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GENETIC LANDSCAPE OF OBESITY: INTERPLAY BETWEEN GENETICS, ENVIRONMENT AND LIFESTYLE - A REVIEW

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Abstract

Obesity is a complex and multifactorial disorder with both environmental and genetic factors. Although such as diet and physical activity are important lifestyle factors in the etiology of obesity, there is growing evidence that hereditary predisposition is a major cause for the susceptibility to excess weight gain. Genome-wide association studies (GWAS) have implicated numerous genetic variants that are linked to obesity, including those that are involved in fat storage, energy metabolism, and appetite regulation. Of these, variants of genes such as FTO (fat mass and obesity-associated gene) and MC4R (melanocortin 4 receptor gene) have been strongly associated with elevated body mass index (BMI) and obesity risk. In addition to single-gene effects, obesity is a polygenic disorder, where multiple genes interact with each other and with environmental determinants to determine obesity outcomes. DNA methylation and histone modifications are Epigenetic marks that can also modulate gene expression in response to diet, exercise, and early life exposures. It affect obesity risk. Recent technological advances in next-generation sequencing (NGS) and multi-omics have also provided more insight into how genetic and epigenetic obesity determinants function. Most importantly, the gut microbiome has also emerged as an important determinant, with studies indicating that host genetics can modulate the composition of the microbiota, which in turn affects metabolism and energy balance. Current evidences of genomic and genetic studies shows that obesity is affected by several genes involved in appetite regulation, energy metabolism, hormonal control and environmental factors. These discoveries demonstrate the genetic, lifestyle and epigenetic factors involved in obesity and it also explain the concept of personalized patient care.

Keywords: *BMI, Gut microbiome, GWAS, Melanocortin 4 receptor gene, NGS*

INTRODUCTION

Obesity has many root causes and is a complex syndrome that can be defined as the excess storage of body fat and is of serious concern to health. It is associated with a spectrum of chronic conditions, including type 2 diabetes, cardiovascular disease, and cancer. Obesity increased globally and has emerged as a priority in public health (1). It is considered that diet, activity, and environment are the determinants of the general population of obesity. However, some evidences indicates that there is a tremendous role played by genetics in the determination of a person's vulnerability to obesity (2). Genetics influence obesity by acting through multiple pathways, including genetic variation regulating appetite, metabolism, fat storage, and energy expenditure (3). GWAS, family and twins studies have shown a prudent interaction between obesity and genetics of individuals which shows the deviation of BMI between 40 to 70%, after the revealing of certain gene's function it become clear that they have pragmatic activity and majestic role in the regards of obesity such as FTO and MC4R studies yields that these genes have repercussion of weight control. Like sickle cell animea and some types of cancers it does not depend only a single gene but is the result of different genes dealing with the environment (4). Although there are some evidences regarding monogenic origin of obesity are present but are very scarce and rare, mostly required mutations in more than one genes in which each one plays a key role in this condition. Despite all these genetic mutations, the epigenetic factors like methylation and histone modifications also whopping and robust influence and can have magnificent role in gene regulation. It is significant to analyze and understand the genomic role of obesity to vindicate

personalized medical prevention and remedy dependent strategies (5). The modern techniques in accuracy of medicine delivery and nutrigenomics lifestyle and diet pattern of an individual are being studying by researcher in accord to their genetics providing valuable avenues in the regard of treating obesity more effectively. With the continual of research the genetic analysis with environmental and behavioral relations could provide better management and silver bullets of obesity (6).

GENETICS OF OBESITY

Obesity relies on different factors including genetic, environmental, gut microbiota and lifestyle factors. A majestic amount of research to decipher the genetic vulnerability to obesity has established that the scarce and rare genetic mutants in an individual deliberate to verdict the susceptibility of overweight (7). Variations in the melanocortin-4 receptor (MC4R) gene is the great significant genomic determinants and assiduous to encounter an individual with obesity. Which is a prominent determinant of voracity and energy metabolism? MC4R gene variants infest the singling pathways and cause chronic obesity in early childhood by controlling food intake(8). Genome-wide association studies (GWAS) also found various indels linked with obesity, especially in the FTO (fat mass and obesity-associated) gene, regulating fat accumulation and metabolism. Polygenic obesity due to combined actions of numerous genetic variants is much more common than monogenic obesity due to single-gene mutations (9). Epigenetics is also an important cause of obesity, where dietary intake, exercise, and stress can regulate the expression of genes without actually altering the sequence of DNA itself. For instance, DNA methylation and histone modification can influence genes in energy homeostasis and thus predispose to obesity (10). Moreover, rare syndromic obesity disorders such as Prader-Willi syndrome and Bardet-Biedl syndrome also demonstrate the genetic abnormality of the disease (11). Nevertheless, even with the strong genetic predisposition, obesity is not fully explained by heredity and that lifestyle factors and socio-economic status also equally decide body weight. Demystifying the genetic pathogenesis of obesity is essential. Because it helps to develop personalized medicine, such as drugs and gene therapy, to treat this rapidly growing epidemic of global obesity (12) (Fig. 1).

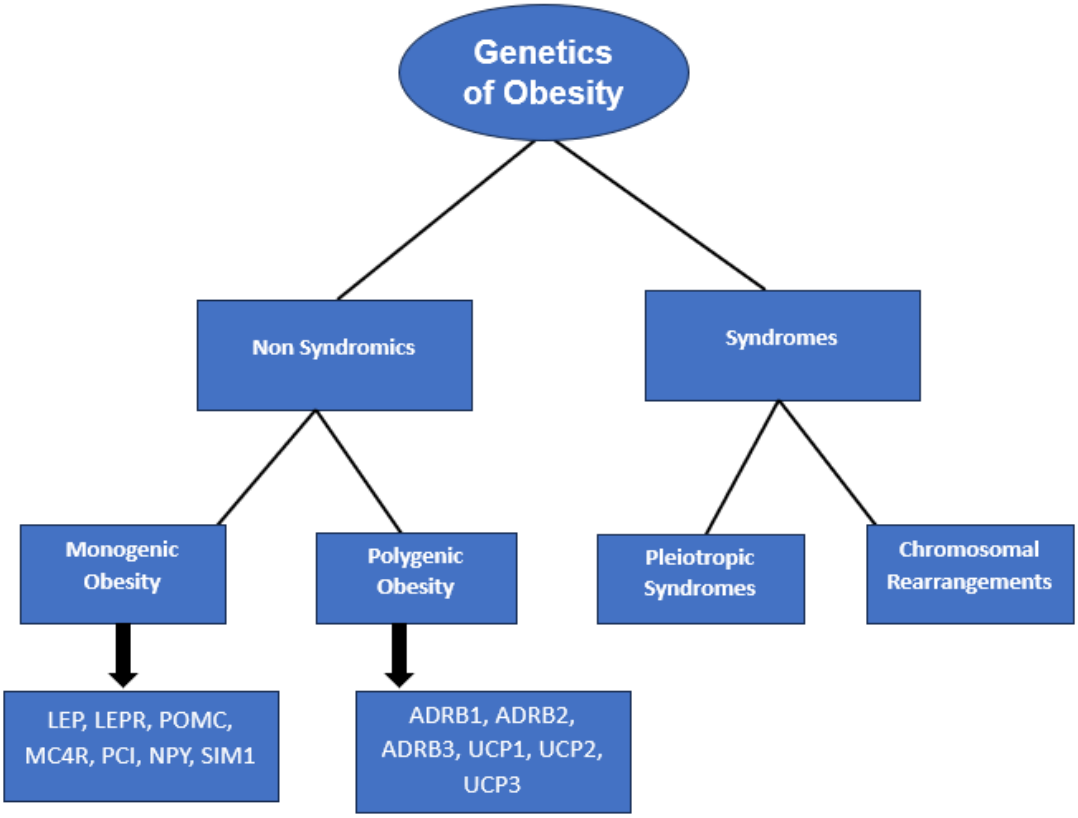

Fig. 1. Schematic classification of the genetic architecture underlying obesity

MONOGENIC OBESITY

Monogenic obesity is an extreme form of obesity caused by mutations in a single gene that directly affect the regulation of appetite, energy expenditure, and metabolism (13). Unlike common obesity, which

results from complex interactions between multiple environmental and genetic factors, it is primarily caused by genetic defects in the most critical elements of the leptin-melanocortin pathway, an essential system in the hypothalamus that regulates appetite (14). The pathway is disrupted by mutations in genes such as LEP (leptin), LEPR (leptin receptor), MC4R (melanocortin-4 receptor), PCSK1 (proprotein convertase subtilisin/kexin type 1), and POMC (pro-opiomelanocortin), leading to increased appetite (hyperphagia) and early-onset obesity, which typically begins in infancy or childhood. Patients with this type of disease typically have insatiable hunger, reduced energy expenditure, and metabolic disturbances, and it is extremely difficult to lose weight with conventional techniques such as diet and exercise (15). Since the condition is genetically predisposed, ineffective anti-obesity drugs are usually employed, and some drugs such as leptin replacement (in LEP mutations) or MC4R agonists (in MC4R mutations) have been explored as therapeutic drugs (16). Early diagnosis and genetic analysis are crucial to the management of the condition and the delivery of personalized treatment plans. This type of obesity is the research area that is extremely significant because the mechanisms can be used to make important observations about the underlying genetic and biological etiology of the condition of obesity and metabolic disorders (17) (Fig. 2).

POLYGENIC OBESITY

Polygenic obesity is a complex and heterogeneous disorder caused by numerous genetic variants, each with a small effect on the overall susceptibility to obesity in an individual (18). Instead of obesity which is caused by mutations in a single gene, polygenic obesity arises due to the additive effect of numerous loci, frequently compounded by environmental and lifestyle determinants such as diet, physical activity, and socioeconomic status (19) (Fig. 2).

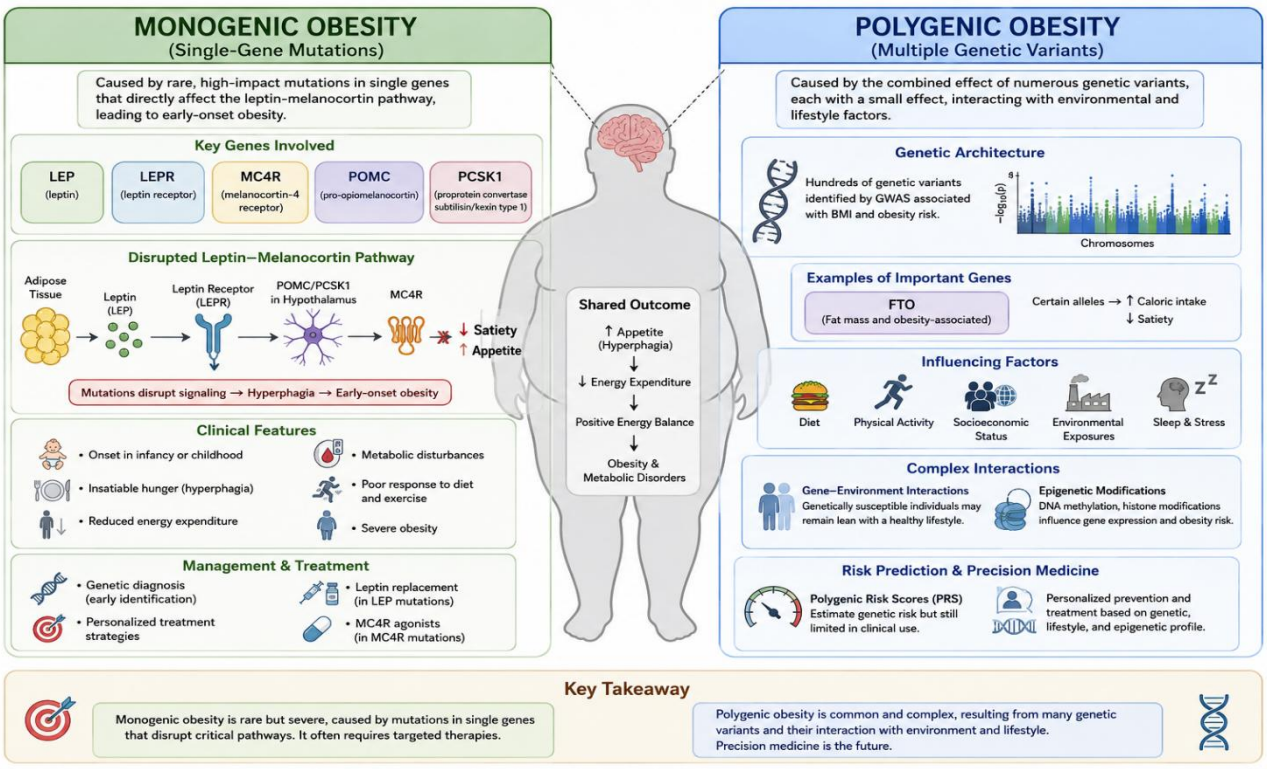

Fig. 2. Monogenic and polygenic obesity

Genome-wide association studies (GWAS) have identified numerous hundreds of genetic variants for body mass index (BMI) and risk of obesity, many of which map in or close to genes for regulation of appetite, energy metabolism, adipogenesis, and neural signaling (20). Among these, FTO (fat mass and obesity-associated) gene variants are some of the most intensively investigated, with certain alleles leading to enhanced caloric intake and reduced satiety. Nevertheless, the genetic architecture of polygenic obesity is immensely complex, with each variant contributing relatively modestly, so that prediction of an individual's risk of obesity is hard to make from genes alone (21). Moreover, gene-environment interactions alter the expression of genes associated with obesity; for instance, genetically susceptible persons to obesity might remain lean if they lead a healthy lifestyle with a proper diet and physical activity (22). Polygenic risk scoring

(PRS) has become progressively refined in predicting an individual's genetic risk to obesity, although applications in the clinic are in their infancy (23)., DNA methylation and histone modifications are Epigenetic changes that can also influence gene expression and lead to obesity susceptibility, adding yet another level of complexity to the genetic architecture of the disease (24). As science further unravels the complex interaction between genetics, environment, and lifestyle, an increasingly personalized approach to obesity prevention and treatment is unfolding, emphasizing the importance of precision medicine in addressing the booming global obesity epidemic (25).

GENE-ENVIRONMENT INTERACTIONS

Gene-environment interactions are the dynamic interplay between the individual's genetic makeup and external environmental exposures, both combining to shape physiological characteristics, disease susceptibility, and even behavioral predispositions (26, 27). While genes set a biological template, they are not employed in solitude—environmental exposures can modify their expression, at times profoundly, and lead to variation in health outcomes even in genetically comparable individuals. This interplay is a fundamental principle in complex diseases, where genetics and environment both play a role but none of them alone is the sole perpetrator, but their interplay decides risk, course, and severity (28, 29). For instance, while an individual may have inherited genetic variants for increased risk of type 2 diabetes, their risk of developing the disease is a function of lifestyle parameters like diet, exercise, and stress levels. Sedentary lifestyle and unbalanced diet can trigger expression of genes related to insulin resistance, while a balanced diet and exercise program can suppress these effects, illustrating the function of environmental exposures in modifying gene expression (30, 31).

One of the most significant biological processes through which gene-environment interaction takes place is epigenetics, which refers to reversible changes in gene expression without actual modification of the DNA sequence. Epigenetic changes, such as DNA methylation, histone modification, and non-coding RNA function, are also regulated by a number of environmental exposures like exposure to toxins, stress, diet, and even social environment. For example, it has been found through studies that children who have been exposed to early severe stress or trauma are susceptible to developing long-term epigenetic changes of stress response genes, and hence they become vulnerable for mental illness conditions like depression and anxiety disorders in adulthood. Likewise, exposure to cigarette smoke or air pollution results in epigenetic changes and a risk for lung disease even in subjects without any considerable genetic risks for such conditions (32-34). Gene and environment correlation is another very significant concept in the theory of gene environment interaction. Its correlation explains the process by which the genetic risk tends to cause the individual to expose him or herself to a particular environment. This means that individuals like to select or alter their environment according to their genetic risk consciously or unconsciously. For example, a genetically high intelligence individual will attempt to reach difficult intellectual environments in the form of higher studies and professional activity, which in turn raise the level of intellectual capacity. Some genetic risks may drive the individual towards dangerous habits like drug abuse, which enhances negative outcomes even more (35-38).

Examples in the real world further demonstrate the role of gene and environment interactions. Perhaps the most famous example is the interaction of the FTO gene and obesity. Although certain versions of the FTO gene confer an increased risk of obesity, research has demonstrated that this risk can be reduced by several-fold by changes in lifestyle, such as diet and exercise. This indicates that even if there is a genetic component, this is not deterministic but is subject to modification by environmental factors. Another famous example is the interaction of the BRCA1 and BRCA2 genes and the environment in the risk of breast cancer. Those women who get these mutants genes will have increased and surged risks of developing breast cancer, but this risk can be further worsen or lessen by epigenetic factors that regulate the functioning of genes and other factors such as alcohol abuse ,procreative factors and hormone therapy (39-41) (Fig. 3).

According to psychiatry, in depression and any stress the serotonin transporter gene (5HTTLPR) has been analyzed which make it ostensible that gene carrier of this gene have high risk of having depression

exacerbated by abuse or losing beloved, but people with the same gene having supportive environment and caring circle may not develop depression revealing that environment have a great role in the expression of a particular gene (42-44).

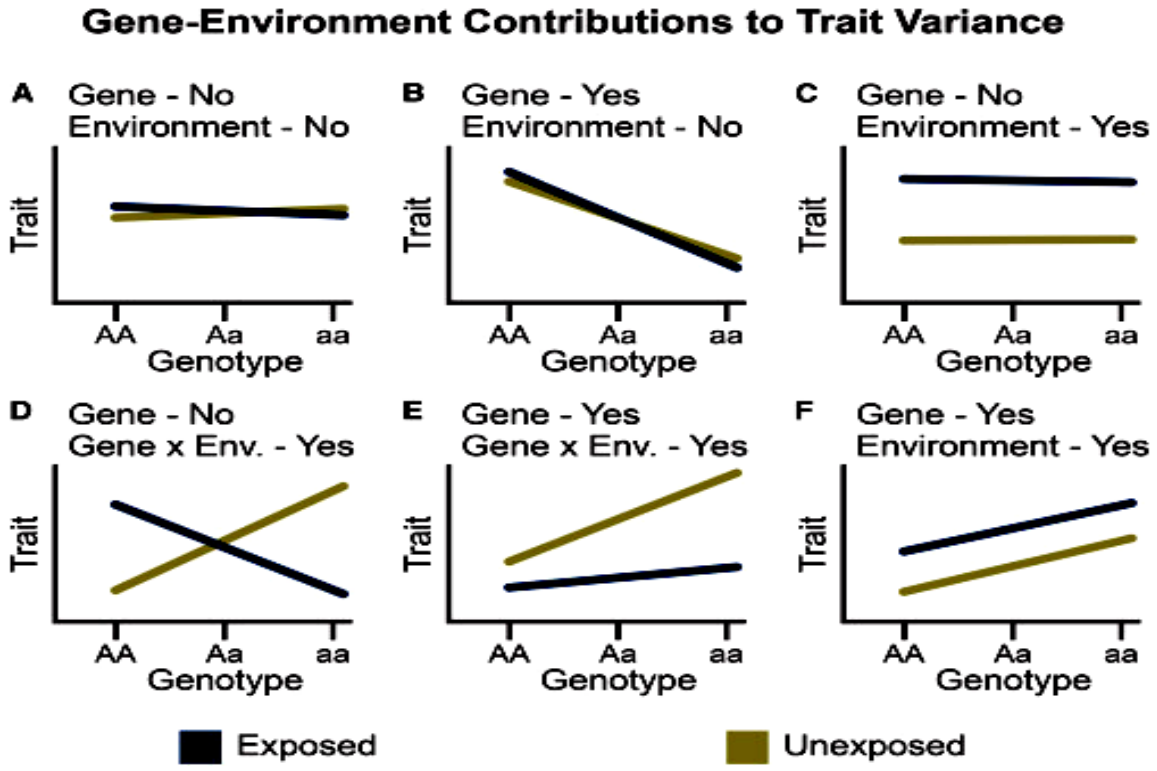

Fig. 3. Gene-Environment contributions to trait variance given a genetic locus of interest (X Axis) and an exposure of interest (exposed = blue), the ways in which they can be related to a trait of interest

The study about the relationship between environment and gene activity has vast impact on the implications for public health and medicine. It centered on the personalized medicine by analyzing genetics and environment of a particular individual by exposing genetic susceptibilities in early life, the professionals can utilize the specific techniques and health related precautions , such as recommending to change the lifestyle which can cause obesity or may worsen including counseling of that particular individual .moreover health policies for public can be devised to curtail the detrimental environmental encounters such as curbing air pollution or mitigating chemicals in food so that their impact can be alleviated on susceptible individuals (45-49).

THE FUTURE OF OBESITY RESEARCH

The future of obesity research will be very vast because of the technological advancements. Through these advancements we can analyze the complexity of the genes related to the origin of obesity and tread towards the personalized medicines having less side effects and more pragmatic activities (50-52). As obesity is becoming the major problem for the considerable population of people and causing different diseases sequelae such as cardiovascular disorders, diabetes and certain carcinomas .The researchers are looking and analyzing the new causative agents of obesity (53-55). Gut microbiota research is one of the most burning topic which having a key role in one's health even effecting to the mode of individuals .Gut microbes have a role in the metabolism of individuals ,appetite and energy balance which constitute in obesity. By decrypting the particular communities of microbes which play role in obesity one may develop effective therapies such as prebiotic , probiotic and fecal transplants (56-59). Moreover the advancements in genetic and epigenetic studies one can analyze the role of specific genes like tubby gene and the expression of these particular genes which contribute in the development of obesity. Another major advancement is the use of AI and machine learning in the study like we can analyze the specific genes and inactivation of genes or the genes having surrogate effects by bioinformatics. Some devices like smart phone apps and smartwatches also playing role in obesity, these devices provide feedback and support in delivering personalized guidance (60-62). Adding more there is insurgence of awareness about the environmental

determinants of obesity such as food insecurity, social and economic status .Future research will be focused on interventions by cultural response ,gut health and genetics of individuals . While these developments have occurred, challenges persist, including the need for long-term trials to ascertain the efficacy and persistence of novel treatments, the ethical considerations of genetic and microbiome-based therapies, and the need for interdisciplinarity to combat the disease's etiology (63-65). By combining frontier science with insight into the biological, behavioral, and societal origins of obesity, the future of obesity research is poised to unlock enormous potential to revolutionize prevention, treatment, and policy and ultimately to improve the health and well-being of populations worldwide (66, 67).

INTEGRATION OF MULTI-OMICS DATA IN OBESITY RESEARCH

Integration of multi-omics data is a game-changer approach to obesity research that offers unprecedented insight into the multidimensional biological processes of the disease. Multi-omics is the combined analysis of two or more "omics" fields, such as genomics, transcriptomics, proteomics, metabolomics, and epigenomics, each with its own degree of biological information (68-70). Genomics analyzes the genetic code and variation that predisposes to obesity, transcriptomics analyzes patterns of gene expression that show how genes are turned on and off in response to environmental and lifestyle factors, proteomics analyzes the proteins made by cells, the functional molecules that orchestrate biological processes, and metabolomics analyzes the metabolites, the small molecules made by cellular metabolism, that provide a snapshot of the biochemical health of the body. Epigenetics analyzes the impacts of lifestyle, diet and environmental factors that affect the DNA expression without altering the genetic code decrypting the relation of these factors with obesity (71-73). By combining all this available data and fusing all the stories scientists can picturize the exact causes and remedies of obesity which have different faces like genes, metabolism, proteins and environmental factors playing a certain character in obesity. Suppose combing the metabolic profiles with the genome having particular data of genes will show how genetic mutations manipulate the metabolic pathways such as weight gain and insulin resistance (74-76) (Fig. 4).

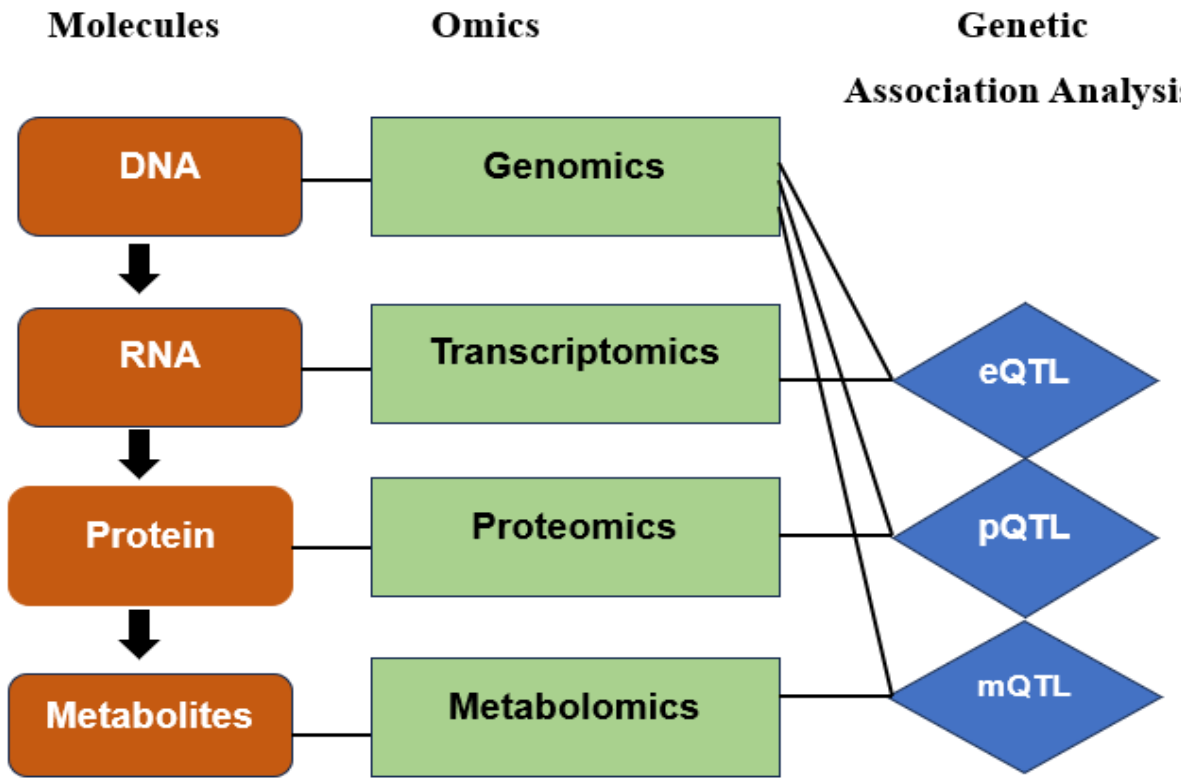

Fig. 4. Multi-omics Study for the Interpretation of Genome

Reiteratively analyzing the proteomic and transcriptomics data collectively make it blatant clear about the certain biomarkers and molecular pathways disrupted in obesity and demanding new therapies. Powerful machine learning algorithms and computational methods are needed to analyze and interpret these huge, complex datasets to find patterns and correlations that are impossible to find with single-omics

methods. Further, multi-omics integration can potentially facilitate the design of personalized medicine strategies, whereby interventions are tailored to an individual's unique genetic, molecular, and metabolic constitution. Such an initiative is extremely promising for the treatment of obesity for its heterogeneity, as it would allow researchers to characterize discrete disease subtypes each with its own unique etiology and therapeutic needs. However, multi-omics integration is not without its challenges, such as the requirement for standardized data acquisition, storage, and analysis protocols. There is also need of access to large heterogeneous datasets to derive robust and generalizable conclusions (77-79). Despite such constraints, multi omics integration holds the promise of transforming the study of obesity and yielding a greater insight into the disease that will drive innovative, precision medicine-based prevention and treatment strategies to Next-Generation Sequencing (NGS) in Obesity Research.

PERSONALIZED PATIENT CARE: REVOLUTIONIZING HEALTHCARE THROUGH INDIVIDUALIZED TREATMENT

Personalized patient care, or personalized medicine or precision medicine, is a new model of healthcare that individualizes medical treatment based on the individualistic characteristics of the patient (80-82). Such a paradigm shift is a departure from the traditional "one-size-fits-all" paradigm, where treatments are designed based on average response in populations. Instead of targeting the individualistic genetic, molecular, environmental, and lifestyle determinants of an individual's health. Building on the development of genomics, biotechnology, data analytics, and artificial intelligence, personalized patient care holds the promise of optimizing treatment efficacy, minimizing the risk of adverse effects, and optimizing general health outcomes (83-86). An example of personalized patient care is genetic testing to detect discrete mutations or biomarkers of an individual's response to particular medicines, thus allowing healthcare providers to prescribe the optimal therapy with minimal risk of adverse effects. Similarly, wearable devices and mobile health applications can monitor patients' vital signs, physical activity, and other health markers continuously, providing real-time data to inform individualized interventions. Such intervention can be particularly useful in the case of complicated and chronic diseases such as cancer, cardiovascular diseases, and diabetes, where individualized treatment regimens can more effectively enhance quality of life and survival (86, 87). Apart from this, personalized patient care does not only concern being familiar with the patient as much as biology is involved but also the patient's psyche, the patient's social network, and the external environment too. Personalized patient care facilitates more patient and physician relationships. Activate patient's participation in their own medical care, and preventive interventions based on individualized risk factors. However, there are limitations in the widespread adoption of personalized patient care, including high economic costs, the ethical issues of genetic privacy, and adequate infrastructure to tackle big health data. Setting aside these impediments, the benefits of personalized patient care are limitless, promising an era of precision, proaction, and empowering healthcare for all. As medicine and technology progress, personalized patient care is certain to be the pillar of evidence-based medicine in the future, revolutionizing the, diagnosis, prevention, and treatment of diseases and on the path to a healthy, just world (88-90).

CONCLUSION

Obesity is degenerative disease caused by an interaction among lifestyle, genetic and environmental factors. The predominant cause is excess energy consumption and physical inactivity, but novel evidence demonstrates the significant role of genetic predisposition in defining the susceptibility of an individual to obesity. Numerous genes have been linked with obesity, particularly the genes with function in energy metabolism, appetite, fatty acid storage, and hormonal regulation. Variations in genetic structures such as FTO, MC4R, and LEP are linked with BMI gain and the risk of obesity. Genomic analysis innovation, particularly by next-generation sequencing (NGS) and multi-omics, has improved the understanding of the genetic component in obesity. Furthermore, epigenetic changes like DNA methylation and histone modification reveal how environment influence the genes and alter their function without changing the DNA sequence. Understanding the genetic pathogenesis of obesity offers new models of targeted

prevention and therapy. Precision medicine interventions use an individual's genetic marker to tailor treatment, for example, genotype-guided dietary recommendation and microbiome-driven interventions. Genetic information can be used to identify individuals at risk of obesity early in life, thereby allow early lifestyle modification and intervention before excessive body weight gain. While further research continues to unravel the complex genetic etiology of obesity. The future of obesity treatment will likely progress towards more effective, targeted, and sustainable results. By leveraging the power of genomics and multi-omics information, researchers and clinicians can develop tailored interventions. These can be transcend one-size-fits-all approaches, ultimately improving public health and prevention of the global burden of obesity-related disease.

Conflict of interest:

All authors declare no conflict of interest.

Authors' contribution:

MG Data collection and writing; MUH Data analysis and manuscript editing; IJ & TA Contributed and assisted in writing and formal analysis; MG & ZM Supervised the overall study.

Declaration of generative AI-assisted tools:

Authors declared that no AI-assisted tools were used.

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