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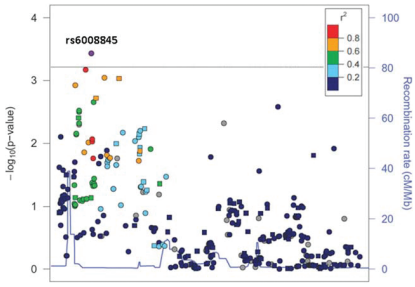
In This Issue of *Diabetes*

By Max Bingham, PhD

PPARA Polymorphism Can Identify Patients With Type 2 Diabetes Who Would Benefit From Fenofibrate Treatment

A specific polymorphism influences the cardiovascular benefits of fenofibrate, and it might be possible to use the marker to identify patients with type 2 diabetes who would benefit from such a treatment, according to Morieri et al. (**p. 771**). They also estimate that use of the marker would at least double the proportion of patients with type 2 diabetes eligible for fenofibrate therapy, which would have clear public health implications. Previous trial data have supported the use of fenofibrate treatment in patients with atherogenic dyslipidemia but not in wider populations, including type 2 diabetes. The study is a post hoc genetic analysis of the ACCORD-Lipid trial, which investigated fenofibrate treatment as an add-on to statin therapy in type 2 diabetes, and was directed at the *PPARA* gene as this is the known pharmacological target of fibrates. The authors found that a single nucleotide polymorphism, rs6008845 C/T, reached study-wide significance in terms of its influence on the effect of fenofibrate on major cardiovascular events (MACE). Approximately 3,000 individuals were included in the initial analysis. Individuals who were T/T homozygous, ~36% of the population, experienced a reduction in MACE of 51% in response to fenofibrate (hazard ratio 0.49; 95% CI 0.34–0.72). Other genotypes (i.e., C/T and C/C) experienced no benefit. Notably, the authors also found the same relationship in African American participants in the same trial and in a series of external cohorts, indicating external validity of the analysis. While touching on mechanisms with further experiments, which they caution are preliminary, they conclude that the *PPARA* variant appears to influence the cardiovascular effects of fenofibrate and so can be used to identify patients with type 2 diabetes who might benefit from using the treatment. Personalized medicine in action? Commenting more widely, author Alessandro Doria told *Diabetes*: "We need more evidence before these findings can be translated into new therapeutic protocols, but this is an example of how genetic information can be potentially harnessed to improve the cost-effectiveness of available treatments."

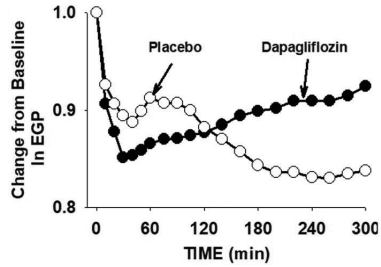


Regional plot of *PPARA* gene region with rs6008845 locus highlighted.

Morieri et al. *PPARA* polymorphism influences the cardiovascular benefit of fenofibrate in type 2 diabetes: findings from ACCORD-Lipid. Diabetes 2020;69:771–783

Insulin and Glucagon Levels Do Not Explain Increased Endogenous Glucose Production With SGLT2 Inhibitors

The "paradoxical" increase in endogenous glucose production associated with the use of sodium–glucose cotransport 2 inhibitors (SGLT2i) in type 2 diabetes is not primarily related to changes in insulin or glucagon concentrations or reduced plasma glucose concentrations, according to Alatrach et al. (**p. 681**). Their study looked at the effects of dapagliflozin (an SGLT2i) on endogenous glucose production alone and also while clamping plasma glucose or insulin and glucagon. A total of 38 patients with type 2 diabetes completed the study, with 26 receiving dapagliflozin (10 mg) and 12 receiving placebo. The assessments included three 8-h measurements of endogenous glucose production via a tracer method to cover the nonclamped and clamped scenarios. They found that dapagliflozin resulted in a greater reduction in plasma glucose concentrations compared with placebo; however, at the same time, there was an increase in endogenous glucose production with dapagliflozin, while placebo resulted in a reduction. There was also a significant increase in plasma glucagon and decrease in plasma insulin levels. When glucose was clamped in the second part of the study, insulin levels remained the same and there was a reduction in glucagon in both groups. Notably, there was still the same difference in endogenous glucose production with dapagliflozin compared with placebo. When insulin and glucagon were clamped in the third part of the study, dapagliflozin resulted in an initial large drop in endogenous glucose production but then rose in the remaining hours. What explains the rise? Author Ralph DeFronzo told us: "These results demonstrate the existence of a previously undiscovered renal glucoregulatory mechanism. This opens a new avenue of research to unravel the biological mechanism(s) that regulate glucose metabolism in patients with diabetes. The ultimate benefits will rest upon the development of novel pharmacological agents that can modulate this newly discovered renal-hepatic response to SGLT2i-induced glucosuria."



Change from baseline in total endogenous glucose production during glucose infusion and pancreatic clamp in subjects receiving dapagliflozin or placebo.

Alatrach et al. Evidence against an important role of plasma insulin and glucagon concentrations in the increase in EGP caused by SGLT2 inhibitors. Diabetes 2020;69:681–688

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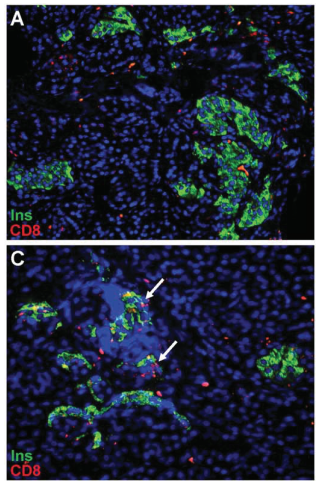
Novel Low-Frequency Genetic Variants Have Large Effects on Type 1 Diabetes Risks

Estimates suggest that about 80% of the genetic risk for type 1 diabetes has so far been identified, leaving about 20% still to be characterized. There is a wide expectation that rare and low-frequency genetic variants will account for this missing risk and in doing so offer up potential new targets for interventions. With these expectations, Forgetta et al. (**p. 784**) use deep imputation of genotyping data and genome-wide association studies to identify rare novel single nucleotide polymorphisms (SNPs) with large effect sizes on type 1 diabetes. The genome-wide association study looked at ~9 million SNPs in ~9,400 case subjects with type 1 diabetes and ~15,700 control subjects taken from across 12 cohorts to identify candidate SNPs that had not previously been identified. Candidate variants identified at the discovery stage were then replicated and validated in two further cohorts. They identified 27 variants that met the authors' inclusion criteria, and specifically three were novel, met the definition of rare, and retained sufficient significance in the replication stage. Further in silico analyses allowed them to prioritize variant rs60587303 from within the first intron of *STK39*. The effect size of the variant approximated that of previously identified common variants linked to type 1 diabetes risks. To validate their findings, they then turned to primary murine $CD4^+$ T cells treated with closantel, an inhibitor of *stk39*. Inhibition had no effect on T-cell activation and proliferation, but it did enhance secretion of IFNγ and IL-2. They suggest this might be indicative of enhanced inflammatory responses and possibly the basis for a mechanistic hypothesis. They stress that much more work will be needed to validate this. They ultimately conclude that their findings demonstrate the utility of the approach to identify low-frequency or rare genetic variants and might also offer novel insights into the pathophysiology of the disease and the potential identification of drug targets.

Forgetta et al. Rare genetic variants of large effect influence risk of type 1 diabetes. Diabetes 2020;69:784–795

"Curative Potential": Immune Cells and Gene Expression Levels in LADA Pancreases Explored

Jörns et al. (**p. 624**) report an assessment of a range of immune cells and gene expression analyses in islets from adult humans with latent autoimmune diabetes (LADA), type 1 diabetes, or type 2 diabetes or from healthy control subjects. For comparison, they also report the same analyses in the LEW.1AR1-*iddm* rat model of autoimmune diabetes that develops either type 1 diabetes at an earlier stage, LADA at a later stage, or no diabetes at all. Based on the analyses, they conclude there are differences among the various forms of diabetes in terms of immune cell infiltration into islets and also the gene expression of various cell cycle and cytokine markers. They also propose that the evidence explains why LADA has a slower progression and results in a milder form of autoimmune diabetes. Following removal of pancreases, tissue specimens were subjected to immunohistochemistry and gene expression analyses with in situ RT-PCR and quantitative RT-PCR. Targets for measurement included various immune cells (including CD8 T cells and CD68 macrophages), while gene expression analyses covered various cytokines and cell cycle markers. The authors describe finding differences in both human and rat pancreases in terms of immune cell infiltration and particularly a changed ratio between CD8 T cells and macrophages, which were the two most dominant types in type 1 diabetes and LADA. In terms of gene expression, there were changed ratios between various markers and differences between LADA and type 1 diabetes, with the most striking result being a near total absence of expression in LADA pancreatic areas without immune cell infiltration. Commenting more widely, author Sigurd Lenzen told us: "The detailed insight into the pathomechanisms underlying autoimmune diabetes allows the development of specific treatment schedules for the different forms of the disease. They can be expected to become available in the form of combination therapies with therapeutic antibodies with curative potential in the future."



Human islets without (*A*) and with (*C*) immune cell infiltration. Green, β-cells; red, CD8 T cells.

Jörns et al. Pancreas pathology of latent autoimmune diabetes in adults (LADA) in patients and in a LADA rat model compared with type 1 diabetes. Diabetes 2020;69:624–633

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