Health & Medicine

Untangling Minds

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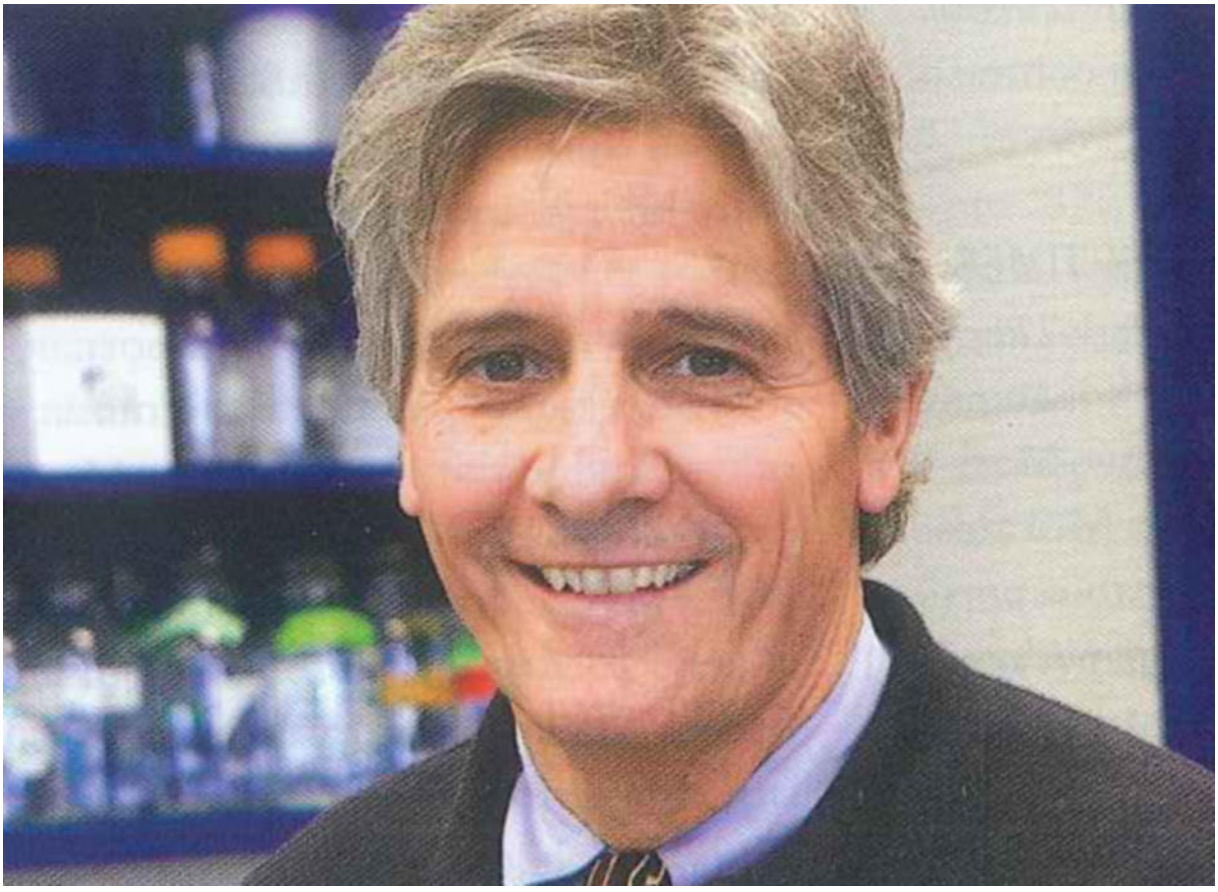

Richard Mayeux (Charles Manley).

Treatments for Alzheimer’s disease today are modest in effect, merely slowing the progression of symptoms. That’s partly because scientists until recently had identified only four genes that contribute to the disease. Many more genes are believed to be involved, setting off numerous biological malfunctions that together create the sticky, fibrous plaque that destroys the diseased brain.

Columbia researchers led by Richard Mayeux ’91PH have discovered another piece of that puzzle. They recently concluded that a fifth gene, called SORL1, is associated with Alzheimer’s. The gene is only the second identified as contributing to late-onset Alzheimer’s, the most common form of the disease, affecting people over the age of

65 and accounting for 90 percent of all cases. The first gene, ApoE4, was linked to late-onset Alzheimer's in 1993.

Mayeux, codirector of Columbia's Taub Institute for Research on Alzheimer's Disease and the Aging Brain, published the findings in the February issue of *Nature Genetics* in collaboration with scientists at the University of Toronto, Boston University, and 12 other institutions. The federally funded researchers examined the DNA of more than 6000 people, including several hundred Dominicans living in the Washington Heights neighborhood of Manhattan.

They examined members of six ethnic groups in several cities and found that variants in the gene SORL1 are more common in people with late-onset Alzheimer's than in healthy individuals of the same age. The finding held true across four ethnic groups: Caribbean-Hispanic, Northern European, African-American, and Israeli-Arab.

The researchers aren't sure exactly where the relevant mutations are on SORL1. That's the next stage of their research, and it's a tricky challenge, because SORL1 is thought to have upward of 500 common variations, an unusually large number. The scientists have examined about 30 so far and haven't yet found a single mutation that is clearly linked to the disease among any of the ethnic populations.

"The causal mutations we're looking for are probably quite subtle, because if they were major mutations they would cause disease earlier in life," says Mayeux, the Gertrude H. Sergievsky Professor of Neurology, Psychiatry, and Epidemiology. "That SORL1 is involved in late-onset Alzheimer's would indicate that it functions pretty normally until old age, and then for some reason it peters out."

What exactly is SORL1's role in causing the disease? Scientists have known for a few years that SORL1 produces a protein, also called SORL1, which acts as a sort of intercellular traffic cop, directing other proteins and molecules down pathways where they'll metabolize properly. A key molecule that's directed by the protein SORL1 is amyloid precursor protein (APP), which turns into the obstructive plaque found in diseased brains, most Alzheimer's experts believe.

Mayeux says that mutations in the gene SORL1 reduce the amount of protein it produces, which in turn allows APP to stray into cellular regions where it takes on its toxic form. Physiologic research supports that working hypothesis: The scientists last year found that levels of the protein SORL1 are very low in individuals with late-onset Alzheimer's.

The scientists hope that by identifying exactly which SORL1 mutations are at work in this process, they'll eventually help develop new treatments, as well as genetic screening tools to identify susceptibility to Alzheimer's. Researchers say it's too early to determine what percentage of Alzheimer's cases the gene SORL1 might help explain; the gene ApoE4 is implicated in about 20 percent of late-onset Alzheimer's cases, and SORL1 is thought to be involved in causing a smaller percentage.

"Alzheimer's vaccines that get rid of some proteins in the body have been developed, but they cause other illnesses, like encephalitis, and so they've never become available," says Mayeux. "If we can develop a genetic test that determines, without a doubt, that some people will develop Alzheimer's, then they can decide whether to take those risks."

Guide to school abbreviations

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