

Genetics of Human Obesity: An Overview

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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/m² (under weight), 18.5 – 24.9 kg/m² (normal weight), 25.0 – 29.9 kg/m² (over weight) 30.0-30.9 kg/m² (obese) and $\epsilon \geq 40$ kg/m² (extremely obese).

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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 is 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 supriliac 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 Model ^a	TE ratio	RFPI
	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

^aModel 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.

^bPC, Parent-Child correlation (i.e. FS =FD = MS = MD).

^cSibling 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 brackets 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).

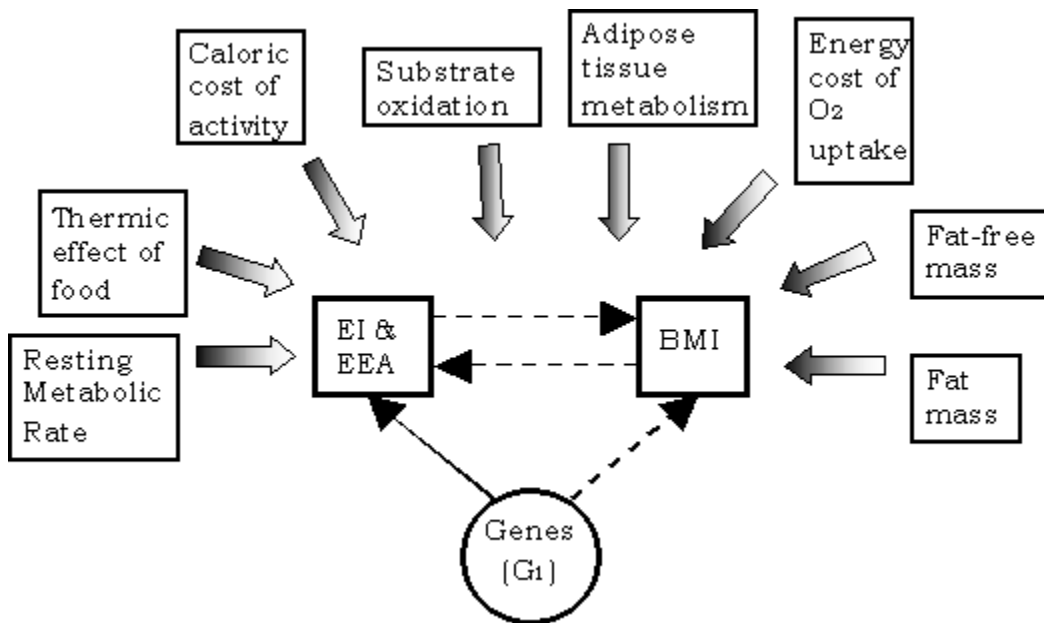


Fig. 1. Schematic representation of the factors that underlie the association between Body Mass Index (BMI), Energy Expenditure at Activity (EEA), Energy Intake (EI). Genes (G₁, in the circle) is a hypothetical familial factor (one or more major genes and/or polygenetic effects) that underlies each of the energy and BMI traits (squares). Whether the effect of G₁ on BMI is direct (dashed line from G₁ 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 Framingham 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 Framingham 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	Wu X, 2002
		(Black)		
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* KO and Tg				2	6	6	6	6	6	6/7	10	11
Mendelian disorders with map location	8	12	13	16	16	20	24	25	33	38	55	166
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 under-powered 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.

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 well 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

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

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.

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