Johnson, *Int. J. Obes.* **22**, 39 (1998).
3. J. P. Foreyt and G. K. Goodrick, *Lancet* **346**, 134 (1995).
4. R. P. Troiano and K. M. Flegal, *Pediatrics* **101**, 497 (1998).
5. F. X. Pi-Sunyer. *Ann. Intern. Med.* **119**, 655 (1993).
6. J. O. Hill, M. J. Pagliassotti, J. C. Peters, *Genetic Determinants of Obesity*, C. Bouchard, Ed. (CRC Press, Boca Raton, FL, 1994), pp. 35–48.
7. J. P. Flatt, *Diab. Rev.* **4**, 433 (1996).
8. T. J. Horton *et al.*, *Am. J. Clin. Nutr.* **62**, 19 (1995); M. E. J. Lean and W. P. T. James, *Int. J. Obes.* **12**, 15 (1988).
9. S. Chang *et al.*, *Am. J. Physiol.* **259**, R1096 (1990); A. Sclafani, *Ann. N.Y. Acad. Sci.* **575**, 281 (1989).
10. D. M. Salmon and J. P. Flatt, *Int. J. Obes.* **9**, 443 (1985).
11. L. Lissner, D. A. Levitsky, B. J. Strupp, H. J. Kalkwarf, D. A. Roe, *Am. J. Clin. Nutr.* **46**, 886 (1987); B. J. Rolls and V. A Hammer, *ibid.* **62**, 1086S (1995); R. J. Stubbs, P. Ritz, W. A. Coward, A. M. Prentice, *ibid.*, p. 330; B. J. Rolls and D. J. Shide, *Nutr. Rev.* **50**, 283 (1992).
12. M. S. Westerterp-Plantenga *et al.*, *Int. J. Obes.* **22**, 14 (1998).
13. R. J. Stubbs, C. G. Harbron, P. R. Murgatroyd, A. M. Prentice, *Am. J. Clin. Nutr.* **62**, 316 (1995).
14. E. A. Bell *et al.*, *ibid.* **67**, 412 (1998).
15. W. C. Willett, *ibid.*, p. 556S.
16. N. D. Ernst *et al.*, *J. Am. Diet. Assoc.* **97**, S47 (1997); A. Astrup, S. Toubro, A. Ruben, A. R. Skov, *ibid.*, p. S82.
17. U.S. Department of Health and Human Services, *Physical Activity and Health: A Report of the Surgeon General* (U.S. Department of Health and Human Services, Atlanta, GA, 1996).
18. R. J. Stubbs, *Nutr. Bull.* **19**, 53 (1994).
19. L. L. Birch, S. L. Johnson, G. Andersen, J. C. Peters, M. C. Schulte, *N. Engl. J. Med.* **324**, 232 (1991).
20. M. L. Klem, R. R. Wing, M. T. McGuire, H. M. Seagle, J. O. Hill, *Am. J. Clin. Nutr.* **66**, 239 (1997).
21. We thank A. Kriketos for help in preparing this manuscript. Supported by NIH grants DK42549, DK38088, and DK48520. Because of space limitations, it was not possible to include a comprehensive list of references for all of the work discussed. References (*1*) and (*6*) provide a more comprehensive reference list. The Procter and Gamble Company markets both regular and low-fat food products.

The Search for Human Obesity Genes

Anthony G. Comuzzie and David B. Allison

Understanding of the genetic influences on obesity has increased at a tremendous rate in recent years. By some estimates, 40 to 70 percent of the variation in obesity-related phenotypes in humans is heritable. Although several single-gene mutations have been shown to cause obesity in animal models, the situation in humans is considerably more complex. The most common forms of human obesity arise from the interactions of multiple genes, environmental factors, and behavior, and this complex etiology makes the search for obesity genes especially challenging. This article discusses the strategies currently being used to search for human obesity genes and recent promising results from these efforts.

One of the greatest challenges in biomedical research today is the elucidation of the underlying genetic architecture of complex phenotypes such as obesity. At first glance, body weight seems exceptionally simple. It can be defined precisely and measured with great accuracy and reliability. However, recent research on obesity has revealed that body weight is in fact a truly complex phenotype. As an amalgamation of literally everything we are physically, body weight is influenced by any factor that influences the weight of any individual tissue, organ, or fluid. Indeed, obesity may represent the archetype of the so-called "complex phenotypes." In contrast to simple Mendelian disorders, in which there is generally a one-to-one relationship between genotype at a single locus and the presence or absence of the disorder, obesity arises as a result of numerous behavioral, environmental, and genetic factors. The role of behavior and environment in the development of obesity is described elsewhere in this issue (*1*). Here, we discuss our current understanding of the genetics of human obesity, with an emphasis on some of the special challenges this complex condition poses to would-be gene finders.

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Genetic Approaches to Human Obesity

Although there is longstanding evidence that genetics plays an important role in the body weight of livestock and laboratory rodents, an appreciation of the genetic contribution to human obesity is a relatively recent development. Twin, adoption, and family studies have now established that an individual's risk of obesity is increased when he or she has relatives who are obese (*2*). Other studies have shown consistently that ~40 to 70% of the variation in obesity-related phenotypes, such as body mass index (BMI), sum of skinfold thickness, fat mass, and leptin levels, is heritable (*3*). Finally, numerous segregation analyses (studies evaluating the evidence and mode of transmission for a major gene based on observed patterns of phenotypic inheritance among related individuals) have provided evidence that among the genes that influence these obesity-related phenotypes, at least a few exert relatively large effects. In fact, anonymous major genes accounting for as much as 40% of the variation in BMI (*4*) and ~40% of the variation in fat mass (*5*) have been reported, along with major genes influencing specific measures of adipose tissue distribution (*6*). Importantly, some of these genes appear to exert their effects across various ethnic populations. While there will undoubtedly be rare obesity-predisposing alleles whose phenotypic effect is restricted to isolated populations or even families, the possible existence of at least a few common alleles with measurable effects on obesity has particularly important public health implications. It is these genes that may reveal new avenues for treatment and allow identification of at-risk individuals for the largest portion of the population.

Emphasis has shifted from the question of whether human obesity has a genetic component to which specific genes are responsible. Studies of animal models (*7*) have identified several genes with measurable effects on body weight and composition, supporting the concept that such genes exist. A key point of debate in the search for these genes is the optimal sampling strategy, both in terms of the unit of study (for example, sibling pairs versus extended families) and in the mode of ascertainment (for example, affected individuals versus randomly selected probands). Four sampling procedures are being used:

(i) Random or haphazard sampling, in which individuals are selected without regard to their phenotype or family structure. This method has the advantages of representativeness and convenience but offers low statistical power.

(ii) Sampling of large sibships or pedigrees. This method also allows analysis of individuals who are phenotypically representative of the population but offers higher statistical power than random sampling. Al-

though the most common unit of study has been that of sibling pairs, in large part due to the relative simplicity involved in collection and analysis, there is evidence that larger sibships and pedigrees can offer substantial power advantages (*8*). Thus, in recent studies, more elaborate family structures are being used as the sampling unit (*9*, *10*).

(iii) Sampling of phenotypically extreme (very obese or very thin) individuals. This method increases statistical power and has been widely advocated (*11*), but it remains controversial (*12*). Loci best identified by this sampling method are predicted to have obesity-predisposing alleles that are rare, recessive in action, and capable of conferring massive obesity or extreme thinness in an individual (*13*), but may still have a rather modest effect at the population level.

(iv) Sampling of special populations that are geographically or culturally isolated and descended from a relatively small founder population. This method is advantageous because such populations are thought to exhibit greater homogeneity and linkage disequilibrium, both of which can increase statistical power. Populations currently under study for these reasons include Pima Indians, Old Order Amish, Mennonites, and inhabitants of the Island of Kosrae, all of whom have high rates of obesity. Other populations being evaluated largely because of availability, the desire to study multiple ethnic groups, and, in some cases, high rates of obesity, include African Americans, Mexican Americans, European Americans, French Canadians, rural Chinese, and several European populations.

A second key point of debate among obesity geneticists is the optimal obesity phenotype for genetic research. Some investigators favor the use of BMI, which can be measured reliably and inexpensively and is convenient for large sample numbers. Others favor the use of intermediary phenotypes such as resting metabolic rate, respiratory quotient, or insulin sensitivity because they are less likely than BMI to be influenced by extrinsic factors unrelated to obesity and may therefore provide more statistical power. In many cases, an intermediary position, in which one measures multiple phenotypes that characterize obesity—such as weight, total fat mass, and visceral adipose tissue area—may be preferable. Like BMI, these phenotypes can be measured reliably and in some cases (such as bio-impedance analysis of total fat mass) inexpensively, thereby allowing evaluation of large sample numbers.

Candidate Gene Approach. Until recently, the analysis of candidate genes (known genes identified a priori on the basis of their effects in animal models or suspected physiological involvement in a particular disorder) was the primary strategy used in the search for potential obesity genes. There are now scores of such candidate genes described in the literature [reviewed in (*14*)], some with an obvious link to the obesity phenotype (see Table 1 for a selected list) and others whose postulated mechanism of action in obesity is more speculative. Many candidate genes have been identified as a result of the agricultural community's intense interest in breeding livestock (pigs, cows, sheep) that grow large but lean on the smallest amount of feed possible (*7*). The growing number of rodent obesity models has also provided many new candidate genes.

Traditionally, statistical support for linkage has been presented in the form of a LOD score (logarithm of the likelihood ratio for linkage). A LOD score of 3, taken as strong evidence of linkage and corresponding to a P value of 0.0001, is a condition in which the hypothesis of linkage is 1000 times more likely than the alternative of no linkage. To date, most linkage studies of candidate genes for human obesity have failed to reach this level of significance, although a few studies offer suggestive evidence of linkage (LOD score >2) (*14*). The low LOD scores in these studies could reflect the fact that some of the candidate genes initially identified in animal models of obesity may play a less important role in human obesity. Alternatively, they may simply reflect the small sample size, and therefore the low statistical power, of many human studies.

Despite these problems, the candidate gene approach has yielded intriguing insights into the genetics of human obesity. A study of Mexican Americans revealed a significant multipoint linkage (LOD score = 3.1) for sum of extremity skinfolds and *D7S514*, an anonymous marker near the leptin gene (*LEP*) on chromosome 7q31.3. This marker accounts for ~55% of the variation in this trait (*15*). In an analysis of French Canadian families, four phenotypes were examined using three markers spanning a 5-centiMorgan (cM) region around the gene for uncoupling protein 2 (*UCP2*) on chromosome 11 (*9*). The uncoupling proteins have been implicated in obesity because they appear to increase thermogenesis and energy expenditure (*9*, *16*). Based on a two-point linkage analysis, the authors reported a P value of 0.000002 (this represents a LOD score equivalent of 4.6) between one of these markers (*D11S911*) and resting energy expenditure.

Thus far, a total of nine humans have been reported to carry mutations in homologs of three rodent obesity genes, *LEP* (encoding leptin), *LEPR* (encoding the leptin receptor), and *FAT* (encoding car-

Table 1. Selected list of candidate genes for human obesity and body composition, identified on the basis of animal models, physiology, and prior human research.*

Gene	Phenotype	Chromosomal location		References†
		Mouse	Human	
ASIP	obesity	2-88.8	20q11.2-q12	Michaud *et al.*, 1997
CPE	obesity	8-32	4q28	Prochazka *et al.*, 1991 (mouse); Hall *et al.*, 1993 (human)
LEP	obesity	6-10.5	7-q32	Geffroy *et al.*, 1995
LEPR	obesity	4-46.7	1-p31	Tartaglia *et al.*, 1995
TUB	obesity	7-51.45	11p15.4-p15.5	Klyen *et al.*, 1996
UCP1	energy balance	8-37	4q31	Cassard *et al.*, 1990
UCP2	energy balance	7-50	11q13	Fleury *et al.*, 1997
UCP3	energy balance	7-50	11q13	Solanes *et al.*, 1997
MC3R	feeding behavior	2-100	20q13	Magenis *et al.*, 1994
MC4R	feeding behavior	1 or 18 (predicted)	18q21.3-q22	Huszar *et al.*, 1997
POMC	obesity (leptin levels?)	12-4	2p23.2	Boston *et al.*, 1997; Mountjoy and Wong, 1997
NPYR5	appetite regulation	8-33	4q31-q32	Nakamura *et al.*, 1997
MSTN	skeletal muscle growth	1 or 2 (predicted)	2q32.1	McPherron and Lee, 1997
CCKAR	satiety	5-34.0	4p15.1	Huppi *et al.*, 1995
TNFA	obesity	17-19.1	6p21.3	Norman *et al.*, 1995
PPAR-γ	adipocyte differentiation	6-53.0	3p25	Chawla *et al.*, 1994
ADRB3	adipocyte differentiation	8-10	8p11.1-p12	Mitchell *et al.*, 1998

*This list is not intended to be comprehensive. †Detailed reference information is in (*29*). Abbreviations: ASIP, agouti signaling protein; CPE, carboxypeptidase E; LEP, leptin; LEPR, leptin receptor; TUB, tubby; UCP, uncoupling protein; MCR, melanocortin receptor; POMC, pro-opiomelanocortin; NPYR, neuropeptide Y receptor; MSTN, myostatin (also called growth differentiation factor 8); CCKAR, cholecystokinin A receptor; TNFA, tumor necrosis factor α; PPAR-γ, peroxisome proliferator activated receptor-γ; ADRB3, beta-3-adrenergic receptor.

boxypeptidase E) (*17*). Although such mutations are rare (given the thousands of individuals screened, the frequency of individuals homozygous for such mutations is likely to be $\ll 10^{-3}$), suggesting that they are not responsible for the most common forms of obesity in the population, these results confirm that these gene products play a role in human obesity and may allow further elucidation of their signal transduction pathways. Finally, several groups have searched for linkage between obesity-related phenotypes and the chromosomal region encompassing *LEP*; a recent meta-analysis suggests that there may be linkage with BMI (*18*).

Genome Scanning Approach. In a genome scan, linkage analysis is conducted using a series of anonymous polymorphisms, spaced at relatively constant intervals over the entire genome [for example, ~350 to 370 markers with an average spacing of 10 cM] to identify quantitative trait loci (QTLs) affecting the phenotype under study. In contrast to the traditional candidate gene approach, with genome scanning there are no a priori assumptions about the potential importance of specific genes or chromosomal regions. Instead, the results of the scan are used to identify candidate chromosomal regions, or in some cases positional candidate genes, which then become the focus of more intensive follow-up analyses. A positional candidate gene differs from a traditional candidate gene in that it is only considered a candidate after the establishment of its proximity to a QTL identified in the genome scan. Thus, this approach offers the potential of identifying genes previously unsuspected of having an influence on the phenotype of interest. Genome scans are complicated by the fact that instead of a single test for linkage, one must conduct multiple tests across the entire genome. In light of this, it has been proposed that a LOD score ≥ 3.3 can be taken as strong evidence of linkage and a LOD score ≥ 1.9 but < 3.3 as evidence suggestive of linkage (*19*).

To date, the results of two genome scans for obesity-related phenotypes have been reported, one in Mexican Americans (*10*), and the other in Pima Indians (*20*). In the latter study, a genome scan for percent body fat (%BF) was conducted using an ~10 cM map for 283 sibling pairs from 88 nuclear families. In two-point linkage analysis, two genomic regions were detected that showed suggestive evidence of linkage (LOD score = 2.0) to %BF, one at chromosome 3p24.2-p22 and the other at chromosome 11q21-q22 (*20*). In a subsequent multipoint analysis the chromosome 11 LOD score was increased to 2.8, and it may improve as the size and complexity of the sample increases. Thus far, no obvious candidate genes have been mapped to either chromosomal region.

In the second study, 10 families of Mexican Americans (representing 459 individuals and comprising 5667 relative pairs ranging from parent-offspring to double second cousins) were evaluated for several obesity-related phenotypes in a 20-cM genomic scan (*10*). Significant linkages were detected for QTLs on chromosome 2 (~74 cM from the tip of the short arm) and chromosome 8 (~65 cM from the tip of the short arm) and leptin levels (LOD scores = 4.3 and 2.2, respectively). A significant linkage was also detected between fat mass (FM) and the chromosome 2 QTL (LOD score = 1.9). Multipoint analysis of the leptin linkages increased the LOD score to 4.95 for the QTL on chromosome 2 and 2.2 for the chromosome 8 QTL. Multipoint analysis of the FM linkage on chromosome 2 increased this LOD score to 2.75. These analyses were conducted using a variance component approach, which not only allows gene localization but also provides an estimate of the magnitude of the gene's effect on the phenotype (*21*). In the case of the chromosome 2 linkages, the QTL was estimated to account for 47% of the variation in serum leptin levels and 32% of the variation in FM.

The areas of linkage on chromosomes 2 and 8 each contain strong positional candidate genes for obesity. For example,

Table 2. Evidence for the presence of linkage with human obesity phenotypes.*

Gene or marker	Chromosomal location	N pairs	Phenotype	Inferential statistics	References†
D1S202	1q31-32	large pedigree	BMI	$P = 4.7 \times 10^{-5}$	Murray *et al.* (1994)
ACP1	2p25	>300	BMI	$P = .004$	Bailey-Wilson *et al.* (1993)
GRL	5q31-q32	88	BMI > 27	$P = .009$	Clement *et al.* (1996)
BF	6p21.3	>168	skinfolds	$.01 < P < 0.03$	Wilson *et al.* (1991)
TNFA, Tnfir24, D6S273, 291	6p21.2	>255	% body fat	$.002 < P < .048$	Norman *et al.* (1995)
GLO1	6p21.2	>168	skinfolds, relative weight	$.004 < P < 0.05$	Wilson *et al.* (1991)
SUR (D11S419)	11p15.1	67	BMI > 27	$P = .0032$	Hani *et al.* (1997)
D1S200	1p32-p22	137 sibships	BMI	$P = .009$	Chagnon *et al.* (1997)
ADA to *MC3R*	20p12 to 20q13.3	258	% body fat; BMI, fasting insulin	$.008 > P > .0005$	Lembertas *et al.* (1997)
D2S1788	2p21	pedigrees	serum leptin	LOD = 4.95; $P \sim 1.8 \times 10^{6}$	Comuzzie *et al.* (1997)
LEP region	chromosome 7	>1000	BMI	$P < 2 \times 10^{-5}$	Allison and Heo (1998) (meta-analysis of 5 studies)
KEL	7q33	402	BMI, skinfolds	$P < .0001$	Borecki *et al.* (1994)
ESD	13q14.1-q14.2	194	% body fat, skinfolds	$P < 0.04$	Borecki *et al.* (1994)
ADA	20q12-q13.11	428	BMI, skinfolds	$.02 < P < .001$	Borecki *et al.* (1994)
P1	22q11.2-qter	>168	relative weight	$P = .03$	Wilson *et al.* (1991)
D3S2432	3p24.2-p22	874	% body fat	LOD = 2.0	Norman *et al.* (1997)
D11S2000, 2366	11q21-q22	874	% body fat	LOD = 3.1	Norman *et al.* (1997)
MC5R	18p11.2	242-289	BMI, Σ 6 skinfolds, fat mass, % body fat	$0.001 < P < 0.02$	Chagnon *et al.* (1997)
ADA, MC3R, D20S17,120	20q12-q13	258	BMI, Σ 6 skinfolds, fat mass, % body fat	$0.004 < P < 0.02$	Lembertas *et al.* (1997)

*Adapted from a table compiled by Y. C. Chagnon, L. Pérusse, and C. Bouchard. Reprinted with permission from *Obes. Res.* **6**, 76 (1998). †Detailed reference information is in (*29*). Most results were obtained with the single point sib-pair method. Abbreviations: ACP1, acid phosphatase; SUR, sulfonylurea receptor; MCR, melanocortin receptor; GRL, glucocorticoid receptor; BF, properdin factor B; TNFir24, dinucleotide repeat marker locus near the tumor necrosis factor α gene; GLO1, glyoxylase I; LEP, leptin; KEL, Kell blood group; ESD, esterase D; ADA, adenosine deaminase; P1, P blood group; BMI, body mass index.

the chromosome 2 region encompasses *POMC*, which codes for the prohormone pro-opiomelanocortin. This hormone is the precursor of several hormones in the hypothalamic-pituitary axis (among them, melanocyte-stimulating hormones and adrenocorticotropic hormone) that have long been suspected of playing a role in obesity (*22*). *POMC* was originally identified as a candidate gene on the basis of its location (*10*), and its gene product has recently been implicated in appetite regulation (*23*). A search is now being conducted for polymorphisms in *POMC* that might be associated with variation in leptin levels or other obesity-related phenotypes. The region of linkage on chromosome 8 encompasses *ADRB3*, the gene for the β-3-adrenergic receptor, which was previously identified as a candidate because of its role in the regulation of energy expenditure. Although the cumulative evidence of linkage between the well-known tryptophan to arginine mutation (Trp64Arg) in *ADRB3* and BMI is weak (*24*), the argument that *ADRB3* is a human obesity gene has been strengthened by follow-up analyses of Mexican Americans (*25*); these analyses have revealed an association between *ADRB3* variants and BMI, FM, and waist circumference after first conditioning on the stronger QTL signal on chromosome 2. Table 2 presents a selected list of genes and markers that have been linked to obesity phenotypes [for more information, see (*14*)].

Future Prospects

Research into the genetics of human obesity is continuing at a rapid pace (*26*), with the goal now increasingly focused on the identification of specific causative genes. There are at least three genome scanning efforts underway that have obesity phenotypes as a primary focus (the San Antonio Family Heart Study, the San Antonio Family Diabetes Study, and the Pima Indian Study) and at least three others that should be operational shortly (the MRC-Obesity Genes Project, a study of French Canadians, and a study of nonhuman primates). Other ongoing genome scans, in which obesity phenotypes are involved but not the primary focus (for example, the Strong Heart Study and the Amish Family Diabetes Study), should also aid in the discovery of human obesity genes.

Although early results from the genome scan in Mexican Americans suggests the existence of a few genes with substantial effects on obesity, the large number of genetic loci likely to be involved means that many of these genes on their own may account for only a small portion of the total phenotypic variance. The power to map genes that exert a truly small effect will likely remain unacceptably low given the sample sizes that any single investigator can realistically collect (*27*). One solution is to pool data across many laboratories and investigators. The simplest way to do this is through meta-analysis (*24*), although such pooling of summary statistics has several well-recognized limitations (*28*). Pooling of raw data from multiple studies may be a stronger approach because it should increase statistical power. This strategy is now being applied in genetic studies of other complex disorders such as type-II diabetes and autism. Thus, our ability to fully understand the genetic contribution to obesity may ultimately depend on the extent to which we can overcome the practical and social barriers to collaborative gene finding efforts in an intensely competitive arena.

REFERENCES AND NOTES

1. J. O. Hill and J. C. Peters, *Science* **280**, 1371 (1998).
2. C. B. Davenport, *Body-build and Its Inheritance* (Carnegie Institution of Washington, Washington, DC, 1923); A. J. Stunkard *et al.*, *N. Engl. J. Med.* **314**, 193 (1986); H. H. M. Maes, M. C. Neale, L. J. Eaves, *Behav. Genet.* **27**, 325 (1997); J. M. Meyer and A. J. Stunkard, in *Obesity: Theory and Therapy*, A. J. Stunkard and T. A. Wadden, Eds. (Raven Press, New York, 1993); J. M. Meyer, in *Behavior Genetic Approaches in Behavioral Medicine*, J. R. Turner, L. R. Cardon, J. K. Hewitt, Eds. (Plenum Press, New York, 1995).
3. D. B. Allison *et al.*, *Int. J. Obes.* **20**, 501 (1996); A. G. Comuzzie *et al.*, *Am. J. Hum. Biol.* **5**, 725 (1993); A. G. Comuzzie *et al.*, *Int. J. Obes.* **18**, 413 (1994); A. G. Comuzzie *et al.*, *J. Clin. Endocrinol. Metab.* **81**, 597 (1996).
4. P. Moll, T. Burns, R. Lauer, *Am. J. Hum. Genet.* **49**, 1243 (1991); R. Ness, P. Laskarzewski, R. A. Price, *Hum. Biol.* **63**, 39 (1991); R. A. Price, R. Ness, P. Laskarzewski, *ibid.* **62**, 747 (1990); R. A. Price, *Int. J. Obes.* **20**, 1044 (1996).
5. A. G. Comuzzie *et al.*, *Genet. Epidemiol.* **12**, 475 (1995); T. Rice, I. B. Borecki, C. Bouchard, D. C. Rao, *Am. J. Hum. Genet.* **52**, 967 (1993).
6. I. B. Borecki, T. Rice, L. Pérusse, C. Bouchard, D. C. Rao, *Obes. Res.* **3**, 1 (1995); S. J. Hasstedt, M. E. Ramirez, H. Kuida, R. R. Williams, *Am. J. Hum. Genet.* **45**, 917 (1989).
7. L. Grobet *et al.*, *Nature Genet.* **17**, 71 (1997); Zhang, D. L. Kuhlers, W. E. Rempel, *J. Anim. Sci.* **70**, 1307 (1992); D. Pomp, *Behav. Genet.* **27**, 285 (1997).
8. J. T. Williams, R. Duggirala, J. Blangero, *Genet. Epidemiol.* **14**, 1065 (1997).
9. C. Bouchard, L. Pérusse, Y. C. Chagnon, C. Warden, D. Ricquier, *Hum. Mol. Genet.* **6**, 1887 (1997).
10. A. G. Comuzzie *et al.*, *Nature Genet.* **15**, 273 (1997).
11. L. Eaves and J. Meyer, *Behav. Genet.* **24**, 443 (1994); N. Risch and H. Zhang, *Science* **268**, 1584 (1995); *Am. J. Hum. Genet.* **58**, 836 (1996).
12. D. B. Allison, M. Heo, N. J. Schork, S. L. Wong, R. C. Elston, *Hum. Hered.* **48**, 97 (1998).
13. R. A. Price, in *Regulation of Body Weight: Biological and Behavioral Mechanisms*, C. Bouchard and G. A. Bray, Eds. (Wiley, Chichester, UK, 1996).
14. C. Bouchard and L. Pérusse, *Obes. Res.* **4**, 81 (1996); C. Bouchard, *J. Nutr.* **127**, 1887S (1997); Y. C. Chagnon, L. Pérusse, C. Bouchard, *Obes. Res.* **6**, 76 (1998).
15. R. Duggirala *et al.*, *Am. J. Hum. Genet.* **59**, 694 (1996).
16. C. Fleury *et al.*, *Nature Genet.* **15**, 269 (1997).
17. R. S. Jackson *et al.*, *ibid.* **16**, 303 (1997); C. T. Montague *et al.*, *Nature* **387**, 903 (1997); A. Strobel, T. Issad, L. Camoin, M. Ozata, A. D. Strosberg, *Nature Genet.* **18**, 213 (1998).
18. D. B. Allison and M. Heo, *Genetics* **148**, 859 (1998).
19. E. Lander and L. Kruglyak, *Nature Genet.* **11**, 241 (1995).
20. R. A. Norman *et al.*, *Am. J. Hum. Genet.* **60**, 166 (1997).
21. L. Almasy and J. Blangero, *ibid.* **62**, 1198 (1998).
22. G. A. Bray and D. A. York, *Physiol. Rev.* **59**, 719 (1979); P. De Vos, R. Saladin, J. Auwerx, B. Staels, *J. Biol. Chem.* **270**, 15958 (1995); W. Fan, B. A. Boston, R. A. Kesterson, V. J. Hruby, R. D. Cone, *Nature* **385**, 165 (1997); D. Huszar *et al.*, *Cell* **88**, 131 (1997); R. J. Miltenberger, R. L. Mynatt, J. E. Wilkinson, R. P. Woychik, *J. Nutr.* **127**, 1902S (1997); E. J. Michaud *et al.*, *J. Endocrinol.* **155**, 207 (1997).
23. B. A. Boston, K. M. Blaydon, J. Varnerin, R. D. Cone, *Science* **278**, 1641 (1997); R. J. Seeley *et al.*, *Horm. Metab. Res.* **28**, 664 (1996); R. J. Seeley *et al.*, *Nature* **390**, 349 (1997); M. W. Schwartz *et al.*, *Diabetes* **46**, 2119 (1997).
24. D. B. Allison, M. Heo, M. S. Faith, A. Pietrobelli, *Int. J. Obes.*, in press.
25. B. D. Mitchell *et al.*, *J. Clin. Invest.* **101**, 584 (1998).
26. D. B. Allison and M. S. Faith, *Behav. Genet.* **27**, 273 (1997).
27. D. B. Allison and N. J. Schork, *ibid.*, p. 401.
28. K. K. Steinberg *et al.*, *Am. J. Epidemiol.* **145**, 917 (1997).
29. J. D. Murray, D. E. Bulman, G. C. Ebers, G. M. Lathrop, G. P. A. Rice, *Am. J. Hum. Genet.* **55**, A197 (1994); J. E. Bailey-Wilson, A. F. Wilson, V. Bamba, *Genet. Epidemiol.* **10**, 665 (1993); K. Clément *et al.*, *Int. J. Obes.* **20**, 507 (1996); A. F. Wilson, R. C. Elston, L. D. Tran, R. M. Siervogel, *Am. J. Hum. Genet.* **48**, 862 (1991); M. Prochazka, H. Mochizuki, L. J. Baier, P. T. Cohen, C. Bogardus, *Diabetologia* **38**, 461 (1995); R. A. Norman, C. Bogardus, E. Ravussin, *J. Clin. Invest.* **96**, 158 (1995); E. H. Hani *et al.*, *Diabetes* **46**, 688 (1997); Y. C. Chagnon *et al.*, *Obes. Res.* **5**, 115 (1997); L. Pérusse, C. Bouchard, F. T. Dionne, Y. C. Chagnon, *ibid.*, p. 49; A. G. Comuzzie *et al.*, *Nature Genet.* **15**, 273 (1997); D. B. Allison and M. Heo, *Genetics* **148**, 859 (1998); M. Prochazka *et al.*, *Mouse Genome* **89**, 280 (1991); I. B. Borecki, T. Rice, L. Pérusse, C. Bouchard, D. C. Rao, *Obes. Res.* **2**, 213 (1994); C. Hall, E. Manser, N. K. Spurr, L. Lim, *Genomics* **15**, 461 (1993); S. Geffroy *et al.*, *ibid.* **28**, 603 (1995); L. A. Tartaglia *et al.*, *Cell* **83**, 1263 (1995); A. M. Cassard *et al.*, *J. Cell. Biochem.* **43**, 255 (1990); R. E. Magenis, L. Smith, J. H. Nadeau, *Mamm. Genome* **5**, 503 (1994); G. Solanes, A. Vidal-Puig, D. Grujic, J. S. Flier, B. B. Lowell, *J. Biol. Chem.* **272**, 25433 (1997); D. Huszar *et al.*, *Cell* **88**, 131 (1997); B. A. Boston, K. M. Blaydon, J. Varnerin, R. D. Cone, *Science* **278**, 1641 (1997); B. D. Mitchell *et al.*, *J. Clin. Invest.* **101**, 584 (1998); K. G. Mountjoy and J. Wong, *Mol. Cell. Endocrinol.* **128**, 171 (1997); A. Chawla, E. J. Schwarz, D. D. Dimaculangan, M. A. Lazar, *Endocrinology* **135**, 798 (1994); M. Nakamura, M. Yokoyama, H. Watanabe, T. Matsumoto, *Biochim. Biophys. Acta* **1328**, 83 (1997); P. W. Kleyn, W. Fan, S. G. Kovats, J. J. Lee, *Cell* **85**, 281 (1996); C. Fleury *et al.*, *Nature Genet.* **15**, 269 (1997); A. C. McPherron and S. J. Lee, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 12457 (1997); K. Huppi, D. Siwarski, J. R. Pisegna, S. Wank, *Genomics* **25**, 727 (1995); E. J. Michaud *et al.*, *J. Endocrinol.* **155**, 207 (1997); R. A. Norman *et al.*, *Am. J. Hum. Genet.* **60**, 166 (1997); Y. C. Chagnon *et al.*, *Mol. Med.* **3**, 663 (1997); A. V. Lembertas *et al.*, *J. Clin. Invest.* **100**, 1240 (1997).

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