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Role of Genetics in Obesity

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Abstract
Obesity is a worldwide pandemic as well as a remarkably significant health-related issue. Excessive weight gain is a normal yet complex, multifactorial problem with high heritability, where as much as 80% of the difference in the Body Mass Index (BMI) is attributable to hereditary elements. Literary works on the additional variables of the present obesity epidemic, and hereditary basis of human weight gain, were examined in compilation of this report. The current prevalence of obesity is fairly recent worldwide event driven by our modern way of life as well as nutritional routines. Usual Obesity is the outcome of interaction between various hereditary variants and ecological aspects. The function of obesity genes in this present epidemic is passive, yet its effect is extremely substantial, due to the fact that people with these genes might be predisposed to serious or perhaps morbid obesity when exposed to the modern "obesogenic" environment. The human weight regulation mechanism evolved and became effective in preventing weight loss, however is reasonably inefficient in preventing excess weight gain. The modern-day obesogenic environment urges a less active way of living and offers easy accessibility to processed foods, which leads to reduced energy expenditure and increased calorie consumption. We have unintentionally created a biological and environmental imbalance, as the human weight regulation is unable to evolve fast enough to keep up with the environmental changes. This has led to maladaptation of an otherwise sound and metabolically reliable physiological mechanism, with severe metabolic repercussions.

Keywords
Genes, Maladaptation, Obesity, Obesogenic, GWAS.

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INTRODUCTION:
Obesity is a global pandemic and a significant health concern due the consequent morbidity and premature death; obesity predisposes to severe morbidities such as type 2 diabetes, high blood pressure as well as coronary cardiovascular diseases. Industrialization and innovation are rightly criticized for increasing obesity occurrence throughout the world, as it created an "obesogenic" environment with calorie abundance and ubiquitous automation that encouraged sedentary lifestyles, causing energy intake and expenditure imbalance and also favors the deposition of excess calories as fat. Although this trend of increasing body girth is majorly driven by the

obesogenic environment, but it is promoted by the person's genetic susceptibility to excessive weight gain.

Obesity is usual yet complex, multifactorial condition with high rate of heritability. While it is well developed that obesity runs in families, the familial clustering is not simply because of a common lifestyle and shared environment. Research studies in twins, adoptees and family members suggest that as much as 80% of the variance in the Body Mass Index (BMI) is attributable to Genetic Elements. Relative risk of obesity amongst siblings was approximated to be 3 to 7, the concurrence rate of obesity is greater between monozygotic twins than dizygotic twins, and adoptee's weight is typically closer to their birth parents than their adoptive parents. These and several other thorough researches integrating twins, adoptees and family data have estimated that the heritability of BMI or body fat to be 25% to 40%. These research studies sustained the role of genetics in the pathogenesis of human obesity.

Nevertheless, Obesity has a broad phenotypic irregularity, ranging from slightly overweight to the morbidly obese, along with the spectrum of early childhood to late adult beginning. The relative contribution of the environment and gene sensitivity towards the pathogenesis of obesity varied between various obese individuals, even within the same families, and might contribute to phenotypic variability. The environment and a sedentary lifestyle might be the leading contributing factor in the advancement of late onset obesity in a grown-up, while genetic factors may exert a greater influence in a child that developed early onset obesity in the obesogenic environment, and such concept is supported by the knowledge that the heritability of early-onset obesity might be considerably greater than that of adult-onset obesity. This heterogeneity maybe even extends to the individual's response to weight loss measures. Among individuals where environmental factors are predominant, they might find it much easier to lose weight in contrasted to individuals whose genetics predominate.

While family, twins and adoption research studies in addition to various linkage and association studies have provided substantial proof which supported the genetic basis for human obesity, the presently increasing prevalence of obesity is a fairly recent worldwide event which took place just in the last few decades. It is impossible that genetic anomalies or major changes in allelic regularities of obesity related genes are responsible for this surge, given the stable gene pool of the world's population in this brief time period. However, though the role of obesity genes in present epidemic is passive, its effect is extremely considerable, since people with these genes maybe predisposed to severe or perhaps morbid obesity when exposed to the modern obesogenic environment. Historically, the human race has dealt with extended durations of hunger as well as hardships, and was constantly required to collect or hunt for food. The ability to preserve energy in the form of adipose tissue would certainly give a considerable survival benefit, where the body is enriched with genes that favor the storage of energy, as well as diminished energy expenditure (Thrifty Gene Hypothesis), and for that reason most likely to survive natural selection process over the centuries. The human weight regulation mechanism advanced and became effective in preventing against fat burning, yet reasonably inefficient in preventing against excessive weight gain.

The modern obesogenic environment of industrialized countries developed over the past few decades in our bid to minimize work and enhance efficiency and quality of lifestyle. The population has ended up being sedentary and reliant on machines and automation. Paired with easy access to processed foods, this has led to a reduce expenditure and increased calorie intake. While human resourcefulness has been successful in creating an atmosphere of work efficiency and lot of things, it has likewise accidentally developed a biological and environmental imbalance, as the human weight regulation is incapable of evolving quick enough to keep pace the environmental changes. This resulted in maladaptation of an otherwise sound and metabolically efficient physiological mechanism, with serious metabolic consequences. Subsequently, the percentage of obese individuals has increased continuously throughout the years. Particularly, there is a noticeable rise in morbid obesity that cannot be justified by a simple shift in population mean. The hypothesis is that the obesogenic environment has triggered a subgroup of the population, genetically prone to severe weight gain, to come to be exceedingly obese. These populations may hold 'Thrifty Genes' or as we call them, Obesity Genes which would otherwise be protection against starvation and for that reason prove beneficial. However, in the modern obesogenic environment, high-risk groups such as the Pima Indians, Pacific Islanders, Afro-Americans, Asians and Hispanic-Americans may develop severe obesity.

Obesity gene research has progressed rapidly over the past 2 decades, which has provided discovery of the molecular mechanism of energy homeostasis

while doing so. Conventional techniques were employed reveal these Obese genes consisting of genome-wide scans that studied unrelated obese people, linkage studies that took a look at pairs or families with history of obesity, as well as association studies which examined the connection between obesity and polymorphic variations of prospect genes thought to influence weight regulation. Unlike various other multifactorial disorders, these approaches have not been much of assurance for common obesity, since the obese phenotype is very heterogeneous, even within the very same family members. There variable contribution from genetic, environmental and behavioral influences that varies for each obese individual, confounding efforts to evaluate this condition. While a number of syndromic forms of human obesity such as the 'Prader-Willi disorder' and 'Bardet-Biedl disorder' have been genetically mapped and causative genes identified, their specific functions in the pathogenesis of obesity and the underlying molecular mechanisms have not been isolated yet.

In 2001, 6 genes were linked to monogenic human obesity and no common variants were reproducibly related to polygenic obesity. By 2008, development in the field resulted in the identification of 8 monogenic genes as well as 4 polygenic genes namely, FTO, PCSK1, MC4R, CTNNBL, from associate researches at the genome-wide level of significance. The current development of the Genome-Wide Association Studies (GWAS) has brought about more developments in gene recognition and currently 9 loci are identified to be associated with Mendelian forms of obesity along with 58 loci contributing to polygenic obesity.

Another lesson of the observed continuum between monogenic and polygenic form of obesity is that GWAS-derived unique loci must be considered as highly relevant prospect gene for monogenic obesity, particularly if added arguments in human or animal models strengthen the candidateship of the gene. The SH2B1 gene is for instance an intriguing candidate as SNPs at the SH2B1 locus are linked with BMI by GWAS, rare deletions consisting of SH2B1 are associated with a Mendelian form of obesity as well as inactivation of SH2B1 in mice causing hyperphagia, leptin resistance and obesity. However, notable exemptions have been reported for other promising candidate genes. As an example, FTO is the significant contributor to polygenic obesity and mice down or over-expressing FTO are resistant or susceptible to develop obesity. However, heterozygous loss-of-function mutations in FTO are found in both lean and overweight subjects and do not contribute to monogenic obesity.

Direct genotyping in GWAS and viable imputation making use of original HapMap reference panels only covers a limited variety of SNPs and range of allele regularities. The advancement in denser genotyping chips and imputation techniques utilizing information from the HapMap 3 as well as 1,000 genomes project will certainly make it possible for expansion to a larger set of variants and will certainly enable targeted resequencing and systematic fine mapping to produce a complete portfolio of sequence variations. Such sequence variations are most likely to include rare variants, present in less than 1 % of the population, the limit for polymorphism in standard GWAS, with potentially larger penetrance effects than previously recognized common variants. More than 100 different mutations have been identified within the MC4R region and, although many of these variants are very rare, together they represent a higher proportion of total variation in adiposity.

The search for genetic factors predisposing to usual weight gain is tough and also the development has been slow, as it is most likely that each individual genetic variant exerts subtle impact on body weight and therefore confirming its association with increased adiposity can be challenging. It is still uncertain if the genes of common obesity validate to the "Common variant- Common disease model", where usual polymorphisms in several loci contribute collectively to the danger of obesity, or the "Rare variants- Common disease model" where multiple rare alleles collectively exert an effect. The availability of advanced computer systems and modern technologies such as high-density single nucleotide polymorphism (SNP) microarrays and high throughput sequencing equipment have made it feasible to analyze various combination of multiple SNPs or haplotypes in candidate genes related with weight regulation, and hopefully human population will certainly be wiser concerning the genetic architecture of common obesity in the near future. A unique but converse approach to identify genes affecting weight regulation is to examine people that are slim and have trouble gaining weight, having obesity resistance, such as youngsters with a failing to thrive and without recognizable disorders. Much like obesity, leanness is heritable, and it is consequently possible that research studies of reverse phenotype can increase the chances to reveal the obesity genes.

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