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In This Issue of *Diabetes*

By Max Bingham, PhD

Diabetes Prevention Improves Cardiovascular Risk Factors Regardless of Genetic Risk for Heart Disease

Intensive lifestyle modification designed to reduce risks for diabetes, and to a lesser extent metformin, have a beneficial effect on a range of cardiovascular risk factors in individuals with elevated blood glucose after 1 year, according to Merino et al. (**p. 112**). Specifically, this benefit was independent of genetic risk for heart disease, underscoring the importance of physical activity, weight loss, and improved diet to reduce cardiovascular and diabetes risks. The findings come from an analysis of the 1-year changes in cardiovascular risk factors in ~2,700 individuals involved in the U.S. Diabetes Prevention Program. In the original randomized controlled trial, investigators tested the effects of lifestyle intervention and metformin versus placebo on the incidence of diabetes in glucose-intolerant individuals. Based on that cohort, they went on to analyze individuals with samples available for DNA analysis to construct a polygenic risk score based on 201 variants associated with heart disease. They also included measures of numerous risk factors for cardiovascular disease. They found that participants in both the lifestyle and metformin interventions had greater improvements in a majority of risk factors compared with placebo irrespective of genetic risks for heart disease. They also highlight that changes in body weight improved most cardiac risk factors and changes in dietary quality and physical activity improved blood lipids and blood pressure within the lifestyle intervention group. They suggest that further studies will be needed to confirm the findings and also address some of the limitations of the current study, which include the possibility that some of the findings may have emerged by chance and require confirmation. They also point out that there may be undiscovered genetic markers of risk for heart disease that might alter their result. Commenting further, author Jose C. Florez told us: "This work, which focused on heart disease risk in a clinical trial, extends our earlier findings that intensive lifestyle modification is effective regardless of type 2 diabetes genetic risk and confirms more recent results from observational cohorts."

Merino et al. Interaction between type 2 diabetes prevention strategies and genetic determinants of coronary artery disease on cardiometabolic risk factors. Diabetes 2020;69:112–120

More Genetic Variants Associated With Declines in First-Phase Insulin Response

Certain genetic variants outside of the class II HLA region are associated with altered first-phase insulin response (FPIR), according to Koskinen et al. (**p. 12**). Specifically, they found that in children with multiple islet-specific autoantibodies, the change in FPIR over time was different according four different genotypes (*PTPN2, FUT2, CTSH,* or *IKZF4*) or the class I HLA *A*24* allele. They also found that children with susceptibility alleles for type 1 diabetes experienced a much more rapid decline in insulin secretion compared with individuals without them. The findings come from an examination of associations between FPIR, a number of class I HLA alleles, and eight single nucleotide polymorphisms located outside the HLA region. A total of 438 children were involved in the study and were included in this analysis if they had one or more FPIR results and were assessed for seroconversion to one or more of the islet-specific autoantibodies (against insulin, GAD, IA2, and zinc transporter 8). The authors found that FPIR increased over time in children without multiple autoantibodies, with very few progressing to type 1 diabetes. In contrast, in children with multiple autoantibodies, FPIR declined and the majority progressed to type 1 diabetes. Using hierarchal linear mixed models, they found modest associations between FPIR and a number of the gene regions included in the analysis. Children with the alleles associated with the risk for type 1 diabetes had steeper declines in FPIR compared with those without the risk alleles. The same was true for the class I HLA allele *A*24*. Commenting further, author Maarit K. Koskinen told *Diabetes*: "We have previously observed that FPIR is decreased several years before the onset of type 1 diabetes in children with multiple autoantibodies. This effect was, however, independent from class II HLA genotype. Here we found that certain genetic variants other than class II HLA genes have an effect on FPIR."

Koskinen et al. Longitudinal pattern of first-phase insulin response is associated with genetic variants outside the class II HLA region in children with multiple autoantibodies. Diabetes 2020;69:12–19

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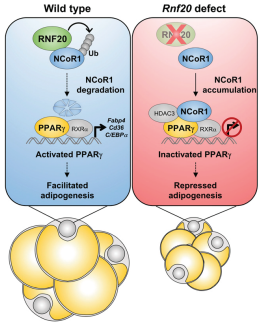
RNF20: a Potential Target in Obesity-Induced Metabolic Disorders

Ring finger protein 20, or RNF20, promotes adipogenesis by regulating peroxisome proliferator–activated receptor-γ (PPARγ), according to Jeon et al. (**p. 20**). Specifically, they suggest that RNF20 regulates nuclear corepressor 1 (NCoR1) degradation, which eventually potentiates the transcriptional activity of PPARγ. The relevance of this is that excessive and deficient adipogenesis is highly relevant to energy metabolism issues such as obesity and type 2 diabetes and PPARγ is regarded as a key factor for it. The findings come from a series of experiments in mice and cells but centered around the *Rnf20*$^{-/-}$ knockout mouse model and comparisons with wild-type mice. The authors then used a series of techniques to systematically investigate the role of RNF20 in adipocytes. They found that *Rnf20*$^{-/-}$ mice on either a normal or high-fat diet had reduced fat mass and fat cell size compared with wild-type mice, suggesting that RNF20 has a role in adipose tissue. A high-fat diet also resulted in reduced body weight gain in the knockout mice. Wild-type mice on a high-fat diet also had immune cell infiltration in adipose tissue, but this was alleviated in equivalently fed knockout mice. Using proteomics, they found that levels of PPARγ target proteins were prominently downregulated in adipose tissue of *Rnf20*$^{-/-}$ mice. Moving to cells with a knockdown of *Rnf20*, they found suppressed lipid accumulation and adipogenic gene expression and, to confirm, found the opposite when RNF20 was overexpressed. Mechanistic studies then uncovered a role for NCoR1, specifically that RNF20 appears to promote its degradation, which then led to stimulation of transcriptional activity of PPARγ in adipocytes. Author Jae Bum Kim added: "In obese subjects, metabolic improvements are often associated with a reduction in adipose tissue mass and adipocyte size. With our findings, it is feasible to propose that the moderation of adipocyte differentiation by RNF20 could be a potential therapeutic option against obesity-induced metabolic diseases."



In wild-type adipocytes (left), RNF20 promotes degradation of NCoR1, which leads to activation of PPARγ and adipogenesis. In *Rnf20* defective adipocytes (right), NCoR1 accumulates, which suppresses PPARγ and adipogenesis. Ub, ubiquitination.

Jeon et al. RNF20 functions as a transcriptional coactivator for PPARγ by promoting NCoR1 degradation in adipocytes. Diabetes 2020;69:20–34

High Prevalence of Monogenic Diabetes in Han Chinese Diagnosed With Type 1 Diabetes

Around 6% of the Han Chinese population with type 1 diabetes may in fact have monogenic diabetes, according to Li et al. (**p. 121**). As a result, they suggest the findings support the use of universal sequencing of autoantibody-negative cases as standard of care in East Asian patients with a clinical diagnosis of type 1 diabetes. In addition, the authors also found that nonsyndromic diabetes with *WSF1* mutations is not rare in the population, and while treatment implications are not yet clear, they point toward incretin interventions as a possible route and add that the gene should be included in any panel of tests that might be implemented for monogenic diabetes diagnosis. The findings come from efforts to sequence the exome of 82 Han Chinese individuals who were clinically diagnosed with type 1 diabetes but were negative for three of the autoantibodies commonly used to diagnose this type of diabetes. The sequencing targeted known or proposed genes linked to monogenic diabetes. They found credible mutations in 18 of the individuals, with all mutations having pathogenicity according five different algorithms. The most common gene was *HNF1A* (encoding MODY3), which was found in six of the individuals. Concurrently, they found that diallelic mutations occurred in *WFS1* at almost the same rate. Based on the known rate of 27.4% autoantibody negativity and 22% mutation rate in the Chinese population, they propose that 6% of those with a diagnosis for type 1 diabetes may actually have monogenic diabetes. Commenting further, author Constantin Polychronakos told us: "Six percent may sound like a small percentage, but for these few patients, it can be a life-changing diagnosis. Modern methods make their detection feasible logistically and financially—a year's worth of insulin in China would represent a considerable saving for some."

Li et al. High prevalence of a monogenic cause in Han Chinese diagnosed with type 1 diabetes, partly driven by nonsyndromic recessive *WFS1* mutations. Diabetes 2020;69:121–126

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