Int J Hum Genet, 8(1-2): 217-226 (2008)
PRINT: ISSN 0972-3757 ONLINE: 2456-6360
DOI: 10.31901/24566330.2008/08.01-2.18

Genetics of Human Obesity: An Overview

A. Nirmala[1], B. M. Reddy[2] and P.P. Reddy[1,3]

1. School of Human Genome Research and Genetic Disorders, Mahatma Gandhi National Institute of Research and Social Action, Hyderabad, India
2. Molecular Anthropology Group, Biological Anthropology Unit, Indian Statistical Institute, Hyderabad, India
3. Institute of Genetics and Hospital for Genetic Disorders, Begampet, Hyderabad, India

KEYWORDS Body mass index; genetic predisposition; environment; familial aggregation; candidate genes; whole genome scans; association; population based samples

ABSTRACT Obesity is a complex, heterogeneous group of disorders that is determined by genes, environmental factors and interaction between genes and environment. Body Mass Index (BMI) is a proxy measure for obesity and is the most commonly studied marker for it. Obesity is becoming an increasingly important clinical and public health challenge through out the world. It is associated not only with an increased burden of non-insulin diabetes, hypertension, cardiovascular diseases, some types of cancers and premature mortality but also with the social and psychological effects of excess weight. Because of its larger population size, the developing world has faced with larger burden of overweight and obesity. Several studies have shown that changes in dietary patterns, physical activity levels and life styles associated with diet and urbanization are related to increasing incidence of obesity in India. The risk of obesity is about two to three times higher for an individual with a family history of obesity and it increases with the severity of obesity. In this paper, we present a broad historical overview of the studies on the genetic etiology of human obesity, including the recent studies involving candidate gene and whole genome scan approaches using case-control and family samples. The uniqueness of Indian population structure and its relevance to understanding and/or for disentangling the genetic etiology of complex genetic disorders in general and particularly of human obesity has been emphasized.

INTRODUCTION

Obesity is a complex, heterogeneous group of disorders that is determined by genes, environmental factors and interaction between genes and environment. Although there is considerable controversy as to the relative influence of the genetic and environmental contributions on the expression of human obesity it is known that both factors are essential in the determination of this complex trait (Bouchard and Perusse 1985). Body Mass Index (BMI) is a proxy measure for obesity and is the most commonly studied marker for it. The World Health Organization (WHO) recommended the following cut off points for body mass index to classify weight status in adults 20years of age or older: 18.5 kg/m^2 (under weight), 18.5 – 24.9 kg/m^2 (normal weight), 25.0 – 29.9 kg/m^2 (over weight) 30.0-30.9 kg/m^2 (obese) and $\varepsilon \geq 40$ kg/m^2 (extremely obese).

Address for correspondence: Dr. A. Nirmala, Ph.D.
School of Human Genome Research and Genetic Disorders, Mahatma Gandhi National Institute of Research & Social Action, 1-2-17, Street No. 17, Gagan Mahal Road, Domalguda, Hyderabad 500 029, Andhra Pradesh, India
Telephone: 040-27672492; *Fax:* 040-27664920
E-mail: allanirmala@gmail.com

Obesity is becoming an increasingly important clinical and public health challenge throughout the world. Although this epidemic is not of infectious origin, it is clearly communicable, moving rapidly in association with globalization within and across populations all of which appear to be genetically susceptible at some level, and is being transmitted through eating and physical activity (Kumanyika 2007). Obesity is associated not only with an increased burden of non-insulin diabetes, hypertension, cardiovascular diseases, some types of cancers and premature mortality but also with the social and psychological effects of excess weight (Bell et al. 2005). Recently the International Obesity Task Force estimated a total of 1.1 billion overweight (including 320 million obese) adults worldwide (International Obesity Task Force 2005). Prevalence of obesity is higher in the economically developed regions of the world (Haslam and James 2005) compared to the developing regions. However, with increasing adoption of western lifestyles, those in the developing countries are also rapidly catching up with the obesity. Because of larger population size, the developing world is actually faced with larger burden of overweight and obesity (Gu et al. 2005; Reddy et al. 2002).

Several studies have shown that changes in

dietary patterns, physical activity levels and life styles associated with diet and urbanization are related to increasing incidence of obesity in India (Reddy BN 1998). National Foundation of India (Joshi and Joshi 2002) reported higher incidence of obesity among people above 40 years. They also noted that obesity as an emerging problem. The risk of obesity is about two to three times higher for an individual with a family history of obesity and it increases with the severity of obesity. Obesity is a major chronic disorder affecting 20-40% adults in India.

GENETIC PREDISPOSITION TO OBESITY

For more than 50 year it is clear that both familial and non-familial factors played an important role in the development of obesity (Davenport 1923) and also that the genetic basis was behind much of the familial components. From mid 1980's onwards the systematic studies, hence the knowledge in this field, progressed rapidly. By studying identical twins, most of the investigators reported the heritability estimates in the range of 50% - 90% (Bouchard et al. 1988; Stunkard et al. 1990). Recent studies in the United States have shown disproportionate levels of obesity in African American and Hispanic Americans compared with Caucasians (Cossrow and Falkner 2004). These ethnic differences are not only due to variations in lifestyles and economic factors alone but also indicate an important role of genes. With increasing trends in the prevalence of obesity and also with the evidence of strong genetic influence in the development of obesity, many research groups started to study the genetics of obesity for better understanding the pathogenesis of the disease. Candidate gene approach and whole genome scans are two important methods that are commonly used to unravel the complex nature of underlying genetic etiology of obesity. With this background, we try to outline the recent developments in the field of genetics of obesity by providing information from heritability studies, genome wide linkage studies and candidate gene association studies.

Monogenic Forms of Obesity

Some forms of obesity are caused by mutations in single genes. These forms of obesity are rare and very severe, generally starting in childhood (Farooqi and Rahilly 2004). Currently 176 human obesity cases due to single gene mutations in 11 different genes have been reported (Yang et al. 2007), including the leptin, leptin receptor, proopiomelanocortin (POMC) and the melanocortin four receptor genes (MC4R). MC4-R is the most frequent autosomal dominant form of obesity which is caused by mutations in the gene that encodes MC4R. It represents the most common monogenic obesity disorder present in 1-6% of obese individuals from different ethnic groups (Bell et al. 2005). Till date, 50 loci related to Mendelian syndromes relevant to human obesity have been mapped to a genomic region and causal genes or strong candidates have been identified for most of the syndromes (Rankinen et al. 2006).

Syndromic Forms of Obesity

At least 20 rare syndromes due to discrete genetic defects or chromosomal abnormalities, both autosomal and X-linked, are characterized by obesity. For example, Prader Willi Syndrome (PWS) is an autosomal- dominant disorder that is characterized by obesity and it is usually caused by a paternally inherited deletion at the chromosomal region 15q11.2 – q12 and less frequently by maternal uniparental disomy (Bell et al. 2005). Molecular causes that underlie the etiology of syndromic obesity are more complex than for monogenic cases and further studies are necessary to reveal their genetic basis.

Genetics of Common Obesity

The more common forms of obesity are the result of both gene-gene and gene-environment interactions. However, unlike the monogenic obesity, identification of specific susceptible genes is difficult. Currently over 430 genes or chromosomal regions have been implicated in the etiology of obesity. It is clear from the twin, adoption and family studies that obesity in highly heritable and an individual's risk of obesity increases when one has relatives who are obese (Stunkard et al. 1986a,b; Rice et al. 1999). The first evidence about the important role of genetics in obesity came from the National Heart Lung and Blood Institute (NHLBI) Twin study in 1977, which indicated the possibility that the observed familial aggregation for obesity was due to genetic factors rather than environment (Feinleib

et al. 1977). Heritability estimates for obesity related phenotypes varied from 6% to 85% among various populations (Review by Yang et al., 2007). Significant familial correlations (Nirmala et al 1993; Tables 1 & 2) and transmissibility estimates (Mitchell et al. 1993) have been documented for numerous obesity phenotypes and energy variables. Heritability estimates ranged from 16% to 85% for body mass index (Allison et al. 1996; Pietilainen et.al. 1999; Adeyemo et al. 2003; McQueen et al. 2003; Platte et al. 2003). Hasstedt et al. (1989) reported a recessive mode of inheritance for the ratio of sub-scapular thickness to the sum of sub-scapular and suprailiac skin fold thickness, while Selby et al. (1989) using the same ratio as a measure of central body fat estimated heritability of 0.43 after correction for overall obesity. Turula et al. (1990) and Moll et al. (1991) also reported similar findings. Pietilainen et al. (1999) estimated that 80% of the inter-individual variation in BMI was due to genetic effects, which was supported by a similar study from UK (Koeppen – Schomerus et al. 2001).

Influence of major genes was also reported for several obesity phenotypes including the body mass index (BMI), fat mass, relative fat pattern index, the abdominal visceral fat area and the ratio of trunk to extremity skin folds adjusted for total fat (Feitosa et al. 1999). Multi-factorial effect (that is polygenic and/or familial environmental etiologies) is also reported for obesity measures (Bouchard and Perusse 1985). Feitosa et al. (2000) by using segregation analysis on 1691 individuals belonging to 432 nuclear families from India investigated the evidence of major gene effect for BMI and reported putative major locus accounting for 37% of the phenotypic variance**.** However after adjusting the BMI for energy intake (EI) and energy expenditure of activity (EEA), no evidence in support of major

Table 1: Maximum likelihood parameter estimates (± SE) of the familial correlations for obesity/adiposity measures estimated under the parsimonious models in Telugu families, after adjusting for age and energy measures (Nirmala et al. 1993).

Age-adjusted phenotypes	*SF6*	*TSF3*	*BMI*	*TE ratio*	*RFPI*
			Model[a]		
	II	*II*	*II*	*V*	*V*
FM	0.46 ± 0.04	0.44 ± 0.04	0.37 ± 0.04	0.01 ± 0.05	0.06 ± 0.05
PC[b]	0.38 ± 0.03	0.36 ± 0.03	0.24 ± 0.03	0.22 ± 0.03	0.11 ± 0.03
BB	0.68 ± 0.04	0.65 ± 0.05	0.55 ± 0.06	0.22 ± 0.03	0.11 ± 0.03
SS	0.43 ± 0.07	0.36 ± 0.08	0.28 ± 0.09	0.22 ± 0.03	0.11 ± 0.03
BS	0.50 ± 0.05	0.48 ± 0.05	0.36 ± 0.06	0.22 ± 0.03	0.11 ± 0.03
Age and energy adj. phenotypes			*Model*		
	IV	*V*	*IV*	*V*	*III*
FM	0.04 ± 0.05	0.00 ± 0.05	0.14 ± 0.05	-0.06 ± 0.05	0.04 ± 0.05
FS	0.18 ± 0.03	0.23 ± 0.03	0.17 ± 0.03	0.19 ± 0.03	0.07 ± 0.03
FD	0.18 ± 0.03	0.23 ± 0.03	0.17 ± 0.03	0.19 ± 0.03	0.06 ± 0.07
MS	0.18 ± 0.03	0.23 ± 0.03	0.17 ± 0.03	0.19 ± 0.03	-0.03 ± 0.05
MD	0.18 ± 0.03	0.23 ± 0.03	0.17 ± 0.03	0.19 ± 0.03	0.17 ± 0.05
Siblings[c]	0.40 ± 0.04	0.23 ± 0.03	0.40 ± 0.05	0.19 ± 0.03	0.11 ± 0.05

[a]Model I, FS = FD and MS = MD; model II, FS =FD = MS = MD; model III, BB=SS=BS; model IV, FS = FD = MS = MD and BB=SS=BS; model V, FS = FD = MS = MD = BB=SS=BS.
[b]PC, Parent-Child correlation (i.e. FS =FD = MS = MD).
[c]Sibling correlation (i.e. BS = SS = BS).

Table 2: Maximum Likelihood estimate (±Se) of familial correlations of EI, EI/Kg, EE/Kg (Nirmala et al. 1993).

P	*EI*	*EI/Kg*	*EE*	*EE/Kg*
FM	0.52±0.03	0.66±0.02	0.32±0.05	0.72±0.02
PC	0.15±0.04	0.28±0.04	0.02±0.04	0.40±0.04
SS	0.69±0.03	0.68±0.03	0.74±0.02	0.74±0.02

P = pair of relatives; FM = Father-Mother; PC = Parent-Child; SS = Sib-Sib. EI = Energy Intake; EE = Energy Expenditure

gene could be observed suggesting either EI or EEA mediate the expression of major gene effect on BMI or that the same major gene may influence both traits (Fig. 1 and Table 3). Energy intake (EI) and energy expenditure of activity level (EEA) are two important influencing factors of obesity. These variables tend to aggregate within families (Perusse et al. 1988a, b, 1989) and their contribution in the development of obesity has also been explained using twin studies. It is generally accepted that there is association between BMI and EEA within individuals (Pacy et al. 1986) although the BMI – EI association is less robust across studies (Ballard – Barbash et al. 1996). However, very little is known whether the heritable factors underlying BMI are related to those for EEA and/or EI. Studies that specifically examined the familial nature of energy association showed that familial factors are involved (Bouchard et al. 1990). Faith et al. (2004) reported familial association with total energy and macronutrient intakes independent of anthropometric measures such as height and weight indicating genetic or home environmental

Table 3: Maximum Likelihood Estimates of Cross-Trait Correlation ± Standard Errors Feitosa et al. (2000)

	Correlation	*General*	*Parsimonious*
Spouse	f_1m_2	0.39±0.05	0.39±0.04
	f_2m_1	0.35±0.05	0.35±0.05
Parent-offspring	f_1s_2	0.23±0.05	0.25±0.04
	f_2s_1	0.28±0.06	0.26±0.04
	f_1d_2	0.25±0.06	[0.25]
	f_2d_1	0.21±0.06	[0.26]
	m_1s_2	0.24±0.05	[0.25]
	m_2s_1	0.25±0.05	[0.26]
	m_1d_2	0.27±0.07	[0.25]
	m_2d_1	0.25±0.06	[0.26]
Siblings	s_1s_2	0.42±0.07	0.33±0.05
	d_1d_2	0.30±0.08	[0.33]
	s_1d_2	0.32±0.06	[0.33]
	s_2d_1	0.26±0.07	[0.33]
Intra-individual	f_{12}	0.87±0.01	0.87±0.01
	m_{12}	0.91±0.01	0.91±0.01
	s_{12}	0.84±0.02	0.84±0.01
	d_{12}	0.85±0.02	[0.84]

Note: Parameters in square brockets were equated with a preceding correlation.
Subscript 1 is BMI, while 2 is BMI/E (e.g., f_1m_2 = father's BMI with mother's BMI/E).

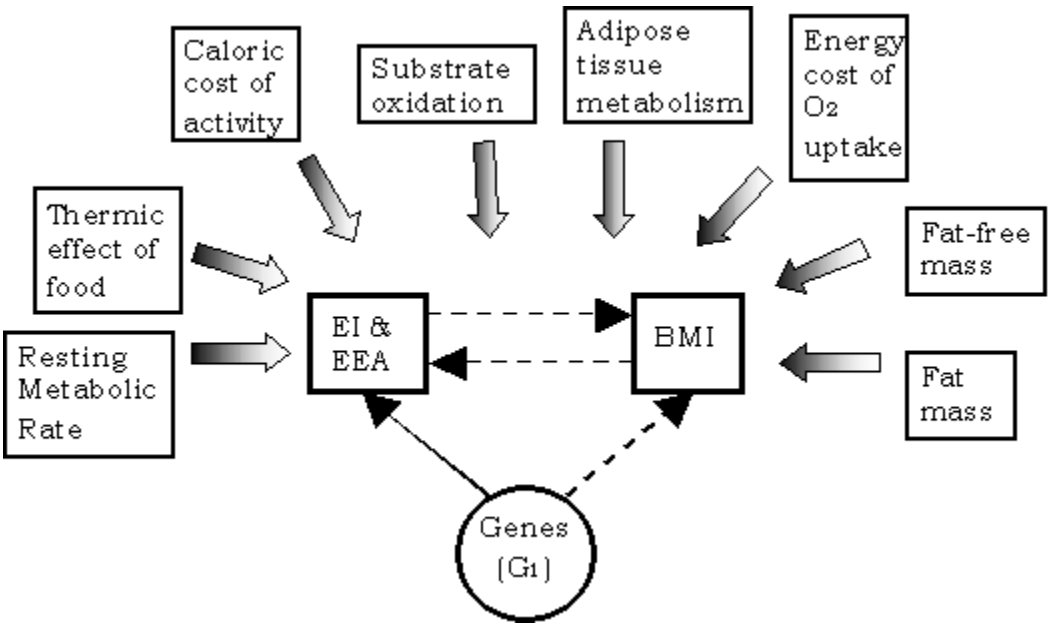

Fig. 1. Schematic representation of the factors that underlie the association between Body Mass Index (BMI), Energy Expenditure at Activity (EEA), Energy Intake (EI). Genes (G_1, in the circle) is a hypothetical familial factor (one or more major genes and/or polygenetic effects) that underlies each of the energy and BMI traits (squares). Whether the effect of G_1 on BMI is direct (dashed line from G_1 to BMI) or indirect through the energy variables is not resolved here. Additional factors that may impact on the energy balance-BMI relationship are shown in the top portion of the figure (Adapted from Feitosa et al. 2000).

influences that are specific to these behaviors. Mitchell et al. (1993) by studying the relationship between EI and EEA with BMI using the familial aggregation (path methods) reported that the familiarity for BMI was reduced after adjusting for the energy measures suggesting that BMI, EI and EEA shared some of the same polygenic and/ or common environmental causes. Feitosa et al. (2000) concluded that part of the familial relationship between BMI and the energy variables may be due to the non-additive effects of a pleiotropic major gene as well as to common multi-factorial (additive) factors. The source of the additive effect may be primarily familial environmental in origin.

Genome Wide Linkage Studies

Human obesity is a complex trait found to be determined by the interaction of multiple genes and environmental factors. Genome wide linkage scans exploit familial relationship and rely on use of highly polymorphic markers that spread across the whole genome to pinpoint the location of genes, followed by calculating the degree of linkage of the marker to a disease trait. For obesity, genome wide scans have been performed in two kinds of samples: (1) Families from the general population (2) Families that include one obese proband. For quantitative trait analysis, large families from a general population with high prevalence of obesity are required (Bell et al., 2005). In fact, the first genome wide scan using this method for obesity phenotype was reported by Comuzzie et al. (1997). They studied Mexican American families from the San Antonio Family Heart Study for leptin levels and fat mass at 2p21. The first genome wide analysis using nuclear families ascertained specifically for obesity also found a locus for obesity at 2p21 and another at 10p12 (Hager et al. 1998). Subsequently, many loci have been identified with the evidence of linkage with numerous obesity related phenotypes. As of October 2005, 253 quantitative trait loci for obesity related phenotypes have been derived from 61 genome wide linkage studies in human populations. Fifty two genome regions harbour quantitative trait loci supported by two or more studies (Rankinen et al. 2006). Linkage of body mass index to almost every chromosomal region except Y was reported by many genome-wide linkage studies. Evidence for the presence of linkage with body mass index was given in Table 4 (adapted from Yang et al. 2007). Stone et al. (2002) obtained the hitherto strongest linkage evidence for linkage for obesity in Utah pedigrees. Few studies have also found evidence of linkage with waist circumference which was located at 1q21-q25 in the Hong Kong Family Diabetes Study (Ng et al. 2004) and 6q23-25 region in the Framinghan Heart Study (Fox et al. 2004). Price et al. (2002) reported suggestive linkage in European Americans and African Americans at the xp21.3 and xp11.3 region.

Evidence of linkage with body fat was also reported by many researches (see Yang et al. 2007). Li et al. (2004) and Dong et al. (2005) observed the evidence of linkage with the same genetic marker in chromosome 21q22.3. By studying non-Hispanic whites and African Americans Lewis et al. (2005) reported sex specific findings i.e., evidence of linkage in the chromosome 15q25.3 for men and in the chromosome 12q24 for women. Reports of chromosomal regions linked to obesity and body composition from most of the studies are not robust. Only few regions have been replicated in some studies. The most promising genetic regions in chromosomes 2, 3, 6, 11, 13 and 20 were replicated in many studies with reference to body mass index (Yang et al. 2007).

There is a reduced time of environmental impact in extreme childhood obesity. Hence studying such cases help in reducing the effect of environmental contribution. A genome scan by Meyre et al. (2004) in children with a BMI that is greater than or equal to ninety–seventh percentile identified significant linkage at 6q22.31 – q23.2. This was supported by the US Framigham Heart Study which identified linkage in the same region, using BMI and waist circumference measurements (Atwood et al. 2002; Fox et al. 2004).

The inconsistencies in the replication of results of genome scans may be partially due to varying sample sizes from study to study. Moreover, small sample sizes tend to limit the power of genome scans to detect linkage. When considering inconsistencies of results the nature of study population is also an important issue. Population heterogeneity decreases the power to detect the true linkage signals with in the studies and also makes it difficult to compare across the studies (Altmuller et al. 2001). The useful strategies to increase the precision in the identification of the genetic effects of obesity in the groups studied and to improve the power of studies to detect linked loci are: (i) making use of

Table 4: Evidence for the presence of linkage with body mass index (Adapted from Yang et al. 2007)

DNA marker	*Chromosomal Location*	*Study Sample*	*Lod Score*	*First Author, Year (Reference No.)*
D2S1788	2p22.3	66 White families (349 subjects)	3.08	Palmer L, 2003
D2S347	2q14.3	1,249 White European-origin sibling pairs	4.44	Deng HW, 2002
D2S347	2q14.3	53 Caucasian families (758 subjects)	3.42	Liu Y, 2004
	2q37	451 Caucasian families (4,247 subjects)	3.34	Guo YF, 2006
D3S1764	3q22.3	1,055 pairs (White, Black, Mexican American, and Asian)	3.45 (Black)	Wu X, 2002
D3S2427	3q26.33	507 Caucasian families (2,209 subjects)	3.3	Kissebah A, 2000
D3S2427	3q26.33	128 African-American families (545 subjects)	4.3	Luke A, 2003
D3S2427	3q26.33	1,055 pairs (White, Black, Mexican American)	3.4	Wu X, 2002
D3S3676	3q26.33	128 African-American families (545 subjects)	4.3	Luke A, 2003
D4S1627	4p13	37 Utah families (994 subjects)	3.4	Stone S, 2002
D4S3350	4p15.1	37 Utah families (994 subjects)	9.2	Stone S, 2002
D4S2632	4p15.1	37 Utah families (994 subjects)	6.1	Stone S, 2002
D6S403	6q23.3	27 Mexican-American families (261 subjects)	4.2	Arya R, 2002
D6S1003	6q24.1	27 Mexican-American families (261 subjects)	4.2	Arya R, 2002
D7S817	7p14.3	182 African families (769 subjects)	3.83	Adeyemo A, 2003
D7S1804	7q32.3	401 American families (3,027 subjects)	4.9	Feitosa MF, 2002
D8S1121	8p11.23	10 Mexican-American families (470 subjects)	3.2	Mitchell B, 1999
D10S212	10q26.3	18 Dutch families (198 subjects)	3.3	van der Kallen CJ, 2000
Chromosome 10 region	10q26.3	279 White families (1,848 non-Hispanic subjects)	3.2	Turner S, 2004
D11S2000	11q22.3	182 African families (769 subjects)	3.35	Adeyemo A, 2003
D11S912	11q24.3	264 Pima Indian and American families (1,766 pairs)	3.6	Hanson RL, 1998
D12S1052	12q21.1	66 White families (349 subjects)	3.41	Palmer L, 2003
D12S1064	12q21.33	66 White families (349 subjects)	3.41	Palmer L, 2003
D12S2070	12q24.21	260 European-American families (1,297 subjects)	3.57	Li W, 2004
	12q24	933 Australian families (2,053 subjects)	3.02	Cornes BK, 2005
D13S257	13q14.2	401 American families (3,027 subjects)	3.2	Feitosa MF, 2002
D13S175	13q12.11	580 Finnish families	3.3	Watanabe RM, 2000
D13S221	13q12.13	580 Finnish families	3.3	Watanabe RM, 2000
D13S1493	13q13.2	1,124 American families (3,383 subjects)	3.2	North K, 2004
D19S571	19q	109 French Caucasian families (447 subjects)	3.8	Bell CG, 2004
D20S149	20q13.31-qter	92 American families (513 subjects, 423 pairs)	3.2	Lee JH, 1999
D20S476	20q13	92 American families (513 subjects, 423 pairs)	3.06	Lee JH, 1999
D20S438	20q12	103 Utah families (1,711 subjects)	3.5	Hunt SC, 2001
D20S107	20q12	92 American families (513 subjects, 423 pairs)	3.2	Lee JH, 1999
D20S211	20q13.2	92 American families (513 subjects, 423 pairs)	3.2	Lee JH, 1999

* LOD score: In genetics, a statistical estimate of whether two loci (the sites of genes) are likely to lie near each other on a chromosome and are therefore likely to be inherited together as a package. ''LOD'' stands for logarithm of the odds (to the base 10). (A LOD score of three means that the odds are a thousand to one in favor of genetic linkage.)

extreme phenotypes, (ii) reducing environmental pressure and (iii) studying homogenous populations (Bell et al. 2005).

Candidate Gene Association Studies

Obesity is a complex non-mendelian trait and may depend on several susceptible genes with low or moderate effects. Loktionov (2003) stated firm evidence on the influence of genes in energy homeostasis and thermogenesis adipogenesis leptin-insulin signaling transduction and hormonal signaling peptide to play a role in the development of obesity. Many studies reported association between DNA sequence variation in specific genes and obesity phenotypes (Rankinen et al. 2006). So far, 426 findings of positive associations in 127 genes have been reported. Evolution in the status of the Human Obesity Gene Map is given in Table 5 (Adapted from Rankinen et al. 2006). Among them, 22 genes are prominent and each supported by at least five positive studies, while 12 of those are supported by at least 10 positive replication studies (Table 6). In order to detect genetic variants that influence susceptibility to common diseases, genetic association studies are useful. But failure to replicate findings is a major problem. The

Table 5: Evolution in the status of the Human Obesity Gene Map (Adapted from Rankinen et al. 2006)

	1994	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*	*2003*	*2004*	*2005*
Single gene mutations*				2	6	6	6	6	6	6/7	10	11
KO and Tg									38	55	166	244
Mendelian disorders with map location	8	12	13	16	16	20	24	25	33	41	49	50
Animal QTLs	7	9	24	55	67	98	115	165	168	183	221	408
Human QTLs from genome scans				3	8	14	21	33	68	139	204	317
Candidate genes with positive findings	9	10	13	21	29	40	48	58	71	90	113	127

* Number of genes, not number of mutations

inconsistency in the findings of genetic association across the studies may be due to (i) false positive results, (ii) for complex diseases like obesity with modest genetic effects a true association may fail to replicate in an underpowered replication attempt and (iii) population heterogeneity. Further, a true association in one population may not be true to another population because of the variation in genetic and environmental factors (Tan et al. 2004; Colhoum et al. 2003). Unmeasured factors such as selection bias and differential misclassification of exposures may also be responsible for some non-replications (Clayton et al. 2005). A recent meta-analysis of genetic association studies concluded that 20% to 30% of genetic associations are real and have modest effects on the risk of common diseases, in spite of the abundant false positive associations (Lohmueller et al. 2003). This suggests that as many as 20% to 30% of the obesity candidate genes identified might contribute to the risk of obesity in humans. Refined study designs and statistical testing are required for having appropriate power in the genome wide association studies, to detect genes with lower relative risk. More stringent criteria for interpreting results of association studies are also needed.

Table 6: The genes that show the most consistent association with obesity with related phenotype. (Summarized from Rankinen et al., 2006)

S. No.	*Gene*	*Chromosomal location*	*No. of studies showing replication of results*
1	PPARG	3p25	30
2	ADRB3	8p12-p11.2	29
3	ADRB2	5q31-q32	20
4	LEPR	1p31	16
5	GNB3	12p13.31	14
6	UCP3	11q13	12
7	ADIPOQ	3q27	11
8	LEP	7q31.3	11
9	UCP2	11q13	11
10	HTR2C	xq24	10
11	NR3C1	5q31	10
12	UCP1	4q28-q31	10

CONCLUSION

The global emergence of obesity is one of the greatest challenges in public health research. Unhealthy diet and physical activity are two primary factors responsible for the increase in the incidence of obesity. In spite of the key role of modern lifestyles in developing obesity, genes seem to be important in the development of most severe early onset forms of obesity. Their characterization has still to be completed. By the discovery of novel genes, new etiological pathways can be revealed and innovative therapies and preventive measure can be established. Kumanyika (2007) suggested that more specific characterization of obesity phenotypes may also help to consider the differences in the evolution of obesity in diverse socio-environmental and racial/ethnic context. Race and ethnicity, key markers of excess risk for obesity, may reflect any or all of a host of variables and causal pathways. Understanding the aspects of energy intake, expenditure of utilization differences among different racial/ethnic groups will provide valuable clues as will as ideas about the different types of interventions that may be needed to reduce the excess risk. Despite all these, the primary goal that still remains unfulfilled is to identify the right combination of genes and mutations that are associated with this increased risk and to determine the risk. Despite these limitations, understanding the genetic mechanisms underlying human obesity is rapidly increasing because of the completion of the Human Genome Project and recent advancements in the International Hap Map Project. However, complete understanding of this complex trait will be possible only by the

integration of many disciplines, combining advances in genetic epidemiology with the fields of functional genomics and proteomics.

The Indian Context and Its Relevance

As the environment and life styles of the populations differ widely in different countries it is expected that they may provide knowledge of the relative roles of genes and environment in the formation of obese phenotype. Future studies on non-modernized traditional homogenous populations and the transitional populations hold the key to understanding the process of development of obesity. India is inhabited by many diverse tribal and caste populations which are expected to be genetically homogenous because of the practice of endogamy. For historical reasons, India also offers immense genetic and cultural heterogeneity, yet constituting precisely defined Mendelian populations with impermeable genetic boundaries. This situation provides the most ideal framework to untangle the complex nature of the development of obesity. Unfortunately most of the studies in India did not include population based samples. Future studies on Indian populations might be fruitful in establishing the precise nature of association between obesity and gene polymorphisms and/or identifying new genes/ mutations specific to Indian populations. Further, the transitional nature of many of the Indian populations provides an opportunity to study the gene environment interactions in an apt fashion. A better understanding of gene-gene and gene environment interaction is necessary for realizing the pharmacogenetic treatment of obesity.

The process of rapid urbanization and changing lifestyles in India and other developing countries has brought many complex diseases related to cardiovascular system, diabetes etc to manifest in menacingly high proportions in the recent years. The unique Indian population situation with highest levels of endogamy and inbreeding offers immense possibilities for dissecting genetic etiology of these complex as well as single gene disorders. It is possible to meet these challenges given the revolutionary developments in DNA technology.

ACKNOWLEDGEMENT

The authors are thankful to Dr. D. Swaminadhan, President, MGNIRSA, and Director, ISI for logistic support and to Mr. T. Nagaraja, and Dr. V. Tripathy, Indian Statistical Institute, Hyderabad, for assistance during the preparation of this manuscript.

REFERENCES

Adeyemo A, Luke A, Cooper R et al. 2003. A genome-wide scan for body mass index among Nigerian families. *Obes Res*, **11**: 266-273.

Allison DB, Kaprio J, Korkeila M et al. 1996. The heritability of body mass index among an international sample of monozygotic twins reared apart. *Int J Obes Relat Metab Disord*, **20**: 501-506.

Altmuller J, Palmer L.J, Fischer G, et al 2001. Genome-wide scans of complex human diseases: true linkage is hard to find. *Am J Hum Genet*, **69**: 936-950.

Arya R, Blangero J, Williams K et al. 2002. Factors of insulin resistance syndrome related phenotypes are linked to genetic locations on chromosome 6 and 7 in nondiabetic Mexican-Americans. *Diabetes* **51**: 841-847.

Atwood LD et al. 2002. Gennome wide linkage analysis of body mass index across 28 years of the Framingham Heart Study. *Am J Hum Genet*, **71**:1044-1050.

Ballard Barbash RI, Graubard SM, Krebs–Smith et al. 1996. Contribution of dieting to the inverse association between energy intake and body mass index. *Europ J Clin Nutr*, **50**: 98-106.

Bell CG, Benzinou M, Siddiq A et al. 2004. Genome wide linkage analysis for severe obesity in French Caucasians finds significant susceptibility locus on chromosome 19q. *Diabetes*, **53**: 1857-1865.

Bell CG, Walley AJ, Froquel. P 2005. The genetics of human obesity. *Nature Rev Gen*, **6**: 221-234.

Bouchad. C, Peusse L 1985. Genetics of obesity. *Ann Rev Nutr*, **13**: 337 -354.

Bouchard C, Perusse L, Lebalanc C, Tremblay. A and Theriault G 1988. Inheritance of the amount and distribution of human body fat. *Int J Obes*, **12**: 205 -215.

Clayton DG, Walker NM, Smyth DJ et al. 2005. Population structure, differential bias and genomic control in a large scale, case-contorl association study. *Nat Genet*, **37**: 1243-1246.

Colhoun HM, McKeigue PM, Smith DG 2003. Problems of reporting genetic asoociations with complex outcomes. *Lancet*, **361**: 865-872.

Comuzzie AG et al. 1997. A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2. *Nature Genet*, **15**: 273 – 276.

Cornes BK, Medland SE, Ferreira MA et al. 2005. Sex-limited genome wide linkage scan for body mass index in an unselected sample of 933 Australian twin families. *Twin Res Hum Genet*, **8**: 616-632.

Cossrow N, Falkner B 2004. Race/Ethnic issues in obesity and related comorabidities. *J Clin Endocrinol Metab*, **89**: 2590-2594.

Davenport CB 1923. *Body Build and Its Inheritance*. Washington: Carnegie Institution

Deng HW, Deng H, Liu YJ et al. 2002. A genome wide

linkage Scan for quantitative trait loci for obesity phenotypes. *Am J Hum Genet*, **70**: 1138-1151.

Dong CH, Li WD, Li D et al 2005. Interaction between obesity susceptibility loci in chromosome regions 2p25-p24 and 13q13-q21. *Eur J Hum Genet*, **13**: 102-108.

Faith MS et al. 2004. Familial aggregation of energy intake in children. *Am J Clin Nutr*, **79**: 844-850.

Farooqi IS and Rahilly S 2004. Monogenic human obesity syndromes. *Recent Prog Horm Res*, **59**: 409-424.

Feinleib M et al 1977. The NHLBI twin study of cardiovascular disease risk factors. Methodology and Summary of ruslts. *Am J Epidemiol*, **106**: 284-285.

Feitosa MF, Borecki IB, Rich SS et al 2002. Quantitative-trait loci influencing body-mass index reside on chromosomes 7 and 13: the National Heart, Lung and Blood Institute Family Heart Study. *Am J Hum Genet*, **70**: 72-82.

Feitosa MF, Rice T, Nirmala A, Rao DC 1999. Segregation analysis of regional fat distribution in families from Andhra Pradesh, India. *Int J Obesity*, **23**: 874-880.

Feitosa MF, Rice T, Nirmala A and Rao DC 2000. Major gene effect on body mass index: The role of energy intake and energy expenditure. *Hum Biol*, **72**:781-799.

Fox CS et al 2004. Genome Wide Linkage to chromosome 6 for waist circumference in the Framingham Heart Study. *Diabetes*, **53**: 399-1402.

Gu D, Reynolds K, Wu X et al 2005. Prevalence of the metabolic syndrome and overweight among adults in china. *Lancet*, **365**: 1398-1405.

Guo YF, Shen H, Liu YJ et al 2006. Assessment of genetic linkage and parent of origin effects on obesity. *J Clin Endocrinol Metab*, **91**:4001-4005

Hager J. et al 1998. A genome wide scan for human obesity genes reveals a major susceptibility locus on chromosome 10. *Nature Genet*, **20**: 304-308.

Hanson RL, Ehm MG, Pettitt DJ et al 1998. An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. *Am J Hum Genet*, **63**: 1130-1138.

Haslam DW, James WP 2005. Obesity. *Lancet*, **366**: 1197-1209.

Hasstedt SJ, Ramirez ME, Kuida H, Williams RR 1989. Recessive inheritance of a relative fat pattern. *Am J Hum Genet*, **45**: 917–925.

Hunt SC, Abkevich V, Hensel CH et al 2001. Linkage of body mass index to chromosome 20 in Utah pedigrees. *Hum Genet*, **109**: 279-285.

International Obesity Task Force 2005. About obesity. London-United Kingdom (Http://www.iotf.org/about obesity. asp).

Joshi SR, Joshi SS 2002. Obesity therapeutics the Indain Consensus SB Gupta (Ed.). API Medicine update. *Association of Physicians of India*, **12**: 492-504.

Kissebah A, Sonnenberg G, Myklebust J et al 2000. Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. *Proc Natl Acad Sci* USA, **97**: 14478-14483.

Koeppen Schomerus G, Wardle J, Plomin R 2001. A genetic analysis of weight and overweight in 4 year old twin pairs. *Int J Obes Relat Metab Disord*, **25**: 838-844.

Kumanyika SK 2007. The obesity Epidemic: Looking in the Mirror. *Am J Epidemiol*, **166**: 243-245.

Lee JH, Reed DR, Li WD et al 1999. Genome scan for human obesity and linkage to markers in 20q13. *Am J Hum Genet*, **64**: 196-209.

Lewis CE, North KE, Arnett D et al 2005. Sex-specific findings from a genome wide linkage analysis of human fatness in non-Hispanic Whites and African Americans: the HyperGen study. *Int J Obes* (Lond.), **29**:639-649.

Li W, Dong C, Li D, et al 2004. An obesity-related locus in chromosome region 12q23-24. *Diabetes*, **53**: 812-820.

Liu Y, Xu F, Shen H et al 2004. A follow-up linkage study for quantitative trait loci contributing to obesity related phenotypes. *J Clin Endocrinol Metab*, **89**:875-882.

Lohmueller KE, Pearce CL, Pike M et al 2003. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet*, **33**: 177-182.

Loktinov A 2003. Common gene polymorphisms and nutrition: emerging links with pathogenesis of multifactorial chronic diseases (review). *J Nutr Biochem*, **14**: 426-451.

Luke A, Wu X, Zhu X et al 2003. Linkage for BMI at 3q27 region confirmed in an African-American Population. *Diabetes*, **52**: 1284-1287.

Mc Queen MB, Bertram L, Rimm EB et al 2003. A QTL genome scan of the metabolic syndrome and its component traits. *BMC Genet*, **4** (suppl. 1): s96.

Meyre D et al 2004. A genome wide scan for childhood obesity associated traits in French families shows significant linkage on chromosome 6q22.31-q23.2. *Diabetes*, **53**: 803-811.

Mitchell B, Cole S, Comuzzie A, et al 1999. A quantitative trait locus influencing BMI maps to the region of the beta-3adrenergic receptor. *Diabetes*, **48**: 1863-1667.

Mitchell LE, Nirmala A, Rice T et al 1993. The impact of energy intake and energy expenditure of activity on the familial transmission of adiposity in an Indian Population. *Am J Hum Biol*, **5**: 331-339.

Moll PP, Burns TL, Lauer RM 1991. The genetic and environmental sources of body mass index variability: The Muscatine Ponderosity Family Study. *Am J Hum Genet*, **49**: 1243-1255.

Ng MCY, Lam VKL et al 2004. Genome wide scans for metabolic syndrome and related quantitative traits in Hong Kong Chinese and confirmation of a susceptibility locus on chromosome 1q21-q25. *Diabetes*, **53**: 2676-2683.

Nirmala A, Mitchell LE, Rice T et al 1993. Assessment of adiposity in an Indian population: Familial correlations. *Genet Epidemiol*, **10**: 133-143.

North K, Rose K, Borecki I et al 2004. Evidence for a gene on chromosome 13 influencing postural systolic blood pressure change and body mass index. *Hypertension*, **43**: 780-784.

Pacy PJ, Webster J, Garrow JS 1986. Exercise and obesity. *Sports Med*, **3**: 89-113.

Palmer L, Buxbaum S, Larkin E et al. 2003. A whole genome scan for obstructive sleep apnea and obesity. *Am J Hum Genet*, **72**: 340-350.

Perusse L, Leblac C, Bouchard C 1988a. Familial resemblance in lifestyle components: Results form the Canada Fitness Survey. *Can J Pub Health*, **79**: 201-2005.

Perusse L, Tremblay A, Leblanc C et al 1988b. Familial resemblance in energy intake: Contribution of genetic and environmental factors. *Am J Clin Nutr*, **47**: 629-635.

Perusse L, Tremblay A, Leblanc C et al 1989. Genetic and environmental influences on level of habitual activity and exercise participation. *Am J Epidemiol*, **129**: 1012-1022.

Pietilainen KH, Kaprio J, Rissanen A et al 1999. Distribution and heritability of BMI in Finnish adolescents aged 16 years and 17 years: A study of 4884 twins and 2509 singletons. *Int J Obes Relat Metab Disord*, **23**: 107-115.

Platte P, Papanicolaou GJ, Jhonson J et al 2003. A study of linkage and association of body mass index in the old order Amish. *Am J Med Genet, C Semin Med Genet*, **121**: 71-80.

Price RA, Kilker R, Lil WD 2002. An X-chromosome scan reveals a locus for fat distribution in chromosome region Xp21-22. *Diabetes*, **51**: 1989-1991.

Rankinen T, Zuberi A, Changnon Y.C et al. 2006. The human obesity gene Map: the 2005 update. *Obesity (Silver spring)*, **14**: 529-644.

Reddy BN 1998. Body mass index and its association with socioeconomic and behavioral variables: A study among socioeconomically heterogeneous populations of Andhra Pradesh, India. *Hum Biol*, **70**: 901-917.

Reddy KS, Prabhakaran D, Shah P et al 2002. Differences in body mass index and waist: hip ratios in North Indian rural and urban populations. *Obes Rev*, **3**: 197-202.

Rice T, Perusse L, Bouchard C et al 1999. Familial aggregation of body mass index and subcutaneous fat measures in the longitudinal Quebec Family Study. *Genet Epodemiol*, **16**: 316-334.

Selby JV et al 1989. Evidence of genetic influence on central body fat in middle aged twins. *Hum Biol*, **61**: 179-194.

Stone S, Abkevich V, Hunt SC et al 2002. A Major predisposition locus for severe Obesity at 4p15-p14. *Am J Hum Genet*, **70**: 1459-1468.

Stunkard AJ, Fuch TT, Hrubec Z 1986b. A twin study of human obesity. *JAMA*, **256**: 251-254.

Stunkard AJ, Harris JR, Pedersen NL and McClearn GE 1990. The body mass index of twins who have been reared apart. *N Engl J Med*, **322**:1483-1487.

Stunkard AJ, Sorensen TI, Hanis C et al 1986a. An adoption study of human obesity. *N Engl J Med*, **314**: 193-198.

Tan NC, Mulley JC, Berkovic SF 2004. Genetic association studies in epilepsy: "the truth is out there". *Epilepsy*, **45**: 1429-1442.

Turner S, Karida S, boerwinkle E, et al 2004. Multivariate linkage analysis of blood pressure and body mass index. *Genet Epidemiol*, **27**: 64-73.

Turula M, Kaprio J, Rissanen A and Koskenvuo M 1990. Body weight in the Finnish Twin Cohort. *Diabetes Res Clin Pract*, **10** (Spppl. 1): 33-36.

Van der Kallen CJ, Cantor RM, Van Greevenbroek MM et al 2000. Genome scan for adiposity in Dutch dyslipidemic families reveals novel quantitative trait loci for leptin, body mass index and soluble tumor necrosis factor receptor super family 1A. *Int J Obes Relat Metab Disord*, **24**: 1381-1391.

Watanabe RM, Ghosh S, Langefeld CD et al 2000. The Finland-United Stated investigation of non-insulin-dependent diabetes mellitus genetics (FUSION) study.II. An autosomal genome scan for diabetes-related quantitative trait. *Am J Hum Genet*, **67**: 1186-1200.

WHO Technical Report Series 2000. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation.

Wu X, Cooper RS, Borecki I et al 2002. A combined analysis of genome wide linkage scans for body mass index from the National Heart, Lung and Blood Institute Family Blood pressure Program. *Am J Hum Genet*, **70**: 1247-1256.

Yang W, Kelly T, He J 2007. Genetic epidemiology of obesity. *Epidemiologic Rev*, **29**: 49-61.