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In This Issue of *Diabetes*

By Max Bingham, PhD

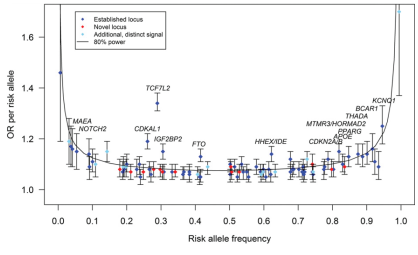
IGF2: A New Type 2 Diabetes Therapeutic Target?

A variant in the gene that encodes IGF2 is likely associated with a ~20% reduced risk for type 2 diabetes. Mercader et al. (**p. 2903**) say their findings suggest that reducing the expression of isoform 2 of *IGF2* in certain tissues is potentially a new therapeutic target for type 2 diabetes. The claims come from a study that compared many thousands of genetic variants in ~8,200 individuals with type 2 diabetes and just under 13,000 individuals without the disease. All were of Latino descent. As well as identifying variants that had previously been linked to type 2 diabetes, the authors detail a novel site in *IGF2* that is potentially protective. Reportedly, individuals who were heterozygous carriers of the variant had a 22% reduced risk of type 2 diabetes, whereas homozygous carriers had a 40% reduced risk. Overall, the authors found that 17% of the population in Mexico carries the protective allele. They go on to describe a series of experiments in which they show that the variant prevents splicing between exons 1 and 2 of *IGF2* and is specifically associated with an allele-dosage–dependent reduction in the expression of isoform 2 of *IGF2*. On that basis, they say that targeting the variant pharmacologically could yield positive outcomes in individuals without the protective allele, including those from populations where the variant is not present. Author Jose C. Florez told *Diabetes*: "Finding a genetic association is only the first step toward elucidating molecular mechanism and direction of effect, both of which we have pursued here to begin translating genetics into therapeutics. Our study also illustrates the advantages of studying diverse populations to undertake genetic discovery and the power of philanthropy and collaboration in driving new understanding."

Mercader et al. A loss-of-function splice acceptor variant in *IGF2* is protective for type 2 diabetes. Diabetes 2017;66:2903–2914

More Gene Targets Identified for Type 2 Diabetes

A meta-analysis by Scott et al. (**p. 2888**) of genome-wide association data has increased the number of genetic signals (loci) identified for type 2 diabetes. As well as suggesting that the extent of the genetic component of the disease is still only partially determined, the study also underlines the diversity of mechanisms likely involved and potentially expands the number of therapeutic targets that could be investigated. According to the authors, the study combined genome-wide data from 30 studies of individuals with type 2 diabetes and control subjects without diabetes. In addition to confirming many previous associations, the authors say they have now refined the location of causal DNA variants at 13 novel and 69 established loci. The analyses reportedly involved many more individuals than any previous genome-wide association study alone and so had much increased statistical power. The authors suggest that it should be possible to detect those potential genetic links that have low frequency but still might be relevant to type 2 diabetes. Author Mark I. McCarthy said: "We already see a strong overlap between the genetic signals we find and the drugs already used to treat diabetes. This gives us confidence that new genetic signals are likely signposts to ways of treating or preventing this disease." Going further, author Michael Boehnke added: "Our study has focused on identification of DNA variants that influence risk of type 2 diabetes in individuals of European ancestry. But as we have seen these newly identified variants have similar impact across many ancestries. These findings highlight a shared genetic basis of type 2 diabetes across human populations, an important consideration for subsequent drug discovery." Author Inga Prokopenko commented: "While the overwhelming majority of established type 2 diabetes loci are common noncoding DNA variants, in our study we were able to stratify them by inferred physiological mechanism. We also highlight enrichment in regulatory elements that are specific for relevant tissues. This demonstrates how genetic variants can impact the pathophysiological processes leading to type 2 diabetes."



The effect sizes of the established (blue diamonds), novel (red diamonds), and additional distinct (sky blue diamonds) signals according to their risk allele frequency.

Scott et al. An expanded genome-wide association study of type 2 diabetes in Europeans. Diabetes 2017;66:2888–2902

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Adipose Tissue Remodeling Following Bariatric Surgery Changes Fat Disposal and Might Explain Diabetes Remission

Bariatric surgery routinely results in significant weight loss in obese individuals and a concurrent remission of type 2 diabetes for many who have the disease. Quite why this happens has been the subject of numerous hypotheses and speculation. According to Grenier-Larouche et al. (**p. 2743**), it seems likely that yet another mechanism might be involved, namely that bariatric surgery results in complete remodeling of the way adipose tissues deal with fatty acids and that this in turn affects glycemic control and improves insulin sensitivity. They report their year-long investigation of a small group ($n = 17$) of severely obese individuals who underwent a bariatric surgery procedure and were then followed to determine various measures relating to obesity and diabetes. A significant weight reduction (a mean excess weight loss of 84% after 1 year) and partial or complete remission of type 2 diabetes in all of the patients was achieved. The authors also revealed a number of mechanistic changes and a picture of how adipose tissues likely change the way they handle fat following surgery. Author André C. Carpentier said: "What is striking in our study is the highly dynamic metabolic adaptation of lean and adipose tissues over very large changes in total body adiposity. Very early after surgery before weight loss had occurred, we saw very important improvement in hepatic insulin resistance closely associated with a reduction in adipose tissue free fatty acid spillover. However, at later stages with important weight loss, this adipose tissue mechanism was completely gone and replaced by improved lean tissue handling of free fatty acids secreted at large rates again by adipose tissues. In the end, remission of diabetes appears related to adipose tissue cell size reduction but not reduction of its free fatty acid secretion as we thought initially. This shows that the current view held by many of the link between high adipose tissue free fatty acid secretion and type 2 diabetes is too simplistic."

Grenier-Larouche et al. Fatty acid metabolic remodeling during type 2 diabetes remission after bariatric surgery. Diabetes 2017;66:2743–2755

A Method to Recapitulate Hypoglycemia-Associated Autonomic Failure Using Morphine

The vicious combination of bouts of hypoglycemia and hypoglycemia unawareness breeding more hypoglycemia is one of the limiting factors in type 1 diabetes that precludes patients achieving near-normal glycemia with insulin. This so-called hypoglycemia-associated autonomic failure (HAAF) is likely linked to the activation of the opioid system (although other hypotheses exist), and so uncovering underlying mechanisms might point toward potential treatment routes. According to Carey et al. (**p. 2764**), one of the issues facing researchers is that recapitulating HAAF in humans in a meaningful (and safe) way has limited such studies, despite some evidence pointing toward the potential of opioid receptor blockade as a method to prevent the development of HAAF. As such, they report an approach involving the use of an opioid receptor agonist, morphine, that can reproduce some of the key features of HAAF in healthy humans without diabetes and in the process provide more evidence that opioid receptors are likely involved in the failure. The highly mechanistic study involved 12 healthy individuals in two protocols in random order centered on receiving either saline or morphine infusions on day 1, followed by stepped hypoglycemic clamps on day 2. Various relevant hormonal responses were then assessed along with endogenous glucose production and symptoms of hypoglycemia. The authors report that morphine induced a ~30% reduction in epinephrine response and reduced both endogenous glucose production and (awareness of) symptoms of hypoglycemia—all key features of HAAF. Further studies then elucidated more precisely the likely link among opioid receptors in the brain, hormones, and the regulation of glucose. Author Meredith Hawkins said: "A lot of exciting research is currently happening in this field. We hope that better defining the role of the opioid system in HAAF might lead to an effective way of preventing HAAF from occurring in patients with recurrent episodes of hypoglycemia, ultimately hopefully reducing death and disability."

Carey et al. Opioid receptor activation impairs hypoglycemic counterregulation in humans. Diabetes 2017;66:2764–2773

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