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## **RESEARCHERS FIND THAT VARIATIONS IN FOUR INFLAMMATORY GENES MAY PREDISPOSE MEXICAN AMERICANS TO INSULIN RESISTANCE, A PRECURSOR OF DIABETES**

LOS ANGELES (June 11, 2005, 10:00 a.m., PDT) – Although numerous studies have shown that low-grade inflammation is linked to heart disease and diabetes, more recent studies have shown that inflammation plays a role in insulin resistance, a syndrome that leads to diabetes and heart disease and affects about one in four adults in the United States. But exactly how inflammation triggers insulin resistance is not fully understood.

Now, researchers at Cedars-Sinai Medical Center and the University of California, Los Angeles, have found that variations in four genes that control inflammation are linked to insulin resistance, the precursor of diabetes, in Mexican Americans. Their findings, reported at the American Diabetes Association's 65<sup>th</sup> Annual Scientific Sessions, may enable physicians to identify patients at the highest risk for developing diabetes and to design therapies that target these genes to prevent insulin resistance.

“This study is the first to show that four inflammatory pathway genes – IL4, IL4R, IL6 and C5 – contribute to the development of insulin resistance,” said Jerome I. Rotter, M.D., director of research, Medical Genetics Institute at Cedars-Sinai Medical Center.

Low-grade inflammation originates in numerous places throughout the body, including excess fat, and is often triggered by some type of injury or infection. In heart disease, the idea is that the coronary arteries become inflamed, causing the plaque or fatty build-up in the arteries to rupture. But because the inflammation is internal and not “seen,” doctors use a simple blood test to measure for high levels of C-reactive protein (CRP) – a marker for inflammation. High levels of CRP are linked to an increased risk of heart attack, stroke, diabetes and more recently, insulin resistance.

Insulin, which is secreted by the pancreas, helps cells to take in glucose and convert it to energy. Insulin resistance occurs when muscle, fat, and liver cells do not use insulin properly. As a result, the pancreas tries to keep up with the demand for insulin by producing more, causing excess sugar to build up in the blood. Over time, insulin resistance leads to heart disease, diabetes, high blood pressure, obesity and polycystic ovarian syndrome. In fact, about 25 percent – 68 million – adult Americans have insulin resistance, with Mexican Americans having the highest prevalence.

“Because insulin resistance and heart disease are so common in the Mexican American population and we know that chronic low-grade inflammation is associated with these diseases, our group wanted to investigate whether specific inflammatory genes might be involved,” Rotter said.

To determine whether specific variations in the genes that control inflammatory responses were directly linked to insulin resistance, researchers at Cedars-Sinai and the University of California, Los Angeles, studied a large, high-risk population of Mexican Americans. Using the most precise diagnostic and genetic tests, the

tests, the investigators examined the link between variations in 31 of the most common inflammatory genes and insulin resistance.

The researchers examined the DNA of 656 Mexican American family members participating in the study and identified 41 variations in the 31 inflammatory genes. Among these family members, 394 adult offspring and their spouses were then tested for insulin sensitivity with the glucose clamp, the most precise diagnostic test for insulin resistance, by receiving an infusion of insulin in one arm over a two-hour period. At the same time, blood samples were drawn from the other arm to measure how much glucose was present in the blood. Depending on blood glucose levels, sugar was added to see how well the cells used it. Patients were found to be less insulin resistant when the samples showed low blood sugar levels even when glucose was added, indicating that the cells were taking up glucose. However, when little or no glucose needed to be added, the patients were found to be insulin resistant, i.e., their blood sugar levels remained too high, indicating that the cells were not using the glucose as they should.

The investigators then compared patients' level of insulin resistance to each of the 41 inflammatory gene variations. They found that four specific gene variations were significantly linked with high levels of insulin resistance. Among these inflammatory genes, IL4, IL4R and C5 were found to have significant variation despite the patient's age, sex, or body mass index (BMI), while variations in IL6 affected insulin resistance only through excess body fat.

“Essentially, our study shows that these inflammatory genes cause insulin resistance,” Rotter said. “In other words, it appears that low grade inflammation causes insulin resistance and is not just a consequence of insulin resistance.”

To be doubly certain that these gene variations were linked to insulin resistance, the investigators analyzed larger portions, or haplotypes, of both IL4 and IL6. Haplotypes represent the majority of common variation passed down in families, encompassing sections of the gene that have remained unbroken by evolution over time. Consequently, haplotypes are more likely to identify disease associations than single gene variations. The researchers found that insulin resistance was associated with the fourth most common haplotype of the IL4 gene and the most common haplotype of the IL6 gene, providing further support for the involvement of these genes.

“These data suggest that the relationship between chronic inflammation and insulin resistance, as well as that between these inflammatory markers and the later development of Type 2 diabetes, may well have a genetic basis encompassing such inflammation genes as IL4, IL4R, IL5 and C5,” Rotter said.

Future studies will investigate the role these genes play in the development of insulin resistance, diabetes and heart disease.

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One of only four hospitals in California whose nurses have been honored with the prestigious Magnet designation, Cedars-Sinai Medical Center is one of the largest non-profit academic medical centers in the Western United States. For 17 consecutive years, it has been named Los Angeles' most preferred hospital for all health needs in an independent survey of area residents. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. It ranks among the top 10 non-university hospitals in the nation for its research activities and was recently fully accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). Additional information is available at [www.csmc.edu](http://www.csmc.edu).

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