Characterising the genetic contribution to type 2 diabetes

WHA T WE DID

- We have over the past 8 years led, or contributed to, efforts that have resulted in the discovery of around two-thirds of the ~80 T2D risk loci now confirmed; these collectively explain ~10% of individual risk of type 2 diabetes.

- We have comprehensively catalogued the contribution of common variants to T2D predisposition and demonstrated that most common variant signals influence T2D risk across all major ethnic groups.

- We have shown that most T2D risk loci exert their effects through a predominant action on insulin secretion, with only a minority acting via insulin action.

- We have demonstrated substantial overlap with genes implicated in monogenic forms of diabetes, and with those which encode proteins which are the therapeutic targets of existing diabetes medication.

- At many of these loci (including KLF14, MTNR1B, PAM, ZMIZ1), we have made substantial progress towards elaborating the specific mechanisms through which these variants exert their metabolic effects.

WHA T WAS KNOWN

- Type 2 diabetes (T2D) represents a major challenge to global health, but poor understanding of the mechanisms responsible frustrates efforts to develop more effective approaches to prevention and treatment.

- Twin and family studies highlight the genetic contribution to individual risk of T2D.

- Before the advent of genome wide association approaches, efforts to identify T2D risk variants had been dominated by spurious claims of association generated from underpowered studies. Only a handful of robust associations had been reported.

REFERENCES

- Genome wide association study of 14,000 cases of seven common diseases and 3,000 shared controls.
- Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes.
- Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis.
- Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes.
- Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility.
- Genetic fine-mapping and genomic annotation defines causal mechanisms at type 2 diabetes susceptibility loci.