Robinson Awarded Five-Year R01 Grant

Bowles Center for Alcohol Studies Researcher Donita Robinson, Ph.D., recently received her first Research Project Grant (R01) from the National Institutes of Health's National Institute on Alcohol Abuse and Alcoholism. Totaling just over a million dollars, the five-year project will examine dopamine release and neural activity in rat models of habitual alcohol drinking and cue-induced relapse.

The project, titled 'Habits and cues in alcohol drinking: Dynamic striatal activity,' will look at the major factors that contribute to habitual alcohol drinking, such as the learning processes underlying habit formation and the degrees to which habits versus goal-directed behaviors may influence the susceptibility to relapse.

"Alcoholism is a chronic disorder that typically spans several decades and may be perpetuated by learned, habitual behavior. Studies in rats can model the contribution of habit to alcohol drinking and allow direct measurement of brain function during these behaviors," said Robinson.

Dopamine is a neurotransmitter, important in many functions, including learning, movement, attention and reward. Robinson is focused on the key role of dopamine in the association between cues and drug experience. Addiction links cues and drug experiences leading to cues, e.g. seeing an alcohol advertisement or establishment prompts hunger for the reward, e.g. craving for drug. Psychologists have found that addicted individuals respond to cues that they learned were rewarding when first experimenting with drugs, even after they stop being rewarding, e.g. continued drug seeking in the absence of reward (and likely presence of negative consequences). The psychological shifts from goal-directed behavior to automatic habitual behavior are thought to be based on changes in dopamine neurotransmission.

Donita Robinson, Ph.D.

Robinson can measure neuronal activity in brain in subsecond time spans that follow synaptic transmission in moving, behaving rats. This allows the determination of brain region-specific synaptic plasticity, and neuronal activity being related to behavior at various stages of alcohol experience, experimentation, learning use, dependence, abstinence and relapse She will test the overall hypothesis that subsecond dopamine release and ongoing neuronal activity differ in the brain areas active during goal-directed alcohol reinforcement compared to the areas preferentially active during habitual alcohol reinforcement and cue-induced relapse.

Data from this study will provide important information on how the brain differentially encodes goal-directed versus habitual alcohol drinking. Robinson thinks that these studies could potentially identify novel mechanisms that would be of crucial importance to understand the development and treatment of alcohol abuse and alcoholism. ■

The Bowles Center for Alcohol Studies

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Center Line

Bowles Center for Alcohol Studies
School of Medicine, University of North Carolina at Chapel Hill

Our mission is to conduct, coordinate, and promote basic and clinical research on the causes, prevention, and treatment of alcoholism and alcoholic disease.

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Wilhelmsen Lab: On the Cutting Edge of Efforts to Elucidate the Genetic Determinants of Alcoholism

"It's no wonder he's a drinker; alcoholism runs in his family." This statement could as easily have been made a hundred years ago as it could be made today. That a person's heritage influences his susceptibility to alcoholism and other addictions has been recognized by both scientists and lay people for centuries. The importance of genetic factors in alcoholism is supported by the finding of higher risk of alcoholism among relatives of an alcoholic than among the general population, as well as a higher risk among genetically identical twins than among fraternal twins or non-twin siblings (who are genetically similar but not identical). The evidence that children of alcoholics who are adopted and raised by their non-alcoholic parents are at heightened risk of alcohol dependence also reflects a significant genetic contribution to alcoholism. Indeed, family and twin studies suggest that a person's genetic make-up explains approximately 40% to 60% of the risk for alcoholism.

While the conclusion that there is a genetic contribution to alcoholism and addiction is inescapable, success in identifying genes that play a major role in alcohol addiction has been limited. Anticipating that the effect of genes on alcohol use behavior would be complex, several investigators have been focusing on developing strategies to dissect complex genetic systems. Dr. Kirk Wilhelmsen, Distinguished Scholar and Associate Professor in the Departments of Genetics and Neurology and the Bowles Center for Alcohol Studies at UNC, is at the forefront of these efforts. Wilhelmsen is famous in neurology circles for his discovery a decade ago of the role of genetic mutations in a protein known as tau in neurodegenerative diseases such as frontal-lobe dementia and Parkinson's. While he continues to study the role of genetic mutations in neurodegeneration, Wilhelmsen has developed a twin interest in the genetic determinants of addiction, including alcohol and nicotine dependence. "I can think of few conditions that involve more complex interactions between genes and the environment than addiction," says Wilhelmsen. "Gaining insight into addiction, which is medically important, will also tell us important things about how the brain works. Addiction is the subversion of biologic processes that affect learning and these processes drive behavior."

Wilhelmsen Lab (Left to Right): Scott Chasse, Ph.D., Kirk Wilhelmsen, M.D., Ph.D., Gabi Cameron, B.S., Amy Webb, B.S., Jackie Ellis, B.S., and Ian Gizer, Ph.D.

Dr. Wilhelmsen believes the principal reason that genetic analysis of alcoholism has had such limited success is that a change in approach is needed. Geneticists have learned that without correctly defining a trait that gene mapping will usually fail. Dr. Wilhelmsen's group has focused on deter-mining the attributes of alcohol use behavior that are linked to the chromosomes they implicate in alcoholism. This approach has produced much stron-ger evidence for the location of genes that affect alcoholism than the conventional approach. The unique aspects of this approach are that it could find genetic subtypes of alcoholism and/or genetic linkage to characteristics that overlap with other mental diseases like anxiety. This novel approach of careful behavioral phenotyping and genotyping to the specific phenotypes may uncover strong associations not previously recognized.

Wilhelmsen began his study of addiction at the Gallo Clinic and Research Center and the University of California at San Francisco, where he established clinical and laboratory programs to identify addiction

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Kirk C. Wilhelmsen, M.D., Ph.D.

Affiliations

Associate Professor, Departments of Genetics and Neurology and the Bowles Center for Alcohol Studies, UNC-Chapel Hill.

Education and Training

M.D., University of Wisconsin, Madison, 1986; PhD in Molecular Biology, University of Wisconsin, Madison, 1984; BS in Chemistry, University of California, San Diego, 1978.

Recent Publications

Webb A, Miller B, Bonasera S, Boxer A, Karydas A, **Wilhelmsen KC**. Role of the tau gene region chromosome inversion in progressive supranuclear palsy, corticobasal degeneration, and related disorders. Arch Neurol. 2008 Nov;65(11):1473-8.

Ehlers CL, Lind PA, **Wilhelmsen KC**. Association between single nucleotide polymorphisms in the mu opioid receptor gene (OPRM1) and self-reported responses to alcohol in American Indians. BMC Med Genet. 2008 Apr 23;9:35.

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Website

www.med.unc.edu/alcohol/wilhelmsen

susceptibility genes. At the Gallo Center, Wilhelmsen was the only geneticist among clinical and animal researchers who studied the physiological and behavioral effects of alcohol, and he was charged with establishing, from the ground up, the incredibly complex computing and databasing infrastructure required for genetic analysis. He moved to UNC in the fall of 2004 in part to take advantage of the university's network of investigators with interest in human genetics, neurobiology, and complex traits. UNC has benefited from Wilhelmsen's vast experience in creating the infrastructure necessary for genetic analysis.

At UNC, Wilhelmsen has developed large-scale, highly automated systems for genotyping, which is the process of determining the genetic makeup of an individual by using biological assays. The data derived from these systems enable analysis of large numbers of traits for the entire human genome. Two types of analysis—linkage analysis and association analysis—are performed. Linkage analysis involves sequencing portions of chromosomes to search for genetic markers of disease. Association analysis involves comparing the genotypes, or genetic makeups, of a population of individuals with a disease to those of a control population without the disease to identify genetic variations responsible for a trait.

Wilhelmsen's lab has completed the laboratory analysis for four large-scale, family-based projects and has identified several chromosome locations for behavioral traits related to alcohol addiction. They found that chromosome locations implicated in alcoholism and other forms of drug dependence are also related to consumption behavior in general. Furthermore, they determined that body mass index was strongly linked to the same chromosome region. By a systematic exploration of alcoholism trait definition, the Wilhelmsen group has been able to integrate the evidence supporting the gene mapping data from many studies. Such consistency between studies is rare in behavioral genetics, suggesting that proper trait definition matters and will lead to success in the identification of alcohol addiction genes.

Wilhelmsen's expertise in genetic analysis and infrastructure has led to collaborations across institutions. Wilhelmsen is integrally involved in the Renaissance Computing Institute (RENCI), a collaborative, multidisciplinary organization that involves government, industry, and academic institutions including UNC, Duke University, and North Carolina State University. Supported by the state of North Carolina, RENCI was launched in 2004 to bring world-class computing and technology resources to bear on addressing research questions and identifying solutions to scientific and medical problems affecting North Carolina, the nation, and the world. Many of the RENCI initiatives are directed at identifying means of improving healthcare and people's overall health.

"Identifying these genes will eventually lead to biologically based individualized therapies."

Wilhelmsen is co-principal investigator of a large new multidisciplinary initiative called Carolina Center for Exploratory Genetic Analysis (CCEGA). This project brings geneticists, statisticians, and computer scientists together to develop the technological infrastructure needed to identify the genetic determinants of human diseases. An important focus of CCEGA's is developing the tools to support the genetic analysis of complex traits like alcohol addiction. Funded by the National Institutes of Health, CCEGA has developed tools to analyze the relationships between genotypes and physical and behavioral traits in three contexts: (1) *family linkage studies*, which examine the relationships between genotypes and susceptibility to alcoholism; (2) *gene expression profile studies*, which identify genetic and cellular patterns or signatures associated with disease; and (3) *public health studies*, which identify risk factors in specific communities. Conducting these studies requires analysis of a vast quantity of genetic data at a rate fast enough to provide information meaningful to the scientists interpreting it. Wilhelmsen is a leader in these efforts.

The increasingly sophisticated genetic tools, developed by Wilhelmsen, could contribute to enormous advances in the treatment of alcoholism and other addictions. Two of these tools which the Wilhelmsen Group has developed, called Convergent Haplotype Association Tagging and Genometric Linkage Analysis, require supercomputing capability. Together with computer scientists at RENCI, the Wilhelmsen group is developing web portals so that these tools can be used by the wider genetics community. One potential future application of genetic data is prediction of risk or susceptibility for alcoholism. Genetic information on risk combined with information on family history of alcoholism and personal history of alcohol consumption could improve the ability to predict risk of becoming an alcoholic. Armed with knowledge of their genetic risk, individuals could modify their behavior to minimize the chance that they will become alcohol dependent. Another potential application of genetic data is the ability to tailor medicine to the genetic make-up of an individual. One day, it may be possible to select pharmacotherapy for alcoholism based on a person's genotype in order to maximize the efficacy of therapy. Some progress in this area has already been realized: the efficacy of naltrexone in the treatment of alcohol dependence has been found to depend partly on a polymorphism (i.e., a genetic variant) in a specific type of receptor on nerve cells (the mu opioid receptor).

"People who drink excessively do so because environmental influences and inherited biological factors interact in complex ways," says Wilhelmsen. "Human genetic analysis has allowed disease-causing genes to be identified for many conditions, and I am confident that we will one day identify key genes for alcoholism. Identifying these genes will improve our understanding of the biological causes of excessive drinking and eventually lead to biologically based individualized therapies." ■

The Director's Column

Fulton T. Crews, Ph.D.
Director,
Bowles Center for Alcohol Studies

The genetics of alcoholism is one of the great challenges of 21st century medicine. We know that alcoholism is associated with families. Genetics are important, although family association likely includes both genetic and environmental factors, since alcohol exposure differs in families with alcoholism. Both protective and risk genes are likely very important in the genetics of alcoholism. We know genes that metabolize alcohol play a role in the genetics of alcoholism. Individuals who have very fast alcohol dehydrogenase and/or slow aldehyde dehydrogenase gene alleles have an endogenous Antabuse®-like reaction to alcohol that protects them from becoming alcoholic. The endogenous Antabuse®-like reaction makes them sick when they drink alcohol, yet these metabolic alleles do not protect all from becoming alcoholics.

Many factors, including animal genetic models of alcoholism, suggest genes that regulate brain function may be important in alcoholism. Family history and risk for alcoholism are genetically linked to a low sedative response to alcohol. We don't know which genes. The sedative response to alcohol is likely due to differences in the brain. There is a lot of effort to understand the sedative response, alcohol tolerance and physical dependence, but it is complicated and not well understood.

Likely equally important, not every alcoholic is the same. They have various alleles of about 20,000 genes, some of which are silenced depending upon if they came from the mother or father. Environmental factors, including nutrition, nurture, and all that shapes our development, make each human unique. Mental disease phenotypes that characterize a disease can include differences in tolerance, withdrawal, compulsive drive, impulsive actions promoting negative consequences, anti-social and social anxiety factors that contribute to the diagnosis of alcohol dependence. Another part of the complexity is that other mental diseases, such as depression and anxiety, are often diagnosed as co-morbid when combined with alcohol dependence. All of these factors make it very difficult for geneticists to find which alleles of genes associate with alcoholism.

What is exciting about Kirk Wilhelmsen's work is the use of novel combinations of genes, unique environmental – gene associations and specific phenotypic aspects of the diagnosis that associates individuals with similar symptoms and allelic genotypes. This novel and interesting new direction requires incredible computing and mathematics but may unravel the tremendous complexity within the thousands of alleles of genes and different ways the brain drives our activity. ■

continued from previous page

CONGRATULATIONS

Dr. Linda P. Spear
Received the 2008
Bowles Lectureship Award

This annual award honors distinguished researchers that have made significant contributions to our understanding of the causes, prevention and/or treatment of alcoholism and alcohol abuse.