SUPPLEMENTARY METHODS

Cohorts

The Hertfordshire Cohort study is a population-based cohort study comprising 3,000 men and women born in the English county of Hertfordshire between 1931-1939 and still resident there. At age 60-75 years, all participants attended a clinic for detailed physiological investigations during which medical and social histories were ascertained. Furthermore, data was collected on anthropometry, blood pressure, glucose tolerance and fasting serum cholesterol and triglycerides. Cohort details have been described previously (1). Genotypic and phenotypic data were available for 2,901 individuals (Supplementary table 1).

The Fenland study is an ongoing population-based cohort study designed to investigate the association between genetic and lifestyle factors on the risk of obesity, insulin sensitivity, hyperglycaemia and related metabolic traits in men and women aged 30 to 55 years. Potential volunteers were recruited from General Practice sampling frames in the Fenland, Ely and Cambridge areas of the Cambridgeshire Primary Care Trust in the U.K. All participants were measured at the MRC Epidemiology Unit Clinical Research Facilities in Ely, Wisbech and Cambridge. Participants attended after an overnight fast for a detailed clinical examination and blood samples were collected. Cohort details have been described previously (2). For the current analysis data on 1,865 individuals were included (Supplementary table 1).

The MRC Ely study is a population-based cohort study of the aetiology and pathogenesis of T2DM and related metabolic disorders. Study participants were randomly selected from people living in Ely and surrounding villages (East Anglia, UK), an ethnically homogenous white European population. None of the participants had diagnosed T2DM, although 139
individuals met the WHO criteria for T2DM on oral glucose tolerance testing performed as part of the study. All participants attended a clinical examination that included standard anthropometric measurements, medical questionnaires and a 75-g OGTT. The study design, methods and measurements of the three phases of this cohort study have been described in detail elsewhere (3-5). The current analysis includes 1,699 men and women aged 35-79 years, for whom genotypic and phenotypic data were available from phase 3 (Supplementary table 1).

The MONICA study includes participants recruited as part of the WHO-MONICA population survey conducted from 1995 to 1997 in three different parts of France: the Lille Urban Community in northern France (n=1,195), the Bas-Rhin county in eastern France (n=1,131) and the Haute-Garonne county in southern France (n=1,182). Participants (aged 35-64 years) were randomly selected from electoral rolls after stratification by town size, gender and age in order to obtain 200 participants for each gender and each 10-year age group (WHO-MONICA Project protocol) (6). The whole MONICA Lille sample was used for this study as well as individuals presenting with T2D in the two other French centers to obtain 282 individuals with T2D (fasting glycemia ≥ 126 mg/dl or use of antidiabetic treatment) and 854 normoglycaemic individuals. For quantitative trait analysis, only participants from the MONICA-Lille study without antidiabetic treatment were included (n=1,097) (Supplementary table 1).

The HELENA participants were recruited as part of the Healthy Lifestyle in Europe by Nutrition in Adolescence-Cross Sectional study (HELENA, http://www.helenastudy.com) performed from 2006 to 2007 in 10 centres from 9 European countries as previously described (7). Participation in the study was voluntary. The sample included a total of 3,865
adolescents (mean age 14.8 ± 1.4 years) recruited through schools. In order to investigate clinical biochemistry assays and genetic analyses, one third of the classes (n=1,155) were randomly selected for blood collection. Blood samples were drawn at school according to a standardised collection protocol (after a 10-hour overnight fast), and were sent to a central laboratory (the Analytical Laboratory at the University of Bonn [IEL], Germany) for subsequent biochemical measurements (8). DNA was extracted from white blood cells with the Puregene kit (QIAGEN, Courtaboeuf, France) by the Genomic analysis Laboratory at the Institut Pasteur de Lille (Lille, France) (Supplementary table 1).

The Addition study is a T2DM case series that together with non-diabetic individuals of the MRC Ely study forms a case-control study. The ADDITION study was designed to evaluate the costs and benefits of screening for prevalent undiagnosed T2DM and to determine the benefits of intensive cardiovascular risk reduction in people with screen-detected disease. Previously undiagnosed prevalent cases of T2DM, defined using WHO OGTT criteria, were identified via a population-based stepwise screening strategy among 40 to 69 year olds participating in the UK Cambridge arm of the ADDITION study. Current analyses include 800 white European men and women who had DNA available and information on BMI (6). Participants of the MRC Ely study were confirmed as controls (n=1,607) or classified as cases (n=891) for the case-control comparison (Supplementary table 1).

The Cambridgeshire Case–Control Study consists of 552 patients with T2DM aged 45–76 years, randomly sampled from a population-based diabetes register and 552 controls, recruited from the same population and individually matched for age, sex and geographical location. Cases were defined by onset of diabetes after the age of 30 years without insulin treatment in the first year following diagnosis. Diabetes was excluded in controls by medical
record search, and by an HbA1c measurement of <6%. The study design and methods have been described in detail elsewhere (9). For the current analysis genotypic data was available in 531 controls and 538 cases (Supplementary table 1).

Ethical permission

Ethical permission for all the studies was granted by the respective Local Research Ethics Committee, and study participants provided informed consent. In the HELENA study, written informed consent was obtained from each participant and both of his/her parents or legal representatives (10).

References


2. Willer CJ, Bonnycastle LL, Conneely KN et al. Screening of 134 single nucleotide polymorphisms (SNPs) previously associated with type 2 diabetes replicates association with 12 SNPs in nine genes. Diabetes 2007; 56:256-64.


