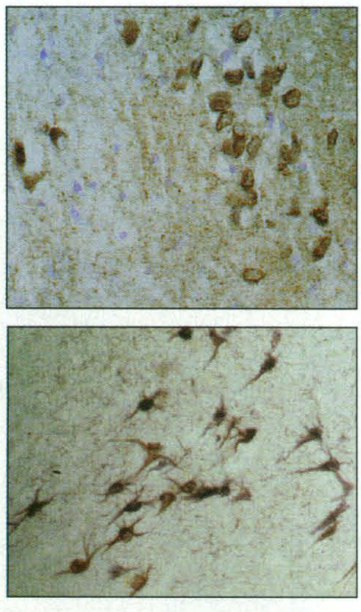
NEURODEGENERATIVE DISEASE

Tau Protein Mutations Confirmed as Neuron Killers

Long a suspect in the neuronal wreckage of Alzheimer's disease, the protein called tau looked like it was going to get off scot-free. Circumstantial evidence linking tau to the disease is plentiful. It is the major component of "tangles"—abnormal twists of proteins found in the dead brain cells of Alzheimer's sufferers—and the number of tangles seems to correlate with the severity of dementia. But no one could ever nail tau's guilt once and for all. Now, however, fresh revelations have reignited the case against tau.

In the 3 June issue of *Annals of Neurology*, a team led by Gerard Schellenberg of the Veterans Affairs Puget Sound Health Care System in Seattle reports evidence suggesting that *tau* gene mutations cause a type of inherited dementia that is also characterized by brain tangles. And in the *Proceedings of the National Academy of Sciences (PNAS)* later this month, Maria Grazia Spillantini of the Centre for Brain Repair at Cambridge University in the United Kingdom and her colleagues will report that another mutation in *tau* causes a slightly different genetic condition. The list won't stop there. As-yet-unpublished work from other labs has linked *tau* mutations to more than a dozen more of these hereditary dementias, collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17).



M. G. SPILLANTINI/CAMBRIDGE UNIV.

Deadly tangles. Abnormal tau filaments (stained brown) appear in brains from both FTDP-17 *(top)* and Alzheimer's *(bottom)* patients.

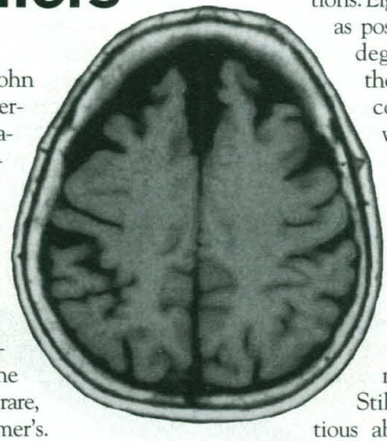
To longtime tau researchers, these discoveries are welcome, as they establish at last that the protein can play a primary role in causing at least some cases of neurodegenerative disease. That idea had lost favor because genetically engineered mice that make no tau at all suffer no obvious ill effects. More important, no one could find anything wrong with the *tau* gene in people with Alzheimer's or other neurodegenerative diseases. "When we would go around the country and give lectures [on tau], people would ask, 'So when are you going to find a mutation?' " says John Trojanowski of the University of Pennsylvania in Philadelphia, one of the researchers who continued to work on the protein. If tau had any role at all, it was believed to be secondary to the neurodegenerative events set in motion by abnormal deposits of another protein, β amyloid, the product of a gene mutated in rare, hereditary forms of Alzheimer's.

But the new work "really brings the tau pathway to the forefront" as an important contributor to neurodegeneration, says neurologist Kirk Wilhelmsen of the University of California, San Francisco. That doesn't mean that β amyloid isn't at fault in Alzheimer's disease. Some researchers suspect that it may work with tau to kill cells. But with the new evidence linking tau to neurodegeneration, researchers hope they'll be able to piece together what triggers formation of the protein's ruinous tangles and perhaps how that formation could be prevented.

Schellenberg's team had been trying to find a cause of FTDP-17s for several years. The symptoms of the diseases that fall under that rubric vary widely, ranging from psychoses that resemble schizophrenia to difficulty speaking to Parkinson's-like tremors. And because many patients develop dementias, they are often misdiagnosed as having Alzheimer's disease. The *tau* gene was a prime suspect in the FTDP-17 diseases. Not only did the patients have dementias and tangles, but genetic studies by Wilhelmsen and other researchers had linked all of the FTDP-17s to a region on chromosome 17 where the gene is located.

Even so, initial searches failed to find anything wrong with the gene in FTDP-17 patients. "The trend was to give up," says neurologist Thomas Bird of the VA Puget Sound, a co-author on the Schellenberg paper. But "to be thorough," says Schellenberg, postdoctoral fellow Parvoneh Poorkaj continued her search, looking for variations in the gene that might be found only in patients.

After screening members of two affected families, she came up with nine gene variations. Eight of them were eliminated as possible causes of the neurodegenerative disease when they also turned up in healthy controls. Apparently, they were normal gene variations. But the ninth proved to be found only in the ill members of one family. Still, the researchers were cautious about concluding that the gene change caused the disease. It did not appear in a family with similar symptoms, and previous negative results had made them wary. "We had taken it as far as we could," says Schellenberg, so they began presenting their findings at seminars and meetings, hoping to find corroboration from other groups.



T. BIRD/VA PUGET SOUND, SEATTLE

Brain atrophy. Magnetic resonance image shows frontal lobe loss in an FTDP-17 patient.

They soon found it. A team led by Spillantini, Michel Goedert of the Medical Research Council Laboratory of Molecular Biology in Cambridge, U.K., and Bernardino Ghetti of Indiana University School of Medicine in Indianapolis had been analyzing the *tau* gene in a family with an FTDP-17 disease called familial multiple system tauopathy with presenile dementia (MSTD). As they report in *PNAS*, they also found a *tau* gene anomaly in affected family members.

Since then, Schellenberg's group has found a mutation in the gene in a second Seattle family with a different FTDP-17, and at least three other teams, including one led by Michael Hutton of the Mayo Clinic in Jacksonville, Florida, have reported at closed meetings that they have found mutations in other FTDP-17 dementias, their colleagues say. Hutton declined to comment on his own work, as it has been submitted to *Nature*.

Many of the families have slightly different mutations, says Spillantini, which may explain why the patients often vary in their dementia symptoms and show different kinds of brain damage after death. But many researchers think all these defects might kill cells in roughly the same way: by somehow preventing tau from binding to the microtubules. These are the protein filaments that help provide support for cell structures such as axons, the long projections that form connections between neurons.

In Schellenberg's families, for instance, the mutations occur right in the gene sequence coding for the part of the protein where it contacts the microtubules, prevent-

ing it from binding. Some researchers think this disruption could cause the microtubules to collapse. The destabilized axons would lose contact with their target neurons—and neurons die when they lose their connections.

The Spillantini group's mutation may also affect tau binding to microtubules, she says, although the mutation is more subtle. It is not in the gene's protein-coding regions but in one of its introns—regions that are spliced out of the messenger RNA made from a gene before the mRNA is translated into the actual protein. In humans, the tau protein occurs in six different forms of varying lengths, depending on where the splices are made and which exons are included in the finished protein. The mutation seems to encourage the cell's protein-making machinery to grind out abnormal amounts of three of the longer forms.

In fact, the brains of MSTD sufferers have several times as much of the longer tau versions as do normal brains, the Spillantini team reports. This imbalance, says Spillantini, may prevent proper binding to the microtubules, which could then destabilize the axons. She notes, however, that the disrupted-axon scenario faces a serious challenge, posed by the genetically engineered mice that make no tau protein yet seem healthy. She favors another possibility: that a disruption in binding leads to an excess of tau floating loose in the cell. Like out-of-work loiterers, the unbound proteins might aggregate and disrupt cell function.

Although Alzheimer's patients don't seem to have any tau mutations, the protein may get more respect from Alzheimer's researchers now that there's more direct proof that tau defects can lead to nerve cell death. Indeed, John Hardy of the Mayo Clinic, whose team discovered the first mutation in the gene that encodes β amyloid, thinks that β amyloid may somehow work through disruption of tau function. That could explain the correlation between the degree of dementia in patients and the abundance of tangles in their brains, he notes. "The pathway from amyloid to dementia is likely to go through tangles," he predicts. The big question now is how the two might interact to make tau into a killer.

Understanding how tau turns deadly could have benefits beyond Alzheimer's and the tau diseases. Hardy and others have noted that a familial form of Parkinson's disease described last year (*Science*, 27 June 1997, p. 1973) is also caused by a mutated protein that accumulates in brain cells. Indeed, Goedert thinks the tau diseases could be a model for understanding how abnormal protein filaments might kill cells in a whole range of diseases, including sporadic dementias, Parkinson's disease, and Huntington's disease. "I would argue that cells die because they have these filaments," he says. Just months ago, tau was a marginal suspect in brain diseases, but now it might help close several other unsolved cases.

–Gretchen Vogel

HUMAN ORIGINS

Old, Old Skull Has a New Look

The origins of our species, *Homo sapiens*, are lost in a gaping hole in the fossil record. Between 1.4 million and 600,000 years ago, traces of human ancestors more or less vanish in Africa, where many researchers believe *H. sapiens* originated. Now a well-preserved skull of an early human found in the northeast African country of Eritrea has landed right in the middle of that gap.

Dated to 1 million years ago, the skull shows a tantalizing mix of ancient and modern features, says Ernesto Abbate, a geologist at the University of Florence in Italy and head of the multinational team—including members from Italy, South Africa, and Switzerland—that reported the discovery in this week's issue of *Nature*. Although it has yet to be studied in detail, the skull "could be evidence of the emergence of *H. sapiens* characters earlier than previously thought," says Lorenzo Rook, a paleontologist at the University of Florence. It also underscores earlier hints that northeastern Africa was a focal point of human evolution, says Tim White, a paleoanthropologist at the University of California, Berkeley: "This discovery is another significant step in establishing the Horn of Africa as the key to understanding human origins and evolution."

The skull was found in the remote, arid lands of the Northern Danakil Depression of Eritrea, about 50 kilometers from the Red Sea and 400 kilometers north of the famed Awash Valley in Ethiopia, which has yielded the remains of several other human ancestors. Rook was walking along a hilly slope in December 1995 when he noticed the right side of the skull, ear-side up, poking out of the sand and rock. "I called to my colleagues, and we immediately realized it was a *Homo* skull," says Rook.

When they had dug it out of the rock, their first impression was that the nearly complete brain case resembles that of *H. erectus*, a human ancestor that appeared in Africa 1.7 million years ago and persisted until at least 1.4 million years ago in Africa and much later in Asia. Like *H. erectus*, it has a pronounced brow ridge and elongated brain case, among other features, says Rook.

E. ABBATE / UNIVERSITY OF FLORENCE

Filling a gap. The Eritrean skull dates from the dawn of *Homo sapiens*.

The new skull would be the youngest African *erectus*. To date the stratum where it was found, the team looked in the rocks for the signature of known reversals in Earth's magnetic field and identified fossils from mammals that went extinct at known times. The resulting age of 1 million years puts the fossil right between the youngest *H. erectus* found in Africa—a 1.4-million-year-old fossil from Olduvai, Tanzania—and the oldest archaic form of *H. sapiens*, a 600,000-year-old specimen from Bodo, Ethiopia.

A closer look at the fossil revealed modern-looking features mixed with the old. The skull is remarkably narrow, reaching its greatest width near the top, as in *H. sapiens*, rather than at the base, as in *erectus*. This suggests that some traits typical of *H. sapiens* had begun to develop 200,000 to 300,000 years earlier than expected, says Rook. "It contributes to the perception that *H. erectus* and *H. sapiens* have no distinct boundary between them," adds paleoanthropologist Milford Wolpoff of the University of Michigan, Ann Arbor, who has seen photos of the skull.

But others say such conclusions are preliminary because half the skull is still embedded in rock. Further hampering study, the skull, along with two incisors and pelvic fragments, has been kept under wraps at the Eritrea National Museum in Asmara. Eritrea, a nation just 5 years old, has yet to write regulations governing the study of such antiquities. The Italian team is working with Eritrean scientists and officials to arrange for the skull to be restored and studied.

Ultimately, the fossil could help anthropologists make sense of other fossils found outside Africa that fall in the critical time gap, such as 800,000-year-old remains at Atapuerca, Spain, and *H. erectus* in Asia. No one knows whether these creatures are evolutionary dead ends or transitional players on the path to *H. sapiens*, but the new skull may help to sort out where they fit on the family tree. "This is clearly going to be a major player in future scenarios, but it has to be studied," says Ian Tattersall, a paleoanthropologist at the American Museum of Natural History in New York.

–Ann Gibbons