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Genetic determinants of glucose homeostasis

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Type 2 diabetes is a complex metabolic disorder characterised by varying degrees of impairment in insulin secretion and resistance to the action of insulin. Considerable progress has been made recently in understanding the genetic determinants of diabetes. A logical next step is to describe how these variants relate to the underlying pathophysiological processes that lead to diabetes as this may provide insights into pathways to disease. These quantitative traits are, of course, of direct interest in themselves and a growing literature is now emerging on the genetic determinants of insulin secretion and insulin resistance. This review article focuses on describing the complex associations between type 2 diabetes risk variants and quantitative glycaemic traits and the relationship between variants initially discovered in association studies of these traits and risk of type 2 diabetes.

Genetic association studies of type 2 diabetes and quantitative metabolic traits

Type 2 diabetes is a complex metabolic disorder characterised by varying degrees of impairment in insulin secretion and resistance to the action of insulin. Considerable progress has been made recently in understanding the genetic determinants of diabetes. A logical next step is to describe how these variants relate to the underlying pathophysiological processes that lead to diabetes as this may provide insights into pathways to disease. These quantitative traits are, of course, of direct interest in themselves and a growing literature is now emerging on the genetic determinants of insulin

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secretion and insulin resistance. The variants discovered through this approach are interesting candidates for diabetes. Although diabetes is defined and treated clinical as a binary disorder that people either do or do not have, the reality is that glucose is continuously distributed and there is no distinct line that defines abnormality. Various quantitative measures of hyperglycaemia are available which define not only diabetes and categorical states of non-diabetic hyperglycaemia but also predict the micro- and macrovascular complications of diabetes. These hyperglycaemia traits have been the focus of genetic investigation largely through the large international Meta-Analyses of Glucose and Insulin related traits Consortium (MAGIC) and the results of these studies are directly relevant to understanding the determinants of these quantitative measures and are also more indirectly important candidates to examine for association with diabetes. This article describes each of the following approaches in turn.

- Investigation of association of proven T2DM loci with insulin resistance and secretion.
- Investigation of the genetic determinants of insulin resistance and secretion.
- Association with T2DM of variants shown to be related to insulin resistance and secretion.
- Investigation of the genetic determinants of quantitative measures of glycaemia.
- The association with measures of insulin secretion and resistance of variants associated with quantitative measures of glycaemia.
- The association with T2DM of variants associated with quantitative measures of glycaemia.

Investigation of association of proven T2DM loci with insulin resistance and secretion

Genetic association studies aimed at understanding the aetiology of T2DM have predominantly followed a clinical approach by investigating type 2 diabetes status as the outcome in case–control studies and after a long period of slow progress there has been a recent explosion in the rate of discovery of genetic loci associated with diabetes. This successful model has been driven by technological advances in genotyping and reduction in costs, facilitating the conduct of genome-wide association studies and by large-scale collaborative meta-analyses between studies. Common variants in nearly 40 loci have now been identified to be robustly and consistently linked to type 2 diabetes risk. The majority of studies have been performed in individuals of European descent,[1–6] but a number of studies have successfully identified type 2 diabetes associated loci in other ethnic groups including Chinese and Japanese.[7,8]

Physiological characterisation has been performed previously for type 2 diabetes associated loci in follow up studies[9–14] and has highlighted that the vast majority of type 2 diabetes risk loci are associated with impaired insulin secretion – a topic which has been comprehensively reviewed elsewhere.[11] Recently, however, a large meta-analysis of GWAS (designated "DIAGRAM+") reported a further 12 loci associated with type 2 diabetes at genome-wide significance (*HMGA2*, *CENTD2*, *KLF14*, *PRC1*, *TP53INP1*, *ZBED3*, *ZFAND6*, *CHCHD9*, *KCNQ1*, *BCL11A*, *HNF1A* and *DUSP9*).[6] To date a single physiological characterisation study in 5722 people reported that only *CENTD2* showed an association with insulin secretion and the remaining loci did not show reproducible associations with any trait.[15] This is consistent with physiological characterisation studies performed on variants identified in the initial DIAGRAM GWAS and it is presumed that the modest effect size of these variants identified from larger GWAS of type 2 diabetes will require physiological characterisation to be performed in much larger sample sizes.

Physiological characterisation of variants identified in studies of type 2 diabetes has resulted in very few associations with measures of insulin sensitivity, which begs the question why genetic variants identified in GWAS of type 2 diabetes may be more likely to be associated with impaired insulin secretion than impaired insulin sensitivity. A number of possibilities may explain this observation.[16] Previous GWAS for type 2 diabetes tended to use selected cases below a defined BMI cut-off and controls matched for BMI which could have reduced the chances of finding loci associated with insulin resistance. OGTT-derived metrics of insulin resistance are less heritable than those for secretion and environmental determinants may, therefore, be more important for insulin sensitivity than secretion.