Example of gad2 gene candidate gene for obesity essay

Abstract

Obesity is a heritable and genetically influenced disorder. Recent studies have proved that obesity is a biochemically driven neurological disorder. Obesity has a complex and heterogeneous genetic and phenotypic manifestation. Familial obesity is monogenic and common obesity is polygenic. Leptin and its receptor (LEPR), the α-melanocortin-stimulating hormone receptor (MC4R), pro-opiomelanocortin (POMC) and prohormone subtilisin/kexin type 1 (PCSK1) are some of the single genes involved in monogenic obesity. Glutamate Decarboxylase 2 gene (GAD2) gene is thought to be part of a polygene system resulting in common obesity. GAD2 coding sequence is present on chromosome 10p locus and encodes for a protein GAD65. This protein catalyzes the formation of the neurotransmitter γ-aminobutyric acid (GABA) responsible for increasing the food intake. Cohort studies have contradicting views on GAD2 gene as a possible obesity gene. However, this contradiction is thought to be due to lack of large studies and statistical backing.

GAD2 gene as a candidate gene for obesity

Introduction

Obesity is not new to the human population. However, it was not as frequent or common as one sees in today's population. According to the studies, if the current lifestyle trend continues, by the year 2030 more than 50% of the people in the US and 1. 12 billion people worldwide will be categorized as obese. The main reasons for this increase is the consumption of processed food and less active lifestyle. Besides the lifestyle and food habits, there

have been studies linking genes as significant factors for causing obesity (Walley, Blakemore & Froguel, 2006). Since families tend to share both the lifestyle and the genes, it is difficult to weed out the exact cause. Fatness can be measured in terms of adiposity and is one of the heritable traits. Such heritable factors cause 45-75% of variation between related individuals, such as twins. Obesity is a complex condition and cannot be attributed to a single gene. The interaction of multiple factors imposes the condition. Genome wide scans have been done to look for genetic markers that segregate along with the related trait of the disease. 250 quantitative trait loci (QTL) have been identified for obesity. Glutamate Decarboxylase 2 gene (GAD2) is one of them. (Farooqi & O'Rahilly, 2007).

Evidence for genetic contribution to obesity

In general, families with obese parents tend to have children with obesity. It is a combination of lifestyle and genetics. Familial studies on nuclear families have shown that overweight parents or relatives need not have overweight children. However, children of obese parents tend to be obese. This indicates that obesity tends to run in the family and that it is hereditary. (Farooqi & O'Rahilly, 2007).

Hypotheses on genetics of obesity

There are many hypotheses that aim at elucidating the mechanism of obesity in correlation to genetics. Walley, Asher & Froguel (2009) have briefly explained some of those hypotheses.

Thrifty gene hypothesis. The genes have evolved over time in such a manner that weight gain is favored to overcome famine and prevent starvation. The

control mechanism of the body is not designed to regulate weight gain.

Predation release hypothesis. The method of Natural Selection would have not favored survival of obese humans. However, once humans learnt how to defend themselves, this predator pressure was released and the obesity-bestowing genes drifted randomly.

Sedentary lifestyle hypothesis. High calorie food intake with less physical activity is a trend that has been around for the past few decades. This could have resulted in genetic changes in the metabolic enzymes.

Genetic variants of obesity

The discovery of genetic correlation of obesity has helped see the disorder in new light. It is not an act of voluntary overeating. Obesity is a biochemically driven urge to eat. Unveiling the genetic and biochemical connection has helped patients and common people to realize that obesity is a serious condition comparable to coronary risk, stroke and cancer. (Farooqi & O'Rahilly, 2007).

Monogenic obesity. Monogenic obesity is associated with familial obesity that displays the Mendelian inheritance pattern. Single genes involved in appetite regulation are responsible for only 4% to 5% of the obesity cases. Monogenic obesity is characterized by early onset of the disease due to hyperphagia (overeating). Some of the single genes involved are leptin and its receptor (LEPR), α-melanocortin-stimulating hormone receptor (MC4R), pro-opiomelanocortin (POMC) and prohormone subtilisin/Kexin type 1 (PCSK1). (Walley, Blakemore & Froguel, 2006). Leptin gene was identified using mouse models. It was the first single gene to be associated with obesity in

humans. Recently, three more genes have been identified that cause a rare kind of monogenic obesity. These genes are, single-minded homolog 1 (SIM1), brain-derived neurotrophic factor BDNF and neurotrophic tyrosine kinase receptor type 2 (NTRK2; also known as tropomyosin-related kinase B, TRKB). These genes are associated with energy balance. (Walley, Asher & Froguel, 2009).

Polygenic obesity. Polygenic obesity, which is also called as common obesity, shows no Mendelian inheritance pattern. Multiple genes with relatively small individual effect may combine to cause common obesity under favorable environmental conditions. Scientists have not yet devised a method to analyze candidate genes that could cause polygenic obesity. However, two genes have been found common to monogenic and polygenic obesity: MC4R and BDNF. One approach that is being explored currently is using genome wide scans. These scans are done on nuclear families with specific requirements to detect linkage with obesity. The specific requirements were that at least one of the family members must have a body mass index (BMI) of more than 40 kg/m2 and at least one of the siblings must have a BMI of 27 kg/m2. The scans have revealed that chromosome 10p locus shows high linkage to obesity. (Boutin et al, 2003). Positional cloning has revealed candidate genes such as GAD2, solute carrier family 6 (amino acid transporter), member 14 (SLC6A14) and ectonucleotide pyrophosphatase/phosphodiesterase1 (ENPP1). The gene of interest for this paper, GAD2 is responsible for catalyzing γ-aminobutyric acid (GABA), a neurotransmitter that is responsible for increasing food intake. (Walley, Asher & Froguel, 2009).

Physiological basis of obesity

Energy balance disorder. Obesity is a disorder of energy balance in the body. That is, there is more consumption of energy in the form of food and very less expenditure in the form of physical activity. The less expenditure could be due to non-oxidation of fat, unregulated fat deposition in the body due to an impaired lipolysis in the adipocytes and low basal metabolism. At a biochemical level, the energy balance in the body is regulated by leptin that is encoded by LEP gene. When the adiposity increases, leptin is released to decrease the appetite. The energy expenditure is implemented by leptin through thermogenesis in brown adipose tissue (BAT). Previously BAT was thought to be metabolically inactive. However, research shows that BAT has a significant role in fat metabolism and obesity. (Walley, Asher & Froguel, 2009).

Adipocyte disorder. Fat is stored in the form of triacylglycerol in the adipocytes. The number of adipocytes increases steadily until an individual reaches adolescence. Once a person reaches adulthood, the number remains the same, but adipocyte size differs. When these adipocytes enlarge due to accumulation of fat, it results in weight gains in humans. It has also been found that children with early onset of obesity have increased the number of adipocytes compared to normal children. Thus, obese adolescent children go on to become obese adults. Even after losing weight, adults who were previously obese show higher number of adipocytes. This indicates that the adipocyte numbers never change irrespective of weight loss and continue to promote leptin deficiency and low energy expenditure. (Walley, Asher & Froguel, 2009).

Neurobehavioral disorders. Obesity was never looked upon as a neurological problem until the role of leptin-melanocortin pathway in appetite was discovered. Obesity is now defined as a neurological disorder driven by a biochemical urge to overeat. (Walley, Asher & Froguel, 2009).

Epigenetics and obesity

Gene variations can occur in the form of insertion or deletion mutations in the DNA sequence. Such changes in a single nucleotide are called as single nucleotide polymorphism (SNPs). Most of them are harmless and may cause no significant difference in gene expression. However, some SNPs could change the protein function. Epigenetic variations do not cause any change in the actual DNA sequence, but changes the way in which the DNA folds. Such a change may be in the form of methylation or histone modification, which in turn can influence protein transcription. The modifications can change the amount or rate at which the protein is encoded. Sometimes the epigenetic modifications cause gene silencing due to methylation. Role of epigenetics on obese individual is evident from studies of genetic imprinting. Imprinting causes only one allele (either paternal or maternal) to expresses. Loss of imprinting in certain chromosomes has been associated with hyperphagia leading to obesity. (Walley, Blakemore & Froguel, 2006).

GAD2 and obesity

GAD2 coding sequence, present on chromosome 10p locus, encodes for the protein GAD65. This protein catalyzes the formation of the neurotransmitter GABA. This coding sequence is home for a marker gene D10S197 that shows strong linkage to obesity. D10S197 is present on the intron 7 of the GAD2

gene. GABA stimulates hunger by interacting with the neuron neuropeptide Y (NPY) present in the paraventricular nucleus. Studies done on class III obesity indicated the presence of a haplotype and an SNP residing within the GAD2 sequence, differing in their occurrence frequency. The affected obese individuals had +61450 C> A and +83897 T> A SNPs. That is, at the upstream position +61450 Cytosine was replaced by Adenine and at +83897 Thymine was replaced by Adenine. The unaffected normal weight individuals had the excessive amounts of the normal +61450 C and +83897 T. Another variant of GAD2 that was studied had -243 A> G. That is, downstream -243 had guanine instead of adenine and had strong associations with class III obesity. When a luciferase reporter gene was spliced with GAD2 promoter, the -243 A> G from the 5' region resulted in 6 times more production of protein when compared to the wild type -243 A in murine cells. It has been concluded that -243 A> G might be responsible for influencing potential physiological changes. There are conflicting evidences of association between GAD2 and severe obesity in humans. The research by Boutin et al (2003) proves an association of this gene with morbid obesity. However, Swarbrik et al (2005) could not corroborate this result owing to smaller study group. Nevertheless, it does not eliminate GAD2 as a potential candidate. (Swarbrick et al, 2005).

Obesity associated health risks

How and where the body fat accumulates is a gene driven mechanism. The preferential visceral fat accumulation in insulin sensitive tissues such as the pancreas and liver is life-threatening. Such a condition brings about insulin

resistance and leads to inflammation due to macrophage infiltration. However, the situation can be maintained at neutral if the body can generate insulin sensitive subcutaneous adipocytes for storing fat. Obesity can lead to associated risks such as asthma, sleep apnea, cancer, osteoarthritis, renal failure, diabetes, insulin resistance, microvascular problems, etc. Biomarkers are now available to detect the type of obesity and the associated health problems. Bariatric surgery is a sought after method to control body weight. However, it has been discovered that individuals who underwent such surgeries to lose weight died earlier when compared to individuals who did not undergo the surgery and did gain more weight. Thus, obesity is much more complex than it seems. (Walley, Blakemore & Froguel, 2006).

Future of genetic studies in obesity

Phenotype selection. Genotypes are expressed through different phenotypes. Thus, the phenotypes must be selected based on their robustness, reproducibility and accuracy to the disease being studied. Obesity studies must not be solely based on BMI. More attributes that are physical in nature must be taken into consideration before starting an obesity study. Some diagnostic tools used for this purpose these days are: Photonic scanners. Measure BMI, waist-hip ratio and other measurements. Air-displacement plethysmography. Allows measurement of full body volume and weight. In addition, it measures fat mass and fat-free mass. Computed tomography (CT) and magnetic resonance imaging (MRI). Gives accurate measurement of the body fat mass and its distribution. Ultrasonography (US). Results from US are very similar to that obtained from

CT and MRI.

Cellular and molecular phenotyping are also being explored for accurate measurements and effects of obesity related genes. This method might be able to shed light on the relation between the candidate gene and the phenotype. Transcriptomes are being used to uncover new candidate genes through genomic techniques. RNA transcripts are analyzed from tissue samples of members of the same family in a microarray. The amount of transcripts is quantified and studied for associated phenotypes. (Walley, Asher & Froguel, 2009).

Genome wide studies. There is a severe lack of statistical data for backing the data obtained from experiments. Genome wide studies will not only help with statistical power, but also help in analyzing new variants and SNPs. Most obesity studies are case-control studies as subjects can be easily found for such studies. However, such studies tantamount to being false due to population substructure. (Walley, Asher & Froguel, 2009).

Conclusion

Obesity is more complex than it was thought to be. It is heterogeneous in terms of genotype and phenotype. That is, obese individuals differ greatly in their fat deposition patterns, genes that cause them and associated factors. Both genetics and epigenetics influence the expression and manifestation of obesity. GAD2 gene is a potential candidate whose role in obesity needs to be more powerfully established using large study groups that are selected with more uniformity. Statistical backing will also help the study. Chromosome 10p12 is a very potential location to look for more potential

candidates that might be the driving force for polygenic and possibly monogenic obesity. However, with current amount of genetic and phenotypic data, GAD2 does not make a very compelling obesity causing gene candidate. (Walley, Blakemore & Froguel, 2006).

Reference

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