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Facing Your Genetic Destiny

The use of predictive genetic tests is still limited to a handful of relatively rare and highly hereditary diseases, but that's about to change

By Sergio Pistoì

Marina, a young woman living near Varese, Italy, stood chatting with her neighbors one day two years ago when she suddenly dropped to the floor, clutching her chest. People around her panicked. But after a seemingly endless second, a violent spasm shook her body and Marina awakened. She was shocked but alive and well.

For doctors at the local hospital, the diagnosis was easy: Marina had suffered from ventricular fibrillation, a potentially lethal block of the heart muscle. After a quick checkup, she returned to her normal life. But this was no miracle: Marina survived because she was aware of a defect in her heart and took the necessary precautions.

| TYPES OF GENETIC TESTS | |
|-------------------------------|---|
| DIAGNOSTIC TESTS: | establish or confirm the diagnosis for an individual already affected. |
| PRE-SYMPTOMATIC TESTS: | tell with certainty if someone will develop some disease in the future. This category includes the test for Huntington's disease. |
| PREDICTIVE TESTS: | can indicate an increased risk for a disease but cannot tell if and when a person will be affected. |

Indeed, years before, two of her sisters had died from a rare inherited disease called stress-induced polymorphic ventricular tachycardia (VTSIP). People with this disease are at risk of fibrillation at any moment but especially after physical or emotional stress. Standard exams, such as an electrocardiogram, are usually unable to reveal the condition, but a genetic test can.

"VTSIP is caused by mutations in a gene called Ryr-2 that regulates the electric activity of the heart," says Silvia Priori, a cardiologist at the Maugeri Foundation in Pavia, Italy, who discovered the genetic alteration together with colleagues about three years ago. When doctors performed the gene test on Marina's DNA, they discovered that she carried the defective form of the gene. "Her risk of a having a heart attack was high," Priori says--"about 70 percent" during her lifetime.

So before any life-threatening symptoms could appear, Marina and another sister, who also tested positive, had miniature automatic defibrillators implanted in their chests. When Marina's heart fibrillated in front of her neighbors, the lifesaving device was able to jump-start the organ. An ambulance, and a regular defibrillator, would have probably arrived too late.

Know Your Genes, Save Your Life

Marina's story is an extreme example of a gene test that made a difference between life and death. But like Marina, hundreds of people around the world take advantage of genetic testing to detect and alter the course of various disorders. For example, hereditary hemochromatosis, or "iron disease," causes a slow accumulation of iron in many organs. Among Caucasians, it affects about 1 in 300 people, resulting in liver damage, diabetes and impotence after their 40s or 50s. Genetic testing can spot the disease in children or young adults before symptoms appear, and regular bloodletting can then prevent the condition's consequences.

The use of predictive gene tests is still limited to a handful of relatively rare and highly hereditary diseases. But that scenario is about to change: scientists in academic and corporate laboratories are tirelessly digging through human DNA to find genetic variations that make individuals susceptible to common diseases, including Alzheimer's, cancer, cardiovascular diseases, diabetes and stroke. Whereas today doctors calculate our risk profile for disease using a few one-size-fits-all parameters, such as cholesterol levels, blood pressure and the number of cigarettes we smoke, tomorrow they might instead consider our complex, and personalized, genetic risk pattern.

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| RISKY ANTIGENS | | |
|------------------------|-----------|----------|
| DISEASE | HLA TYPE | RISK |
| Ankylosing spondylitis | | |
| Uveitis and arthritis | B27 | 40 - 70x |
| Juvenile diabetes | DR 3/4 | 15x |
| Rheumatoid arthritis | DR4 | 6 - 14x |
| Psoriasis | Cw6 | 13x |
| Celiac disease | DRB1*0301 | 11x |
| Multiple sclerosis | DRB1*1501 | 6x |

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Perseus 2001, modified

French Nobel laureate Jean Dausset was first to see the predictive value of genetic testing. "[...]medicine was, in its history, first of all curative, then preventive and finally predictive, whereas today the order is reversed: initially predictive, then preventive and finally, only in desperation, curative," he wrote. In the 1960s Dausset discovered the HLA antigens, molecules on the surface of white blood cells that are necessary for the immune response. The same antigens determine whether a transplanted organ will be rejected, which explains why it is often difficult to find a match: there are many genetically determined HLA "flavors."

Dausset found that certain HLA flavors were often associated with inflammatory and autoimmune diseases, such as juvenile diabetes or rheumatoid arthritis (see chart). For example, one in five people carrying a version of HLA called B27 will develop ankylosing spondylitis, an inflammatory disease of the vertebrae. And subsequent studies on twins and families have revealed strong hereditary components to virtually all common disorders--from diabetes, asthma, hypertension and cancer to many mental disorders, including depression, schizophrenia and autism.

Criminal Gangs

Geneticists distinguish between monogenic disorders--in which a single gene rules as an absolute master--and multifactorial disorders. The latter result from "criminal gangs" of genes--often tens of them--and the influence of environmental variables, such as diet and smoking habits, as well as infections or contact with toxic agents.

Thousands of known monogenic diseases, such as cystic fibrosis, muscular dystrophies and retinitis pigmentosa, are caused by single defective genes and are inherited in a predictable way, according to the classic laws of Mendelian genetics. Testing for monogenic diseases, when available, gives clear-cut results: people with the bad copy of the gene will generally manifest symptoms.

But most common disorders are instead multifactorial. Individual genetic variations may render someone susceptible, but they are neither necessary nor sufficient to cause such a disease. People with a genetic tendency toward diabetes, for example, have an increased statistical chance of being affected one day but are also likely to live in good health to a ripe old age. On the other hand, people without any evident predisposition may become diabetics, against all odds. Therefore, genetic tests for multifactorial disorders give only an estimated risk; they will never indicate whether the disease will actually develop.

Probing the Genomic Minefield

During this past decade, thanks to the advances of the Human Genome Project and improved techniques, scientists have started to extricate from a tangle of genetic and environmental factors the causes of many multifactorial diseases. "Researchers have developed more and more effective ways to pinpoint significant variations in the genome," says Dale R. Pfof, CEO at Orchid, a company based in Princeton, N.J., that specializes in the analysis of genetic diversity.

For years geneticists have been using polymorphic markers--regions of DNA that are extremely variable among individuals--as signposts along the genome. Using a method called linkage, for example, researchers can look for markers that are common among the diseased individuals of one family and not their healthy relatives. Because DNA regions that are close to each other in the chromosome are usually inherited together, disease genes are expected to lie near these markers.

"The density of markers in the genome has increased dramatically in the last years, allowing more and more accurate analysis," Pfof explains. Researchers have identified hundreds of gene variations that predispose their carriers to common disorders. For instance, a particular form of the gene coding for angiotensinogen--an important blood pressure regulator--is carried by 35 percent of Caucasians and triples the risk of hypertension and heart attack. The good news is that the same variation makes these people more responsive to preventive measures in the form of low-sodium



TWIN STUDIES have revealed a great deal about hereditary conditions.

diets and a class of anti-hypertensive drugs called ACE-inhibitors.

But the revolution in genetic research could soon send the old markers in search of pensions. Most genetic differences between individuals are a result of variations in single "letters" of the DNA, variations that scientists call single nucleotide polymorphisms, or SNPs. Using new techniques, researchers can home in on the SNPs that are associated with specific diseases and analyze thousands of variations in minutes (see part II of this story next week for more on this subject). In the not-too-distant future, your doctor will test for your genetic profile as easily as he screens your cholesterol levels today.

The Boomerang Effect

What is the real utility of a predictive test? It depends, geneticists say. A test is useful when it warns about a serious and clear risk of disease and, most of all, when there is a real possibility of preventing it, as in Marina's case. But the same information can boomerang when no countermeasure is at hand. Learning simply that a disease may or may not occur can lead to undue anxiety and limitations in our lives. Even worse, the results of such a test might give employers or insurance companies new grounds for discrimination.

Today only a few genetic tests escape from this boomerang effect. They include susceptibility tests for certain cancers among people with strong family histories of the disease. Analyses of *BRCA1* and *BRCA2* or *MLH1* and *MSH2* genes, for example, reveal high risks of breast and ovarian cancer or colorectal cancer. In both cases, preventive options exist. Another susceptibility test for multiple endocrine neoplasia (MEN)--a rare cancer of the thyroid--is particularly useful: people with a mutation in a gene called *Ret*--which practically guarantees that they will develop MEN--can have their thyroid glands removed before the cancer arises.



BOOMERANG EFFECT: The results of genetic testing can boomerang, producing more worry than useful information.

But not all susceptibility tests are so successful. Take, for instance, a test for Alzheimer's disease. In 1993, after years of difficult work, researchers discovered that people with a variant of the gene for the fat-transporter apolipoprotein E, ApoE(4), face a 10-fold risk of Alzheimer's. Excitement for the discovery waned, however, when it became clear that up to 70 percent of all people with the ApoE variant would never develop the disease. Again, it is the boomerang effect: about 15 percent of all Caucasians carry the "bad" ApoE(4) version, but they hardly need to know that before an effective prevention becomes available. For this reason, guidelines from expert groups in Europe and in the U.S. recommend that the ApoE exam be used to confirm the disease in affected individuals but not as a predictive test in healthy people.

More generally, experts agree that the utility of a predictive test depends on the possibility of an effective prevention. Most likely, a growing number of diseases will be preventable in the future with drugs, vaccines, or gene therapies and stem cell transplants. When that happens, many predictive tests, which now are useless and even dangerous, will become powerful tools for helping us to secure our health.

IN PART II OF THIS STORY:

Available at www.sciam.com beginning next Monday, February 25, 2002

- How SNP hunters are reshaping the future of genetics.
- Reading your destiny using genetic chip technology.
- Genetically tailored medical treatment: Is it around the corner?

FURTHER READING:

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