Towards precision medicine for type 2 diabetes

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The key to establishing precision medicine for type 2 diabetes (T2D) is to use single nucleotide polymorphisms (SNPs) to determine susceptibility to T2D. Since 2007, genome-wide association studies (GWASs) based on the common disease–common variant hypothesis have been conducted and have identified ~100 T2D susceptibility SNPs, although these SNPs influence the T2D susceptibility only weakly [1]. The major SNPs can explain approximately 10% of the T2D heritability; the rest is called the “missing heritability” [2]. Whole-genome or exome sequencing was expected to find SNPs with low minor allele frequencies and relatively strong effects. However, T2D susceptibility is unlikely to be mainly determined by low-frequency SNPs [3].

Since T2D results from heterogeneous pathogenesis, artificial classification of diseases or phenotypes could reduce the statistical power available to identify relevant SNPs. Many of the T2D susceptibility SNPs identified so far are related to impaired insulin secretion, probably because diabetes remains undiagnosed as long as insulin secretion can overcome insulin resistance. Precise classification of T2D based on pathogenesis could help to identify SNPs with stronger effects on specific phenotypes.

Other targets include SNPs that determine continuous parameters which are logically responsible for pathogenesis, such as cytokines. For example, resistin is a cytokine that is secreted from adipocytes and induces insulin resistance in mice, making it a candidate gene for T2D [4]. We

reported that the G allele of SNP –420 in the human resistin gene promoter is tightly associated with circulating resistin in Japanese subjects through the binding of specific transcription factors [5]. The identification of such factors that have their gene expression regulated by functional SNPs should be pursued. The precise classification of T2D and the integration of SNPs that determine clinically relevant factors could facilitate the establishment of precision medicine for T2D.

References

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