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the newsletter of

Research into the Causes of Schizophrenia and Bipolar Disorder

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Welcome to Concordance, the newsletter providing updates on the work of the Program for Genetics and Psychoses at the University of Pittsburgh. Our research studies focus on finding out more about the underlying genetic causes of schizophrenia and related illnesses. Dr. Vishwajit Nimgaonkar, MD, PhD, Professor of Psychiatry and Human Genetics, oversees our research efforts. We are currently seeking volunteers for the studies described below. If you or a family member has a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or a related illness, you may be eligible to participate.

Please call 800 994 8182 for more information. We pay participants for time and travel

Look for Us in the Community

As researchers, we don't spend all of our time in the laboratory; we like to meet the people who contribute to our work by participating in our studies. Exchanging ideas with consumers at mental health conferences and other community events helps keeps us in touch with the people we hope to help with our studies.

In coming months, we will be hosting panel discussions at several community events. You'll find us at the Southwest Pennsylvania NAMI Conference in Pittsburgh on April 22; at the Pennsylvania Mental Health Consumers' Association's Elements Conference in State College, PA on June 8th; and at the Ohio Advocates for Mental Health conference in Akron on July 29th. We will be joined by past participants in research speaking on the theme of "Research and Recovery." Many research participants find that the experience of taking part in a study is both informative and empowering, and we look forward to hearing consumers speak on this topic.

Updates from our Laboratory

Why are we doing this research?

Research to date indicates that mental illnesses are to some degree heritable; it is likely that some combination of genetic predisposition and environmental factors combine to cause mental illness to manifest itself in affected individuals. We believe that if we can find the causes of these illnesses, we will be able to design better medications and treatments. Through research, medications and treatments have improved greatly, but we believe there is still room for improvement.

Here are some examples of projects we have started:

Infections and schizophrenia: Many researchers feel that infections with viruses may contribute to the risk for schizophrenia. For example, infection with herpes simplex virus 1, the virus that causes cold sores, was noted more frequently among patients in some studies. Not all researchers agree with such conclusions. It is possible that variations in an individual's genetic makeup could be another factor. We have been trying to see if variants of genes modulating the immune system could be analyzed together with exposure to particular viruses among patients and comparable individuals. Several scientists have reported that a variant of a gene called tumor necrosis factor (TNF) increases schizophrenia risk. TNF is a gene that activates the immune system response. We recently completed a study where we investigated several variants of the TNF gene along with exposure to common viruses such as

herpes simplex virus 1. We did not find any 'gene-virus' interaction despite comprehensive analyses. This work is due to be published in the journal 'Schizophrenia Research' (*Shirts et al.*).

Regulator of G-protein Signaling 4 gene (RGS4): *RGS4* is a gene with important regulatory effects in the brain. Since Dr. Nimgaonkar's group first discovered a possible link between *RGS4* and schizophrenia several years ago, a number of other researchers have had similar findings. To understand this link better, we have collected genetic data from consumers with schizophrenia, their parents, and unrelated comparison individuals from 13 different institutions in the U.S., U.K., Ireland, India, China, and Brazil. In sum, we have analyzed data from 13,807 individuals, making this one of the largest single gene studies ever conducted in schizophrenia genetic research. Collectively, our results suggest *RGS4* may have a role in the development of schizophrenia, but much research remains to understand what that role may be. The results of this study and a review paper of this gene are currently in press (Talkowski et al., *Biological Psychiatry*; Talkowski et al., *Schizophrenia Bulletin*)

Mitochondrial function in Schizophrenia: Some investigators have suggested that mitochondria, the powerhouses of cells, may not function properly among some patients. We are evaluating variations in the DNA located in mitochondria. We have observed many DNA alterations, some of which were earlier reported to be associated with other known diseases. We are planning further studies aimed at understanding the function of these DNA variants.

New Method of DNA Extraction: We are collaborating with a group that is interested in bipolar disorder among children. To obtain DNA from these children without blood draws, we have tested kits that require only saliva. We can obtain DNA in acceptable amounts from saliva. Although we prefer blood samples, the saliva collection will offer acceptable results in DNA collection for children and those who are afraid of needles.

Studies of circadian function: All of us have daily routines for sleep and work. These routines are tied to basic body functions called 'circadian rhythms'. It is thought that circadian rhythm disruption may play a role in producing illnesses such as depression. In fact, manipulating circadian rhythms using light therapy can treat some forms of depression. We are investigating circadian rhythm disturbances among patients with bipolar disorder or schizophrenia and their relatives. If particular problems can be identified, we hope to target treatment based on circadian rhythm.

Schizophrenia Studies- US

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We currently have three schizophrenia studies underway in the United States: The African American Paartners Study, The Family Study of Schizophrenia and Related Conditions, and the Genetic Susceptibility Study. Our goal is to identify genes that play a role in predisposing people to schizophrenia.

To date, over 600 people have participated in our studies by providing blood samples and interviews to support our research efforts. This includes controls from the same areas where we have interviewed affected families. If one or more of your family members is affected by schizophrenia or schizoaffective disorder, your family may be eligible to participate in one of these studies. This study is not confined to the Pittsburgh area: relatives from across the country can participate.

Bipolar Studies

Recent Findings: Meta- Analysis Suggests Chromosomes 6 and 8 Worthy of Further Study

Since our last Concordance publication, the Genetic Repository for STEP-BD Participants (GRP), a large study taking place at the University of Pittsburgh and eleven other sites around the country, concluded recruitment with over 2,000 participants enrolled! The purpose of the study is to search for genes that may increase the risk of

bipolar disorder or influence response to treatment. Participants provided blood samples to enable genetic studies of bipolar disorder.

Now that the enrollment period is over, scientific inquiry using the samples collected can begin. The first phase of inquiry is a meta-analysis of existing genetic research on bipolar disorder – this means that the data from previous studies is scientifically analyzed to look for genes that seem consistently implicated in bipolar disorder across studies, and thus might be worthy of further study using this large collection of samples. The analyses consistently suggest variation at genes on the long arms of chromosomes 6 and 8 may be related to bipolar disorder. This finding suggests further study of these particular regions may be especially valuable.

Family Study in STEP-BD

A study related to the GRP, FaSt STEP, or the Family Study in STEP-BD, continues to recruit participants. Recent changes in the study allow us to recruit individuals diagnosed with bipolar disorder, and when possible their parents, from the community. This is an exciting development; previously, the study was closely tied to the STEP BD clinical trial, and we were limited to inviting only patients in STEP BD and their family members to enroll. Over 400 families have participated so far, and we hope that with our new community recruitment efforts, many more will take part.

Candidate Gene Alleles

We have recently begun recruiting individuals diagnosed with bipolar disorder and their family members for another genetic study of bipolar disorder. We are specifically interested in seeing if abnormalities in the circadian rhythms could explain the onset of bipolar disorder. We hope that by studying the DNA of people who have been diagnosed with the illness as well as their family members, we will learn more about the genetic underpinnings of bipolar disorder.

Work in India

We are currently into the second year of a five-year grant funded by the Fogarty International Center of the NIH. The Training Grant for Psychiatric Genetics and Ethics in India will provide an opportunity for four pre and post-doctoral trainees to train for research in psychiatric epidemiology and ethics in India. At present our four trainees have returned to India for the next 2.5 years, to conduct their field training while continuing their education via web based distance education. Over the next four years, they will travel to and from India, enabling them to train in the field, and will then have opportunities to formulate their own psychiatric genetics and ethics research endeavors in India.

We also have on going work with our NIMH funded grant, Genetic Susceptibility in Schizophrenia. We recruit participants and their family members, for which we seek to identify the genetic and environmental causes of schizophrenia, bipolar disorder, and other related illnesses. We are into the forth year of funding and have recruited over 383 families to date.

Family studies in Egypt

We have initiated a collaboration at Mansoura University to investigate the genetics of bipolar disorder and schizophrenia in Egypt. We wish to see if marriages involving close relatives alter the risk for these conditions. Dr. Mansour, an Egyptian psychiatrist who trained in our lab, has started enrolling participants. To date, 23 families have participated in our research

THANK YOU TO ALL WHO HAVE PARTICIPATED IN OUR STUDIES!

Your help and support has enabled this important research to continue.

We are always excited to meet new families who would like to take part in our studies. *At this time we particularly need help connecting with families in which two individuals (two siblings or a parent and child) have a diagnosis of schizophrenia or schizoaffective disorder. If you know families who might be interested, please encourage them to contact us* ***as soon as possible*** *at our toll-free number:* ***1-877-363-5895****.*

Thank you!