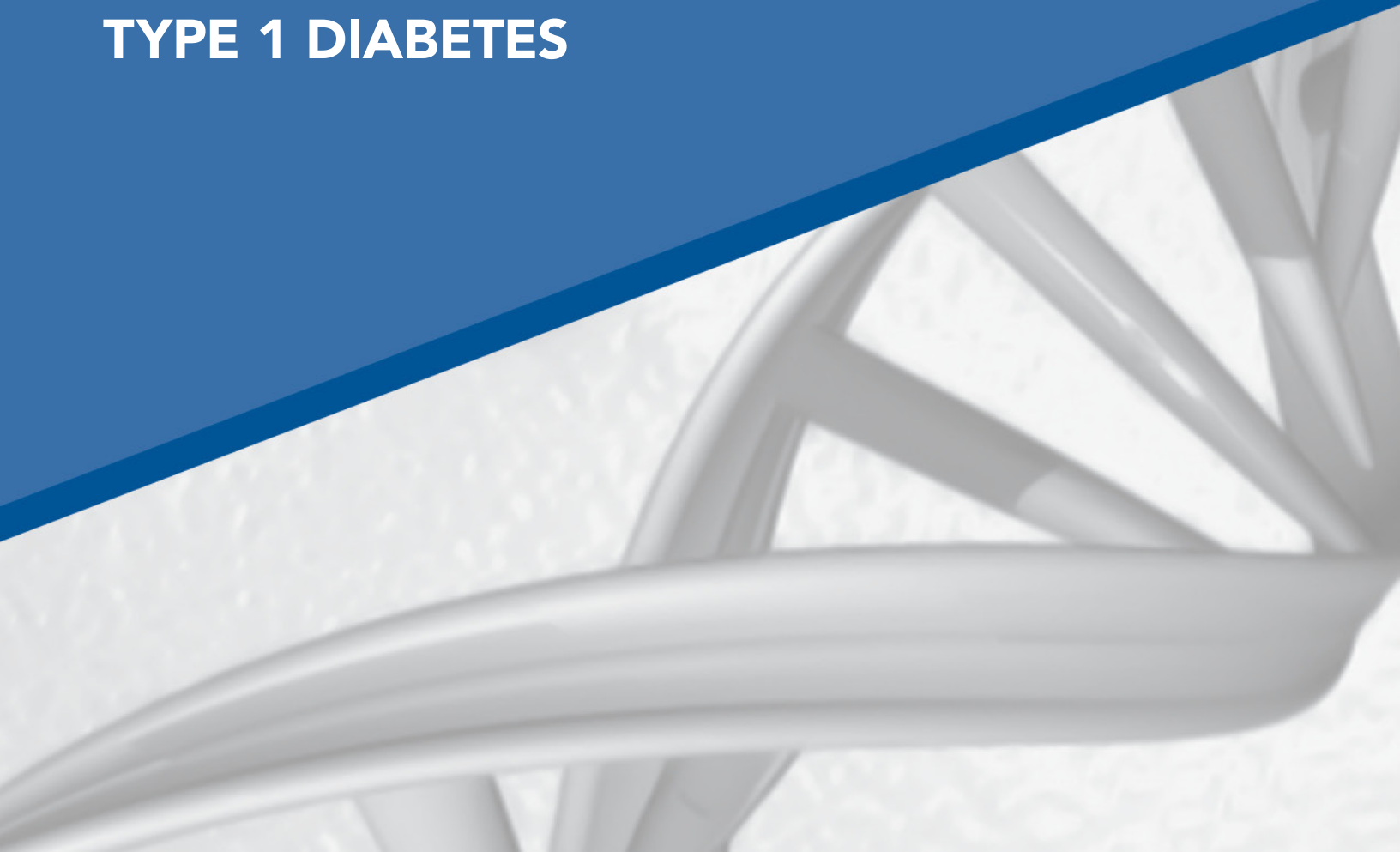# GOAL I

IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

T he *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of large-scale, long-term clinical research studies and clinical trials that are essential for identifying the genetic and environmental causes of type 1 diabetes and testing interventions to prevent the disease. In addition to the significant research progress described in this chapter, information on the program evaluation related to Goal I can be found in Appendix A (Allocation of Funds), Appendix B (Assessment), and Appendix C (Evaluation of Major Research Consortia, Networks, and Resources).

Type 1 diabetes results from an interaction of genetic and environmental factors that triggers the autoimmune destruction of insulin-producing pancreatic beta cells. Discovering those genetic and environmental risk factors and determining how they interact to cause disease are key steps toward being able to identify individuals who are at risk for type 1 diabetes and accurately assess their specific level of risk. Moreover, research on type 1 diabetes triggers can reveal the molecular mechanisms associated with the development of autoimmune disease and aid in the development of new therapies to delay, prevent, or reverse type 1 diabetes.

The *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program or Program)* has invested significant resources into multiple large-scale, long-term clinical research studies aimed at identifying the genetic and environmental causes of type 1 diabetes or testing interventions to prevent the disease. Collectively, these studies are recruiting and intensively monitoring thousands of families and individuals affected by type 1 diabetes. This substantial investment of financial resources, along with the considerable time and effort of researchers and patients, has already led to new scientific advances. As a result of these studies, we now know how many children in the United States have diabetes, and are poised to see how rates of childhood diabetes are changing over time. Nearly 50 genetic regions that influence risk for type 1 diabetes are now known—up from three genes known a decade ago. Genetic evidence linking type 1 diabetes with other autoimmune diseases, such as celiac disease, suggests that research on the environmental risk factors for type 1 diabetes may benefit a larger patient group than originally anticipated. These and other findings represent only a fraction of the knowledge that is expected to accrue from the long-term investment in research on genetic and environmental risk factors of type 1 diabetes supported by the *Special Diabetes Program.*

Graphic: Drawing of DNA double helix. Image credit: National Human Genome Research Institute, NIH.

HIGHLIGHTS OF RECENT RESEARCH ADVANCES RELATED TO GOAL I

Identification of Genetic Regions Involved in Type 1 Diabetes Susceptibility: Researchers have analyzed data from the Type 1 Diabetes Genetics Consortium (T1DGC) collection and other genetic studies to identify over 40 genetic regions that are associated with type 1 diabetes risk. Most of the newly identified genes seem to be associated with T cells or other components of the immune system. For example, the genes *SH2B3*, *IL2RA*, *PRKCQ*, *TAGAP*, and *UBASH3A* are all implicated in T cell activation, and *IL2* and *IL27* are involved in T cell proliferation and differentiation, respectively. Another gene, *GLIS3*, is associated with development of the insulin-producing beta cells of the pancreas. Mutations in *GLIS3* have also been found in people who have a form of neonatal diabetes. Other implicated regions contain genes of unknown function, and further research on these genes may uncover new biochemical pathways involved in the pathogenesis of type 1 diabetes.

Completion of Recruitment for TEDDY and TRIGR: Major research accomplishments have been the completion of recruitment for The Environmental Determinants of Diabetes in the Young (TEDDY) study to find environmental triggers of type 1 diabetes and the Trial to Reduce IDDM in the Genetically At-Risk (TRIGR) study to test a dietary intervention to prevent type 1 diabetes. In TEDDY, over 425,000 infants were screened and over 8,000 children were enrolled for long-term monitoring. TRIGR recruited over 5,600 pregnant women and enrolled 2,160 eligible newborns. Recruitment of the TEDDY and TRIGR cohorts sets the stage for successful completion of these important clinical studies that could have great impact on public health efforts to prevent type 1 diabetes.

Epidemiology of Childhood Diabetes in the United States: The SEARCH for Diabetes in Youth study (SEARCH) is providing data on how many children and youth in the United States have diabetes and how those rates are changing over time. SEARCH found that in children under the age of 10 years, type 1 diabetes was the most common form of diabetes in all racial/ethnic groups examined. Type 2 diabetes was rarely diagnosed in this age group. Among youth under the age of 10 years, the rate of new cases was 19.7 per 100,000 each year for type 1 diabetes and 0.4 per 100,000 for type 2 diabetes. Among youth 10 years of age and older, the rate of new cases was 18.6 per 100,000 each year for type 1 diabetes and 8.5 per 100,000 each year for youth with type 2 diabetes. Non-Hispanic white youth had the highest rate of new cases of type 1 diabetes. While still infrequent, rates of type 2 diabetes were greater among youth aged 10 to 19 years compared to younger children, with higher rates among U.S. minority populations compared with non-Hispanic whites. Among non-Hispanic white youth aged 10 to 19 years, the rate of new cases was higher for type 1 than for type 2 diabetes. For Asian/Pacific Islander and American Indian youth aged 10 to 19 years, the opposite was true—the rate of new cases was greater for type 2 than for type 1 diabetes. Among African American and Hispanic youth aged 10 to 19 years, the rates of new cases of type 1 and type 2 diabetes were similar.

Increasing Role of Environmental Triggers in Type 1 Diabetes: A SEARCH site in Colorado found that the incidence of type 1 diabetes has increased 1.6-fold among non-Hispanic white and Hispanic youth aged 0-17 years

from 1978-1988 to 2002-2004. Emerging evidence indicates that increasing environmental exposures might account for trends in the diagnosis of type 1 diabetes over time. For example, non-Hispanic white and Hispanic children diagnosed with type 1 diabetes between 2002 and 2004 were found to be less likely to have the highest risk Human Leukocyte Antigen (HLA) class II genotypes than those diagnosed between 1978-1988. This observation suggests that environmental factors might now be able to trigger disease in individuals who have lower genetic susceptibility to type 1 diabetes. SEARCH investigators also found that the age of type 1 diabetes diagnosis in Colorado children decreased by 9.6 months from the period 1978-1983 to 2002-2004. An increase in the height of children over this time period accounted for about 15 percent of the decreasing age of diagnosis, but the major environmental pressures affecting risk of type 1 diabetes remain unknown.

Diabetes Control in Youth with Type 1 Diabetes: In addition to providing the first national data on rates of childhood diabetes, SEARCH also provides information on the health status of children with diabetes. SEARCH investigators found that 17 percent of youth with type 1 diabetes have hemoglobin A1c (HbA1c) levels greater than 9 percent that reflect poor glycemic control. African American, American Indian, Hispanic, and Asian/Pacific Islander youth with type 1 diabetes were significantly more likely to have higher HbA1c levels than non-Hispanic white youth (rates for poor glycemic control of 36 percent, 52 percent, 27 percent, and 26 percent versus 12 percent respectively). Another analysis showed that insulin pump use, which is associated with the lowest HbA1c levels in all age groups, was more frequently used by older youth, females, non-Hispanic whites, and families with higher incomes and education. These findings point to the need to develop more effective treatment strategies to improve metabolic control in all youth with type 1 diabetes.

COMPLEXITY OF TYPE 1 DIABETES SUSCEPTIBILITY

By 1998, at the start of the *Special Diabetes Program*, scientists had long been studying patterns of type 1 diabetes in families and groups around the world to look for the causes of this disease. Their research efforts uncovered wide variations in an individual's chance of developing type 1 diabetes and suggested that complex interactions of multiple genetic and environmental factors might be involved in disease onset.

Studies of Large Populations Provide Insight into Type 1 Diabetes: By studying large populations, researchers noted a significant geographical variation in the rate of type 1 diabetes. Several decades ago wide variation in the rates of type 1 diabetes around the world were recognized ranging from more than 20 cases diagnosed per 100,000 persons per year to fewer than 3 cases diagnosed per 100,000 persons per year.[13] In the United States, based on limited local data, rates were thought to be intermediate between those extremes.[14] More recent data on incidence of type 1 diabetes worldwide is presented in Figure 2. This great variability in disease incidence across national borders could reflect genetic differences among diverse racial and ethnic

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[13]   Dorman JS , McCarthy BJ, O'Leary LA, et al.: Risk Factors for Insulin-Dependent Diabetes. In *Diabetes in America* (pp. 165-178). Bethesda, MD: National Diabetes Data Group, NIH, 1995.
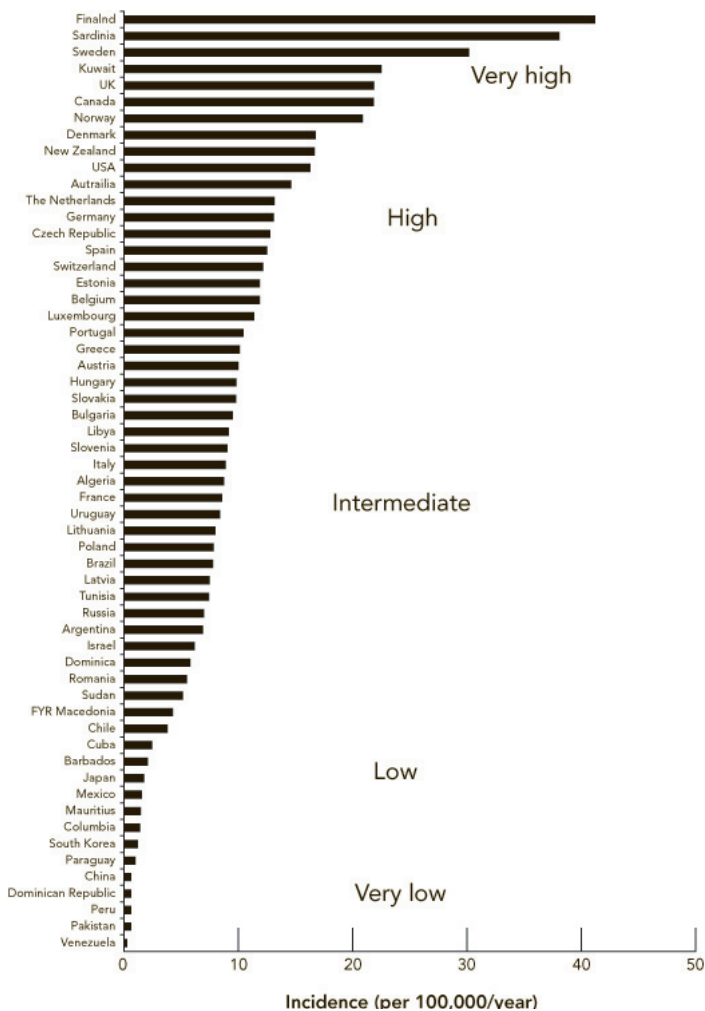
[14]   *Ibid.*

Figure 2: Worldwide Incidence of Type 1 Diabetes in Children Standardized rates (per 100,000/year) of type 1 diabetes in children aged 14 years or under worldwide 1990-1999. Countries are arranged in descending incidence rate. Reprinted with permission from the DIAMOND Project Group and *Diabetic Medicine* 23: 857-866, 2006, John Wiley and Sons Inc. publisher.

populations; environmental differences, such as variations in dietary practices or the level of exposure to sunlight; or a combination of genetic and environmental risk factors.

Insights from Individual Families with Type 1 Diabetes: Results from studies of individuals with type 1 diabetes and their families, as well as individuals without diabetes, strongly support the hypothesis that genetic susceptibility in combination with environmental factors is required for disease onset. Researchers found that a person who has a close relative with type 1 diabetes has up to a 15-fold higher[15] risk of developing the disease than someone with no close relative with type 1 diabetes. If an identical twin has type 1 diabetes, then his or her twin has a substantially greater risk of developing type 1 diabetes.[16] The second twin, however, still only develops type 1 diabetes about 40 percent of the time,[17] even though identical twins have the same genetic make-up. Importantly, more than 80 percent of people with type 1 diabetes have no close relative with the disease.[18] Together, these research findings indicated that genetic factors have a significant effect on disease susceptibility, but the autoimmune process leading to type 1 diabetes seems to also require an as-yet unknown environmental triggers.

Investing in Critical Infrastructure for Research on Genetic and Environmental Risk Factors for Type 1 Diabetes: The *Special Diabetes Program* has enabled the creation of large-scale research efforts to identify the genes that confer increased susceptibility to or protection from type 1 diabetes, as well as the environmental factors that trigger the autoimmune process in genetically susceptible individuals. With support from the *Special*

15   Tillil H and Köbberling J: Age-corrected empirical genetic risk estimates for first-degree relatives of IDDM patients. Diabetes 36: 93-99, 1987.
16   Kyvik KO, Green A, and Beck-Nielsen H: Concordance rates of insulin dependent diabetes mellitus: a population based study of young Danish twins. BMJ 311: 913-917, 1995.
17   Rich SS: Mapping genes in diabetes: genetic epidemiological perspective. Diabetes 39: 1315-1319, 1990.
18   Dorman JS, McCarthy BJ, O'Leary LA, et al.: Risk Factors for Insulin-Dependent Diabetes. In *Diabetes in America* (pp. 165-178). Bethesda, MD: National Diabetes Data Group, NIH, 1995.

Diabetes Program, T1DGC, TEDDY, SEARCH, and clinical trials to prevent type 1 diabetes, such as TRIGR, have begun a new era in research on the genetic and environmental causes of type 1 diabetes.

GENETIC CAUSES OF TYPE 1 DIABETES

A decade ago, scientists had identified three genetic regions that influence the risk for type 1 diabetes. As much as 50 percent of genetic susceptibility to type 1 diabetes is attributable to variations in the *HLA* class II regions of the Major Histocompatibility Complex. Proteins encoded by the *HLA* genes help a person's immune system distinguish their own cells from foreign cells, such as disease-causing bacteria. For reasons that are still being studied, some variations in the *HLA* genes make it more likely that the immune system will not recognize the body's cells as "self," and therefore launch an attack on these cells, triggering type 1 diabetes or another autoimmune disease. Other regions linked with type 1 diabetes included a portion of DNA that regulates the insulin gene and a gene called *CTLA4* that encodes a protein found in T cells of the immune system. While these three genetic regions together accounted for a large proportion of type 1 diabetes cases, it was clear that many genes for type 1 diabetes had yet to be discovered.

The search for genetic causes of type 1 diabetes is complicated by the fact that some genes might have small effects in many people across the population and other genes might have larger effects but only in a small group of individuals or families. In addition, some genetic risk factors might interact with each other such that increased risk in certain individuals might result from disease-associated variations in two or more genes. Scientists knew that identifying all genetic variants that affect the risk of type 1 diabetes would require a large-scale, coordinated effort to systematically search the genomes of thousands of people with type 1 diabetes and their close relatives who do or do not also have the disease.

Coordinating and Implementing International Efforts To Discover the Genetic Causes of Type 1 Diabetes: In 2001, with support from the *Special Diabetes Program*, the T1DGC was established with the goal of organizing and implementing international efforts to identify genes that determine an individual's risk of type 1 diabetes. The Consortium is led by NIDDK in collaboration with NIAID, NHGRI, NICHD, and JDRF. The T1DGC established four international networks to coordinate the work of researchers across the globe.

The Consortium aimed to collect, store, and analyze DNA from 2,800 families with two or more siblings with type 1 diabetes. In populations with low rates of type 1 diabetes, families with only one child with type 1 diabetes, as well as individuals with or without type 1 diabetes, were also recruited to participate in the study. The T1DGC made significant efforts to collect DNA from non-Caucasian populations for which little information is available about the genetics of type 1 diabetes. The Consortium also created an extensive database containing clinical, genetic, and medical history information from each participant. With DNA samples and data from approximately 38,000 individuals, the T1DGC collection has amassed the statistical power needed to facilitate the search for type 1 diabetes genes and genetic interactions. To maximize scientific output from this unique genetic collection, the resources known as the NIDDK Central Repositories coordinate sharing of available T1DGC biosamples and data with qualified

investigators for approved research studies. For more information on the T1DGC, please see the Investigator Profile of Dr. Stephen Rich in this chapter.

Newly Identified Genes Associated with Increased Susceptibility to Type 1 Diabetes: The T1DGC investment has already begun to pay off—researchers have used data gleaned from the T1DGC collection and other studies to identify nearly 50 genetic regions that are associated with type 1 diabetes risk. Most of these newly identified genes seem to be associated with T cells or other components of the immune system. More research is needed to understand how each of the genes associated with type 1 diabetes actually causes or contributes to the disease. The identification of these genetic regions sets the stage for new insights about type 1 diabetes. Because many of the genes that increase risk for type 1 diabetes are also associated with other autoimmune diseases, learning how the genes alter risk will shed light on multiple autoimmune disorders.

Fine-mapping Genetic and Genomic Variants that Contribute to Type 1 Diabetes: To build on the research resources made available by the T1DGC, the *Special Diabetes Program* is supporting new research to more finely map the newly identified susceptibility regions and to uncover the mechanisms by which the genes influence risk of type 1 diabetes. Researchers are taking a closer look at the susceptibility regions, each of which contain up to 27 genes, to identify the exact genes and sequence variants that are associated with disease risk. They are also exploring how variations in the *CTLA4* gene create subtle differences in the amount of protein that is produced from the gene and how those differences relate to the pathogenesis of type 1 diabetes, and testing the hypothesis that genetic changes that do not affect the DNA sequence can also influence type 1 diabetes

risk. By expanding knowledge of the pathogenesis of type 1 diabetes, this research could inform new strategies for prevention and treatment. It can also improve predictive abilities and enable the design of more specific clinical trials to test personalized interventions for patients with similar risk profiles.

ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

By the start of the *Special Diabetes Program* in 1998, scientists had garnered some clues to potential environmental causes of type 1 diabetes. Research uncovered an apparent seasonal pattern to type 1 diabetes onset with fewer cases diagnosed in warm summer months. This observation suggested to researchers that infectious agents, such as viruses, that are more common during colder months might be potential triggers of type 1 diabetes. Other studies found evidence of nutritional factors in disease onset. Breastfeeding was associated with a lower risk of type 1 diabetes in children, while early exposure to cow's milk or the introduction of cereal before 3 months or after 7 months of age were associated with a higher risk. Type 1 diabetes risk has also been linked to factors as diverse as levels of vitamin D in the blood, stress, maternal age, birth order, and socioeconomic status. Despite a wealth of research demonstrating significant associations between type 1 diabetes and a variety of potential risk factors, no single environmental factor has been definitively identified as a causative agent for type 1 diabetes.

Many early studies on the environmental causes of type 1 diabetes focused on individuals with existing type 1 diabetes and examined their history to try to determine potential environmental influences before or around the time of diagnosis. Such studies were limited

by imprecision, recall bias, and failure to account for exposures early in life. Other studies enrolled too few children or followed participants for time periods that were too short to generate statistically significant results. Identifying environmental triggers of type 1 diabetes with certainty would require a prospective clinical study that allows for intensive observation of thousands of at-risk individuals before the onset of disease. Because the autoimmune process in type 1 diabetes can take years in some individuals, such a study would have to follow its participants over a long period of time.

Intensive Long-term Monitoring To Identify Environmental Triggers of Type 1 Diabetes:

With support from the *Special Diabetes Program*, NIDDK, NIAID, NICHD, NIEHS, CDC, and JDRF established the long-term TEDDY study to provide a coordinated, multidisciplinary approach to understanding the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. TEDDY is an international consortium of six research groups located in the United States and Europe.

TEDDY investigators have screened over 425,000 newborns from the general population or who have either a parent or sibling with type 1 diabetes to identify infants with *HLA* gene sequences that predict an increased risk of type 1 diabetes. Over 8,000 high-risk infants are now being followed in the TEDDY study from birth through 15 years of age. For a decade and a half, investigators will regularly collect information on the child's diet, illnesses, vaccinations, and psychosocial stresses; biological samples, including blood, stool, and toenail clippings, will be collected and stored for future analysis as new

technologies and hypotheses are developed. In addition, TEDDY children will be frequently tested for evidence of the autoimmune process that characterizes type 1 diabetes, enabling researchers to study the very early stages in the development of the disease.

Because the study is scheduled to continue until 2023, TEDDY has been rigorously designed to maximize the probability of successfully identifying one or more environmental triggers of type 1 diabetes. Biosamples from TEDDY participants will be made available to researchers worldwide through the NIDDK Central Repositories so that innovative hypotheses related to the environmental causes of type 1 diabetes can be efficiently tested without the need to duplicate costly infrastructure and human resources. The substantial investment in TEDDY can reap major rewards and revolutionize the ability to prevent type 1 diabetes. For example, identification of a dietary or infectious cause of type 1 diabetes could have an enormously positive impact on public health through a diet change or vaccine for disease prevention.

Benefits of Research on Type 1 Diabetes for Other Autoimmune Diseases: Benefits of the TEDDY study are expected to extend more broadly to include people with celiac disease, a digestive disorder caused by autoimmunity directed at gluten proteins in wheat and other grains. Celiac disease and type 1 diabetes share some genetic susceptibility factors, and many people have both diseases. Celiac disease affects about 2 million Americans and, like type 1 diabetes, rates of the disorder are rising.[19] Because the newborns studied in TEDDY are at high risk of celiac disease, the researchers are studying the development of both autoimmune

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[19]   Fasano A, Berti I, Gerarduzzi T, et al: Prevalence of celiac disease in at-risk and not-at-risk groups in the United States. Archives of Internal Medicine 163: 268-292, 2003.

disorders. Thus, the intensive study of at-risk youth over many years to uncover environmental risk factors for type 1 diabetes will also identify factors that contribute to celiac disease and other autoimmune diseases.

Testing a Dietary Strategy for Type 1 Diabetes Prevention: While TEDDY represents an unbiased, prospective, long-term investment in finding the environmental causes of type 1 diabetes, scientists are also studying whether modification of specific potential triggers can prevent or reduce the incidence of type 1 diabetes. TRIGR, which is led by NICHD, is an international clinical trial testing whether weaning high-risk infants to a formula in which milk proteins have been broken down (hydrolyzed) into much smaller pieces can reduce the risk of diabetes-associated autoimmunity or type 1 diabetes compared to weaning to standard cow's milk formula. Families from 15 countries across North America, Europe, and Australia participate in TRIGR.

Research suggests that standard cow's milk proteins might interfere with the normal development of the immune system in genetically susceptible individuals and that hydrolyzed milk might be less likely to trigger that deleterious effect on the immune system. To test the hypothesis that hydrolyzed formula could reduce the risk of type 1 diabetes, TRIGR recruited over 5,600 pregnant women who have type 1 diabetes or have a relative with type 1 diabetes to participate in the early phases of the study. Ultimately, 2,160 of their infants were identified as being at high risk for type 1 diabetes and enrolled in TRIGR. Mothers of enrolled infants were encouraged to breastfeed for as long as possible. At weaning, infants were randomly assigned to receive either standard or extensively hydrolyzed formula. TRIGR investigators are monitoring these children for signs of diabetes-related autoimmunity or the development of type 1 diabetes

until they are 10 years of age. The last baby enrolled in TRIGR was born in 2007, so results from the trial are expected after 2017. If the TRIGR hypothesis is proven to be correct, a simple dietary intervention could have significant benefits for families that carry a high genetic risk of type 1 diabetes.

EPIDEMIOLOGY OF DIABETES IN AMERICAN YOUTH

A major challenge for understanding childhood diabetes in the United States has been the lack of reliable national information on the rates, types, and clinical course of diabetes in children and youth. With support from the *Special Diabetes Program*, CDC and NIDDK launched SEARCH, a multicenter epidemiologic study to identify cases of diabetes in children and youth under 20 years of age in six geographically dispersed regions across the United States. The SEARCH centers cover a large population of American youth with significant racial/ethnic, socioeconomic, and geographic diversity.

Understanding the Complexity of Diabetes in Youth: SEARCH has revealed a more complicated picture of childhood diabetes than was previously assumed. In children under 10 years of age, type 1 diabetes represented the predominant form of new cases of diabetes in all racial/ethnic groups studied. Type 2 diabetes was only rarely diagnosed in this age group. In youth from 10 to 19 years of age, type 1 diabetes was the main form of newly diagnosed diabetes in non-Hispanic white children, while type 2 diabetes was more common in Asian/Pacific Islander and American Indian youth. New cases of diabetes were about equally split between type 1 and type 2 diabetes in older African American and Hispanic youth. Interestingly, SEARCH investigators found some diabetic youth had features of both forms of the disease. SEARCH is now leading efforts to better

classify diabetes type in youth for both research and clinical purposes.

Discovering Risk Factors for Childhood Diabetes: SEARCH is contributing to the hunt for the genetic and environmental triggers of diabetes, which could inform new therapeutic strategies. SEARCH data showed that obesity—typically thought of as a risk factor for type 2 diabetes—might accelerate the onset of type 1 diabetes in children who already have reduced beta cell function. Ongoing investment in SEARCH will allow researchers to quantitate changes in the rates of childhood diabetes over time and better characterize the natural history and risk factors for all forms of diabetes in children and youth. For more information on SEARCH, please see the Investigator Profile of Dr. Dana Dabelea in Goal V.

Summary

Research to identify the genetic and environmental causes of type 1 diabetes has profound implications for at-risk individuals, as well as those already living with the disease. Understanding the genetic risk factors will help scientists and clinicians better identify individuals with higher susceptibility for type 1 diabetes so that they can be offered enrollment in clinical trials of potential preventive strategies or be given interventions to prevent diabetes once such interventions are tested and validated. Even in the absence of prevention strategies, at-risk individuals can be closely monitored for early signs of autoimmunity. Research has shown that at-risk children who are monitored before diabetes onset have lower rates of diabetic ketoacidosis, a potentially fatal complication of untreated diabetes, and are less likely to be hospitalized at diagnosis. Similarly, identifying environmental risk factors might point to simple behavioral modifications—such as choosing a

different infant formula as is being tested in TRIGR—that can reduce the chance of developing type 1 diabetes. Defining the genetic and environmental risk factors could also reveal the biological pathways that go awry in type 1 diabetes and elicit autoimmune destruction of the beta cells. The design and development of drugs that correct those pathways could potentially reverse type 1 diabetes even in individuals with long-standing disease.

The *Special Statutory Funding Program for Type 1 Diabetes Research* has supported the establishment of unprecedented research infrastructure and resources that have already significantly advanced knowledge of the genetic and environmental causes of this complex disease. Nonetheless, the potential payoff from the investment in these large-scale, long-term studies is only beginning to be realized. All research consortia described in this chapter have invested substantial time, human resources, and effort to screen and enroll thousands of families and individuals affected by type 1 diabetes (see the Feature on "Critical Investment in Infrastructure for Type 1 Diabetes Research" later in this chapter). Likewise, the dedicated volunteers in these research studies have contributed significant amounts of time and effort toward the goal of attaining new knowledge about type 1 diabetes that would not otherwise be possible to attain without their participation. These efforts have set the stage for future research progress that is expected to be fully realized in the years to come. This important line of research could not be undertaken at all, or at least not at an unprecedented scale, without the financial and organizational resources of the *Special Diabetes Program* and the dedicated participation of the diabetes research and patient communities.

RESEARCH CONSORTIA AND NETWORKS RELATED TO RESEARCH ON THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

Evaluation of research consortia and networks supported by the *Special Diabetes Program* and related to Goal I is found in Appendix C. Highlights of these programs are summarized below.

Type 1 Diabetes Genetics Consortium (T1DGC): The T1DGC coordinates and implements research to identify the genes that affect a person's risk for type 1 diabetes. Since its establishment in 2001, the T1DGC has collected DNA samples, as well as clinical, genetic, and medical history data, from 38,000 individuals, including members of 2,800 families with two or more siblings with type 1 diabetes. The T1DGC operates four clinical recruitment networks in Asia-Pacific, Europe, North America, and the United Kingdom. Because of the efforts of the Consortium and other studies, scientists have identified nearly 50 genetic regions that contribute to the risk of type 1 diabetes—up from only three susceptibility genes that were known a decade ago.

The Environmental Determinants of Diabetes in the Young Study (TEDDY): The TEDDY study provides a coordinated, multidisciplinary approach to understanding the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. Six clinical sites located in the United States, Finland, Germany, and Sweden screened more than 425,000 infants to determine their level of genetic risk for type 1 diabetes. Study investigators enrolled and will monitor over 8,000 infants who have been found to be at high risk for type 1 diabetes until 15 years of age to determine if and when diabetes-related autoimmunity or type 1 diabetes begin. This ambitious, long-term study is critically important for informing the development of new prevention strategies.

Trial To Reduce IDDM in the Genetically At-Risk (TRIGR): TRIGR is an international clinical trial testing a dietary intervention to prevent type 1 diabetes in children with a high genetic risk of developing the disease. More than 2,160 infants enrolled in TRIGR have been randomly assigned to receive either extensively hydrolyzed infant formula or standard cow's milk-based formula after weaning. Researchers will monitor these infants until 10 years of age for signs of diabetes-related autoimmunity or type 1 diabetes to determine whether hydrolyzed formula decreases the risk of developing type 1 diabetes.

SEARCH for Diabetes in Youth (SEARCH): SEARCH is a multicenter epidemiological study to identify cases of and characterize diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States. SEARCH has defined prevalence and incidence of diabetes in youth, which has provided the most comprehensive picture to date of rates of childhood diabetes in the United States. SEARCH is now poised to evaluate how rates of diabetes are changing over time and better characterize the natural history and risk factors for all forms of diabetes in children and youth.

The goals of identifying the causes of type 1 diabetes, and determining strategies for curing, reversing, treating, and preventing the disease are challenging ones. Specific research questions in type 1 diabetes require large-scale team efforts to address and complement investigator-initiated studies. In particular, determination of the numerous genetic contributors to type 1 diabetes, discovery of environmental triggers that influence development of the disease, characterization and nationwide surveillance of diabetes in children, and the conduct of clinical trials, especially for prevention of the disease, necessitate significant, coordinated efforts and infrastructure. The *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of extensive, collaborative clinical research networks that are carrying out unprecedented studies to accelerate the pace of research on type 1 diabetes. As examples, the four research consortia described below each have unique requirements for a large infrastructure to achieve these important goals. Results from these vital projects have the potential to revolutionize the health and quality of life of people with and at risk to develop type 1 diabetes.

Type 1 Diabetes Genetics Consortium (T1DGC)

Type 1 diabetes is not caused by a single gene; rather, variations in many genes can affect susceptibility to the disease and these variants can be rare within a population. In addition, unique variants may be present in different ethnic/racial populations. Therefore, to identify comprehensively and confidently all of the variants that affect risk of type 1 diabetes, genomes from a large number of ethnically diverse individuals need to be screened. In 2001, the T1DGC, led by NIDDK, was established with the overarching goal of searching through the genome to identify the genes that determine an individual's risk of developing type 1 diabetes. To collect the significant number of samples necessary, the consortium includes four international clinical recruitment networks in Asia-Pacific, Europe, North America, and the United Kingdom, as well as a coordinating center, autoantibody laboratory, and Human Leukocyte Antigen genotyping laboratory that collectively represent more than 200 individual recruitment sites and nearly 350 Consortium members.

The T1DGC has used its clinical infrastructure to recruit, screen, and collect DNA from a large cohort of families and individuals affected by type 1 diabetes. As of spring 2010, the T1DGC has recruited and taken biosamples from 2,800 Caucasian families with two or more siblings with type 1 diabetes, 500 trios (father, mother, and a child with type 1 diabetes), 600 cases (people with type 1 diabetes), and 700 controls (people with no history of type 1 diabetes). The participation of minority populations is particularly valuable as little information is currently available on the genetic causes of type 1 diabetes in these populations. As many minority populations have a low prevalence of type 1 diabetes, it is difficult to achieve sufficient numbers of participants. Recruitment of trios, cases, and controls is ongoing in these populations, including African Americans and Mexican Americans. The approximately 38,000 DNA samples collected to date and samples currently being collected by the T1DGC should provide sufficient statistical power to find not only common genetic variants that influence type 1 diabetes risk in many people but also rare risk variants that affect few individuals.

In addition to its clinical infrastructure, the T1DGC requires substantial resources for biosample processing, information technology, and database storage capacity. Generation, analysis, and storage of sequence information from the 38,000 collected DNA samples are not trivial, and the productive T1DGC continues to generate more data from these valuable DNA samples as new technologies become available. Already, the investment in the T1DGC infrastructure is paying off. The T1DGC and its collaborators have identified over 40 genes or gene regions associated with type 1 diabetes, bringing the total number of known regions to near 50—up from only three genes that were known a few years ago. This remarkable explosion in knowledge opens exciting new opportunities for the development of improved strategies to identify and profile individuals at risk who could benefit from future prevention efforts, and novel avenues for the discovery of therapies to prevent or reverse the disease. For more information on the T1DGC, please see the Investigator Profile of Dr. Stephen Rich in this chapter.

The Environmental Determinants of Diabetes in the Young (TEDDY)

Several potential environmental triggers of type 1 diabetes have been suggested, but none have been demonstrated conclusively to cause the disease. These, or any number of unknown environmental triggers, might interact with specific genetic factors to induce development of type 1 diabetes. Identifying the environmental factors that trigger the disease in genetically susceptible individuals requires a herculean effort of large numbers of volunteers, over 2 decades of dedication, and significant quantities of collected biosamples and data. The thousands of participants are needed to ensure that any observed links between

environmental exposure and disease development are meaningful and not coincidence. Also, it is not known if or when the genetically susceptible participants will develop the disease; therefore, they are being followed in large numbers from newborn to 15 years of age. Finally, great quantities of biosamples and data are being collected to capture every potential exposure to an environmental trigger as it is unknown where this exposure will appear.

Launched in 2002, TEDDY, led by NIDDK, represents a coordinated, multidisciplinary effort to unravel this complex puzzle. It is an international consortium of six clinical centers located in the United States and three countries in Europe, as well as a data coordinating center. More than 45 staff members, including principal investigators, project managers, and study coordinators, are involved in this intensive, 20-year effort. To identify potential participants with specific genetic markers indicating a high risk of type 1 diabetes, TEDDY investigators drew a blood sample and sequenced DNA of nearly 419,000 newborns from the general population, as well as over 6,000 newborns who have a first degree relative with type 1 diabetes. Screening these 425,000 newborns identified over 20,000 genetically at-risk infants; the parents of over 8,000 of these infants chose to enroll their child in TEDDY. TEDDY completed enrollment in 2010 and is anticipated to continue through 2023.

Participation in TEDDY requires families to dedicate a significant investment of time and effort. Parents keep regular, detailed records of their child's diet, illnesses, allergies, and other life experiences. Every 3 months for 4 years, parents bring their child to a TEDDY clinic for a 60 to 90 minute visit that includes a blood draw. After 4 years, children are seen at the clinic every

6 months until the child turns 15 years of age or develops type 1 diabetes. Other biosamples, such as stool and nail clippings, are also collected by parents at regular intervals and shipped to the study sites. Some biosamples are analyzed immediately for evidence of autoantibodies that indicate the early stages of type 1 diabetes. Other specimens and data are being stored for future analysis after the investigators learn which children develop type 1 diabetes and which do not. This consortium is creating an unparalleled and invaluable collection of data and biosamples that has the potential to transform research on the causes and progression of type 1 diabetes and have an enormous impact on public health efforts to prevent the disease.

SEARCH for Diabetes in Youth (SEARCH)

Research and public health efforts on childhood diabetes have been hampered in the United States by the lack of national epidemiologic data. This type of data requires a large sample size to collect accurate information. It is necessary to collect this information from diverse populations as these data are likely to vary among racial/ethnic groups. To generate these critical data, the SEARCH study, led by CDC and co-supported by NIDDK, was initiated in 2000 with the overarching goal of characterizing diabetes in individuals less than 20 years of age. SEARCH collects data in six geographically dispersed locations across the country from a racially and ethnically diverse population that includes non-Hispanic white, Hispanic, African American, American Indian, and Asian/Pacific Islander children and youth.

Over 5 million individuals are under surveillance by SEARCH as they reside within a geographic area or participate in a health plan covered by one of the research centers. Children newly diagnosed with diabetes or their parents are invited to fill out an initial

patient survey that requests basic information on the child's diagnosis, processes of care, and quality of life. To date, more than 12,000 youth or families have completed this 20-minute survey, and over 6,000 also participated in baseline in-person visits at SEARCH clinics. Each 1 to 3 hour visit included a physical exam, collection of blood and urine samples, measurement of C-peptide levels, and collection of data related to family medical history, quality of life, depression, diet, and other issues. Children are asked to return for follow-up clinical visits 1, 2, and 5 years later. It is necessary for SEARCH investigators to observe the same individuals over a substantial period of time to monitor disease progression and long-term outcomes in these children. Therefore, mailings are sent periodically to maintain contact with SEARCH participants and encourage them to remain in the study. The SEARCH study is being conducted by staff at six research centers, a coordinating center, and a central laboratory.

Through the committed efforts of its investigators and participants, SEARCH has generated an unprecedented understanding of type 1 and type 2 diabetes in children and youth in the United States. SEARCH has generated incidence and prevalence data for diabetes in children, including racial/ethnic data, and findings from SEARCH point to the need for better treatment strategies and technologies to improve diabetes management in children and youth. Investigators are capitalizing on the data collected by SEARCH to conduct 11 ancillary studies on novel research questions. For more information on the use of SEARCH data to inform understanding of heart-related complications of diabetes, see the Investigator Profile of Dr. Dana Dabelea in Goal V. The investment in large-scale infrastructure for SEARCH has produced substantial contributions to characterizing diabetes in American children and will

continue to lead to a better understanding of the natural history, complications, and risk factors of diabetes in childhood and adolescence.

Type 1 Diabetes TrialNet (TrialNet)

TrialNet, led by NIDDK, supports the development and implementation of clinical trials of agents aimed at preventing type 1 diabetes in people at risk for the disease and slowing disease progression in people who are newly diagnosed. TrialNet's mission is carried out by a large, multidisciplinary network consisting of 18 clinical centers in North America, Europe, and Australia; more than 150 additional patient recruitment sites; a biostatistical coordinating center; a Chairman's office; and various core facilities including six laboratories and a central pharmacy. Without the TrialNet infrastructure, every investigator wanting to evaluate a new potential type 1 diabetes prediction model, screening methodology, or therapy for prevention or treatment would have to create and support a framework for recruiting, screening, treating, and monitoring hundreds (for new-onset trials) or tens of thousands (for prevention trials) of individuals. This approach would be prohibitively expensive and duplicative, and would possibly limit the comparison of scientific outcomes across studies due to the absence of standard laboratory procedures. The TrialNet infrastructure ultimately saves time and resources by facilitating the efficient and timely conduct of clinical trials.

The TrialNet Natural History Study (NHS) was created to identify risk factors for type 1 diabetes and document disease characteristics and progression. As of mid-2010, over 79,000 individuals with a close relative with type 1 diabetes have participated in the NHS by consenting to a blood test for the presence of autoantibodies predictive of the disease. TrialNet expects to screen about 20,000

individuals per year in the future. So far, nearly 2,000 individuals have been found to be autoantibody positive. At-risk individuals are invited to continue in the NHS by visiting a TrialNet clinic every 6 months. At each visit, researchers conduct a series of tests to evaluate the individual's risk factors and monitor progression to type 1 diabetes. The number of autoantibody-positive individuals (2,000) compared to the total number screened (79,000) underscores the need for large-scale infrastructure to implement the NHS. Only 3 to 4 percent of relatives of people with type 1 diabetes have autoantibodies in their blood, and some autoantibody positive individuals never progress to diabetes. So, many geographically dispersed sites are needed to recruit, screen, and monitor the at-risk population—this research could not be done by an individual site.

At-risk or newly diagnosed individuals are invited to participate in clinical trials of new therapies for prevention or new-onset intervention. To date, approximately 200 individuals identified through the NHS and over 700 additional individuals with type 1 diabetes (mostly new-onset) have enrolled in TrialNet intervention trials. TrialNet has supported five trials of promising interventions in people newly diagnosed with type 1 diabetes and two prevention trials in individuals at risk for the development of the disease. TrialNet plans to launch one additional intervention trial in newly diagnosed individuals and two additional prevention trials in at-risk individuals in 2010 and 2011. In 2009, TrialNet reported that a drug targeting B lymphocytes in the immune system preserved the function of insulin-producing beta cells in people newly diagnosed with type 1 diabetes. The finding suggests that targeting these immune cells can be used as a strategy to prevent or treat type 1 diabetes. For more information on this study, see the

Investigator Profile of Dr. Mark Pescovitz in Goal II. The infrastructure developed by TrialNet allows clinical trials to be launched quickly and conducted efficiently. This ensures that promising therapies and preventative strategies are tested, and that the investment in basic research, as well as the investment in TrialNet, is fully maximized.

Coordination of Infrastructure and Resources for Type 1 Diabetes Research

To extend and capitalize on research infrastructure and resources supported by the *Special Diabetes Program*, NIH and CDC have made a concerted effort to promote collaboration and coordination across research groups. These interactions have been particularly important and fruitful among the consortia charged with understanding the etiology and epidemiology of type 1 diabetes. For example, TEDDY and the Trial to Reduce IDDM in the Genetically at-Risk (TRIGR) both required massive international screening programs to identify newborns with a high degree of genetic risk for type 1 diabetes. Thus, TEDDY and TRIGR implemented similar standards for data collection, quality control, and analysis so that results obtained in each study can be directly compared. In another example, all TrialNet sites and four SEARCH centers served as recruitment centers for T1DGC, allowing eligible individuals with type 1 diabetes to contribute to multiple research studies. Additional information on collaboration across consortia can be found in Appendix D.

Conclusion

In 1983, the NIH began the 10-year landmark Diabetes Control and Complications Trial (DCCT) with 1,441 volunteers. The DCCT ultimately demonstrated that intensive insulin therapy to control blood glucose could dramatically reduce the risk of complications of the eyes,

kidneys, and nerves in people with type 1 diabetes. Since 1994, researchers have continued to monitor the health of about 95 percent of the DCCT participants in the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study to determine the impact of intensive insulin therapy on complications that take longer to manifest. The long-term duration of this effort enabled EDIC to show, among other results, that intensive blood glucose control reduces the risk of cardiovascular complications of type 1 diabetes and that the benefits of intensive control in reducing eye, nerve, and kidney disease extended long after the trial was completed. Moreover, insights from this trial established biomarkers that the U.S. Food and Drug Administration has used to approve multiple classes of medications for type 2 diabetes and is considering for approval of new therapeutics to preserve beta cell function in type 1 diabetes. Thus, for more than a quarter of a century, NIH investment in the DCCT/EDIC studies has continued to yield unique and important scientific insights that have changed the standard of care for daily management of type 1 diabetes. Because type 1 diabetes is a chronic disease that progresses at variable rates in individuals over the course of decades, these landmark discoveries would not have been possible without NIH's commitment to long-term support of DCCT/EDIC at a scale that permitted statistically significant outcomes to be achieved.

Likewise, the T1DGC, TEDDY, SEARCH, and TrialNet consortia, all supported by significant resources and investment from the *Special Diabetes Program*, offer exceptional opportunities to accelerate the pace of scientific discovery related to type 1 diabetes. These challenging projects require large scales, long durations, and substantial efforts to complete. The investment

in infrastructure by the *Special Diabetes Program* is not limited to clinical research, but also includes basic research studies critical to the development of new therapeutics. For example, the Beta Cell Biology Consortium (BCBC) brings together over 50 multidisciplinary principal investigators and over 200 affiliates to work collaboratively toward the development of cell replacement therapy as a potential cure for type 1 diabetes. The goal of cell replacement therapy requires addressing both the developmental biology of the insulin-producing beta cell as well as modulation of the immune system to prevent an immune attack on the newly introduced cells and therefore benefits from a multidisciplinary team approach (more information on the BCBC can be found in Goal III and Appendix C).

The investment to date in these infrastructures ensures that this research can be carried out in the most scientifically productive manner. Benefits of the NIH investment in these consortia have already been realized and are expected to accrue for years to come as new technologies are developed and new insights emerge. Importantly, the time and efforts of tens of thousands of dedicated volunteers affected by type 1 diabetes have been instrumental to the success of these consortia. With sustained involvement by NIH, researchers, and volunteers, T1DGC, TEDDY, SEARCH, and TrialNet have the potential to shift existing paradigms of type 1 diabetes prediction, prevention, and treatment, benefitting individuals who are living with or at risk for type 1 diabetes and improving public health.

Investigator Profile

Stephen S. Rich, Ph.D.

Making Unprecedented Contributions to the Genetics of Type 1 Diabetes
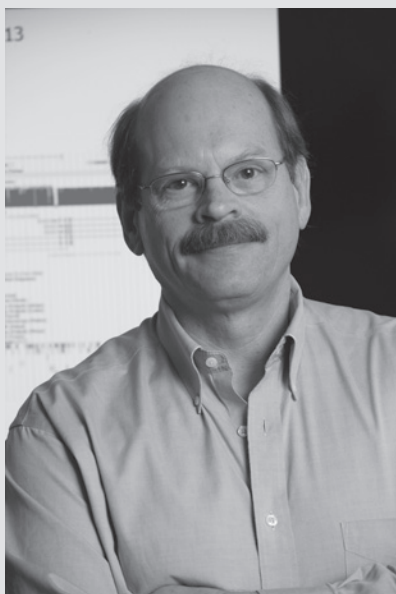
Stephen S. Rich, Ph.D.

Stephen S. Rich, Ph.D., is a Professor of Public Health Sciences at the University of Virginia School of Medicine. Since 2002, Dr. Rich has served as Chair of the Steering Committee and Director of the coordinating center of the Type 1 Diabetes Genetics Consortium (T1DGC), which is led by NIDDK and supported by the Special Statutory Funding Program for Type 1 Diabetes Research. *The T1DGC aims to organize and implement international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. This profile describes the unparalleled resources created by the T1DGC and how those resources are being used by Dr. Rich and other investigators to uncover the genetic causes of type 1 diabetes.*

A 30-Year Commitment to Research on the Genetics of Type 1 Diabetes

In 1980, Dr. Rich began his academic career as a faculty member at the University of Minnesota working on a project related to the genetics of type 1 diabetes. At the time, Dr. Rich notes, "We knew very little about the disease and the genetics of it. So, this was a very new, emerging field." Researchers had shown through studies of twins that the risk of developing type 1 diabetes is heavily influenced by genes—identical twins have about a 40 percent risk[20] of developing type 1 diabetes if their twin already has the disease compared to about 0.2 percent risk[21] in the general population. In the mid-1970s, other scientists had found that type 1 diabetes is triggered by an autoimmune reaction and that genes of the HLA (Human Leukocyte Antigen) system are associated with risk for type 1 diabetes. Over roughly the next 15 years, Dr. Rich and other genetics researchers identified other genes involved in type 1 diabetes risk— namely, the *insulin*, *CTLA4*, and *PTPN22* genes. Still, researchers knew that many more genes affecting type 1 diabetes risk had yet to be discovered.

A turning point in the field of type 1 diabetes genetic research occurred in the late 1990s. Scientists from around the world with an interest in this subject met in Denmark at a meeting sponsored, in part, by NIDDK and JDRF. "We realized that part of our problem was lack of available clinical resources, data resources, and the ability to leverage emergent technology," says Dr. Rich. "We decided that instead of a group of investigators working individually and perhaps in competition with each other with limited resources, why not form a group of investigators working along the same path?" Dr. Rich

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[20] Rich SS: Mapping genes in diabetes: genetic epidemiological perspective. <u>Diabetes</u> 39: 1315-1319, 1990.
[21] SEARCH for Diabetes in Youth Study Group, et al: The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. <u>Pediatrics</u> 118: 1510-1518, 2006.

accepted primary responsibility for writing the grant application that resulted in funding for and creation of the T1DGC. Subsequently, as chair of the T1DGC Steering Committee, Dr. Rich has worked to build consensus on the scientific directions and methods of the Consortium and overseen general operations.

Scientists and Families Working Together To Combat Type 1 Diabetes

The T1DGC represented a new paradigm of collaboration in the field of genetics research for type 1 diabetes. Dr. Rich points out that the Consortium made it possible to conduct research studies that could not have been accomplished in individual laboratories. He emphasizes, "No one investigator typically has the resources to collect an adequate number of samples to robustly investigate [genetic] risk. No one investigator typically has sufficient numbers of people who can clinically phenotype patients or perform the genetic analyses in a genome-wide, robust, unbiased way. No individual investigator typically would have the analytic, bioinformatic, and informatic infrastructure to handle this type of data." Moreover, the collaborative nature of the T1DGC gave researchers an opportunity to openly discuss complex problems with other leaders in the field without concerns about scientific competition.

T1DGC investigators recognized early on that the success of the Consortium's mission would rely not only on the willingness of scientists to work together but also on the voluntary participation of sufficient numbers of families affected by type 1 diabetes. Researchers estimated that genetic material would need to be collected from 4,000 families with at least two siblings affected by type 1 diabetes ("affected sib-pair families") in order to identify all genes that have a major effect on type 1 diabetes risk. After pooling samples that some investigators had already collected, the T1DGC would need to recruit at least 2,800 additional affected sib-pair families from around the world.

From the beginning, the T1DGC was sensitive to the concerns that potential participants in a genetics study might have regarding ethics, social and legal issues, and protection of their individual rights. Because those concerns differ not only across the United States, but also among different countries, the international T1DGC made a concerted effort to be transparent about the nature of the study and the rights of individual participants. Dr. Rich observes that these efforts paid off in terms of families' willingness to contribute their DNA to the T1DGC study, noting that "The overall impact on the research by the participation of these individuals has been phenomenal. Even though it was an extraordinarily hard task to identify 2,800 families to provide this [T1DGC] resource, whenever they've been identified, they've been willing to participate. And, I think part of this is the transparency and the understanding of the [participants'] needs and expectations."

A New Resource for Research on the Genetics of Type 1 Diabetes

According to Dr. Rich, a major accomplishment of the T1DGC has been the assembly of an unprecedented collection of material and data for research on the genetic causes of type 1 diabetes. In addition to the newly collected 2,800 sib-pair families, the Consortium has collected genetic materials from a large number of unrelated individuals with type 1 diabetes, as well as from individuals without the disease. Importantly, materials have been collected in populations that are thought to be at lower risk for type 1 diabetes, such as those of African American or Mexican American ancestry, in which little is known about the genetic causes of type 1 diabetes.

These materials, along with data from the genetic analyses conducted with the samples, are all available to the scientific community through the NIDDK repositories. In this way, Dr. Rich says, "The funding of the T1DGC is exponentially multiplied in terms of the leverage and the use of the materials that the [NIH] provided. People can access collections of DNA, plasma, and serum to perform additional studies without their having to invest in [collecting their own samples]."

The rapid evolution of technologies for genetic and genomic research that occurred over the past decade has made the T1DGC collection even more valuable than originally envisioned. Better technology, accompanied by a dramatic reduction in the cost of genotyping, allowed T1DGC researchers to accomplish their original goal of identifying all genes or gene regions that have a major effect on type 1 diabetes risk and also to search for genes that have a modest or small effect on risk. To date, the T1DGC and its collaborators have identified over 40 genes or gene regions associated with type 1 diabetes, bringing the total number of known regions to near 50—a far cry from the 3 genes that were known a decade ago when the Consortium was first envisioned.

"My feeling personally is that by having a type 1 diabetes genetics consortium, we've probably reduced the time that it may take to really identify the genetic bases of type 1 diabetes not by the 5-10 years that the consortium has been in existence, but probably by 20 years simply because we've been able to assemble the resources and make them available to everyone," stresses Dr. Rich.

Looking to the Future

The T1DGC directly examined differences at individual base pairs—called single nucleotide polymorphisms—to identify genes that influence type 1 diabetes risk. In addition, NIH solicits and supports research proposals from individual investigators to make use of the T1DGC collection for novel genetic studies. In fiscal year 2009, Dr. Rich and his collaborators were awarded two of five grants from NIDDK and with support from the *Special Diabetes Program* aimed at building on the T1DGC findings by fine-mapping and functional analysis of genetic and genomic contributors to type 1 diabetes risk. Dr. Rich's group is looking for structural variations in the genome, such as duplications, insertions, deletions, or rearrangements of DNA segments, that could contribute to risk. Other funded investigators are exploring the role of variants in gene expression or epigenetic modifications to the DNA in type 1 diabetes risk. Now that the T1DGC and its collaborators have identified the genes and genetic regions involved in type 1 diabetes, this new research will help us to understand how they exert their effects.

The T1DGC collection contains a renewable resource—existing clinical and genetic data as well as immortalized cell lines created for most participants supply unlimited amounts of DNA for analysis. Thus, valuable scientific insights resulting from the T1DGC collection will continue to accrue in the future as technologies for genetic research evolve. As Dr. Rich observes, "The T1DGC has been extraordinarily successful in performing genetic studies and providing resources to the scientific

community. But, the resources themselves are not finite in their utility. They are going to be critically important for the next phase of genetic research in type 1 diabetes." Thus, the collaboration and vision of the T1DGC investigators, coupled with the willing participation of thousands of people affected by diabetes, have transformed type 1 diabetes genetics research from the emerging, undeveloped field that Dr. Rich first entered 30 years ago to a vibrant field of research that continues to expand our understanding of the genetic risk factors and biochemical pathways involved in type 1 diabetes.

Patient Profile
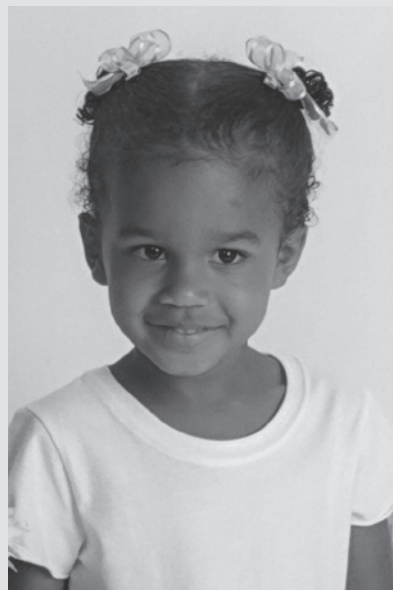
Nilia Olsen

Participating in TEDDY To Identify What Triggers Type 1 Diabetes in Children

Four-year-old Nilia Olsen has no idea she's participating in a study that has determined she has an elevated risk for developing type 1 diabetes. She just knows that, every 3 months, she goes to the doctor's office to have her blood drawn, and, of all things, "she loves it," says her mom, Sonya.

"She likes the different colors on the tops of the vials," says Sonya, referring to the collection vials for blood samples. "Her favorite color is pink, so she likes to fill that one up first."

Nilia is one of over 8,000 children participating in The Environmental Determinants of Diabetes in the Young study, otherwise known as TEDDY. TEDDY is led by the NIDDK and supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*. The international study's long-term goal is to try to identify infectious agents, dietary factors, or other environmental agents, including psychosocial factors, that trigger type 1 diabetes in genetically susceptible individuals or protect against the disease.

But such details don't concern Nilia right now. She's a typical little girl who attends pre-school, likes to dress up—as well as dig for worms. "She's high energy," her mother laughs.

Nilia Olsen

About the TEDDY Study

Researchers have discovered that children who develop type 1 diabetes have certain kinds of "high-risk" genes. Analyzing DNA from Nilia's blood shortly after she was born indicated that she was genetically at high risk to develop the disease. Researchers also know that some children with high-risk genes develop type 1 diabetes, while others don't. This has led them to think that something in the environment "triggers" or causes a child with high-risk genes to actually get type 1 diabetes. The purpose of TEDDY, therefore, is to try to identify the environmental triggers that cause children to get the disease. TEDDY has enrolled genetically susceptible newborns into the study from two populations: those with a sibling or parent with type 1 diabetes, and those from the general population with no family history of the disease. Nilia falls into the general population group because she has no family history of type 1 diabetes.

Like Nilia, the other children in this study, all of whom were identified within 3 months of their birth as being at high genetic risk for developing type 1 diabetes, will be followed until age 15. During that time, information will be collected about their diets, illnesses, allergies, and other life experiences. Blood samples will be collected every 3 months and stool samples will be collected monthly for the first 4 years. After 4 years, these samples will be collected every 6 months until the children turn 15 years old. Parents are also asked to fill out questionnaires at regular intervals, and to record events, such as illnesses, in the child's "TEDDY Book."

From these numerous samples and other information collected about the children, researchers hope to identify a factor or factors that lead some genetically predisposed children to develop type 1 diabetes while others do not. This information is critically important for identifying strategies for disease prevention. For example, if a virus were found to trigger type 1 diabetes, a vaccine could possibly be developed. If a dietary factor were found to be causative, then changes to children's diets could be made.

It is only through the dedicated efforts of families, such as the Olsen family, that the TEDDY study could be conducted. Responsibilities such as making regular doctor's visits for blood draws, taking monthly stool samples for 4 years, and keeping detailed notebooks with information about their child's health is no small task. It is clear that TEDDY families are dedicated to the study and its goals. This commitment can reap major rewards if an environmental trigger is discovered, which could pave the way toward being able to prevent type 1 diabetes and help future generations of children.

One Family's Experience with the TEDDY Study

The day after Nilia was born, Sonya was asked if her daughter's blood could be sampled for a study to see if the child had an elevated risk for type 1 diabetes. Although there is no history of type 1 diabetes in the family, Sonya was aware that nearly all of the women on her father's side have type 2 diabetes (formerly called adult-onset diabetes). Sonya immediately agreed and enrolled Nilia into TEDDY when researchers found that Nilia carried high-risk genes for type 1 diabetes.

"I don't have diabetes, and neither does my husband, Thomas," says Sonya. Thomas is in the military and was deployed to Iraq on his second tour of duty in October 2009. Beyond her daughter's increased genetic risk for type 1 diabetes, Sonya says that an additional motivation for her to enroll Nilia into TEDDY was "knowing that type 2 diabetes runs on my father's side of the family." Both forms of diabetes can lead to serious health complications.

At the time this profile was written, it's been 4 years since Nilia's blood was originally sampled, and although it was discovered that she has an elevated risk for developing type 1 diabetes, fortunately she remains diabetes-free. Sonya says that knowing Nilia has an elevated risk "was something that as a family we knew we would take in stride." Not only have they taken it in stride, they have remained dedicated to contributing to an important research study that can lead to new ways to prevent type 1 diabetes. According to TEDDY staff, Sonya has always gone the extra mile to do everything she could for TEDDY research, including participating in optional fun events designed to build community among local TEDDY

families. However, the Olsen family lived in Augusta, Georgia, when Nilia first entered the study. Since then, the family has been transferred by the military to Alabama. "The study staff has been very flexible," says Sonya. "We do everything through the mail. Every time Nilia's blood and stool samples get tested, they mail us the results. It's great. The continuity provides us with a sense of peace."

"I would strongly encourage other families to participate in clinical trials like TEDDY," says Sonya. "Knowing that our daughter is in a trial like TEDDY gives us a great deal of peace of mind."

As with all other study participants, the Olsen family was provided a calendar, "and we record whenever Nilia goes to the doctor," says Sonya. "We write down when she's sick and what kind of medication she may be taking. We record if she goes to the hospital." But so far, according to Sonya, Nilia has not had any hospitalizations or health issues related to diabetes. As for filling out the calendar and other paperwork related to the study, "It's not difficult, at all," says Sonya. "It just takes a few minutes to record."

Nilia may be a big reason the family is able to cope so well. At age 4, she is proving to be a real trooper when it comes to participating in the study. "Whenever she goes to the bathroom, she asks if she needs to poop in the cup," Sonya says, with a slight laugh. "And she's really good at having her blood drawn. She never cries about it and never has." In fact, Nilia is so good about having her blood drawn that she is featured in a video about blood draws for TEDDY that has been distributed to other TEDDY sites.

"I would strongly encourage other families to participate in clinical trials like TEDDY," says Sonya. "Knowing that our daughter is in a trial like TEDDY gives us a great deal of peace of mind."

Nilia's father, Thomas, calls home once a week from Iraq and asks how Nilia is doing. "It pleases me to be able to tell him she's doing well."

EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE *SPECIAL DIABETES PROGRAM*

The *Special Statutory Funding Program for Type 1 Diabetes Research* has fueled the emergence of a wide range of research opportunities. These opportunities were identified in a strategic planning process as being critically important for overcoming current barriers and achieving progress in diabetes research. Key questions and research opportunities relevant to type 1 diabetes, including those related to identifying the genetic and environmental causes of type 1 diabetes, are outlined in Appendix F.