Svenska Läkaresällskapet

Berzelius symposium 91

Precision Medicine in Type 2 Diabetes and Cardiovascular Disease

31 August–1 September 2016 in Båstad · Sweden

Programme · General information · Lectures abstracts · Poster abstracts

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Precision Medicine in Type 2 Diabetes and Cardiovascular Disease

Purpose statement: Cardiovascular disease (CVD) and type 2 diabetes are devastating and costly diseases whose prevalence is increasing rapidly around the world, projected to exceed billions of people worldwide within the next decades. Although drug and lifestyle interventions are used widely to prevent and treat CVD and diabetes, neither is highly effective; for example, in high risk adults, intensive lifestyle intervention delays the onset of disease by roughly 3-years and with metformin by 18-months compared to placebo control intervention (Knowler et al, Lancet, 2009), with diabetes "prevention" being the exception, rather than the rule.

Moreover, whilst some patients respond very well to therapies, others benefit little or not at all, progressing rapidly through the pre-diabetic phase of beta-cell decline and later developing life-threatening complications such as retinopathy, nephropathy, peripheral neuropathy, and CVD. As such, there is an urgent need to develop innovative and effective prevention and treatment strategies. Human biology is complex and people differ in their genetic and molecular characteristics, which underlies the variable response to interventions and rates of disease progression. Thus, a huge, as yet unrealised opportunity exists to optimize the prevention and treatment of CVD and type 2 diabetes by tailoring therapies to the patient's unique biology. This concept is often termed "precision medicine". This conference will bring together thought-leaders in diabetes precision medicine who will present the state-of-the-science and discuss future prospects.

Description

The aetiology, clinical presentation, and consequences of CVD and type 2 diabetes are highly heterogeneous. Hence, the diseases are likely to represent multiple pathophysiological subclasses, each conveying the common clinical characteristic, such as chronically elevated blood glucose concentrations in diabetes. Efforts to tackle CVD and type 2 diabetes are further hindered because susceptibility to risk factor exposure and response to therapy can vary widely from one person to the next, in part owing to inter-individual biological differences such as genetic and epigenomic variations. Thus, the prevention and treatment of these diseases is likely to require approaches that are tailored to the specific disease subclass and biological characteristics of the patient. Recognizing this, private and public sector entities have made major investments in research programmes focused on the discovery of biomarkers that help optimize prevention and treatment regimes for CVD and type 2 diabetes through disease stratification and personalized therapy; this concept is broadly termed precision medicine. This congress will bring together the world's thought leaders in CVD and type 2 diabetes precision medicine to hear state-of-the-art lectures and to promote national and international research collaborations around this topic. The major themes of the congress will focus on: i) technologies and methods, ii) recent research findings, iii) clinical translation, and iv) future prospects.

Significance

The work leading to genome-guided treatment of monogenic diseases such as congenital obesity, maturity onset diabetes in the young (MODY), partial familial lipodystrophy, and some cancers began almost two decades ago. However, precision medicine in complex diseases is a relatively new concept, with the first major research programmes for CVD and type 2 diabetes launched by the EU as part of the Innovative Medicines Initiative (IMI) in 2010, followed by the Precision Medicines Initiative and the Accelerating Medicines Partnership (AMP) in the US in 2012. Nonetheless, tremendous progress building collaborative networks, developing technologies and methods, and identifying biomarkers and functional mechanisms has been made in this short time. Thus, the timing of this meeting, its content and the opportunities it will afford for building collaborative networks are excellent. Moreover, the meeting will raise the profile of precision medicines research in Sweden at a time when many new national and international collaborative networks are forming with Swedish investigators at their hearts.

Paul Franks
Professor of Genetic Epidemiology

Programme

Wednesday, 31 August 2016

09.00–09.15 Welcome and introduction.
Paul Franks, Lund University Diabetes Center, Sweden

09.15–10.00 Precision medicine: where are we and where are we going?
Leif Groop, Lund University Diabetes Center, Sweden

Chair: **Tim Frayling**, Exeter, UK

10.00–10.45 What industry wants from academic partnerships in precision medicine.
Hartmut Ruetten, Sanofi, Germany

Chair: **Tim Frayling**, Exeter, UK

10.45–11.15 Coffee break (poster session 1)

11.15–12.15 Why national initiatives and global collaborations are needed and how they are taking shape. **Phil Smith**, NIDDK, US

Chair: **Tim Frayling**, Exeter, UK

12.15–13.30 Lunch

13.30–14.15 The genetics of therapeutic response. **Jose Florez**, Harvard, US

Chair: **Maria Gomez**, Malmö, Sweden

14.15–15.00 Is genotype-guided lifestyle therapy on the horizon?
Anna Krook, Karolinska Institutet, Sweden

Chair: **Maria Gomez**, Malmö, Sweden

15.00–15.30 Coffee break (poster session 2)

15.30–16.15 A translational approach to resolve T2D pathogenesis.
Hindrik Mulder, Lund University Diabetes Center, Sweden

Chair: **Guy Rutter**, London, UK

16.15–17.00 From genomics to precision medicine: Uncovering and manipulating the circuitry of non-coding variants. **Manolis Kellis**, MIT, US

Chair: **Guy Rutter**, London, UK

17.00–17.45 Using human genetics and genomics to unravel causal mechanisms for diabetes. **Anna Gloyn**, Oxford, UK

Chair: **Guy Rutter**, London, UK

19.00–22.00 Symposium dinner

Thursday, 1 September 2016

09.00–09.45 Genetics of obesity: Can an old dog teach us new tricks?
Giles Yeo, Cambridge, UK

Chair: **Tove Fall**, Uppsala, Sweden

09.45–10.30 New insights from combining genetics with clinical diabetes.
Andrew Hattersley, Exeter, UK

Chair: **Tove Fall**, Uppsala, Sweden

10.30–11.15 Making precision medicine personal. **Mike Snyder**, Stanford, US

Chair: **Tove Fall**, Uppsala, Sweden

11.15–12.00 Innovation in big data analysis. **Mark McCarthy**, Oxford, UK

Chair: **Tove Fall**, Uppsala, Sweden

12.00–13.00 Lunch

13.00–14.00 Debate: precision medicine will transform patient care for the better:
for: **Ewan Pearson**, University of Dundee, UK
against: **Simon Griffin**, University of Cambridge, UK

Chair: **Nick Timpson**, Bristol, UK

14.00–14.45 Current trends and standards in the genomics of clinical traits and complex diseases. **Myles Axton**, Cheif Editor, Nature Genetics

Chair: **Marju Orho-Melander**, Malmö, Sweden

14.45–15.00 Closing remarks. **Paul Franks**, Lund University Diabetes Center, Sweden

General information

When & Where?

31 August–1 September 2016 at the Congress Hall at Hotel Skansen, Kyrkogatan 2 in Båstad, Sweden.

Lunches and coffee are included in the participation cost and will be served in the on-site restaurant at the Hotel Skansen.

Symposium website

www.sls.se/precisionmedicine/

Speakers' biographies

Paul Franks

Since 2010, Paul has been Professor of Genetic Epidemiology at Lund University Diabetes Center in Sweden, where he leads the *Genetic and Molecular Epidemiology Unit*. He trained at the University of Cambridge in the UK and the *Diabetes Epidemiology and Clinical Research Branch* of National Institutes of Health (NIH) in the US. Paul's research focuses on the interplay of genetic variation, pharmacotherapy and lifestyle in type 2 diabetes and cardiovascular disease. He is also an adjunct professor at Harvard University and the Principal Investigator of a number of national and international collaborative research projects funded by the European Union, NIH, and the Swedish Research Council etc. Paul has authored ~270 papers, delivered ~125 invited lectures, and has an H-index of 58 according to Google Scholar.

Leif Groop

Leif Groop, M.D., Ph.D. is since 1993 Professor in Endocrinology at Lund University, Sweden.

He received his MD at University of Berne, Switzerland and PhD at University of Helsinki, Finland. After a PostDoc period at Yale University he devoted his research to dissection of the heterogeneity of diabetes but also to explore the pathogenic events leading to type 2 diabetes. As an important tool to achieve this goal, he initiated the Botnia Study on the west coast of Finland, one of the world's largest family studies on type 2 diabetes. This has been an invaluable tool in dissecting the phenotypic and genotypic heterogeneity of type 2 diabetes.

His research group has been involved in a number of keynote studies delineating the role of genetic variants for risk of type 2 diabetes. In 2007 they carried out together with international collaborators the first whole genome association study for type 2 diabetes, which by Science was called Breakthrough of the Year. More recently he has adopted a systems biology approach to dissect the functional consequences of such genetic variants. He has served on numerous editorial boards and achieved several international recognitions, including the Claude Bernard, Anders Jahre and Fernströms awards. He is also a Distinguished Professor of the Academy of Finland as well as member of the Swedish Royal Academy of Science.

Hartmut Ruetten

In 2016, Hartmut Ruetten has been appointed as Head of the Translational Medicine Clinical Pharmacology group in the German HUB of sanofi. The primary task of his group is to translate basic research into 'proof of concept' in patients in the area of diabetes, obesity and cardiovascular complications of diabetes.

He is the coordinator of the IMI (Innovative Medicine Initiative of the European Union) consortium DIRECT (DIabetes REsearCh on patient straTification) and co-project leader of RHAPSODY (Assessing risk and progression of pre-diabetes and type 2 diabetes to enable disease modification), which are private-public partnerships between academia and pharmaceutical companies.

Phil Smith

Dr. Smith received his PhD from the University of Virginia, and came to the NIH in 1991.

Dr. Smith is currently Deputy Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases, and Director of the Office of Obesity Research in the National Institute of Diabetes and Digestive and Kidney Diseases. He chairs two Common Fund trans-NIH programs, The Metabolomics Program and the 4D-Nucleome Program. Dr. Smith helped develop and now chairs the Accelerating Medicines Partnership in Type 2 Diabetes. AMP-T2D is an innovative collaboration between NIH and pharmaceutical companies focused on translating genetic discoveries into novel therapeutic targets.

Jose C. Florez

Jose C. Florez, M.D., Ph.D. is the Chief of the Diabetes Unit at the Massachusetts General Hospital, an Associate Professor at Harvard Medical School, and an Institute Member at the Broad Institute.

He and his group have contributed to the performance and analysis of high-throughput genomic studies in type 2 diabetes and related traits, in international consortia such as MAGIC, GENIE, DIAGRAM, T2D-GENES and SIGMA. He leads the genetic research efforts of the Diabetes Prevention Program, and is the Principal Investigator of the Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR-MGH). In addition to his research and teaching duties, he is clinically active, serves on several Editorial Boards and has received numerous professional awards.

Anna Krook

Anna Krook's research focuses on the regulation of skeletal muscle insulin sensitivity at the molecular level. Studies have included exercise effects, which enhance insulin sensitivity as well as obesity and type 2 diabetes, which are characterized by skeletal muscle insulin resistance. The role of different inflammatory factors in this context have also been addressed.

Anna Krook received her Ph.D. from University of Cambridge and then went on to pursue post-doctoral studies at Karolinska Institutet where she is currently Professor at the Department of Physiology and Pharmacology. Anna Krook is currently an Associate Editor of Diabetes and Scientific Secretary of the Swedish Diabetes Association.

Hindrik Mulder

Hindrik is a professor and senior consultant diabetologist, based at Lund University Diabetes Centre in Sweden. He received his MD and PhD from Lund University. His graduate work was devoted to the role of Islet Amyloid Polypeptide in the β-cells, GI tract and sensory nervous system. During a Post Doc period at Gifford Diabetes Center at UT Southwestern, Dallas, Tx, he developed one of the most widely used clonal insulin-secreting cells used in β-cell research. His attention focused on the metabolic control of islet hormone secretion. He unraveled lipolytic pathways in β-cell stimulus-secretion coupling and lipotoxicity. Another novel line of research was the link between neurodegeneration and diabetes – this work elucidated the role of frataxin and huntingtin in β-cell function, proteins responsible for Friedreich's Ataxia and Huntington's disease, respectively.

In the wake of GWAS, his group has devoted its effort to understanding how genetic variants actually cause disease. These efforts have unraveled the role mitochondrial transcription and translation in the pathogenesis of type 2 diabetes. Along similar lines, understanding how a genetic variant in the gene encoding the receptor for melatonin has been a major task for the group in recent years.

Hindrik was awarded the DPLU/LUDC Nordic Prize for an Outstanding Young Diabetes Investigator in 2007. He is the co-ordinator of Metabolic Center at Lund University, and has served on the board of numerous committees and foundations, such as Swedish Diabetes Foundation, Påhlsson Foundation and Swedish Research Council.

Manolis Kellis

Manolis Kellis is a Professor of Computer Science at MIT, an Institute Member of the Broad Institute of MIT and Harvard, and a member of the Computer Science and Artificial Intelligence Lab at MIT where he directs the MIT Computational Biology Group (compbio.mit.edu).

He has helped direct several large-scale genomics projects, including the NIH Common Fund Roadmap Epigenomics project, the comparative analysis of 29 mammals, the human and the Drosophila Encyclopedia of DNA Elements (ENCODE) project, and the Genotype Tissue-Expression (GTEx) project. He received the US Presidential Early Career Award in Science and Engineering (PECASE), the NSF CAREER award, the Alfred P. Sloan Fellowship. He obtained his Ph.D. from MIT, where he received the Sprowls award for the best doctorate thesis in computer science. He lived in Greece and France before moving to the US.

Anna Gloyn

Anna is currently a Wellcome Trust Senior Fellow in Basic Biomedical Science & Professor of Molecular Genetics & Metabolism based jointly at the Oxford Centre for Diabetes Endocrinology and Metabolism (OCDEM) and the Wellcome Trust Centre for Human Genetics (WTCHG) at the University of Oxford.

Anna completed her DPhil at the University of Oxford under the supervision of the late Professor Robert Turner. Her post-doctoral training was carried out at the University of Exeter under the mentorship of Professors Andrew Hattersley & Sian Ellard and at the University of Pennsylvania in Philadelphia under the mentorship of Professor Franz Matschinsky.

Anna's research is focused on using naturally occurring mutations in humans as tools to identity critical regulatory pathways and insights into normal physiology. Anna's early post-doctoral research led to the identification a new genetic aetiology for permanent and transient neonatal diabetes due to *KCNJ11* mutations and resulted in one of the first examples of the determination of the molecular genetic aetiology leading to improved treatment options for patients. Whilst in Oxford Anna's team discovered a novel genetic cause of constitutive insulin sensitivity in humans due to mutations in the *PTEN* gene highlighting the complex interplay between pathways involved in cell-growth and metabolism.

Anna's current research projects are focused on the translation of genetic association signals for type 2 diabetes and glycaemic traits mechanisms for beta-cell dysfunction and diabetes. Her group uses a variety of complementary approaches, including human genetics, genomics, physiology and islet-biology to dissect out the molecular mechanisms driving disease pathogenesis.

Anna's work has been recognized both nationally and internationally as she is a recipient of a European Association for the Study of Diabetes (EASD) Rising Star Award (2005), the RD Lawrence Named Lecturer (Diabetes UK Annual Professional Conference 2009), the GB Morgagni Silver Medal (2014) and the EASD Minkowski Prize (2014).

Giles Yeo

Giles joined Prof Sydney Brenner at the University of Cambridge for his PhD studies. In 1998 he began his post-doctoral training with Prof Sir Stephen O'Rahilly working on the genetics of severe human obesity. He was the first to report that mutations in the melanocortin-4 receptor (MC4R) and in the neurotrophic receptor TRKB resulted in severe human obesity.

In 2007, Giles became Director of the core Genomics facilities and a group leader at the University of Cambridge Metabolic Research Labs. He is interested in studying the brain control of food intake and bodyweight, and how these are dysregulated in obesity.

Andrew Hattersley

Professor Andrew Hattersley FRCP, FMedSci, FRS is the Professor of Molecular Medicine at the University of Exeter.

He has published over 500 papers with > 32000 citations in both molecular and clinical science research.

He has been working on monogenic diabetes since 1989. His work combines clinical observations, cutting edge molecular genetics and in depth clinical and physiological studies. He has described 12 new subtypes of monogenic diabetes and developed diagnostic and treatment approaches for monogenic diabetes that are adopted throughout the world. With Professor Sian Ellard he taken Exeter from a centre without a genetics lab in 1995 to being the top international lab for monogenic diabetes and has had over 7,000 referrals from over 80 countries worldwide. He was appointed as a fellow of The Royal Society in 2010.

Michael Snyder

Michael Snyder is the Stanford Ascherman Professor and Chair of Genetics and the Director of the Center of Genomics and Personalized Medicine.

Dr. Snyder received his Ph.D. training at the California Institute of Technology and carried out postdoctoral training at Stanford University. He is a leader in the field of functional genomics and proteomics, and one of the major participants of the ENCODE project. His laboratory study was the first to perform a large-scale functional genomics project in any organism, and has developed many technologies in genomics and proteomics. These including the development of proteome chips, high resolution tiling arrays for the entire human genome, methods for global mapping of transcription factor binding sites (ChIP-chip now replaced by ChIP-seq), paired end sequencing for mapping of structural variation in eukaryotes, de novo genome sequencing of genomes using high throughput technologies and RNA-Seq. These technologies have been used for characterizing genomes, proteomes and regulatory networks. Seminal findings from the Snyder laboratory include the discovery that much more of the human genome is transcribed and contains regulatory information than was previously appreciated, and a high diversity of transcription factor binding occurs both between and within species. He has also combined different state-of–the-art "omics" technologies to perform the first longitudinal detailed integrative personal omics profile (iPOP) of person and used this to assess disease risk and monitor disease states for personalized medicine. He is a cofounder of several biotechnology companies, including Protometrix (now part of Life Technologies), Affomix (now part of Illumina), Excelix, and Personalis, and he presently serves on the board of a number of companies.

Mark McCarthy

Mark McCarthy is the Robert Turner Professor of Diabetes Medicine at the University of Oxford, based at the Oxford Centre for Diabetes, Endocrinology and Metabolism and the Wellcome Trust Centre for Human Genetics.
Following 8 years at Imperial College, Professor McCarthy moved to Oxford in 2002. He is a physician-scientist and human geneticist, interested in the biological basis of complex disease. His research group is focused on the identification and characterisation of genetic variants influencing risk of type 2 diabetes and related traits, and on using those discoveries to drive biological inference and translational opportunities.

Ewan Pearson

Ewan Pearson is a Professor in Diabetic Medicine at the University of Dundee, UK, and is Honorary Consultant in Diabetes and Endocrinology at Ninewells Hospital and Medical School in Dundee. 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. His research interests are the phenotypic and genotypic determinants of drug response and drug side effects, the aetiology of young-onset diabetes and the mechanisms driving progression of diabetes.

He is the academic lead on the €46M IMI-DIRECT project on stratification in Type 2 diabetes and is Strand 2 lead on the £6M MRC funded MASTERMIND project. Professor Pearson's New Investigator Award funding by the Wellcome Trust aims to gain deeper phenotypic, physiological and molecular insights into the mechanism of action of metformin and other diabetes drugs and how patients respond differently and experience different side effects to these agents.

Simon Griffin

Simon Griffin MBBS MSc DM FRCGP is Professor of General Practice at the University of Cambridge.

He qualified from the London Hospital in 1986 and trained in Clinical Epidemiology and Public Health at the University of Southampton and the London School of Hygiene and Tropical Medicine. He leads a Medical Research Council programme, now in its third quinquennium, which contributes to efforts aimed at preventing the growing burden of diabetes, obesity and related disorders by translating epidemiological knowledge into preventive action, and evaluating the effectiveness of a range of strategies from behaviour change to screening. Away from work Simon plays soccer and surfs.

Myles Axton

Myles Axton is the editor of Nature Genetics.

He was a university lecturer in molecular and cellular biology at the University of Oxford and a Fellow of Balliol College from 1995 to 2003. He obtained his degree in genetics at Cambridge in 1985, and his doctorate at Imperial College in 1990, and between 1990 and 1995 did postdoctoral research at Dundee and at MIT's Whitehead Institute. Myles's research made use of the advanced genetics of Drosophila to study genome stability by examining the roles of cell cycle regulators in life cycle transitions. His interests broadened into human genetics, genomics and systems biology through lecturing and from tutoring biochemists, zoologists and medical students from primary research papers. Helping to establish Oxford's innovative research MSc. in Integrative Biosciences led Myles to realize the importance of the integrative overview of biomedical research. As a full time professional editor he is now in a position to use this perspective to help coordinate research in genetics.

Speakers abstracts

Precision medicin: where are we and where are we going?

Leif Groop, Lund University Diabetes Centre, Malmö, Sweden

In the State of the Union address on January 20, 2015 President Obama conveyed an important message to the scientific community "Tonight I am launching a new precision medicine initiative to bring us closer to curing diseases like cancer and diabetes and to give all of us access to the personalized information we need to keep ourselves and our families heathier". While the cancer field is much more advanced when it comes to precision medicine, the diabetes field has clearly been limping behind. The current classification of diabetes into two main forms is imprecise and poor in predicting disease outcome. Moreover, a diagnosis of diabetes based simply on measuring glucose is too crude. A refined diabetes classification could provide a powerful tool to implement individualized care from diagnosis in the same way as a genetic diagnosis of monogenic forms of diabetes guides clinicians to optimal treatment (1). However, there have been few attempts to provide a better diabetes sub-classification (2). Data mining of patient records have generated new interesting data, but is entirely dependent upon current diagnostic criteria (3). I will here present data from a study where were we have applied information from six quantitative variables measured at diagnosis to a data-driven cluster analysis of three large cohorts (N =19,000) of newly diagnosed diabetic patients (age 0–94 years). By linking this information to data from patient records and national drug prescription registry, it was possible to classify diabetes patients into five subgroups predicting disease progression and development of early diabetic complications more precisely than the current classification. This new classification may help to target early intensified treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

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2. Klonoff D. Precision medicine for managing diabetes. J Diab Science and Technology 9;3-7,2015.

3. Li L et al. Identification of type 2 diabetes subgroups through topological analysis of patient similarity. Sci Transl Med 7, 1–16, 2015.

What industry wants from academic partnerships in precision medicine

Hartmut Ruetten, MD PhD, Sanofi

Pharma industry has been quite successful to develop and market therapeutic offers for common diseases such as hypertension, cardiovascular diseases, cancer, diabetes, to name just a few in recent decades. For example, today 12 different classes of glucose-lowering agents are available on the market for the treatment of type 2 diabetes. However, the phenotype of people who develop type 2 diabetes is highly variable, as is the rate at which their diabetes progresses, how they respond to diabetes therapy and who develops micro- and macrovascular complications. This variable development, progression and treatment response of diabetes is likely to reflect subtypes of diabetes with different pathophysiology. Current practice in diabetes, both clinically and in drug development, is to assume an 'average' response to a diabetes treatment. However, some subgroups of patients do not respond to medication and others have an extreme response or extreme adverse reaction. Pharma industry is well positioned to identify, optimize and develop novel medicines but has limited capabilities, expertise and resources to reveal the fundamental mechanisms underlying complex and heterogeneous diseases such as diabetes. In contrast, in academia there is very specialized knowledge, technical expertise in the forefront of science and access to cohorts from epidemiological, non-interventional studies. Thus, combining the strength of academia and industry increases the chance of success in precision medicine.

The genetics of therapeutic response

Jose C. Florez, M.D., Ph.D., Massachusetts General Hospital

In recent years technological and analytical advances have led to an explosion in the discovery of genetic loci associated with type 2 diabetes. However, their ability to improve prediction of disease outcomes beyond standard clinical risk factors has been limited (1). On the other hand, genetic effects on drug response may be stronger than those commonly seen for disease incidence. Pharmacogenetic findings may help to uncover new drug targets, illuminate pathophysiology, clarify disease heterogeneity, aid in the fine-mapping of genetic associations, and contribute to personalized or precision treatment (2). In diabetes, precedent for the successful application of pharmacogenetic concepts exists in monogenic forms of the disease, such as maturity onset diabetes of the young or neonatal diabetes (3). Whether similar insights will be produced for the common form of type 2 diabetes remains to be seen. With recent advances in genetic approaches, the successive application of candidate gene studies, large-scale genotyping studies and genome-wide association studies (4) has started to generate suggestive results that may lead to changes in clinical practice (5). However, many potential barriers to the translation of pharmacogenetic discoveries to the clinical management of diabetes still remain. In this presentation, we will offer a contemporary overview of the field in its current state, identify potential obstacles, and highlight future directions.

References

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2. Zhou K, Pedersen HK, Dawed AY, Pearson ER: Pharmacogenomics in diabetes mellitus: insights into drug action and drug discovery. Nat Rev Endocrinol 2016;12:337–346

3. Greeley SA, Naylor RN, Philipson LH, Bell GI: Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment. Curr Diab Rep 2011;11:519–532

4. Zhou K, Bellenguez C, Spencer CC, Bennett AJ, Coleman RL, Tavendale R, Hawley SA, Donnelly LA, Schofield C, Groves CJ, Burch L, Carr F, Strange A, Freeman C, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Dronov S, Duncanson A, Edkins S, Gray E, Hunt S, Jankowski J, Langford C, Markus HS, Mathew CG, Plomin R, Rautanen A, Sawcer SJ, Samani NJ, Trembath R, Viswanathan AC, Wood NW, Harries LW, Hattersley AT, Doney AS, Colhoun H, Morris AD, Sutherland C, Hardie DG, Peltonen L, McCarthy MI, Holman RR, Palmer CN, Donnelly P, Pearson ER: Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. Nat Genet 2011;43:117–120

5. Manolopoulos VG, Ragia G, Tavridou A: Pharmacogenomics of oral antidiabetic medications: current data and pharmacoepigenomic perspective. Pharmacogenomics 2011;12:1161–1191

Learning objectives

1. To understand the potential and limitations of genetic information in the prediction of drug response

2. To assimilate the cases where pharmacogenetic data influences treatment decisions in monogenic forms of diabetes

3. To obtain a contemporary view of the state of the field in the pharmacogenetics of type 2 diabetes

Is genotype-guided lifestyle therapy on the horizon?

Anna Krook, Department of Physiology and Pharmacology,
Karolinska Institutet

Daily physical activity remains an effective strategy to prevent obesity and type 2 diabetes. Skeletal muscle is an insulin-responsive organ and the primary site for post-prandial glucose disposal. Skeletal muscle insulin resistance, leading to a reduction in insulin-stimulated glucose disposal, is often an early defect contributing to the development of type 2 diabetes. Physical exercise has a profound effect on muscle insulin-sensitivity and impacts on whole-body metabolism.
Not all people respond in the same way, or with the same magnitude, to a given exercise intervention, and a proportion of people have disappointing clinical outcomes even when the exercise appears to have been adequately performed. Careful analysis of the exercise response at a molecular level in high- as well as low-responders will give insights into the relative roles of different exercise-activated molecular pathways, and may be able to inform personalised exercise-intervention programs to ensure maximum benefits.

Key Learning Points
- Skeletal muscle insulin-sensitivity as a modifiable risk factor to metabolic disease
- Effect of physical exercise
- Differential response to exercise interventions

Suggested reading1–4

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A translational approach to resolve T2D pathogenesis

Hindrik Mulder, Lund University

Type 2 Diabetes (T2D) is a polygenic disease. Genome-wide association studies have identified > 100 genetic variants associated with T2D but the mechanisms whereby they cause disease have rarely been defined. I will describe a translational study of one such risk gene encoding the melatonin receptor 1 B *(MTNR1B)*. It employed a recruit-by-genotype study, human islets, insulin-producing cells and knock out mice.

Such an approach may be useful in future studies of risk variants to either better understand disease mechanisms or find/evaluate drug targets.

- The rs10830963 variant of *MTNR1B* confers increased expression, i.e., it is an expression quantitative trait locus (eQTL)
- The resulting increase in melatonin signaling inhibits insulin release due to lower levels of cAMP
- Conversely, MTNR1B knock out mice release more insulin
- Administering melatonin to risk variant carriers has a stronger negative effect on glucose and insulin levels

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From genomics to precision medicine: Uncovering and manipulating the circuitry of non-coding variants

Manolis Kellis, Ph.D., Professor, MIT Computer Science and Artificial Intelligence Lab, Institute Member, Broad Institute of MIT and Harvard

Perhaps the greatest surprise of human genome-wide association studies (GWAS) is that 90% of disease-associated regions do not affect proteins directly, but instead lie in non-coding regions with putative gene-regulatory roles. This has increased the urgency of understanding the non-coding genome, as a key component of understanding human disease. To address this challenge, we generated maps of genomic control elements across 127 primary human tissues and cell types, and tissue-specific regulatory networks linking these elements to their target genes and their regulators. We have used these maps and circuits to understand how human genetic variation contributes to disease and cancer, providing an unbiased view of disease genetics and sometimes re-shaping our understanding of common disorders. For example, we find evidence that genetic variants contributing to Alzheimer's disease act primarily through immune processes, rather than neuronal processes. We also find that the strongest genetic association with obesity acts via a master switch controlling energy storage vs. energy dissipation in our adipocytes, rather than through the control of appetite in the brain. We have shown that we can manipulate these circuits by genome editing or gene targeting in human cells and in mice, indicating tissue-autonomous therapeutic avenues can alter metabolism. In addition to dissecting known disease-associated regions, we have combined genetic information with regulatory annotations and with epigenetic variation to discover new disease regions in cardiovascular disease, Alzheimer's disease, and prostate cancer. These results span the spectrum of common, rare, and somatic variants, and illustrate the power and broad applicability of regulatory annotations and circuits for understanding human disease and cancer.

Using human genetics and genomics to unravel causal mechanisms for diabetes

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Over the past decade, common variant genome wide association studies (GWAS) have emerged as the dominant strategy for human genetics discovery. In terms of locus detection this approach has proved extremely effective with hundreds of loci identified which influence type 2 diabetes risk and glycaemic traits. Each of these loci has the potential to reveal novel insights into biology, and to underpin future translational advances. However several of the characteristics of these loci – in particular the modest effect size of most common variant risk-loci, and their predilection for regulatory sequence – have served as an obstacle to efforts to connect each of these signals to the gene through which the effect on diabetes risk is mediated, the so called "effector transcript" and thereby access knowledge and functional approaches which are generally focused on transcript biology. Recent developments in high throughput genomics has provided strategies for data generation and integration which now offer highly-efficient approaches for connecting the risk-variants and haplotypes revealed by common variant GWAS studies, to their effector transcripts. These include sequence-based quantification of RNA expression in human pancreatic islets and exome sequence and exome variant genotyping studies which enable the identification of disease-associated coding variants which provide signposts to the effector transcript and clues to the direction of effect. This presentation will focus on recent efforts to use a variety of these approaches to unlock the biology at GWAS signals for type 2 diabetes.

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Genetics of obesity: Can an old dog teach us new tricks?

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It is clear that the cause of obesity is a result of eating more than you burn. What is more complex to answer is why some people eat more than others? Over the past 20 years, insights from human and mouse genetics have illuminated multiple pathways within the brain that play a key role in the control of food intake. We now know that the brain leptin-melanocortin pathway is central to mammalian food intake control, with genetic disruption resulting in extreme obesity. These, however, remain rare, with the major burden of disease carried by those of us with 'common obesity'. In recent years, genome-wide association studies have revealed more than 100 different candidate genes linked to BMI, with most, including many components of the melanocortin pathway, acting in the CNS and influencing food intake. So while severe disruption of the melanocortin pathway results in severe obesity, subtle variations in these same genes influence where you might sit in the normal distribution of BMI. As we now enter this 'post-genomics' world, can this new information influence our treatment and management of obese patients?

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New insights from combining genetics with clinical diabetes

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Background

There have been considerable advances in defining the molecular genetic aetiology of monogenic diabetes. Finding a new genetic subtype gives new insight into the underlying aetiology and pathophysiology and so is scientifically important. In addition, we have shown for maturity-onset diabetes of the young (MODY) and neonatal diabetes the specific genetic aetiology has a profound impact on treatment and clinical management and is clinically important. This is most dramatically shown by the way C peptide negative patients with neonatal diabetes due to a mutation in the beta-cell potassium channel can achieve excellent glycaemic control on high dose sulphonylurea therapy. The rapid adoption of molecular genetic testing in neonatal diabetes was greatly helped by the simply applied clinical definition of all cases of diabetes diagnosed before 6 months. In MODY, despite a clear impact of a genetic diagnosis on therapeutic response, most cases are misdiagnosed as Type 1 or Type 2 diabetes mainly because there is no single, simple, clinical criteria to identify cases.

Recent advances

Next generation sequencing has led to rapid gene discovery in genes not previously known to be candidate genes – resulting in novel scientific insights

The main recent advances in clinical care have been the implementation of molecular genetics into clinical practice outside specialist centres and monogenic diabetes experts. Universal, systematic antibody testing as performed in Sweden paediatric practice results in rapid accurate testing of monogenic diabetes and may offer the rest of the world a model for how to get the diagnosis right soon after diagnosis. In Exeter we recently introduced a Type 1 diabetes genetic risk score that can help to make or exclude a diagnosis of Type 1 diabetes. The challenge of appropriately integrating molecular genetics into routine care is at least as important as gene discovery if most patients are to benefit from the clinical insights that arise from a diagnosis of monogenic diabetes.

Making precision medicine personal

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Understanding health and disease requires a detailed analysis of both our DNA and the molecular events that determine human physiology. We performed an integrated Personal Omics Profiling (iPOP) of 100 healthy and prediabetic human subjects over three years including periods of viral infection as well as during controlled weight gain and loss. Our iPOP integrates multiomics information from the host (genomics, epigenomics, transcriptomics, proteomics and metabolomics) and from the gut microbiome. Longitudinal multiomics profiling reveals extensive dynamic biomolecular changes occur during times of perturbation, and the different perturbations have distinct effects on different biological pathways. Overall, our results demonstrate a global and system-wide level of biochemical and cellular changes occur during environment exposures and omics profiling can be used to manage health.

Innovation in big data analysis

Mark McCarthy, Oxford Centre for Diabetes, Endocrinology & Metabolism

The growing prevalence of type 2 diabetes highlights the limitations of available preventative options, and high rates of diabetes complications attest to the inadequacies of current treatments. Novel therapeutic strategies need to be informed by a more complete understanding of the molecular and physiological basis of disease, delivering validated interventional targets and biomarkers to define disease risk, progression, and subtype. My group, working within large global consortia, uses human genetics to deliver this understanding. Growing availability of exome sequence and array data now delivers coding variant associations that can plug directly into functional studies. However, the main repository of variant association for T2D remains ~100 common variant signals uncovered by GWAS, most of which map outside coding sequence. We are implementing a multifaceted approach that combines genome-scale and focused functional studies to unlock the biology within these loci.

We use fine-mapping to improve localisation of causal variants, and map these onto regulatory annotations from key tissues, most notably the human islet. This provides a platform for identifying downstream transcripts through tissue-specific cis-eQTL analyses and conformational capture. We combine these "regulatory variant" data with transcript level information to define the best-supported transcripts in each GWAS region. Finally, we connect loci through analyses of protein-protein interaction, co-expression and pathway data. These efforts are starting to bear fruit, with around one-third of GWAS signals now featuring a well-supported priority transcript. We follow up these priority candidates through cellular, molecular, rodent and human studies to consolidate mechanistic evidence. To build engagement, we are co-developing, via the Accelerating Medicines Partnership, a dedicated T2D knowledge portal that facilitates access to these data for the wider research community.

We are also interested in the ways in which the integration of multiple omics data types ("holistomics") may provide a route from biological understanding to translational opportunities, for example through the identification of complex dynamic biomarkers of disease progression and mechanistic stratification. We are pursuing these efforts in the context of several large-scale international consortia including DIRECT, RHAPSODY, BEAT-DKD and MultiMUTHER.

Debate:
Precision medicine will transform patient care for the better

For the motion.

Ewan Pearson, University of Dundee, UK

Precision medicine – what's not to like? This conceptually broad approach to medicine aims to use information about the individual to be more precise about how we treat our patients. To some extent this is just the practice of medicine, but the developments in our ability to phenotype individuals enables the incorporation of the molecular signature of disease – be it from blood or a diseased tissue. There can be no doubt that precision medicine will transform patient care – it already has in the field of cancer therapy and for the avoidance of some extreme drug reactions. In diabetes, it is also clear that there have been transformative discoveries that enable 'precise' treatment choice in monogenic diabetes. The challenge is how we apply precision medicine in the complex heterogeneous disease that is Type 2 diabetes. Here I will argue that we have started to dissect the aetiology of this condition and identify how different strata have different diabetes trajectories, and that we are identifying clinically and genetically defined subgroups who respond differently to common diabetes treatments. It will not be too long before we begin to incorporate these approaches into clinical care.

Debate:
Precision medicine will transform patient care for the better

Against the motion.

Simon Griffin, University of Cambridge, UK

Enabled by scientific vision, technological advances and worldwide collaborations, the increase in our understanding of the genetic architecture of common chronic conditions has been remarkable. However, translation of this knowledge into improvements in routine clinical practice and prediction, prevention and management of disease has been limited and fallen considerably short of expectations. I will argue that this was foreseeable and is unlikely to change in the near future.

Genes add little predictive utility to simple models incorporating routinely available data, in spite of estimates of performance of genetic scores being biased due to the spectrum effect.

Diseases like diabetes are defined by somewhat arbitrary biomarker thresholds. Biomarker levels are influenced by diverse pathophysiological mechanisms and interactions between numerous genes and environmental exposures. The genes have not changed for generations. The key mutable determinants informing preventive efforts are behavioural.

The use of genes to predict effects of treatment is based on the flawed assumptions that we know how the drugs exert their pleiotropic effects and that molecules predict medication adherence. The expectation that genetic information would influence behaviours has been shown to be unrealistic in several trials.

The primacy of the positivist medical/pharmaceutical narrative has reinforced the erroneous belief that the solution to diabetes lies solely in tailored interventions for individuals. It has also deflected attention and resources, both health service and research, away from alternative paradigms such as public health and societal approaches targeting the wider collective determinants of disease and shifting their distributions in populations.

Current trends and standards in the genomics of clinical traits and complex diseases

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Genomic analysis of the basis for complex diseases has moved into a new phase recently as it becomes possible to conduct genome wide screens in populations of African ancestry with different exposures, shorter regions of linkage disequilibrium and enriched for heterogeneous rarer variants. The expectation that most GWAS SNPs associated with disease risk will correlate with expression quantitative traits in relevant tissues may only rarely be confirmed, suggesting there is much new genome biology for us to discover. At best, systems models of the mechanisms of trait associated genetic variation will require integration of genetic epidemiology, annotation, chromatin and RNA expression data. I will also discuss various methods current association data can be analyzed for causal inference between pairs of traits. Some of these lead to conflicting conclusions about the roles of clinical traits such as serum triglycerides and lipoproteins in diabetes and cardiovascular disease. Participants at this meeting have an important role in setting strategic priorities and standards for the journal in this field.

Poster abstracts

A Prospective Study of Dietary and Supplemental Zinc Intake and Risk of Type 2 Diabetes Depending on Genetic Variation in SLC30A8

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Funding sources: VR, ERC, HLF, NNF, SDF, PF, LF

Aims/hypothesis
The solute carrier family 30 member 8 gene *(SLC30A8)* encodes a zinc transporter in the beta cell and individuals with the major C-allele of the missense variant (rs13266634; C/T; R325W) in *SLC30A8* demonstrate a decreased early insulin response to glucose and an increased risk of type 2 diabetes (T2D). While data from human studies are scarce, high zinc intake has been associated with a decreased risk of T2D. We hypothesized that the association between zinc intake and T2D may differ by *SLC30A8* rs13266634 genotype.

Methods
We carried out a prospective study among subjects with no history of diabetes or cardiovascular disease in the population-based Malmö Diet and Cancer Study cohort (N=26,132, 38% men; 85.8 % with genotype data). Dietary zinc intake was assessed using a diet history method combining a diet questionnaire with a 7-day food record. During a median follow-up of 19 years 3,676 T2D cases occurred. A BMI-stratified Cox proportional hazards regression model with attained age as the time-scale was used to model the association between total and dietary zinc intake, zinc supplement use, zinc:iron ratio, and risk of T2D with adjustment for both dietary and non-dietary factors. Interactions with BMI and *SLC30A8* genotype were tested.

Results
The median total zinc intake was 11.4 mg/day (interquartile range 9.2–14.7) and the median dietary zinc intake was 10.7 mg/day (interquartile range 8.8-12.9). Zinc supplement users (17%) had a median total zinc intake of 22.4 mg/day (interquartile range 17.1–25.5). Total zinc intake was non-linearly associated with T2D risk, and dietary zinc associated with increased risk of T2D (P trend <0.0001). In contrast, we observed a lower risk of T2D among zinc supplement users (HR=0.79, 95% CI: 0.70–0.89). The *SLC30A8* CC-genotype was associated with a higher risk of T2D (HR=1.16, 95% CI: 1.07–1.24), and the effect was stronger among subjects with higher BMI (P interaction = 0.007). We observed no significant modification of the zinc-T2D association by *SLC30A8* genotype. However, a three-way interaction between *SLC30A8* genotype, BMI, and zinc:iron ratio was observed (P interaction = 0.007). A high zinc:iron ratio conferred a protective effect on T2D risk among obese subjects, and the effect was more pronounced among T-allele carriers.

Conclusions
Zinc supplementation may lower risk of T2D and a high zinc:iron intake ratio may lower risk of T2D in a *SLC30A8* genotype-specific way among subjects with high BMI.

Proteomic profiling and development of heart failure

Precision Medicine in Type 2 Diabetes and Cardiovascular Disease

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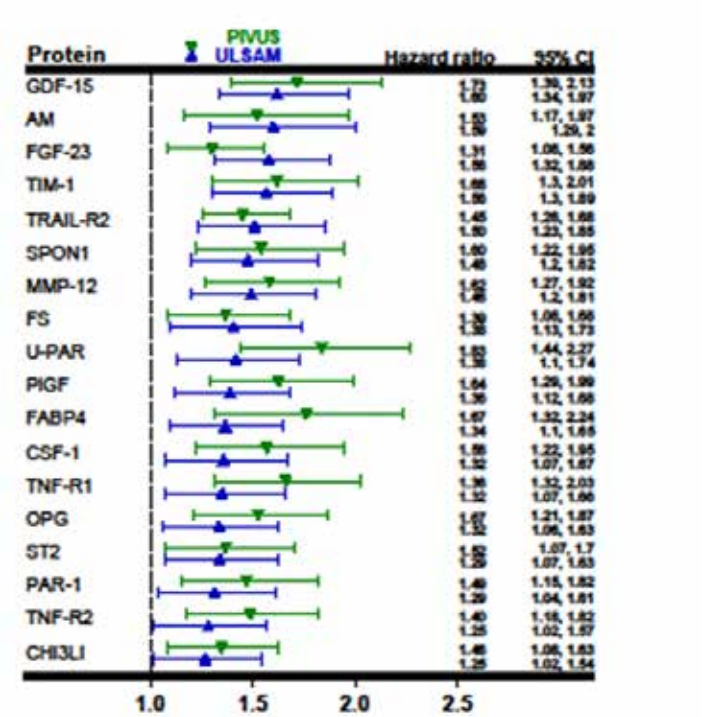
Emerging technologies have made it possible to simultaneously measure a large number of circulating proteins. The utility of this approach to identify novel heart failure biomarkers has not been reported.

We explored and validated associations between 92 plasma proteins, assessed by a proximity extension assay (Proseek Multiplex CVD, OLINK Bioscience), and the risk of heart failure in two independent community based cohorts; Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS; women 50%, n=904; median age, 70 years; 80 heart failure events during 10 years follow-up), and Uppsala Longitudinal Study of Adult Men (ULSAM; n=685; median age 78 years; 90 heart failure events during 8 years follow-up).

In PIVUS, 30 proteins were significantly associated with heart failure incidence in age and sex-adjusted cox proportional hazard models after taking into account the multiple testing using a false discovery rate of 5%. The association between 18 of these proteins and heart failure incidence were replicated in ULSAM at nominal p-values (figure). When adjusting for established cardiovascular disease risk factors nine of these remained significantly associated with incident heart failure.

Using a state-of-the-art proteomics chip, several novel independent heart failure risk markers were discovered and replicated in two independent cohorts. Our data suggest that large scale proteomic analyses is a promising way of discovering new and relevant heart failure risk markers.

Figure. Proteins and heart failure risk.



Data are hazard ratio (HR) adjusted for age and gender expressed per standard deviation increase of protein levels.

Stig Cronberg, M.D., Docent in practical medicine 1968, University of Lund, Malmö Hospital

Case history: I myself like my father and two brothers have diabetes type 2. I developed it in the United Arab Emirates in 1995. Detected after my return. Every year I worked 6 weeks in the bush in rural Kenya, living the same simple life as the indigenes. Buying food at the marked once a week: Fruit, vegetables, bread, egg and drinking water. I decided to live the simple African way in Sweden: Drinking only water, eating no sugar, much exercise.

Results: Gradually my bodyweight decreased with 1–2 kg every year from 90 kg back to 73 kg now. My abdominal circumference decreased from 104 cm to 88 cm now. My blood pressure decreased from 180/105 to 135/60. My blood glucose was normalized but has come back as has my glucose in the urine.

Discussion: I have not taken any single tablet for years. Always feeling well. I have had diabetes for 22 years without taking any medicine I will soon be 82 years old.

Interaction between genes and macronutrient intake on the risk of deve-loping type 2 diabetes: systematic review and findings from EPIC-InterAct

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Background: Gene-diet interactions have been reported to contribute to the development of type 2 diabetes (T2D). However, to date, few examples have been consistently replicated.

Objective: To identify existing evidence for gene-macronutrient interactions and T2D, and to examine the reported interactions in a large-scale study (EPIC-InterAct).

Design: We systematically reviewed studies reporting gene-macronutrient interactions and T2D that were identified using electronic databases including MEDLINE, HuGE-Net and the WHO clinical trials registry (to October 2015). Studies including macronutrient quantity (e.g. percentage of total energy intake from carbohydrate) or indicators of quality (e.g. dietary fibre) were eligible. Additionally both self-report and objective biomarkers of intake were eligible. Identified interactions from the review were subsequently examined in the EPIC-InterAct case-cohort study (n=15,652 with 6,902 cases; 7 European countries). Prentice-weighted Cox regression was used to estimate country-specific HRs, 95%CI and p for interaction, which were then pooled by random effects meta-analysis. A primary model was fitted using the same covariates as reported in the published study, and a second model adjusted for additional covariates alongside estimating effects of isocaloric macronutrient substitution.

Results: Thirteen observational studies were reviewed (n<1,700 cases). Eight unique interactions were reported to be significant between macronutrients (carbohydrate, fat, saturated fat, dietary fibre, and glycemic load derived from self-report of dietary intake and circulating n-3 polyunsaturated fatty acids) and genetic variants in or near *TCF7L2, GIPR, CAV2* and *PEPD* (p for interaction <0.05). In an analysis in EPIC-InterAct which duplicated the models from previous studies reporting these interactions, we found no evidence of interaction (p for interaction ≥0.23). Additionally, no interactions were detected when further adjusted for potential confounders and isocaloric macronutrient substitutions performed.

Conclusion: Findings from previous studies were not confirmed in EPIC-InterAct. There is currently no convincing evidence for interaction between macronutrient intake and selected genes in the development of T2D. This highlights the importance of independent replication in identifying gene-diet interactions.

Metabolite trajectories during an oral glucose challenge reveal new associations with clamp-measured insulin sensitivity

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Impaired insulin sensitivity (IS) – i.e. insulin resistance – predisposes to the development of type 2 diabetes and cardiovascular disease. Metabolic challenges like an oral glucose tolerance test (OGTT) can uncover early pathogenic mechanisms in healthy individuals. Our aim was to discover metabolite profiles during an OGTT that are associated with clamp-measured IS and to explore the causality.

In 470 non-diabetic men (age 70.6 ± 0.6 years), we studied 192 metabolites identified by untargeted liquid chromatography/mass spectrometry metabolomics analysis of plasma samples taken at 0, 30, and 120 min during an OGTT. The outcome was IS measured by the hyperinsulinemic-euglycemic clamp method. Linear regression adjusted for age and sample quality identified 35 metabolites associated with IS at any time point, of which 9 showed significant associations between the rates of change from 0–30 min and 30–120 min and IS. Two medium-chain acylcarnitines had the strongest trajectory associations. In bidirectional Mendelian Randomization (MR) analysis using a validated IS genetic risk score and findings from our own genome wide association study of metabolite levels (n = 3,624) as instrumental variables, we found a trend ($P < 0.1$) for a positive causal effect of impaired IS on rising C10-carnitine levels during the OGTT. No evidence for a causal effect of acylcarnitine levels on IS was found, but the statistical power was limited and MR analysis was based on fasting levels rather than trajectories. Unsupervised cluster analysis separated metabolites into different OGTT profiles that corresponded to metabolites' chemical classes.

In summary, based on a large community sample with gold standard measurement for IS, untargeted metabolomics profiling during an OGTT revealed new associations between changes in medium-chain acylcarnitine levels and IS. *In vitro* studies are planned for validation and biological insights.

Dog ownership and the risk of cardiovascular disease: a nationwide cohort study

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Background
Conflicting results surround the effect of pet ownership on human health. We aimed to investigate the association of dog ownership with cardiovascular disease (CVD) and mortality in a nation-wide prospective cohort.

Methods
All Swedish residents aged 40–80 years on January 1st, 2001 were identified through the Register of the Total Population and record linkage to other national registers for information on dog ownership, hospital admissions, socio-economic status and death performed. Individuals with previous CVD hospitalization were excluded. Outcomes included ischemic and hemorrhagic stroke, acute myocardial infarction, heart failure, CVD and CVD-specific and all-cause mortality and were assessed up to December 31st 2012. Multivariable-adjusted Cox proportional hazard models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI).

Results
Of the 3 357 244 eligible individuals, 162 091 (4.8%) were registered dog owners. In both single and multiple person households, dog ownership was associated with lower cardiovascular mortality (HR 0.61 [95 % CI, 0.54 to 0.69] and 0.85 [0.80 to 0.90)]), and all-cause mortality (HR 0.65 [0.62 to 0.68] and HR 0.80 [0.86 to 0.90]). Dog ownership was inversely associated with incident ischemic stroke (HR 0.80 [0.82 to 0.96]), myocardial infarction (HR 0.90 [0.84 to 0.96]) and composite CVD risk (HR 0.91 [0.87 to 0.95] in single-occupancy households.

Conclusion
In this large prospective study, dog ownership was associated with decreased all-cause mortality and mortality from CVD. This effect was larger in single occupancy households. In single occupancy households, dog ownership was also associated with lower risk of incident myocardial infarction and ischemic stroke.

Using genome editing to identify and characterise functional variants that determine response to metformin

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Genetic variation between individuals is likely to account for some of the observed heterogeneity in the glucose lowering effect of metformin. Several pharmacogenetics studies have identified that the minor allele at rs2289669 in intron 10 of the *SLC47A1* gene, which codes for the metformin transporter multidrug and toxin extrusion 1 (MATE1), is associated with a greater reduction in HbA1c levels. However, it is currently not known if rs2289669 is itself causal or how the functional variant operates at the molecular level. To address these questions we have combined *in silico* analysis with *in vitro* genome engineering using the CRISPR-Cas9 system.
Functional annotation of those SNPs in tight LD with rs2289669 using the UCSC genome browser identified rs8065082 in intron 12 of *SLC47A1* as the top ranking functional candidate. Sanger sequencing of the regions of *SLC47A1* containing rs2289669 and rs8065082 confirmed that no preexisting mutations were present in the Huh-7 human hepatocyte cell line. With this information, two gRNAs per SNP target were designed, cloned into a Cas9 plasmid vector and optimised for high transfection efficiency in Huh-7. To test both the gRNA targeting capacity and to generate *SLC47A1*/MATE1 KO cells for pre-testing of functional interaction with metformin, paired gRNAs were used to excise a ~2kbp region. This included exons 11 and 12 resulting in ~60% reduction in *SLC47A1*/MATE1 mRNA expression in a heterogeneous population of transfected cells. Clonal cell populations of *SLC47A1*/MATE KO cells were generated and metformin-dependent inhibition of glucagon-induced glucose output and gluconeogenic enzyme expression were compared to WT cells. Using these validated gRNAs, independent Huh-7 clonal cell populations homozygous and heterozygous for the minor allele at rs2289669 or rs8065082 will be generated for functional analysis in the next phase of this work.

Glycaemic control before and after the onset of type 2 diabetes: A description of the baseline data from the epidemiological cohorts within the IMI DIRECT Consortium

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Background and aims: Disentangling the heterogeneous aetiology, clinical presentation and prognosis of type 2 diabetes and optimizing treatment might be facilitated by using biomarkers to characterise risk factor susceptibility and treatment response. The DIRECT (Diabetes Research on Patient Stratification) Study is a European Union (EU) Innovative Medicines Initiative (IMI) project that seeks to test these hypotheses in two recently established epidemiological cohorts; here we describe the baseline characteristics of these cohorts.

Materials and methods: From a sampling frame of 24,196 participants from European population-based cohorts with detailed health information, 2281 participants at risk of glycaemic deterioration were identified using a risk prediction algorithm and enrolled into a prospective cohort study undertaken at four study centres across Europe (Cohort 1). Using ADA-2011 glycaemic categories, 22% (n=490) were healthy, 24% (n=545) had isolated impaired A1c (iIA1c), 16% (n=369) had isolated impaired fasting glucose (iIFG), 2% (n=38) had isolated impaired glucose tolerance (iIGT), and 36% (n=805) had combined impaired glucose control of more than one impairment (cIGC). We also recruited 804 participants with newly diagnosed T2D (Cohort 2) at six study centres across Europe, of whom 66% (n=527) were lifestyle treated (LS) and 34% (n=277) were metformin + lifestyle treated (Met+LS), from general practice and other registries. Beta-cell function and glycaemic control were modelled from frequently sampled 75g oral glucose tolerance and mixed meal tolerance tests in the two cohorts respectively.
Body composition was assessed using MRI and lifestyle through self-report and triaxial accelerometry. Both cohorts also include measures that are not presented here. These include genomic, transcriptomic, proteomic, metabolomic and faecal microbiome assessments.

Results: Statistics are presented as mean±SEM, *P*-values are shown to illustrate differences by glycaemic/treatment strata within cohort. Cohort 1 (prediabetes); 76% of participants were male, age 62±0.1 years. Age, sex and centre adjusted means were: BMI = 28.7±0.2 kg/m^2 ($P<1.6\times10^{-21}$); fasting glucose was 5.5±0.02 mmol/l ($P<2.5\times10^{-295}$); glucose sensitivity was 112±2 pmol/min/m2/mM (P=9.8×10-15); oral glucose insulin sensitivity was 381±2 ml/min/m^2 ($P=6.6\times10^{-165}$); and liver fat was 5.6±0.6 percent ($P=1.9\times10^{-6}$). Cohort 2 (diabetes); Age, sex and centre adjusted means for: BMI was 30.4 ±0.2 kg/m^2 (P =0.4); fasting glucose was 7.1±0.06 mmol/l (P =0.012); glucose sensitivity was 81±3 pmol/min/m^2/mM (P=0.004); oral glucose insulin sensitivity was 300±3 ml/min/m2 (P =0.09); and liver fat was 8.5±0.3 percent ($P=9.8\times10^{-4}$).

Conclusion: These baseline characteristics provide an insight to the heterogeneous pathophysiology within established stratifications of prediabetes and diabetes. The epidemiological cohorts within DIRECT represent one of the most intensively characterised prospective studies of glycaemic deterioration to date designed for stratification of diabetes for improved treatment and prevention.

Who was Berzelius?

Jöns Jacob Berzelius, one of the most prominent natural scientists of the 19th century, was born in 1779 in Väversunda, in the county of Östergötland in southern Sweden, a region with rich cultural traditions.
Orphaned at an early age, he went to several foster-homes and received his schooling in nearby Linköping. After graduating in medicine at the University of Uppsala, he moved to Stockholm, where he became assistent master without pay at the so-called »Surgical School«, and earned his keep by working as a doctor for poor people. At the age of 28 he became professor of medicine and pharmacy.

In 1808 Berzelius was one of the seven men who founded The Swedish Society of Medicine »For the perfection of science through mutual mediation of knowledge and collective experience, for the promotion of friendly confidence between doctors«.

Berzelius have enriched our knowledge of nature of life phenomena, established the atomic weights of most of the known elements, presented his electrochemical theory for the understanding of the nature of chemical compounds and laid the foundation for the sciences of the chemistry of rock types. He also found that elements combine with each other according to fixed numerical relationships. In addition to this, in his striving for order and method, with his talent for simplicity and clarity in expression, he created the chemical symbolic language in 1813, which since that time has been an essential instrument of chemistry.
With time he became a practised lecturer but preferred to express himself in writing and this he did superbly. Impressive are the great scientific works where he also demonstrated his interest and ability to spread knowledge about the latest advances of natural sciences.

Berzelius delight in research and debate was united with a great humility before the great scientific questions. Both his attitude and artistery of formulation is illustrated by the following passage in his Manual of Cheamistry (vol 3, 1818):

»All our theory is but a means of conistently conceptualizing the inward processes of phenomena, and it is presumable and adequate when all scientifically known facts can be deduced from it. This mode of conceptualization can equally well be false and, unfortunately, presumable is so frequently. Even though, at a certain period in the development of science, it may match the purpose just as well as a true theory. Experience is augmented, facts appear which do not agree with it, and one is forced to go in search of a new mode of conceptualization within which these facts can also be accomodated; and in this manner, no doubt, modes of conceptualization will be altered from age to age, as experience if broadened, and the complete truth may perhaps never be attained. But even if the goal can never be reached, let us never abondon our endeavor to get closer to it.«

Parts of this text is found in: Berzelius – Creator of the chemical language, by Carl Gustaf Bernhard, the Royal Swedish Academy of Sciences

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