Public Health Genomics Approach to Type 2 Diabetes

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Type 2 diabetes is a leading cause of morbidity and mortality worldwide (1). In the last 15 years, the number of people in the U.S. with diagnosed diabetes has more than doubled. Strong risk factors for type 2 diabetes include age, sex, obesity, physical inactivity, and family history (2). Several measured genetic variants have recently emerged as risk factors for type 2 diabetes. In this commentary, we discuss the impact of new gene discoveries on prediction and prevention of type 2 diabetes. We propose that the new multidisciplinary field of public health genomics can help translate gene discoveries into appropriate actions to reduce the burden of type 2 diabetes in the population.

Role of genetic factors in type 2 diabetes. It has long been recognized that type 2 diabetes runs in families even though only a few diabetes-related genetic diseases have been identified (3). Until recently, the quest for genetic susceptibility to type 2 diabetes has frustrated researchers. Since the completion of the Human Genome Project in 2003 (4), and the Haplotype Mapping (HapMap) Project in 2005 (5), the stage was set for using large-scale collaborative genome-wide association studies (GWAS) to search for genetic factors for many common diseases of public health importance, including type 2 diabetes (6). Since 2007, the scientific community has begun to reap the benefits of GWAS, with >170 studies published and many replicated genetic "hits" found across the genome for a variety of common diseases. These findings fuel expectations that genetic factors can be used to construct susceptibility profiles that will help in the prediction, prevention, and early detection of human diseases, thus ushering in a new era of personalized health care and disease prevention (7).

Current findings on the genetics of type 2 diabetes. In this issue, van Hoek et al. (8) and Lango et al. (9) take GWAS findings in type 2 diabetes to the next logical level by asking the question of whether genetic risk factors for type 2 diabetes discovered using GWAS can be combined to improve the prediction of risk of type 2 diabetes among adults. van Hoek et al. genotyped 18 genetic variants from recent GWAS on type 2 diabetes in a prospective population-based study among almost 6,544 individuals ≥55 years of age. Lango et al. assessed 18 variants in 2,598 control subjects and 2,309 case subjects from a population-based study of individuals of white European descent living in the Tayside region in the U.K. There was considerable overlap between the set of genes in the two studies. Despite different study designs, methods, and case definitions, the two studies essentially showed similar findings. van Hoek et al. found that when genetic variants are combined together to predict the incidence of type 2 diabetes, they had only weak predictive ability in their population. The area under the curve, a measure of discriminative accuracy, was 0.60 for prediction based on the genetic polymorphisms; 0.66 for age, sex, and BMI; and 0.68 for the genetic polymorphisms and clinical characteristics combined. Lango et al. also found that individuals carrying more risk alleles had higher risk of type 2 diabetes. However, the area under the curve for these variants was 0.60. The area under the curve for age, BMI, and sex was 0.78, and adding the genetic risk variants only marginally increased this to 0.80.

Both studies have strengths and limitations, as acknowledged by the investigators. These include the relatively small sample sizes; the lack of the prospective nature of the Lango study; the various ethnic groups and the potential lack of generalizability of findings; the lack of power to examine interactions; the potential that genetic effects could be mediated through other measured risk factors such as BMI leading to possible collinearity; and the fact that these genetic markers may not be the true causal variants in type 2 diabetes (with misclassification due to linkage disequilibrium and weakening of effect sizes). An additional methodological issue is the lack of a comparable and standardized case definition of the type 2 diabetes phenotype between the two studies. Lastly, neither study considered family history for type 2 diabetes, which is likely a strong and independent risk factor (reflecting both genetic and environmental factors).

Can genetic factors be used to predict the risk of type 2 diabetes? The results of these two studies clearly indicate that currently we have a limited ability to predict the risk of type 2 diabetes in the general population based on genetic profiles, especially when added to established risk factors. This finding also is consistent with recent findings on genetic factors from other common diseases such as prostate cancer (10) and coronary heart disease (11). Clearly, our ability to predict type 2 diabetes using genetic risk factors is likely to improve as more variants are discovered, especially if these variants have stronger effect sizes than the current ones (most current ones have odds ratios under 2), if strong gene-gene and gene-environment interactions are found, or if biochemical or physiological biomarkers that are more proximal to the development of type 2 diabetes are discovered and validated. Nevertheless, GWAS findings have great implications in terms of understanding disease biology and pathogenesis and the future development of preventive and treatment interventions.

The public health genomics approach to type 2 diabetes. So, while exciting gene discoveries are being made, what can we do? The answer may lie in the relatively new

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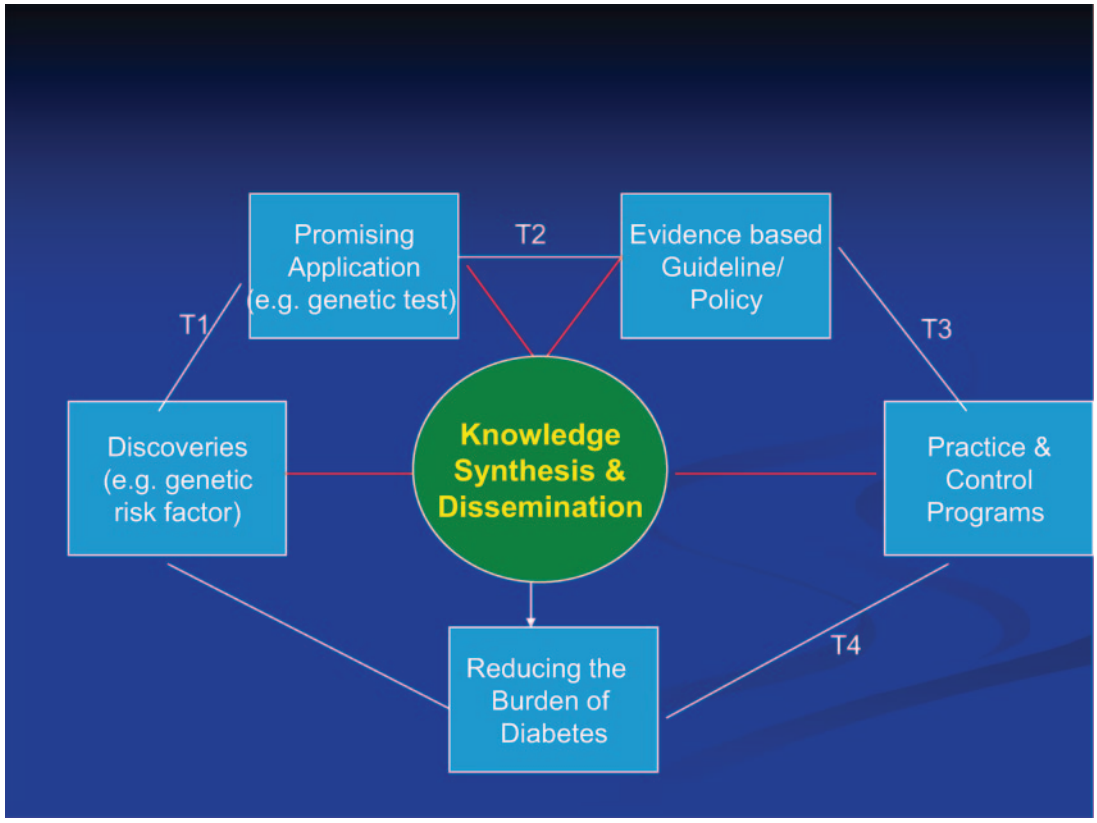

FIG. 1. A public health genomics framework for translating human genetic discoveries into diabetes control and prevention. Diagram modified from Khoury et al. (14)

field of public health genomics, "a multidisciplinary field concerned with the effective and responsible translation of genome-based knowledge and technologies to improve population health" (12). Researchers, policymakers, and practitioners in public health genomics use population-based data on genetic variation and gene-environment interactions to develop, implement, and evaluate evidence-based tools for improving health and preventing disease. They also apply systematic evidence-based knowledge synthesis and appraisal of the clinical validity and utility of genomic applications in health practice. Validated genomic information is then integrated into disease control and prevention programs (13).

Like many areas of public health, public health genomics uses translation phases to progress from discovery to population health impact (14). Because multiple disciplines participate, the process encourages feedback loops and ongoing knowledge synthesis and dissemination. Although many translation schemas are available, we show in Fig. 1*a* continuum adapted from Khoury et al. for type 2 diabetes. Phase one (T1) research seeks to move a basic genomic discovery into a candidate health application (e.g., promising genetic test/intervention). Phase two (T2) research assesses the value of a genomic application for health practice leading to the development of evidence-based guidelines. Phase three (T3) research attempts to move evidence-based guidelines into health practice through knowledge transfer, delivery, dissemination, and diffusion research. Phase four (T4) research and evaluation seek to assess the "real world" health outcomes of a genomic application in practice. Because the development of evidence-based guidelines is a moving target, multiple disciplines are involved in translation research and provide feedback loops to allow integration of new knowledge into practice. Table 1 lists examples of translation genomics research activities related to type 2 diabetes. The two articles published in this issue are examples of T1 research. Most current human genomics research is discovery based. We have recently estimated that no more than 3% of published human genomics studies focus on T2 and beyond (14). Indeed, evidence-based guidelines and T3 and T4 research in genomics currently are rare (except in newborn screening programs for rare metabolic disorders). At present, there are no evidence-based recommendations for the use of genomics in the prevention or treatment of type 2 diabetes.

Knowledge synthesis and dissemination to providers, consumers, and policymakers is at the core of the public health genomics enterprise (Fig. 1). Because of the rapidly emerging information on the genetics of common disease, such as the information reported in the two articles, we need authoritative and credible processes to rapidly summarize what we know and what we don't know about the role of genetic factors in human diseases and to determine whether or not the use of such information is likely to lead to health benefit at the individual and population levels. The Centers for Disease Control and Prevention has developed two knowledge synthesis initiatives in genomics. The first is the Human Genome Epidemiology Network (HuGENet), which is a global collaboration of individuals and networks interested in developing the knowledge base on genes and diseases (15). An online, searchable, and continuously updated database is available (16). As of 1 August 2008, 431 genes have been studied in relation to type 2 diabetes with more than 1,340 publications and 50 meta-analyses as well as 15 GWAS.

TABLE 1
The continuum of translation research in human genomics: types of research and examples related to type 2 diabetes

Translation research phase	Notation	Types of research	Examples
T1	Discovery to candidate health application	Phases I and II clinical trials; observational studies	Can genetic variants be used singly and in combinations to predict type 2 diabetes
T2	Health application to evidence-based practice guidelines	Phase II clinical trial; observational studies; evidence synthesis and guidelines development	What are the benefits and harms for using genetic variants in type 2 diabetes prediction? Can we reduce the burden of type 2 diabetes?
T3	Practice guidelines to health practice	Dissemination research; implementation research: diffusion research phase IV clinical trials	How can we move evidence-based guidelines for genetic testing for type 2 diabetes into practice? Are there barriers to testing?
T4	Practice to population health impact	Outcomes research (includes multiple disciplines); population monitoring of morbidity, mortality, benefits, and risk	Do genetic testing for type 2 diabetes and targeted interventions reduce the burden of type 2 diabetes in the population?

The second knowledge synthesis enterprise is the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative (17). This is an independent multidisciplinary expert panel that commissions evidence-based reviews of the clinical validity and utility of genetic tests in specific clinical and population health scenarios. The EGAPP working group is developing evidence-based clinical guidelines for a variety of diseases. The first such guideline was published on the use of cypP450 genetic polymorphism in the treatment of depression with antidepressive medications (18). Currently, the EGAPP working group is evaluating emerging tests with multiple variants that purport to predict future risk of type 2 diabetes (similar to what the authors of the two articles were trying to assess). Details on EGAPP methodology are published elsewhere (19).

Concluding remarks. Can genetic risk factors be used for the prediction of type 2 diabetes? The answer is not yet. It is certainly possible that as the discoveries of genetic factors continue at a rapid pace, we may have enough variants that, when combined with other risk factors and clinical variables, may lead to more predictive risk profiles. Even then, we need to figure out how such information can be communicated and whether or not it will affect the adoption of healthy lifestyles and the seeking of medical interventions that could lead to overall reduction in type 2 diabetes burden. This is a long process involving different fields of clinical and population studies, both observational studies and clinical trials. In the meantime, in spite of our incomplete knowledge of the genetics of type 2 diabetes today, the burden of type 2 diabetes can be ameliorated at the population level. Recent studies have found that lifestyle changes through diet and exercise can prevent or delay the onset of type 2 diabetes. For people already living with diabetes, much of this burden could be prevented with early detection, improved delivery of care, and adequate management (1). Concerted clinical and public health efforts are underway to assist in reducing the burden of diabetes in the population. In addition, a simple tool such as family history of type 2 diabetes can raise the level of awareness about the role of shared genes and environments in families and the need for risk-reducing behaviors. In the final analysis, traditional risk factors, including family history (20), still provide the most reliable approach to defining different levels of risk for developing type 2 diabetes in the population.

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