Type 2 diabetes mellitus: from genes to disease

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Abstract:
The development of type 2 diabetes (T2DM) is determined by two factors: genetics and environment. The genetic background of T2DM is undoubtedly heterogeneous. Most patients with T2DM exhibit two different defects: the impairment of insulin secretion and decreased insulin sensitivity. This means that there are at least two pathophysiological pathways and at least two groups of genes that may be involved in the pathogenesis of T2DM. As far as genetic background of T2DM is concerned, the disease may be divided into two large groups: monogenic and polygenic forms. In this review, we present genes known to cause rare monogenic forms of diabetes with predominant insulin deficiency (MODY – maturity-onset diabetes of the young, MIDD – maternally inherited diabetes with deafness) and uncommon syndromes of severe insulin resistance. We also describe some of the main approaches used to identify genes involved in the more common forms of T2D and the reasons for the lack of spectacular success in this field. Although major genes for T2DM still await to be discovered, we have probably established a "road map" that we should follow.

Key words: diabetes, gene, polygenic, monogenic

Introduction

Diabetes is one of the most common metabolic disorders. It is estimated that the number of diabetes patients worldwide has already exceeded 200 million [92]. This creates a need to understand the etiology of the disease, genetic and environmental factors influencing development of diabetes. Diabetes is a group of metabolic diseases that are characterized by elevated glucose level. Poorly controlled or undiagnosed disease may be associated with so called late complications of diabetes such as accelerated atherosclerosis, blindness, renal insufficiency, stroke, and amputation of extremities. Diabetes is also associated with a decrease in life expectancy. These facts make diabetes a major health problem. There are two main forms of diabetes: type 1 and type 2. It is type 2 diabetes (T2DM), previously known as non-insulin dependent, that is the much more prevalent form, responsible for 90% of the disease prevalence [92, 125]. In the majority of the industrialised world societies this disease affects a few percent of the entire population [125]. Recent publications indicate an increase in the prevalence of diabetes world-wide, especially in younger people [80] affecting a substantial percentage of the pediatric age group in some populations [30]. T2DM is characterised by the presence of two basic abnormalities: impairment of insulin secretion and decrease in insulin sensitivity [52]. The disease creates a large pathophysiological spectrum from a predominantly secretory defect with moderate, if any, degree of insulin resistance to a predominantly insulin resistant disease with relative insulin deficiency. Whereas insulin resistance can be demonstrated early in life, many