

WORKSHOP REPORT

Diabetes Genetics. A Seventh Sense for the Successful Sequel of ‘Come Together’ “The Genotypes and Phenotypes of Diabetes”. Bergen, Norway. April 22-26, 2009 2nd Meeting of ‘EASD Study Group on Genetics of Diabetes’ and 44th Annual Meeting of the ‘Scandinavian Society for the Study of Diabetes’

Pål Rasmus Njølstad^{1,2}, Anders Molven^{3,4}, Leif Groop^{5,6}

¹Department of Clinical Medicine, University of Bergen; ²Department of Pediatrics, Haukeland University Hospital; ³The Gade Institute, University of Bergen; ⁴Department of Pathology, Haukeland University Hospital. Bergen, Norway. ⁵Unit of Diabetes and Endocrinology, Department of Clinical Sciences in Malmö, Lund University Diabetes Centre, University Hospital. Malmö, Sweden. ⁶Department of Medicine, Helsinki University Central Hospital, and Research Program of Molecular Medicine, University of Helsinki. Helsinki, Finland

Since the first meeting in Ystad, Sweden in 1997 [1], a core of key players in diabetes genetics has been coming together in a series of workshop-like meetings. The seventh follow-up meeting, “The Genotypes and Phenotypes of Diabetes”, took place at Solstrand, outside Bergen, Norway on April 22-26 this year, highlighting the recent success in diabetes genetics in terms of finding diabetes genes [2]. Future prospects now are to dissect their role in the pathogenesis of diabetes and use the information for targeted treatment. ‘Come together’ has become a mantra for this series of meetings which have had a European basis and input from American researchers. Along the way, the ‘EASD Study Group for the Genetics of Diabetes’, was formed. At the initial meeting, 12 years ago in Ystad, the main point was that different research groups working on the genetics of diabetes needed to collaborate in order to have the power necessary to find diabetes genes [1]. In subsequent meetings (Table 1) other groups of actors have been added due to the constant need for the agenda to ‘evolve’ along with the

changing research in the field. The following meetings have included beta cell physiology and genetics, obesity, rare diabetes syndromes, common forms of diabetes, clinical applications, and pharmacogenetics. The recent, successful advances in dissecting the genetics of polygenic diabetes using genome-wide association studies (GWAS) in large patient materials from collaborating, large consortia should leave no doubt that Lund University Professor Leif Groop’s welcome address at Ystad was futuristic.

Key words Diabetes Mellitus; Exocrine Pancreatic Insufficiency; Genes; Genetics; Genome-Wide Association Study; Polymorphism, Single Nucleotide

Abbreviations EASD: European Association for the Study of Diabetes; GWAS: genome-wide association studies; MODY: maturity-onset diabetes of the young; SNP: single nucleotide polymorphism

Correspondence Pål Rasmus Njølstad
Department of Pediatrics, Haukeland University Hospital,
University of Bergen, N-5021 Bergen, Norway
Phone: +47-5597.5153; Fax: +47-5597.5159
E-mail: pal.njolstad@uib.no

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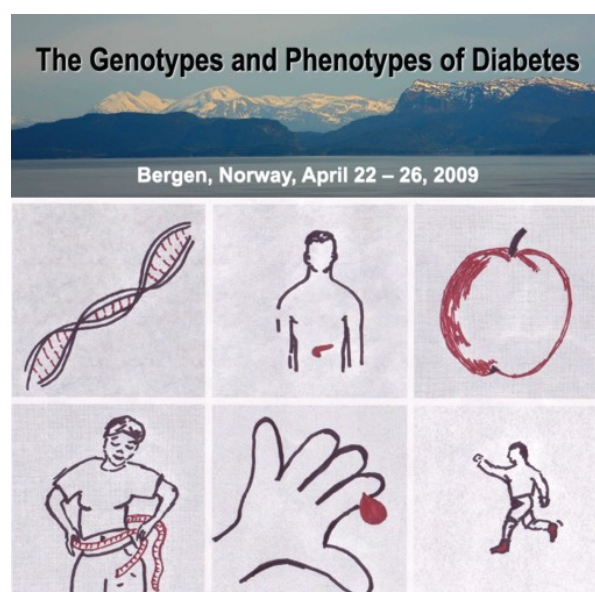


Figure 1. The Genotypes and Phenotypes of Diabetes. Bergen, Norway, April 22-26, 2009 (Photo: Janniche Torsvik; Illustration: Jens Kristoffer Hertel).

Table 1. Meetings in this series.

Year	Place	Title
1997	Ystad, Sweden	Genetics of Diabetes
2002	Ystad, Sweden	Diabetes - A Focus on the Beta Cell
2003	Lille, France	Genomics of Diabetes and Associated Diseases in the Post Genome Era
2003	Bergen, Norway	Disorders of Signaling Mechanisms in the Pancreatic Beta Cell: From Rare Diseases to General Principles
2004	Malaga, Spain	Managing Beta Cell Diseases in the Post-Genomic Era
2006	Elsinore, Denmark	Genomics of Hyperglycemia
2007	Malaga, Spain	Understanding Diabetes in the Pharmacogenomic Age
2009	Bergen, Norway	The Genotypes and Phenotypes of Diabetes

The recent meeting in Bergen (Figure 1, the complete program and abstracts of which can be found at <http://www.uib.no/diabetes>), was the seventh sequel of the original idea of ‘coming together’ and 2nd formal meeting of the ‘EASD Study Group for the Genetics of Diabetes’. This time, researchers interested in diabetes syndromes also affecting the beta cells’ neighbors, namely, the pancreatic exocrine cells joined the party. As leader of the organizing committee, Professor Pål R Njølstad from the University of Bergen, Norway, pointed out in his talk, it may be time to join researchers and clinicians interested in beta cells and exocrine cells, respectively, since these cell types indeed reside within one organ and there are distinct diabetes syndromes affecting both cell types. The Bergen meeting had seminars and keynote lectures that summed up what has been learnt from the previous gatherings and addressed the ever demanding question of what the next experiment should be?

Genome-Wide Association Studies in Common Diabetes

Dr. David Meyre from the Pasteur Institute in Lille, France, opened the session on genome-wide association studies. He pointed out that in the pre-GWAS area, the first genes associated with a predisposition to type 2 diabetes were identified by positional cloning (*CAPN10*, *ENPP1*, *HNF4A* and *TCF7L2*) [3, 4, 5, 6] or a candidate gene approach (*PPARG*, *KCNJ11*, *HNF1A* and *WFS1*) [7, 8, 9, 10]. The progress was slow and only *PPARG*, *KCNJ11* and *TCF7L2* discovered in 2000, 2003, and 2006, respectively, were robustly replicated in the following years. Interaction with confounding variables (obesity status, ethnicity, family history of type 2 diabetes) should explain the heterogeneity found in replication efforts at least for some of the remaining genes. Then two main things happened: technology made a great leap forward and the analysis of thousands of patients became possible through the collaboration between the large genetic consortia.

In the 1980s, genetic variants had to be analyzed one by one. Ten years later, it had become possible to perform detailed studies of individual genes, including some hundreds of single nucleotide polymorphisms (SNPs) illustrated by the identification of *CAPN10* associated with diabetes in Mexican-Americans [3]. The breakthrough came in 2006 with DNA chips on which genetic information of at least one million SNPs can be analyzed. Thus, it became possible to

investigate whether common variants of the genome were connected with a susceptibility to common diseases by association studies using cases and controls.

The first wave of diabetes-associated SNPs was published in 2007. The beauty of this wave was not only that it was possible to find these SNPs, but also that scientists from Diabetes Genetics Initiative (DGI), the Wellcome Trust Case Control Consortium (WTCCC)/UK Type 2 Diabetes Genetics Consortium collection and the Finland-United States Investigation of NIDDM Genetics (FUSION) had come together by replicating each other’s studies in the three papers published in “Science” [11, 12, 13] which followed the first paper published in “Nature” by Froguel *et al.* [14]. In this first wave, the previously identified genes, *PPARG*, *KCNJ11* and *TCF7L2* loci were confirmed. Six additional type 2 diabetes risk loci were identified: *FTO*, *CDKN2A/B*, *IGFBP2*, *CDKAL1*, *SLC0A8* and *HHEX*. Subsequent large-scale association studies added two more genes to the list, *TCF2* and *WFS1*, before the second wave from the diabetes Genetics Replication And Meta-analysis (DIAGRAM) consortium identified six more (*ADAMTS9*, *TSPAN8*, *CAMK1D*, *NOTCH2*, *THADA* and *JAZF1*) [15]. GWAS performed in Asian subjects last year identified *KCNQ1* as a type 2 diabetes risk gene [16].

Keynote lecturer, Professor Mark I McCarthy from the University of Oxford, United Kingdom, described how even larger efforts at GWAS meta-analysis, such as that conducted by the DIAGRAM+ consortium were able to identify additional novel loci influencing type 2 diabetes. Professor McCarthy highlighted three challenges: turning the genetic signals into function, explaining more of the variance, and translating the findings into clinical practice [17]. In some instances, the connection from association signal to genes is apparent, i.e. obesity and *MC4R*, fasting glucose and *MTNR1B*, and diabetes and *SLC30A8*. Still, most of the signals detected so far are not associated with a clear mechanism of action. Professor McCarthy said that it seems many of the variants have a modest effect only and there seems to be little evidence for interactions between the signals. Interestingly, most of the signals found to date are associated with genes expressed in the beta cell. Professor McCarthy pointed out that type 2 diabetes in simple terms is due to insulin resistance, in which *PPARG*, possibly *WFS1* and *FTO* via obesity are risk genes; and/or reduced insulin secretion. *KCNJ11*, *TCF7L2*, *IGF2BP2*, *SLC30A8* and possibly

WFS1 are risk genes associated with beta cell dysfunction while *HHEX*, *CDKAL1*, *CDKN2A/B* and *HNF1B* are potentially associated with reduced beta cell mass. There are some hints at pathways, for instances Wnt-signalling and cell cycle regulation, and overlap between type 2 diabetes and cancer variants. The relationship between *CDKN2A*, melanoma and other tumors, and reduced beta cell regeneration illustrates the yin and yang of diabetes and cancer, Professor McCarthy said. There are a number of approaches that can be deployed to find the “dark matter” of heritability including fine mapping within the regions already discovered as well as resequencing to find low frequency and rare variants that contribute to diabetes risk.

The recent debate, challenging the GWAS results and whether this approach has failed due to small effects and individual prediction seems unlikely [18, 19, 20, 21], was discussed. Professor Groop asked the provocative question whether type 2 diabetes really is inherited at all. Still, data from the Botnia study including 6,421 individuals from 1,131 families demonstrate that the predictive value of family history of type 2 diabetes exceeds that of 2-hour glucose load. Also, the Malmö preventive study showed that a family history of type 2 diabetes clearly was a more important risk factor than body mass index over 30 kg/m² and fasting glucose over 5.5 mmol/L [22]. Still, Groop *et al.* show that clinical risk factors are far more important than 16 type 2 diabetes-associated risk SNPs either alone or in combination [23]. Thus, he concluded that although the type 2 diabetes-associated SNPs cannot explain the familial risk of type 2 diabetes, they contribute largely to the population risk and screening for these variants could reduce the number of individuals needed to be included in trials aiming at prevention of type 2 diabetes. Maybe they can also offer the possibility of real primary prevention!

Monogenic Beta Cell Diseases: Don't Forget Positional Cloning!

Some researchers have proclaimed that ‘MODY is dead’, some have resurrected MODY; so what is the present status? Professor Sian Ellard from Peninsula Medical School, Exeter, United Kingdom, opened the session on monogenic diabetes by providing an overview of the phenotypes of various subtypes of MODY and the best practice in diagnostics of MODY based on guidelines recently published by the European Molecular Genetics Quality Network MODY group [24]. The term MODY may be confusing since the definition excludes, for instance, many cases of neonatal diabetes due to spontaneous mutations. Moreover, mutations in genes previously only associated with neonatal diabetes, for instance *ABCC8*, *KCNJ11* and *INS*, have now been found also in adolescents with monogenic diabetes. Although the term MODY survived this meeting as well, ‘monogenic diabetes’ may be the name for the future.

If one were asked to put a bet on one gene causing diabetes in man, it would probably be the insulin gene! Although some rare forms of insulin resistance were described about 20 years ago, it was only in 2007 that the insulin gene (*INS*) was found to cause diabetes in man [25]. Keynote lecturer, Professor Graeme I Bell from the University of Chicago, IL; U.S.A., was crucial in this finding and the story has turned a full circle since he was also decisive for the cloning and sequencing of the human insulin back in 1979. In addition to the discovery that mutations in *INS* can cause neonatal diabetes [25, 26], MODY [27] and antibody-negative type 1 diabetes [27] have been added to the list. Bell revealed how he will use fruit flies in the struggle to find ways to stop the likely apoptotic process in the beta cells of insulin gene mutation carriers.

Keynote lecturer, Professor Andrew Hattersley from Peninsula Medical School, Exeter, United Kingdom, reviewed how recent advances in the genetics of neonatal diabetes and neonatal hyperinsulinism give key insights to beta cell physiology as well as offering improved clinical management. In the key beta cell genes *KCNJ11*, *ABCC8* and *GCK*, different mutations will result in both activating and inactivating mutations and result in the opposing phenotypes of hypo- and hyper-glycemia, whilst in mutations of *HNF4A*, the same loss of function mutations will result in both transient neonatal hypoglycemia and also later in beta cell failure and diabetes [28].

A molecular genetic diagnosis is now possible for most patients with transient or permanent neonatal diabetes, Hattersley said. In permanent neonatal diabetes, the commonest cause results from *KCNJ11* mutations, but *ABCC8* and *INS* mutations which may present as dominant or recessive mutations, are frequent as well. Neurological features, which are present in approximately 20% of the patients with *KCNJ11* mutations, are rarely seen in *ABCC8* patients and are not a feature of *INS* mutations. The major reason that genetics has been so important in neonatal diabetes is that it has altered treatment. Most patients with *ABCC8* and *KCNJ11* mutations, even if apparently insulin-dependent, can improve metabolic control by replacing insulin injections with sulfonylurea tablets [29, 30]. Neonatal diabetes is now an area where a molecular genetic diagnosis is not a luxury but a necessity.

It is still possible to find diabetes genes by positional cloning! Dr, Khalid Hussain from University College, London, United Kingdom, revealed the strategy for the recent finding of a gene causing pigmentary hypertrichosis, insulin-dependent diabetes and exocrine dysfunction. By careful clinical phenotyping and collecting five consanguineous families with similar cases, homozygosity analysis mapped the locus to a 1.4-Mb region on chromosome 10. Of 14 known and predicted genes, they identified different homozygous mutations in *SLC29A3* encoding the human equilibrative nucleoside transporter-3 protein (hENT3)

in all five probands [31]. Also Hussain put forward the fruit fly as a tool for deciphering the protein's dysfunction.

Beyond the Beta Cell in Diabetes

Although localized within the same organ, endocrine and exocrine cells are involved in different diseases which are treated by distinctive specialists and discussed at different congresses, Professor Njølstad said. Studies of monogenic pancreatic diseases have confirmed that exocrine and endocrine dysfunctions often occur together and have elucidated some of the mechanisms involved. Mutations in key regulators of the pancreatic progenitor cells, such as *IPF1*, *PTF1A*, *HNF1B* and *EIF2AK3*, affect both endocrine and exocrine cells. A typical feature in patients with mutations in such genes is pancreatic aplasia which subsequently will lead to permanent neonatal diabetes and exocrine insufficiency. Mutations in *HNF1B* cause a multisystemic disease with malformation in pancreas, kidneys and the genital system. The structural changes in the pancreas are of particular interest, Professor Njølstad revealed, since new data suggest that the body and tail of the pancreas is absent or severely atrophic in *HNF1B*-MODY [32].

Diseases primarily affecting the pancreatic exocrine cells, such as chronic pancreatitis and pancreatic cancer, are often associated with diabetes. There are also monogenic diseases where the primary defect resides in the exocrine cells, e.g. cystic fibrosis and *CEL*-MODY. Exocrine dysfunction can generally be detected in infancy. Three of four subjects with cystic fibrosis will have diabetes by 30 years of age while all cases reported with *CEL*-MODY [33] had developed diabetes at 50 years of age, Professor Njølstad said. The precise mechanism for the development of diabetes in these diseases might be pancreatic inflammation and fat infiltration [34]. Concerning diseases which primarily affect the pancreatic endocrine cells, 10-25% of patients with type 1 diabetes as well as *HNF1A*- and *HNF4A*-MODY have exocrine dysfunction [35]. It is conceivable that the mechanism relates to insulinopenia affecting the exocrine tissue.

Professor Philip Hardt, from the Giessen University Hospital, Giessen, Germany, said that there are few studies on the effects of enzyme treatment on exocrine dysfunction in the various forms of diabetes. Further studies are needed to explore the sensitivity and specificity of tests for exocrine dysfunction in various forms for diabetes and to decide when pancreatic enzyme supplement therapy could be warranted.

Keynote speaker Dr. Rohit Kulkarni from Harvard Medical School, Boston, MA, U.S.A., provided genetic data supporting a role of insulin signaling in the regulation of alpha cell function [36]. Knockout mice were created for the insulin receptor in pancreatic alpha cells. In the fed state, adult male knockout mice had elevated glucagon, glucose intolerance, hyperglycemia, and elevated glucagon response to L-arginine stimulation. Clamp studies showed that there was an

enhanced glucagon secretory response in the knockout mice. These findings were supported by cell line experiments. Dr. Kulkarni proposed that alpha cell insulin resistance contributes to dysregulation of glucagon secretion in distorted glycemic states. Hence, modulating alpha cell growth and function may be a future treatment target for improving glucose homeostasis in patients with diabetes.

What's Next?

Several of the speakers were challenged to look into the future. Professors Groop and McCarthy advocated the 1,000 genomes project aiming at a catalogue of human DNA variance created using next-generation sequencing. This will find the rare variants with high or modest effects. Professor Groop showed data on two families with diabetes where several affected members carried a variant in the *CDKN2A/B* region on chromosome 9. Professor Graeme I Bell strongly argued that going back to families would be to go back to where the field was in the nineties and then nothing new would have really emerged from the very costly studies.

Professor Torben Hansen from Hagedorn Research Institute, Gentofte, Denmark, asked the very provocative question: Are obesity and obesity-associated type 2 diabetes in part caused by an imbalance of the gut bacteria? Obese mice have a 50% higher representation of the gut *Firmicutes* division and a proportionally lesser representation of the *Bacteroidetes* division than the matched lean mice. This trait is transmissible: colonization of germ-free mice with an 'obese microbiota' results in a significantly greater increase in total body fat than colonization with a 'lean microbiota'. The *Firmicutes* have a higher capacity for breaking down complex carbohydrates than *Bacteroidetes*. Studies have shown that obese individuals have a higher proportion of *Firmicutes* and a lower proportion of *Bacteroidetes* than lean persons. As subjects lost weight, the proportional representation of the *Firmicutes* decreased and the relative amount of *Bacteroidetes* increased. Thus, weight loss in obese was associated with a gut flora resembling more that of a lean person. Hansen and colleagues are involved in the "Metagenomics of the Human Intestinal Tract" (MetaHIT) project, which is a EU-sponsored project. The major tasks are shotgun sequencing of all genes in the human metagenome, sequencing of 100 selected microbe genomes, functional characterization of selected genes, gene variants and gene products, construction of microbiome RNA- and DNA-arrays for large-scale metagenome profiling studies, metagenome RNA- and DNA-profiling studies in human obesity and obesity-associated diabetes as well as in human inflammatory diseases.

The Meeting Continues and Evolves

The 2009 "The Genotypes and Phenotypes of Diabetes" meeting was permeated by a pioneer atmosphere which has been apparent at each workshop

in this series, although the focus has constantly changed. One might predict that the next meeting (2011 in Malmö, Sweden) will include exciting updates on deep sequencing in complex and monogenic diabetes, and new insights from copy-number variation analyses and studies of epigenetic effects. A challenge will be bioinformatics and database developments which are critical for integrating the vast amount of genotype/phenotype information. The core researchers will come together and invite new groups along with the need to 'evolve' along with the changing research in the field, but it remains focused on a desire to understand how human genomes vary, how diabetes develops and how this information can be used to improve treatment.

Competing interest statement The authors declare that they have no competing financial interests

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