International Journal of Pharma Medicine and Biological Sciences

ISSN 2278 – 5221 www.ijpmbs.com
Vol. 3, No. 1, January 2014

Review Article

HERITABILITY OF BODY WEIGHT: AN EVIDENCE FOR OBESITY?

Balakrishna Shetty[1] and Manjula Shantaram[2]*

*Corresponding Author: ***Manjula Shantaram*** ✉ manjula59@gmail.com

Excess body weight has reached epidemic proportions globally, with more than 1 billion adults being either overweight or obese. Increase in the body weight has been observed across all age groups. Excess body weight is a multi-factorial and heterogeneous condition that results from alterations of various genes. The inheritance pattern of obesity is thus complex, and environmental factors play an important role in promoting or delaying its development. Even though genetic contribution to inter-individual variation in common obesity has been estimated at 40-70%, the search for obesity susceptibility genes has been not achieved to a large extent. This article reviews progress made in the field of genetics for the understanding of heritability of body weight with an emphasis on established overweight or obesity susceptibility loci identified through candidate gene, genome wide linkage and genome-wide association studies. Although it is not clearly understood the strength of the genetic effects on obesity, it is evident that human adiposity and a propensity towards weight gain is influenced by genes.

Keywords: Body weight, Body mass index, Heritability, Obesity, Genetics

INTRODUCTION

Body weight is one of the physiological characteristics and its increase or decrease is caused by an imbalance between the energy intake and energy expenditure. This results from the complex interactions between genes, other biological factors, behavior, life course experiences and exposures to biophysical and socioeconomic environments (Emily *et al.,* 2009). Many people maintain a near-constant body weight throughout adult life. This ability is a demonstration of caloric homeostasis, a physiological condition in which energy needs match energy intakes. Various signal molecules act on the brain to control hunger and appetite. Short term signals like cholecystokinin (CCK) and Glucagon-like peptide-1(GLP-1) relay satiety signals to the brain while eating is in progress. Long term signals include leptin and insulin, leptin being secreted by the adipose tissue mass is an

[1] Department of Biochemistry, S.D.M. College of Naturopathy and Yogic Sciences, Ujire, Karnataka - 574 240.
[2] Department of Biochemistry, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka - 575 018.

indication of fat stores. Leptin inhibits eating by binding to a receptor in brain neurons, which initiates signal transduction pathways that reduce appetite. Insulin also works in the brain, signaling carbohydrate availability (Woods, 2009). Thus body weight is strongly under the control of biological system which regulates the balance between the energy intake and energy output. Increase in food intake results in part from increases in the production of the hormone, ghrelin that signals hunger and decreases in the production of the hormone, leptin that signals fullness (Friedman, 2009).

Most of the scientific conclusions made related to body weight are based on Body Mass Index (BMI) calculation. Body mass index is expressed as weight in kilograms divided by height in meters squared (kg/m^2)—is commonly used (Han *et al.,* 2006) to classify underweight (BMI <18.5 kg/m^2), healthy or normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obesity (BMI >30.0 kg/m^2), and extreme obesity (BMI >40.0 kg/m^2).

Epidemiological studies show that there is an increase in the average body weight in many industrialized countries increased since a last few decades. The increasing prevalence of overweight (BMI > 25 kg/m^2) and obesity (BMI > 30 kg/m^2), with the associated risks of cardiovascular disease, type 2 diabetes, various cancers, and joint disease, is arousing considerable and growing interest in the underlying risk factors (Malnick and Knobler, 2006). The populations of modern industrialized countries are exposed to a multitude of environmental factors that favor a positive energy balance. Energy uptake frequently exceeds energy consumption to such an extent that body fat increases to an above average level, resulting in overweight or obesity. The two primary causes are thought to be the low cost and availability of a wide range of tasty, high-energy foodstuffs and a lack of exercise both at work and during leisure. Psychosocial factors play a role in how individual or people cope with their obesity-facilitating environment (Emily *et al*., 2009).

The scientific reviews show dramatic rise in the body weight of children which resulted in childhood obesity in the past 15 years (Lobstein *et al*., 2006). It is clearly due to the changes in the environment, because genes have not altered. However, not all children are overweight. This difference could be due to inherited genetic differences between children or to differences in their rearing environment. Most of the studies give evidence of overweight and obesity rates being continued to increase. A study by Rokholm *et al.* (2010) shows that 'obesity' rates for children, adolescents and adults is stabilized in Australia, Europe, Russia, USA and Japan. But on the contrary, there is an increase in the prevalence of obesity in Asian adults especially of India, Nepal, Bangladesh and Malaysia. However, average body weight is still increasing to some degree in specific population groups as well as in countries that are rapidly industrializing (Bouchard, 1997) and so, it is important to study the factors that may be contributing to this trend. Presently we are trying to explore the role of genetic factors on the body weight.

HERITABILITY LEVEL

The results of level of heritability particular to any trait are from the studies based on large number of twins, adoption and family studies. The level of heritability of body weight is simply the fraction of the population variation in body weight that can be explained by genetic transmission. Two

comprehensive studies incorporating twins, adoptees and nuclear family data have yielded heritability estimates of 25-40% of the individual differences in BMI or body fat (Bouchard, 1997). The relative contribution of genetics to the variability in body weight in a population is referred to as heritability. Research on monozygotic (identical) twins, nonidentical twins and siblings provides strong evidence for the heritability of body weight (Hsu *et al*., 2005; Wardle, 2008). These studies have shown that between 70 and 80% of the variability in body weight can be attributed to genetic variation within the population to which the twins belong. Heritability does not refer to the contribution of genetics to the weight of an individual, or the relative chance of being fat if one's parents are fat. Heritability is high when genes contribute proportionately more to the variation of body weight within the population than the environment.

STUDIES ON HERITABILITY OF BODY WEIGHT

Genetic contribution can arise from either specific locations of genetic sequences within a gene that makes an individual more susceptible to higher body weight or variant forms of whole genes associated with increased susceptibility. Studies related to the search of heritability of body weight can be grouped into three types: Identification of candidate genes, genome wide linkage studies and genome wide association studies.

CANDIDATE GENE STUDIES

Candidate gene studies rely on the current understanding of the biology and pathophysiology that underlies the susceptibility to obesity. Genes, for which there is evidence for a role in regulation of the energy balance in animal models or monogenic forms of obesity, are tested for association with obesity-related traits at the population level. Recent update of the Human Obesity Gene Map reported more than 127 candidate genes for which at least one study reported a positive association with obesity-related traits (Rankinen *et al.,* 2006). Since the replication of results in successive studies has been inconsistent, the overall conclusion on association of candidate genes remains unclear. But strong association with obesity was found for melanocortin 4 receptor (MC4R), prohormone convertase 1/3 (PCSK1), Brain-Derived Neurotrophic Factor (BDNF), and β-adrenergic receptor 3 (ADRB3) genes. MC4R is widely expressed in the central nervous system and plays a key role in the regulation of food intake and energy homeostasis (Huszar *et al*., 1997). Rare functional mutations in MC4R are the commonest monogenic cause of severe early onset obesity (Farooqi *et al*., 2003). The PCSK1 gene is another strong candidate, as it encodes an enzyme that converts pro-hormones into hormones involved in energy metabolism regulation. Individuals with rare mutations in PCSK1 are born with a PC1/3 deficiency resulting in a syndrome characterized by extreme childhood obesity (Jackson *et al.,* 1997). Animal studies have shown the role BDNF in eating behavior, body weight regulation and hyperactivity (Kernie *et al*., 2000) and a rare mutation in BDNF probably causes severe obesity and hyperphagia (Gray *et al.,* 2006). ADRB3 is a candidate gene involved in the regulation of lipolysis and thermogenesis. A recent meta-analysis that combined data of 44,833 individuals found a significant association between the Arg64Trp variant and BMI in East Asians (Kurokawa *et al*., 2008). Large scale studies and meta-analyses

of at least five variants in four candidate genes have been found to be robustly associated with obesity-related traits.

GENOME-WIDE LINKAGE STUDIES

These studies rely on the relatedness of study subjects and test whether certain chromosomal regions co-segregate with a disease or trait across generations by which to identify new, unanticipated genetic variants associated with a disease or trait of interest (Loos, 2009). Results of study by Dong *et al.* (2005) suggest that there are at least three genetic loci—in chromosome regions 10p12, 12q24, and 13q32—that may influence susceptibility to obesity when it is maternally or paternally transmitted. A meta-analysis of 37 genome wide linkage studies of European origin, could not locate a single obesity or BMI locus with convincing evidence (Saunders *et al.,* 2007). This meta-analysis indicates that genome-wide linkage might not be an effective approach for identifying genetic variants for common obesity.

GENOME WIDE ASSOCIATION STUDIES

Genome-Wide Association (GWA) study is a whole genome association study. It is an examination of many common genetic variants in different individuals to see if any genetic variant is associated with a certain trait (Manolio, 2010). Recently, several GWA study results have expanded the number of genetic susceptibility loci for obesity by identifying several new Single Nucleotide Polymorphisms (SNPs) consistently associated with both BMI and weight, and thus, contributing to obesity risk (Thorleifsson *et al.,* 2009). The study by Zhao *et al.* (2009) on 6078 children with obesity showed several genetic variants of BDNF gene. The product of the gene Brain-derived neurotrophic factor is a nerve growth factor. The relevance between BDNF and children obesity in 1097 European cases and 2760 controls further confirmed by the same authors in 2011. A study of 6078 European children identifies the association between Fat mass and obesity associated (FTO) gene variants and childhood obesity. FTO is located in chromosome 16, which has been considered as one of the most important genes related to obesity (Zhao *et al.,* 2009). Glucosamine-6-phosphate deaminase 2(GNPDA2) is an enzyme in humans which is encoded by the GNPDA2 gene located in chromosome 4p12. Results of study by Zhao *et al.* (2011) on 1097 obese cases of European population found that the genetic variants of GNPDA2 were correlated with pediatric BMI and obesity. Zhao *et al* (2009) reported Insulin induced gene2 (INSIG2) as an identified gene with children obesity in European cases. Renström *et al* (2009) conducted a study on 4923 adults from northern Sweden and reported that Mitochondrial carrier homolog 2 (MTCH2) is significantly associated obesity correlates with obesity. Zhao *et al.* (2011) performed a GWA meta-analysis on 1097 obesity case together with 2760 lean controls aged 2-18 years old in European Americans and found the association between Neurexin-3-alpha (NRXN3) loci and childhood obesity.

CONCLUSION

Based on the results of several genetic and GWA studies, many genes are identified which may have significant effect on bodyweight and thereby on obesity, ultimately suggesting that obesity is partly due to genetic variance. Confounding variables such as environmental influence and

unknown gene-gene interactions may also be present. The results of these studies are based on subjects corresponding to difference in ethnicity, age and different study sample sizes. Hence, there are many unknown factors which may also have played their role in the identification of genes related to excess bodyweight. As a result, it is clear that the occurrence of overweight is complex, and our current knowledge is not sufficient to explain the exact mechanism of obesity. Consequently, future studies with a larger sample size, newer methodologies and a complete meta-analysis of all the genuine studies may lead to a new gateway for the better understanding of the heritability of overweight or obesity.

REFERENCES

1. Bouchard C (1997), "Genetics of human obesity: recent results from linkage studies", *J Nutr* , Vol. 127, pp. 1887-1890.
2. Dong C, Li Wei-Dong, Geller F, Lei Lei, Li Ding, and Gorlova O Y (2005), "Possible genomic imprinting of three human obesity-related genetic loci", *Am J Hum Genet ,* Vol. 76, pp. 427–437.
3. Emily J. McAllister, Nikhil V. Dhurandhar, Scott W. Keith, Louis J Aronne, Jamie Barger and Monica Baskin (2009), "Ten Putative Contributors to the Obesity Epidemic", *Crit Rev Food Sci Nutr* , Vol. 49, pp. 868–913.
4. Farooqi I S, Keogh J M, Yeo G S H, Lank E J, Cheetham T and O'Rahilly S (2003), "Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene", *N Engl J Med ,* Vol. 348, pp. 1085–1095.
5. Friedman J M (2009), "Obesity: Causes and control of excess body fat", Nature, Vol. 459, pp. 340-342.
6. Gray J, Yeo G S H, Cox J J, Morton J, Adlam A L and Keogh J M (2006), "Hyperphagia, severe obesity impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene", *Diabetes,* Vol. 55, pp. 3366–3371.
7. Han T S, Sattar N and Lean M (2006), "Assessment of obesity and its clinical implications", *BMJ*, Vol. 333, pp. 695-698.
8. Hsu F C, Lenchik L, Nicklas B J, Lohman K, Register T C and Mychaleckyj J (2005), "Heritability of body composition measured by DXA in the diabetes heart study", *Obes Res* , Vol. 13, pp. 312-319.
9. Huszar D, Lynch C A, Fairchild-Huntress V, Dunmore J H, Fang Q and Berkemeier L R (1997), "Targeted disruption of the melanocortin-4 receptor results in obesity in mice", *Cell,* Vol. 88, pp. 131–141.
10. Jackson R S, Creemers J W M, Ohagi S, Raffin-Sanson M L, Sanders L and Montague C T (1997), "Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene", *Nat Genet* , Vol. 16, pp. 303–306.
11. Kernie SG, Liebl DJ and Parada L F (2000), "BDNF regulates eating behavior and locomotor activity in mice", *EMBO J,* Vol. 19, pp. 1290–300.
12. Kurokawa N, Young E H, Oka Y, Satoh H, Wareham N J and Sandhu M S (2008), "The ADRB3 Trp64Arg variant and BMI: a meta-analysis of 44 833 individuals", *Int J Obes*, Vol. 32, pp. 1240–1249.

13. Lobstein T, Baur L and Uauy R (2004), "Obesity in children and young people: a crisis in public health", *Obes Rev* , Vol. 5, pp. 4 –104.

14. Loos R J (2009), "Recent progress in the genetics of common obesity", *Br J Clin Pharmacol* , Vol. 68, pp. 811-829.

15. Malnick S D H and Knobler H (2006), "The medical complications of obesity", *Q J Med*, Vol. 99, pp. 565–579.

16. Manolio T A (2010), "Genome wide association studies and assessment of the risk of disease", *N Engl J Med* , Vol. 363, pp. 166-176.

17. Rankinen T, Zuberi A, Chagnon Y C, Weisnagel S J , Argyropoulos G and Walts B (2005), "The human obesity gene map: the 2005 update", *Obes Res* , Vol. 14, pp. 529–644.

18. Renström F, Payne F, Nordström A, Brito E C, Rolandsson O and Hallmans G (2009), "Replication and extension of genome-wide association study results for obesity in 4923 adults from northern Sweden", *Hum Mol Genet* , Vol. 18, pp. 1489-1496.

19. Rokholm B, Baker J L and Sorensen T I A (2010), "The levelling off of the obesity epidemic since the year 1999 – a review of evidence and perspectives", *Obesity Reviews*, Vol. 11, pp. 835-846.

20. Saunders C L, Chiodini B D, Sham P, Lewis C M, Abkevich V and Adeyemo A A (2007), "Meta-analysis of genome-wide linkage studies in BMI and obesity", *Obesity* (Silver Spring), Vol. 15, pp. 2263–2275.

21. Thorleifsson G, Walters GB, Gudbjartsson D F, Steinthorsdottir V, Sulem P and Helgadottir A (2009), "Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity", *Nat Genet* , Vol. 41, pp. 18-24.

22. Wardle J, Carnell S, Haworth C M and Plomin R (2008), "Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment", *Am J Clin Nutr* , Vol. 87, pp. 398-404.

23. Woods SC (2009), "The control of food intake: behavioral versus molecular perspectives", *Cell Metab*, Vol. 9, pp. 489-498.

24. Zhao J, Bradfield J P, Li M, Wang K, Zhang H and Kim C E (2009), "The role of obesity-associated loci identified in genome-wide association studies in the determination of pediatric BMI", *Obesity* (Silver Spring), Vol. 17, pp. 2254- 2257.

25. Zhao J, Bradfield J P, Zhang H, Sleiman P M, Kim C E and Glessner J T (2011), "Role of BMI-associated loci identified in GWAS meta-analyses in the context of common childhood obesity in European Americans", *Obesity* (Silver Spring), Vol. 19, pp. 2436-2439.