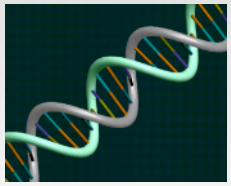
Genes, Circuits, Behavior: From psychiatry genetics to personalized medicines

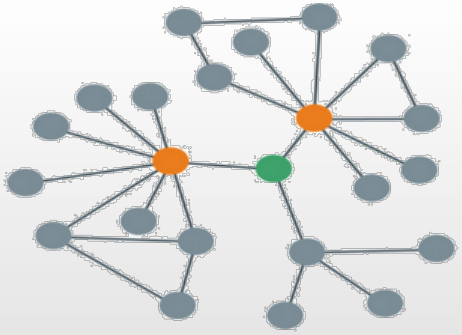
Anirvan Ghosh, F. Hoffmann-La Roche

Imagine this…

Treatment of mental illness based on individual genome sequence

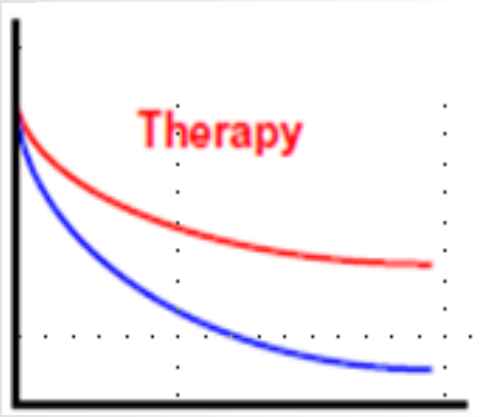


Risk genes



Co-expression networks

Patient stratification



Personalized treatment

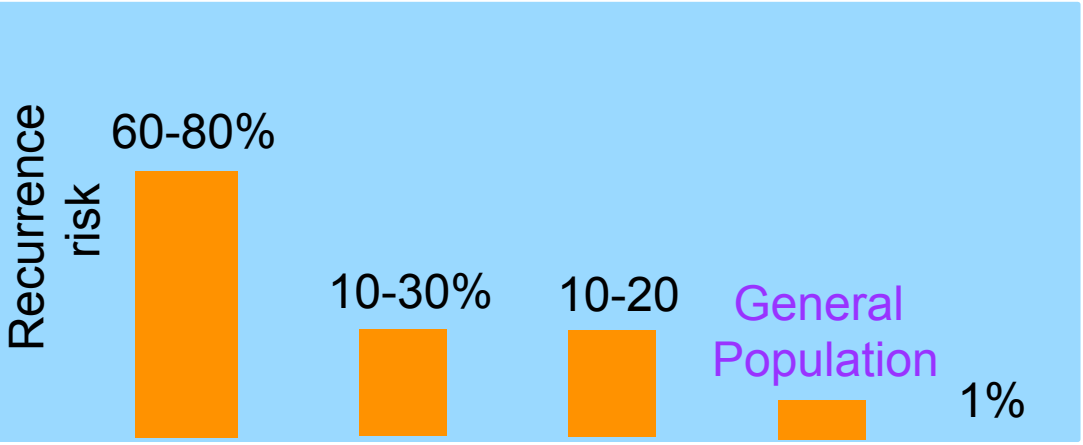
Psychiatric disorders are highly heritable

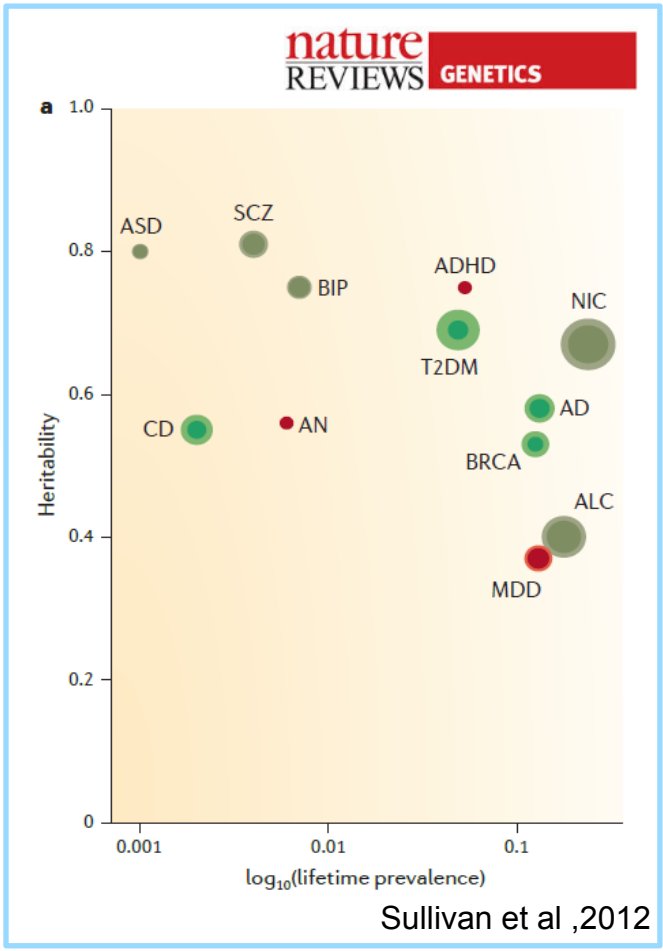
Genes play a major role

MZ twins

DZ twins

Siblings





Sullivan et al ,2012

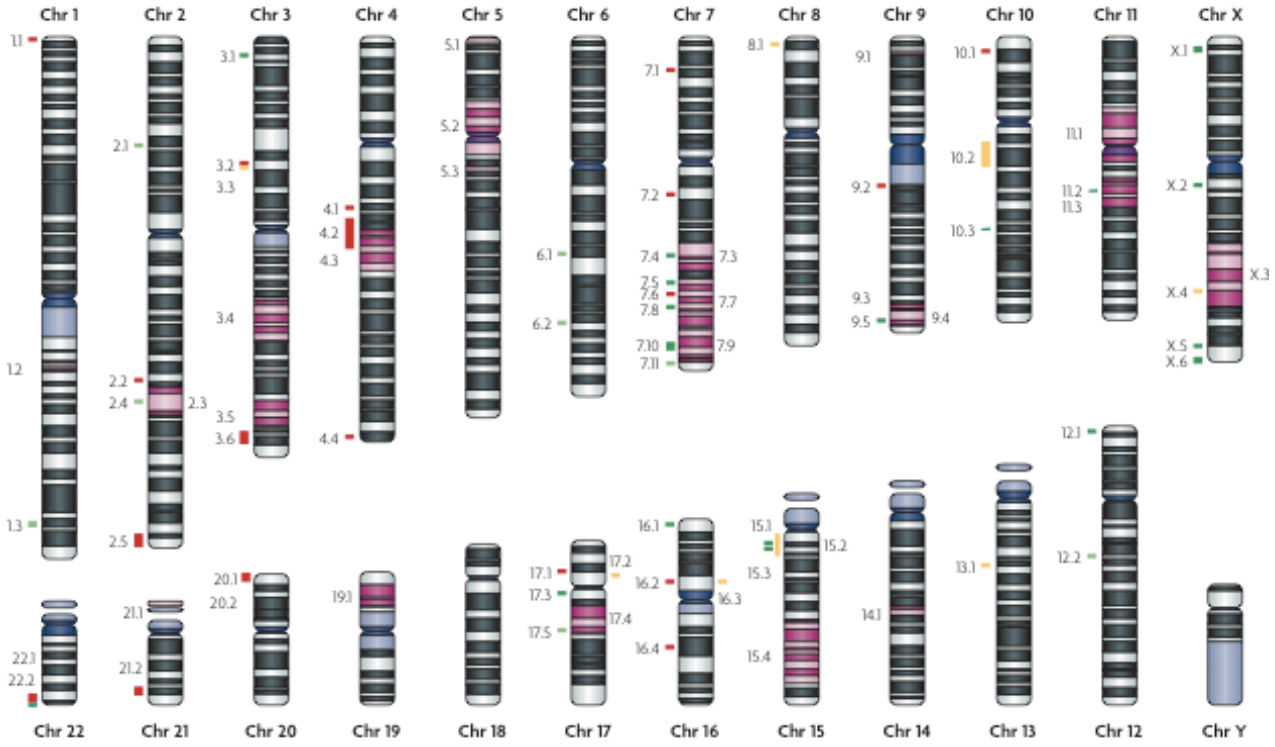
NDD and schizophrenia are highly heritable disorders

Risk genes are widely distributed in the genome

SNP- single nucleotide polymorphisms

RM - rare mutations

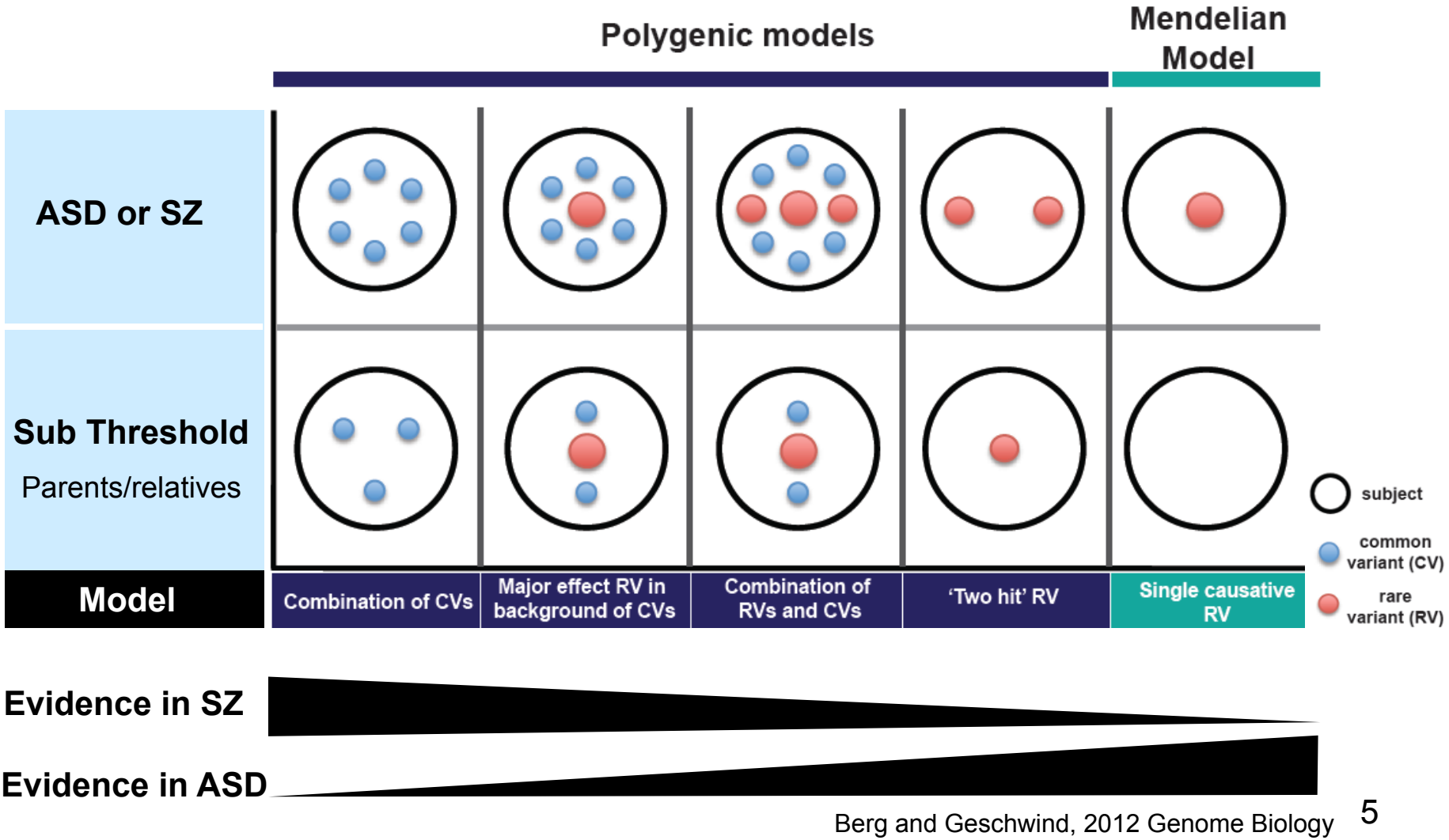
CNV - copy number variations



Geschwind et al.

Genetic architecture of schizophrenia and autism

Common & rare mutations in hundreds of genes



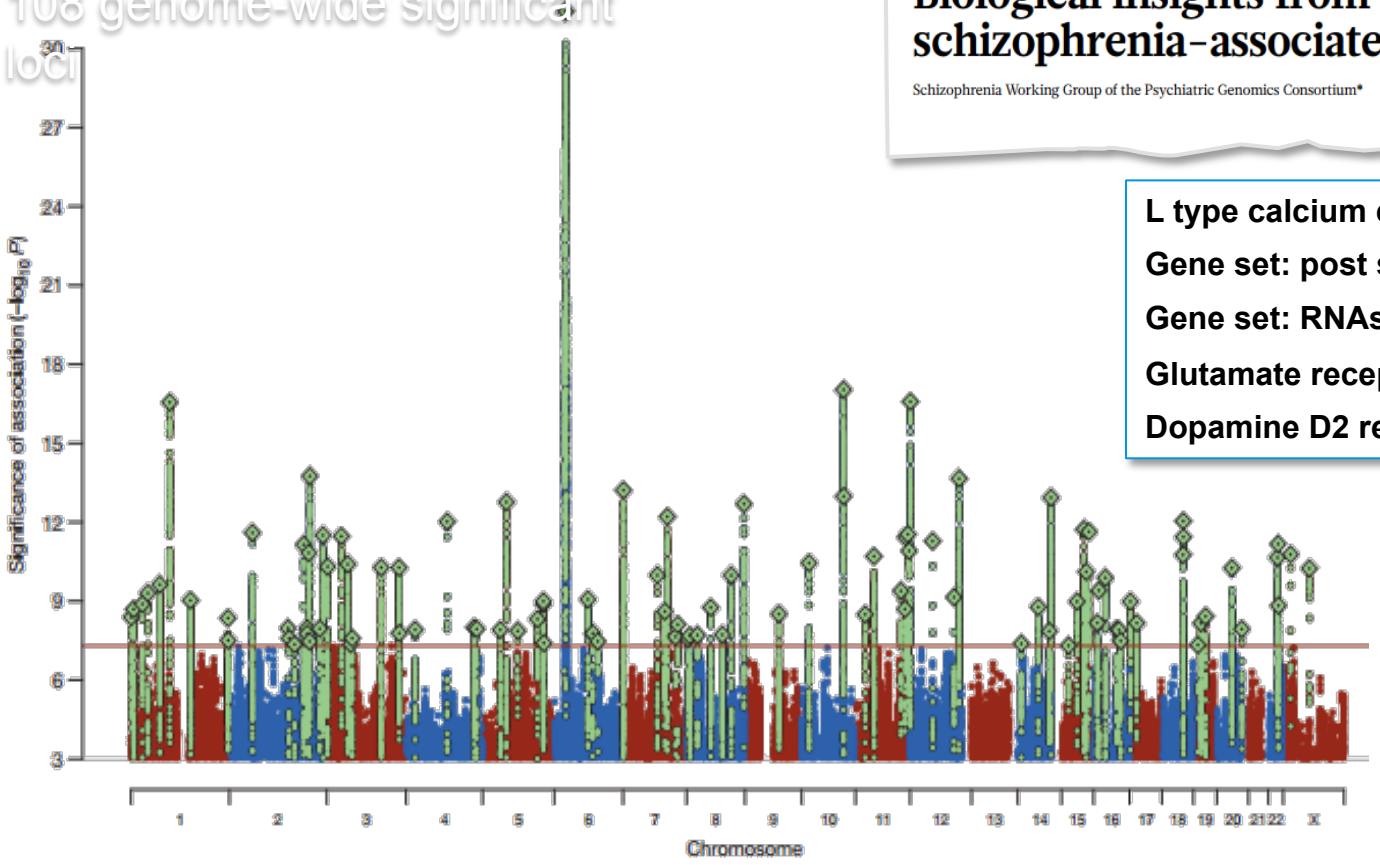
Berg and Geschwind, 2012 Genome Biology

Schizophrenia: genes implicated by common variants

Genome-wide association studies (GWAS)

36,989 cases & 113,075 controls

108 genome-wide significant loci



ARTICLE

doi:10.1038/nature13595

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

L type calcium channels (4 subunits)

Gene set: post synaptic density

Gene set: RNAs bound by FMRP

Glutamate receptors

Dopamine D2 receptors

Autism: genes implicated by rare variants

Whole exome sequencing studies

Nature: Oct 29,2014

The contribution of *de novo* coding mutations to autism spectrum disorder

2517 families

Nature: Oct 29,2014

Synaptic, transcriptional and chromatin genes disrupted in autism

2270 families

1601 ASD

5397 controls

Voltage-gated ion channels

Gene set: Synaptic transmission

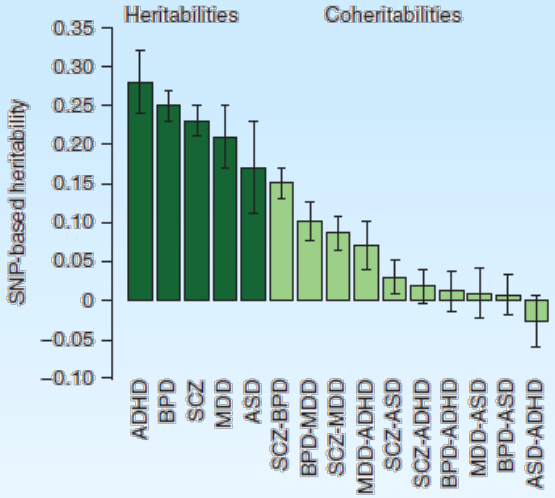
Gene set: FMRP targets

Gene set: Chromatin modifiers

Emerging themes from psychiatric genetic studies

Risk genes are shared across multiple psychiatric disorders

Common variants

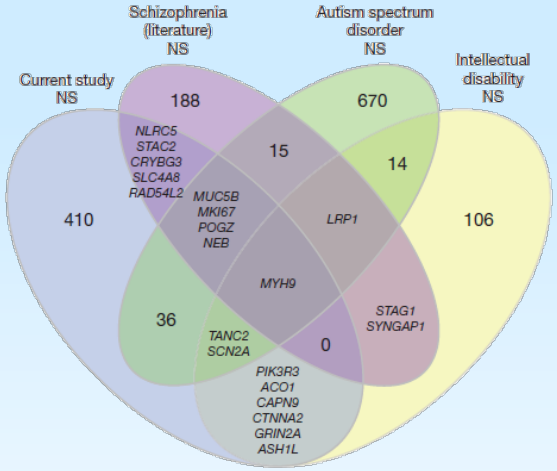


Nature Genetics, 2014

Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

Cross-Disorder Group of the Psychiatric Genomics Consortium*

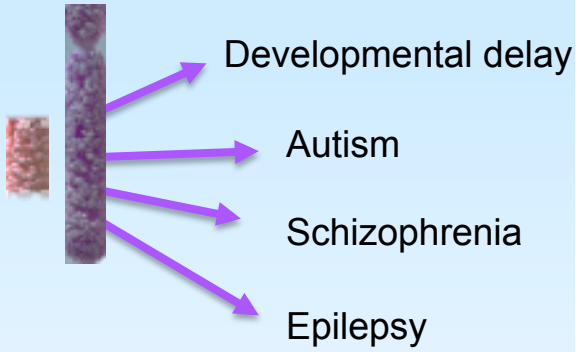
Rare variants



Fromer et al, Nature, 2014

Iossofov et al, Nature 2014

Copy number variants

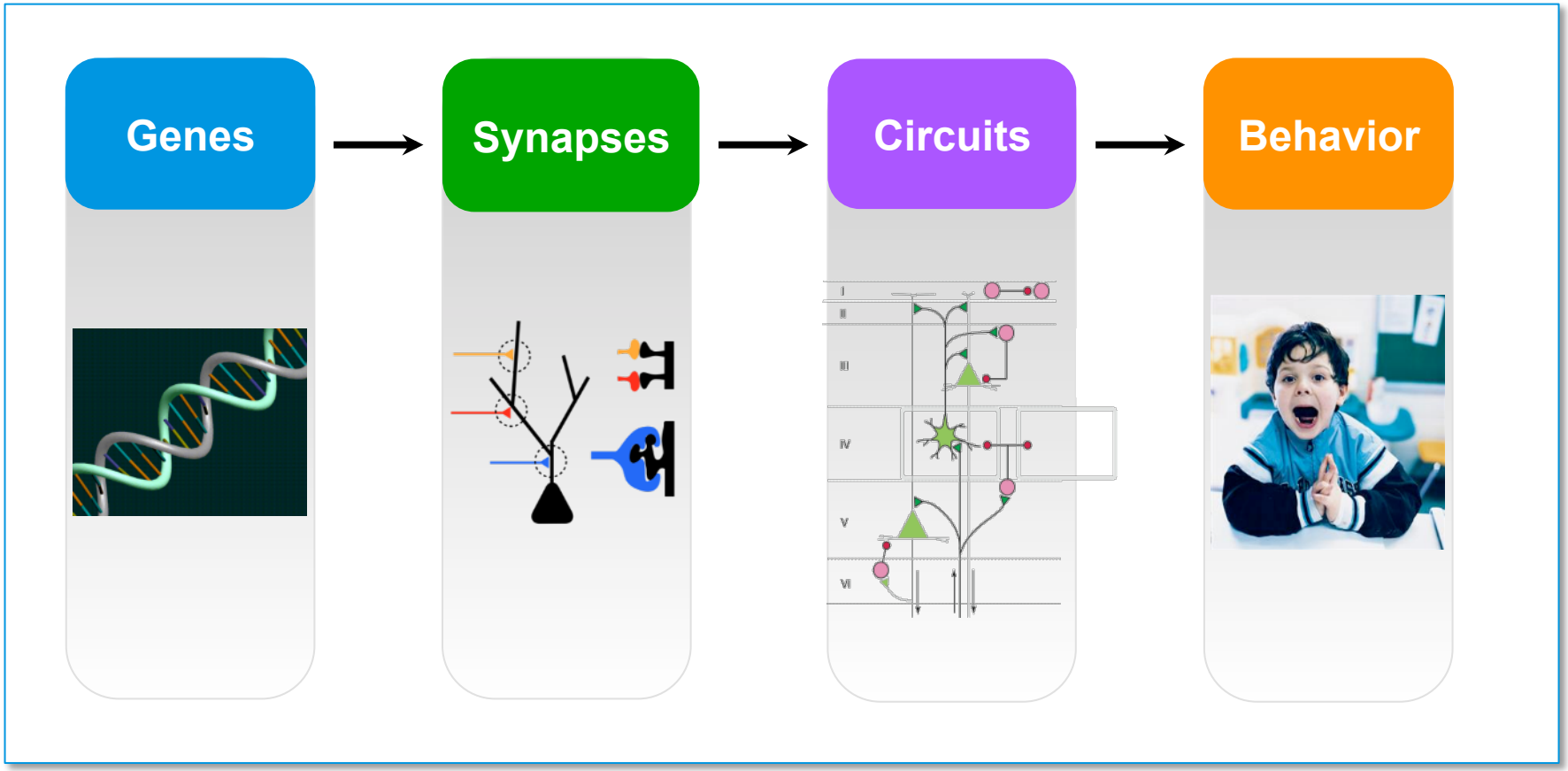


15q13.3 deletion

Malhotra et al, Cell 2012

A framework for drug discovery in psychiatry & NDD

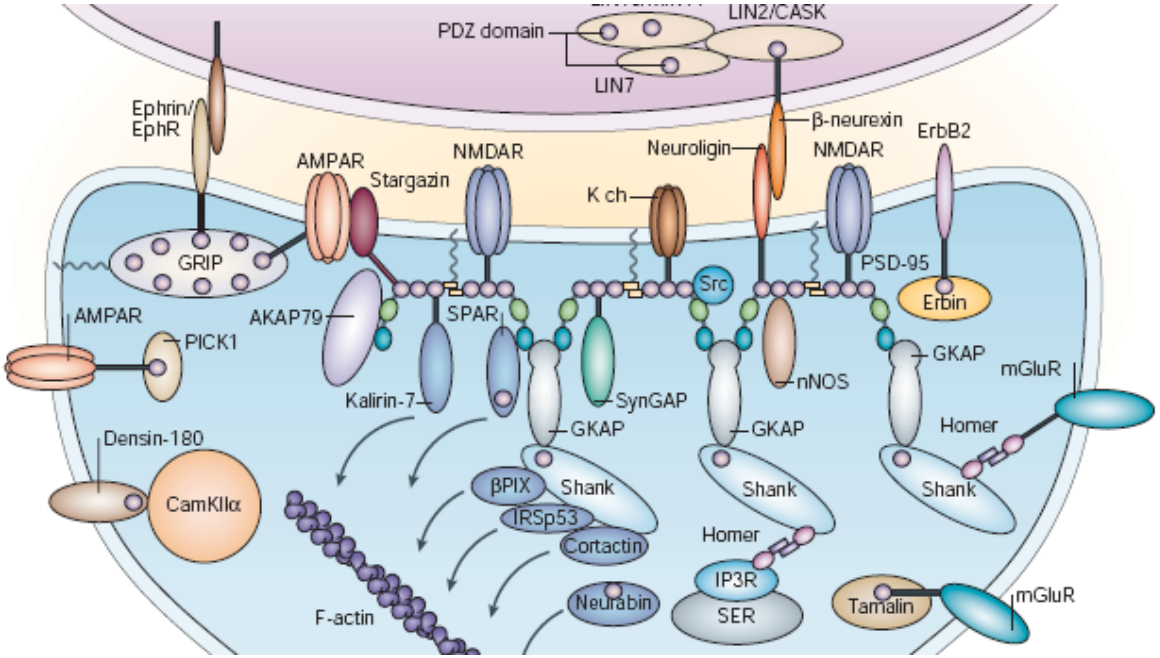
Synapses & circuits as the point of intervention

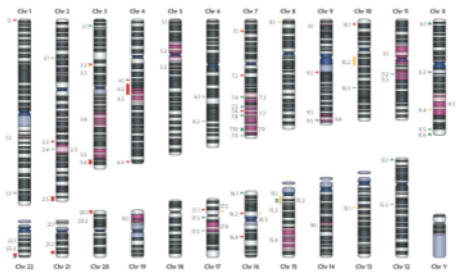


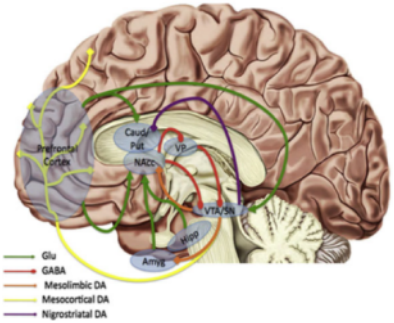
Next generation of targets in NDD and psychiatry

Synapse and Signaling modulators

- Compelling **genetic association** and **target tractability**
- **Disease-relevant phenotypes** in cellular (iPS) and animal models
- Evidence of **circuit dysfunction** for key behavioral domains from human imaging and behavioral studies

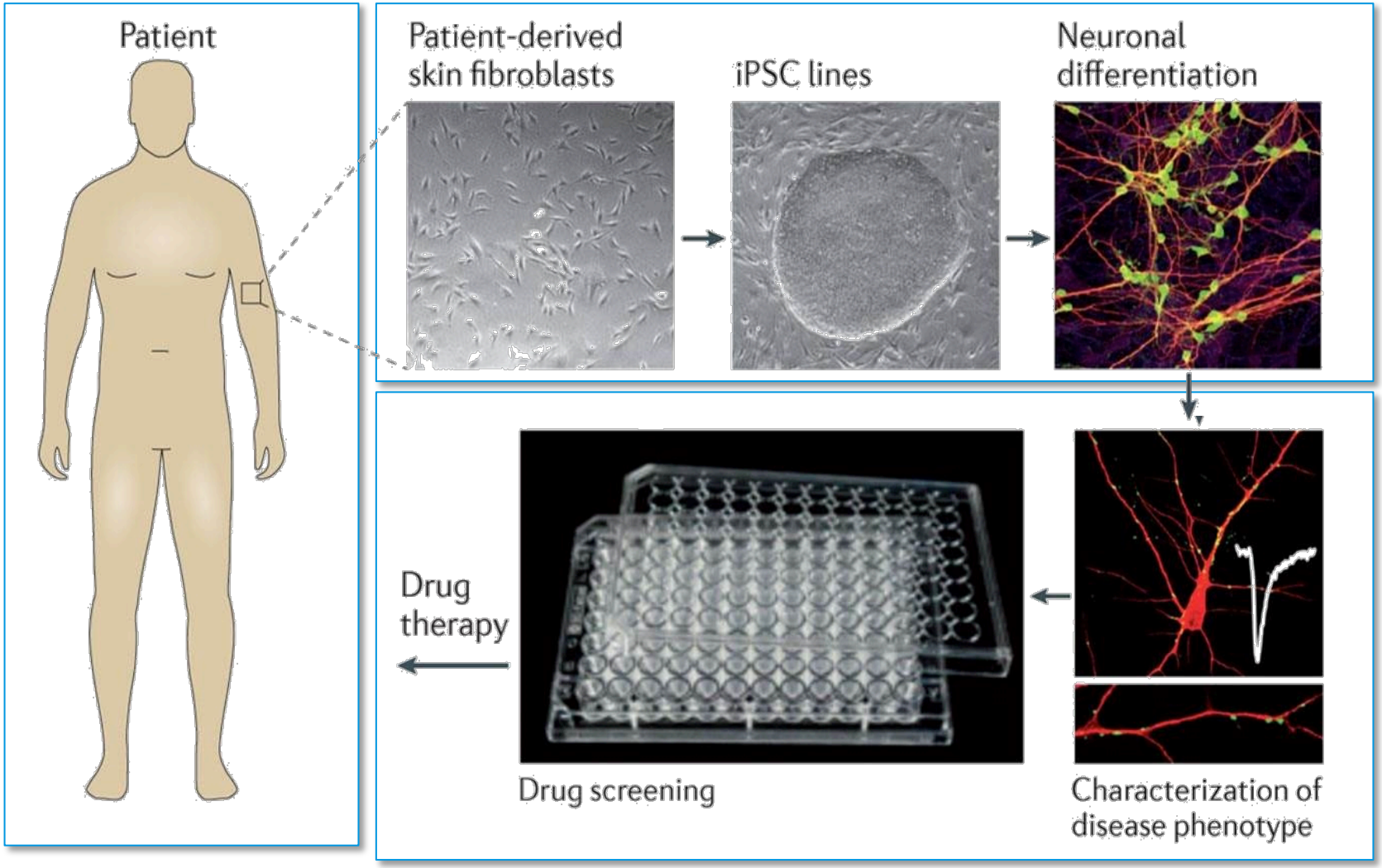






Cellular phenotype identification using iPSCs

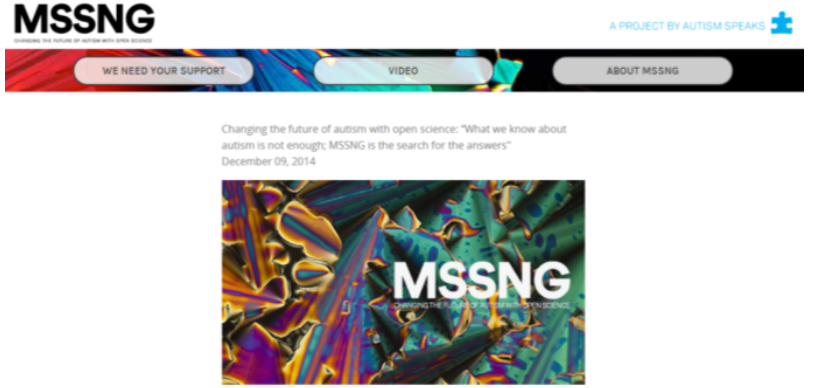
Modeling neurobehavioral disorders



Ghosh *et al.* 2013, Nature Reviews Drug Discovery 12(10): 777-790

Large-scale whole genome sequencing in psychiatry

Big science will drive novel discoveries & precision treatment



MSSNG is a groundbreaking collaboration between Google and Autism Speaks to create the world's largest genomic database on autism.

Whole genome sequencing of 10,000 autism cases

The Genomic Psychiatry Cohort: Partners in Discovery

Michele T. Pato,[1] Janet L. Sobell,[1] Helena Medeiros,[1] Colony Abbott,[1] Brooke M. Sklar,[1] Peter F. Buckley,[2] Evelyn J. Bromet,[3] Michael A. Escamilla,[4] Ayman H. Fanous,[5] Douglas S. Lehrer,[6] Fabio Macciardi,[7] Dolores Malaspina,[8] Steve A. McCarroll,[9,10] Stephen R. Marder,[11] Jennifer Moran,[9] Christopher P. Morley,[12] Humberto Nicolini,[13] Diana O. Perkins,[14] Shaun M. Purcell,[15] Mark H. Rapaport,[16] Pamela Sklar,[17] Jordan W. Smoller,[18] James A. Knowles,[1] The Genomic Psychiatry Cohort Consortium, and Carlos N. Pato[1]*

Whole genome sequencing of 10,000 schizophrenia and bipolar disorder cases

From genomics to personalized medicine: The way forward for drug discovery for mental illness

Risk genes for ASD and SZ

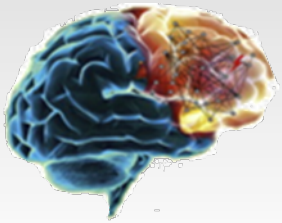
Molecular pathways and endophenotypes

Convergent cellular phenotypes

Circuit and behavior analysis in model systems

Target development

Large-scale whole genome sequencing



Molecular maps of human brain

- co-expression networks
- protein-protein interaction networks

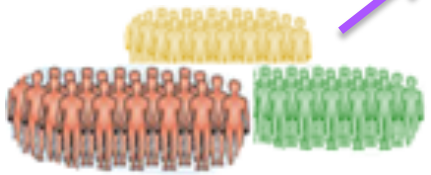
Imaging maps

- EEG
- MRI

iPSCs

Precision trials

Personalized medicine



Molecular/genetic subtypes of ASD and SZ


Doing now what patients need next

Backup slides

A new era of gene discovery in psychiatric disorders

Risk and causal genes can be reliably identified

Key drivers of gene discovery

- Genome resources
  - Human Genome, HapMap and 1000 genomes project

- Genomic technologies :
  - Microarrays
  - Exome sequencing
  - Whole genome sequencing

- Large scale collaborations
  - Psychiatric Genomics Consortium (PGC)
  - Autism Genome Project (AGP), Simons Simplex Collection (SSC)

From exome to whole genome sequencing

Whole genome sequencing (WGS) will reveal causative mutations in majority of ASD cases

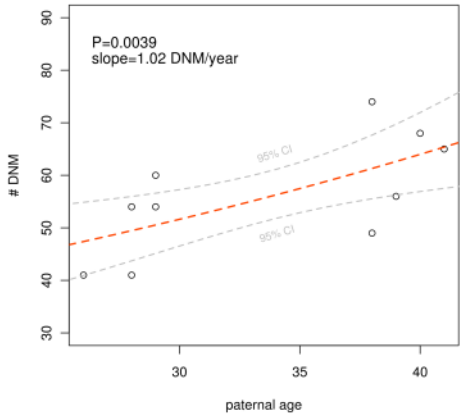
Whole-Genome Sequencing in Autism Identifies Hot Spots for De Novo Germline Mutation

Cell, 2012

Whole-genome sequencing of quartet families with autism spectrum disorder

Nature Medicine, 2015

- Increase in diagnostic yield by WGS
  - 70% of WGS cases have a clinically relevant rare penetrant mutation
- Paternal age effect: denovo mutations increase with increasing father's age
  - partially explains increased risk of ASD in older fathers



Autism: Rare de novo mutations contribute significant genetic risk for ASD

Evidence from exome sequencing and CNV studies

Neuron :June, 2011

Rare De Novo and Transmitted Copy-Number Variation in Autistic Spectrum Disorders

Nature: Oct 29,2014

The contribution of *de novo* coding mutations to autism spectrum disorder

Nature: Oct 29,2014

Synaptic, transcriptional and chromatin genes disrupted in autism

A list of authors and their affiliations appears at the end of the paper

2517 families

2270 families

- denovoCNVs and coding point mutations contribute 30% of ASD risk.
- 30 novel causal ASD genes identified
  - with recurrent(>2) loss of function de novo mutations in the same gene
- New causal genes implicate novel biological pathways such as chromatin modifier genes in ASD risk

Schizophrenia: genes implicated by rare variants

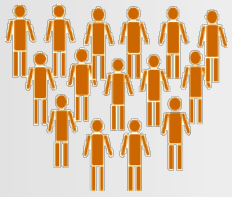
Whole exome sequencing studies

Nature: Feb13, 2014

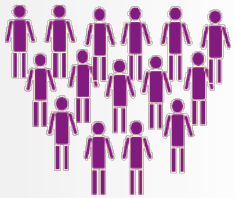
A polygenic burden of rare disruptive mutations in schizophrenia

Nature: Feb13, 2014

De novo mutations in schizophrenia implicate synaptic networks



2500 SZ



2500 controls

623 families

Voltage-gated calcium channels

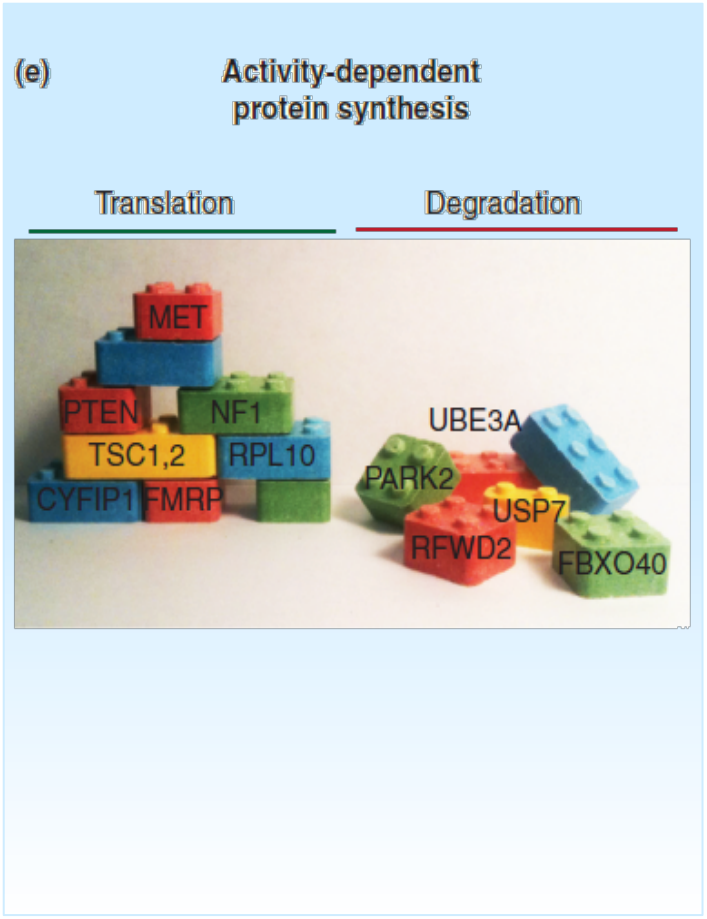
Gene set: post synaptic density-95

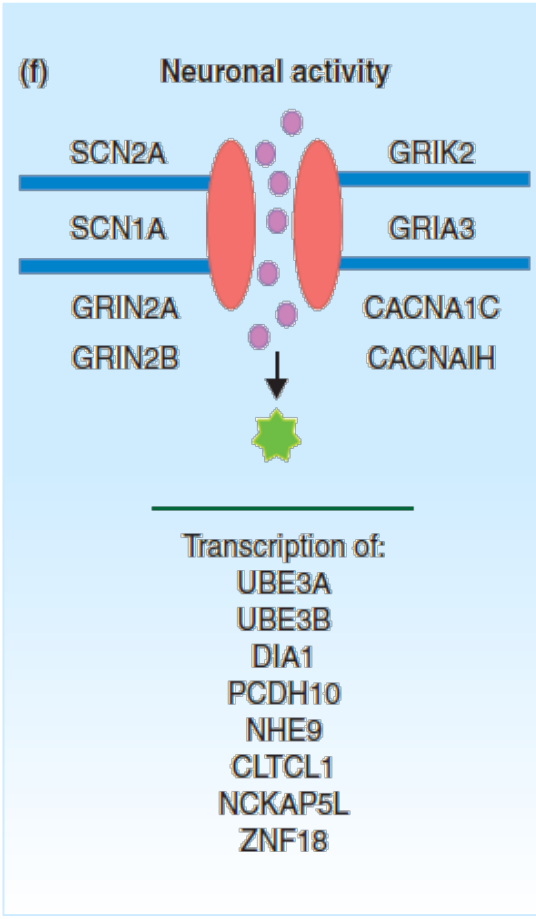
Gene set: ARC complex

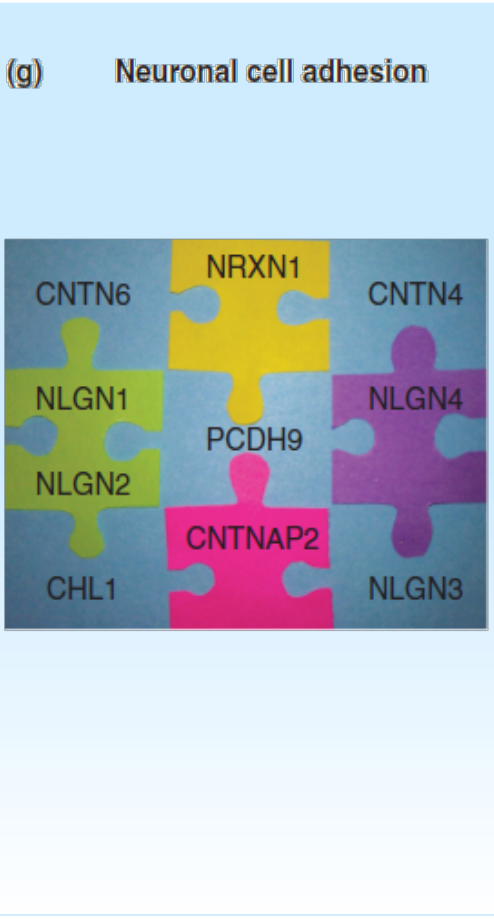
Gene set: NMDAR complex

Notably, both common and rare variants implicate convergent gene sets

ASD risk genes cluster into specific cellular and molecular processes



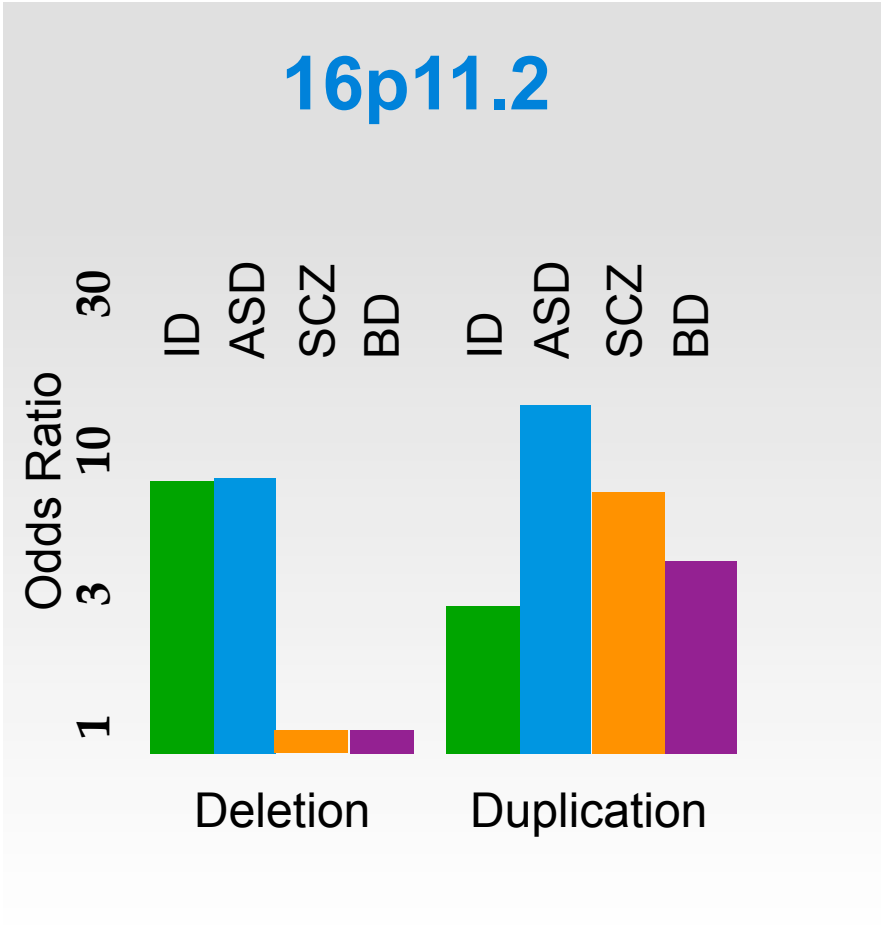


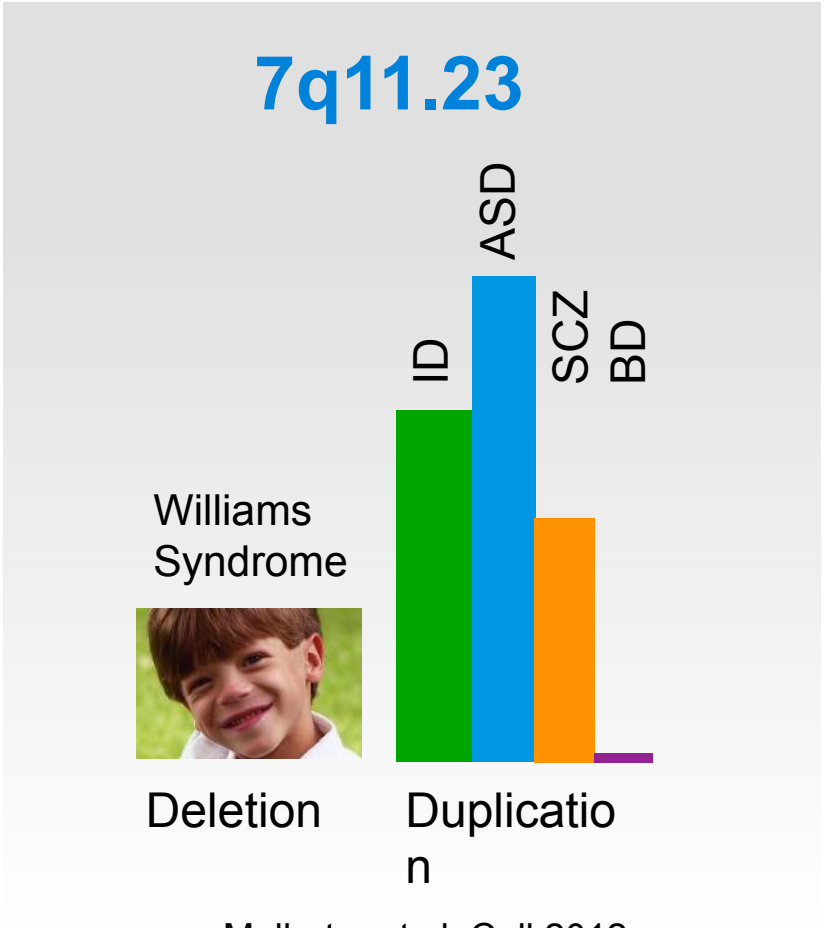


Chen JA, et al. 2015.
Annu. Rev. Pathol. Mech. Dis. 10:111–44

Emerging themes from psychiatric genetic studies

Reciprocal mutations associated with psychiatric traits



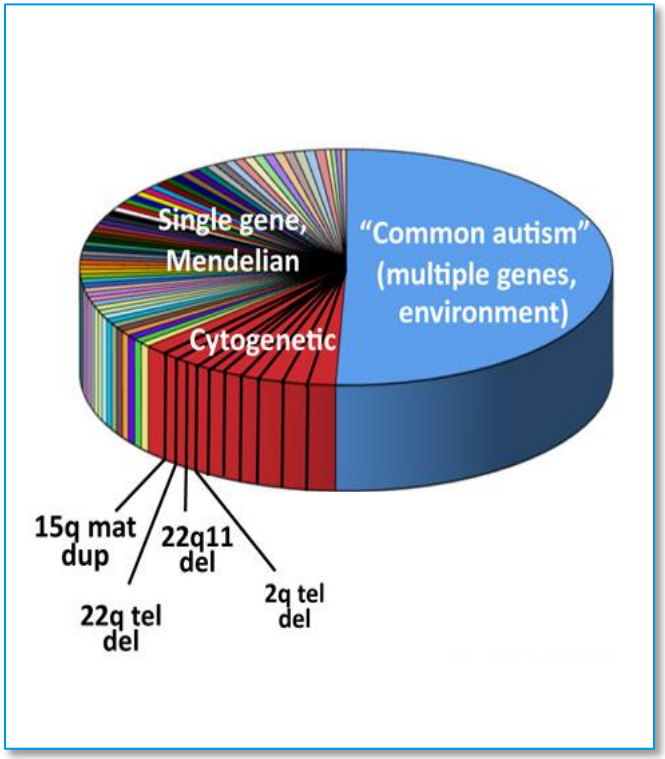


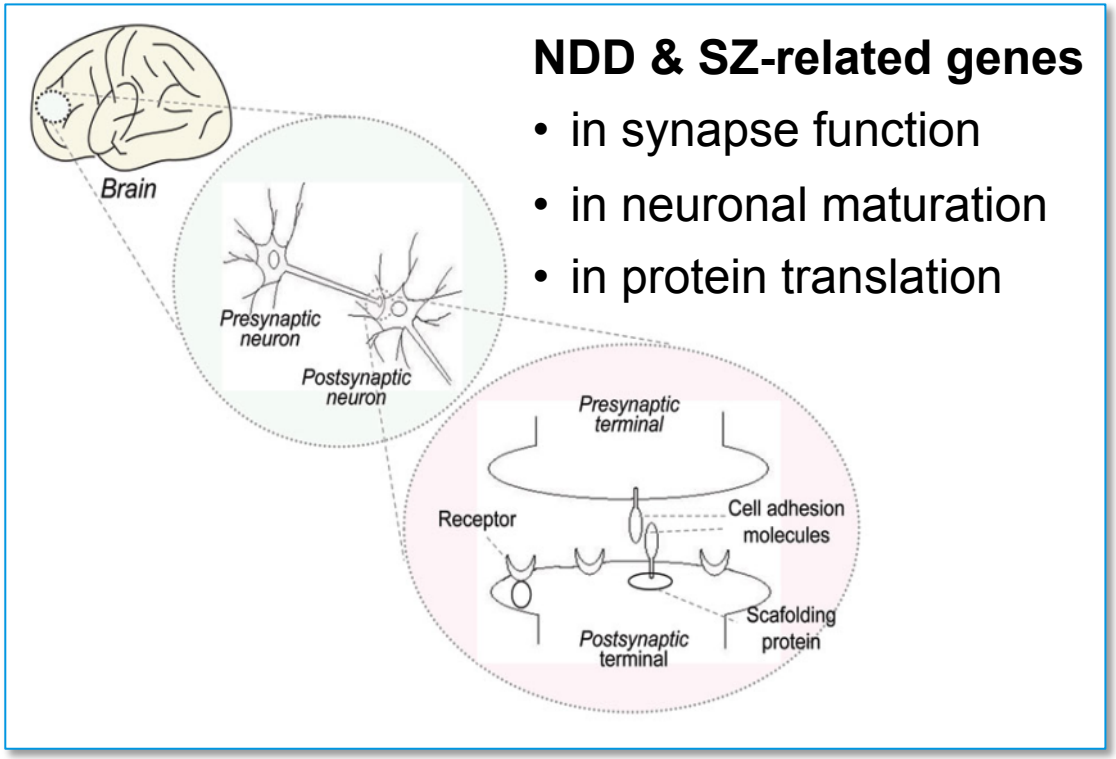
Malhotra et al, Cell 2012

Synapses are convergence pathways for risk genes

Relationship of susceptibility genes to synaptic dysfunction

Neuronal synapses harbor many tractable targets including GPCRs and ion channels

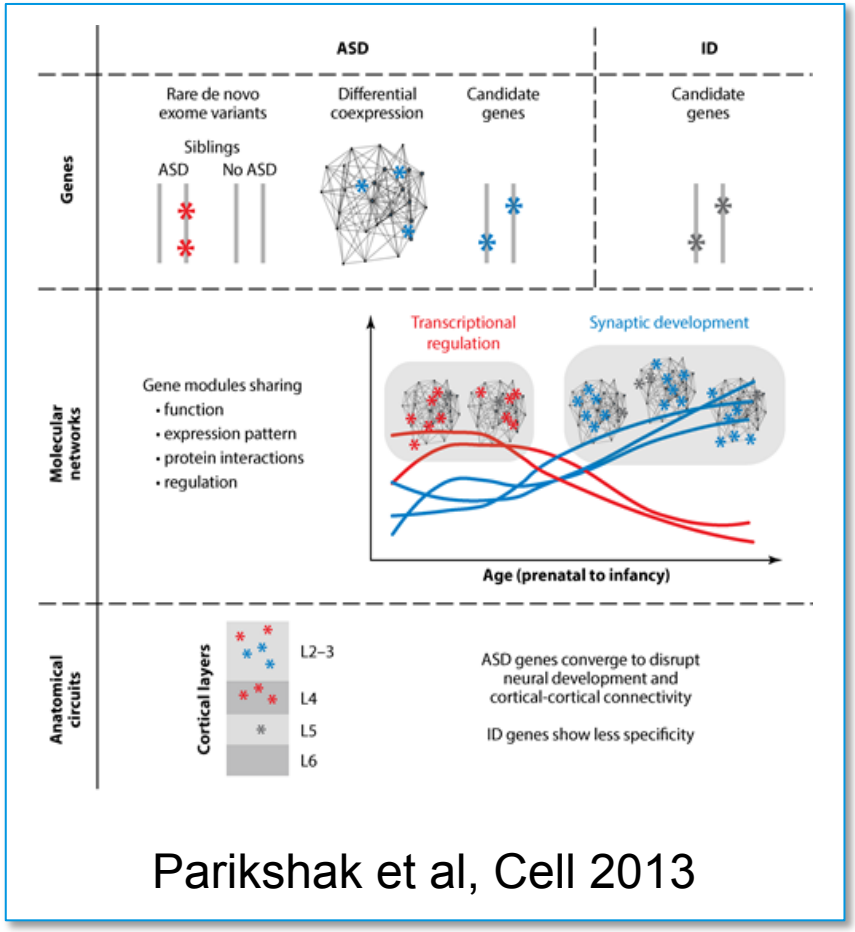




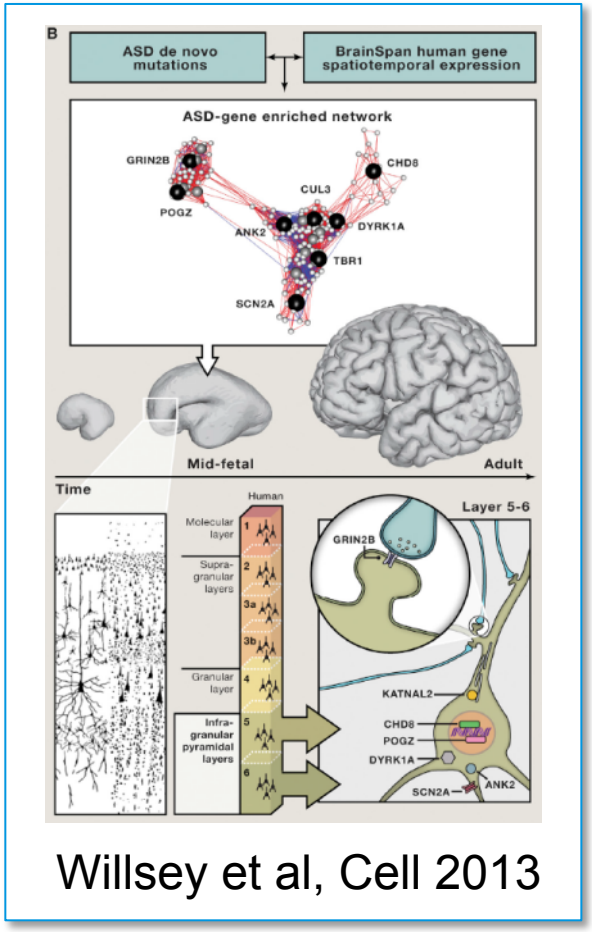
NDD & SZ-related genes

- in synapse function
- in neuronal maturation
- in protein translation

Developmental timing and cellular specificity of the molecular pathways disrupted by ASD risk genes



Parikshak et al, Cell 2013



Willsey et al, Cell 2013

Integrative genomics implicate mid-fetal cortical glutamatergic neurons