What have we learnt from genetic studies of type 2 diabetes in Chinese?

The prevalence of diabetes is increasing at an alarming rate throughout the world, posing a considerable public health concern. Once a country with the second highest number of diabetic patients, China has now become the worldwide epicenter of the diabetes epidemic[1]. Type 2 diabetes accounts for 85–95% of all diabetic patients in developed countries and an even higher percentage of those in developing countries, so it is imperative to gain a greater understanding of the etiological mechanisms of type 2 diabetes, including genetic mechanisms. Considerable evidence suggests that there is ethnic heterogeneity in the development of diabetes. Compared with populations of European descent, Han Chinese exhibit stronger genetic susceptibility to type 2 diabetes and develop diabetes at lower degrees of obesity and at much higher rates given the same amount of weight gain, which may be caused by more prominent central obesity and earlier β-cell failure in Chinese populations. Given these differences between Han Chinese and populations of European descent, investigations into specific genetic factors for type 2 diabetes in Chinese populations are considered necessary.

The recent advent of genome-wide association studies (GWAS) has led to a striking increment of the number of genes conferring risk for type 2 diabetes. Most of the GWAS were conducted in samples of European populations, with 27 loci being newly identified as susceptibility loci for type 2 diabetes. This gives a total of 32 loci contributing to type 2 diabetes susceptibility in European populations. Based on our study of 3410 cases versus 3412 controls, 10 of the 32 loci identified in European populations showed significant associations with type 2 diabetes in Shanghai Chinese, with ORs range from 1.13 to 1.40 (Figure 1). But why did we fail to replicate most of the effects of the susceptible loci identified in European populations? Take *TCF7L2* as an example. This locus was considered the strongest genetic risk factor for type 2 diabetes in European samples, with rs7903146 as the top single nucleotide polymorphism (SNP) within the locus. Recently, this SNP was reported to be located in a region of allele-specific open chromatin with greater enhancer activity for the T risk allele carriers, suggesting that it is a functional variant participating in the development of type 2 diabetes. Despite this, most studies have failed to replicate the association between rs7903146 and the disease in Chinese samples. Two important reasons could explain this discrepancy. First, thousands of case control samples may not have sufficient statistical power to replicate the association because of a much lower risk allele frequency and effect size in Chinese populations compared with European counterparts. Second, different loci other than rs7903146 may be associated with type 2 diabetes in the Chinese

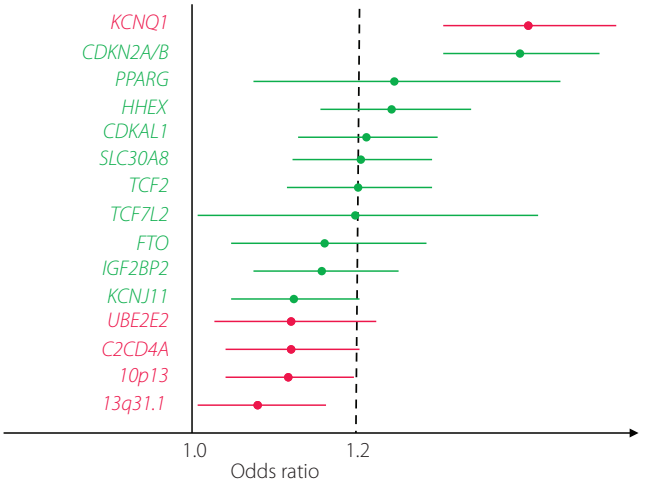

Figure 1 | Associations between loci and type 2 diabetes in Chinese samples. Loci initially identified in populations of European descent are shown in green, whereas those identified in east Asian populations are shown in red. Data show the odds ratio with 95% confidence intervals.

population, as suggested by several studies, which may indicate that different but independent signals in the same gene predispose to type 2 diabetes in different ethnic groups.

GWAS of type 2 diabetes have started in east Asian populations. Although not as advanced as the studies in European populations, these GWAS in Asian populations have resulted in the identification of seven risk loci since 2008, namely *KCNQ1*, *SRR*, *PTPRD*, *UBE2E2*, *C2CD4A-C2CD4B*, 10p13 and 13q31.1. Five of these seven loci discovered in east Asian populations were replicated in our Chinese samples (Figure 1), with a much higher success rate than loci identified in the European populations. Of these susceptible genes indentified in the Asian population, *KCNQ1* showed the strongest association with type 2 diabetes in our samples, with an odds ratio (OR) reaching 1.53, closely resembling the initial findings in Japanese populations[2]. It should also be noted that, in 2010, a second independent signal at this locus was found in populations of European descent, which provides evidence for the existence of independent signals at the same locus in different populations. Together all the findings regarding *KCNQ1* indicate that it is necessary to validate initial signals and to explore potential independent signals in populations of different ethnicities.

Identifying genetic variants that participate in glucose metabolism may shed light on the pathogenesis of type 2 diabetes. GWAS on these quantitative traits has revealed 14 loci

contributing to variance in fasting plasma glucose levels and five loci influencing 2-h glucose levels. Interestingly, genetic variants significantly modulating fasting glucose concentrations only partially overlap with those predisposing to type 2 diabetes and their effects on fasting glucose levels do not predict their role in the susceptibility to the disease. In previous studies, we replicated the association of *G6PC2*, *GCK*, *MTNR1B*, *DGKB*, *MADD* and *SLC30A8* with fasting plasma glucose, and the association of *G6PC2*, *GCK* and *PROX1* with 2-h glucose levels in Chinese populations. Intriguing findings were observed in our studies that *G6PC2* and *MADD* were both associated with fasting glucose levels as well as type 2 diabetes in our Chinese samples; however, they were only associated with fasting glucose levels in populations of European descent[3,4]. Such pleiotropic effects of the same genes in different populations may arise from poorer β-cell function in Chinese populations compared with European populations because *G6PC2* is involved in insulin secretion and *MADD* is involved in insulin processing, which further highlights the importance of genetic investigations for type 2 diabetes in populations with different ethnicities.

The exploration of genetic factors for type 2 diabetes according to ethnic background may increase opportunities for the discovery of novel susceptible loci. Previously, we have attempted to find novel loci predisposing to type 2 diabetes in Chinese populations through genome-wide linkage studies. We demonstrated that chromosome 1q21-q24 harbored susceptible gene(s) for type 2 diabetes, which has also been suggested by studies in other different ethnic groups. The International Type 2 Diabetes 1q Consortium conducted a detailed fine-mapping study in eight populations, including a Chinese population from Shanghai, and found a nominal association located in *NOS1AP*. However, the association was not validated in additional European samples. Given that European samples accounted for 95.9% of all the participants in that study and a significant association between *NOS1AP* and type 2 diabetes was shown in the preliminary analysis in the Shanghai 1q samples, we further examined the association between *NOS1AP* and type 2 diabetes in our samples through fine mapping on 1q23.3 and suggested that *NOS1AP* genetic variant rs12742393 may have a minor effect on susceptibility to type 2 diabetes in Chinese[5]. Trying to elucidate the mechanisms that underlie the association between *NOS1AP* and type 2 diabetes, we performed expression profile analysis and proteomic analysis in addition to traditional approaches with molecular and cellular tools. Preliminary data suggest diverse liver expression profiles in different genotypes of *NOS1AP* and also a potential role of this gene in fatty acid metabolism in the liver (Jia W, unpublished data, 2011).

It is of note that the loci identified thus far account for only a small proportion of the heritability of type 2 diabetes, despite the growing number of loci discovered in recent years. In an attempt to explain the remaining heritability of complex diseases, including type 2 diabetes, much attention has focused on the exploration of multiple, low-frequency, or rare variants, which are considered to confer high risks for these diseases. Newer approaches through which these variants can be better captured than GWAS are needed and exome sequencing appears to be an attractive and cost-effective technique. However, more in-depth investigation into type 2 diabetes and its related traits through GWAS in east Asians and other non-European populations remains necessary because the exploration of genetic factors related to type 2 diabetes in these populations is still in the early stages. All these efforts should provide novel insights into the pathogenesis of type 2 diabetes, and may also contribute to the translation of genetic advances into personalized therapeutics for type 2 diabetic patients.

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