News, Literature, and Events in Braingenethics

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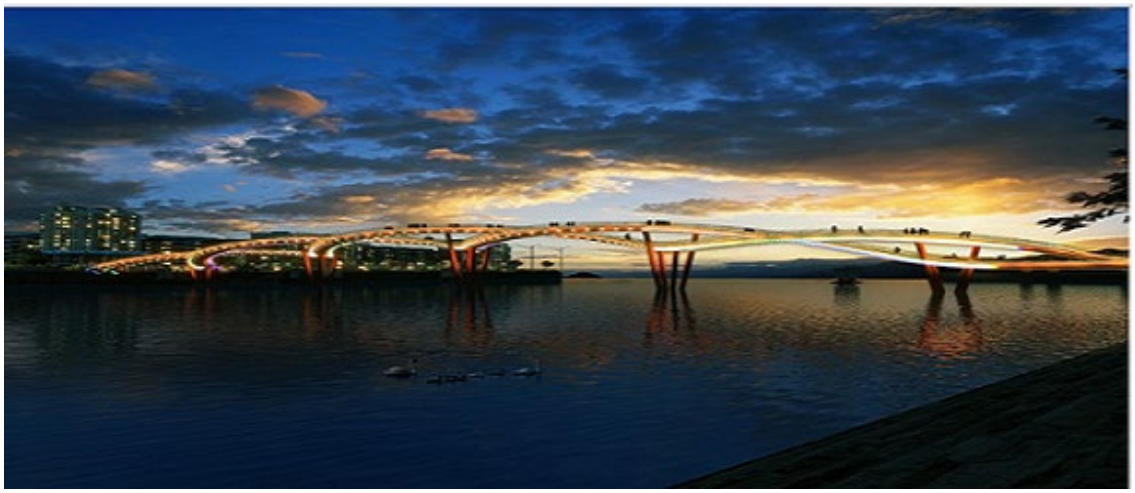

In the Literature

Successes and Challenges in Precision Medicine in Psychiatry
Edwin van den Oord et al.
Beyond new drug development, which is slow and costly, pharmacogenomics promises to improve psychiatric care by tailoring drug administration to patient genotype. The development of the genome-wide association study (GWAS) has made pharmacogenomics possible even without a deep understanding of the mechanism of drug action.

Precision Psychiatry—Yes, but Precisely What?
Ana Gómez-Carillo et al.

In the Media

Polygenic Risk Scores for Three Psychiatric Disorders Linked to Depression Diagnoses
GenomeWeb
Higher polygenic risk scores for depression and other psychiatric disorders are associated with an increased risk of a diagnosis of depression within a general population cohort, according to a new study by Kathrine Musliner and colleagues published in JAMA Psychiatry. In this case-cohort study of 34,573 individuals, each 1 SD increase in the polygenic risk for major depression was associated with a 30% increase in the hazard for a depression diagnosis in

Responding to a July Viewpoint by Jordan Smoller and Murray Stein in *JAMA*, Gómez-Carillo and colleagues take Smoller and Stein to task for identifying the crisis of care in psychiatry, then suggesting precision medicine as the solution, without attention to the social context in which psychiatric illnesses occur. Smoller and Stein reply here.

Integrating Genomics into Psychiatric Practice: Ethical and Legal Challenges for Clinicians
Eric T. Ward et al.
This article reviews how clinicians encounter and use genomics in the clinic, summarizes existing literature on how clinicians feel about the use of genomics in psychiatry, and analyzes foreseeable ethical and legal challenges for the responsible integration of genomics into psychiatric care at the structural and clinic levels.

Thinking About Schizophrenia in an Era of Genomic Medicine
Daniel R. Weinberger
In his commentary in the *American Journal of Psychiatry*, Weinberger addresses how the genomic era is changing our understanding of schizophrenia, despite having little predictive power in individuals. He further reflects that genetics is only part of the story.

Predicting Polygenic Risk of Psychiatric Disorders
Alicia Martin et al.
Though still in its nascence, there is great promise for the use of GWAS in predicting risk for psychiatric disorders. The authors review the current state of the field and identify

hospital-based psychiatric care, or "first depression." Polygenic liabilities for schizophrenia and bipolar disorder were also associated with an increased hazard of depression, but to a lesser extent.

Can We Blame Our Genes for Our Decisions?
Nathaniel Scharping
Though there's a strong cultural belief in genetic determinism, the truth lies between the facts that genes are implicated in every action we take and that genetic influence on behavior is much more nuanced and complex than the story of determinism leads us to believe.

Sure, You Can Learn Your Genetic Risk for Alzheimer's. But Do You Really Want to Know?
Tony Dearing
Genetic tests for AD are popular, but interpreting them is fraught.

Twins Get some 'Mystifying' Results when They Put 5 DNA Ancestry Kits to the Test
Charlsie Agro and Luke Denne
Despite having virtually identical DNA, the twins did not receive matching results from any of the companies. In most cases, the results from the same company traced each sister's ancestry to the same parts of the world — albeit by varying percentages. But the results from California-based 23andMe seemed to suggest each twin had unique twists in their ancestry composition.

Hong Kong Genome Project to Sequence, Analyze 20K Patients
GenomeWeb

opportunities and potential pitfalls as progress continues.

[A Systematic Review of the Psychological Implications of Genetic Testing: A Comparative Analysis Among Cardiovascular, Neurodegenerative and Cancer Diseases]

Serena Oliveri et al.

A systematic review of studies examining psychological correlates of receiving genetic information regarding predisposition to disease finds no significant effect on measures of depression or anxiety, with the exception of Huntington's disease.

[De Novo Variants in MAPK8IP3 Cause Intellectual Disability with Variable Brain Anomalies]

Konrad Platzer et al.

Using exome sequencing, Platzer et al. identified *de novo* variants in *MAPK8IP3* in 13 unrelated individuals presenting with an overlapping phenotype of mild-to-severe intellectual disability. They then used CRISPR-Cas9 to test effects of these variants in C. elegans. Platzer et al. conclude that *de novo* variants in *MAPK8IP3* are a cause of a neurodevelopmental disorder with intellectual disability and variable brain anomalies.

[Association Studies of up to 1.2 Million Individuals Yield New Insights into the Genetic Etiology of Tobacco and Alcohol Use]

Mengzhen Liu et al.

In sample sizes up to 1.2 million individuals, the authors discovered 566 genetic variants in 406 loci associated with tobacco and alcohol

Hong Kong plans to sequence and analyze the genomes of 20,000 patients and, in some cases, their families as part of the $87 million Hong Kong Genome Project (HKGP). Goals include increasing the diagnostic rate for patients with rare genetic disorders, gaining insight into genomic changes that cause cancer, and developing more quality genomic data for Chinese-ancestry populations.

[Myriad Pushing Ahead with Payors on GeneSight as Data from Large Randomized Study Is Published]

Turna Ray

Myriad Genetics is hoping that data from the [GUIDED study], a randomized controlled trial of GeneSight, their tool for enabling pharmacogenomic testing-guided depression treatment, will encourage payors to cover its use in the clinical context. Although the study failed to meet its primary endpoint, and symptom improvement at eight weeks was not statistically significant for patients in the pharmacogenetic testing arm compared to the treatment-as-usual arm, the study did show that patients receiving GeneSight-guided treatment had significant improvements in remission and response rates.

[We Won't Use CRISPR to Make Super-smart Babies—But Only Because We Can't]

Antonio Regalado

A primary fear of human germline gene editing, such as with CRISPR, is that it could enable genetic inequality that would exacerbate social inequality. GWAS studies

use, with 150 loci in common. Smoking phenotypes were genetically correlated with increased prevalence of many health conditions, whereas alcohol use was negatively correlated with these conditions, such that increased genetic risk for alcohol use is associated with lower disease risk.

Genome-wide Study Identifies 611 Loci Associated with Risk Tolerance and Risky Behaviors

Richard K. Linnér et al.

A new GWAS produced in collaboration with 23andMe identifies new loci associated with various aspects of risk, including 124 with general risk tolerance. There is no evidence found of enrichment for genes previously hypothesized to relate to risk tolerance. **This is a pre-print and is not peer-reviewed.**

Autism Spectrum Disorders: Autistic Phenotypes and Complicated Mechanisms

Xi-Cheng Zhang et al.

This review summarizes recent progress in ASD research, focusing on its genetic and epigenetic mechanisms. It also discusses current animal models of ASD and the application of high-throughput sequencing technologies in studying ASD.

The ASD Living Biology: From Cell Proliferation to Clinical Phenotype

Eric Courchesne et al.

This review considers genetic, genomic, cellular, postmortem, animal model, and cell model evidence that shows that ASD begins in the womb. This leads

show, however, that complex traits like intelligence and musical ability involve potentially thousands of genes, making intervention for enhancement exceedingly difficult, if not wholly unlikely.

PsychENCODE

The PsychENCODE Consortium, an NIH-funded initiative aimed at discovering and investigating the role of non-coding genomic elements in the human brain, has published 11 research papers resulting from the study of over 2000 individual brains. The papers focus on functional genomics in the developing and adult brain as well as psychiatric disorders. For more background on the project and its implications, see Kelly Servick's article in Science. In a critical take on the project, neurogeneticist Kevin Mitchell questions the limited efficacy of a project that barely addresses how genetic risk ultimately affects pathophysiology and causes psychopathology

Early Experiences with Genome Sequencing in Newborns

John Lantos, editor

This supplemental issue of Pediatrics focuses on the new ethical issues in newborn genetic testing that have come with whole genome sequencing (WGS). Among the articles are three from the BabySeq project. Other topics include issues in genomics in the NICU, return of results, and concept

to a new theory that ASD is a multistage, progressive disorder of brain development, spanning nearly all of prenatal life. The authors introduce the ASD Living Biology paradigm, which seeks knowledge of prenatal beginnings of ASD by linking genetic and in vitro prenatal molecular, cellular and neural measurements with in vivo post-natal molecular, neural and clinical presentation and progression in each ASD child.

Genetic and Environmental Influences on Structural Brain Measures in Twins with Autism Spectrum Disorder

John Hegarty et al.

Twin pairs with and without ASD were recruited for this structural brain imaging study. Twins with ASD showed more environmental influence on some structural brain structures. This is especially relevant regarding the role of genetic and environmental factors in the development of ASD, in which certain brain structures may be more sensitive to specific influences.

Meta-analysis of Alzheimer's Disease on 9,751 Samples from Norway and IGAP Study Identifies Four Risk Loci

Aree Witoelar et al.

Witoelar and colleagues identify new loci implicated in Alzheimer's disease.

Genome-wide Meta-analysis Identifies New Loci and Functional Pathways Influencing Alzheimer's Disease Risk

Iris Jansen et al.

Jansen and colleagues performed a

of the "false-negative phenotype."

James Watson's Views on Race

James Watson, co-discover of the double helix structure of DNA and a giant in the field, has been widely criticized over views on racial differences that were included as part of a documentary on him. Amy Harmon covers the story here, with further analysis in a guest entry in Lauretta Charlton's column here. Cold Spring Harbor Laboratory, his academic home for many years, issued this statement rebuking his statements and announcing that they were stripping him of his chancellorship and honorary titles.

Elsewhere, C. Brandon Ogbunu, a professor of ecology and evolutionary psychology at Brown and a mentee of a student of Watson's, discusses what it's like to be a black biologist who owes much to James Watson. He wonders, "Is it much ado about nothing, or might the black scientist occupy a special place in modern conversations about scientific racism?"

large GWAS of clinically diagnosed AD and AD-by-proxy (71,880 cases, 383,378 controls). AD-by-proxy, based on parental diagnoses, showed strong genetic correlation with AD ($r_g = 0.81$). Meta-analysis identified 29 risk loci, implicating 215 potential causative genes. Associated genes are strongly expressed in immune-related tissues and cell types (spleen, liver, and microglia). Mendelian randomization results suggest a protective effect of cognitive ability on AD risk.

Assessment of Racial Disparities in Biomarkers for Alzheimer Disease

John Morris et al.

Differences between African American and non-Hispanic white individuals in Alzheimer biomarkers, namely concentrations of tau protein in cerebrospinal fluid, suggest possible race-dependent biological mechanisms that contribute to expression of disease. This editorial by Lisa Barnes in response to the study identifies recruitment of African Americans into AD research studies as a key issue In AD research.

Return of Individual Genomic Research Results: Are Laws and

More In the Literature

Harnessing Genetic Complexity to Enhance Translatability of Alzheimer's Disease Mouse Models: A Path toward Precision Medicine

Sarah Neuner et al.

This work both introduces a novel AD mouse population as an innovative and reproducible resource for the study of mechanisms underlying AD and provides evidence that preclinical models incorporating genetic diversity may better translate to human disease.

Diagnostic Utility of Whole Exome Sequencing in the Neuromuscular Clinic

Megan Waldrop et al.

The authors looked at patient records in their clinic to describe the impact of WES on diagnosis. They conclude that their results confirm the clinical utility of WES and that it can provide an end to the diagnostic odyssey for parents.

Genetic Testing in a Cohort of Patients with Potential Epilepsy with Myoclonic-atonic Seizures

Katie Angione et al.

This study reviewed genetic testing results for a cohort of EMAS (epilepsy with myoclonic-atonic seizures) patients. The

Policies Keeping Step?

Adrian Thorogood et al.

Across 20 countries, laws and policies governing return of genomic results vary widely and often contradict each other. International best practices are needed inform ethical return of results and future legislative and policy efforts.

authors conclude that while EMAS is widely accepted to have a strong genetic component, the diagnostic yield of genetic testing remains low. This may be because several genes now thought to be associated with EMAS are not included on the more commonly ordered epilepsy panels, or have only recently been added to them.

Upcoming Events and Jobs

Seminar on Ethical, Legal and Social Implications of Genetics

Center for Research on Ethical/Legal/Social Implications of Psychiatric, Neurologic & Behavioral Genetics

Department of Psychiatry, Columbia University Medical Center

Monday, February 11th, 2019 12:00-1:00pm

Rm. 10-405A&B, Irving Institute for Clinical and Translational Research

10th Floor, Presbyterian Hospital (PH) Building, 622 W. 168th Street

Precision Pediatric Oncology: An Ethical Perspective

Steve Joffe, MD, MPH

Emanuel and Robert Hart Professor of Medical Ethics

Professor of Pediatrics

Chief, Division of Medical Ethics

University of Pennsylvania

|MC:SUBJECT|

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21 Malcolm Gordon Rd.
Garrison, NY 10524