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Review

Genetic factors for human obesity

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Abstract. Obesity is a multifactorial and heterogeneous condition that results from alterations of various genes, each having a partial and additive effect. The inheritance pattern of obesity is thus complex, and environmental factors play an important role in promoting or delaying its development. The identification of susceptibility genes and genetic variants for obesity requires various methodological approaches. Obesity is classified into three main categories on the basis of genetic etiology: monogenic, syndromic, and polygenic obesity. Here we review monogenic and syndromic obesity. We also review the linkage analysis studies followed by the candidate gene approaches and genome-wide association studies. Identification of the underlying genetic causes of obesity will likely provide a basis both for the development of new therapeutic agents and for the personalized prevention of this condition.

Keywords. Obesity, susceptibility gene, polymorphism, candidate gene, genome-wide association study.

Introduction

Obesity has become a major public health problem as a result of its increasing prevalence in most developed countries. It is a risk factor for type 2 diabetes, dyslipidemia, hypertension, and atherosclerosis [1]. Adipose tissue constitutes a major endocrine system that secretes a variety of bioactive substances termed adipocytokines. Altered adipocytokine secretion profiles increase the risk of obesity-related cardiovascular disorders and diabetes mellitus [2, 3]. Environmental factors such as behavior (overeating, physical inactivity) and socioeconomic conditions affect an individual's risk for obesity [4]. Obesity also results from the effects of multiple genetic factors. The identification of susceptibility genes for obesity is therefore important for its predictive value and for potential intervention to avert future cardiovascular events. Numerous epidemiological studies have recognized the contribution of genetic factors to individual susceptibility to obesity [5], and substantial progress has been made in identifying susceptibility genes and in understanding the molecular mechanisms of obesity. This article reviews these advances in our knowledge of monogenic, syndromic, and polygenic obesity disorders in humans.

Classification of obesity according to genetic etiology

Although environmental factors play an important role in obesity, genetic variants also contribute substantially to its pathogenesis. Obesity is classified into three main categories on the basis of genetic etiology. The identification of genes that underlie these categories of monogenic, syndromic, and polygenic obesity has greatly increased our knowledge of the mechanisms responsible for this condition [6].

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Monogenic obesity

Monogenic obesity results from an alteration of a single gene. Several monogenic forms of human obesity have been identified by searching for mutations homologous to those causing obesity in mice. Although murine models are useful to understand the molecular pathogenesis of human obesity, such monogenic obesity syndromes are rare in human.

Leptin gene (*LEP*) mutation (*ob*). *LEP* maps to human chromosome 7q31.3 and comprises three exons separated by two introns [7]. The naturally occurring *ob*/*ob* mouse harbors a nonsense mutation in codon 105 of *Lep* of the parental mouse strain [8]. This mutation abolishes leptin production and results in profound obesity. The corresponding mutation has not been detected in *LEP* of humans [9]. However, a different *LEP* mutation was detected in two severely obese children belonging to a highly consanguineous pedigree [10]. The homozygous frameshift mutation resulted in deletion of a single guanine nucleotide in codon 133 of *LEP*. These children produced a very small quantity of leptin and presented with early-onset obesity and hyperphagia but with normal body temperature and plasma concentrations of cortisol and glucose.

Leptin receptor gene (*LEPR*) mutation (*db*). *LEPR* maps to human chromosome 1p31 and encodes at least five protein isoforms [11]. In mice, *Lepr* was shown to map to the same 6-cM interval on chromosome 4 as *db*. The *db*/*db* mouse produces an alternatively spliced transcript of *Lepr* with a 106-nucleotide insertion that results in premature termination of the intracellular domain of the encoded protein [12, 13]. A spliced variant form of rat LEPR cDNA that encodes a protein with a short intracellular domain was also identified in the Zucker *fa*/*fa* rat [14]. These mutations cause severe obesity in the rodents that is not reversible by administration of leptin. In humans, a homozygous mutation in *LEPR* that results in the production of a truncated leptin receptor lacking both the transmembrane and intracellular domains has been described [15]. Individuals with this mutation presented with early-onset morbid obesity, lack of pubertal development, and a reduced level of secretion of both growth hormone and thyrotropin.

Pro-opiomelanocortin gene (*POMC*) mutation. *POMC* maps to human chromosome 2p23 [16] and generates the melanocortin peptides adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH) α, β, and γ, as well as the opioid-receptor ligand β-endorphin. Two individuals congenitally lacking *POMC* products were initially described [17, 18]. One patient was a compound heterozygote for two mutations in exon 3 that interfered with appropriate synthesis of ACTH and α-MSH. The second patient was homozygous for a mutation in exon 2 that abolished POMC translation. Subsequently, three additional unrelated children with congenital POMC deficiency who were either homozygous or compound heterozygous for *POMC* mutations, as well as an individual homozygous for a loss-of-function *POMC* mutation that resulted in the loss of all POMC-derived peptides, were described [19]. These genetic defects in *POMC* resulted in early-onset obesity, adrenal insufficiency, and red hair pigmentation.

Melanocortin 4 receptor gene (*MC4R*) mutation. MC4R is a member of the G protein-coupled receptor family and signals through the activation of adenylyl cyclase. Mice expressing an activated form of this receptor as a result of gene targeting developed a maturity-onset obesity syndrome associated with hyperphagia, hyperinsulinemia, and hyperglycemia [20]. In humans, two frameshift mutations in *MC4R* resulting in truncation of the encoded protein were found to be associated with a dominant form of obesity [21, 22]. About 100 different obesity-associated *MC4R* mutations that result in a change of amino acid in the encoded protein have since been described in various ethnic groups [23, 24]. In spite of the autosomal dominant mode of transmission exhibited by most families with *MC4R*-linked obesity, the penetrance of the disease is sometimes incomplete and its clinical expression is variable.

Prohormone convertase 1 gene (*PC1*) mutation. PC1 is a neuroendocrine convertase that belongs to a family of subtilisin-like serine endoproteases and acts on a range of substrates including proinsulin, proglucagon, and POMC. An adult female with severe early-onset obesity, hypogonadotropic hypogonadism, abnormal glucose homeostasis, and increased plasma concentrations of proinsulin and POMC was found to be a compound heterozygote for *PC1* mutations [25]. One of the mutations, Gly483Arg, prevents maturation of the inactive propeptide form of PC1 (pro-PC1), resulting in its retention in the endoplasmic reticulum, whereas the other mutation, 4A→C, in the donor splice site of intron 5, results in exon skipping, a frameshift, and the generation of a premature stop codon in the region of the gene encoding the catalytic domain of the protein. A second case of human PC1 deficiency due to compound heterozygosity for novel missense and nonsense mutations has also been described [26]; the affected individual manifested severe refractory neonatal diarrhea due to absorptive dysfunction in the small intestine, suggesting that PC1

in enteroendocrine cells is essential for the normal absorptive function of the human small intestine.

Single-minded, drosophila, homolog of, 1 gene (*SIM1*) mutation. A *de novo* balanced translocation involving chromosomes 1p22.1 and 6q16.2 was identified in a girl with early-onset obesity [27]. This translocation separates the 5′ promoter region and the region encoding the basic helix-loop-helix domain of *SIM1* on chromosome 6 from the regions of the gene encoding the PAS (3′ period, aryl hydrocarbon receptor, and Single-mind) and putative transcriptional regulatory domains. SIM1 is expressed in the developing central nervous system and appears to be a physiological target of α-MSH, which inhibits food intake. The disruption of *SIM1* is thus associated with the dysregulation of food intake rather than with that of energy expenditure [28].

Neurotropic tyrosine kinase receptor type 2 gene (*NTRK2*) mutation. A *de novo* heterozygous missense mutation Tyr722Cys in *NTRK2* was identified in a boy with severe early-onset obesity and impairment of memory, learning, and nociception [29]. Brain-derived neurotrophic factor (BDNF) regulates the development, survival, and differentiation of neurons through its high-affinity receptor, tyrosine receptor kinase B (TrkB), which is encoded by *NTRK2*, and it also contributes to the regulation of body weight and food intake [30]. The identified mutation of *NTRK2* results in impairment of receptor autophosphorylation and signaling to mitogen-activated protein kinase, leading to a unique human disorder of hyperphagic obesity.

Syndromic obesity

Syndromic obesity refers to obesity that occurs in the context of a distinct set of associated clinical phenotypes, such as mental retardation, dysmorphic features, and organ-specific developmental abnormalities. About 25 genetic obesity syndromes have been identified to date [31]. These syndromes arise from discrete genetic defects or chromosomal abnormalities and can be either autosomal or X-linked disorders.

Prader-Willi syndrome (PWS). PWS is characterized by central obesity, neonatal hypotonia, hyperphagia, hypothalamic hypogonadism, and mild mental retardation with somatic abnormalities such as short stature, peculiar facial features, and small hands [32]. It is caused by defects in the inheritance of imprinted genes in the chromosomal region 15q11.2-q12 [33]. Most (75%) cases of PWS result from paternal deletions of this chromosomal region, with 22% of cases resulting from maternal uniparental disomy, less than 3% from imprinting errors caused by microdeletions of the imprinting center at the small nuclear ribonucleoprotein polypeptide N (SNRPN) upstream reading frame (*SNURF*)–*SNRPN* locus or an abnormal imprint without a detectable microdeletion, and less than 1% from paternal translocations [34]. Other candidate genes in the responsible interval include *NDN*, which encodes necdin (a growth suppressor present in virtually all postmitotic neurons in the brain and found at the highest levels in the hypothalamus) [35], and three families of C/D-box small nucleolar RNA genes (HBII-13, HBII-52, HBII-85) [36]. Several patients with clinical features of PWS but with a normal chromosome 15 have also been described; these individuals manifested cytogenetic alterations of chromosome 6q [37].

Bardet-Biedl syndrome (BBS). BBS is characterized by early-onset obesity associated with progressive rod-cone dystrophy, morphological finger abnormalities, dyslexia, learning disabilities, and progressive renal disease [38]. Linkage studies indicate that this syndrome may be caused by genetic defects at various chromosomal loci, with several mutations having been identified within *BBS1* on chromosome 11q13, *BBS2* on 16q21, *BBS3* on 3p12-q13, *BBS4* on 15q22.3-q23, *BBS5* on 2q31, *BBS6* on 20p12, *BBS7* on 4q27, *BBS8* on 14q32.1, *BBS9* on 7p14, *BBS10* on 12q21.2, *BBS11* on 9q31-q34.1, and *BBS12* on 4q27 [39–42]. Although BBS was originally thought to be a recessive disorder, clinical manifestation of some forms of the disease requires a homozygous recessive mutation in one of six loci and an additional mutation at a second locus, a pattern of inheritance referred to as triallelic [43]. Heterozygosity for a mutation of *BBS3* was thus found to modify the expression of homozygosity for a Met390Arg mutation of *BBS1* [44]. Despite the identification of several genes that contribute to BBS, the genetic basis of the syndrome remains unknown in more than 50% of affected families. The common Met390Arg mutation of *BBS1* accounts for about 80% of all *BBS1* mutations and is found on a similar genetic background across populations [45]. The BBS3 form of the disease has been shown to be caused by a mutation in the ADP-ribosylation factor (ARF)-like-6 gene (*ARL6*) on chromosome 3p12-q13 [44], whereas BBS6 is caused by mutation of *MKKS*, which is located on 20p12 and is also mutated in McKusick-Kaufman syndrome [46, 47]. Mutation of a gene for a tetratricopeptide repeat protein, *TTC8*, causes BBS8, and mutation of parathyroid hormone-responsive gene B1 (*PTHB1*) causes BBS9 [48, 49]. The recently identified loci *BBS10*, *BBS11*, and *BBS12* encode chromosome 12 open reading frame 58

(C12orf58), tripartite motif-containing protein-32 (TRIM32), and chromosome 4 open reading frame 24 (C4orf24), respectively [41, 42].

Alström syndrome (ALMS). ALMS is an autosomal recessive and genetically homogeneous disorder. The syndrome is characterized by mild truncal obesity associated with small stature, dilated cardiomyopathy, and type 2 diabetes. It is also associated with other clinical traits of variable severity such as hyperthyroidism, retinal cone dystrophy, progressive sensorineural hearing loss, chronic nephropathy, and hepatic dysfunction. Although this disorder shows many similarities to BBS, there is no mental defect, polydactyly, or hypogonadism [50]. The gene *ALMS1*, located on chromosome 2p13, has been shown to be defective in ALMS. This gene is ubiquitously expressed at low levels and encodes a protein that contains a large tandem-repeat domain comprising 34 imperfect repetitions of a 47-amino acid sequence but whose function is unknown [51, 52]. ALMS is caused by a balanced translocation of chromosome 2p13 that disrupts *ALMS1* or by a small number of nonsense or frameshift mutations in the gene.

Börjeson-Forssman-Lehmann syndrome (BFLS). BFLS is an X-linked dominant disease characterized by late-childhood truncal obesity, severe intellectual disability, epilepsy, microcephaly, long ears, short stature, and gynecomastia [53]. Affected males manifest hypotonia, failure to thrive, big ears, and small external genitalia as infants and moderately short stature with emerging truncal obesity, gynecomastia, macrocephaly, tapering fingers, and shortened toes as boys. Some heterozygous females show milder clinical features as a result of skewed X inactivation [54]. The gene associated with BFLS was originally localized to a 17-Mbp region at Xq26-q27 [55]. The interval of the BFLS locus was subsequently narrowed to an ~ 9-Mbp region containing more than 62 genes, and a novel, widely expressed zinc-finger plant homeodomain (PHD)-like finger gene (*PHF6*) was identified as a causative gene [56]. *PHF6* encodes a protein with two zinc-finger domains that accumulates in the nucleolus and may play a role in transcription. Eight different missense or truncation mutations of *PHF6* have been identified in seven familial and two sporadic cases of BFLS [56].

Cohen syndrome (COH1). COH1 is an autosomal recessive disorder that is overrepresented in the Finnish population. The syndrome is characterized by mild truncal obesity, thin extremities, and short stature. A specific clinical phenotype has been delineated in a homogeneous cohort of Finnish COH1 patients, consisting of nonprogressive mild to severe psychomotor retardation, motor clumsiness, microcephaly, characteristic facial features, hypotonia and joint laxity, progressive retinochoroidal dystrophy, myopia, intermittent isolated neutropenia, and a cheerful disposition [57]. Haplotype analysis of the critical region on chromosome 8q22 resulted in identification of the responsible gene for COH1 as that for vascular protein sorting 13, yeast, homolog of B (*VPS13B*). Several frameshift, premature termination, and missense mutations of this gene have been identified in patients with COH1 [58]. On the basis of its homology with *Saccharomyces cerevisiae* VPS13 proteins, VPS13B is thought to function in vesicle-mediated sorting and transport of proteins within the cell.

Polygenic obesity

Polygenic obesity results from the effects of several altered genes. Two main approaches have been adopted to find the genetic variants that affect obesity: linkage analysis and association studies. Although linkage analysis has been highly successful in mapping genes responsible for single-gene disorders, it has generally been less successful for multigenic diseases. Whole-genome scans often identify chromosomal regions as being linked to obesity, but the results of such studies vary greatly, probably because of the low capacity of linkage to find genes with modest effects or because of differences in study design or populations. Association studies have been successful in identifying genes for common diseases and complex traits, but their results are also often not replicated consistently because of differences in study design or insufficient power of the population size.

Linkage analysis. The information available on the location of repeated sequences throughout the genome has led to the increasingly rapid identification of genes responsible for mendelian diseases and of chromosomal regions associated with susceptibility to the development of complex diseases. The strategy of gene mapping or positional cloning is based on analysis of the inheritance or segregation of genetic markers in multigeneration families or extensive groups of sib-pairs affected by the disease under study, with the purpose of identifying responsible genes according to their chromosomal location. Whole-genome search studies have demonstrated the presence of different obesity susceptibility loci in different ethnic groups (Table 1). The results of these studies support the notion that different genes and gene combinations are responsible for the pathogenesis of obesity in different populations.

Table 1. Whole-genome linkage analyses of obesity in various ethnic groups.

Study population	Chromosome	Markers (candidate gene)	Score	Reference
Pima Indians	11q23.3	D11S1998	LOD = 2.7	[59]
	11q24.1	D11S4464	LOD = 2.7	[59]
	11q24.3	D11S912	LOD = 3.6	[60]
Mexican Americans	2q12.2-q14.3	D2S293–D2S383	LOD = 2.9	[61]
	4q16.1	D4S912 (*PPARGC1*, *CCKAR*)	LOD = 4.5	[61]
	7q32.2	D7S514 (*OB*)	$p = 0.0001$	[62]
	7q34	D7S495	$p = 0.0001$	[62]
	8p11.23	D8S1121 (*ADRB3*)	MLS = 3.2	[63]
	11p15.5	D11S984–D11S988	LOD = 2.5	[61]
	11q24.1	D11S4464	LOD = 2.3	[61]
Amish	5q35.3	D5S408	$p = 0.0039$	[64]
	7q34	D7S1823	$p = 0.0008$	[64]
	7q35	D7S2195	$p = 0.001$	[64]
	14q22.2	D14S276	LOD = 1.8	[65]
African Americans	3p26.3	D3S2387	LOD = 3.67	[66]
	3q26.33	D3S2427 or D3S3676	LOD = 4.3	[67]
	4q24	D4S1647	LOD = 2.63	[68]
	5p15.2	D5S817	LOD = 1.9	[69]
	8q21.3	GATA8B01	LOD = 2.56	[68]
European or African Americans	3q13.33	ATA28H11	LOD = 2.8	[70]
	10p11.23	D10S208	$p = 0.0005$	[71]
	10q21.1	D10S107	$p = 0.0005$	[71]
	10q22.1	D10S1646	LOD = 2.5	[72]
	Xp21.3	DXS997	LOD = 2.7	[71]
	Xp11.3	DXS1003	LOD = 2.7	[71]
Hispanic Americans	3p26.3	D3S2387	LOD = 3.67	[66]
US (in blacks)	3q22.1	D3S1764	LOD= 3.45	[73]
US (in Mexican Americans)	3q26.33	D3S2427	LOD = 3.4	[74]
US	1p36.32	D1S468	LOD = 2.8	[74]
	1p36.32	D1S468	LOD = 2.32	[75]
	2q14.3	D2S347	LOD = 4.04	[74]
	2q14.3	D2S347	LOD = 3.42	[75]
(Framingham Heart Study)	2p22-p21	D2S1356	$p = 0.0004$	[76]
(Framingham Heart Study)	2p16.3	D2S1352	$p = 0.0004$	[76]
	2p22.3	D2S1788	LOD = 3.08	[77]
(NHLBI Family Heart Study)	2q35-q36.3	D2S1363–D2S1279	LOD = 3.34	[78]
	3q26.33	D3S2427	LOD = 3.3	[79]
	3q12.3	D3S3045	LOD = 3.66	[80]
(in Utah pedigrees)	4p13	D4S1627	LOD = 3.4	[81]
(in Utah pedigrees)	4p15.1	D4S3350	LOD = 9.2	[81]
(Framingham Heart Study)	6q23.3	D6S1009	LOD = 2.79	[82]
(Framingham Heart Study)	6q23.3	D6S1009	LOD = 2.79	[83]
	7q22.3	D7S692	LOD = 2.75	[84]
	7q31.1	D7S523	LOD = 2.11	[84]
(NHLBI Family Heart Study)	7q32.3	D7S1804	MLS = 4.9	[85]
(Framingham Heart Study)	11q24.3	D11S912	$p = 0.0003$	[76]
	12q21	D12S1052	LOD = 3.41	[77]
	12q21.33	D12S1064	LOD = 3.41	[77]
	12q24.21	D12S2070	MLS = 4.01	[80]
(NHLBI Family Heart Study)	13q14.2	D13S257	MLS = 4.9	[85]
	13q21.32	D13S800	LOD = 2.7	[86]
	13q31.3	D13S793	LOD = 4.79	[80]
	13q32.2	D13S779	LOD = 2.82	[86]
	16p13.2	D16S404	LOD = 1.7	[87]
(Framingham Heart Study)	16q12.2	D16S3253	LOD = 3.21	[82]
	20p13	D20S482	LOD = 3.55	[87]
	20p12.2	D20S851	LOD = 4.08	[87]
(in Utah pedigrees)	20q12	D20S438	LOD = 3.5	[88]
	20q12	D20S107	LOD = 3.2	[89]
	20q13	D20S476	LOD = 3.2	[89]
	20q13.2	D20S211	LOD = 3.2	[89]
	20q13.31-qter	D20S149	LOD = 3.2	[89]

Table 1 *(Continued)*

Study population	Chromosome	Markers (candidate gene)	Score	Reference
Canadian (in Québec City)	7q35	KEL	$p = 0.0001$	[90]
	20q13.12	ADA	$p = 0.001$	[90]
French	2q33.2-q36.3	D2S112–D2S396	LOD = 2.73	[91]
	5q14.3	D5S1463	LOD = 2.68	[92]
	6q22.31-q23.2	D6S462–D6S441	LOD = 3.27	[91]
	10p12.2	D10S197	LOD = 4.9	[93]
	17q23.3	D17S944	LOD = 3.16	[92]
	19q13.3-q13.43	D19S418	LOD = 3.21	[92]
	20q13.2	D20S120 (*MC3R*)	$p = 0.004$	[94]
Finnish	18q21.32	D18S1155	LOD = 2.4	[95]
	Xq24	DXS6804 (*HTR2C*)	LOD = 3.1	[95]
	3p22.3	D3S2432	LOD = 3.4	[96]
	13q12.11	D13S175	LOD = 3.3	[96]
	13q12.13	D13S221	LOD = 3.3	[96]
German	10p12.2	D10S197	LOD = 2.24	[97]
	10p12.1	D10S1932	LOD = 2.32	[98]
	10p11.2	D10S1781	LOD = 2.32	[98]
Dutch	1p31.1	D1S1665 (*LEPR*)	LOD = 1.2	[99]
	6p25.1	SE30	LOD = 2.13	[100]
	7p21.1	D7S3051	LOD = 2.4	[100]
	10q26.3	D10S212	LOD = 3.3	[99]
Africans	1p11.2	D1S534	LOD = 2.24	[101]
	7p14.3	D7S817	LOD = 3.83	[101]
	8p22	GATA151F02	LOD = 2.34	[101]
	11q22.3	D11S2000 (*NPY*, *DRD2*, *APOA4*, *LMNA*, *LPL*)	LOD = 3.35	[101]
Hong Kong Chinese	1q23.1-q23.2	D1S194-D1S196	MLS = 3.71	[102]

LOD, logarithm of odds; MLS, maximum lod sores.

Candidate gene approach. In association studies of obesity, genes or gene variants are selected as candidate disease determinants if they have a known or hypothesized role in metabolism or if they are located within a region of the genome implicated in obesity by linkage analysis. In the simplest form of such studies, the frequency of the variant allele of a particular gene is compared between obese and nonobese individuals, or between obese individuals and their nonobese relatives [103]. Some representative polymorphisms associated with human obesity are listed in Table 2 and are discussed below.

Peroxisome proliferator-activated receptor γ gene (PPARG). A Pro115Gln polymorphism of *PPARG* was found to be associated with the rate of adipocyte differentiation as well as with greater cellular accumulation of triglyceride [104]. In addition, the Ala allele of a Pro12Ala polymorphism of *PPARG* was associated with a lower body mass index (BMI), lower plasma insulin level, higher insulin sensitivity, and higher plasma high density lipoprotein (HDL)-cholesterol level [105]. The transactivation activity of PPARγ containing Ala12 was found to be reduced compared with that of the protein containing Pro12 [105], suggesting that this difference in activity of this transcriptional regulator of adipogenesis may underlie the effect of this polymorphism on the accumulation of adipose tissue mass.

β2-Adrenergic receptor gene (ADRB2). An Arg16Gly polymorphism of *ADRB2* has been associated with BMI and the fasting plasma concentration of nonesterified fatty acids [106]. A longitudinal study further revealed that the Gly16 allele was associated with a higher frequency of weight gain and blood pressure elevation over a 5-year period [107]. Another polymorphism of *ADRB2*, Gln27Glu, has also been associated with obesity, with the association depending on physical activity [108].

β3-Adrenergic receptor gene (ADRB3). A Trp64Arg polymorphism of *ADRB3* has been associated with obesity [109]. The variant allele of this polymorphism was also shown to be associated with increased BMI, fat mass, and waist circumference in a paired-sibling analysis of Mexican Americans [110]. However, about half of the subsequent large studies examining this polymorphism demonstrated an association with BMI, whereas the other half did not [111, 112]. Because there is no evidence that *ADRB3* is expressed and translated into a protein in human adipose tissue, genotype for *ADRB3* may not prove reliable for assessment of genetic risk for obesity.

Table 2. Summary of association studies for candidate gene markers and obesity.

Gene	Locus	Polymorphism	Effect of variant allele	dbSNP no.	Reference
Angiotensin-converting enzyme (*ACE*)	17q23	Intron16 (I/D)	Associated with plasma ACE level		[118]
		–240A→T	Associated with plasma ACE level	rs4291	[119]
β2-Adrenergic receptor (*ADRB2*)	5q31-q32	Arg16Gly	Decreased receptor activity	rs1042713	[106, 107]
		Gln27Glu	Decreased receptor activity	rs1042714	[108]
β3-Adrenergic receptor (*ADRB3*)	9p12	Trp64Arg	Decreased receptor activity	rs4994	[109, 110]
G protein β3 subunit (*GNB3*)	12p13.3	825C→T	Modified G protein activation	rs5443	[120–122]
Leptin (*LEP*)	7q31	–2548G→A	Changed leptin concentration	rs7799039	[123]
		19A→G	Changed leptin concentration	rs2167270	[124, 125]
Leptin receptor (*LEPR*)	1p31	Arg223Glu	Changed receptor function	rs1137101	[126, 127]
		Lys656Asn	Changed receptor function	rs8179183	[128]
Peroxisome proliferator–activated receptor γ (*PPARG*)	3p25	Pro115Gln	Reduced transactivation activity	rs1800571	[104]
		Pro12Ala	Reduced transactivation activity	rs1801282	[105]
Tumor necrosis factor-α (*TNFA*)	6p21.3	–308A→G	Changed transcriptional activity	rs1800629	[117]
Uncoupling protein 1 (*UCP1*)	4q28-q31	–3826A→G	No	rs1800592	[113, 114]
Uncoupling protein 2 (*UCP2*)	11q13	–866G→A	Changed UCP2 mRNA abundance	rs659366	[115]
Uncoupling protein 3 (*UCP3*)	11q13	–55C→T	No	rs1800849	[116]

Uncoupling protein (UCP) genes. A -3826A→G polymorphism of *UCP1* was shown to be associated with weight gain during adult life in individuals with morbid obesity [113]. This polymorphism was also associated with postprandial thermogenesis after a high-fat meal in healthy boys, suggesting that impaired UCP1-mediated thermogenesis may have adverse effects on the regulation of body weight [114]. A -866G→A polymorphism of *UCP2* was found to be associated with the risk of obesity in middle-aged humans [115]. In addition, a -55C→T polymorphism in the 5′ flanking region of *UCP3* was associated with BMI as a result of an effect on the benefit of physical activity [116].

Tumor necrosis factor-α gene (TNFA). The *A* allele of a -308G→A polymorphism in the 5′ untranslated region of *TNFA* was shown to be associated with an increased BMI, waist-to-hip ratio, and abdominal sagittal diameter. This allele was also associated with an increased plasma concentration of cortisol in the morning as well as with increased postprandial cortisol secretion, possibly accounting for its association with obesity [117].

Angiotensin-converting enzyme gene (ACE). An insertion/deletion (I/D) polymorphism in intron 16 of *ACE*, which contributes to a large extent to variability in plasma ACE levels, was found to be associated with higher percentage of body fat in older adults [118]. Another polymorphism of *ACE*, -240A→T, was also associated with BMI in Japanese individuals, with the *T* allele protecting against obesity [119].

G protein β3 subunit gene (GNB3). An 825C→T polymorphism of *GNB3* was shown to be associated with obesity in Caucasians, Africans, and Asians [120]. In each of these three cohorts, the frequency of the 825*T* allele was significantly increased in obese individuals compared with those of normal weight. The 825*T* allele of this polymorphism was also found to be associated with postpregnancy weight retention as well as with low birth weight in babies born to women without other risk factors for reduced fetal growth [121, 122].

Leptin gene (LEP). Several variants of *LEP* have been identified. A -2548G→A polymorphism in the 5′ region of the gene was shown to be associated with plasma leptin concentration and the prevalence of obesity [123]. In addition, obese individuals homozygous for the *G* allele of a 19A→G polymorphism of *LEP* had significantly lower leptin concentrations than did those either heterozygous or homozygous for the *A* allele [124]. This polymorphism was also associated with obesity in women [125].

Leptin receptor gene (LEPR). A G→A (Arg223Glu) polymorphism of *LEPR* was found to be associated with plasma leptin levels as well as with BMI, fat mass, and the insulin response to an oral glucose tolerance test in postmenopausal Caucasian women [126, 127]. In addition, a Lys656Asn polymorphism of *LEPR* was associated with the leptin response and weight loss secondary to a lifestyle modification in obese patients [128] as well as in those with impaired glucose tolerance [127].

Genome-wide association studies. Several associations between obesity and single nucleotide polymorphisms (SNPs) spanning candidate genes in chromosomal regions implicated in genome-wide scans have been demonstrated. Polymorphisms of the genes encoding solute carrier family 6 member 14 (*SLC6A14*) on chromosome X [129], glutamic acid decarboxylase (*GAD2*) on chromosome 10 [130], and ecto-nucleotide pyrophosphatase 1 (*ENPP1*), also known as plasma cell membrane glycoprotein-1 (*PC-1*), on chromosome 6 [131] were thus shown to be associated with obesity. Recent advances in high-throughput SNP typing technology have made genome-wide association studies a realistic approach to the identification of genes responsible for common diseases or complex genetic traits. The many genetic variants and patterns of common variation elucidated by the human HapMap Project will also facilitate the selection of variants for testing in association studies [132]. Several genome-wide association studies for common diseases were published in 2007 [133–136]. The identification of susceptibility variants for type 2 diabetes in these independent genome-wide association studies was replicated. A genome-wide association study of obesity-related traits showed that a polymorphism (rs9930506) of the fat mass- and obesity-associated gene (*FTO*) was markedly associated with BMI, hip circumference, and body weight [137]. Variation in *FTO* was demonstrated to contribute to childhood and adult obesity in different populations [138, 139]. The results of other ongoing genome-wide association studies of obesity are expected to identify additional susceptibility variants and loci for obesity in the near future.

Gene-environment and gene-gene interactions. Although the importance of gene-environment and gene-gene interactions in the onset and progression of obesity is well recognized, these interactions are not well understood because of the complexity both of designing studies to characterize them and of processing the data generated [140]. Advances in knowledge of the human genome as well as the development of new technologies for performing and analyzing the results of such studies will be necessary to shed light on this issue.

Conclusion

Obesity has become a major public health problem as a result of its increasing prevalence in most developed countries. The World Health Organization (WHO) estimates that ~1.6 billion adults were overweight (BMI $\geq$ 25 kg/m^2) and at least 400 million adults were clinically obese (BMI $\geq$ 30 kg/m^2) worldwide in 2005 [141]. WHO further predicts that ~2.3 billion adults will be overweight and more than 700 million will be obese by 2015. The pathogenesis of obesity is complex, with environmental factors affecting an individual's inherent risk for this condition, which is determined by the effects of multiple genetic factors. The identification of susceptibility genes for obesity is therefore important for its prediction. The adoption of various methodological approaches that address both gene-gene and gene-environment interactions as well as an individual's genetic and metabolic profiles will be required to determine the genes and sequence variants that increase susceptibility to the common forms of obesity. The definition of the genomic basis of obesity will have a substantial impact on clinical practice and potentially facilitate intervention to avert future cardiovascular events for each patient. The interaction of environmental factors, such as behavior (overeating and physical inactivity) and socioeconomic conditions, affects an individual's risk for obesity. In addition to new knowledge through research that integrates social, behavioral, cultural, and physical factors to prevent obesity, such a genomic approach to the understanding and treatment of obesity will eventually lead to increased survival and better quality of life.

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