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Genome wide association study of obesity

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ABSTRACT Obesity is a great risk factor for type 2 diabetes and certain types of cancer, which become a major burden for public health worldwide. As a classic complex disease, obesity is regarded as the interaction of genetic and environmental factors. However, it is controversial which of these two factors have greater effect on obesity. Several genetic loci have recently been reported to contribute to the development of obesity reported in genome-wide association study (GWAS) these years. GWAS play an important role in complex disease research and explore the potential effect of genetic variance. To further understand the genetic influence on obesity risk, we reviewed and collected articles on Pubmed for genes that reported in recent GWAS. We summarized the publications in GWAS and found 49 candidate genes, which were strongly suggested to relate to obesity risk in human. Despite the findings of this and other similar, contemporary research projects, much of the single nucleotide polymorphism details and underlying mechanism in this field of study remains, to a great extent, unknown. As a result, future studies are needed for obesity risk in human beings.

KEY WORDS obesity; genome wide association study (GWAS); genes

肥胖的全基因组关联研究

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[**摘要**] 肥胖是 2 型糖尿病和某些癌症的重要危险因子，同时也是影响世界范围内公众健康的重要负担。作为一

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种传统的复杂疾病，肥胖症被认为是基因与环境交互作用的产物。然而上述两个因素中哪一个对肥胖的产生发挥更大的作用尚存争议。近年来，通过全基因组关联分析 (GWAS) 发现了一些影响肥胖进展的基因位点。GWAS 研究对探寻基因变异在复杂疾病中的潜在作用发挥日益重要的作用。为进一步了解遗传因素导致肥胖的风险，笔者回顾并收集 Pubmed 上近期有关 GWAS 研究报道的基因，总结已发表的关于 GWAS 的研究论文，共找出与人类肥胖患病风险强相关的 49 个候选基因。尽管该发现与当前的研究存在相似性，但这一研究领域的许多单核苷酸多态性 (SNPs) 的详细信息和潜在机制尚未阐明。因此，有必要对人类肥胖症患病风险进行更为深入的研究。

[**关键词**] 肥胖；全基因组关联分析；基因

1 Introduction

Obesity is becoming a global epidemic in both adult and children[1]. Obesity is defined as a medical condition in which excess body fat has accumulated and may adverse effect on health. Body mass index (BMI), which is calculated based on height and weight, defined people as overweight if their BMI is between 25 and 30 kg/m^2, and obese when it is greater than 30 kg/m^2 [2]. Epidemical research shows that in 2005–2006, 35.3% of adults in United States were obese[3]. Obesity increases the likelihood of various diseases, such as type 2 diabetes mellitus, cardiovascular diseases, certain types of cancer, and hypertension[4-6].

A combination of excessive food energy intake and a lack of physical activity were considered as the main reason of obesity[7]. However, in the past decades, more and more research suggests that like many other medical conditions, obesity is the result of interplay between both environmental and genetic factors[8]. Genetic polymorphism in various genes controlling appetites and metabolism predispose to obesity when sufficient food and energy present[9]. Researchers also has focused some studies on inheritance patterns rather than single genes, which found that 80% of the offspring of two obese parents were obese, in contrast to less than 10% of the offspring of two parents who were of normal weight[10].

Genome-wide association study (GWA study, or GWAS), which is also known as whole genome association study, is an examination of many common genetic variants in difference individuals to see if any genetic variant is associated with a certain trait[11]. GWAS is widely used for complex disease research right now[12]. Recently, several GWAS results have expanded the number of genetic susceptibility loci for obesity by identifying several new single nucleotide polymorphisms (SNPs) consistently associated with both BMI and weight, and thus, contributing to obesity risk[13]. This review set out to investigate the obesity related loci from recently GWA studies, and explore the association with abdominal obesity—an important contributor to increased morbidity and mortality. By reviewing the articles collected on Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) with keywords “obesity AND GWAS AND gene”, 49 obesity candidate genes were included (Table 1). Including hormones, cytokines, interleukins et al, these genes were epidemically and functionally reported to correlate with body status. In this review, we also have summarized the novel founding of GWA study based on obesity people as well as health controls.

Obesity is highly attributed to genetic factors: the heritability is estimated to be as much 0.4–0.8 for BMI [14], suggesting that genetic factors play an important role in this diseases. A large number of candidate genes influencing obesity were identified by mutation analysis, linkage studies, and association studies. We reviewed GWA studies from Medline database as well as meeting abstracts, including reported obesity GWAS results from multiply ethnics, European, Asian and American and so on. In summary, we believe that further more functional and genetic studies of these genes are needed in the future to help understand the mechanism of obesity and its induced diseases.

2 Significant genes of obesity in GWA studies

2.1 Brain-derived neurotrophic factor (BDNF)

BDNF is a member of neurotropic family of growth factors, which are related to the nerve growth factor. In 2009, several genetic variants within BDNF gene were found to be associated with obesity in 6078 children[15]. This group confirmed this relevance between BDNF and children obesity in 1097 European cases and 2760 controls

in 2011[16]. Another study in different ethnic populations also replicated this significant association in Singaorean Chinese, Malay and Asian-Indian subjects published in 2011 by Dorajoo et al[17].

2.2 FTO

FTO is fat mass and obesity-associated protein located in chromosome 16, which has been considered as one of the most important genes related to obesity. Certain genetic variants of FTO gene appear to be correlated with obesity in humans and reported widely recent years. A study of 6078 European children identifies the association between FTO variants and childhood obesity[15]. The relationship also has been replicated in 1097 European cases in 2011[16], 1400 obese Europeans in 2011[18]. Wang et al also reported a GWAS and candidate SNP genotyping study of obesity in 2011. For the binary trait of obesity, they found 16 genome-wide significant signals within the FTO gene in 520 obesity case and 540 control subjects[19].

2.3 GNPDA2

Glucosamine-6-phosphate deaminase 2 also known as GNPDA2 is an enzyme that in humans is encoded by the GNPDA2 gene located in chromosome 4p12. Zhao et al has reported that the genetic variants of GNPDA2 were correlated with pediatric BMI and children obesity in in 6078 European children[15] and 1097 European obese cases[16].

2.4 INSIG2

INSIG2 is insulin induced gene 2, which could be activated and regulated by insulin, Akt as well as MCHR2. Zhao et al reported the INSIG as an identified gene with children obesity in European cases[15]. rs7566605 in INSIG2 gene showed to correlated with severe obesity in Japanese (n=908) published in 2008[20]. Campa et al analyzed the associate between INSIG2 rs7566605 and female BMI in 3937 European women and 2194 controls. Furthermore, they studied the association between this polymorphism and break cancer risk in this case cohort including 1269 invasive breast cancer cases. However, there were no statistic results between this SNP and BMI, nor did breast cancer risk[21].

2.5 LYPLAL1

LYPLAL1 gene encoding lysophospholipase-like 1 and locates in 1q41. Bille et al reported that rs2605100 in LYPLAL1 was statistically associated with BMI, waist circumference (WC) in all 15326 Danish subjects enrolled. The minor allele associated with WC among women, but the major allele of this polymorphism also correlated with fasting serum triglyceride concentrations, fasting serum insulin concentrations, and increased insulin resistance[22]. However, Hotta et al reported that there was no significant association between LYPLAL1 and BMI, visceral fat area (VFA), or subcutaneous fat area (SFA) in 1228 Japanese population[23].

2.6 MSRA

Peptide methionine sulfoxidereductase is an enzyme that in humans is encoded by the MSRA gene. In 2011, Bille et al reported that MSRA variants were significantly associated with quantitative metabolic traits in adult Danes. The MSRA rs545854 showed nominal associations with central obesity in large scale populations[22]. However, another study in Japanese population in 2010 did not find significant association between MSRA variants and BMI in 1228 subjects[23].

2.7 MTCH2

Mitochondrial carrier homolog 2 also known as MTCH2 is suggested to correlate with obesity. MTCH2 rs4752856 was reported significantly associated obesity in 4923 adults from northern Sweden in 2009 by Fenstrom et al. They extended this study in 3885 non-diabetic and 1038 diabetic individuals[24]. In 2011, Delahanty et al performed a GWAS to identify multiple genetic markers for obesity, and their samples comprised 832 endometrial cancer cases and 2049 controls. MTCH2 loci variants not only presented associated with BMI, but also correlated with the risk of endometrial cancer[25].

2.8 NRXN3

NRXN3 (Neurexin-3-alpha) belongs to neurexin family that function in the vertebrate nervous system as cell adhesion molecules and receptors. In 2011, Zhao et al performed a GWA meta-anlysis in 1097 obesity case together with 2760 lean controls aged 2–18 years old in European Americans. This study found the association between NRXN3 loci and childhood obesity[16]. However, there was another publication in 2011 suggested NRXN3 correlated with waist circumference among women but no associations with obesity related metabolic traits in a large scare adult Danes[22].

2.9 SEC16B

SEC16B is named as protein transport protein Sec16B. In 2011, SEC16B was suggested to associate with childhood obesity in European Americans. Zhao et al performed a GWA meta-anlysis in 1097 obesity case together with 2760 lean controls [16]. However, this relevance has not been replicated by Sandholt et al in Danes. This study investigated the association between SEC16B variants and metabolic phenotypes in 18014 middle-aged Danes, but no significant results were found this time[26].

2.10 SOX6

SOX6, also known as transcription factor SOX-6 belongs to SOX gene family which encodes a group of transcription factors defined by the conserved high mobility group (HMG) DNA-binding domain. A powerful bivariate genome-wide association analyses suggest the SOX6 gene influencing obesity phenotypes in homogeneous Caucasians males. rs297325 and rs4756846, located in intron 1 of SOX6 gene, were significantly associated with both BMI and hip BMD[27]. In 2011, SOX6 variants have been replicated correlated with BMI in Chinese population comprised by 832 endometrial cancer cases and 2049 controls[25].

2.11 TFAP2B

TFAP2B is transcription factor AP-2 beta, a member of the AP-2 family of transcription factors. Bille et al performed an implication of central obesity-related variants on quantitative metabolic traits in adult Danes in 2011. TFAP2B rs987237 showed nominal associations with central obesity. However, when investigating quantitative metabolic traits, no underlying metabolic phenotypes became obvious[22]. Another publication in 2011 also reported that TFAP2B variants significantly associated with BMI in Singaporean Chinese, Malay and Asian-Indian populations[17].

2.12 TMEM18

Transmembrane protein 18, TMEM18, has been connected to cell migration and obesity recent years. Two SNPs near TMEM18, rs6548238 and rs756131, were reported significantly associated with severe childhood obesity 502 severely obese and 527 healthy Swedish children[28]. Another study in Children's Hospital of Philadelphia from 2006 to 2008 showed that variants of TMEM18 were also correlated with childhood obesity consisted of 6078 children of European ancestry with BMI information[15].

2.13 TNNI3K

TNNI3K, located to 1p31.1, belongs to a tyrosine kinase-like branch in the kinase tree of the human genome. In 2011, TNNI3K variant was reported as significant association with childhood obesity in European Americans. Zhao et al performed a GWA meta-analysis in 1097 obesity case together with 2760 lean controls aged between 2 and 18 years old[16]. Another multiple ethnic study in 2011 replicated that TFAP2B variants significantly associated with BMI in Singaporean Chinese, Malay and Asian-Indian populations[17].

3 Summary

Based on the results of genome wide association, we have selected 49 genes that likely have significant effect on obesity. Furthermore, most of these genes have been replicated by other genetic studies, ultimately suggesting that obesity is on some degree influenced by genetic variance. Confounding variables such as environmental influence and unknown gene-gene interactions do undoubtedly exist. Additionally, unidentified associations corresponding to differences in ethnicity, age, study sample sizes, and study-specific methods of analysis do further complicate the situation. As a result, it is clear that the occurrence of obesity is complex, and our current lack of knowledge concerning it is currently hindering our ability to fully explain the exact mechanism of obesity. Consequently, future studies encompassing larger sample sizes and novel perspectives are called for in overcoming current problems. If allowed to transpire, these studies will ultimately facilitate a better understanding of the regulatory pathways in obesity in human beings.

Table 1 Significant genes for obesity from genome-wide association study

Gene	Full name	Location
A2BP1	RNA binding protein, fox-1 homolog 1	16p13.3
ALCAM	Activated leukocyte cell adhesion molecule	3q13.1
APBB2	Amyloid beta (A4) precursor protein-binding, family B, member 2	4p13
APBB2	Amyloid beta (A4) precursor protein-binding,	4p13
BDNF	family B, member 2 Brain-derived neurotrophic factor	11p13
C11orf53	Chromosome 11 open reading frame 53	11q23.1
CD36	CD36 molecule (thrombospondin receptor)	7q11.2
CDH12	Cadherin 12, type 2 (N-cadherin 2)	5p14.3
CDH13	Cadherin 13, H-cadherin	16q23.3
FAIM2	Fas apoptotic inhibitory molecule 2	12q13
FDX1	Ferredoxin 1	11q22
FER1L4	Er-1-like 4	20q11.22
FHIT	Fragile histidine triad gene	3p14.2
FTO	Fat mass and obesity associated	16q12.2
GNPDA2	Glucosamine-6-phosphate deaminase 2	4p12
GNPDA2	Glucosamine-6-phosphate deaminase 2	4p12
GNPDA2	Glucosamine-6-phosphate deaminase 2	4p12
INSIG2	Insulin induced gene 2	2q14.2
KCTD15	Potassium channel tetramerisation domain containing 15	19q13.11
LRRN6C	Leucine rich repeat neuronal 6C	9p21.2
LRRN6C	Leucine rich repeat neuronal 6C	9p21.2
LYPLAL1	Lysophospholipase-like 1	1q41
MC4R	Melanocortin 4 receptor	18q22
MSRA	Methionine sulfoxidereductase A	8p23.1
MTCH2	Mitochondrial carrier 2	11p11.2
MTNR1B	Melatonin receptor 1B	11q21-q22
MYLIP	Myosin regulatory light chain interacting protein	6p23-p22.3
MYLIP	Myosin regulatory light chain interacting	6p23-p22.3
NEGR1	protein Neuronal growth regulator 1	1p31.1
NPC1	Niemann-Pick disease, type C1	18q11-q12
NRXN3	Neurexin 3	14q31
NUDT12	Nudix (nucleoside diphosphate linked moiety X)-type motif 12	5q21.2
NUDT12	Nudix (nucleoside diphosphate linked moiety X)-type motif 12	5q21.2
OTOL1	Otolin 1	3q26.1
PTBP2	Polypyrimidine tract binding protein 2	1p21.3
QPCTL	Glutaminyl-peptide cyclotransferase-like	19q13.32
SDCCAG8	Serologically defined colon cancer antigen 8	1q43
SEC16B	SEC16 homolog B	1q25.2
SH2B1	SH2B adaptor protein 1	16p11.2
SOX6	Sry (sex determining region y)-box 6	11p15.3
SP7	Sp7 transcription factor	12q13.13
TFAP2B	Transcription factor AP-2 beta	6p12
TFAP2B	Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	6p12
TMEM18	Transmembrane protein 18	2p25.3
TNNI3K	TNNI3 interacting kinase	1p31.1
UBE2E3	Ubiquitin-conjugating enzyme E2E 3	2q32.1

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