Behavioral Genetics and Polygenic Inheritance

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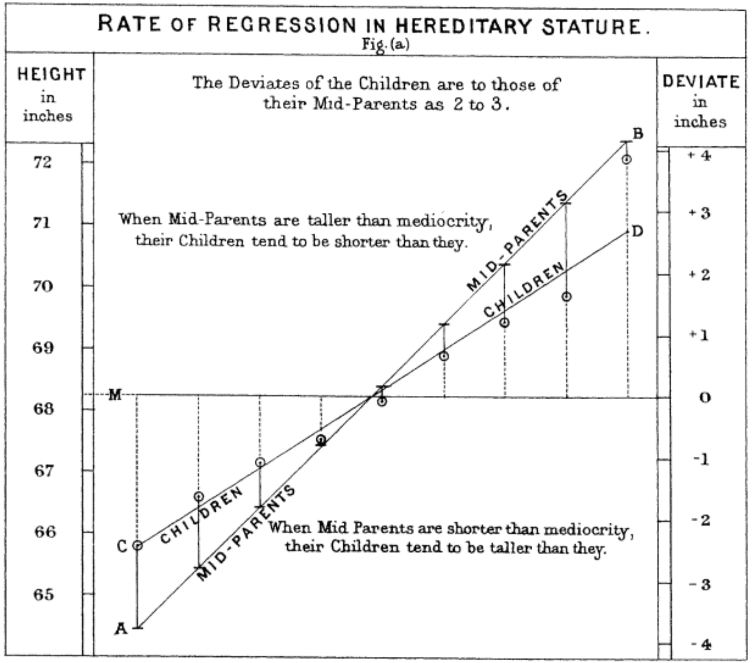
Why genetics?

- Genetics influences almost all human traits



The Deviates of the Children are to those of their Mid-Parents as 2 to 3.

When Mid-Parents are taller than mediocrity, their Children tend to be shorter than they.

When Mid Parents are shorter than mediocrity, their Children tend to be taller than they.

True for:
schizophrenia
bipolar
autism
ADHD
height
diabetes
...

Technology to rescue
Genome-wide association

15 February 2001

nature

www.nature.com

the human genome

Nuclear fission
Five-dimensional energy landscapes

Seafloor spreading
The view from under the Arctic ice

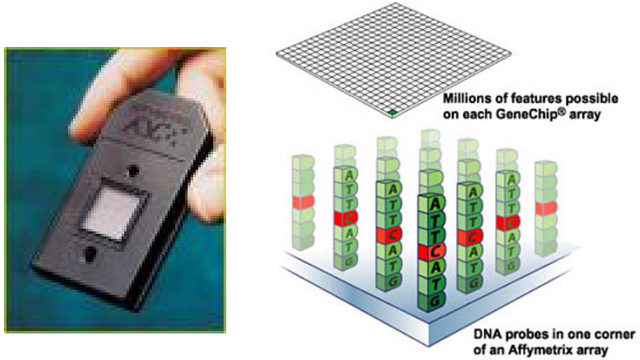
Career prospects
Sequence creates new opportunities

naturejobs
genomics special

2001

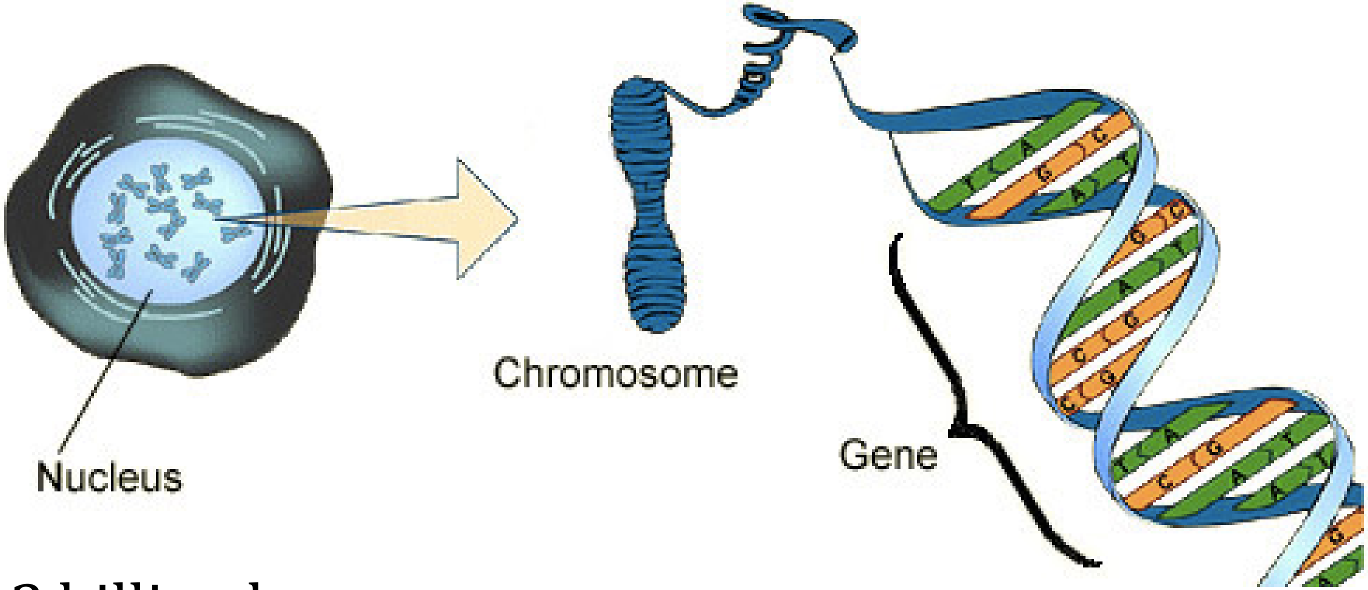
2003 - 2007

Genome-wide association (GWAS)



2005-present

Scope of the challenge

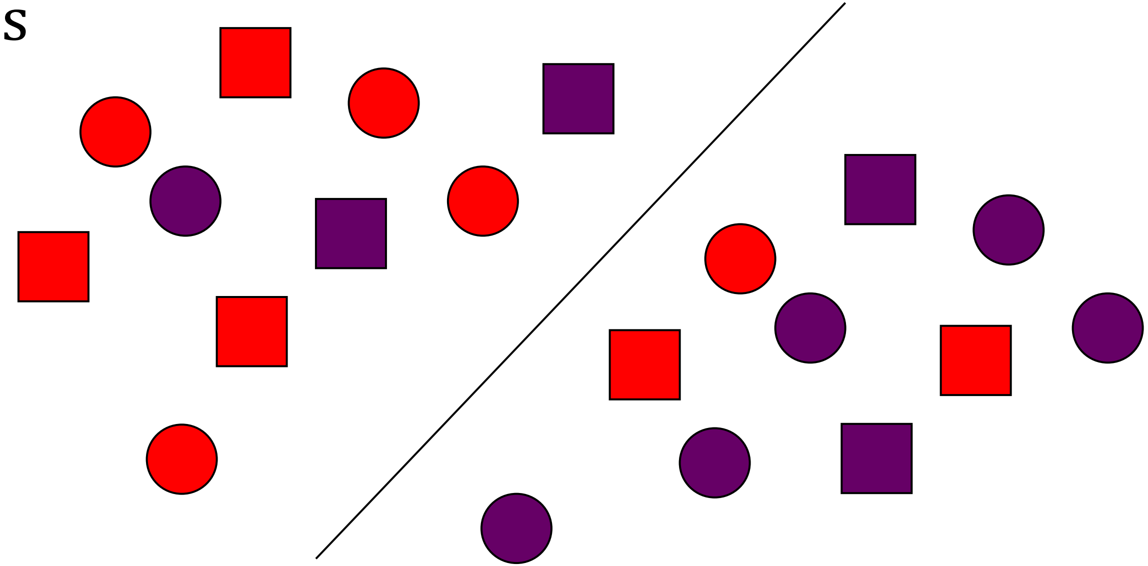


3.3 billion bases

18-20,000 genes

30 million+ common SNPs – single base changes

Genetic association study



Cases

Controls

🟥 allele 1

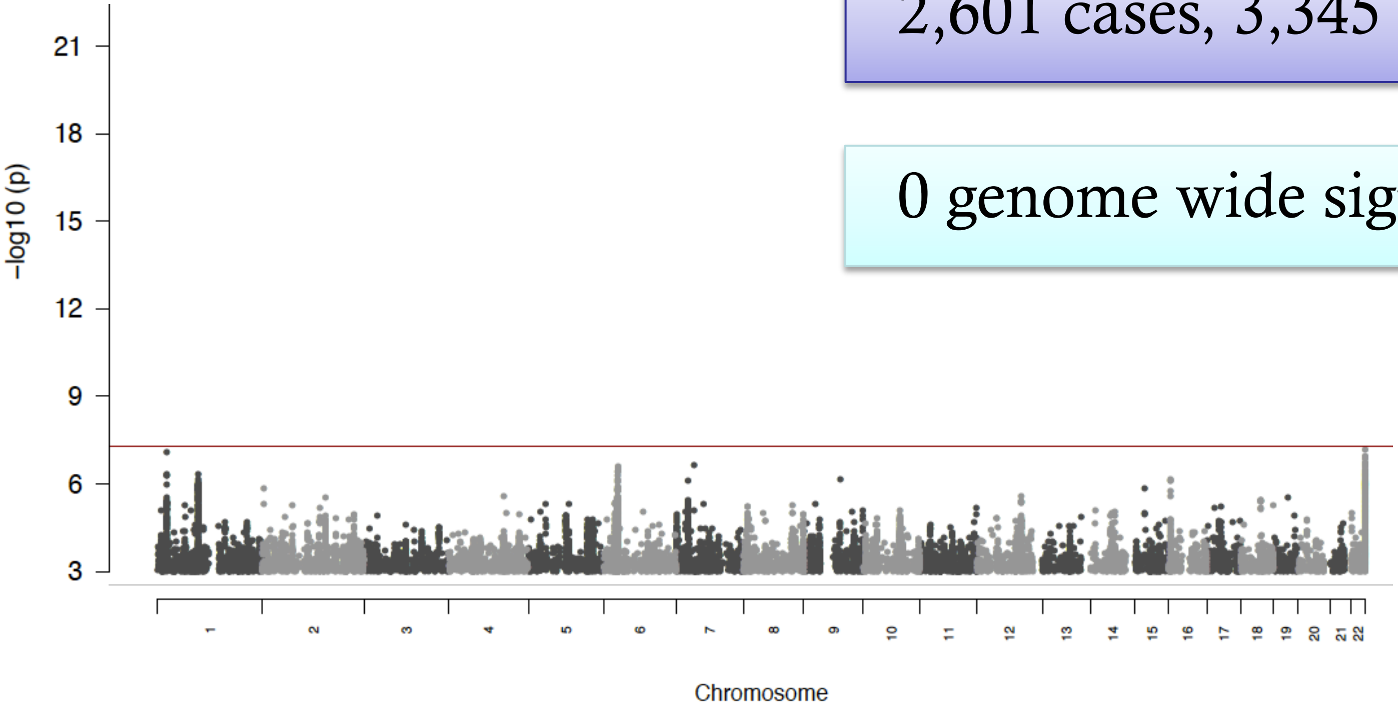
🟪 allele 2

Test allele 1 frequency

ISC 2009 GWAS of schizophrenia
Not so fast?

2,601 cases, 3,345 controls

0 genome wide significant sites



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
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Thomas Lehner
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PGC stats group

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Naomi Wray
Frank Dudbridge
Peter Holmans
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Edwin van den Oord
Shaun Purcell
Nick Craddock
Danielle Posthuma
Ken Kendler

Mark Daly

Genetic Cluster Computer

Psychiatric Genomics Consortium (PGC)

300+ investigators
80 institutions
20 countries

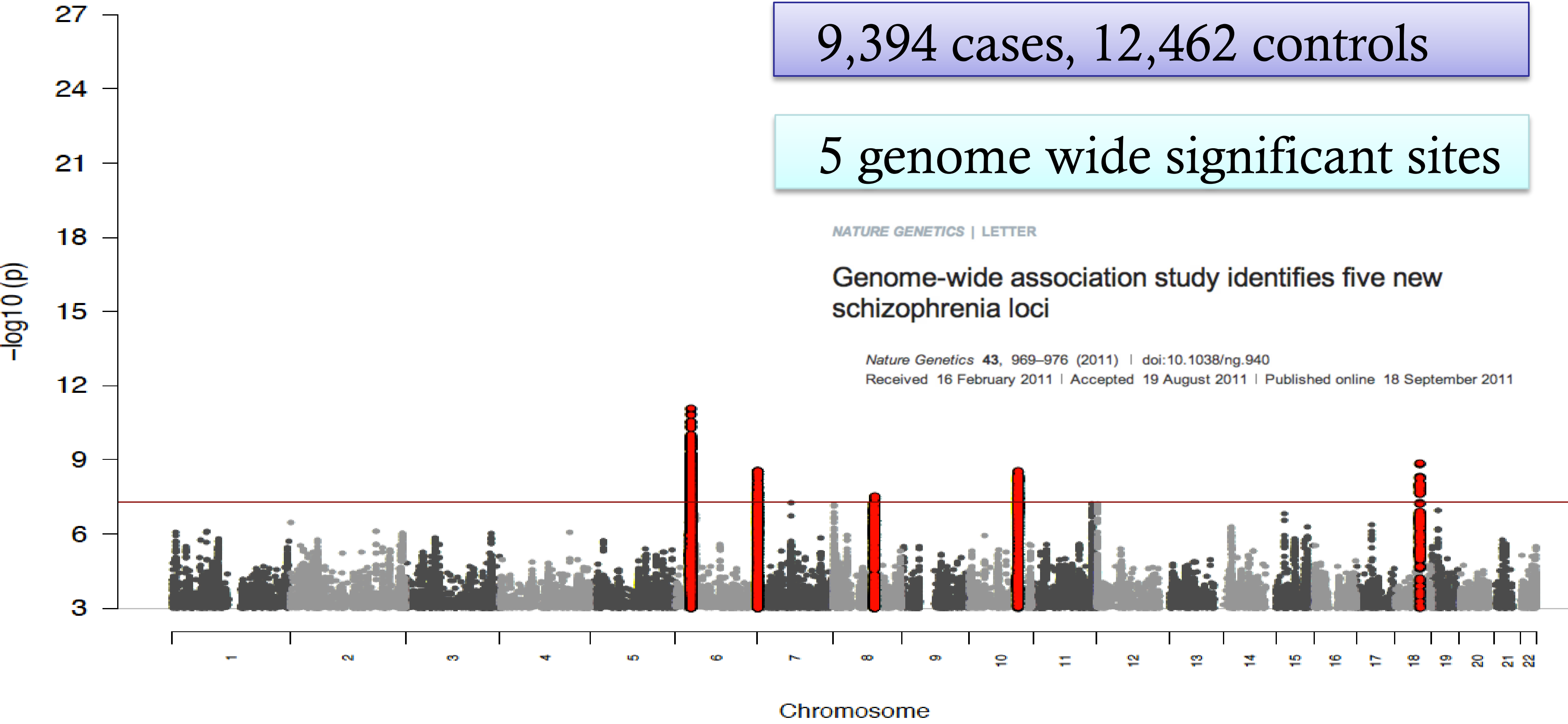
Huge thanks to
Thomas Lehner
Pat Bender

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

PGC - The Past - 2011

9,394 cases, 12,462 controls

5 genome wide significant sites

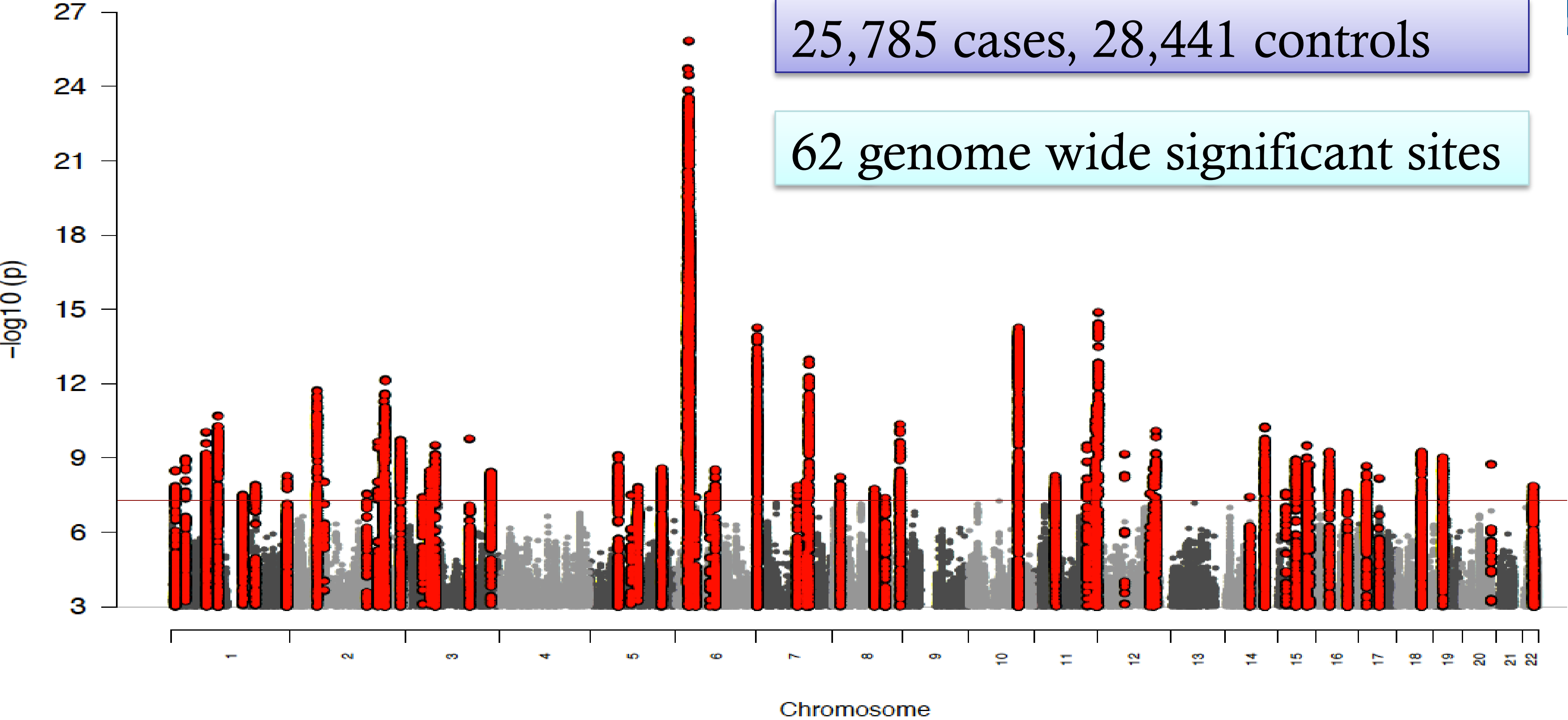


NATURE GENETICS | LETTER

Genome-wide association study identifies five new schizophrenia loci

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

PGC SCZ, WCPG 2012, Hamburg



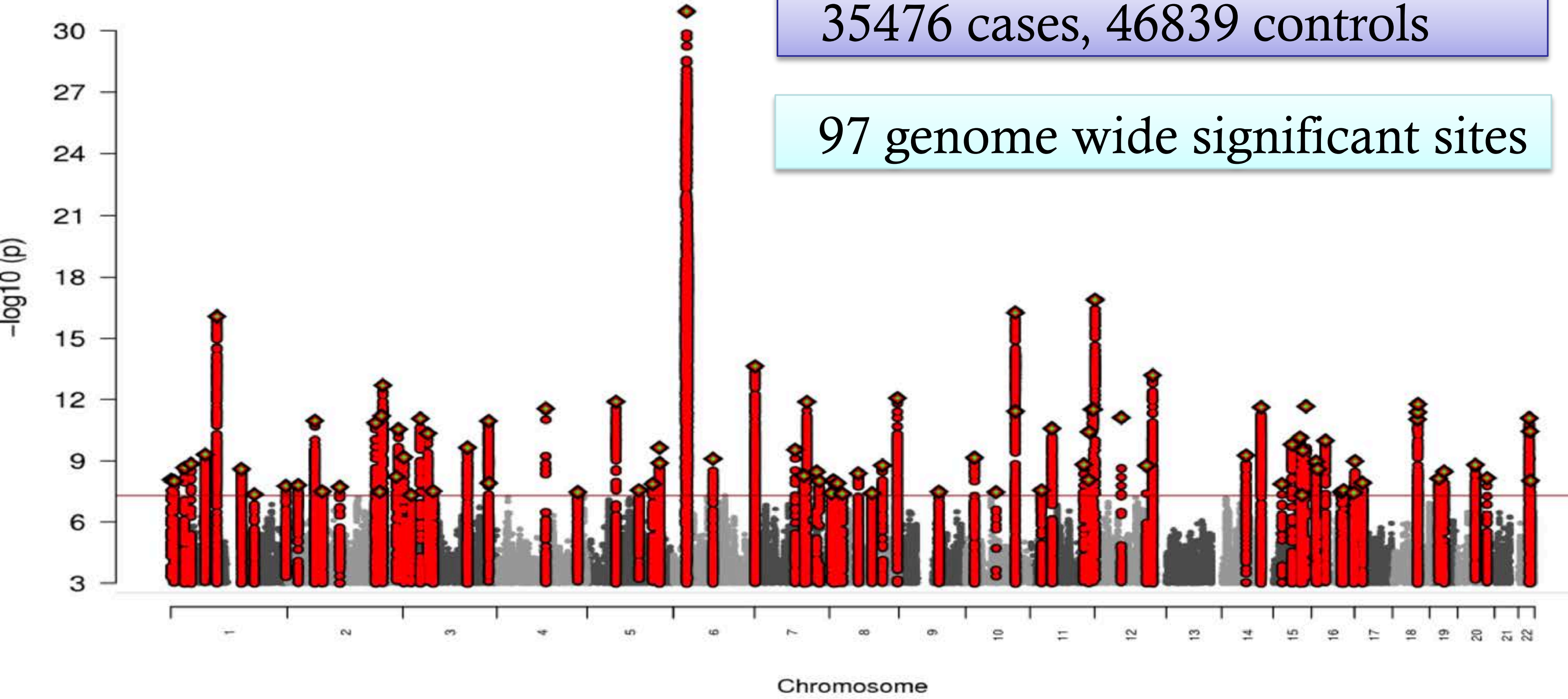
25,785 cases, 28,441 controls

62 genome wide significant sites

PGC SCZ, June 2013

35476 cases, 46839 controls

97 genome wide significant sites



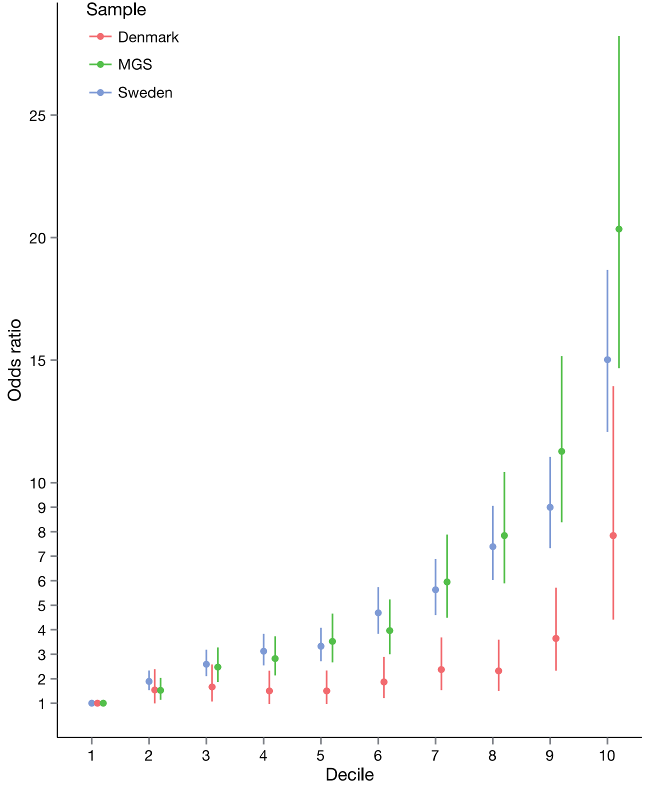
Building a predictor...

Take all SNPs with $p<0.05$

Create a score:

$\Sigma\beta_i{*}g_i$

Use as a predictor of schizophrenia



ISC Nature 2009; PGC Nature 2014

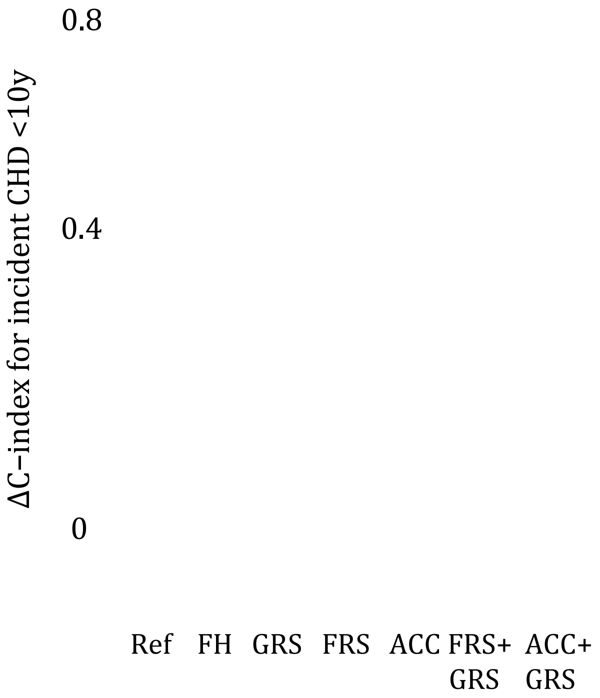
Perhaps we can do better? Example from heart attack

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



JAMA 2001, 285:2486-97; Abraham et al, Eur Heart J, 2016

Conclusions

- Most behavioral traits have some genetic basis
- Genetic prediction improves as sample size of discovery cohort increases
- Integration of genetic and phenotypic data creates better predictors
- Overall prediction is challenging, especially for rare outcomes