The Genetic Determinants of Common Human Obesity

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The genetic determinants of common human obesity have been elusive until recently, when work from several groups led to the identification of 16 loci that reproducibly associate with common human obesity. These loci reveal that the genetic architecture of common human obesity likely involves rare high penetrant loci, common low penetrant loci, and likely intermediate loci that are yet to be discovered. These loci implicate central nervous system processes in the pathophysiology of common human obesity, are not limited to effects in the central nervous system, and confirm a genetic susceptibility to obesity that may be harder for some individuals to overcome compared with others.

Introduction

Obesity is one of the most menacing medical problems facing our society today. In the United States, more than 65% of individuals are overweight and more than 33% are frankly obese [1]. Obesity affects more than 1 billion people worldwide and its prevalence is increasing. Concomitant with an increase in obesity is an increase in obesity-related medical complications, such as diabetes, hypertension, dyslipidemia, coronary artery disease, nonalcoholic fatty liver disease, and cancer [2]. Unfortunately, we have no effective medical treatments for obesity at this time. Fundamentally, obesity is a disorder of energy balance. Some individuals manage to balance their energy intakes with energy expenditure and have normal weight. However, many individuals in our current society have an imbalance of energy intake and energy expenditure, which results in them becoming obese. A fundamental biological question is whether or not there are factors that contribute to this energy balance. If there are biological factors that contribute to energy balance, how do we identify and target them for therapeutic intervention?

A Genetic Approach to Common Human Obesity

The prevalence of obesity has increased markedly since the mid 1980s, both in the United States and throughout the world [2]. Certainly, this is not due to a change in our genetics; therefore, it reflects a change in our environment. Nevertheless, even in this current obesogenic environment, the predisposition of some individuals to become obese or stay thin varies. Therefore, by studying the predisposition of individuals to stay thin or become obese in such an environment we may be able to uncover the underlying genetic elements that contribute to this variation. One common measure of overall obesity is body mass index (BMI), which is defined as someone's weight in kilograms divided by their height in meters squared. Based on population norms, the World Health Organization has deemed individuals of European ancestry with a BMI $\geq$ 30 kg/m^2 to be obese. From family studies, we know that BMI is about 40% to 60% heritable (ie, genetic). In particular, there is ample evidence that twins raised apart develop a BMI and body habitus that is more congruent with their identical twin, regardless of their different environments, suggesting a strong genetic component [3,4]. Similar experiments in families suggest a very strong genetic component. Measures of abdominal obesity, which is often more strongly correlated with metabolic complications of obesity, include waist circumference (WC) and waist-to-hip ratio (WHR), both of which are also heritable (45%–60%), even after controlling for BMI (to which they are correlated) [5,6]. Despite this strong genetic predisposition to common obesity, identifying the underlying elements that contribute to this obesity has been quite difficult until recently.

Monogenic Human Obesity

Certainly, monogenic obesity syndromes in humans exist. Individuals who lack function in leptin [7], the leptin receptor [8], or the melanocortin receptor [9] all develop severe early-onset obesity. These are inherited mostly as Mendelian conditions passing clearly from one generation to another as single gene defects. Furthermore, we know that there are other syndromes that have obesity as a component in humans. These include Prader-Willi syndrome, Bardet-Biedl syndrome, Fragile X syndrome, and more recently WAGR syndrome (Wilms tumor, aniridia,

genitourinary anomalies, and mental retardation) [10,11]. However, all of these conditions are rare in humans and even if all of these monogenic obesity cases are summed they do not come close to the 33% of individuals in our society who are obese or the 66% who are overweight.

Advances in Genomics

After the sequencing of the human genome, it was discovered that more than 99.5% of human DNA was identical between individuals and that most of the other differences between us were in the form of single nucleotide polymorphisms (SNPs) [12]. The International HapMap Project then went on to characterize common genetic variation in three different populations: one of European ancestry, one of African ancestry, and one of Asian ancestry [13,14••]. With these new tools, it became possible to ask whether or not common genetic variants were associated with measures of obesity. Common genetic variants at a locus in the genome could be determined by genotyping in many individuals, and then by using regression techniques, it could be determined whether a locus is associated with a particular phenotype of interest. Initially, many studies reported associations between genetic variants and BMI; however, many of these could not be reproduced. There are many reasons for this, including lack of power, population stratification artifacts (where an association with the trait is caused by an uneven distribution of individuals from different populations in which the allele exists at different frequencies), and genetic artifacts. Since then, methods have been developed to improve genotyping quality and better filter data to control population stratification. Also, cost-effective commercial products have been developed for genotyping SNPs throughout the whole genome, making it possible to screen the human genome with less bias for associations of SNPs with measures of obesity. As more and more individuals are genotyped on such platforms, we increase our power to detect variants that associate with obesity measures. The culmination of all this technological advancement and human cooperation has recently led to the publication of the first reproducible common variants that associate with common human obesity.

The First Common SNP Variants to Associate with BMI

The first variants to be associated with common human obesity were variants in the previously unknown gene fatso (*FTO*) [14••]. A group of investigators conducting a case-control analysis of diabetes noted that one of their top diabetes-associated hits also associated with BMI and the entire effect on diabetes was abolished once they controlled for BMI. They went on to replicate the association of this variant with BMI in over 38,000 samples. Another group performing a whole-genome scan in another population also noted that the variants around this gene were associated at a genome-wide significance threshold ($P < 5 \times 10^{-8}$) with BMI and reported this shortly after the initial report [15••]. Many groups have since gone on to confirm that variants around the gene *FTO* reproducibly associate with human BMI. What became obvious after the publication of these papers was that the effect size on BMI of this variant was about 0.1 population standard deviation per allele (which is quite small), suggesting that large numbers of individuals would be needed to find other variants with similarly small effect sizes. Multiple groups studying BMI using whole-genome association data started to meta-analyze their data to see if they could find such similar variants. Indeed, from such collaborative efforts the second common variant to be associated with BMI was found and this was just downstream of an excellent candidate gene: the melanocortin 4 receptor (*MC4R*) [16••]. This variant turned out to have about a 0.05 population standard deviation per allele effect on BMI. Furthermore, individuals that carried this gene also had slightly taller stature [16••], similar to what had previously been reported for more severe mutations in *MC4R* [9]. These results strongly suggested that this variant downstream of the *MC4R* gene may affect the melanocortin 4 receptor in a manner congruent with but less severe than more severe mutations in this gene.

Large-Scale Meta-Analyses of BMI Uncover Many SNP Variants That Associate With BMI

Two groups have since gone on to do large-scale meta-analyses of genome-wide association data: one from the Genetic Investigation of Anthropometric Traits (GIANT) consortium [17••] and the other from deCODE genetics (Reykjavik, Iceland) [18••] (Table 1). These groups confirmed *FTO* and *MC4R* as real BMI-associated loci and also identified variants that reproducibly associated with BMI around several other genes: potassium channel tetramerization domain 15 (*KCTD15*), SH2 domain-containing protein 1B (*SH2B1*), mitochondrial carrier homolog 2 (*MTCH2*), glucosamine-6-phosphate deaminase 2 (*GNPDA2*), trans membrane protein 18 (*TMEM18*), neuronal growth regulator 1 (*NEGR1*), brain-derived neurotrophic factor (*BDNF*), ets variant gene 5 (*ETV5*), leucine zipper transcription regulator 2 (*LZTR2*), and Fas apoptotic inhibitory molecule 2 (*FAIM2*) [17••,18••]. These groups reported no heterogeneity of these variants across studies and genders and found that these variants associated more with weight and fat mass than height, suggesting that they were adiposity loci more than height loci [17••,18••]. Furthermore, the frequency of the BMI-increasing alleles varied anywhere from 21% to 84% in individuals of European ancestry, suggesting that these are common in this population [17••,18••]. This finding is important, because at these frequencies most individuals in the population would carry at least one BMI-increasing allele. These elements alone, however, do not cause obesity but rather

Table 1. Variants that associate with increasing obesity measures

SNP	Chromsome	Position	Allele	Frequency*	Nearest gene
rs9939609	16	52378028	A	0.46	*FTO*
rs6548238	2	624905	C	0.85	*TMEM18*
rs17782313	18	56002077	C	0.265	*MC4R*
rs10938397	4	45023455	G	0.446	*GNPDA2*
rs7498665	16	28790742	G	0.381	*SH2B1*
rs11084753	19	39013977	G	0.69	*KCTD15*
rs10838738	11	47619625	G	0.363	*MTCH2*
rs2815752	1	72524461	A	0.637	*NEGR1*
rs4074134	11	27603861	G	0.77	*BDNF*
rs7647305	3	187316984	C	0.796	*ETV5*
rs10913469	1	176180142	C	0.254	*LZTR2*
rs7138803	12	48533735	A	0.345	*FAIM*
rs987237	6	50911009	G	0.164	*TFAP2B*
rs7826222 (rs545854)	8	9897490	G	0.177	*MSRA*
rs2605100†	1	217710847	G	0.686	*LYPLAL1*
rs10146997	14	79014915	G	0.248	*NRXN3*

*In International HapMap Project CEU group.
†Affects waist-to-hip ratio in women only; all other SNPs affect overall body mass index in both men and women.
CEU—Utah residents with ancestry from northern and western Europe; SNP—single nucleotide polymorphism.

increase the probability of becoming obese in a large proportion of the population. The different patterns of inheritance of these variants that influence BMI contribute to the variation in BMI that we see in this population and make us all unique.

Large-Scale Meta-Analyses of WC and WHR Uncover Variants That Associate With Measures of Central Obesity

Recently, two groups, one from the GIANT consortium [19••] and the other from the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) consortium [20••], reported variants near transcription factor–activating enhancer-binding protein 2 beta (*TFAP2B*), methionine sulfoxide reductase A (*MSRA*), neurexin 3 (*NRX3*), and lysophospholipase-like protein 1 (*LYPLAL1*) that associated with measures of central obesity (ie, WC and WHR). Variants near *TFAP2B*, *MSRA*, and *NRX3* were associated with WC in both men and women and their association with WC was diminished considerably when controlling for BMI, suggesting that these loci affect overall as well as central adiposity [19••,20••]. In contrast, *LYPLAL1* was associated with WHR in women more than men and its effect on WHR remained strong even after controlling for overall BMI, making it one of the first gender-specific and central obesity–specific variants to date [19••]. The frequency of the central obesity measure alleles range from 16% to 67% and, like the BMI-associating variants, are common (Table 1).

Genetic Architecture of Common Human Obesity

One striking revelation from these studies is that many of the best-associating variants are in noncoding areas of the genome. The best example of this was a variant that mapped to a 10.8-kb region in a gene desert approximately 400 kb downstream of *GNPDA2* and 900 kb upstream of gamma-aminobutyric acid A receptor, alpha 2 (*GABRA2*) [17]. The best-associating variants were found also in introns of *FTO*, neurexin 3 (*NRXN3*), and *LZTR2* downstream of *MC4R*, transmembrane protein 18 (*TMEM18*), potassium channel tetramerization domain 15 (*KCDT15*), *BDNF*, *LYPLAL1*, *TFAP2B*, and *FAIM2* and upstream of *NEGR1*, *MSRA*, and *ETV5* [17••–20••]. For the other two cases, the association signal overlapped the coding regions of multiple genes, which makes it possible that the causal variant lies in the coding region of one of the underlying genes [17••,18••]. Nevertheless, for other association signals it is more likely than not that the causal variant will lie outside the protein coding regions of nearby genes. Many of the Mendelian mutations that have been identified affect the coding regions of the genes or completely eliminate the function of genes. It remains to be determined how these newly identified variants that do not lie in the coding regions of genes affect nearby genes. One can certainly speculate that they may affect tissue-specific enhancers, elements that affect global chromosomal structure, or processes that we have yet to discover. Nevertheless, it is clear that these variants causally affect variation in obesity measures, perhaps to a lesser degree than completely eliminating gene function. For example, individuals with

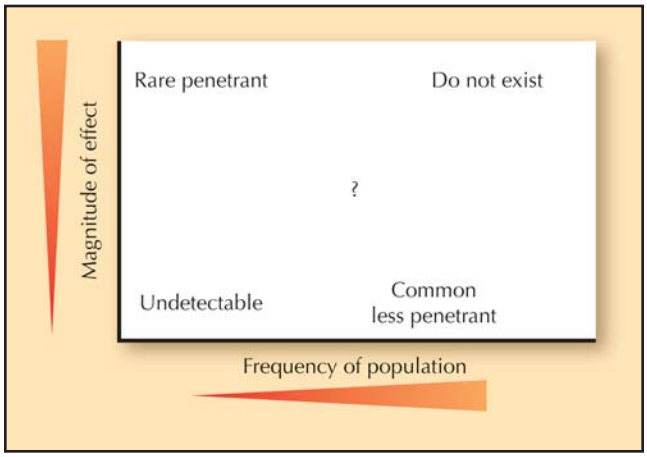

Figure 1. Genetic architecture of human obesity.

a variant downstream of *MC4R*, which is present in 38% of individuals of European ancestry, have a slightly higher BMI than individuals who do not carry these alleles [16••]. However, variation in the protein coding region of *MC4R* leads to severe early-onset pediatric obesity [9]. Similarly, variants downstream of *BDNF* lead to slightly higher BMI in individuals that carry these variants [18••]; however, as was recently reported by Han et al. [11], individuals who carry deletions in *BDNF* or severe mutations in *BDNF* have early-onset pediatric obesity. This gives us a framework for thinking about the genetics of common human obesity (Fig. 1). Prior to this work, we knew that rare severe mutations existed in genes that led to more Mendelian-like syndromes that can be inherited clearly from one generation to another. From this work, we have now learned that there are common less penetrant variants that can be inherited that affect population variation in BMI. Investigators have looked for common very penetrant variants that affect obesity, but such variants have not been detected, at least in European populations to date. Certainly there may also be rare variants with weak effects that cannot be detected by current methods. Finally, there are also likely variants that span the spectrum between common less penetrant mutations and rare penetrant mutations that may be discoverable by sequencing exons in individuals with extreme phenotypes to find variants that have stronger effects on the phenotype but that may not be quite as rare as the Mendelian mutations identified to date.

Copy Number Polymorphisms and Common Human Obesity

One group also discovered that a copy number variant was associated with common human obesity [17••]. None of the samples used for meta-analysis of BMI by Willer et al. [17••] were genotyped on a platform that had any information on copy number variants, which are duplications or deletions in the genome. However, by combining the association data with a linkage disequilibrium map of SNPs that were in high linkage disequilibrium with copy number variants from genotyped International HapMap Project samples from individuals of European ancestry on newer platforms that included both SNP and copy number information, Willer et al. [17••] were able to discern that the best associating SNP variants all fell on one haplotype that contained a 45-kb deletion upstream of *NEGR1*. This deletion eliminated noncoding elements upstream of *NEGR1* [17••]. Without further functional studies, it not clear whether the SNP variants or the deletion is the real causal variant, but certainly something on that haplotype is causally related to development of obesity. This is exciting because it is the first copy number variant to be associated with human obesity and the second copy number variant to be associated with any common genetic disorder. This suggests that other types of genetic variation beyond SNPs may also contribute to common genetic disorders and that further work may uncover these.

Hypotheses Related to the Biology of Common Human Obesity

Many new hypotheses regarding the biology of common human obesity have been generated from these studies. Prior to this work, we knew that mice that lacked *sh2b1* had hyperphagia obesity, hyperglycemia, hyperinsulinemia, and insulin and leptin resistance [21]. We also knew that mice that lacked *mc4R* had hyperphagia obesity, hyperglycemia, and hyperinsulinemia [22]. Both of these genes are thought to act in the hypothalamus. Within the hypothalamus there are pro-opiomelanocortin (POMC) neurons that decrease food intake by signaling through *mc4r*. If *mc4r* is disrupted, the signal to decrease food intake through that receptor is not propagated and animals become obese. Leptin, which is made by adipose tissue, acts positively on POMC neurons to decrease food intake. *sh2b1* is part of the leptin signaling pathway and, if disrupted, POMC-mediated signaling to decrease food intake does not occur and animals become obese [23]. Sixty-five percent and 38% of individuals of European ancestry carry variants in *SH2B1* or downstream of *MC4R*, respectively, that increase BMI [16••–18••]. This suggests that, as in mice, variations around these genes in humans likely contribute to common human obesity. Similarly, mice that have *bdnf* or the BDNF receptor deleted develop obesity compared with their otherwise genetically identical littermates [24–26]. Analogously, humans that have deletions in *BDNF* develop severe early-onset obesity [11]; specific variants in this gene have also been associated with human anorexia and bulimia [27]. Thirty percent of individuals carry a BMI-increasing allele downstream of *BDNF* that contributes to increased population BMI [18••]. These results in aggregate are extremely exciting because an unbiased screen of the human genome has revealed variants near three genes that are clearly known to affect obesity in animals and are known to cause monogenic human disorders, suggesting that genes near variants identified through genome-wide

association studies may have evolutionarily conserved actions on body weight.

In addition to these three loci, there are another 13 verified loci that contribute to common human obesity. Although the precise gene that any of the associated SNPs influence remains to be verified, as was the case with *SH2B1*, *MC4R*, and *BDNF*, the genes nearest to these variants often are good candidates for affecting obesity measures. Two of these, *NEGR1* and *NRXN3*, may affect neuronal processes [28–30]. *FTO* is part of a cluster of genes that is thought to play a role in brain patterning [31], and one report suggests that it plays a role as a nucleic acid demethylase [32]. However, upstream of *FTO* is a gene called protein fantom (*FTM*), also known as retinitis pigmentosa GTPase regulator (RPGR)-interacting protein 1L (*RPGRIP1L*). *RPGRIP1L* is located in the ciliary basal body and is necessary for left-right symmetry and patterning of the neural tube and in limbs [33–36]. It is also associated with celial-related Hedgehog signaling in response to sonic Hedgehog [37]. *FTO* and *RGRIP1L* are expressed in similar tissues and may be jointly transcriptionally regulated [38]. Missense and truncation mutations in *RPGRIP1L* are linked to cerebellar oculo-renal syndrome (also called Joubert's syndrome type B or Meckel's syndrome [34–36]), which belongs to a group of developmental autosomal recessive disorders associated with primary cilium dysfunction, which also includes the Bardet-Biedl syndrome, in which obesity is a prominent component. Thus, *RPGRIP1L* is a prime candidate for being the gene causing increased BMI by variants in the first intron of *FTO*. Variants between *GNPDA2* and *GABRA2* also reproducibly associate with BMI. *GNPDA2* by homology is thought to play a role in protein glycosylation. γ-Aminobutyric acid receptors are known to play a role in the anxiety response, and the variants around these loci have been found to be associated with human alcohol addiction [39]. Variants that associate with BMI in the region of mitochondrial carrier homologue 2 (*MTCH2*) overlap many genes in this region. *MTCH2* has been reported to play a role in apoptosis [40], but otherwise, not much is known about its function. Other candidates, such as *FAIM2*, a signaling molecule, and *TFAP2B*, a transcription factor, also protect against programmed cell death [41,42]. Furthermore, both *TFAP2B* and *LYPLAL1*, which are similar to triglyceride lipases, are expressed in adipose tissue and may affect fat accumulation [43,44]. Associations with variants around *KCTD15* and *TMEM18* are also reproducible, but these genes are named by homology to other proteins, and their function is not known. When the homologue of *ETV5*, a transcription factor, is knocked out in mice, it results in low birth weight [45], but the mechanism of this low birth weight is not known. LZTR2 is a protein whose homologue in yeast, *sec16*, is part of the endoplasmic reticulum and might play a role in secretion [46]. Its function in higher mammals is not worked out. Finally, *MSRA* may play a role in reduction of methionine and in antioxidant stress response and aging [47], but the exact mechanism by which this protein and the other proteins that these candidate genes encode affect obesity remains to be determined. This opens up many exciting new avenues of research in the field of obesity.

Expression of the Best BMI-Affecting Candidate Genes

Interestingly, expression of many of the best candidate genes in these regions seems to be very high in the central nervous system, particularly in the hypothalamus [17••]. Willer et al. [17••] did reverse transcription polymerase chain reaction testing of the best candidates in various human tissues and found that seven of eight of the nearest/best candidate genes in the region of their associated variants were expressed at very high levels in the cortex and hypothalamus. These include *FTO*, *MC4R*, *TMEM18*, *GNPDA2*, *KCTD15*, *NEGR1*, and *SH2B1* [17••]. *MTCH2* was expressed at high levels in the liver, kidney, and testes [17••]. *BDNF*, as its name implies, and *NRXN3* are also known to be expressed at high levels in the brain. Precise expression patterns of *ETV5* and *SEC16* in humans remain to be determined. Taken together, these data suggest that central nervous system processes may be important for the regulation of BMI in human obesity. This is not surprising given that many monogenic obesity syndromes affect genes in the central nervous system, including *MC4R*, leptin, leptin receptor, and *BDNF*. Although their precise function in the brain remains to be determined, these genes may affect appetite, mood, behavior, development, energy expenditure, energy balance, or other processes that we do not fully understand or have not yet characterized. However, the effects of candidate genes are not limited to the central nervous system; *TFAP2B* and *LYPLAL1* are expressed in fat cells and likely exert their effects there [43,44].

Effect Sizes of Variants That Associate With BMI

The variants reported have effect sizes of anywhere from 0.06 to 0.23 BMI units per allele [17••]. This translates to about 0.4 to 2.0 pounds in normal-height individuals. In the study by Willer et al. [17••], the authors went on to genotype variants around *FTO*, *MC4R*, *TMEM18*, *GNPDA2*, *MTCH2*, *KCTD15*, *NEGR1*, and *SH2B1* in over 14,000 individuals from the European Prospective Investigation of Cancer (EPIC)-Norfolk population in England. They went on to show that individuals who carried more than 13 BMI-increasing alleles (1.2% of the population) had a BMI that was 1.5 units higher than individuals who carried fewer than three BMI-increasing alleles (1.4% of the population). This translates to a difference of about 8.5 to 10.5 pounds between those individuals [17••], which can result in medically significant differences in development of metabolic dis-

ease. These authors weighted the alleles and examined whether a person's allele score (how many BMI-increasing alleles they carried) could predict the dichotomous outcome of obesity defined as a BMI ≥ 30 kg/m^2 versus non-obesity defined as a BMI less than 30 kg/m^2 using a receiver operator curve analysis. A perfect test would have an area under the curve of 1 and a worthless test is an area under the curve of 0.5; most medically significant tests lie somewhere above 0.6. They found that with eight variants, the area under the curve was 0.548 [17••]. Thus, knowing one's genotype at these eight loci can help predict obesity somewhat better than by chance, but not by much. This is not a clinically viable test at this time, but with the discovery of more variants our predictive power will increase. Indeed, the variance in BMI explained by these eight loci identified is only about 1% [17••,18••]. Given that about 40% to 60% of BMI is genetically influenced, there are many more genetic variants that will need to be identified to explain this variance. Indeed, larger meta-analyses are already underway that without a doubt will identify more common variants that associate with human BMI. Furthermore, sequencing studies of individuals with extreme BMI may identify severe variants in parallel in genes that also affect population-based BMI.

Future Studies

This work has already given us new potential targets for therapeutic intervention, a better sense of which individuals are at higher or lower risk of developing obesity, and may also give us clues as to whether individuals have different propensities to respond to different treatments for obesity. This genetic information will need to be combined with environmental risks that we know promote obesity to give us a more accurate prediction of personal risk for obesity. We can then use this to tailor preventive and therapeutic treatments to personal need. To do this we will need to expand this work to other ancestries, as so far these studies have been limited to individuals of European ancestry. Furthermore, we need to identify not only genes but also pathways that affect BMI to open up more possibilities for therapeutic intervention above and beyond the first genes identified. This will involve integrative work bringing genetics together with expression data, text mining, biochemical pathway data, RNA interference signatures, and protein interaction data.

Conclusions

Variants at 16 loci have been reproducibly shown to associate with measures of common human obesity, and more are likely to be discovered in the next few years. This work opens up many new avenues of research. With new genetic tools, we are gaining insights into not only the genetics of human obesity, but the very essence of who we are and why we do things. As much as we would like to think that we have full control over our actions and being, some of that is genetically influenced, as is shown by these variants that affect appetite, and may be harder for some people than others to change. Furthermore, medicine has done an excellent job of keeping many people from dying prematurely. Many individuals will thus live to older ages where they will go on to suffer from diseases that reflect our endogenous susceptibilities, including obesity, diabetes, and cancers. With these new genetic tools, we hope to better understand and treat these endogenous susceptibilities so that we can improve health, increase the efficiency of health care delivery, and decrease costs.

Disclosure

No potential conflict of interest relevant to this article was reported.

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