What genetic factors contribute to obesity?

Obesity has increasingly become a challenging epidemic and is now a global concern which has shown no sign of lessening (McAllister et al, 2009, p. 868). While considerable efforts have been invested in stressing the importance of physical activity and the choice of food intake, studies have shown compelling evidence that genetic determinants brought by the inter-individual differences have high responsibility in obesity susceptibility (O'Rahilly & Farooqi, 2006, p. 1095). Substantive evidences about the molecular constituents of the major pathways involved in the balance of mammalian energy have only been recently deciphered. Therefore, this provides a gateway to a mechanistic understanding of obesity that will soon be a useful resource in the designing of effective drugs against obesity. Linkage studies and associations based on populations have identified specific loci where genetic variations occur among obese individuals. Efforts to indentifying and characterizing the monogenic obesity syndromes have also shown considerable success (O'Rahilly & Farooqi, 2006, p. 1095). While a number of researchers have come into a consensus that genetic factors predispose individuals to obesity, some still slightly differ by appreciating the role of such factors like the influence on metabolic rate as well as the effect of selective partitioning of the excess energy in the human body into fats (O'Rahilly & Farooqi, 2006, p. 1095). This paper specifically identifies various genetic factors which contribute to obesity and provides recommendations for addressing the epidemic. To date, there are five main constituent genes known to be involved in food intake and energy expenditure pathways which ultimately contribute to obesity progression. These genes are leptin, leptin receptor, melanocortin-4 receptor, pro-opiomelanocortin as well as prohormone convertase genes (Bouchard, 2009, p. 1499). The role of these

genes in the occurrence of obesity and mutation consequences of such genes, which are studied in different experiments, are elaborated and explained under different gene headings below.

Leptin gene

Efforts to perform leptin gene cloning in 1994 opened an avenue for rapid research in biomedicine and large scale genetic studies followed thereafter (Hinney, Vogel & Heberbrand, 2010, p. 297). Finally, these efforts made success stories after effectively managing to treat leptin deficiency children using the recombinant leptin protein. The treatment of leptin deficiency children also provided other insights to biomedical researchers that single gene mutations could potentially lead to disorders such as obesity and hyperphagia (Hinney, Vogel & Heberbrand, 2010, p. 297). Since its discovery, leptin has posed a potential possibility for the treatment of obesity. The development of obesity treatments has been centered in identifying main targets in leptin gene which was the first to be implicated for the genetic cause of obesity. The leptin hormone is mainly secreted depending on the body fat and is responsible for the regulation of appetite and energy metabolism mainly in the brain (Ahima, 2002, p. 196). Results obtained from linkage studies have deciphered that leptin is basically an assembly of 167 different amino acids that are produced by the leptin gene right from the adipose tissue. The protein encoded by the leptin gene displays a number of biological roles associated with obesity by binding with a defined receptor located in the hypothalamus. These biological roles of leptin include the control of food intake pathways, body weight regulation and homeostasis of energy (Wang et al, 2006, p. 183). French studies and

investigations into populations in Pennsylvania have associated leptin to cases of severe obesity. Among humans, the chromosomal locations of the genes for leptin receptor and leptin have been mapped to 1p31 and 7q31. 3 respectively (Wang et al, 2006, p. 183). Research had earlier shown that the variant G-2548A occurring in the LEP promoter was responsible for reductions in the BMI among overweight women. In addition, a few studies have shown correlations between obesity development and the presence of LEPR gene polymorphisms (Geller et al, 2004, p. 572).

According to Ioffe, Moon, Connolly and Friedman (1998, p. 11852), subset of obese humans have considerably lower levels of leptin plasma. The findings imply that abnormal regulation of the gene in the adipose tissue could be the main cause of pathogenesis in obesity. Ioffe et al (1998, p. 11852) carried out an experiment to test the propensity that decrease in the production of leptin could impact the body’s metabolism thus cause obesity. They performed their experiment by mating animal models that carried lowly expressed adipocyte specific aP2-human leptin transgene with mice that did not express any leptin gene. The leptin treatment of the mice that never expressed leptin resulted to a marked reduction in weight which resembled the results obtained after wild-type mice treatment. Usually, a subset of obese individuals expresses relatively low levels of leptin in plasma. The decreased rates of leptin production among obese individuals by the adipocytes have been implicated for the cause of obesity (Ioffe et al, 1998, p. 11854). Mutations in the leptin gene or the leptin receptor gene have been found to cause increased appetite, overeating, massive weight gain, impaired thermoregulation, insulin resistance and diabetes, immune

dysfunction, sexual maturation failures and a number of neuroendocrine derangements in both human subjects and rats (Ahima, 2002, p. 196).

Melanocortin-4 receptor gene (MC4R)

Mutations in the melanocortin 4 receptor have been said to be the most common genetic factors which contribute to obesity. While the gene coding for the protein, MC4R has been implicated for regulating the body weight of individuals and obesity, there are no convincing reports associating the gene with the increased binge eating among obese individuals. Contrary to what had been observed in the previous studies, the MC4R deficiency does not actually cause hyperinsulinemia. However, a frameshift mutation in the gene coding for the protein MC4R has been associated with dominant human obesity (Hinney, et al, 2003, p. 4258). The protein also acts as an antagonist for the agouti-related peptide (AgRP) gene that code for an endogenous antagonist for the receptor. The homologous of the MC4R gene, the MC3R gene has also been found to be a good candidate for causing genetic susceptibility to glucose intolerance in type II diabetes mellitus (Hinney, et al, 2003, p. 4258). In order to prove that MC4R is influential in causing obesity, researchers have sequenced the introns of the gene among the Pima Indians who among them, 300 were severely affected by obesity and 126 of them were neither obese nor diabetic. In their study, the researchers have addressed the assertion that substitution of G-A at codon 103 of the MC4R gene is responsible for influencing abdominal obesity and lipid, glucose and insulin metabolism. The substitution has also been implicated for its effect in inflecting the circulatory hormones such as the salivary cortisol (Hinney, et al, 2003, p. 4260).

Genome wide association studies (GWAS) have been potential tools for identifying a number of candidate genes in specific regions of the chromosomes which harbor genes responsible and other phenotypes (Zlot et al, 2007, p. 31). GWAS also provide critical tools for indentifying the common variants with reduces penetrance relevant as traits of interests or risk factors. Genes such as melanocortin-4 receptor gene occur in a coding region which also harbors other polygenic variants which regulate weight in healthy individuals apart from the mutations responsible for obesity (Yang et al, 2002, p. 20328). These minor alleles that have been identified include various polymorphisms which code for isoleucine amino acid instead of valine at position 103 (103I) and the other that codes for leucine instead of isoleucine at 251L of the receptor protein. These polymorphisms are all negatively associated with the problem of obesity (Zlot et al, 2007, p. 31). Homozygous carriers of such alleles have slightly reduced basal metabolic rate (BMI) which is a risk factor for obesity.

The biological mechanism of the MC4R gene has been suggested to involve the activation of the MC4R receptor which leads to a significant decrease in food intake. The MC4R has therefore been marked as the main therapeutic target for obesity treatment. The new regulatory biological mechanism has also been detected in cell lines which are derived from the murine hypothalamic neurons that express MC4R endogenously. This therefore points to the physiological importance of the endocytosis promoted by AgRP. In a study involving a number of obese children and adults, 6 percent of them were found to posses MC4R SNPs (Zlot et al, 2007, p. 29). Following agonist stimulation, the MC4R usually signals via the intracellular adenylate

cyclase pathway of signal transduction. Studies among the obese subjects have detected large quantities of MC4R mRNA in the membranes of the astrocytes contrary to the HEK-rMC4R cell membranes.

Pro-opiomelanocortin (POMC)

Feeding in humans follows habitually trained rhythms which are regulated by the hypothalamus. The amount of food one consumes happens as a response to the energy status in the body that depends on the hormones. Even though this is a complex process, there exists an integrated relationship between the energy needs of the body and the amount of food that is required by the body. As a result, the brain through the hypothalamus triggers the release of responsible hormones that regulate food intake. This happens through the release of pro-opiomelanocortin (POMC) (Millinvgton, 2007, p. 4). The initial stage of the production of pro-opionmelanocortin starts with the production of the release of the POMC at the hypothalamus.

Through a series of active enzymatic reaction steps, the pro-opiomelanocortin (POMC) plays an initial role in the production of corticotrophin (ACTH), melanocyte-stimulating hormones (MSH) and endorphin (Millinvgton, 2007, p. 4). The MSH leads to the production of melanocortin peptides that plays a high role in the development of appetite. The melanocortin peptides also continue to have a role in body weight regulation. As the body continues to produce the necessary genes that regulate its development, some genes that develop in the central nervous system give rise to the production of the melanocortin peptides. According to Zemel and Shi (2000, p. 179), melanocortin peptides work by coating the melanocortin-4 receptors through the formation of a layer around these

receptors. This covering inhibits the food absorption and intake. The absence of this through the degeneration of the melanocortin peptide cover marks the onset of obesity. This means that melanocortin receptors POMC peptides plays a significant role in the development of obesity.

As seen earlier, feeding is a process that happens through responses of habitual rhythms such as circadian rhythms. These rhythms are controlled by the genes that are adapted to a given type of system. The lack of POMC in the body exhibits itself through adrenal failure, altered pigmentation and increment in height onset of obesity (Millington, 2007, p. 8). The processing of POMC occurs partially in the pituitary cells and neurons of the hypothalamus. However, POMC derivatives can be discharged differently through varying hypothalamic sites. These are sites that are involved in feeding process. This process of release leads to slight variations in the amount of signal sent to the sites.

From the above discussion, dietary related aspects especially obesity emanates from a complex combination of various genes that makes their significant contributions. Environmental factors are also known to have their equivalent contributions to the role of the genes in the dietary habits and their effects on the body. The melanocortin that is produced as a result of POMC stimulation plays a central role in the direct processes of food absorption. Additionally, the signals sent by the POMC maintain the hormonal levels that controls amount of food to be absorbed at any given moment. This is depending on the homeostatic energy requirement at any specific time. However, in the instance when the levels of POMC released by the hypothalamus get reduced to minimal levels, the immediate effect that

follows is the reduced production of melanocortin peptides. This means that the body no longer has the ability to control the amount of food being taken up by the body. Obesity develops as a result of the body absorbing food at a higher level than required.

Prohormone convertase 1 (PCSK1)

Researchers have reported that common variants in the PCSK 1 gene could be a potential cause of obesity. The proprotein convertase subtilisin/kexin type 1(PCSK 1) has been suggested to play a critical role in proteolytic cleavage, a step which is also important in the maturation process of a number of hormones which are produced as precursors (Heni et al, 2010, p. 86). The PCSK 1gene codes for the prohormone convertase 1 which is actively involved in peptide maturation. The protease is selectively expressed in the endocrine and neuronal tissues where its main substrates include the hormones which regulate energy metabolism such as proinsulin, proopiomelanocortin and proglucagon (Heni et al, 2010, p. 86). Rare mutations in the PCSK 1 gene have been identified to be responsible for causing childhood obesity as well as the abnormal metabolism of glucose, proinsulin and insulin and the C-peptide. Common single nucleotide polymorphisms (SNPs) in the PCSK 1 gene, the rs6232 and rs6235 have been associated with incidences of obesity (Heni et al, 2010, p. 86). Various mutations of the PCSK1 gene cause monogenic obesity. The SNP rs6235 has a high correlation to the non-synonymous rs6234 which encodes the Q665E. This substitution occurs at the protein in the C-terminal region (Tuomas et al, 2009, 3499). This research found that there exist a significant correlation

between age and crs6232 in the initiation and proliferation of obesity (Tuomas et al, 2009, 3499).

Another research by Qibin et al (2010, p. 456) found that the rs6234 has significant association with an increased risk of a combined obesity phenotype and an overall overweight condition. The PCSK 1 gene was also found to have a higher association to obesity among men as compared to women. The result of this gene is that it influences the increment in fat storage around the waist region. The study also found that there exist enough evidence that associates PCSK1 rs6234 with overweight and the level of body mass index in men. It was also revealed that PCSK1 rs6234 plays no role in the weight gain among women.

There have been various recommendations in the use of several mechanisms in the management of obesity. This has been based on the knowledge of the fact that eating habits are part of acquired characteristics. However, studies have revealed that eating habits are controlled by genes. This has therefore called for more understanding on the gene make up of a person. The understanding of the role of PCSK1 gene in the control in insulin and consequent glucose synthesis is a breakthrough in the ongoing research in the search of the appropriate weight management measures.

Studies conducted by Martin et al (2010, 9) have found that small amounts of alleles of PCSK1 and SNPs are associated in high levels of stimulation of glucose proinsulin levels. This gave an indication that the two are related in the reduction of proinsulin conversion with little effect on insulin itself. Under the normal conditions, prohormone convertase cleaves a substantial amount

of proinsulin. The study further found that PCSK1 and SNPs alters the sequence of the amino acid sequence of the protein which makes up this hormone. The change that is initiated by the SNP rs6232 on asparagines is the reduction of the enzymatic activity. The similar change also occurs on the location of the protein thereby reducing its effectiveness in regulating insulin. The end result is the increment of body weight, a condition that is referred to as obesity.

Fat Mass and Obesity Associated Gene (FTO)

The FTO gene has also been identified, using the GWAS approach, to be associated with type II diabetes and obesity. The A-allele of the FTO variant rs9939609 in intron 1 has been shown to be associated with an increased risk to develop obesity complication by 31 percent (Hinney, Vogel & Heberbrand, 2010, p. 302). The association of genes in obesity and overweight problems has been suggested to be high in both monogenic obesity and polygenic forms. The FTO gene is one of the best examples of the common variants which play a role in increasing the BMI and thus important among obesity individuals. The FTO gene is known to be found in chromosome 6 among humans and variants of the gene have closely been associated with human obesity. The gene is widely distributed in both adult tissues and fetal tissues but there is much expression in the pancreatic islets as well as in the hypothalamus.

Transcribed amino acid sequence of the FTO gene has shown high homology with AlkB, an enzyme which demethylates DNA oxidatively. The FTO recombinant protein has the potential to catalyze 3-methylthymine demethylation in single-stranded DNA. Animal studies have shown that gene

expression in FTO is usually upregulated in rats especially in the hypothalamus following food deprivation. The gene is also negatively correlated with the orexogenic galanin like peptide expression that is commonly involved in food intake stimulation. The increase in the expression of hypothalamic FTO is often associated with energy intake regulation but not the feeding reward. These consequences make the gene to be identified as a critical in causing obesity.

An obesity risk allele of the FTO variant has been identified. Usually, the carriers with a single copy of the FTO allele are more susceptible to develop obesity than individuals without the copies. In another observation, the carriers of the two copies of the FTO gene weigh even more than those with a single copy of the gene. This implies that the gene causes an increased risk of obesity among the carriers compared to those without a copy of the gene. At the same time, researchers have identified the association of the single nucleotide polymorphisms (SNPs) in the similar region (rs14210850) of the FTO gene. The variation has been identified as the cause for some percentage of population variance in BMI and even a higher number of attributable obesity cases. The risk allele, according to the researchers, is found in cluster 10 SNP in intron 1 of the FTO gene known as the rs9939609. Morbid obesity has also been shown to be associated with both the INSIG2 SNPs and the FTO gene. Variants of the FTO have also found to be associated with the obesity condition using GWAS of BMI. In the study, individuals with AA and AT alleles at rs993909 have been found to consume more energy per day compared to the individuals having the protective genotype of TT. However, the similar studies have indicated no variation in energy

expenditure based on polymorphisms. In other studies, the consequences of variations in the two different types of SNPs in the FTO gene have shown the possibility of the gene impacting the levels of circulating leptin as well as the energy expenditure. The SNPs that affect the energy expenditure and the circulating levels of leptin include the rs1421085 and rs17817449. Although the studies have not pointed on the biological mechanisms of the FTO gene in contributing to obesity and weight control, researchers have postulated that the gene could be responsible for regulating appetite through its influence in the hypothalamus.

Discussion and Recommendations

The pathogenesis of complex diseases such as obesity has always been associated with the interaction of environmental and genetic factors. This complexity has made it difficult for researchers to tease apart the accurate relationship between the genotype, phenotype and environmental factors by only using conventional experimental designs. Using genetic information maintained in databases, researchers have been able to identify critical molecular pathways responsible for obesity which are specifically brought by the interaction of the environmental factors and the genetic factors (Gohlke et al, 2009, p. 46). Bioinformatics techniques and the Internet have offered critical tools for synthesizing data on the relationship between genes and diseases such as obesity. Methods such as genome-wide association scans have shown a number of genetic variants in the FTO gene which might be associated with phenotypes related to obesity (Scuteri et al, 2007, p. 115). Researchers have identified the potential benefits of genomic-wide association studies (GWAS) approaches in obesity intervention and

prevention strategies such as the design of highly specific drugs targeting the identified molecular pathways (Zlot et al, 2007, p. 31).

The role of epigenetics in obesity has been explored by a number of researchers including McAllister et al (2009, p. 892). Epigenetics encompasses the study of a number of inheritable variations mechanisms in gene expression which do not necessarily originate from alterations in the DNA sequence. These mechanisms are often established at the early stages of postnatal development and during the prenatal stages and they act to maintain a number of gene expression patterns throughout the life of an individual (McAllister et al, 2009, p. 892). Because of this, some environmental factors have become common in the recent past and have commensurately deranged the epigenetic mechanism establishment which results in the regulation of body weight (McAllister et al, 2009, p. 892). The roles of cytosine methylation within the CpG dinucleotides, the modification of histone proteins which package the DNA into the nucleus and the cell-dependent expression of a number of autoregulatory DNA binding proteins have been investigated and shown to perpetuate the conformation of regional chromatic which dictates which type of gene will be competent transcriptionally in specific type of cells (McAllister et al, 2009, p. 892). This literally implies that apart from the genetic basis of obesity, the epigenetic studies shed light and provides extra information that is layered above the common understanding of gene sequences. Like the DNA sequence, epigenetic factors are also replicated at cell division during mitosis and meiosis thus bestowing transgenerational epigenetic inheritance (McAllister et al, 2009, p. 892).

As reported by McAllister et al (2009, p. 896), the understanding of the environmental factors on the epigenetic processes has always remained elementary. Therefore, there has been little evidence to point out specific environmental exposures whose increasing levels might affect epigenetic mechanisms. Maternal obesity has however been identified as one of the main environmental exposure which results into obesity. It is accepted that the obesity epidemic affects even the childbearing women and feed-forward transgenerational obesity amplification has been proposed to result among children born of obese mothers. This is because the intrauterine environments of obese mothers are likely to induce developmental adaptations in the developing fetus which consequently predispose them to obesity. In an observation made to support this assertion, children born of obese mother after bariatric surgery were found to have reduced risks for obesity than the children born of the same mothers before bariatric surgery (McAllister et al, 2009, p. 893). Bariatric surgery is one of the medical procedures carried out with an objective of losing weight and has shown exciting evidence in reducing the chances of obesity among the born children.

There are two types of disorders that have been identified to be caused by single-gene defects. The first class of these disorders is the Mendelian disorders which cause a variety of clinical features including obesity. The second class of single-gene defects is mainly characterized by disease conditions in which obesity is one of the main clinical features. 11 different genes have been reported to be closely associated with monogenic obesity and 52 genomic regions which harbor quantitative trait loci have also been

indentified to have associations with human obesity. Five of the genes have been considered to be of clinical importance since they account up to 5 percent of the early obesity onset and severe cases of childhood obesity. These genes are leptin, leptin receptor, pro-opiomelanocortin, melanocortin 4 receptor as well as prohormone convertase genes. One of the most interesting observations is that all the five genes are associated with encoding receptors and peptides involved in satiety and appetite regulation. Therefore, there is need to intensify research efforts in marking the five genes and developing molecular drug targets for critical receptors which control appetite and satiety. Apart from the five common genes that have been associated with obesity, other minor genes with smaller effects such as ACE, LDLR and VDR have also been implicated for causing obesity. These minor genes are more than 20 in number (Bouchard, 2009, p. 1499).

Conclusion and Recommendation

The prevalence of obesity is increasing globally as biomedical researchers step up their efforts to indentify the specific genetic causes of the epidemic. A number of technological and conceptual advances have made it possible for a shift to an approach centered in single-gene search for interventions aimed at treating and preventing obesity. Before these advances, traditional approaches involved studying obesity from the polygenic approach which was very difficult to mark out the exact molecular processes that occur in at cellular level. A few complex segregation analyses maintained the assertion that obesity was mainly caused by more than a single segregating genes having large effects on the adiposity and body weight. Later studies supported the evidence that obesity could be caused by both polygenic and

oligogenic determinants. With the improved technology and scanning of the entire genome, it has been possible to identify individual genes responsible for obesity using polymorphic microsatellite markers. Among the enabling technologies in sequencing the human genomes involve SNP identification, bioinformatics and SNP genotyping technologies. At present, these technologies have made it possible to study the anatomy of the human genome with improved details and this is expected to yield newer insights into pointing out the exact genetic causes of obesity.