The end or the start of understanding the genetics of type 2 diabetes

For centuries, the clinical characterization and hereditary transmission of diabetes have been of interest. The continuous change in diagnostic cut-offs of glucose levels categorizing diabetes, used before 1979 in the absence of anything better, reflects the difficulty of classifying a person with the disease or syndrome of diabetes. Cases of diabetes as currently defined, in particular type 2 diabetes (T2D), are increasing in epidemic proportions globally. Yet, when one day the etiologies of type 2 diabetes are fully understood, we might find the numbers of cases of the so-called 'garden-variety' common type 2 diabetes very much reduced, as most of the cases will have been redesignated by or reclassified as 'other specific types of diabetes'!

So, what is our current understanding of the disease causes of type 2 diabetes? Great effort has been expended (by geneticists) and technologies have been improved (by engineers) to tease out the genetic architecture of the disease. Looking back over recent decades, we are beginning to understand how difficult the work is to appreciate the number of T2D susceptibility genes that were identified during these years. From the classic candidate gene approach, fortunately we are increasing our understanding of the pathophysiology of type 2 diabetes; that is, increased insulin resistance and decreased beta cell function, by the widely replicated genes, exemplified by the gene for insulin sensitivity, *PPARG*, and another for insulin secretion, *KCNJ11*. Even with dozens of genome-wide linkage scans worldwide, we have only witnessed successful gene location down to *TCF7L2*, identified so far with the highest genetic risk of all known type 2 susceptibility loci and widely replicated in almost all populations worldwide. In the subsequent and more powerful genome-wide association studies (GWAS), this gene was repeatedly identified as having the highest genome-wide significance level. There still remain some loci identified by linkage scans to be further tested for, as these chromosomal regions might harbor positional candidate gene(s) that contribute to the development of type 2 diabetes. These tests, combined with GWAS or regional single nucleotide polymorphism (SNP) study, have the potential to identify the gene(s) hidden in these linkage peaks.

With more GWAS covering more and more populations, the gene list for type 2 diabetes and its related phenotypes has grown to more than 20 in only a few years[1]. Most of the early GWAS were carried out in European patients, successfully finding genes or loci, even with a very small genetic effect (OR = 1.1–1.5). Due to a potential ethnic heterogeneity, additional GWAS in other populations are considered necessary and important. And indeed, after Japanese scans, the *KCNQ1* gene was added to the list of T2D susceptibility genes. Interestingly, the association of T2D and genetic variants of the *KCNQ1* gene was also replicated in other populations, including Chinese and European[1]. In a very recent GWAS of T2D in people of Chinese ethnicity, we reported two additional susceptibility genes, *SRR* and *PTPRD*, together with the one known *KCNQ1* gene[2]. Subsequent replications in other populations are mandatory and would represent a new wave of replication study, pooled analyses and meta-analyses. When replicating a particular SNP of a gene, it is worthwhile testing the tag SNP covering the whole gene as we had shown that the SNP of the *TCF7L2* gene that are associated with T2D in Chinese people in Taiwan were different from the SNP reported (rs7903146) in other populations. It is therefore important to consider whether we are testing the SNP or the gene[3].

Intriguing findings from these studies include the multiple disease susceptibility genes of little effect, mostly related to beta cell functions and/or pancreatic development. Of the genes that we reported, the *PTPRD* gene might prove to be the first example of an insulin resistant gene from the GWAS. Based on the known effect of receptor type tyrosine phosphatase for interference with insulin signaling, it is a highly plausible candidate gene for involvement in insulin resistance that is integral to the pathogenesis of T2D. As another aspect, we also consider that the pleiotropic effects of one gene might explain its effect on disease pathogenesis or phenotypes. We have shown that both insulin secretion (with the well-known SNP rs7903146) and insulin resistance (with the SNP rs290481) are associated with genetic variants of the same gene *TCF7L2*[4]. Whether the effect of genetic variants of the *TCF7L2* in different populations is the result of interaction with different environmental factors or the corresponding varying genetic effects from different SNP remains unanswered.

What about the role of other approaches in searching for further T2D susceptibility genes in the GWAS and post-GWAS eras? Taking the simulation results from predictions of T2D achieved through adding the alleles of most genetic risk into the modeling, it has been estimated that the cumulative effect of these genetic factors contribute just 5–10% of the total variance of genetic heritability at most. Therefore, one can either go back to the traditional candidate gene approach or go one step further to whole genome sequencing. The signals of previously identified candidate genes were not remarkable in the GWAS analyses. Therefore, the candidate gene approach, especially analyzing all the genes of the specific biological pathway(s), might still be viable in the game of gene hunting. On the other approach, one might turn to pursuing a new generation DNA

sequencing with the hope of finding rare variants that promise a higher genetic effect. Whether this will prove productive or not is just a question of time. In between these two extremes, one can consider genome-wide pathway analyses as a way of understanding the etiology of complex diseases like T2D. Or, one can analyze the correlation with quantitative traits in nondiabetic individuals to further identify genes that correlate with insulin secretion or insulin resistance. Then, traditional case–control studies for an association with T2D can be tested. Through these different approaches, some additional genes are believed to be the new T2D susceptibility genes. As for the common copy number variants (CNV) on the existing platform for GWAS, it has recently been found to be unlikely to contribute greatly to the genetic basis of common human diseases. More studies will be needed to confirm the functional role of CNV on gene expression and molecular mechanisms leading to diabetes.

During just a relatively short period in human evolution, the prevalence of T2D has increased at a phenomenal speed, much faster than can be accounted for by the nucleotide incorporation error rate, gene selection and genetic drifting. Apparently, the development of this complex disease is boosted by the prevalence of obesity. It gives rise to a highly probable hypothesis that the enormous environmental impact on genetic expression, either through gene–environment interaction or epigenomic effect, leads to the manifestation of disease. Indeed, some nutrigenomic studies have partially validated these proposed hypotheses. More confirmative examples come from the findings that high glucose and glucose variability affect the long-term effect of gene expression through the modification of the methylation status of the selective set of genes. Understanding of this highly interesting field is just beginning and needs to be further explained in a more precise way[5].

Increasing knowledge of the pathogenesis of T2D produces several implications. First, one can find a new avenue to meet the need for better diabetic control. Therapies targeting all aspects of etiopathogenetic abnormalities of diabetes will be vital to best care for individuals with this disease. Second, we can optimistically expect a better choice of antidiabetic regime based on individual genetic architecture. In contrast, we might expect to avoid medications that could harm patients. Third, preventive medicine can be designed according to our understanding of etiological factors, especially focusing on modifiable factors that might produce an effect through interaction with susceptible genotypes. Fourth, a better understanding of genetic and ethnic heterogeneities will benefit region-specific strategies for prevention and better treatment of diabetes. Therefore, testing or replication of genetic factors identified in other regions should be considered mandatory in Asian populations.

With all these new discoveries in understanding the genetic architecture of complex diseases such as T2D, it is expected that we can resolve the complexity of genetic factors as well as environmental factors that are also relevant. Hopefully, these advances can be translated into therapeutic potential to counter the global pandemic of diabetes.

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