Scientists Probe Role of Genes, Environment in Parkinson Disease

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WASHINGTON, DC—Although scientists have found about a dozen genes associated with familial Parkinson disease and identified environmental factors linked to altered risk for developing the sporadic form of the disorder, its etiology remains elusive. But now, researchers are applying molecular and genomic tools to develop a better understanding of this devastating illness.

As reports from the first World Parkinson Congress held here in February indicate, such tools are indeed helping scientists make headway in deciphering the precise molecular events underlying the disorder and understanding how these might interact with environmental factors. One researcher presented the results of a large-scale whole genome survey of genes associated with Parkinson, identifying one novel gene variant linked to the disorder and pointing to two potential molecular mechanisms. Two other studies suggest how particular gene variants might interact with environmental factors to modulate risk.

A COMPLEX DISEASE

“The vast majority of Parkinson disease is not inherited in a simple way,” said Harvey Checkoway, PhD, MPH, a professor of epidemiology at the University of Washington, Seattle. “It’s a complex disease and probably has many different factors that influence risk, including genes that interplay with environmental factors.”

Large epidemiological studies have helped identify several environmental factors that are associated with risk of developing the disorder. Compounds that have been frequently associated with an increased risk of Parkinson disease are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a compound that is sometimes accidentally produced in the manufacture of certain illegal drugs; pesticides; certain metals; and polychlorinated biphenyls. Several factors, including smoking, coffee and tea drinking, nonsteroidal antiinflammatory drugs, and having increased uric acid levels in the blood, have also been associated with a reduced risk, said Caroline M. Tanner, MD, PhD, director of clinical research at the Parkinson Institute in Sunnyvale, Calif.

Alberto Ascherio, MD, DrPH, associate professor of nutrition and epidemiology at the Harvard School of Public Health, presented findings bolstering earlier evidence that uric acid, a powerful antioxidant found in serum and in the brain, is protective against Parkinson. Using a nested case-control analysis of 84 individuals with Parkinson and 168 controls from the Health Professionals Follow-up Study, Ascherio and colleagues found that elevated levels of uric acid in the blood were associated with a significant reduction in the risk of Parkinson disease. This finding also held in a meta-analysis that pooled their study data with that from two previous studies that had found a marginally significant reduction in risk associated with higher uric acid levels (Davis JW et al. Am J Epidemiol. 1996;144:480-484, and de Lau LM et al. Ann Neurol. 2005;58:797-800).

There is a plausible biological explanation for why elevated uric acid levels might be protective against Parkinson disease, which results from the progressive loss of dopamine neurons in the substantia nigra of the brain. Researchers hypothesize that oxidative stress contributes to the loss of such neurons; if that’s the case, elevated levels of an antioxidant like uric acid might be protective. Because uric acid levels can be...
manipulated through diet and other interventions, these data may point to potential therapies or preventive strategies, Ascherio said. “We’re still in the very early days,” he added, noting that more research is necessary to determine whether this strategy could actually help treat or prevent Parkinson and whether raising the levels of uric acid or some other antioxidant would be associated with any adverse events.

GENOMIC CLUES
Other researchers have used high-throughput genomic technologies to hunt for genes and identify the molecular pathways these genes might influence.

Using such technologies, Demetrius Maraganore, MD, professor of neurology at the Mayo Clinic in Rochester, Minn, and colleagues identified 11 genomic markers of Parkinson disease in 11 distinct locations in the human genome (Maraganore DM et al. Am J Hum Genet. 2005;77:685-93). In the first part of the analysis, which involved 43 sibling pairs in which one sibling had Parkinson (either familial or sporadic) and the other did not, the investigators individually genotyped nearly 200,000 single-nucleotide polymorphisms (SNPs) in the DNA of these sibling pairs. (SNPs are DNA sequence variations that occur when a single nucleotide, or “letter” in the genome sequence is altered.) In the second part of the study, which involved 332 case-unrelated control pairs, they genotyped more than 1700 Parkinson disease-associated SNPs and 300 control SNPs.

One of the SNPs found by the analysis to be associated with Parkinson disease is located within the gene encoding semaphorin 5A protein (SEMA5A), which plays a crucial role in guiding the development of the axons of dopamine neurons. Maraganore said this is a particularly interesting finding because it suggests a plausible explanation for why variation in this gene might lead to dopamine deficiency in the striatum, the presumed cause of the symptoms of Parkinson disease. He explained a gene variant encoding abnormal SEMA5A protein would lead to abnormal dopamine neuron connections in the striatum and could lead to a congenital deficiency of dopamine in this region.

“If you are born with less dopamine in the striatum to begin with, it would probably take fewer other insults to lower you below the threshold at which symptoms would become apparent,” Maraganore said.

The SEMA5A protein also initiates apoptosis (programmed cell death) of dopamine nerve cells, so a variant of the gene might cause the die-off of dopamine neurons documented in patients with Parkinson.

In this case, fishing through the whole genome for genes relevant to the disease seems to have paid off, turning up a possibility researchers had not previously considered.

“We would have never anticipated this genetic association with a candidate gene approach,” Maraganore said. “This was nowhere on the radar screen for Parkinson disease.”

The analysis also provided a higher resolution map of two regions of the genome that have been linked to familial forms of Parkinson disease and suggests that genes within these regions might also play a role in sporadic cases of the disorder. In addition, the scientists identified a gene called LOC200008 within one of these regions that is highly associated with the risk of developing Parkinson disease. There is evidence that LOC200008 may encode a protein involved in electron transport in the mitochondria, explained Maraganore. Animal studies have previously found that MPTP and a pesticide called rotenone cause Parkinson-like symptoms by disrupting electron transport in the mitochondria, he noted. If a variant of LOC200008 produces an abnormal protein that somehow compromises electron transport, it would provide a plausible explanation why this gene might heighten susceptibility to Parkinson disease, perhaps by interacting with environmental factors that have the same disruptive effect, Maraganore said.

If the results of the study are verified, it could provide pharmaceutical companies with new therapeutic targets. For example, a drug might be able to slow the death of dopamine neurons in the brains of patients with Parkinson disease by targeting the receptors that bind the SEMA5A protein, preventing it from signaling that the cells should die.

GENE-ENVIRONMENT LINKS
Two other studies provided possible explanations for how genetic susceptibilities might interact with environmental factors to determine an individual’s risk of developing Parkinson disease.

One study provided further clues about the role that excessive nitric oxide levels in the brain might play in Parkinson disease and how this damage might be modulated by smoking. Scientists have demonstrated that high nitric oxide levels are neurotoxic and that inhibiting nitric oxide–producing enzymes such as inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) is neuroprotective. A French study published in 2003 suggested that polymorphisms in the genes for iNOS and nNOS are associated with an increased risk of Parkinson disease and suggested that nNOS might interact with smoking (Leveque C et al. Hum Mol Genet. 2003;12:79-86). Now a larger gene-association analysis of more than 1142 individuals with Parkinson disease and 1197 controls from 752 families has found that two variants of the gene for iNOS are associated with Parkinson disease risk in families with earlier onset disease. The study, presented by Dana Hancock, a graduate student working in the laboratory of William Scott, PhD, at Duke University, in Durham, NC, also suggested that individuals who carry these variants may not benefit from the protective effects of smoking that have been observed in previous studies. The findings indicate that these variants may not only increase the risk of developing Parkinson disease but also possibly lower the age of onset, said Hancock.

Based on these findings and a recent study that suggested smoking in-
Avian Flu Risk to Humans Probed
Viral Adaptation to Human Cells Would Aid Spread

Tracy Hampton, PhD

As change is one of the constants with viruses, scientists are vigilantly monitoring variances that arise in the H5N1 avian influenza virus that might lead to a pandemic in humans. And in an attempt to stay one step ahead of the H5N1 virus, researchers are trying to predict how it could change its characteristics and cell-binding preferences in the future. Recent efforts with these endeavors have resulted in new information that might be used to prevent the H5N1 virus from gaining a foothold in the human population.

LUNG LOCALE

Two recent articles reveal that, contrary to the notion that avian influenza virus has little affinity for cells of the human respiratory tract, the H5N1 virus preferentially binds to cells deep within the human airway. The studies’ findings indicate that while human influenza virus binds to molecules that are prevalent on the surface of cells in the upper airway, avian virus preferentially targets molecules that tend to be found on the surfaces of cells lining alveoli, deep within the lungs. This finding may explain why human-to-human transmission of current strains of the H5N1 virus is inefficient.

The molecules bound by avian and human influenza viruses are receptors called SAα2,3Gal and SAα2,6Gal, respectively. Researchers led by University of Wisconsin–Madison’s Yoshihiro Kawaoka, PhD, analyzed human tissues and found that avian-type SAα2,3Gal receptors were absent in cells in the upper portions of the respiratory system but prevalent in cells in the lower portions (Shinya K et al. Nature. 2006; 440:435-436). Conversely, human-type SAα2,6Gal receptors were abundant in the upper regions but lacking in the lower regions of the respiratory tract.

Another group, led by Thijs Kuiken, DVM, PhD, of the Erasmus Medical Center in Rotterdam, the Netherlands, compared the pattern of H5N1 exhibit iNOS (Mazzio EA et al. Neurotoxicology. 2005;26:49-62), Hancock hypothesizes that by binding iNOS, cigarette smoking may prevent toxic levels of nitric oxide from developing, although she noted that biological evidence to support this idea is currently very limited. Scott, an associate research professor at the Center for Human Genetics at Duke, said further studies by his laboratory will focus on determining the functional significance of these or other variants of the iNOS gene.

In another presentation, Maria Angeles Mena, PhD, an investigator in the department of neurobiology at the Hospital Ramón y Cajal, in Madrid, said that she and her colleagues found that neuronal cells cultured from mice that carry the Park-2 gene variant were more susceptible to rotenone-induced apoptosis than were neuronal cell cultures from control mice. Additionally, they found that microglia activation is involved in such damage. Microglia play an important role in the immune response of the central nervous system, but some scientists have suggested that in such disorders as Alzheimer disease, a brain injury or insult might trigger excessive microglia activation, leading to inflammation and, ultimately, neurodegeneration. Treating Park-2 cultures with minocycline, an inhibitor of microglia activation, prevented rotenone’s damaging effects on these cultures.

“This animal model is very nice because it proves the interaction between genetic and environmental factors in Parkinson disease,” said Mena.