HUMAN GENETICS

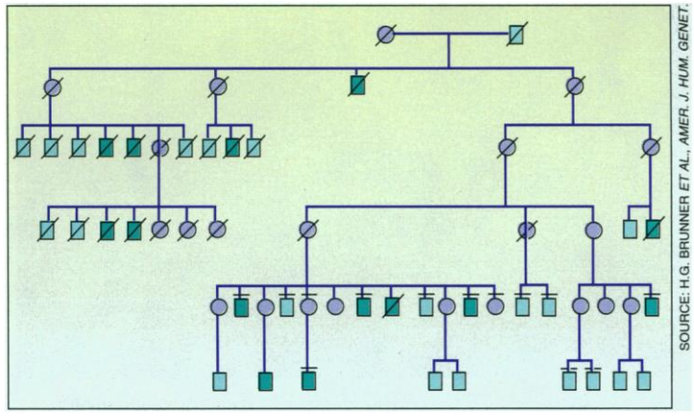
Evidence Found for a Possible 'Aggression Gene'

Researchers in the Netherlands are hot on the track of a genetic mutation in a large Dutch family that may cause periodic outbursts of aggression in its possessors. In this month's issue of the *American Journal of Human Genetics*, Han G. Brunner and his colleagues at University Hospital in Nijmegen report evidence suggesting that a mutation in the gene for an enzyme called monoamine oxidase A (MAOA) may underlie the aggressive and sometimes violent behavior displayed by certain males in this family.

Other researchers are cautious about what the new findings might mean. They point out, for example, that previous studies that appeared to link behaviors to genetic defects were subsequently disproven. "There have been many false starts in this field, and those have given it a bad name," notes Markku Linnoila, scientific director at the National Institute on Alcohol Abuse and Alcoholism (NIAAA). But, he adds, "this study seems solid and is therefore very exciting." What's more, a linkage between an MAOA gene defect and behavioral problems would make biological sense because the enzyme encoded by the gene helps break down several neurotransmitters that might, if their concentrations build up abnormally, cause a person to respond excessively—and at times even violently—to stress.

If this original report is borne out by further work, it would be the first time that a specific gene defect has been found to predispose its bearers to aggressive behavior. And while so far the suspected mutation has been found in just one family, the work raises the possibility that MAOA gene defects contribute to aggressive or violent tendencies in members of the population at large. If so, it might be possible to identify people who are prone to commit violent acts by screening for MAOA gene mutations, and then treat those individuals with either diet or drugs to counteract the mutation's effects. Any such proposals would, of course, be highly controversial. Indeed, research into the biological causes of violence has already come under fire because of concerns that the information it produces might be used to stigmatize individuals or groups of people (*Science*, 9 October 1992, p. 212).

Brunner, a clinical geneticist, originally became interested in looking for the suspected "aggression gene" in 1978, when a woman serendipitously stopped by his office to ask for help with a problem in her family. For generations, she told Brunner, many of the men had been prone to seemingly unprovoked aggressive outbursts. The problem was so remarkable that 30 years ago an unaffected maternal granduncle had compiled a record about nine male relatives who displayed the aberrant behavior. Since then, five more males in the family developed the disorder.



SOURCE: H.G. BRUNNER *ET AL., AMER. J. HUM. GENET.*

Tracing the pedigree. The dark green rectangles represent the affected males in the Dutch family.

Those studied by Brunner and his colleagues include, for example, one who raped his sister, and later, in a mental institution, attacked his warden with a pitchfork. Another sometimes threatened his sisters with a knife, forcing them to undress; a third had attempted to run over his employer with a car, after his boss told him his work wasn't up to snuff; and two were arsonists. All affected males are also mildly retarded with a typical IQ of about 85. None of the women in the family, however, has been either mentally deficient or prone to aggressive outbursts. This suggested that the disorder is caused by a recessive gene on the X (female) chromosome. Men have only one X chromosome and therefore develop symptoms whenever they inherit the bad gene, while women are protected because their second X chromosome carries a good copy of the gene.

But even though the researchers had good reason to suspect that the gene was on the X chromosome, finding it was not easy. "For 10 years, it was a problem that couldn't be solved," Brunner says. "We didn't have a clue." That began to change in the late 1980s with the discovery of new, highly informative markers, essentially genetic landmarks that can be used in linkage studies to locate the genes that cause hereditary diseases. The idea is that a marker that is consistently inherited with a disease must be located very near the causative gene. Using markers for the X chromosome, Brunner and his colleagues then identified the MAO gene region as the likely site for the diseased gene in this family.

But the linkage study didn't prove that the MAOA gene was at fault. For one thing, humans have two genes for monoamine oxidase enzymes—the other is called MAOB—and the two are located next to each other on the X chromosome. But the Nijmegen group also has biochemical evidence pointing to a MAOA gene defect as the cause of the Dutch family's problems.

The normal function of the two enzymes is to assist in the breakdown of the neurotransmitters dopamine, epinephrine, norepinephrine, and serotonin, and analysis of urine samples from family members indicated that one or both enzymes wasn't doing its job in affected men. They were excreting higher than normal amounts of chemicals that the monoamine oxidases work on. Presumably MAOA is the enzyme at fault since the men's MAOB variant appears normal.

Other researchers also have evidence that MAOA activity may be disturbed in individuals displaying aberrant behavior. "In our studies [of arsonists and impulsive alcoholics] we have neurochemical findings that could implicate an MAOA deficiency," says NIAAA's Linnoila. Although the cause of the deficiency is not known, it's not the result of a defect in the MAOA gene. "These are not X-linked families," Linnoila explains. "And this tells us that other genes and factors are involved in these behaviors."

Still, it would come as no surprise if a MAOA gene defect resulted in episodic violent or other abnormal behavior. "Dennis Murphy [of the NIAAA] predicted long ago that a mutation on the MAOA gene would cause altered behavior," says Xandra Breakefield, a neurogeneticist at Massachusetts General Hospital, who cloned the two MAO genes in 1988, and who has been searching for people with an MAOA deficiency for the past 15 years. "It looks like this prediction is now no longer a fantasy; it's reality." Breakefield is now collaborating with Brunner to try to pin down the exact mutation in the Dutch family and show that it is indeed linked to the behavioral disorder.

The reason for thinking that a MAOA deficiency could lead to behavioral disturbances is that the neurotransmitters it helps break down come into play during the body's so-called fight or flight responses to threats

and other stresses. If they were to accumulate abnormally, those responses would effectively be in high gear all the time. "If these individuals have a defect on the MAOA gene, right away you can see that they would have trouble handling any stressful situation, even ones the rest of us easily cope with," explains Breakefield. The two arsonists in the Dutch family, for example, set fires following the deaths of close relatives.

Diet, too, may trigger abnormal behavior if the MAOA gene is malfunctioning. The enzyme also helps detoxify "false transmitters," such as tyramine that can alter the effects of the natural neurotransmitters and occur in some foods, including chocolate, red wine, and certain cheeses. Eliminating foods with a high tyramine content might therefore help people with a defective MAOA gene. And diet might help in another way as well.

The neurotransmitters broken down by MAOA are synthesized from the amino acids phenylalanine and tryptophan. Breakefield speculates that restricting the intake of those amino acids may help people with an MAOA deficiency by preventing the neurotransmitter buildup. Another, perhaps less onerous, possibility is the use of drugs to block the neurotransmitter activity. Such drugs—the beta blockers used to treat high blood pressure, for example—already exist for some neurotransmitters. "What we hope is that this insight into a new type of metabolic deficiency will help these patients to diminish their outbursts so that they can lead more productive lives," says Breakefield.

But while the results may hold some promise for helping the aggression-prone members of the Dutch family, geneticists caution that it would be premature to apply them to the population at large. After all, to date the suspected mutation has been found only in that one family, and even if it should be found in other families, its expression might well be modified by social, economic, and cultural factors. "There are always serious doubts about extending these extreme situations to the general population, because so many societal factors come into play," says Jonathan Beckwith, a Harvard University geneticist and a member of the Human Genome Project's working group on the ethical, legal, and social implications of human genetics research. He points out that Brunner's paper provides no information about whether the Dutch family's environment might have influenced their behavioral problems. Referring to the now discredited idea that there is a linkage between violent behavior by males and the possession of an extra copy of the Y (male) chromosome, Beckwith warns: "It would be a disaster if people suddenly decided to begin screening babies for monoamine oxidase deficiencies—as some did for the XYY defect."

–Virginia Morell

TECHNOLOGY

Recognizing Handwriting in Context

Computerized handwriting recognition, once a sleepy field populated by a few software engineers, has been jolted awake by an explosion of interest in hand-held computers that work with a pen. It is now a hotbed of activity. But even the best commercial systems today are hardly able to recognize half of the inconsistently scrawled words they tackle. So most systems restrict the vocabulary a user can employ and outlaw script, making the user print—slowly and carefully—instead. Now a research team at the University of Buffalo has given some old grade school rules a new spin, placed them into a writing recognition system, and nearly doubled its accuracy. The system, presented last month at a University of Buffalo handwriting recognition conference, identifies words by their context, relying on a series of probabilities known as "statistical grammar."

Conventional recognition systems identify a written word by guessing at each letter based on an analysis of its lines and curves, and then picking a word from the dictionary that most closely matches the string of guessed letters, along with a few alternative guesses. The new system, developed by Rohini Srihari, Stayvis Ng, Charlotte Baltus, and Jackie Kud of the University of Buffalo, evaluates the grammar of these guessed words as they appear in a sentence and determines which ones make the most sense.

To do that, the researchers had to overcome the basic challenge of "context-dependent" recognition: Standard rules of grammar permit words to be put together in many different ways. If the system gave each word candidate one of 60 different grammar "tags," based on categories like "noun," "verb," and individual pronouns, a computer would still come up with thousands of grammatically correct ways in which these tags could be strung together. "There are just too many ways to make a sentence," explains Srihari. "It leads to a combinatorial explosion."

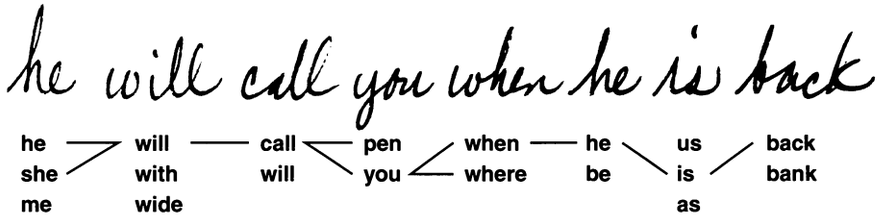
To muffle the explosion, Srihari dumped formal grammar in favor of "statistical grammar": She had a computer pore over thousands of electronic mail messages, noting the probability of each grammar tag being followed by another particular tag. (E-mail messages tend to employ the same informal language typical of handwritten messages, notes Srihari.) Other researchers have already applied this technique to character recognition, so that, for example, a system might know that the letter after a "q" is likely to be a "u," even if it looks more like an "n." Similarly, the Buffalo system can figure out that a "determiner" such as "the" or "a" is likely to be followed by a noun.

The context-based system works in tandem with a conventional recognition system. Once the conventional system makes a pass at a sentence and generates a list of candidate words, Srihari's system can on a first pass eliminate an average of 60% of the guesses because they represent an unlikely word transition. To narrow the choice down to a single, best-guess sentence, the system takes a second pass looking for the proper order of "hypertags": phrases such as the noun phrase "the cat", the verb phrase "probably is," and the prepositional phrase "under the table."

One limitation of the context-based system is that the conventional system underlying it must at least list the correct word, though it doesn't have to identify it as such; otherwise the context-based system has nothing to pick from. But if the right word is in the list, Srihari has found that her system improves accuracy from the conventional system's paltry 58% to an impressive 95%.

Srihari's group's work is "quite good," says Kai-FuLee, manager of speech and language technologies at Apple, adding that "the use of context will be one of the key techniques that will make handwritten computer communications possible."

–David H. Freedman



Sentence structure. The Buffalo handwriting recognition system picks correct words from lists of alternatives by determining which word is likely to follow another from a grammatical point of view. Lines between words indicate the most likely transitions.

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