News, Literature, and Events in Braingenethics

View this email in your browser

# Braingenethics Update

**Vol. 5, No. 2**
**March 2018**
braingenethics.cumc.columbia.edu/

## In the Literature

The Daunting Polygenicity of Mental Illness: Making a New Map
**Steve E. Hyman**
An epochal opportunity to elucidate the pathogenic mechanisms of psychiatric disorders has emerged from advances in genomic technology, new computational tools and the growth of international consortia committed to data sharing. Yet a sobering picture is coming into view; it reveals daunting genetic and phenotypic complexity portending enormous challenges for neurobiology. Psychiatric neuroscience must develop a new scientific map to guide investigation through a polygenic terra incognita.

A Polygenic P Factor for Major Psychiatric Disorders

The Myth of Optimality in Clinical Neuroscience
**Avram Holmes et al.**
This paper challenges the idea that "health" possesses a single ideal state, arguing that there is no universally optimal profile of brain functioning. Instead of examining behaviors in isolation, psychiatric illnesses can be best understood through the study of patterns of variation across distributed brain systems.

## In the Media

How Genetics Is Changing Our Understanding of 'Race'
**David Reich**

**Saskia Selzam**

It has been proposed that a single dimension, called the p factor, can capture a person's liability to mental disorder. Relevant to this p hypothesis, recent genetic research has found surprisingly high genetic correlations between pairs of psychiatric disorders. This paper compares genetic correlations from different methods and examines their support for a genetic p factor.

Overlap Between the General Factor of Personality and Trait Emotional Intelligence: A Genetic Correlation Study

**Dimitri van der Linden et al.**

The present study examines whether the strong phenotypic correlation between the General Factor of Personality (GFP) and trait emotional intelligence (EI) has a genetic component. In a sample of monozygotic and dizygotic twins, the heritability estimates for the GFP and trait EI were 53 and 45%, respectively. Moreover, there was a strong genetic correlation between the GFP and trait EI. These findings are discussed in light of evolutionary accounts of the GFP.

Genome-wide Association Study of Dimensional Psychopathology Using Electronic Health Records

**Thomas H. McCoy Jr. et al.**

Genetic studies of neuropsychiatric disease strongly suggest an overlap in liability. This study applied a newly developed natural language processing method to extract five symptom dimensions, and conducted a genome-wide association study to examine whether common variants were associated with each of these dimensions as quantitative traits. Loci in three of five domains exceeded a genome-wide threshold for statistical significance.

Genome-wide Analyses of Self-Reported Empathy: Correlations with Autism,

The average genetic differences between people of different subgroups are small, but that fact has created an orthodoxy out of the idea that those small differences don't matter. The author argues that contending that there are no significant differences between racial subgroups, even when genetic evidence suggests that there might be, invites the kind of racist reasoning that the denial of difference aims to prevent.

Jermaine Jones Seeks to Untangle the Genetics Behind Substance Abuse

**Katarina Zimmer**

Studying pharmacogenetics in lab rodents prepared the Columbia University professor to investigate the biological underpinnings of substance use disorders in humans.

UK Judges Receive Primers on Forensic Science

**Catherine Oxford**

Scientists in the U.K., in collaboration with members of the judiciary, have launched the first in a series of explanatory documents designed to help integrate science into the courtroom.

Environment, Not Genetics, Primarily Shapes Microbiome Composition

**Jim Daley**

A study published in Nature suggests that environment plays a much greater role than host genetics in determining the composition of the human gut microbiome, and that including microbiome characteristics when predicting people's traits makes those estimates more

Schizophrenia, and Anorexia Nervosa

**Varun Warrier**

This study marks the largest genome-wide association study (GWAS) of empathy to date using a well-validated self-report measure of empathy, the Empathy Quotient (EQ), in 46,861 research participants from 23andMe, Inc.The results suggest that the genetic variations associated with empathy also play a role in psychiatric conditions and psychological traits.

More In the Media: The Ability to Feel Empathy—Or Not—Is Shaped by Your Genes, by Olivia Goldhill

Parkinson's Foundation Launches Genetic Testing Initiative to Optimize Patient Care

The Parkinson's Foundation has launched an effort to support CLIA-approved genetic testing for people with Parkinson's disease (PD). The initiative, which stemmed from discussions with Center Steering Committee member Roy Alcalay, MD, MS, Florence Irving Assistant Professor of Neurology at Columbia, would make clinical genetic testing accessible for people with PD through their clinicians. It aims to accelerate recruitment to precision medicine clinical trials, and explore the role of genetic testing in the management of PD. To understand the significance of the initiative, some background is necessary.

***Dr. Roy Alcalay, with more on the project:*** Until recently, only a fraction of people with PD were referred to genetic counseling, usually people with either a significant family history or very early-onset PD. However, extensive

accurate than only personal history.

## More In the Literature

Differences in Exam Performance Between Pupils Attending Selective and Non-Selected Schools Mirror the Genetic Differences Between Them

**Emily Smith-Wooley et al.**

On average, students attending selective schools outperform their non-selective counterparts in national exams. This study examined the role of genetic and environmental differences between these two groups, finding that genetic and exam differences between school types are primarily due to the heritable characteristics involved in pupil admission.

More: Critical reflection by Erik Turkheimer

Measuring and Estimating the Effect Sizes of Copy Number Variants on General Intelligence in Community-Based Samples

**Guillaume Huguet et al.**

Copy number variants (CNVs) classified as pathogenic are identified in 10% to 15% of patients referred for neurodevelopmental disorders. This study identified all CNVs that were 50 kilobases (kb) or larger in 2 general population cohorts with measures of IQ. This represents a new framework to study variants too rare to perform individual association studies and can help estimate the cognitive effect of undocumented deletions in the neurodevelopmental clinic.

research on two genes, *LRRK2* and *GBA*, may change this practice. 5-10% of all people with PD and >30% of Ashkenazi Jews with PD carry a mutation or a variant in *LRRK2* or *GBA*. Carrier status has been shown in multiple studies to predict rate of progression (slower in *LRRK2* and faster in *GBA*, when compared to non-carriers). More recently, potential interventions targeting carriers have reached various stages of clinical trials. In these settings, where genotype status may be used to infer both clinical outcomes and eligibility to test potential treatments, the interest in obtaining clinical genetic testing has grown. The new initiative will demonstrate whether people with PD are interested in obtaining genetic data, in part to determine clinical trial eligibility, or will refrain from testing, as observed in other neurodegenerative conditions. It will also evaluate whether clinicians change treatment recommendations based on genotype.

Physician-Assisted Death for Psychiatric Patients — Misguided Public Policy

**Frank G. Miller and Paul S. Appelbaum**

Physicians in the Netherlands and Belgium have helped a small but growing number of patients with mental illness but no terminal condition to end their lives. In some U.S. states, attempts to extend physician-assisted death to psychiatric patients appear inevitable.

Please Test My Child for a Cancer Gene, but Don't Tell Her

**Johan Bester et al.**

A 38-year-old woman with Li-Fraumeni syndrome has an 11-year-old daughter,

The Speed of Progression to Tobacco and Alcohol Dependence: A Twin Study

**Spencer B. Huggett et al.**

This study investigated the role of genetic and environmental influences for age of initiation and speed of progression to dependence (latency) of tobacco and alcohol use. Latencies to dependence were heritable traits for tobacco and alcohol. Genetic influences contributing to early age of initiation were associated with faster latencies but sometimes were counteracted by environmental factors, the extent to which depended on substance and sex.

Antidepressant Outcomes Predicted by Genetic Variation in Corticotropin-Releasing Hormone Binding Protein

**Chloe P. O'Donnell et al.**

This study investigated whether variation within the hypothalamic-pituitary (HPA) axis genes predicts antidepressant outcomes within two large clinical trials. The authors found that the rs28365143 variant within the corticotropin-releasing hormone binding protein (CRHBP) gene predicted antidepressant outcomes for remission, response, and symptom change.

Common Schizophrenia Alleles are Enriched in Mutation-intolerant Genes and In Regions Under Strong Background Selection

**Antonio F. Pardiñas et al.**

Through a genome-wide association study and meta-analysis with existing data, this study identified 50 novel loci and 145 loci in total associated with schizophrenia. Through integrating genomic fine-mapping with brain expression and chromosome conformation data, researchers also found candidate causal genes within 33 loci.

who the geneticist recommends testing for the Li-Fraumeni genetic variant. The mother is concerned about the impact of testing and diagnosis on Karen's psychological well-being. She requests that testing be done without disclosing it to the child and requests that the results only be revealed if they are positive. Experts in genetics, law, and bioethics discuss whether it is permissible to test the child without her knowledge or assent.

Genome-wide Association Study Identifies a Regulatory Variant of RGMA Associated with Opioid Dependence in European Americans

**Zhongshan Cheng et al.**

This study completed an opioid dependence (OD) genome-wide association study in 3058 opioid-exposed European Americans, 1290 of whom met criteria for a DSM-IV diagnosis of OD. Analysis revealed that RGMA messenger RNA expression was associated with OD and four genes implicated in other psychiatric disorders.

Heredity Beyond the Gene

**Russell Bonduriansky & Troy Day**

Biologists are now faced with the monumental challenge of making sense of a rapidly growing menagerie of discoveries that violate deeply ingrained ideas. Something is clearly missing from the conventional concept of heredity, which asserts that inheritance is mediated exclusively by genes and denies the possibility that some effects of environment and experience can be transmitted to descendants.

Dark DNA: The missing matter at the heart of nature

The Biological Contributions to Gender Identity and Gender Diversity: Bringing Data to the Table

**Tinca J. C. Polderman**

This paper reviews the evidence that gender identity and related socially defined gender constructs are influenced in part by innate factors including genes. Based on the data reviewed, it hypothesizes that gender identity is a multifactorial complex trait with a heritable polygenic component, and argues that increasing the awareness of the biological diversity underlying gender identity development is relevant to all domains of social, medical, and neuroscience research and foundational for reducing health disparities and promoting human-rights protections for gender minorities.

Are the Brains of Transgender People Different from Those of Cisgender People?

**Shawna Williams**

Research into the biological basis of gender identity is in its infancy, but clues are beginning to emerge.

-Editorial here: The Skin We're In, Bob Grant

Damaging de Novo Mutations Diminish Motor Skills in Children on the Autism Spectrum

**Andreas Buja et al.**

In individuals with autism spectrum disorder (ASD), de novo mutations have previously been shown to be significantly correlated with lower IQ but not with the core characteristics of ASD. This study demonstrates that damaging de novo mutations in ASD individuals are also significantly and convincingly correlated

**Adam Hargreaves**
The discovery of dark DNA is so recent that researchers are still trying to work out how widespread it is and whether it benefits those species that possess it. However, its very existence raises some fundamental questions about genetics and evolution.

## Call for Submissions

*Neuropsychiatric Genetics* will publish a special issue entitled, "**Ethical, Legal, and Social Implications of Advances in Neuropsychiatric Genetics**." The journal anticipates accepting submissions until June 1, 2018. **If you are interested in this opportunity, please let the guest editors know by completing this short online form.** If you have any questions, please contact guest editors Christian Lenk (christian.lenk@uni-ulm.de) and Gabriel Lázaro-Muñoz (glazaro@bcm.edu).

with measures of impaired motor skills. This correlation is not explained by a correlation between IQ and motor skills.

Dysregulation of the Epigenetic Landscape of Normal Aging in Alzheimer's disease
**Raffaella Nativio et al.**
Aging is the strongest risk factor for Alzheimer's disease (AD). This study compares the genome-wide enrichment of the H4K16ac chromatin state marker in AD individuals against younger and elderly cognitively normal adults, finding that normal aging leads to H4k16ac enrichment, while AD entails dramatic loss of the mark.

Rare Variants in Axonogenesis Genes Connect Three Families with Sound–Color Synesthesia
**Amanda K. Tilot et al.**
Synesthesia is a rare nonpathological phenomenon where stimulation of one sense automatically provokes a secondary perception in another. The trait appears to be more common among people with autism spectrum disorder and savant abilities. This study used whole-exome sequencing with three families with sound–color (auditory–visual) synesthesia, and identified rare genetic variants that fully cosegregate with synesthesia in each family, uncovering 37 genes of interest.

A Comprehensive Analysis of Nuclear-encoded Mitochondrial Genes in Schizophrenia
**Vanessa F. Gonçalves et al.**
Mitochondrial dysfunction may play a role in schizophrenia (SCZ). This study conducted analyses using results from the Schizophrenia Psychiatric Genomics Consortium GWAS (PGC-SCZ2). It provides evidence that specific aspects of mitochondrial function may play a role in

SCZ, but did not observe its broad involvement even using a large sample.

Looking for the Psychosocial Impacts of Genomic Information

Watch the archive from last month's conference here.

## Upcoming Webinar

A webinar sponsored by The Scientist will feature expert panels on neurodevelopment and neurodegenerative diseases.

Are All Neurodegenerative Diseases Made Equal?

Wednesday, April 11th, 2018, 2:30-4:00 pm

This webinar will focus on the neurodegenerative processes resulting in the development of diseases like Alzheimer's (AD), Parkinson's (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). Recent studies have suggested common mechanisms underlying these pathologies. A panel of experts will share their research, discuss current therapeutic approaches, and offer their insights on the mechanisms that drive this array of neurodegenerative diseases.

*|MC:SUBJECT|*

**Our mailing address is:**
The Hastings Center
21 Malcolm Gordon Rd.
Garrison, NY 10524