Research Highlight

Genome-wide Association Studies of Common Obesity: Now and Future*

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Obesity has become a major public health concern worldwide[1]. Obesity is a complex disease influenced by both genetic and environmental factors. Epidemiological studies have indicated that environmental factors, such as excessive energy intake and lack of physical activity, might contribute to the development of obesity. Genetic factors also play an important role in the pathogenesis of obesity. Indeed, approximately 40%-70% of the variation in body mass index (BMI) can be attributed to genetic factors[2].

Before 2006, two approaches, including linkage study and candidate gene association study were used to understand genetics of obesity. However, few of the identified genes could be successfully confirmed in the following independent studies[3]. Genome-wide association study (GWAS) is a promising way for identification of novel loci for BMI/risk of obesity. To date, a number of GWASs have identified more than 50 BMI/obesity susceptibility loci in populations of European and non-European origins[4-13] (Table 1). The variants in/near *FTO* (*fat mass and obesity associated*) gene and *MC4R* (*melanocortin receptor 4*) gene are the first two loci detected by GWAS[4-5]. Other loci include variants in/near *TMEM18*, *GNPDA2*, *BDNF*, *FAIM2*, *NPC1*, *SEC16B*, *SH2B1*, *PCSK1, KCTD15,* and so on[6-13]. However, the following studies have reported inconsistent results in different ethnic groups. The discrepant findings might be due to differences in the sample size, participants recruited, and genetic and environmental backgrounds. Several meta-analyses have confirmed the positive association between *FTO*[14] and *MC4R* genes[15] and obesity, but further meta-analyses are needed to clarify the association betwen other genetic loci and BMI/obesity.

FTO

In 2007, Frayling et al.[4] firstly reported that variant in *FTO* gene was associated with type 2 diabetes. However, the *FTO*-type 2 diabetes association disappeared after adjustment for BMI, suggesting that the effect of *FTO* on type 2 diabetes was completely mediated by BMI/obesity. That is, *FTO* is an obesity associated gene. Although the conflicting findings were reported in the following studies, the GWASs[6-7,10-12] and the majority of studies[14,16-17] also confirmed the significant association between variants in *FTO* gene and BMI/obesity in both European and non-European populations, in both adults and children. For Chinese population, Li et al.[18] firstly reported that three variants (rs9939609, rs8050136, and rs9930506) in *FTO* were not associated with obesity. Subsequently, the controversial results were published, some suggested non-significant association while others indicated positive association. A recent meta-analysis of 3994 obesity cases and 11 205 controls confirmed that variant in *FTO* was associated with the risk of obesity in Han ethnic group (OR=1.27, 95% CI=1.16-1.39)[19]. The results above suggested that there is not an ethnic difference in the effect of *FTO* on human common obesity although the genetic background is different for European and non-European populations.

The mechanism causing the association between *FTO* variants and obesity risk remains unclear. *FTO* is highly expressed in the central nervous system, which regulates energy metabolism[7]. Interestingly, rs9939609 variant in *FTO* was found to influence energy-dense food intake rather than regulation of energy expenditure in a British children population[20]. The majority of following studies also supported the important role of *FTO* variants in the control of choice and intake of food.

Environmental factors, e.g., physical activity and diets, might modulate gene expression and thus influence the effect of gene variants. Investigation of the impact of interaction between genetic factor and environmental factor on obesity might be helpful in suggesting intervention strategies against the risk effect of genetic variants. To date, many studies have attempted to investigate the influence of physical

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Table 1. Risk Loci for Common Obesity Identified by Genome-wide Association Studies

Chr.	SNP	Nearby Genes	Effect Allele Frequency (Allele)	Odds Ratio (95% CI) for Obesity	Explained Variance (%) of BMI	Reference
16	rs9939609	*FTO*	0.46 (A)	1.32 (1.26-1.39)	0.34	[4,10]
18	rs17782313	*MC4R*	0.26 (C)	1.12 (1.08-1.16)	0.10	[5,10]
2	rs7561317	*TMEM18*	0.85 (G)	1.20 (1.13-1.27)	0.15	[6,10]
1	rs2568958	*NEGR1*	0.64 (A)	1.07 (1.02-1.12)	0.04	[6,10]
1	rs10913469	*SEC16B, RASAL2*	0.25 (C)	1.11 (1.05-1.18)	0.07	[6,10]
3	rs7647305	*SFRS10, ETV5, DGKG*	0.80 (C)	1.11 (1.05-1.17)	0.03	[6,10]
6	rs2844479	*NCR3, AIF1,BAT2*	0.33 (C)	1.07 (1.02-1.12)	NR	[6,10]
11	rs6265	*LGR4, LIN7C, BDNF*	0.19 (T)	1.12 (1.06-1.19)	0.07	[6,10]
12	rs7138803	*BCDIN3D, FAIM2*	0.34 (A)	1.14 (1.09-1.19)	0.04	[6,10]
16	rs7498665	*SH2B1, ATP2A1*	0.38 (G)	1.08 (1.03-1.13)	0.05	[6,10]
19	rs29941	*CHST8, KCTD15*	0.68 (G)	1.10 (1.04-1.15)	0.00	[6,10]
4	rs10938397	*GNPDA2*	0.45 (G)	1.12 (1.07-1.17)	0.08	[7,10]
5	rs6235	*PCSK1*	0.27 (G)	1.22 (1.15-1.29)	0.01	[8,11]
18	rs1805081	*NPC1*	0.47 (C)	1.41 (1.19-1.61)[a]	NR	[9]
16	rs1424233	*MAF*	0.44 (C)	1.39 (1.23-1.54)[a]	NR	[9]
10	rs10508503	*PTER*	0.09 (T)	1.47 (1.02-2.63)[a]	NR	[9]
13	rs9568856	*OLFM4*	0.13 (A)	1.22 (1.14-1.29)	NR	[13]
17	rs9299	*HOXB5*	0.63 (T)	1.14 (1.09-1.20)	NR	[13]
2	rs713586	*RBJ, ADCY3 (Q, M), POMC (Q,B),*	0.47 (C)	1.07 (1.05-1.09)	0.06	[10]
16	rs12444979	*GPRC5B (C,Q), IQCK (Q)*	0.87 (C)	1.08 (1.04-1.11)	0.04	[10]
15	rs2241423	*MAP2K5, LBXCOR1 (M)*	0.78 (G)	1.07 (1.04-1.10)	0.03	[10]
19	rs2287019	*QPCTL, GIPR (B,M)*	0.80 (C)	1.09 (1.05-1.12)	0.04	[10]
1	rs1514175	*TNNI3K*	0.43 (A)	1.04 (1.02-1.07)	0.02	[10]
4	rs13107325	*SLC39A8 (Q,M)*	0.07 (T)	1.10 (1.05-1.15)	0.03	[10]
5	rs2112347	*FLJ35779 (M), HMGCR (B)*	0.63 (T)	1.05 (1.03-1.08)	0.02	[10]
9	rs10968576	*LRRN6C*	0.31 (G)	1.04 (1.02-1.06)	0.02	[10]
19	rs3810291	*TMEM160 (Q), ZC3H4 (Q)*	0.67 (A)	1.06 (1.03-1.08)	0.02	[10]
2	rs887912	*FANCL*	0.29 (T)	1.05 (1.03-1.08)	0.03	[10]
3	rs13078807	*CADM2*	0.20 (G)	1.03 (1.00-1.06)	0.02	[10]
14	rs1184769	*PRKD1*	0.04 (T)	1.10 (1.04-1.17)	0.01	[10]
2	rs2890652	*LRP1B*	0.18 (C)	1.05 (1.02-1.08)	0.02	[10]
1	rs1555543	*PTBP2*	0.59 (C)	1.02 (1.00-1.04)	0.01	[10]
13	rs4771122	*MTIF3, GTF3A (Q)*	0.24 (G)	1.05 (1.01-1.08)	0.02	[10]
5	rs4836133	*ZNF608*	0.48 (A)	1.03 (1.01-1.05)	0.01	[10]
11	rs4929949	*RPL27A, TUB (B)*	0.52 (C)	1.03 (1.01-1.05)	0.01	[10]
6	rs206936	*NUDT3, HMGA1 (B)*	0.21 (G)	1.03 (1.01 1.06)	0.01	[10]
6	rs2206734	*CDKAL1*	0.59 (C)	1.13 (1.07-1.19)	0.06	[11]
9	rs11142387	*KLF9*	0.46 (C)	1.10 (1.04-1.16)	0.04	[11]
16	rs12597579	*GP2*	0.80 (C)	1.06 (1.02-1.10)	0.05	[12]
11	rs652722	*PAX6*	0.61 (C)	1.05 (1.02-1.08)	0.04	[12]

Note. [a]Morbid obesity (BMI≥40kg/m^2); NR, not reported.

activity on the association between *FTO* variants and obesity but revealed conflict results[21]. Recently, a meta-analysis performed by Kilpeläinen et al.[22] suggested that physical activity could reduce the influence of *FTO* variants on obesity risk in adults but not in children. In addition, several studies observed that high intake of saturated fatty acids strengthened the association between *FTO* and BMI/risk of obesity[23]. These findings highlighted the importance of physical activity and healthy diet against the risk of genetic variants on obesity.

MC4R

In previous studies, several rare mutations in *MC4R* gene were found to be associated with monogenic forms of extreme, early-onset obesity. Also, the association between two common variants (V103I, I251L) in *MC4R* gene and common obesity was extensively investigated. The following meta-analyses confirmed that both I-allele of V103I variant and L-allele of I251L variant could reduce the risk of obesity in general population[24-25]. In 2008, Loos et al.[5] firstly reported that rs1778231 variant, 188 kilobase (kb) downstream of *MC4R*, was associated with BMI/obesity in European population by GWAS. In the same year, another GWAS identified rs129070134 variant (~150 kb downstream of *MC4R*) was associated with BMI/obesity in Indian Asians[27]. The significant association was further confirmed in Europeans and East Asians, in adults and children[15]. In Chinese, *MC4R* variant was reported to has consistent positive association with risk of obesity except one study suggesting non-significant association by Tao et al.[26]. A meta-analysis of 4515 obesity cases and 9415 controls further confirmed the positive association in Chinese population (OR=1.31, 95% CI=1.23-1.39)[15].

Like *FTO, MC4R* also plays an important role in the central regulation of energy homeostasis. Most studies reported that variant near *MC4R* was associated with increased food intake and unhealthy eating behavior although some studies did not.

For other obesity-related loci, only a few independent studies had been conducted and only few loci could be successfully replicated[17,28]. More GWASs are needed to confirm the association between obesity and other new obesity-related loci.

Predictive Value of Obesity Related Loci

Although more than 50 obesity related loci have been identified, the effect of each variant was modest, with odds ratio ranging from 1.1 to 1.5 for per-risk allele. Of all obesity related loci, *FTO* locus only accounts for 0.34% of variation in BMI; each of other loci explains even less BMI variation (Table 1). The finding from a population-based study involving 20 431 participants suggested that all 12 variants combined only explained 0.9% of BMI variation, with an area under the curve (AUC) of 0.574 for the prediction of obesity[29]. In another population-based study involving 8120 individuals, the result based on the genetic risk score of 32 loci was similar, with explained variance in BMI of 1.45% and the AUC for obesity of 0.575[10]. In a word, the predictive value of genetic loci identified by GWAS is very limited. In contrast, the traditional factors, including parental obesity and childhood obesity, were reported to have higher predictive value, with the AUC for adulthood obesity of about 0.70[30]. However, as two genetic studies above did not collect the information on parental and childhood obesity, it is impossible to estimate the predictive value of the genetic and traditional factors combined.

Although the identified obesity related loci have limited predictive value, they are still very important in personalized medicine. That is, individuals who carry more risk alleles can be suggested to improve their lifestyle, such as having healthy diets and spending more time on physical activity against the risk of obesity caused by genetic factors. However, the development of new drugs based on the newly identified loci by GWAS is still at early stage.

Future Perception

To date, the majority of obesity-related loci are identified in non-coding regions, often in areas that are several kbs away from the coding region of a gene. Thus, it is unclear which variant or gene is on the causal pathway towards obesity. In addition, as the identified loci by GWAS could explain only a fraction of the heritability, more loci remain to be identified. The following are the four trends in future. First, many rare variants, unable to be detected by GWAS, might have stronger effect on obesity. The new sequencing techniques, including exome or whole genome sequencing, would be useful to identify these low frequency variants. Second, methylation scan, using techniques such as DNA methylation-specific microarrays, might facilitate the understanding of gene expression modified by environmental and/or developmental factors. Third, more effective statistical and computational methods should be developed to detect interaction

of gene-gene or gene-environment. Fourth, conducting large studies to investigate the association between obesity related loci and obesity associated diseases, including type 2 diabetes[31], hypertension[32-33], metabolic syndrome, cardiovascular disease, and cancer, to further clarify the mechanisms of these obesity related diseases.

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