid profiling to demonstrate that obese subcutaneous adipose tissue has a distinct fatty acid signature compared to lean subcutaneous adipose tissue [46]. Finally, the short-term consumption of an isocaloric low-carbohydrate/high-protein diet in obese subjects with non-alcoholic fatty liver disease revealed marked shifts in gut bacteria, plasma metabolite profiles, and hepatic gene expression [47]. These examples suggest that results obtained from integrative 'OMIC studies could be readily used to better personalize treatments in healthcare [44]. Future observational studies and clinical trials should consider using several 'OMIC techniques to obtain a more holistic understanding of phenotype and response to lifestyle factors.

Furthermore, *in vitro* and animal studies can also use 'OMIC technologies to characterize the metabolic pathways associated with health and disease risks [48, 49]. For example, an animal study used an integrated 'OMIC approach to characterize the effects of high-amylose-maize-resistant starch on the cecal microbiome, liver metabolome, and transcriptome under obesogenic conditions [50]. It is anticipated that integrative 'OMIC studies will help improve our understanding of complex mechanisms and responses to interventions, thereby increasing the likelihood of discovering novel biomarkers and/or therapies.

An ongoing challenge of using 'OMIC tools is the huge demand for data processing and analysis. However, the fields of bioinformatics and biostatistics have progressed impressively over the years and have kept pace with the enormous amounts of data generated by large-scale 'OMIC studies. Despite this progress, a lack of standardization of methods, both in regard to laboratory techniques and data analyses, often hinders the opportunity to compare results between studies. To address this issue, working groups have been established to develop guidelines to help standardize methods. For example, Grimaldi et al. [51] developed and proposed a framework to assess the strength of evidence regarding the scientific validity of diet-gene interactions. This is particularly important given the numerous direct-to-consumer genetic companies that currently provide their customers with personalized lifestyle recommendations.

Overall, 'OMIC tools should be incorporated into all types of studies that aim to explore the interactions between lifestyle factors and health outcomes. Such approaches will not only

help to answer specific hypotheses, but will also generate new avenues of investigation that were previously unknown. Ultimately, integrative 'OMIC analyses will enable researchers to predict more accurately which treatment and prevention strategies should be used for a particular individual or subset of the general population to mitigate disease risk. This will consequently lead to a more widespread adoption of personalized medicine and personalized nutrition in the healthcare system [52, 53].

Regulation of the Epigenome by Lifestyle Factors

Common complex diseases are polygenic and influenced by numerous non-genetic factors, such as the epigenome. Alterations in the epigenome are associated with the development of chronic diseases, including various cancers, obesity, T2D, metabolic syndrome, cardiovascular disease, and neurodegenerative disorders [54, 55]. These epigenetic changes may be inherited and/or acquired throughout the life span following exposure to environmental factors. Consequently, differences in the epigenome of a diseased individual compared to a healthy individual are widely reported in the literature. Further research is necessary to better understand how the timing and duration of exposure, amongst other considerations, to lifestyle factors influences the epigenome.

Epigenetics describes heritable modifications to DNA that regulate gene expression without changing the nucleotide sequence [56]. These mechanisms are key for understanding genomic function. Several major epigenetic mechanisms have been described to date: DNA methylation, histone modification, and, more recently, regulation by non-coding RNAs [57]. The first two mechanisms “*write*, *erase*, and *read*” information on DNA or histone proteins to direct structural modifications in chromatin that influence gene expression by controlling the accessibility of regulatory regions on DNA. In contrast, non-coding RNAs are transcribed from DNA, but not translated into protein. These functional RNA molecules regulate gene expression at the transcriptional and post-transcriptional level. Regardless of the mechanism, epigenetics is involved in a wide range of processes that include cell programming, development, aging, and adaptation to environmental factors.

DNA methylation generally occurs in regions containing promoters and other regulatory sequences in order to influence gene expression. This process is mediated by a family of DNA methyltransferase (DNMT) enzymes that transfer a methyl group to cytosine residues, producing 5-methylcytosine. Dietary methyl donors (e.g., folate and choline) are critical to support this process. Increased promoter methylation is typically associated with transcriptional suppression, while reduced methylation does the opposite [58, 59]. Similarly, histone modification is a second epigenetic mechanism that also regulates gene expression. Specific enzymes add methyl, acetyl, phosphate, and other functional groups to create marks on histone tails that modify the affinity between DNA and histone pro-

teins. This ultimately controls gene expression by relaxing or tightening chromatin. These marks may be removed enzymatically in response to a variety of factors, including dietary components [60].

Diet is known to have a key role in the regulation of the epigenome. Many nutrients and other bioactive compounds in foods regulate gene expression by influencing, either directly or indirectly, the epigenome [61]. Moreover, the availability of nutrients at critical developmental stages, such as pregnancy and infancy, can have profound effects on epigenetic patterns that persist in later stages of life [62, 63]. Indeed, some epigenomic marks may be conserved across generations, as demonstrated using the agouti viable yellow mouse model [63]. During the adult life, the epigenome becomes relatively more stable, although modifications still occur in response to environmental factors such as diet, pollutants, medication, aging, and physical activity. Overall, a large number of epigenetic studies have been conducted using in vitro and animal models to generate insights into this critically important area of genomic regulation. However, comparatively fewer studies have been conducted in humans due to their longer life span, large inter-individual variation, and the cell and tissue specificity that exists in epigenetic mechanisms controlling gene expression.

The field of nutriepigenomics investigates the interplay between food compounds and the epigenome [61, 64–66]. Evidence of the role of dietary components on epigenetic mechanisms is well-established and the field has grown rapidly thanks to the accessibility and affordability of 'OMIC technologies. The effects of phytochemicals and other bioactive compounds have been studied and results suggest that the impact of these molecules on human health may be partly explained by their effects on the epigenome [61, 66]. Substances such as resveratrol from grapes [67], epigallocatechin gallate from green tea [68], genistein from soy [69], and epicatechin from cocoa [70] have been shown to regulate enzymes controlling DNA and histone modifications. Some of these compounds have been attributed anti-inflammatory and anti-tumoral effects, in addition to a variety of other effects that are still under investigation. Consequently, there is considerable interest to use phytochemicals to prevent and/or treat diseases [65]. The physiological benefits of physical activity and adaptation to exercise are also associated with changes in the epigenome. For example, it has been demonstrated that exercise during pregnancy can induce modifications in the offspring that are associated with a reduced risk for obesity [71]. Collectively, these examples highlight the breadth of lifestyle factors that can influence gene expression through epigenomic regulation.

In summary, lifestyle factors affect human health by modifying the epigenome. Moreover, these effects may, in some cases, be transgenerational and persist in future generations after exposure to a given factor. Indeed, these modifications may be related to maternal conditions before and during pregnancy [72], but may also be transmitted through the paternal line [73]. Research of epigenetic mechanisms in humans has enormous

potential to shed light into lifestyle-gene interactions and to provide a better understanding of the aetiology of disease. Further research is required to characterize these mechanisms in depth and translate knowledge into recommendations aimed to improve disease prevention, diagnosis, and therapy in a personalized manner.

Conclusion

The examples presented in this Editorial highlight only a fraction of the topics that fall under the purview of *Lifestyle Genomics*. It is evident that the landscape for personalized health strategies continues to expand into new areas, but more research is necessary to substantiate the science and support the value for customers of direct-to-consumer genetic companies.

Chrononutrition, gut bacteria, alcohol and drug consumption, and xenobiotics are important areas to consider when studying lifestyle-gene interactions. We believe this Editorial will help potential contributing authors better appreciate the scope and breadth of *Lifestyle Genomics*. If you are addressing an important area related to lifestyle factors, genes, and biological function/human health, we invite you to send us your manuscript. We hope that you will share our enthusiasm for the journal, and that you will become both a devoted contributor and reader of *Lifestyle Genomics*.

Disclosure Statement

We declare that the authors have no conflict of interest. However, all authors are members of the Editorial Board for *Lifestyle Genomics*.

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