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Revitalizing Translational Psychiatry

Steven E. Hyman
Stanley Center for Psychiatric Research
Broad Institute of Harvard and MIT

Psychiatric drug efficacy long stalled
Same molecular targets as 1950's prototypes

Drug Class	Prototype (date)	Targets
Lithium	Lithium (1949)	GSK3β; IMPase
Antipsychotics	Chlorpromazine (1951)	D_2 DR
Antidepressants	Imipramine (1957) Isoniazid (1957)	NET, SERT MAO
Benzodiazepines	Chlordiazepoxide (1957)	$GABA_AR$ BZD site

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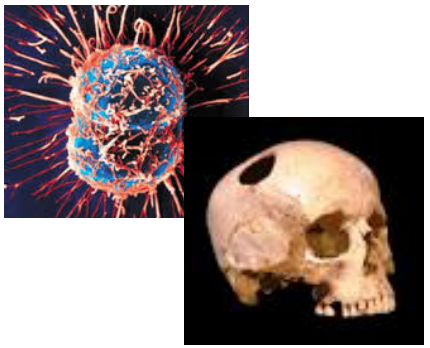
Despite high disease prevalence & burden; despite unmet need industry is exiting psychiatry

Scientific reasons:

- Dearth of molecular insights to nominate new targets
- Inaccessibility of human brain tissue
- Lack of disease models (except rare monogenic forms of autism)
- No biomarkers for clinical trials or treatment selection



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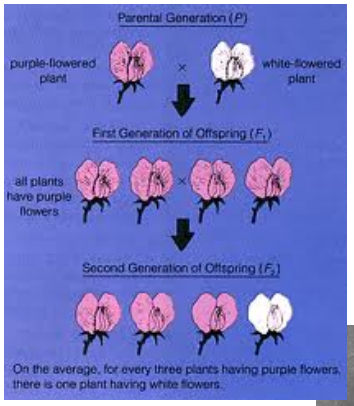
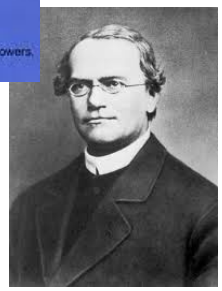
High heritability means that our genomes contain molecular clues to pathogenesis

Disorder	λ	heritability
Autism	25	0.65-0.8
Schizophrenia	9	0.8
Bipolar Disorder	8	0.7-0.8
Major Depression	2-5	0.35

Twin-based estimates





But our brains are not like Mendel's peas

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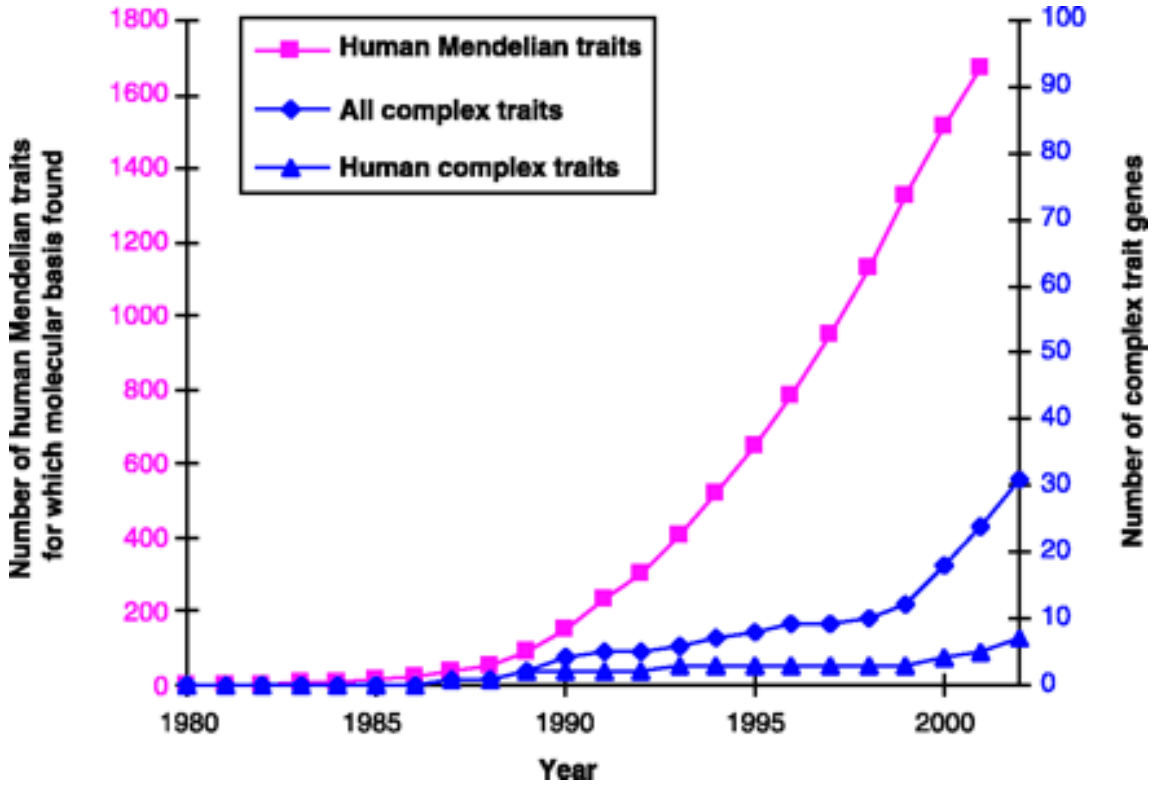
Dark ages of complex trait genetics: Linkage and candidate gene association assumed alleles of large effect



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Source; Glazier, Nadeau, Aitman, *Science* 2002

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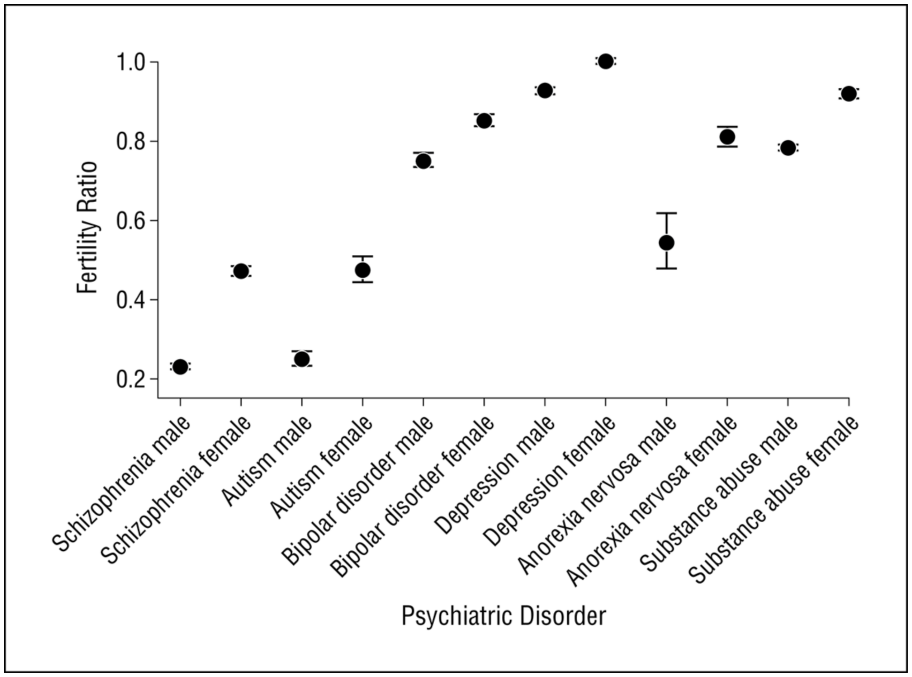
Insight into low penetrance:
Fecundity of patients with psychiatric disorders



Fertility ratios by disorder and gender.
A fertility ratio of 1 = that of the general population.

Power et al. JAMA Psychiatry. 2013;70(1):22-30.

Ramifications:
Common and Rare Variants can readily be transmitter at very low effect sizes (OR < 1.1)

Transmission of large effect alleles must be extremely rare

Source Mark Daly and Ben Neale

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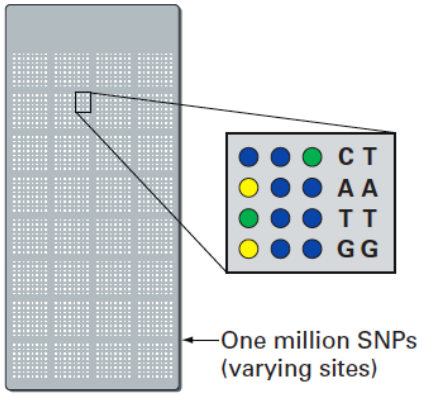
Technology and collaboration have enabled genetics at the necessary scale



Inexpensive microarrays for common variants.

>10 million common SNPs

Sequencing for rare variants

Many millions of rare and ultra-rare variants

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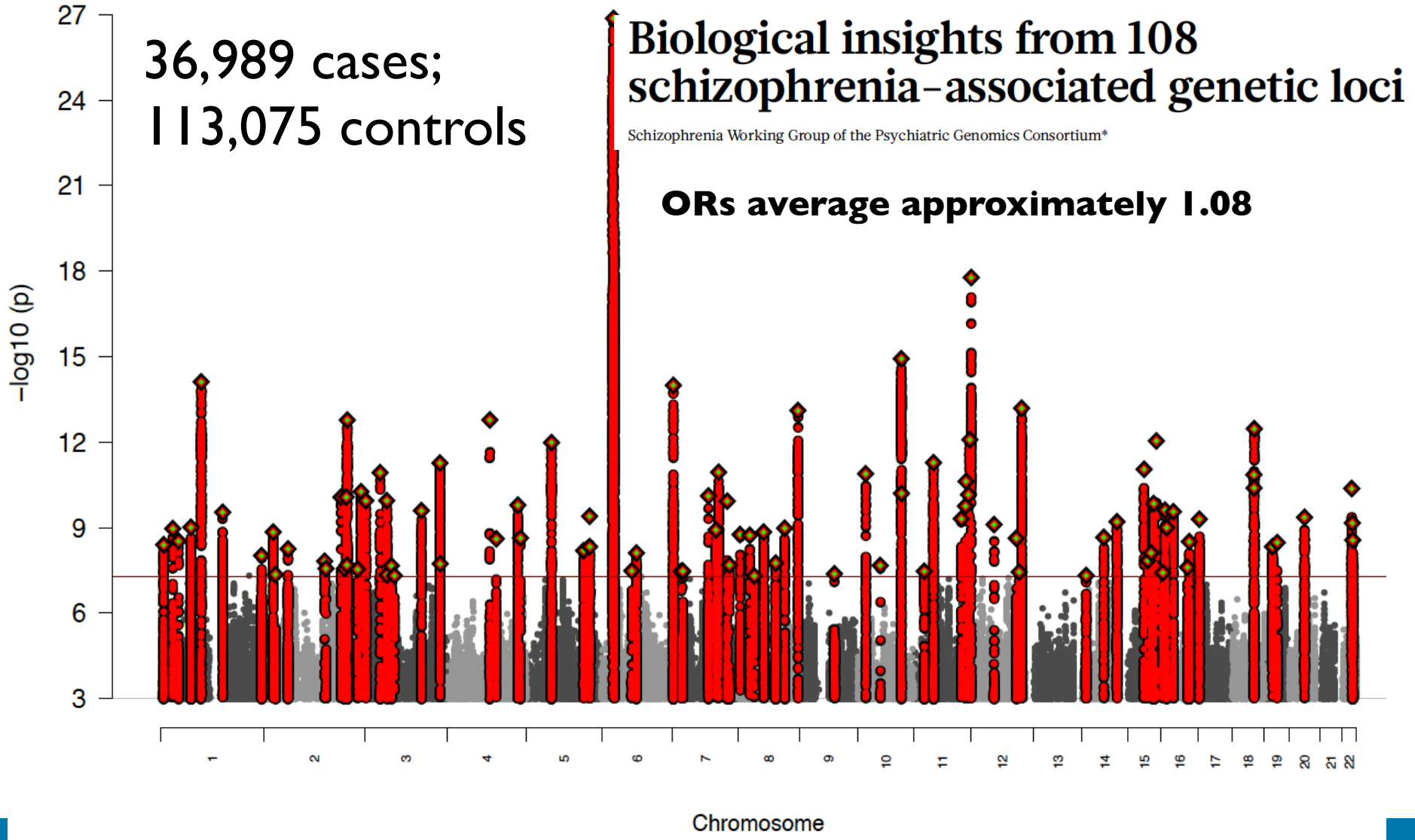
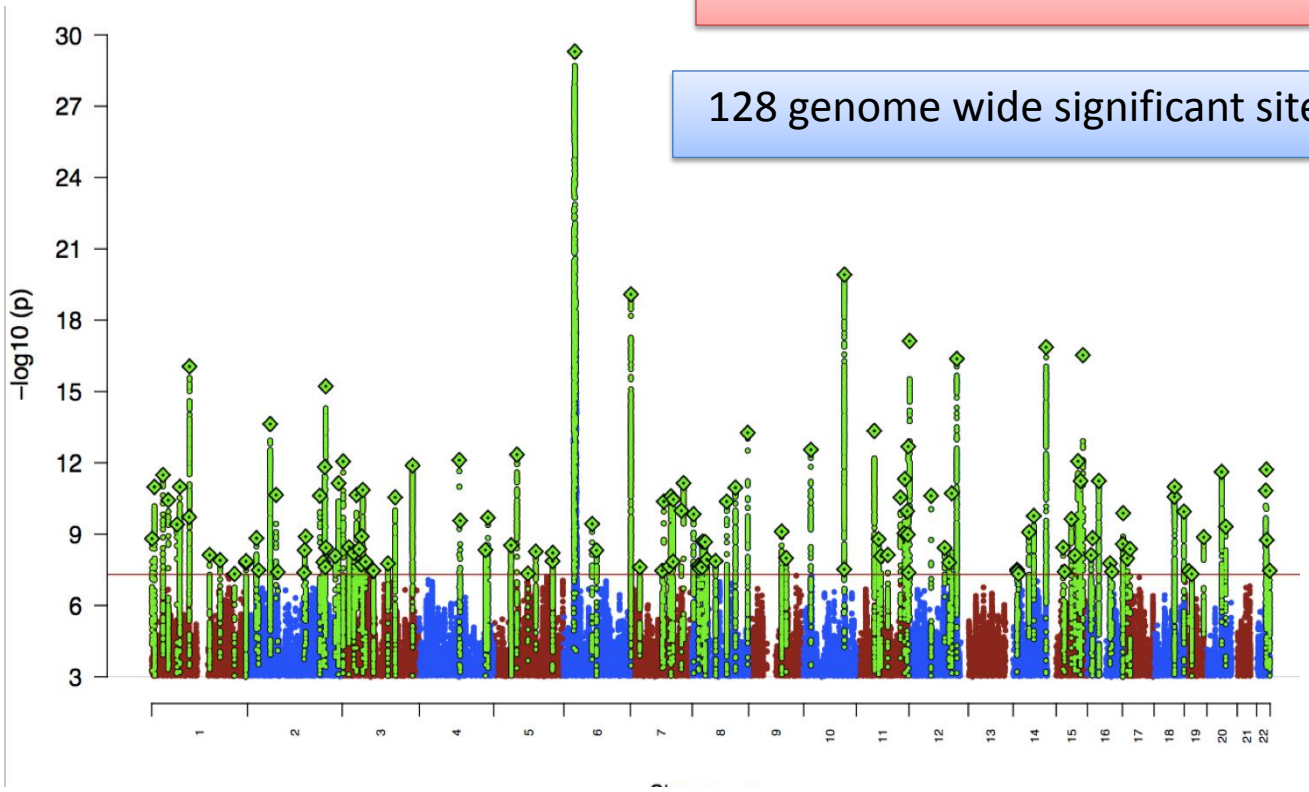
PGC Genome-wide common variant association in schizophrenia 2014



Current state of schizophrenia GWAS

47121 cases, 68221 controls

128 genome wide significant sites



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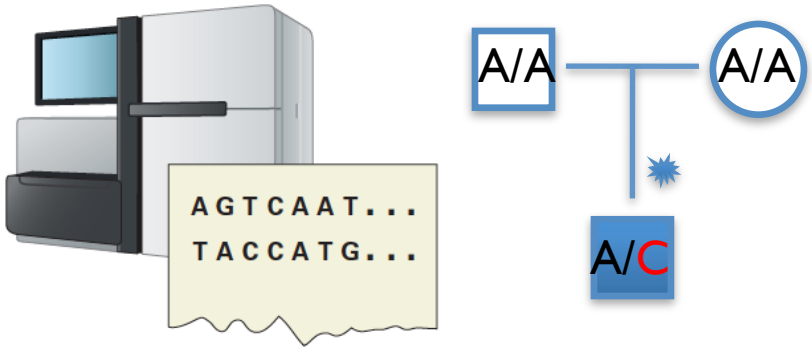
Rare protein altering alleles are more readily *experimentally "actionable"*

Sequencing in required to find rare, protein-altering alleles, both *de novo* and transmitted



Trio studies to identify *de novo* mutations

Significant results in ASDs, not schizophrenia

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ASDs: Genes constrained by evolution significantly enriched for *de novo* mutations

Gene	Mutations	# LoF Observed	# LoF Expected	p-value
SYNGAP1	missense, nonsense, frameshift, frameshift, nonsense, frameshift	6	0.0258	9.38E-11
DYRK1A	frameshift, splice, nonsense, frameshift	4	0.0153	2.26E-09
SCN2A	missense, missense, missense, frameshift, missense, nonsense, nonsense, missense, splice	4	0.0378	8.27E-08
ARID1B	nonsense, nonsense, frameshift, frameshift, missense	4	0.0380	8.45E-08
SUV420H1	nonsense, miss, splice, miss, frameshift	3	0.0171	8.17E-07

Source: Ben Neale

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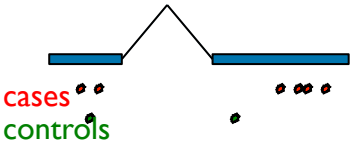
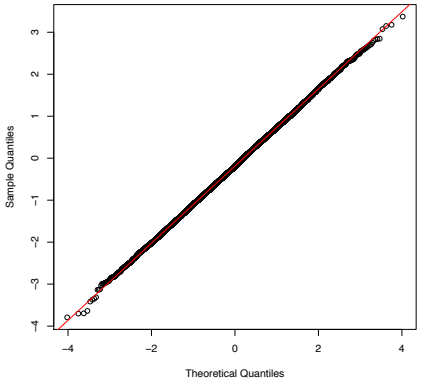
Case-control whole exome sequencing studies to find transmitted, rare protein altering alleles





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- **Challenge: very high background rates of neutral variation**
- **Rarity and low penetrance decreases power to detect**
- **WEX of 6,0000 schizophrenia cases, no gene yet statistically significant**
- **No significance to date without theory-laden clustering**

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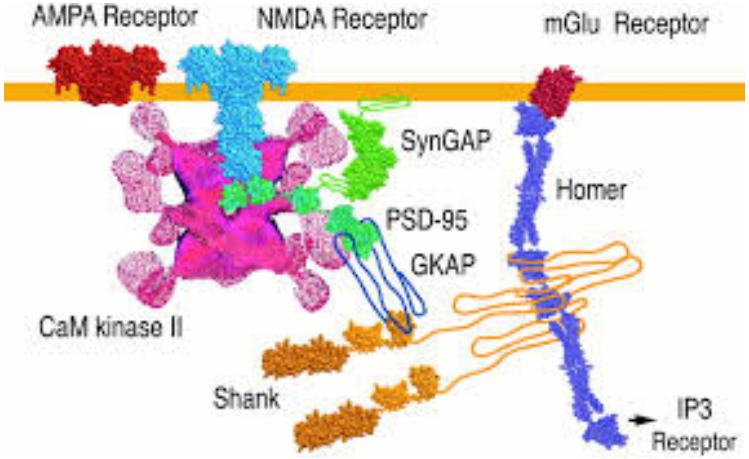
Why care about alleles of small effect?

Central hypothesis: The many risk associated genes converge on a far smaller number of cell types, molecular 'machines' and pathways

- *Confidently* associated alleles of *any effect size* implicate specific genes.
- Genes implicate protein networks, physiologic processes, and cell types
- Alleles indicate directionality for therapeutics



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Basic Thesis

1. Therapeutics for neuropsychiatric disorders has endured a long period of stasis—recycling a small number of hypotheses
2. Unbiased, large scale genetics provides a window onto new biology—but reveals daunting polygenicity
3. Key hypothesis: Many hundreds of disease-associated genes will reduce to a far smaller number of 'molecular pathways'
4. This requires that we 'finish the job' in genetics

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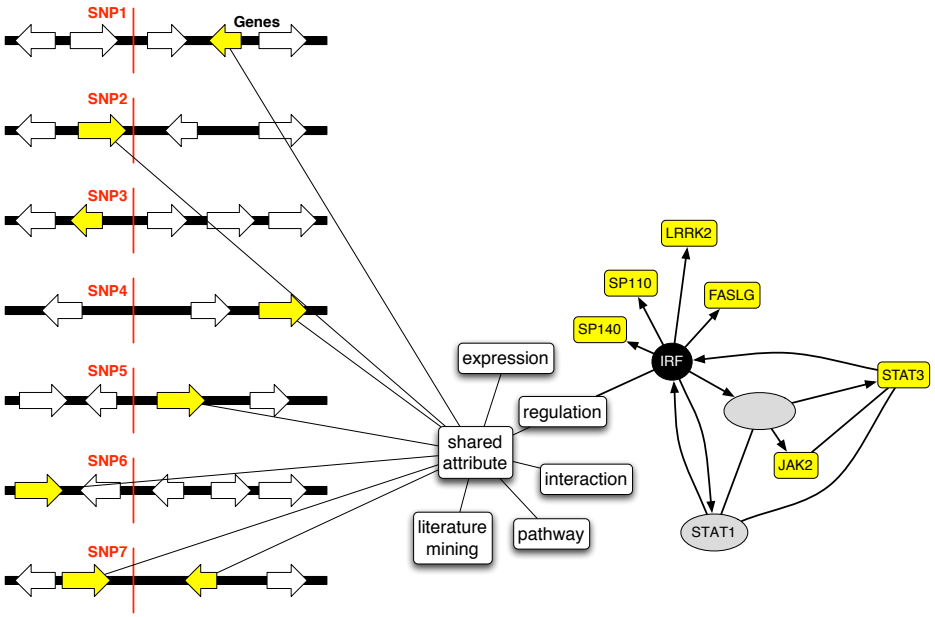
We must finish the job and share all the data

- Genes have many different functions
- Combinatorial information places genes in relevant cell types, pathways



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Goal: finish the job and make all data public

	Schizophrenia			Autism Spectrum Disorders		
Year	**GWAS**	**Exome Seq.**	**Genome Seq.**	**GWAS**	**Exome Seq.**	**Genome Seq.**
2015	40K	13K	3.7K	18K	6K	None
2016-2017	70K	40K	10K	25K	25K	5K
2018-2019	>100K	60K	20K	40K	40K	10K

Estimates

National Human Genome Research Institute

NIMH

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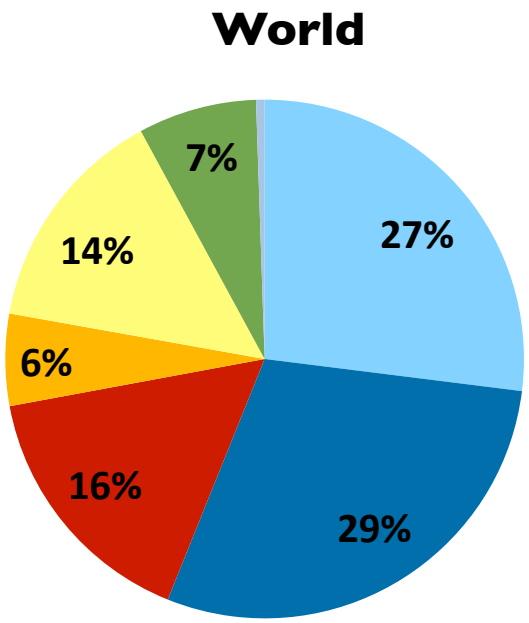
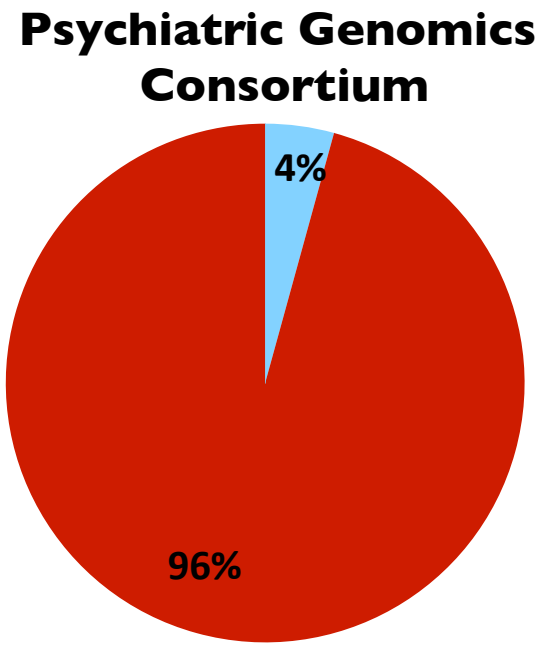
‘Finishing the job’ requires genetic diversity





Courtesy of Laramie Duncan

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New collaborations to increase global genetic diversity of samples

Country	Schizophrenia/ Bipolar Disorder	Autism Spectrum Disorder	Controls
China	15,000	N/A	15,000
Japan	5,000	N/A	5,000
Mexico	5,000	2,000	7,000
Ethiopia	2000	N/A	TBD
Kenya	2,000	500	2,500
South Africa	4,800	800	5,600
Uganda	500	200	700

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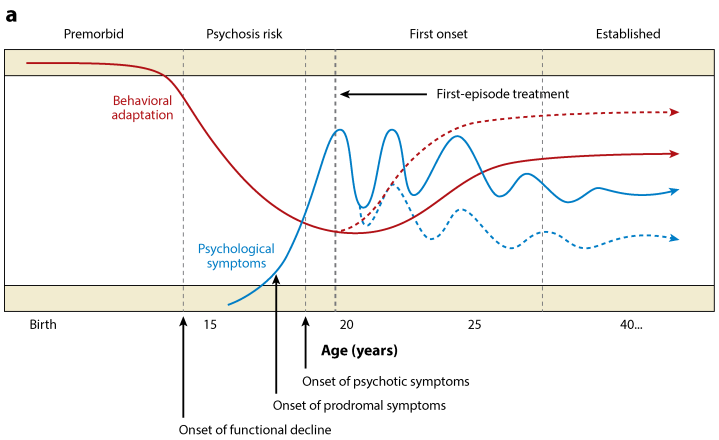
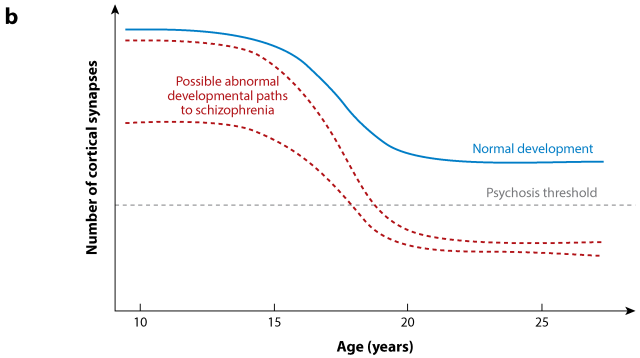
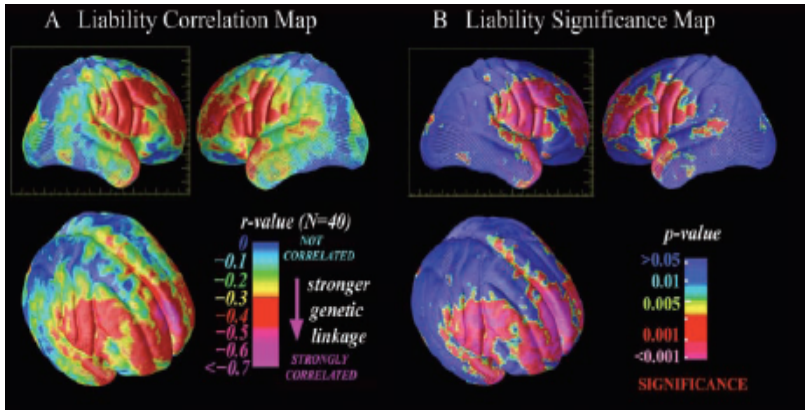
Course of schizophrenia and pathologic findings

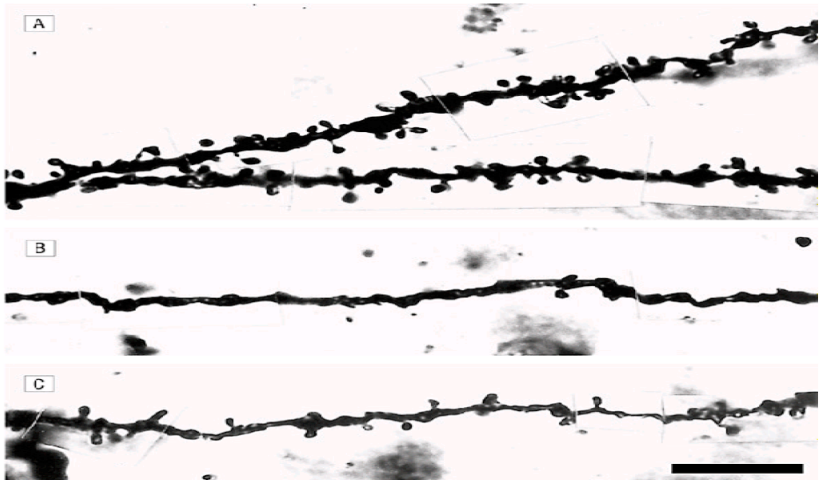




Fusar-Poli P, et al. 2014.
Annu. Rev. Clin. Psychol. 10:155–92



Cannon et al. Proc Natl Acad Sci U S A. 2002 99:3228-33



Glantz and Lewis, 2000

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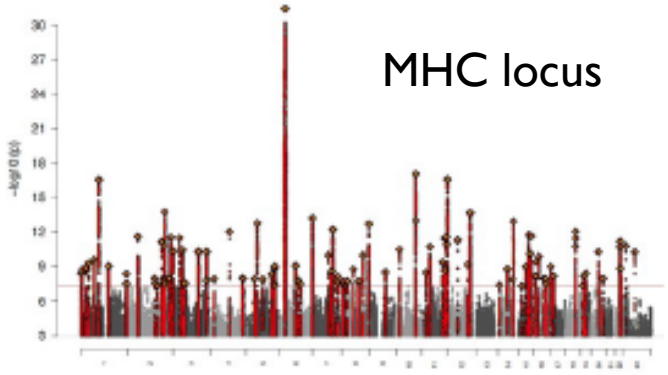
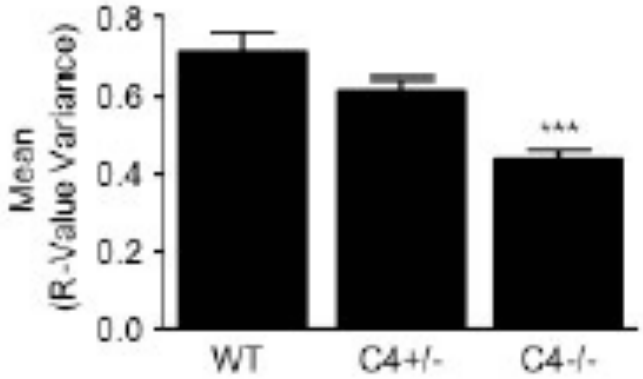
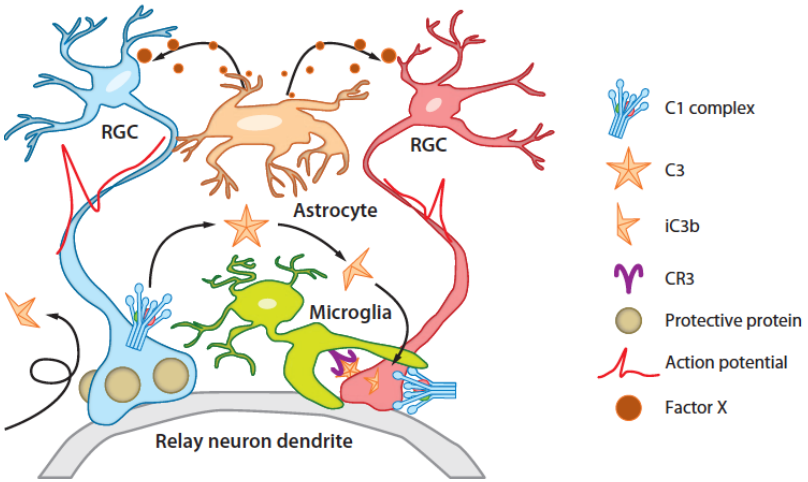
Alleles implicate synapse elimination in schizophrenia



MHC locus

Schizophrenia GWAS





C4-dependent synapse elimination in mouse visual cortex. Source: Beth Stevens

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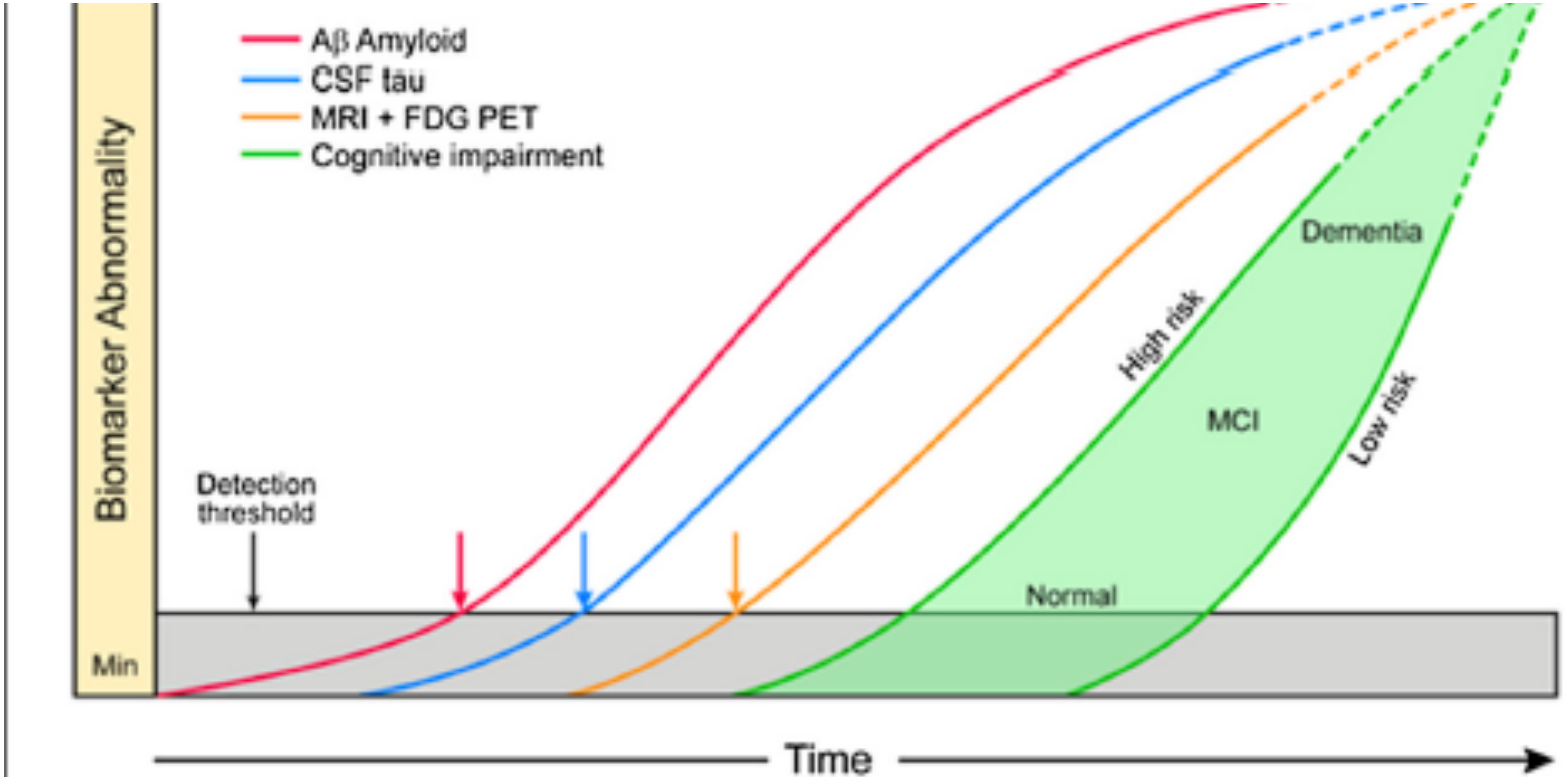
Biomarkers: model in AD



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Shared common variant risk across disorders: *Genetic background matters* in biological models

Significant

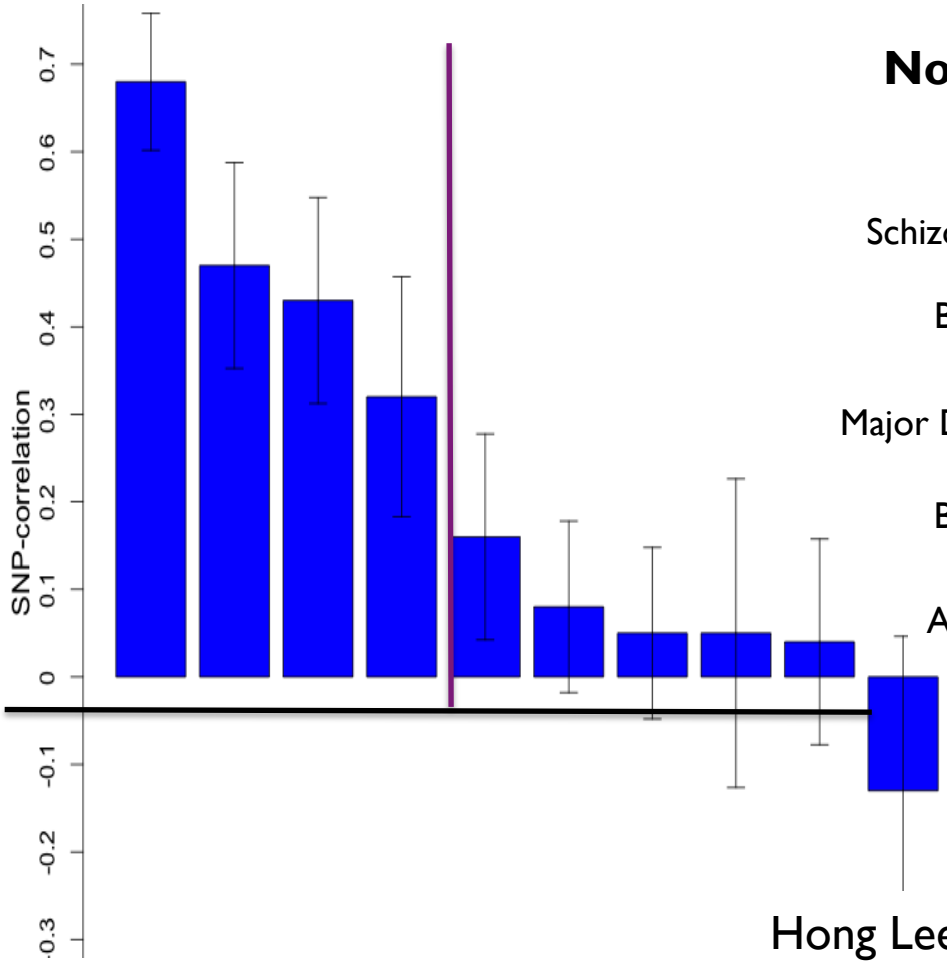
Schizophrenia/Bipolar

Bipolar/Major Depression

Schizophrenia/Major Depression

Major Depression/ADHD

Schizophrenia/Autism



Non-significant

Schizophrenia/ADHD

Bipolar/ADHD

Major Depression/Autism

Bipolar/Autism

ADHD/Autism

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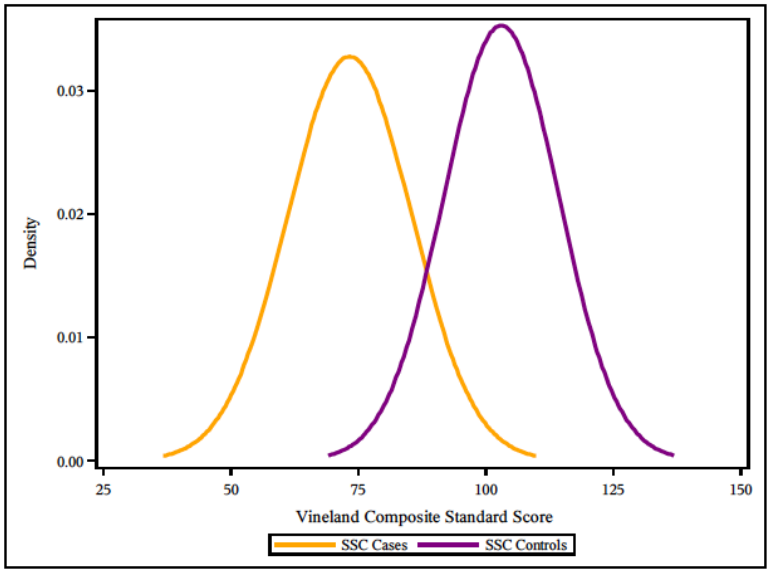
Hong Lee, Naomi Wray

For normally distributed traits, phenotypic variation overlaps in cases and controls



- Affected individuals vary considerably in symptoms and impairments
- Unaffected individuals may have overlapping distributions of some of the same symptoms and impairments

Source: Elise Robinson, Stanley Center

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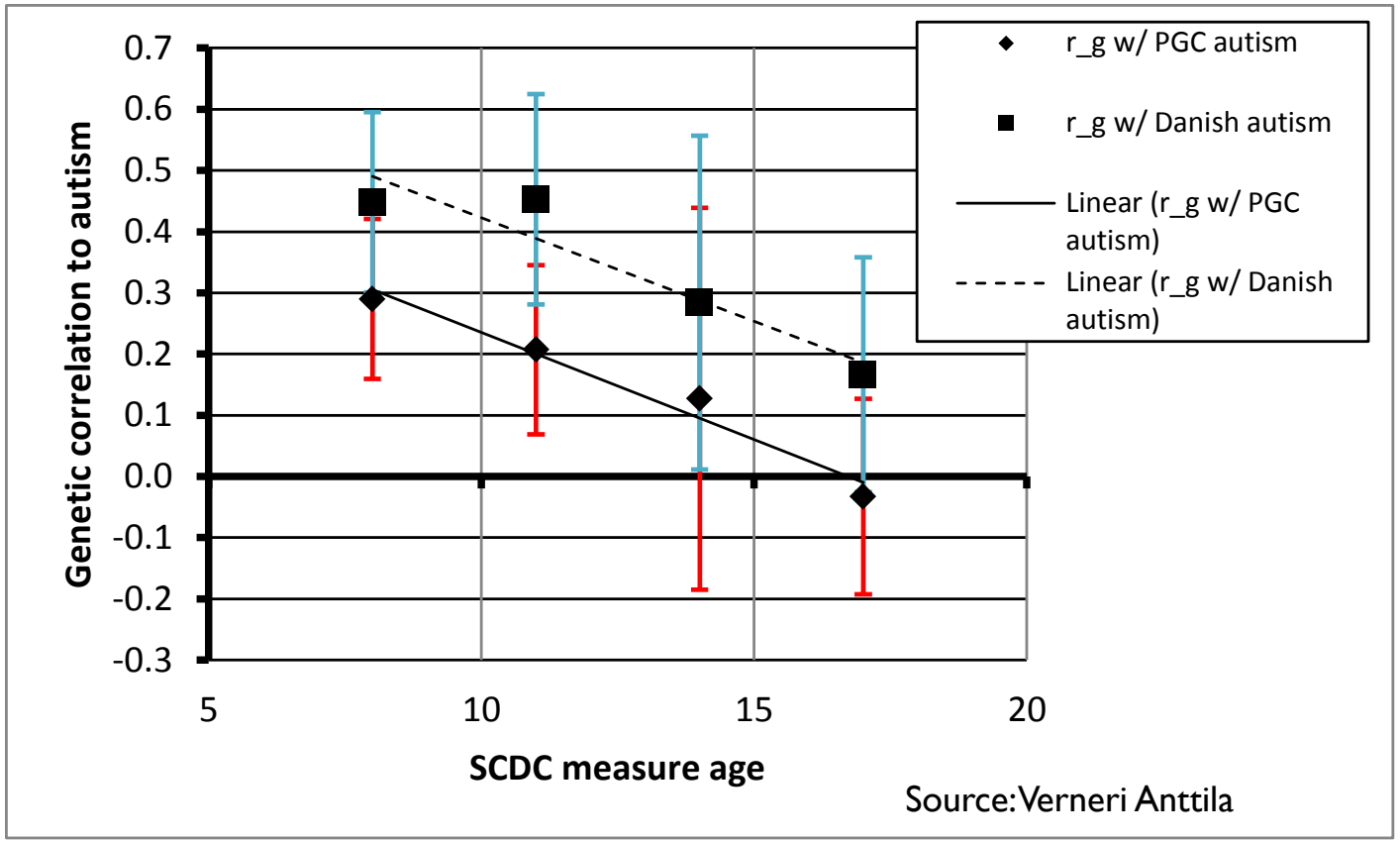
The common variant influences on ASDs are also associated with social and communication differences in the pediatric general population

Univariate SCDC Heritability

Age	h2g	SE
8	0.2026	0.1028
11	0.1847	0.0957
13	0.0606	0.1174
17	0.1722	0.1101



Source: Verneri Anttila

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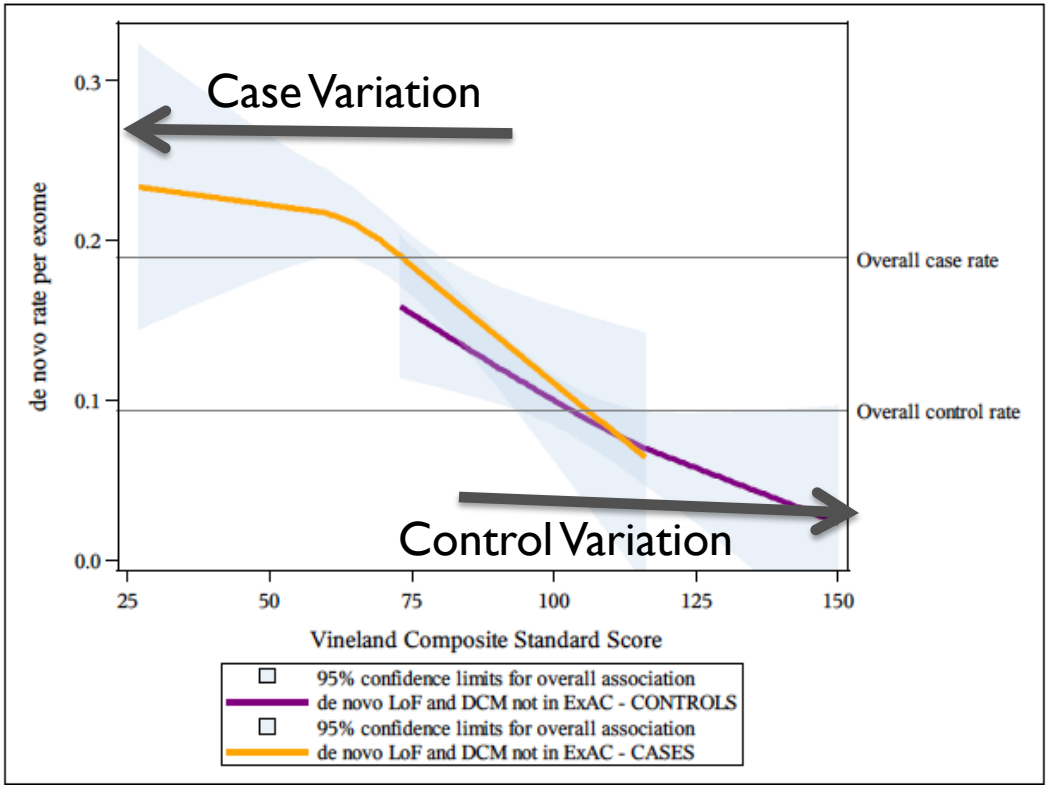
Variation within cases and within controls blurs the categorical distinction

Intellectual disability, seizures, lack of language



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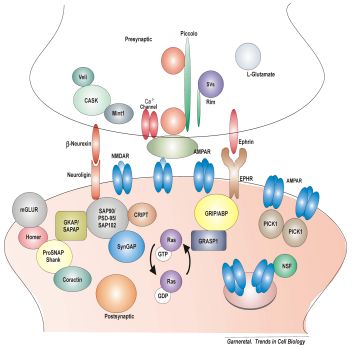
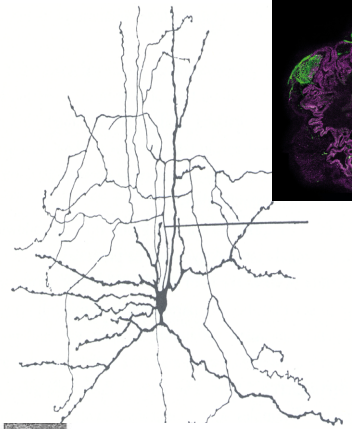
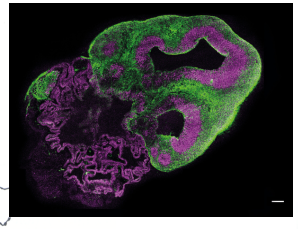
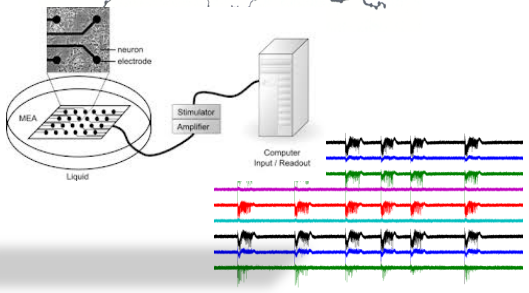
The challenge of translation: taking evolution into account

As a community we must develop informative assays, based on genetics results, in cells, organoids, animals, humans

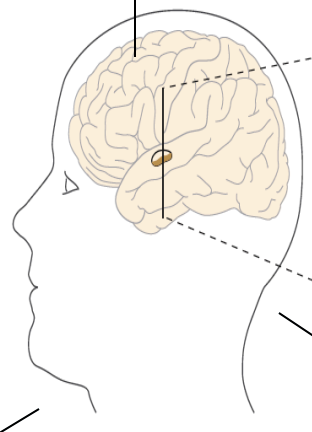


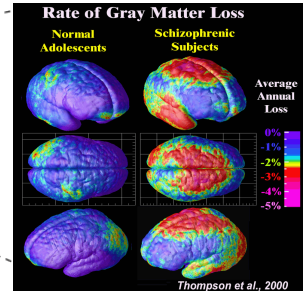






90 myr





Abnormal cortical thinning in schizophrenia (Thomson et al 2000

40 myr

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The extended community

Broad Institute, Harvard, & MIT

Genetics
Steve McCarroll
Mark Daly
Ben Neale
Elise Robinson
Aarno Palotie
Karestan Koenen
Stephan Ripke
Giulio Genovese

Epidemiology
Elise Robinson

Neurobiology
Guoping Feng
Beth Stevens
Jen Pan
Bernardo Sabatini
Zhanyan Fu

Stem Cell Biology
Kevin Eggan
Paola Arlotta
Lee Rubin

Therapeutics
Ed Scolnick
Jeff Cottreell

Proteomics
Wade Harper
Kasper Lage

Genome Engineering
Feng Zhang

Karolinska Institute, Stockholm
Christina Hultman
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Patrick Sullivan

iPsych Denmark
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Shaun Purcell

Johns Hopkins
Rick Huganir
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Novartis Institute for Biomedical Research
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