An island in the Mediterranean is furthering diabetes research in New Jersey

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Lisa Denzin, left, is working with postdoctoral research fellow and former Sardinian graduate student Francesca Virdis, to understandthe role of DM in preventing the development of type 1 diabetes in humans." Credit: John Emerson

One look at Sardinia's white-sand beaches and turquoise water would lead you to assume that this part of the world is devoted entirely to

idyllic getaways and sun-filled vacations. You'd never guess that the island's population is also contributing evidence to diabetes research in the United States. Geneticists from Sardinia – the second-largest island in the Mediterranean, with a population of a little more than one and a half million – are working with Lisa Denzin, and associate professor of pediatrics at Rutgers Robert Wood Johnson Medical School and resident scientist, Child Health Institute of New Jersey, to understand the genetic underpinnings that trigger type 1 diabetes mellitus.

Why Sardinia?

Sardinians suffer from the world's second-highest rate of type 1 diabetes – one of the most common chronic childhood diseases, which results from an autoimmune destruction of insulin-producing beta cells. Since 1990, the Insulin-Dependent Diabetes Mellitus Sardinia Project has been investigating preclinical phases of type 1 diabetes in a large cohort of people. The goal is to learn why some people who are genetically at risk for type 1 diabetes don't develop the disease.

There's another reason Sardinia is the perfect location for this research. The island has proved to be a rich source of data mining for this and other projects because of its isolated population. It's simpler to investigate the environmental, immunological, and genetic factors related to the cause and development of diseases such as type 1 diabetes.

Understanding the disease

"Most autoimmune diseases' genetic susceptibility is linked to genes in the major histocompatibility complex (MHC) called human leukocyte antigens (HLA)," says Dr. Denzin. The HLA genes control and regulate the immune system. "There are HLA class I and class II genes, and the class II genes have a stronger link to autoimmunity," she adds. Although

50 percent of genetic components are linked to HLA molecules, other genes in the MHC are also involved. "Because HLAs occur in so many different forms, the diversity makes them difficult to study in terms of autoimmune disease," says Denzin. The Sardinian team was interested in knowing if not only HLA class II genes but also other genes encoded within the MHC region were mediating protection from developing type 1 diabetes.

When the Italian geneticists mapped the genes further, they discovered that an allele of a gene encoding a protein that Dr. Denzin's laboratory works on – called DM – is associated with protection from type 1 diabetes. DM controls the presentation of HLA class II proteins at the cell surface – known to trigger immunity. Finding a specific allele of DM that is mediating protection from type 1 diabetes suggests that this allele – or version of DM – might in fact alter this process, thereby leading to protection.

Opening the door to collaboration

Dr. Denzin was approached by Sardinian researchers Francesco Cucca, a physician professor of medical genetics, University of Sassari, Italy, and director of the National Research Council of Italy's Institute of Genetic and Biomedical Research, and Valeria Orrú, permanent researcher, University of Cagliari, Italy. "We received an email from Dr. Orrú expressing an interest in our mouse model results – where we showed if we altered activity of the DM protein, we could protect a non-obese diabetic mouse for diabetes," says Dr. Denzin. "They suggested to us that modulating DM activity could be the mechanism by which the people in the Sardinian study are protected from type I diabetes."

The partnership of the labs was formalized when Francesca Virdis, a former Sardinian graduate student of Orrú's, became part of the project, working in Denzin's lab as a postdoctoral research fellow. Virdis's goal is

to use biochemical and cell biological assays established in Dr. Denzin's lab to answer the question of altered activity. "If we can show that this DM has altered function, we could make a significant discovery in type 1 diabetes," says Denzin.

A potential druggable target for type 1 diabetes

"HLA class II and DM are needed to fight infection, so you can't simply get rid of them. What's important about this idea is that rather than trying to eliminate molecules, we simply change the way they function," says Dr. Denzin. "DM could be a druggable target. Potentially changing the way the molecule works might be enough." A protective genetic variant could lead to a useful treatment. "Usually people are looking for lots of things," says Denzin. "We're fortunate to be focusing on one specific molecule to find an answer.."

The data from these experiments represent steps toward understanding the role of DM in preventing the development of type 1 diabetes in humans.

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