Researchers find gene mutations in scleroderma patients that could point to new treatments

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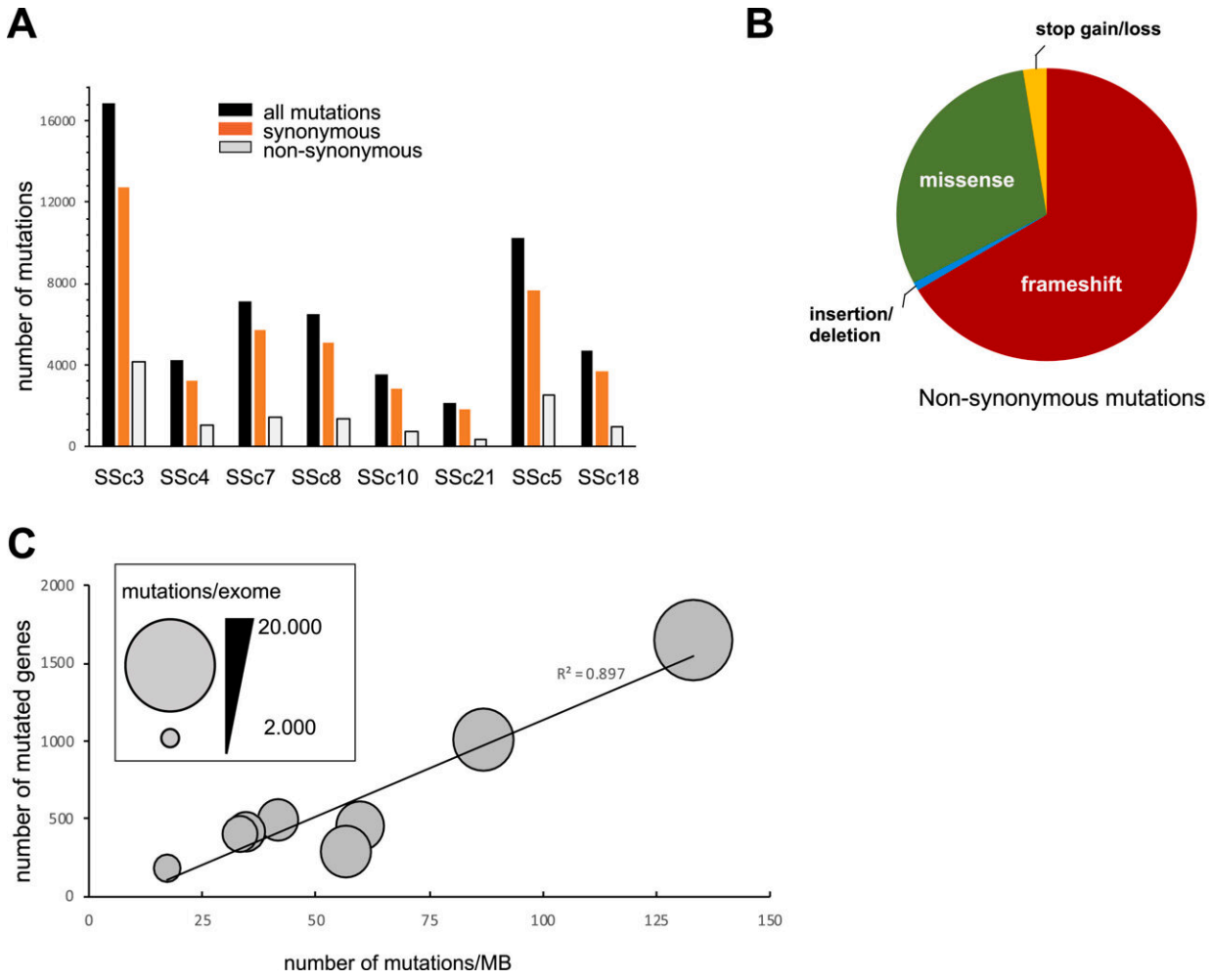

Mutation burden in the skin of patients with SSc. Skin biopsies were obtained from the distal forearm, the sequencing libraries were prepared from the microdissected areas of fibrosis and analyzed by whole exome sequencing. A:

The number of synonymous and non-synonymous mutations in the samples; B: the types of non-synonymous mutations in all SSc samples; C: correlation between number of mutations and number of mutated genes. Credit: *Journal of Autoimmunity* (2022). DOI: 10.1016/j.jaut.2022.102847

Researchers have uncovered cancer-like genetic mutations in the affected cells of people with scleroderma, pointing the way to potential new ways to treat the debilitating and sometimes fatal skin and connective tissue disease.

"Of all rheumatic diseases, scleroderma has the worst outcomes," says lead investigator Mohamed Osman, rheumatologist and assistant professor in the Faculty of Medicine & Dentistry.

"By uncovering some of the mechanisms linking abnormal DNA damage responses with fibrosis and inflammation, we hope to uncover novel mechanisms which we can use to better treat patients in the clinic."

One in 2,500 people suffer from scleroderma, according to Osman. Also known as "systemic sclerosis," scleroderma causes hardening of the skin due to an overproduction of collagen. In severe cases it can lead to fibrosis (scarring or thickening) of vascular and organ tissues such as lungs, kidneys and the gastrointestinal tract, which can be fatal. In some patients, the disease starts as Raynaud's, a disease that causes spasms in the arteries of the hands and feet.

Women and smokers have a higher risk than others of developing scleroderma, but the cause is unknown. Scleroderma patients have an elevated risk for lung, breast, ovarian or colon cancers. Medication, diet and exercise may slow progression and ease symptoms, but there is no cure.

Although scleroderma is generally considered an inflammatory autoimmune disorder, immunosuppressive treatments—which turn the immune system down or off and are typically used for other autoimmune disorders—are not as effective for scleroderma.

"This is a preliminary study that gives us a lot of insight into the pathogenesis of this disease and explains why we see inflammation that doesn't respond as well to immunosuppressive therapy, which until now has been an enigma," says Osman.

Immune suppression versus immunotherapy

The researchers examined tissues from eight patients, taking samples from the scleroderma-affected skin and from mouth swabs as a control sample. Using a next-generation sequencing platform, they sequenced all the exons in the genome, which are called the exome. Exons are the part of the genes that contain code to produce proteins.

They found nearly 2,000 mutations, including "clock-like" mutations that drive premature aging and cancer, and 25 oncogenes that have cancer-causing potential. At the same time, they noted that some of the mutations that are always present in cancer were not seen in the scleroderma cells.

Based on these new findings, the researchers posit that immunotherapy treatments such as those used on some cancers may turn out to be effective. Immunotherapy boosts certain parts of the immune system to target particular cells.

"Our study shows that there is a parallel between the mutations driving cancer and the mutations driving the development of scleroderma," says co-investigator Robert Gniadecki, professor and director of the division of dermatology.

"The endpoint in cancer is aggressive tumor growth, and in scleroderma it is fibrosis. The immune response is at the core of both processes."

Osman and Gniadecki intend to continue their work by examining cells from more patients. The two first met in an airport lounge after a conference and realized in conversation that while they work in different disciplines—rheumatology and dermatology—they share an interest in solving the mystery of scleroderma. They now work together in a combined dermatology and rheumatology clinic seeing patients, as well as carrying out the joint research project.

The research was published in the *Journal of Autoimmunity*.

More information: Robert Gniadecki et al, Genomic instability in early systemic sclerosis, *Journal of Autoimmunity* (2022). DOI: 10.1016/j.jaut.2022.102847

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