REVIEWS

Human genetics illuminates the paths to metabolic disease

Stephen O'Rahilly[1]

Metabolic diseases represent a growing threat to world-wide public health. In general, these disorders result from the interaction of heritable factors with environmental influences. Here, I will focus on two important metabolic disorders, namely type 2 diabetes and obesity, and explore the extent to which human molecular genetic research has illuminated our understanding of their underlying pathophysiological mechanisms.

Definitive measures of the heritability of a human trait or disease are unattainable as the precise extent to which inherited factors determine inter-individual differences in risk varies between populations and over time. When considered as quantitative traits, measures of 'fatness' are highly heritable with about 70% of inter-individual difference in indices of adiposity being attributable to genetic factors[1]. Twin studies suggest that although glucose tolerance is highly heritable, non-genetic factors also have a role, particularly in determining the timing of transition to frank diabetes[2]. It is clear that there has been, in many countries, a rapid recent increase in both obesity and the type 2 diabetes, especially in children, and changes over this time frame are unlikely to be driven by genetic alterations[3]. Nevertheless, even in the midst of the 'obesity epidemic', genetic factors still seem to have a major role in determining who becomes obese[4] and/or develop diabetes.

Understanding the heritable component of metabolic disease

Although simple curiosity remains a noble impetus to scientific effort, the enormous investment in human genomics has been driven by the promise that increasing genetic knowledge would translate into improved tools for the treatment and prevention of disease. This promise currently sits uncomfortably with the paucity of novel, safe and effective treatments emerging from the pharmaceutical sector. In engaging with the public and our funders we need to emphasize the long-term view of the war against complex chronic metabolic disease, while celebrating any successes we achieve along the way. In the case of obesity and diabetes we already have compelling examples where genetic knowledge has improved the health and well being of some people[5,6]. In the future, increasing knowledge of the genetic architecture of metabolic disease is likely to deliver tangible benefits to human health. First, by discovering and validating key nodal points in the control of key elements of metabolic homeostasis, human genetics is likely to inform decisions regarding the selection of molecular targets for novel therapeutics. Second, we can predict that the reliable dissection of genetic and pathophysiological heterogeneity within metabolic diseases that are currently artificially grouped as single entities should lead to improvements in personalized diagnosis, prognostication, therapy and prevention. However, it is likely that such impacts will occur in a gradual and stepwise manner.

Type 2 diabetes

Diabetes is a condition defined by a state of chronic elevation of plasma glucose levels, the adverse impact of which occurs predominantly, but not exclusively, through its effects on the health of small and large blood vessels. Much effort has gone into the classification of diabetes. In simple terms, type 1 diabetes results from an autoimmune destruction of the insulin-producing pancreatic beta cells, and forms of diabetes that result from defined causes such as monogenic disorders of insulin secretion or action, or as a secondary consequence of acquired pancreatic, endocrine or other disorders are classified individually according to their primary cause[7]. However, with our current knowledge, these subtypes together only account for $<$10% of all cases of diabetes[7]. The term 'type 2 diabetes' is currently used for the remainder, which is very unlikely to be a homogenous entity.

The view of type 2 diabetes in the 'pre-molecular genetic' era. It has long been clear that (1) people with type 2 diabetes are very often obese or overweight; (2) the majority of patients with type 2 diabetes have an impaired metabolic response to administered or endogenous insulin; and (3) obesity, even in non-diabetic individuals, tends to lead to a state of insulin resistance[8]. Beginning in the 1960s, when it first became possible to measure plasma levels of insulin, a vast body of pathophysiological investigation of people with diabetes and 'prediabetes' led to a general (if not universal) consensus that the inherited defect predisposing to type 2 diabetes was likely to involve a primary defect in insulin action[9]. As the major tissue responsible for glucose disposal after a meal, skeletal muscle was widely considered to be the location at which such a defect would primarily express itself[10]. Thus, insulin resistance, exacerbated by obesity, would result in chronic overwork of pancreatic beta cells, ultimately leading to their 'exhaustion' and decompensation to a hyperglycaemic state. However, throughout this period, some investigators continued to draw attention to the fact that normoglycaemic 'at risk' individuals seemed to have both quantitative and qualitative defects in pancreatic beta-cell function that indicated the existence of an intrinsic problem with islet function[11].

Lessons from monogenic forms of diabetes. Over the past 20 years or so, arguably the major contribution of molecular genetics to 'non-type-1 diabetes' has been the identification of a range of single gene disorders that result in chronic hyperglycaemia (Table 1). The elucidation of the precise molecular basis for a number of these conditions has been illuminating in terms of the basic understanding of critical components in the control of human glucose homeostasis and in the lessons they have taught us that are relevant to our concepts of the pathophysiology of common forms of diabetes. Importantly, these discoveries have also brought some practical improvements in diagnosis and management.

[1]University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK.

Table 1 | Monogenic disorders of glucose tolerance

Gene	Functional defect or consequence	Reference
Inherited disorders largely impacting on insulin secretion		
HNF4a *HNF1A* *IPF1* (also called *PDX1*) *HNF1B* *NEUROD1*	Defects in transcription factors responsible for beta-cell development, maintenance, function or survival	14 15 16 17 18
GCK (Glucokinase) *ABCC8* (sulphonylurea receptor) *KCNJ11* (Kir6.2 potassium channel) Mitochondrial 3243 variant	Defects in the glucose sensing/ metabolism/secretory function of pancreatic beta cells	13 19 20 49
Chromosome 6q22-6q23 *ZFP57*	Imprinting disorders causing transient neonatal diabetes	79 80
EIF2AK3 *WFS1* *INS* *CEL*	Defects leading to increased beta-cell death; increased ER stress (*WFS1* and *INS*)	53 50 21 81
Inherited disorders largely impacting on insulin action		
*AGPAT2**	Defects in adipocyte triglyceride synthesis	31
*PPARG** *BSCL2* (Seipin)*	Defects in adipocyte development	28 30
LMNA (lamin A/C)* *CAV1* (Caveolin 1)*	Mechanism unclear	20 32
*CIDEC**	Dysregulated lipolysis	33
INSR† *AKT2*† *TBC1D4*† (also known as *AS160*)		23 25 26
ALMS1‡	Alstrom's syndrome; mechanism unclear	82,83

Examples of mechanisms whereby mutations in single human genes lead to disorders characterized by impaired glucose tolerance. This list is not comprehensive. For a fuller review see ref. 84.
* Primary lipodystrophies.
† Disorders of insulin signalling.
‡ Pleiotropic syndromes associated with severe insulin resistance.

Inherited disorders of insulin secretion. In the early 1970s clinicians reported a form of 'non-type-1' diabetes that presented in young adult life, appeared to be highly familial, and did not require insulin therapy for its control. They termed this 'maturity onset diabetes of the young' (MODY) and it subsequently became clear that, at least in some families, inheritance of this disorder followed an autosomal-dominant pattern[12]. Physiological studies suggested that, in most cases, MODY resulted from a defect in insulin secretion, rather than action[12]. The first MODY gene to be identified encodes glucokinase, an enzyme involved in the sensing of glucose by the pancreatic beta cell[13]. Subsequently, the application of linkage analysis identified mutations in a number of transcription factors, several in the HNF family of basic-loop-helix transcription factors, to be the cause of other subtypes of MODY[14–18]. More recently it has been realized that some children who presented with diabetes very early in life did not have 'typical' type 1 diabetes but rather had monogenic forms of neonatal diabetes arising from mutations that result in impaired beta-cell development or function or increased beta-cell destruction[19–21]. In the case of MODY, the best estimates are that the aetiology of >80% of cases of early-onset, autosomal-dominant, familial hyperglycaemia is now identifiable[22]. The vast majority of genetic causes identified so far involve a primary deficiency in insulin secretion[22].

Inherited disorders of insulin action. The normal control of glucose metabolism requires not only a normal secretion of insulin but also its normal action in its key target tissues including muscle, liver and fat. It might, therefore, be considered surprising that when monogenic forms of diabetes are parsed, insulin secretory defects seem to be grossly overrepresented. Why are genetic disorders of insulin action not more prominent? Studies of familial forms of inherited insulin resistance provide at least some of the answer to this. Mutations in the human insulin receptor gene were the first form of primary genetic disorder of human insulin action to be described[23]. Intriguingly, not all patients carrying such mutations present with diabetes, as the response of the healthy pancreas to such intrinsic insulin resistance is to expand islet beta-cell mass and hypersecrete enormous quantities of insulin[24]. In some individuals at least, this could maintain normoglycaemia for many decades, although most subjects do finally decompensate to develop diabetes, which is then extremely difficult to treat[24]. The capacity of compensatory hyperinsulinaemia to ward off diabetes for many years explains why, in contrast to single gene disorders affecting insulin secretion, single gene disorders impacting on insulin action frequently do not manifest themselves as diabetes until rather late in life. So far, other than mutations in the insulin receptor, only a single human family (with a mutation in *AKT2*) has been reported in which a primary defect in the insulin signal transduction pathway leads to a clearly monogenic form of diabetes[25]. We have recently described a human family where a nonsense mutation in *TBC1D4*, which encodes a Rab-GAP protein involved in glucose transporter translocation in skeletal muscle and fat, causes severe selective post-prandial insulin resistance[26]. However, the compensatory capacity of the beta cell is such that diabetes does not necessarily ensue.

Although monogenic disorders directly impairing the action of insulin have been hard to find, there is another group of single gene disorders leading to insulin-resistant forms of diabetes where considerable progress has been made. The failure to develop, or adequately store triglyceride in, adipose tissue leads to ectopic deposition of stored lipid in muscle, liver, pancreas and elsewhere, and this phenomenon, through mechanisms that are being aggressively explored, severely impairs insulin action in those tissues[27]. Although compensatory hyperinsulinaemia prevents diabetes for a time, diabetes frequently supervenes. The genetic defects underlying several forms of recessive and dominantly inherited lipodystrophic disorders have been identified[28–33]. Several of these causative genes are uniquely expressed in adipocytes and thus demonstrate that adipose tissue 'failure' alone can initiate a pathophysiological cascade that can lead to an insulin-resistant form of human diabetes.

Lessons from genetic studies in 'common' type 2 diabetes. Much effort has been expended in the attempt to identify common genetic variants which underpin 'common' type 2 diabetes (Table 2). However, it is only recently, when the key challenges of adequate

Table 2 | Common genetic variants associated with type 2 diabetes

Chromosome	Nearby genes	How identified	Reference
1	*NOTCH2*	GWAS meta-analysis	85
2	*THADA*	GWAS meta-analysis	85
2	*IRS1*	GWAS	77
3	*ADAMTS9*	GWAS meta-analysis	85
3	*PPARG*	Candidate gene	86
3	*IGF2BP2**	GWAS	87,88,89
4	*WFS1*	Candidate gene	51
6	*CDKAL1**	GWAS	87,88,89,90
7	*JAZF1*	GWAS meta-analysis	85
8	*SLC30A8**	GWAS	91
9	*CDKN2A/B**	GWAS	87,88,89
10	*CDC123, CAMK1D*	GWAS meta-analysis	85
10	*HHEX**, *KIF11, IDE*	GWAS	91
10	*TCF7L2**	Linkage analysis/region-wide genotyping	92
11	*KCNJ11**	Candidate gene	93
11	*MTNR1B**	GWAS	41
12	*TSPAN8, LGR5*	GWAS meta-analysis	85
16	*FTO*	GWAS	69
17	*HNF1B*	Candidate gene	94

Susceptibility loci associated with type 2 diabetes have been described in detail in several recent reviews (for example, ref. 34). Increasing numbers of SNPs replicably associated with type 2 diabetes are rapidly emerging and it is unlikely that this table will be up to date at the time of publication. GWAS, genome-wide association study.
* SNPs associated with decreased insulin secretion in non-diabetic humans[35–39].

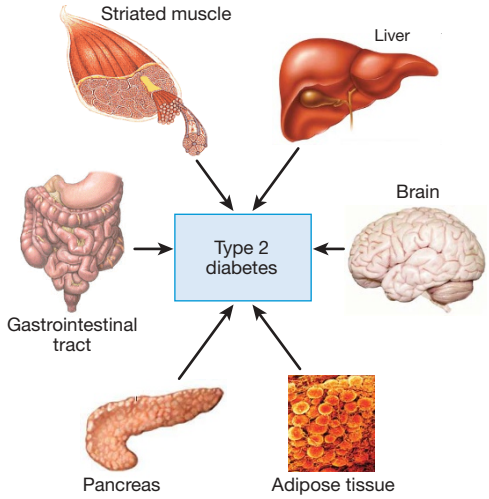
sample size and genome-wide coverage of genetic variation have been met, that reliable and reproducible information has finally emerged. There are now at least 19 common alleles (present in at least 1% of the populations that have been studied) that are generally accepted as being truly associated with type 2 diabetes[34]. More are very likely to emerge. A major scientific challenge over the forthcoming years will be to put mechanistic flesh on the bare bones of these associations. Although a minority of these diabetes single nucleotide polymorphisms (SNPs) are actually known to affect the structure or expression of a gene product with a credible link to glucose metabolism, the majority are not. It is likely that the physical location of these SNPs in the genome will give some clue to their ultimate biological effect, with the most closely co-located functional gene most likely to be the culprit; however, 'guilt by proximity' cannot be universally assumed. Nevertheless, it is striking that a large number of diabetes SNPs are close to genes expressed highly in the adult or developing pancreas and many have been shown to be associated with reduced beta-cell dysfunction in non-diabetic subjects[35–39]. Investigators have also used genome-wide approaches to examine genetic determinants of fasting glucose levels as a quantitative trait and it is intriguing that there is only limited overlap with 'diabetes' genes[40–42].

Human genetics informs pathophysiology of type 2 diabetes. The results from studies of monogenic diabetes remind us of the salient facts that the normal pancreatic beta cell can upregulate its function and maintain normoglycaemia for some considerable time in the face of severe insulin resistance, but that even a modest inherent defect in beta-cell function leads to hyperglycaemia[22]. That said, it is still formally possible that the majority of genes predisposing to common type 2 diabetes would exert their effect on insulin resistance with 'normal' beta cells simply failing in response to decades of compensatory overwork. The recent genome-wide association studies suggest that this simple scenario is likely to be incorrect. It seems more probable that a substantial part of the inherent susceptibility of an individual to develop type 2 diabetes in mid-life relates to the extent to which pancreatic beta-cell function can be maintained (Box 1). Looking back at the 'pre-molecular genetic' literature, could we have predicted that? There actually was a 'contrarian' tendency, much of it emanating from Europe, which in the 1970s and 1980s tried to draw attention to the presence, in non-diabetic people at high risk of later type 2 diabetes, of subtle quantitative and qualitative abnormalities of insulin secretion[11,43].

This reformulation of the general view of type 2 diabetes does not mean that insulin resistance is not important in its aetiology. Indeed most behavioural or pharmacological interventions that are proven to delay the onset of type 2 diabetes have their major impact on insulin sensitivity[44]. However, rather than viewing such interventions as targeting the sole and fundamental mechanism of type 2 diabetes, we should now perhaps better see them as protecting the inherently vulnerable pancreatic beta cell from overwork. That said, even in the absence of hyperglycaemia, insulin resistance is strongly associated with, and may even have a causative role in, important and highly prevalent conditions such as atherosclerosis, dyslipidaemia, hypertension, non-alcoholic steatohepatitis and polycystic ovarian syndrome, and thus improving our understanding of its aetiology is a biomedical priority.

For several decades diabetes researchers tended to focus their research on the pancreatic beta cell or on the two principal targets controlling glucose production and utilization in the whole body, namely liver and skeletal muscle. As only a small fraction of ingested glucose ended up in adipose tissue, the latter was, for some time, relatively ignored. The dawning realization that the healthy handling of carbohydrate metabolism was crucially interconnected with and dependent on lipid metabolism led to the emergence of the adipocyte as the 'fourth musketeer' of diabetes[27,45]. The molecular genetic era has clearly shown us that genetic defects solely impairing the development and/or function of adipose tissue (as in the hereditary lipodystrophies) are sufficient to result in the early and inevitable appearance of diabetes, providing compelling proof of the importance of that previously neglected organ.

Box 1 | The complex landscape of type 2 diabetes



Monogenic causes of diabetes impact mostly on pancreatic islet function, and many 'common' type 2 diabetes SNPs map close to genes expressed in islets and some are associated with beta-cell dysfunction in non-diabetic subjects. These findings have shifted the 'model' of type 2 diabetes from one where intrinsically normal pancreatic islets become 'exhausted' as a result of prolonged attempts to compensate for a primary defect in insulin action to one where intrinsic genetic variability in islet function is a major determinant of the susceptibility to develop diabetes.

Unlike muscle and liver, adipose tissue is not a major site of either glucose disposal or production. However, monogenic disorders of adipose tissue development/function lead to severe insulin resistance/diabetes as a result of 'fat failure' and diversion of nutrient delivery to muscle and liver, which impairs insulin action in these tissues through mechanisms that remain to be determined conclusively.

The brain clearly has a leading role in the control of energy balance, and obesity is a major risk factor for type 2 diabetes. In animal models, physiological/pharmacological manipulations in the brain influence glucose metabolism independent of energy homeostasis. So far, human genetic variants associated with both obesity and type 2 diabetes seem to exert most of their effects on glucose tolerance through an effect on adiposity (which itself increases insulin resistance in muscle and liver).

Muscle and liver are the major sites of insulin-regulated glucose disposal/production. Although insulin resistance, especially in muscle, is a key, early feature of type 2 diabetes and is heritable, surprisingly few 'diabetes genetic hits' primarily affect these tissues. Why is this so? First, environmental factors (diet, exercise, and so on) have major, highly labile impacts on these tissues. Insulin resistance is therefore an unstable phenotype and genetic influences are hard to 'pin down'. Second, effects of inherited variation in insulin action on glucose metabolism are masked by the capacity of normal pancreas to compensate.

Physiological and pharmacological studies indicate a powerful influence of hormonal products of entero-endocrine cells on glucose homeostasis. Human genetics has not, as yet, convincingly contributed to the notion that variation in entero-endocrine cell function has a role in determining susceptibility to diabetes. However, *TCF7L2*, which is at the site of the first discovered and most significant SNP associated with 'common' type 2 diabetes, is expressed in entero-endocrine cells and might influence their function.

Research efforts into possible pathogenic mechanisms in type 2 diabetes continue to be intense, with novel and potentially unifying hypotheses continually emerging. Of these, I will briefly consider three—namely mitochondrial dysfunction[46], endoplasmic reticulum (ER) stress[47] and inflammation[48]—and explore the extent to which human molecular genetics has supported the potential aetiological importance of these processes in human diabetes. Certain mutations in the mitochondrial genome are consistently associated with maternally inherited forms of human diabetes, and those mutations seem to cause

diabetes largely by impairing insulin secretion rather than insulin action[49]; however, there is currently little evidence to implicate common variation in the mitochondrial genome, or indeed in nuclear encoded/mitochondrially expressed genes in type 2 diabetes. *WFS1* was found to be mutated in Wolfram syndrome[50], a pleiotropic recessive disorder associated with diabetes. Subsequently, mutations in *WFS1* were found in children with non-syndromic forms of insulinopaenic diabetes and common variants in *WFS1* influence pancreatic beta-cell function and type 2 diabetes risk[51]. WFS1 has been implicated in the control of ER stress responses[52], and some other monogenic forms of diabetes (*EIF2AK3*[53] and *INS*[46]) have also been found to impair pancreatic beta-cell function by interfering with, or overwhelming, normal ER stress responses. As with mitochondrial dysfunction the principal impact of these disorders is on insulin secretion with little evidence yet for an effect on insulin resistance. There is good evidence that patients with pre-diabetes and type 2 diabetes have low levels of activation of inflammatory pathways[48], but the evidence that such activation is aetiologically involved in the disease is currently lacking. In contrast with, for example, type 1 diabetes or inflammatory bowel disease[54], the genome-wide studies of type 2 diabetes do not suggest an inflammatory 'genetic signature'. Results in genome-wide association studies of insulin-resistant phenotypes are awaited with interest.

Clinical implications of genetic discoveries in diabetes. At present, the information that has emerged regarding the genetic basis of common type 2 diabetes has not penetrated into clinical practice. Even taking all the known diabetes risk SNPs together adds only marginally more predictive power to that provided by conventional risk factors[55,56]. In contrast, the work in MODY has led to real clinical utility and patient benefit[22]. It is now clear that patients with glucokinase mutations have life-long, stable modest hyperglycaemia and do not need aggressive glucose-lowering therapy, whereas patients with other forms of MODY tend to progress and eventually require insulin therapy[22]. Notably, patients with HNF1-α mutations seem to be supersensitive to sulphonylurea drugs[57], a fact that can be used to harness these drugs to patient benefit while avoiding dangerous hypoglycaemia. Finally, and most strikingly, a rare group of patients with mutations that result in the voltage-gated potassium channel of the pancreatic beta cell being constitutively open[19,20] and who consequently develop insulin-dependent diabetes in the neonatal period have been shown to respond to sulphonylurea drugs[5]. Such patients can stop insulin injections and achieve improved control with an oral medication, resulting in a dramatic improvement in their quality of life and likely long-term health.

Obesity

Obesity is most simply defined as a state in which the total amount of triglyceride stored in adipose tissue is abnormally increased. It is strongly associated with a wide variety of adverse health outcomes, including diabetes, vascular disease and certain cancers[58]. Obesity results from a chronic, positive imbalance between energy intake and energy expenditure (Box 2). Intuitively, it seems that simple measurements of the components of these two sides of the energy equation should be readily able to identify the major contributor to obesity in any single affected individual. In practice, however, the accrual of excess fat mass usually occurs gradually and the daily imbalance of energy required to result in obesity is so small as to seriously challenge the resolution of existing measures of energy intake or expenditure. Additionally, obesity is highly susceptible to the 'Hawthorne' effect, with individuals who know they are being studied consciously or unconsciously altering their behaviour. The fact that adiposity is a highly heritable trait does, however, provide the opportunity to use modern molecular genetics to obtain mechanistic insights that were previously unobtainable. If we could find variants in genes with known or at least tractable functions that are unequivocally associated with obesity we might start to be able to build up a picture of what sorts of biological factors determine why, in the face of a highly 'obesogenic' environment, some people are susceptible to obesity whereas others remain lean.

The view of obesity in the 'pre-molecular genetic' era. Much effort was expended in exploring the hypothesis that obese people had a reduced basal metabolic rate (BMR). This was convincingly demonstrated not to be the case[59]. Indeed obesity was generally found to be associated with increased BMR because the parallel increase in lean mass is the main determinant of BMR. Obese people generally reported a low daily caloric intake, certainly insufficient to explain their obesity[60]. Several studies showed that obese people tended to underestimate consistently their daily caloric intake[60]. This challenging set of observations did not help to make human obesity a particularly attractive area in which to pursue a scientific or medical career.

Lessons from monogenic disorders. It had long been known that human obesity could result from a disorder in a single gene. Clinically defined genetic syndromes such as Prader–Willi and Bardet–Biedl were strongly associated with obesity and a voracious appetite but the coexistence of developmental delay and more generalized brain dysfunction complicated interpretation. However, in the mid-1990s the first human single genetic defects were found that led to severe obesity in the absence of developmental delay[61,62]. These discoveries

Table 3 | Monogenic disorders leading to human obesity

Disorders without generalized disturbance of higher nervous system functions

Gene	Encoded product	Comment	Reference
LEP	Leptin	Adipocyte-derived hormone	61
LEPR	Leptin receptor	Receptor for adipocyte-derived hormone	95
POMC	Pro-opiomelanocortin	Hypothalamic neuropeptide	96
PCSK1	Proprotein convertase 1	Processes pro-peptides (including POMC) to active moieties	62
MC4R	Melanocortin 4 receptor	Receptor for POMC products αMSH and βMSH	97,98
SIM1	SIM1, homologue of *Drosophila* single minded 1,	Transcription factor necessary for hypothalamic development	99

Disorders associated with developmental delay/cognitive dysfunction due to generalized disturbance of CNS function

Gene	Syndrome	Comment	Reference
–	Bardet–Biedl syndrome	At least 12 genes identified, most of which affect the function of the primary cilium	68
–	Prader–Willi syndrome	Imprinted locus on chromosome 15q including snoRNA cluster	100
GNAS	Pseudohypoparathyroidism	Encodes α-subunit of the stimulatory G protein	101
BDNF	WAGR syndrome	Deletion of *BDNF* in a subset of patients with WAGR syndrome is associated with obesity	102,103
NTRK2	–	Encodes TrkB, a receptor for brain-derived neurotrophic factor (BDNF) and neurotrophin 5 (NTF5). *NTRK2* mutations are associated with developmental delay and severe childhood obesity	104

Examples of human genes, mutations in which lead to a highly penetrant form of obesity. In disorders where careful phenotypic measurement has been undertaken, obesity is largely driven by increased appetite and/or diminished satiety. The mutations either have effects largely restricted to areas of the brain concerned with energy homeostasis, in which case obesity is usually the dominant presenting clinical feature, or impact on more generalized CNS functions, in which case obesity presents in the context of a more global developmental disorder. For a more comprehensive review of monogenic disorders leading to obesity see ref. 105.

were greatly facilitated by an explosion of research into the control of energy balance in obese animal models and in particular by the discovery of leptin as an adipocyte-derived hormone influencing the central control of energy balance[63], and the recognition of the brain melanocortin system as a major mediator of leptin action[64]. There are now at least 20 single gene disorders that clearly result in an autosomal form of human obesity (Table 3). Notably, so far all these disorders affect the central sensing and control of energy balance[65]. When energy balance is studied in detail in affected subjects it is clear that there is a major increase in appetite and reduction in satiety and that spontaneous measured food intake is greater than can be explained by increased body size[65]. In contrast, studies of energy expenditure in these subjects tend to reveal subtle if any decrement, although in MC4R deficiency there is a modest, but significant, tendency towards reduced metabolic rate[66] and reduced lipid oxidation[67]. The discovery that all of the genetic defects leading to Bardet–Biedl syndrome have a role in the structure and function of the primary cilium has focused attention on that organelle as a potentially crucial one in hypothalamic neurons responsible for the control of energy balance[68]. The marked reversal of the severe obesity seen in human leptin deficiency on administration of recombinant human leptin demonstrated the principle that, if a clear molecular basis for an individual's obesity could be found, then mechanism-based therapeutics could be highly effective[6].

Lessons from studies of the genetic basis for common obesity. Genome-wide association studies are beginning to identify the common genetic variation that underpins difference in adiposity across the normal population (Table 4). SNPs in the first intron of *FTO* were the first to emerge as unequivocally associated with human obesity[69,70]. *FTO* is a paradigm of how challenging it will be to move from proven genetic association to an understanding of the biology underpinning such an association. *FTO* is highly expressed in hypothalamus, where its expression is regulated by feeding and fasting[71]. Carriers of obesity-risk SNPs consistently show an increased appetite or measured food intake[72], and thus it seems clear that, like the monogenic disorders, the mechanism underlying the impact of this common genetic variant on human adiposity is principally through energy intake. However, there are still many questions. Intriguingly, mice rendered null for *Fto* are very small and have increased energy expenditure[73]. As yet, no one has demonstrated that the risk SNPs affect *FTO* expression. Although FTO has been shown to be a dioxygenase with an ability to demethylate 3-methylthymine in DNA *in vitro*, we don't know the true physiological substrate and we don't yet understand how its enzymatic function is linked to its role in energy balance[71].

The second obesity-risk SNP to be reported lies on chromosome 18, with its closest gene being *MC4R* (ref. 74). The association of this SNP with height[74] and with increased food intake[75] is reminiscent of the phenotype of severe MC4R deficiency and suggests that the SNP may indeed be operating through an effect on *MC4R*. Like *PPARG* and *KCNJ11* in diabetes, *MC4R* is an example of where disorders causing highly penetrant forms of a phenotype also harbour common variants which contribute to the phenotype in the broader population. Recently, several further SNPs robustly associated with obesity have been reported. Intriguingly, many of these are closely located to genes that are known to be expressed in the central nervous system[76].

Clinical implications of genetic discoveries. Leptin is a life-saving therapy for a very rare group of severely obese patients with congenital leptin deficiency. MC4R deficiency is present in up to 5% of severely obese children and we have argued that the determination of *MC4R* sequence should be a routine part of the evaluation of any severely obese child[65]. Although at the moment such information does not lead to any obvious specific therapy, it is important for carers, patients and parents to know that there is a powerful underlying biological drive promoting weight gain and that any success that diet and exercise have in restricting weight gain should be celebrated as an achievement. The definition of a clear genetic basis for a child's severe obesity may also prevent inappropriate and potentially highly damaging actions taken by health and social care agencies, who, in cases of severe childhood obesity, occasionally suggest temporary removal of a child from the parental home. As yet we know of only a small fraction of the genetic variants that underpin variation in adiposity in the general population, and it is unlikely that those SNPs which we know thus far will, on their own, have clinical utility. However, they have pointed the way towards new pathways, the pharmacological manipulation of which may ultimately be therapeutically beneficial.

Human genetics informs pathophysiology of obesity. Although it is likely that genetic variants influencing factors such as basal metabolic rate, or the propensity to take exercise, will, in time, be found, when we look at the information gleaned from the past 15 years of molecular genetic activity we cannot avoid concluding that, as much as type 2 diabetes is clearly a disease in which pancreatic beta-cell dysfunction is a critical element, obesity is a condition in which inherent genetic predisposition is dominated by the brain. Perhaps we will gradually come to see obesity not so much as a metabolic disease (although it can have grave metabolic consequences) but more of a neurobehavioural disorder, albeit one highly susceptible to the environment[65]. Most of the monogenic causes of human obesity seem to operate through increasing the 'set point' at which body adipose stores stabilize in the individual. Individuals with mutations in leptin, the leptin receptor and *MC4R*, for example, become obese at a very young age and remain severely, but not necessarily increasingly, obese throughout their lives. Other individuals, included among which are some of the most massively obese, gradually and progressively become more severely obese over time. Could some of these individuals have a progressive neurological disorder whereby instead of the adipostatic system simply functioning at an abnormal set point, the neuronal machinery controlling energy balance itself gradually degenerates? There is a dearth of information about hypothalamic histomorphometry in the severely obese, and this is a field ripe for further study.

Table 4 | Common genetic variants associated with body mass index

Chromosome	Nearby genes	How identified	Reference
1	*NEGR1**	GWAS meta-analysis, GWAS	76, 106
1	*SEC16B, RASAL2*	GWAS	106
2	*TMEM18*	GWAS meta-analysis, GWAS	76, 106
3	*SFRS10 (TRA2B), ETV5, DGKG*	GWAS	106
4	*GNPDA2*	GWAS meta-analysis	76
5	*PCSK1**	Candidate gene	107
6	*NCR3, AIF1, BAT2*	GWAS	106
10	*PTER†*	GWAS	108
11	*MTCH2*	GWAS meta-analysis	76
11	*LGR4, LIN7C, BDNF*	GWAS	106
12	*BCDIN3D, FAIM2*	GWAS	106
16	*MAF†*	GWAS	108
16	*SH2B1*, ATP2A1*	GWAS meta-analysis, GWAS	76, 106
16	*FTO**	GWAS	69, 70
18	*NPC1†*	GWAS	108
18	*MC4R**	GWAS	74
19	*KCTD15, CHST8*	GWAS meta-analysis, GWAS	76, 106

GWAS, genome-wide association study.
* Several of the genes most closely adjacent to the associated polymorphisms (mostly SNPs but some indels (insertions and deletions)) are expressed particularly highly in the CNS.
† Reported to be associated with early onset and/or extreme obesity but, so far, not confirmed in common adult obesity.

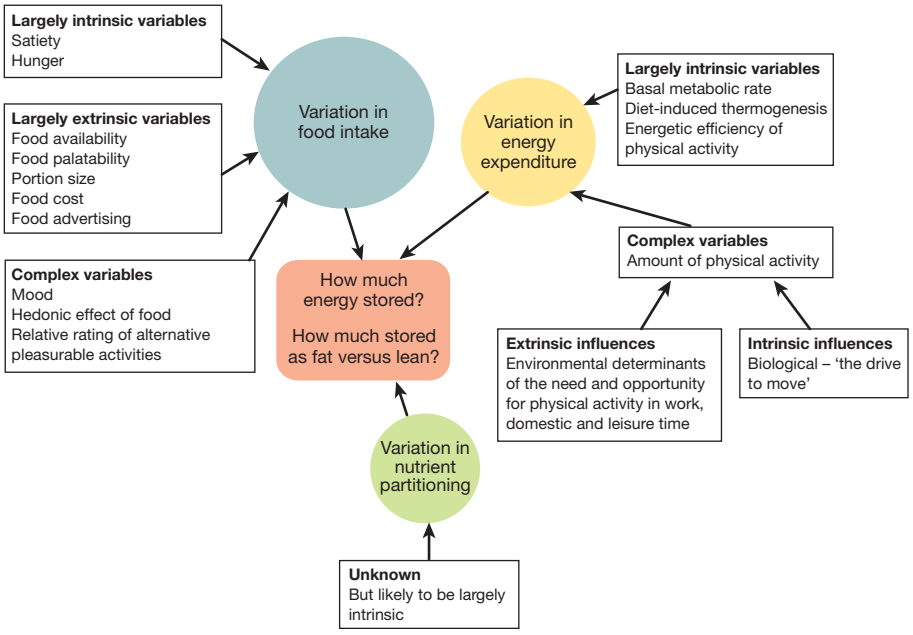
The remaining challenges

Although recent advances in the genetics of common metabolic disease have been exciting, the variants thus far detected only explain a very small fraction of the heritability of these disorders. It will be intriguing to see to what extent the remaining heritability is attributable to minor effects of common alleles, variation in gene copy number and rare mutations, and to watch the unfolding story of how they interact with environmental and epigenetic factors.

Box 2 | Variables influencing an individual's risk of becoming obese

Why are some people overweight and some people lean? This outcome results from the complex interaction between the cumulative intake and expenditure of energy and the tendency to deposit any excess of energy as either fat or lean mass (so-called nutrient partitioning). The major impact of molecular genetics on our understanding of the intrinsic variables that have an impact on energy balance is the unexpected finding that genetic variants causing severe familial obesity largely influence food intake through effects on hunger and satiety.

Importantly, many common SNPs broadly influencing adiposity across the human population are located in genes that are predominantly expressed in the brain. SNPs in the first intron of *FTO*, which are the most highly replicated common variants associated with human adiposity, are associated with alterations in appetite and food intake in humans.



Insulin resistance is a major feature of many common metabolic diseases and clearly has high heritability. It is perhaps surprising that so few genes having an impact on insulin action have thus far emerged from genome-wide approaches[77]. Gene discovery in this area is complicated by the major impact of recent diet and exercise on measures of insulin sensitivity and the fact that the measures of insulin sensitivity available in most sizeable epidemiological studies are indirect proxies that generally focus on the fasting state. The molecular mechanisms of insulin action in liver (the key target tissue in the fasting state) and both muscle and fat (the key target tissues in the post-prandial state) are known to have key differences, and it is likely that different sets of genetic variants will underpin inter-individual differences in basal and post-meal insulin sensitivity. The distribution of body fat has effects on insulin sensitivity and diabetes risk independent of its total amount and it is intriguing that SNPs affecting measures of fat distribution are now emerging[78].

As exemplified by *FTO* (see above), much effort and ingenuity will need to be expended to understand the precise mechanisms whereby risk alleles influence pathophysiology. This will need a multidisciplinary approach using cell biology, animal models and detailed pathophysiological studies in humans carrying risk variants.

Will the growing body of credible human genetic data help the pharmaceutical and biotechnology sectors in their efforts to design and develop better drug therapies for common metabolic diseases? In the 'drug discovery' part of the pipeline, knowledge that a particular potential therapeutic target, when genetically altered in humans, has an appropriate phenotype can provide reassurance about the relevance of that particular target. Additionally, knowledge that major loss- or gain-of-function mutations in that target do not result in other non-metabolic phenotypes in humans increases confidence that pharmacological manipulation of the target may have some specificity for the phenotype of interest. In this regard, information from rare highly penetrant mutations causing severe metabolic phenotypes may be of more direct utility to drug developers than common variants with subtle effects on metabolic phenotypes. Genetic studies of people with extreme familial leanness or severely obese subjects who avoid metabolic sequelae may be of particular interest.

Can human genetics accelerate or improve the development phase of the drug pipeline? When testing an antiobesity agent in terms of its ability to reduce metabolic risk it might, for example, be possible to enrich that group with genetic variants predisposing to type 2 diabetes so that an impact of weight loss on adverse metabolic outcome might be demonstrable earlier. The power of the currently available genetic information is probably insufficient for this to have a major impact at this stage. However, it would seem wise to continue to ensure that genetic material is obtained on participants from all clinical trials and to undertake post-hoc analysis examining whether one or other genetically defined subgroup had particularly pronounced therapeutic, or indeed adverse, effects.

Conclusions

Those of us who have grappled for decades with the challenge of understanding the fundamental mechanisms underlying type 2 diabetes and obesity are vulnerable to the assertion that we have been essentially misguided. It is clear that in environments where calories are difficult and expensive to access and much physical activity is required to be expended in acquiring them, obesity and type 2 diabetes are uncommon diseases[3]. It is difficult to refute the assertion that if modern populations returned to a hunter-gatherer state then obesity and diabetes would not be the major public heath threats that they now are. Nevertheless, the genetic loading that some unfortunate people receive is so adverse that they are likely to suffer metabolic disease despite their best efforts to avoid it. Human molecular genetics has allowed us to identify significant subsets of patients with obesity and/or diabetes where intrinsic biological factors have a major role, and some patients with these disease subtypes exhibit beneficial therapeutic responses to specific interventions targeted to underlying mechanism. It is also likely to have a continuing role in the validation of therapeutic targets for common forms of metabolic disease as well as the continued pathophysiological dissection of

superficially similar diseases into more refined and therapeutically relevant subtypes.

1. Maes, H. H., Neale, M. C. & Eaves, L. J. Genetic and environmental factors in relative body weight and human adiposity. *Behav. Genet.* **27,** 325–351 (1997).
2. Poulsen, P., Kyvik, K. O., Vaag, A. & Beck-Nielsen, H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance – a population-based twin study. *Diabetologia* **42,** 139–145 (1999).
3. Wild, S. *et al.* Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* **27,** 1047–1053 (2004).
4. Wardle, J., Carnell, S., Haworth, C. M. & 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).
5. Pearson, E. R. *et al.* Switching from insulin to oral sulphonylureas in patients with diabetes due to Kir6.2 mutations. *N. Engl. J. Med.* **355,** 467–477 (2006).
Describes dramatic clinical benefits resulting from identification of a specific molecular subtype of diabetes.
6. Farooqi, I. S. *et al.* 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).
Describes reversal of severe human obesity in congenital leptin deficiency by administration of recombinant leptin.
7. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF Consultation. ⟨http://www.idf.org/webdata/docs/WHO_IDF_definition_diagnosis_of_diabetes.pdf⟩ (2006).
8. Petersen, K. F. & Shulman, G. I. Etiology of insulin resistance. *Am. J. Med.* **119,** S10–S16 (2006).
9. Reaven, G. M. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* **37,** 1595–1607 (1988).
10. Cline, G. W. *et al.* Impaired glucose transport as a cause of decreased insulin-stimulated muscle glycogen synthesis in type 2 diabetes. *N. Engl. J. Med.* **341,** 240–246 (1999).
11. Turner, R. C. *et al.* Pathogenesis of NIDDM—a disease of deficient insulin secretion. *Baillieres Clin. Endocrinol. Metab.* **2,** 327–342 (1988).
12. Tattersall, R. Maturity-onset diabetes of the young: a clinical history. *Diabet. Med.* **15,** 11–14 (1998).
13. Vionnet, N. *et al.* Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus. *Nature* **356,** 721–722 (1992).
Describes first causative mutation to be identified in a familial form of diabetes.
14. Yamagata, K. *et al.* Mutations in the hepatocyte nuclear factor-4α gene in maturity-onset diabetes of the young (MODY1). *Nature* **384,** 458–460 (1996).
15. Yamagata, K. *et al.* Mutations in the hepatocyte nuclear factor-1α gene in maturity-onset diabetes of the young (MODY3). *Nature* **384,** 455–458 (1996).
Refs 14 and 15 highlight the importance of mutations in the HNF family of transcription factors in the causation of familial forms of diabetes.
16. Stoffers, D. A., Ferrer, J., Clarke, W. L. & Habener, J. F. Early-onset type-II diabetes mellitus (MODY4) linked to *IPF1*. *Nature Genet.* **17,** 138–139 (1997).
17. Horikawa, Y. *et al.* Mutation in hepatocyte nuclear factor-1 β gene (*TCF2*) associated with MODY. *Nature Genet.* **17,** 384–385 (1997).
18. Malecki, M. T. *et al.* Mutations in *NEUROD1* are associated with the development of type 2 diabetes mellitus. *Nature Genet.* **23,** 323–328 (1999).
19. Babenko, A. P. *et al.* Activating mutations in the *ABCC8* gene in neonatal diabetes mellitus. *N. Engl. J. Med.* **355,** 456–466 (2006).
20. Gloyn, A. L. *et al.* Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N. Engl. J. Med.* 350, 1838–1849 (2004); erratum **351,** 1470 (2004).
Refs 19 and 20 demonstrate that mutations constitutively activating the voltage-gated potassium channel in the pancreatic beta cell could lead to insulin-deficient diabetes from birth.
21. Støy, J. *et al.* Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc. Natl Acad. Sci. USA* **104,** 15040–15044 (2007).
22. Gill-Carey, O. & Hattersley, A. T. Genetics and type 2 diabetes in youth. *Pediatr. Diabetes* **8** (Suppl. 9), 42–47 (2007).
23. Yoshimasa, Y. *et al.* Insulin-resistant diabetes due to a point mutation that prevents insulin proreceptor processing. *Science* **240,** 784–787 (1988).
24. Accili, D. *et al.* Insulin resistance due to mutations of the insulin receptor gene: an overview. *J. Endocrinol. Invest.* **11,** 857–864 (1992).
25. George, S. *et al.* A family with severe insulin resistance and diabetes due to a mutation in *AKT2*. *Science* **304,** 1325–1328 (2004).
26. Dash, S. *et al.* A truncation mutation in *TBC1D4* in a family with acanthosis nigricans and postprandial hyperinsulinemia. *Proc. Natl Acad. Sci. USA* **106,** 9350–9355 (2009).
27. McGarry, J. D. What if Minkowski had been ageusic? An alternative angle on diabetes. *Science* **258,** 766–770 (1992).
A highly influential commentary that helped switch attention from glucose to lipid metabolism in type 2 diabetes.
28. Barroso, I. *et al.* Dominant negative mutations in human PPARγ associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* **402,** 880–883 (1999).
The first evidence in any species that disruption of PPARγ function has a severe impact on insulin sensitivity.
29. Shackleton, S. *et al. LMNA*, encoding lamin A/C, is mutated in partial lipodystrophy. *Nature Genet.* **24,** 153–156 (2000).
30. Magré, J. *et al.* Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. *Nature Genet.* **28,** 365–370 (2001).
31. Agarwal, A. K. *et al. AGPAT2* is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. *Nature Genet.* **31,** 21–23 (2002).
32. Kim, C. A. *et al.* Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy. *J. Clin. Endocrinol. Metab.* **93,** 1129–1134 (2008).
33. Rubio-Cabezas, O. *et al.* Partial lipodystrophy and insulin resistant diabetes in a patient with a homozygous nonsense mutation in *CIDEC*. *EMBO Mol. Med* **1,** 280–287 (2009).
34. McCarthy, M. I. & Zeggini, E. Genome-wide association studies in type 2 diabetes. *Curr. Diab. Rep.* **9,** 164–171 (2009).
35. Stancáková, A. *et al.* Association of 18 confirmed susceptibility loci for type 2 diabetes with indices of insulin release, proinsulin conversion, and insulin sensitivity in 5,327 non-diabetic Finnish Men. *Diabetes* **58,** 2129–2136 (2009).
36. Pascoe, L. *et al.* Common variants of the novel type 2 diabetes genes *CDKAL1* and *HHEX/IDE* are associated with decreased pancreatic beta-cell function. *Diabetes* **56,** 3101–3104 (2007).
37. Grarup, N. *et al.* Studies of association of variants near the *HHEX, CDKN2A/B,* and *IGF2BP2* genes with type 2 diabetes and impaired insulin release in 10,705 Danish subjects: validation and extension of genome-wide association studies. *Diabetes* **56,** 3105–3111 (2007).
38. Palmer, N. D. *et al.* Association of *TCF7L2* gene polymorphisms with reduced acute insulin response in Hispanic Americans. *J. Clin. Endocrinol. Metab.* **93,** 304–309 (2008).
39. Palmer, N. D. *et al.* Quantitative trait analysis of type 2 diabetes susceptibility loci identified from whole genome association studies in the Insulin Resistance Atherosclerosis Family Study. *Diabetes* **57,** 1093–1100 (2008).
40. Bouatia-Naji, N. *et al.* A polymorphism within the *G6PC2* gene is associated with fasting plasma glucose levels. *Science* **320,** 1085–1088 (2008).
41. Bouatia-Naji, N. *et al.* A variant near *MTNR1B* is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nature Genet.* **41,** 89–94 (2009).
42. Prokopenko, I. *et al.* Variants in *MTNR1B* influence fasting glucose levels. *Nature Genet.* **41,** 77–81 (2009).
43. Porte, D. Jr & Kahn, S. E. The key role of islet dysfunction in type II diabetes mellitus. *Clin. Invest. Med.* **18,** 247–254 (1995).
44. Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* **344,** 1343–1350 (2001).
45. Reaven, G. M. The fourth musketeer—from Alexandre Dumas to Claude Bernard. *Diabetologia* **38,** 3–13 (1995).
46. Højlund, K., Mogensen, M., Sahlin, K. & Beck-Nielsen, H. Mitochondrial dysfunction in type 2 diabetes and obesity. *Endocrinol. Metab. Clin. North Am.* **37,** 713–731 (2008).
47. Harding, H. P. & Ron, D. Endoplasmic reticulum stress and the development of diabetes: a review. *Diabetes* **51** (Suppl. 3), S455–S461 (2002).
48. Shoelson, S. E., Lee, J. & Goldfine, A. B. Inflammation and insulin resistance. *J. Clin. Invest.* **116,** 1793–1801 (2006).
49. van den Ouweland, J. M. *et al.* Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nature Genet.* **1,** 368–371 (1992).
50. Inoue, H. *et al.* A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nature Genet.* **20,** 143–148 (1998).
51. Sandhu, M. S. *et al.* Common variants in *WFS1* confer risk of type 2 diabetes. *Nature Genet.* **39,** 951–953 (2007).
52. Fonseca, S. G. *et al.* WFS1 is a novel component of the unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic beta-cells. *J. Biol. Chem.* **280,** 39609–39615 (2005).
53. Delépine, M. *et al. EIF2AK3*, encoding translation initiation factor 2-α kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nature Genet.* **25,** 406–409 (2000).
54. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447,** 661–678 (2007).
55. Meigs, J. B. *et al.* Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N. Engl. J. Med.* **359,** 2208–2219 (2008).
56. Lyssenko, V. *et al.* Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N. Engl. J. Med.* **359,** 2220–2232 (2008).
57. Hattersley, A. T. & Pearson, E. R. Minireview: pharmacogenetics and beyond: the interaction of therapeutic response, beta-cell physiology, and genetics in diabetes. *Endocrinology* **147,** 2657–2663 (2006).
58. Kopelman, P. G. Obesity as a medical problem. *Nature* **404,** 635–643 (2000).
59. Jéquier, E. Energy expenditure in obesity. *Clin. Endocrinol. Metab.* **13,** 563–580 (1984).
60. Lissner, L. Measuring food intake in studies of obesity. *Public Health Nutr.* **5,** 889–892 (2002).
61. Montague, C. T. *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **387,** 903–908 (1997).

62. Jackson, R. S. *et al.* Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nature Genet.* **16,** 303–306 (1997).
Refs 61 and 62 describe the first two genetic defects found to cause familial forms of human obesity.
63. Zhang, Y. *et al.* Positional cloning of the mouse obese gene and its human homologue. *Nature* **372,** 425–432 (1994).
Paper describing the discovery of leptin as an adipocyte-derived hormone with a role in the control of energy balance.
64. Huszar, D. *et al.* Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* **88,** 131–141 (1997).
First definitive evidence for the role of melanocortin 4 receptor in the control of body weight.
65. O'Rahilly, S. & Farooqi, I. S. Human obesity: a heritable neurobehavioral disorder that is highly sensitive to environmental conditions. *Diabetes* **57,** 2905–2910 (2008).
66. Krakoff, J. *et al.* Lower metabolic rate in individuals heterozygous for either a frameshift or a functional missense *MC4R* variant. *Diabetes* **57,** 3267–3272 (2008).
67. Nogueiras, R. *et al.* The central melanocortin system directly controls peripheral lipid metabolism. *J. Clin. Invest.* **117,** 3475–3488 (2007).
68. Badano, J. L., Mitsuma, N., Beales, P. L. & Katsanis, N. The ciliopathies: an emerging class of human genetic disorders. *Annu. Rev. Genomics Hum. Genet.* **7,** 125–148 (2006).
69. Frayling, T. M. *et al.* 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).
First description of a common human obesity gene discovered through a genome-wide association approach.
70. Dina, C. *et al.* Variation in *FTO* contributes to childhood obesity and severe adult obesity. *Nature Genet.* **39,** 724–726 (2007).
71. Gerken, T. *et al.* The obesity-associated *FTO* gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science* **318,** 1469–1472 (2007).
72. Cecil, J. E. *et al.* An obesity-associated *FTO* gene variant and increased energy intake in children. *N. Engl. J. Med.* **359,** 2558–2566 (2008).
73. Fischer, J. *et al.* Inactivation of the *Fto* gene protects from obesity. *Nature* **458,** 894–898 (2009).
74. Loos, R. J. *et al.* Common variants near *MC4R* are associated with fat mass, weight and risk of obesity. *Nature Genet.* **40,** 768–775 (2008).
This study reports a common variant in the vicinity of *MC4R* associated with human obesity.
75. Qi, L., Kraft, P., Hunter, D. J. & Hu, F. B. The common obesity variant near *MC4R* gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. *Hum. Mol. Genet.* **17,** 3502–3508 (2008).
76. Willer, C. J. *et al.* Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nature Genet.* **41,** 25–34 (2009).
77. Rung, J. *et al.* Genetic variant near *IRS1* is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. *Nature Genet.* **41,** 1110–1115 (2009).
78. Lindgren, C. M. *et al.* Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. *PLoS Genet.* **5,** e1000508 (2009).
79. Temple, I. K. *et al.* An imprinted gene(s) for diabetes? *Nature Genet.* **9,** 110–112 (1995).
80. Mackay, D. J. *et al.* Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in *ZFP57*. *Nature Genet.* **40,** 949–951 (2008).
81. Ræder, H. *et al.* Mutations in the *CEL* VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nature Genet.* **38,** 54–62 (2006).
82. Hearn, T. *et al.* Mutation of *ALMS1*, a large gene with a tandem repeat encoding 47 amino acids, causes Alström syndrome. *Nature Genet.* **31,** 79–83 (2002).
83. Collin, G. B. *et al.* Mutations in *ALMS1* cause obesity, type 2 diabetes and neurosensory degeneration in Alström syndrome. *Nature Genet.* **31,** 74–78 (2002).
84. McCarthy, M. I. & Hattersley, A. T. Learning from molecular genetics: novel insights arising from the definition of genes for monogenic and type 2 diabetes. *Diabetes* **57,** 2889–2898 (2008).
85. Zeggini, E. *et al.* Meta analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type-2 diabetes. *Nature Genet.* **40,** 638–645 (2008).
86. Deeb, S. S. *et al.* A Pro12Ala substitution in PPARγ2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nature Genet.* **20,** 284–287 (1998).
The first association between a common SNP in PPARγ and type 2 diabetes.
87. Saxena, R. *et al.* Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* **316,** 1331–1336 (2007).
88. Zeggini, E. *et al.* Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* **316,** 1336–1341 (2007).
89. Scott, L. *et al.* A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* **316,** 1341–1345 (2007).
90. Steinthorsdottir, V. *et al.* A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes. *Nature Genet.* **39,** 770–775 (2007).
91. Sladek, R. *et al.* A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* **445,** 881–885 (2007).
The first genome-wide association study in type 2 diabetes, focusing on more severe and early onset cases; identified SNPs are close to several islet genes.
92. Grant, S. F. *et al.* Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. *Nature Genet.* **38,** 320–323 (2006).
The first and, so far, most significant common type 2 diabetes gene identified initially through linkage and positional candidate screening in a large Icelandic population.
93. Florez, J. C. Haplotype structure and genotype-phenotype correlations of the sulphonylurea receptor and the islet ATP-sensitive potassium channel gene region. *Diabetes* **53,** 1360–1368 (2004).
94. Gudmundsson, J. *et al.* Two variants on chromosome 17 confer prostate cancer risk, and the one in *TCF2* protects against type 2 diabetes. *Nature Genet.* **39,** 977–983 (2007).
95. Clément, K. *et al.* A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* **392,** 398–401 (1998).
96. Krude, H. *et al.* Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by *POMC* mutations in humans. *Nature Genet.* **19,** 155–157 (1998).
97. Vaisse, C., Clement, K., Guy-Grand, B. & Froguel, P. A frameshift mutation in human *MC4R* is associated with a dominant form of obesity. *Nature Genet.* **20,** 113–114 (1998).
98. Yeo, G. S. *et al.* A frameshift mutation in *MC4R* associated with dominantly inherited human obesity. *Nature Genet.* **20,** 111–112 (1998).
Refs 97 and 98 are the first descriptions of human melanocortin 4 receptor deficiency, the commonest single gene disorder causing obesity in humans.
99. Holder, J. L. Jr, Butte, N. F. & Zinn, A. R. Profound obesity associated with a balanced translocation that disrupts the *SIM1* gene. *Hum. Mol. Genet.* **9,** 101–108 (2000).
100. Sahoo, T. *et al.* Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster. *Nature Genet.* **40,** 719–721 (2008).
101. Spiegel, A. Albright's hereditary osteodystrophy and defective G proteins. *N. Engl. J. Med.* **322,** 1461–1462 (1990).
102. Gray, J. *et al.* 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).
103. Han, J. C. *et al.* Brain-derived neurotrophic factor and obesity in the WAGR syndrome. *N. Engl. J. Med.* 359, 918–927 (2008); erratum **359,** 1414 (2008).
104. Yeo, G. S. *et al.* A *de novo* mutation affecting human TrkB associated with severe obesity and developmental delay. *Nature Neurosci.* **7,** 1187–1189 (2004).
105. Beales, P. R., Farooqi, I. S. & O'Rahilly, S. (eds) *Genetics of Obesity Syndromes* (Oxford Univ. Press, 2009).
106. Thorleifsson, G. *et al.* Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nature Genet.* **41,** 18–24 (2009).
107. Benzinou, M. *et al.* Common nonsynonymous variants in *PCSK1* confer risk of obesity. *Nature Genet.* **40,** 943–945 (2008).
108. Meyre, D. *et al.* Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nature Genet.* **41,** 157–159 (2009).

Acknowledgements I thank M. Adams for assistance with this manuscript. I also thank A. Hattersley for many helpful suggestions, and I. Barroso, T. Coll, S. Farooqi, R. Loos, J. Rochford, D. Savage, R. Semple, N. Wareham and G. Yeo for discussions over many years. I acknowledge the support of the MRC Centre for Obesity and Related Metabolic Diseases, the Wellcome Trust, the NIHR Cambridge Biomedical Research Centre, and the EU for their continuing support of our work in this area.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The author declares competing financial interests: details accompany the full-text HTML version of the paper at www.nature.com/nature. Correspondence should be addressed to S.O.R. (so104@medschl.cam.ac.uk).