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Fired up to fight kidney failure

By ABIGAIL KLEIN LEICHMAN/ISRAEL21C
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Israeli researchers have identified culprit gene.

By identifying the gene that increases the risk of kidney failure, Israeli researchers may revolutionize the prevention, detection, and treatment of kidney disease in people with markedly increased risk, including people of Hispanic and, particularly, sub-Saharan African heritage.

A team led by Dr. Karl Skorecki of Israel's Rambam Medical Center in Haifa and the Technion-Israel Institute of Technology has identified the gene that increases the risk of kidney failure in people of African heritage.

Skorecki revealed his findings at a June lecture at Sunnybrook Health Sciences Center at the University of Toronto, his alma mater. An article describing his findings is currently under review at a major scientific journal.

Uncovering mutations to find clues

Two years ago, independent research teams, including Skorecki's, pinpointed a region of 34 genes involved in the risk disparity. One in particular, MYH9, was tagged as the culprit.

"Everyone jumped all over MYH9 like a herd and we joined the herd as well," Skorecki tells ISRAEL21c. "We all focused our energy on looking for how it caused increased risk. But in the back of my mind I was always concerned about these other 'guys' in the region."

In March, Skorecki received an update from the 1,000 Genomes Project, which provides data on the sequence of genes in 1,000 individuals from different parts of the world. Skorecki assigned members of his team, including a data mining expert, to search the update for mutations found frequently in sub-Saharans and not in Europeans.

"Lo and behold, they found several such mutations never previously described," says Skorecki.

Israel has virtually no sub-Saharan population, but its sizable Ethiopian population was known not to be at greater risk for kidney disease. "We observed at Rambam that Ethiopian Jews have a profile unlike the sub-Saharan profile and therefore we wanted to find a mutation that would be very infrequent in Ethiopians," Skorecki explains. "A few candidates came out as fitting these criteria."

With so much at stake, his team raced to figure out which of MYH9's 'neighbors' was altering the function of the key protein in the gene region. "It's like being interested in the driver, but you've only got the hitchhiker," he says.

Targeting prevention and therapy

Within months, after genotyping 1,631 blood samples from African and Hispanic individuals with and without kidney disease - in collaboration with researchers in the UK, the US, and Ethiopia - Skorecki's team found

the "driver." It was a gene called APOL1.

Genetic variations in many genes, including the APOL family, are known to protect against tropical diseases such as malaria and African sleeping sickness, but at the same time put carriers at risk for other conditions.

"We proved APOL1's association with kidney disease," Skorecki declares. "We have not proven, but have made a circumstantial link between the mutation and the protection."

With a grant from the Israel Science Foundation and from Technion donors, Skorecki's team is pursuing further studies in collaboration with a leading Canadian nephrologist and with Ethiopian scientists. "We're interested in global human health and are not parochial in our approach," relates Skorecki, 57, who was director of nephrology at the University of Toronto and chief nephrologist at the Hospital for Sick Children before moving to Israel in 1995.

If the findings are verified, doctors may rethink the current strategy of using relatives as kidney donors because those relatives probably carry the same mutated gene. They might start hypertension and HIV treatment earlier in those with the risk marker, as both these conditions can lead to kidney failure. They may also start routinely testing certain populations, particularly sub-Saharan groups such as Caribbeans.

"The holy grail, though, is the mechanistic connection," Skorecki tells ISRAEL21c. "We have started looking at the effect of the non-risk variant versus the risk variant of the APOL protein on various functions in the blood and kidneys. Once you figure out the mechanism of how APOL gets into cells, binds to a certain protein, and causes the cells to inflame or die, you'll find a target for prevention or therapy. I've diverted a lot of time and energy to this and we are all fired up."

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