Contribution of genetics to behavioral prediction

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Why genetics?



• Genetics influences almost all human traits



True for: schizophrenia bipolar autism ADHD height diabetes

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Technological revolution



International HapMap Project

2003 - 2007

Genome-wide association & Sequencing







2001

Scope of the challenge



3.3 billion bases
18-20,000 genes
30 million+ common SNPs – single base changes

Genetic association study



ISC 2009 GWAS of schizophrenia Not so fast?





Psychiatric Genomics Consortium

PGC schizophrenia

Michael O'Donovan Pamela Sklar

> **Patrick Sullivan Doug Levinson** Ed Scolnick Pablo Gejman Aiden Corvin Anil Malhotra **Ayman Fanous** D Blackwood Hugh Gurling Kenneth Kendler Michael Gill Michael Owen Leena Peltonen

Ole Andreassen **Roel Ophoff** David St. Clair Sven Cichon **Thomas Schulze** Peter Holmans Thomas Lehner **Aarno** Palotie Alan Sanders Thomas Werge Dan Rujescu Bryan Mowry Mathew Keller

PGC stats group **Stephan Ripke** Naomi Wray Frank Dudbridge Peter Holmans Danyu Lin Edwin van den Oord Shaun Purcell Nick Craddock Danielle Posthuma Ken Kendler Mark Daly

Genetic Cluster Computer

Psychiatric Genomics Consortium (PGC)

300+ investigators80 institutions20 countries

Huge thanks to Thomas Lehner Pat Bender

NINH

National Institute of Mental Health Reducing the burden of mental illness and behavioral disorders through research on mind, brain, and behavi

PGC - The Past - 2011



9,394 cases, 12,462 controls

5 genome wide significant sites

Genome-wide association study identifies five new

Nature Genetics 43, 969-976 (2011) | doi:10.1038/ng.940 Received 16 February 2011 | Accepted 19 August 2011 | Published online 18 September 2011

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PGC SCZ, WCPG 2012, Hamburg



PGC SCZ, June 2013



Building a predictor...



Perhaps we can do better? Example from heart attack

Risk scores to predict 10-year risk of heart attack:

Framingham Risk Score (FRS):

age, sex, LDL, HDL, blood pressure, diabetes, and smoking

Updated score from American College of Cardiology/ American Heart Association (ACC/AHA) using same measures





Potential pitfalls



Use of polygenic risk does not generalize well across populations

Martin et al. 2017 American Journal Human Genetics

What the future holds

- Increased resolution of score
- Wider set of phenotypes beyond medical genetics applications
- Increased availability of score generation

Things to bear in mind

- Genes are not fate
- These scores are probabilistic and carry with them great uncertainty
- Much of the prior art (e.g., MAOA/warrior gene) has not held up to scrutiny