Genetic markers in diabetes mellitus: the need and promise for specific drug therapies in defined subtypes of diabetes patients

"Present knowledge of genetic factors in Type 2 diabetes establishes both an opportunity and a mandate to examine the potential for improved diabetes management by individualizing drug choices..."

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An estimated 24 million people in the USA (>8% of the population) and approximately 250 million people worldwide have diabetes [101]. When it is poorly controlled, diabetes has acute medical consequences resulting from osmotic diuresis, disturbed fluid and electrolyte balance, compromised immune function and, in extremely insulin-deficient patients, ketoacidosis. Of equal or greater importance, the diagnosis of diabetes brings with it a markedly increased risk of long-term complications. Diabetes-associated macrovascular disease contributes to an increased occurrence of myocardial infarction, congestive heart failure, stroke and peripheral vascular disease, and microvascular complications of diabetes often lead to loss of vision, renal insufficiency and disabling symptomatic neuropathies. In the USA, diabetes is the seventh leading cause of death, largely from the impact of its long-term complications, with financial costs that exceed US$150 billion per year [101].

The development of diabetes in most individuals results from an unfavorable confluence of environmental and genetic factors. In Type 1 diabetes, it is thought that yet unidentified environmental insults (toxic, infectious or other), acting in a susceptible genetic background, lead to initiation and progression of autoimmune β-cell destruction. In Type 2 diabetes, lifestyle factors (excess calorie intake, decreased exercise and possibly specific dietary components), again acting in a susceptible genetic background, typically result in both insulin resistance and compromised insulin secretion. The common defining biomarker for diabetes is hyperglycemia and, irrespective of the underlying cause, compelling data indicate that improved control of blood glucose in diabetes relieves acute symptoms, reduces long-term complications, and decreases associated morbidity and mortality. Although there is ongoing debate on the preferred target level for glycemia [1], the accepted fundamental principle is one of bringing blood glucose as close as possible to normal without inducing an unacceptable frequency or severity of hypoglycemia. Further benefit is often attained from additional treatment directed to normalizing blood pressure and circulating lipids, as well as specific interventions for diabetes complications, such as laser therapy for retinopathy. This article will focus on current approaches to blood glucose control.

The management of glycemia in diabetes typically includes attention to diet and exercise combined with pharmacologic agents selected from a palette of injectable and oral drugs. Advances in available forms of insulin and other drugs over the past two to three decades, plus home glucose meters and, for some patients, devices such as insulin pumps and continuous glucose monitoring systems, has substantially increased the capacity of diabetes patients to control their blood glucose levels and to decrease the associated long-term risks. However, current therapeutic strategies still often fail to bring patients to glycemic targets. In the USA, data from the National Health and Nutrition Examination Survey (NHANES) indicates that only approximately 50% of diabetes patients are at or below the conservative hemoglobin A1c goal of 7% [2].

In considering strategies for improving glycemic therapy, there is increasing interest in approaches that better link treatment to specific diabetes subtypes in individual patients. It has long been known that diabetes is a heterogeneous disorder. Recognition of different forms of the disease corresponding to today's Type 1 and 2 diabetes is evident in medical writing dating back 2000 years [3]. Standard treatment approaches to these two forms of diabetes differ, with early initiation of insulin in patients recognized to have Type 1 diabetes and often long periods of management with oral hypoglycemic agents in patients with Type 2 diabetes. More refined examination of individual phenotypes, biochemical markers, and inheritance patterns over the past several decades has progressively identified additional diabetes subtypes, such as maturity onset diabetes of the young (MODY),

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various forms of lipoatrophic diabetes and syndromes of extreme insulin resistance. With rapid advances in molecular genetic technologies, there has been remarkable recent progress in our understanding of the reality and complexity of diabetes subtypes. There are presently more than 27 monogenic forms of diabetes for which a specific mutant causal gene has been identified [4,5]. Most of these disorders are rare and thus account for only a small fraction of diabetes. An exception is MODY, which accounts for 1–2% of diabetes in various populations [6]. MODY patients were first recognized based on characteristic clinical features that include autosomal dominant inheritance, onset under age 25 years in some but not all family members, and often long periods of successful management with oral agents versus insulin (an otherwise unusual feature of early onset diabetes) [7]. A total of six genes have thus far been identified as monogenic determinants of the various forms of MODY [8].

Patients with monogenic forms of diabetes demonstrate the potential for utilization of genetic data to guide preferred choices for specific drug therapy. For example, mutations in the *KCNJ11* gene have been identified in approximately half of patients with neonatal diabetes (onset prior to 6 months of age) [9]. These patients have functional defects in the *KCNJ11*-encoded Kir6.2 subunit of the pancreatic β-cell K_{ATP} channel, which is a target for sulfonylurea drugs. Even after many years on insulin injections, patients recognized to have *KCNJ11* mutations often can be successfully transitioned to oral sulfonylureas, with a resulting decrease in hemoglobin A1c levels. The MODY2 form of diabetes provides a second example of genetic diagnosis guiding therapeutic strategy [10]. MODY2 results from mutations in the glucokinase gene that lead to a decrease in its affinity for glucose and a consequent altered set point for insulin secretion. Blood glucose is precisely regulated, but to a slightly higher than normal concentration. These patients typically have mildly elevated blood glucose levels, with little change in hemoglobin A1c from an average value of 6–7% whether on insulin, oral agents or no treatment. They appear to have little or no increased risk of long-term complications irrespective of treatment strategy and, once recognized, are best maintained off all therapy except during pregnancy, when insulin may be needed to protect a non-MODY2 fetus from developing β-cell hyperplasia in response to the mild maternal hyperglycemia. The most common forms of MODY diabetes (MODY1 and -3) result from mutations in the HNF4α and HNF1α transcription factors, respectively [10,11]. The specific mechanisms linking these transcription factors to the development of diabetes are not known, but these patients have been observed empirically to be highly sensitive to sulfonylureas. Although MODY1 and -3 patients are often treated with insulin prior to genetic diagnosis, they can frequently be transitioned when correctly diagnosed to sulfonylureas, with a resulting improvement in blood glucose control. With the exception of the UK, where a highly successful program has focused on the genetic diagnosis of MODY, most MODY patients throughout the world are not correctly diagnosed and often unnecessarily treated with insulin. In the USA, a conservative estimate is that 1% of all diabetes patients have undiagnosed MODY1 or -3 diabetes, and fewer than 15% of these patients are correctly diagnosed [Hattersley AT, Pers. Comm.]. This projects to more than 200,000 individuals in the USA alone who might be more effectively and less expensively treated with an oral sulfonylurea if correctly diagnosed by gene sequencing. Although data analyzing the cost–effectiveness of intensified screening for MODY, neonatal diabetes and other forms of monogenic diabetes have not been published, it can be anticipated that genetic screening for these subtypes of diabetes by primary care physicians as well as endocrinologists will become a standard part of disease management as the cost of gene sequencing continues to decline.

The known monogenic forms of diabetes illustrate the types of molecular abnormalities that can lead to diabetes and the potential for individualizing drug therapy based on specific diabetes subtype. What is our current knowledge of genetic factors that contribute to the much more common Type 2 diabetes phenotype, and what is the potential for individualizing therapy of patients with Type 2 diabetes based on their genetic makeup? These questions were recently addressed by an expert panel assembled by the US Endocrine Society and the American Diabetes Association, which resulted in the publication of a set of guidelines for future investigation [5]. A combination of candidate gene and genome scanning approaches has now identified at least 23 genes with sequence variations that are significantly associated with Type 2 diabetes in multiple populations [12]. Numerous additional genes have been linked to diabetes through smaller scale studies in single populations. Each

of these genetic factors, most of which consist of sequence polymorphisms, makes a statistically significant but quantitatively small contribution to overall diabetes risk (typically on the order of a 1.5-fold increased risk). The genetic determinants of risk in most patients with Type 2 diabetes are thought to derive from the combined effects of many genes (a polygenic disorder), and the totality of genes identified to date is estimated to account for less than 10% of the overall genetic risk. Unless dominant genetic factors are unexpectedly identified, full understanding of the genetic determinants of Type 2 diabetes is likely to require the discovery of many more diabetes genes and probably new approaches to analyze the combinatorial effects of multiple, low impact genetic variants. Although this is a daunting prospect, such knowledge may in fact progress rapidly with advancing sequencing technologies, the accelerating generation of full genome sequence data, and new insights into genetic organization and regulation (e.g., the role of small RNAs [13]).

Even with the limited number of Type 2 diabetes genes thus far identified and the modest contribution of individual genes, there are encouraging early data suggesting that some of the currently recognized genetic polymorphisms can have practical impact on choices for therapy in Type 2 diabetes management. For example, in a recently published study on a Chinese Type 2 diabetes population, patients with a 359Ala/Ala as compared with a Ser/Ser polymorphism in the *ABBC8* (Sur1) sulfonylurea receptor gene were found to have a modest but significant increase in sulfonylurea responsiveness [14]. In another study, a non-sequence-changing G to A single nucleotide polymorphism in the *SLC47A1* gene (encoding the multidrug and toxin extrusion protein 1 [MATE1]) was associated with significantly greater effectiveness of metformin [15]. This appears to make mechanistic sense, since the MATE1 protein is involved in biliary and urinary excretion of metformin. Other studies have provided data suggesting potential links of polymophisms in the *TCF7L2* transcription factor gene to sulfonylurea responsiveness [16], the *PPARγ* gene to thiazolidinedione responsiveness [17] and the *OCT1* gene to metformin responsiveness [18]. For each of these observations, further studies are needed to confirm the association with specific drug responsiveness and define the significance for cost–effectiveness and outcomes in Type 2 diabetes.

Current algorithms for treatment of Type 2 diabetes focus on combining lifestyle modification (diet and exercise) with drug therapy [19]. Decisions on sequential choices of oral agents and insulin have been based on analyses of efficacy, potential synergy in mechanisms of action and cost. Despite extensive evidence for heterogeneity of Type 2 diabetes, these treatment algorithms have for the most part approached all patients as if Type 2 diabetes is a homogeneous disorder. Present knowledge of genetic factors in Type 2 diabetes establishes both an opportunity and a mandate to examine the potential for improved diabetes management by individualizing drug choices based on patient genotype.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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