Short Communication

The Crosstalk between Genetic and Epigenetic Factors in Multifactorial Disorders

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Introduction

In the late 20th and early 21st centuries, global demographics began to stand out a paradigm shift toward an older population, largely due to advancements in public health, medical practices, and socioeconomic conditions. Multifactorial disorders are characterized by a complex interplay of genetic, epigenetic, and environmental factors tend to occur more frequently in older adults because of cumulative exposure to risk factors over the years and pose a significant challenge to modern medicine. Among the most common multifactorial disorders, diabetes, cardiovascular diseases (CVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), metabolic dysfunction associated fatty liver disease (MAFLD), neuropsychiatric disorders and malignancies are of particular interest that accumulate with age.[1,2] While the traditional genetic research has provided invaluable insights into the heritable components of these conditions, it has become increasingly clear that genetics alone cannot fully account for their development, variability, or progression. In recent years, epigenetics has emerged as a critical layer of regulation that bridges the genome and the environment, offering a deeper understanding of how gene expression is modulated without altering the underlying DNA sequence.[3] Multifactorial disorders are influenced by many genetic variants (polygenic) and non-genetic factors such as lifestyle, diet, toxins, or infections. Unlike monogenic diseases that are caused by a single gene mutation and follow simple Mendelian inheritance pattern, multifactorial disorders mostly remain polygenic in inheritance. Recognition is steadily improving that there is dynamic crosstalk between genetic and epigenetic factors underlying the multifactorial disorders. This short communication highlights the integration of genetic variants such as single nucleotide polymorphisms (SNPs) with epigenetic mechanisms like DNA methylation, histone modification, and non-coding RNA activity in conjunction with the role of environmental factors in multifactorial disease susceptibility and resilience.[4] This intricate dialogue not only enhances our ability to decode the molecular basis of these complex diseases but also opens new avenues for identifying novel biomarkers, predicting disease prognosis, and developing personalized therapeutic strategies. Moreover, recent discoveries in artificial intelligence and machine learning provide powerful tools to analyze vast datasets, enabling the identification of patterns and interactions that contribute to disease onset and progression.

Genetic Basis of Multifactorial Disorders

Genetics refers to the study of DNA sequence and mutations such as single nucleotide polymorphisms (SNPs), insertions/deletions as well as structural variations. A genetic predisposition, also called genetic susceptibility is an increased likelihood of developing a particular disease based on individual's genetic profile that is often inherited from a parent. Although genetic variants and susceptibility factors contribute to multifactorial disease, they lack a direct cause and effect relationship. Polygenetic inheritance involves cumulative effect of many genes, where each gene may contribute a small effect to disease risk but their compound effects increase disease risk significantly.[5] Changes in many genes, each with a small effect, may underlie susceptibility to many multifactorial diseases, including cancer, obesity, diabetes, heart disease, and neuropsychiatric illness. Multiple genetic loci that contribute for the genetic basis of multifactorial disorders (e.g., >100 loci contribute to type 2 diabetes risk) are often identified using genome-wide association studies (GWAS).[6,7] SNPs represent a difference in a single DNA nucleotide at a specific location in the genome that occur naturally and are present in roughly every 1,000 nucleotides on average. An individual's genome contains around 4 to 5 million SNPs, which are the most studied common variant in humans that contribute to the genetic basis of multifactorial disorders. Based on their location either in protein-coding and non-coding RNA genes, the SNPs are classified as neutral and functional. The neutral have no effect, while the functional SNPs affect different biological processes and continually confer the risk of multifactorial diseases. Overwhelming majority of SNPs are located in non-coding regions (e.g., promoters, enhancer sequence) but still have a functional impact on gene expression, regulation, or other processes. For example, they can alter transcription factor binding sites, affecting mRNA processing, or influence chromatin structure.[4] Polygenic Risk Scores (PRS) aggregate the effects of many SNPs to estimate an individual's likelyhood of developing the disease and can have large or small effects on the likelihood of developing a particular disease. Populations can be stratified into low, medium, and high genetic risk groups based on PRS.[8]

Some individuals may carry rare but high-impact variants that significantly elevate the risk and are typically identified through whole-exome or whole-genome sequencing. The effect of one gene may depend on the presence or absence of others, called gene-gene interaction (epistasis), which can amplify or mask the risk of multifactorial disorders. There are a number of challenges in understanding the genetic basis of many multifactorial disorders like missing heritability (GWAS variants account for only a portion of heritability), ancestry bias (most studies are based on European populations), non-coding variants (hard to interpret the function of many associated SNPs) and epigenetic regulation (not captured directly in DNA sequence).[9]

Epigenetic Basis of Multifactorial Disorders

Epigenetics refers to the study of heritable changes in gene expression that do not involve alteration of the DNA sequence. Changes in gene activity, driven by lifestyle and environmental

exposures, are the focus of epigenetics, which controls the activation or suppression of genes. Unlike genetic mutations, epigenetic changes do not alter the base sequence of DNA and are reversible, but they can modify how a DNA sequence is read and the information is translated for biological functions. The epigenetic basis of multifactorial disorders refers to how heritable changes in gene expression without actual alterations in the DNA sequence itself, contribute to the onset of complex diseases. Epigenetic modifications often interact with genetic predisposition and environmental exposures, playing a critical role in disease susceptibility, progression, and variability in response to treatment.[10,11] The main mechanisms dictating epigenetics include:

(a) DNA methylation: Addition of methyl groups to cytosines (mostly at CpG sites), typically turns genes off, while demethylation (removal of methyl group) turns genes on. DNA methylation has emerged as a key regulator of gene function and genomic stability during early stages of human development and cellular differentiation. As such, methylation defects have long been known to play a role in human diseases including imprinting disorders, trinucleotide expansion disorders, and acquired conditions including cancer.

(b) Histone modifications: Chemical changes to histone proteins (e.g., acetylation, methylation) alter chromatin structure to ensure how tightly or loosely DNA is packed and accessibility of genes. For example, altered histone acetylation and methylation affect genes involved in insulin signaling and glucose metabolism leading to type 2 diabetes mellitus. Likewise, abnormal histone methylation and acetylation patterns affect oncogene and tumor suppressor gene expression found in case of breast, colorectal and prostate cancers.

(C) Non-coding RNAs: These include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) that can bind to messenger RNAs to degrade them or block their translation, regulating gene expression post-transcriptionally. It has been observed that altered miRNA expression can dysregulate neuronal genes and inflammatory responses leading to Alzheimer's disease and miRNA-21 is often upregulated in various cancers (e.g., breast, lung, colon).

(D) Chromatin remodeling: Structural changes to chromatin that impact access of transcription factor has huge mastery in gene expression. Chromatin remodeling influences the expression of insulin signaling and glucose metabolism genes (e.g., Factors like SETDB1, HDACs, and SWI/SNF influence pancreatic β-cell function and insulin resistance) leading to type 2 diabetes mellitus. Similarly, chromatin remodeling defects have been implicated in a range of neurological disorders, such as autism spectrum disorder (mutations in genes encoding chromatin remodeling complexes, such as CHD8), and schizophrenia.

Further, epigenetic mechanisms can translate environmental exposures (e.g., diet, stress, toxins, infections) into biological outcomes. For example, fetus exposed to maternal smoking during pregnancy exhibits methylation changes in genes regulating lung development and immunity. Some epigenetic changes can be passed from one generation to the next, contributing to familial patterns of disease but unlike genetic mutations, epigenetic marks can potentially be reversed, making them potential targets for therapy.[12]

Environmental and Lifestyle Factors In Multifactorial Disorders

There is truth in the saying that 'genetics loads the gun and environment pulls the trigger'. Environmental and lifestyle factors play a critical role in the development and progression of multifactorial disorders, often interacting with a person's genetic makeup to trigger, enhance, or suppress disease expression. Since multifactorial disorders are caused by interactions between genetic susceptibility and non-genetic factors, the external influences can alter gene expression via epigenetics contributing to cellular stress, immune and metabolic modulations to accelerate or delay the disease onset.[1] Certain genetic variants may have increased susceptibility to environmental exposures (e.g., variants in the APOE gene elevate Alzheimer's risk especially in smokers).[13] Environmental factors, including smoking, physical activity and living conditions, have a greater impact on health and premature death than genes themselves. It has been estimated that environmental factors explained 17% of the variation in risk of death, compared to less than 2% explained by genetic predisposition. The environmental risk factors include pollution, radiation, noise, land use patterns, work environment, and climate change. Early life exposure to environmental risks such as chemicals, radiation, and air pollutants might increase the likelihood of developing multifactorial diseases, also called non-communicable disease (NCD). Parrallel to environmental factors, life style associated factors such as lack of physical activity, poor nutrition, not getting enough sleep, tobacco use, excessive alcohol consumption are equally important to give rise to multifactorial diseases and deaths.[11,14]

Crosstalk Between Genetic and Epigenetic Factors

Mutual interaction between genetic and epigenetic factors facilitate their crosstalk for a fine tune gene expression to modulate disease susceptibility and progression. Genetic variants affected by epigenetic regulation serve as a key link between genotype and phenotype, especially in multifactorial disorders.[15] Genetic factors that affect epigenetic regulation play a crucial role in shaping gene expression patterns without altering the underlying DNA sequence. These variants can influence how genes are turned on or off by the epigenetic markers such as DNA methylation, histone modification, chromatin accessibility, and non-coding RNA expression.[11,16] Followings are the major mechanisms of crosstalk between genetic and epigenetic factors.[17]

A. Genetic variants affecting epigenetic regulation: Examples of this process include SNPs in regulatory regions (promoters/enhancers), that can change transcription factor binding, impacting epigenetic marks (e.g., DNA methylation patterns). Another example is methylation quantitative trait loci (meQTLs), that control methylation levels at specific

sites and impact gene expression through epigenetic mechanisms.

B. Epigenetic changes modifying genetic effects: Epigenetic marks can silence or activate genes, modifying the impact of genetic mutations. In some cancers, tumor suppressor genes are silenced by methylation, even if there is no genetic mutation. Further, genomic imprinting (epigenetic silencing of one allele) can make a person functionally hemizygous and increases the vulnerability to mutations in the active allele.

C. Environmental interactions: Environmental exposures such as diet, toxins, stress, infections, etc. can influence epigenetic marks and unmask latent genetic susceptibilities, e.g., smoking-induced methylation changes can exacerbate genetic risk factors for lung cancer.

Followings are example of multifactorial diseases due to genetics-epigenetics crosstalk:

Cancers: Hypermethylation of tumor suppressor genes (e.g., p16, BRCA1) and global DNA hypomethylation promote tumorigenesis. Histone modifications can activate oncogenes or silence repair genes and dysregulation of chromatin remodeling can lead to uncontrolled cell growth and tumor formation. Genetic mutations (e.g., in TP53, BRCA1) interact with epigenetic changes (e.g., hypermethylation of CDKN2A/p16) to give rise to many cancers. Similarly, global hypomethylation and promoter-specific hypermethylation are hallmarks of many cancers.[18]

Neurological disorders**:** DNA methylation can influence brain development and function, contributing to conditions like Alzheimer's disease, autism spectrum disorder (ASD), schizophrenia, and Huntington's disease. In Alzheimer's disease, SNPs in the APOE gene correlate with methylation and histone modifications in nearby regions. Rett syndrome is caused by mutations in the MECP2 gene, which encodes a protein that interprets DNA methylation marks.[19]

Autoimmune diseases: Epigenetic modifications, including DNA methylation and histone modifications, can influence the behavior of immune cells and contribute to the loss of immune tolerance and development of autoimmune diseases. Epigenetic dysregulation (e.g., hypomethylation in T cells) combined with genetic variants (e.g., in HLA genes) contributes to diseases like lupus and multiple sclerosis.[20]

Metabolic disorders: DNA methylation changes in pancreatic β-cells affect insulin production and high fat diets induce methylation patterns that can predispose to insulin resistance In type 2 diabetes, genetic risk loci (e.g., TCF7L2) interact with altered methylation in pancreatic islet cells, affecting insulin secretion.[21]

Conclusion

The intricate interplay between genetic variants and epigenetic regulations lies at the cornerstone of multifactorial disorders, where complex traits emerge from the convergence of inherited DNA sequences and dynamic regulatory processes. Genetic variants can shape the epigenetic landscape by influencing DNA methylation, histone modifications, chromatin accessibility, and non-coding RNA expression, thereby modulating gene activity in a context-dependent manner. Conversely, epigenetic states can mediate the effects of environmental exposures on genetically predisposed individuals, offering a mechanistic explanation for variable disease outcomes. This genetic-epigenetic crosstalk not only enhances our understanding of disease etiology but also opens new avenues for precision medicine.[10] By integrating genomic and epigenomic data, we can better identify at-risk individuals, predict disease progression, and develop targeted interventions. With continuous evolution of high-throughput technologies and computational tools, the comprehensive mapping of these interactions for unraveling the complexity of multifactorial diseases such as cancer, diabetes, cardiovascular disorders, and neuropsychiatric conditions is likely to be feasible. Recognizing and exploring the interaction between genetics and epigenetics is essential for advancing beyond simplistic, single-cause views of disease, and for developing a more comprehensive, systems-based perspective on human health and illness. Future directions include multi-omics integration (combining genomics, epigenomics, transcriptomics, and proteomics), single-cell epigenomics and CRISPR-based epigenetic editing for comprehensive disease modeling. This integrated approach is crucial for identifying novel biomarkers, predicting disease prognosis, and developing personalized therapeutic strategies.[22]

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