The performance of genes contributing to a person's risk of developing diabetes has been difficult to determine. The development of diabetes is complex and multifactorial involving genetics (alleles, or genetic variants), nutrition, activity level and the nutritional status and neonatal environment during gestation. However, people with an affected parent have a 3.5 fold risk of developing Diabetes compared to individuals with no affected family members.1 Despite the powerful role played by genetics in the development of diabetes, geneticists have failed to find a single diabetes gene. In the early 1980s, after the breakthrough in the understanding of childhood diabetes, the hunt for other underlying genetic causes for diabetes started.

Diabetes in most people has been characterized into type-1, type-1.5 or type-2.2 Other forms of insulin resistant Diabetes also can be seen in gestational Diabetes, polycystic ovary disease, acanthosis nigricans, and Maturity-Onset Diabetes of the Young or MODY. These rare forms like MODY are inherited in a Mendelian manner either dominant (needing one of two mutant alleles) or recessive (needing two of two mutant alleles). Insulin resistant Diabetes can also be unmasked by medications like prednisone. In rare cases, nonresistant forms of Diabetes may also be seen following trauma to the pancreas or pancreatic surgery.3

Nearly 20 different regions of the genome may be involved in genetic susceptibility to type-1 Diabetes (T1D). Two of the best studied genes in type-1 Diabetes are the HLA (human leukocyte antigen) region and the insulin gene. The HLA region has several hundred genes which are known to be involved in immune response. Those most strongly associated with the disease are the HLA class II genes (i.e., HLA-DR, DQ, DP).2 There are at least two genes in the HLA region (HLA-DQB1, locus: 6p21.3) that account for 40 to 50 percent of the diabetes risk that people inherit from their parents. Different versions (or alleles) of these genes called DR can put a person at risk for or prevent them from developing type-1 Diabetes. People can inherit one form of DR from their mother and one form of DR from their father. It is the combination of these two forms of the gene that determine a person's overall risk. Two forms of DR, designated DR3 and DR4, are present in 95 percent of type-1 Diabetics, and 30 percent have inherited both DR3 and DR4. The two alleles DR3 and DR4 alleles cause slight differences in the disease.4 People who inherit DR3 (but not DR4) develop Diabetes at an older age, and tend to have antibodies against pancreatic beta cells but not against insulin. These people are also more likely to develop thyroid autoimmune disease. People with allele DR4 (but not DR3) tend to develop diabetes earlier in life and have an immune reaction against insulin. People with both alleles DR3 and DR4 develop diabetes at the youngest age and have the highest levels of antibodies against insulin. In terms of absolute risk, Caucasian individuals with two susceptibility haplotypes have an approximately 6% chance of developing T1D through age 35 years compared to < 1% among Asians.

In addition to these genes, two other genes are now known to influence T1D risk, INS (locus:11p15.5) and CTLA (locus: 42q31-35).5

The changes in insulin gene located on chromosome 11p15.5, has been designated as IDDM2. This region, determines how much insulin the gene makes. It is composed of a repeated section of DNA called the Variable Number of Tandem Repeats (VNTR). Patients with smaller VNTR regions are two to five times more likely to develop type 1 Diabetes than a person with at least one long VNTR. The longer (protective) VNTR region seems to decrease the amount of insulin produced in the pancreas as well as protects a person from developing Diabetes. It has also been found that during development the longer VNTR causes more insulin to be produced. Researchers think that when developing immune cells are exposed to high levels of insulin, they learn to identify insulin and are less likely to react against it and cause diabetes later in life.6 Recent studies of the insulin gene locus demonstrate that the allele “C” of the -2221Msp(C/T) and “A” -23HphI(A/T) insulin gene polymorphisms confer susceptibility to T1D.7

The CTLA-4 (cytotoxic T lymphocyte-associated 4) gene, located on chromosome 2q31-35 has been found associated with T1D. Its Thr17Ala variant may increase T1D risk. CTLA-4 negatively regulates T-cell function and its variants have also been associated with other autoimmune diseases.5
type-2 Diabetes (T2D) is more common in some ethnic groups. Although researchers deduce from studying family histories that one can inherit a risk for type-2 diabetes, it has been difficult to identify specific gene mutations that cause the disease. Many genes are involved in controlling body's fuel intake and regulation. Mutation in any one gene will probably not lead to diabetes, but mutations in several genes could add up to pose an increased risk. Any two people with type-2 diabetes may have mutations in a different subset of genes, making it difficult to identify or pin point a single gene. One well studied gene is the Beta3-adrenergic receptor gene. The Beta3-adrenergic receptor gene makes a protein in fat cells that is involved in determining how much energy body uses in the resting state. A mutation in this gene slows the process of fat burning, increasing the tendency of such person to be obese. One specific mutation in this gene, called TRP64ARG, is almost four times more common in Pima Indians than in people of European descent, and is one and a half times more common in people of African or Mexican descent. The prevalence of the TRP64ARG gene mutation probably accounts at least in part for a higher rate of type-2 Diabetes in these populations. People with two copies of the TRP64ARG mutation tend to be more obese because of slower metabolism than people without the mutation even if they do not go on to develop Diabetes. They also have a harder time losing weight than the general population. In addition, people with the TRP64ARG mutation develop diabetes at an earlier age than type-2 Diabetics without the mutation. This mutation is not present in all type-2 Diabetics, but it appears to change the course of diabetes in those who carry it. The TRP64ARG mutation causes the Beta3-adrenergic receptor gene to make a different protein sequence that has the amino acid Arginine (ARG) at the 64th position instead of Tryptophan (TRP). Researchers think that mutations in similar genes like Beta3-adrenergic receptor gene may also put a person at risk for diabetes. With this ongoing research in high-risk groups and families researchers will be able to find additional gene mutations. Other candidates contributing are PPARγ (peroxisome proliferator-activated receptor-γ), the gene important in adipocyte and lipid metabolism, increases T2D risk by several fold in Europeans, 98% of whom carry at least one copy of the Pro allele ABCC8 (ATP binding cassette, subfamily C, member 8), is another identified which is part of the ATP-sensitive potassium channel, which plays a key role in regulating the release of hormones, such as insulin and glucagon, in the beta cell. Since this gene is located near the INS gene, current studies are evaluating whether they work in concert with each other, or rather have an independent effect on T2D susceptibility. Another contributing candidate is CAPN10 (calpain 10)U. CAPN10 encodes an intracellular calcium-dependent cysteine protease that is ubiquitously expressed. Studies from different ethnic groups indicate that the contribution of this locus to increased T2D risk may be much larger in Mexican-American than Caucasian populations.

Maturity-Onset Diabetes of the Young (MODY) is the cause of an uncommon form of T2D (accounting for <5% of all T2D cases) that generally occurs before age 25 years. Because of advances in molecular genetics, it is now known that there are at least six forms of MODY, each of which caused by a mutation in a different gene that is directly involved with beta cell function. Because approximately 15% of MODY patients do not carry mutations in one of these genes, it is anticipated that other genes that cause MODY will be discovered in the near future. Studies on identical twins reveal that often one twin develops type-1 diabetes while the other twin remains disease-free.

The critical difference between health and disease might thus reside not in an individual's genetic blueprint but in how those genes are "expressed", that is how the translation of genetic information into proteins or RNA is switched on and off during disease progression. Most of us can help keep ourselves from developing diabetes by remaining lean and physically active. We cannot do anything about the effects of our genetics or our maternal and neonatal environment, but we can choose to have a healthy diet and lifestyle.

REFERENCES


