Chapter 7
Genes and Human Obesity

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Introduction

Obesity has increased dramatically over the last few decades. Since 1990 the prevalence of obesity has more than tripled and by 2007 approached one-third of the population, with another third that was overweight (CDC, http://www.cdc.gov/NCCDPHP/dnpa/obesity/trend/index.htm). Highest rates are found in the United States and the United Kingdom among developed countries, and in the Middle East and Pacific Islands in the developing world (WHO: http://www.who.int/infobase/comparestart.aspx). The increase in obesity rates in developing countries has coincided with "westernization" [1–3]. Life in the developed and developing world has become increasingly sedentary while relatively inexpensive, highly palatable food with high caloric content has become widely available. Although many lifestyle factors have been suggested to contribute to the dramatic obesity increase, the primary cause is, as one would expect, excess caloric intake [4, 5]. Diet accounts in part for national differences, but change within countries appears to be driven primarily by overall food availability [6]. Food is readily available and people are overeating.

Heritability

Gene frequencies do not change over short periods in large populations, and the large secular increases must have an environmental origin. This fact may lead some to wonder whether the heritability of obesity has declined during the same period, but this is not the case. There have been a large number of studies that estimated heritability of body mass index (BMI) and related variables [7], and they are consistent in finding moderate to high heritability. Furthermore, the estimates do not depend

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on the period of the study. For example, two studies on twins conducted almost 20 years apart found virtually identical estimates of overall heritability of BMI of about.80 [8, 9]. So, while estimates from particular studies vary, there is no trend toward decreasing (or increasing) heritability.

Gene–Environment Interaction

Bouchard and colleagues completed a series of landmark studies that helped to explain the role of inherited variation in environmentally influenced change. Bouchard's research group studied monozygotic twins exposed to long-term positive or negative energy balance. There were considerable individual differences in weight gain or loss under the different conditions, but changes were similar in the genetically identical co-twins, both in overall weight and visceral fat. The results indicate that genotype mediates response to the environment [10]. In other words, response to environmental change is itself heritable.

The major environmental changes that are credited with causing the obesity pandemic occurred at a population level, but, as with the study on twins, individuals differ in their response. While two-thirds of populations of developed countries are overweight or obese, the remaining third, living in the same environment, are of normal weight or thin. At the least, this implies a behavioral interaction, and, given the heritability of obesity and coordinate changes in twins, gene–environment interaction must play a major mediating role. A few studies have tried to identify environmental interactions with specific genes, focusing of weight gain or loss as phenotypes, and diet or exercise as components of the environment. One review identified some 13 studies that reported associations with some measure of exercise and 15 with diet and/or exercise [11]. However, most associations have not been replicated. The interaction most consistently supported was with the Trp64Arg polymorphism in the adrenergic receptor beta 3 (ADRB3) gene [11]. Limited power due to small sample size may in part contribute to the inconsistency of results. However, in the end most reported associations will be false positives while a few failures to replicate could be false negatives. The pairing of new technologies with larger sample sizes could prove more robust for examining gene–environment interactions, but this possible outcome will depend on the nature and magnitude of the individual interactions.

Candidate Genes

The phenotypic response in susceptible individuals must be influenced by variability in genes that influence energy balance. Energy homeostasis requires the coordination of appetite and satiety with energy expenditure and storage. A great deal has been learned about how energy homeostasis is maintained [12]. It is a complex process involving genes that regulate appetite, energy metabolism, and fat deposition.

Many genes that lie in associated regulatory pathways have become candidates for weight gain and obesity. These have included Leptin, Leptin Receptor, MC4R, UCPs, PPARG, NPY, and Ghrelin as well as genes in signaling pathways.

Candidate gene studies have identified mutations in humans or introduced them in animal models [13]. The last comprehensive count of human studies identified associations with 127 genes, most with at best mixed records of replication. The positive side of a candidate gene approach is that the genes derive from an emerging understanding of biology. Any associations that are detected with common obesity fit into a preexisting framework. Candidate gene studies have had their successes. Major gene mutations have been associated with obesity. However, they tend to be rare and account for a few cases of extreme obesity [13].

Common Obesity and Rare Gene Variation

Overall, candidate gene studies have been unsuccessful in explaining common forms of obesity. Genes central to energy balance tend to have low variability, presumably because of strong selection pressure. Even so, some have argued that mutations in a large number of genes may account for most human obesity and other common diseases. This view is sometimes called the common trait rare gene hypothesis (CTRV, [14, 15]), as opposed to the common trait common variant (CTCV) hypothesis.

Substantial progress in finding rare variants has come with a focus on copy number variation (CNV, a variant in a DNA segment of 1 or more kb in length). While major deletions, duplications, and rearrangements of DNA sequence associated with rare diseases have been know for some time, the scale of CNV was not appreciated until the last few years. One whole-genome survey found more than 4,000 variants, affecting more than 600 Mb of genomic DNA sequence [16]. Large-scale screening has identified associations of CNVs with a number of phenotypes [17] including type 1 diabetes, neuropsychiatric conditions [18], and several other common disorders [19].

To date, there have been few studies of CNVs associated with obesity. An association between BMI and a chromosome 10q11 CNV was recently reported in a Chinese cohort [20]. Two genes in this region are *GPRIN2* and *PPYR1*, which are worthy of follow-up studies in larger samples. In other studies, a deletion on 16p11.2 was recently reported to be associated with obesity [21, 22].

We recently completed a genome-wide CNV survey of obese cases and never-overweight control subjects [23]. CNVs larger than 1 Mb were found to be over-represented in obese cases compared with never overweight control subjects (odds ratio (OR) = 1.5), and CNVs larger than 2 Mb were present in 1.3% of the cases but absent in control subjects. When focusing on rare deletions that disrupt genes, even more pronounced effect sizes were observed (OR = 2.7 for CNVs larger than 1 Mb). Interestingly, obese cases that carry these large CNVs have only moderately high BMI. Several CNVs were found to disrupt known candidate genes for obesity, such as a 3.3 Mb deletion disrupting *NAP1L5* and a 2.1 Mb duplication disrupting *UCP1* and *IL15*. Our results suggest that large CNVs, especially rare deletions,

confer risk of obesity in individuals with moderate to extreme obesity. The genes affected by these CNVs thus become candidates for obesity.

Linkage Studies

One source of motivation for proposing the CTRV hypothesis was that attempts, through linkage and association, to identify common genes had been unsuccessful, at least until recently. The search for common genes has generally taken a genomic approach in which the entire genome is screened without prior hypotheses. Linkage studies were the first to take a whole-genome approach. There have been more than 60 of them for obesity-related traits [13], for example, but the results have been disappointing. A meta-analysis of 37 of these studies found only two regions to be significantly supported at the 1% level [24]: chromosome 13q for BMI and chromosome 12q for obesity (BMI ≥ 30).

The outcome of the meta-analysis helps to explain why most comprehensive searches for gene associations under linkage peaks have been unsuccessful. Many factors may account for this lack of success, but some are particularly important. Linkage studies tended to be underpowered, often in the extreme, and have had inadequate marker coverage. A particularly unfortunate aspect of low power is that most "significant" results are likely to be false positives, and because of this most studies that follow will fail to replicate. Another difficulty with low power is that even some weak positives may be true and therefore missed.

Whole-Genome Association Studies

Whole-genome association (WGA) studies made it possible to address the two most serious deficiencies of previous approaches, in that new genotyping technology has been combined with very large sample sizes. Moreover, WGA studies have several advantages over whole-genome linkage scans. The resolution is two to three orders of magnitude greater, 2–5 Mb in linkage studies compared with 10–100 kb with association. Cases and controls are much easier to collect than families, and the sample sizes required while large are much smaller than those required for linkage [25] and well within reach for collaborative groups, if not individual investigators. The advantages of a WGA approach were recognized some time ago [26], but the available technology was insufficient at that time. Circumstances have changed.

Recent GWA studies have depended upon advances in marker identification and genomic technology for high-throughput genotyping. The International HapMap Project (http://www.hapmap.org/) has identified more than 4 million single-nucleotide polymorphisms (SNPs) and 550,000 of them provide about 95% coverage of the genome in most populations, with about double that number needed for Africans [27]. High-throughput technology makes it possible to type up to 1 million genotypes in a single pass (Affymetrix and Illumina). Greatly reduced costs have made the

technology widely accessible. Finally, large sample sizes have been developed through the cooperation of investigators at multiple sites.

WGA studies have become widely available only within the past 3 years. Yet, there already have been a number of them related to obesity. The first few had relatively low genome coverage and found no associations that met a genome-wide level of significance (2×10^{-7}) [28, 29]. Not surprisingly, replication of the early findings has been mixed at best, for example, the reported association with the gene INSIG2 [30].

The breakthrough for WGA studies came from the Wellcome Trust Case Control Consortium (WTCCC) study that included 490,000 SNPs and a total of almost 39,000 individuals, although the initial phase utilized a much smaller number of cases and controls, about 2,000 and 3,000, respectively [31]. The study was unprecedented in size and in the strength of the association with FTO. An association with MC4R has also been reported based on the WTCCC sample [32]. The association with FTO has been replicated in most studies that followed. MC4R has been replicated as well, although not as consistently. A summary of reported associations with obesity-related traits that reached genome-wide significance is summarized in Table 1, while Table 2 lists those with the strongest support. The amount of variance in BMI accounted for by variants in these genes is disappointedly low, about two-thirds of 1% [30].

Table 1 Whole-genome association studies for obesity related traits reaching genome-wide significance as of April 2010

Study	N SNPs	Sample size	Genome-wide significance
Fraling et al. 2007 [61]	490k	38,759	FTO
Scuteri et al. 2007 [62]	361k	4,000+	FTO
Liu et al. 2008 [63]	500k	1,000	CTNNBL1
Loos et al. 2008 [32]	490	16,876	MC4R (FTO)
Thorleifsson et al. 2009 [64]	306k	38,112	FTO, MC4R, NEGR1, TMEM18, SH2B1, and 6 other loci
Meyre et al. 2009 [65]	300k CNV370	2,796	FTO, MC4R, NPC1, MAF, PTER
Willer et al. 2009 [30] Meta-analysis	Various	32,000	FTO, MC4R, TMEM18, CTD15, GNPDA2, SH2B1, MTCH2, NEGR1
Lindgren et al. 2009 [66] Meta-analysis	Various	38,580 Original 70,689 replications	FTO, MC4R, TFAP2B, MSRA
Johansson et al. 2010 [67]		3,448 linkage 3,925 associations	MGAT1
Wang et al. 2010 [23]	550k	2,363	FTO

Table 2 Obesity-related trait gene associations replicated at genome-wide level of significance. Together, these 5 genes account for less than 1% of the variance in BMI, ~0.67%

Gene	Proportion of variance (%)
FTO, fat mass associated gene	0.33
MC4R, melanocortin receptor 4	0.10
TMEM18, transmembrane protein 18	0.13
SH2B1, Src domain homology 2 B adaptor protein 1	0.08
NEGR1, neuronal growth regulator 1	0.03

From Willer et al. 2009 [30].

Larger sample sizes should help to identify more associations and improve replication, however, the effect sizes will only grow smaller. These finding on obesity are consistent with those for stature, a complex trait with an even higher heritability of at least.80. A large GWAS of stature involving some 63,000 subjects found 54 associated genes that accounted for only about 5% of the total variation in height [33–35]. This finding led to much discussion and speculation as to what happened to the so-called "missing heritability" [36]. Suggestions have included gene–environment interaction, as well as epigenetics. As discussed in an earlier section, gene–environment interaction can play an important role in the development of obesity, although it should be borne in mind that this may only complicate things further, as environmental response is itself heritable. Epigenetics will be discussed later in this chapter.

Disparate Approaches Appear to Converge

WGAS results have demonstrated that there are indeed common variants in genes that increase risk for obesity. This is particularly true for FTO that has been widely replicated. However, the proportion of variance in BMI these common genes account for is quite small, less than 1% [30]. Major gene mutations such as those in leptin, leptin receptor, and POMC have dramatic effects on individuals but are so rare that they account for essentially no common variance. CNVs are much more common than major gene mutations, but they are still relatively rare and account for little variance overall. While there are marked differences in frequency, each approach has been successful. However, the identified variants individually and together account for very little of the overall variance.

Taken on face value, the results from the different approaches suggest polygenic inheritance. The classic polygenic model was devised by R. A. Fisher as a way of incorporating Mendelian inheritance into quantitative variation [37]. For convenience he assumed there were multiple causal genes, each with small and roughly equal effects. The particulars, however, give a somewhat different picture. It turns out there are indeed multiple causal genes, and each variant accounts for little overall variance. However, the variants have a wide range of effects on the individuals that carry them. There is as yet no evidence the effects sum to create the phenotype. Studies published so far show little or no overlap in the genes identified by the different approaches.

Unanticipated Genes

Whole-genome approaches have the capacity to detect associations with genes that could not have been anticipated based on current knowledge. FTO for example falls outside any of the pathways that were known to affect appetite and energy balance. FTO had been identified previously through large-scale mutigenesis in mice [38] and received the acronym Fto because mice having a deletion of this gene had fused toes on the fore limbs. Ironically, it was called "fatso", not because of an obese phenotype (there was none) but because of a relatively large gene footprint.

Epigenetic Modification

There has been much discussion of late about the possible effects of epigenetic changes on risk for common disorders [39]. Epigenetic modification refers to changes in gene expression that are heritable, that is, which are maintained during somatic cell division and may in some cases be passed on to offspring.

Genomic imprinting is the most studied form of epigenetic modification, and involves the differential marking of parental chromosomes during gametogenesis. Imprinting appears to occur in all marsupial and placental species, and many of the imprinted genes are related to body size and/or metabolism [40–42]. The conflict theory suggests the association of imprinting with body size arose due to differential parental investment in offspring in polyandrous animals. Males are invested in larger body size of their offspring while females have an equal investment in all offspring regardless of the father. The theory is supported by fetus size in deer mice (peromyscus) hybrids of monogamous and polyandrous species [43].

The best known example relating to obesity is the Prader-Willi and Angelman syndromes, which are due to imprinting of the paternal or maternal chromosome, respectively, of region 15q11–13. Another imprinted gene is insulin-like growth factor 2, and paternal expression is strongly related to several measures of fat deposition in pigs [44]. In addition, quantitative trait loci (QTL), inferred genes based on linkage, have been identified in mice. Imprinting is suggested because linkage depends on parent of origin. In one study, five QTL were found, two paternal, two maternal, and one with no parent of origin effect [45].

Parent of origin effects have also been identified in humans. A large survey reported parent of origin-dependent associations of variants in known imprinted regions on chromosomes 7q32 and 11p15 with several complex disorders, including type 2 diabetes [46]. In our own work, we have found parent of origin effects on linkage in chromosome regions 10p12 and 12q24, where the linkage signal is due entirely to maternal transmission [47]. Chromosome 12q24 was one of the best supported linkage results in a meta-analysis [24], which seems to indicate that the linkage signal is detectible even if parent of origin is not modeled in the analyses. The chromosome 10p12 region (19.4–33.3 Mb) is homologous to a largely overlapping segment of mouse chromosome 2A3 (15–23 Mb) that has been predicted to be imprinted based on a machine learning model [48]. Two genes in this region have

previously been associated with obesity, glutamate decarboxylase 2 (GAD2), and G protein receptor 158 (GPR158) [49]. The concordance is intriguing, although imprinting mechanisms remain to be identified through molecular studies. A further suggestion of imprinting effects in humans is our recent finding of a CNV deletion of a region of chromosome 4 including the NAP1L5 gene [23]. The gene is normally expressed only on the paternal chromosome, which is deleted, apparently leading to an absence of gene expression.

Environmentally induced epigenetic modification has been recognized in cancer for some time, but a role in complex disorders such as obesity has only recently begun to be examined at a genomic level. However, indirect evidence demonstrating environmental effects on risk for obesity has been known for some time. For example, an early study found increased rates of obesity in men who had been *in utero* or neonatal during the height of the Dutch famine of 1944–1945 [50]. Other studies of this type also have found that maternal malnutrition contributes to risk for obesity and other aspects of the metabolic syndrome [51]. Another study [52] found that prenatal exposure to maternal diabetes increased the risk for obesity in Pima Indians. Animal studies similarly have shown that maternal exposure to malnutrition, high fat diets, stress, and other factors increase risk for obesity and the metabolic syndrome. It is of some interest that both under- and over-nutrition during fetal development can increase risk [53].

More recent studies have focused on epigenetic changes associated with prenatal exposure. A follow-up study on the Dutch famine cohort, for example, found that exposure indeed led to decreased methylation of the imprinted IGF2 gene [54]. Gene expression differences in monozygotic twins discordant for obesity also suggest the possibility of epigenetic modification [55]. While overall differences in expression could be state dependent, mitochondrial DNA copy number differences in adipose tissue of discordant twins are consistent with epigenetic effects.

The obesity state affects expression of many genes, with perhaps as many as 17,000 transcripts related to BMI in adipose tissue according to one estimate [56]. Gene expression in normal weight animals has also been related to later obesity. Inbred C57BL/6J mice are susceptible to diet-induced obesity, but there is variation in adiposity from an early age and the differences are maintained under both high-fat and restricted low-fat diets [57]. Microarray analysis found parallel pre-obesity differences in the expression of genes in several known metabolic pathways. The causes of the expression differences are unclear but could be due to prenatal or early postnatal environment.

Applications: Prevention and Therapy

One goal of genetic research, whether stated or implicit, is that findings will eventually make it possible to use genotype to make decisions about appropriate approaches to prevention and therapy. The nature of the genetics of human obesity complicates

its application, particularly in identifying individuals most at risk. Odds ratios for most variants will be even smaller than for FTO (about 1.65) and have been estimated to be in the range of 1.2. Prediction will therefore involve only small increments in risk. In most cases, familial obesity will continue to be the best predictor of risk. This difficulty will not only limit application but can also raise ethical concerns in providing risk assessments to individuals who may never develop obesity or become overweight for different reasons. While overall heritability is substantial, the contribution of individual genes or genotypes is likely to be very small relative to the major environmental influences of diet and lifestyle.

The identification of protective genes may have the earliest application in the form of more individualized pharmacological treatment, for example, identifying individuals with resistance to drug-induced weight gain. To do so, it is not necessary to identify genes involved in etiology, only those genes that directly influence drug effectiveness or side effects. Research in other areas has already made it possible to tailor medication to individual genotype, particularly for cancers. Response to tamoxifen treatment for breast cancer, for example, appears to be ineffective in 5–8% of women with a variant of the CYP2D6 gene [58]. With regard to obesity, several genes have been identified that may influence drug-induced weight gain, for example, due to olanzapine, including PMCH, 5HT2A, ADRA2A, and PKHD1 [59]. In addition, SLC6A2 and GRIN1 have been associated with weight loss in response to norepinephrine/dopamine transporter inhibitors [60]. Further research will be needed before genomic screening is practical on a large scale, but applications may be generally available in the not too distant future.

What Lies Ahead

Genomic approaches may well detect other previously unknown genes that are common and exert their influence though unanticipated pathways. Whole-genome sequencing will permit the identification of new variants, particularly CNVs that are individually rare but have larger effects than common SNP alleles on obesity phenotypes. Environmental influences can be better understood by the identification of interactions with specific, measured genotypes. New genes will provide additional targets for pharmacological intervention. Genotypes at these loci may be used in therapeutic interventions through knowledge of their influence on drug effectiveness or side effects.

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