



TSC ALERT

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December 2004

Welcome to the December 2004 edition of *TSC Alert* – an online research newsletter for individuals interested in Tuberous Sclerosis Complex (TSC) research and clinical care. This online newsletter contains information of interest to the TSC research and health care community. Please forward this newsletter to colleagues who are interested in TSC. To be added/deleted to/from the mailing list for *TSC Alert* and/or to submit information for the January 2005 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org

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IMPORTANT DEADLINES

TSC/LAM International Research Symposium – Call for Abstracts!

Deadline for submission of abstracts: January 14, 2005

Deadline for submission of Late-breaking Abstracts: March 15, 2005

Deadline for Registration: February 18, 2005

(See information below in Conferences)

SOLICITING NOMINATIONS FOR MANUEL R. GOMEZ AWARD

Deadline for submission of nominations: February 1, 2005

(See information below in News)

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM (TSCR) IN THE CDRMP

Deadline: February 22, 2005

(See information below in Grant Announcements)

GRANT ANNOUNCEMENTS

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM (TSCR) IN THE CDRMP

Deadline: February 22, 2005

The Fiscal Year 2005 (FY05) Defense Appropriations Act provides \$3.2 million to the Department of Defense Tuberos Sclerosis Complex Research Program (TSCR) to support innovative research directed toward improved prevention, diagnosis, and treatment of TSC. This program is administered by the US Army Medical Research and Materiel Command through the Office of the Congressionally Directed Medical Research Programs (CDMRP). The deadline for the receipt of electronic submissions is February 22, 2005 at 5:00 p.m. Eastern time.

FY05 TSCR Program Announcements for the following mechanisms can be found on the DCMRP Web site.

- **Natural History Study Awards - New**
- **Natural History Development Awards**
- **Concept Awards**
- **Idea Development Awards**

Detailed descriptions of each mechanism are provided in the FY05 TSCR Program Announcements on the CDMRP Web site. For more information about the TSCR or other CDMRP-sponsored programs, please visit the CDMRP website at:

<http://cdmrp.army.mil/funding/05tscrp.htm>

James S. McDonnell Foundation: 21st Century Science Initiative - 2005

Research Award Application Deadline: 6:00 pm CST March 7, 2005

The James S. McDonnell Foundation (JSMF) announces updated program descriptions and application guidelines for its 21st Century Science Initiative Research Awards. The 21st Century Research Awards support investigator-initiated research. Funding is available for research projects in Brain Cancer; Bridging Brain, Mind, and Behavior; and Studying Complex Systems. Program information, application guidelines, and proposal preparation instructions are available at: <http://www.jsmf.org>. No geographic restrictions; international applications are encouraged. Information on the Foundation's 21st Century Collaborative Activity Awards is also available on the website.

NIH Establishes Website for New Investigators (NOT-OD-05-014)

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-014.html>

Request for Information (RFI): NIH Knockout Mouse Inventory Project (NOT-OD-05-015)

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-015.html>

Innovative Technologies for Molecular Analysis of Cancer (RFA-CA-06-002)

National Cancer Institute

Application Receipt Date(s): February 17, 2005; June 17, 2005; October 18, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-06-002.html>

Application of Emerging Technologies for Cancer Research (RFA-CA-06-003)

National Cancer Institute

Application Receipt Date(s): February 17, 2005; June 17, 2005; October 18, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-06-003.html>

Innovations in Cancer Sample Preparation (RFA-CA-06-004)

National Cancer Institute

Application Receipt Date(s): February 17, 2005; June 17, 2005; October 18, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-06-004.html>

Heart Failure Clinical Research Network (RFA-HL-05-003)

National Heart, Lung, and Blood Institute

Application Receipt Date(s): August 16, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-05-003.html>

Assay Development for High Throughput Molecular Screening (RFA-RM-05-011)

NIH Roadmap Initiatives

Application Receipt Date(s): February 14, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-011.html>

Research on Mind-Body Interactions and Health (PA-05-027)

Office of Behavioral and Social Science Research

National Center for Complementary and Alternative Medicine

National Cancer Institute

National Heart, Lung, and Blood Institute

National Institute on Aging

National Institute on Alcohol Abuse and Alcoholism

National Institute of Child Health and Human Development

National Institute on Drug Abuse

National Institute of Dental and Craniofacial Research

National Institute of Environmental Health Sciences

National Institute of Mental Health

Application Receipt Date(s): Multiple dates, see announcement.

<http://grants.nih.gov/grants/guide/pa-files/PA-05-027.html>

Shared Instrumentation Grant Program (PAR-05-028)

National Center for Research Resources

Application Receipt Date(s): March 22, 2005

<http://grants.nih.gov/grants/guide/pa-files/PAR-05-028.html>

INTERDISCIPLINARY TRAINING: BEHAVIOR, ENVIRONMENT AND BIOLOGY (RFA-RM-05-010)

Letters of Intent Receipt Date(s): January 14, 2005

Application Receipt Date(s): February 11, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-010.html>

PILOT-SCALE LIBRARIES FOR HIGH-THROUGHPUT SCREENING(RFA-RM-05-014)

Letters of Intent Receipt Date(s): January 14, 2005

Application Receipt Date(s): February 15, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-014.html>

NLM Grants for Scholarly Works in Biomedicine and Health (PAR-05-025)

National Library of Medicine

Application Receipt Date(s): Multiple dates, see announcement.

<http://grants.nih.gov/grants/guide/pa-files/PAR-05-025.html>

Community Participation in Research (PAR-05-026)

Office of Behavioral and Social Science Research

Agency for Healthcare Research and Quality

National Cancer Institute

National Heart, Lung, and Blood Institute

National Institute on Alcohol Abuse and Alcoholism

National Institute of Child Health and Human Development

National Institute on Deafness and Other Communication Disorders

National Institute of Dental and Craniofacial Research

National Institute of Environmental Health Sciences

National Institute of Mental Health

National Institute of Nursing Research

National Institute for Occupational Safety and Health

Application Receipt Date(s): May 17, 2005, 2006, 2007

<http://grants.nih.gov/grants/guide/pa-files/PAR-05-026.html>

NIDCD P30 Grants for Translational Research (NOT-DC-05-001)

National Institute on Deafness and Other Communication Disorders

<http://grants.nih.gov/grants/guide/notice-files/NOT-DC-05-001.html>

NIDDK Medical Student Research Training Program (MSRT) (NOT-DK-05-004)

National Institute of Diabetes and Digestive and Kidney Diseases

<http://grants.nih.gov/grants/guide/notice-files/NOT-DK-05-004.html>

National Children's Study Coordinating Center (NOT-HD-05-001)

National Institute of Child Health and Human Development

<http://grants.nih.gov/grants/guide/notice-files/NOT-HD-05-001.html>

National Children's Study Vanguard Centers (NOT-HD-05-002)

National Institute of Child Health and Human Development

<http://grants.nih.gov/grants/guide/notice-files/NOT-HD-05-002.html>

Pre-Application Meeting for RFA NS-05-005, "Centers of Excellence in Translational Human Stem Cell Research" (NOT-NS-05-002)

National Institute of Neurological Disorders and Stroke

National Heart, Lung, and Blood Institute

National Institute of Diabetes and Digestive and Kidney Diseases

<http://grants.nih.gov/grants/guide/notice-files/NOT-NS-05-002.html>

Building Interdisciplinary Research Careers in Women's Health (RFA-OD-05-002)

Agency for Healthcare Research and Quality

Office of Research on Women's Health

National Institute of Child Health and Human Development
National Institute on Alcohol Abuse and Alcoholism
National Institute of Allergy and Infectious Diseases
National Institute on Drug Abuse
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of Mental Health
Office of Dietary Supplements
Application Receipt Date(s): February 23, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-05-002.html>

Decision Making in Health: Behavior Maintenance (PA-05-016)

National Cancer Institute
National Institute on Drug Abuse
National Institute on Alcohol Abuse and Alcoholism
Application Receipt Dates: Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PA-05-016.html>

Decision Making in Cancer: Single-Event Decisions (PA-05-017)

National Cancer Institute
Application Receipt Dates: Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PA-05-017.html>

Research on Co-Morbid Mental and Other Physical Disorders (PA-05-018)

National Institute of Mental Health
Application Receipt Dates: Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PA-05-018.html>

Health Behavior Change in People with Mental Disorders (PA-05-019)

National Institute of Mental Health
Application Receipt Dates: Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PA-05-019.html>

NIDCR Exploratory and Developmental Grants in Clinical Research (PAR-05-020)

National Institute of Dental and Craniofacial Research
Application Receipt Date(s): Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PAR-05-020.html>

NIDCD Translational Research Grants (PAR-05-023)

National Institute on Deafness and Other Communication Disorders
Application Receipt Date(s): Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PAR-05-023.html>

SKIN DISEASES RESEARCH CORE CENTERS (RFA-AR-05-002)

Letters of Intent Receipt Date(s): April 26, 2005
Application Receipt Date(s): May 24, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-05-002.html>

RESEARCH SUPPLEMENTS TO PROMOTE DIVERSITY IN HEALTH-RELATED RESEARCH (PA-05-015)

Letters of Intent Receipt Date(s): Not Required
Application Receipt Date(s): Multiple receipt dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PA-05-015.html>

Identifying Autism Susceptibility Genes (RFA-MH-05-007)

National Institute of Mental Health
Cure Autism Now
Canadian Institutes of Health Research
Health Research Board, Ireland
Institute of Genetics
Institute of Human Development, Child and Youth Health
Institute of Neurosciences, Mental Health and Addiction
National Alliance for Autism Research
National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Environmental Health Sciences
National Institute of Neurological Disorders and Stroke
Southwest Autism Research & Resource Center
Application Receipt Date(s): April 19, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-05-007.html>

Exploratory Centers for Cheminformatics Research (RFA-RM-05-012)

NIH Roadmap Initiatives
Application Receipt Date(s): March 10, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-012.html>

Predoctoral Clinical Research Training Programs (RFA-RM-05-015)

NIH Roadmap Initiatives
Application Receipt Date(s): March 25, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-015.html>

Social and Cultural Dimensions of Health (PA-05-029)

Office of Behavioral and Social Science Research
National Center for Complementary and Alternative Medicine
National Cancer Institute
National Human Genome Research Institute
National Heart, Lung, and Blood Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development
National Institute on Drug Abuse
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of Mental Health
National Institute of Nursing Research
Application Receipt Date(s): Multiple receipt dates, see announcement.
<http://grants.nih.gov/grants/guide/pa-files/PA-05-029.html>

SMALL GRANTS PROGRAM FOR CANCER EPIDEMIOLOGY (PAR-04-159)

National Cancer Institute
Application Receipt Date(s): November 21, 2005; March 20, 2006;
July 20, 2006; November 20, 2006; March 20, 2007; July 20, 2007;
November 20, 2007; March 20, 2008; July 21, 2008; November 21, 2008

<http://grants.nih.gov/grants/guide/pa-files/PA-04-159.html>

SKIN DISEASES RESEARCH CORE CENTERS (RFA-AR-05-002)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Application Receipt Date(s): May 24, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-05-002.html>

TYPICAL/DISORDERED LANGUAGE: PHENOTYPE ASSESSMENT TOOLS (RFA-DC-05-001)

National Institute on Deafness and Other Communication Disorders

National Institute of Child Health and Human Development

Application Receipt Date(s): February 24, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-DC-05-001.html>

TSC RESEARCH RESOURCES

NEW TSC ANIMAL MODEL AVAILABLE Jack Arbiser, M.D., Ph.D. and his colleagues have developed a new animal model of TSC (see Basic Science Spotlight in TSC Publications below). Dr. Arbiser is happy to collaborate with investigators who are interested in utilizing this animal model for their TSC research. Dr. Arbiser may be contacted at: jarbise@emory.edu, Tel: 404-727-5063

Announcing the NIA Aged Non-Human Primate Tissue Bank (NOT-AG-05-002)

National Institute on Aging

<http://grants.nih.gov/grants/guide/notice-files/NOT-AG-05-002.html>

NIH AWARDS \$1 MILLION TO UNC FOR GENOME FINGERPRINT SCANNING

PROGRAM The National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), announced today it will provide more than \$1 million over three years to the University of North Carolina at Chapel Hill to further develop and make more widely available a Genome Fingerprint Scanning (GFS) program. The tool allows researchers to match mass spectrometry data directly to raw, unannotated genetic sequences to identify proteins and locate novel genes. Proteomics, the study of how proteins interact and respond to changing conditions in complex systems, is increasingly being used to help decipher diseases such as cancer, diabetes, and Alzheimer's.

"This powerful genome fingerprint scanning tool will allow researchers to overcome a major bottleneck that has hampered their capacity to make full use of the vast information generated by sequencing dozens of genomes," said NCRR Director Judith L. Vaitukaitis, M.D. "This is the equivalent of being able to harness a whole library of information without an index."

Current software for protein identification is limited mainly to those for which a gene or protein entry exists in one of the public databases. Protein identification cannot be effectively performed for organisms whose annotations are incomplete, missing, or incorrect. By contrast, the GFS program is capable of matching mass spectrometry data from proteomic studies directly to raw, or even unfinished, genome sequences. The program has already been used to identify novel proteins in "Francisella tularensis," the bacterium that causes the infectious disease tularemia, and in "Tetrahymena thermophila," a model organism for studies of cellular and molecular biology.

"This support from NCRH will allow us to transform our Genome Fingerprint Scanning program from an experimental, beta-quality tool, into a free, widely-used resource that will benefit the global proteomics community," said Morgan C. Giddings, Ph.D., assistant professor at the University of North Carolina at Chapel Hill School of Medicine and the GFS project director.

An enhanced GFS program will greatly assist researchers who are studying proteins to better understand complex diseases. The most common approach compares proteins expressed in diseased versus normal tissues to determine proteins whose expression levels or forms are significantly changed, indicating a potential role in the disease. One example is a recent study identifying some of the important regulatory gene clusters controlling glucose responsiveness in a key metabolic pathway affecting diabetes. Another is the discovery of the genes producing many abnormal regulatory proteins found in Alzheimer's disease.

This grant will allow Giddings and her team to upgrade the project's current Web site, <<http://gfs.unc.edu>>, to include numerous enhancements for end users of the program. They plan to greatly improve the program's output to include peptide maps that users can browse overlaid on a genome, expand the list of built-in searchable genomes, provide a multi-genome simultaneous search capability, and automate both updates of the genome databases and distribution of the computing load to ensure rapid response times. In addition, Giddings intends to enhance the GFS to extend its applicability to large, multi-exon genes. She also will make the program, developed on Unix under the Macintosh operating system, available for Linux, Microsoft Windows and other common platforms; and will develop documentation aimed at all user levels.

NCRH is part of the National Institutes of Health, an agency of the Department of Health and Human Services. NCRH is the nation's leading federal sponsor of resources that enable advances in many areas of biomedical research. NCRH support provides the scientific research community with access to a diverse array of biomedical research technologies, instrumentation, specialized basic and clinical research facilities, animal models, genetic stocks, and such biomaterials as cell lines, tissues, and organs. Additional information about NCRH can be found at <<http://www.ncrh.nih.gov>>.

NEW TSC PUBLICATIONS

Journal of Child Neurology September 2004 Issue Focused on TSC

The September 2004 issue of the Journal of Child Neurology, Vol. 19, Number 9, contains 15 articles on TSC that were presented at the 2003 Child Neurology Society meeting in the "Neurobiology of Disease in Children" Symposium organized by Bernard L. Maria, MD, MBA. E. Steve Roach, MD and David Gutmann, MD, PhD co-chaired the symposium. You may access the PDF of this issue on the Tuberous Sclerosis Alliance Web site at:

<http://www.tsalliance.org/pages.aspx?content=131>

Basic Science Spotlight: Govindarajan B, Brat D, Csete M, Martin WD, Murad E, Litani K, Cohen C, Cerimele F, Nunnelle M, Lefkove B, Yamamoto T, Lee C, Arbiser JL (2004)

Transgenic expression of dominant negative tuberin through a strong constitutive promoter results in a tissue-specific tuberous sclerosis phenotype in the skin and brain. J Biol Chem. 2004 Dec 2 [Epub ahead of print]

Tuberous sclerosis (TS) is a common autosomal dominant disorder caused by loss or malfunction of hamartin (tsc1) or tuberin (tsc2). Many lesions in TS do not demonstrate loss of heterozygosity (LOH) for these genes, implying that dominant negative forms of these genes may account for

some hamartomas and neoplasms in TS. In order to test this hypothesis, Dr. Govindarajan and colleagues at Emory University expressed a dominant negative allele of tuberin (DRG) behind the CMV promoter in NIH3T3 cells and transgenic mice. This allele binds hamartin, but has a deletion in the C-terminus of tuberin, leading to constitutive activation of rap1 and rab5/rabaptin. Expression of DRG in NIH3T3 cells led to a strong induction of reactive oxygen species (ROS), induction of VEGF, and malignant transformation in vivo. Expression of DRG driven by the constitutive cytomegalovirus promoter (CMV) led to high level expression in all murine tissues examined, including skin, kidney, liver, and brain. Surprisingly, mice expressing the DRG transgene developed a fibrovascular collagenoma in the dermis, which closely resembles the Shagreen patch observed in human patients with TS. In addition, deficient migration of periventricular external granule cells in the cerebellum was observed, which may be the murine equivalent of subependymal giant cell astrocytomas (SEGAS) or tubers commonly seen in TS patients. Thus, expression of a dominant negative tuberin in multiple tissues can lead to a tissue-specific phenotype resembling some of the findings in human TS. Their data is the first to demonstrate that specific signaling abnormalities underlie specific hamartomas in a model of a human genetic disorder.

Basic Science Spotlight: Meikle L, McMullen JR, Sherwood MC, Lader AS, Walker V, Chan JA, Kwiatkowski DJ (2004) **A mouse model of cardiac rhabdomyoma generated by loss of Tsc1 in ventricular myocytes.** Hum Mol Genet 2004 Dec 15 [Epub ahead of print]

Tuberous sclerosis is a hamartoma syndrome due to mutations in TSC1 or TSC2 in which cardiac rhabdomyomas are seen in about 60% of patients. These lesions have an unusual natural history as they are usually most prominent immediately after birth, and spontaneously resolve in most cases. To develop a mouse model of this lesion, L. Meikle and collaborators at Brigham & Women's Hospital in Boston used a conditional, floxed allele of Tsc1 and a modified myosin light chain 2v allele in which cre recombinase expression occurs in ventricular myocytes. Mice with ventricular loss of Tsc1 had a median survival of 6 months, and developed a dilated cardiomyopathy with the occurrence of scattered foci of enlarged ventricular myocytes. The enlarged cells were periodic acid-Schiff positive indicating the presence of excess glycogen and expressed elevated levels of phospho-S6, similar to findings in patient rhabdomyoma cells. The observations confirm that rhabdomyomas occur through a two hit mechanism of pathogenesis. However, the mice showed no evidence of fetal/neonatal demise, and there was no evidence of proliferation in the lesions. The researchers propose that these differences are due to the timing of loss of Tsc1 in the ventricular myocytes and/or the truncated gestational period in the mouse compared to humans, during which progesterational hormones may accentuate the growth of patient rhabdomyomas.

Clinical Science Spotlight: Prather P, de Vries PJ (2004) **Behavioral and cognitive aspects of tuberous sclerosis complex.** J Child Neurol 19(9):666-74

Tuberous sclerosis complex is a multisystem genetic disorder. Of all the possible manifestations of this complex disorder, the cognitive and behavioral problems represent the area of greatest concern to parents and caregivers. This review outlines the current evidence regarding global intellectual abilities, behavioral problems, psychiatric diagnoses, learning disorders, and specific neuropsychologic deficits for which individuals with tuberous sclerosis complex are at particularly increased risk, and outlines approaches to intervention. Approximately half of individuals diagnosed with tuberous sclerosis complex present with global intellectual impairment and developmental psychopathologies. Those with normal intellectual abilities are also at high risk of specific neuropsychologic deficits and behavioral, learning, and other psychiatric disorders. There is no evidence for an inevitable decline in cognition or behavior, and any such changes should be investigated. The evolving neurocognitive literature suggests that frontal brain systems might be

most consistently disrupted by tuberous sclerosis complex-related neuropathology, thus leading to abnormalities in regulatory and goal-directed behaviors.

New TSC Publications:

Ali M, Girimaji SC, Markandaya M, Shukla AK, Sacchidanand S, Kumar A (2005) Mutation and polymorphism analysis of TSC1 and TSC2 genes in Indian patients with tuberous sclerosis complex. *Acta Neurol Scand* 111(1):54-63

Astrinidis A, Henske EP (2004) Aberrant cellular differentiation and migration in renal and pulmonary tuberous sclerosis complex. *J Child Neurol* 19(9):710-5

Au KS, Williams AT, Gambello MJ, Northrup H (2004) Molecular genetic basis of tuberous sclerosis complex: from bench to bedside. *J Child Neurol* 19(9):699-709

Avruch J, Lin Y, Long X, Murthy S, Ortiz-Vega S (2005) Recent advances in the regulation of the TOR pathway by insulin and nutrients. *Curr Opin Clin Nutr Metab Care* 8(1):67-72

Bailey SN, Sabatini DM, Stockwell BR (2004) Microarrays of small molecules embedded in biodegradable polymers for use in mammalian cell-based screens. *Proc Natl Acad Sci U S A* 101(46):16144-9. Epub 2004 Nov 16

Billings B, Hamrick LC, Bueschen AJ, Kenney PJ (2004) Coexisting angiomyolipoma and renal cell carcinoma in a kidney of an elderly woman: case report and review of the literature. *ScientificWorldJournal* 4 Suppl 1:27-30

Birkhaeuser F, Ackermann C, Flueckiger T, Guenin MO, Kern B, Tondelli P, Peterli R (2004) First description of a PEComa (perivascular epithelioid cell tumor) of the colon: report of a case and review of the literature. *Dis Colon Rectum* 47(10):1734-7

Brugarolas J, Lei K, Hurley RL, Manning BD, Reiling JH, Hafen E, Witters LA, Ellisen LW, Kaelin WG Jr (2004) Regulation of mTOR function in response to hypoxia by REDD1 and the TSC1/TSC2 tumor suppressor complex. *Genes Dev* 2004 Dec 1 18(23):2893-904 Epub 2004 Dec 1

Chao CH, Lin CY, Chan SC, Chen KS (2004) Concurrent hepatic and ruptured renal angiomyolipoma in tuberous sclerosis complex. *Chang Gung Med J* 27(9):696-700

Conrad GR, Sinha P (2005) FDG PET Imaging of Subependymal Gray Matter Heterotopia. *Clin Nucl Med* 30(1):35-6

Cook JD, Walker CL The Eker rat: establishing a genetic paradigm linking renal cell carcinoma and uterine leiomyoma. *Curr Mol Med* 4(8):813-24

Crapanzano JP (2005) Fine-needle aspiration of renal angiomyolipoma: Cytological findings and diagnostic pitfalls in a series of five cases. *Diagn Cytopathol* 32(1):53-7

Crino PB (2004) Molecular pathogenesis of tuber formation in tuberous sclerosis complex. *J Child Neurol* 19(9):716-25

Crooks DM, Pacheco-Rodriguez G, Decastro RM, McCoy JP Jr, Wang JA, Kumaki F, Darling T, Moss J (2004) Molecular and genetic analysis of disseminated neoplastic cells in

- lymphangi leiomyomatosis. *Proc Natl Acad Sci U S A* 2004 Dec 6 [Epub ahead of print]
- Curatolo P, Porfirio MC, Manzi B, Seri S (2004) Autism in tuberous sclerosis. *Eur J Paediatr Neurol* 8(6):327-32
- Dhanasekaran SM, Dash A, Yu J, Maine IP, Laxman B, Tomlins SA, Creighton CJ, Menon A, Rubin MA, Chinnaiyan AM (2004) Molecular profiling of human prostate tissues: insights into gene expression patterns of prostate development during puberty. *FASEB J* 2004 Nov 17 [Epub ahead of print]
- DiMario FJ Jr (2004) Brain abnormalities in tuberous sclerosis complex. *J Child Neurol* 19(9):650-7
- D'Souza J, Hendricks M, Le Guyader S, Subburaju S, Grunewald B, Scholich K, Jesuthasan S (2004) Formation of the retinotectal projection requires Esrom, an ortholog of PAM (protein associated with Myc). *Development* 2004 Dec 8 [Epub ahead of print]
- Finkelstein R (2004) Advances in tuberous sclerosis complex research: the October 1, 2003, Child Neurology Society Workshop. *J Child Neurol* 19(9):734-5
- Fischli S, Gassmann Ch, Stanga Z, Cottagnoud P, Stucki A (2004) [Dyspnea and hemoptysis in a young woman with unclear renal alterations] *Schweiz Rundsch Med Prax* 93(46):1923-8 [Article in German]
- Franz DN (2004) Non-neurologic manifestations of tuberous sclerosis complex. *J Child Neurol* 19(9):690-8
- Goncharova E, Goncharov D, Noonan D, Krymskaya VP (2004) TSC2 modulates actin cytoskeleton and focal adhesion through TSC1-binding domain and the Rac1 GTPase. *JCB*, 167 (6):1171-1182
- Govindarajan B, Brat D, Csete M, Martin WD, Murad E, Litani K, Cohen C, Cerimele F, Nunnolley M, Lefkove B, Yamamoto T, Lee C, Arbiser JL (2004) Transgenic expression of dominant negative tuberin through a strong constitutive promoter results in a tissue-specific tuberous sclerosis phenotype in the skin and brain. *J Biol Chem*. 2004 Dec 2 [Epub ahead of print]
- Henske EP (2004) The genetic basis of kidney cancer: why is tuberous sclerosis complex often overlooked? *Curr Mol Med* 4(8):825-31
- Kenerson H, Dundon TA, Yeung RS (2004) Effects of Rapamycin in the Eker Rat Model of Tuberous Sclerosis Complex. *Pediatr Res*. 2004 Nov 19 [Epub ahead of print]
- Lee L, Sudentas P, Donohue B, Asrican K, Worku A, Walker V, Sun Y, Schmidt K, Albert MS, El-Hashemite N, Lader AS, Onda H, Zhang H, Kwiatkowski DJ, Dabora SL (2004) Efficacy of a rapamycin analog (CCI-779) and IFN-gamma in tuberous sclerosis mouse models. *Genes Chromosomes Cancer*. 2004 Dec 1 [Epub ahead of print]
<http://www3.interscience.wiley.com/cgi-bin/fulltext/109801674/HTMLSTART>
- Mak BC, Yeung RS (2004) The tuberous sclerosis complex genes in tumor development. *Cancer Invest* 22(4):588-603
- Maria BL (2004) Tuberous sclerosis complex: future research directions. *J Child Neurol* 19(9):631
- Maria BL, Deidrick KM, Roach ES, Gutmann DH (2004) Tuberous sclerosis complex: pathogenesis,

- diagnosis, strategies, therapies, and future research directions. *J Child Neurol* 19(9):632-42
- Meikle L, McMullen JR, Sherwood MC, Lader AS, Walker V, Chan JA, Kwiatkowski DJ (2004) A mouse model of cardiac rhabdomyoma generated by loss of Tsc1 in ventricular myocytes. *Hum Mol Genet* 2004 Dec 15 [Epub ahead of print]
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CONFERENCES

January 27-28, 2005

National Coalition for Health Professional Education in Genetics (NCHPEG) & Genetics Resources on the Web (GROW) 8th Annual Meeting: Focus on Family History

Hyatt Regency Bethesda, Bethesda, MD

For more information: <http://www.nchpeg.org>

February 19-20, 2005

West Coast Regional TSC Conference

Mission Inn, Riverside, CA

Sponsored and organized by the Community Alliance of the Tuberous Sclerosis Alliance

For more information and to register, visit the TS Alliance Web site at: <http://www.tsalliance.org>

April 8-10, 2005

TSC/LAM Research Conference & TSC Adult Conference

The Hyatt Regency, Downtown Cincinnati, OH

Organized by the Tuberous Sclerosis Alliance, LAM Foundation, and Rare Lung Disease Consortium

The Tuberous Sclerosis Alliance and the LAM Foundation invite you to attend the first joint TSC/LAM conference in Cincinnati, Ohio in April 2005. Sessions will include:

- The TSC Genes in the Brain – What Do They Do?
- Signaling Pathways and Basic Biology of TSC1/TSC2
- TSC-LAM Translational Research
- What Causes Epilepsy in TSC?
- Behavioral Phenotypes in TSC
- Late-Breaking Science and Roadmap for a Cure for TSC

CALL FOR ABSTRACTS

Platform and poster presentations will be selected from submitted abstracts based on scientific merit and thematic considerations. The application and instructions are enclosed and may also be completed electronically or downloaded from the Tuberous Sclerosis Alliance Web site at <http://www.tsalliance.org> or The LAM Foundation website at <http://lam.uc.edu>

Deadline for submission of abstracts: January 14, 2005

Deadline for submission of Late-Breaking TSC Abstracts: March 15, 2005

Deadline for Registration: February 18, 2005

For more information, Call for Abstracts, Agenda and Registration information:
<http://www.tsalliance.org>

Save the date! May 4-5, 2006
TSC International Research Conference 2006
Berlin, Germany
More information coming soon!

NEWS

BRAINS OF PEOPLE WITH AUTISM RECALL LETTERS OF THE ALPHABET IN BRAIN AREAS DEALING WITH SHAPES: Finding Supports Theory That Autism Results From Failure of Brain Areas To Work Together In contrast to people who do not have autism, people with autism remember letters of the alphabet in a part of the brain that ordinarily processes shapes, according to a study from a collaborative program of the National Institute of Child Health and Human Development of the National Institutes of Health.

The study was conducted by researchers in the NICHD Collaborative Program of Excellence in Autism (CPEA) at the University of Pittsburgh and Carnegie Mellon University. It supports a theory by CPEA scientists that autism results from a failure of the various parts of the brain to work together. In autism, the theory holds, these distinct brain areas tend to work independently of each other. The theory accounts for observations that while many people with autism excel at tasks involving details, they have difficulty with more complex information.

The study and the theory are the work of Marcel Just, Ph.D., Professor of Psychology at Carnegie Mellon University in Pittsburgh, Pennsylvania and Nancy Minshew, M.D., Professor of Psychiatry and Neurology at the University of Pittsburgh School of Medicine and their colleagues.

The study is in the November 29 on-line publication in the journal "Neuroimage," at <http://www.sciencedirect.com>.

"This finding provides more evidence to support a promising theory of autism," said Duane Alexander, M.D., Director of the NICHD. "If confirmed, this theory suggests that therapies emphasizing problem solving skills and other tasks that activate multiple brain areas at the same time might benefit people with autism."

People with autism typically have difficulty communicating and interacting socially with others. The old saying "unable to see the forest for the trees" applies to people with autism, describing how many of them excel at matters of detail, yet struggle to comprehend the larger picture. For example, some children with autism may become champions at spelling bees, but have difficulty understanding the meaning of a sentence or a story.

"The language pattern in autism is a microcosm for the disorder," Dr. Just said. "People with autism are good at a lower level of analysis but have a deficit at the higher level."

In the current study, the researchers used a brain imaging technique known as functional magnetic resonance imaging (fMRI) to measure the brain activity of 14 individuals with high functioning autism while they performed a simple memory task involving letters of the alphabet. Specifically, the study volunteers were shown a sequence of letters. After each letter, they were asked to name the letter that preceded it. In some cases, they were asked to name the letter

that appeared two letters previously. The autism volunteers' brain activation patterns were compared to a control group of people who did not have autism, but were of a similar age and I.Q. level.

Both groups successfully completed the task. However, the fMRI scans revealed different brain activation patterns between the two groups. Compared to the control group, the volunteers with autism showed more activation in the right hemisphere, or half, of the brain, and less activation in the left hemisphere. The left hemisphere takes the lead in processing letters, words and sentences, whereas the right hemisphere plays a larger role in processing shapes and visual information.

Dr. Just said that the brain could interpret letters either spatially, as geometric shapes, or linguistically, by the names of the letters. The imaging data indicated that the volunteers with autism remembered letters as shapes, while the control group remembered them by their names. The brain activation patterns of the two groups also differed in other ways. While performing the task, the group with autism showed less activation in the anterior, or front, parts of the brain, and more activation in the posterior, or rear parts of the brain. Dr. Just explained that the brain's anterior portions carry out higher-level thinking and reasoning while the posterior portion is more involved with perceiving details.

Compared to the control group, the different brain areas of the people with autism were less likely to work in synchrony (at the same time) while recalling the letters. Such synchronization between brain areas takes place during many kinds of higher-level thinking and analysis that prove difficult for many people with autism.

These current findings provide evidence in support of the theory developed by these researchers. Called the theory of underconnectivity in autism, it maintains that autism results from a failure of the brain's neurological wiring -- the fibers of nervous system tissue that interconnect the individual parts of the brain. Deprived of effective connections, the different brain areas must work independently, sometimes performing at a higher level individually than they do in people who do not have autism. This may allow some people with autism to excel at spelling and other detail-oriented tasks but make it difficult for them to comprehend more complex material.

The researchers published their theory in the July issue of "Brain," in conjunction with the results of another fMRI study of volunteers with autism. In that study, volunteers were asked a question about a simple sentence that they had just read. When the people with autism performed the task, their brains showed less synchronization than did the brains of the control group. Moreover, the brains of the group with autism had less activation in an anterior part of the brain that integrates the words of a sentence, and more activation in a posterior brain area that comprehends individual words.

Many behavioral therapies to treat autism stress rote learning, Dr. Minshew explained. Such strategies are helpful, particularly early in a child's development. However, if the theory of underconnectivity proves valid, therapies that stimulate brain areas to work in synchrony might also offer some benefit. Such therapies might stress problem solving skills and creative thinking, and attempt to foster flexibility in thinking.

Dr. Just noted that more evidence to support the theory might come from the group's on-going studies of other cognitive abilities. The researchers are attempting to determine if underconnectivity is a general feature of the brain in autism, and are using brain imaging studies to examine the brain's white matter in people with autism. White matter is the part of the brain that consists of the larger neurological connections spanning different parts of the brain.

The NICHD is part of the National Institutes of Health (NIH), the biomedical research arm of the federal government. NIH is an agency of the U.S. Department of Health and Human Services. The NICHD sponsors research on development, before and after birth; maternal, child, and family health; reproductive biology and population issues; and medical rehabilitation. NICHD publications, as well as information about the Institute, are available from the NICHD Web site, <<http://www.nichd.nih.gov>>, or from the NICHD Information Resource Center, 1-800-370-2943; e-mail NICHDInformationResourceCenter@mail.nih.gov.

FEW AMERICANS ARE AWARE THEY HAVE CHRONIC KIDNEY DISEASE Ten to 20 million people in the United States have kidney disease but most don't know it, according to researchers at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health, the Johns Hopkins Bloomberg School of Public Health, and the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention. The findings are in the "Journal of the American Society of Nephrology."

Over the past decade the number of people with kidney failure doubled and the number starting dialysis or having a first kidney transplant increased by 50 percent, so that more than 400,000 Americans are now being treated for kidney failure at a cost of \$25 billion annually. In contrast to these dramatic increases, the study also found that the number of people with earlier stages of kidney disease remained stable. About 7.4 million people have less than half the kidney function of a healthy young adult. Another 11.3 million have at least half of what's considered normal function, but they also have persistent protein in their urine, a sign of kidney disease. The researchers can't explain the paradox between stable prevalence of kidney disease and rising incidence of kidney failure, but they suggest that fewer patients may be dying and more may be progressing faster to dialysis.

"Given the high prevalence of chronic kidney disease, we need to increase awareness, diagnosis and treatment if we are going to reduce the rate of progression and complications. Most critical are control of diabetes and hypertension," said Josef Coresh, M.D., Ph.D., lead author of the study and professor of epidemiology, medicine and biostatistics at the Bloomberg School of Public Health in Baltimore.

Coresh and his colleagues estimated awareness of chronic kidney disease among 4,101 people in the United States from 1999 to 2000 and compared disease prevalence in those years with that from 1988 to 1994, when 15,488 people were surveyed. Data were from two National Health and Nutrition Examination Surveys by NCHS of nationally representative, non-institutionalized adults.

In the most recent survey, participants were asked: "Have you ever been told by a doctor or other health professional that you had weak or failing kidneys (excluding kidney stones, bladder infections, or incontinence)?" Less than 10 percent of adults with moderately decreased kidney function (one half to one quarter the filtering capacity of a young healthy adult) reported being told they had weakened or failing kidneys. Awareness was low in all but the most severe stages of kidney disease. Women with moderately decreased kidney function were significantly less aware of their illness compared to similarly affected men. The researchers determined actual kidney function from blood and urine tests and estimated glomerular filtration rate (GFR), a measure of how well the kidneys are filtering waste from the blood.

Lack of awareness may be due in part to doctors' sole reliance on the blood level of a substance known as creatinine. Because muscle mass and other person-to-person variables can alter creatinine levels, a "normal" reading can provide a false sense of security. Instead, creatinine should be considered along with a patient's age, gender, and race to estimate GFR.

"Kidney disease can be well advanced before it's found with creatinine alone. GFR is a more accurate gauge of how well the kidneys work, and our free calculator makes finding the rate a snap," said Thomas H. Hostetter, M.D., senior author of the study and director of NIDDK's National Kidney Disease Education Program (NKDEP). "The earlier we identify kidney disease the sooner we can treat it," said Hostetter.

NKDEP is asking labs to streamline the process for identifying kidney disease. "The GFR calculator is a great tool, but it's still one more step for busy doctors' offices. We are really pleased that several major labs have agreed to automatically report estimated GFR whenever creatinine is measured, removing a potential barrier to finding kidney disease early," said Hostetter. "We are still working quite hard to standardize tests for kidney disease by all labs."

People with chronic kidney disease are at high risk for premature death, heart attacks and strokes as well as hypertension, anemia, bone disease and malnutrition. NKDEP strives to increase awareness about kidney disease and offers the GFR calculator and other free tools at <<http://www.nkdep.nih.gov>>.

"Chronic Kidney Disease Awareness, Prevalence and Trends among U.S. Adults, 1999 to 2000" was written by Josef Coresh, Danita Byrd-Holt, Brad C. Astor, Josephine P. Briggs, Paul W. Eggers, David A. Lacher and Thomas H. Hostetter. The paper was published online on November 24, 2004, and will appear in print January 2004 in the "Journal of the American Society of Nephrology."

Funding for the study was provided by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Center for Research Resources at the National Institutes of Health and by the American Heart Association Established Investigators Award.

NEW CONTRACT ALLOWS NIGMS CELL REPOSITORY TO CONTINUE PROVIDING KEY GENETIC RESEARCH RESOURCES

The National Institute of General Medical Sciences (NIGMS) has awarded a \$14.6 million, 5-year contract to the Coriell Institute for Medical Research in Camden, NJ, to continue operation of the NIGMS Human Genetic Cell Repository (HGCR). The repository is now in its 32nd year as an NIGMS-funded research resource.

The HGCR provides cells and DNA for use in human genetic and genomic research, speeding the discovery and investigation of genes linked to disease. Using the repository collection, scientists can study both common and rare disorders without having to locate appropriate cell donors. Since its establishment in 1972, the HGCR has distributed more than 100,000 cell cultures and 282,000 DNA samples.

"High-quality, publicly available research resources are a critical piece of the 21st-century scientific toolkit," said Jeremy M. Berg, Ph.D., NIGMS director. "The NIGMS Human Genetic Cell Repository continues to provide researchers with essential materials for studying the role genetic variation plays in human disease."

Genetic factors appear to contribute to virtually every human disease. But in most cases it is combinations of genes and environmental influences that cause illness, and researchers do not yet understand most of the combinations of factors. The HGCR plays an important role in advancing this knowledge by establishing specialized collections of DNA and cell cultures and making them available to the research community for a modest fee.

Within the repository are thousands of cell lines from people with genetic abnormalities as well as from unaffected family members. For the many genetic disorders represented, a large number of the cell lines have been characterized at the molecular level. This fine level of detail helps

researchers understand how slight genetic differences can lead to very different forms and severities of a disease. The HGCR also houses extensive panels of cell lines and DNA representing nearly all the variations of certain disease genes such as the BRCA1 breast and ovarian cancer gene and the cystic fibrosis gene. Researchers have successfully used HGCR cell lines harboring defects in individual chromosomes to pinpoint the locations of disease genes within the human genome and to search for new genes, enabling further studies of many health conditions.

While humans share 99.9 percent of their DNA sequence, within the 0.1 percent that is different lies important information about disease risks and individual responses to medications. To help researchers find this information, the HGCR contains samples from the HapMap consortium, a global partnership of scientists and funding agencies whose goal is to catalog genetic variation among all humans, as well as from the Centre d'Etude du Polymorphisme Humain (CEPH) family resource. This latter collection contains DNA samples and cell lines from a well-characterized group of families including grandparents, parents, and children. Scientists use the popular CEPH collection to clarify the roles of genes in health and disease.

Because genetic studies can raise concerns about donor privacy, samples deposited in the repository are stripped of individual identifying information and they may not be used for commercial purposes. To address the possible implications of genetic studies for the larger populations to which individual donors belong, the HGCR requires that researchers consult in advance with the communities from which they propose to collect samples and make plans for ongoing consultation with those communities.

"In addition to maintaining a very high level of scientific quality, the NIGMS Human Genetic Cell Repository has stayed well ahead of the curve on the important issue of protecting the privacy of individuals and the interests of communities," said Judith H. Greenberg, Ph.D., director of the NIGMS Division of Genetics and Developmental Biology and project officer on the repository contract. "Individuals, communities and scientists are partners in the research process, and policies like those established by the repository help advance genetic research while maintaining high ethical standards."

The repository Web site, <<http://locus.umdj.edu/nigms>>, lists available cell lines and DNA collections, along with detailed background information on their characteristics.

NIGMS is one of the 27 components of NIH, the premier federal agency for biomedical research. The NIGMS mission is to support basic biomedical research that lays the foundation for advances in disease diagnosis, treatment and prevention. More information about the HGCR can be found at <http://www.nigms.nih.gov/about_nigms/repository.html>.

MUTANT GENE LINKED TO TREATMENT-RESISTANT DEPRESSION A mutant gene that starves the brain of serotonin, a mood-regulating chemical messenger, has been discovered and found to be 10 times more prevalent in depressed patients than in control subjects, report researchers funded by the National Institutes of Health's National Institute of Mental Health (NIMH) and National Heart Lung and Blood Institute (NHLBI). Patients with the mutation failed to respond well to the most commonly prescribed class of antidepressant medications, which work via serotonin, suggesting that the mutation may underlie a treatment-resistant subtype of the illness.

The mutant gene codes for the brain enzyme, tryptophan hydroxylase-2, that makes serotonin, and results in 80 percent less of the neurotransmitter. It was carried by nine of 87 depressed patients, three of 219 healthy controls and none of 60 bipolar disorder patients. Drs. Marc Caron,

Xiaodong Zhang and colleagues at Duke University announced their findings in the January 2005 "Neuron," published online in mid-December.

"If confirmed, this discovery could lead to a genetic test for vulnerability to depression and a way to predict which patients might respond best to serotonin-selective antidepressants," noted NIMH Director Thomas Insel, M.D.

The Duke researchers had previously reported in the July 9, 2004 "Science" that some mice have a tiny, one-letter variation in the sequence of their tryptophan hydroxylase gene (Tph2) that results in 50-70 percent less serotonin. This suggested that such a variant gene might also exist in humans and might be involved in mood and anxiety disorders, which often respond to serotonin selective reuptake inhibitors (SSRIs) -- antidepressants that block the re-absorption of serotonin, enhancing its availability to neurons.

In the current study, a similar variant culled from human subjects produced 80 percent less serotonin in cell cultures than the common version of the enzyme. More than 10 percent of the 87 patients with unipolar major depression carried the mutation, compared to only one percent of the 219 controls. Among the nine SSRI-resistant patient carriers, seven had a family history of mental illness or substance abuse, six had been suicidal and four had generalized anxiety.

Although they fell short of meeting criteria for major depression, the three control group carriers also had family histories of psychiatric problems and experienced mild depression and anxiety symptoms. This points up the complexity of these disorders, say the researchers. For example, major depression is thought to be 40-70 percent heritable, but likely involves an interaction of several genes with environmental events. Previous studies have linked depression with the same region of chromosome 12, where the tryptophan hydroxylase-2 gene is located. Whether the absence of the mutation among 60 patients with bipolar disorder proves to be evidence of a different underlying biology remains to be investigated in future studies.

The researchers say their finding "provides a potential molecular mechanism for aberrant serotonin function in neuropsychiatric disorders."

Also participating in the study were: Raul Gainetdinov, Jean-Marin Beaulieu, Tatyana Sotnikova, Lauranell Burch, Redford Williams, David Schwartz, and Ranga Krishnan, Duke University.

In addition to grants from NIMH and NHLBI, the study was also funded by the Human Frontiers Science Program and the Canadian Institute of Health Research. NIMH and NHLBI are part of the National Institutes of Health (NIH), the Federal Government's primary agency for biomedical and behavioral research. NIH is a component of the U.S. Department of Health and Human Services.

To learn more, visit the following links:

Depression: <<http://www.nimh.nih.gov/HealthInformation/Depressionmenu.cfm>>

Bipolar Disorder:

<<http://www.nimh.nih.gov/healthinformation/bipolarmenu.cfm>>

PUBMED Abstract of July 9, 2004 SCIENCE Article

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15247473>

INTERNATIONAL HAPMAP CONSORTIUM WIDENS DATA ACCESS: Mapping of Human Genetic Variation Will Speed Search for Disease Genes

The International HapMap Consortium announced that it is ending computer-based "click wrap" license restrictions on data generated by its effort to create a map of human genetic variation. As

a result, all of the consortium's data are now completely available to the public, a move that will provide researchers with even easier access to tools for identifying genetic contributions to disease.

The consortium is developing a map of common patterns, or haplotypes, of human genetic variation that can be used as a resource for scientists searching for genes related to health and disease. To create the HapMap, DNA was taken from blood samples collected by researchers in China, Japan, Nigeria and the United States. No medical or personal identifying information was obtained from the 270 individuals providing the samples. However, the samples are identified by the population from which they were collected.

The \$130 million project, which was launched in October 2002 and is expected to be completed in September 2005, is a public-private partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom and the United States. The U.S. component is led by the National Human Genome Research Institute (NHGRI) on behalf of the 19 institutes, centers and offices of the National Institutes of Health (NIH) that contributed funding. For more information on the International HapMap Project, see <<http://genome.gov/10001688>>.

From the outset, the consortium followed the example of the Human Genome Project and made most of its data quickly and freely available through public databases on the Internet. However, concerns existed that outside groups might be able to combine some of the HapMap data with their own data to generate patentable inventions -- a process referred to by some as "parasitic patenting." Such patents could potentially be used to exclude other researchers from being able to freely use the HapMap data. To prevent this from happening, the HapMap consortium required users to sign, using a simple mouse click from their computers, a free, non-exclusive, non-royalty-bearing licensing agreement to obtain access to certain types of data the project had collected on individuals' DNA sequences, specifically the genotypes. Under terms of that license, users agreed not to prevent others from using the individual genotype data and to share data only with those who had also agreed to this condition.

"The licensing agreement was quite non-restrictive and enabled most researchers to use HapMap data as they wished. However, there was an unavoidable consequence of the license: it did prevent HapMap data from being incorporated into other public genomic databases," said NHGRI Director Francis S. Collins, M.D., Ph.D. "We are pleased that researchers around the globe will now have swift and easy access to all HapMap data, free of any restrictions."

Several recent developments prompted the consortium's decision to drop the licensing requirement. First, consortium researchers already have publicly released data on about one million single nucleotide polymorphisms (SNPs) in the individual DNA samples that have been genotyped for the HapMap project. Second, Perlegen Sciences, Inc., of Mountain View, Calif., has publicly released genotype data on about 1.6 million SNPs. Third, new methods have been developed to analyze the data and are being used to determine the genome-wide patterns of genetic variation in the HapMap data. These advances led the consortium to conclude that the patterns of human genetic variation can readily be determined clearly enough from the primary genotype data to constitute prior art. Thus, in the view of the consortium, derivation of haplotypes and "haplotype tag SNPs" from HapMap data should be considered obvious and thus not patentable. Therefore, the original reasons for imposing the licensing requirement no longer exist and the requirement can be dropped. This decision will allow the HapMap project's Data Coordination Center to post all of the consortium's monthly release of data and to distribute this data to other public databases, such as the NIH-funded National Center for Biotechnology Information's dbSNP <<http://www.ncbi.nlm.nih.gov/projects/SNP/>> and the JSNP Database in Japan <<http://snp.ims.u-tokyo.ac.jp/>>.

"We are excited that the HapMap data will be even more easily available for researchers to use in their efforts to find genes that influence many common diseases, such as diabetes, hypertension and arthritis. Gene mappers have been using the HapMap data almost as rapidly as we have been able to generate them," said Yusuke Nakamura, M.D., Ph.D., director of the University of Tokyo's Human Genome Center, as well as leader of the RIKEN SNP Research Center and the Japanese group working on the International HapMap Project.

Researchers are already using the HapMap data to study conditions such as type 2 diabetes, asthma and dyslexia, as well as genes related to differences in how individuals metabolize and react to certain medications. When the HapMap is completed next year, those studies will be able to be carried out even more efficiently.

"We are delighted that our public databases will now be able to integrate the HapMap data with other genomic data," said Ewan Birney, Ph.D., who heads Ensembl, one of the public databases that had been unable, until today, to incorporate the HapMap data, and which is a joint genome browser project between the European Bioinformatics Institute and the Wellcome Trust Sanger Institute in Cambridge, England. "Now, researchers will be able to study how this new information about human genetic variation relates to genes and their function. Such studies are essential to efforts to develop better ways of diagnosing, treating and preventing human disease."

NHGRI is one of the 27 institutes and centers at the NIH, which is an agency of the Department of Health and Human Services. The NHGRI Division of Extramural Research supports grants for research and for training and career development at sites nationwide. Additional information about NHGRI can be found at <<http://www.genome.gov>>.

ARCHIVED ISSUES OF TSC ALERT

For previous issues of the TSC Alert, visit the TS Alliance Web site at:

<http://tsalliance.easycgi.com/pages.aspx?content=25>

TSC INFORMATION

For information about TSC, visit the TS Alliance Web site at: <http://www.tsalliance.org> or call the Tuberous Sclerosis Alliance at 1-800-225-6872.

INTERESTING LINKS

NIH will develop network for quantifying patient-reported outcomes.

<http://nihroadmap.nih.gov/clinicalresearch/promis.asp>

NIH has created a Web page about policy on public access and research archiving.

http://www.nih.gov/about/publicaccess/publicaccess_background.htm

Psychotherapy, Meds Best for Youth With Obsessive Compulsive Disorder
<http://www.nimh.nih.gov/press/pryouthocd.cfm>

Stress Impairs Thinking Via Mania-Linked Enzyme
<http://www.nimh.nih.gov/press/preenzyme.cfm>

Report of the National Advisory Mental Health Council's Workgroup on Clinical Trials
http://www.nimh.nih.gov/council/interventions_research.cfm