The genetics of type 2 diabetes

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Introduction

Of the various subtypes of diabetes, type 2 diabetes has the greatest impact on health worldwide. Around 150 million people have type 2 diabetes, and the prevalence will rise by 40% by 2010 [1]. Type 2 diabetes and its complications already consume 5–10% of health budgets in many countries [2]. Yet, despite the manifest importance of this condition, and many years of detailed metabolic study, understanding of the basic aetiological mechanisms remains fragmentary [3]. This contrasts with the other major subtype of diabetes, type 1, where it is well-established that the major aetiological process involves autoimmune destruction of the insulin-secreting pancreatic beta-cells. Type 2 diabetes displays a clear association with obesity, and the clustering of type 2 diabetes, hypertension, dyslipidaemia and macrovascular disease within individuals and families, indicates that reduced sensitivity to the peripheral actions of insulin (i.e. insulin resistance) plays a key role in disease pathogenesis [4]. However, since many individuals with marked insulin resistance still manage to maintain normal glucose homeostasis, variation in the compensatory capacity of the pancreatic beta–cell must be an equal partner in disease progression [5]. Efforts to characterize further the crucial intermediate metabolic steps in the development of full-blown type 2 diabetes have largely foundered on the rocks of individual heterogeneity and the complicating effects of hyperglycaemia (and its treatment) on the very intermediate traits that investigators might wish to measure.

Improved glycaemic control has been clearly shown to reduce the burden of diabetic complications [6]. Since currently available treatments rarely achieve the goal of lifelong restoration of normoglycaemia, there is manifest need for improved therapeutic and preventative modalities targeted to the key pathogenetic steps. As with the other complex inherited traits, the hope is that genetic analyses will deliver the molecular understanding that will inform future drug development.

Nature and nurture

The earliest evidence for a major genetic contribution to the development of type 2 diabetes came from classical experimental paradigms including twin, family and population studies. These clearly demonstrate that the closer the genetic relationship between two individuals, the more likely they are to share the same glucose tolerance status. Thus, identical twin pairs show a higher concordance rate for diabetes than do fraternal twins [7, 8] and first-degree relatives of diabetic individuals have lifetime rates of diabetes up to four times the background population prevalence [9]. Marked differences in diabetes prevalence between distinct ethnic groups living in adjacent, similar environments (as a result of cultural isolation and/or migration) provide additional evidence for genetic effects [10]: in some instances, the risk of diabetes is clearly related to the relative proportions of genetic contribution from high-risk and low-risk ancestral populations [11]. Recent successes in identifying susceptibility loci for type 2 diabetes provide the clearest arguments for the role of genes.

As with other complex traits, genetic predisposition is only part of the story: nongenetic (environmental) factors determine whether, and how, risk-associated genotypes lead to overt disease. Lifestyle-related factors such as physical activity levels and diet are, next to age, the most important determinants of the penetrance of a given set of diabetes-susceptibility genotypes. Thus, the prevalence of type 2 diabetes often increases dramatically when populations switch from rural and/or low risk dietary and physical activity patterns and adopt more urban, Western lifestyles [12, 13]. Physical activity has been shown to reduce insulin resistance [14] whereas a diet rich in fat and carbohydrate, but poor in fibre content, can aggravate it [15]. The consistent association between type 2 diabetes and measures of obesity, especially central obesity, almost certainly reflects common environmental as well as genetic factors underlying both conditions.

In recent years, a robust association between low birthweight and metabolic and cardiovascular disease

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(including type 2 diabetes) in adulthood has led to the hypothesis that suboptimal fetal nutrition represents an important environmental stimulus to future diabetes risk [16]. Though studies seeking direct support for this 'thrifty phenotype' mechanism in humans have proven inconclusive [17], the balance of evidence does favour the concept that lifelong metabolic 'programming' can be initiated in early life by the complex interaction of fetomaternal environment and fetal genotype. The plausibility of a genetic contribution to the observed association between fetal and adult phenotypes is enhanced by the realization that the genes expected to contribute to variation in fetal growth and survival (those involved in regulation of insulin action and secretion) are precisely the same genes implicated in the susceptibility to adult disease [18].

On the trail of diabetes genes

Several, complementary, approaches to disease gene identification are being actively pursued in the study of type 2 diabetes.

In some families, diabetes appears to be inherited as a monogenic trait, segregating in either classical Mendelian or maternal (mitochondrial) fashion. Autosomal dominant, early onset diabetes (known as maturity-onset diabetes of the young, MODY) has been revealed to be a genetically heterogeneous condition, with mutations in the gluco-kinase gene [19] and in genes for various transcription factors (hepatocyte nuclear factor (HNF)-1α [20], HNF-1β [21], HNF-4α [22], insulin promotor factor 1 (IPF1) [23] and neurogenic differentiation 1 (NEUROD1) [24]), each capable of producing a phenotype in which beta-cell dysfunction predominates. In other families, diabetes results from defects in the insulin gene leading to mutant–insulin syndromes [25], and in the genes for the insulin receptor [26] and peroxisome proliferation-activated receptor gamma [27], producing extreme insulin-resistance. In yet other families, diabetes is one component of a broader syndrome (e.g. Wolfram syndrome, familial partial lipo-dystrophy [28]). The syndrome of maternally inherited diabetes with sensorineural deafness (MIDD) [29] results from a mutation in the mitochondrial tRNA$^{Leu(UUR)}$ gene, at a site also implicated in a neurological condition named MELAS mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. By and large, studies of these genes in typical multifactorial type 2 diabetes, have not revealed them to be major players. However, there is no clear clinical demarcation between monogenic and multifactorial forms, and some genes (e.g. *IPF1*) seem capable of producing either phenotype [23, 30]. Such discoveries are providing crucial insights into the mechanisms responsible for the maintenance of normal glucose homeostasis. In particular, identification and characterization of the various MODY genes is shedding new light on the hidden inner workings of the beta-cell and the biochemical and transcriptional networks responsible for normal glucose-regulated insulin secretion.

The seminal studies on the ob/ob mouse demonstrate how rodent genetics can transform our understanding of human pathophysiology [31]. There are several rodent models of type 2 diabetes and related traits, but polygenic models such as the Goto-Kakizaki (GK) and Otsuka long Evans Tokushima fatty (OLETF) rats are likely to provide the most appropriate resources for identifying those genes relevant to human disease [32–34]. The GK rat, for example, shows, without evidence of overt obesity, the main metabolic, hormonal and vascular features described in human diabetes. Results from two independent studies have identified at least seven loci controlling diabetes-related subphenotypes (mainly glucose intolerance, impairment of insulin secretion and adiposity/body weight) and emphasize the complex physiology (different loci seem to influence fasting and postload blood glucose) [32, 33]. Though there is no guarantee that the genes causing diabetes in these polygenic rodent models are the same as those involved in human disease, these analyses (like those of human subtypes) provide examples of 'real' diabetes genes and clues to the key metabolic pathways responsible for the maintenance of normal glucose homeostasis. Similar insights are also likely to come through large-scale mutagenesis projects [35], and from transgenic manipulation of either single [36] or multiple [37] candidate genes.

Advances in our understanding of the physiology of nutrient regulation and of diabetes pathogenesis, generate a constantly expanding list of genes that, on the grounds of biology and/or implication in the development of human single-gene or rodent diabetes, are candidates for a role in typical multifactorial type 2 diabetes. The screening of these genes for nucleotide variants that are associated with type 2 diabetes is a core component of much diabetes genetics research. Such association analyses seek to demonstrate that a particular variant has higher than expected prevalence on 'disease-gene-carrying' chromosomes through, for example, comparison of genotype frequencies between groups of unrelated cases and control subjects. Because such studies rely on linkage disequilibrium for detection of a signal, positive results are only likely at, or very close to, functional variants. Association studies therefore provide a powerful approach for analysis of small regions, but remain problematical for screens of larger genomic regions. In type 2 diabetes, consistent susceptibility effects have only been identified at a small number of loci to date, including (arguably) the variable region upstream of the insulin gene (insulin variable number random repeat (INS-VNTR)) [38], and the genes for IPF-1 [30, 39], the sulphonylurea receptor

[40, 41] and insulin–receptor substrate-1 [42]. This may, of course, mean that researchers have failed to study the 'right' candidates. However, there is no doubt that type 1 error, inadequate power, population stratification effects and the vagaries of linkage disequilibrium relationships in different populations have all contributed to the often contradictory results of such candidate gene studies [43]. A further limitation is that many studies have hitherto focused on coding regions, leaving regulatory gene sequences mostly unexplored. Given that so many of the MODY genes are involved in gene regulation, this may be a serious omission. It is clear that the revolution in the understanding of human genetic variation arising from the human genome project will, in the future, encourage more systematic and rational approaches to the evaluation of candidate loci for disease risk, characterized by large study populations, family–based association methods [43] and assessment of variation at the level of the haplotype rather than individual alleles.

All the methods described above make implicit assumptions about the likely biology of the genes contributing to multifactorial type 2 diabetes. In contrast, the genome-wide linkage approach attempts to locate such genes through their genomic position alone [43]. The rationale is straightforward: if family members share a given phenotype, they will also show excess sharing of chromosomal regions immediately surrounding genes contributing to that phenotype. Diabetes-susceptibility genes can therefore be revealed by finding regions of increased allele-sharing in collections of small multiplex families (typically affected sibpairs) [43]. This approach has been successfully applied to several complex inherited traits including type 1 diabetes, obesity, and psoriasis [44–46]. Because such studies depend on the detection of cosegregation within families (i.e. linkage) and, unlike association studies, do not require allele-specific effects (i.e. linkage disequilibrium), they are capable of detecting a signal over a wide area (10–30 centimorgan), thereby allowing analysis of the entire genome with only a few hundred polymorphic markers.

Around 25 genome-wide scans for type 2 diabetes are underway worldwide, involving over 5000 pedigrees from diverse ethnic groups [47–52]. The relatively low sibling relative risk for diabetes (about 3.5 fold increase compared with the general population [9]) sets a limit to the size of linkage signal that can be expected, and massive family collections and meticulous attention for detail are essential for success. In the UK, for example, the British Diabetic Association Warren 2 consortium is currently scanning over 1000 British type 2 diabetic sibpairs. These daunting experimental requirements have certainly slowed the delivery of results, but some consistent patterns can now be discerned through the fog of data [47–52]. It is clear that there is no single major gene of overwhelming importance

in type 2 diabetes (nothing akin to HLA in type 1). However, several genomic regions (e.g. on chromosomes 1, 7, 11, 12 and 20) are showing interesting replications across datasets and thus represent foci for detailed exploration. New statistical methodologies (e.g. to exploit multilocus effects [53] and to analyse quantitative, as opposed to discrete, traits [54]) promise to permit us to squeeze more power from our existing studies.

Such genome-wide scans can identify regions of interest, but these may still contain up to 20 million base-pairs: finding the precise site(s) of aetiological variation within these regions represents a major challenge. Here, researchers stand to benefit from explosive technological developments (single nucleotide polymorphism (SNP) genotyping, proteomics, transcriptional profiling) and the burgeoning genomics databases (cataloguing human gene sequences, expression profiles and genomic variation) [55, 56]. These enable a multifaceted attack which utilizes linkage disequilibrium mapping to refine disease gene location, together with bioinformatics and transcriptional profiling tools to pick out the regional genes with the strongest biological candidacy. These approaches are now bearing fruit, as amply demonstrated by the recent report implicating the calpain-10 gene as a major susceptibility gene in Mexican Americans [47, 57].

The road ahead

What can we infer from the current state of knowledge about the genetics of type 2 diabetes? It is clear that predictions of single major susceptibility genes were overly optimistic: individual susceptibility is almost certainly governed by the interaction of multiple genetic and environmental effects. There are good theoretical and biological reasons to believe that many of these susceptibility variants will be common polymorphisms in key regulatory genes [58]. As Neel pointed out several decades ago [59], genetic variants which today (given sedentary lifestyle and cafeteria diets) predispose to diabetes and obesity, might, in prehistoric times (when food supply was erratic) have been positively advantageous, and therefore maintained at high frequency. Whilst some of these diabetes-susceptibility variants might be very old indeed (predating the out-of-Africa expansion of modern humans) and contribute to disease worldwide, others may have become enriched in particular ethnic groups through interaction with specific environment, and/or genetic drift. Such effects may help to explain the marked ethnic differences in diabetes prevalence [1], and some of the difficulty replicating genome scan results across different populations [47–52]. In addition, there is an increasing suggestion that the seeds of adult diabetes are sown in early life. Recent data demonstrating parent-specific transmission effects at the insulin gene

[38], together with the evidence for excess diabetes in the mothers of subjects with type 2 diabetes [60], and the known associations between foetal growth and adult disease [16], all suggest that susceptibility to adult diabetes may be initiated by genetic and environmental events operating in early life.

The spectacular advances in information and technology arising out of the Human Genome Project [55], combined with the massive clinical resources available to the research community and a spirit of international collaboration (exemplified by the efforts of the International Type 2 Diabetes Linkage Analysis Consortium, which acts as a forum for joint analysis of much of the world's type 2 diabetes genome scan data) provide a solid basis for future developments in this field. The expectation is that the coming decade will see the molecular basis of susceptibility to type 2 diabetes (and a host of other related conditions) laid bare.

Where will the genetic information take us? The hope is that it will inform future drug discovery programs and deliver targeted treatments that allow lifelong restoration of normal metabolic homeostasis. By identifying the pathways and tissues involved in the gradual metabolic decompensation that precedes full-blown diabetes, genetic studies should identify new therapeutic targets in fundamental pathways, and direct efforts to target therapies to relevant tissues. By allowing those individuals at greatest personal risk of future diabetes to be identified (on the basis of genotype as well as family history and environmental exposure), preventative measures and presymptomatic therapeutics can be targeted to those likely to benefit. By improving our nosological classification of type 2 diabetes and our understanding of pharmacogenetics, and thereby providing a sound basis for subdividing patients according to the predominant pathophysiological defect and predicted therapeutic response, rational individualized treatment selection becomes an achievable goal.

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