FUT2 Nonfunctional Variant: A "Missing Link" Between Genes and Environment in Type 1 Diabetes?

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Recent worldwide epidemiological studies demonstrate that the incidence for type 1 diabetes in most regions has been increasing by 2–5% and that type 1 diabetes prevalence in the U.S. is approximately 1 in 300 by the age of 18 (1). In other regions, the rate of increase has been even higher. For example, just 35 years ago type 1 diabetes was a very rare disorder in China, but recent rapid economic development along with changes in lifestyle and, presumably, the living environment have rendered this country with an annual increase of 7.4% for type 1 diabetes prevalence (2). Indeed, the incidence of type 1 diabetes among different geographic/ethnic regions varies up to 500-fold (3). The dramatic increase of type 1 diabetes incidence worldwide in genetically stable populations, the significant international discrepancies for disease incidence, and reports of increased incidence when individuals migrate from low-incidence to high-incidence areas (4,5) cannot be accounted for by the genetic factors alone—thus demonstrating the implication of the complex interactions between susceptibility genes, the environmental/stochastic factors, and the immune system in type 1 diabetes etiology.

The famous "hygiene hypothesis" has been frequently used to explain the rapid increase and discrepancy of type 1 diabetes incidence (6). It is believed that our increasingly hygienic environment, resulting from improvements in health care delivery and sanitation, has decreased the frequency of childhood infections, perhaps resulting in concomitant alterations in the gut microbiome, leading to a modulation of the developing immune system in genetically predisposed individuals and favoring the development of autoimmunity. Indeed, recent studies revealed that the composition of gut bacteria in children is linked to the risk for type 1 diabetes development (7). Studies in animals further support that exposure to an appropriate amount and composition of bacteria provides protection for NOD mice against type 1 diabetes development (8). Nevertheless, how a type 1 diabetes–susceptible gene reshapes the gut microbiome predisposing an individual to the development of autoimmune responses against β-cell self-antigens is yet to be elucidated.

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DOI: 10.2337/db11-1104

See accompanying original article, p. 3081.

This said, the *FUT2* gene represents an ideal candidate that bridges genetic susceptibility and alterations in the gut microbiome to modulate the immune system in early life (Fig. 1). *FUT2* is located on Chr19q-13.33 and encodes the α(1,2) fucosyltransferase responsible for the synthesis of H antigen, which is the precursor of the ABO histo-blood group antigens in body fluids and on the surface of the intestinal mucosa. Individuals that are homozygous for any nonfunctional *FUT2* allele fail to present ABO antigens in secretions and on the intestinal mucosa (called nonsecretors or se individuals), while those subjects carrying at least one functional *FUT2* allele can express ABO on secretions (called secretors or Se individuals) (9). It is noteworthy that the FUT2 nonsecretor phenotype has been noted to be associated with alterations in the gut microbiome (10), with recent studies demonstrating that it confers genetic susceptibility to Crohn's disease (11,12). Keeping these facts in mind, Smyth et al. (13) conducted a genetic study for the *FUT2* nonsecretor allele in type 1 diabetes susceptibility using 8,344 type 1 diabetic case subjects, 10,008 control subjects, and 3,360 type 1 diabetic families. They genotyped the nonfunctional allele se^{428} (single nucleotide polymorphism rs601338, A>G) that is unique to subjects of European origin, which encodes a stop codon at position 143 (X143 W). They demonstrated convincing evidence supporting a recessive association between type 1 diabetes and rs601338. Specifically, in the case/control dataset, the odds ratio for the homozygous nonfunctional allele A/A against A/G and G/G was 1.29 (95% CI 1.20–1.37; $P = 7.3 \times 10^{-14}$). Similarly, the familial dataset demonstrated a relative risk of 1.22 (95% CI 1.12–1.32; $P = 6.8 \times 10^{-6}$) for A/A against A/G and G/G. The evidence was further strengthened by combining the two datasets ($P = 4.3 \times 10^{-18}$). To determine whether rs601338 is the only causative variant within this chromosomal region, they combined the rs601338 genotype data with another dataset containing 116 single nucleotide polymorphisms flanking this region and originating from a genome-wide association study (14), followed by a stepwise regression analysis in 3,419 case and 3,524 control subjects—an analysis that failed to obtain convincing evidence supporting independent effects in Chr19q-13.33 region.

Failure to secrete ABO blood group antigens on the intestinal mucosa has been noted to alter the gut microbiome (10) associated with resistance to a variety of infectious diseases (15–18). Therefore, the study by Smyth et al. provides a unique target to dissect the underlying mechanisms between the interactions of genetic risk factors and environmental impacts in type 1 diabetes pathogenesis. The gastrointestinal tract contains the largest surface area of the body, which is also the greatest area with constant exposure to a variety of environmental insults such as microorganisms, food antigens, and toxins. Diverse microorganisms inhabit the gastrointestinal tract and are unlikely to be just innocent bystanders but active players in modulating host immune defense. The microbiome may

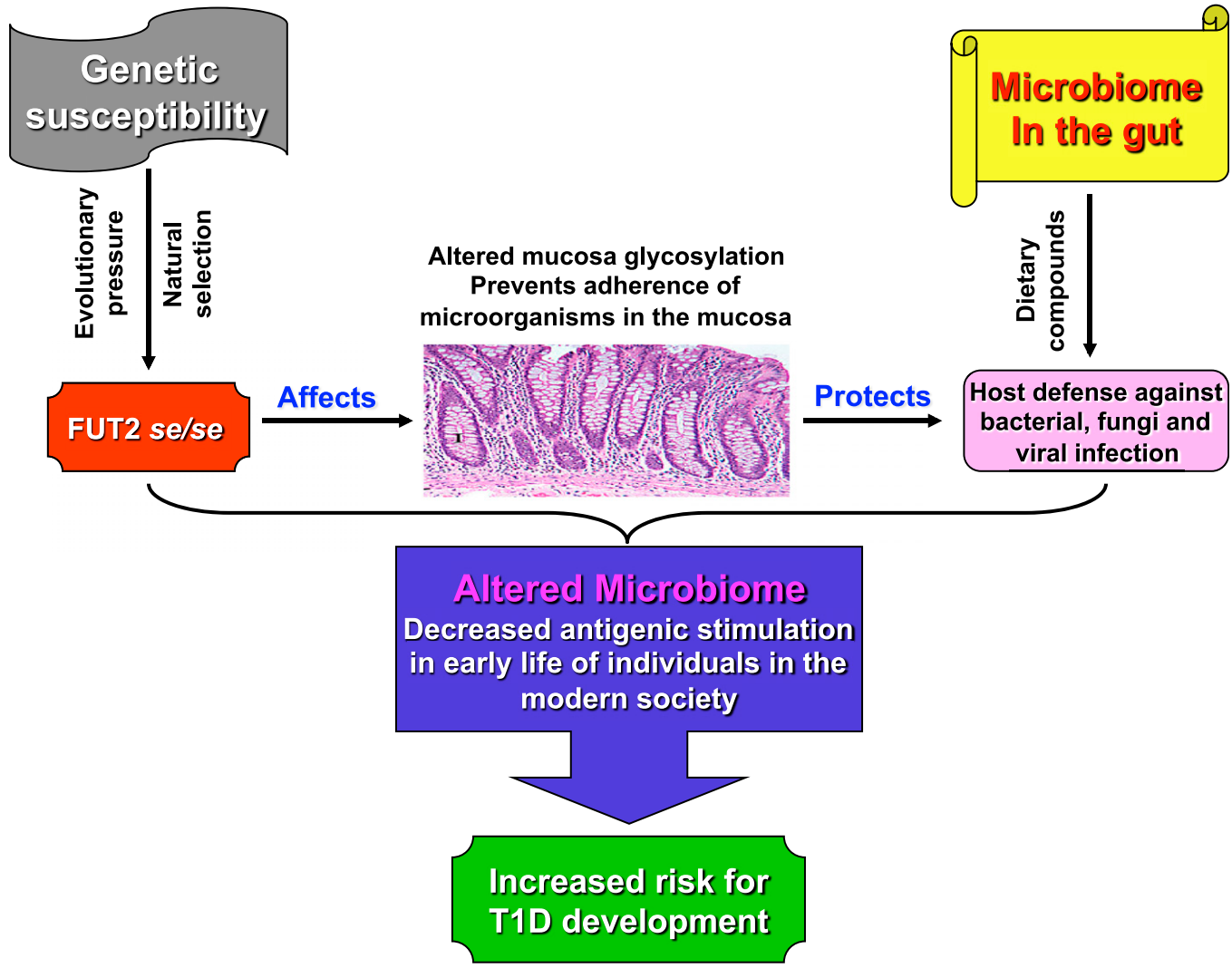

FIG. 1. A model for the potential implication of interactions between the FUT2 nonsecretor status and the gut microbiome in the pathogenesis of type 1 diabetes (T1D). The FUT2 nonsecretor (se) allele was naturally selected under evolutionary pressure to protect hosts against bacterial, fungi, and viral infections by altering the profile of mucosa glycosation, which then prevents the adherence of microorganisms to the mucosal epithelial cells and the mucus layer lining the gastric epithelium. While this protective effect is beneficial for host defense, it also imbalances the microbiome in the gut associated with decreased antigenic stimulation to the immune system in early life of subjects in the modern society, which would predispose those individuals homozygous for the nonsecretor allele with increased risk to the development of type 1 diabetes. (A high-quality digital representation of this figure is available in the online issue.)

also be modulated by dietary compounds and host (i.e., genetic) factors from the early days of life (19). In line with this notion, the *FUT2* se[428] null allele was found to be selected under evolutionary pressure (9). This natural selection on the one hand is beneficial for humans against bacterial (10), fungi (15) and viral infections (17,18), but on the other hand may affect gastric mucosa glycosylation, an essential process for the adherence of microorganisms to the mucosal epithelial cells and the mucus layer lining the gastric epithelium (20). As a consequence, it reshapes microbiome composition in the gut (7,10), potentially contributing to decreased antigenic stimulation in early life in the modern society, which would predispose those individuals with increased risk to the development of autoimmune responses against β-cell self-antigens (Fig. 1).

Yet, functional data relevant to the FUT2 nonsecretor phenotype in type 1 diabetes susceptibility are currently lacking. But there is evidence that the *Fut2-null* mice surface mucosal cells mimic nonsecretor gastric epithelial cells in humans (20). Therefore, it would be interesting to examine whether the *Fut2-null* mice confer increased risk for type 1 diabetes development. It would also be important to examine whether other FUT2 nonsecretor genotypes related to the corresponding populations confer genetic susceptibility to type 1 diabetes development. These and other studies (including analysis of the gut microbiome in various FUT2 genotypes) will be required to tie in the complex interplay between genetics and environment in type 1 diabetes pathogenesis.

ACKNOWLEDGMENTS

C.-Y.W. is supported by the Juvenile Diabetes Research Foundation International and the EFSD/CDC/Lilly Program for Collaborative Diabetes Research between China and Europe.

No potential conflicts of interest relevant to this article were reported.

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