NEWS

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NEW STUDIES SHED LIGHT ON PARKINSON DISEASE

San Diego—October 26, 2007. Three reports on important genetic breakthroughs related to Parkinson disease will be presented at the 57th Annual Meeting of the American Society of Human Genetics in San Diego, California, October 23-27.

- **Nitric Oxide, Smoking, Pesticides, and Parkinson Disease**
- **MicroRNA Involvement in Parkinson Disease Is "Tip of Iceberg"**
- **New Locus Detected for Parkinson Disease**

Brief descriptions of the major findings of these three reports are presented below.

Parkinson disease (PD) affects approximately 1% of the population over the age of 50, and is the second most common neurodegenerative disease after Alzheimer disease.

Nitric Oxide, Smoking, Pesticides, and Parkinson Disease
Researchers at the University of Miami and Duke University have shown that variants of two nitric oxide synthase (NOS) genes are risk factors for Parkinson disease (PD). They have also shown that some of these gene variants can interact with established environmental risk factors (smoking and pesticide exposure) for PD and may, in this way, also influence susceptibility to PD. The researchers believe that further investigations of these gene-environment interactions may reveal key biochemical pathways related to PD susceptibility, and that these pathways may provide targets for effective clinical intervention.

Nitric oxide (NO) is famous as the molecule whose levels are increased by administration of erectile dysfunction medications, but NO has numerous physiologic roles as a biological messenger molecule. In 1992, it was declared "Molecule of the Year" by *Science* magazine, and in 1998, the significance of work on NO as a signaling molecule was recognized with awarding of the Nobel prize. NO also has a metabolite that is a free radical that can contribute to oxidative stress and induce numerous negative changes in cells, including lipid peroxidation, functional alterations in proteins, DNA damage, and mitochondrial energy dysfunction.

Nitric oxide synthase genes *(NOS1, NOS2A,* and *NOS3)* have been thought to be candidate genes for PD, as excess NO levels are associated with depletion of dopamine-producing neurons in the substantia nigra region of the brain—and this is a cardinal finding in PD. And earlier work by these researchers and others has suggested a possible association between NOS gene polymorphisms and PD

In particular, *NOS1* and *NOS2A* are believed to be especially good candidate genes for PD susceptibility—*NOS1* because it is expressed specially in neurons and *NOS2A* because it is triggered by inflammatory mediators to produce high NO levels in the brain and other tissues. Many have suggested that PD is triggered by neuroinflammation. *NOS3* is perhaps a less likely candidate gene because it is expressed predominantly in the endothelium of blood vessels throughout the body. It is this gene that is associated with erectile dysfunction medications.

In addition to the possible gene effects, it is thought that NO levels can be affected by putative PD environmental risk factors-- smoking (reduced risk of PD), caffeine (reduced risk of PD), non-steroidal anti-inflammatory drugs (reduced risk of PD), and pesticide exposure (increased risk of PD). Therefore, it has been suggested that NOS genes might interact with these environmental factors to alter NO levels and thus also affect susceptibility to the development of PD.

In the current work, genotyping studies of particular gene variations (SNPs) in *NOS1* (27 SNPs), *NOS2A* (18 SNPs), and *NOS3* (5 SNPs) showed significant association of seven *NOS1* SNPs and seven *NOS2A* SNPs with PD. No associations between the *NOS3* SNPs and PD were found. In addition, significant associations between pesticide exposure and two of the *NOS1* SNPs, and between smoking and two of the *NOS2A* SNPs were found in relation to PD.

The results support *NOS1* and *NOS2A* as genetic factors for PD, and demonstrate that the interactions of these genes and/or their products with environmental factors may also influence susceptibility to PD development. The authors note that there is prior evidence for a possible biological explanation for smoking interacting with *NOS2A* to inhibit the production of NO. To their knowledge, however, there is no prior evidence for a biological explanation for the interaction of pesticides with NOS1. Future work will focus on unraveling these gene-environment interactions with the goal of possibly revealing underlying biochemical pathways that might prove amenable to targeted clinical intervention.

The authors of this work are Ph.D. candidate Dana Hancock, of Duke University, and Eden Martin, Ph.D., Jeffrey Vance, M.D., Ph.D., and William Scott, Ph.D., all formerly of Duke University and now of the University of Miami. Dr. Vance is chair of the Division of Human Genetics, Department of Medicine, and director of the Center for Genomic Medicine at the University of Miami Miller School of Medicine. He is also director of the Morris K. Udall Parkinson Disease Research Center of Excellence at the University of Miami.

MicroRNA Involvement in Parkinson Disease is "Tip of the Iceberg"

Researchers at the University of Miami have shown that a known genetic risk factor for Parkinson disease (PD) likely operates via disruption of a microRNA (miRNA)-mediated regulatory mechanism. They have further shown that this disruption is likely to lead to overexpression of -synuclein, which, in excess, is known to cause PD.

The authors suggest that the newly described mechanism of regulatory disruption may prove to be commonly involved in the modulation of individual susceptibility to various complex diseases. In fact, they postulate that their current finding represents "just the tip of the iceberg" for future research in the area of miRNA-influenced susceptibility to complex diseases.

miRNAs are small, non-coding transcripts of approximately 22 nucleotides that negatively regulate the translation of complementary mRNA, usually by binding in the 3' untranslated region (UTR) of the mRNA. It is believed that miRNAs play important roles in development, cell death, and cell proliferation.

Previous work by the authors had demonstrated linkage of chromosome 8p to PD and subsequent work by others had identified a gene in this region *(FGF20*—fibroblast growth factor 20) as a risk factor for PD.

Multiple lines of evidence support this association, the authors noted. These include evidence that *FGF20* is preferentially expressed in the substantia nigra region (the most affected region in PD) compared to other regions of the brain and a recent report that FGF20 protein has neurotrophic properties and promotes survival of dopaminergic neurons. PD is characterized, in part, by the depletion of dopaminergic neurons in the substantia nigra region of the brain.

In the current work, the authors further examined the association between *FGF20* and PD and found the strongest disease association with a SNP in the 3' UTR of *FGF20.* Functional analysis showed that this SNP disrupts a binding site for a particular miRNA (miR-433) and leads to increased translation of *FGF20* both in vitro and in vivo. miR-433 is highly expressed in brain, but not in heart, liver, or kidney, the authors noted.

The authors further noted that, in a cell-based assay and in PD brains, the increase of *FGF20* translation is correlated with increased expression of □-synuclein, which has previously been shown to cause PD through both over-expression and point mutations.□-synuclein is the principal component of Lewy bodies, the defining pathological hallmark of PD.

The authors conclude that the risk-conferring SNP in *FGF20* disrupts a key miRNA binding site leading to the upregulation of *FGF20* and the correlated increased expression of □-synuclein, which can cause PD.

They suggest that this novel mechanism of regulatory disruption by a gene variation may prove to be of much wider general significance in individual susceptibility to complex diseases.

Future work will include efforts to determine if miR-433 and FGF20 will potentially be useful in PD diagnosis and treatment.

The first author of this paper is Gaofeng Wang, Ph.D., assistant professor of medicine at the University of Miami's Center for Genomic Medicine and Center for Molecular Genomics. The senior author is Jeffery Vance, M.D., Ph.D., chair of the Division of Human Genetics, Department of Medicine, and director of the Center for Genomic Medicine at the University of Miami Miller School of Medicine. He is also director of the Morris K. Udall Parkinson Disease Research Center of Excellence at the University of Miami.

New Locus Detected for Late-Onset Parkinson Disease

In a genome-wide association study of a genetically isolated population, scientists have identified a novel locus for susceptibility to late-onset Parkinson disease (PD). The locus, as defined by disease-associated SNPs, is a 1.1 Mb region on chromosome 9. The authors noted that several interesting candidate genes for PD, most notably *GRIN3A* and *PPP3R2*, are located within 1.5 Mb of the locus.

GRIN3A (glutamate receptor, ionotropic, 3A) is also known as N-methyl-D-aspartate (NMDA) receptor 3A. NMDA receptors belong to superfamily of glutamate-regulated ion channels and are present in neurons throughout the CNS. Calcium flux through NMDA receptors is thought to play a critical role in synaptic plasticity, a cellular mechanism related to learning and memory.

PPP3R2 (protein phosphatase 3, regulatory subunit B) is also known as calcineurin B, type II. Calcineurin is especially abundant in the brain where it constitutes 1% of total protein.

The current study was carried out on a genetically isolated Turkish population that shows increased prevalence of late-onset PD relative to the general (Turkish) population. An Affymetrix 10KSNP Chip was used to genotype 31 late-onset PD patients and 27 unrelated controls. The results demonstrated that one SNP was strongly associated with the disease in this population. 30 additional SNPs covering a 1.1 Mb region surrounding the initial SNP were tested and multiple SNPs in this group confirmed the initial association.

Because associations found in isolated populations are often not found in different populations, the authors tested the association in two additional isolated populations and the general Dutch population by screening for association with tagging SNPs for six candidate genes in the region of the locus. They said that results showed that multiple tagging SNPs for these candidate genes were significantly associated with PD in the additional isolates and the general Dutch population.

The first author of this report is Zoltan Bogdanovits, Ph.D., of the VU Medical Center in Amsterdam, the Netherlands. The senior author is Peter Heutink, Ph.D., also of the VU Medical Center.

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