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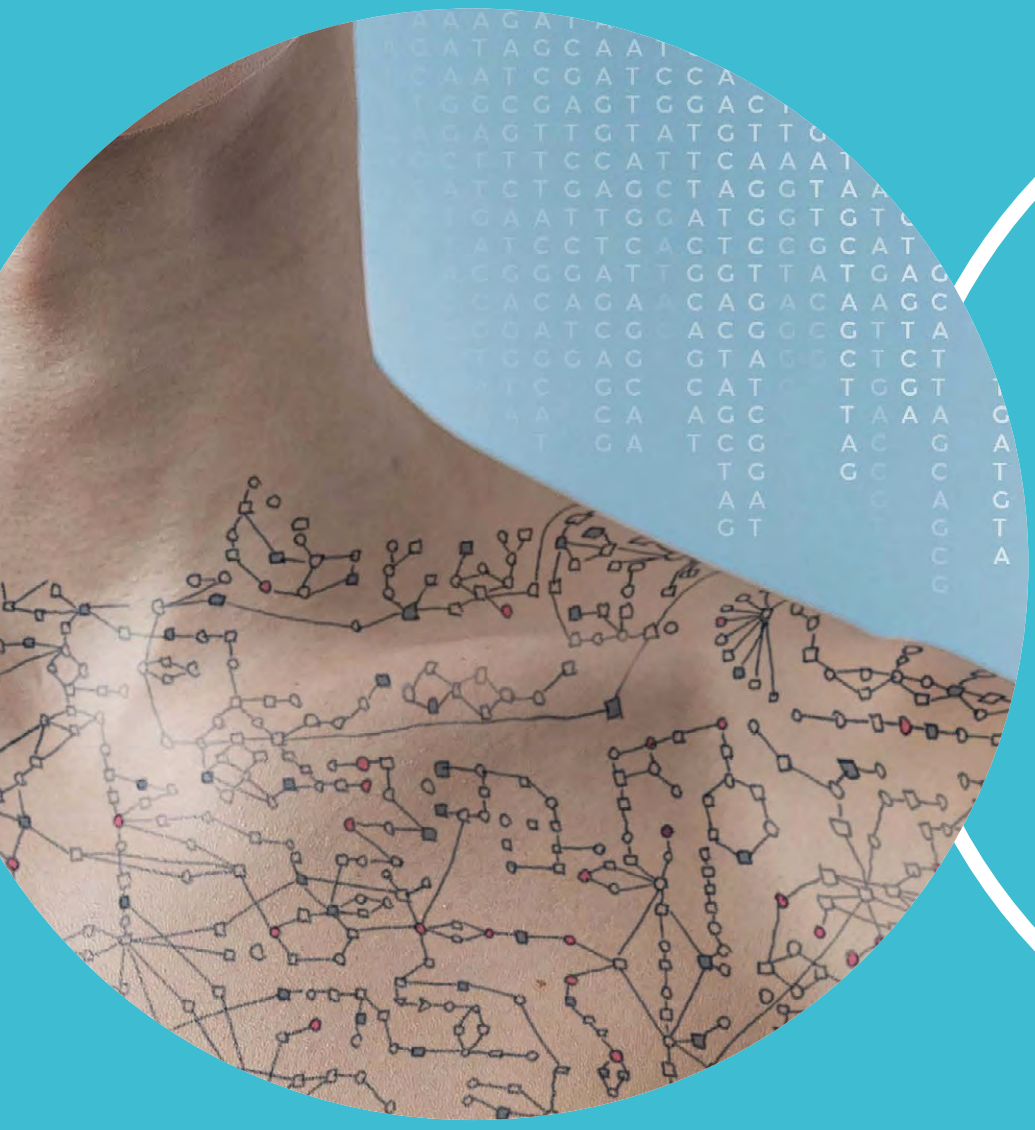
Multi-omics in Metabolic Disease

7–9 June 2023

Wellcome Genome Campus, UK



Abstract book

Multi-omics in Metabolic Disease

Wellcome Genome Campus Conference Centre,
Hinxton, Cambridge, UK
7–9 June 2023

Scientific Programme Committee:

Jules Griffin
University of Aberdeen, UK

Claudia Langenberg
Queen Mary University of London, UK & Berlin Institute of Health at Charité, Germany

Ruth Loos
University of Copenhagen, Denmark

Giles Yeo
University of Cambridge, UK

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Dear Colleague,

I would like to offer you a warm welcome to the Multi-omics in Metabolic Disease 2023 conference, which is being delivered as a hybrid conference, with delegates from around the world joining us on campus or online. I hope you will find the talks interesting and stimulating, and find opportunities for networking with colleagues and potential collaborators during the breaks and at the poster sessions, or by participating in the online discussions though our virtual event portal. We hope you make connections that lead to new and exciting collaborations throughout your time here with us.

This event is organised by Wellcome Connecting Science (WCS), with core funding from the Wellcome Trust. WCS funds, develops and delivers training and conferences that span basic research, cutting-edge biomedicine, and the application of genomics in healthcare. Our programme includes a range of conferences and laboratory, computational, and discussion based courses at the campus or in lower and middle income countries, providing hands-on training in the latest biomedical techniques for research scientists and healthcare professionals. We have also developed a series of MOOCs, accessible to learners for free. Our recently introduced podcast Your Digital Mentor, explores topics around mentoring and career development, tackling the challenges through real stories and honest discussions from expert guests across the world. To find out more about our programme, please visit: **https://coursesandconferences.wellcomeconnectingscience.org/**

We have a strong commitment to equality, diversity and inclusion across the programme. To promote a culture of inclusion and equal representation at our events, we ensure that 50% of our programme committees, session chairs and invited speakers are women. We also work with our programme committees to invite speakers from a range of countries. To read more about our policies, please visit: **https://coursesandconferences.wellcomeconnectingscience.org/about-us/policies/**

The events team will be onsite and online to help this event run smoothly, so drop by the registration desk email us at **conferences@wellcomeconnectingscience.org**, or contact us through the event portal if you have any queries.

Finally, I hope you enjoy the conference.

Best wishes,

Dr Treasa Creavin
Head of Conferences and Online Training
treasa.creavin@wellcomeconnectingscience.org

Event sponsors

We would like to acknowledge the generous support of the following organisations for the Multi-omics in Metabolic Disease conference.

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LMIC bursaries were generously supported by:

Journal of Neuroendocrinology

BSN British Society for Neuroendocrinology

Prizes were generously supported by:

Molecular Omics

Hybrid Conference Programme

Start (GMT)	Finish (GMT)	Presenter details
Wednesday 7 June 2023		
12:00	**13:00**	**Registration, lunch and networking**
12:30	12:50	Briefing for Keynote & Session 1 speakers, chair, moderator & committee - Auditorium
12:50	**13:00**	**Welcome**
		Scientific Programme Committee:
		Julian Griffin, University of Aberdeen, UK
		Claudia Langenberg, Berlin Institute of Health at Charite, Germany
		Ruth Loos, University of Copenhagen, Denmark
		Giles Yeo, University of Cambridge, UK
13:00	**14:00**	**Keynote 1**
		Chair: Claudia Langenberg
		Moderator: Julian Griffin
		Personalized medicine based on deep human phenotyping
		Eran Segal, Weizmann Institute of Science, Israel
14:00	14:10	**Comfort break**
14:10	**15:40**	**Session 1: Genomics in metabolic disease**
		Chair: Eleanor Raffan, Universty of Cambridge, UK
		Moderator: Claudia Langenberg
14:10	14:40	**Unravelling mechanisms for islet-cell dysfunction in diabetes using multi-omic data**
		Anna Gloyn, Stanford University, USA
14:40	15:10	**Mapping cellular processes across multiple phenotypic scales in the context of type 2 diabetes genetic variation**
		Melina Claussnitzer, Broad Institute, USA
15:10	15:25	**Dissecting the genetic heterogeneity of type 2 diabetes using untargeted plasma metabolomics reveals unique molecular signatures of disease subtypes**
		Alice Williamson, University of Cambridge, UK
15:25	15:40	**Genetic architecture of body size change from childhood to adulthood**
		Germán Carrasquilla, University of Copenhagen, Denmark
15:40	16:10	**Refreshment break**

15:55	16:10	**Briefing for Session 2 speakers, chair & moderator - Auditorium**
16:10	**17:40**	**Session 2: Epigenomics & transcriptomics** *Chair: Julian Griffin* *Moderator: Giles Yeo*
16:10	16:40	**Single-cell mapping of body weight-regulatory hindbrain cell populations** *Tune Pers, University of Copenhagen, Denmark*
16:40	17:10	**Skeletal muscle response to an exercise bout** *Anna Krook, Karolinska Institute, Sweden*
17:10	17:25	**Transcriptomic Response of Postprandial Blood, Fat and Muscle to a combined lifestyle intervention in older adults** *Fatih Bogaards, Leiden University Medical Center, Netherlands*
17:25	17:40	**Spatial mapping of GLP-1R populations in the human hypothalamus** *Georgina Dowsett, University of Cambridge, UK*
17:40	**18:10**	**Poster pitches for odd number posters**
18:10	**18:25**	**Sponsor talk**
18:10	18:25	**Characterizing the differential health outcomes of metabolic health studies in smaller, shorter studies. The magic of proteomic surrogates** *Steve Williams (Chief Medical Officer), SomaLogic*
18:25	**19:25**	**Poster session 1 - odd numbers with drinks reception - Sponsored by SomaLogic**
19:25	21:30	Dinner Bar open (card payments only)

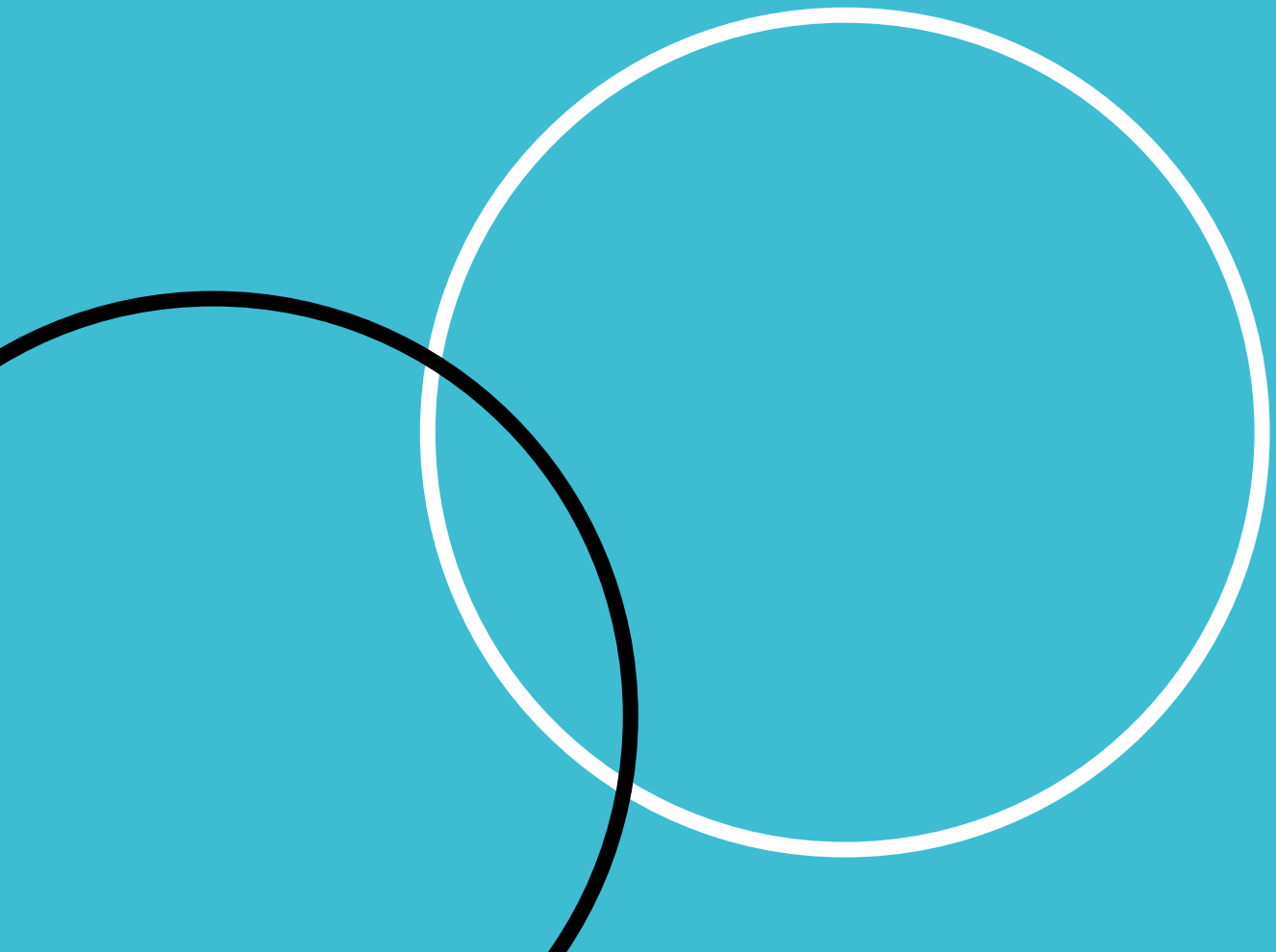
Thursday 8 June 2023		
07:30	09:00	Breakfast
09:15	09:30	Briefing for Session 3 speakers, chair & moderator - Auditorium
09:30	**11:00**	**Session 3: Proteomics**
		Chair: Richard Kay, Wellcome Trust MRC Institute of Metabolic Science, UK
		Moderator: Julian Griffin
09:30	10:00	**High-throughput proteomics for clinical cohort studies and to discover missing gene function**
		Markus Rasler, Berlin Institute of Health at Charite, Germany
10:00	10:30	**Insights into type 2 diabetes from islet single-cell genomics**
		Maike Sander, Max Delbrück Center for Molecular Medicine, Germany
10:30	10:45	**Metabolic moonlighting and single-cell heterogeneity drive functional phenotypes in human cells**
		Chrisitan Gnann, KTH Royal Institute of Technology, Sweden
10:45	11:00	**Proteomic and lipidomic adaptations in liver upon acute reversal of insulin resistance demonstrate molecular rewiring**
		Xiaowen Duan, Institute of Metabolic Science, UK
11:00	11:45	Refreshment break
11:30	11:45	Briefing for Session 4 speakers, chair & moderator - Auditorium
11:45	**13:15**	**Session 4: Metabolic disease research in diverse populations and global settings**
		Chair: Giles Yeo
		Moderator: Claudia Langenberg
11:45	12:15	**No one left behind: considerations for multi-omic research in low resource settings**
		Simon Anderson, The University of the West Indies, Barbados
12:15	12:45	**Exploring African genetic diversity for novel gene discovery & genetic risk prediction**
		Segun Fatumo, Medical Research Council/Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit, Uganda
12:45	13:00	**XBP1 expression in pancreatic islet cells is associated with poor glycaemic control especially in young non-obese onset diabetes across diverse ancestries**
		Moneeza K Siddiqui, University of Dundee, UK
13:00	13:15	**Genetic studies of urine metabolomics to elucidate metabolic disease processes in Polynesian-ancestry individuals**
		Khánh-Dung Nguyen, Variant Bio, USA

13:15	14:45	Lunch and networking
14:30	14:45	Briefing for Session 5 speakers, chair & moderator - Auditorium
14:45	**16:15**	**Session 5: Metabolomics & lipidomics**
		Chair: Julian Griffin
		Moderator: Giles Yeo
14:45	15:15	**Where have "omic" studies in obesity led us?**
		Karine Clement, Sorbonne University, France
15:15	15:45	**The impact of multiomics to inform precision health - virtual**
		Jessica Lasky-Su, Harvard University, USA
15:45	16:00	**TLCD1 and TLCD2 regulate cellular phosphatidylethanolamine composition and promote the progression of non-alcoholic steatohepatitis**
		Kasparas Petkevicius, University of Cambridge, UK
16:00	16:15	**Unravelling the interplay between type 2 diabetes, genetics and metabolite levels**
		Ozvan Bocher, Helmholtz Munich, Germany
16:15	**16:45**	**Poster pitches for even number posters**
16:45	**17:45**	**Poster session 2 - even numbers with drinks reception**
17:45	18:30	Free time/networking
18:30	20:30	Dinner
		Bar open (card payments only)

Friday 9 June 2023		
07:30	09:00	Breakfast
09:15	09:30	Briefing for Session 6 speakers, chair & moderator
09:30	**11:00**	**Session 6: Application of multi-omics to disease**
		Chair: Julian Griffin
		Moderator: Claudia Langenberg
09:30	10:00	**Integrating genetics with proteomics to inform drug discovery and development** *Joanna Howson, Novo Nordisk Research Centre Oxford, UK*
10:00	10:30	**Leveraging metabolite and protein QTLs to dissect GWAS loci** *Eric Fauman, Pfizer, USA*
10:30	10:45	**Linking inter organ communications: A systemic approach to understand pathogenesis of Diabetes** *Dominik Lutter, Helmholtz Munich, Germany*
10:45	11:00	**A CRISPR-inhibition library to investigate non-alcoholic fatty liver disease genetic loci** *Kelly De Coteau, Imperial College London, UK*
11:00	11:45	Refreshment break
11:30	11:45	Briefing for Keynote, chair, moderator & committee
11:45	**12:45**	**Keynote 2**
		Chair: Giles Yeo
		Moderator: Julian Griffin
		Genetic effects on the epigenome and transcriptome at genomic loci for metabolic disease *Karen Mohlke, University of North Carolina, USA*
12:45	**13:00**	**Closing remarks and prize presentation**
		Scientific Programme Committee:
		Julian Griffin, University of Aberdeen, UK
		Claudia Langenberg, Berlin Institute of Health at Charite, Germany
		Ruth Loos, University of Copenhagen, Denmark
		Giles Yeo, University of Cambridge, UK
13:00	13:50	Lunch and departures
13:50		**Coach departures for Stansted and Heathrow airports**
14:00		**Coach departures for Cambridge train station and city centre**

Spoken Presentation Abstracts

These abstracts should not be cited in bibliographies. Materials contained herein should be treated as personal communication and should be cited as such only with consent of the author.



Personalized medicine based on deep human phenotyping

Eran Segal

Weizmann Institute of Science, Israel

Recent technological advances allow large cohorts of human individuals to be profiled, presenting many challenges and opportunities. I will present The Human Phenotype Project, a large-scale (>10,000 participants) deep-phenotype prospective longitudinal cohort and biobank that we established, aimed at identifying novel molecular markers with diagnostic, prognostic and therapeutic value, and at developing prediction models for disease onset and progression. Our deep profiling includes medical history, lifestyle and nutritional habits, vital signs, anthropometrics, blood tests, continuous glucose and sleep monitoring, and molecular profiling of the transcriptome, genetics, gut and oral microbiome, metabolome and immune system. Our analyses of this data provide novel insights into potential drivers of obesity, diabetes, and heart disease, and identify hundreds of novel markers at the microbiome, metabolite, and immune system level. Overall, our predictive models can be translated into personalized disease prevention and treatment plans, and to the development of new therapeutic modalities based on metabolites and the microbiome.

Notes:

Unravelling mechanisms for islet-cell dysfunction in diabetes using multi-omic data

Anna L Gloyn, DPhil

Departments of Pediatrics & Genetics, Stanford University, USA

Human genetics offers a power tool to investigate causal mechanisms for diabetes. In recent years genome-wide association studies (GWAS) have identified hundreds of regions of the genome which alter risk for developing type 2 diabetes. Each of these is a chance to discover mechanistic insight into how cells fail to produce, secrete, or respond to insulin. In our lab we are particularly interested in why pancreatic beta-cells fail to produce sufficient insulin to meet demand. A major bottleneck moving from a genetic association signal to underlying biology is our inability to identify the precise causal variants and then understand how they impact gene function. Most signals are in non-coding regions of the genome and influence gene regulation in a context - cell type, developmental time point, stimulus - dependent manner which makes this even more challenging. Our lab uses multi-omic approaches to link genetic variants to regulatory elements and changes in gene expression and then studies gene perturbation in authentic human cell models to establish if it results in disease relevant cellular phenotypes. We work both genome-wide (pooled CRISPR screens) and take a “deeper dive” at individual loci by combining studies in model organisms, human physiology, stem-cell biology and genome-editing. My presentation will cover examples of our efforts to work at scale (genome-wide screens) and at individual type 2 diabetes loci to deliver insights into cellular and molecular mechanisms underlying beta-cell failure in type 2 diabetes.

Notes:

Mapping cellular processes across multiple phenotypic scales in the context of type 2 diabetes genetic variation

Melina Claussnitzer

Broad Institute, USA

The Claussnitzer team is enthusiastic about adding function to large-scale genetic association study results (Variant-to-Function, V2F) in the context of metabolic disease. The motivation of my research program has been that those genetic studies succeeded in identifying more than 1,000 associations between genetic loci and metabolic disease in humans. Yet, the next grand challenge — systematically dissecting the mechanisms by which these variants affect disease — has still to be solved and scaled. We have previously developed V2F frameworks for going from variants to genes to cells to biological pathways for the FTO obesity risk locus, and shown that this framework generalizes to other genetic risk loci. In this presentation, I will introduce novel experimental and computational strategies to scalably map cellular processes across multiple phenotypic scales in the context of type 2 diabetes genetic variation.

Notes:

Dissecting the genetic heterogeneity of type 2 diabetes using untargeted plasma metabolomics reveals unique molecular signatures of disease subtypes

Alice Williamson(1,2), Maik Pietzner(1,3,6), Laura B L Wittemans(1,4,5), Isobel D Stewart(1), Victoria P W Auyeung(1), Nicholas J Wareham(1), Claudia Langenberg(1,3,6)

1. MRC Epidemiology Unit, Wellcome-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK 2. Metabolic Research Laboratories, Wellcome-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK 3. Computational Medicine, Berlin Institute of Health at Charité–Universitätsmedizin Berlin, Germany 4. Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK 5. Nuffield Department of Women's and Reproductive Health, Medical Sciences Division, University of Oxford, Oxford, UK 6. Precision Healthcare University Research Institute, Queen Mary University of London, London, UK

Background: Type 2 diabetes (T2D) is a major global health burden and patients present with a high heterogeneity in symptoms and aetiology. Part of the heterogeneity has been attributed to distinct genetic endotypes of T2D, but the molecular characteristics of such subtypes are still unclear.

Methods: Here, we integrated information on genetic risk using (partial) polygenic risk scores (PGS) for T2D with comprehensive untargeted metabolomic profiling in >10,000 individuals. We assessed a putative causal role of metabolites in mediating genetic risk towards T2D incidence using a mediation framework and bespoke follow-up including genetic colocalisation and Mendelian randomisation analysis.

Results: More than 350 metabolites were significantly associated with T2D incidence spanning almost all biological pathways. Of 134 metabolites associated with a PGS for T2D, 71 were also associated with incident T2D with significant and directionally consistent associations, covering well-known pathways, as well as less established ones such as steroid metabolism. These pathways were attributable to distinct underlying genetic architectures as demonstrated by the analysis of genetic T2D endotypes, which were associated with non-overlapping metabolomic signatures. While we observed evidence for 18 metabolites to be potentially on a causal pathway from genetic liability to T2D onset, bespoke follow-up analysis at biobank-scale for the most prominent candidate, glycine, suggested reverse causality via insulin resistance.

Conclusions: Here, we demonstrate the utility of integrating measures of genetic risk of T2D with large-scale metabolomics profiling to allow the refinement of key aetiological pathways in T2D. We propose a genetically guided strategy to reveal the biological mechanisms that underlie confounded observational associations.

Ongoing work: This analysis framework is currently being expanded to proteomics measures, to further refine the aetiological signatures of T2D endotypes.

Notes:

Genetic architecture of body size change from childhood to adulthood

G.D. Carrasquilla, M.R. Christiansen, G.J. Rodríguez, M. García-Ureña, T.O. Kilpeläinen, and R.J.F. Loos

Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Background: Genome-wide association studies (GWAS) have identified numerous genetic loci associated with body size in childhood or adulthood separately. However, no genetic loci have been identified for the change in body size from childhood to adulthood.

Methods: We conducted a GWAS for body size change from childhood to middle age in 418,139 individuals of European ancestry from the UK Biobank. Participants self-reported their body size at age 10 as "thin", "average" or "plump" as compared to their peers. We then created a corresponding three-category variable for body size in adulthood, utilizing measured adult BMI. Body size change was calculated as the difference in body size category between age 10 and middle-age.

Results: We identified 12 loci that were associated with body size change ($P<5x10-9$) that have not been identified in previous GWAS of child or adult BMI. Three of the loci were previously reported for association with psychiatric traits in adulthood, such as depression, neuroticism, and insomnia. Five loci were associated with body fat distribution, body composition, or height in adulthood. Three loci were linked to sexual maturation, including age at menarche and testosterone levels.

Conclusion: Our findings suggest that the genetic mechanisms responsible for regulating changes in body size over time are distinct from those involved in controlling body size at a single point in time. Deeper understanding of these mechanisms will be important to design more effective interventions for promoting healthy body size from childhood to adulthood

Funding: Novo Nordisk Foundation (NNF18CC0034900, NNF17SA0031406, NNF17OC0026848, NNF20OC0059313) and Horizon2020 MSCA (No846502).

Notes:

Single-cell mapping of body weight-regulatory hindbrain cell populations

Mette Q. Ludwig1, Bernd Coester1, Petar Todorov1, Oliver Pugerup Christensen1, Dylan M. Rausch1, Wenwen Cheng2, Desiree Gordian2, Sofia Lundh3, Paul Kievit4, Marina Kjærgaard Gerstenberg3, Anna Secher3, Kirsten Raun3, Kristoffer L. Egerod1, Martin G. Myers, Jr2, Tune H. Pers1

1 Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark, 2 Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA, 3 Global Drug Discovery, Novo Nordisk A/S, Måløv, Denmark, 4 Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, Oregon, USA

The amylin receptor agonist cagrilintide induces weight loss in part through activation of incompletely understood neuronal circuits in the brainstem dorsal vagal complex (DVC). The weight loss effect is more pronounced in humans and rats than in mice, a difference that is unlikely to be explained by receptor pharmacokinetics. We recently characterized calcitonin receptor (Calcr)-expressing neuronal populations in the mouse area postrema (AP) and the nucleus of the solitary tract (NTS), which are capable of sensing amylin and amylin-related peptides. However, it remains unknown whether additional DVC Calcr populations exist across species and how cagrilintide engages primary and secondary responders to induce long-term effects on energy balance.

To identify DVC cell populations and molecular pathways that mediate cagrilintide-induced weight loss effects, we first used single-nucleus RNA-sequencing (snRNA-seq) to establish a comprehensive atlas of the DVC, comprising both rhesus macaque, mouse, and rat cells. In diet-induced obese mice, following either acute or subchronic treatment with cagrilintide, we then systematically identified cagrilintide-responsive genes and regulons across cell populations.

Sequencing more than 35,000 rhesus macaque, 160,000 mouse, and 40,000 rat DVC cells, we constructed an atlas of nine glial cell types and 28 neuronal cell populations. Among these, five neuronal populations showed a high expression of Calcr. Expectedly, we found that cagrilintide enhanced expression of regulons controlled by primary response genes in a population of AP Calcr neurons in mice. Interestingly, upon subchronic treatment, these regulons were not upregulated in mice, whereas the same regulons were upregulated in rats. In rats, we further identified prolactin releasing hormone (Prlh), a gene that, when overexpressed in mice, can abrogate obesity and is co-expressed with Calcr in a population of NTS neurons, was among the most differentially expressed genes.

Together, our data provides a comprehensive resource of species-specific and conserved DVC cell populations and suggest that cagrilintide treatment induces sustained activation of neurons in the rat DVC, including Prlh-expressing Calcr neurons, but not in the mouse DVC.

Notes:

Skeletal muscle response to an exercise bout

Anna Krook

Karolinska Institute, Sweden

Regular exercise can lead to a number of changes in skeletal muscle, including changes in muscle size, strength, and endurance. Exercise is a physiologically relevant stressor for skeletal muscle. In response to muscle contraction skeletal muscle mobilises exercise stores, increases energy metabolism and initiates a number of transcriptomic changes. Of relevance to metabolic disease, a single exercise bout also enhances skeletal muscle insulin sensitivity. This lecture will explore coordinated response to a single bout of exercise in people with normal glucose tolerance and people with type 2 diabetes from whole body glucose control to transcriptomic and metabolomic changes.

Notes:

Transcriptomic Response of Postprandial Blood, Fat and Muscle to a combined lifestyle intervention in older adults

Fatih Bogaards1,2,3, Thies Gehrmann1,2, Marian Beekman1, Lisette de Groot3, Marcel Reinders2,4, Eline Slagboom1,4,5

1 Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, 2 Leiden Computational Biology Center, Leiden, The Netherlands, 3 Human Nutrition and Health, Wageningen University & Research, Division of Human Nutrition, Wageningen, The Netherlands, 4 Delft Bioinformatics Lab, Delft University of Technology, Delft, The Netherland, 5 Max Planck Institute for Biology of Aging, Cologne, Germany

Lifestyle interventions have shown a range of beneficial health gains. Their effects can be studied by traditional blood-based markers of metabolic health and omics-based assays, including the transcriptome. Generally, a strong effect of such interventions is observed on the transcriptome of fat and muscle (Wahl and LaRocca, 2021), but not on the blood transcriptome, where effects are milder and more variable (Day et al., 2021). To understand how variation in omics profiles relate to health, one often relies on population-based omics studies, which are mostly focused on the blood transcriptome. Here we study the relation of short-term changes in lifestyle, the corresponding effects of omics changes in blood, fat and muscle on one hand and to the health gain on the other. Due to the systemic nature of lifestyle interventions, we speculate that some of the transcriptomic changes in different tissues align, and that part of changes in the blood transcriptome reflect the responses in fat and muscle. Hereto, an integrative analysis was explored of postprandial fat, muscle and blood transcriptomic responses to a 13-week physical activity and dietary lifestyle intervention in older adults (age 50-75) (Growing Old TOgether (GOTO) study; van de Rest et al., 2016).

Integrative data analysis methods pool data from different datasets to jointly analyze them. Joint and Independent Variation Explained (JIVE) is one such method (Lock et al., 2013). JIVE decomposes the variation across the different datasets in three components: 1) the joint variation between the datasets, 2) dataset-specific variations, and 3) residual noise. Even though the blood transcriptome response is often minimal, JIVE may reveal the part that represents the joint response across tissues. We are interested in this joint response, as it might capture the intervention effects on metabolic health stronger than the blood transcriptome alone.

Applying this integrative data analysis approach on the GOTO dataset, we report on the sex specific intervention effects of the transcriptome within each of the different tissues, how they associate with health improvements across the intervention, and on the characteristics of the observed joint transcriptional effect.

The GOTO intervention had virtually no effect on the postprandial blood transcriptome, while the fat and muscle transcriptomes were significantly responding. In fat, pathways involved in HDL remodeling and signaling were overrepresented, while in muscle, collagen and extracellular matrix pathways were significantly overexpressed. Additionally, we found that the effects of the fat transcriptome closest associated with gains in metabolic health. Lastly, in males, we identified a shared variation between the transcriptomes of the three tissues. Using the joint variation modeled in the postprandial blood transcriptome, we detected an intervention effect that was significantly associated with the changes in whole-body and trunk fat%, which was not present in the original transcriptome of postprandial blood.

We propose that this method could be used to estimate part of the effect of an intervention on fat and muscle transcriptomes, when only blood expression data is available. Currently we are investigating the shared effects of the intervention on the proteome, transcriptome and metabolome.

Our work is part of the VOILA consortium, which focuses on stimulating healthy ageing by improving immune-metabolic, gut and muscle health and identifying novel biomarkers that can indicate the health status of older individuals and monitor response to novel interventions.

Notes:

Spatial mapping of GLP-1R populations in the human hypothalamus

Georgina Dowsett, Sofia Lundh, Henning Hvid, John Tadross, Lotte Bjerre Knudsen, Joseph Polex-Wolf, Brian Lam, Charles Pyke, Giles SH Yeo

Wellcome-MRC Institute of Metabolic Science-Metabolic Research Laboratories

Novo Nordisk A/S

The hormone and neurotransmitter GLP-1 acts on receptors in multiple organs in the body, including the brain. Previous studies in animal models show that GLP-1 acts in several brain regions, including the hypothalamus, to modulate food intake. With GLP-1R agonists such as liraglutide and semaglutide used for treating obesity, it is important to understand the mechanisms of GLP-1 action in the human brain. We previously used single-cell RNA-sequencing and RNAscope to characterise hypothalamic GLP1R populations in mice. Here, we utilise the latest spatial transcriptomics technology, which allows for whole transcriptome profiling across a tissue section at a resolution of 1-10 cells. Using Visium spatial transcriptomics we profile 7 human hypothalamic sections and characterise transcript expression of hypothalamic nuclei. Additionally, we characterise distinct GLP1R populations and confirm transcript co-expression with RNAscope. Using this, we can begin to delineate the cellular targets of GLP1R agonists which mediate their weight loss effects.

Notes:

High-throughput proteomics for clinical cohort studies and to discover missing gene function

Markus Rasler

Berlin Institute of Health at Charite, Germany

Understanding the interactions between metabolites and small molecules on one hand, and the proteome on the other, are vital for our understanding of biological phenotypes, metabolism and drug action. In this presentation I'll summarize our efforts in developing methods for high-throughput proteomics. I'll further show examples that illustrate how high-throughput proteomic datasets allow to bridge genome, proteome and metabolome. The results indicate that genome-scale proteomic data opens new avenues for understanding gene function and interactions within biological systems, could impact drug discovery, and lead to a new generation of diagnostic and prognostic tests in medicine.

Notes:

Insights into type 2 diabetes from islet single-cell genomics

Maike Sander

Max Delbrück Center for Molecular Medicine, Germany

Altered function and gene regulation of pancreatic islet beta cells is a hallmark of type 2 diabetes (T2D), but a comprehensive understanding of mechanisms driving T2D is still missing. We integrated information from measurements of chromatin accessibility, gene expression and function in single beta cells with genetic association data to identify disease-causal gene regulatory changes in T2D. Using machine learning on chromatin accessibility data from non-diabetic, pre-T2D and T2D donors, we identified two transcriptionally and functionally distinct beta cell subtypes that undergo an abundance shift in T2D. Subtype-defining accessible chromatin are enriched for T2D risk variants, suggesting a causal contribution of subtype identity to T2D. Both subtypes exhibited activation of a stress-response transcriptional program and functional impairment in T2D, which is likely induced by the T2D-associated metabolic environment. Our findings demonstrate the power of multimodal single-cell measurements combined with machine learning for identifying mechanisms of complex diseases.

Notes:

Metabolic moonlighting and single-cell heterogeneity drive functional phenotypes in human cells

Christian Gnann, Christian Gnann1, Sanem Sariyar1, Trang Le2, Anthony J. Cesnik2, Diana Mahdessian1, Rutger Schutten3, Manuel D. Leonetti4, Cecilia Lindskog3, Emma Lundberg1,2,4

1 KTH Royal Institute of Technology, Science for Life Laboratory, Department of Protein Science, Stockholm, Sweden

2 Stanford University, Department of Bioengineering, Palo Alto, CA, USA

3 Uppsala University, Rudbeck Laboratory, Department of Immunology, Genetics and Pathology, Uppsala, Sweden

4 Chan Zuckerberg Biohub, San Francisco, CA, USA

Non-genetic cellular heterogeneity in the spatial expression of metabolic enzymes has been implicated in a variety of cellular processes such as drug resistance, metastasis, differentiation or immune cell activation. In our work, we integrate single-cell transcriptomics and public protein-protein interaction data with the imaging-based spatial proteomics data from the Human Protein Atlas to provide insight into the extent of subcellular metabolic complexity.

Our data highlights the spatiotemporal complexity of the metabolic proteome as over 50% of all enzymes localize to multiple cellular compartments, suggesting potential multifunctional properties. By integrating public affinity purification-based protein-protein interaction data with subcellular location data from the HPA, we identified several enzymes with potentially novel non-canonical functions. In addition, we show that metabolic enzymes exhibit higher degrees of single-cell expression variability compared to the human proteome. Interestingly, this metabolic heterogeneity arises independently of cell cycle progression and is established at the post-transcriptional level. Furthermore, we reveal that metabolic heterogeneity is strongly correlated between related pathways, indicating that cellular states are manifested through intra- and intercellular fluctuations of the respective enzymes. Altogether, we believe that the spatial complexity and single-cell variability of metabolic enzymes can establish dynamic metabolic states which can provide a readout for cell and tissue phenotypes ultimately allowing for targeted studies of their impacts on cell function in normal and pathological cell systems.

Notes:

Proteomic and lipidomic adaptations in liver upon acute reversal of insulin resistance demonstrate molecular rewiring

Xiaowen Duan, Satish Patel, Afreen Haider, David Savage

Metabolic Research Laboratories, Wellcome-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge, CB2 0QQ, UK

Insulin resistance is the major factor underpinning the association between obesity and metabolic diseases, however the mechanisms responsible for causing insulin resistance remain unclear. In order to determine the mechanisms underlying the remarkably rapid reversal of insulin resistance after reduced caloric intake (e.g. after bariatric surgery), we have established a mouse model which phenocopies this phenomenon. This model involves 8 weeks of high fat feeding (HFD) followed by 3 days calorie restriction induced by switching diet to chow (CD). Mice undergoing HFD or CD for the duration of the study were used as controls. Body weight and cage food intake were monitored throughout the study and ITT among other plasma parameters were measured at the end of the study. Insulin-responsive tissues including liver, adipose tissue and muscle were collected and multi-omics studies including proteomics and lipidomics together with biochemical characterization were performed. Our data suggest that 3 days' caloric restriction via diet-switching from HFD to CD was sufficient to reverse whole body insulin sensitivity. Biochemical characterisation of liver suggests subtle changes in Peroxiredoxins dimerization ratio among diet groups, however, total Prdx2 and Prdx3 levels were elevated in HFD group compared to CD group and remained unchanged in diet switching group. ER stress markers including phospho-eIF2α and phospho-JNK were elevated in HFD group versus CD group and were further elevated after diet-switching. Liver lipidomics suggests a dramatic increase of DAG and TAG in HFD group compared to CD group and they were largely reduced after diet-switching. Lipid families including Lyso-phosphatidyl-choline (LPC), Monogalactosyldiacylglycerol (MGDG), Mono-lyso-CL were also increased in HFD group compared to CD group and normalised to the level of CD group after diet-switching. Certain species from Ceramide and Cadiolipin families showed a similar trend. Liver proteomics suggest that proteins involved in canonical insulin signalling pathway and gluconeogenesis were largely unchanged in abundance among diet groups, proteins involved in de novo lipogenesis were mostly unaffected between HFD and CD group, however, proteins including Scd1, Fasn and Acly were significantly downregulated by diet-switching compared to the other two groups. With hypothesis-free method, we demonstrated that proteins including Retsat, Cdo1 were significantly changed in abundance in HFD group compared to CD group and reversed in diet-switching group, suggesting a potential role in diet-induced insulin resistance. Future directions include the determination of liver-specific insulin sensitivity in this model and the mechanisms of action of the potential regulators of insulin resistance.

Notes:

No one left behind: considerations for multi-omic research in low resource settings

Simon Anderson

The University of the West Indies, Barbados

Beyond the genome and its role in human health and disease are the dynamic realms of the transcriptome, proteome and metabolome that sit at the table of discovery. At the heart of these are the untapped repositories of rich information which, if integrated through multi-omic technology, could unravel the significant impact of diseases on human health. Often the lens of discovery is turned to focus on the capacity and findings from resource-replete settings leaving behind the potential of data from studies of people living in low-resourced and a low-to-middle-income setting. Heeding the call for the equitable inclusion of data from diverse populations in multi-omic research ensures that this multi-dimensional approach does not further exacerbate health disparities by facilitating discoveries that will disproportionately benefit some population groups. Multi-omic research should leave none behind.

Notes:

Exploring African genetic diversity for novel gene discovery and genetic risk prediction

Segun Fatumo PhD, FHEA

Medical Research Council/Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit, Uganda

Since the first human genome was sequenced about twenty years ago, advances in genome technologies have resulted in whole-genome sequencing and microarray-based genotyping of millions of human genomes. However, genetic and genomic research is primarily focused on populations of European ancestry. As of June 2021, for example, the vast majority of genomics studies, including genome-wide association studies (GWAS), had been conducted in people of European descent (86.3%), followed by East Asian (5.9%), and African (1.1%) populations. While the proportion of samples from people of European ancestry has increased from 81% in 2016 to 86% in 2021, the proportion of samples from underrepresented groups has either remained stagnant or decreased.

As a result, the many underrepresented populations may miss out on the potential benefits of genomic research, such as a better understanding of disease aetiology, early detection and diagnosis, rational drug design, and improved clinical care. In my presentation, I will discuss the importance of genomic diversity and how we are using Africa's limited human genome resource to 1) discover novel disease susceptibility genetic loci, 2) refine association signals at new and existing loci, 3) develop and test polygenic scores to determine disease risk, 4) assess causal relationships in diseases, and 5) develop capacity for genomics research in Africa.

Notes:

XBP1 expression in pancreatic islet cells is associated with poor glycaemic control especially in young non-obese onset diabetes across diverse ancestries

Moneeza K Siddiqui, Theo Dupuis1, Ranjit Mohan Anjana2,3, Sundararajan Srinivasan 1, Adem Y Dawed 1, Alaa Melhem 1, Margherita Bigossi 1, Alasdair Taylor1, Ebenezer Tolu Adedire 1, Jebarani Saravanan 3, Ambra Sartori 4, David Davtian 1, Venkatesan Radha3, Sam Hodgson 5, Alison McNeilly 6, James Cantley 6, Naveed Sattar7, Rohini Mathur 5, Sarah Finer 5, Genes & Health Research Team 5, , Ewan R Pearson1, Ana Viñuela8, Rajendra Pradeepa 3, Viswanathan Mohan 2,3, Colin N A Palmer 1, Andrew A Brown 1

1 Division of Population Health and Genomics, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9 SY, United Kingdom, 2Dr Mohan's Diabetes Specialities Centre and Madras Diabetes Research Foundation, Chennai, India, 3 Madras Diabetes Research Foundation, Chennai, India, 4 Department of Genetic Medicine and Development, Geneva University Hospital and University of Geneva Medical School, Geneva, Switzerland, 5 Wolfson Institute of Population Health, Queen Mary University of London, 6 Division of Systems Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee DD19DSY, United Kingdom, 7 Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK, 8 Biosciences Institute, Faculty of Medicine, Newcastle University, Newcastle Upon Tyne, United Kingdom

Individuals from certain ancestry groups such as South Asians and East Asians have higher rates of type 2 diabetes mellitus (T2DM), in part, driven by insulin deficiency. This can be due to beta-cell insufficiency, low cell mass, or early apoptosis. The transcription factor XBP1 has a key role in maintaining beta-cell function and preventing apoptosis by mitigating cellular endoplasmic reticulum stress. We examine if expression quantitative trait loci (eQTL) that predict XBP1 expression levels in pancreatic islets are associated with T2DM. Using trans-ancestry biobanks, we explore whether this association is driven by lower beta-cell function leading to poor glycaemic control and if this genetic variation has implications for drug response.

Methods: eQTL data for pancreatic tissue and pancreatic islet cells as well as T2DM summary statistics from trans-ancestry studies were used to determine if expression of XBP1 was associated with T2DM risk. Clinical data for beta-cell function was available from South Asian Indians. Further, HbA1c at T2DM diagnosis were available from individuals of South Asian Indian, Bangladeshi and Pakistani ancestries and white Europeans, while summary data was available also from East Asians. Pharmacogenetic associations for drugs designed to improve insulin secretion were examined.

Results: We show that variants affecting XBP1 expression in pancreatic islets colocalised with variants associated with T2DM risk, and this effect was stronger in East Asians than in white Europeans. Lower expression of XBP1 was associated with higher risk of T2DM. Further the gene region shows evidence of recent selection in Europeans and an XBP1 eQTL variant rs7287124 has a higher risk allele frequency in East (65%) and South Asians (50%) compared to white Europeans (25%). In 470 South Asian Indians with newly diagnosed T2DM, the variant was associated with lower beta-cell function (log HOMAB =-0.14,P=5x10-3). The effect of the variant on HbA1c was meta-analysed across East Asians, white Europeans, and South Asian Indian, Pakistani, and Bangladeshis and was found to be 4.32 mmol/mol (95%CI:2.60,6.04,P=8x10-7) per allele. The effect is driven by those with young-onset diabetes with non-obese BMI in whom the per allele effect was 6.41 mmol/mol (95%CI:3.04,9.79,P=2x10-4). Variant carriers had impaired response to insulin secretagogues.

Conclusion: XBP1 is a novel target for beta-cell dysfunction in T2DM with particular value for individuals of under-researched ancestries who have greater risk of young, non-obese onset diabetes. The effect of XBP1 eQTL variant was found to be comparable with or greater than the effect of novel T2DM therapies.

Notes:

Genetic studies of urine metabolomics to elucidate metabolic disease processes in Polynesian-ancestry individuals

Khánh-Dung H. Nguyen1, Megan Leask2,3, Anne-Katrin Emde1, Jaye Moors1, Nicola Dalbeth4, Lisa Stamp5, Janak de Zoysa4, Rinki Murphy4, Phillip L. Wilcox2, Laura M. Yerges-Armstrong1, Kaja A. Wasik1, Tony R. Merriman2,3, Stephane E. Castel1**

1 Variant Bio, Seattle, Washington, USA;

2 University of Otago, Dunedin, New Zealand;

3 University of Alabama Birmingham, Birmingham, Alabama, USA.

4 Department of Medicine, University of Auckland, Auckland, New Zealand;

5 Department of Medicine, University of Otago, Christchurch, New Zealand;

** these authors contributed equally*

Metabolic disorders such as chronic kidney disease (CKD), gout and type 2 diabetes (T2D) are prevalent in Indigenous populations of the Pacific. Recent discoveries have unfurled protective genetics in these populations. Despite this, the underlying genetic mechanisms remain elusive. Large-scale multiomics analysis may provide novel insights by identifying population-enriched functional genetic variation. Here we have mapped genetic associations to metabolites and assessed whether these are also associated with metabolic disease. Specifically, we evaluated variations of up to 1,605 untargeted mass spectrometry-based urine metabolites measured on the Metabolon platform in a population-based cohort of 1,395 people of Aotearoa New Zealand Māori and Pacific (Polynesian) ancestry accompanied by mid-pass (4x coverage) whole-genome sequencing data. Our analysis identified 191 genetic-metabolite associations (metabolite quantitative trait loci, mQTLs) at 45 unique genomic loci with 119 urine metabolites (significance threshold p-value ≤5x10-8 ÷ 807 principal components explaining 99% metabolomic variation). Of these, 90 metabolites are also differentially expressed in disease, i.e., their levels are significantly different in patients compared to participants without disease of interest (FDR ≤0.01). Specifically, 62 metabolites are differentially expressed across CKD stages (linked to 96 genetic associations at 29 loci), 33 metabolites in gout (54 associations at 16 loci) and 53 metabolites in T2D (85 associations at 29 loci). Interestingly, of the 191 identified mQTLs (95% finemapped credible sets), 115 (60%) span a putatively functional (protein coding, splicing or regulatory) region, and 42 (22%) contain at least one variant enriched in Polynesian-ancestry individuals (minor allele frequency, MAF ≥5%) compared to gnomAD population reference (MAF <1%), and 98 (51%) have not been previously reported in the GWAS catalog. Furthermore, we identified metabolite-associated, Polynesian-enriched missense variants in DMGDH, ABCC4, and PIPOX where the metabolites were also differentially expressed in CKD and T2D. This study provides novel insights for further understanding of the genetics of metabolic disease among Pacific populations. It is addressing health inequities via the verification of existing and identification of new druggable targets and precision medicine initiatives.

Notes:

Where have “omic” studies in obesity led us

Karine Clement

Sorbonne University, France

Obesity is a chronic disease linked to multiple environmental and biological factors including genetic factors. Once established, obesity is chronic and is associated with alterations in organ biology and inter-organ dialogues. The "omics" approach provides tools to approach this complexity and our team has worked on both genomic and transcriptomic dimensions extended to adipose tissues in order to show the importance of fibro-inflammatory alterations in these tissues. More recently, we have extended our approaches to the study of the gut bacterial metagenome to demonstrate the alterations in the composition and function of the intestinal microbiota during obesity. Thus, the "omics" approach has allowed us to approach some fundamental mechanisms involved in the development of obesity and its chronicization.

Notes:

The impact of multiomics to inform precision health

Jessica Lasky-Su

Harvard University, USA

Biological age provides a synthesized measure of an individual's physiological state and is a critical predictor of morbidity and mortality risk. While other omics have been used developed to predict biological age, to date, limited research has assessed the relationship between biological aging and metabolomics, which may provide important clues into the molecular drivers of the aging process. In this study, we developed a robust biological aging phenotype using ~30 clinical labs from electronic medical records on >30.000 people from the Mass General Brigham Biobank. We demonstrated the robustness of BioAge by applying this Lasso/Cox approach at four time points in the associated electronic medical records (01/01/2008, 01/01/2010, 01/01/2012, 01/01/2014). BioAge had correlations of >0.98 with the other estimates, demonstrating that our prediction model is highly reproducible when created using different EMR data. We created biological ageing predictive models for three omic data types (DNAm, metabolomics, proteomics) using individuals from the MGB-Biobank. For each omic model, the sample was split into training and testing sets and applied elastic net regression to select the omic variants to be retained in the final predictive model. For all three predictive models, the training and testing correlations were greater than 0.90 and 0.84 respectively. We further created a multiomic-informed BioAge predictor by using the metabolomic and proteomic data to further reduce the error in the DNAm model. Using this approach, we created a final multiomic model with an RSME = 2.4 and a training and testing correlation of 0.97 and 0.92 respectively. We identified that the multiomic predicted biological age is associated with significantly increased risk of adverse health outcomes, including all-cause mortality, cardiovascular disease, and cancer. Our results highlight the potential of multiomics for predicting biological age and establishing personalized anti-aging strategies and further elucidate the molecular mechanisms of aging that may ultimately promoting healthy aging and longevity.

Notes:

TLCD1 and TLCD2 regulate cellular phosphatidylethanolamine composition and promote the progression of non-alcoholic steatohepatitis

Kasparas Petkevicius, Henrik Palmgren, Matthew S. Glover, Andrea Ahnmark, Anne-Christine Andréasson, Katja Madeyski-Bengtson, Hiroki Kawana, Erik L. Allman, Delaney Kaper, Martin Uhrbom, Liselotte Andersson, Leif Aasehaug, Johan Forsström, Simonetta Wallin, Ingela Ahlstedt, Renata Leke, Daniel Karlsson, Hernán González-King, Lars Löfgren, Ralf Nilsson, Giovanni Pellegrini, Nozomu Kono, Junken Aoki, Sonja Hess, Grzegorz Sienski, Marc Pilon, Mohammad Bohlooly-Y, Marcello Maresca, Xiao-Rong Peng

1. Medical Research Council Mitochondrial Biology Unit, University of Cambridge, Hills Road, CB2 0XY Cambridge, UK.

2. Bioscience Metabolism, Research and Early Development Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

Non-alcoholic steatohepatitis (NASH) is one of the major comorbidities of obesity and type 2 diabetes with no approved treatment. The primary cause of NASH is aberrant lipid metabolism, leading to hepatic lipotoxicity, inflammation and fibrosis. Human genetic NASH risk variants are associated with dysregulated hepatic phospholipid levels, suggesting the importance of hepatocyte phospholipid metabolism in NASH development.

Phosphatidylethanolamine (PE) is the second most abundant mammalian phospholipid, and is enriched in mitochondria and the inner layer of plasma membrane. However, our understanding of cellular PE metabolism - particularly how cells regulate PE fatty acyl chain composition - is limited. In our study, we utilised mouse genome-lipid association data to identify a genetic locus on mouse chromosome 11, containing two poorly characterized genes Tlcd1 and Tlcd2, that had the strongest association to the abundance of hepatic PE species.

Next, we used CRISPR-Cas9 genome editing to generate Tlcd1 and Tlcd2 single-knockout, and Tlcd1/2 double-knockout mice. Using lipidomics, we found that both single and double Tlcd1/2 knockout mice have strongly reduced hepatic monounsaturated fatty acid-containing PE levels. We then employed stable isotope lipid tracing to demonstrate that TLCD1 and TLCD2 act in a cell-intrinsic manner to promote the incorporation of monounsaturated fatty acids specifically into PEs. Furthermore, we performed immunoprecipitation and proteomics to uncover that both human TLCD1/2 and their C. elegans homologue FLD-1 interact with the mitochondria. We also showed that TLCD1/2 regulate mouse hepatic mitochondrial PE fatty acyl chain composition.

As aberrant hepatic mitochondrial PE metabolism had been implicated in the development of liver disease in animal models, we subjected Tlcd1/2 double-knockout mice to a high-fat diet and Western diet feeding regimes. We found that Tlcd1/2 double-knockout mice had attenuated development of fatty liver disease and NASH in both dietary challenge models, indicating that monounsaturated fatty acid-containing PE species promote the progression of NASH.

Overall, our findings establish TLCD1/2 proteins as key regulators of cellular PE fatty acyl chain composition and implicate them in the development of fatty liver disease. My current research aims to decipher the precise biochemical mechanism of action of TLCD proteins, as well as to understand how they affect mitochondrial function.

Reference: Petkevicius et al. TLCD1 and TLCD2 regulate cellular phosphatidylethanolamine composition and promote the progression of non-alcoholic steatohepatitis. Nature Communications 13, 6020 (2022).

Notes:

Unravelling the interplay between type 2 diabetes, genetics and metabolite levels

Ozvan Bocher (1), Archit Singh (1,2), Ana Arruda (1,2), Peter Kreitmaier (1,2), Andrei Barysenka (1,3), William Rayner (1,3), Eleftheria Zeggini (1,3)

1. Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

2. Technical University of Munich (TUM), TUM School of Medicine, Munich, Germany

3. Technical University of Munich (TUM) and Klinikum Rechts der Isar, TUM School of Medicine, Munich, Germany

Type 2 diabetes (T2D) represents a major health burden and is forecast to increase dramatically in the upcoming years. The genetics of the disease have been successfully investigated in large GWAS but the remaining challenge lies in fully understanding the role of these variants in the biology giving rise to the disease. Metabolomics offers an opportunity to answer this question by giving insights into these biological mechanisms and into why certain patients progress to specific complications. We sought to investigate the interplay between genetics, metabolomics and T2D risk in the UK Biobank cohort. We first conducted a bidirectional Mendelian Randomization (MR) study using the UK Biobank to assess the effects of metabolites on T2D risk and the DIAMANTE GWAS meta-analysis results to assess the effects in the opposite direction. Within the power constraint of the study, we found suggestive evidence for some metabolites to be causal of T2D, including glucose and metabolites linked to HDL cholesterol. In the reverse direction, statistical power was much higher reflecting the larger study size of the DIAMANTE meta-analysis. We find changes in half of the 164 absolute metabolite levels tested to be caused by T2D (with p-value down to 10-61), including an increase in amino acids and glucose levels, and a decrease in metabolite levels from cholesterol classes. Some of these metabolite levels are also seen to be associated with specific T2D complications in the UK Biobank cohort such as HDL cholesterol showing lower values in T2D individuals with kidney complications compared to T2D individuals without complications (β=-0.49, p=1.61x10-6). Secondly, we assessed the interaction between T2D status and genetic variants through a differential metabolite QTL analysis. We find 26 metabolites that are differentially genetically regulated in individuals with and without type 2 diabetes, including glycine (β=0.41, p=5x10-25 for the most significant SNP) and low-density lipoproteins (β=0.52, p=1.08x10-10) which show the most prominent signals. Almost half of these 26 metabolites were found to be caused by T2D. This work provides a better understanding of the metabolic changes that are causative of T2D as well as metabolic changes that are induced by the occurrence of the disease. While further work is needed to confirm these results and better disentangle the underlying biology, they provide potential directions to investigate T2D consequences and subsequent complications.

Notes:

Integrating genetics with proteomics to inform drug discovery and development

Joanna Howson

Novo Nordisk Research Centre Oxford, UK

ABSTRACT TBC

Notes:

Leveraging metabolite and protein QTLs to dissect GWAS loci

Eric Fauman

Pfizer, USA

Genome-wide association studies have been very successful at identifying genomic regions reproducibly associated with a wide variety of human phenotypes including risk of disease. However, the mechanisms by which genetic variations manifest as phenotypic variations are not always clear. One approach to better understand these mechanisms is to start with traits such as protein or metabolite abundance where the basic biology and biochemistry are relatively well-established permitting confident assignment of the true causal genes mediating the genetic signals. Knowledge of the causal gene can lead to a richer understanding of the role of pleiotropy and indirect effects in different genetic findings. Applying rules gleaned from molecular traits to complex disease traits allows us to hone in on likely causal disease genes and in some cases assess potential horsepower or therapeutic benefit.

Notes:

Linking inter organ communications: A systemic approach to understand pathogenesis of Diabetes

Dominik Lutter, Dominik LutDominik Lutter1, Kenneth Dyar2, Shogo Sato3, Jonas T. Treebak4, Sonja Schriever1, Bryan Bergman5, Paul Pfluger1, Juleen Zierath4,6, Susanna Hofmann7,8ter1, Kenneth Dyar2, Shogo Sato3, Jonas T. Treebak4, Sonja Schriever1, Bryan Bergman5, Paul Pfluger1, Juleen Zierath4,6, Susanna Hofmann7,8

1, Institute for Diabetes and Obesity (IDO), Helmholtz Diabetes Center (HDC), Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany, 2, Metabolic Physiology, Institute for Diabetes and Cancer, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany, 3, Center for Epigenetics and Metabolism, INSERM U1233, Department of Biological Chemistry, School of Medicine, University of California, Irvine, Irvine, CA, USA, 4, Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, 5, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 6, Department of Physiology and Pharmacology, Integrative Physiology, Karolinska Institutet, Stockholm, Sweden, 7, Institute for Diabetes and Regeneration (IDR-H), Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany, 8, Department of Medicine IV, University Hospital, LMU Munich, Munich, Germany

The development of Type 2 Diabetes Mellitus (T2DM) is a slow progressive process involving multiple tissues and organs. To date, the systemic character and its implications on tissue/organ communications are only partly understood. Although, T2DM is generally the result of an impaired glucose and energy metabolism, it is typically diagnosed late in the majority of cases and its progression varies from individual to individual. Furthermore, the clinical standard to diagnose diabetes is still maily based on fasting glucose levels, which is imprecise in the prediction of pre-diabetes or obese individuals with impaired insulin sensitivity. To enable identification of accessible early predictive markers for pre-diabetes, diabetes and organ damage, and to develop individualized intervention strategies, a better understanding of the molecular and physiological changes during development of T2DM is needed.

Starting from metabolic profiling across multiple tissues under different conditions, we show how diet and timed exercise rewires tissue-specific and systemic metabolism. By arteriovenous sampling across hindlimb muscle and the liver, we highlight differential tissue production and distribution of exerkines. Subsequently, we integrated transcriptomics and metabolomics data from murine livers and identified genes with potential regulatory effects on hepatic metabolism. Among those, we found genes including the hepatokine INHBE, to correlate with diabetes-related traits such as overweight, hepatic fat content, and insulin resistance. Finally, we investigated interactions between gene expression and clinical diabetes markers in skeletal muscle and inter muscular adipose tissue (IMAT) from individuals with obesity with and without diagnosed T2D. We used multivariate regression to model the tissue specific gene expression impact on the two key IR markers, glucose infusion rate (GIR) during a hyperinsulinemic/euglycemic clamp and fasting glucose (FG). Out of the 65 top predictive genes, we identified three distinct clusters characterizing different states of gene expression patterns associated with glucose metabolism. Followed by an unsupervised classification of our study participants we revealed a refined view on an individual's metabolic state that partly differs from the clinical classification. In an independent lifestyle and exercise intervention study including individuals with obesity, with and without impaired glucose tolerance and impaired FG, we could validate previously selected gene candidates and identify four genes with significant potential to predict individual intervention responses.

Notes:

CRISPR-inhibition library to investigate non-alcoholic fatty liver disease genetic loci

Kelly De Coteau, Hannah Maude, Dorka Nagy, Lowri Morris, Inês Cebola

Section of Genetics and Genomics, Department of Metabolism, Digestion & Reproduction, Imperial College, London, UK

Non-alcoholic fatty liver disease (NAFLD) is characterised by excessive accumulation of fat in the liver and recent estimates give a global prevalence of ~30%. The lack of approved treatments for this disease is partly attributed to the poor understanding of genetic mechanisms that contribute to NAFLD development. Previous analyses have shown that NAFLD risk variants are enriched in liver cis-regulatory elements (CREs), including enhancers specifically active in hepatocytes and liver sinusoidal endothelial cells (LSECs). The goal of this work is to link NAFLD GWAS loci to disease effector genes implicated in the development of NAFLD. Therefore, we designed a pooled single-guide RNA (sgRNA) library to carry out a CRISPR inhibition screen, targeting genes and CREs associated with NAFLD and related liver traits by genome-wide association studies (GWAS). We integrated a total of 20 GWAS for NAFLD and NAFLD-related traits. The library design included curated CREs with GWAS variants, as well as the transcription start sites of genes which (1) had coding variants, (2) promoter variants, (3) were putative targets of CREs. Specifically, we prioritised noncoding variants overlapping CREs (promoters and enhancers) active in human hepatocytes and/or LSEC, using a combination of publicly available and in-house datasets: ATAC-seq from whole liver, Hep3B and LSEC, as well as ChIP-seq data from primary LSECs. Assignment of CREs to genes were as follows: (1) Variants overlapping active gene promoters were assigned to that gene, (2) variants overlapping active enhancers in at least one of the two cell types were assigned to target genes using a combination of GREAT, GeneHancer, and GTEx liver eQTLs. The list of putative target genes was further filtered for genes expressed in human liver and/or in primary hepatocytes or LSEC. Target regions were used as input for sgRNA design using CRISPick, aiming for a coverage of 10 sgRNAs per TSS and 15 sgRNAs per enhancer. Altogether, the final library included 8,063 sgRNAs, targeting 425 TSS, 218 CREs and 10 locus-specific negative control regions. This sgRNA library will be cloned into the CROP-seq-Opti backbone, which in combination with KRAB-dCas9 expressing Hep3B and endothelial cells, will be deployed in future work using Perturb-seq to identify the targets of noncoding NAFLD-associated variants. The pooled design will also enable the repurposing of the library in FACS-based assays, such as lipid staining with BODIPY. Altogether, this ongoing work will contribute to further our understanding of how specific genetic risk loci contribute to NAFLD.

Notes:

Genetic effects on the epigenome and transcriptome at genomic loci for metabolic disease

Karen Mohlke

University of North Carolina, Chapel Hill, NC, USA

Genome-wide association studies (GWAS) have identified variants in thousands of genome regions associated with metabolic disease risk or variation in quantitative traits, but the genes and variants responsible for most associations remain to be defined. To detect candidate genes and variants that may influence disease risk, genetic data can be integrated with transcriptome and epigenome data from disease-relevant tissues. To identify genes that may be altered by trait-associated variants, we detect genetic variants associated with gene expression levels, or expression quantitative trait loci (eQTL), and to identify variants that may affect gene regulation, we generate epigenome data using the assay for transposase-accessible chromatin and detect variants associated with chromatin accessibility (caQTL). We performed an eQTL meta-analysis in subcutaneous adipose tissue from 2,256 individuals in five studies and identified 34K conditionally distinct eQTL signals in 18K genes. More than 3,819 eQTL signals for 1,981 genes colocalized with GWAS signals for one or more of 28 metabolic traits. In addition, 15 genes with allelic series of at least two colocalized eQTL and GWAS signals showed a mediating gene dosage effect on a metabolic trait. QTL studies depend on sample size, and the larger study available by meta-analysis enabled more comprehensive detection of candidate genes that may affect these traits. In a separate study, we performed a caQTL analysis in liver tissue from 138 individuals and identified caQTL signals for 30K putative regulatory elements. The caQTL variants are enriched in liver tissue promoter and enhancer states and disrupt binding motifs of transcription factors expressed in liver. We identified hundreds of caQTL that colocalize with GWAS signals for 12 metabolic traits, and for at least one-third of these, the peak could be linked to a predicted target gene. Together, these eQTL and caQTL characterize human adipose and liver gene regulation and help identify molecular mechanisms and genes at GWAS loci for metabolic disease.

Poster Presentation Abstracts

Meat intake in relation to gut microbiota in the population-based Swedish CardioPulmonary bioImage Study

Shafqat Ahmad, Susanna C Larsson1,2, Ulrika Ericson3, Koen F. Dekkers4, Sergi Sayols-Baixeras4,5, Ulf Hammar4, Gabriel Baldanzi4, Diem Nguyen4, Ulf Risérus6, Karl Michaëlsson1, Johan Sundström7,8, J Gustav Smith9,10,11, Gunnar Engström3, Johan Ärnlöv12,13, Tove Fall4, Marju Orho-Melander3, Shafqat Ahmad4,14

1Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University, SE-751 85 Uppsala, Sweden; 2Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden.; 3Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden.; 4Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, EpiHubben, MTC-huset, 751 85, Uppsala, Sweden; 5CIBER Cardiovascular diseases (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain.; 6Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala University, Uppsala, Sweden.; 7Department of Medical Sciences, Clinical Epidemiology, Uppsala University, Uppsala, Sweden; 8The George Institute for Global Health, Sydney, Australia; 9The Wallenberg Laboratory/ Department of Molecular and Clinical Medicine, Institute of Medicine, Gothenburg University and the Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; 10Department of Cardiology, Clinical Sciences, Lund University and Skåne University Hospital, Lund, Sweden; 11Wallenberg Center for Molecular Medicine and Lund University Diabetes Center, Lund University, Lund, Sweden; 12Division of Family Medicine and Primary Care, Department of Neurobiology, Care Science and Society, Karolinska Institutet, Huddinge, Sweden.; 13School of Health and Social Studies, Dalarna University, Falun, Sweden.; 14Preventive Medicine Division, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, United States

Background and aims: Emerging evidence indicates that meat intake decreases the gut microbiome diversity and affects its composition. The present work aimed to identify the meat-associated gut microbiome features and its association with host factors including metabolites, traditional lipids, and inflammation biomarkers.

Methods: Gut microbiome species were profiled and compared by deep shotgun metagenomics sequencing in 9,678 individuals from the Swedish CArdioPulmonary bioImage Study (SCAPIS). Intake of red meat, including unprocessed and processed, and white meat was collected using a food frequency questionnaire. The associations of meat intake with alpha- and beta-diversity indices and relative abundance of gut microbiome species were tested using linear regression models and distance-based ANOVA with adjustment for age, sex, analytical plate, study site, total energy intake, dietary fiber intake, BMI, smoking, and education. Meat-associated species were further assessed in association with plasma metabolites, microbial gene enrichments, biomarkers of traditional lipid metabolism and inflammation related C-reactive protein measures.

Results: Higher intake of processed red meat was associated with reduced overall microbiome diversity and with 125 microbiome species, including 67 positive associations. Species positively associated with processed red meat were enriched for microbial gene functions threonine degradation and Bifidobacterium shunt energy metabolism, and were associated with increased plasma levels of creatine, carnitine, and carnosine metabolites, and C-reactive protein measures. Unprocessed red meat and white meat intake was not associated with overall microbiome diversity. Unprocessed red meat intake was positively associated with 4 species while white meat was associated with 27 species, including positive associations with 19 species.

Conclusion: This large-scale population-based study may suggest an important role of processed red meat intake in shaping the gut microbiome composition and function. Microbiome species associated with processed red meat are linked to host metabolism and health.

Metabolic reprogramming induced by periodic veganism in humans

Ozvan Bocher (1), Anargyros Skoulakis (2)

Konstantinos Rouskas (2,3)

Panagiotis Mantas(2)

Y.C. Park(1)

Stavros Glentis(2)

Alexandros C. Dimopoulos(4,5)

Gabi Kastenmüller(6)

Eleftheria Zeggini(1,7)

Antigone S Dimas(1,2)

1. Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

2. Institute for Bioinnovation, Biomedical Sciences Research Center 'Alexander Fleming', Fleming 34, 16672, Vari, Greece.

3. Institute of Applied Biosciences, Centre for Research & Technology Hellas, Thessaloniki, Greece

4. Institute for Fundamental Biomedical Science, Biomedical Sciences Research Center "Alexander Fleming", Fleming 34, 16672, Vari, Greece

5. Hellenic Naval Academy, Hatzikyriakou Avenue, Pireaus 185 39, Greece

6. Institute of Computational Biology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

7. Technical University of Munich (TUM) and Klinikum Rechts der Isar, TUM School of Medicine, Munich, Germany

The effects of dietary restriction on health have been previously described in studies focusing mostly on model organisms. Challenges around human diet studies include lack of consistency in following a particular diet, but also heterogeneity in dietary groups studied. To address these issues, we present the FastBio (Religious Fasting Biology) study comprising 200 periodic vegan (PV) individuals who follow a highly consistent diet involving alternating periods of veganism and omnivory throughout the year. PV individuals were profiled at two timepoints: during omnivory, and during a vegan type of dietary restriction, where they had abstained from meat, fish, dairy products and eggs for 3 to 4 weeks. For comparison purposes, FastBio includes 211 non-vegan (NV) individuals, who follow an omnivorous diet throughout the year. Molecular profiles including 1455 proteins from the OLINK Explore panel and 249 metabolites from the Nightingale panel were measured for all individuals at both timepoints. To evaluate the molecular impact of switching from an omnivorous to a vegan diet, we used paired differential expression analysis to compare measured traits for each dietary group across timepoints and considered significant results with FDR-corrected p-value lower than 5%. We report 410 and 201 differentially expressed proteins (DEPs) for PV and NV groups respectively, of which 146 were shared, likely reflecting seasonal effects. We also report 264 PV-unique DEPs, including proteins with a role in browning of adipose tissue, bone degradation, T cell function and cognition. From a metabolite perspective, NV individuals are almost identical at both timepoints, whereas PV individuals display a significant shift in 168 metabolites. These metabolites have directions of associations compatible with preventive effects for complex diseases including coronary heart disease and type 2 diabetes. The metabolic shift documented, encompasses decreased percentages of saturated fatty acids and omega-3, decreased levels of valine and cholesterol classes but increased levels of alanine, glycine and glutamine at the restriction timepoint, with absolute log-fold changes up to 0.25 and corrected p-values down to 2.6x10-40. Furthermore, this metabolic shift in PV individuals renders their biological age at the restriction timepoint approximately one year lower than their actual chronological age. Overall, our study highlights a rapid metabolic shift in PV individuals that is driven by 3-4 weeks of abstinence from animal products. While further work is needed to elucidate the biological pathways impacted, our results suggest that periodic veganism has mostly positive effects on human health.

Multi-“omics” prediction of incident type 2 diabetes

Julia Carrasco-Zanini(1), Maik Pietzner (1,2,3), Eleanor Wheeler(1), Nicola D. Kerrison(1), Nicholas Wareham(1), Claudia Langenberg(1,2,3)**

1. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge, CB2 0QQ, UK.

2. Computational Medicine, Berlin Institute of Health at Charité-Universitätsmedizin Berlin, 10117 Berlin, Germany.

3. Precision Healthcare University Research Institute, Queen Mary University of London, UK

The identification of people who are at high risk of developing type 2 diabetes (T2D) is a key part of population-level prevention strategies. Previous studies have evaluated the predictive utility of "omics" measurements but have considered these separately. The improvement that combined "omics" biomarkers can provide over and above current clinical standard models is unclear.

We developed sparse interpretable prediction models in a prospective, nested T2D case-cohort study (N=1105, T2D cases=375, 10,792 person years of follow-up) selecting from 5759 features across the genome, proteome, metabolome and clinical biomarkers using least absolute shrinkage and selection operator (LASSO) regression. We compared the predictive performance of "omics" derived predictors to a clinical model including the variables from the Cambridge T2D risk score and HbA1c.

The top 10 proteins alone achieved the highest performance (concordance index (C-index) = 0.82 (95% confidence interval (CI) 0.75 - 0.88)) among single "omics" predictors, suggesting the proteome as the most informative single "omics" layer. Prediction of T2D incidence was only significantly improved over and above the clinical model by the top 10 features across several "omics" layers (C-index = 0.87 (95% CI 0.82 - 0.92), delta C-index = 0.05, p-value = 0.045). This improvement was most relevant in individuals with HbA1c below the threshold for prediabetes (C-index = 0.84 (95% CI 0.77 - 0.90), delta C-index = 0.07, p-value = 0.03), in whom prediction would be most useful as they are not targeted for preventative interventions by current clinical guidelines. In this subgroup, the T2D-polygenic risk score (PGS) was the mayor contributor to the improvement in prediction, which alone, resulted in a comparable improvement in performance over the clinical model (C-index = 0.83 (95% CI 0.75 - 0.90), delta C-index = 0.06, p-value = 0.002). However, individuals at high polygenic risk were at around half the absolute risk for T2D compared to individuals with prediabetes over a 20-year follow-up period.

"Omics" approaches provided significant improvements in prediction of incident T2D. However, while a PGS does improve prediction in people with an HbA1c in the normoglycaemic range, the group in whom prediction would be most useful, even individuals with a high polygenic burden in that subgroup had a low absolute T2D risk. This suggests a limited feasibility of implementing targeted population-based genetic screening for preventative interventions.

Subcellular proteomics identifies novel insulin-responsive proteins in adipocytes

Olivia J. Conway, Josie A. Christopher (2), Lisa M. Breckels (2), Dougall M. Norris (1), Satish Patel (1), David B. Savage (1), Kathryn S. Lilley (2), Daniel J. Fazakerley (1)

(1) Wellcome-MRC Institute of Metabolic Science – Metabolic Research Laboratories, University of Cambridge, Cambridge, UK.

(2) Department of Biochemistry, University of Cambridge, Cambridge, UK.

Adipocytes provide a site of energy storage after feeding, and release energy during fasting. In the fed state, insulin promotes glucose and lipid uptake and storage, whereas β3-adrenergic signalling promotes lipolysis and fatty acid/glycerol release during fasting. Both these metabolic states are mediated by changes in protein localisation. For example, insulin acutely increases the abundance of glucose transporters at the plasma membrane, whilst β3-adrenergic signalling increases lipase localisation to lipid droplets.

Given the importance of protein translocation in adipocyte function, we have generated a subcellular map of the 3T3-L1 adipocyte proteome in unstimulated cells, and under conditions that mimic feeding (100 nM insulin, 30 min), or fasting (1 nM CL316,243, 30 min). We used two orthologous proteomic approaches: Localisation of Organelle Proteins by Isotopic Tagging after Differential UltraCentrifugation (LOPIT-DC) to map the whole-adipocyte spatial proteome, and plasma membrane-specific biotinylation to give greater resolution of changes in the adipocyte plasma membrane proteome.

This approach has revealed novel subcellular protein translocation events in response to insulin and β3-adrenergic signalling, including movement between intracellular organelles and from intracellular sites to the plasma membrane. Focussing on insulin-responsive translocation to the plasma membrane, we identified c3orf18, an uncharacterised protein-of-interest that translocates to the adipocyte plasma membrane in response to insulin. Initial characterisation suggests this transmembrane protein plays a role in insulin-stimulated glucose uptake by regulating insulin signalling. Work is ongoing to characterise the precise role of c3orf18 in insulin-stimulated glucose uptake.

Variant-to-function translation of obesity-associated loci through multi-omics data integration

Virginia Díez-Obrero, Roelof A J Smit, Marta Guindo-Martínez, Ruth J.F. Loos

Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background

Genome-wide association studies (GWAS) have identified hundreds of loci associated with body mass index (BMI). However, the variant-to-function translation of only a handful of these loci has been successful.

Objectives

Here, we aim to identify candidate effector genes within BMI-associated loci, and reveal their molecular effects, to ultimately provide new biological insights into obesity pathogenesis.

Methods

We integrated GWAS summary statistics of BMI reported by the GIANT Consortium (Yengo et al, 2018) with multi-omics quantitative trait loci (QTLs), including plasma-derived gene expression, protein, and metabolite QTLs (e/p/metabQTLs), and brain and adipose tissue-derived eQTLs from different studies. We performed colocalization analyses to detect shared genetic signals between BMI and -omic traits. We used cis-e/pQTLs to identify candidate effector genes within loci, and trans-e/p/metabQTLs to pinpoint the molecular effects of cis-colocalizing loci. We implemented a two-sample Mendelian Randomization approach to assess the causal relationship between -omic traits and BMI.

Results: Cis-e/pQTLs of 916 genes colocalized at 259 of the 536 BMI-associated loci. The integration of multiple QTL datasets from different tissues maximized the power for discovery. In 18 of the 259 loci, the same genes colocalized both at the gene expression- and protein-level (e.g., TTC12 and LYZ). Trans-e/pQTLs and/or metabolite-QTLs colocalizing in 181 of the 259 cis-colocalizing loci pointed to molecular mechanisms. For example, we found that genetic variants in GIPR that are associated with higher BMI and cardiovascular disease, also associate with higher protein levels of GIP, lower protein levels of SCGB3A1, QPCTL, and MSMB, and lower levels of X-12818 metabolite in plasma. Furthermore, the protein levels in plasma of 62 genes, such as SNX1 and PRKCB, are causally associated with BMI, which may provide new biomarkers of obesity risk. We developed a web browser for visualizing the results, which will be available at https://shinyapp01.ku.dk/BMI_multiomics/.

Conclusion

Integrating multi-omics data with GWAS results successfully provided new molecular insights into the variant-to-function translation of BMI-associated loci.

Identifying potential therapeutic targets in liver fibrosis using SCINDY, a computational pipeline for profiling cell-cell interactions

Pengwei Dong, Linshan Zhang, Yifan Liang, Shitong Ding, Wei Xiong Wen, Bethan Psaila, Supat Thongjuea, Adam Mead, Kang Zhu, Guanlin Wang

Institute of Metabolism and Integrative Biology, Fudan University, Shanghai, P.R. China, 200438

Single cell transcriptomics (scRNAseq) enables high-resolution insights into cellular composition, heterogeneity and molecular pathways. However, the cell-cell interactions and spatial details of the native tissue architecture are lost during sample processing, which are crucial in the development and function of organisms. To overcome this limitation, we have developed a novel machine learning-based computational tool - an open access R package SCINDY to profile and predict key ligand and receptor interactions and reconstruct cellular communications using scRNAseq data. SCINDY includes a new curated ligand-receptor database of more than ~3000 ligand-receptor pairs and a removal of interaction 'noise' step to reduce the false positive interactions, which is not included in other widely used pipelines such as CellPhoneDB and NicheNet. The interaction prioritization model is adjusted and validated using spatial transcriptomics datasets. As an example, we applied the SCINDY package to liver fibrosis, a pathological process characterized by the excessive accumulation of extracellular matrix proteins in the liver. Using SCINDY, we found upregulated TGFB1 expression and elevated fatty acid oxidation and IL4 signals in the fibrotic liver using integrated scRNAseq datasets of >500,000 cells from control and patients with liver fibrosis. These results suggest that interactions between immune cells and hepatocyte cells in the fibrotic liver undergo metabolic reprogramming. Furthermore, we also detected an 'inflammatory' microenvironment with significant cytokine/chemokine interactions between immune cells and stromal cells, particularly in hepatocytes (e.g., CCL2-CCR2). We further validated these ligand-receptor interactions using a publicly available cirrhosis spatial transcriptomics dataset. In summary, SCINDY has the ability to identify potential therapeutic targets for anti-liver fibrosis and can be further applied to other diseases.

Multimolecular screening of human physiologies with infrared molecular fingerprinting

Tarek Eissa, Mihaela Zigman, Cristina Leonardo, Kosmas Kepesidis, Frank Fleischmann, Christian Gieger, Birgit Linkohr, Daniel Meyer, Viola Zoka, Lothar Richter, Annette Peters

[1] Ludwig Maximilian University of Munich, Department of Laser Physics, Garching, Germany

[2] Max Planck Institute of Quantum Optics, Laboratory for Attosecond Physics, Garching, Germany

[3] Technical University of Munich, Department of Informatics, Garching, Germany

[4] Helmholtz Munich Zentrum München, Institute of Epidemiology, Neuherberg, Germany

Describing human health physiologies in an accurate, high-throughput, and cost-effective manner is a long standing challenge. Multimolecular gateways probing the composition of biological substances thus have the potential to contribute to medical screening, enabling timely diagnostics and early therapeutic interventions. Infrared spectroscopy is a powerful analytical technique that has great potential with its capability of decoding the molecular content of biological samples and, thereby, enabling the detection of a multitude of conditions linked to human physiologies. The technology relies on the fact that every molecule absorbs light in a unique spectral pattern that depends on its chemical structure. When biological samples are exposed to broadband infrared radiation, the resulting spectra provide information on the types of chemical bonds, as well as their concentrations, present within. In this sense, infrared spectra integrate the entire set of omes of a sample and allow for label-free profiling.

However, the translation of this technology into clinical practice has not been achieved. It faces several challenges, which include the standardization of protocols, interpretation of complex spectra, and the need for large-scale validation studies. In a large-scale population-based study (n = 5184), we combined Fourier transform infrared (FTIR) spectroscopy of blood plasma with machine learning analysis of spectral patterns to assess whether the approach meets the prerequisites of population-wide medical screening. Specifically, we assessed the efficacy of detecting a set of highly prevalent, co-occurring health phenotypes-dyslipidemia, hypertension, prediabetes, type-2 diabetes, and healthy states-in a parallel fashion. We find that infrared molecular spectra encode information which facilitates the simultaneous detection of multiple phenotypic states-ranging from healthy to multimorbid states-in a robust and dataset-independent fashion. Furthermore, we reveal that infrared spectra of blood plasma heavily correlate to multiple commonly measured clinical chemistry analytes, which facilitates their interpretability through a clinical context.

Given the size of the population examined and medical data evaluated, involving realistic multi-year variations in clinical sample collection and measurement times, we identify a new practical application for an established technology that shall be further tailored for defined use-cases. Especially relevant in light of the high level of within-person stability of blood-based infrared molecular spectra over time, which was confirmed in a previous study. Altogether, we present a proof-of-concept that blood-based infrared molecular probing offers a robust and minimally invasive multi-phenotyping platform that delivers clinically-actionable evaluations.

Longitudinal multi-omic analyses in the MultiMuTHER study reveal cross-sectional and longitudinal interplay between gene expression and metabolite levels in whole blood

JS El-Sayed Moustafa1, A Ramisch2,3, Y Raza1, G Leday4, Y Jiao5,6,7, G Nicholson7, D Wang1, M Stevens2,3, M Abdalla5,6,7, C Menni1, C Holmes7, MI McCarthy5,6,8, ET Dermitzakis2,3, S Richardson4, TD Spector1 and KS Small1

1. Department of Twin Research and Genetic Epidemiology, King's College London, UK

2. Department of Genetic Medicine and Development, Faculty of Medicine, University of Geneva, Switzerland

3. Institute of Genetics and Genomics in Geneva, Switzerland

4. Medical Research Council Biostatistics Unit, Cambridge, UK

5. Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, UK

6. Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, UK

7. Department of Statistics, University of Oxford, UK

8. Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Trust, UK

Multi-omic datasets represent a snapshot of the system's physiological state, and are increasingly being considered for health monitoring and earlier identification of disease risk. Deeper understanding of context-specificity, longitudinal stability, cross-sectional and longitudinal interplay between concurrently-measured 'omics is critical to our understanding of the molecular evolution of ageing and complex disease.

We explored longitudinal multi-omic stability as well as cross-sectional and longitudinal patterns of co-variation in the MultiMuTHER study, which comprises gene expression (RNASeq-16,292 genes) and metabolomics (Metabolon-1,197 metabolites) data in whole blood at three or more timepoints over up to eight years per individual from 335 TwinsUK subjects [age range 32-80; median=61yrs]. TwinsUK is a deeply-phenotyped cohort of twins with extensive 'omics data and repeat phenotypic measures. Longitudinal gene expression and metabolome-wide association analyses revealed expression levels of ~30% of genes and over 35% of metabolites showed significant change over time (FDR 5%), revealing systemic effects of time on the transcriptome and metabolome.

We next employed multiple complementary multi-omic approaches to assess the relationships between whole blood gene expression and metabolite levels. We first fitted mixed effects models to identify gene-metabolite pairs whose levels were associated across all timepoints. We identified 105,629 metabolite-gene associations at 5% FDR. Expression of each gene was associated with a median (1st-3rd quartiles) of 4 (2-10) metabolites, while each metabolite was associated with a median (1st-3rd quartiles) of 37 (13-119) genes. Expression levels of 18 genes were found to be associated with levels of more than 10% of metabolites. These included a number of genes whose expression levels were shown to change over time, including CPT1A, SLC25A20, PDK4, ACAA2 and GATA2.

Taking a system-wide approach to identify relationships in the patterns of longitudinal change in genes and metabolites, we assessed the pattern of correlations between individual-level longitudinal slopes for all genes and metabolites whose levels exhibited longitudinal change. In longitudinally-correlated gene-metabolite pairs, we identified a number of hub genes and metabolites exhibiting high connectivity in this subset, including the metabolite quinolinate, and the genes PDK4, SLC25A20, ST14 and CPT1A.

In summary, we have performed one of the largest multi-omic longitudinal studies of concurrently-measured gene expression and metabolite levels in whole blood, identifying patterns of multi-omic changes over time, as well as over 100,000 gene-metabolite associations. This study provides novel insight into the interplay between gene expression and metabolite levels, and may inform systems-wide approaches to projection of temporal progression of age-related diseases.

Establishing the proteomic and metabolomic signature of weight loss

Lucy J. Goudswaard, Madeleine L. Smith, David A. Hughes, Naveed Sattar, Roy Taylor, Michael E. J. Lean, Alex McConnachie, Paul Welsh, NIHR By-Band-Sleeve Trial Management Group, Laura J. Corbin, Nicholas J. Timpson

University of Bristol, University of Glasgow, Newcastle University

Background

Adiposity is associated with an increased risk of type 2 diabetes (T2D) and cardiovascular disease. It is likely that a change in circulating proteins and metabolites plays a role in obesity-related disease risk. This study aimed to triangulate evidence from randomized controlled trials of caloric restriction and bariatric surgery, along with Mendelian randomisation (MR) to characterise the effects of body mass index (BMI) on circulating molecular traits.

Methods

Data from trials of surgically and medically induced weight loss were compared along with evidence from Mendelian randomisation. Participants from a subset of the By-Band-Sleeve trial of surgically induced weight loss (N=125) had samples available from baseline and 3-years post randomisation, where circulating proteins were measured by Olink Explore 1536 and metabolites were measured using Metabolon. The Diabetes Remission Clinical Trial (DiRECT, N=292) included participants with overweight/obesity (baseline mean BMI 35 kg/m2, SD 4.5 kg/m2) who underwent either a low energy total diet replacement (intervention) or were allocated to guideline T2D care (control). Plasma samples were taken at baseline and after 1-year and SomaLogic and Metabolon were used to quantify plasma proteins and metabolites, respectively. Lastly, molecular traits with consistent evidence across both trials were also explored using MR to estimate the causal effect of BMI.

Results

Changes were observed in 191 proteins and 44 metabolites following bariatric surgery. Protein effects include a decrease in pro-inflammatory proteins, e.g., leptin and interleukin-1 antagonist protein (IL1RN). Metabolites that were associated with surgery were largely from lipid and amino acid pathways. In a comparative analysis, 23 proteins and 15 metabolites were found to be associated with both surgical and dietary interventions (weight loss non-specific), whilst 161 proteins and 107 metabolite changes were unique to one or other study (intervention specific). MR analyses provided a separate line of evidence for a causal role of BMI in regulating the levels of six proteins including insulin-like growth factor binding protein-1 and IL1RN.

Conclusion

This study made use of distinct study designs and analytical approaches to explore the effect of BMI on molecular traits. Molecular effects that are specific to only one intervention may provide valuable biological insight into either bariatric surgery or caloric restriction mechanisms. Observing consistency across such analyses provides greater confidence that the effects we see reflect genuine physiological responses to differential BMI. These consistent molecular traits are currently being explored as potential intermediates of obesity and disease outcomes.

Association of ceramide with rapid decline in kidney function and end stage kidney disease in patients with type 2 diabetes

Resham L Gurung1, Yiamunaa M1, Jian-Jun Liu1, Sylvia Liu1, Wai Kin Tham2, Janus Lee1, Federico Tesio Torta2, Keven Ang1, Marcus Wenk2, Su Chi Lim1,3,4,5

1Clinical Research Unit, Khoo Teck Puat Hospital, Singapore; 2 Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; 3Diabetes Centre, Admiralty Medical Centre, Singapore; 4Saw Swee Hock School of Public Heath, Singapore; 5Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Objective

Earlier identification of patients with type 2 diabetes (T2D) at risk for kidney disease is important to prevent kidney function decline and kidney failure. Plasma ceramides have been linked to diabetic kidney disease (DKD). We aimed to investigate the association between plasma ceramide and ceramide scores and a rapid decline in kidney function (RDKF) and end-stage kidney disease (ESKD) in patients with T2D.

Method

This prospective study involved 1746 T2D participants aged 21-65 with an estimated glomerular filtration rate (eGFR) of more than 30/min/ 1.73m2 at baseline. RDKF and ESKD were defined as a decline of more than 5ml/min/1.73m2/yr and eGFR less than 15/min/ 1.73m2 for at least three months on dialysis or renal death at follow-up, respectively. Linear mix model was used to generate the eGFR slope including patients with > 2 eGFR reading and minimum of 2 years follow-up period.

High risk ceramide levels Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/24:0) and Cer(d18:1/24:1) were measured using Liquid chromatography-mass spectrometry (LC-MS) at baseline. Ceramides were analyzed as continuous variables (per SD), ratios (natural log-transformed), and categorical (3 groups) based on ceramide scores with adjustment for age, sex, ethnicity, current smoking status, history of cardiovascular disease, body mass index, HbA1c, diabetes duration, mean arterial pressure, LDL-cholesterol, triglyceride, eGFR and urine albumin to creatine ratio (uACR) and usage of Renin-Angiotensin System (RAS) antagonist.

Results

During a median (interquartile range) follow-up period of 7.7 (4.7-8.9) years, 197 (11%) patients experienced RDKF. Ceramide Cer(d18:1/24:0) (OR=0.71, 95%CI 0.56-0.90, P=0.005, per SD), and ceramide ratios Cer(d18:1/16:0)/Cer(d18:1/24:0) (OR=3.54, 95%CI 1.70-7.35, P=0.001), Cer(d18:1/18:0)/Cer(d18:1/24:0) (OR=1.89, 95%CI 1.10-3.25, P=0.022) and Cer(d18:1/24:1)/Cer(d18:1/24:0) (OR=4.01 95%CI, 1.93-8.31, P=0.0002) remained significantly associated with RDKF after adjusting for covariates. Participants in the higher ceramide score group had 1.66-fold (95%CI 1.04-2.64, P=0.032) higher odds of RDKF than those in the lower ceramide score group.

A total of 124 patients experienced ESKD. Ceramide ratios Cer(d18:1/16:0)/Cer(d18:1/24:0) (HR=3.10 95%CI 1.44-6.64, P=0.004), and Cer(d18:1/24:1)/Cer(d18:1/24:0) (HR=4.66 95%CI 1.93-11.24, P=0.001) were significantly associated with higher risk of ESKD. Participants in the higher ceramide score group had a higher risk for ESKD than those in the lower ceramide score group but were not independent of baseline kidney function.

Discussion

Distinct ceramides, ceramide ratios and scores were significantly associated with a decline in kidney function in T2D patients, independent of conventional risk factors. Further studies are warranted to determine the clinical diagnostic value of distinct ceramides in identifying T2D patients at risk of kidney failure.

Aerobic exercise training and gut microbiome-associated metabolic shifts in women with overweight: A multi-omic study

Jukka E Hintikka, Juha P Ahtiainen, Perttu Permi, Marko Lehtonen, Satu Pekkala

Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Department of Biological and Environmental Science, Nanoscience Center, University of Jyvaskyla, Jyvaskyla, Finland

Faculty of Health Sciences, School of Pharmacy, University of Eastern Finland, Kuopio, Finland

Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Physical activity is essential in weight management, improves overall health, and mitigates obesity-related risk markers. Besides inducing changes in systemic metabolism, habitual exercise may improve gut's microbial diversity and increase the abundance of beneficial taxa in a correlated fashion. Since there is a lack of integrative omics studies on exercise and overweight populations, we studied the metabolomes and gut microbiota associated with programmed exercise in obese individuals subjected to programmed exercise. We measured the serum and fecal metabolites of 17 adult women with overweight during a six-week endurance exercise program. Further, we integrated the exercise-responsive metabolites with variations in the gut microbiome and cardiorespiratory parameters. We found clear correlation with several serum and fecal metabolites, and metabolic pathways, during the exercise period in comparison to a preceding control period, indicating increased lipid oxidation and oxidative stress. Especially, exercise caused co-occurring increase in levels of serum lyso-phosphatidylcholine moieties and fecal glycerophosphocholine. This signature was associated with several microbial metagenome pathways and the abundance of Akkermansia. The study demonstrates that, in the absence of body composition changes, aerobic exercise can induce metabolic shifts that provide substrates for beneficial gut microbiota in individuals with overweight or obesity.

Body mass regulation is associated with genetic variation at ribosomal DNA

Michelle L. Holland, Pui Pik Law, Francisco Rodriguez-Algarra*, Fredrika Asenius, Maria Gregori, Robert A E Seaborne, Robin Mesnage, Michael N. Antoniou, Weilong Li, Qihua Tan, Sara L Hillman, Vardhman K Rakyan, David J Williams*

nt of Medical and Molecular Genetics, School of Basic and Medical Biosciences, King's College London, UK.

The Blizard Institute, School of Medicine and Dentistry, Queen Mary University of London, UK.

UCL EGA Institute for Women's Health, University College London, London, UK.

4

Population Research Unit, University of Helsinki, Helsinki, Finland.

5

Epidemiology, Biostatistics and Biodemography, Department of Public Health, University of Southern Denmark, Denmark.

Modern lifestyles have driven a surge in obesity incidence, presenting a significant public health issue. The understanding of the genetic basis of an individual's response to an obesogenic environment is therefore an important area of enquiry. So far, much has been learnt about how variation in single copy loci contribute to body mass (BM) regulation. However, due to technical reasons, large scale studies of repetitive parts of the genome in relation to trait variation have been more challenging. One such region is the 45S-ribosomal DNA (45S-rDNA). There are 100s of 45S-rDNA copies in mammalian genomes, as they encode for the 18S, 5.8S and 28S rRNAs and therefore are essential for ribosome production and protein synthesis. 45S-rDNA is not included in genome assemblies because of its repetitive organisation and as such is excluded from studies of genetic variation. However, extensive interindividual genetic variation in 45S-rDNA has been shown in mice and humans. Our previous work identified 45S-rDNA to be epigenetically responsive to early life nutrition in mice. Therefore, we used a novel approach to analyse whole genome bisulfite sequencing data from blood of obese and lean men. 45S-rDNA was the only repetitive genome feature to show altered DNA methylation between the groups. On further analysis, this result was driven by a strong correlation between 45S-rDNA copy number (CN) and methylation, with obese individuals having lower 45S-rDNA CN. We validated the CN-BM association in adipose tissue from an independent cohort not selected for the extremes of BM, replicating the negative correlation between BM and 45S-rDNA CN. Analysis of a separate cohort of BM-discordant monozygotic twins showed that 45S-rDNA CN was not altered, suggesting the association is due to germ-line inherited 45S-rDNA CN. 45S-rDNA CN variation is not strongly influenced by genetic variation elsewhere in the genome, including that previously implicated in BM associations. The association between 45S-rDNA CN and BM is not unique to humans. Using longitudinally collected weight data from rats, we show that 45S-rDNA CN is negatively correlated with the growth rate between sexual maturity and young adulthood. The cross-sectional association of BM and 45S-rDNA CN only emerges at the end of this period, suggesting that the critical developmental window for any mechanism through which this association is acting is likely to be up to this point. In summary, our work highlights that 45S-rDNA CN may be a previously unknown genetic factor associated with BM variation.

Temporal intra-individual variability of multi-omics signatures and their dependence of the nutritional status in metabolic disease

Aimo Kannt, Nicole Ziegler, Sonja Luckhardt

Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Frankfurt am Main, Germany

Omics technologies and multiplex analysis systems have opened new possibilities for comprehensive disease phenotyping and precision medicine, including the identification of biomarkers predicting disease progression or response to therapy. In contrast to, for example, genomic characteristics, circulating metabolites and proteins are more prone to variations due to environmental factors, circadian fluctuations and in response to nutrition. However, such biomarkers might particularly be relevant in the context of metabolic disorders.

Thus, we investigated intra-individual variabilities of the metabolic and proteomic signatures in a tightly controlled clinical study over four weeks (3 visits) in patients with type-2 diabetes (T2D), in pre-diabetic individuals and healthy controls (n=10 each), before and after intake of a mixed meal. In total, more than 1400 metabolites and 350 proteins were included in the current analysis, allowing for a comprehensive characterization of disease-related parameters in relation to nutritional status.

Our data reveal that the serum metabolome is generally stable over time, indicated by a median intra-class correlation coefficient (ICC) of 0.65 across all metabolites. As expected, disease groups vary significantly in their metabolite profile, healthy controls thereby being most different from the two other groups. Interestingly, differences between T2D patients and pre-diabetic as well as healthy individuals became larger after meal intake compared to the fasting state.

Similar results were obtained with the proteomics approach. While intra-individual variability is, except for some specific markers, rather low, protein signatures varied considerably between the three groups. Among many other proteins, for example, Cadherin-2 (CDH2), Hepatocyte growth factor (HGF) and Fibroblast growth factor (FGF)-21 were increased in T2D patients and pre-diabetic individuals compared to healthy controls.

Differences in response to meal intake were much more pronounced in the metabolome than the protein profile. While 381 out of 1438 metabolites (~26%) significantly changed upon meal intake, with 114 being differentially regulated between T2D patients and healthy controls, only approximately 2.5% of proteins were significantly affected by the nutritional status, among them FGF-21, Ghrelin (GHRL) and Keratin (KRT) 19.

Our data will further serve as a basis for the identification and validation of disease-associated protein and metabolite signatures that might unveil potential biomarkers for clinical applications.

Multi-omics analysis of the human gut microbiome in relation to human disease and quantitative traits

Maria Kardakova, Sergey Musienko2, Kirill Danilov2, Murad Omarov2, Anna Popenko2, Julien Terroire1,3, Inga Prokopenko1,3, Ayse Demirkan1,3.

1 Section of Statistical Multi-Omics, Department of Clinical & Experimental Medicine, University of Surrey, Guildford, UK

2 Atlas Biomed Group Limited, London, UK

3 People-Centred Artificial Intelligence Institute, University of Surrey, Guildford, UK

The human gut microbiome is determined by lifestyle, diet, medication and host genetics. The composition of the microbiome is a potential predictor of host health. Using the Atlas Biomed Group (ABG) dataset of 4548 individual-level 16S rRNA gene sequence data, we captured changes in the gut microbiome across multiple self-reported phenotypes, including T2D, obesity, depression, PCOS, hypothyroidism, migraine, psoriasis, lactose intolerance, celiac disease and inflammatory bowel diseases (IBD): ulcerative colitis and Crohn's disease. The 16S rRNA data were processed using the QIIME-2 method. Association of gut microbial relative abundance (RA) with phenotypes was performed using linear models in MaAsLin2 and ANCOM-BC software packages in parallel. Models were adjusted for a geographical region, age and gender and included RA as an outcome.

Over 50 unique taxa were significantly associated (q-value<0.05) with various phenotypes of interest with concordance between ANCOM-BC and Maaslin2 tests. IBD status and obesity status were inversely associated with Catabacter RA. Victivallis presence was negatively associated with a history of depression, IBD and obesity. Terrisporobacter RA was lower in the T2D and depression groups; Lachnospira RA was significantly lower among those with Crohn's disease, T2D and IBD. Bacteroides were more abundant in the IBD and Crohn's disease groups than in the controls. The beta diversity has been investigated during the analysis. Differences in a geographical region, age and gender of participants led to variations in microbiome richness, beta and alpha diversity and composition across the cohort. The alpha diversity of the microbiome was significantly different (p-value<0.05) in individuals with obesity, PCOS, T2D, IBD and depression compared to controls.

In the current study, we provide a broad basis and hypotheses for further identification of the role of the gut microbiome in various health complications. Future multi-omics analyses will also incorporate genetic information using GWAS analysis and will consider physical activity levels, sleep duration, medications, smoking status and dietary patterns, which will account for the environmental component of the effects found.

Peptidomics – the missing piece of the multi-omics puzzle

Richard Kay, Vian Azzu 1,2, Amy George1, Gabriele Mocciaro1, Fiona Gribble1, Frank Reimann1, Mattia Frontini2, Michael Allison2, Richard Kay1

1. Wellcome-MRC Institute of Metabolic Science, University of Cambridge, UK

2. Liver Unit, Addenbrookes Hospital, Cambridge, UK.

Introduction

The mass spectrometric analysis of endogenous peptides is still a relatively new field, with very few laboratories performing peptidomics studies. However, endogenous peptides have many physiological roles, especially in energy homeostasis and metabolism, highlighting their importance as bioactive molecules. Despite this, compared to metabolomics or proteomic studies, only very few peptidomics analyses have been performed on disease cohorts mainly due to the challenge of extracting peptides from the background of high abundant plasma proteins.

Methodology

A plasma peptidomics pipeline has been developed based around organic solvent precipitation and solid phase extraction, which can rapidly and accurately extract peptides from plasma for subsequent LC-MS/MS analysis and has been applied to multiple clinical challenges. High resolution mass spectrometry systems have been used to characterise the presence of complex peptides such as des 31-32 and des 64-65 proinsulin in patients with insulin auto immune syndrome and prohormone convertase deficiency. Whilst targeted quantitation on triple quadrupole systems have enabled the detection and quantitation of peptides which don't currently have suitable commercial immunoassay reagents such as motilin and insulin-like peptide 5.

Non-Alcoholic Fatty Liver Disease (NAFLD) Clinical study

Using an established peptidomics pipeline, serum samples from patients with NAFLD were extracted and analysed using an untargeted peptidomics approach, and identified a significant number of peptide biomarkers that were capable of distinguishing NAFLD patients from controls. These included oxidised intact apolipoproteins such as APOC3 (affecting all three major glycoforms - APOC30, APOC3i and APOC3ii) as well as oxidised and degraded fragments of the same proteins. Once these biomarkers had been characterised using bioinformatics programs, a triple quadrupole analysis was performed to quantify these peptides on a larger sample cohort (87 patients, 20 controls). This high throughput analysis was performed using equipment already used in clinical biochemistry laboratories, with a short 10 minute analyses using only 10 µL of starting serum. Monitoring these biomarkers enabled the characterisation of liver disease samples with high accuracy (ROC values of 0.95 and higher). This methodology could potentially be transferred to clinical labs as a screening technique for NAFLD once validated.

Conclusions

The peptidome is a highly under studied space in clinical research, and has potential to contain novel biomarkers of metabolic disease which are being completely missed by metabolomics and proteomics approaches.

Cross-omic analysis highlights epigenetic setpoints following a polyphenol-rich diet: DIRECT PLUS trial

Anne Hoffmann, Anne Hoffman, Anat Yaskolka Meir, Tobias Hagemann, Luise Müller, Beatrice Engelmann, Ulrike Rolle-Kampczyk, Gal Tsaban, Hila Zelicha, Ehud Rinott, Alon Kaplan, Ilan Shelef, Michael Stumvoll, Matthias Blüher, Liming Liang, Uta Ceglarek, Berend Isermann, Martin von Bergen, Peter Kovacs, Maria Keller, Iris Shai

1 Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Center Munich at the University of Leipzig and University Hospital Leipzig, Leipzig, 04103, Germany

2 The Health & Nutrition Innovative International Research Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, 84101 Beer-Sheva, Israel

3 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

4 Medical Department III – Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Leipzig 04103, Germany

5 Department of Molecular Systems Biology, Helmholtz Centre for Environmental Research – UFZ, 04318 Leipzig, Germany

6 Soroka University Medical Center, 84101 Beer-Sheva, Israel

7 Deutsches Zentrum für Diabetesforschung e.V., 85764 Neuherberg, Germany

8 Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, Universitätsklinikum Leipzig, Leipzig University, 04103 Leipzig, Germany.

9 Institute of Biochemistry, Faculty of Life Sciences, University of Leipzig, 04103 Leipzig, Germany

10 Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

Abstract

Background: The capacity of a polyphenol-enriched diet to modulate the epigenome in vivo is partly unknown. Given the beneficial metabolic effects of a Mediterranean (MED) diet enriched in polyphenols and reduced in red/processed meat (greenMED) in the 18-month DIRECT PLUS randomized controlled trial, we analyzed the effects of the greenMED diet on methylome and transcriptome to highlight molecular mechanisms underlying the observed metabolic improvements.

Methods: The study included 260 participants (baseline BMI= 31.2 kg/m2, age=51 years) of the DIRECT PLUS trial, initially randomized to one of the intervention arms: healthy dietary guidelines (HDG), MED (further 440mg polyphenols were provided by walnuts) and green-MED (further 1240mg polyphenols were provided by walnuts, green tea and green duckweed shake). Blood methylome and transcriptome of all study subjects were analyzed at baseline and after completing the 18-month intervention using Illumina EPIC and RNA sequencing technologies.

Results: A total of 1,573 Differentially Methylated Regions (DMRs; false discovery rate (FDR)<5%) was found in the greenMED compared to the MED (177) and HDG (377) intervention. This corresponded to 1,753 Differentially Expressed Genes (DEGs; FDR<5%) in the greenMED arm compared to MED (7) and HDG (738). Consistently, the highest number (6%) of epigenetic modulating genes was transcriptionally changed by the greenMED diet. Weighted Cluster Network Analysis for the greenMED intervention between transcriptional and phenotype changes, including urine polyphenol intensities, identified candidate genes in association with folic acid change (all P<1x10-3) and highlighted one module including the KIR3DS1 locus, being negatively correlated with the polyphenol changes (e.g. P-value<1x10-4) but positively with the superficial subcutaneous adipose area-, weight- and waist circumference-change (all P<0.05) after the greenMED diet. Amongst others this module also included the Cystathionine Beta-Synthase a DMR gene playing a major role in homocysteine reduction.

Conclusion: Overall, the greenMED diet renders a high capacity to regulate individual's epigenome. Our findings suggest epigenetic key drivers such as folate to mediate this capacity but also indicate a direct effect of dietary polyphenols on the one-carbon metabolism.

The causal effects of lipids on Kidney function in Africans: bidirectional and multivariable Mendelian-randomization study

Christopher Kintu, Opeyemi Soremekun 1, Mayanja Richard 1,2, Abram B. Kamiza 1,3, Allan Kalungi 1,5, Robert Kalyesubula 5, Bagaya S. Bernard 2, Daudi Jjingo 2, Tinashe Chikowore 1,6, Segun Fatumo 1, 4,5, 7

1The African Computational Genomics (TACG) Research Group

2Department of Immunology and Molecular Biology, School of Biomedical Sciences, Makerere University College of Health Sciences, Kampala, Uganda.

3Malawi Epidemiology and Intervention Research Unit, Lilongwe, Malawi

4H3Africa Bioinformatics Network (H3ABioNet) Node, Centre for Genomics Research and Innovation, NABDA/FMST, Abuja, Nigeria

5Medical Research Council/ Uganda Virus Research Institute/London School of Hygiene and Tropical Medicine (MRC/UVRI/LSHTM) Uganda research unit, Entebbe, Uganda

6MRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

7Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom

Background: Observational studies have investigated the effect of serum lipids on kidney function, but these findings are limited by confounding, reverse causation and have reported conflicting results. Mendelian randomization (MR) studies address this confounding problem. However, they have been conducted mostly in Europeans. We, therefore, set out to investigate the effect of lipid traits on the estimated glomerular filtration rate (eGFR) in individuals of African ancestry.

Methods: We used the Two-sample and multivariable Mendelian Randomization approaches; in which instrument variables (IVs) for the predictor (lipid traits) were derived from summary-level data for the meta-analysis of The African Partnership for Chronic Disease Research (APCDR) (n= 13,612) & the Africa Wits-IN-DEPTH partnership for Genomics studies (AWI-Gen) dataset (n=10603,). The outcome IVs were computed from the eGFR summary-level data of African-ancestry individuals within the Million Veteran Program (n=57336). A random-effects inverse variance method was used in our primary analysis, and pleiotropy was adjusted for using robust and penalized sensitivity testing.

Results: A significant association between genetically predicted low-density lipoprotein (LDL) cholesterol and eGFR in African ancestry individuals (= 1.1, 95% CI = [0.411-1.788]; p=0.002). Similarly, total cholesterol (TC) levels were significantly associated with low eGFR (= 1.619, [0.412-2.826]; p=0.009). In the multivariable analysis inverse-variance weighted (MVIVW) method, there was substantial evidence for a causal association between LDL and TC with eGFR after adjusting for collinearity between lipid traits (= 1.228 [0.477-1.979]; p=0.001) and (= 1.357 [0.444-2.27]; p=0.004) respectively. A protective effect of Triglycerides (TG) on eGFR was observed in the MVIVW analysis (= -1.412 [-2.714- -0.109]; p=0.034). We found no evidence of a reverse causal impact of eGFR on serum lipids. All our sensitivity analyses indicated no pleiotropy or heterogeneity between our instrumental variables.

Conclusion: Genetically predicted LDL-C and TC are causally associated with low eGFR levels in African-ancestry individuals.

Key words: Mendelian Randomization, Kidney function, serum lipids, eGFR

A multi-omic obesity biobank

Daniel Lam, Holger Klein, Adhideb Ghosh, Christian Wolfrum, Mattias Blüher

Global Computational Biology and Digital Sciences, Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach/Riss, Biberach, Germany

Institute of Food, Nutrition and Health, ETH Zurich, Schwerzenbach, Switzerland

Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum Munchen at the University of Leipzig and University Hospital Leipzig, Leipzig, Germany

We report the establishment of a multi-omic resource based on the Leipzig Obesity Biobank (LOBB). LOBB consists of three cohorts: a cross-sectional, predominantly obese, cohort (2000+ subjects), a bariatric surgery cohort (with matched samples before and after surgery), and a relatively small cohort of obese subjects who are either insulin sensitive or resistant. Omic data generated include whole genomes, adipose tissue bulk and single nucleus transcriptomes, adipose tissue proteomes, and blood lipidomes and metabolomes.

One analytical objective is to identify molecular subtypes of obesity that are interpretable and ideally clinically actionable. To achieve this, we use single-omic unsupervised clustering as well as decomposing multiple omic layers to a common latent representation. In both cases, subtypes emerge in an unsupervised fashion. These subtypes are annotated (e.g. with clinical parameters) to facilitate interpretability and actionability of the subtypes.

A second objective is to construct novel and useful resources, such as detailed e/p/mQTL maps of human adipose tissue depots. These are employed in GWAS fine mapping and Mendelian Randomization approaches. Finally, we will enrich the genomic architecture of obesity, for example through multi-omic subtype-based GWAS.

Overall, our approach contributes to the understanding of the molecular and genomic basis of obesity, the clinically informative and therapeutically actionable segmentation of the obese population, and the discovery of novel therapeutic targets and biomarkers.

Chromosome 16p11.2 BP2-BP3 deletion encompassing SH2B1 associated with accelerated metabolic disease

Katherine Lawler[1], Ruth Hanssen[1], Chiara Auwerx[2,3], Maarja Jõeloo[4], Marie C. Sadler[2,3], Elana Henning[1], Julia Keogh[1], Rebecca Bounds[1], Miriam Smith[1], Helen Firth[5], Zoltán Kutalik[2,3], Alexandre Reymond[2], I. Sadaf Farooqi[1]

1. University of Cambridge Metabolic Research Laboratories, Wellcome-MRC Institute of Metabolic Science, UK. 2. University of Lausanne, Switzerland. 3. Swiss Institute of Bioinformatics, Lausanne, Switzerland. 4. University of Tartu, Estonia. 5. Department of Clinical Genetics, Cambridge University Hospitals NHS Foundation Trust & Wellcome Sanger Institute, UK.

Background:

Obesity and type 2 diabetes (T2D) are prevalent, heterogeneous conditions associated with significant morbidity and mortality. Identifying subgroups of people whose obesity and T2D is driven by shared pathogenic mechanisms can inform precision medicine approaches.

Disruption of SH2B1, an adaptor protein involved in leptin-melanocortin signalling, impairs leptin, insulin and Brain-derived Neurotrophic Factor signaling. We investigated the metabolic consequences of the obesity-associated 16p11.2 BP2-BP3 deletion, which encompasses SH2B1 and eight other protein-coding genes.

Methods:

We detected 79 carriers of 16p11.2 BP2-BP3 deletions among 0.5 million people in UK Biobank and 0.2 million people from the Estonian Biobank. We performed a phenome-wide association scan (PheWAS) and body mass index (BMI)-matched cohort analyses of metabolic traits and disorders and serum metabolomic biomarkers.

Results:

In comparison to the whole UK Biobank and Estonian Biobank populations, and to BMI-matched controls, deletion carriers (DEL) had early-onset obesity (DEL=41%; ctrl=23%; p=0.003) and T2D (DEL=38%; ctrl=14%; p=1.8x10-6) which appeared to be difficult to treat and had an increased rate of diabetes-associated co-morbidities. Serum lipid profiles were significantly altered, and the increased risk of accelerated metabolic disease persisted in comparison to BMI-matched controls. Mendelian randomization suggested that decreased SH2B1 expression increases T2D risk (p=8.1x10-6), suggestive of a causative role for SH2B1 haploinsufficiency.

Conclusion:

We identify a subgroup of individuals with early-onset complex obesity and T2D, in whom early and targeted treatments may be effective at reducing the risk of long-term metabolic complications.

Therapeutic Target Discovery using proteome-wide analyses in large population health studies like the UK Biobank

Cindy Lawley, Lotta Wik, Niklas Nordberg, John Broberg, Johan Björkesten, Erika Assarsson, Sara Henriksson, Ida Grundberg, Christina Westerberg, Elin Liljeroth, Adam Falck, Martin Lundberg, Lasse Folkersen, Anders Malarstig

Understanding the dynamics of the human proteome is crucial for identifying biomarkers to be used as measurable indicators for disease severity and progression, patient stratification, and drug development. The Proximity Extension Assay (PEA) is a technology that translates protein information into actionable insights across large samples sizes in both healthy and disease samples. Here we have combined the unique PEA technology with automated sample preparation and high-throughput sequencing readout for parallel measurement of ~3,000 proteins for up to 384 samples at a time, generating over 1 million data points per run. Characterizing the proteome alongside genetic and clinical data enables a protein quantitative trait loci (pQTL) framework to not only validate known clinical targets and identify new clinical targets but to also suggest repurposing opportunities of clinical candidates for new indications. We will discuss goals and results of large population health studies integrating proteomics, genomics and clinical data like the UK Biobank Pharma Proteomics Project and SCALLOP Consortium and summarize publicly available data resulting from these efforts.

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Untargeted Metabolomics Analysis of Urine Samples Reveals Diet-Dependent Metabolites Fingerprints Using Machine Learning Algorithms

Yifan Liang, Pengwei Dong, Shitong Ding, Zengguang Jin, Chaoqun Niu, Terasa G. Valecak, Alex Douglas, Kang Zhu, John Speakman, Guanlin Wang

Institute of Metabolism and Integrative Biology, Fudan University

Diet plays a crucial role in the diagnosis and treatment of many disorders. However, traditional methods of dietary intake assessment, such as food frequency questionnaires and 24-hour dietary recalls, are limited by subjectivity and recall bias. Metabolomics is an emerging field that offers a promising and powerful approach to assess dietary intake and quality, identify markers of nutritional status, and predict health outcomes based on the unique metabolic fingerprints of different diets. Metabolic fingerprints are unique chemical signatures that reflect the various metabolic processes and environmental interactions of an organism. Here, we performed untargeted metabolomics analysis on urine samples collected from 28 healthy females who were provided with two distinct diets (noodles and burgers) as lunch for 14 consecutive days and whose body composition was measured. No significant body fat percentage and WHR changed during this experiment. We identified 962 metabolites in the urine metabolomics data. We found the metabolite profiles of the participants in the two diet groups were significantly different, indicating that diet has a profound impact on metabolism. We further applied non-linear dimensional reduction methods combined with machine learning algorithms to identify biomarkers from urine metabolites. These results demonstrated that the metabolic signature from the same diet changed over time and that a specific combination of 10 metabolites can be used to distinguish between diets. We further applied this method to another independent urine untargeted metabolomics dataset with known food intake and the method demonstrated a high predictive capacity for 'tracing' the food intake. Our results provide new insights into the metabolic effects of different diets and certain urine metabolites as diagnostic markers of individual's nutritional status. Our new machine learning algorithm-based method shows great potential in tracing food intake and highlights urine metabolites as non-invasive biomarkers for assessing the nutritional status of metabolic diseases.

Unsupervised clustering revealed metabolic syndrome endophenotypes with differing phenotypic and genotypic traits in UK and Taiwan Biobanks

Aylwin Ming Wee Lim, Evan Unit Lim, Pei-Lung Chen, Cathy SJ Fann

National Yang Ming Chiao Tung University

Institute of Biomedical Sciences, Academia Sinica

ASUS Intelligent Cloud Services (AICS)

Background: Metabolic syndrome (MetS) is highly heterogenous with detrimental clinical outcomes and high worldwide prevalence.

Methods: Clinically-relevant endophenotypes were identified through unsupervised clustering in UK Biobank (UKB) MetS individuals. GWAS were performed to identify genotypic traits associated with each endophenotypes. Potential drug repurposing targets were established from GWAS results and unbiased identification of drugs targeting associated genes. Heritability and polygenic risk score models for each endophenotypes were calculated. MetS endophenotypes were further explored in Taiwan Biobank (TWB).

Results: Five MetS endophenotypes were identified in UKB which were Cluster 1 (C1): non-descriptive (n=33,707), Cluster 2 (C2): hypertensive (n=23,215), Cluster 3 (C3): obese (n=30,089), Cluster 4 (C4): lipodystrophy-like (n=13,116) and Cluster 5 (C5): hyperglycaemic (n=3,869). C1 had higher risks for most clinical outcomes and highest cardiovascular risk after adjustment for T2D. Similar MetS endophenotypes with similar proportions were also identified in TWB with comparable phenotypic traits and clinical outcomes.

LPCAT2, NUDT21 and OGFOD1 were associated with all clusters in UKB except C2, this finding was validated in C1 and C3 of TWB. When analysing the cluster-specific genes in UKB, C1 had 156 distinct genes while C2 had 16, C3 had 98, C4 had 133 and C5 had 8. C1 GWAS revealed cardiac-specific TRIM63 and MYBPC3, skeletal muscle-specific MYLPF and RAPSN. C5 GWAS identified known T2D genes such as TCF7L2, IRS1, BBIP1 and GIN1. C1, C3 and C4 were associated with genes highly expressed in brain tissues such as CN1H2, TMEM151A, MT3 and C1QTNF4. Comparing genotypic traits between TWB and UKB, C1 of TWB overlapped at 43 genes, C3 overlapped at 21 genes and C4 overlapped at 112 genes with UKB. Example of overlapped genes for C1: MT3, LPL, TOMM40, C3: FTO, SLC6A2 and C4: LPL, APOA1, APOC1, PCSK7, GCKR.

C1-associated genes were enriched in gene-set targeted by cardiovascular system drugs such as diuretics targeting SLC12A3 and SLC12A4; C3 by anti-obesity drugs targeting SLC6A2 and antithrombotic drugs targeting F2, TFPI and VEGFA; C4 by lipid-modifying drugs targeting APOB and LPL; C5 by drugs of alimentary tract targeting CES1. Using 3,800 cases subsets in UKB, our first-of-its-kind PRS for endophenotypes performed better (C1 R2=0.0114, C3 R2=0.0094, C4 R2=0.0572, C5 R2=0.0175) than the heterogenous all MetS category (R2=0.0052), with exception of C2 (R2=0.0018) which had lowest heritability of h2=0.2198.

Conclusion: The combination of unsupervised clustering and GWAS allowed for identification of clinically important MetS endophenotypes across two populations, representing a key step towards precision medicine.

The transcriptional response to acute exercise is HIF1□ dependant and time-of-day specific.

MacGregor Kirstin, Ehrlich Amy M

Ashcroft Stephen P

Small Lewin

Treebak Jonas T

Zierath Juleen R.

Deparment of Molecular Medicine and Surgery, Integrative Physiology, Karolinska Institutet, Stockholm, Sweden

Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

The regulation of metabolism in peripheral tissues is mediated by pathways that are under circadian control. Intimate links have been reported between the circadian clock and the expression of genes that regulate metabolism in response to energetic stress, such as physical activity. There is a bi-directional relationship between the circadian clock and HIF1a, which is specific to time-of-day exercise. The aim of this study was to elucidate the interplay between HIF1a and time-of-day in the skeletal muscle transcriptional response to acute exercise. Skeletal muscle specific HIF1a knock out (HIF1a-mKO) and wild type (WT) mice (N = 8 per group) were subjected to 60 min treadmill running (16 m/min, 5 % incline) or a sham treatment at zeitgeber time (ZT) 3 and ZT 15. RNA sequencing was performed on gastrocnemius tissue of mice 3 hr following the intervention. Transcriptomic analysis determined a HIF1a dependant, time-of-day specific transcriptional expression profile in exercised, but not sedentary, mice. In exercised mice, a greater number of transcripts were differentially expressed between HIF1a-mKO and WT at ZT 3 (516) compared to ZT 15 (91). Within these differentially expressed transcripts between HIF1a-mKO and WT mice, 477 transcripts were specific to exercise at ZT 3 and 50 transcripts were specific to exercise at ZT 15. Conversely, in sedentary mice, similar skeletal muscle transcriptional profiles were observed between HIF1a-mKO and WT mice at ZT 3 and ZT 15. We detected 17 differently expressed transcripts at ZT 3 and 89 differently expressed transcripts at ZT 15 between sedentary HIF1a-mKO and WT mice. Over enrichment analysis of altered transcriptional profiles between HIF1a-mKO and WT mice in response to exercise determined a positive enrichment of gene ontology terms involved in oxidative metabolism (oxidative phosphorylation, aerobic respiration, cellular respiration) and mitochondrial function (mitochondrial respiratory chain complex assembly, ATP synthesis coupled electron transport and respiratory electron transport chain) at ZT 3, but not ZT 15. Collectively these results indicate that the transcriptional profile of skeletal muscle is time-of-day and HIF1A dependant following an acute bout of exercise. Specifically, following HIF1a KO, a greater transcriptional response is observed in exercised mice at ZT 3 compared to ZT 15, coupled with an overrepresentation of oxidative metabolism and mitochondrial function gene ontology pathways. Thus, the time-of-day specific response of skeletal muscle to acute exercise may be partly driven by the interaction between the muscle circadian clock and HIF1a.

A multi-omic study on human pluripotent stem cell-derived brown adipocyte differentiation

Iman Mali1,2, Sonia Rodríguez-Fdez1,2, Ioannis Kamzolas1,3, Possawee Prasertsuk1,2, Maria Harkiolaki4, Archana Jadhav4, Chindinma Okolo4, Stefania Carobbio5, Antonio Vidal-Puig1,2

1Wellcome-MRC Institute of Metabolic Science and MRC Metabolic Diseases Unit, Metabolic Research Laboratories, University of Cambridge, Cambridge, UK

2Heart Lung Research Institute, Royal Papworth Hospital NHS Foundation Trust/University of Cambridge, Cambridge, UK

3European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton, UK

4Diamond Light Source, Harwell Science and Innovation Campus, Didcot OX11 0DE, UK

5Centro de Investigacion Principe Felipe, 46012 Valencia, Spain

Brown adipocytes (BA) are the main sites of non-shivering thermogenesis. These cells are characterised by high abundance of mitochondria and presence of multi-locular lipid droplets. An increased in the abundance and activity of BA is positively correlated with improved glucose metabolism, resistance to fatty liver disease, and better cardiometabolic health. This has led to the idea that turning on BA therapeutically may be protective against obesity and metabolic disorder. However, existing approaches have been unsuccessful due to both long-term secondary effects of available drugs and the low amount of mature BAs present in obese and diabetic patients. Fortunately, these patients do still conserve adipocyte precursors that could be differentiated into functional BAs. To achieve this goal, a deeper understanding of human BA differentiation is required. We are using a human stem cell-derived BA in vitro differentiation model to identify novel regulators and stage-specific markers in human brown adipogenesis. To accomplish this, we have collected phospho-proteomic, proteomic, and transcriptomic data at each stage of the differentiation. Furthermore, to complement our multi-omic results we have collected high-resolution imaging data combining soft X-ray tomography (cryoSXT) and structured illumination microscopy (cryoSIM) to quantify subcellular features (i.e. mitochondria number, volume and cristae organisation, and lipid droplet distribution). Using this integrated omics approach in addition to high-resolution imaging, we hope to identify candidate targets to either promote the differentiation of endogenous BA precursors or to increase the thermogenic capacity of existing BA.

Association of body composition with blood gene expression in late childhood – a cross-section analysis in the HELIX Project and the Generation R Study

Irene Marques 1,2, Dolors Pelegrí 3,4, Martine Vrijheid 3,4,5, Vincent W. V. Jaddoe 1,2, Mariona Bustamante 3,4,6, Janine F. Felix* 1,2*

1. Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands 2. Department of Pediatrics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands 3. ISGlobal, Institute for Global Health, Barcelona, Spain; 4. Universitat Pompeu Fabra (UPF), Barcelona, Spain; 5. CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain 6. Center for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Barcelona, Spain

** Shared authorship*

Background: Adult body mass index (BMI) has been associated with the expression of several genes. Whether similar associations are present in children is unknown. We aimed to evaluate associations of body composition with blood gene expression in children and to assess replication in a population measured using a different method.

Methods: Cross-sectional discovery transcriptome-wide analyses of childhood BMI, total fat mass percentage (FM), and waist circumference (WC) were conducted in 901 8-year-old children from the population-based Human Early-Life Exposome (HELIX) project. Whole blood gene expression was assessed with the Affymetrix Human Transcriptome Array 2.0 array. We fitted linear regression models with the limma R package, adjusting for ethnicity, cohort, maternal education and maternal smoking during pregnancy. Sensitivity analysis included: (i) additional adjustment for blood cell composition, (ii) restriction to European-ancestry children, and (iii) restriction to samples with RNA integrity number □6.5. We attempted replication, using RNA sequencing data and information on BMI, FM and android fat mass (instead of WC) from 172 10-year-old children from the population-based Generation R Study. Here, the regression models were run with EdgeR, adjusting for batch, maternal education and maternal smoking during pregnancy. Functional pathway enrichment analyses were conducted with the enrichR tool and Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Results: In HELIX, mean (sd) BMI, FM, and WC were 16.8 (2.5) kg/m2,22.5 (7.9) %, and 58.3 (7.5) cm, respectively. Correlations between the phenotypes ranged from 0.64 to 0.82. After correction for false discovery rate (FDR) at 5%, BMI was associated with expression of 26 genes, FM with 18, and WC with 19 genes, with 17 common and 26 unique genes across the phenotypes. Top significantly enriched KEGG pathways included NOD-like receptor signaling pathway, staphylococcus aureus infection and cytosolic DNA-sensing pathway. In the Generation R Study, FM was associated with expression levels of 3 (LTF, CRISP3, CEACAM8) out of the 18 genes, and android fat mass with 6 (LCN2, LTF, CEACAM8, CRISP3, DEFA1B, DEFA1) out of the 17 genes. None of the childhood BMI associated genes replicated in this much smaller population.

Conclusion: Measures of childhood body composition are associated with blood gene expression in two population-based cohorts, using different methods. Further functional analyses of these genes may provide insights in potential biological mechanisms underlying the development or consequences of body composition.

Discovery and fine-mapping of novel genetic loci associated with estimated glomerular filtration rate of cystatin C in Africans

Richard Mayanja, Richard Mayanja1,2, Tafadzwa Machipisa3, Opeyemi Soremekun1, Abram Bunya Kamiza1,4 , Christopher Kintu1,2, Allan Kalungi1, Robert Kalyesubula5, Obondo J. Sande6, Daudi Jjingo7, June Fabian8,9, Nora Franceschini10, Dorothea Nitsch11 , Moffat Nyirenda4,11, Andrew P. Morris12, Tinashe Chikowore 13,14, Segun Fatumo1,4,11

1The African Computational Genomics (TACG) Research Group, MRC/UVRI and LSHTM, Entebbe, Uganda; 2College of Health Sciences, Makerere University, Kampala Uganda; 3Department of Medicine, University of Cape Town & Groote Schuur Hospital, Cape Town, South Africa; 4Malawi Epidemiology and Intervention Research Unit, Lilongwe, Malawi; 5Medical Research Council/ Uganda Virus Research Institute/London School of Hygiene and Tropical Medicine (MRC/UVRI/LSHTM) Uganda research unit, Entebbe, Uganda; 6 Department of Immunology and Molecular Biology, School of Biomedical Sciences, Makerere University College of Health Sciences, Kampala, Uganda; 7African Center of Excellence in Bioinformatics (ACE-B), Makerere University, Kampala 10101, Uganda; 8Medical Research Council/Wits University Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; 9Wits Donald Gordon Medical Centre, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; 10Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC.US ; 11London School of Hygiene and Tropical Medicine London, United Kingdom; 12Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, UK; 13Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; 14MRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Background: Chronic kidney disease prevalence is increasing in Africa and its genetic determinants are poorly understood. As a marker of kidney function, the glomerular filtration rate is estimated (eGFR) using equations that model the excretion of endogenous biomarkers (creatinine and cystatin C) in non-African populations. Emerging evidence confirms these equations perform poorly in African populations, with cystatin C performing better than creatinine. However, most genome-wide association studies (GWASs) focus on creatinine and variants associated with cystatin C-based eGFR are yet to be determined.

Method: Using data from the Uganda Genomic Resource (UGR), we performed GWAS of cystatin C-based eGFR (eGFRcys) in 5878 Ugandans and evaluated replication in independent studies. Putatively causal variants were identified through Bayesian fine mapping. Functional annotation of the GWAS loci was performed using FUMA. Phenome-wide association analysis (PheWAS) was conducted to identify other human phenotypes/traits associated with our lead variants.

Results and Discussion: Lead SNPs at three loci (from 64 genome-wide significant (p-value <5x10-8) SNPs) were identified; rs59288815 (ANK3), rs4277141(OR51B5) and rs911119 (CST3). Of these three loci, fine mapping yielded one credible set with 99% posterior probability for each of the two loci (rs59288815 and rs911119). Ultimately, the PheWASs showed a strong association with kidney traits, particularly for rs911119.

Conclusion: Our study is the first GWAS of eGFRcys from Africa. In a Ugandan population sample, we identified novel loci in ANK3 and OR51B5, and replicated CST3 gene's association with cystatin C, linking to kidney dysfunction. Large GWAS for eGFRcys are warranted in Africa to enhance discovery.

Keywords: Cystatin C; Estimated glomerular filtration rate; Kidney Function; Genome-wide association study; Fine-mapping.

In patients with non-alcoholic fatty liver disease, HDL lipidomics identifies a novel player in its pathogenesis

Gabriele Mocciaro1,2, Michael Allison3, Benjamin Jenkins4, Vian Azzu3, Isabel Huang-Doran3, Richard Kay4, Davies Susan3, Mattia Frontini5, Antonio Vidal-Puig4, Albert Koulman4, Michele Vacca1,2,4,6, Julian L. Griffin1,7

1 University of Cambridge, Department of Biochemistry, Cambridge, United Kingdom; 2 Roger Williams Institute of Hepatology, Foundation for Liver Research, United Kingdom, 3 Addenbrooke's Hospital, Cambridge Biomedical Research Centre, Department of Medicine, United Kingdom; 4 Wellcome Trust-MRC Institute of Metabolic Science Metabolic Research Laboratories, United Kingdom; 5 National Institute for Health Research BioResource, Cambridge University Hospitals, United Kingdom; 6 Aldo Moro University of Bari, Department of Interdisciplinary Medicine, Clinica Medica "C. Frugoni"; 7 University of Aberdeen, The Rowett Institute, United Kingdom, jules.griffin@abdn.ac.uk.

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a spectrum of diseases ranging from simple steatosis to steatohepatitis and advanced liver disease while being a major risk factor for cardiovascular diseases. Lipidomic studies have consistently reported a characteristic hepatic and VLDL lipid signature in NAFLD, while plasma traits are more debated. Surprisingly, the high-density lipoprotein (HDL) lipidomic composition has not been characterised by mass spectrometry across the NAFLD spectrum, despite HDL being a possible source of lipids delivered from peripheral tissues to the liver.

Method: We studied 89 patients with a biopsy confirmed NAFLD and 20 healthy volunteers (CTRL), matched for age and sex, whole serum (20 CTRL, 36 NAFL, 53 NASH) and the HDL lipoprotein (9 CTRL, 11 NAFL, 20 NASH) lipidomics by liquid chromatography-mass spectrometry. HDL were isolated using fast protein liquid chromatography.

Results: In whole serum, NAFLD patients displayed significantly higher saturated free fatty acids (FFA) and lower polyunsaturated FFA as compared to controls; a similar trend was also observed in other lipid species. The lipoprotein lipidomic analysis demonstrated that different phospolipids and their PUFA component were significantly lower in HDL of NASH versus controls, with phosphatidylcholine (PC) being the most affected lipid class. Moreover, total, and saturated ceramides (Cer) in HDL were significantly higher in NASH compared to controls. HDL-PC, and HDL-Cer were also strongly correlated with insulin resistance, transaminases, and liver histology (hepatocyte ballooning) suggesting that the concentration of these lipids in HDL might be associated with peripheral organ dysfunction and/or with the necro-inflammatory milieu in NASH.

Conclusion: Taken together, these data show for the first time that NAFLD is associated with a reduced absolute content of polyunsaturated FFA and PUFA-HDL-phospholipids that correlate with metabolic impairment and liver damage. We, therefore, speculate that an impaired PUFA transport from peripheral tissues to the liver (via FFA and HDL) might be a contributing factor in NAFLD pathophysiology.

Investigating the contribution of sinusoidal endothelial cell gene regulatory networks to liver disease

Dorka Nagy, Hannah Maude, Angelos Manolias, Lowri Morris, Inês Cebola

1 – Section of Genetics and Genomics, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK.

2 – Section of Biomolecular Medicine, Department of Metabolism, Digestion and Reproduction, Imperial College London, UK

Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, is estimated to affect ~30% of the global population, constituting a growing public health concern. Common diseases like NAFLD are characterized by risk variants predominantly at enhancer elements, that may act by disrupting transcription factor (TF) binding sites. Enhancer elements are highly cell-type specific, which renders the investigation of the cis-regulatory network of all relevant cell types regardless of abundance in the tissue. Liver sinusoidal endothelial cells (LSECs) make up <20% of the liver cell mass, and their dysfunction plays a key role in the progression of NAFLD; however, their epigenomic landscape and its potential role in cardiometabolic disease have not been investigated.

Our lab created epigenomic maps of primary LSECs under control and lipotoxicity-mimicking conditions (high concentration of saturated free fatty acids), observing widespread changes in both gene expression (RNA-seq), chromatin activity (ATAC-seq and active chromatin marks ChIP-seq) in palmitate-treated primary LSECs. Enrichment analysis of NAFLD-associated variants surprisingly showed stronger enrichment at regulatory elements of LSECs than of hepatocytes, despite detecting similar numbers of CREs. Looking specifically at LSEC CREs, we also observed significant enrichment of NAFLD risk variants at LSEC-specific CREs (i.e., CREs that are not active in hepatocytes) and at palmitate-responsive LSEC CREs. These results underpin the special role of LSEC CREs in NAFLD development.

LSEC enhancers that displayed differential activity under palmitate treatment were tested for TF motif disruption by NAFLD-associated variants, identifying variants of interest for functional follow-up. Three prioritized enhancers containing NAFLD-associated variants showed significantly allele-dependent activity by luciferase reporter assay.

Future plans include identification of the target gene(s) of fatty acid responsive CREs containing NAFLD risk variants by CRISPR-mediated activation and UMI-4C. This workflow may identify pathways suitable for therapeutic targeting, something that is unavailable for NAFLD to date.

Safety and efficacy evaluation of Uvaria chamae P. Beauv (Annonaceae): preclinical stage in development of hypoglycaemic agent

Jonathan Emeka, Emordi 1, Esther Oluwatoyin, Agbaje 2; Ibrahim Adekunle2 , Oreagba;*

Osede Ignis, Iribhogbe 1; Matthew Obaineh, Ojezele 3

1 Department of Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University, Ekpoma, Nigeria.

2 Department of Pharmacology, Therapeutics and Toxicology, College of Medicine, University of Lagos, Lagos, Nigeria.

3 Department of Pharmacology, College of Health Sciences, Delta State University, Abraka, Nigeria.

Background

The study aimed to evaluate pilot toxicity and antidiabetic activity of the ethanolic root extract of Uvaria chamae P. Beauv (Annonaceae) in diabetic Wistar rats

Methodology

Acute toxicity was evaluated using graded oral doses and median lethal dose (LD50) determined. The glucose lowering properties of CEUC was assessed using oral glucose tolerance test (OGTT) and the single dose study. Diabetes mellitus was induced using two different models. Streptozotocin induced diabetic rats were treated for 7 days with CEUC (100, 250 and 400 mg/kg) and insulin (0.5 I. U/kg as reference hypoglycaemic agent) while, alloxan induced diabetic rats were treated for 14 days with CEUC (100, 250 and 400 mg/kg), glibenclamide and pioglitazone (71µg/kg, 429 µg/kg respectively as reference hypoglycaemic agents). The CEUC was partitioned into chloroform, ethyl acetate and ethanolic fractions via silica-gel column chromatography. Alpha amylase and alpha glucosidase inhibition by the root extract of CEUC and its fractions were evaluated. Percentage inhibition and IC50 values were determined. Effect of Uvaria chamae on the formation of fluorescent Advance Glycation End products (AGEs) was assessed using in vitro glycation of bovine serum albumin.

Results

The LD50 of the extract was found to be >2 g/kg body weight. The single dose study and OGTT revealed that CEUC significantly decreased blood glucose levels. Results showed that there was statistically significant reduction in blood glucose levels of all the diabetic rats treated with CEUC compared with diabetic untreated rats and comparable with reference hypoglycaemic agents. The CEUC significantly elevated HDL cholesterol with a reduction in total cholesterol and LDL cholesterol levels. This study revealed that CEUC and its fractions caused significant inhibition of advanced glycation end products.

Conclusion

In conclusion, the study showed that Uvaria chamae is safe for use and has antidiabetic properties which may be through alpha-amylase and alpha-glucosidase inhibition. The findings of this study also showed that the plant has hypolipidaemic and antioxidant activity thereby inhibiting the formation of toxic advance glycation end products responsible for the complications of diabetes mellitus.

MINEARALS COMPOSITION ENHANCE HYPOGLYCAEMIC ACTIVITIES OF BIOACTIVE COMPOUNDS FROM NATURAL PRODUCTS.

Omolara Jemimah OJEZELE1, Matthew Obaineh OJEZELE2, Shedrach Oludare AGUNBIADE3

1Chemistry unit, Science Laboratory Department, Federal College of Animal Health & Production Technology, Nigeria.

2Department of Pharmacology, Delta State University, Nigeria

3Department of Biochemistry, Lead City University, Nigeria

Background: Diabetes is a chronic disorder of glucose intolerance. This disease is epidemiologically alarming and has been described as a major cause of disability and death. It is characterized by high blood glucose level and glycosuria resulting from dysfunction of pancreatic beta-cells and insulin resistance. Mineral deficiencies are common in diabetes and can exacerbate insulin resistance. Several of these minerals are co-factors for signalling intermediaries of insulin action and key enzymes of glucose metabolism. Many plants with antidiabetic properties probably act in part through their content of fibre, vitamins, bioactive or mineral content

Objectives: This study investigated the mineral, proximate, phytochemical compositions and hypoglycaemic effect of

Commelina africana and Ageratum conyzoides extracts in diabetic rats, and the likely relationship between this property and the mineral, proximate and phytochemical compositions of the plants.

Methods: The mineral, proximate composition and phytochemical contents of the plants were analysed. Experimental diabetic animals were administered 500mg/kg body weight aqueous extracts.

Results: Aqueous extract of Ageratum conyzoides reduced fasting blood glucose of experimental animals by 39.1% while Commelina africana reduced the same by 78.0%. Alkaloids, cardenolides, saponins, and tannins were detected in both plants. Anthraquinones was absent in C. africana but a trace of it was detected in A. conyzoides. The hypoglycaemic effect of Commelina africana was comparable with the reference hypoglycaemic agent. Ageratum conyzoides showed comparably weaker hypoglycaemic effect than exhibited by reference hypoglycaemic agent. Comparatively, Commelina africana had higher mineral concentrations (except Na) than Ageratum conyzoides.

Conclusions: Plants' extracts minerals (magnesium, potassium and iron) and bioactive components (alkaloids and cardenolides) seemingly enhanced their hypoglycaemic effect. Furthermore, these minerals, alkaloids and cardenolides could be helpful in ameliorating complications of diabetes like hypertension and cardiovascular disease.

The case for the multi-dimensional ‘omics: phenomics & longitudinal sample analysis to understand Metabolic Syndrome

Andrew Parton, Ariella Cohain, Celia Antonio Schell, Henrietta Bull, Rebecca Cripps, Robert Thong, Slaven Stekovic

Multiomic Health

Metabolic syndrome, a complex tapestry of interrelated diseases, stands as a global threat affecting over half a billion people and its mortality is projected to increase by 7.5 million people in the next 20 years. This multifaceted, progressive disorder demands a comprehensive approach to uncover its intricacies, as DNA-centric investigations fall short in capturing the full picture. To truly decode metabolic syndrome, we must venture beyond genomics, embracing a holistic, multiomics perspective that accounts for both individual molecular responses and environmental influences.

As research predominantly emphasises single omics for patient cohorts, the declining costs of sequencing and other emerging technologies necessitate a shift towards generating multiomics data from individual subjects. Although some progress has been made in this realm, the dynamic nature of metabolic syndrome requires us to incorporate temporal data capturing the progression of the disease. Longitudinal sample collection and omics data generation, while crucial, must be complemented by in-depth clinical data and outcomes analysis to truly unravel the complexities of this ever-changing condition.

Out of all the published datasets available for Metabolic Syndrome on GEO, only 1 dataset contains >100 samples, multiple omics and clinical data and even that study doesn't contain any outcomes (eg. death, heart attack, etc). And looking at the UKBiobank which is a phenomenal resource to the research community, while it contains outcomes data and deep clinical data, in the context of Metabolic Syndrome, it is still lacking a lot of the dynamic elements that track disease (e.g. cholesterol levels, blood pressure, blood glucose, etc.) as well as multiple sample collections for patients.

Our solution at MultiOmic Health is to partner with strategic centres that have Metabolic Syndrome patients data with multiple collection points along with deep clinical data and outcomes information. By integrating machine learning and AI to analyse these longitudinal samples 'omics, we are able to start to untangle not only the differences between the disease and healthy state but also the different trajectories of the disease and the underlying biology.

Sequence-based Meta-omic Methodology Alters Stool Microbiome Profiles & Observed Health Outcomes

Molly Pratt (1)(2), Morag Graham (1,2), Denice Bay (1), Charles Bernstein (3,4), Gary Van Domselaar (1,2)

1 Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, MB.

2 National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB.

3 Department of Internal Medicine, University of Manitoba, Winnipeg, MB.

4 University of Manitoba IBD Clinical and Research Centre, Winnipeg, MB.

Disease-associated changes to the gastrointestinal (GI) microbiome have been detected in a variety of chronic human illnesses. Currently, GI microorganisms are thought to play a major role in systemic health and homeostasis through interactions with the immune system of their host. In recent years, the available technology for capturing and characterizing the GI microbiome has expanded greatly, resulting in a rapid expansion of the field. In particular, culture-independent technologies allowing for direct analysis of microbial genes, transcripts, proteins, and other metabolites (collectively referred to as meta-omics) from stool samples show potential for personalized disease detection and monitoring through non-invasive screening. However, due to the high degree of variability inherent in microbiome profiles, establishing a consensus for microbial signatures or biomarkers of disease across studies is difficult. Differences in study methodology can further complicate comparisons, since the laboratory protocols for sequence-based data capture and analysis are varied, and there are several commercial kits and reagents available for the storage and isolation of microbial DNA and RNA from stool for downstream microbiome profiling. Research has shown that the choice of nucleic acid extraction kit and storage method can affect resulting nucleic acid quality. In the current methodological study, a single stool sample from a healthy donor is divided and processed using multiple commercially available methods for nucleic acid stabilization and isolation in order to evaluate the effect of processing on observed sequence-based microbiome profiles. The research herein demonstrates that the experimental methodology used to stabilize and isolate nucleic acids from human stool samples can significantly impact the ability to capture GI microbiome diversity from metagenomic and metatranscriptomic data. Notably, GI microbiome characteristics commonly used as health markers in disease research are differentially impacted by the specific combination of preservative reagent and nucleic acid extraction kit. This study additionally describes important considerations for future meta-omic microbiome research, including the choice of bacterial lysis approach, bioinformatic analysis methodology, and potentially detrimental vendor mismatching. Ultimately, the current research supports the use of informed experimental design and expands current understanding of how biological sample integrity and experimental bias may affect observed meta-omic microbiome profiles.

Dogs are a compelling model organism for studying the genomics of metabolic disease

Eleanor Raffan, Natalie J. Wallis1, 2, Alyce McClellan2, Anna Morros Nuevo2, Marie Dittmann1, Jodie Wainwright1, Gabriella Lakatos1, Alexander Mörseburg1, Justine Chan2, Sambhavi S. Kumar2, Ellen Schofield3, Jacek Mokrosinski1, Katherine Kentistou4, John Perry1, 4, Felix Day4, Sadaf Farooqi1, Giles Yeo1, Stephen O'Rahilly1, Eleanor Raffan1, 2, 5

1 Wellcome-MRC Institute of Metabolic Science, Cambridge, UK

2 University of Cambridge Department of Physiology Development and Neuroscience, Cambridge, UK

3 University of Cambridge Department of Veterinary Medicine, Cambridge, UK

4 MRC Epidemiology Unit, Cambridge, UK

5 Presenting author.

The high heritability of obesity is well established and gene mapping studies have lead to a plethora of genetic obesity associations in human populations, making it hard to prioritise genes for further study. In dogs, an obesity epidemic shares many clinical features with that in people but selective breeding means gene mapping is relatively straightforward. We study pet dogs as a model for human disease and use genomics coupled with follow-on molecular, epidemiological and physiological studies to understand the mechanistic links between genes and obesity in dogs and humans.

In an obesity prone breed, Labrador retrievers, we identified a mutation in the gene POMC associated with obesity and food motivation. Affected dogs have greater motivational salience in response to a food cue and lower resting energy expenditure, consistent with impaired signalling thought the hypothalamic melanocortin pathway and providing evidence that β-MSH is a critical neuropeptide in energy homeostasis. A GWAS study for obesity in Labradors identified further obesity-associated loci used to generate genomic scores that were predictive in Labradors and to a lesser extent in a related retriever breed, but not more distantly related breeds. However, individual risk loci are associated in different breed and mixed breed populations, demonstrating the heterogeneity of complex trait genetics across breeds. Genomic scores illuminate how obesity risk differs in working vs pet populations and provides insight into the penetrance of the POMC variant. In Labradors and >16,000 dogs with data on food motivation and owner management, we have shown how polygenic risk is in large part mediated via eating behaviour but moderated by environmental exposure to dietary risk factors and exercise. Finally, genes shown to have large effect on fat mass in dogs can also prioritise study of previously overlooked human obesity genes, a tactic we have used to highlight the importance of SEMA3D and DENND1B on energy homeostasis.

Abdominal fat distribution is associated with higher non-fasting triglycerides and an increased risk of cardiovascular disease

Malene Revsbech Christiansen, Germán D. Carrasquilla

Tuomas O. Kilpeläinen

Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Background: Elevated fasting triglyceride (TG) levels are a major risk factor for cardiovascular disease (CVD). While most previous studies have focused on the association between fasting TG levels and CVD risk, non-fasting TG levels may be more predictive of CVD, as they reflect changes in remnant cholesterol levels. In a recent study of 755 individuals with obesity undergoing an oral fat tolerance test, we discovered that abdominal obesity elevates postprandial TG levels, whereas lower-body fat decreases them. These differences may reflect the relatively high lipolytic activity of visceral fat, compared to lower-body fat that stores excess fatty acids after a meal, acting as a "metabolic sink". However, it is unclear whether these findings are generalizable to the broader population and whether they have implications for CVD risk.

Objective: We aimed to study how abdominal obesity affects non-fasting and fasting TG levels and assess the impact on the risk of CVD in the UK Biobank.

Methods: Data on non-fasting TG levels (collected within 8 hours of last meal) were available for 382,203 individuals while data on fasting TG levels (collected after 8 hours of fasting) were available for 15,175 individuals. We examined the effect of abdominal obesity, measured by waist-hip ratio adjusting for BMI (WHRadjBMI), on TG levels and CVD risk using both phenotypic and genetically instrumented exposures, to minimize the influence of confounding and reverse causation on our results.

Results: The genetic score for WHRadjBMI showed a 24% greater effect on non-fasting TG levels (beta=0.0072 SD per allele) than fasting levels (beta=0.0058 SD per allele). The WHRadjBMI score was associated with an increased risk of CVD (HR=1.003/allele), and this effect was reduced after adjustment for non-fasting but not fasting TG levels.

Conclusion: Genetic predisposition to abdominal obesity has a stronger effect on non-fasting than fasting TG levels. Including non-fasting TG levels in CVD risk assessment may provide additional information beyond that obtained from fasting TG measurement alone.

Multi–omics in Metabolic Disease: The Importance of Circadian Time

Jean-Michel Fustin, Ben Saer

The University of Manchester

Faculty of Biology, Medicine and Health

Centre for Biological Timing

Studies seeking to define the impact of genetic and dietary metabolic deficiencies in model rodents have often measured the metabolome or transcriptome from tissue samples harvested during the day, by convenience for the researchers. Mice and rats being nocturnal, means that these measurements were made during the resting/fasting phase of these animals. Thus, conclusions may have been affected with consequences of these deficiencies underestimated.

We have previously shown a bidirectional link between 1-carbon metabolism and the circadian clock in many species, such that 1-carbon metabolism regulates the circadian clock and vice-versa. It is therefore very likely that the consequences of 1-carbon metabolism deficiencies on metabolome or transcriptome will be dependent on the time of day at which they are measured.

Here, we show that mice fed a methionine/choline deficient (MCD) diet rapidly and dramatically lose normal circadian rhythms at the behavioural and molecular levels. The MCD diet is commonly used to induce steatohepatitis as a model for human NASH, but the weight loss and insulin hypersensitivity of mice under this diet are opposite to what is seen in NASH, questioning the validity of this model. Indeed, we demonstrate that, far from only affecting fatty acid metabolism in the liver, the MCD diet causes widespread changes in the liver and brain circadian transcriptomes and metabolomes, commensurate with changes in circadian locomotor activity rhythms, highlighting the systemic effects of this diet. Importantly, we show that conclusions on the impact of dietary deficiencies are highly influenced by the time at which measurements are made, calling for the inclusion of circadian time in metabolic disease study designs.

Deep multi-omic integration to understand inter-organ relationships that regulate systemic immunometabolism

Misha Siddiqui1,2, Stephanie Ling1, Marco Bezzi2, Azam Hamidinekoo1, Jennifer Tan1, Bader Zarrouki4, Renata Leke4, Benjamin Challis3, Yinyin Yuan5, and Giovanni Pellegrini6

1. Imaging and Data Analytics, Clinical Pharmacology and Safety Sciences, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK

2. Molecular Pathology, The Institute of Cancer Research (ICR), London, UK

3. Translational Science & Experimental Medicine Research and Early Development, Cardiovascular, Renal & Metabolism, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK

4. Bioscience metabolism, Clinical Pharmacology and Safety Sciences, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

5. The University of Texas MD Anderson Cancer Center, Texas, US

6. Pathology, Aptuit, an Evotec Company, Verona, Italy

Most people living with non-alcoholic fatty liver disease (NAFLD) have isolated liver steatosis that is considered benign, and approximately 20% develop non-alcoholic steatosis hepatitis (NASH), which can progress into cirrhosis and hepatocellular carcinoma (HCC). NAFLD was recently redefined as metabolic-associated fatty liver disease and immunopathogenesis is crucial in NAFLD development and progression. Our knowledge is not sufficient to propose an integrated view of the crosstalk of immune cells in NASH and its interplay with metabolism.

This study investigates the immune cell landscape and its interactions as well as immune cell pathways dysregulated in NAFLD in transcriptomics and metabolomics data. Mice fed Gubra Amylin NASH (GAN - diet-induced obesity (DIO) NASH model), or chow were housed for 25 weeks at thermoneutral (TN) temperature and 25, 33 and 46 weeks at standard temperature.

Over-representation pathway analysis of bulk-level transcriptomics data revealed that inflammation and extracellular matrix pathways were significantly upregulated whereas metabolic-related pathways were significantly downregulated in the GAN-DIO model. Comparing publicly available clinical transcriptomics data to the GAN-DIO model demonstrated the relative similarity of time course data to clinical disease progression. To unravel metabolic changes, I have started analysis of metabolomics data and knowledge integration of transcriptomics and metabolomics data.

Identified immune cell phenotypes and tissue zonation patterns in livers by image mass cytometry. Immune infiltration (F480, neutrophil, CD4, CD8, Treg) was significantly increased in the GAN-DIO model compared to the control. Furthermore, immune cell infiltration increased with the pathologist's steatosis and fibrosis score. TN-housed mice showed the most significant, immune cell infiltration and, change in pathways dysregulated, and were most similar to clinical transcriptomics data as they are a more accurate representation of clinical NAFLD/NASH. Investigation of zonal infiltration revealed that the lobules of the liver contain a spatially polarized immune system and a statistically significant relationship between NASH severity and zonation patterns of inflammation and fibrosis has been reported. Adopted spatial statistic, G-function to deconvolve the immune cell interactions by comparing to complete spatial randomness and between disease and control group. This revealed many significant interactions that changed in the GAN-DIO model from the control group for example neutrophils were statistically clustered with Treg, B cells and CD8 cells in the GAN model at 30 microns.

Establishing a systematic model of the role of metabolic regulation and its crosstalk with the immune system will enable a greater understanding of the physiological systems in place to defend against metabolic stress.

Genome-Wide Association Studies on Coronary Artery Disease: A Systematic Review and Implications for Populations of Different Ethnicities

Sarah Silva, Dorothea Nitsch and Segun Fatumo

The London School of Hygiene & Tropical Medicine

Background: Having a different subset of genes pertaining to the relationship between a specific ancestry group and CAD contributes towards understanding the variety of genetic architecture of coronary artery disease (CAD) across populations.

Aim: To investigate the evidence for differences in the genetic architecture of CAD in populations of diverse ancestries, in order to contribute towards a more global understanding of the pathophysiology of CAD.

Methods: Systematic review. Hypothesis-free genome-wide association studies on coronary artery disease were screened for inclusion. Studies which were published in English, included only human subjects, were published between 2005-2022 and had any form of coronary artery disease as a primary outcome were included. Embase, Medline, Global Health and Cochrane Library were screened on the 6th of October, 2022, with the GWAS Catalog included as a positive control.

Results: We identified 3100 studies, of which, 36 relevant studies were included in this research. Notably, three of the included papers were not included in the GWAS Catalog at the time of the analysis. 743,919 CAD case participants from 25 different countries were analysed, with 58% of the studies identified in this research conducted in populations of European ancestry. No studies investigated populations of admixed American ancestry or Africans living in continental Africa, while limited sample sizes of population groups besides Europeans and East Asians were included. A combined total of 631 unique lead SNPs were identified from the included studies; three ancestry-specific genetic loci were identified in South Asian and African ancestry populations respectively and 95 genetic loci were identified within studies of East Asian ancestry, which were not detected in studies of other ancestries. Of the total number of identified unique lead SNPs, 71 genetic loci were identified to be associated with coronary artery disease in more than one study.

Discussion: The large number of SNPs identified in ancestry-specific cohorts such as the East Asian ancestry group is indicative of the value of conducting research in more diverse settings. With an increasing number of studies identifying novel population-specific CAD loci, findings should be added to the GWAS reference panel in order to capture a more accurate representation of the global population.

Machine learning derived liver fat predictions from multiple orthogonal data sources to drive genetic discovery of NAFLD

Hari Somineni, Sumit Mukherjee, Jingwen Pei, Karl Guo, David Light, Santhosh Satapati, David Lloyd, Philip Tagari, Daphne Koller, Colm O'Dushlaine and Thomas Soare

Insitro, South San Francisco, CA, USA

Proxy phenotypes, phenotypes that are associated with a disease of interest, where the association is suspected to be due to shared biology, allow for the utilization of genetic data from large population cohorts to gain a better understanding of the genetic architecture of complex diseases. Nonalcoholic fatty liver disease (NAFLD), liver with more than 5.5% fat content, is a leading risk factor for end-stage liver disease and is associated with a range of cardio-metabolic conditions. Here we used machine learning to predict liver fat content using three different data modalities, including magnetic resonance imaging (MRI; n=25,474 participants), blood-based clinical and anthropometric markers (biomarkers; n=262,927), and plasma metabolites (n=82,138) in the UK Biobank, and leveraged them, separately, to further understand the genetic architecture of NAFLD. A genome-wide association study of ML-derived liver fat content identified over 2000 independent signals (up to 62 from MRI, 2220 from biomarkers, and 706 from metabolites), significantly expanding the catalog of likely genetic contributions to fat accumulation. Among these signals were well known associations, including PNPLA3, TM6SF2 and GCKR, with consistent effect estimates confirming established biology. In addition, we replicated previously published MRI-derived liver fat associations, including APOE and MAST3. By comparing our results to publicly available summary statistics from clinical NAFLD (n=49 signals) or MRI-derived proton density fat fraction (PDFF; n=92 signals), we observed that MRI modality was most concordant (up to 57% precision and 41% recall value when compared to clinical NAFLD GWAS; up to 93% precision and 28% recall (likely to do with reduced sample sizes in our data and subsequent reduction in power; however, we note a 98% recall at nominal significance) with PDFF). On the other hand, plasma metabolites were least informative (up to 8% precision and 20% recall with clinical NAFLD; up to 8% precision and 14% recall with PDFF). Lastly, liver fat content from biomarkers yielded a 76% recall value, but only had a 5% precision when compared to clinical NAFLD and 58% recall and 7% precision when compared to PDFF). Pairwise genetic correlation analyses indicated a strong positive correlation between liver fat content from across data modalities (rg ranging from 0.79 to 0.97) and with clinical NAFLD (rg ranging from 0.73 for metabolite-derived liver fat to 0.87 for MRI-derived liver fat). Overall, these findings demonstrate the value of leveraging ML-based trait predictions across orthogonal data sources to identify potentially novel genetic associations.

The development of a comprehensive LC-MS method for the quantitation of candidate lipid biomarkers for gestational diabetes.

Dr. Albert Koulman, Jamila Sullivan-Al-Kadhomiy, Benjamin Jenkins & Claire Meek

Dr. Albert Koulman

Core Metabolomics and Lipidomics Laboratory

Institute of Metabolic Science

University of Cambridge

Pathology building Level 4

Addenbrooke's Hospital

CB2 0QQ

UK

tel: +44 (0) 1223 763202

Intro: Lipid metabolism is dynamically influenced by pregnancy in humans. Gestational diabetes mellitus (GDM) is characterised by development of hyperglycaemia, typically in the second or third trimester of pregnancy, preceded by changes in lipid metabolism. Previous work suggests that specific lipid species may be able to identify women at high risk of GDM. In this study, we aimed to identify if certain candidate-biomarker lipid species present in early-pregnancy maternal blood are able to predict GDM incidence/ prognosis.

Methods: Using a literature search, we identified a range of lipid-related candidate-biomarkers of GDM. These proposed biomarkers were investigated using a quantitative analytical method utilising liquid chromatography and high-resolution mass spectrometry (LC-MS). In previous studies, the lipids were measured by direct infusion mass spectrometry and different LC-MS methods. The current study brings all these candidate-biomarker lipids together into one LC-MS method for quantitative profiling, determined by both accurate mass and retention time. While the previous studies looked at temporal GDM predictors, metabolic biomarkers and specific lipid groups separately, this study aimed to develop an overarching measurement of the 66 lipids individually as well as collectively.

The plasma samples were prepared using a high-throughput single phase extraction previously published by Jenkins et al 2020. Chromatographic separation was performed on a Waters Acquity Premier UPLC® CSH C18 column; 1.7 µm, I.D. 2.1 mm X 50 mm, along with a Q-Exactive scanning at 4 Hz (equivalent to 35,000 resolution) using positive/negative switching. Targeted data processing was done using the Thermo Xcalibur software, briefly: extracted ion chromatogram peaks for each target lipid specie were integrated at their expected retention time and normalised to an appropriate labelled internal standard. These were then further normalised, quality processed and then transformed into absolute concentrations (µM).

Results: We here present a novel robust method of analysis of key candidate-biomarkers for GDM. The method is 12 min per sample and can work with a 384 well plate format. This method provided quantitative and detailed coverage of the candidate lipid biomarkers that had been and is suitable for the analysis of plasma, serum and/or tissue samples from studies on complications in pregnancy.

Conclusion: This novel method will be applied on sample sets to validate which lipid biomarkers are most effective as early predictors of GDM, with possible roles in the underlying biological processes resulting in GDM.

Adults prenatally exposed to the Dutch Famine have a metabolic signature predictive of type-2 diabetes risk.

Jazmin Taeubert1, Thomas B. Kuipers1, Jiayi Zhou2, Chihua Li3, Shuang Wang4, Tian Wang4, BBMRI-NL Metabolomics consortium, Daniel W. Belsky2,3, L. H. Lumey1,3, Bastiaan T. Heijmans1.

1. Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

2. Butler Columbia Aging Center, Columbia University, New York, United States

3. Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, United states

4. Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, United states

Introduction: Exposure to famine in the prenatal period is associated with an increased risk of metabolic disease. Here, we employ nuclear magnetic resonance (NMR) metabolomic profiling to define and refine the metabolic profile associated with intrauterine exposure to malnutrition during the Dutch Famine.

Methods: NMR metabolomics data were generated in 480 individuals prenatally exposed to famine (mean 58.8 years, 0.5 SD) and 464 controls (mean 57.9 years, 5.4 SD) participating in the Dutch Hunger Winter Families Study. We examined the association of prenatal famine exposure with log-transformed concentrations of 168 metabolic markers (lipoprotein subclass-specific cholesterol and triglycerides, amino acids, ketone bodies, and others). Regression models included age, sex, and use of cholesterol-lowering drugs as covariates. Effect-size estimates are reported in standard-deviation (SD) units of the log-transformed metabolites.

Results: Prenatal famine exposure was associated with higher concentrations of tyrosine, leucine, glucose, and isoleucine in later life (b = 0.2-0.3, p<3x10-3 for all). Associations were robust to covariate adjustment for BMI, diabetes, and polygenic scores of the metabolites. In metabolome-wide analysis, effect sizes for in-utero-famine exposure were strongly correlated with effect-sizes estimated in UK Biobank data for risk of incident type-2 diabetes (r = 0.77, p = 2x10-16) and BMI (r = 0.87; p = 2x10-16).

Conclusion: Prenatal famine exposure is associated with metabolomic differences later in life. These include higher levels of branched-chain amino acids, aromatic amino acids, and glucose, as well as an overall metabolomic profile characteristic of risk for obesity and type-2 diabetes. Our findings illuminate the metabolome as a mechanism through which in-utero undernutrition contributes to development of metabolic diseases in later life.

Are you drowning your cells? The importance of oxygen tension in cell culture

Joycelyn Tan (1), Sam Virtue (1), Dougall M. Norris (1), Olivia J. Conway (1), Ming Yang (2,3), Christopher Gribben (4), Fatima Lugtu (4), James R. Krycer (5,6), Richard J. Mills (5,6), Ioannis Kamzolas (1,7), Martin Dale (1), James A. Horscroft (9), Alice P. Sowton (9), Marcella Ma (1), Evangelia Petsalaki (7), Andrew J. Murray (9), James E. Hudson (5,6,10), Ludovic Vallier (4), Christian Frezza (2,3), Antonio Vidal-Puig (1), Daniel J. Fazakerley (1)

(1) Metabolic Research Laboratories, Wellcome-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge, UK; (2) MRC Cancer Unit, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK; (3) CECAD Research Center, Faculty of Medicine, University Hospital Cologne, Cologne, Germany; (4) Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge, Cambridge, UK; (5) QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; (6) Faculty of Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia; (7) European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, UK; (8) Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK; (9) Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK; (10) Faculty of Medicine, School of Biomedical Sciences, The University of Queensland, Brisbane, Queensland, Australia

Cell culture is generally considered to be at non-physiological hyperoxia. However, when compared to well-evolved circulatory systems, passive diffusion of oxygen through the culture medium column represents a fundamental limitation in cell culture systems. We hypothesised that oxygen consumption by cultured cells, along with limited oxygen diffusion through the culture medium, would establish a gradient of oxygen concentrations from the air-media interface to the cell monolayer. The resulting pericellular hypoxia may have major effects on cellular metabolism and function. To study this, we manipulated cellular oxygen availability in cultured cells, focussing predominantly on terminally differentiated metabolic cell types. We used a broad range of metabolic and biochemical assays, alongside multi-omics analyses to provide the most detailed characterisation to-date of the cellular metabolic, transcriptomic, and functional responses to changes in oxygen availability. Under standard culture conditions, 3T3-L1 adipocytes are hypoxic and highly glycolytic. Increasing oxygen availability altered 13C-glucose flux toward mitochondria, simultaneously increasing glucose oxidation and use of glucose-derived carbon for lipogenesis. These metabolic changes were coupled to thousands of gene expression changes, and rendered adipocytes more sensitive to insulin and lipolytic stimuli. Importantly, pathway analyses revealed increasing oxygen tension made in vitro adipocytes more similar to in vivo white adipose tissue. Metabolic and phenotypic responses to increased oxygen were also observed in other post-mitotic cells, revealing a consistent enhancement in cellular function and differentiation of hPSC-derived hepatocytes and cardiac organoids. These data reflect major metabolic and transcriptional rewiring during cell culture when oxygen availability is increased. Our study highlights that cell culture is not a state of artificially high oxygen tension, but a state of variable oxygen tension depending on both the oxygen consumption rate of the cell monolayer and the oxygen diffusion distance. Manipulating oxygen levels has dramatic effects on many aspects of cellular metabolism, with important implications for cell models and their translation to in vivo settings.

The complex cross-talk diet-microbiota-epigenome: the case of Akkermansia in type 1 diabetic children in Qatar

Annalisa Terranegra, Shaikha Alabduljabbar1, Arun P Lakshmanan1, Goran Petrovski2, Fawziya Al Khalaf2, and Annalisa Terranegra1

1 Research department, Sidra Medicine, Doha, Qatar

2 Endocrinology clinic, Sidra Medicine, Doha, Qatar

Introduction: Type 1 diabetes (T1D) is one of the common pediatric diseases in Qatar. Bacterial dysbiosis and diet have been shown to be contributing factors to T1D. Our previous results revealed that the genus Akkermansia was significantly elevated in the Qatari pediatric T1D subjects with poorly controlled HbA1c levels (>7.5%) and consuming an Arabic diet. Thus, in this pilot study, we aim to explore the correlation of Akkermasia abundance with clinical status, nutrient intake and blood DNA methylation in the pediatric T1D population of Qatar.

Methodology: Thirty-seven pediatric T1D patients aged 6-12 years were enrolled in the study and matched with 23 healthy control subjects (HC). Clinical data were collected from the medical records together with blood and fecal samples, as well as 24-hour dietary recalls. Illumina Miseq 16S rDNA sequencing was used for the microbiome analysis from stool samples (previously puclished), Illumina Infinium 850 K array for DNA-methylation (DNAm) analysis from blood samples, and the dietary data were analyzed by the Axxya Nutritionist Pro system. GenomeStudio (Illumina Inc.) pipelines were used for the methylome analysis. Statistical analysis was conducted using Prism GraphPad, with a statistical significance of p-value<0.05.

Results: Spearman correlation showed that Akkermansia is significatively correlated with dietary intake of cholesterol (r=0.311), linolenic acid (r=-0.0.501), iron (r=-0.0.345), magnesium (r=-0.298), manganese (r=-0.486), maltose (r=-0.301), and proline (r=-0.311), and with the serum levels of vitamin D (r=-0.424) and the insulin/carbs ratio (r=0.336) in T1D patients. While Akkermansia in the HC group showed correlations with dietary beta-carotene (r=-0.440), serum levels of AST (r=-0.463) and HbA1c (r=-0.471), triglycerides (r=0.596) and HDL (r=0.518). DNAm analysis identified multiple differentially methylated loci among which STAG1, TMEM63C, FOXK1, AKR1B15, ACSF3 hypermethylated, and ZNF709, UQCRC1, KLHL7, EMILIN1, LINC01359 hypomethylated in T1D subjects with HbA1c levels (>7.5%) compared to T1D subjects with HbA1c levels (<7.5%). Moreover, the total level of CpG is significatively correlated with the levels of HbA1C (r=0.215), AST (r=0.3845), SBP (r=0.286), and dietary intake of EPA and DHA (r=-0.4785, r=-0.503, respectively), beta-tocopherol (r=-0.339) in T1D and contrariwise many amino acids in both T1D and HC.

Conclusion: Akkermansia, previously associated with negative glycemic control in T1D, is found to be correlated to multiple dietary and clinical factors in pediatric T1D. Moreover, a change in the methylation pattern is also associated with glycemic control (level of HbA1C) and diet. In particular, multiple differentially methylated loci involved in metabolic and protein metabolism pathways are able to discriminate T1D subjects according to glycemic control (HbA1c levels >7.5%). The findings show a complex interaction between diet, gut microbiota, and epigenetic modification in controlling glycemia in T1D and can open the routes to dietary and probiotic therapies for T1D.

The effect of diet on the inflammatory and lipid biomarkers for Cardiovascular Diseases Risk in the Obese Qatari population

Annalisa Terranegra, Yasmin Olabi1, Salma Hayder Ahmed1, Arun Prasath Lakshmanan 1, Shana Jacob 2, Sahar Al-Shamari 3, Hala Taha Khalil Taha Shabana 3, Wahiba Elhag 3, Yassmin Salaheldin Mohamed Ibrahim 3

1Precision Nutrition, Research Department, Sidra Medicine, Doha, Qatar.

2Advanced Cell Therapy Core, Research Department, Sidra Medicine, Doha, Qatar.

3Bariatric and Metabolic Surgery Department, Hamad Medical Corporation, Doha, Qatar.

Introduction: The increasing prevalence of obesity and the vast amount of research linking it to the etiology of cardiovascular diseases (CVD) have driven the interest in further assessing the underlying molecular mechanisms. Numerous studies and ongoing research highlight the association between CVD and both the Dietary Inflammatory Index (DII) and Healthy Eating Index (HEI) where it has been shown that a Pro-Inflammatory diet increases the risk of CVD. Lipid profile is routinely used as a biomarker for CVD, particularly HDL/LDL. However, lipid metabolism is still not clearly elucidated as well as the effect of diet on it.

In this study, we aimed to assess any interaction between diet, inflammatory biomarkers, and serum lipidomic profiles associated with CVD risk in the obese population of Qatar.

Methodology: We enrolled 55 adult subjects classified in the CVD risk group (≥10 risk score) and no-risk group (<10 risk score) according to the Framingham risk formula. We measured body composition by bioimpedance, dietary intake by 24hrs recalls, inflammatory biomarkers by multiplex protein array, and serum lipid metabolites by liquid chromatography-mass spectrometry (HPLC-MS). Dietary habits were assessed by calculating DII and HEI scores. Mann-Whitney U test was used to compare between CVD risk group and the no-risk group. Correlation analysis between dietary scores and the biomarkers was performed using Spearman Correlation. Statistical analyses were conducted using Prism GraphPad, with a statistical significance of p-value<0.05.

Results: The inflammatory biomarker, Thymic stromal lymphopoietin (TSLP) (p=0.01), the lipid biomarkers, Phosphatidylinositol (p=0.03); Zymosterol ester (p=0.01), and Sphiganine-1-Phosphate (p=0.02) were higher in the CVD-risk group vs the no-risk one. Conversely, the inflammatory biomarker Matrix metalloproteinase (MMP-1) was significantly higher in the no-risk group (p=0.04). The correlation analysis confirmed the interaction between dietary habits and multiple lipid and inflammatory biomarkers, among which both HEI and DII inversely correlated with Osteopontin (vs HEI r=0.83, p=0.016; vs DII r= -0.76, p=0.037); Sterol ester (vs HEI r= 0.45, p=0.002; vs DII r=-0.42, p=0.004), Phosphatidic acid (vs HEI r=0.39, p= 0.008; vs DII r=-0.36, p=0.016); Phosphatidylcholine (vs HEI r=0.38, p= 0.011; vs DII - 0.33, p= 0.025).

Conclusion: The role of diet in the modulation of the lipid profile indicates its importance and effective potential in the prevention and treatment of CVD in the obese population. Further studies need to confirm the findings and better elucidate the molecular mechanism underlying the effect of diet on the lipid and inflammatory biomarkers for CVD.

Identifying hypothalamic cell type-specific regulatory mechanisms driving obesity and type 2 diabetes predisposition

Cecilia E Thomas, Helle K. Lilja-Fischer [1], Marie A. Bentsen [1], Colin Smith [2], Istvan Adorjan [3], Kristoffer L. Egerod [1], Tune H. Pers [1]

1 Novo Nordisk Foundation Center for Basic Metabolic Research, Copenhagen University, Copenhagen, Denmark

2 Academic Neuropathology, Centre for Clinical Brain Sciences, Edinburgh, United Kingdom

3 Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, Hungary

Despite insights from animal studies and >2000 genetic variants having been associated with metabolic disease, the genes and pathways mediating susceptibility to obesity and type 2 diabetes are largely unknown. Both human genetics and mouse studies point to the brain as the major regulator of metabolic fuel homeostasis.

We will use human postmortem brain tissue and map regulatory networks across individuals with and without metabolic disease. Focusing on the mediobasal hypothalamus, we will generate data on gene expression, chromatin accessibility and enhancer activity using single-cell RNA, assay for transposase-accessible chromatin, and cleavage under targets and tagmentation sequencing. To identify candidate cell type-specific effector genes, molecular functions, and pathways mediating the genetic risk of metabolic disease, we will (i) identify active enhancers and predict enhancer-to-gene pairs using the activity-by-contact model; (ii) map genetic variants to active enhancers and their predicted target genes; and (iii) apply computational analysis to identify regulatory networks.

Key outcomes of this study include (i) cell type-specific human hypothalamic atlases of cells defined by their gene regulatory networks; (ii) maps of genetic variants' likely target genes, effector cell types and molecular processes; and (iii) regulatory networks linking obesity with diabetes predisposition. The focus will be on providing testable hypotheses on specific combinations of cell types and molecular phenotypes involved in metabolic dysfunction that are amenable to in vitro experiments using stem cell-derived hypothalamic cell type models.

A Multi-Omics Approach to Identify Markers of Diabetic Neuropathy for Precision Medicine

Dr Gurjeet Kaur 1, Tina Okdahl 2, Alberto Santos Delgado 3,4, Tarunveer Singh Alhuwalia 1,1a, Christian Stevns Hansen 1, Tine Willum Hansen 1, Nicolai J. Wewer Albrechtsen 3, David Wishart 5, Benedikt Kessler 6,7, Peter Rossing 1, Troels Staehelin Jensen 8,9, Christina Brock 2, Cristina Legido-Quigley 1,10, Karolina Sulek 1

1 Steno Diabetes Center Copenhagen, Herlev, Denmark

1a The Bioinformatics Center, Department of Biology, University of Copenhagen, Copenhagen, Denmark

2 Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital and Clinical Institute, Aalborg University, Aalborg, Denmark

3 NNF Center for Protein Research, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

4 Li-Ka Shing Big Data Institute, University of Oxford, UK

5 University of Alberta, Edmonton, Alberta, Canada

6 Target Discovery Institute, Centre for Medicines Discovery, University of Oxford, UK

7 Chinese Academy for Medical Sciences Oxford Institute, Nuffield Department of Medicine, University of Oxford, UK

8 Danish Pain Research Centre, Department of Clinical Medicine, Aarhus University, Denmark

9 Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

10 Institute of Pharmaceutical Science, School of Life Science & Medicine, King's College London, London UK

In type 1 diabetes (T1D), lack of insulin production leads to hyperglycemia with a cascade of metabolic dysregulations in the body. Longstanding diabetes might lead to different microvascular complications: one severe complication being neuropathy that damages the nerves. Most common among diabetic neuropathies is distal symmetric polyneuropathy (DSPN) (75%), which clinically is defined as presence or symptoms of peripheral nerve dysfunction. Early detection of DSPN is essential to prevent the onset of nerve damage and its complications, such as foot ulcers, infections, and amputations. There is no causal treatment for the neuropathy or for its associated pain.

Through combination of clinical characteristics, plasma metabolomics, lipidomics, and proteomics data, the study aims on development of clinically actionable biomarkers and their setup at Steno Diabetes Center Copenhagen. Our optimized workflow will be used to profile plasma from two established cohorts including 150 and 700 T1D patients with serum samples available. Discovery will be made in individuals already diagnosed with DSPN and validation will include longitudinal data of T1D individuals followed for development of DSPN.

Our study will potentially contribute towards development of novel biomarkers for the early detection of DSPN in T1D individuals, which will impact improved clinical outcomes and better quality of life for T1D individuals. Furthermore, the study will allow discovery of molecular pathways and mechanisms underlying DSPN development and progression, opening the path for future research towards drug discovery.

GWAS in Labrador retrievers identifies novel obesity genes in dogs and humans.

Natalie J. Wallis 1, 2, Alyce McClellan 2,

Justine Chan 2,

Sambhavi S. Kumar 2,

Ellen Schofield 3,

Jacek Mokrosinski 1,

Alexander Mörseburg 1,

Katherine Kentistou 4,

John Perry 1, 4,

Giles Yeo 1,

Sadaf Farooqi 1,

Stephen O'Rahilly 1,

Eleanor Raffan 1, 2

1 Wellcome-MRC Institute of Metabolic Science, Cambridge, UK

2 University of Cambridge Department of Physiology Development and Neuroscience, Cambridge, UK

3 University of Cambridge Department of Veterinary Medicine, Cambridge, UK

4 MRC Epidemiology Unit, Cambridge, UK

Background: In dogs, selective breeding and population bottlenecks simplify gene mapping for disease. Similarities between canine and human obesity means genetic associations in dogs can prioritise candidates from human genomic studies for further investigation.

Methods/Results: A genome wide association study for obesity in Labrador retrievers identified multiple obesity genes. Genetic scores for obesity predict phenotypes in related but not unrelated breeds. Polygenic background influences penetrance of well characterised mutations in the leptin-melanocortin pathway. In human cohorts, we found canine obesity genes are associated with both common and monogenic forms of obesity. Selective sweep mapping highlighted regions containing known obesity genes including a missense variant in MC4R which affects receptor function.

Conclusion: We have identified novel obesity-related genes in humans by studying a canine obesity model. This demonstrates the benefits of studying complex disease in non-traditional animal models such as the dog.

Integration of genomics and untargeted metabolomics data for the diagnosis of patients with suspected inherited metabolic disorders

Robin Wijngaard1,7, Judith J. Jans2,7, Anke P. Willems2,7, Nanda M. Verhoeven2,7, Leo A.J. Kluijtmans3,7, Udo F.H. Engelke3,7, David Koolen1, Elise A. Ferreira4,7, Saskia N. van der Crabben5,7, Mirjam Langeveld6,7, Christian Gilissen1, Lisenka E.L.M. Vissers1, Clara D.M. van Karnebeek4,7, Machteld M. Oud1,7

1Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, The Netherlands; 2Department of Genetics, university Medical Center Utrecht, Utrecht, The Netherlands; 3Department of Laboratory Medicine, Translational Metabolic Laboratory, Radboud university medical center, Nijmegen, The Netherlands; 4Department of Pediatrics, Emma Children's Hospital Amsterdam University Medical Centers, Amsterdam NL; 5Department of Human Genetics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; 6Department of Endocrinology and Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; 7On behalf of United for Metabolic Diseases (UMD),The Netherlands.

The ZOEMBA study ("ZOektocht naar Erfelijke MetaBole Aandoeningen") is a Dutch national multicenter study initiated by the United for Metabolic Diseases consortium. The main objective of the study is to diagnose patients suspected of having an inherited metabolic disease (IMD), but who remain undiagnosed after diagnostic care.

The study cohort includes 150 patients with a clinical and/or biochemical profile compatible with IMD and no diagnosis upon exome sequencing in routine diagnostic care. For all patients, 30x short read genome sequencing was performed (including parents when possible) as part of the ZOEMBA study. In addition, untargeted metabolomics was performed on two different specimens from each patient, including ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (plasma) and Hybrid Quadrupole-Orbitrap mass spectrometry (dry blood spots).

The study consists of two parts. First, existing data integration tools will be tested and compared on data with known pathogenic variants and metabolites (controls), followed by an analysis of the ZOEMBA cohort. The obtained insights into the strengths and limitations of each tool and its approach will be used in the second part, where we aim to improve the methods by making them more suitable for patients with diseases of unknown etiology. Furthermore, we would like to include data derived from other sources such as genome-wide metabolic quantitative trait locus analysis studies. In cases where we find variants of uncertain significance (VUS) in good candidate genes, functional follow-up will be performed to validate the pathogenicity of the variants. In addition, metabolites in abnormal concentrations will be studied for their function as potential biomarkers.

In this study we will integrate genomic and untargeted metabolomic data to improve diagnostic care and evaluate the clinical utility for patients suspected of having an IMD. With this study we aim to increase the diagnostic yield, to elucidate new IMD genes and to discover new biomarkers useful for diagnosis or monitoring of IMD.

RNA sequencing in hypothalamic nuclei reveals distinct gene expression profiles in response to exercise and sex difference

Robby Zachariah Tom, Shiqi Zhang, Sebastian Cucuruz, Brian Lam, Giles Yeo, Susanna M Hofmann

1)Institute of Diabetes and Regeneration Research, Helmholtz Zentrum, Munich, Germany

2)Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität München, Munich

3)Wellcome-MRC Institute of Metabolic Science-Metabolic Research Laboratories, University of Cambridge, UK

Introduction: Exposure to an energy dense diet and reduced physical activity drive obesity and metabolic disorders in both sexes, but differences in rate and response to exercise interventions are apparent. The hypothalamus regulates food intake, body weight, and energy balance, but sex-specific differences in hypothalamic function that contribute to obesity and response to interventions are unclear. We used laser capture microdissection and RNA-sequencing to profile the transcriptome of arcuate (ARC), ventromedial (VMH), dorsomedial (DMH) and paraventricular (PVN) hypothalamic nuclei in male and female mice with access to standard (SD) or high-fat diets (HFD) and voluntary running wheels (VR).

Results: VR reduced diet-induced weight gain in both males and females, but males displayed proportionally greater weight reduction than females. Dietary choices were also influenced by exercise, with VR increasing calorie consumption in male mice exposed to both SD and HFD, while total calorie consumption in females were unaltered. Here, we show that the transcriptional profile of all four hypothalamic nuclei in response to VR is influenced by sex. In ARC, exercise reduced stress signaling pathways in both males and females. AMPK signaling and apoptosis signaling pathways were dominant in ARC and were differentially regulated by exercise and sex. Glial fibrillary acidic protein (GFAP) which forms structural filament of astrocytes and regulates neuronal functions also showed sexual dimorphic differences. In VMH, exercise modulated pathways associated with DNA damage and repair in a sex independent manner. Signaling pathways associated with synapse formation and neurogenesis were differentially regulated by exercise and sex. In DMH, pathways related to neural plasticity were regulated by exercise independent of sex, while sexual dimorphic differences were observed in synaptogenesis pathways in DMH. In PVN, exercise facilitated vascular remodeling pathways in both sexes, with sex-specific variations observed in inflammatory signaling pathways. Furthermore, in a separate study, we cross verified the sex specific increase in GFAP expression in ARC. The number of astrocytes in ARC from female mice were higher than males and was independent of diet. But HFD exposure reduced the number of primary projections ($p < 0.05$) and total length of primary projections only in males. Conclusion: We have identified signaling pathways that are modulated by exercise in four hypothalamic nuclei in a sexual dimorphic manner and argues for sex specific lifestyle interventions in the treatment of obesity and other metabolic disorders.

Virtual Poster Presentation Abstracts

A case of Methylmalonic Aciduria: The genomics approach towards a confirmed diagnosis

Nadir Aman,

Sandor Speciality Diagnotics Pvt. Ltd., Banjara Hills, Hyderabad-5000134

Background-Methylmalonic acidemia with homocystinuria (MMACHC) is an inherited disorder in which the body is unable to properly process protein building blocks (amino acids), certain fats (lipids), and a waxy fat-like substance called cholesterol. When the condition begins early in life, affected individuals typically have failure to thrive, IUGR, pallor, hypotonia, seizures. Most infants and children with this condition have microcephaly, delayed development and intellectual disability. Less common features of the condition include eye problems and a blood disorder called megaloblastic anemia. When methylmalonic acidemia with homocystinuria begins in adolescence or adulthood, the signs and symptoms usually include psychiatric changes and cognitive problems. In addition, these individuals can begin to lose previously acquired mental and movement abilities, resulting in a decline in school or work performance, difficulty controlling movements, memory problems, speech difficulties, a decline in intellectual function (dementia), or an extreme lack of energy (lethargy).

Case History- A 3-years male child born of third-degree consanguineous marriage presented with: Global developmental delay, Recurrent Spasms, Epileptic Encephalopathy, Nystagmus, Increased brisk reflexes, Visual Inattention

Investigations- EEG- Showed generalized epileptiform activity over both hemispheres. TMS, GCMS, biotinidase study, Amino acid profile, acyl carnitine protein was NORMAL

NGS based whole exome sequencing was suggested for genomic diagnosis.

Results- The patient showed a likely pathogenic homozygous mutation at Exon 3 of MMACHC [c.394C>T (p.Arg132Ter)] gene, located at chromosome 1p34.1 known to cause Methylmalonic Aciduria and Homocystinuria cblC type.

Genetic Counselling-MMACHC is a rare autosomal recessive disorder with an incidence ranging from 1 /100,000 to 1/200,000 births worldwide. The clinical suspicion of cblC disease should lead to the immediate analysis of urine organic acids, serum MMA, tHcy, plasma amino acids and an acylcarnitine profile followed by mutation analysis. Individuals with combined methylmalonic acidemia and homocystinuria respond to a combined treatment consisting of supplementation of hydroxy cobalamin, betaine, folic acid, vitamin B6 and L-carnitine with clinical and biochemical improvement. The early prenatal diagnosis of cblC disease is possible by molecular analysis of chorionic villus cells or cultured amniocytes. Exome sequencing along with measurement of enzyme activity analysis can significantly improve the diagnostic yield. Parents were counselled regarding the risk of having another child with MMACHC is 25% with each pregnancy with the same two partners. Hence parental testing as well prenatal testing should be recommended.

Autozygosity and type 2 diabetes phenotype and risk prediction in British Pakistani and Bangladeshi individuals: results from the Genes & Health study

Sam Hodgson, Daniel Malawsky2, Qinqin Huang2, Teng Heng2, Fabiola Eto1, Daniel Stow1, Miriam Samuel1, The Genes & Health Research Team1, David van Heel1, Rohini Mathur1, Hilary C Martin2 & Sarah Finer1

1: Queen Mary, University of London

2: Wellcome Sanger Institute

Background: Autozygosity is a form of extensive homozygosity mediated through identity-by-descent associated with consanguinity and endogamy, and increases risk of type 2 diabetes (T2D). The fraction of the genome in runs of homozygosity (FROH), a common measure of individual-level autozygosity, is higher in British Pakistani and Bangladeshi (BPB) individuals than other ancestral groups, as are rates of T2D.

Aims: Explore phenotypic features associated with autozygosity in T2D subgroups, and assess the utility of autozygosity in predicting incident T2D and its complications.

Methods: G&H combines electronic health record and genetic data from 44k BPB individuals. The distribution of FROH in unrelated individuals was compared across five phenotypic subgroups of T2D in a clinical model (n = 3527) clustering individuals on the basis of clinical variables at the time of diagnosis using latent class analysis. FROH was added as a clustering variable in an integrated clinical-genetic model of T2D subgroups. Progression to micro- and macrovascular complications was compared between subgroups for both clinical and integrated models using Cox proportional hazards models adjusted for statin use and hypertension. Prediction of 10-year diabetes risk was compared between two models (QDiabetes, and a QDiabetes-FROH integrated risk tool (IRT)).

Results: In clinical clustering analysis, FROH was highest in the mild obesity-related diabetes (MOD) cluster (mean value 0.022, 95% CI 0.020 - 0.024) and lowest in the insulin-resistant diabetes (IRD) cluster (mean value 0.013, 95% CI 0.011 - 0.015)(ANOVA across all five clusters $p < 0.001$); in contrast T2D polygenic risk score was highest in the clinically-undifferentiated diabetes (CUD) and IRD clusters and lowest in MOD (ANOVA across all clusters $p<0.001$). Progression to microvascular complications was highest in CUD and lowest in MOD ($p<0.001$). In the integrated clinical-genetic model a novel subgroup emerged, characterized by high FROH (0.059), low PRS (-0.447), and moderately high BMI (30.0kg/m^2), which we term autozygosity-related diabetes, and which had lowest rates of progression to microvascular complications. Prediction of incident diabetes was moderately improved in females aged less than 40 years for QDiabetes model A (NRI 0.59%, 95% CI 0.09 - 1.09%) but not in other subgroups, nor overall for QDiabetes models B or C.

Conclusions: Autozygosity is associated with distinct type 2 diabetes phenotypes in BPB individuals, and may offer clinical utility in prediction of microvascular complications.

Two cases of D-bifunctional protein deficiency as a cause of neonatal onset seizures and hypotonia

Fatma Mejdoub, Guirat Manel 1 , Regaieg Chiraz 2, Gharbi Nourhene 1 , Guidara Souhir1, Cheillan David 3 , Frikha Hela1, Kamoun Hassen 1, Hamida Nadia2, Ben Ayed Ikhlas1

1-Medical Genetic Department, Hedi Chaker Hospital, Sfax, Tunisia, Sfax, Tunisia

2-Neonatology department Hedi Chaker Hospital, Sfax, Tunisia

3-Service Biochimie et Biologie Moléculaire, CHU de Lyon HCL

D-bifunctional protein (DBP) deficiency, caused by recessive mutations in HSD17B4 gene, is a severe, infantile-onset disorder of peroxisomal fatty acid oxidation. It is characterized with neonatal hypotonia, seizures, craniofacial dysmorphisms, psychomotor delay, visual and hearing impairment and death typically within the first 2 years of life. We reported here two cases of Tunisian unrelated new-borns (P1 and P2) suffered from generalized hypotonia and seizures. The evolution was characterized, for both, by early death due to respiratory and neurological distress.

A whole exome sequencing was performed for P1, and Sanger sequencing of exon 16 of the HSD17B4 gene followed by Targeted panel sequencing for P2.

P1 was homozygote for N457Y, and P2 was compound heterozygote for N457Y and R506C. Segregation study of these mutations in the P2's parents is in progress. Both missense mutations are located in the hydratase subunit of the protein. The variant N457Y represents a hotspot mutation responsible for more than 12% of cases of DBP type II deficiency and reduces the hydratase activity of this protein to less than 10%. The R506C variant is located also in a hotspot region and is known to be responsible for a disturbance in the dimerization of the DBP protein.

Molecular confirmation of DBP deficiency provided a better genotype-phenotype correlation in our patients and allowed accurate genetic counselling to their families. The study of other DBP deficiency patients could help us to estimate the allelic frequency of the N457Y mutation in the Tunisian population.

Genetic counseling in inherited metabolic disorders: current challenges and insights

Brinda Ramanathan, Deepika Karthik Kumar, Dr. Vidhya Vishwanathan, Dr. Meenakshi J, Dr. Subramanian Sethuraman

NISHTA Integrated Neurodevelopment Centre, Chennai, Tamil Nadu, India

Background: Inherited metabolic disorders, though individually rare, cumulatively form a considerable number, often compounded by genetic and clinical heterogeneity. We discuss here three cases of metabolic disorders that present unique challenges in genetic counseling. Method: A 3-generation pedigree, family history, and medical history were taken for the patient's families. Genomic testing was carried out using next-generation sequencing. Case 1 (preconception counseling)- 5-month-old female with elevated 4-hydroxybutyric acid and glycolic acid, found to harbor compound heterozygous variants in the ALDH5A1 associated with succinic semialdehyde dehydrogenase deficiency. Case 2 (to understand diagnosis and management) a 2 year-old-male with global developmental delay was found to harbor compound heterozygous variants in the SDHA gene suggestive of a mitochondrial deficiency related disorder. Case 3 (to confirm if there is a genetic diagnosis)- 12-year-old male with congenital bilateral sensorineural hearing loss and late onset bilateral ptosis was found to harbor compound heterozygous variants in the USH2A gene alongside homozygous variants in the BTD gene. Genetic counseling and conclusion: All three cases were unique in their clinical and genetic manifestations and involved counseling aimed at addressing their respective concerns and context. We aim to highlight through this series that while genomic testing has improved our ability to detect and diagnose metabolic diseases multi-fold, we still have the arduous task of correlating and counseling among clinical and genetic heterogeneity.

Associations of four biological age markers with child development: A multi-omic analysis in the European HELIX cohort

Oliver Robinson, ChungHo Lau, Lida Chatzi, Hector C. Keun, Regina Grazuleviciene, Kristine B. Gützkow, Léa Maitre, Dries S. Martens, John Wright, Tim Nawrot, Mariona Bustamante, Martine Vrijheid

Medical Research Council Centre for Environment and Health, School of Public Health, Imperial College London, London, United Kingdom

Mohn Centre for Children's Health and Well-being, School of Public Health, Imperial College London, London, United Kingdom

Department of Environmental Science, Vytautas Magnus University, Kaunas, Lithuania

Universitat Pompeu Fabra (UPF), Barcelona, Spain

Institute for Global Health (ISGlobal), Barcelona, Spain,

CIBER Epidemiologa y Salud Pública (CIBERESP), Madrid, Spain,

Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, United States

Division of Systems Medicine, Department of Metabolism, Digestion and Reproduction, Imperial College London, UK

Cancer Metabolism & Systems Toxicology Group, Division of Cancer, Department of Surgery & Cancer; Imperial College London, UK

Division of Climate and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium

Department of Social Medicine, School of Medicine, University of Crete, Heraklion, Crete, Greece

Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK

While biological age in adults is often understood as representing general health and resilience, the interpretation of accelerated biological age in children and its relationship to development remains unclear. We aimed to clarify the relationship of accelerated biological age, assessed through telomere length and three omics-derived biological clocks, to child developmental outcomes, including growth and adiposity, cognition, behaviour, lung function and onset of puberty, among European children participating in the HELIX exposome cohort.

The study population included up to 1,173 children, aged between 5 and 12 years, from study centres in the UK, France, Spain, Norway, Lithuania, and Greece. Telomere length was measured through qPCR, blood DNA methylation and gene expression was measured using microarray, and proteins and metabolites were measured by a range of targeted assays. DNA methylation age was assessed using Horvath's skin and blood clock, while novel blood transcriptome and "immunometabolic" (based on plasma protein and urinary and serum metabolite data) clocks were derived and tested in a subset of children assessed six months after the main follow-up visit. Associations between biological age indicators with child developmental measures as well as health risk factors were estimated using linear regression, adjusted for chronological age, sex, ethnicity and study centre.

Transcriptome and immunometabolic clocks predicted chronological age well in the test set ($r = 0.93$ and $r = 0.84$ respectively). Generally, weak correlations were observed, after adjustment for chronological age, between the biological age indicators. Higher birthweight was associated with greater immunometabolic Δ age, smoke exposure with greater DNA methylation Δ age and high family affluence with longer telomere length. All biological age markers were positively associated with BMI and fat mass, and all markers except telomere length were associated with height, at least at nominal significance ($p<0.05$). Immunometabolic Δ age was associated with better working memory ($p = 4e-3$) and reduced inattentiveness ($p = 4e-4$), while DNA methylation Δ age was associated with greater inattentiveness ($p=0.03$) and poorer externalizing behaviours ($p = 0.01$). Shorter telomere length was also associated with poorer externalizing behaviours ($p=0.03$).

In children, as in adults, biological ageing appears to be a multi-faceted process and adiposity is an important correlate of accelerated biological ageing. Patterns of associations suggested that accelerated immunometabolic age may represent build-up of biological capital while accelerated DNA methylation age and telomere attrition may represent a "wear and tear" model of biological ageing in children.

C. elegans multiomics supports the identification of core gene regulatory networks involved in host-gut bacterium interactions

Alejandra Zárate-Potes1,#,, Irtiqa Ali1, Laila Rees1, Hayley Brownless1, Margarida Camacho1, Eleanor Crago1, Jack Martin1, Natália S. Jardim1, Rajal Patel1, Leah Catchpole2, Karim Gharbi2, Alexandre Benedetto1,**

1Division of Biomedical and Life Sciences, FHM, Lancaster University, Lancaster, UK

2 Earlham Institute, Norwich Research Park, Norwich, UK.

 # presenter.

**Corresponding authors: a.zarate-potes@lancaster.ac.uk, a.benedetto@lancaster.ac.uk*

Animal health is majorly influenced by microbial commensals that impact metabolism, behaviour, disease, response to treatments and ageing. To develop interventions that promote life-long health, it is critical to understand the complex interplay of molecular pathways that regulate these interactions.

To address this challenge, we first conducted a metanalysis of available RNAseq datasets to identify host genes most frequently differentially regulated upon microbial exposure. We then reasoned that studying naïve worms' early exposure to Gram+ or Gram- gut pathogens would reveal core gene regulatory networks involved in host-gut microbe communication beyond contexts of infection. Using deadly gut pathogens would also enable pangenome host genetic screening via simple automated survival assays (LFASS).

We thus adopted a multiomics approach, performing paired host-microbe transcriptomics, proteomics, and targeted metabolomics of wild type N2 and long-lived, Insulin-Like Receptor daf-2 mutant, worms exposed to E. coli OP50 control, Enterococcus faecalis OG1RF or Pseudomonas aeruginosa PA14 for 2, 4, 6 and 12 hours. To enable analysis of concomitant host and microbe transcriptional changes we developed a dual RNA extraction method yielding ~5% bacterial and ~95% host sequencing reads. We combined these approaches with parallel whole-genome phenotypic screens on RNAi-sensitive rrf-3 mutants using the commercially available whole-genome RNAi Ahringer clone library (phenomics).

Currently, we have completed the genetic screen for chromosomes X, I, II, III, yielding expected hits such as the GATA transcription factor elt-2, and hedgehog-like signalling genes such as grl-21, ptr-18 and qua-1 that were flagged in previous studies. Analysis of host gene expression changes identified new genes of interest, including the HN4-gamma orthologue and predicted immunoregulator nhr-112, with knockdown of nhr-112 impacting the metabolite flow through the kynurenine pathway of tryptophan metabolism and resulting in hypersensitivity to PA14 but increased resistance to OG1RF.

Here we will be presenting our methodologies and progress to date, including novel insights from our ongoing genetic screens, transcriptomics, proteomics, and targeted metabolomics analyses relevant to innate immunity and ageing.

DNA methylation surrogates of metabolites as ageing predictors: a UK cohort study

Kexin Xu, Chungho Lau, Oliver Robinson

Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London

Variability in ageing trajectories between individuals may lead to differences in biological age, reflecting differing health states. Omics data, including metabolomics and DNA methylation, have been used to construct biological 'clocks' that are often used to assess biological age. Metabolomics, while reflecting physiological reactions, suffers from poor temporal stability, while DNA methylation captures longer-term variation and has therefore been used as a surrogate marker for other biomarkers including proteins. Here, we aimed to develop a DNA methylation clock that can capture metabolic ageing, through the development of DNA methylation surrogate markers for metabolites and combining these surrogates into an overall prediction model of chronological age.

Within the UK Airwave cohort (N = 820), methylation was measured using the EPIC array and 594 metabolites were annotated following NMR and LCMS in blood. Data were split 4:1 into training and test sets. Within the training set, lasso regression was used to develop a surrogate score (DNAm-metabolite) for each metabolite, and then elastic net regression was used to develop age prediction models from the original metabolites or the DNAm-metabolites. Associations of "age acceleration" (residuals of predicted age regressed on chronological age) with ageing risk factors were assessed using linear regression. Enrichment analysis was performed to investigate the biological roles of the DNA methylation sites used in the DNAm-metabolite clock.

371 (~62%) DNAm-metabolites show significant ($p < 10\text{-}4$) correlations; in the test set with the original metabolites (range r: 0.30 - 0.74). On average, these DNAm-metabolites have stronger age associations than the original metabolites. Twenty-four DNAm-metabolites together predict chronological age with a correlation of 0.86 in the test set, higher than a correlation of 0.68 predicted by 24 metabolites. Age acceleration derived from the DNAm-metabolite clock was associated ($p < 0.05$) with being male, depression and heavy alcohol use. The CpG sites included in the DNAm-metabolite clock were enriched for multiple metabolic traits, including hepatic fat and serum liver enzyme levels.

We have shown that DNA methylation may be used to develop surrogate markers for metabolites, which may be useful where metabolomic data is unavailable. We developed a novel DNAm-metabolite clock that provides improved prediction of chronological age compared to a clock trained on metabolites alone and appears to capture some aspects of metabolic ageing. Hence, we present a stable and convenient way to assess metabolic ageing, which may have use for personalised and preventative medicine for chronic diseases.

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conferences@wellcomeconnectingscience.org

+44 (0) 1223 495100