## Why It Is Important To Find The Genetic and Environmental Causes of Type 1 Diabetes

- Unraveling the Complexities of Type 1 Diabetes
- Finding Culprit Genes and Their Role in Autoimmunity
- Consortia for Pooling of Genetic Resources and Talent
- Pursuit of Candidate Genes and Insights from Animal Models
- Environmental Factors
- Long-Term Studies
- Future Implications of This Research

## Patient Profile

Katie and Ellie Clark: Mother and Daughter Living with Type 1 Diabetes
Type 1 diabetes is an insidious, destructive, and costly disease that can strike anyone. Those who don’t have the disease usually know someone who does—a family member, friend, neighbor, or coworker. They ask themselves: “Am I also at risk for this disease, can I be tested for it, and how can I prevent it from striking me or my child? Are there any changes I could make to prevent the disease in my family?” Patients living with type 1 diabetes ask: “How did I get this disease? Do I have a bad form of the disease? Will my children or my grandchildren be likely to get it too?”

**WHY IT IS IMPORTANT TO IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES**

Unraveling the Complexities of Type 1 Diabetes

In type 1 diabetes, an interplay of genetic and environmental factors is at the root of the immune system’s misguided attack on the body’s insulin-producing cells (beta cells found in clusters within the pancreas called “islets”). Until these factors are completely deciphered, it will not be possible to know with certainty all those who are at risk for the disease and their specific risk profiles. This knowledge is urgently needed to develop and tailor the most effective clinical strategies for completely preventing the disease. This knowledge would also facilitate research aimed at reversing the disease as soon as possible after its onset—before complications take hold of the eyes, kidneys, nerves, heart, and other parts of the body.

Type 1 diabetes is an extremely complex disease, believed to involve many genes that work in concert and can have both large and small effects. If altered from their healthy state, the genes can cause a person to have a predisposition for the disease. When this genetic susceptibility is “triggered” by an environmental agent, the body’s immune defense system will then turn against itself. Ironically, when provoked, the normally protective immune system—which fights against bacteria, viruses, and other foreign invaders—will launch an assault on the body’s own insulin-producing cells. This immune system attack on “self” makes type 1 diabetes an “autoimmune” disease.

Finding Culprit Genes and Their Role in Autoimmunity

It is important to find out why some individuals develop type 1 diabetes, while others do not. The likelihood that a person will develop the disease is known to be higher the more closely related he or she is to someone who has type 1 diabetes. However, 80 percent of new patients with type 1 diabetes do not have close relatives with the disease (15). Moreover, even in identical twins, who have the same genetic makeup, it is possible for the disease to affect one, but not the other.

Many research advances have been achieved in the search for “culprit” genes, their variations, and their influence on the immune system. Strong evidence points to four genetic regions that contain suspect genes. However, both laboratory and clinical studies indicate that as many as 20 other regions may contain genes that influence disease susceptibility, and some of these genes may influence it only in certain populations. Moreover, it is possible that greater risk is conferred by specific gene combinations and gene-gene interactions, whereas smaller risk may accompany the presence and interplay of other genes. Teasing apart these differences is extremely difficult.

Research indicates that one of the implicated genetic regions (the major histocompatibility complex or “MHC”) may contribute up to 50 percent of the total genetic risk for type 1 diabetes. Moreover, the protein products of genes in this region are of central importance to the body’s immune response. It is possible that these gene products affect key immune system cells (T cells) leading them into attacking proteins in the pancreas as if they were invading bacteria or viruses. Other studies have confirmed that some people have a version of the insulin gene that makes them more susceptible to type 1 diabetes. In particular, they have shown that the degree of disease susceptibility is likely to be directly
influenced by the number of repeated elements in a region of this gene that regulates its expression. Still other research has revealed genes that dampen or eliminate proteins that protect the body against an aberrant immune response.

Consortia for Pooling of Genetic Resources and Talent

Type 1 diabetes research benefits greatly from generic, large-scale projects, such as the Human Genome Project, which have accelerated the study of genes and their function in health and disease. These types of broad efforts provide a knowledge base that can be greatly amplified by the addition of disease-specific genetic data, such as that being garnered by the ongoing NIH-funded international Type 1 Diabetes Genetics Consortium (T1DGC). The Consortium is collecting biosamples from 2,800 families in which two or more siblings have type 1 diabetes. This resource provides a powerful tool for unraveling the complex underpinnings of the disease, which will be interrogated through the combined expertise of many investigators. Analyses of large study groups offer the statistical power needed to identify and confirm genetic and environmental contributors to complex diseases. Such pooled resources increase the probability of not only defining genetic risk, but also identifying targets toward which new preventive strategies can be directed.

Pursuit of Candidate Genes and Insights from Animal Models

To narrow the gene hunt, researchers have identified and are continuing to focus their efforts on genes believed to be likely “candidates” for contributing to disease onset. Many additional candidate genes will be identified by general immunology studies, research on insulin-producing cells, and investigations of animal models that mirror type 1 diabetes in humans. Discovery of diabetes-causing genes in animal models will propel research on corresponding genes in human tissue samples, and will thus help to uncover the pathways in which the genes function. Every “culprit” gene and pathway that is identified represents a potential target for heading off the disease before its onslaught, or for intervening in the disease before it progresses to serious complications.

Environmental Factors

In parallel with the search for disease-causing genetic factors, it is imperative to uncover the environmental triggers that spark type 1 diabetes. Many people may have a genetic susceptibility to the disease, but may never actually develop it unless something in the environment initiates that genetic machinery. Environmental triggers remain elusive—although research suggests that viruses, diet, environmental toxins, and stress may be implicated. Observed patterns of disease outbreak, as well as seasonality of onset, lend support to the possibility that an infectious agent may act as a trigger. If a viral trigger is revealed, then a vaccine could possibly be developed to prevent disease onset in genetically susceptible individuals. Studies have also suggested that dietary factors, such as vitamins B and D, as well as certain fatty acids, may have protective effects, but more research is needed on the role of these and other dietary factors in disease development.

Importantly, the studies of environmental factors that play a role in type 1 diabetes may also contribute to understanding the development of other autoimmune diseases, such as celiac disease, which primarily affects the gastrointestinal tract. In the United States, the prevalence of celiac disease has been estimated to be approximately one percent (16). Some genes
confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Therefore, ongoing studies to identify environmental triggers of type 1 diabetes are also investigating development of celiac disease. These studies may uncover environmental factors initiating both disorders, benefitting not only patients with type 1 diabetes, but also people suffering from celiac disease.

**Long-Term Studies**

Very long-term studies are required to understand the causes and natural history of type 1 diabetes. Such lengthy studies are needed because environmental triggers of disease may occur in infancy and early childhood, but the disease’s onset may be later in childhood, adolescence, or early adulthood. Important efforts to this end are already under way in NIH-funded consortia and should be continued. Recently, scientists directing six independent studies of environmental triggers of type 1 diabetes in the United States and high-risk areas of Europe joined forces to create a united study (The Environmental Determinants of Diabetes in the Young [TEDDY]) with much greater power to uncover potential environmental triggers. Samples from the TEDDY study will be made widely available to researchers worldwide. Already, elimination of early exposure to one potential dietary trigger of type 1 diabetes, cow’s milk-based infant formula, is being tested in a clinical trial (Trial to Reduce IDDM in the Genetically at Risk [TRIGR]). While costly, such long-term studies could answer critically important questions about disease risk and onset. The payoff for this substantial investment could be huge—such as a vaccine against an infectious trigger, or dietary change that might protect against development of type 1 diabetes.

**Future Implications of This Research**

With new insights into the interplay of genetic-environmental factors and immune mechanisms in type 1 diabetes, researchers may be able to identify with great precision those individuals at risk for the disease, and to develop and test prevention-oriented strategies. It is possible, for example, that such new knowledge could point the way toward the screening of newborns, and to even more widespread screening to identify individuals at risk in the general population. This knowledge would facilitate the design of more specific clinical trials for testing interventions specifically tailored to patients with similar risk profiles. If researchers find that an infectious agent is an environmental trigger of the disease, efforts could be directed toward the development of a preventive vaccine. Alternatively, if a dietary component is found to be causative or protective, individuals at risk could take steps to either eliminate or add it to their diets. These are just a few examples of the enormously important and practical strides forward that can be envisioned and possibly attained once the underlying causes of type 1 diabetes are fully delineated.

Diabetes is an extremely costly disease to treat in both human and financial terms. It places an enormous burden on families and on the U.S. health care system. By pinpointing the constellation of type 1 diabetes disease genes, their environmental triggers, and their cascading effects on the immune system, researchers may be able to entirely prevent or reverse disease onset. Combating the disease at the front end is especially beneficial, because early steps could preclude or arrest the development of disease complications—including kidney failure, blindness, lower limb amputations, heart attacks, and strokes. Research on the underpinnings of the disease thus offers the real hope of preventing type 1 diabetes from ever ravaging the body. For individuals at risk, it would clearly be far better to completely prevent the disease than to undergo a difficult and suboptimal treatment regimen of daily insulin administration after the disease has begun wreaking havoc within the body. Likewise, the Nation as a whole would benefit from building a sound knowledge base for developing prevention-oriented strategies.
Katie Clark spent weeks denying her 5-year-old daughter’s symptoms of type 1 diabetes. Up to that point, Katie thought that the fact that everyone wanted to touch Ellie’s beautiful curly blond hair would be her daughter’s burden to bear. She was wrong.

When sugar was found in Ellie’s urine on what was supposed to be her first day at a new preschool, Katie learned that Ellie had type 1 diabetes. Katie was devastated. She spent her 30th birthday at the hospital, and was deeply depressed for most of the next 2 weeks. She was also so very angry. “Anger isn’t the most common emotion at the beginning,” Katie observes. “However, we’re not new to the disease. I’ve had type 1 diabetes for 28 years.”

At the time this profile was written, 10 months after being diagnosed, Ellie had already suffered many unwanted side effects from disease treatment. She had calluses on her fingers. Her bottom had scar tissue from her insulin pump sites. She had undergone 1,494 finger pricks and 98 pump site changes. Ellie’s insulin pump site must be changed every three days. Ellie will ask, out of the blue, “Is it day three?” Katie laments, “I cannot tell you how heartbreaking it is for me to see my daughter worrying about an impending pump site change. There is relief on her face on those days when we can say, ‘No honey, not today.’ The devastation in her eyes is almost more than I can stand when we have to say, ‘Yes, today is day three, sweetheart.’” Katie is concerned that “Ellie is spending her time worrying about diabetes when she should be playing with her baby dolls and learning to read.”

One of the greatest difficulties Katie finds in dealing with Ellie’s disease is knowing firsthand the challenges that Ellie will face as she grows up. Katie knows just how type 1 diabetes will affect every detail of Ellie’s life. Katie states, “There is no escape...there are no vacations from type 1 diabetes.” Ellie will have to endure constant finger sticks and worry about when her next meal will be. Like Katie, Ellie is at risk of developing devastating disease complications, such as blindness, kidney disease, and heart disease, which could ultimately reduce her life span by approximately 15 years. Katie recalls, “I can very vividly remember reading a magazine article about the complications of diabetes when I was 8 years old. I was horrified. I can see Ellie will be going through these same thoughts and dealing with these same issues, and it’s horrible. This is not the life I dreamt of for my precious daughter.”

Other less common but very memorable events will leave their imprint as well, as they have during some of the happiest moments of Katie’s life. Recalling the insulin reaction she had on her wedding day, Katie laments, “My newly styled hair got messed up, and orange juice I needed to take immediately to adjust my blood sugar level was spilled on my veil.” For each of her pregnancies, Katie saw her high-risk pregnancy obstetrician once a week, and in the months leading up to the births, she saw her doctors twice a week. While in labor, Katie was forced to check her blood sugar every hour. After

“\textbf{This is not the life I dreamt of for my precious daughter.}”
the births, the nurses whisked the babies away to check their blood sugar levels, because newborns of mothers with diabetes often have low blood sugar (hypoglycemia). The nurses had to put a tube down their throats to pump sugar into their stomachs to normalize their blood sugar levels.

Ellie’s diabetes hits Katie and her husband particularly hard when they’re tucking Ellie into bed at night. That’s when she asks questions such as: “Mommy, why do some people get diabetes and some people don’t?” Or she says, “Daddy, I don’t want diabetes anymore.” Katie and her husband face a new challenge, now that Ellie has begun school. “We have to teach Ellie’s teachers how to take care of her,” Katie observes.

The Clarks dream of giving Ellie back the life she was living before her diagnosis and having a future brighter than one clouded by diabetes. “I’d give everything I have—even my own life—for Ellie not to have to endure another day of this dreadful disease,” Katie stresses. “We must do everything we can to find a cure. Our sweet little girl with the curls deserves it.”

Hope Through Research

In type 1 diabetes, a genetic predisposition for the disease is believed to be triggered by environmental factors. Researchers have already identified genetic regions that play a key role in disease development. However, there are other important genes that have not yet been identified, and it is still unclear how gene-environment interactions may promote the disease. Therefore, the NIH is supporting multifaceted research efforts to uncover important genes and environmental factors that promote the onset of, or confer resistance to, type 1 diabetes. For example, the T1DGC is a monumental effort to analyze the genetic makeup of families in which two or more siblings have type 1 diabetes to determine which genes confer disease susceptibility. Because not just a single gene "causes" type 1 diabetes, this type of large-scale effort is crucial to understanding the complex genetic underpinnings of the disease. Another example is a multicenter, multinational, NIH-funded epidemiological study called TEDDY. In this study, researchers are following newborns who are known to be genetically at risk for developing type 1 diabetes until they are 15 years old, to see who develops the disease. Researchers will use the population to pinpoint the environmental factors that either triggered the disease or provided protection from it. An NIDDK website describes opportunities for patients and family members to enroll in these and other type 1 diabetes clinical research studies: www.T1Diabetes.nih.gov/patient.

How will new knowledge about genes and environmental triggers help patients with type 1 diabetes, like Katie and Ellie Clark? The potential for this research to positively affect the lives of patients with type 1 diabetes is far-reaching. Genetic and environmental factors identified through these research efforts could be used as targets for researchers to develop novel disease prevention strategies. If a certain virus were found to contribute to disease onset, researchers could pursue the development of a vaccine against the virus. In addition, knowledge about which genes are passed down from one generation to the next will allow researchers to more easily identify who is at high risk for developing the disease, and therefore, intervene earlier in the disease process, before the destruction of insulin-producing beta cells even starts. Preventing disease onset means that children like Ellie would never have to endure the thousands of finger sticks or pump changes/insulin injections that are now part of their everyday lives. Disease prevention also prevents the development of life-threatening complications. Therefore, pursuing research on the genetic underpinnings and environmental triggers of type 1 diabetes has great potential for allowing children, like Ellie, to live the life that their parents dreamt for them.