Association analysis of 29,956 individuals confirms that a low frequency variant at CCND2 halves the risk of type 2 diabetes by enhancing insulin secretion.

Paper commentary

Recently, whole-genome sequencing and imputation techniques were combined to identify one of the first robust associations between low frequency variants and type 2 diabetes (Steinthorsdottir et al., 2014). KASP genotyping of one of the identified SNPs (G allele at rs76895963) over 21,394 samples confirmed association of a low frequency SNP variant in CCND2 that halves the risk of type 2 diabetes by enhancing insulin secretion (Yaghootkar et al., 2015).

Highlights of the paper

• Validation of a rare, low frequency variant at CCND2 that halves type 2 diabetes risk
• Large replication study performed with KASP genotyping
• Combining genotyping data from multiple populations (ALSPAC, Go DARTS, METSIM and RISC) to boost significance.

Commentary

A large number of sequence variants are known to be associated with type 2 diabetes. Many common variants only confer modest to small effects on risk; the initial phase of this study was designed specifically to target low frequency SNPs with significant effects.

Initially, the whole genome sequencing which involved 2,630 Icelandic participants was combined with additional Icelandic cases and controls and further independent samples to boost the association data. This method successfully identified four new rare SNP variants that affect type 2 diabetes risk.

The large replication study that has followed confirms that carriers of low frequency G allele at rs76895963 are at approximately half the risk of type 2 diabetes compared to non-carriers. The rare G allele is associated with lower fasting glucose levels and higher insulinogenic index suggesting an effect on insulin secretion.

Genetic associations with human diseases need replicating and validating in independent studies to rule out false positives and to establish an unbiased effect size. Confirming a genetic association with a disease is a significant step towards understanding the underlying physiological mechanisms, diagnosis options, disease prediction and drug therapy targets. This study is just one of many studies worldwide which illustrate that following SNP discovery, KASP genotyping is the ideal choice for robust and successful replication and validation studies worldwide.

Other articles you may be interested in

Identification of low-frequency and rare sequence variants associated with elevated or reduced risk of type 2 diabetes.