# THL Diabetes Studies

## Information for researchers interested in using stored samples and data

## Introduction

THL Diabetes Studies is a large study collection of samples and data collected from diabetic patients and their family members in several studies between 1986 and 2013 by The National Public Health Institute of Finland (currently The Finnish Institute for Health and Welfare, THL).

Type 1 diabetes is more common in Finland than in any other country in the world. Compared to type 1 diabetes, the prevalence of type 2 diabetes is higher, but the incidence does not differ from other developed countries. A combination of genetic and environmental risk factors is involved in the pathogenesis of both type 1 and type 2 diabetes, although the diseases have different causes. The focus of the studies has been on the genetic background and environmental triggers of diabetes in Finland.

### DiMe, IDDMGEN, and T1D-GEN studies

**The Childhood Diabetes in Finland (DiMe)** study started in 1986 and it is the largest population-based family study of type 1 diabetes mellitus (T1DM) in Finland. The aim was to evaluate the role of genetic, environmental and immunological factors and the interaction between genetic and environmental factors in the development of T1DM. Nationwide, all insulin dependent diabetes mellitus (IDDM) cases under the age of 15 in Finland were identified between September 1987 and April 1989 in pediatric wards in Finland. During the enrolment period 801 families participated in the study (participation rate ~95%). Parents and siblings of 801 probands were also asked to participate. Participants filled out questionnaires and were interviewed for example about life events, viral exposure and dietary habits. Blood samples were taken from the participants. More detailed information about the study can be found in a published study article (Tuomilehto et al 1992).
**IDDMGEN, a follow-up study for DiMe**, investigated the epidemiology and genetics of insulin dependent diabetes mellitus (IDDM) in Finland, with a special focus on follow-up of non-diabetic siblings of the probands of the DiMe study. The original study which started in 1994 was called 'Epidemiology and genetics of IDDM in Finland'. The research plan was updated in 2001 and the updated study was called 'Identification of type 1 diabetes susceptibility genes and their interactions in the Finnish population'. In 2008, the name and research plan were updated to **'A genome-wide genetic analysis of childhood and adult onset type 1 diabetes (T1D) in Finland' (T1D-GEN)** and the research frame was changed from collecting diabetic families to a case-control study**.** The aim of this study was to find the genes conferring susceptibility to T1D in the Finnish population. Blood samples were taken, and questionnaires were filled by IDDMGEN and T1D-GEN participants.

### YA and YA-EPID studies

While the DiMe, IDDMGEN and T1D-GEN studies focused on type 1 diabetes which has manifested in children under the age of 15, the **YA and YA-EPID studies** investigated individuals who were diagnosed with type 1 or type 2 diabetes at the age of 15–39 years. 'The Epidemiology of diabetes in young adults' (YA) study started in 2000 and was updated in 2003 as 'The risk of type 1 and type 2 diabetes among young Finns' (YA-EPID) study. YA included patients who were diagnosed with T1DM or T2DM in health care between 1992 and 1996, were residents of Finland and aged 15–39 at the time of diagnosis. Data were obtained from different Finnish national/health registries and the inclusion criterion was the consistent diagnosis of diabetes across at least two data sources. Family members were also invited to participate. In YA and YA-EPID studies the data were collected from registries and by questionnaires, and samples were retrospectively collected between 2002

and 2005. More detailed information about the YA study can be found in a published study article (Lammi et al 2007).

**FUSBIOPS - Study on metabolism of abdominal adipose tissue, skin, and thigh muscle**
FUSION (Finland-United States Investigation of NIDDM Genetics) is a large study investigating genetic variants that predispose to T2D, or are responsible for variability in T2D-related quantitative traits (QTs). FUSBIOPS was a sub-study of FUSION concentrating on expression studies of the skin, muscle and adipose biopsies collected from a selected group of the participants of the FUSION study as well as other studies. The aim of FUSBIOPS was to investigate these insulin sensitive tissues that are associated with glucose utilization and are sources of several proteins that may play a role in T2D development. Adipose, skin and muscle biopsies were collected from 100 individuals with normal glucose tolerance (NGT), 100 individuals with impaired glucose tolerance (IGT) and 100 newly diagnosed T2D individuals, who currently had no drug treatment for diabetes. Biopsies were collected in 2009–2013 in 3 different study sites (Helsinki, Kuopio and Savitaipale). Blood samples, OGTT and other measurements were taken from participants at the first visit. Questionnaires concerning health history, medication and lifestyle were also filled out. The second visit included physical examination and biopsy, while biopsy stiches were removed during a third visit.

## Ethical considerations

The ethical committee of the National Public Health Institute has approved the DiMe and the IDDMGEN study protocols. DiMe and IDDMGEN (until 1999) studies precede current legislation on ethics in medical research and agreeing to participate in the baseline clinical visit was taken to indicate informed consent. The National Advisory Board on Health Care Ethics approved the YA and YA-EPID research plans. The FUSBIOPS study was approved by the coordinating ethics committee of the Hospital District of Helsinki and Uusimaa. A written informed consent was obtained from all the participants of the T1D-GEN, IDDMGEN (1999 onwards), YA, YA-EPID and FUSBIOPS studies.

The THL Diabetes Studies sample collection has been transferred to THL Biobank on April 4th, 2018, following a public announcement that appeared in the Official Newspaper in February 2018. The transfer of the THL Diabetes Studies sample collection to the biobank has been approved by the Coordinating Ethics Committee of Helsinki University Hospital on December 12, 2015 and by the Ministry of Social Affairs and Health on September 14, 2017.

## THL Diabetes Studies samples available for biobank research

The following samples are available from over 13 600 sample donors

- DNA
- Serum (subset)
- Cells (subset)

## THL Diabetes Studies phenotype and omics data available for biobank research

The following data is available for most of the study participants

- Age
- Gender
- Diabetes status
    - Diagnosis
    - Diagnosis date and age

  - Family history of diabetes
  - Information about treatment
- C-peptide measurement
- Genome-wide SNP data

For detailed availability of genome-wide genotypes and sequencing data, see more information in the 'Omics data availability table' at the THL Biobank sample collection page.

**Questionnaire data**
The following questionnaire data is available most of the **YA** and **FUSBIOPS** study participants

- Sociodemographic characteristics
  - ✓ Region of birth
  - ✓ Education
  - ✓ Marital status
- Health status
  - ✓ Digestive system diseases
  - ✓ Heart and cardiovascular diseases
  - ✓ Medication
  - ✓ Endocrine, nutritional and metabolic diseases
  - ✓ Pulmonary diseases
  - ✓ Pregnancy, child birth
  - ✓ Self-reported weight and height
- Functional capacity
- Use of health services
- Lifestyle
  - ✓ Physical activity
  - ✓ Smoking
  - ✓ Nutrition
  - ✓ Alcohol

**Biological/Physical test results**
The following biological and physical measurements are available for the **FUSBIOPS** study participants

- Weight, height, BMI, waist and hip circumference
- Blood pressure, pulse
- OGTT
- Blood lipid values (total cholesterol, HDL cholesterol, triglycerides, apolipoproteins A-1 and B)
- Blood sugar value (glucose, HbA1c, i.e. glycated haemoglobin)
- Liver function (ALAT, glutamyltransferase)
- Inflammation level (CRP)
- Kidney function (urates and creatinine)

**Registry data**
Information from the Finnish national health registries, such as Care Register for Health Care (HILMO), Cancer Register, Cause-of-Death Register and Drug Imbursement Registers etc., can be linked to sample donors by a separate application process.

## Key references

Tuomilehto J, Lounamaa R, Tuomilehto-Wolf E, Reunanen A, Virtala E, Kaprio EA, Åkerblom HK: Epidemiology of childhood diabetes mellitus in Finland – background of a nationwide study of type 1 (insulin-dependent) diabetes mellitus. The Childhood Diabetes in Finland (DiMe) Study Group. Diabetologia 1992; 35:70–76

Harrela M, Koistinen H, Kaprio J, Lehtovirta M, Tuomilehto J, Eriksson J, Toivanen L, Koskenvuo M, Leinonen P, Koistinen R, Seppälä M. Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. J Clin Invest 1996; 98: 2612-2615

Pitkäniemi J, Onkamo P, Arjas E, Tuomilehto-Wolf E, Tuomilehto J and the DiMe Study Group: Estimation of transmission probabilities in families ascertained through a proband with variable age-at-onset disease: Application to the HLA A, B and DR loci in Finnish families with type 1 diabetes. Hum Hered 2000; 50:308-317

Podar T, Sointsev A, Karvonen M, Padaiga Z, Brigis G, Urbonaite B, Viik-Kajander M, Reunanen A, Tuomilehto J. Increasing incidence of childhood-onset Type 1 diabetes in 3 Baltic countries and Finland 1983-1998. Diabetologia 2001; 44: B17-B20

Ronningen KS, Keiding N, Green A on behalf of Genomic Marker Contributors and the EURODIAB ACE Study Group (Tuomilehto J, Karvonen M). Correlations between the incidence of childhood-onset Type 1 diabetes in Europe and HLA genotypes. Diabetologia 2001; 44: B51-B59

Rytkönen M, Moltchanova E, Ranta J, Taskinen O, Tuomilehto J, Karvonen M. The incidence of type 1 diabetes among children in Finland-rural-urban difference. Health Place 2003; 9: 315-325

Pitkäniemi J, Onkamo P, Tuomilehto J, Arjas E. Increasing incidence of Type 1 diabetes – role for genes? BMC Genetics 2004; 5: 5

Pitkäniemi J, Hakulinen T, Näsänen J, Tuomilehto-Wolf E, Tuomilehto J; DiMe Study Group. Class I and II HLA genes are associated with susceptibility and age at onset in Finnish families with type 1 diabetes. Hum Hered. 2004;57(2):69-79

Lammi N, Taskinen O, Moltchanova E, Notkola IL, Eriksson JG, Tuomilehto J, Karvonen M. A high incidence of type 1 diabetes and an alarming increase in the incidence of type 2 diabetes among young adults in Finland between 1992 and 1996. Diabetologia. 2007 Jul;50(7):1393-400

Todd JA, Walker NM et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 2007; 39: 857-64

Lammi N, Blomstedt PA, Moltchanova E, Eriksson JG, Tuomilehto J, Karvonen M. Perinatal risk factors in young adult-onset type 1 and type 2 diabetes - a population-based case-control study. Acta Obstet Gynecol Scand. 2009;88(4):468-674

Klinker MW, Schiller JJ, Magnuson VL, Wang T, Basken J, Veth K, Pearce KI, Kinnunen L, Harjutsalo V, Wang X, Tuomilehto J, Sarti C, Ghosh S. Single-nucleotide polymorphisms in the IL2RA gene are associated with age at diagnosis in late-onset Finnish type 1 diabetes subjects. Immunogenetics 2010; 62: 101-7

Sjöberg L, Pitkäniemi J, Haapala L, Kaaja R, Tuomilehto J. Fertility in people with childhood-onset type 1 diabetes. Diabetologia 2013; 56: 78-81

Scott LJ, Erdos MR, Huyghe JR, Welch RP, Beck AT, Wolford BN, Chines PS, Didion JP, Narisu N, Stringham HM, Taylor DL, Jackson AU, Vadlamudi S, Bonnycastle LL, Kinnunen L, Saramies J, Sundvall J, Albanus RD, Kiseleva A, Hensley J, Crawford GE, Jiang H, Wen X, Watanabe RM, Lakka TA, Mohlke KL, Laakso M, Tuomilehto J, Koistinen HA, Boehnke M, Collins FS, Parker SC. The genetic regulatory signature of type 2 diabetes in human skeletal muscle. Nat Commun. 2016 Jun 29;7:11764

Manning A et al. A Low-Frequency Inactivating AKT2 Variant Enriched in the Finnish Population Is Associated With Fasting Insulin Levels and Type 2 Diabetes Risk. Diabetes. 2017 Jul;66(7):2019-2032

Taylor DL, Jackson AU et al. Integrative analysis of gene expression, DNA methylation, physiological traits, and genetic variation in human skeletal muscle. Proc Natl Acad Sci U S A. 2019 May 28;116(22):10883-10888