

Evidence Uncovered for a Second Alzheimer's Gene

Alzheimer's disease may be caused by more than one gene. If this is confirmed to be the case, efforts to understand the genetic basis of the disease will be hindered

LAST YEAR a great deal of excitement was generated when researchers implicated a gene located on chromosome 21 as the cause of an inherited form of Alzheimer's disease. The discovery appeared to be another important advance in the new age of medical genetics, and it seemed to open the way to isolating the gene and thereby gaining some much needed insight into what causes the progressive mental deterioration that makes Alzheimer's disease such a devastating affliction.

On page 1507 of this issue of *Science*, however, a second group of researchers reports that they do not find an association between the chromosome 21 site and Alzheimer's disease in the families they are studying. The researchers, who include Gerard Schellenberg and George Martin of the University of Washington School of Medicine in Seattle and Thomas Bird of the Veterans Administration Medical Center in that city, suggest that the disease is genetically heterogeneous, that is, that it may be caused by more than one gene, located at different chromosomal sites.

If so, the results would mean not only that the etiology of Alzheimer's disease is even more complex than already thought, but also that efforts to isolate the disease-causing gene may be hindered. "It really will hold up progress if the disease is randomly heterogeneous," says John Hardy of St. Mary's Hospital Medical School in London. "It's going to make finding the gene extraordinarily difficult."

A large group of investigators led by Peter St George-Hyslop and James Gusella of Harvard Medical School made the original identification of chromosome 21 as the probable site of a gene defect that causes Alzheimer's disease (*Science*, 20 February 1987, p. 846). They had identified four large families, spanning five or more generations, in which the neurological condition appeared to be transmitted by a single autosomal dominant gene. This means that an inheritance of a single copy of the gene is sufficient to produce the condition. A hallmark of this familial type of Alzheimer's disease is that it develops relatively early in

life, usually when an individual is in his or her fifties.

With nothing known about the Alzheimer's gene or its product, St George-Hyslop and his colleagues turned to a standard genetic method known as linkage analysis to trace the gene location. The idea is to find particular DNA features or "markers" that are inherited together with disease. This would mean that the marker and the disease-

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causing gene are situated near one another on the same chromosome, although the marker is generally otherwise unrelated to the disease etiology. By mapping the marker position then, an investigator can locate the disease-causing gene.

In the families studied by the Boston workers, Alzheimer's disease was inherited with markers that the investigators mapped to the long arm of chromosome 21, a particularly interesting location. The chromosome had already been implicated as the possible site for an Alzheimer's gene. Down syndrome is caused by the inheritance of an extra copy of chromosome 21. People with this condition frequently develop Alzheimer's symptoms in their thirties and forties and have pathological changes in their brains like those seen in the brains of Alzheimer's patients.

Moreover, Hardy and his colleagues have recently completed their own linkage analysis with a group of families with early-onset Alzheimer's disease. "We've got very good evidence for linkage to chromosome 21 in the families we looked at," he says. "Essen-

tially our data confirm and extend the Boston group's."

That is not what the Seattle group found, however, when they looked for linkage between Alzheimer's disease and the chromosome 21 markers identified by the Boston group. "We tested the same markers and got negative results, excluding linkage to that region," Schellenberg says.

The absence of linkage for 6 of the 15 families in the Seattle study may not be surprising. Members of these families develop the disease much later in life than the early-onset patients studied by the Harvard and St. Mary's workers. Moreover, neither Hardy's group nor that of Alan Roses at Duke University Medical Center in Durham, North Carolina, have been able to detect linkage between late-onset Alzheimer's and the chromosome 21 markers.

Either this form of the disease is caused by a gene located elsewhere or it is not of genetic origin. "Just because you see families with multiple cases, it doesn't mean that the disease is genetic," Hardy cautions. He notes that the late-onset form of the condition is very common in the elderly. It may be that this form of the disease has an environmental cause, such as a chemical or virus, instead of a genetic origin.

The best way to tell whether late-onset Alzheimer's disease is genetic is to find a positive association between it and a specific gene locus, and that has not yet been done. Genetic studies of late-onset Alzheimer's disease are more difficult than those of the early-onset form. Only rarely are families with several affected members from two or more generations available for a condition that does not develop until the seventh, eighth, or ninth decade of life.

The other nine families in the Seattle study have early-onset Alzheimer's disease and are more comparable to those in which the linkage to chromosome 21 has been found. Exactly how comparable they are is a subject of some disagreement, however.

Seven of the nine families belong to an ethnic group known as the Volga Germans. These people are American descendants of a group of approximately 1000 Germans who moved to Russia in the 1760's and settled in two small towns near the Volga River. The supposition is that the members of the Volga German families all inherited their Alzheimer's gene from a common ancestor. This fortuitous historical event should make them a good homogeneous group for doing genetic studies.

Both St George-Hyslop and Hardy suggest that one possible explanation for the Seattle group's failure to find linkage between Alzheimer's disease and chromosome 21 is that the Volga Germans, who provided

the bulk of the data, may not have true Alzheimer's disease. Although these patients have typical Alzheimer's symptoms, the two researchers point out that previous reports indicate that they also display pathological and clinical changes, such as a spongy degeneration in the cerebral cortex of the brain and the presence of jerky movements (known as myoclonus), that do not usually occur in Alzheimer's patients.

Nevertheless, the Seattle workers note that the Alzheimer's diagnosis was confirmed by autopsy for at least one patient in all of the German Volga families except one on which no autopsies were performed. The disease can be hard to diagnose, but the brains of patients show characteristic pathological changes, called plaques and tangles, that can be detected by autopsy. Moreover, Schellenberg notes that myoclonus does occur in a minority—perhaps 25 or 30%—of Alzheimer's patients. "Everything we know about the Volga Germans suggests that they are typical, mainstream Alzheimer's patients," he maintains.

As things now stand then, two groups have found linkage between early-onset Alzheimer's disease and chromosome 21 and one group has not. This raises the possibility that the condition may be caused by more than one gene defect, as Schellenberg and his colleagues suggest. The issue is a critical one for the purposes of gene isolation. If two or more different genes can cause a disease, and if they are randomly distributed in the patient population, then gene isolation efforts will be impeded.

Researchers have been trying to zero in on the Alzheimer's gene on chromosome 21, for example, by finding new markers that are progressively closer to the gene. But the presence of a second disease-causing gene randomly distributed in the patient population can essentially cause them to lose their place on the gene map by making a new marker appear to be farther away from the target gene than it actually is.

Among the additional evidence that would help to confirm the genetic heterogeneity of early-onset Alzheimer's disease is a positive demonstration of linkage to markers located somewhere other than the long arm of chromosome 21. The Seattle group is now pursuing that goal. If such a second chromosomal location can be found, the apparent genetic homogeneity of the Volga Germans may facilitate efforts to isolate the gene itself.

In addition, St George-Hyslop is currently participating in a 40-family study that may also help to resolve the issue of the genetic heterogeneity of Alzheimer's disease. Results are expected in a few months.

■ JEAN L. MARX

Hip Joints: Clues to Bipedalism

The distinctly odd human habit of walking around exclusively on two limbs rather than four, as most good mammals do, has long demanded an explanation from anthropologists, and for good reason. For instance, if our ape-like ancestor of some five or so million years ago had not adopted this bipedal mode of locomotion, then farther down the evolutionary line the development of manipulative skills—the basis of material "culture"—might not have emerged as it did. Whatever was the immediate engine for the evolution of hominid bipedalism—and almost certainly it had to do with the energetics of collecting food—there also remains the question of how quickly and completely it was adopted. Two schools of thought exist. The first, promulgated principally by Owen Lovejoy of Kent State University, is that right from the beginning hominids were fully bipedal, much like modern humans. The second, collectively argued by several researchers at the State University of New York at Stony Brook, is that the adoption of bipedalism was a more gradual affair, with our early ancestors dividing their time between walking upright on the ground and climbing in trees.

The question is, how to distinguish between these two possibilities? The debate so far has centered on the anatomy of the pelvis, which is shaped dramatically differently between apes and humans, for instance, and the form of the hands and feet. In apes, which spend a lot of time climbing, the hand and foot bones are curved, the result of the stresses of climbing. In humans, these bones are more or less straight. And in early hominids? Somewhat in between, which can be taken as merely a genetic holdover, having no functional significance (school 1) or to indicate some continued adaptation to climbing (school 2). This debate has ranged back and forth now for half a dozen years, apparently with no resolution in sight.

The latest contribution to the debate is from William Jungers, one of the Stony Brook team, and it shifts the focus of attention from bones to the joints between them. As anyone with a "bad back" knows, the human habit of walking around exclusively on two limbs has its special stresses and strains. A less obvious sign of these stresses and strains than the nagging pain in the lower back is the unusually large size of the joints involved in keeping us upright: specifically, the junction between the spine and the pelvis, and the hip and knee joints. Following an extensive statistical analysis of limb joints in apes and humans, Jungers concludes that "Regardless of the method, the observation that emerges conspicuously is that modern humans possess exceptionally large hindlimb and lumbo-sacral joints for their body size." The obvious biomechanical reason for this pattern is that humans must bear all their weight on two limbs rather than distributing it among four. As a result, the joints have to be considerably more extensive in surface area so as to maintain stresses within safe limits.

In all the diagrammatic representations of the analyses, the apes cluster rather closely together on one side while humans stand alone on the other. And what of early hominids, specifically "Lucy," the specimen of *Australopithecus* that Jungers chose to examine? Once again the early hominid falls in between modern humans and apes: the size of her thigh joint, for instance, was bigger for her body size than the average ape's, but not as big as a human's. The clear implication is that Lucy routinely experienced less total pressure across her thigh joint than modern humans do. "When on the ground, Lucy no doubt walked bipedally," says Jungers. "However, the decidedly nonhuman degree of relative joint size in [Lucy] implies that this adaptation was far from complete and scarcely full-blown or functionally equivalent to that seen in modern humans."

If, as Jungers claims, the first known hominid was not a habitual biped in the sense that modern humans are, when did our ancestors develop the habit? "It seems highly likely that a Lucy-like locomotor adaptation was a stable one that persisted perhaps until the time of *Homo erectus*," says Jungers. *Homo erectus*, which first appeared about 1.6 million years ago, was different from other hominids in several respects, perhaps including an adaptation to a habitual striding gait. If Jungers is correct, the origin of *Homo erectus* would indeed have involved a real adaptive transition in hominid history.

■ ROGER LEWIN

ADDITIONAL READING

William Jungers, "Relative joint size and hominoid locomotor adaptations," *J. Hum. Evol.* 17, 247 (1988).