year) that will estimate how much CO_2 plants absorb. Another aim is to pool data on the World Wide Web so that modelers can combine them with data from inventories, satellites, land-use studies, and CO_2 measurements from airplanes. They can then test predictions of how much carbon the different ecosystems now sequester and how much they will absorb as greenhouse gas levels rise.

Early results are exceeding expectations. For example, tower data appear to confirm that in temperate zones, landscapes nearer to the equator are likelier to serve as CO_2 sinks. In Italy, for instance, forests absorb as much as 5 tons per hectare each year. The amount stored drops off further north, and a Swedish boreal forest, where peat may have begun to thaw, actually releases about 0.5 tons of carbon per hectare a year. Thus, the towers may be more helpful than expected in terms of closing in on the missing sink, proponents say. Inspired by these results, NCAR's Schimel has suggested to a White House panel on climate change research that Ameriflux expand its network to perhaps 100 towers, if the cost per tower could be brought down.

Some are even more optimistic. At a Fluxnet meeting last month, scientists reported preliminary findings that European forests absorb a net total of up to 0.28 petagrams of carbon a year—a third of the continent's industrial emissions. According to Valentini, who directs Euroflux, the next step is to add data from grasslands and croplands and plug them into "more sophisticated models" of fluxes between soils, plants, and the atmosphere.

A global network of 250 towers coupled with satellite and weather data might allow monitors to see whether countries are living up to their Kyoto commitments. It "can be an independent way to verify what the Kyoto protocol requires," Valentini says. But such statements make some U.S. scientists antsy. If the towers are seen as "tools for the carbon police," says one Ameriflux researcher, Congress may set out to kill the flux program. Others worry that tower fever will lead agencies to underfund other methods needed to ferret out the missing sink. Even with a larger network, it will be difficult to extrapolate local CO_2 fluxes to a regional level, says land-use expert Richard Houghton of the Woods Hole Research Center in Massachusetts. "I don't think they can do it at the accuracy you'd need," he notes.

Flux tower scientists acknowledge that the program is still proving itself—but they say it is on the right track. Until recently, Wofsy admits he had doubts about how useful the towers would be for closing the carbon cycle: "A year ago, I would have said we're not trying to do that." Now, he adds, the data are more encouraging. "We might be able to make more progress than we thought." –JOCELYN KAISER

NEUROGENETICS

New Gene Tied to Common Form of Alzheimer's

Amutation in a protein that may help scour toxins from between neurons appears to increase the risk of late-onset Alzheimer's disease

Over the past half-dozen years, researchers hoping to pin down the cause of the devastating brain degeneration of Alzheimer's disease have seen their list of potential culprits grow. They've found, for example, that mutations in any of three different genes can cause some cases of early-onset Alzheimer's, which strikes in middle age. In addition, they've identified a variant of another gene that increases an individual's risk of developing the much more common form of the disease that occurs later in life. But researchers have been all too aware that none of these discoveries could fully explain the late-onset Alzheimer's disease that afflicts so many families. Now, they have an important new suspect to add to their lineup.

Earlier this week, at the Sixth Annual International Conference on Alzheimer's Disease and Related Disorders, which was held in Amsterdam, neurogeneticist Rudy Tanzi of Harvard's Massachusetts General Hospital in Boston reported genetic evidence indicating that a common mutation in the gene encoding a protein called α_2-macroglobulin (α_2M) makes the people carrying it more susceptible to developing the neurodegenerative condition as they age. (The results will also appear in the August issue of *Nature Genetics*.) At present, no one knows how many Alzheimer's cases might be linked to the mutation, but the number could be large, given that an estimated 30% of the population carries the mutation. "I think that [the new mutation] is probably the strongest risk factor for whether you get Alzheimer's late in life—as strong as or stronger than *ApoE4*," says Alzheimer's expert Sam Sisodia of the University of Chicago, referring to the only other gene currently linked to the late-onset form of the disease.

The new gene and its protein could also make sense of how several other proteins already implicated in Alzheimer's might contribute to the disease. Work by other researchers suggests that the normal α_2M protein acts as a kind of cleanup crew for neurons by binding to several proteins that could have toxic effects and sweeping them out of the space between neurons. These include, for example, the small protein β amyloid, already notorious as a possible cause of Alzheimer's. The mutation may put this cleanup crew out of commission, or at least slow it down, leading to β amyloid deposition and nerve cell death.

ApoE4, a variant of a lipid-carrying protein called apoE, may fit into this picture as well, for one way α_2M may prevent β amyloid deposition is by binding the peptide and transporting it into cells for degradation—a step that uses the very same receptor that apoE uses to enter cells. ApoE4 or excess amounts of other apoEs might block the α_2M–β amyloid complex from binding to the receptor, preventing the cleanup crew from removing its sweepings. All that makes the Tanzi team's discovery "scientifically very interesting," says Steven Hyman, director of the National Institute of Mental Health (NIMH)—and perhaps a clue to new Alzheimer's therapies.

The apoE4 link was one of the clues that first alerted Tanzi and his colleagues to the gene encoding α_2M. They reasoned that if *ApoE4* is a risk factor for Alzheimer's, then other proteins that bind to the apoE4 receptor, a cell surface protein known as LRP (for low-density lipoprotein receptor–related

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Gene team. Among those tracking *A2M*'s role are, from left to right: Marilyn Albert, Deborah Blacker, Linda Rodes, and Rudy Tanzi.

protein), might be risk factors as well. α_2M, which was then known primarily as an inhibitor of many of the body's proteases, or protein-splitting enzymes, is one such protein. The researchers then performed a standard genetic linkage analysis to see whether a common variant of the *A2M* gene that lacks a particular five-nucleotide deletion is associated with Alzheimer's in a group of families which they and teams at Johns Hopkins University School of Medicine and the University of Alabama at Birmingham had collected under the aegis of the NIMH's Alzheimer's Disease Genetics Initiative. The results of this test were disappointing, however.

But other work began suggesting that the researchers might nonetheless be on the right track. "While we were screening," Tanzi recalls, "papers began appearing implicating α_2M biologically in Alzheimer's disease." For example, Dennis Selkoe's team, also at Harvard, found that α_2M has paradoxical effects on one protease: While preventing the protease from degrading large proteins, it apparently triggers the protease to break down β amyloid, an action that should prevent toxic β amyloid deposits from forming. The α_2M protein also interacts with a variety of cytokines, molecules that influence immune activity, suggesting that it might somehow damp down dangerous inflammatory reactions in the brain.

In addition, several teams, including those of Steven Paul at Lilly Research Laboratories in Indianapolis; Sudhir Sahasrabudhe at Hoechst Marion Roussel Inc. in Bridgewater, New Jersey; and Guojun Bu at Washington University School of Medicine in St. Louis, showed that α_2M binds to β amyloid itself, with two potentially protective effects. In test tube assays, it prevents the formation of the insoluble β amyloid fibrils that are considered most toxic to neurons—and does so effectively enough, Paul's group showed, to protect cultured neurons against β amyloid toxicity. What's more, Bu's team showed that cells take up and degrade the α_2M–β amyloid complex, apparently as a result of its binding to the LRP receptor.

These protective functions suggested that a defective *A2M* gene should be an Alzheimer's risk factor, so the Tanzi team tried again to find an association in the Alzheimer's families. This time, though, they turned to a powerful new method of analysis called "family-based association." Using methods developed by statistician Nan Laird of the Harvard School of Public Health and Tanzi's Harvard colleague Deborah Blacker, the researchers compared the frequencies of the mutant *A2M* allele in Alzheimer's patients and their unaffected siblings. And here they struck paydirt.

GENES LINKED TO ALZHEIMER'S DISEASE

Gene	Chromosome	Age of Onset	% of Early Onset Cases	% of All Cases
APP	21	45 to 66	<1	<0.1
Presenilin 1	14	28 to 62	40	1 to 2
Presenilin 2	1	40 to 85	<1	<0.1
ApoE4	19	>60	---	>50 (Risk factor)
A2M	12	>70	---	? (Risk factor)

The analysis showed a highly significant association between the *A2M* deletion and the presence of Alzheimer's disease—as strong as the association with *ApoE4*, Tanzi says. For instance, when researchers removed the possible confounding influence of *ApoE4* by looking only at families lacking that *ApoE* variant, they found that the frequency of the mutant *A2M* gene in Alzheimer's patients was four times greater than in their unaffected siblings. The result was "pretty striking," Tanzi says. "Somehow not having the deletion [in *A2M*] protects you against Alzheimer's disease when you get old."

At least one additional recent genetic study also points to *A2M* as a possible Alzheimer's gene. Alison Goate of Washington University School of Medicine and her colleagues have been conducting a genomewide screen looking for such genes. In a paper in press at the *Journal of the American Medical Association*, they report that a genetic linkage study of a subset of the families studied by the Tanzi team picked up the region on chromosome 12 where *A2M* is located. "I can't say our linkage is to *A2M*, but I can say it is a good candidate for what we are seeing," Goate says. What's more, the deletion the Tanzi team is studying may not be the only *A2M* mutation associated with Alzheimer's. Brad Hyman of Harvard, working with Tanzi, has identified a second, independent mutation in the gene that also appears to increase the risk of the disease.

> "I think that [the new mutation] is probably the strongest risk factor for whether you get Alzheimer's late in life."
>
> —Sam Sisodia

If these common mutations do predispose carriers to Alzheimer's, the discovery could help explain a puzzling observation about *ApoE4*. Some people carrying *ApoE4*, even those with two copies, appear not to get Alzheimer's, an idea supported by another study reported in the August *Nature Genetics*. In it, John Breitner of Johns Hopkins School of Medicine and his colleagues screened nearly 5000 people for Alzheimer's disease as well as their *ApoE4* status.

In agreement with previous work, they found that people with two *ApoE4* copies get the disease earlier than people with one, who get it earlier than people with none. But the analysis also indicated that some *ApoE4* carriers would not get the disease no matter how long they lived. "This suggests that there is a window of time in which if you're going to get Alzheimer's disease, you do. *ApoE4* is defining the window, but not who is getting it," Breitner says. Other genes—such as *A2M*—may determine that "whether," he suggests.

Still, before researchers conclude that *A2M* mutations do in fact play such a role, they would like to see the Tanzi team's finding confirmed in other populations besides the NIMH families. Even before that happens, though, they will begin focusing on just how the *A2M* mutations might lead to Alzheimer's. "It's certainly exciting, but at this point, it's still early and it's not clear how the biology of this will work out," Paul says.

But thanks to the previous biological work, researchers have several hypotheses to test. They will want to know, for example, whether the deletion affects α_2M's ability to carry β amyloid into cells or prevent β amyloid fibril formation. They will also want to test whether *ApoE4* fits into the picture as Tanzi and others propose. Paul's team has already shown that mice lacking the gene for apoE are protected against amyloid deposition, although it remains to be seen whether that's because apoE can interfere with α_2M's cleanup operation. If it does, that could explain how apoE4 accelerates the development of Alzheimer's.

Those kinds of possibilities, sure to spur a new round of research, are what make the new work "very, very interesting," says neurobiologist Steven Moldin of NIMH. "It offers a set of very explicit hypotheses that can be tested."

—JEAN MARX