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Genetics of diabetes – Are we missing the genes or the disease?

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ABSTRACT

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action (American Diabetes Association, 2011). The vast majority of cases of diabetes fall into two broad categories. In type 1 diabetes (T1D), the cause is an absolute deficiency of insulin secretion, whereas in type 2 diabetes (T2D), the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. However, the subdivision into two main categories represents a simplification of the real situation, and research during the recent years has shown that the disease is much more heterogeneous than a simple subdivision into two major subtypes assumes.

Worldwide prevalence figures estimate that there are 280 million diabetic patients in 2011 and more than 500 million in 2030 (http://www.diabetesatlas.org/). In Europe, about 6–8% of the population suffer from diabetes, of them about 90% has T2D and 10% T1D, thereby making T2D to the fastest increasing disease in Europe and worldwide. This epidemic has been ascribed to a collision between the genes and the environment. While our knowledge about the genes is clearly better for T1D than for T2D given the strong contribution of variation in the HLA region to the risk of T1D, the opposite is the case for T2D, where our knowledge about the environmental triggers (obesity, lack of exercise) is much better than the understanding of the underlying genetic causes. This lack of knowledge about the underlying genetic causes of diabetes is often referred to as missing heritability (Manolio et al., 2009) which exceeds 80% for T2D but less than 25% for T1D. In the following review, we will discuss potential sources of this missing heritability which also includes the possibility that our definition of diabetes and its subgroups is imprecise and thereby making the identification of genetic causes difficult.

1. Type 1 diabetes

T1D is due to autoimmune destruction of pancreatic beta-cells leading to dependence upon insulin injections. It affects an excess of 20 million people worldwide with an increase of 2 to 5 percent per year in several countries. This rise appears to be primarily in younger children (International Diabetes Foundation, 2006; Patterson et al., 2009; Svensson et al., 2009) and T1D accounts for approximately two-thirds of new diagnoses of diabetes in patients <20 years of age in the United States (Group, 2006, 2007). The reasons for the increasing incidence are unknown, but environmental factors seem to play an important role. The incidence of T1D varies based upon geography, age, gender, and family history (International Diabetes Foundation, 2006). Interestingly, when people relocate from a region of low to high incidence, their risk of developing T1D also increases, suggesting a causative role for environmental factor(s). This may imply the existence of some environmental determinants acquired with a more westernized lifestyle and that exposures *in utero* or very early infancy are important risk factors (Söderström et al., 2011; Banin et al., 2010). In contrast, wide variations in incidence between neighboring regions with similar environment emphasize the importance of genetic risk factors.

The risk of T1D is increased in close relatives of patients with T1D of Caucasoid origin: no family history (0.4%t), offspring of an affected mother (2 to 4%), affected father (5–8%), both parents affected (>30%), sibling of affected patient (5%), dizygotic twin (8%), and monozygotic twin (50% lifetime risk with 30% risk within 10 years of diagnosis of the first twin) (Kyvik et al., 1995; Pociot et al., 1993).

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A number of pancreatic autoantigens play an important role in the progression of autoimmune islet injury including autoantibodies to glutamic acid decarboxylase (GAD), insulin, insulinoma-associated protein 2 (IA-2), and zinc transporter, ZnT8. These autoantigens are probably not involved in the initiation of the beta-cell injury but rather represent a secondary phenomenon, being released only after the initial injury (Martin et al., 2001; Pescovitz et al., 2009; Petersen et al., 1993; Wong et al., 2004).

Environmental factors have been implicated in the pathogenesis of T1D both as triggers and accelerators of beta-cell destruction (Knip et al., 2005). The strongest evidence for environmental influence is the demonstration in multiple populations of a rapid increase in the incidence of T1D (Gale, 2002). Environmental factors include viral infections (Filippi and von Herrath, 2008), immunizations (Hviid et al., 2004), diet – especially exposure to cow's milk at an early age (Vaarala, 2005), vitamin D deficiency (Hyppönen, 2010), and perinatal factors such as maternal age, history of preeclampsia, and neonatal jaundice. High birth weight and early weight gain are risk factors for T1D (Harder et al., 2009), while low birth weight increases the risk of developing T2D (Hales et al., 1991).

2. Type 2 diabetes

T2D develops when pancreatic beta-cells no longer can increase their insulin secretion to compensate for increasing insulin resistance imposed by increasing obesity (Lyssenko et al., 2008). In contrast to T1D, there is no formal definition of T2D; therefore, patients who do not fulfill criteria of T1D, LADA (see below), secondary diabetes, or monogenic forms of diabetes are considered to have T2D. Although T2D is a disease of adults, it is not uncommon that T2D is diagnosed already in adolescents in high-risk countries like in Asia, Middle East and USA. The lifetime risk of developing T2D is 40% for individuals who have one parent with T2D and almost 70% if both parents are affected (Köbberling and Tillil, 1982).

In contrast to T1D, the risk is higher if the mother, rather than the father, is affected (Groop et al., 1996). There are many potential reasons for this including a role for the intrauterine environment in programming events later in life. Further, the concordance rate of T2D in monozygotic twins is about 70%, while the concordance in dizygotic twins is only 20–30% (Kaprio et al., 1992; Newman et al., 1987). There are also large differences in prevalence between ethnic groups that seem to depend on genetic factors. In Scandinavia, immigrants from the Middle East or Asia have twofold to threefold increased risk of T2D compared to native Swedes. In addition, they have a stronger family history than Scandinavians (Glans et al., 2008). The T2D epidemic can largely be ascribed to the worldwide increase in obesity during the last 30 years, e.g. more than 60% of individuals older than 15 in the UK and the US are overweight (BMI > 25). One possible reason is that genetic selection has favored energy-preserving genotypes (thrifty genotype); individuals living in an environment with unstable food supply could maximize probability of survival if they could efficiently store energy (Neel, 1962). Although the thrifty gene hypothesis provides an appealing explanation to the obesity and T2D epidemic by suggesting survival advantage of thrifty genes during periods of famine, however, formal proof for this hypothesis is still lacking.

3. LADA, MODY, and spectrum of diabetic disorders

The spectrum of diabetic disorders includes more than T1D and T2D. It is rather likely that they represent the extremes of a continuum with autoimmunity, insulin deficiency and T1D on one end and dysfunctional metabolism, metabolic syndrome and T2D on the other (Fig. 1). This does not exclude the possibility that they may share common pathogenic mechanisms like innate immunity (inflammation) which seems to be present in both forms of diabetes (Pickup and Crook, 1998). Also, diabetes is a progressive disease, and a T2D patient often develops impaired insulin secretion and a T1D-like phenotype after 20 years of duration, whereas it is not uncommon that T1D patients show features of the metabolic syndrome after long duration (Thorn et al., 2005). LADA (Latent Autoimmune Diabetes in Adults) is a common subgroup of diabetes accounting for about 7% of all diabetic patients in Europe (Fig. 2). LADA is usually defined as GAD antibody (ab) positive diabetes with onset greater than 35 years of age (Groop et al., 2006; Tuomi et al., 1999, 1993). No need for insulin treatment during the first 6 months is often a third criterion but definition of insulin need is rather subjective. Leaving out this would miss patients with classical late-onset T1D, but they amount to not more than 10% of patients with GAD ab positive diabetes with onset greater than 35 years. LADA is defined by the presence of GAD ab, but the cutoff for defining GAD ab positivity is the same as for T1D which does not exclude that GAD ab levels below this cutoff would have a pathogenic influence on beta-cell function. Therefore, LADA with high ab titers are found to the left of the spectrum close to T1D, whereas LADA with lower titers is to the right of the spectrum close to T2D. MODY (Maturity-Onset-Diabetes of the Young) represents monogenic forms of diabetes with well-defined mutations in more than 6 different genes, and this number is still increasing. The disease is characterized by autosomal dominant transmission of early-onset (<25 years) diabetes and varying degree of beta-cell dysfunction (Tattersall, 1974). A considerable part of patients originally classified as having T1D without autoantibodies and HLA-risk genotypes, but with a family history of diabetes, may in fact have MODY (Moller et al., 1998). It was long debated whether the MODY genes would harbor common less penetrant variants increasing risk of T2D; now, this seems to be the case for most of them including *HNF1A, HNF4A, HNF1B, GCK, PDX1*, etc (Voight, Scott, Steinthorsdottir et al., 2010). MODY shows extreme allelic heterogeneity meaning that most MODY mutations are unique; to date, there are more than 200 mutations described in the *GCK* (MODY2) and *HNF1A* (MODY3) genes (Murphy et al., 2008).

The drawback of this is that an appropriate diagnosis of MODY requires sequencing. Given the limited sequencing capacity until now, it has not been possible to perform large epidemiological studies, and therefore, the true prevalence of different MODY forms is not known (today estimated to be less than 3% of all diabetic patients), nor it is known whether MODY patients harbor additional modifying mutations.

Maternally inherited diabetes and deafness (MIDD) is due to a A3242G mutation in mitochondrial DNA (mtDNA) (van den Ouweland et al., 1992). As mtDNA is only transmitted from the mother, MIDD shows maternal transmission. In addition to hearing loss, many patients also display neurological problems similar to

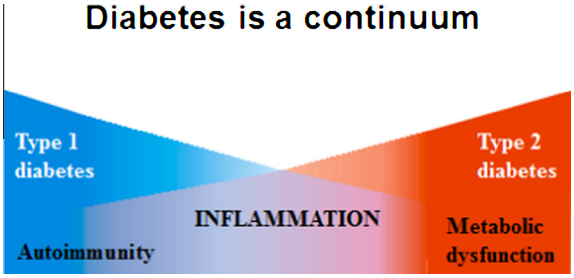

Fig. 1. Diabetes is most likely a continuum where the autoimmunity of type 1 diabetes represents one end of the spectrum and the metabolic dysfunction of type 2 diabetes the other end.