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# GENE IDENTIFIED FOR COMMON NERVE DISORDER

STANFORD—Earlier this spring Stanford researchers, led by professor of neurobiology Dr. Eric Shooter, predicted that a defective gene that makes mice tremble severely may be the same gene involved in one of the most common human nerve disorders.

This month their prediction was confirmed when the Stanford group in collaboration with researchers at Baylor College of Medicine and three other independent research teams published findings in the June issue of the journal *Nature Genetics* showing that the same gene is implicated in *Trembler* mice and in people with Charcot-Marie-Tooth disease (CMT).

An editorial accompanying the four papers credits the Stanford team's recent identification of the location and nature of a mutation in the gene for peripheral myelin protein-22 (PMP-22) in the *Trembler* mouse as responsible for "the current flood of papers" linking that gene to CMT. In a report published in March, the group reported that professor of genetics and pediatrics Dr. Uta Francke and postdoctoral fellow Tayfun Ozcelik located the PMP-22 gene on chromosome 11 in normal mice. Then Shooter and postdoctoral fellows Ueli Suter and Andrew Welcher as well as neuropathology fellow G. Jackson Snipes determined that the PMP-22 gene in *Trembler* mice is mutated.

PMP-22 is a substance made by Schwann cells, companion cells to neurons in the peripheral nervous system. Schwann cells produce myelin, a compound that wraps around nerves to create an insulating sheath.

Charcot-Marie-Tooth, discovered in 1886, is the most common inherited disease of the peripheral nervous system, affecting about one in every 2,500 people. Patients experience muscle weakness and atrophy since defective myelination hampers effective conduction of electrical signals along the nerves to the muscles.

(more — PMP22proof)

In work to track the position of the gene responsible for causing CMT, Baylor researchers Pragna Patel and Jim Lupski had previously determined that CMT is caused by a duplication of DNA sequences in which patients have three copies rather than the usual two of the culprit gene. The finding generated excitement among human geneticists because it was the first time a duplication had been identified as the possible cause of a disease; and, the researchers noted, it may have implications for other genetic diseases. The Baylor group had not, however, identified the specific gene involved.

Together the Stanford and Baylor groups cloned a human PMP-22 gene and mapped it within the region already identified as containing the CMT disease-causing defect. Their newly published study suggests that the PMP-22 gene, when present in three copies instead of the normal two, may lead to CMT.

The findings of the Stanford/Baylor collaborators were independently confirmed by research teams in the Netherlands, Belgium and Utah.

The researchers note that there may be additional mutations to PMP-22 and even other genes involved. But they are hopeful that the duplication offers a potential therapeutic target.

In the meantime, the Stanford research team is studying the fundamental biology of PMP-22 to understand its normal function in the myelin membrane. "Maybe that will give us clues as to what's gone wrong in mice where we see a mutation and in people where there is an excess of the protein," explained Shooter.

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