Human Obesity: A Heritable Neurobehavioral Disorder That Is Highly Sensitive to Environmental Conditions

Stephen O'Rahilly and I. Sadaf Farooqi

The recent increase in the worldwide prevalence of obesity has understandably focused attention on the environmental determinants of this epidemic. Whereas identifying the relative contributions of the factors underlying this recent trend is critical, a comprehensive understanding of the causes of obesity will need to explain why, even in high-risk populations, many people remain lean. Contemporary studies indicate that the heritability of adiposity remains high, even in the face of a strongly obesogenic environment. Whereas the role of inheritance has long been appreciated, only recently have we begun to develop a genuine understanding of the critical role of specific molecules in sensing the state of nutrient storage and regulating food intake and energy expenditure. Notably, a number of single gene disorders resulting in human obesity have been uncovered and, strikingly, all of these defects impair the central control of food intake. Early indications are that common genetic variants influencing adiposity on a population level affect the same processes. While the rising prevalence of obesity is related to increasing ease of access to high-energy palatable food combined with diminishing requirement for physical activity, differences in inter-individual susceptibility to obesity are likely to be related to inherited variation in the efficiency of central control mechanisms influencing eating behavior. Such a construct understandably courts unpopularity, since it can appear to diminish the importance of human free will and is perceived by some as representing a counsel of despair and an "excuse" for otherwise controllable behavior. We argue that a view of obesity that emphasizes the profound biological basis for inter-individual differences in responding to the challenges of achieving a healthy control of nutrient intake should result in a more enlightened attitude toward people with obesity with a consequent reduction in their experience of social and economic discrimination. In the longer term, this may also lead to more efficacious individually targeted approaches to the treatment and prevention of obesity.

The obesity epidemic. Obesity is a major risk factor for premature mortality from cardiovascular and metabolic diseases and certain cancers and for greatly increased morbidity from osteoarticular, gastrointestinal, reproductive, and other disorders (1). It carries an enormous burden of health care costs (2). Therefore, evidence that its prevalence has been increasing and continues to increase in most developed and developing countries (3,4) is a cause for major concern.

Whereas much of the epidemiological data suggest that even moderate degrees of overweight are associated with adverse effects on morbidity and mortality at the population level, there is some controversy about the overall impacts on mortality of moderate weight gain (5). More severe degrees of obesity bring a considerable burden of ill health and social and economic discrimination (6) and have adverse impacts on well-being and psychological and social functioning (7). It is worth noting that the relative importance of particular etiological factors for obesity is likely to be different when considering mild overweight versus morbid obesity and that interventions that may make a clinically significant impact on the overweight may have negligible beneficial effects in a morbidly obese person. Given what we already know about the etiological heterogeneity of obesity, it is important to emphasize that different forms of intervention may be needed for people with different subtypes of this condition.

The contributions of the various environmental factors that are driving increasing obesity rates are hard to quantitate precisely and are likely to differ in degree between populations. They are certainly likely to include factors that make the purchase and consumption of energy-dense food easier and the expenditure of physical activity as part of daily life more difficult. However, it is undoubtedly true that, except for some population isolates, even in geographical areas where obesity rates are highest, a substantial proportion of the population has remained lean (5). In our opinion, there are really only two basic explanations (and they are not necessarily mutually exclusive) for how these people have avoided the "toxic" effects of environment. The one that intuitively appeals to the mass media (and to many lean people) is that this group is largely made up of individuals who have made conscious choices about diet and exercise and have actively fought off the "toxic environment." An alternative explanation, much less frequently cited in public debate, is that this group of subjects are somehow biologically different and achieve their leanness largely through unconscious mechanisms. In this review, we would like to explore this hypothesis in more detail. We will argue that the heritable (and therefore biological) influences on human adiposity are strong and remain so in the midst of the epidemic. We will also argue that while some of that hereditary influence is likely to affect processes such as energy expenditure and nutrient partitioning, what we have discovered thus far about the genes influencing human obesity strongly suggests that heritable differences in neurobehavioral traits influencing habitual eating behavior such as hunger,

satiety, and the hedonic effects of food are likely to be more important.

Hereditary influences on adiposity are profound and continuing. The heritability of human traits such as adiposity is most robustly assessed by studies of monozygotic versus dizygotic twins (8–10). In the case of traits such as BMI, which are readily assessed in large numbers, we have access to the extraordinarily powerful data that can come from the study of adult pairs of identical twins that have been adopted as infants and raised separately by different biologically unrelated families (11,12). There are numerous classical twin studies in obesity, and the average heritability (i.e., proportion of inter-individual difference in a trait explicable by genetic variability) reported consistently in these studies on the order of 40–75% (8,11,12). The classical "adopted-separated twin" study of Stunkard et al. (12) showed no significant correlation between adult BMI of a twin with the members of a family into which they had been adopted, while the correlation coefficient of BMI of one twin with their co-twin (who, in most cases, they had not seen since the first months of life) was 0.7. These remarkable data have never been seriously challenged, and their implications are profound.

Critics of the use of such twin-based methodologies to quantitate the influence of heredity on various traits point to the importance of the prenatal environment and the likely differences in placentation and intrauterine nutrition between twins and singletons, on the one hand, and between monozygotic and dizygotic twins on the other. This has led some to dismiss the utility of such measures of heritability altogether (13). While accepting the likely importance of "prenatal programming" (14), it seems to us that this view is oversimplistic and risks throwing the baby out with the bathwater. In general, where twin and family studies have demonstrated high heritability of a readily measurable trait (e.g., height), appropriately powerful molecular genetic studies are now revealing the identity of these genetic variants and providing conclusive proof that these genetic effects are not "mythical" (15). In the case of adult BMI, in fact, there is little evidence that birth weight (a widely accepted, if crude, measure of intra-uterine nutrition) has any consistently significant association. In brief, if twin (and particularly adopted-separated twin) studies show consistent and strong evidence for a high heritability, then it is very likely that inherited variation in genomic DNA sequence will have a major influence on a trait. There is little serious doubt that the single most powerful determinant of inter-individual differences in adiposity is heredity (16).

It is true that many of the classical twin studies of obesity occurred before the recent obesity epidemic. Might it be the case that the importance of hereditary factors has diminished in recent years as the environmental effects have become more pronounced? Notably, Wardle et al. (17) have recently reported a study of 5,092 8- to 11-year-old twins living in London, U.K., and measured in 2005. Strikingly, the estimate of heritability of both BMI and waist circumference was 77%. Thus, in the midst of the obesity epidemic, the evidence that hereditary factors are important remains unassailable. In the understandable rush to find potentially reversible environmental causes for the epidemic of obesity, it is not surprising that this fact is not infrequently downplayed. For example, Reilly et al. (18) recently reported the most comprehensive prospective studies of risk factors determining obesity at age 7 years. Some environmental factors such as maternal smoking and hours of television viewed daily showed a relationship with BMI with odds ratios reaching 1.5–1.8 at the highest levels of exposure. However, in this study, if both parents were obese, the odds ratio of obesity in the child was 10.4, and if adiposity rebound occurred in a child before 43 months, the odds ratio was 15. Clearly, there are potential unmeasured environmental explanations for both these striking associations, but it is equally (if not more) plausible that biological and inherited factors predominantly underlie both these associations. In the extensive debate that followed the publication of that article (19), it is remarkable that little or no attention was paid to the factors that had been clearly demonstrated to have by far the highest impact. We shall return later to some possible reasons why broad acceptance of the strength of the heritable and biological predisposition to obesity is difficult to secure.

Energy balance is a physiologically controlled process. If genetic variation influences body fat stores, then it must do so through biological and not "metaphysical" processes. A body of work stretching over nearly 70 years has clearly demonstrated that energy balance in mammals is a homeostatically regulated process involving a dialogue between the sites of long-term energy stores, i.e., adipose tissue, and the brain, the organ that coordinates food intake and related behaviors and is the central control of energy expenditure (20–23). Over the past 15 years or so, molecular flesh has been put on the bones of these concepts by the work largely emanating from the study of inherited obesity in rodents, which has firmly established the leptin-melanocortin signaling link as critical to the normal control of energy homeostasis (24–27). The control of energy stores is clearly not subject to the same tight constraints as, say, that of plasma osmolality (another physiological parameter governed by hypothalamic processes involving both a sensation leading to a behavior [thirst drinking] and a hormonal output [i.e., vasopressin]); absolute amounts of fat stored therefore vary between individuals and across a lifetime. But there does tend to be a degree of intra-individual stability, with homeostatic processes kicking in to restore weight to its original levels after periods of weight loss and, in some individuals at least, the tendency of weight to return to its previous level after a period of experimental overfeeding (28–30).

Severe defects in single genes involved in these processes cause human obesity largely through impact on appetite. Over the past decade or so, mutations in specific genes have been found to cause certain monogenic forms of human obesity (31). Certain pleiotropic genetic disorders have long been identified as being associated with obesity as well as features such as mental retardations and various dysmorphisms. Some, such as Prader-Willi syndrome, are well known to be associated with extreme hyperphagia, but the complex nature of the imprinting defect in Prader-Willi syndrome makes it difficult to mechanistically link the genetic defect with the pathophysiology (32). Numerous subtypes of Bardet-Biedl syndrome are also associated with obesity as well as retinitis pigmentosa, renal abnormalities, mental retardation, and other features, and, intriguingly, many of these effects appear to affect proteins localized to the basal body, a key element of the monocilium thought to be important for intercellular sensing (33). However, it is the identification of genetic defects in obese children without the typical features of the classical syndromes that has provided the best evidence to date that the physiological

pathways that underlie energy homeostasis in mice are operative in humans. Homozygous or compound heterozygous loss of function mutations in five different genes operating within the canonical leptin-melanocortin signaling pathway clearly and replicably result in human obesity (34–39). Individual patients with haplo-insufficiency for Sim 1 (a transcription factor necessary for normal hypothalamic development) (40) and for brain-derived neurotrophic factor (41), as well as a heterozygous loss-of-function missense mutation in its receptor Trk B (42), all develop severe obesity in association with other developmental features.

From this body of work, we now know that *1*) humans can become obese as a result of simple genetic defects, *2*) one of those defects (leptin deficiency) is effectively treated by hormone replacement (43), and *3*) MC4R deficiency is a sufficiently common cause of childhood obesity (5.4% in our cohort of ~3,000 children [44]; S.O. and I.S.F., personal observations) for MC4R gene analysis to justify becoming a routine part of the evaluation of the severely obese child. Heterozygous carriers of loss-of-function mutations in leptin (45) and POMC (46) have a substantially increased risk of obesity, indicating that energy balance is sensitive to even relatively subtle disruption in these pathways. Perhaps most interestingly, all genetic defects causing monogenic human obesity thus far described cause obesity principally by disrupting satiety mechanisms. In the case of the MC4R, where directly observed studies of spontaneous food intake at ad libitum meals have been undertaken (44), there is a remarkable relationship with molecular phenotype, with subjects who carry mutations that totally abrogate signaling eating more at a test meal than those who have mutations that only partially disrupt signaling.

Thus, recently acquired information regarding the etiology of monogenic forms of human obesity has demonstrated that obesity can be an inherited neurobehavioral disorder. Indeed, since MC4R deficiency is present in ~1/1,000 U.K. Caucasians (47), this is not a particularly rare phenomenon. However, it is clearly important to consider the extent to which the genetic underpinnings of common forms of obesity might affect the same processes. **Common genetic variants predisposing to obesity are now being identified and appear to affect the same processes.** The study of the genetics of common obesity has been dogged for many years by a profusion of studies of candidate genes, most of which have been inadequately powered to generate firm conclusions. The power of genome-wide association studies undertaken in large sample sets has finally paid dividends, and in 2007, we saw the emergence of the first common genetic variant that unquestionably alters human adiposity. Individuals who are homozygous for the high-risk allele (AA) of FTO weigh on average 3 kg more than individuals with two low-risk alleles, with heterozygotes having an intermediate risk (48). This has been replicated in multiple studies, and the statistical evidence for its association with adiposity, at least in Caucasians, is overwhelming. Gerken et al. (49) recently demonstrated that FTO encodes a member of the 2-Oxoglutatate–dependent dioxygenase family. Importantly, its highest level of expression is in the brain and in the arcuate nucleus of the hypothalamus, where its expression is altered by fasting and feeding (49). Although the single-nucleotide polymorphisms that are most highly associated with obesity are within an intron of the FTO gene, it is still possible that this variant affects the expres-

sion of other genes in the vicinity, so it is not yet conclusively proven that alterations in function or amount of the FTO protein is a key determinant of body weight. Nonetheless, from what we know so far, it seems most likely that intronic variation in the FTO gene influences obesity through its effects on some brain process relevant to energy balance. Interestingly, Tschritter et al. (50) have recently shown evidence that the human brain's cerebrocortical responses to insulin (measured by magnetoencephalogram) are influenced by the FTO genotype.

Whereas many previous candidate gene studies were of inadequate size to come up with conclusive results, the use of meta-analysis can distil information from a variety of sources and come up with more reliable conclusions regarding associations. Of the meta-analyses done to date, those investigating a specific amino acid variant in the MC4R receptor have provided the most convincing evidence for an effect on body weight (51,52). Again, as we know that disruption of MC4R function effects appetite and food intake, it is highly likely that commoner variants in the same gene will have effects that are different only in degree.

Over the next few months, a larger number of genetic variants will emerge as genome-wide association results are pooled and replicated. We predict that these studies will reveal variants in a number of other genes expressed in the central nervous system and influencing appetite and satiety.

How do these genetic variants interact with environmental factors to explain the obesity epidemic? Only in very recent human history has the majority of people in developed and many developing countries had ready access to more daily calories than are required to sustain health and maintain adequate nutritional stores. This has principally resulted from two factors: the reduction in the need for strenuous physical activity in the workplace and in the home, which has reduced the requirements for ingested energy, and the abundance, ready availability, palatability, and relative cheapness of food augmented by its aggressive commercial promotion (4). The relative importance of these factors probably varies across geographical locations and socioeconomic groups. Although there have always been some obese people in all societies, other than those with very limited access to food, these factors have conspired in the very recent past to ensure that all individuals with an intrinsic tendency to gain weight over time can readily do so. However, it is important to point out that, even in places where obesity is very common, there are still many lean people (5). The very high heritability of adiposity suggests that the reasons for those inter-individual differences in susceptibility are likely to have a biological rather than a moral explanation.

One consistent epidemiological finding that requires explanation is the fact that, in highly developed countries at least, the prevalence of obesity is inversely associated with both socioeconomic status and educational status (4). At first glance, this seems to be powerful evidence that poor and/or less educated people are either subject to more of the environmental factors that drive obesity or are less able to consciously counteract the same environmental obesogenic forces that are exerted across the whole population. An implied corollary of the second interpretation is that economic poverty and/or lack of education impairs a person's ability to resist the current obesogenic environment. Although these conjectures may well be true, there is a third potential contributor to the associa-

tion between low socioeconomic/educational status and obesity that is much less frequently discussed. In a classic paper, Gortmaker et al. (6) demonstrated that obese teenagers, when matched for parental income and scholastic achievement, had considerably higher rates of economic poverty in adult life, strongly suggesting that, in highly developed societies, obesity may be a cause of economic disadvantage rather than simply a consequence. These data have been replicated elsewhere and strongly suggest that, at least in developed Westernized countries, obesity can drive downward social and economic drift (53). Thus, it is at least plausible that those who may be biologically and genetically predisposed to obesity run the risk of acquiring less social, economic, and educational capital throughout their life.

An evolutionary perspective. For more than 40 years, the Neel Thrifty Gene hypothesis has dominated thinking about the evolution of susceptibility to human obesity (54). However, there are a number of serious problems with this hypothesis, including that, even in areas where obesity is very common, a large number of people remain lean. If there are strong environmentally based evolutionary drivers for particular traits (exemplified by the case of sunlight exposure and skin color [55]), alleles that favor survival tend to become rapidly fixed in populations. Speakman (56–58) recently expounded what we find to be a more compelling coherent evolutionary scenario, incorporating modern knowledge of the biology of energy balance to a satisfying degree. He hypothesizes that random natural variation in "hypothalamic energy balance set points" has occurred over millions of years of primate evolution. Whereas variants that would tend to produce a state of low energy stores would have been systematically selected against, at least in part because of their adverse impact of reproductive success, upward drifts in such set points would have been allowed to persist (rather than being positively selected for, as the "thrifty gene" hypothesis would have it). This upward drift would be particularly prominent because the formation of organized social groups and the discovery of fire, both of which occurred around 2,000,000 years ago, made our ancestors less susceptible to predation. Not particularly emphasized by Speakman, but likely to be important, is the probability that such natural tendencies toward an upward drift in adipose stores may rarely have actually manifested themselves as obesity because of the high energy cost of obtaining food during most of human evolution. It is only in the past 50 years or so, when for the first time in human history the majority of people in the developed and developing world can readily access sufficient daily calories to exceed the calories expended in acquiring them, that those with intrinsically higher set points have manifested their "obesity potential" on a grand scale. Unlike the "thrifty gene" hypothesis, this scenario provides a credible explanation for the fact that even in places where obesity is very common, a substantial proportion of the population remains lean.

Conclusions. For medical, social, and economic reasons, most obese people are highly motivated to lose weight but find it difficult to lose weight and, if they succeed, even more difficult to maintain weight loss (59). The biology that underpins those difficulties is at last becoming clear. However, such information is certainly failing to filter through to the public. Here is a respected (if avowedly acerbic) *Sunday Times* journalist responding to thoughts that the U.K. government might financially motivate

healthy eating: "Perhaps instead of offering fat people money, which they will only spend on pies, we should once again stigmatise them. Schoolchildren could be encouraged to pelt fat classmates with cakes, exclude them from playground activities, and subject them to cruel jibes. And pinch them on their horrible fleshy arms during assembly. Fat adults could be forced to pay for two seats on public transport, could be given the worst seats in restaurants, and scolded over their choice of dessert. 'Have the fruit salad, you fat pig,' and so on. Most obesity is, after all, a consequence of stupidity and indolence and not of some genetic affliction. It is a lifestyle choice which people would be less inclined to adopt if they knew we all hated them for it . . . " (*Sunday Times*, 27 January 2008).

There is an obvious element of "playing to the gallery" in this tirade, but it reveals an interesting attitude that we strongly suspect is not restricted to journalists. It is puzzling that obesity can engender such moral revulsion and even "hatred" when it is a condition that only afflicts the sufferer. Despite this, rather than eliciting sympathy for a serious medical condition, obesity seems often to elicit a reaction that might be more understandable if directed at people parking inappropriately in disabled parking spaces or serially cheating on their spouses. The reasons for this revulsion are complex, culture specific, and more likely to be illuminated by philosophers and social anthropologists than by biologists, but it is clear that we have a long way to go before convincing the public and even many doctors that obesity is an affliction worthy of sympathy and serious medical research.

As the fruits of current large-scale genetic approaches continue to emerge, we predict that many, and perhaps the majority, of genetic variants predisposing to obesity will do so through influencing appetitive phenomena such as satiety and the response to food cues, many of which have been shown to be heritable. Indeed, we have known for 40 years or more that quantitative measures of such appetite-related variables are clearly linked to obesity (60) and that measurable and stable measures of eating behavior are heritable (61). The notion that genes can affect our apparently voluntary behavior is understandably uncomfortable to many. It can be perceived as a challenge to the concept of human "free will" and the notion that we are in full conscious control of all our behaviors. However, the history of human science from Copernicus through Darwin to modern neurobiology has continually challenged the notion of human centrality to, and control over, the processes of nature. As evidence for the biological basis for inherited influences over certain basic human behaviors becomes more established and accepted, we hope that this will lead to a more enlightened attitude toward people with obesity and a reduction in discrimination against them. Importantly, a better understanding of the detailed biology of appetite should lead to improved targeted pharmacotherapy. It is highly plausible that the inherent appetite-related factors that promote increased food intake and drive obesity (e.g., impaired satiety, enhanced responsiveness to visual food-related cues, or increased sense of hunger between meals) will vary markedly between people and that pharmacological and/or behavioral tools could be specifically targeted based on a much greater understanding of the neurobiological basis for these different aspects of appetitive behavior.

A commonly expressed belief of people who are naturally lean is that, as they find little difficulty in controlling their weight, they are puzzled as to how people who are

obese have "let that happen to themselves" and therefore assume that this is some sort of adverse life choice born of moral weakness. Whereas there is no doubt that emotional stresses and other factors can predispose to overeating, it is crucial that we recognize that the drive to eat varies enormously between people, with a strong genetic underpinning for that variability. Because of this, the conscious effort that needs to be made by the obese to slim down to a normal body weight is likely to be far greater than that required for a naturally lean person to remain so. This not only refers to the issue of greater appetitive drive but also to the neuroendocrine adaptations to weight loss that tend to conserve energy in the "reduced obese" state, making continued weight loss harder still (62,63).

ACKNOWLEDGMENTS

REFERENCES

1. Kopelman PG: Obesity as a medical problem. *Nature* 404:635–643, 2000
2. Wolf AM, Colditz GA: Current estimates of the economic cost of obesity in the United States. *Obes Res* 6:97–106, 1998
3. Seidell JC: Time trends in obesity: an epidemiological perspective. *Horm Metab Res* 29:155–158, 1997
4. Prentice AM: The emerging epidemic of obesity in developing countries. *Int J Epidemiol* 35:93–99, 2006
5. Flegal KM, Graubard BI, Williamson DF, Gail MH: Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 298:2028–2037, 2007
6. Gortmaker SL, Must A, Perrin JM, Sobol AM, Dietz WH: Social and economic consequences of overweight in adolescence and young adulthood. *N Engl J Med* 329:1008–1012, 1993
7. Sarlio-Lahteenkorva S, Stunkard A, Rissanen A: Psychosocial factors and quality of life in obesity. *Int J Obes Relat Metab Disord* 19 (Suppl. 6):S1–S5, 1995
8. Maes HH, Neale MC, Eaves LJ: Genetic and environmental factors in relative body weight and human adiposity. *Behav Genet* 27:325–351, 1997
9. Allison DB, Kaprio J, Korkeila M, Koskenvuo M, Neale MC, Hayakawa K: The heritability of body mass index among an international sample of monozygotic twins reared apart. *Int J Obes Relat Metab Disord* 20:501–506, 1996
10. Allison DB, Heshka S, Neale MC, Lykken DT, Heymsfield SB: A genetic analysis of relative weight among 4,020 twin pairs, with an emphasis on sex effects. *Health Psychol* 13:362–365, 1994
11. Stunkard AJ, Foch TT, Hrubec Z: A twin study of human obesity. *JAMA* 256:51–54, 1986
12. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE: The body-mass index of twins who have been reared apart. *N Engl J Med* 322:1483–1487, 1990
13. Phillips DI, Hales CN, Barker DJ: Can twin studies assess the genetic component in type 2 (non-insulin-dependent) diabetes mellitus? *Diabetologia* 36:471–472, 1993
14. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD: Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 303:1019–1022, 1991
15. Weedon MN, Lettre G, Freathy RM, Lindgren CM, Voight BF, Perry JR, Elliott KS, Hackett R, Guiducci C, Shields B, Zeggini E, Lango H, Lyssenko V, Timpson NJ, Burtt NP, Rayner NW, Saxena R, Ardlie K, Tobias JH, Ness AR, Ring SM, Palmer CN, Morris AD, Peltonen L, Salomaa V, Davey Smith G, Groop LC, Hattersley AT, McCarthy MI, Hirschhorn JN, Frayling TM: A common variant of HMGA2 is associated with adult and childhood height in the general population. *Nat Genet* 39:1245–1250, 2007
16. Friedman JM: Modern science versus the stigma of obesity. *Nat Med* 10:563–569, 2004
17. Wardle J, Carnell S, Haworth CM, Plomin R: Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr* 87:398–404, 2008
18. Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, Steer C, Sherriff A: Early life risk factors for obesity in childhood: cohort study. *BMJ* 330:1357, 2005
19. Greenhalgh T: Early life risk factors for obesity in childhood: the hand that rocks the cradle rules the world. *BMJ* 331:453, 2005
20. Kennedy GC: The role of depot fat in the hypothalamic control of food intake in the rat. *Proc R Soc Lond* 140:578–596, 1953
21. Hervey GR: The effects of lesions in the hypothalamus in parabiotic rats. *J Physiol London* 145:336, 1959
22. Hetherington AW, Ranson SW: Hypothalamic lesions and adiposity in the rat. *Anat Rec* 78:149–172, 1940
23. Coleman DL, Hummel KP: Effects of parabiosis of normal with genetically diabetic mice. *Am J Physiol* 217:1298–1304, 1969
24. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM: Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425–432, 1994
25. Chen H, Charlat O, Tartaglia LA, Woolf EA, Weng X, Ellis SJ, Lakey ND, Culpepper J, Moore KJ, Breitbart RE, Duyk GM, Tepper RI, Morgenstern JP: Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. *Cell* 84:491–495, 1996
26. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W, Kesterson RA, Boston BA, Cone RD, Smith FJ, Campfield LA, Burn P, Lee F: Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* 88:131–141, 1997
27. Leibel RL, Chung WK, Chua SC Jr: The molecular genetics of rodent single gene obesities. *J Biol Chem* 272:31937–31940, 1997
28. Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Theriault G, Dussault J, Moorjani S, Pinault S, Fournier G: The response to long-term overfeeding in identical twins. *N Engl J Med* 322:1477–1482, 1990
29. Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Moorjani S, Theriault G, Kim SY: Overfeeding in identical twins: 5-year postoverfeeding results. *Metabolism* 45:1042–1050, 1996
30. Larson DE, Rising R, Ferraro RT, Ravussin E: Spontaneous overfeeding with a "cafeteria diet" in men: effects on 24-hour energy expenditure and substrate oxidation. *Int J Obes Relat Metab Disord* 19:331–337, 1995
31. Farooqi IS, O'Rahilly S: Monogenic obesity in humans. *Annu Rev Med* 56:443–458, 2005
32. Goldstone AP: Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* 15:12–20, 2004
33. Badano JL, Mitsuma N, Beales PL, Katsanis N: The ciliopathies: an emerging class of human genetic disorders. *Annu Rev Genomics Hum Genet* 7:125–148, 2006
34. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S: Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 387:903–908, 1997
35. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougneres P, Lebouc Y, Froguel P, Guy-Grand B: A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 392:398–401, 1998
36. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM,

Lank E, Bottomley B, Lopez-Fernandez J, Ferraz-Amaro I, Dattani MT, Ercan O, Myhre AG, Retterstol L, Stanhope R, Edge JA, McKenzie S, Lessan N, Ghodsi M, De Rosa V, Perna F, Fontana S, Barroso I, Undlien DE, O'Rahilly S: Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N Engl J Med* 356:237–247, 2007

37. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Gruters A: Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 19:155–157, 1998

38. Jackson RS, Creemers JW, Ohagi S, Raffin-Sanson ML, Sanders L, Montague CT, Hutton JC, O'Rahilly S: Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat Genet* 16:303–306, 1997

39. Yeo GS, Farooqi IS, Aminian S, Halsall DJ, Stanhope RG, O'Rahilly S: A frameshift mutation in MC4R associated with dominantly inherited human obesity (Letter). *Nat Genet* 20:111–112, 1998

40. Holder JL Jr, Butte NF, Zinn AR: Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. *Hum Mol Genet* 9:101–108, 2000

41. Gray J, Yeo GS, Cox JJ, Morton J, Adlam AL, Keogh JM, Yanovski JA, El Gharbawy A, Han JC, Tung YC, Hodges JR, Raymond FL, O'Rahilly S, Farooqi IS: Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene. *Diabetes* 55:3366–3371, 2006

42. Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, Sivaramakrishnan S, O'Rahilly S, Farooqi IS: A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat Neurosci* 7:1187–1189, 2004

43. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F, Fontana S, Lechler RI, DePaoli AM, O'Rahilly S: Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* 110:1093–1103, 2002

44. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S: Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med* 348:1085–1095, 2003

45. Farooqi IS, Keogh JM, Kamath S, Jones S, Gibson WT, Trussell R, Jebb SA, Lip GY, O'Rahilly S: Partial leptin deficiency and human adiposity. *Nature* 414:34–35, 2001

46. Farooqi IS, Drop S, Clements A, Keogh JM, Biernacka J, Lowenbein S, Challis BG, O'Rahilly S: Heterozygosity for a POMC-null mutation and increased obesity risk in humans. *Diabetes* 55:2549–2553, 2006

47. Alharbi KK, Spanakis E, Tan K, Smith MJ, Aldahmesh MA, O'Dell SD, Sayer AA, Lawlor DA, Ebrahim S, Davey Smith G, O'Rahilly S, Farooqi S, Cooper C, Phillips DI, Day IN: Prevalence and functionality of paucimorphic and private MC4R mutations in a large, unselected European British population, scanned by meltMADGE. *Hum Mutat* 28:294–302, 2007

48. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI: A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 316:889–894, 2007

49. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, Robins P, Prieur X, Coll AP, Ma M, Jovanovic Z, Farooqi IS, Sedgwick B, Barroso I, Lindahl T, Ponting CP, Ashcroft FM, O'Rahilly S, Schofield CJ: The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science* 318:1469–1472, 2007

50. Tschritter O, Preissl H, Yokoyama Y, Machicao F, Haring HU, Fritsche A: Variation in the FTO gene locus is associated with cerebrocortical insulin resistance in humans. *Diabetologia* 50:2602–2603, 2007

51. Heid IM, Vollmert C, Kronenberg F, Huth C, Ankerst DP, Luchner A, Hinney A, Bronner G, Wichmann HE, Illig T, Doring A, Hebebrand J: Association of the MC4R V103I polymorphism with the metabolic syndrome: the KORA Study. *Obesity* 16:369–376, 2008

52. Young EH, Wareham NJ, Farooqi S, Hinney A, Hebebrand J, Scherag A, O'Rahilly S, Barroso I, Sandhu MS: The V103I polymorphism of the MC4R gene and obesity: population based studies and meta-analysis of 29 563 individuals. *Int J Obes (Lond)* 31:1437–1441, 2007

53. McLaren L: Socioeconomic status and obesity. *Epidemiol Rev* 29:29–48, 2007

54. Neel JV: Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 14:353–362, 1962

55. Rees JL: Genetics of hair and skin color. *Annu Rev Genet* 37:67–90, 2003

56. Speakman JR: A nonadaptive scenario explaining the genetic predisposition to obesity: the "predation release" hypothesis. *Cell Metab* 6:5–12, 2007

57. Speakman JR: Thrifty genes for obesity and the metabolic syndrome: time to call off the search? *Diab Vasc Dis Res* 3:7–11, 2006

58. Speakman JR: Obesity: the integrated roles of environment and genetics. *J Nutr* 134:2090S–2105S, 2004

59. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL: Is the energy homeostasis system inherently biased toward weight gain? *Diabetes* 52:232–238, 2003

60. Schachter S: Obesity and eating: internal and external cues differentially affect the eating behavior of obese and normal subjects. *Science* 161:751–756, 1968

61. Rankinen T, Bouchard C: Genetics of food intake and eating behavior phenotypes in humans. *Annu Rev Nutr* 26:413–434, 2006

62. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, Gallagher D, Mayer L, Murphy E, Leibel RL: Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest* 115:3579–3586, 2005

63. Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL: Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab* 87:2391–2394, 2002