# Fragile X syndrome: link to Parkinson's?

The grandfathers of individuals with fragile X syndrome may be at risk for Parkinson's-like neurological symptoms, according to research by Randi Hagerman and colleagues. Fragile X, the most common inherited cause of mental retardation, often causes autistic-like symptoms.

Fragile X occurs when a mutation in the FMR1 gene "turns off" the instructions to make a protein called FMRP. The mutation involves a repeated segment of DNA, with affected individuals having more than 200 repeats and carriers exhibiting 50 to 200. Carriers do not have fragile X syndrome, but may exhibit mild cognitive or emotional problems.

Hagerman et al. report that they have identified five fragile X carriers, all grandfathers of children with full-blown fragile X syndrome, who exhibit neurodegenerative symptoms resembling those seen in Parkinson's disease. *(Editor's note: the authors have identified five additional cases since publishing their article.)* The patients began exhibiting symptoms in their 50s or early 60s, with a Parkinson's-like tremor appearing first. Additional symptoms include memory problems, impotence, memory loss, a "mask-like" appearance, and deficits in executive function (higher-level cognitive skills including the ability to plan and carry out events), wide-based gait and difficulty in walking, and slow movement and speech. Brain scans of the subjects revealed atrophy.

"We have known that men and women who carry a mutation of the fragile X gene are more likely to have problems with anxiety, attention deficit and hyperactivity disorder or premature menopause," Hagerman says. "But this is the first time we have found a group of men in their 50s and 60s who suffer from this unique tremor problem and whose grandchildren suffer from fragile X syndrome."

The researchers say the prevalence of Parkinson's-like symptoms among grandfathers of individuals with fragile X syndrome is unknown. They conclude, "It is imperative that additional individuals with both [the premutation and the full mutation] be screened for tremor, and that individuals with action tremor associated with cognitive decline and mild parkinsonism be screened for fragile X."

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"Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X," R. J. Hagerman, M. Leehey, W. Heinrichs, F. Tassone, R. Wilson, J. Hills, J. Grigsby, B. Gage, and P. J. Hagerman, *Neurology*, Vol. 57, No. 1, July 10, 2001, 127-30. Address: Randi J. Hagerman, M.I.N.D. Institute, UC Davis Medical Center, 4860 Y Street, Suite 3020, Sacramento, CA 95817.

—and—

"Parkinson's-like neurological disorder discovered in grandfathers of children with fragile X syndrome," press release, M.I.N.D. Institute, July 2001.

# Cholinergic abnormalities seen in autistic adults

New research implicates abnormalities of cholinergic neurons—brain cells that synthesize and use the neurotransmitter acetylcholine—as a factor in autism.

Elaine Perry et al. performed post-mortem studies on brain samples from seven autistic adults and 10 non-disabled adults. The researchers found three times more brain-derived neurotrophic factor, a chemical that affects the development and function of cholinergic neurons, in basal forebrain tissue from autistic subjects than in samples from controls. In addition, they found significantly less nicotinic receptor activity in the cerebral cortex of autistic subjects than in controls. (Nicotinic receptors are one of two types of receptors to which acetylcholine binds.)

The researchers also examined brain tissue samples from 16 retarded, non-autistic subjects, but did not see the same pattern of abnormalities detected in the autistic subjects.

Perry et al. note that previous research by Margaret Bauman and Thomas Kemper identified abnormalities in basal forebrain cholinergic neurons, including larger-than-normal size and numbers in children and small size and numbers in adults. The researchers say their findings and those of Bauman and Kemper "implicate the cholinergic system in developmental disorders such as autism," and suggest that treatment approaches that modify the function of cholinergic receptors may be effective.

Other research groups have recently reported cholinergic abnormalities in schizophrenia, Alzheimer's disease, Parkinson's disease, and Tourette syndrome, and some are experimenting with the use of nicotine, which affects cholinergic system activity, as a treatment.

**Editor's note: Although Perry et al. do not suggest a cause for the abnormalities they identified, Sallie Bernard et al. note in *Autism: A Unique Type of Mercury Poisoning* (see ARI's web site) that exposure to low levels of mercury can affect the cholinergic system in multiple ways. Research on cholinergic system abnormalities should consider the possible role of mercury exposure from vaccinations.**

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"Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain," E. K. Perry, M. L. Lee, C. M. Martin-Ruiz, J. A. Court, S. G. Volsen, J. Merrit, E. Folly, P. E. Iversen, M. L. Bauman, R. H. Perry, and G. L. Wenk, *American Journal of Psychiatry*, Vol. 158, No. 7, July 2001. Address: Elaine Perry, Centre Development in Clinical Brain Aging, MRC, Newcastle General Hospital, Newcastle Upon Tyne NE4 6BE, U.K.

# Is self-injurious behavior linked to neuropathy?

A pilot study suggests that some cases of self-injury may stem from neuropathy, a form of nerve damage or dysfunction that can lead to a loss of feeling in an area, a pins-and-needles feeling, pain, or other abnormal sensations.

Frank Symons and colleagues studied four nonverbal, mentally retarded adults who exhibited severe self-injury. Noting that skin temperature changes can be indicative of neuropathy, the researchers tested the skin temperatures of the subjects at the site they most often injured, a site they injured less often, and a site they did not injure.

"For each participant," the researchers report, "the body site targeted most frequently for self-injury was associated with altered skin temperature." They note that while self-injury may itself change skin temperature, evidence from other animal and human studies suggests that neuropathy can lead to self-injury. For instance, they note, self-mutilation is a common finding in animals with dysesthesia, or abnormal sensations caused by lesions of the sensory nerve pathways. In addition, cases of intellectually normal individuals who targeted self-injury toward areas with neuropathy and altered skin temperature have been documented.

The researchers suggest that self-injury may provide temporary relief of neuropathy-caused pain or discomfort (as when a child scratches at a scab or chicken pox lesion), but may lead in the long run to more irritation that in turn generates more self-injury.

The researchers note that all four of their subjects responded well to naltrexone, a substance that blocks opioid receptors and alters the perception of pain. They suggest that further studies examine whether naltrexone treatment, although it has no known effect on neuropathy itself, is more effective in individuals with skin temperature differences at self-injury sites.

In addition, Symons and colleagues say, "One clinical implication of a pain-related model of self-injurious behavior (SIB) is that treatments for peripheral neuropathies may provide an effective treatment option for some subset of SIB cases." They note that several studies show decreased self-injury during treatment with transcutaneous electrical nerve stimulation (TENS), a treatment that blocks peripheral pain signals.

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"Preliminary study of altered skin temperature at body sites associated with self-injurious behavior in adults who have developmental disabilities," Frank J. Symons, Kelly A. Sutton, and James W. Bodfish, *American Journal on Mental Retardation*, Vol. 106, No. 4, 2001, 336-43. Address: Frank Symons, Dept. of Educational Psychology, 227 Burton Hall, 178 Pillsbury Dr SE, College of Education and Human Development, University of Minnesota, Minneapolis, MN 55455.