Geneticists hunt for scleroderma triggers

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At its most benign, the autoimmune disease scleroderma can discolor parts of the skin of its sufferers. At its most pernicious, it can thicken and harden their skin, their blood vessels, and their internal organs before, in many cases, killing them.

In all its forms, scleroderma gives Dartmouth geneticist Michael Whitfield, his graduate students, and his postdoctoral researchers a sense of urgency in their search for the triggers of the chronic condition. In a study that the Journal of Investigative Dermatology published in its October 2009 edition, Whitfield's team reports a closer connection between a gene profile for the profibrotic pathway TGF-beta and a tendency in some scleroderma sufferers to develop lung problems. Jennifer Sargent, who recently earned her Ph.D. in molecular and cellular biology from DMS, is lead author of the study, which analyzed the previously-identified TGF-beta pathway signature in skin biopsies from patients and healthy control subjects from around the country.

"The finding that a gene signature expressed in skin is associated with the occurrence of lung disease is surprising and to our knowledge is previously unreported," the report says. "ILD [interstitial lung disease] is the leading cause of death among patients with dSSc [diffuse systemic sclerosis]. . . . Recent work has developed tools and methods for diagnosis, staging, and characterization of ILD in dSSc patients; however, biomarkers that reliably predict who will develop lung complications before they become symptomatic would be beneficial."

In collaboration with M. Kari Connolly, a professor of dermatology at the University of California-San Francisco, Whitfield, an associate professor of genetics at DMS, and his researchers began creating a map of skin to profile the molecular behavior of genes in scleroderma in 2001.

For the current study, he received support from the Scleroderma Research Foundation, as well as a biomedical research award to Dartmouth from the Howard Hughes Medical Institute.

"Several different pathways likely contribute to the gene expression subsets in scleroderma, and each subset may need to be treated differently," Whitfield says, before adding, "We're getting inquiries from rheumatologists and companies that are looking at drug trials."

In 2008, with DMS postdoctoral fellow Ausra Milano as lead author, Whitfield's group profiled gene expression to divide scleroderma patients into different categories. Those findings prompted Sargent, who participated in the 2008 study, to start mapping the genetic pathways that the disease follows in the subset of patients with the most severe cases. She will continue her experiments as a postdoctoral fellow with Whitfield, before going to work at the National Institutes of Health in January of 2010.

Source: Dartmouth Medical School (news : web)