7th MEETING OF EASD STUDY GROUP
PRAGUE
EASD-SGGD

7th Meeting of EASD Study Group on Genetics of Diabetes [EASD-SGGD]

16 – 19 May, 2019,
Prague - Motol

Programme & Abstract Book

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Content

Acknowledgement of Partners

Welcome

Dear Colleagues and Friends,

It is our honour and pleasure to welcome you to the 7th Meeting of EASD Study Group on Genetics of Diabetes (EASD-SGGD) in Prague.

Welcome to Czechia, the motherland of Johann Gregor Mendel, the inventor of modern genetics, and Jan Evangelista Purkynje, the founder of the first ever Institute of Physiology, at the Charles University in Prague. Our university was founded in 1348 by Charles IV, Czech king and Emperor of the Holy Roman Empire. It was the first university located north of the Alps and east of Paris at that time.

The host institution of the 7th EASD-SGGD is the 2nd Faculty of Medicine, Charles University in Prague which is focused on research in the field of Paediatric Medicine and Genetics. The meeting will take place at our hospital premises at the University Hospital Prague - Motol.

The mission of SGGD is to promote research into the genetic basis of all forms of diabetes, as well as to promote the interaction and transfer of knowledge between basic scientists and the clinical community. Also, its 7th meeting aims to provide participants with an opportunity to present and discuss the latest achievements in the field of genetics of diabetes, its complications and related conditions, and their impact on medical understanding and the improvement of patient care.

We are grateful that you, together with other leading genetics of diabetes experts, will be contributing to an excellent scientific programme which offers a mixture of keynote lectures, invited talks, and oral and poster presentations. We hope that you will not only enjoy the science and novel medical knowledge, but also the charm of our city of Prague, spanning from its medieval history to its vibrant present and promising future. Please, also accept our invitation to participate at the welcome reception and at the meeting dinner. Both events will take place in the very heart of the historic city centre, each of them on either side of the well-known Charles bridge.

We hope that you will enjoy this meeting as well as our Czech hospitality!

Štěpánka Průhová & Jan Lebl, on behalf of the organising committee

EASD-SGGD Steering Committee

Emma Ahlqvist

Lund University Diabetes Centre

Department of Clinical Sciences Malmö, section Genomics, Diabetes & Endocrinology

Malmö, Sweden

Amélie Bonnefond

CNRS UMR 8199, European Genomic Institute for Diabetes (EGID), Institut Pasteur de Lille, University of Lille

Lille, 59000, France

Niels Grarup

Section of Metabolic Genetics, The Novo Nordisk Foundation Center for Basic Metabolic Research

Faculty Of Health and Medical Sciences, University of Copenhagen

Copenhagen, Denmark

Leen t' Hart

Leiden University Medical Center, Department of Cell and Chemical Biology & Department of Biomedical Data Sciences, section Molecular Epidemiology

Leiden, The Netherlands

Keynote Speakers and Lectures

OMICS – session on the epigenomics of diabetes and obesity

Roderick C Slieker (Leiden, the Netherlands)

My research focuses on the intersection of clinical epidemiology and molecular epidemiology to improve prevention and treatment of diabetes and diabetes-related complications. During my PhD I have investigated DNA methylation, a key regulatory mechanism of cells. I investigated how regulatory mechanisms are established in fetal development and how they define adult tissues. Aberrant gene expression and DNA methylation play an important role in the development diseases. In a next step, I investigated the DNA methylation and gene expression changes (linear changes and variability) that occur during aging to the normal regulation of multiple tissues. From this research, I wanted to focus more on type 2 diabetes and as such I joined the diabetes groups in the LUMC and VUmc for a dual appointment. To get a better understanding how changes in molecular markers contribute or mark disease progression, my research now focuses on the integration and utility of multiple omics in prevention, prediction and treatment of type 2 disease and related complications. Part of this research is performed within RHAPSODY that focuses on diabetes progression and patient stratification.

A multi-omics approach towards type 2 diabetes

People with type 2 diabetes are heterogeneous in their disease progression, which requires adequate biomarkers, but also insight into the etiology of disease progression. Accelerated by technological advances an increasing number of molecular measures are measured. These measures will bring individually, but especially together, more insight into type 2 diabetes progression and etiology.

To achieve this, we explore and combine multiple omics layers, including genetic, mRNA and miRNA expression and metabolomics to track progression of type 2 diabetes. For example, we combine genetic data with public data to improve the insight in the tissue and genes involved.

Here, I will provide examples of how multiple omics contribute to the understanding of the etiology and prediction of type 2 diabetes.

Jan-Wilhelm Kornfeld (Köln, Germany; Odense, Denmark)

Jan-Wilhelm Kornfeld is Professor for Molecular Biology of Metabolic Diseases at the Department for Biochemistry and Molecular Biology of the University of Southern Denmark. His research group focusses on dissecting the functional contribution of noncoding RNAs and epigenetic regulator complexes to liver nutrient sensing and adipose tissue plasticity. He utilizes system-wide noncoding RNA and chromatin profiling approaches in conjunction with generation of gene-modified mouse models.

Personal information

Date of birth: August 10, 1976
Nationality: German
Family status: Married. Two children born 2013 and 2016

Education

2003	Diploma in Biochemistry, Medical University of Hanover, Germany
2008	PhD in Cell Biology, University of Kiel, Germany

Professional experience

2008–09	Post doc at L-Boltzmann Institute for Cancer Research (Supervisor: R. Moriggl, Vienna, AT)
2009–13	Post doc at University of Cologne, Germany (Supervisor: Prof. Jens C. Brüning, Köln, DE)
2013–18	Adjunct Principal Investigator at Cologne Cluster of Excellence (CECAD, Köln, DE)
2014–18	Group leader at Max Planck Institute for Metabolism Research (MPI-mR, Köln, DE)
2018–	Full professor for Molecular Biology of Metabolic Diseases, University of Southern Denmark

Awards and honors

2009–13	Long-Term Fellowship of the European Molecular Biology Organization (EMBO)
2015–	Elected member of the Young Academy of Europe (YAE)

Roles in Research Consortia

2018	Co-Founder of ADIPOSIGN, an intl. Center for Adipocyte Signaling, established by a donation from the Nordisk Foundation CHALLENGE grant call.

Educational activities

Principal supervisor since 2014 of: 10 post docs, 6 PhD, 3 MSc and BSc bachelor students.

Commissions of trust

- Ad-hoc reviewer for the following research institutions and science foundations:
  German Research Foundation (DFG, DE)
  German Leibniz Society (DE)
  Austrian Science Fund (FWF, AT)
  French National Center for Scientific Research (CNRS, FR)
  National Institute of Health and Medical Research (INSERM, FR)
  Fondation pour La Recherche Médicale (FRM, FR)
  Medical Research Council (MRC, UK),
  European Research Council (ERC)
  National Research Agency (ANR, FR)
- Ad-hoc reviewer for *Nat Commun, Nat Cell Biol, Front Genet, J Clin Invest, Mol Metab, FEBS, Sci Rep, JoVE, Nucl Acids Res and Cell Cycle*

Recent Grants and Awards

2014–18	Emmy-Noether Program Grant (11.53 m DKK)
2014–15	CECAD Program Grant (0.6 m DKK)
2015–	European Research Council (10 m DKK)
2017–	Novo Nordisk Program Grant on Basic Bioscience (1.8 m DKK)
2018–	Danish Independent Research Council DFF1 Grant (2.4 m DKK)
2018–	Novo Nordisk Foundation Challenge Grant (1 out of 4 cofounders, 60 m DKK)

Patents

Identification of microRNA802 as novel target for treatment of obesity-associated insulin resistance, diabetes mellitus type 2 and metabolic comorbidities of obesity. Patent rights relayed to Max-Planck Society. Internal Reference No.: M0802-4568-MSG-JK

International meetings

Invited speaker at >60 intl. meetings and institutional seminars since 2012 in the field of RNA biology, liver metabolism and adipose tissue function.

Meeting organization

2013–2015	2 international meetings on noncoding RNAs and metabolism (Köln, DE)
2017	1 international symposium on adipose tissue metabolism (Potsdam, DE)
2019	1 international meeting on noncoding RNAs and metabolism (Copenhagen, DK)

Most important publications:

Pradas-Juni M, Hansmeier NR, […], de Aguiar Vallim T, **Kornfeld JW.** A MAFG-lncRNA axis links systemic nutrient abundance to hepatic glucose metabolism. *Nat Commun (under revision).*

Hansmeier NR, Widdershoven PJM, […], **Kornfeld JW.** Rapid Generation of Long Noncoding RNA Knockout Mice Using CRISPR/Cas9 Technology. *Non-Coding RNA* (2019).

Klemm P, Frommolt P, **Kornfeld JW.** s•nR: a visual analytics framework for contextual analyses of private and public RNA-seq data. *BMC Genomics* (2019).

Schmidt E, Dhaouadi I, […], Bilban M, **Kornfeld JW.** LincRNA H19 protects from dietary obesity by constraining monoallelic gene expression in brown fat. *Nat Commun* (2018).

Awazawa M, […] **Kornfeld JW**, Blüher M, Brüning JC. A microRNA screen reveals that elevated hepatic ectodysplasin A expression contributes to obesity-induced insulin resistance in skeletal muscle. *Nat Med* (2017).

Duteil D, […] **Kornfeld JW**, […], Schüle R. Lsd1 Ablation Triggers Metabolic Reprogramming of Brown Adipose Tissue. *Cell Rep* (2016).

Oliverio M, Schmidt E, […], Brüning JC, **Kornfeld JW.** Age- and Obesity-Induced Decline of Brown Fat Function as Consequence of Impaired miR-328 Dependent Silencing of Bace1. *Nat Cell Biol* (2016).

Kornfeld JW, Baitzel B, […], Stoffel M, Brüning JC. Obesity-Induced Overexpression of miR-802 Impairs Glucose Metabolism Via Silencing of Hnf1b. *Nature* (2013).

*Mueller KM, ***Kornfeld JW**, […], Moriggl R. Impairment of hepatic growth hormone and glucocorticoid receptor signaling causes steatosis and hepatocellular carcinoma in mice. *Hepatology* (2011). *equally contributed.

*Blaas L, ***Kornfeld JW**, […], Casanova E. Disruption of the GH-STAT5-IGF-1 axis severely aggravates liver fibrosis in a mouse model of cholestasis. *Hepatology* (2010). *equally contributed.

*Engblom D, ***Kornfeld JW**, […], Schütz G. Direct glucocorticoid receptor-Stat5 interaction in hepatocytes controls body size and maturation-related gene expression. *Genes Dev* (2007). *equally contributed.

Regulation of metabolism by long, noncoding RNAs.

Biosketch:

Jan-Wilhelm Kornfeld is Danish Diabetes Academy-endowed Professor for Molecular Biology of Metabolic Disease at the University of Southern Denmark. His scientific curiosity revolves around the intriguing questions why genomes in higher organisms are, on one hand, largely devoid of protein-coding information, but, on the other hand, 'invest' a great deal of cellular energy into expressing thousands of non-protein coding or 'Noncoding' RNAs. We are particularly interested in a newly described class of Noncoding RNAs termed *long*, *noncoding* RNAs (lncRNAs) with elusive functions in cellular metabolism and physiology, but also in metabolic diseases like obesity and type 2 diabetes. Specifically we study the role that lncRNAs play in liver metabolism, adipose tissue differentiation and fat tissue plasticity.

Summary:

In the present study, we used Next-Generation RNA-Sequencing to find an unexpectedly high fraction of lncRNAs, but not protein-coding mRNAs, repressed during diet-induced obesity and refeeding, whilst nutrient deprivation induced lncRNAs in mouse liver. Accordingly, lncRNAs were repressed in obese and diabetic humans liver. LncRNA and coding mRNA promoter analyses in conjunction with MAFG cistrome and gain-of-function analyses confirmed that increased signaling activity of transcription factor MAFG during DIO is specifically linked to lncRNA repression. RNA interference using locked nucleic acid (LNA)-mediated gene silencing of MAFG elicited a fasting-like gene expression profile *in vitro*, improved glucose tolerance *in vivo*, derepressed lncRNAs and prevented insulin-induced mammalian target of rapamycin (mTOR)-signaling thus, potentially, inhibiting also mTOR-dependent mRNA translation.

In addition we found obesity-repressed lncRNA *lincIRS2* repressed by MAFG. Studying the function consequences of *lincIRS2* deficiency in mice, we found that LNA-mediated *lincIRS2* silencing caused insulin resistance, whereas CRISPR/Cas9-mediated knockout of *lincIRS2* elevated blood glucose levels,

derepressed gluconeogenic gene expression and impaired induction of the hepatic fasting gene program, thus eliciting a state of metabolic 'inflexibility' in these mice.

Taken together, we identified a novel MAFG-*lincIRS2* axis controlling hepatic glucose metabolism and metabolic flexibility in health and metabolic disease.

Different subgroups in diabetes

Emma Ahlqvist (Malmö, Sweden)

Higher education degrees

2017	Docent, Genetic Epidemiology, Lund University, Sweden
2007	Ph.D., "Identification of Arthritis Susceptibility Genes in Mice and Humans"; supervisor: Rikard Holmdahl, Lund University, Sweden
2002	M.Sc Biomedicine, specialisation in bioinformatics, Lund University, Sweden

Positions

2016	Associate Professor, Diabetes and Endocrinology, dept. of Clinical Sciences Malmö, Lund University, Sweden
2009–2016	Assistant Professor, Diabetes and Endocrinology, dept. of Clinical Sciences Malmö, Lund University, Sweden

Postdoctoral position

2008	Redoxis AB (Lund/Gothenburg) / Medical Inflammation Research (Lund University)

Degrees

2017	Docent, Genetic Epidemiology, Lund University, Sweden
2007	Ph.D. "Identification of Arthritis Susceptibility Genes in Mice and Humans"; supervisor: Rikard Holmdahl
2002	M.Sc Biomedicine, specialisation in bioinformatics, Lund University, Sweden

Interruption in research

2014–2015	12 months parental leave 100 %
2011	9 months parental leave 100 %

Honors

Scientific coordinator for the ANDIS cohort (2017–)
Member of the ANDIS management team (2016–)
EASD-SGGD committee (2017–)

Awards

The 2017 year Ulf Andersson/Hjelt Foundation Award for outstanding achievements in research, granted by the Bo and Kerstin Hjelt Foundation.

Publications

Number of published/accepted original peer-reviewed articles: 48
Number of review articles: 3
Book chapters: 2
Total number of citations: 3069
H-index = 20
(Scopus 2019-04-16)

Clinical and genetic subtypes of diabetes

Type 2 diabetes is a highly heterogeneous disease with great variability in risk of complications and response to medication. Last year we suggested a new classification of diabetes patients based on six simple variables measured at diagnosis: age at diagnosis, BMI, insulin resistance (HOMA2-IR),

insulin secretion capacity (HOMA2-B), HbA1c and presence of GAD autoantibodies (Ahlqvist et al. 2018). Using a simple clustering algorithm, we divided patients from the Swedish ANDIS cohort into five subgroups: severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), moderate obesity-related diabetes (MOD) and moderate age-related diabetes (MARD). The insulin-resistant group had an increased risk of kidney disease in spite of relatively good glycemic control, whereas the insulin-deficient group had the highest risk of diabetic retinopathy.
Recently, we and others have replicated these findings in multiple populations and further compared the clinical characteristics of the subtypes. We have also studied the genetics of each subtype and related traits using genome-wide association analysis and genetic risk scores, identifying both common and subtype-specific genetic associations. Given that genetics is a powerful tool to investigate the mechanisms underlying disease, this gives us an opportunity to start disentangling differences in disease mechanisms.

Amelie Bonnefond (Lille, France)

Amélie Bonnefond is a Senior Research Associate and currently works in the lab of Prof. Philippe Froguel in Lille, where she is head of the next-generation sequencing platform.

Her research is focused on the contribution of rare genetic events to the risk of type 2 diabetes and related disorders including obesity.

To date, Amélie Bonnefond (H-index: 44) has been co-author of more than 100 articles.

She was recipient of the Rising Star award from the EASD in 2012, and the Loubatières award from the French-speaking Society of Diabetes (SFD) in 2018.

Towards the genetic continuum between common type 2 diabetes and monogenic diabetes

Type 2 diabetes (T2D) is a complex genetic metabolic disorder which has developed into major health problem responsible for early morbidities and mortality, with a burden increasing globally. Estimates of T2D heritability range from 40 to 75 %. Genome-wide association studies (GWAS) have identified more than 200 frequent loci associated with T2D risk. Despite this success, all these loci explain less than 20 % of T2D heritability, and the translation of these discoveries into advances in pathophysiology and precision medicine has been modest so far. In contrast, the genetic investigation of monogenic forms of diabetes has revealed several key regulators of glucose homeostasis and insulin secretion from pancreatic beta cells, leading to textbook cases of genomic and precision medicine. During my talk, I will present unpublished data, based on a large-scale resequencing project, showing the unexpectedly high rate of monogenic diabetes among French patients presenting with late T2D onset. These results have strong implications for the future care and follow-up of mutated patients and their families.

› MODY

Andrew Hattersley (Exeter, UK)

Professor Andrew Hattersley is a consultant diabetologist at the Royal Devon and Exeter hospital and the Professor of Molecular Medicine at the University of Exeter. His clinical training in diabetes and endocrinology was at the Hammersmith and Birmingham and his research training with Prof. Robert Turner in Oxford. With Professor Sian Ellard he has taken Exeter from a centre without a genetics lab in 1995 to being the top international lab for monogenic diabetes that has had over 16,000 referrals from over 95 countries worldwide. His work combines clinical observations, cutting edge molecular genetics and in depth clinical and physiological studies. With the Exeter team he has described 16 new subtypes of monogenic diabetes and developed diagnostic

and treatment approaches for monogenic diabetes that are adopted throughout the world. Recent work has focused on "Precision Diabetes" identifying subgroups in Type 1 and Type 2 diabetes with different treatment responses. He has published over 550 papers with over 55,000 citations, given over 300 national and international lecturers and received many awards for his work including being appointed as a fellow of The Royal Society in 2010 and awarded a CBE in 2017.

New genes and new insights in monogenic diabetes

This lecture will be on new advances in monogenic diabetes. The talk will give examples of recently discovered novel causes and also changes in management that result from using state of the art techniques in clinical care. This can lead to difficult clinical situations as well as improved diagnosis.

Lise Bjørkhaug Gundersen (Bergen, Norway)

Lise Bjørkhaug Gundersen is a professor in molecular pathology at the Western Norway University of Applied Science, Norway. She has since 2000 focused on studying naturally occurring coding variants in genes associated with MODY and type 2 diabetes, including HNF-1A, GCK, and HNF4A, and identified in different population cohorts (MODY, type 2 diabetes, general population), with aim to identify the molecular causes for dysregulation of insulin secretion.

Lise has also been interested in the role of posttranslational modifications in the normal regulation and function of glucokinase and the hepatocyte nuclear factor-1alpha (HNF-1A), and potential relevance in diabetes development. Here, she has identified two novel mechanisms for the regulation and function of glucokinase by protein ubiquitination and SUMOylation, both affecting glucokinase activity and stability. Ubiquitination was also found to play a role in the aggregation and degradation of selected GCK-MODY associated mutant forms. She also identified SUMOylation as a novel mechanism for the regulation of HNF-1A transcription factor function, and the protein inhibitor of activated STAT (PIASgamma) as a novel repressor of HNF-1A transactivation, and affecting the translocation and subnuclear localization of HNF-1A. Her team uses a variety of complementary molecular, cell biological and biochemical approaches in their research.

This keynote will discuss opportunities and challenges of currently used functional tools to predict pathogenic effect of genomic signals within selected HNFs and as cause for diabetes disease.

Significance of functional studies of HNF- gene coding variants for diabetes classification

L. Bjørkhaug[1], A. Kaci[2,3], L.A. Najmi[2,4], J. Hjaltadottir[3], K.A. Mohamed[3,4], J. Molnes[2,4], P. Svalastoga[4], B.B. Johansson[4], P.R. Njølstad[3,4], I. Aukrust[2,4].

1 *Department of Biomedical Laboratory Sciences and Chemical Engineering, Western Norway University of Applied Sciences, Bergen, Norway*
2 *Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway*
3 *Department of Pediatrics and Adolescents, Haukeland University Hospital, Bergen, Norway*
4 *Center for Diabetes Research, Department of Clinical Science, University of Bergen, Norway*

Precision medicine increasingly relies on an accurate interpretation of the consequence of genetic variation. Large-scale multi-ethnic genetic sequencing studies have challenged our understanding of the relationship between coding variants in Mendelian disease genes, including those in clinically actionable genes such as the hepatocyte nuclear factor genes *HNF1A* and *HNF4A*. The consensus has been that heterozygous highly penetrant loss-of-function variants in *HNF1A* and *HNF4A* give rise to the clinically distinct monogenic diabetes subtypes characterized by non-obesity, young age of onset (<25 years), dominant inheritance, and progressive decrease in insulin secretion (Maturity-onset Diabetes of the Young, MODY3 and MODY1). A reliable, clinical translation of the effect of any *HNF1A* and *HNF4A* variant is important for correct diabetes diagnosis. As many individuals carrying such variants are often misdiagnosed as insulin-dependent diabetes, a correct interpretation of variant effect is a requisite for improved treatment (insulin replaced by sulfonylureas). According to ACMG guidelines, validated functional analyses provide a strong evidence for predicting variant pathogenic effect.

Increased access to exome-sequencing data requires a need for detailed mapping of *HNF1A* and *HNF4A* sequence-function relationships at high fidelity, using molecular characterization and analytical pipelines with sensitivity to capture a range of variant effects (severe-mild-benign). In our registry-based studies (MODY, Norwegian Childhood Diabetes Registry, T2D), we examine the effect of variants in *HNF1A*, *HNF4A* and *HNF1B* genes using functional assays investigating transactivation, DNA binding, protein expression and subcellular localization. Variant effect on normal protein function is used to support reclassification of variants and potential assessment of candidates for precision medicine.

These studies are supported by Helse Vest, Norwegian Diabetes Association and foundation of Kristian Gerhard Jebsen.

Genetics of Type 1 diabetes

Matthew Johnson (Exeter, UK)

Matt graduated with a bachelor's degree in Biological sciences from the University of Birmingham in 2011 and began working in Exeter diagnostic genetics laboratory in 2013. He completed his PhD on the genetics of autoimmune forms of neonatal diabetes in 2017 in Exeter under the supervision of Sarah Flanagan, Sian Ellard and Andrew Hattersley. Since then he has been a postdoctoral researcher at the University of Exeter Medical School, continuing to work on the genetics of autoimmunity, monogenic forms of diabetes and extremely early-onset type 1 diabetes. He has published 15 research papers and 2 review articles, including a study showing that known polygenic risk loci for type 1 diabetes do not modify the phenotype in monogenic autoimmunity and the identification of LRBA as a novel cause of autoimmune neonatal diabetes. Current projects include studying the phenotypic variation in monogenic autoimmunity and applying new approaches to increase diagnoses and gene discovery.

Monogenic forms of autoimmune diabetes; challenges and opportunities

Monogenic autoimmune diabetes results from a single highly penetrant mutation that causes autoimmunity leading to destruction of the beta-cells. Identifying monogenic autoimmune diabetes can be a challenge; early-onset type 1 diabetes (T1D) can cluster with additional autoimmune diseases due to shared polygenic risk, particularly from the HLA DR3 and DR4 alleles, and islet and other organ specific autoantibodies are present in patients with both monogenic and polygenic aetiologies. Gene discovery approaches based on phenotype and family structure have had some success in monogenic autoimmune diabetes, with 11 genes described to date. Integration of genetic risk scores shows promise to improve the yield of gene discovery by removing more common clustering of T1D and additional autoimmunity.

Identifying novel causes of monogenic autoimmune diabetes provides insights into pathways of autoimmunity which may improve understanding of more common polygenic autoimmune disease. For patients, a diagnosis of monogenic autoimmune diabetes is important as it can have treatment implications, with specific therapies for some subtypes (e.g. Abatacept in LRBA deficiency) and optimal immunosuppression in others (e.g. Sirolimus in IPEX syndrome). Furthermore, a genetic diagnosis is desirable before undertaking stem cell transplantation which can be curative but carries high risk. Families can also benefit from knowledge of recurrence risk and the availability of prenatal testing.

In 2014 our group identified gain of function STAT3 mutations as a cause of autoimmune diabetes with onset in the neonatal period, and further studies have shown that diabetes is actually a smaller component than initially thought. We also showed in 2017 that recessively inherited LRBA mutations can cause autoimmune neonatal diabetes and recently demonstrated that trisomy 21 can cause autoimmune diabetes before 6 months that is autoimmune but not HLA associated. This demonstrates that there is a unique subset of diabetes caused by trisomy 21 amongst the more common co-incidence of T1D and Down syndrome.

Per-Henrik Groop (Helsinki, Finland)

Professor Per-Henrik Groop, MD, DMSc, FRCPE graduated from the University of Helsinki in 1982. It was here where he defended his thesis on *'The relationship between GIP and beta-cell function in man'* in 1989. Following post-doctoral studies at Guy's Hospital, University of London, under Professor Giancarlo Viberti, Professor Groop returned to Helsinki as Consultant of Nephrology. He served as Professor of Nephrology (Chair) 2010–2015 and is currently Professor of Internal Medicine (Chair) at the University of Helsinki. He is also Chief Physician at the Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital and Principal Investigator of the Finnish Diabetic Nephropathy (FinnDiane) Study at the Folkhälsan Research Center in Helsinki, Finland. He is Adjunct Professor at the Department of Diabetes, Monash University, Melbourne, Australia.

His research is focused on the dissection of the pathogenesis of diabetic complications with special emphasis on diabetic nephropathy. In order to provide a unique set of clinical resources with high power to identify genes and genetic variants associated with diabetic complications, Professor Groop initiated the large, nationwide FinnDiane Study in 1997. To date, this landmark study comprises 8400 patients with Type 1 Diabetes and their family members recruited via a comprehensive network of 92 hospitals and healthcare centres throughout Finland. His FinnDiane Research Group represents an inter-disciplinary team of 45 scientists, post-graduate students and personnel.

Professor Groop served as Associate Editor of *Diabetologia*, 2005–2007, and as member of the Advisory Board, 2008–2011. He served as Associate Editor of *Kidney International and International Diabetes Monitor*, 2007–2011. He was Chairman of the EASD Scientist Training Course, 2007–2013, President of the European Diabetic Nephropathy Study Group (EDNSG), 2008–2010, Chairman of the Signe and Ane Gyllenberg Foundation since 2011, and Honorary Secretary of the EASD 2013–2016. He was awarded the prestigious EASD Castelli Pedroli Prize – 24th Camillo Golgi Lecture in 2009 as well as the Novo Nordisk Foundation Lecture in 2012.

Professor Groop has published more than 350 peer-reviewed original articles in high-impact journals, 33 reviews and book chapters, 47 papers in his native languages Swedish and Finnish as well as more than 600 abstracts presented at major international meetings.

The genetic landscape of renal complications in type 1 diabetes

Roughly 30 % of individuals with type 1 diabetes develop diabetic nephropathy, a devastating late complication, that is accompanied with a manifold increased risk of premature mortality and cardiovascular complications. Already at the early stage of microalbuminuria there is a 3-fold increased risk of premature mortality, 9-fold risk at the stage of macroalbuminuria and 18-fold risk when the individual has reached the stage of ESRD. The reason why one third of those with type 1 diabetes carries risk of diabetic nephropathy is still not fully understood, but a number of manageable environmental factors such as long-term exposure to hyperglycemia, insulin resistance, presence of metabolic syndrome, lipid abnormalities, increased BMI, smoking, lack of intensive physical activity, contribute. However, these risk factors do not explain the total risk of diabetic nephropathy. Since there is an obvious familial clustering regarding diabetic nephropathy, there is now also focus on the search for genetic factors behind the complication. However, the genetic impact might not be as strong as for the type 1 diabetes disease itself, a fact that has certainly contributed to the rather low number of genes that has been linked to diabetic nephropathy. Another factor that has jeopardized the search has been the lack of populations with and without diabetic nephropathy with enough power to detect potential genetic links. The Finnish Diabetic Nephropathy (FinnDiane) Study is to date one of the largest populations that has recruited a large number of individuals with and without diabetic nephropathy, and this landmark study has been a major part alongside collaborative efforts on both sides of the Atlantic Ocean to decipher the genetic enigma of diabetic nephropathy. The presentation will provide an overview of recent data from these efforts, i.e. genetic findings that might explain some of the risk of diabetic nephropathy including data from GWAS, exome and whole genome sequencing as well as epigenetics. The most promising observation so far is the association with a SNP in the gene encoding the alpha-3 subunit

of type IV collagen, a major structural component of the glomerular basement membrane. Notably, this association with *COL4A3* shows a protective effect on the development of diabetic nephropathy.

Flemming Pociot (Copenhagen, Denmark)

Professor, MD, DMSc.

Department of Type 1 Diabetes Biology, Steno Diabetes Center Copenhagen and University of Copenhagen, Denmark.

Research areas:

Genetics, epidemiology, proteomics, bioinformatics – systems biology with focus on type 1 diabetes (T1D) and beta-cell function. Long-standing involvement in T1D genetics. Has been involved in identification of several T1D susceptibility loci and was amongst the first to address the functional aspects of these. His group was also one of the first to use proteomics to address the pathogenic processes in the beta cell leading to T1D development. During the last few years the research focus has specifically on translating observations from genome-wide association studies (GWAS) into understanding type 1 diabetes (T1D) pathogenesis. A specific focus area is to explore the role of non-coding RNA (ncRNAs) both in diabetes and other diseases.

Genetics of beta-cell dysfunction during T1D development

Genetic studies have identified >60 loci associated with the risk of developing type 1 diabetes (T1D). The vast majority of these are identified by genome-wide association studies (GWAS) using large case–control cohorts of European ancestry. More than 80 % of the heritability of T1D can be explained by GWAS data in this population group. However, with few exceptions, their individual contribution to T1D risk is low and understanding their function in disease biology remains a huge challenge. GWAS on its own does not inform us in detail on disease mechanisms, but the combination of GWAS data with other omics-data is beginning to advance our understanding of T1D etiology and pathogenesis. Current knowledge supports the notion that genetic variation in both pancreatic β cells and in immune cells is central in mediating T1D risk. The majority of the genes in the T1D susceptibility loci are expressed in human islets and β cells, where they according to recent studies modulate the β-cell response to the immune system. Their possible involvement in T1D pathogenesis will be discussed.

› Microbiome

Oluf Pedersen (Copenhagen, Denmark)

Dr. Oluf PEDERSEN is Principal Investigator and Group Leader at Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen; and Professor of Human Metabolism, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Applying a variety of biological samples, technologies and statistical-genetics methods the team of Oluf Pedersen is focused on discovering genomic variation that predisposes for common cardio-metabolic disorders. The genomic discoveries are characterized in genetic-physiology studies of disease intermediary traits and in large-scale studies of genetic-epidemiology elucidating the interaction of gene variants with health behavior.

During recent 10 years among the pioneers in the nascent research of the human intestinal microbiome – from basic conceptual contributions to the first bacterial gene catalogues of the human gut and definition of metagenomic species to several studies of aberrant microbiomes in common diseases. Suspected human pathogenic microbiota is studied mechanistically in animal models.

The intestinal microbiota and human metabolism

Traditionally, human-associated microbes have been viewed through the lens of a single species and primarily related to infectious diseases. However, recent advances in culture-independent technologies and computational biology have offered brute force approaches demonstrating the enormous diversity, functional capacity, and dynamics of the astronomic number of bacteria for which humans are the hosts.

The far majority of microbes resides in the distal gastrointestinal tract and imbalances of intestinal bacteria associate with a range of diseases including obesity, diabetes and their comorbidities.

In my lecture, I will discuss ongoing research in genetic and non-genetic factors regulation the human gut microbiota and focus on a potential role of dysbiosis in the pathogenesis of insulin resistance, pre-diabetes and overt type 2 diabetes.

Ondřej Cinek (Prague, Czech Republic)

Ondrej Cinek is Professor in Medical Biology at Charles University in Prague. Presently he holds a position of Senior Researcher, leading a small molecular laboratory at the University Hospital Motol. His research interests include the virome and bacteriome in the development of type 1 diabetes mellitus, as well as specific molecular detection, quantification and genotyping of infectious agents. As other people in this field, he is also involved in bioinformatics and programming (e.g. for virome sequencing, bacteriome profiling and for research of human monogenic conditions). He has published more than 140 international papers, mostly on type 1 diabetes or virology.

Microbiota components and the development of type 1 diabetes – bacteria, viruses, and beyond

The advent of massive parallel sequencing has dramatically changed the methods for studying environmental factors in the pathogenesis of type 1 diabetes. Instead of investigating individual microbes for their putative association with type 1 diabetes, the novel techniques have made it possible to characterize the whole microbiota, and compare its composition between cases (subjects at various stages of type 1 diabetes), and matched controls. The change in the paradigm is comparable to what happened to genetic association studies after the advent of SNP arrays and genome-wide association techniques. This has not come without costs in terms of accuracy. While individual testing of candidate microbes using established PCR techniques is a mature strategy, often under regular proficiency control, the massive parallel sequencing techniques are still rapidly developing.

The microbiome consists of the bacteriome, the virome, the mycobiome (all fungi in a niche or a sample) and the parasitome. Abundant studies are available especially on the gut bacteriome, both in connection to islet autoimmunity, and to diabetes. However, only exceptionally two studies agree on any single agent or a well delineated group of bacteria that would be associated with the conditions. Surprisingly, the larger a study was, the less likely it was to pinpoint a putative causative bacterium. For viruses, the situation is even more complicated: having no pan-viral signature, viruses can be investigated only by metagenomic methods. Their standardisation is extremely poor, and the same applies to the statistical methods for detection of associations with various elements of virus taxonomy, or with measures of virome diversity. Almost nothing is known about the effects of fungi or single-cell parasites, although they are by no means scarce even in developed populations.

The presentation will review recent developments in the association studies of type 1 diabetes with microbiome components, highlighting methodological challenges and unresolved obstacles.

Personalized medicine from a genetic perspective

Ewan Pearson (Dundee, UK)

Division of Public Health and Genomics, School of Medicine, University of Dundee, UK

Ewan Pearson is Professor of Diabetic Medicine at the University of Dundee, Visiting Professor at the University of Edinburgh, and Honorary Consultant in Diabetes and Endocrinology at Ninewells Hospital and Medical School in Dundee. In the School of Medicine, he is the Head of Division for Population Health and Genomics and the Director of the Dundee Clinical Academic Track.

Professor Pearson obtained his medical degree from the University of Cambridge School of Clinical Medicine, UK. He undertook a Wellcome Trust Clinical Training fellowship with Prof Andrew Hattersley at the University of Exeter Medical School, UK and completed his PhD in the physiology and treatment of monogenic diabetes. He then moved to Dundee where he was supported by a Chief Scientist Office Clinician Scientist fellowship and, more recently, by a Wellcome Trust Investigator Award. Over the last ten years in Dundee his research interests have been in the phenotypic and genotypic determinants of drug response in diabetes, and in stratified approaches to the management of diabetes. He leads the IMI-DIRECT project on stratification in type 2 diabetes and is strand 2 lead on the ABPI-MRC funded MASTERMIND project. Ewan has been awarded the Royal College of Physicians of Edinburgh Croom Lecture, an EASD Rising Star award, the Diabetes UK RD Lawrence Lecture and the EASD Minkowski Award for his work in these areas.

Pharmacogenomics in diabetes mellitus: insights into drug action and drug discovery

Type 2 diabetes is a common complex disease. In this talk I will establish a framework for considering both how aetiology of diabetes might alter drug response, and how variation in drug response might give insights into aetiology. I will focus on how we can map type 2 diabetes genetics variants on to the glycaemic benefit of diabetes drugs, and how GWAS of diabetes drugs is providing insight into mechanism of action of existing drugs. I will then consider how genetic variation will soon be used in clinical practice to guide patient therapy in type 2 diabetes.

Torben Hansen (Copenhagen, Denmark)

Torben Hansen is Professor of Molecular Metabolism and Director of the Programme Human Genomics and Metagenomics in Metabolism at the Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Denmark.

Dr Hansen's major research interests are the pathophysiology and pathogenesis of type 2 diabetes, obesity and the metabolic syndrome, and the identification of genetic determinants for both mono and polygenic components of diabetes and obesity. Furthermore, his recent research is also focused on the impact of the gut and saliva microbiome on disease and health and the crosstalk between the host genome and the microbiome.

Dr Hansen is Head of The Graduate PhD Programme for Basic Metabolic Research at University of Copenhagen and is involved in pre- and postgraduate educational activities at the Universities of Copenhagen, Aarhus and Odense, and at the Steno Diabetes Center Copenhagen. He has published more than 500 peer-reviewed original scientific articles and he has been cited more than 39,000 times and holds a H-factor of 80 according to web of science.

Genetics of metabolic traits: Lessons from isolated populations

Type 2 diabetes (T2D) affects millions of people worldwide. Improving the understanding of the underlying mechanisms, and ultimately improving the treatment strategies is, thus, of great interest. To achieve this, identification of genetic variation predisposing to T2D is important. A large number of variants have been identified in large outbred populations, mainly from Europe and Asia. However,

to elucidate additional variation, isolated populations have a number of advantageous properties, including increased amounts of linkage disequilibrium, and increased probability for presence of high frequency disease-associated variants due to genetic drift. Collectively this increases the statistical power to detect association signals in isolated populations compared to large outbred populations. In this presentation, I elaborate on why isolated populations are a powerful resource for the identification of complex-disease variants, and describe their contributions to the understanding of the genetics of T2D and other cardio-metabolic traits.

Metabolism and obesity

Ruth Loos (New York, USA)

Ruth Loos is Director of the Genetics of Obesity and Related Metabolic Traits Program, and co-director of The Charles Bronfman Institute of Personalized Medicine at the Icahn School of Medicine at Mount Sinai.

Her research focuses on the etiology of obesity, in particular, on the identification of genes and genetic loci contributing to the risk of obesity and related traits. She has been involved in gene-discovery since 2005. With the GIANT (Genetic Investigation of ANTropometric traits) consortium, she has contributed to the majority of large-scale gene-discovery efforts that thus far have revealed more than 500 obesity-associated loci. Furthermore, she studies more refined adiposity phenotypes and biomarkers to reveal new biology that has not been uncovered by using traditional obesity outcomes.

Besides gene-discovery, Ruth uses epidemiological methods to assess the public health implications of the established loci by examining their predictive value, interaction with lifestyle factors, and their role in precision medicine of common obesity.

Genes that make you fat, but keep you healthy

Obesity prevalence continues to rise worldwide, posing a substantial burden on people's health and wellbeing. However, up to 45 % of obese individuals do not suffer from cardiometabolic complications, also referred to as the metabolically healthy obese (MHO). Concurrently, up to 30 % of normal weight individuals demonstrate cardiometabolic risk factors that are typically only seen in obese individuals; the so called metabolically obese normal weight (MONW). Besides lifestyle (physical activity, diet, smoking, …) and demographic (age, sex, ancestry) factors, innate biological mechanisms are known to contribute to the etiology of the MHO and MONW phenotypes, as well. Experimental studies in animal models have shown that adipose tissue and adipocyte biology are key players, and mechanisms such as adipose tissue expandability, fat distribution, adipogenesis, vascularization of adipose tissue, inflammation, and mitochondrial function are the main mechanisms that uncouple adiposity from its cardiometabolic comorbidities.

I will review the recent studies that take advantage of genetic association data to expand insights into the biology of MHO/MONW phenotypes, focusing on loci that are associated with increased adiposity, but – at the same time – also with lower risk of cardiometabolic disease.

Most loci reported so far were identified through follow-up of results from genome-wide association studies for body fat percentage, insulin levels, and HDL-cholesterol levels. For some of the loci – but not all – the association with increased adiposity, but protective cardiometabolic effects was mediated through favorable effect on body fat distribution. A well-known example is the Pro12Ala variant in *PPARG*. Preliminary (unreported) findings of a purposefully designed genome-wide association study to discover new genes in a hypothesis-free manner, shows that also other mechanisms (e.g. inflammation) and other tissues maybe involved.

Through gene discovery, new biological mechanisms may be revealed that (un)couple adiposity and its cardiometabolic complications. These genes and pathways may eventually translate in new targets for treatment and prevention, such as PPARG for TZDs in the treatment of type 2 diabetes.

Practical Info

Meeting Venue

University Hospital Motol
www.fnmotol.cz
V Úvalu 84
150 06 Prague 5, Czech Republic

Mission and Vision

The mission of University Hospital in Motol is treatment of illnesses based on actual pieces of medical knowledge and to provide complex and specialized high quality care for all stages of human life. The mission is summed up in our motto: fnmotol.cz: "serving generations". Our main plan for future is to make the hospital "flag ship" of Czech health service in general and specialized care. In order to achieve our goals it is extremely important to have an effective plan for operating the hospital, including a plan for increasing the quality of health care. Our hospital:

- Provides basic, specialized and super specialized health care and services in medical fields in form of outpatient and in-patient care for children, adults and elderly patients
- The biggest health care facility in CZ
- Is built in two single blocks that are connected together as well as few separate pavilions – has 2,410 beds
- More than 860,000 people per year are treated as outpatients
- More than 70,000 people are treated as in patients
- Has more than 5,000 employees

About Prague

Heart of Europe

The capital city of the Czech Republic is considered the heart of the European continent. Its history is deeply rooted in every building and you can feel the city's cultural spirit in every step. Different architectural styles have been preserved throughout wars and years of the communist era, providing visitors with a valuable insight into past images of Prague. As visitors travel along the Vltava River, they are taken on a historical rollercoaster; ranging from the Prague Castle, being the largest historical complex, to the Dancing House representing the city's modern contemporary architecture on the opposite side of the river. However, Prague is not only a city of historical monuments but also a city for living, where culture is an integral part of all things. It is not surprising to find that it has been a source of inspiration for many famous Prague residents and personalities, such as Einstein, Kafka, Mozart and van Beethoven.

Today, many years on from the Velvet Revolution, Prague has established itself as the meeting point of the East and West. The city is now host to multiple scientific conferences and cultural events and is in the top 10 of event destinations worldwide. The same goes for movie makers who simply love coming to Prague to enhance the scene and backdrop of their movies. You may have seen Prague in films such as The Bourne Identity (2002), The Illusionist (2006), Casino Royale (2006), Mission: Impossible (1996) and Amadeus (1984).

"Prague isn't just a city, but an entity of some kind."

Sezin Koehler

Practical Info

Registration Opening Hours

16.5.	12:00–18:30
17.5.	8:30–18:15
18.5.	8:30–14:00

Badges

Your name badge, provided during the onsite registration, is an official Meeting document and must be worn at all times for entry to the scientific sessions, exhibition area and social programme. In case of lost or forgotten badges, an administration fee of 20 EUR will be charged.

Language

The Meeting language is English, no simultaneous translation is provided

WiFi

There is a free WiFi internet connection available in the venue.

Lost & Found

A lost and found service is available at the registration desk.

Food and Beverages

Coffee breaks and lunches are included in the registration fee and will be served within the Poster area.

Smoking Policy

Please note that smoking is not permitted anywhere within the venue.

Certificate of Attendance

The certificate of attendance will be provided to all of the participant after the Meeting by email.

Doctor / First Aid

In case of emergency, please contact the Registration desk or dial 112 to get specialised help.

Emergency phone numbers

General emergency	112
Police	158
Fire department	150
Emergency medical service	155

Company Profiles

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HPST, s.r.o.

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Illumina Inc

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Complex diseases affect us all. Illumina is committed to advancing our understanding of complex diseases and how they will be diagnosed and treated.
Complex diseases result from a combination of genetic and environmental factors, many of which are not understood. These diseases include neurodegenerative, psychiatric, and autoimmune disorders, and others.
The expanding Illumina complex disease product portfolio includes array and next-generation sequencing (NGS) technologies that are helping drive a revolution in complex disease genomics. These solutions deliver high-quality, reproducible results that accelerate research on various complex diseases. These discoveries have the potential to lead to life-changing improvements for patients and their loved ones.

ELI LILLY ČR, s.r.o.

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Eli Lilly and company was founded in 1876 by Colonel Eli Lilly, a man committed to creating high-quality medicines that met real needs in an era of unreliable elixirs peddled by questionable characters. His charge to the generations of employees who have followed was this: "Take what you find here and make it better and better."
More than 140 years later, Lilly remains committed to his vision through every aspect of its business and the people it serves starting with those who take Lilly medicines, and extending to health care professionals, employees and the communities.
Lilly unites caring with discovery to create medicines that make life better for people around the world.

Novo Nordisk s.r.o.

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Novo Nordisk is a global healthcare company with more than 95 years of innovation and leadership in diabetes care. This heritage has given experience and capabilities that also enable the company to help people defeat other serious chronic diseases: haemophilia, growth disorders and obesity.

Contact Details and Disclaimer

Meeting Secretariat

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Disclamer – Data Privacy and Security

We take your privacy very seriously and in order to comply with the European General Data Protection Regulation (entered into force as of 25 May 2018) consent requirements we updated our Privacy Policy. You can view it on our website – www.czech-in.org/C-IN/GDPR/privacy-policy.html.

Feel free to contact us with any questions in regards to the Privacy Policy, Data Protection and GDPR in general by an email (gdpr@c-in.eu) or by phone +420 261 174 301.

Programme

Thursday, May 16

12:00–13:30 **Lunch in the poster area**

13:30–13:45 **Welcome and opening**
Jan Lebl, Štěpánka Průhová, Emma Ahlqvist

13:45–15:15 **SESSION 1**

Genetics of Type 1 diabetes
Chairs: Kateřina Kaňková, Sarah Flanagan

13:45–14:15 Flemming Pociot *(Copenhagen, Denmark)* – **Genetics of beta-cell dysfunction during T1D development**

14:15–14:45 Per H Groop *(Helsinki, Finland)* – **The Genetic Landscape of Renal Complications in Type 1 Diabetes**

14:45–15:15 Matthew Johnson *(Exeter, UK)* – **Monogenic forms of autoimmune diabetes; challenges and opportunities**

15:15–16:15 **POSTER SESSION 1**

Posters 1–9 (T1D, MODY)
Chairs: Ondřej Cinek, Zdeněk Šumník

Posters 20–28 (T2D, Metabolism)
Chairs: Ines Barroso, Jan Lebl

COFFEE / TEA BREAK

16:15–18:15 **SESSION 2**

Personalized medicine from a genetic perspective
Chairs: Timothy Frayling, Christine Bellanne-Chantelot

16:15–16:45 Torben Hansen *(Copenhagen, Denmark)* – **Genetics of metabolic traits: Lessons from isolated populations**

16:45–17:15 Ewan Pearson *(Dundee, UK)* – **Pharmacogenomics in diabetes mellitus: insights into drug action and drug discovery**

Oral presentations: Animal models of diabetes

17:15–17:30 OP01 Lucie Šedová *(Prague, Czech Republic)* – **Effects of NME7 CRISPR/CAS9-Targeting on metabolic syndrome-related parameters of Sprague Dawley rats**

17:30–17:45 OP02 Eugenia Mazzaferro *(Uppsala, Sweden)* – **Zebrafish as a model system to characterise causal genes for LDL cholesterol levels and downstream effects on atherosclerosis and diabetes risk**

17:45–18:00 OP03 Marcel den Hoed *(Uppsala, Sweden)* – **Zebrafish as a model system for systematic IMAGE- and CRISPR-CAS9-Based screens in insulin resistance**

18:00–18:15 OP04 Natalie van Zuydam *(Uppsala, Sweden)* – **A Zebrafish model for identifying putatively causal genes from diabetes associated loci**

19:30 DINNER (RESTAURANT PROFESNÍ DŮM)

Friday, May 17

09:00–11:00 **SESSION 3**

Monogenic diabetes
Chairs: Leen M 't Hart, Daniela Gasperíková

09:00–09.30 Andrew Hattersley *(Exeter, UK)* – **New genes and new insights in monogenic diabetes**

09:30–10:00 Lise Bjørkhaug Gundersen *(Bergen, Norway)* – **Significance of functional studies of HNF-coding gene variants for diabetes classification**

Oral presentations: MODY

10:00–10:15 OP05 Jarno Kettunen *(Helsinki, Finland)* – **The family-based assessment of HNF1A-MODY**

10:15–10:30 OP06 Kevin Colclough *(Exeter, UK)* – **Next generation sequencing for monogenic diabetes increases diagnostic yield and identifies patients that would not be diagnosed by single gene testing according to clinical phenotype**

10:30–10:45 OP07 Alexander Sidelmann Christensen *(Copenhagen, Denmark)* – **Both GIP and GLP-1 potentiate Sulfonylurea-induced insulin secretion in patients with HNF1A-diabetes**

10:45–11:00 OP08 Elisa De Franco *(Exeter, UK)* – ***De novo* variants in *EIF2B1* are a novel cause of permanent neonatal diabetes and transient liver dysfunction**

11:00–11:30 COFFEE / TEA BREAK

11:30–13:00 **Oral Presentations: Monogenic beta-cell disorders**
Chairs: Niels Grarup, Katarine Owen

11:30–11:45 OP09 Jayne Houghton *(Exeter, UK)* – **Routine screening of the *KDM6A* and *KMT2D* genes in individuals with hyperinsulinism allows for an earlier diagnosis of Kabuki screening**

11:45–12:00 OP10 Thomas Laver *(Exeter, UK)* – **Large deletions are an underappreciated cause of hyperinsulinism**

12:00–12:15 OP11 Cécile Saint-Martin *(Paris, France)* – **NGS analysis of monogenic diabetes patients showed that maternally inherited diabetes and deafness is underdiagnosed**

12:15–12:30 OP12 Marcus Tuke *(Exeter, UK)* – **Assessing the pathogenicity and penetrance of *HNF1B* deletions and duplications in UK Biobank**

12:30–12:45 OP13 Ingrida Stankute *(Kaunas, Lithuania)* – **High incidence of monogenic diabetes in Lithuanian pediatric and young adult diabetes patients**

12:45 - 13:00 OP14 Kashyap Patel *(Exeter, UK)* – **Different genetic testing strategies for monogenic diabetes are needed in populations with higher rates of consanguinity**

13:00–14:30 LUNCH IN THE POSTER AREA

13:20–14:30 **POSTER SESSION 2**

Posters 10–19 (MODY)
Chairs: Kevin Colclough, Julie Støy

Posters 29–39 (Obesity)
Chairs: Ruth Loos, Roderick C. Slieker

14:30–16:30 **SESSION 4**

Different subgroups of diabetes
Chairs: Antonio Luis Cuesta-Muños, Martine Vaxillaire

14:30–15:00 Emma Ahlqvist *(Malmö, Sweden)* – **Clinical and genetic subtypes of diabetes**

15:00–15:30 Amelie Bonnefond *(Lille, France)* – **Towards the genetic continuum between common type 2 diabetes and monogenic diabetes**

Oral presentations: Different subgroups of diabetes – practical implications

15:30–15:45 OP15 Michael Weedon *(Exeter, UK)* – **Using UK Biobank to assess the pathogenicity, penetrance and expressivity of monogenic diabetes variants**

15:45–16:00 OP16 Matthew Wakeling *(Exeter, UK)* – **Homozygosity mapping from small targeted NGS panel using Savvy homozygosity – getting more from less**

16:00–16:15 OP17 Adem Dawed *(Dundee, UK)* – **Loss of function variants in the *CYP2C9* & *SLCO1B1* are associated with improved glycaemic response to sulphonylureas: A GoDARTS Study**

16:15–16:30 OP18 James W Harrison *(Exeter, UK)* – **A Type 1 Diabetes Genetic Risk Score improves classification of diabetes in India**

16:30–17:00 COFFEE / TEA BREAK

17:00–18:00 **SESSION 5**

Microbioma in Type 1 and Type 2 diabetes
Chairs: Zdeněk Šumník, Torben Hansen

17:00–17:30 Ondřej Cinek *(Prague, Czech Republic)* – **Microbiota components and the development of type 1 diabetes – bacteria, viruses, and beyond**

17:30–18:00 Oluf Pedersen *(Copenhagen, Denmark)* – **The intestinal microbiota and human metabolism**

19:30 DINNER (RESTAURANT MLÝNEC)

Saturday, May 18

09:00–11:00 **SESSION 6**

Metabolism and Obesity I. (OMICS)
Chairs: Michael Weedon, Phillipe Froguel

09:00–09.30 Roderick C Slieker *(Leiden, the Netherlands)* – **A multi-omics approach towards type 2 diabetes**

09:30–10:00 Jan-Wilhelm Kornfeld *(Köln, Germany; Odense, Denmark)* – **Regulation of metabolism by long noncoding RNAs**

Oral presentations: Epigenetics and gene expression

10:00–10:15 OP19 Pradeep Bompara *(Malmö, Sweden)* – **Epigenetic and transcriptome landscapes of glucose-induced histone acetylation in pancreatic islets**

10:15–10:30 OP20 Ji Chen *(Cambridge, UK)* – **Leveraging ancestry differences for glycaemic trait locus discovery and fine-mapping**

10:30–10:45 OP21 Jason Torres *(Oxford, UK)* – **Integration of epigenetic maps and High-Resolution Chromatin Interactions implicates effector transcripts at loci associated with Type 2 diabetes in human pancreatic EndoC- β H1 cells**

10:45–11:00 OP22 Jun Liu *(Rotterdam, the Netherlands)* – **Novel CPG sites of glucose and insulin homeostasis: An integrative Cross-Omics Analysis**

11:00–11:30 COFFEE / TEA BREAK

11:30–13:00 **SESSION 7**

Metabolism and Obesity II.
Chairs: Lenka Petruželková, Jan-Wilhelm Kornfeld

Oral presentations: Population studies

11:30–11:45 OP23 Jessica Tyrrell *(Exeter,UK)* – **Comparing the causal effects of diabetes-related traits on measures of micro-and macro-vascular disease**

11:45–12:00 OP24 Zhanna Balkhiyarova *(London, UK)* – **Common genetic loci associated with Type 2 diabetes mellitus, depressive symptoms and anxiety**

12:00–12:15 OP25 Sadia Saeed *(Lille, France)* – **Augmented exome sequencing (CoDE-Seg) identifies point mutations and copy number variants causing extreme obesity in 48 % of patients from a consanguineous Pakistani population**

12:15–12:30 OP26 Marika Kaakinen *(London, UK)* – **Multiple epigenetic and metabolomic markers predict glycaemic health in middle-aged men and woman**

Genetics of obesity

12:30–13:00 Ruth Loos *(New York, USA)* – **Genes that make you fat, but keep you healthy**

13:00–13:30 **Best poster and oral presentation Award ceremony * and closing of the meeting**

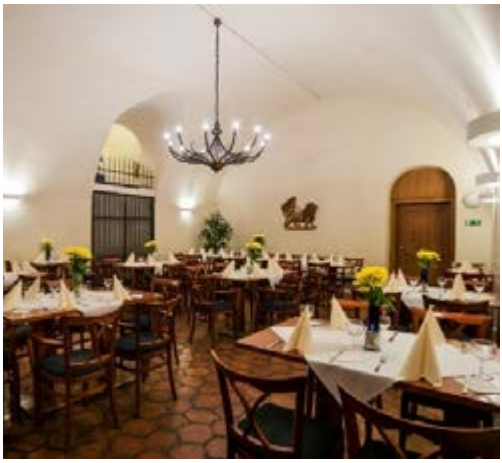
* Mandatory for winners to be present

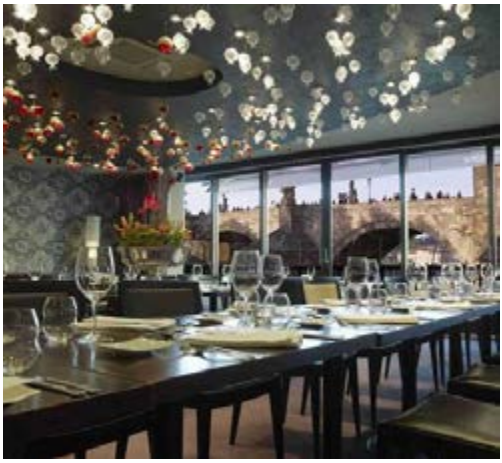
Best poster presentation award
Best oral presentation award
Chairs: Štěpánka Průhová, Jan Lebl, Amelie Bonnefond

Closing remarks

13:30 LUNCH

Social Activities





Welcome Reception

Profesní dům restaurant
Thursday May 16, 19:30
Malostranské nám. 25
118 00 Prague 1

In the centre of Prague, in the university building by the Church of Saint Nicholas, is the stylish subterranean Profesní dům restaurant.

The local masterchefs will prepare for you a rich selection of traditional Czech and international cuisine.

Meeting Dinner

Mlýnec restaurant
Friday May 17, 19:30
Novotného lávka 9
110 00 Prague 1

The river Vltava flowing under your feet, a romantic view of the Charles Bridge and a newly designed interior inspired by the dynamic water surface. Add to that the exceptional food with an emphasis on getting every detail just right and a thorouhly professional approach, and your visit will be a special experience which you will want to repeat.

Executive chef Marek Šáda revives forgotten Czech delicacies for you. To create a dish that will delight you, he doesn't shy from using contemporary culinary methods with respect to traditional meals. The result speaks for itselfs.

Abstract Book

Oral Presentations

Lucie Šedová

OP01: EFFECTS OF NME7 CRISPR/CAS9-TARGETING ON METABOLIC SYNDROME-RELATED PARAMETERS OF SPRAGUE DAWLEY RATS

Šedová L.[1,2], Školníková E.[2], Chambers N.[2], Chalupský K.[2], Makovický P.[2], Včelák J.[3], Bendlová B.[3], Šeda O.[2], Sedláček R.[1]

1) Czech Centre for Phenogenomics, Institute of Molecular Genetics, Vestec, Czech Republic
2) Institute of Biology and Medical Genetics, The First Faculty of Medicine, Charles University, Prague, Czech Republic
3) Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic

Background

We have previously identified an association of genetic variants in NME7 (non-metastatic cells 7, nucleoside diphosphate kinase 7) gene with indices of insulin sensitivity and dyslipidemia in two independent human cohorts

Aims

We aimed to investigate the role of Nme7 in metabolic syndrome using a targeted rat model. Methods: The CRISPR/Cas9 nuclease system was used for generation of Sprague Dawley Nme7 knock-out rats targeting the exon 4 of Nme7 gene. As the homozygous Nme7 targeted allele was not viable mostly due to prominent and severe hydrocephalus, We performed comprehensive metabolic, transcriptomic and histomorphometric comparison of heterozygous SDNme7+/- male and female adult rats with their wild type littermates (SD).

Results

Body weights of SDNme7+/- males compared to SD males started to be significantly higher at week 9 and this difference was preserved till sacrifice at week 22, but body weight of SDNme7+/- and SD females remained comparable. Significant differences were observed in glucose tolerance on standard diet, where both SDNme7+/- male and female rats had significantly higher glucose levels during intraperitoneal glucose tolerance test resulting in larger area under the glycemic curve. There were no differences in organ weights. Islets of Langerhans fibrosis was observed only in SDNme7+/- animals contrasting with wild-type controls. We performed liver and fat pad transcriptomic analyses of SDNme7+/- and SD males, identifying several dysregulated metabolic and signalling pathways in SDNme7+/- including nodes related to cilia such as Ift140, Ift57, Ttc26, Cep290, Bbs5 genes.

Conclusions

We observed glucose intolerance, islet fibrosis and global transcriptome shifts in heterozygous SDNme7+/- rats, suggesting a role of Nme7 in diabetes and metabolic syndrome-related pathologies.

Acknowledgments

Supported by Czech Science Foundation Project 17-13491S.

Eugenia Mazzaferro

OP02: ZEBRAFISH AS MODEL SYSTEM TO CHARACTERISE CAUSAL GENES FOR LDL CHOLESTEROL LEVELS AND DOWNSTREAM EFFECTS ON ATHEROSCLEROSIS AND DIABETES RISK

Mazzaferro E.[1], Bandaru M.[1], Emmanouilidou A.[1], Klingström T.[1], den Hoed M.[1]

1) The Beijer Laboratory and Department of Immunology, Genetics and Pathology, Uppsala University and SciLifeLab, Sweden

Background

Coronary artery disease is the leading cause of death worldwide and results from progression of atherosclerosis, which is triggered in part by elevated plasma concentrations of LDL cholesterol (LDLc). Statins can help prevent cardiovascular diseases by lowering LDLc. However, several trials reported a higher risk of incident diabetes and impaired glycaemic control in diabetes patients treated with statins.

Aim

This project aims to improve our understanding of the genetic aetiology of the regulation of plasma LDLc levels and their effect on atherosclerosis and diabetes risk, with the ultimate goal to identify alternative LDLc targets.

Methods

56 candidate genes were prioritised and results for orthologues of the first six human genes are currently available. The genes abcg5, abcg8, myrf, col4a3bpa, col4a3bpb, st3gal4, ywhaqa and ywhaqb were characterised in vivo using a high-throughput, image- and CRISPR-Cas9-based zebrafish model system. The offspring of founder fish were imaged for vascular accumulation and co-localization of lipids, macrophages and neutrophils. For each larva, whole body levels of triglycerides, total cholesterol and glucose were subsequently quantified enzymatically, and the larvae were sequenced to identify CRISPR-induced mutations.

Results

Each additional mutated allele of the genes col4a3bpb, st3gal4, ywhaqa, and ywhaqb was associated with less vascular lipid deposition and less co-localisation of macrophages with lipids, without affecting glucose, total cholesterol, or triglyceride levels. Larvae with mutations in ywhaqa were also smaller. Mutations in myrf resulted in more vascular accumulation of lipids, and in more co-localisation of macrophages with neutrophils, without affecting whole body levels of triglycerides, total cholesterol and glucose. The GWAS catalog suggests that targeting COL4A3BP and MYRF may have adverse neurological side effects and higher risk of on the colorectal cancer, respectively. CONCLUSION: ST3GAL4 and SNF emerge as alternative targets to pharmaceutically lower LDLc levels and the risk of early-stage atherosclerosis without anticipated adverse side effects.

Marcel den Hoed

OP03: ZEBRAFISH LARVAE AS A MODEL SYSTEM FOR SYSTEMATIC IMAGE- AND CRISPR-CAS9-BASED SCREENS IN INSULIN RESISTANCE

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Background

Systematic characterization of genes in GWAS-identified loci requires novel *in vivo* model systems.

Aims

We developed and validated a zebrafish model system for systematic, large-scale, image-based genetic screens in insulin resistance.

Methods

We metabolically challenged 454 larvae by dietary cholesterol supplementation (4 %) and/or exposure to 3 % glucose solution; treated 571 challenged larvae with 0, 10 or 25 uM rosiglitazone or metformin; and challenged 560 offspring of multiplexed CRISPR-Cas9 founders for *INSR*, *IRS1* and *PPARG*. Interventions from 5 to 10 days post-fertilisation were followed by imaging and quantification of ß-cell number, ß-cell insulin expression, liver size, and subcutaneous and liver fat. Whole-body LDLc, HDLc, triglycerides, total cholesterol and glucose levels were then assessed enzymatically, and larvae were sequenced at the CRISPRtargeted sites if appropriate.

Results

Glucose exposure resulted in more ß-cells, higher ß-cell insulin expression, a larger liver, more liver and subcutaneous fat, and higher glucose. Cholesterol supplementation resulted in higher LDLc and total cholesterol, more liver fat and less subcutaneous fat. Rosiglitazone treatment resulted in lower LDLc, HDLc and total cholesterol, fewer ß-cells, a smaller liver, less liver fat, and similar (lower dose) or lower (higher dose) glucose. Metformin treatment resulted in lower HDLc, higher total cholesterol (trend), more liver fat, and lower glucose (trend). Each additional mutated allele in *insrb* resulted in higher LDLc, lower HDLc, more ß-cells, a larger liver, more liver fat, and higher glucose. Opposite effects were observed for *insra*. Each mutated allele in *irs1* resulted in more ß-cells (trend) and higher glucose; each mutated allele in *pparg* resulted in more liver fat and ß-cells (trends).

Conclusion

Results from metabolic challenges, treatment with insulin sensitizers, and disruption of established insulin resistance genes confirm that zebrafish larvae are suitable for systematic, *in vivo* characterization of candidate genes for insulin resistance.

Natalie Van Zuydam

OP04: A ZEBRAFISH MODEL FOR IDENTIFYING PUTATIVELY CAUSAL GENES FROM DIABETES ASSOCIATED LOCI

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There are hundreds of loci associated with type 2 diabetes (T2D) risk but the majority of genes underlying them have not been identified. To assess the suitability of zebrafish as a model for T2D gene discovery we examined the effects of known causal genes of in monogenic form of diabetes, and the effects of metformin and sulphonlyreas on metabolic traits in zebrafish.

Genome-editing using CRISPR/Cas9 was employed to induce mutations in the zebrafish orthologues of 4 MODY genes (pdx1, gck, hnf1a, hnf1ba and hnfbb). On day 10 post fertilisation (dpf) and after dietary intervention from 5 dpf, 668 zebrafish larvae were phenotypically screened and genotyped for CRISPR induced mutations at targeted sites using paired-end sequencing. Similarly, the effects of metformin (359 treated vs 527 untreated) and tolbutamide (248 treated vs 357 untreated) treatment on metabolic traits were assessed at 10 dpf. The effects of mutations or therapeutic interventions were examined using hierarchical linear models.

Mutations in MODY genes were associated with changes in lipid and glucose homeostasis, and beta-cell morphology: pdx1 mutations were associated ($p \leq 0.05$) with fewer beta-cells and with higher HDLc (βSDunits[SE]=0.26[0.07]); mutations in hnf1a were associated with lower LDLc (-0.25[0.11]); and mutations in hnf1bb were associated with higher glucose levels (0.20[0.07]) and higher total cholesterol (0.33[0.07]). Metformin treatment showed a trend for lower glucose levels consistent with effects in humans, but also with higher total body cholesterol levels (0.23[0.11]) and more liver fat (0.29[0.11]). Tolbutamide treatment was associated with fewer beta-cells (-0.37[0.14]) and higher glucose levels (0.27[0.09]).

Disruption of known diabetes genes in zebrafish was associated with changes in metabolic traits, and metformin treatment showed a trend for lower whole-body glucose, consistent with effects in humans. These data show that zebrafish are likely to be a suitable model for gene discovery in diabetes.

Jarno Kettunen

OP05: THE FAMILY-BASED ASSESSMENT OF HNF1A-MODY

Kettunen J.L.T., Isomaa B., Sarelin L., Kokko P., Groop L., Rajala E., Tuomi T.

Background

The present view of the HNF1A-MODY phenotype is largely based on patients fulfilling predefined criteria for genetic testing, which poses a risk of neglecting possible heterogeneity among the patients.

Aims

To assess the timing of onset of diabetes, clinical features including body mass index, and mortality among carriers of the most common MODY variant in *HNF1A*, p.Gly292fs, we conducted a family-based comparative study in eight HNF1A-MODY families comprising 128 carriers and 122 non-carriers.

Methods

In two large (89 carriers, 92 non-carries) and five other (39 carries, 30 non-carriers) HNF1A-MODY families from the FINNMODY and Botnia studies, we analysed data on glucose, insulin, C-peptide (for a subgroup also glucagon, FFA, and proinsulin) at fasting or during an OGTT, mortality and morbidity (from national registries) and anthropometric measurements. Of 184 individuals with OGTT data, 108 provided an OGTT more than once.

Results

Half of the carriers had diabetes at 25 years, and 25 % remained undiagnosed at 43 years. The median age at diagnosis was 22 (IQR: 17 to 33). The usability of the Exeter MODY probability calculator was limited: 24/108 diabetic carriers were older than 35 years at diagnosis excluding its use. Further, the calculator failed to reach a threshold probability of 20 % in more than 10 % of diabetic carriers. First adult BMI was 2 kg/m^2 lower among the carriers (adjusted BMI -1.5 kg/m^2, adjusted weight -4.8 kg). The carriers had an increased mortality rate during the follow-up (Cox HR 2.4, p=0.04; total N=238, 13 carriers and 13 non-carriers died). Mean HbA1c correlated with the age at diagnosis of coronary artery disease among the carriers.

Conclusions

The presentation of HNF1A-MODY is heterogeneous. The age at diagnosis was higher than expected and the carriers were leaner than the non-carriers.

Kevin Colclough

OP06: NEXT GENERATION SEQUENCING FOR MONOGENIC DIABETES INCREASES DIAGNOSTIC YIELD AND IDENTIFIES PATIENTS THAT WOULD NOT BE DIAGNOSED BY SINGLE GENE TESTING ACCORDING TO CLINICAL PHENOTYPE

Colclough K., Houghton J., Moleirinho A., van Heugten R., Ellard S., Hattersley A. & Patel K.

Background

Monogenic diabetes diagnosed outside the neonatal period is clinically and genetically heterogeneous. Targeted next-generation sequencing (tNGS) for this disorder is replacing Sanger sequencing of single genes, but the diagnostic and clinical utility of tNGS as a first-line genetic test is not known.

Aims

Determine diagnostic yield of first-line tNGS for monogenic diabetes diagnosed aged >1 year compared to *GCK*, *HNF1A* and *HNF4A* sequencing alone, and assess whether clinical characteristics of patients are consistent with diagnosed genetic subtype.

Methods

tNGS of 24 monogenic diabetes genes and the mitochondrial DNA mutation m.3243A>G was performed for 1405 patients diagnosed aged >1 year and a specific genetic subtype was not suspected. Clinical features of patients diagnosed by tNGS were compared to patients with the same genetic subtype identified by single-gene testing.

Results

A diagnosis of monogenic diabetes was made in 296/1405 (21 %) cases. *GCK*, *HNF1A* and *HNF4A* accounted for 69 % (205/296) of cases. Targeted NGS increased diagnostic yield by 91 cases across 15 other genetic subtypes with m.3243A>G the most common (23/91), followed by *HNF1B* (19/91) and *ABCC8/KCNJ11* (16/91).

Diabetes phenotype did not distinguish between *GCK/HNF1A/HNF4A* and the other genetic subtypes. Only 3/23 (13 %) of patients with tNGS-detected m.3243A>G diabetes had a clinician-reported personal or family history of deafness compared to 52/55 (95 %) identified by m.3243A>G testing alone ($p<0.0001$). Similarly, a history renal disease was not reported in the tNGS-*HNF1B* group compared to 45/50 (90 %) patients with diabetes identified by *HNF1B* testing alone ($p<0.0001$).

Conclusions

tNGS that includes the m.3243A>G mutation should be used as a first-line test for monogenic diabetes for all patients not suspected of having a specific genetic subtype. tNGS increases diagnostic yield and identifies patients that would not be diagnosed by single-gene testing based on clinical phenotype.

Acknowledgments

We thank all diagnostic laboratory staff that performed the tNGS testing.

Alexander Sidelmann Christensen

OP07: BOTH GIP AND GLP-1 POTENTIATE SULFONYLUREA-INDUCED INSULIN SECRETION IN PATIENTS WITH HNF1A-DIABETES

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Context (background)

Sulfonylurea (SU) is considered first-line treatment of hepatocyte nuclear factor 1-alpha (HNF1A)-diabetes despite risk of hypoglycaemia and potentially body weight gain. In addition, lasting glycaemic control is rarely obtained with SU why new treatments for patients with HNF1A-diabetes are needed.

Aims

To evaluate the insulinotropic effect of exogenous glucose-dependent insulinotropic peptide (GIP) and glucagon-like-peptide 1 (GLP-1), respectively, as an add on to SU in patients with HNF1A-diabetes.

Methods

Ten patients with HNF1A-diabetes (females=4; [mean±SD] age 35.3±8.1 years; BMI 22.4±1.5 kg/m^2; HbA1c 42.3±6.6 mmol/mol) and ten matched healthy controls (females=4; age 33.9±8.0 years; BMI 22.2±2.4 kg/m^2; HbA1c 31.9±2.8 mmol/mol) were included in this randomised, placebo-controlled, cross-over study. Participants were subjected to six 2-hour glucose clamps (1 h at fasting plasma glucose (FPG) and 1 h at 1.5 × FPG). At time -90 min, participants received 1 mg of glimepiride or placebo. At time 0–120 min a continuous infusion of either GIP (1.5 pmol/l/kg), GLP-1 (0.5 pmol/l/kg) or saline (NaCl) was given. Insulin responses were quantified as baseline-subtracted area under the curves (bsAUC) from 0 to 120 min.

Results

The insulin response was attenuated in patients with HNF1A-diabetes compared to controls. In patients with HNF1A-diabetes both SU+GIP ([mean bsAUC ± SE] 7664 ± 1214) and SU+GLP-1 (6797 ± 1250) potentiated the insulin response compared to SU+NaCl (4224 ± 1280), placebo+GIP (2971 ± 531) and placebo+GLP-1 (3337 ± 803), respectively.

Significant differences ($P<0.05$) in mean insulin bsAUC were observed for SU+GIP vs. placebo+GIP, placebo+GLP-1 and placebo+NaCl, respectively, and for SU+GLP-1 vs. placebo+GIP and placebo+NaCl, respectively.

Conclusion

Both GIP and GLP-1 were insulinotropic in both patients with HNF1A-diabetes and healthy subjects, and their effects were further potentiated when combined with SU.

Elisa De Franco

OP08: *DE NOVO* VARIANTS IN *EIF2B1* ARE A NOVEL CAUSE OF PERMANENT NEONATAL DIABETES AND TRANSIENT LIVER DYSFUNCTION

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Background

Permanent neonatal diabetes (PNDM) diagnosed <6 months is caused by reduced β-cell number or impaired β-cell function. Understanding the genetic basis of PNDM highlights fundamental β-cells mechanisms.

Aim

To identify the genetic causes of PNDM in an international patient cohort.

Methods

We performed trio whole-genome-sequencing for 44 PNDM patients and their unaffected, non-consanguineous parents. Genes with *de novo* variants in >3 patients were followed-up. Replication studies were performed in 114 PNDM patients without a genetic diagnosis.

Results

EIF2B1 was the only gene with novel *de novo* variants (p.(Gly44Asp), p.(Gly44Val), and p.(Ser77Asn)) identified in three patients. Replication studies identified 2 further patients with heterozygous *de novo EIF2B1* variants (p.(Leu34Trp) and p.(*306Thrext*12)). All variants mapped to the same protein surface and were predicted to disrupt protein's function *in silico*. In addition to PNDM, 4/5 patients had hepatitis-like episodes in childhood. No severe neurological features were reported (oldest patient aged 18).

Our patients' phenotype is markedly different from the neurological disease (Leukoencephalopathy with vanishing white matter) caused by biallelic *EIF2B1* variants resulting in loss of the EIF2B complex (formed by EIF2B1 and 4 other proteins). Previous studies in *S.cerevisiae* showed that the p.Gly44 residue (affected in 2 PNDM patients), while not needed for EIF2B complex formation, is essential for interaction with phosphorylated eIF2. Loss of this interaction causes unregulated unfolded protein response and endoplasmic reticulum (ER) stress. This pathway is likely to be essential for β-cell function as absence of one of the eIF2-phosphorylating kinases, PERK (encoded by *EIF2AK3*), also causes PNDM.

Conclusions

We report *de novo EIF2B1* mutations as a novel cause of PNDM and liver dysfunction. These variants are likely to disrupt EIF2B1's interaction with phosphorylated eIF2, causing ER stress. These findings highlight the fundamental role of EIF2B1 in β-cells.

Acknowledgments

Patients, their families and referring clinicians. Funder: Wellcome Trust.

Jayne Houghton

OP09: ROUTINE SCREENING OF THE *KDM6A* AND *KMT2D* GENES IN INDIVIDUALS WITH HYPERINSULINISM ALLOWS FOR AN EARLIER DIAGNOSIS OF KABUKI SCREENING

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Context

Kabuki syndrome is a rare congenital syndrome affecting multiple systems but genetic testing is often not instigated until the full clinical syndrome becomes apparent in childhood (~5 years). Autosomal dominant Kabuki syndrome (*KMT2D)*, accounts for ~56–75 % of cases, whereas X-linked dominant Kabuki syndrome (*KDM6A)* accounts for ~3–8 % of cases. Infancy onset hyperinsulinism (HI) can be a presenting feature of Kabuki syndrome. Testing of *KMT2D/KDM6A* in HI may allow earlier diagnosis of these patients.

Aims

To assess the contribution and characteristics associated with mutations in *KMT2D* or *KDM6A* in patients with HI and Kabuki syndrome.

Methods

We analysed the *KMT2D* and *KDM6A* by targeted next generation sequencing in 324 patients referred for genetic testing between September 2017 and January 2019; 31 patients were referred for Kabuki syndrome testing and 293 were referred for hyperinsulinism testing (negative for *ABCC8, KCNJ11, GLUD1, GCK, HNF4A, HADH, SLC16A1*).

Results

Mutations in *KMT2D/KDM6A* were identified in 15/31 patients referred specifically for Kabuki syndrome testing and 8/293 patients referred for HI testing. Patients referred for HI received a genetic diagnosis of Kabuki syndrome at mean age of 1.1y compared to 5.1y for patients when referred for Kabuki syndrome ($p<0.0001$). There was enrichment of *KDM6A* in HI referrals (6/8) compared to the clinically referred Kabuki syndrome cohort (1/15) ($p<0.001$).

Conclusions

Mutations in *KDM6A* and *KMT2D* are an important cause of hyperinsulinism. The earlier age at genetic diagnosis of patients with hyperinsulinism without clinical suspicion of Kabuki syndrome suggests that hyperinsulinism is an early feature of this syndrome. Systematic testing of the *KDM6A* and *KMT2D* genes in all individuals with hyperinsulinism is warranted as an early genetic diagnosis will allow for early intervention, treatment and the assessment for other features.

Thomas Laver

OP10: LARGE DELETIONS ARE AN UNDERAPPRECIATED CAUSE OF HYPERINSULINISM

Laver T.W., Wakeling M.N., Caswell R., Bunce B., Houghton J.A.L., Patel K.A, Hussain K., Ellard S., Flanagan S.E.

Context

Hyperinsulinism is a disorder where dysregulated insulin secretion leads to hypoglycaemia. 50 % of patients do not have a mutation in a known gene. Large contiguous gene deletions have been reported as an extremely rare cause of hyperinsulinism but are not routinely screened, thus these may be an underappreciated cause of the disorder.

Aims

We aimed to assess the contribution of large deletions to the aetiology of hyperinsulinism.

Methods

Using off-target CNV (copy number variant) calling from targeted next generation sequencing data we screened 865 patients with hyperinsulinism for large deletions (>1 Mb).

Results

We identified causative contiguous gene deletions in 16/865 patients in our cohort. 13 were previously reported to cause hyperinsulinism: X chromosome deletions (Turner syndrome) (n=3), 9p deletions (n=9) and a 16p deletion (n=1). We also identified 3 patients with overlapping *de novo* deletions on chromosome 20. These were the only novel large (>1 Mb) *de novo* deletions within the cohort. They are a new cause of hyperinsulinism.

Conclusions

2 % of patients in our cohort had causative large contiguous gene deletions. This is likely to be an underestimate of the prevalence of large deletions in hyperinsulinism as some patients will have had cytogenetic testing prior to referral for hyperinsulinism genetic testing. Large deletions are a rare but significant cause of hyperinsulinism and should be screened for as part of genetic panel tests for the disease. We also highlight a novel cause of hyperinsulinism: 20p11.2 deletions.

Acknowledgments

We thank the patients and their clinicians without whom this research would not have been possible and acknowledge our funding: Wellcome Trust and the Royal Society (105636/Z/14/Z and WT098395/Z/12/Z).

Cécile Saint-Martin

OP11: NGS ANALYSIS OF MONOGENIC DIABETES PATIENTS SHOWED THAT MATERNALLY INHERITED DIABETES AND DEAFNESS IS UNDERDIAGNOSED

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Context

Maternally inherited diabetes and deafness (MIDD) is a rare form of diabetes typically characterized by a maternal inheritance and by the association with extra-pancreatic features, most predominantly sensorineural hearing loss. It is due to the m.3243A>G variant of the MT-TL1 gene on the mitochondrial DNA.

Aims

Given the clinical variability of MIDD, patients may be undiagnosed or misdiagnosed as type 2 diabetes or MODY patients. The aim of this study was to evaluate the proportion of patients with a clinical suspicion of MODY, who turned out to have a MIDD.

Methods

An NGS capture panel of 20 genes comprising the MT-TL1 locus was analyzed on 480 patients with adult-onset diabetes and referred for MODY genetic testing.

Results

Among 480 patients, 10 (5F, 5M) carried the m.3243A>G mutation (2 %). They had a mean age at diagnosis of diabetes of 30.4 +/-7 years old and were lean (BMI 21.2kg/m² +/-3.2). Diabetes was non–insulin-dependent in 80 % of patients. At the time of study, mean patient age was 40 +/-14 years and median diabetes duration was 6.5 years (0.1–41); only 1 had diabetic retinopathy and chronic renal failure. Despite a relatively important leucocyte heteroplasmy (median heteroplasmy: 29 % (14–47 %)), only 2 patients had associated features: one had hypertrophic cardiomyopathy and one was suspected to be autistic. No hearing loss or macular dystrophy were reported for any of the 10 patients.

Conclusions

Restricting the analysis of MT-TL1 to patients with a traditional MIDD phenotype would miss patients for whom no associated phenotype is reported. m.3243A>G is actually more frequently involved in monogenic diabetes than expected. It represents the 6th most frequent molecular cause after GCK, HNF1A, HNF4A, HNF1B and ABCC8 diabetes subtypes. Phenotype overlapping makes the diagnosis of monogenic diabetes difficult and underlies the benefit of NGS strategies.

Marcus Tuke

OP12: ASSESSING THE PATHOGENICITY AND PENETRANCE OF HNF1B DELETIONS AND DUPLICATIONS IN UK BIOBANK

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Context

The true pathogenicity and penetrance of many of rare putative disease-causing copy number variants (CNVs) is uncertain and may be over-estimated by clinical ascertainment.

Aim

We aimed to use data from 388,714 UK Biobank participants to assess the pathogenicity and penetrance of previously reported pathogenic CNVs in a population-based setting.

Methods

Using SNP chip intensity data in UK Biobank we called and visually-inspected 96 copy number variants overlapping regions known to be associated with developmental syndromes, as well as other large chromosomal events across the genome. We tested the association of these CNVs with diabetes and 401 other clinically-relevant traits in UK Biobank.

Results

We found 15 rare CNVs intersecting known disease genes, including the 17q12 deletion/duplication encompassing the MODY gene HNF1B. Eleven individuals had deletions encompassing HNF1B and a further 106 individuals had duplications. Of the individuals with 17q12 deletions, 6 had diabetes (54.5 % vs. 5.3 % amongst the rest of the UK Biobank; P=2x10−6). The penetrance of diabetes was 30 % by age 40yrs compared to a published estimate of 48 % at 35yrs based on 27 individuals. Two of the 11 individuals with deletions had renal failure. There is some controversy about the impact of duplications of HNF1B. We found no association between the duplication and diabetes (4.4 % vs. 5.3 %; P=0.8) or any renal phenotypes.

Of the remaining CNVs we identified associations between diabetes and the 16p11.2 deletion (n=104; OR=6.2; P=4.5x10−9), although this association was removed after adjusting for BMI. We also detected a novel association between diabetes and the 2q13 duplication (n=51; OR=6.7; P=3x10−6), including genes ACOXL, ANAPC1 and MERTK.

Conclusions

This study identifies a putative new diabetes associated CNV, demonstrates that HNF1B duplications do not cause diabetes and provides a population-based penetrance estimate of HNF1B deletions.

Acknowledgments

This study was conducted using the UK Biobank resource.

Ingrida Stankute

OP13: HIGH INCIDENCE OF MONOGENIC DIABETES IN LITHUANIAN PEDIATRIC AND YOUNG ADULT DIABETES PATIENTS

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Objective

Monogenic diabetes (MD) represents a heterogeneous group of metabolic disorders resulting from defects in single genes. Defects are categorized primarily into three groups: structural defects leading to a decreased number of beta cells, disruption of beta cell function or a progressive cell loss

The aim

To screen the whole pediatric and young adults autoimmune antibody negative diabetes population of Lithuania for MD using targeted next generation sequencing to determine its prevalence and discover additional diabetes genes

Methods

All patients from the national Lithuanian diabetes cohort, covering 100 % of all pediatric and 70 % of the young adult patients in Lithuania were screened for the presence of autoimmune antibodies. We included the IAA positive probands in our study, because the antibodies were tested after introduction of insulin therapy. Genetic analysis was performed by high throughput sequencing from DNA selected for all coding and splicing regions of 323 genes involved in diabetes, including 13 MODY genes

Results

We have analyzed 153 diabetic subjects with suspected MD. Genetic analysis revealed MODY diabetes in 24.1 % of the probands: 13.7 % had mutations in the GCK gene, 5.2 % in the HNF1A gene and 2 % in the HNF4A gene. In 0.65 % we detected variants in the KCNJ11, KLF11 and INS genes. Neonatal diabetes was present in 2 % of the individuals, all had KCNJ11 gene defects. In addition, in 39 % of the probands, we found variants in other potential diabetes genes. Conclusions: This testing approach yields a high rate of positive results. This analysis gives for the first time prevalence for MD in the young Lithuanian population of 1.7 % for GCK mutations, 0.7 % for HNF1A mutations and 0.2 % for HNF4A mutations. Twenty seven % were actionable and led to a change in treatment. Some of the newly detected variants are very distinct for the Lithuanian population.

Acknowledgments

The study was supported by a grant from Lithuanian Research Council Lithuanian-Swiss program "Research and development" (CH-3-ŠMM-01/09) and the Federal Department of Foreign Affairs of Switzerland. Swiss National Science Foundation Grant No. CR33I3_140655 and CR33I3_1166591 to Schwitzgebel VM. The presented work resulted from collaboration made possible through the Merck sponsored educational programme "ESPE Clinical Fellowship" to Stankute I.

Kashyap Patel

OP14: DIFFERENT GENETIC TESTING STRATEGIES FOR MONOGENIC DIABETES ARE NEEDED IN POPULATIONS WITH HIGHER RATES OF CONSANGUINITY

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Background

Nonconsanguineous European populations are over-represented in monogenic diabetes studies. This is important as the resulting recommendations on which genes to test and patient selection for genetic testing may not be appropriate in populations with higher rates of consanguinity.

Aim

To study how genetic aetiologies of monogenic diabetes in a population with higher rates of consanguinity differs from a nonconsanguineous European population.

Method

A Type 1 diabetes genetic risk score (T1D-GRS) based on 30 common polymorphisms was generated for 1093 diabetes children from Turkey (age at diagnosis 0.5–20 y, consanguinity rate 20 %). We tested all 29 monogenic diabetes causes in all patients with low T1D-GRS (<5th centile of T1D, n=111) and patients with moderate T1D-GRS (5–50th centile of T1D) with negative islet autoantibodies (n=125). The results were compared to monogenic diabetes cases identified by the same genetic testing in the same age of diagnosis (0.5–20 y) from the UK(n=102).

Results

Genetic testing confirmed monogenic diabetes in 33/236 (14 %) children: 13 (39 %) had recessive causes, 19 (58 %) dominant and 1 (3 %) mitochondrial (3 %). In contrast, UK patients had only 2/102 (2 %) recessive cases of monogenic diabetes (p<0.0001).

As expected, patients with dominant monogenic diabetes (n=19) compared to the remining of the cohort (n=1060) were more likely to have a higher C-peptide, MODY probability, parental diabetes and rates of non-insulin treatment (all p<0.001). In contrast, patients with recessive causes (n=13) compared to rest of the cohort, had similar levels of C-peptide, MODY probability, parental diabetes and non-insulin treatment (all p>0.05) but had more syndromic diabetes (85 % vs 5 %, p<0.001).

Conclusion

2 in 5 cases of monogenic diabetes are due to recessive aetiologies in population with higher rates of consanguinity. Importantly, the approach to identify these patients is different from nonconsanguineous European population. It is essential that genetic testing in these populations includes recessive genes.

Acknowledgment

Wellcome Trust.

Mike Weedon

OP15: USING UK BIOBANK TO ASSESS THE PATHOGENICITY, PENETRANCE AND EXPRESSIVITY OF MONOGENIC DIABETES VARIANTS

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Context

The true penetrance of many of rare, disease-causing alleles is uncertain and may be over-estimated by clinical ascertainment.

Aim

To use data from 388,714 UK Biobank participants to assess the pathogenicity and penetrance of putatively clinically-relevant rare variants in a population-based setting.

Methods

Although rare variants are harder to genotype accurately than common variants, we were able to classify 1,244 of 4,585 (27 %) putatively clinically relevant rare sequence variants genotyped on the UK Biobank SNP-array as high-quality. We defined ‚clinically-relevant' as variants that were either classified as pathogenic/likely pathogenic in ClinVar or are in genes known to cause monogenic diabetes. We assessed the penetrance, pathogenicity and expressivity of these high-quality variants by testing their association with diabetes and 400 other clinically-relevant traits in UK Biobank.

Results

We identified 27 putatively clinically-relevant rare sequence variants that showed a significant association with one or more traits in UK Biobank, exhibiting reduced penetrance or variable expressivity compared with their associated monogenic disease. We were able to refine the penetrance estimate for the R114W variant, the most commonly reported cause of HNF4A MODY, from 75 % to <10 % by age 40 yrs.

Conclusions

Most rare variant genotype calls from SNP arrays are low quality. Despite this, our study shows that the UK Biobank will help refine the penetrance estimates of monogenic disease variants. The imminent release of exome sequencing data from the UK Biobank will allow a comprehensive survey of the population-based impact of monogenic diabetes variants.

Acknowledgments

This research has been conducted using the UK Biobank Resource

Matthew Wakeling

OP16: HOMOZYGOSITY MAPPING FROM SMALL TARGETED NGS PANELS USING SAVVYHOMOZYGOSITY – GETTING MORE FROM LESS

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Context (Background)

Diagnosis of monogenic diabetes and hyperinsulinism is often achieved using targeted next generation sequencing (NGS). For consanguineous patients without a genetic diagnosis, the identification of regions of homozygosity can assist with both diagnosis and gene discovery. This is usually obtained using a microarray, or it can be calculated from genome sequencing data.

Aims

We aimed to develop a novel method to utilise the off-target reads from existing targeted NGS panel data to identify regions of homozygosity genome-wide.

Methods

We developed SavvyHomozygosity, which uses off-target reads from targeted NGS data in combination with linkage disequilibrium to calculate regions of homozygosity. We used data from 170 samples sequenced using both targeted NGS (average 3.4 M reads per sample) and genome sequencing (mean read depth 35) to estimate the sensitivity and specificity of the method. True homozygous regions were determined from the genome sequencing data, and compared to regions calculated from the targeted NGS data.

Results

Regions of homozygosity larger than 3 Mb were detected with sensitivity and specificity of 77 %, and 10 Mb with sensitivity and specificity of 93 %. Detection was not limited to regions of the genome that are targeted by the sequencing panel.

Conclusions

SavvyHomozygosity identifies regions of homozygosity genome-wide in samples sequenced using a targeted NGS panel. The resulting data can be used to assist the discovery of causative variants, and can also be used with many samples to identify "hot spots" in the genome that may pinpoint an as yet undiscovered disease gene. The homozygosity data can also be used to identify candidate samples for more extensive sequencing.

Acknowledgments

SE and ATH are the recipients of a Wellcome Trust Senior Investigator award (grant number WT098395/Z/12/Z).

Adem Dawed

OP17: LOSS OF FUNCTION VARIANTS IN THE CYP2C9 & SLCO1B1 ARE ASSOCIATED WITH IMPROVED GLYCAEMIC RESPONSE TO SULPHONYLUREAS: A GODARTS STUDY

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Background and aims

Sulphonylureas (SU) are shown to be transported into the liver by OATP1B1 and metabolized by the cytochrome p450 2C9 (CYP2C9) enzyme. Loss of function variants in SLCO1B1 (SLCO1B1*5 (Val174Ala)) and CYP2C9 (CYP2C9*2 (Arg144Cys) and CYP2C9*3 (Ile359Leu)) are associated with reduced transport and impaired metabolism, respectively. In this study we assessed the impact of SLCO1B1*5 and combined CYP2C9*2/*3 genotypes on glycaemic response to SU in patients with type 2 diabetes (T2D).

Methods

We analysed data using 2319 subjects with T2D that are stably treated with SU from the GoDARTS. The association of loss of function variants in SLCO1B1 and CYP2C9 with reduction in HbA1c after one year of SU treatment were assessed using multiple linear regression assuming additive mode of inheritance.

Results

Patients carrying loss of function alleles at SLCO1B1*5 and CYP2C9 achieved better HbA1c reduction (β-per allele for SLCO1B1*5=0.14 %, p=0.01, β-per allele for CYP2C9=0.16 %, p=0.01). A stratified analysis showed significant association of CYP2C9 genotype with SU response only at the background of wild type SLCO1B1 (β=0.14, p=0.01) but not at loss of function SLCO1B1 (β=-0.01, p=0.89). To better assess the impact of these variants in SU response, a composite model consisting of three haplotypes were considered. Compared to those who carry wild type alleles at both SLCO1B1 and CYP2C9, carriers of one or more loss of function alleles at SLCO1B1 with any CYP2C9 background had a 0.26 % (2.8 mmol/mol) (P = 0.002) greater HbA1c reduction. Carriers of one or more loss of function CYP2C9 alleles at wild type SLCO1B1 background had a 0.27 % (3 mmol/mol) (p=0.002) greater response.

Conclusion

These results show that variants in SLCO1B1 and CYP2C9 have clinical impact on the therapeutic response to SUs and highlight the importance of studying transporter and metabolizing genes together in pharmacogenetics.

James Harrison

OP18: A TYPE 1 DIABETES GENETIC RISK SCORE IMPROVES CLASSIFICATION OF DIABETES IN INDIA

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Context

We have previously shown that a type 1 diabetes (T1D) genetic risk score (GRS) can be used to discriminate T1D from type 2 diabetes (T2D) in Europeans. Diabetes is a significant problem in the Indian population – misclassification of T1D and T2D could be a particular problem in young adults in India due to early onset T2D in this population and at lower BMI.

Aims

To test the ability of a T1D-GRS developed in Europeans to discriminate T1D from T2D and controls in Indians with diabetes.

Methods

We studied Indians from Pune, India (T1D (n=262), T2D (n=345) and controls (n=324)) and Europeans from the Wellcome Trust Case Control Consortium (T1D (n=1963), T2D (n=1924) and controls (n=2938)). We genotyped 9 SNPs previously shown to capture common HLA risk allele combinations and non-HLA risk for T1D in Europeans. We calculated a 9 SNP T1D-GRS and assessed its ability to discriminate T1D from T2D and controls in Indians and compare with the Europeans in WTCCC.

Results

We show that the T1D-GRS discriminates T1D from T2D in Indians (ROCAUC[95 % CI]: 0.81[0.77–0.83]) and controls (ROCAUC[95 % CI]: 0.79[0.75–0.83]), although the discriminative power was lower than in Europeans (ROCAUC[95 % CI]: 0.87[0.86–0.88]). We also show that HLA (DR3/DR4) status contributes the majority of discriminative power (ROCAUC[95 % CI]: 0.76[0.720.79]) for DR3/DR4 status). Interestingly we also found the odds ratio for DR3 and DR4 were significantly different in Indians than Europeans (DR3 P=0.002, DR4 P<0.001).

Conclusions

We show that a T1D-GRS using SNPs defined in Europeans is discriminative of T1D from T2D and controls in Indians. Diagnosing diabetes is a particular challenge in the Indian population – this T1D-GRS could be used as a tool to improve classification of diabetes.

Acknowledgments

Diabetes UK and Council for Scientific and Industrial Research (CSIR), India for funding.

Pradeep Bompada

OP19: EPIGENETIC AND TRANSCRIPTOME LANDSCAPES OF GLUCOSE-INDUCED HISTONE ACETYLATION IN PANCREATIC ISLETS

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Background and Aim

Histone acetylation is an essential part of gene regulation controlled by histone acetyltransferase (HAT). Previous studies showed that hyperglycemia induces histone 3 lysine 9 acetylation (H3K9ac) at various gene promoters via HAT p300, which leads to gene expression changes. However, it is not known which regions throughout the whole genome are targeted by p300 at hyperglycemia, or how this may change histone acetylation and subsequently gene expression. In this study, we mapped global H3K9ac enrichment and transcriptome changes induced by high glucose mediated by p300 in pancreatic beta cells.

Materials and Methods

P300 was silenced by CRISPR/Cas9 in rat pancreatic beta cell line INS1 832/13. Wild-type (WT) and p300 knock-out (KO) cells were treated in either 5 or 25 mM glucose for 24 hours. Cells were then subjected to RNA sequencing and chromatin immunoprecipitation (ChIP) sequencing using H3K9ac antibody. Epigenetic and transcriptome changes were then mapped to human islet transcriptome from 24-hour high glucose-treated non-diabetic islets; as well as that of non-diabetes vs. diabetes donors.

Results

High glucose induced H3K9ac enrichment in 211 genomic regions in WT cells mapped by ChIP seq, which were completely abolished in p300 KO cells. RNA seq identified expression changes in 10453 genes induced by glucose, among which 6741 genes were dependent on p300. ChIP seq and RNA seq profiled 162 mutual genes, of which gene expression is dependent on H3K9ac via p300. Mapping to human islet transcriptome identified 62 human genes that are potentially regulated by H3K9ac via p300 in hyperglycemic conditions, among which 3 genes (TXNIP, ACACA and CIART) are specific to short term HG exposure.

Conclusion

Our study provides detailed epigenetic and transcriptome landscape mapping of glucose-induced histone acetylation in islets. We revealed distinct genomic regions that are regulated by high glucose-induced H3K9ac enrichment mediated by HAT p300.

Ji Chen

OP20: LEVERAGING ANCESTRY DIFFERENCES FOR GLYCAEMIC TRAIT LOCUS DISCOVERY AND FINE-MAPPING

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Background

Glycaemic traits are used to diagnose and monitor type 2 diabetes (T2D) and can inform disease pathophysiology. To date, most genetic discovery efforts have focused on European participants, leaving much of trait heritability unexplained. Trans-ethnic genetic studies have previously shown their value for locus discovery and fine-mapping, but have not assessed the relative contributions of sample size and differences in allele frequencies, effect sizes, and linkage disequilibrium (LD) across ancestries.

Aims

In this study, we aimed to investigate the advantages of multiple ancestries for locus discovery and fine-mapping across four glycaemic traits: glycated haemoglobin, fasting glucose, fasting insulin and 2-hour glucose.

Methods

We used MANTRA to combine densely-imputed genome-wide association data in up to 281,416 non-diabetic samples from European, East Asian, Hispanic, African American, South Asian and African ancestries. Loci were fine-mapped using FINEMAP with the sample size weighted mean of LD estimated from multiple cohorts. To assess the contribution of ancestry to locus discovery and fine-mapping, we scaled confidence intervals to emulate the same sample sizes in both within- and trans-ethnic analyses.

Results

We discovered 99 novel loci not previously associated with the four glycaemic traits or T2D. Of these, 21 trans-ethnic loci and three ancestry-driven loci would not have achieved genome-wide significance in equivalent sample sizes of Europeans. Over 81 % of the trans-ethnic signals were homogeneous between ancestries and genetic risk scores performed equivalently across ancestries. In 81/94 fine-mapping regions with single causal variant, trans-ethnic fine-mapping resolution was improved (46 % fewer variants in 99 % credible sets). In 45/81, the improvement was due to differences in allele frequencies, effect sizes and LD, and not just increased sample sizes.

Conclusions

These results highlight the importance of conducting more studies in non-European participants to explore the biology of glycaemic traits.

Acknowledgments

We thank all cohorts, MAGIC collaborators and Wellcome funding.

Jason Torres

OP21: INTEGRATION OF EPIGENETIC MAPS AND HIGH-RESOLUTION CHROMATIN INTERACTIONS IMPLICATES EFFECTOR TRANSCRIPTS AT LOCI ASSOCIATED WITH TYPE 2 DIABETES IN HUMAN PANCREATIC ENDOC- β H1 CELLS

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Context

Large-scale GWAS have revealed over 250 loci that harbour variants significantly associated with type 2 diabetes (T2D). However, identifying causal genes remains a challenge as most of these regions are non-coding and map to regulatory elements in multiple tissues.

Aims

To resolve effector transcripts that mediate disease risk at these loci, we employed next-generation capture-C (NGCC) to map physical chromatin interactions in a human-derived pancreatic β-cell line (i.e. EndoC- β H1). As β-cells serve a central role in systemic glucose metabolism and are highly relevant to T2D pathophysiology, we prioritised variants most likely to have regulatory functions in this cell type.

Methods

To do so, we performed a functional GWAS using summary statistics from the latest DIAMANTE GWAS (900K individuals) and a panel of islet epigenetic chromatin states derived from DNA methylation, open chromatin (ATAC-seq), and histone post-translational modifications (ChIP-seq). Fine-mapped credible sets from this analysis were integrated with maps of open chromatin in EndoC- β H1 cells, eQTLs in human islets, and loci previously implicated in β-cell physiology to generate a set of 283 "high priority" SNPs at 27 T2D-associated loci likely to have regulatory effects in pancreatic β-cells .

Results

We captured enhancers encompassing these variants using NGCC and identified 592 significant chromatin interactions in EndoC- β H1 cells. These interactions were highly enriched for islet transcription factor (i.e. MAFB, PDX1, FOXA2, NKX6.1, NKX6.2) binding sites (p-values < 0.001). Moreover, 52 % of all captured sites physically interact with transcription start sites and corroborate islet eQTL associations involving ADCY5, ZMIZ1 , RREB1 , DGKB , and SLC38A11 . Furthermore, these interactions support putative novel T2D genes regulated by risk-associated variants such DDX51 at the FBRSL1 locus.

Conclusions

These high-resolution chromatin interaction maps in combination with epigenetic and eQTL maps spotlight effector transcripts likely to influence T2D risk in β-cells and prioritise genes that may serve as novel therapeutic targets.

Jun Liu

OP22: NOVEL CPG SITES OF GLUCOSE AND INSULIN HOMEOSTASIS: AN INTEGRATIVE CROSS-OMICS ANALYSIS

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Funding Acknowledgments

The project is mainly funded by Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)–NL (184.021.007).

Background

Despite the growing evidence that differential DNA methylation is implicated in type 2 diabetes (T2D) and obesity, our understanding of the functional relevance of the phenomenon remains limited. Methylation of DNA in blood circulation is one of the key features of obesity. A key question to answer is whether there are functional effects of the differential methylation relevant to the pathogenesis of T2D and whether these effects are explained differential methylation induced by obesity.

Purpose

We used a cross omics integrative analysis to understand the effect of DNA methylation in the early phases of T2D pathology while accounting for body mass index (BMI).

Methods

We performed a blood-based epigenome-wide association study (EWAS) of fasting glucose and insulin with or without BMI adjustment among 4,808 non-diabetic European individuals and replicated the findings among 11 cohorts totaling up to 11,750 trans-ethnic non-diabetic individuals, mainly (58 %) from European ancestry. For the CpGs that are associated with fasting glucose/insulin but partially explained by BMI, we further checked whether the association between BMI and insulin is in part explained by these CpGs. Meanwhile, we also integrated the glycemic methylation loci from the in silico cross-omics databases comprising genomics, epigenomics and transcriptomics collected from public resources.

Results

In the discovery phase, we identified and replicated nine novel differentially methylated sites in whole blood (P-value $<1.27\times10-7$): sites in LETM1, RBM20, IRS2, MAN2A2 genes and 1q25.3 region were associated with fasting insulin; sites in FCRL6, SLAMF1, APOBEC3H genes and 15q26.1 region were associated with fasting glucose. Follow-up in silico cross-omics analyses reveals that the cis-acting methylation quantitative trait loci (meQTLs) near SLAMF1 and its expression in blood are involved in glucose level regulation in the circulation. Moreover, we find that differential methylation in FCRL6 may affect glucose level and the risk of T2D by regulating FCLR6 expression in the liver. In silico cross-omics analyses highlight that differential methylation plays a key role in the crosstalk between the adaptive immune system and glucose homeostasis. Finally, we find the obesity methylation sites are implicated in insulin metabolism. When we adjust the association between obesity and fasting insulin for the CpG sites that associated both to BMI and insulin, the beta for BMI reduces by 16.9 %.

Conclusions

We identify nine novel DNA methylation sites associated with glucose homeostasis and provide new insights into the genetics, epigenetics and transcriptomics of T2D by the integration of cross-omics data in silico. The study shows that differential methylation may explain at least 16.9 % of the association between obesity and insulin.

Jessica Tyrrell

OP23: COMPARING THE CAUSAL EFFECTS OF DIABETES-RELATED TRAITS ON MEASURES OF MICRO- AND MACRO-VASCULAR DISEASE

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Context

Microvascular and macrovascular complications commonly occur in type 2 diabetes, resulting in organ and tissue damage in approximately half of people with the condition. A range of diabetes related traits (e.g. body mass index (BMI), blood pressure, lipid levels) are observationally associated with both micro- and macrovascular damage. However, the causal role of these traits and their relative effects on micro, compared to macro, vascular disease is uncertain.

Aims

To validate the albumin to creatinine ratio (ACR) as a marker of microvascular damage; to test and compare the causal role of 11 metabolic markers on micro and macrovasculature function.

Methods

The association between ACR and two established markers of early microvascular damage were explored in the SUMMIT study. 2-sample Mendelian randomisation (MR) approaches were utilised to test the causal role of 11 metabolic markers on ACR (microvascular damage proxy) and coronary artery disease (CAD; macrovascular damage proxy). MR was performed using up to 450,000 European ancestry UK Biobank participants and data from the most recent ACR and CAD genome-wide association scans.

Results

ACR was confirmed as a proxy for microvasculature damage. Higher triglyceride and LDL-cholesterol levels were causally associated with elevated ACR and higher odds of CAD. However, there was a differential effect of lipids on the micro- and macro-vascular markers: using genetics, higher triglyceride levels were more strongly causal for higher ACR than LDL cholesterol, whereas higher LDL cholesterol was more strongly causal for CAD than triglycerides. Higher BMI, blood pressure, waist hip ratio and type 2 diabetes were causally associated with elevated ACR and CAD risk.

Conclusions

Most diabetes related traits were causally associated with both micro and macrovascular damage. However, lipids demonstrated different causal effects, with triglycerides more strongly causal for microvasculature damage and LDL more strongly causal for macrovascular damage.

Acknowledgments

UK Biobank (Application 9072).

Zhana Balkhiyarova

OP24: COMMON GENETIC LOCI ASSOCIATED WITH TYPE 2 DIABETES MELLITUS, DEPRESSIVE SYMPTOMS AND ANXIETY

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Background

Depression and *anxiety* are highly prevalent in individuals with type 2 diabetes, affecting quality of life and well-being. Epidemiological studies suggest shared aetiology between these conditions. Genetic variants, reportedly associated with them, affect lipid metabolism, cell proliferation, immune and inflammatory response, and oxidative stress, thus suggesting shared pathophysiological processes. However, the phenotypic variance responsible for type 2 diabetes and depression captured by genome-wide association studies (GWAS) explains only ~5 % of susceptibility to these conditions. We aimed to identify genetic factors contributing to their co-morbidity using multi-variable analytical framework.

Methods

We analysed data from population-based Northern Finland birth cohort using 46 years-old clinical examination from 3,597 participants, Haplotype Reference consortium imputed genome-wide Illumina HumanCNV370DUO platform data was quality controlled providing >10M autosomal SNPs for analysis. Using SCOPS software, we performed the multiple-phenotype GWAS (MP-GWAS) as linear combination of residuals for type 2 diabetes, anxiety (Generalized Anxiety Disorder 7-item Scale) and depressive symptoms (Beck Depression Inventory) score, obtained after adjusting for sex and three principal components to control for population structure.

Results

Three loci, at *MICAL2* (rs10765927), *INPP5K* (rs145536147) and *ZNF599* (rs7259475) reached genome-wide significance ($P<5\times10^{-8}$). Expression of target genes at these loci, involved in cell growth, insulin metabolism and transcriptional regulation, takes place primarily in the brain and is decreased in presence of depression. rs10765927, rs145536147 and rs7259475 were associated in GWAS with neuroticism, Parkinson's and Alzheimer's diseases, respectively.

Conclusion

The results of this MP-GWAS provide first evidence for a shared aetiology between type 2 diabetes, depressive symptoms and anxiety.

Sadia Saeed

OP25: AUGMENTED EXOME SEQUENCING (CODE-SEQ) IDENTIFIES POINT MUTATIONS AND COPY NUMBER VARIANTS CAUSING EXTREME OBESITY IN 48 % OF PATIENTS FROM A CONSANGUINEOUS PAKISTANI POPULATION

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Context

Monogenic obesity characterized by extreme adiposity at an early age, is a rare event and accounts globally for <10 % of obese cases. We previously reported prevalence of obesity due to point mutations in Pakistani children but data relating to structural changes (CNVs) leading to obesity are not available for this population

Aims

To elucidate genetic causality of severe obesity in a cohort of 146 affected children from a consanguineous population through an in-house developed augmented whole-exome sequencing (CoDE-seq). This method enables simultaneous detection of CNVs and point mutations in coding regions

Methods

DNA from 146 probands with BMI-SDS>3.0, was sequenced in two successive steps. Direct sequencing of LEP and MC4R genes was followed by CoDE-seq. The variants associated with obesity were graded according to ACMG criteria to predict pathogenicity

Results

We report 59 cases of non-syndromic obesity and 11 cases of syndromic obesity due to 34 different variations, explaining genetic causality of monogenic obesity in 48 % cases. Of these 70 cases, 72 % were identified with homozygous point mutations in the LEP, LEPR, MC4R and ADCY3 genes. Of note is a predominant incidence of LEP mutations (53 %) and a unique 23bp homozygous deletion in ADCY3 gene. Syndromic form of monogenic obesity due to homozygous mutations in BBSs, ALMS1 and VPS13B were identified in 17 % of cases. Additionally, 7 % of cases were identified carrying copy-loss variants associated with syndromic and non-syndromic obesity. Conclusion: Using a sequencing strategy involving augmented WES, we demonstrate a significantly higher frequency (48 %) of monogenic obesity in this consanguineous population than hitherto reported. Large inbred populations provide a valuable and genetically enriched material in our quest of new genes and variants explaining the missing heritability of obesity and discovery of novel mechanisms influencing energy balance

Acknowledgment

The study was funded by French National Research Agency (ANR-10-LABX-46, ANR-10-EQPX-07-01).

Marika Kaakinen

OP26: MULTIPLE EPIGENETIC AND METABOLOMIC MARKERS PREDICT GLYCAEMIC HEALTH IN MIDDLE-AGED MEN AND WOMEN

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Context

Type 2 diabetes (T2D) is a global health burden that will benefit from personalised medicine, with omics data holding promise for it. Most studies have focussed on the improvement in risk prediction of T2D using genetic markers.

Aims

To identify longitudinal predictors of glycaemic traits relevant for T2D from multi-omics data, with special focus on epigenetic and metabolomic markers.

Methods

We used the Northern Finland Birth Cohort 1966 (NFBC 1966) at 31 (T1) and 46 (T2) years to predict fasting glucose (FG) and insulin (FI), glycated haemoglobin (HbA1c) and 2-hour glucose and insulin from oral glucose tolerance test (2hGlu, 2hIns) at T2 in 513 individuals from 1,001 anthropometric, metabolic, metabolomic and epigenetic variables at T1 and T2. We applied six machine learning approaches: random forest (RF), boosted trees (BT) and support vector machine with four different kernels. We further validated our models trained in NFBC1966 in an independent French study with 48 matching predictors (DESIR, N=769, age range 30–65 years at recruitment, interval between data collections: 9 years).

Results

FG and FI were best predicted, with average R^2 values of 0.38 and 0.53. RF and BT showed the most consistent performance. Multiple methylation markers at both time points were amongst the top predictors, including probes within the fatty acid and glucose metabolism regulating genes *CPT1A* and *SREBF1*. Other significant predictors were sex, branched-chain and aromatic amino acids, HDL cholesterol, glycerol, ketone bodies, blood pressure at T2 and measurements of adiposity at T1. In the validation analysis, we reached R^2 values of 0.41/0.55 for FG/FI when trained and tested in NFBC1966 and 0.17/0.30 when trained in NFBC1966 and tested in DESIR.

Conclusions

We identified clinically relevant sets of predictors from multi-omics data and highlight the potential of methylation markers and longitudinal changes in prediction.

Acknowledgments

WCRF UK, WT205915, DynaHEALTH (633595).

Poster Presentations

Type 1 Diabetes

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MODY

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Anni Antikainen

P01: GENOME-WIDE ASSOCIATION ANALYSIS ON CORONARY ARTERY DISEASE IN TYPE 1 DIABETES CONFIRMS CDKN2B-AS1 AND SUGGESTS BETA-DEFENSIN 127 AS A NOVEL RISK LOCUS

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Context

Type 1 diabetes (T1D) is a known risk factor for coronary artery disease (CAD). However, the genetics of CAD have not been extensively studied in T1D. Whether the genetic background is similar to the general population, or loci specific to T1D exist, is not established.

Aims

We aimed to search for loci specific to T1D, describe their role in the pathogenesis and assess the effects of known CAD risk variants.

Methods

A genome-wide association study was performed with RVTEST for 8,744,746 variants on 4869 individuals with T1D (cases/controls: 941/3928). Genotyping of the individuals recruited through the Finnish Diabetic Nephropathy Study and the National Institute of Health and Welfare had been performed with Illumina HumanCoreExome chips at the University of Virginia in addition to imputation with Minimac3 using the 1000 Genomes Phase 3 reference panel. Replication was attempted as a GWAS look-up (434/3123). We evaluated function of the discoveries with a cardio-phenome-wide analysis and assessed the role of the known variants with genetic risk scores (GRS).

Results

Two loci reached genome-wide significance: rs1970112 (OR=1.32) on a known risk locus CDKN2B-AS1 and rs6055069 (OR=0.24) near DEFB127. Replication was successful only for CDKN2B-AS1. Nevertheless, the novel DEFB127 discovery provides an interesting link to inflammation, since β-defensins are involved in the immune system. We discovered eight suggestive loci ($p<1\times10-6$) out of which for instance rs1344228 was also associated with atherosclerosis markers. GRSs suggested that the known risk variants modestly increase CAD risk also in T1D ($p=4.21\times10-7$).

Seth Sharp

P02: DEVELOPMENT AND STANDARDIZATION OF A TYPE 1 DIABETES GENETIC RISK SCORE FOR USE IN NEWBORN SCREENING AND INCIDENT DIAGNOSIS

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Background

There has been increasing interest in genetic risk scores (GRS) in diabetes diagnosis and classification. Type 1 diabetes (T1D) has high heritability with ~50 % of the genetic risk associated with HLA region genes much of which has not been well characterised. We aimed to improve existing capture of genetic risk in HLA and genome-wide and assess an improved GRS as a clinical and research tool.

Methods

We used imputation to identify variants in strong linkage disequilibrium (r^2>0.95) with 14 common HLA-DR/DQ haplotypes in UK Biobank. We modelled pairwise interactions between haplotypes in data from T1DGC (6481 cases, 9247 controls) and generated odds ratios for 18 pairs with significant interaction($p<4.7x10^{-4}$). We used conditional analysis to further identify HLA variants that had not previously been described. We combined results with variants from recent GWAS into a GRS and validated our findings in 542 cases from the UK Biobank.

Results

The improved GRS consisted of 67 variants and was highly discriminative of T1D in UK Biobank from controls (ROC-AUC=0.922, p<0.0001 vs previous GRS) and from T2D (AUC=0.92, p<0.0001) and even greater for early onset T1D (age<5, AUC=0.94). Simulations of GRS for newborn screening demonstrated significantly improved performance versus traditional HLA genotyping (9.5 % vs 20.9 % followed to achieve 77 % sensitivity). Those with a GRS in the top 0.01 % had over 22.8 % risk of T1D in childhood, suggesting a threshold for future intervention trials. Similarly, >78 % of childhood T1D occurred in the top 10 % GRS, suggesting targeting parents for education about presenting symptoms of T1D.

Conclusions

An improved GRS has high utility in diagnosis for identifying T1D and for discriminating from other forms of diabetes and could be used for clinical intervention. Given decreasing genotyping costs newborn screening studies and intervention trials alike can benefit from improved detection and lowered recruitment costs.

Conclusions

We confirmed the CDKN2B-AS1 and suggested a DEFB127 association with CAD in T1D. Our results provide evidence for shared genetic variants with the general population and variants specific to T1D.

Acknowledgments

We acknowledge the participating centers. Funding: EFSD/Sanofi European Diabetes Research Programme in Macrovascular Complications, Finnish Foundation for Cardiovascular Research, JDRF (Grant 17-2013-7) for GWAS genotyping.

Erkka Valo

P03: THE ROLE OF RARE VARIANTS IN DIABETIC NEPHROPATHY IN INDIVIDUALS WITH TYPE 1 DIABETES

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Context

Diabetic nephropathy (DN) is the most severe complication of diabetes. Although several genetic variants have been found to be associated with DN they explain only a small portion of the estimated heritability of the disease. It has been hypothesized that rare variants might explain part of the missing heritability.

Aims

Our aim was to investigate the role of rare variants in the context of DN in individuals with type 1 diabetes (T1D) using whole-genome sequencing (WGS).

Methods

Altogether 593 individuals with T1D from the Finnish Diabetic Nephropathy (FinnDiane) Study were sequenced with Illumina HiSeq X platform. The sequencing reads were aligned and variants called using GATK 4.0 best practices. The individuals represented extreme cases (N=291) and controls (N=292): cases had macroalbuminuria or end-stage renal disease (ESRD) and the controls had remained normoalbuminuric for at least 35 years. The association of genes with DN was evaluated using SKAT-O test implemented in Rvtests software. The analysis was performed restricting to variants with minor allele frequency (MAF) ≤ 0.05 and annotated as protein truncating variants (PTV) or as either PTVs or missense variants.

Results

The data included 14.1 million variants with MAF ≤ 0.05. Of these, 9,381 were PTVs and 97,735 were missense variants. When testing the association with DN using PTVs the top signal was identified in protein coding gene *B4GALT7* ($p=4.1\times10^{-04}$). When analyzing the PTVs and missense variants the strongest association was observed in protein coding gene *WDR1* ($p=5.0\times10^{-05}$). These signals did not replicate in an independent whole-exome sequenced cohort of individuals with T1D of which 250 were cases (macroalbuminuria or ESRD) and 250 were controls (normoalbuminuria).

Conclusions

Further analysis is needed to clarify the role of rare variants in DN in individuals with T1D.

Acknowledgments

Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Novo Nordisk Foundation, Academy of Finland.

Jani Haukka

P04: WHOLE GENOME SEQUENCING OF INDIVIDUALS WITH TYPE 1 DIABETES REVEALS SUGGESTIVE ASSOCIATIONS FOR DIABETIC NEPHROPATHY

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Background and aims

One third of individuals with diabetes develop diabetic nephropathy (DN), which is associated with morbidity and high mortality. With whole genome sequencing (WGS), we aimed to identify low frequency or rare variants for DN, or Finnish population specific variants that were not captured by microarray chip-based study design.

Materials and methods

We performed WGS in 599 individuals with type 1 diabetes from the Finnish Diabetic Nephropathy Study (FinnDiane). The individuals represent extreme phenotypes for DN: 299 cases had developed severe DN (macroalbuminuria or end-stage renal disease), whereas 300 controls have retained normal AER and diabetes duration at least 35 years. The sequencing was conducted using Illumina HiSeq X platform by Macrogen Inc. with at least 30x coverage. The short-read data was processed, and variants were joint called using Broad Institute's best practices guidelines with Genome Analysis Toolkit. Of the 599 samples, 583 samples passed the QC and were considered in the analyses. In this study, we performed single variant analysis for all genomic variants using Rvtest.

Results

After removing variants with <98 % call rate and HWE < 10^{-10}, the number of total variants was 21,92 M. Of these 1,05 M were insertions and 1,43 M deletions. After adjusting the analysis with sex, diabetes duration and two first principal components, no variant reached genome-wide significant P-value. However, one marker from HLA-region of chromosome 6 and three markers from 14 reached suggestive P-values of 7.51×10^{-7} and 9.10×10^{-7} respectively. These common variants were intergenic, the chr14 ones being located close to *CPSF2*-gene that has been associated to dialysis survival rate. None of these variants were present in FinnDiane exome chip study.

Conclusion

This WGS study suggests novel risk loci for the DN, pending replication to confirm their role for DN.

Acknowledgments

Folkhälsan Research Foundation and Academy of Finland for funding this research.

Jana Malíková

P05: FUNCTIONAL ANALYSES OF HNF1A-MODY VARIANTS REFINE INTERPRETATION OF IDENTIFIED SEQUENCE VARIANTS

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Background

While rare variants in the hepatocyte nuclear factor-1 alpha (*HNF1A*) gene can cause Maturity-Onset Diabetes of the Young, HNF1A-MODY, others can be risk factors for development of type 2 diabetes. As suggested by the American College of Medical Genetics (ACMG) guidelines for variant interpretation, functional studies is a strong evidence for classifying a variant as pathogenic.

Aim

We hypothesized that functional evaluation can improve the pathogenicity interpretation of *HNF1A* variants identified in Czech MODY Registry.

Methods

We studied 17 *HNF1A* variants identified in 20 Czech families with diabetes by bioinformatics *in silico* tools and functional protein analyses (transactivation, protein expression, DNA binding, and nuclear localization).

Results

Of 17 variants, 11 (p.Lys120Glu, p.Gln130Glu, p.Arg131Pro, p.Leu139Pro, p.Met154Ile, p.Gln170Ter, p.Glu187SerfsTer40, p.Phe215SerfsTer18, p.Leu383ArgfsTer3, p.Gly437Val, p.Thr563HisfsTer85) exhibited significantly reduced transcriptional activity (<35 %), 3 variants (p.Gly253Arg, pGly288Trp, p.His483Arg) demonstrated mildly reduced activity (45–65 %), while 3 variants (p.Trp113Leu, p.Phe177Ser, p.Thr384Lys) had WT-like activity. Of the 11 low transcriptional activity variants, 8 demonstrated low DNA binding ability (<20 %). Applying our functional data to the *HNF1A* variants caused a reclassification of the pathogenicity class for 10 of the 17 variants (59 %); 6 out of 10 from uncertain significance (class 3) to likely pathogenic (class 4), 1 from uncertain significance (class 3) to benign (class 1) and all 3 originally classified as likely pathogenic (class 4) to pathogenic (class 5). Clinical characteristics of carriers supported the reclassification.

Conclusion

Functional evaluation of *HNF1A* variants is necessary to better predict pathogenic effect and improve diagnostic interpretation, compared to *in silico* prediction tools alone, and particularly in cases where co-segregation data or family history are not available, or where the phenotype is more diverse and overlapping with other diabetes forms.

Alshafi Mohammad

P06: EXPLORING STRATEGIES TO DETECT MODY IN AN EMIRATI POPULATION

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Background

Maturity-onset diabetes of the young (MODY) has been reported sporadically in the UAE. The MODY probability calculator (MPC), developed in white European individuals, uses basic clinical data to calculate the positive predictive value (PPV) of finding MODY, if tested.

Aims

We assessed the performance of the MPC in an Emirati population.

Methods

We recruited individuals diagnosed with any type of diabetes <30 years from a diabetes clinic (cohort-1). We applied the MPC to pancreatic antibody negative individuals and selected those with a PPV>62.4 % for testing using targeted next generation sequencing of all MODY genes. In cohort-2 we retrospectively calculated PPVs in genetically confirmed MODY cases from clinic, selected for testing by their clinician.

Results

Cohort-1: 68 of 644 individuals with a PPV>62.4 % (85 % had PPV>75 %) were tested. Of these, 4.4 % (3/68) were found to harbour MODY mutations in *HNF1A* or *HNF4A*.

Cohort-2: 15 individuals were identified with pathogenic mutations in *HNF1A*, *HNFIB*, *GCK* or *INS*. 73 %(11/15) had a PPV>62.4 % and 27 %(4/15) scored PPVs>21.4–62.4 %. The individuals with confirmed MODY who scored <62.4 % were insulin-treated from diagnosis (n=2), were obese (n=1) or were older with higher HbA1c (n=1).

Comparing the phenotype of MODY cases (n=14) vs no MODY (n=65), in those with PPV>62.4 %, MODY cases were significantly leaner (BMI 21.8 vs 26.2 kg/m^2 p=0.012) but age-at-diagnosis (14.7 vs 17years p=0.72), duration (6.2 vs 7.7years p=0.68) and HbA1c (8.8 % vs 7.3 % p=0.16) were not significantly different. No differences in treatment modality or parental history were observed.

Conclusions

The MPC overestimates the pre-test probability for a significant proportion of Emiratis. The 96 % who tested negative for MODY had features consistent with young-onset type 2 diabetes. 26 % of our confirmed MODY cases had lower PPVs due to atypical features. The MPC requires ethnic-specific refinement to take account of variable diabetes phenotypes in the UAE.

Juraj Staník

P07: AGE OF DIABETES ONSET IN PATIENTS WITH MODY

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Backgroung and Aims

Age of diabetes onset is used in many MODY clinical diagnostic guidelines. We aimed to analyse the age of diabetes onset in MODY patients from Slovakia.

Methods

All people from the Slovak monogenic diabetes database (established in 2003) with diabetes carrying a pathogenic mutation (class 4 or 5) in *GCK*, *HNF1A*, or *HNF4A* gene were included in the study. We analysed the proportion of people with MODY who were diagnosed with hyperglycemia or diabetes under the age of 12, 25, and 35 years, respectively.

Results

Among 267 people with diabetes, 180 had GCK-MODY, 79 had HNF1A-MODY and 8 had HNF4A-MODY. Among GCK-MODY patients currently aged ≤ 40 years (younger group, n=111), 50.4 % were diagnosed with hyperglycemia or diabetes in < 12 years of age, compared to 2.9 % in the group currently aged > 40 years (older group, n=69) ($p<0.001$). On the other hand, 8.1 % and 1.9 % in the younger group compared to 66.7 % ($p<0.001$) and 31.9 % ($p<0.001$) in the older group were diagnosed with hyperglycemia in age >25 and >35 years, respectively. In HNF-MODY 15.7 % patients from the younger group (n=51) had diabetes onset < 12 years of age compared to 0 % patients from the older group (n=36) ($p=0.018$). Furthermore, 5.9 % and 0 % from the younger group were diagnosed with diabetes in age >25 and >35 years compared to 38.9 % ($p<0.001$) and 16.7 % ($p=0.004$) patients from the older group.

Conclusion

Significant proportion of people with MODY aged > 40 years would miss clinical diagnostic criteria for MODY based on age. However, there is apparent tendency of earlier diagnosis of diabetes in the age group ≤ 40 years, probably due to the more frequent testing of glycemia (GCK-MODY) or environmental factors (HNF-MODY).

Supported by

APVV-187-12, VEGA 1/0211/18, VEGA 2/0083/17.

Terézia Valkovičová

P08: HSHS-CRP AS A BIOMARKER FOR HNF1A-MODY

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Introduction

CRP (C-reactive protein) is an inflammatoryinflammatory protein which whose is expressedexpression is regulated also by participating transcription factor HNF1α (Hepatocyte Nuclear Factor 1 alpha). Patients with HNF1A-MODY diabetes carrying a mutation in the *HNF1A* gene have lower plasma concentration of hsCRP (high-sensitivity CRP detection method) compared to patients with another type of diabetes. Therefore, Llow high sensitivity sCRP (hsCRP) was suggestedcould serve as a biomarker for easier diagnosis of patients with HNF1A-MODY patients.

Aim

of the study was to use the hsCRP as a biomarker tofor identifyication of the prevalence of HNF1A-MODY patients from nationwide screening using the hsCRP as a biomarker as a part of the a nationwide project for patients with diabetes in Slovakia.

Population and methods

From the total of 3,539 successive patients with diabetes**,** we selected 50 patients individuals with diagnosed diabetes diagnosed within 8th–40th year of life and hsCRP<0.25 mg/l. We performed the DNA analysis of the *HNF1A* gene by Sanger sequencing and MPLA.

Results

We identified *HNF1A* variants of in three patients, c.737T>G (p.V246G), c.1373_1388dup (p.Q463H fs) and c.1573A>T (p.T525S). The plasma hsCRP concentrations of the identified patients wereas 0.02, 0.01, and 0.07 mg/l, respectively. Age of the disease onset was 17, 18 and 20 years while and all three patients were treated by insulin and classified as T1D in the time of DNA analysis. Although patients with MODY diabetes usually do not have features of the metabolic syndrome, the first patient had hypertension in combination with overweight, and the remaining two patients had hypercholesterolemia on statin treatment.

Conclusion

Usage of hsCRP as a biomarker resulted in a pick-up rate of 6 % in patients with DM onset between 8 and 40 years. We selected 50 patients from 3,539 patients diagnosed with T1D or T2D who were included in nationwide screening of diabetes in Slovakia. We identified three HNF1A-MODY patients from 3,539 diabetics by Sanger sequencingbased on nationwide screening of diabetes in Slovakia. This represents 0.08 % prevalence of HNF1A-MODY. The presence of features of the metabolic syndrome in *HNF1A* mutation carriers is a factor which that complicates the clinical diagnosis of MODY but, at the same time, it indicates the additive value of hsCRP in diagnosis of HNF1A-MODY.

Supported by:

Centre for Research on Serious Diseases and their complications ITMS 26240120038, VEGA 1/0211/18.

Jonathan Locke

P09: A LOWER BIRTH WEIGHT IS ASSOCIATED WITH INCREASED PENETRANCE OF HNF4A-MODY

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Background

The age at which diabetes develops in individuals with HNF4A-MODY is highly variable (age 4–72 years) but the factors that affect penetrance are unknown. Interestingly preceding diabetes HNF4A-MODY is characterised by *in utero* hyperinsulinism leading to a median 790 g increase in birth weight.

Aim

Investigate whether birth weight, as a surrogate measure of fetal insulin secretion, is associated with penetrance of HNF4A-MODY.

Methods

Birth weight and gestational age data was available for 105 white Caucasian individuals (age≥9 years) with; an *HNF4A* mutation absent from gnomAD, and no record of treatment for hyperinsulinism. Sex and gestation-adjusted birth weights were calculated and Kaplan-Meier estimator analyses carried out with birth weight split by tertiles. Given the effect of intrauterine hyperglycaemia on birth weight separate analyses were conducted for individuals with a mother or only father affected (with diabetes/mutation).

Results

In the analysis of HNF4A-MODY individuals with a mother affected (n=61) 95 % (19/20) of lower birth weight offspring had developed diabetes by the age of 25. At the same age only 48 % (10/21) and 50 % (10/20) of individuals in the middle and highest birth weight tertiles had been diagnosed (p=0.002). In HNF4A-MODY individuals with only a father affected (n=44) there was no significant association (p=0.60) between birth weight and penetrance, nor was there any significant association in HNF1A-MODY individuals with a history of maternal (n=72) or paternal (n=38) diabetes.

Conclusions

A strong association between birth weight and MODY penetrance exists in the presence of two major drivers of fetal growth; an *HNF4A* mutation and maternal diabetes.

Acknowledgments

This work is supported by a Wellcome Trust Clinical Postdoctoral Fellowship awarded to KAP.

Yumeng Huang

P10: IMPAIRED PROINSULIN OXIDATIVE FOLDING AND INTRACELLULAR TRAFFICKING CONTRIBUTE TO MODY CAUSED BY INSULIN GENE MUTATIONS

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Background

Insulin gene mutation is the second most common cause of neonatal diabetes. It is also one of the genes involved in maturity-onset diabetes of the young (MODY).

Aims

We aim to investigate the molecular mechanisms underlying phenotypic spectrum of diabetes caused by different insulin gene mutations.

Methods

Three missense insulin gene mutations, p.Gly44Arg, p.Pro52Leu (a novel mutation identified in one French family), and p.Cys96Tyr were used as representative proinsulin mutants in this study. The diabetes phenotypes associated with these mutations range from mild MODY to severe neonatal diabetes. We characterized biological behaviors of these mutants using metabolic labeling, immunoprecipitation, immunoblotting, and confocal immunofluorescence. We also compared the dominant negative effect of these mutants on co-expressed wild-type proinsulin.

Results

Functional analysis showed that these mutations impaired proinsulin oxidative folding in the endoplasmic reticulum (ER), causing proinsulin misfolding and ER stress, decreasing efficiency of the ER export and intracellular trafficking of mutant proinsulin. Importantly, the mutants formed disulfide-linked proinsulin complexes with co-expressed wild-type proinsulin, through which impaired wild-type proinsulin folding and trafficking, limiting insulin production of mature insulin from wild-type proinsulin, contributing to insulin deficient diabetes. Notably, although all three mutants presented similar defects in their folding, trafficking, and dominant negative behavior, the degrees of these defects were clearly different. Specifically, compared with MODY causing mutants (p.Gly44Arg and p.Pro52Leu) that partially affected folding and trafficking of co-expressed wild-type proinsulin, neonatal diabetes causing mutant p.Cys96Tyr resulted in a nearly complete blockade of the ER export of wild-type proinsulin, inducing more severe ER stress, and diminishing insulin production.

Conclusions

The differences of biological behavior of proinsulin mutants and their dominant negative effects on bystander wild-type proinsulin play critical roles in determining the spectrum of diabetes phenotypes caused by insulin gene mutations.

Acknowledgments

This work was supported by research grants from the National Natural Science Foundation of China 81620108004, 81830025, 81700699, 81800733 and 81870533; We acknowledge support of Tianjin Municipal Science and Technology Bureau 17ZXMFSY00150 and 18JCYBJC93900.

Shivani Misra

P11: THE IMPACT OF ETHNICITY ON WOMEN IDENTIFIED FOR GLUCOKINASE MODY TESTING DURING PREGNANCY

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Background

GCK-MODY may be identified during pregnancy. Body mass index (BMI) <30 kg/m^2 and fasting plasma glucose (FPG)≥5.5 mmol/L identified GCK-MODY with 82 % sensitivity and 96 % specificity in white-Caucasian pregnant women. An alternative BMI threshold of <25 kg/m^2 gave 68 % sensitivity and 99 % specificity. We assessed the impact of ethnicity, a known modifier of gestational diabetes risk, on testing rates using these criteria.

Methods

Pregnant women whose self-reported ethnicity was categorised as white, African-Caribbean (AC) or South Asian (SA) were retrospectively reviewed and their FPG and BMI examined. These data were used to predict projected referrals for GCK-MODY genetic testing using BMI and FPG cut-offs.

Results

10,886 of 44,404 women who delivered in our inner-city centre (2014–2018) met the ethnicity criteria, had BMI recorded and underwent a 26–28-week oral glucose tolerance test.

Median BMI significantly varied by ethnicity: 24.0 kg/m^2 white, 27.0 kg/m^2 AC and 24.7 kg/^{2} SA(p=0.0001). Ethnic group impacted the proportions of women in each BMI category: <25 kg/m^2 58 % white, 36 % AC and 53 % SA (p<0.001); <30 kg/m^2 83 %, white 70 % AC and 84 % SA (p<0.001). Median FPG measured 4.3 mmol/L in white, 4.2 mmol/L AC and 4.3 mmol/L SA with overall distributions varying (p=0.0001).

Projected GCK-MODY testing rates in those with FPG≥5.5mmol/L were 0.6 % (BMI<25 kg/m^2) and 1.5 % (BMI<30 kg/m^2). Proportions identified for testing varied by ethnicity for the <30 kg/m^2 but not <25 kg/m^2 cut-off: BMI <25 kg/m^2 0.6 % white, 0.6 %AC, 1.0 %SA (p=0.13), and BMI<30 kg/m^2 1.1 % white, 1.9 %AC and 2.2 %SA(p=0.001).

FPG≥5.5mmol/L favoured AC ethnicity with 36 % of women meeting this criterion, irrespective of BMI, vs 18 % White and 22.6 % SA.

Conclusion

Although existing thresholds identify similar proportions of SA and AC women, the characteristics of these women differ, with higher rates of obesity and fasting hyperglycaemia. These data suggest that existing selection criteria for GCK-MODY testing will need review, once the true prevalence of GCK-MODY is ascertained in these ethnic groups.

Magdalena Szopa

P12: THE UTILITY OF MODY PROBABILITY CALCULATOR IN POLISH PATIENTS WITH DIABETES

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Background

Maturity Onset of the Young (MODY) accounts for 1–2 % of all diabetes cases. There are more than 20 genes linked with MODY. Unfortunately, ca. 90 % of MODY cases are misdiagnosed as type 1 or type 2 diabetes. A proper diagnosis of the type of diabetes is crucial for the use of a tailored treatment. Next-generation sequencing (NGS) enables simultaneous testing of a set of genes responsible for MODY. However, this method is still not reimbursed in many countries and patients selection for testing should be performed preciously. In 2012, an easy-to-use tool have been developed in Exeter, UK, to support the identification of cases appropriate for genetic testing in the British population.

Aims

The aim of the study was to assess the utility of MODY Probability Calculator in Polish patients.

Methods

We have performed a retrospective analysis of 152 probands who were qualified for genetic testing between 2006 and 2018. Patients were recruited for genetic MODY testing according to the classical clinical guidelines that include early age of diagnosis (≤35 years) and a positive, multigenerational family history. If Sanger sequencing for most likely gene was negative, NGS of a set of 28 genes was performed. MODY Probability was calculated on the website: www.diabetesgenes.org.

Results

The study group consists of 64 GCK-, 37 HNF1A-MODY and 51 NGS-negative patients. The mean positive predictive value (PPV) was 66,6±17,7, 46,7±27,3 and 53,3±26,3 % for GCK-, HNF-MODY and NGS-negative, respectively. The optimal statistical cut-off point to distinguish between MODY and NGS-negative patients was 58 % (AUC: 0.568, 95 % CI: 0.47–0.67). In such settings, in the analyzed group sensitivity and specificity was 64,4 % and 49,0 %, respectively. When using cut-off point of PPV for genetic testing of 25 % sensitivity was 87,1 % and specificity 17,6 %.

Conclusions

In the analyzed group of probands that were qualified for genetic testing based on clinical features the use of MODY Probability Calculator would not substantially improve patients selection process for genetic testing. Further improvement of MODY Probability Calculator is desirable.

Acknowledgments

The study was supported by the Diabetes Poland research grant 2016 and the Jagiellonian University Medical College Grant (K/ZDS/006219) awarded to MS.

Bente Berg Johansson

P13: PERSONALIZED MEDICINE IN DIABETES: UNRAVELING THE DISEASE CAUSALTY OF *HNF1B* GENE CODING VARIANTS IN TWO LARGE NORWEGIAN DIABETES REGISTRIES

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Background

Genetic variants in *HNF1B* encoding the transcription factor hepatocyte nuclear factor-1 beta (HNF-1B) can cause Maturity-Onset Diabetes of the Young type 5 (MODY5; HNF1B-MODY) but is also the most common known monogenic cause of developmental kidney disease.

Aim

The aim of this study was to investigate possible pathogenic effects of 13 *HNF1B* variants identified in the Norwegian Childhood Diabetes Registry (NCDR) (n=5400) and the Norwegian MODY Registry (n=2500), using functional protein analyses, and to correlate findings with clinical characteristics of *HNF1B* variant carriers.

Methods

HNF1B variants were classified using a five-tier score system commonly used in clinical diagnostic laboratories. To investigate the effect of HNF1B variants on normal HNF-1B transcriptional activity, we used a Dual-Luciferase assay system in transfected HeLa cells.

Results

13 HNF1B class 3–5 variants were identified in 24 patients (15 families) from the NCDR or the Norwegian MODY Registry. 7 variants were classified as likely pathogenic or pathogenic, 6 variants of unknown significance and 4 variants were interpreted as benign or likely benign. All rare variants were further investigated by functional studies.

All class 3–5 *HNF1B* variants examined inferred reduced HNF-1B transactivation potential except for three variants. Studies are ongoing to assess whether altered RNA stability, protein expression or DNA binding causes reduction in transcriptional activity.

Conclusion

Correlating functional data with clinical characteristics of *HNF1B* variant carriers, could to lead to improved diagnostics, prevent misdiagnosis and thus improve treatment strategies for diabetic patients

Acknowledgments

This work was supported by Helse Vest, the KG Jebsen Foundation, University of Bergen and the Norwegian Diabetes Foundation.

Shenali Amaratunga

P14: RARE GENETIC CAUSES OF DIABETES IN CONSANGUINNEOUS FAMILIES FROM IRAQ

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Context

The spectrum of causative genes and corresponding phenotypes of monogenic diabetes differ according to geographic area, ethnicity and religion. Rare autosomal recessive forms of syndromic diabetes may occur in regions with a high prevalence of consanguinity.

Aims

To elucidate the genetic etiology of non-autoimmune diabetes associated with syndromic features in children from four Kurdish consanguineous families.

Methods

Patients DNA was analyzed by whole exome sequencing methods. Detected variants were filtered using bioinformatic software (Ingenuity and Varaft). If potential variants were not published in the HGMD database, their pathogenicity was evaluated by their absence in the ExAC database, by predictions of in-silico programs and the American College of Medical Genetics (ACMG) standards. Thereafter, selected pathogenic variants were confirmed using Sanger sequencing methods.

Results

In 3 of 4 families, a causative variant was elucidated. 1) A 13 year old girl with insulin-resistant diabetes, hypertrichosis, acanthosis nigricans and dysmorphic features has a biallelic pathogenic variant p.Thr937Met (c.2810C>T) in the INSR gene causing leprechaunism. 2) An 11 year old girl and her brother who both have diabetes and short stature carry a novel biallelic variant p.Ile863Met (c.2589C>G) in the WFS1 gene causing Wolfram syndrome. 3) A 12 year old girl with short stature, non-immune diabetes, hepatosplenomegaly and camptodactyly has a biallelic variant p.Leu349Serfs*56 (c.1045delC) in the SLC29A3 gene known to cause histiocytosis-lymphadenopathy plus syndrome. 4) In two brothers, 8 and 4 years of age with neonatal diabetes and congenital hypothyroidism, a causative variant has not been elucidated yet.

Conclusion

Novel methods of genetic analysis facilitate the efficient identification of rare causal etiologies of diabetes. Even in regions with low consanguinity, it is important to consider syndromic diabetes when encountering a child with diabetes and other apparent phenotypic features.

Acknowledgments

This study is funded by AZV grant number NV18-01-00078.

Martine Vaxillaire

P15: MONOGENIC DIABETES GENES SCREENING IN ELEVEN MEDITERRANEAN COUNTRIES: THE MGSD-MODY STUDY

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Context

Genetic diagnosis of monogenic diabetes (MD) has important clinical implications for long-term follow-up, prognosis and a right targeted treatment. However, estimate of the prevalence and characteristics of MD in many countries is lacking due to poor access to genetic testing, particularly in countries around the Mediterranean area where early-onset diabetes is quite frequent.

Aims

To assess the genetic etiologies of early-onset or atypical non autoimmune diabetes in a multicenter cohort over eleven countries in Europe, North-Africa and Middle-East, and to evaluate the diagnosis rate, distribution of genetic subtypes and specificities at the country level.

Methods

We performed whole-exome sequencing in 217 early-onset diabetes patients (mean age at diagnosis: 26±9 years) clinically selected by 37 outpatient services of eleven countries. The pathogenicity of rare mutations detected in all known MD genes (*n*=35) was assessed using the ACMG criteria. We created an interactive database to store both clinical and genetic anonymized data.

Results

Pathogenic or likely pathogenic mutations in MD genes have been identified in 44 patients, yielding a diagnosis rate of 4 %-to-60 % according to the country. In the whole patient cohort, the main genetic subtypes were: 36 % of MODY2/*GCK*, 21 % of MODY3/*HNF1A*, 10 % of MODY12/*ABCC8*, 6 % of MODY1/*HNF4A*, 2 % of MODY5/*HNF1B* and 2 % of MODY13/*KCNJ11*. Specific genetic etiologies in some countries were observed. The most negative diagnosis rates were found in Morocco, Tunisia and Turkey.

Conclusions

Our study of MODY in the Mediterranean region showed a high, but variable genetic diagnosis rate among several countries, and highlights that MODY is underestimated in this part of the world. Further analysis of whole-exome sequencing data in the unelucidated cases from Turkey and Maghreb will allow us to investigate new genetic causes of early-onset diabetes.

Acknowledgments

The study was funded by the French National Research Agency (ANR-10-LABX-46, ANR-10-EQPX-07-01) and the MGSD.

Cécile Saint-Martin

P16: CHROMOSOME 11 UPD REVEALED BY NGS SEQUENCING

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Context

The past decade witnessed a change in sequencing generations, evolving from a single gene approach to a pan-genomic view of patients. While investigation used to be stopped with the identification of the first potentially pathogenic SNV, we are now facing complex combinations of variants in multiple loci. Thanks to powerful bioinformatic approaches these methodologies should ultimately allow to solve complicated molecular cases.

Aims

Taking advantage of the large amount of data available through next-generation sequencing (NGS) to explore molecular mechanisms beyond reach with Sanger sequencing.

Methods

An NGS-amplicon panel analysis was performed on genes involved in monogenic diabetes and congenital hyperinsulinism in a patient experiencing alternating hypo- and hyperglycemia. Diabetes was diagnosed at 22 months of age, patient was insulin-dependent and without family history of diabetes. Patient also had neuropsychiatric features and epilepsy.

Results

Among the 7 genes included in the panel, 3 are on chromosome 11: *ABCC8*, *KCNJ11* and *INS*. Strangely for this patient all heterozygous SNPs sequenced on these genes (n=5) showed an imbalanced allelic ratio of about 30/70 %. Sanger sequencing confirmed the imbalance ratio and thus excluded an NGS-related bias. MLPA analysis on *ABCC8* excluded a copy number variation of the region. We then performed SNP-array analysis (100 kb resolution) on this patient and her mother. We found there was a 30Mb mosaic segmental UPD of chromosome 11, most probably paternal. SNP-array analysis also allowed the identification of a large deletion encompassing *CHRNA7* and responsible for the inherited epileptic phenotype.

Conclusions

Despite the lack of identification of the event causing the diabetes phenotype, it is interesting to point that this patient has UPD in a region close to an imprinted locus. A pathogenic variant might lie in the intronic or regulatory regions on the paternal chromosome. This highlights the benefits of simultaneous analysis of multiple genes.

Rosa Martinez

P17: MONOGENIC DIABETES DETECTION IN A PAEDIATRIC SPANISH COHORT SUSPECTED OF TYPE 1 DIABETES AND NEGATIVE AUTOIMMUNITY

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Background/Aims

Monogenic diabetes can be misdiagnosed as type 1 (T1D) or type 2 diabetes in children. The right diagnosis is crucial for therapeutic choice and prognosis, and influences genetic counseling.

The aims

of this study were: 1) to assess the further value of screening ZnT8A in addition to the classical autoantibodies for the diagnosis of T1D; and 2) to search for monogenic diabetes (MODY type), in Spanish paediatric patients suspected of T1D with absence of autoantibodies at the onset of the disease.

Methods

400 Spanish paediatric patients with recent-onset diabetes and less than 1 week on insulin replacement therapy were studied. Pancreatic-autoantibodies (IAA, GADA, IA2A and ZnT8A) and HLA-DRB1 risk alleles were analyzed. Genetic testing was performed by a NGS custom gene panel including 12 known MODY genes and by MLPA-MODY.

Results

373 children (373/400, 93.25 %) had at least one positive autoantibody (GAD, IA2 and IAA) at T1DM onset. The ZnT8A analysis showed 229 positive cases, thus we were able to diagnose T1D in 4 additional cases negative for the rest of the antibodies. This increased the T1D diagnosis to 94.3 %.

Genetic screening in the 23 patients with negative autoimmunity identified two heterozygous pathogenic variants (8 %, 2/23); a pathogenic missense variant in *INS* (p.Gly32Ser) and a novel likely pathogenic frameshift variant (p.Val264fs) in *HNF1A* gene which co-segregates with diabetes in family. No partial or whole gene deletions or duplications were detected.

Conclusion

ZnT8A determination improves the diagnosis of autoimmune diabetes in pediatrics. At least 8 % of paediatric patients suspected of T1D and undetectable autoimmunity had pathogenic monogenic diabetes variants and can benefit from the correct diagnosis of the disease by genetic study.

This work was funded by GV2016111035.

Štěpánka Průhová

P18: CHARACTERISTICS OF MONOGENIC DIABETES REGISTERS WITHIN THE ENDO-ERN NETWORK

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European Reference Networks (ERN) are networks of reference centers across Europe, built to manage patients with rare diseases. ENDO-ERN represents a network focused specifically on rare endocrine diseases. Among 71 ENDO-ERN participants, 28 centers from 14 European countries follow rare cases of diabetes. The aim of this study was to map existing registries of monogenic diabetes (MD) and describe the standard care for children with MD in these centers.

Methods

All participating centers were asked to fill in an on-line questionnaire containing 34 questions focused on the basic characteristics of existing registers, care of patients with MD in a particular center and the availability of genetic investigation.

Results

Out of 28 centers, 16 (57 %) originating from 12/14 countries responded. A national register of diabetes, including patients with MD (mostly named as "other types" of diabetes) is present in 9/12 countries. A register, specifically intended for genetically proved monogenic diabetes, is available only in the UK, the Czech Republic, the Netherlands and Spain. In total, data from 1429 children was registered in these registers in 2018. Basal molecular genetic investigation of MD (HNF1A, HNF4A, GCK) was available in 11/12 participating countries, although samples from children with neonatal diabetes (ND) are investigated in Exeter, UK for most countries. The genetic investigation is reimbursed by health insurance companies in 5/12 countries, by research grants in 3/12 countries, by state funded health care systems in 2/12 and by the patients themselves in 2/12. The participating centers take care of more than 760 children with MD (54 children with ND). For many patients these centers serve as a diagnostic center which makes the diagnosis, reports them to the register and starts the treatment, follow-up care is provided by regional clinics. All centers used the ISPAD guidelines for diagnosis and treatment, 7/16 have special transition programs.

Conclusion

Data from the minority of patients with MD are available in existing registries, which implies the need to improve awareness and participation in MD registries.

The genetic investigation in Czech Republic is supported by the research grant NV18-01-00078.

Daniela Vejrážková

P19: DYNAMICS OF GLUCOSE TOLERANCE IN RELATION TO RS10830963 OF THE MTNR1B GENE

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Background
The MTNR1B gene encodes the melatonin receptor. It is expressed primarily in the brain, but also in the pancreas. Variability of the gene is a significant factor influencing glucose metabolism. Rs10830963 shows a robust association with type 2 diabetes.

Aims
To evaluate changes in glucose tolerance during 5–12 (median 7) years of follow-up, depending on rs10830963 genotype.

Methods
The study included 226 re-examined Czech volunteers who underwent the 3-hour oGTT and had normal glucose tolerance at baseline. The mean age, BMI, and interval between the examinations were not significantly different between the genotype groups compared. Genotyping was performed on the TaqMan (LC480, Roche), the data were evaluated by NCSS 2004.

Results
The risk variant G was present in 112 heterozygotes (49 %) and in 21 homozygotes (9 %). 40 participants (18 %) developed impaired glucose tolerance over the years, however, the percentage of such impaired individuals did not differ between the genotypic groups. Rise in blood glucose measured during the oGTT (AUC) was significant in all three genotypes. The HOMA R index of insulin resistance has not increased significantly in non-risk genotype CC (δ=0.22; ns). In contrast, it has increased significantly in CG heterozygotes (δ=0.27; p=<0.05). In GG homozygotes, the change was the most pronounced (δ=0.34), however, given the limited number of individuals, it did not reach statistical significance. Insulin sensitivity calculated according to Matsuda has not decreased significantly in non-risk CC homozygotes (δ=1.4; ns), but it has decreased significantly in CG heterozygotes (δ=1.9; p<0.001) and especially in risk GG homozygotes (δ=2.3; p<0.05).

Conclusions
In line with the worldwide studies demonstrating association of rs10830963 in the MTNR1B gene with diabetes, we observe more pronounced changes in glucose metabolism over time in carriers of the G allele, especially in GG homozygotes.

Acknowledgments
MH CR RVO EÚ00023761 and NV 17-30528A.

David Galuška

T2DM GENETIC RISK SCORE AND MORBIDITY AND MORTALITY ASSOCIATED WITH DIABETIC KIDNEY DISEASE

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Background and aims
Diabetic kidney disease (DKD) is one of the most serious complications of type 2 diabetes mellitus (T2DM). Individual genetic predisposition to development and progression of DKD is still insufficiently explored. Genetic predisposition to T2DM is comprehensively described and genetic risk score (GRS) have been previously established. We hypothesized that GRS might represent a risk factor for DKD progression and cardiovascular morbidity and mortality in T2DM patients in the Czech population.

Materials and methods
A total of 399 patients with T2DM and variable stage of DKD were included and followed up for a median of 43 (IQR 22 – 76) months. The followings endpoints were considered: (a) renal (progression of chronic kidney disease by stage or reaching end-stage renal disease), (b) major adverse cardiovascular event (MACE) and (c) all-cause mortality (ACM). 21 SNPs were selected for evaluating of GRS (OR > 1.1). SNPs were determined using quantitative PCR. Survival analysis using Kaplan-Meier curves was used to assess predictive value of GRS for studied endpoints.

Results
Weighted GRS was calculated considering OR of individual SNPs. Distributions of GRS were divided into quartiles for the purpose of time-to-event analysis. Cumulative incidence of DKD, MACE and all-cause mortality were 47.1 %, 14.9 % and 37.4 %, respectively. Using time to event analysis we did not find any significant differences between groups defined by quartiles of GRS and progression of DKD, MACE and ACM (all $P > 0.05$, log-rank test).

Conclusion
Our results demonstrate that GRS does not predict progression of DKD, MACE or ACM in the Czech population.
Study was supported by the grant NV18-01-00046 from the Ministry of Health of the Czech Republic.

Anna Jonsson

P21: GENOME WIDE ASSOCIATION STUDY OF CIRCULATING LEVELS OF GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AND GLUCAGON-LIKE PEPTIDE-1 DURING AN ORAL GLUCOSE TOLERANCE TEST

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Context

Large-scale genome wide association studies (GWAS) have identified multiple genetic determinants of type 2 diabetes. For most of those validated variants, it is unclear through which mechanisms they exert their effect. One mode of influence may be through an effect on incretin hormone levels since those are important regulators of blood glucose homeostasis.

Aims

Our aims were, firstly, to examine the impact of genetic variants associated with type 2 diabetes and glycemic traits on circulating levels of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) during an oral glucose tolerance test (OGTT), and secondly, to identify novel genomic loci affecting those traits.

Methods

Plasma levels of GIP and GLP-1 were examined in samples obtained at fasting, 30 minutes and 2 hours during an OGTT in a total of up to 2230 individuals. The incremental area under the curve (iAUC) of plasma GIP and GLP-1 were calculated from 0 to 30 minutes and from 0 to 120 minutes during the OGTT. Associations between genetic variants and plasma hormone levels were studied using a linear mixed model (EMMAX).

Results

A variant in the *GIPR* locus (rs2238691) was associated with reduced GIP response to oral glucose stimulation (iAUC 0–30 minutes: Beta (SE) -0.255 (0.037) P= $6.5*10^{-12}$). A variant in the *FADS1* locus, previously reported to associate with elevated fasting glucose level (rs174550) was strongly associated with reduced GIP response at 30 minutes during the OGTT (iAUC 0–30 minutes: -0.151 (0.034) P=6.61×10^{-6}). None of the associations with circulating plasma levels of GLP-1 during the OGTT were significant after correction for multiple testing.

Conclusions

The present meta-analysis identified a genome-wide significantly associated locus containing the GIP receptor gene (*GIPR*).

Acknowledgments

Danish Council for Independent Research, European Union, FP7, Marie Curie Actions, IEF, Novo Nordisk Foundation and Lundbeck Foundation.

Hannah Maude

P22: FINE-MAPPING T2D RISK LOCI REVEALS ALLELIC HETEROGENEITY AND THE POTENTIAL ROLE OF RARER VARIANTS IN REGULATING AMINO ACID AND FATTY ACID CATABOLISM

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Background

Recent analysis based upon high-resolution genetic maps has shown that ~80 Type 2 Diabetes (T2D) disease loci are also expression quantitative loci (eQTL) for nuclear encoded mitochondrial genes with a high degree of co-location with *in silico* functional annotation.

A follow-up fine-mapping study was carried out to investigate two novel loci for evidence of complex association with T2D and mitochondrial function. The first locus, a 79 kb stretch in intron 3 of *FGF14,* was observed to harbour eQTL for genes including *PCCA*, for which the encoded carboxylase catalyses a terminal step in both branched chain amino acid (BCAA) catabolism and odd-chain fatty acid oxidation; two pathways relevant to T2D aetiology. The second is a predicted eQTL for the fatty acid dehydrogenase *ACAD11*.

Aims

Use targeted next-generation sequencing to test for complex genetic mechanisms driving association at these novel loci, including enrichment of intermediate and rare frequency variants and allelic heterogeneity. Identify candidate functional elements for functional studies.

Methods

Sequencing data for independent samples of European ancestry, 94 cases (family-history of T2D) and 94 controls (no family-history), were used to investigate candidate causal variants.

Results

Both loci show locus-wide enrichment of rarer variants (MAF<0.016) at annotated regulatory elements in cases.

Conclusions

We detect enrichment of variants in T2D cases within enhancers at two novel T2D loci. Several candidate elements are being investigated in ongoing functional studies, alongside analysis of a much larger case-control sequencing dataset to replicate allele frequency differences. Similar methodology will be employed to fine-map other novel loci, thus facilitating the discovery of novel pathological mechanisms.

Acknowledgments

WTCCC, NIDDK, MRC (Investigator Award 91993) for supporting this work and Philippe Froguel for pilot DNA samples.

Koen Dekkers

P23: A GENETIC PREDISPOSITION TO KNOWN RISK FACTORS FOR TYPE 2 DIABETES AFFECTS TOLERANCE TEST RESPONSE CURVES AND RESPONSE CURVE PROGRESSION IN PEOPLE WITH (PRE)DIABETES

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Genetic effects on oral glucose tolerance test (OGTT) traits and indices have been investigated in GWAS and increasingly with Mendelian randomization (MR). However, the effect of a genetic predisposition to known risk factors for type 2 diabetes on actual tolerance test response curves and response curve progression in people with (pre)diabetes is largely unknown. Understanding this effect might provide new insights on determinants of diabetes and diabetes progression.

In this preliminary study, we used genetic data and C-peptide, glucose and insulin tolerance test response curve data of the DIRECT consortium. Complete OGTT response curves (3 visits, 7 time points per visit) were available for 1706 people with prediabetes and complete mixed meal tolerance test (MMTT) response curves (3 visits, 5 time points per visit) were available for 507 people with diabetes. First we constructed genetic instruments for BMI, coronary artery disease, diastolic blood pressure, HDL cholesterol, LDL cholesterol, polycystic ovary syndrome, smoking behaviour, systolic blood pressure, triglycerides, waist circumference and waist-to-hip ratio adjusted for BMI (WHRadjBMI), using genetic variants identified in large European GWAS. With these genetic instruments we then estimated the effect of a genetic predisposition to risk factors for diabetes on principal components of OGTT and MMTT response curves and response curve progression using MR. Analyses to evaluate the robustness of this effect still need to be performed.

We identified that a genetic predisposition to high WHRadjBMI affected baseline and progression principal components of C-peptide, glucose and insulin OGTT response curves (people with prediabetes), while a genetic predisposition to high systolic blood pressure affected baseline principal components of the glucose response curve (5 % FDR). Conversely, a genetic predisposition to high triglycerides affected progression principal components of C-peptide MMTT response curves (people with diabetes). Characterization of these effects might reveal novel insights on underlying diabetes pathophysiology and progression.

Acknowledgement

We are grateful to all participants of the DIRECT consortium. The work leading to this publication has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115317 (DIRECT), resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Robert Wagner

P24: INTERACTION BETWEEN GENETIC DIABETES RISK AND PANCREATIC FAT SECRETION IN GENETICALLY PREDISPOSED INDIVIDUALS

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Context

Pancreatic fat (PF) related beta-cell failure might play a role in the pathophysiology of type 2 diabetes (T2D).

Aims

We hypothesized that the effect of PF on beta-cell function can be modeled as a gene x environment interaction. To this end, we investigated the association of PF with insulin secretion in subjects with different genetic predisposition for T2D.

Methods

A genome-wide polygenic risk score (gwPRS) was computed combining summary statistics from a genome-wide association study on diabetes with ~900.000 participants and 480.000 genetic variants in our cohort. The interaction of MRI-measured PF with gwPRS was investigated in 376 non-diabetic participants using oral glucose tolerance test based insulin secretion measures.

Results

While there was no association of PF with insulin secretion in the total cohort, PF interacted with gwPRS on insulin secretion (insulinogenic index) after adjustment for confounders (p=0.001). In participants with low gwPRS, PF associated positively with insulin secretion. In participants with high gwPRS, PF inversely associated with insulin secretion.

Conclusion

Our data suggest that PF contributes to impaired beta-cell function in subjects at high genetic risk for diabetes. In subjects with low genetic diabetes risk, PF is associated with hyperinsulinemia.

Mette Andersen

P25: A COMMON INTERGENIC VARIANT ON CHROMOSOME 11 ASSOCIATES WITH A FAVORABLE METABOLIC PHENOTYPE IN GREENLANDERS

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Context

The small and historically isolated Greenlandic population offers advantages for identification of novel genetic associations. Aims: We aimed to identify genetic loci associated with body-mass index (BMI) and related metabolic phenotypes.

Methods

A population-based sample of Greenlanders were genotyped on the Illumina MetaboChip, 4,674 individuals and 115,182 variants passed quality control.

Results

We identified a common intergenic variant on chromosome 11 (rs4936356), where the minor G-allele was genome-wide significantly associated with lower BMI among Greenlanders (beta (se): -0.14 SD (0.03), p=3.2x10−8), corresponding to 0.64 kg/m^2 lower BMI per G-allele. Moreover, the G-allele was also associated with a leaner body type (weight, -0.13 SD (0.03); waist, -0.12 SD (0.03); hip, -0.11 SD (0.03); fat percent, -0.17 SD (0.03); lean mass, -0.14 SD (0.03); visceral adipose tissue, -0.14 SD (0.03); subcutaneous adipose tissue, -0.12 SD (0.03), all p<0.0003), lower insulin resistance (HOMA-IR, -0.10 SD (0.03), p=0.00021), and a favorable lipid profile (triglyceride, -0.06 SD (0.03), p=0.025; HDL-cholesterol, 0.08 SD (0.03), p=0.0015). The BMI association was replicated in data from the GIANT-consortium (-0.02 SD (0.01), p=8.0x10−4), but not from UK Biobank (-0.03 SD (0.02), p=0.147). The discrepancy between the association in Greenlanders and Europeans might partly be explained by the difference in effect-allele frequency, which was 0.24 among Greenlanders, and 0.07 among Europeans from the UK Biobank.

Conclusions

We identified a variant associated with lower BMI, leaner body type, lower insulin resistance, and a favorable lipid profile. We observed a very large effect in Greenlanders, where the variant was common, while the effect in Europeans was low or absent. Once identified, the causal variant in this locus could be a therapeutic target for improving metabolic health.

Josef Včelák

P26: *NME7* GENE IS ASSOCIATED WITH GLUCOSE LEVELS DURING ORAL GLUCOSE TOLERANCE TEST

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Background

The shape of the glucose curve during oral glucose tolerance test (OGTT) can be considered as predictor of the impaired glucose tolerance and Type 2 Diabetes (T2D). Nucleoside diphosphate kinase 7, non-metastatic cells 7 (NME7) is involved in the biogenesis and function of cilia. Inasmuch as T2D is common in several ciliopathies, we enrolled this gene into the candidate genes for impaired glucose tolerance and T2D.

Aims

to ascertain possible association of the OGTT glucose curves with the genetic background.

Methods

The study included 1219 3-h OGTT glucose curves (blood sampling in 30 min intervals) of 997 women (age median 32 years) and 222 men (age median 31 years) differing in glucose tolerance.

The curves were divided according to their shape: monophasic, biphasic, triphasic and curves with more than three peaks. In these groups we studied the variability of the candidate genes for glucose metabolism: *NME7*, *ATP1B1*, *BLZF1*, *GCK*, *KCNJ11*, *LRP5*, *PPARGC1A*, *PPARG, SLC30A8, TCF7L2, FTO, ZBTB16, THADA, PICALM, BIN1, CLU, CR1, MTNR1B, PNPLA3*. The polymorphisms were genotyped using TaqMan SNP genotyping assays (RealTime LC480, Roche).

Results

Most of the curves were monophasic (48.4 %), then triphasic (26.7 %), biphasic (20 %), and last curves with more than three peaks (4.9 %). Monophasic curves were associated with the lowest insulin sensitivity and insulin secretion and worse lipid spectrum. The shape of curves was associated with *NME7* (rs10732287, p=0.001; rs4264046, p=0.01; rs10800438, p=0.02) with the lowest frequencies of minor alleles in the biphasic curves.

Conclusions

The shape of glucose OGTT curves is related to distinct metabolic profile. Our study found the association of the curve shape with the variability of the *NME7* gene, biological function of which is still not clear. Currently, we are preparing animal *nme7* knock-out model.

Acknowledgments

GACR 17-13491S, NV 18-01-00399, MH CR-DRO (EU 00023761).

Suzanne Jacobs

P27: SLC16A11 DISRUPTION *IN VIVO* CAUSES PHYSIOLGOCIAL CHANGES ASSOCIATED WITH T2D PATHOGENESIS

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Background

Type 2 diabetes (T2D) is heritable, with genetic variation contributing to a disparity in T2D prevalence across populations. An example of this disparity is observed within U.S. populations, where the prevalence of diabetes in individuals of Latin American descent is approximately twice that of non-Hispanic whites. Through a genome-wide association study, we previously identified a variant haplotype in *SLC16A11* that explains ~20 % of the increased T2D prevalence in Mexico. More recently, we carried out genetic fine-mapping, biochemical, molecular, and cellular studies that identified two co-inherited but independent mechanisms by which T2D-associated coding and non-coding variants disrupt *SLC16A11* function: (1) non-coding variants decrease *SLC16A11* expression levels in liver and (2) coding variants in SLC16A11 attenuate activity by disrupting a key interaction with an ancillary protein, thereby reducing plasma membrane localization. These data implicate *SLC16A11* as the causal effector gene at this locus, and suggest reduced SLC16A11 activity as the T2D-relevant direction-of-effect. However, how *SLC16A11* deficiency disrupts glucose homeostasis *in vivo* remains unknown.

Aims

The goal of our current work is to determine the physiological consequences of *Slc16a11* disruption on metabolism.

Results

We used CRISPR/Cas9 to generate a *Slc16a11* knockout mouse model and carried out longitudinal metabolic studies. We demonstrate that *Slc16a11* knock out leads to glucose intolerance and other metabolic phenotypes that are observed as part of the pathophysiology of T2D in humans.

Conclusions

These findings begin to establish the physiological mechanism through which *SLC16A11* disruption alters glycemia, and provide further support for the concept that increasing SLC16A11 function could be therapeutically beneficial for people with T2D.

Acknowledgements

This work was conducted as part of the Slim Initiative for Genomic Medicine, a project funded by the Carlos Slim Foundation in Mexico.

Rashmi Prasad

P28: SIGNATURES OF FETAL PROGRAMMING IN CORD BLOOD FROM MOTHERS WITH GESTATIONAL DIABETES MELLITUS DURING EARLY PREGNANCY

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Context /Background

Gestational diabetes mellitus (GDM) is a transient form of diabetes characterized by impaired insulin secretion and action during pregnancy. GDM is a leading health concern in developing countries like Tanzania. This can result in adverse consequences for mother and offspring. The hypernutrition state in the uterus due to GDM can affect fetal growth leading to macrosomia. This can also result in increased risk of complex disorders such as type 2 diabetes, obesity and cardiovascular diseases in later life (DoHAD hypothesis).

Aims

We aimed to identify signatures of fetal programming as a consequence of GDM during pregnancy.

Methods

We investigated signatures of fetal programming as a consequence of GDM by leveraging RNA sequencing and global methylation data from 21 cord blood samples from mothers with GDM and 119 control women. Simulataneously we also performed GWAS to assess impact of genetic variation on gene expression.

Results

We found the expression of 6 genes to be significantly differentially expressed between cord from GDM mothers compared to controls. This was accompanied by changes in epigenetic patterns of these genes. One such gene was the adenylyl cyclase 9 coding *ADCY9* gene which has previously been shown to have roles in fetal development. We also found multiple genes associated with maternal as well as cord insulin levels. Some of these genes were also associated with offspring birth weight and nutritional status.

Conclusions

Taken together, this study provides novel insights into fetal programming and changes in gene expression in cord blood from mothers with GDM and how this potentially could impact the future health of the offspring.

Acknowledgments

Danish Research Council, European Foundation for Study of Diabetes/Novo Nordisk Programme for Diabetes Research in Europe, Swedish Research Council.

Yanina Timasheva

P29: GENETICS OF TYPE 2 DIABETES, METABOLIC AND BLOOD PRESSURE TRAITS HIGHLIGHTS SHARED BIOLOGICAL PATHWAYS

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Background

Type 2 diabetes (T2D) usually manifests in the metabolic syndrome setting, which also includes abdominal obesity, hypertension, hyperlipidemia and hypercoagulability. Genome-wide association studies (GWAS) identified over 400 distinct association signals for T2D and over 900 for blood pressure traits.

Aims

We aimed to dissect shared genetic factors contributing to the comorbidity of these conditions.

Methods

Using GWAS meta-analyses summary statistics, we defined 3,429 single nucleotide variants (SNVs) associated with 63 cardiometabolic phenotypes (defined as related to T2D, cardiovascular and metabolic traits). We identified 240 unique T2D association signals represented by 478 T2D/glycaemic SNVs overlapping with 596 SNVs reported for other phenotypes and located within 100kb distance. Using hierarchical clustering, we defined groups of shared loci affecting cell-mediated autoimmunity (*CDKAL1* and *G6PC2*), insulin signalling (*GRB14*), beta-adrenergic signalling (*PPP1R3B*), immune response (*CMIP*), cell metabolism (*KCNJ11*), cell cycle regulation and apoptosis (*BCL2*).

Results

We identified 35 distinct signals associated with two or more cardiometabolic phenotypes, including rs560887 in *G6PC2* gene related to higher fasting glucose levels pulse pressure (PP); rs7756992 in *CDKAL1* leading to elevated systolic blood pressure (SBP), increased T2D risk, but lower body mass index (BMI); rs635634 in *ABO* influencing many metabolic endophenotypes, but most notably leading to increased risk of T2D and stroke; rs5219 in *KCNJ11* increasing risk of T2D, related to elevated SBP and PP; and rs12454712 in *BCL2* related to higher SBP and abdominal obesity, but also to lower T2D susceptibility and lower BMI.

Conclusions

We disentangle shared biological pathways between metabolic and blood pressure phenotypes, thus suggesting common pathophysiological mechanisms.

Vicky Au Yeung

P30: UNDERSTANDING THE METABOLIC PATHWAYS LINKING WEIGHT GAIN AND TYPE 2 DIABETES RISK

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Background

Weight gain is a known risk factor for type 2 diabetes (T2D), but the underlying mechanisms are incompletely understood. Recent advances in high-throughput untargeted metabolic profiling may highlight pathways that are important in this association.

Aim

To systematically identify metabolites affected by weight gain and estimate their association with T2D.

Methods

Regression analyses adjusted for age and sex were performed in 9,838 individuals from the EPIC-Norfolk prospective cohort study with metabolite levels measured at baseline using Metabolon's untargeted metabolomics platform. First, linear regression of weight gain, calculated as the average annual difference between measured baseline weight at average 60 years and self-reported weight at age 20 years, was performed on metabolite levels. Logistic regression of metabolite levels on incident T2D (iT2D) was performed in parallel. In a non-overlapping T2D case-cohort of 634 cases and 867 cohort controls nested within EPIC-Norfolk, Bayesian variable selection (BVS) was then performed on metabolites significantly associated with weight gain and iT2D to prioritise potential mediators. Finally, the effect of potential mediators on the association between weight gain and T2D was assessed using individual and stepwise cumulative adjustment in a Prentice-weighted Cox regression model.

Results

Weight gain was significantly associated with 383 of 650 commonly-detected metabolites ($p<7x10-5$). Of these, 128 were also significantly associated with iT2D ($p<7x10-5$). BVS identified 32 potential mediators including amino acids, lipids and biochemically-unidentified compounds. Candidate mediators individually accounted for little, but cumulatively for most of the association between weight gain and iT2D (HR 2.56 (95 % CI 2.19–3.00) vs 1.18 (0.92–1.52) per SD weight gain per SD metabolite before and after metabolite adjustment).

Conclusions

Comprehensive, untargeted metabolic profiling highlights metabolic pathways that may in concert mediate the association between weight gain and T2D risk.

Acknowledgments

We would like to thank the Wellcome Trust and Cambridge Trust for supporting this research.

Nikolas Miniatis

P31: POPULATION-SPECIFIC GENETIC MAPS CAN EFFECTIVELY INTEGRATE RISK LOCI WITH OMICS DATA AND PROVIDE IMPORTANT INSIGHTS INTO THE GENETIC ARCHITECTURE OF T2D

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Background

We recently used metric genetic maps that capture detailed linkage disequilibrium information in European and African-Americans and applied these to large T2D case-control samples in order to estimate accurate locations for putative functional variants in both populations. Replicated T2D locations were tested for evidence of being regulatory hotspots using adipose expression. We identified 111 novel loci associated with T2D-susceptibility locations, 93 of which are cosmopolitan (co-localised on genetic maps for both populations). We found that many previously known T2D signals are also risk loci in African-Americans. Using the same methods, we also showed that the majority of these T2D locations are also regulatory locations (eQTLs) conferring the risk of T2D via the regulation of expression levels for a very large number of cis-regulated genes.

Aims

This is a follow up study on all our T2D locations to obtain insights into their regulatory nature.

Methods

The overlap between T2D locations and chromatin marks for different tissues/cells was investigated for all risk loci. The replication rate for obtaining overlap across tissues was examined. The differences in co-localisation between lead GWAs SNPs and our location estimates on the genetic maps were also studied.

Results

We show that T2D-associated loci, gene expression and cell-specific regulatory annotation can be effectively integrated by localising accurately their effects on population genetic maps. Our T2D locations show a higher degree of accuracy and co-localisation with eQTLs and functional annotation compared to GWAs lead SNPs.

Conclusions

Localising disease loci on genetic maps can provide accurate and detailed information about the implicated functional genes involved. The T2D locations show significant overlap with tissue specific chromatin marks and results provide novel insights for mechanisms in disease aetiology.

Acknowledgments

Wellcome Trust for financial support.

Martin Javorský

P32: *GLP1R* GENE VARIANT IS ASSOCIATED WITH GLYCEMIC RESPONSE TO TREATMENT WITH DPP-4 INHIBITORS

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Background

DPP-4 inhibitors (gliptins) are frequently used for the treatment of type 2 diabetes (T2D). There is considerable variability in the glycemic response to gliptins, partially explainable by genetic factors. Several gene variants were previously associated with GLP-1 stimulated insulin response in physiogenetic studies or with glycemic response to gliptins.

Aims

To examine associations between the selected gene variants and glycemic response to gliptin treatment.

Methods

206 consecutive patients with T2D (46.6 % women) from six outpatient clinics with the mean age 58.9±0.7 years were included in this study. Gliptins were used as the add-on treatment to metformin (n=151), or metformin and sulfonylurea/thiazolidindione combination (n=55). The main study outcome was the reduction in HbA1c (ΔHbA1c) after the 6-month treatment with gliptins. Genotyping of GIPR_rs10423928, GLP1R_rs6923761, GLP1R_rs10305420, TCF7L2_rs7903146, KCNQ1_rs163184, WFS1_rs10010131, CTRB12_rs7202877, LOC105377923_rs1948999 was performed using high-resolution melting curve analysis after real-time PCR. Genotypes followed Hardy-Weinberg equilibrium. Data show mean±SEM. Genetic models were adjusted for age, sex, baseline HbA1c, and serum creatinine.

Results

In the entire study, mean HbA1c was reduced from baseline 7.81±0.07 % (61.9±0.8 mmol/mol) to 7.18±0.07 % (55.0±0.8 mmol/mol) after 6-month gliptin treatment. Mean ΔHbA1c was 0.63±0.07 % (6.9±0.8 mmol/mol). Only GLP1R_rs6923961 G>A variant was significantly associated with ΔHbA1c (adjusted additive model per A-allele: β=-0.27±0.1 %; p=0.006, p_Bonferroni=0.048). ΔHbA1c decreased with number of A-alleles in rs6923961 genotype [GG (n=74): 0.84±0.12 %; GA (n=108): 0.57±0.1 %; AA (n=24): 0.28±0.18 %; p=0.016]. Mean ΔHbA1c was significantly smaller in AA-homozygotes compared with G-allele carriers [0.28±0.18 % vs. 0.68±0.08 % (2.2±1.4 vs. 5.4±0.6 mmol/mol), p=0.016].

Conclusions

We observed a significantly smaller reduction in ΔHbA1c after the 6-month gliptin treatment by 0.27 % per each A-allele of variant GLP1R_rs6923761 G>A (Gly168Ser), which was independent of clinical factors. Our observation might contribute to the individualization of antidiabetic therapy.

Acknowledgments

This study was supported by a research grant from the Ministry of Education of Slovakia VEGA 1/0027/16.

Tanja Dujic

P33: *TCF7L2* GENE VARIANT AND RESPONSE TO METFORMIN IN PATIENTS WITH TYPE 2 DIABETES

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Background

The response to metformin, the most commonly used drug for treatment of type 2 diabetes (T2D), is highly variable, partly due to genetic factors. The common variant rs7903146 C>T within the transcription factor 7 like 2 gene (*TCF7L2*) is the strongest genetic variant associated with T2D to date. A recent study showed that the diabetes risk T allele at rs7903146 is associated with a greater decline in glucose levels after metformin administration in individuals without diabetes.

Aims

In this study we explored the effect of *TCF7L2* rs7903146 genotypes on metformin response in patients with T2D.

Methods

This observational study included 86 newly diagnosed patients with T2D, who were prescribed metformin as their initial hypoglycaemic therapy. Levels of fasting glucose, insulin, HbA_{1c}, total, HDL-, LDL-cholesterol, and triglycerides, and anthropometric parameters were measured prior to metformin therapy, and 6 and 12 months after treatment. Genotyping of *TCF7L2* rs7903146 was performed by the Sequenom MassARRAY® iPLEX® platform.

Results

At baseline, the T allele showed an association with lower triglycerides levels (P=0.037), and a trend of association with lower estimated β-cell function HOMA-%B (P=0.063). After 12 months of metformin treatment, the T allele was associated with 24.0 % lower fasting insulin levels (P=0.003) and lower HOMA-IR index (27.4 % lower levels, P=0.007), after adjustment for baseline values. Moreover, patients with the risk TT genotype had 6.0 % lower fasting glucose levels, adjusted for baseline glucose, after 6 months of metformin treatment (P=0.035), compared to the CC genotype carriers. This effect was more pronounced after adding baseline HOMA-%B to the model (8.4 % lower glucose levels, P=0.002).

Conclusions

Our results suggest that *TCF7L2* rs7903146 variant affects markers of insulin resistance and glycaemic response to metformin in newly diagnosed patients with T2D within first year of metformin treatment.

Acknowledgments

The study was supported by Federal Ministry of Education and Science B&H and Ministry of Civil Affairs B&H awarded to S.S., and EFSD Albert Renold Fellowship awarded to T.D.

Hanieh Yaghootkar

P34: "FAVOURABLE ADIPOSITY" GENETIC FACTORS PINPOINT TO THE ROLE OF SUBCUTANEOUS ADIPOSE TISSUE AND ECTOPIC LIVER FAT IN THE ETHNIC DIFFERENCES IN ADIPOSITY AND DIABETES RISK

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Aims

South Asians have higher risk of type 2 diabetes at lower BMI cut-offs comparing to Europeans. To investigate the genetic aetiology of this difference, we tested whether variants associated with higher adiposity but lower risk of disease – "favourable adiposity" – would have different frequencies and different effects in South Asians.

Methods

We used 10,203 South Asians and 451,000 Europeans from UK Biobank. We generated a genetic score based on the 14 favourable adiposity variants and assessed the collective effect of these variants on adiposity, risk of type 2 diabetes (14,371 Europeans and 1,150 South Asians cases) and MRI scans of abdominal fat (9,600 Europeans and 130 South Asians).

Results

Favourable adiposity alleles were less common in South Asians than Europeans (average number of alleles 10.5 vs 11.6; $P<0.0001$). Each additional allele was associated with higher body fat % (0.148 %, 95 % confidence interval (CI) [0.099,0.197] in South Asians and 0.128 % [0.119,0.136] in Europeans) but lower risk of type 2 diabetes (0.95 Odds Ratio (OR) [0.92,0.97] and 0.97 OR [0.94,0.97] in Europeans). Each additional allele was associated with higher subcutaneous adipose tissue (0.10 Litre [-0.07;0.28]; 0.06 Litre [0.03;0.10]) but lower liver fat (-0.22 % [-0.52;0.13]; -0.09 % [-0.14;-0.05]) in South Asians and Europeans, respectively.

Conclusions

"Favourable adiposity" alleles have similar effects on lower risk of disease in South Asians but are less frequent compared to Europeans. These alleles are associated with higher subcutaneous but lower liver fat which suggests a likely mechanism in the ethnic differences in adiposity and diabetes risk.

Jaroslav Hubáček

P35: *FTO*, *TCF7L2* AND *CDKN2A/2B* VARIANTS WITHIN THE CZECH AND ROMA/GYPSY POPULATIONS

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Background

The incidence of Type 2 Diabetes Mellitus (T2DM) differs significantly between different ethnic groups. The higher prevalence of T2DM is also reported in the case of the Roma/Gypsy population. The Czech-governmental study suggests up to 30 % higher prevalence than within the majority. However, it is not known whether and to what extent these differences have a genetic background and to what extent the unhealthy lifestyle is responsible. Single-nucleotide variants (SNPs) within the genes for FTO (rs17817449), TCF7L2 (rs7903146) and CDKN2A/2B (rs10811661) are considered to be between the most powerful genetic determinants of T2DM development.

Aims

To analyse whether the frequencies of alleles/genotypes of *FTO*, *TCF7L2* and *CDKN2A/2B* genes differs between the two ethnic groups in the Czech Republic.

Methods

Using PCR-RFLP we examined *FTO*, *TCF7L2* and *CDKN2A/2B* genotypes in DNA samples from 300 adult Roma/Gypsies and 300 adult Czechs.

Results

The frequency of genotypes of all three variants differed significantly among the examined ethnicities. Compared to the majority population, Roma/ Gypsies are more likely to carry risky-alleles of *FTO* (26 % vs. 16 % GG homozygotes, P<0.01) and *CDKN2A/2B* (81 % vs. 66 % TT homozygotes, P<0.001) genes, however, less frequently they are carriers of the *TCF7L2* risky-allele (34 % vs. 48 % of the T allele P<0.0005).

Conclusion

The increased prevalence of T2DM in the Roma population may have a background in different frequencies of the risky alleles of some genes associated with the T2DM development. Analysis of a higher number of genetic polymorphisms, interaction analysis and gene score calculation are the further necessary steps – as some protective alleles seems to be more frequent in the Roma/Gypsy population.

Supported by Ministry of Health of the Czech Republic, grant nr. NV18-01-00046.

Ondřej Šeda

P36: GENETICAL GENOMICS OF METABOLIC SYNDROME IN RECOMBINANT INBRED SET OF RAT MODELS

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Background

The genetically designed set of recombinant inbred rat strains PXO serves as a model of human metabolic syndrome, PXO, in which alleles of two rat models of the metabolic syndrome (SHR and PD inbred strains) segregate together with those from Brown Norway rat strain. We have accumulated so far over 100 directly measured metabolic, morphometric and hemodynamic parameters in the complete set of 16 PXO strains and their progenitors, SHR-*Lx* and BXH 2 rat strains.

Aims

Aim of this study was to analyse the genomic architecture of the metabolic syndrome features in this model set using an integrated genomic, phenomic and transcriptomic approach.

Methods

Total RNA was isolated from liver of adult males of all strains, its integrity was checked by Agilent 2000 BioAnalyzer. The transcriptomic assays were run using Affymetrix® Rat Gene 2.1 ST Array Strip. Using the genomic information of > 20,000 SNPs, we have performed a genetical genomic study and correlated the expression profiles with the phenomic dataset. Resulting data were subjected to systems biology-level analyses using Partek Genomics Suite and Ingenuity Pathways Analysis.

Results

We have identified over 55 transcripts and their respective cis- and trans- eQTLs significantly (FDR < 0.05) distinguishing the PXO strains and at the same time correlated to determinants of metabolic syndrome (including *Echdc2, Tmem14c, Miox and Rarres2*). Integrative analysis revealed several networks likely to drive the main differences in metabolic syndrome aspects in the PXO set with *Il1b, Sirt2, Ppara, Ppargc1b, Atp7b* genes as their major nodes.

Conclusions

Using integrative approach, we have identified major biological networks contributing to the pathophysiology of several aspects of metabolic syndrome in the recombinant inbred model set.

Acknowledgments

Supported by Ministry of Health, Czech Republic RVO VFN64165

Hedvika Tůmová

P37: SCREENING OF GENETIC VARIANTS IN CHILDREN SUSPECTED OF MONOGENIC OBESITY

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Context

Obesity in childhood is a very serious problem because it is a high-risk factor of other diseases, e.g. hypertension, diabetes and dyslipidemia in adulthood. Understanding the genetic causes of obesity may allow individual approach to a patient and development of new therapeutic strategies. Less common monogenic obesity is based on a mutation of one of the genes, which participate on development and function of hypothalamus or are a key regulators of energy homeostasis, food intake and body weight.

Aims

Our aim was to sequence selected genes in children suspected of monogenic obesity.

Methods

In our cohort, there were 29 girls and 20 boys (age 0.4–18 years) with BMI over 97.5 percentile of the relevant age (z-BMI 2.17–6.12) from the Czech Republic. Coding regions of 12 genes including their 3' and 5'-UTR were sequenced using the HaloPlex reagent kit (Agilent). Four genes (MC4R, MC3R, POMC and LEP) were verified by sequencing PCR amplicons using Nextera XT (Illumina). Bioinformatics was performed using SureCall v4.0 (Agilent), MiSeq Reporter v2.6 (Illumina), variant interpretation using the available ClinVar, HGMD public databases, dbSNP and PolyPhen, SIFT, MutationTaster and data retrieval in professional publications.

Results

Three already described missense mutations in MC4R (Ile185Phe, Arg165Trp, Thr112Met) causing the reduction or loss of MC4R function were detected.

Conclusions

The number of causal mutations found corresponds with expected frequency of monogenic forms of obesity. Other variants that have been identified in our cohort will be interpreted after obtaining a sufficient number of patients.

Acknowledgments

Supported by MH CZ - DRO (EÚ, 00023761).

Endrina Mujica

P38: IDENTIFICATION OF ALLELIC VARIANTS IN MC4R AND FTO AND THEIR ASSOCIATION WITH OBESITY IN A VENEZUELAN POPULATION

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Background

Obesity is a multifactorial and polygenic disease and a global public health problem leading to diabetes, hypertension and dyslipidemia.

Aims

The aim of this study was to investigate allelic variants in the *MC4R* and *FTO* genes and their association with obesity-related traits in the Venezuelan population.

Methods

We recruited 95 normal weight individuals (controls, BMI≤ 24,99 kg/m^2) and 195 obese individuals (Ob, BMI≥ 30 kg/m^2). The allelic variants were identified by automated exome sequencing (*MC4R*) and quantified using PCR-ARMS (rs9969309 in *FTO*), respectively.

Results

For *MC4R*, four non-synonymous heterozygous variants were detected in 20 individuals (6.9 %). Variant NM_005912.2:c.307G>A(p.Val103Ile), had a higher minor allele frequency (MAF) in the control group than in the Ob group (0.042 vs. 0.008, *P*=0.003). The second most frequent *MC4R* variant (NM_005912.2:c.44T>C(p.Leu15Pro) was observed exclusively in the Ob group (MAF=0.018). The rare NM_005912.2:c.62A>G(p.Tyr21Cys) and NM_005912.2:c.162G>C(p.Gly55Ala) variants were each detected in a single individual with class II obesity. With the exception of Val103Ile, the identified *MC4R* variants have not been reported earlier. Different prediction tools suggest that p.Gly55Ala might have deleterious effects while results were inconsistent for the other variants, so functional studies are desirable. The *MC4R* variants were not associated with circulating glucose and lipid levels, nor with insulin sensitivity.

For *FTO*, the obesity-associated A allele in rs9939609 showed an ~3x higher frequency in Ob than controls (i.e. 0.38 vs. 0.14, P=1E-4. Recessive (AA>GG+AG), dominant (AA+AG>GG) and additive (AA>AT>TT) models show higher ORs of obesity associated with the A allele (OR[95 %CI]) 10.4[2.1–52.2], 2.7[1.4–5.3] and 2.6 [1.5–4.5], respectively. The rs9939609 A allele was also associated with lower HDL-cholesterol levels after adjusting for BMI, age and sex.

Conclusion

The results show that allelic variants in *MC4R* and *FTO* are also associated with obesity in Venezuela.

Acknowledgments

Human Development Council (CONDES) of Zulia University and The Swedish Heart-Lung Foundation.

Keywords

MC4R, FTO, Obesity, automated sequencing*, PCR-ARMS*

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Andy R. Wood

P39: MISALIGNMENT OF CHRONOTYPE GENETICS AND SLEEP TIMING IS ASSOCIATED WITH OBESITY

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Context

Circadian rhythms are fundamental cyclical processes that occur in humans. These daily cycles affect a wide range of molecular and behavioural processes, such as hormone levels, core body temperature and sleep–wake patterns. There is evidence that alterations to circadian timing are linked to adverse metabolic outcomes, including obesity. Chronotype, often referred to as circadian preference, describes an individual's tendency for earlier or later sleep timing. Recent studies have identified several hundred genetic variants associated with chronotype.

Aims

Using 82,442 unrelated European individuals from the UK Biobank with both genetic- and accelerometer data, we tested whether individuals who's sleep timing was misaligned to their genetic chronotype were more likely to be obese.

Methods

We calculated a standardized genetic score for chronotype using 351 genetic variants from the latest genome-wide association study of chronotype. We calculated the degree of misalignment by deriving the absolute values of the genetic score subtracted from standardized values of sleep timing. This misalignment measure was subsequently tested against body-mass-index (BMI).

Results

We observed higher discordance of circadian timing to be associated higher BMI. For example, the 10 % of individuals with the lowest discordance had an average BMI of 26.5 (SD=4.3), whereas the 10 % of individuals with the highest discordance had an average BMI of 27.0 (SD=4.8). These differences were similar between women (26.0 vs 26.6) and men (27.2 vs 27.6). After adjusting for age, sex and assessment centre, and excluding shift-workers, we observed a 0.04 standard deviation increase in BMI (~0.24 kg/m^2) per standard deviation increase in absolute misalignment (P=7×10^{-14}).

Conclusions

Our initial results provide evidence that sleep misalignment relative to genetic chronotype is associated with raised BMI.

Acknowledgments

This work was conducted using the UK Biobank under application 9072.


11TH MEETING OF EASD STUDY GROUP
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