Translating genetic and genomic research in neuropsychiatric conditions: lessons from autism research

IOM Genomics Roundtable Workshop

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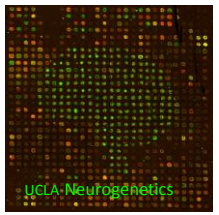
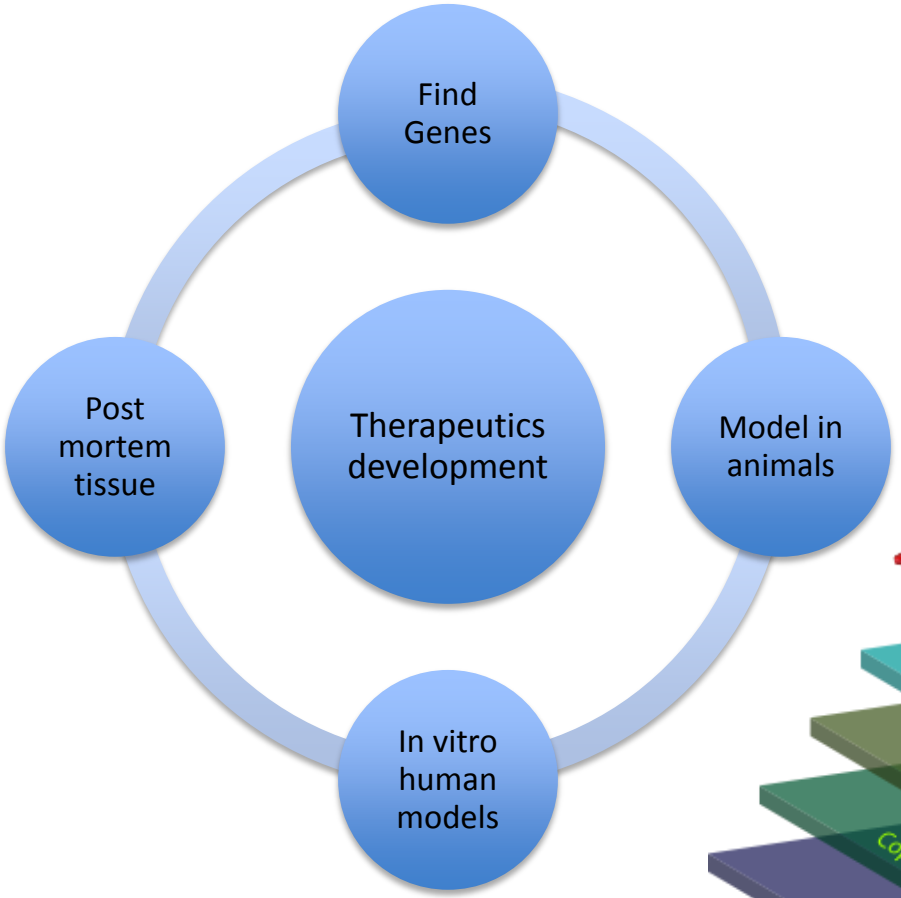
UCLA CART

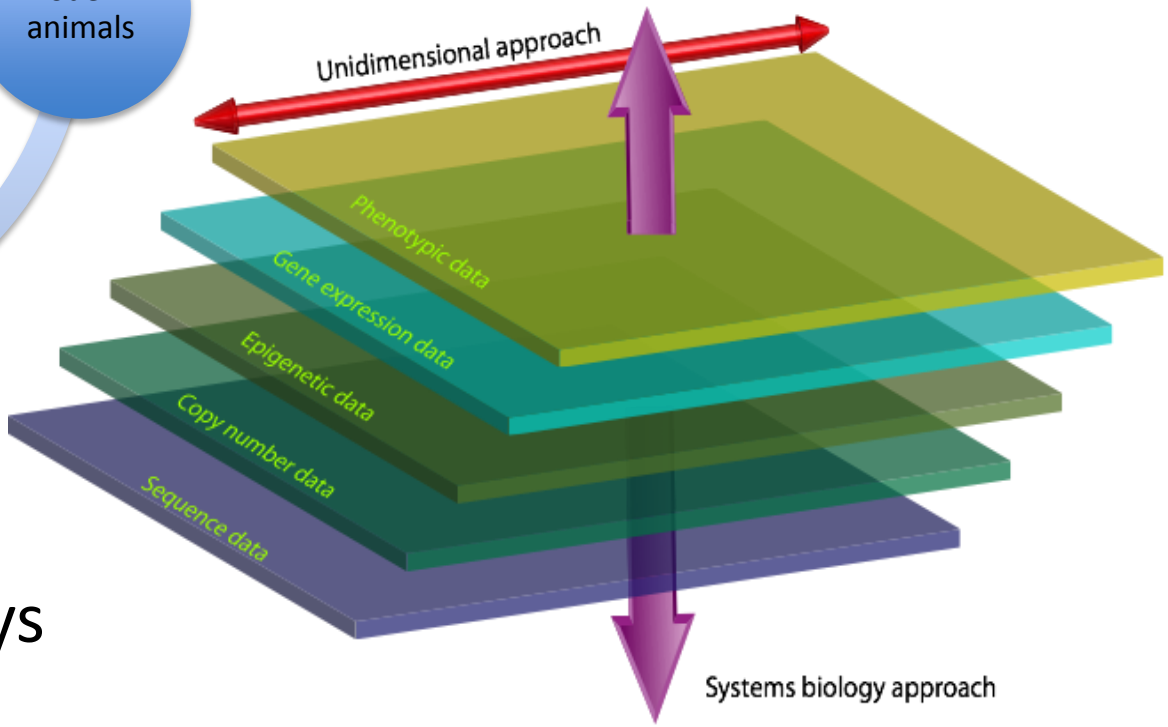
CENTER FOR AUTISM RESEARCH AND TREATMENT



Approach: Moving from Genes to Pathways to Therapeutics



- Identify Genes.
- Human Patients.
- Mouse models.
- Human post mortem tissue.
- Human neural progenitors – primary neurons.



Identify Pathways

Geschwind and Konopka *Nature* 2009

Complexity in neuropsychiatric disorders

AUTISM SPECTRUM DISORDER (ASD) is a prototypical example

Phenotypic

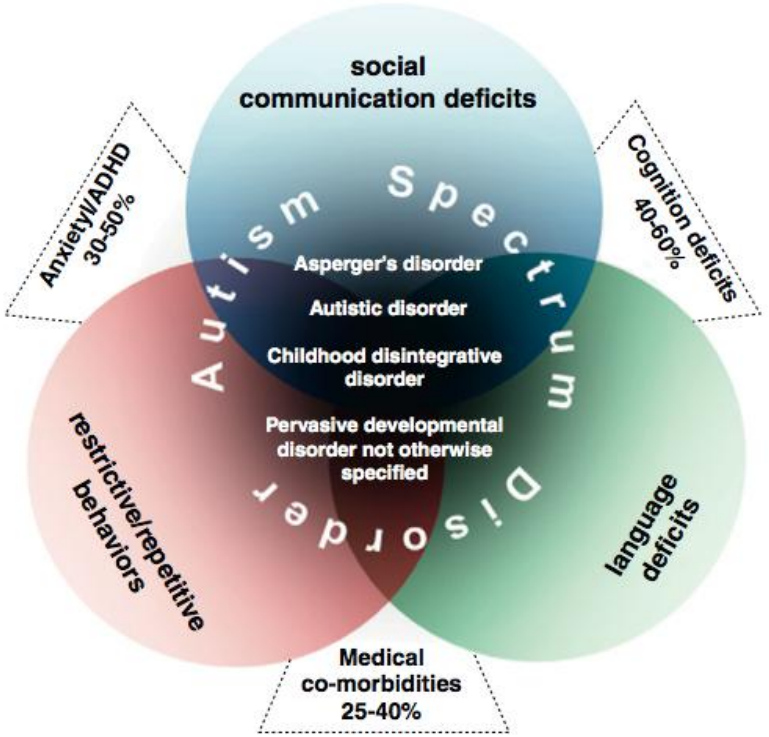
- Disorder Overlap
- Endophenotypes

Etiologic

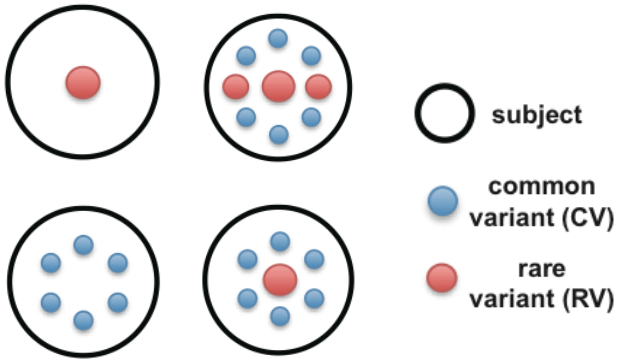
- SNPs, SNVs, CNVs
- Epigenetics
- Environment
- Interactions (GxE, GxG)

Biological pathways

- Molecular
- Cellular
- Circuits
- Behavioral/Cognitive

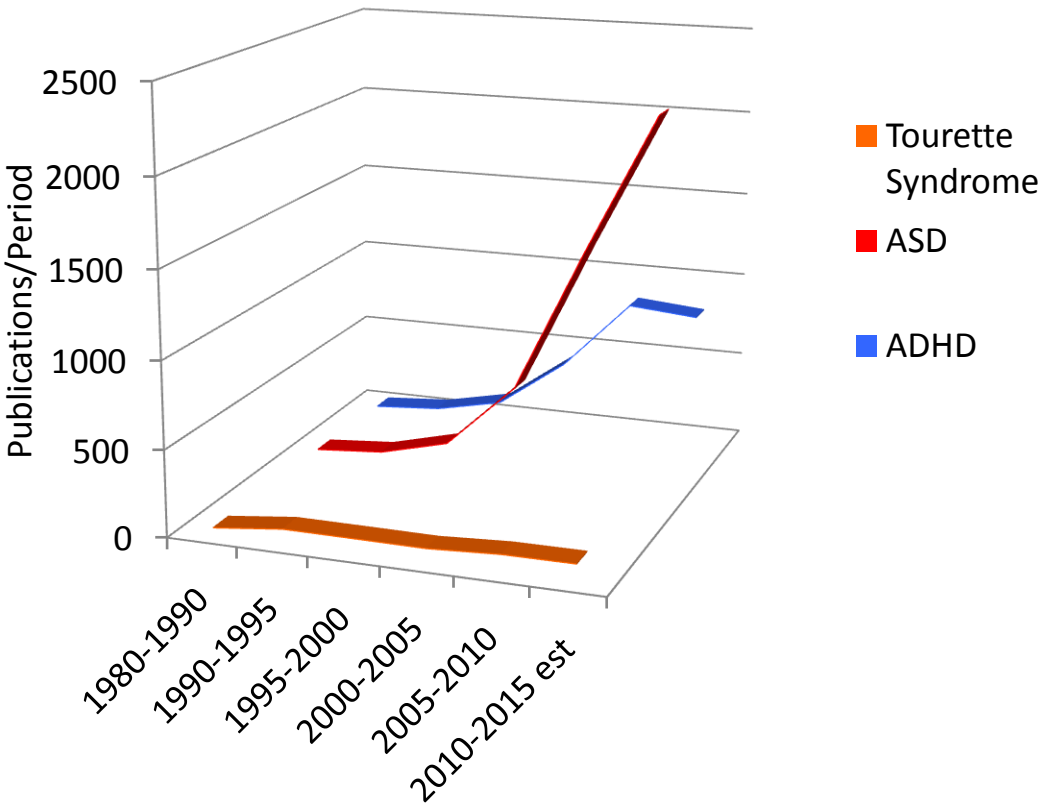


Devlin and Scherer *Curr Opin Genet Dev*, 2012



Berg and Geschwind, *Genome Biol.* 2012

Progress in Understanding ASD Biology



- Genetic variants accounting for about 20% of ASD have been identified (*de novo*).
- Several variants have been studied in human brain to understand circuit level dysfunction..
- Mouse models have been made to understand synapses, cells, circuits.
- In vitro models in IPSCs have been developed.
- Several new pharmacological treatments are in early trials

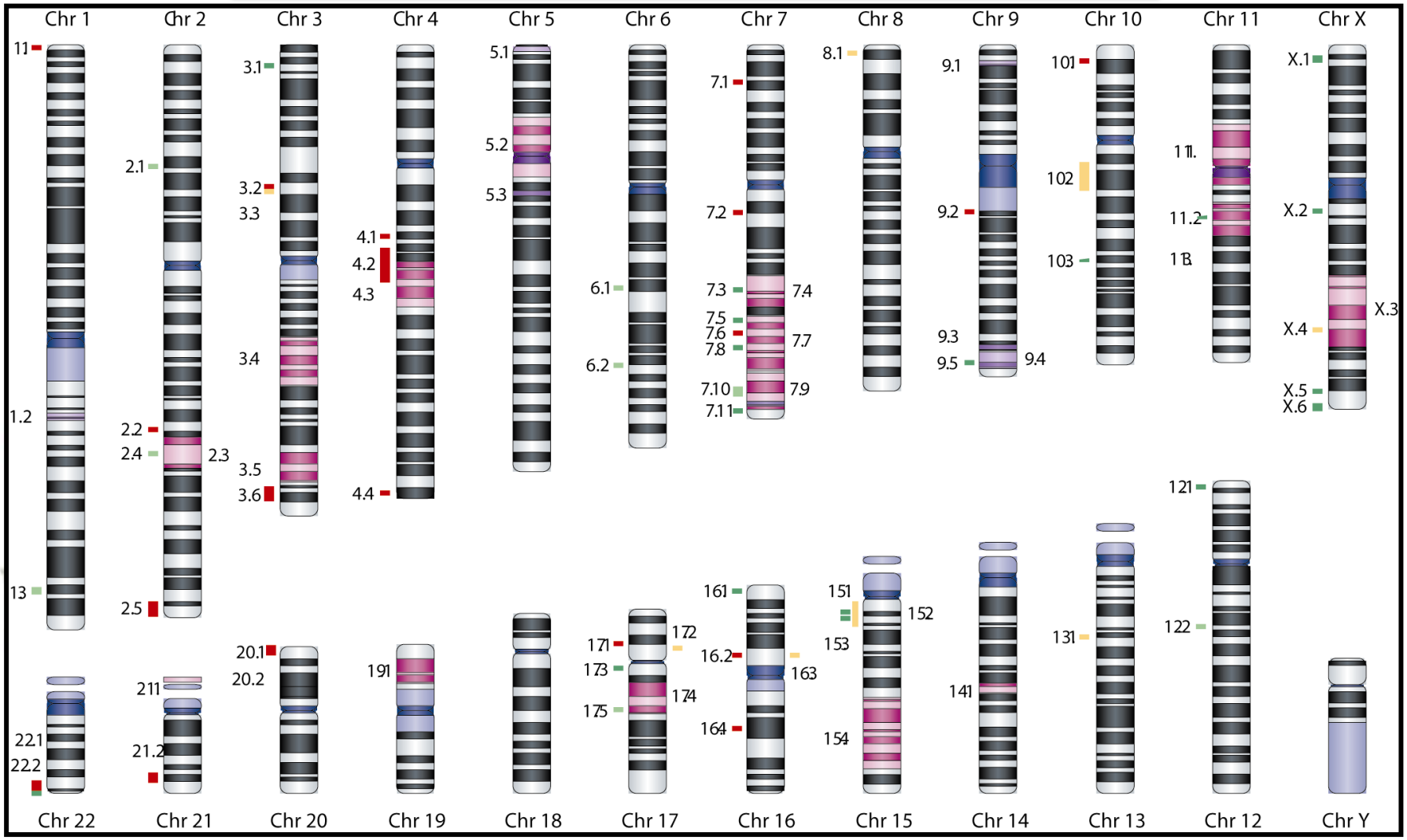
Build it and they will come?

Create a Large, Open Resource

Autism Genetic Resource Exchange

- **An open resource shared with the scientific community**
- **More than 1300 families AND 10,000 DNA samples**
  - **Greatly accelerated the pace of family collection and research.**
  - **>330 researchers and 200 publications since 2001!**
- **Phenotype data:**
  - **ADI-R, ADOS**
  - **basic cognitive and language testing**
  - **physical/neuro exams**
  - **medical histories**
- Biomaterials and Data (Karyotyping/molecular cytogenetics/SNP data).

Progress in Genetics



Abrahams and Geschwind, *Nature Reviews Genetics, 2008*

LETTER

doi:10.1038/nature10945

De novo mutations revealed by whole-exome sequencing are strongly associated with autism

Stephan J. Sanders[1], Michael T. Murtha[1], Abha R. Gupta[2]*, John D. Murdoch[1]*, Melanie J. Raubeson[1]*, A. Jeremy Willsey[1]*, A. Gulhan Ercan-Sencicek[1]*, Nicholas M. DiLullo[1]*, Neelroop N. Parikshak[3], Jason L. Stein[3], Michael F. Walker[1], Gordon T. Ober[1], Nicole A. Teran[1], Youeun Song[1], Paul El-Fishawy[1], Ryan C. Murtha[1], Murim Choi[4], John D. Overton[4], Robert D. Bjornson[5], Nicl
Katl

LETTER

doi:10.1038/nature10989

Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations

Brian J.
Joshua
Elhanan

Neuron
Article

Cell PRESS

De Novo Gene Disruptions in Children on the Autistic S

LETTER

doi:10.1038/nature11011

Ivan Iossifov,[1,6] Michael Ronemus,[1,6]
Yoon-ha Lee,[1] Giuseppe Narzisi,[1] An
Linda Rodgers,[1] Asya Stepansky,[1] Je
Melissa Kramer,[1] Jennifer Parla,[1] Rya
Jennifer C. Darnell,[4] Robert B. Darne
W. Richard McCombie,[1] and Michael

Patterns and rates of exonic *de novo* mutations in autism spectrum disorders

Benjamin M. Neale[1,2], Yan Kou[3,4], Li Liu[5], Avi Ma'ayan[3], Kaitlin E. Samocha[1,2], Aniko Sabo[6], Chiao-Feng Lin[7], Christine Stevens[2], Li-San Wang[7], Vladimir Makarov[4,8], Paz Polak[2,9], Seungtai Yoon[4,8], Jared Maguire[2], Emily L. Crawford[10], Nicholas G. Campbell[10], Evan T. Geller[7], Otto Valladares[7], Chad Schafer[5], Han Liu[11], Tuo Zhao[11], Guiqing Cai[4,8], Jayon Lihm[4,8], Ruth Dannenfelser[3], Omar Jabado[12], Zuleyma Peralta[12], Uma Nagaswamy[6], Donna Muzny[6], Jeffrey G. Reid[6], Irene Newsham[6], Yuanqing Wu[6], Lora Lewis[6], Yi Han[6], Benjamin F. Voight[2,13], Elaine Lim[1,2], Elizabeth Rossin[1,2], Andrew Kirby[1,2], Jason Flannick[2], Menachem Fromer[1,2], Khalid Shakir[2], Tim Fennell[2], Kiran Garimella[2], Eric Banks[2], Ryan Poplin[2], Stacey Gabriel[2], Mark DePristo[2], Jack R. Wimbish[14], Braden E. Boone[14], Shawn E. Levy[14], Catalina Betancur[15], Shamil Sunyaev[2,9], Eric Boerwinkle[6,16], Joseph D. Buxbaum[4,8,12,17], Edwin H. Cook Jr[18], Bernie Devlin[19], Richard A. Gibbs[6], Kathryn Roeder[5], Gerard D. Schellenberg[7], James S. Sutcliffe[10] & Mark J. Daly[1,2]

- Simons Simplex Collection
- AGRE
- Estimate 500-1000 *de novo* mutations.
- Mean effect size = 6

"The Autisms": Many Genetic Syndromes ("the 1%s"), None Specific.

Table 23.4.2 ASD-related syndromes[a] (modified from [3])

ASD-related syndrome	Associated gene(s)	Proportion with ASD	Proportion ASD with syndrome	References
1q21 Duplication	Many	50%	~1%?	[91, 128]
3p Deletion / duplication	CNTN4	<50%	~1%	[51, 61, 110]
15q Duplication (maternal)	Many (including UBE3A, GABRB3, SNRPN, and SNURF)	High	~1%	[41]

Trends in Cognitive Sciences September 2011, Vol. 15, No. 9

Table 1. Pleiotropic effects of major genes/mutations associated with ASD and allied neurodevelopmental disorders

Gene/region	Mechanism	Disorders	References
NRXN1	CNV, PM	ASD, SZ	[36], [50,72,73]
CNTNAP2	CNV, PM, CP	ASD, ID, epilepsy, LD/SLI, TS	[59,61,74,75]
16pdel	CNV	ASD, SZ, DD, LD, normal carrier	[33,37,42,76–78]
16pdup	CNV	SZ, ID, DD, LD, ADHD, normal carrier	[33,39,42,78]
15q13.3del	CNV	SZ, epilepsy, ASD, normal carrier	[42,73,79]
17q12del	CNV	SZ, ASD, ID	[80]
15q11–13dup	CNV	ASD, SZ/psychosis	[33,81]
22q11	CNV	ASD, ADHD, SZ, ID, epilepsy	[73,82–84]
1q21	CNV	ASD, SZ, ID, epilepsy	[42,85,86]

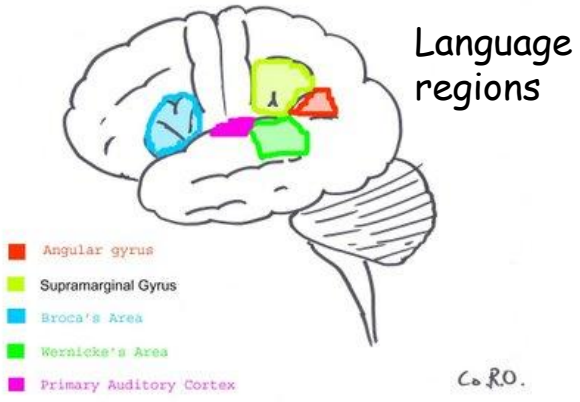
Here we list genes, form of genetic risk variant, clinical disorders where the mutation has been observed, and some representative references. This table is not meant to be exhaustive but illustrative of the pleiotropic effects of known ASD genes or loci with relatively large effect sizes (OR > 5–10 for ASD). New abbreviations are as follows: TS, Tourette syndrome and PM, point mutation.

duplication(17p11)				
Smith–Lemli–Optiz (11q13)	DHCR7 [c]	50%	Negligible	[129]
Prader–Willi (15q11-13)	Paternal deletions	20–25%	Unknown	[45]
Rett (Xq26)	MECP2	N/A	~0.5%	[5]
Timothy syndrome (12p13)	CACNA1C	60–80%	Negligible	[120]
Tuberous sclerosis (9q34 and 16p13)	TSC1, TSC2	20%	~1%	[10]

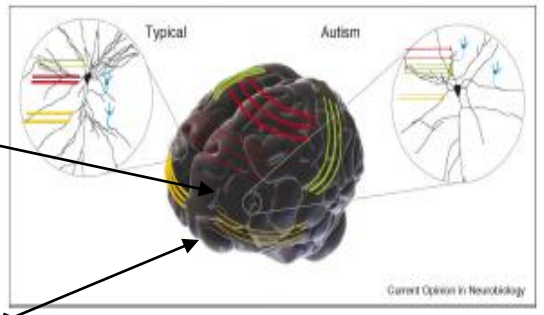
Abrahams and Geschwind *Vogul and Motulsky* 2009

The "endophenotype" concept

- Common neurodevelopmental disorders, such as autism, SLI/dyslexia, ADHD, epilepsy, and MR are not defined based on common etiology.
- The association of genetic factors with specific, measurable components of each disease, called "endophenotypes" will be stronger than the clinical diagnosis alone.
- To be most useful for genetic analysis, endophenotypes should be:
  - Associated with the disease
  - Heritable
  - Relatively stable
  - Identified in first degree relatives more than the general population.
  - Quantifiable



Language regions

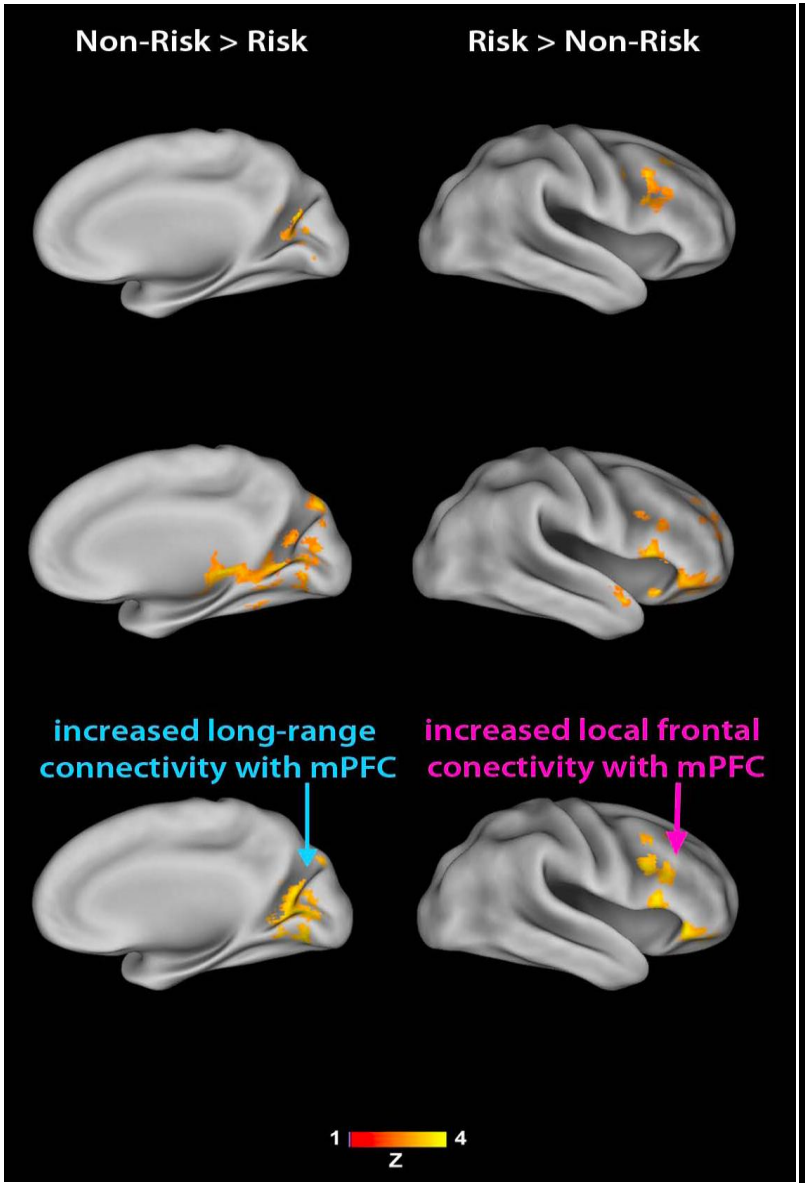


working memory

Social cognition, attention, implicit learning

Studying ASD risk variants in humans

CNTNAP2



Van Zeeland et al. Science *Trans Med 2011*

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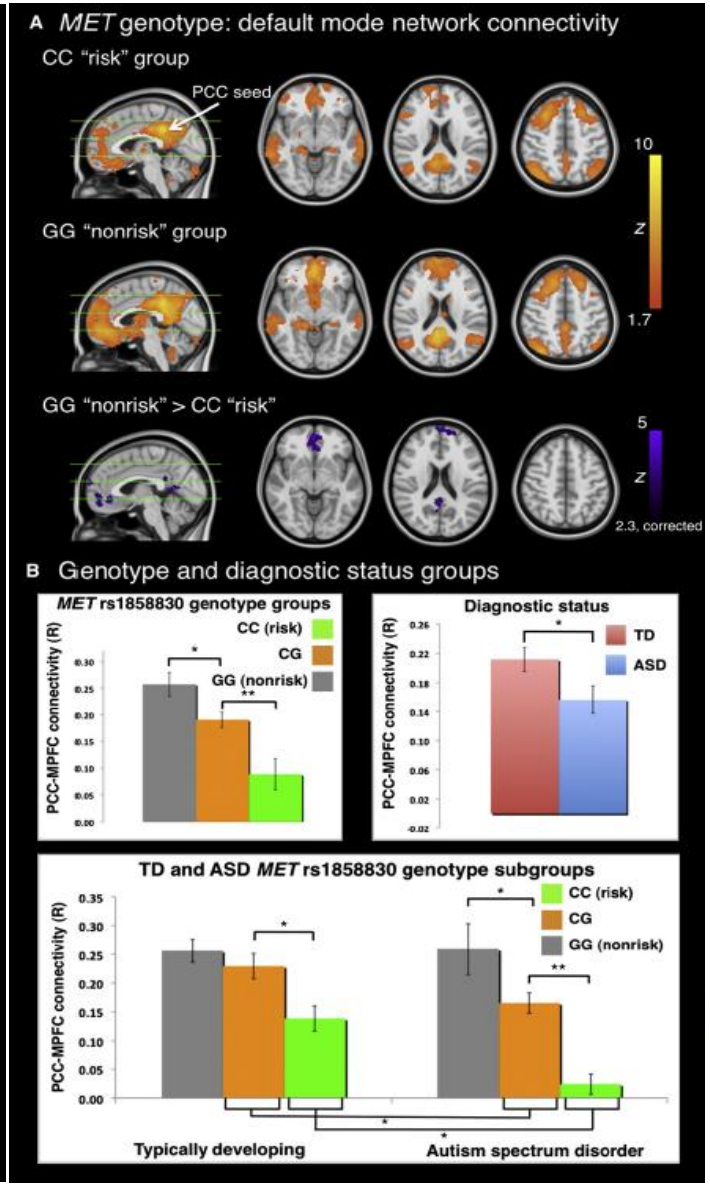
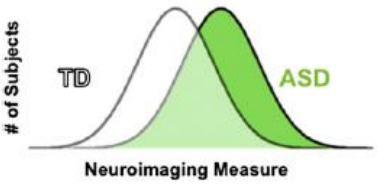


Rudie et al. *Neuron 2012*

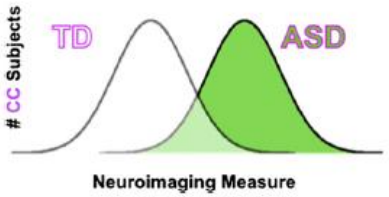
1. Heterogeneity of Neuroimaging Phenotypes



2. Stratify Neuroimaging Phenotype (diagnosis independent)

3. Stratify Using Risk Variant(s) That Modulates Phenotypes Across Human Populations

4. Reduce Heterogeneity Using Genotype And Diagnosis



Open access, freely available online PLOS BIOLOGY

Ultrasonic Songs of Male Mice

Timothy E. Holy*, Zhongsheng Guo

Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri, United States of America

Previously it was shown that male mice, when they encounter female mice or their pheromones, emit ultrasonic vocalizations with frequencies ranging over 30–110 kHz. Here, we show that these vocalizations have the characteristics of song, consisting of several different syllable types, whose temporal sequencing includes the utterance of repeated phrases. Individual males produce songs with characteristic syllabic and temporal structure. This study provides a quantitative initial description of male mouse songs, and opens the possibility of studying song production and perception in an established genetic model organism.

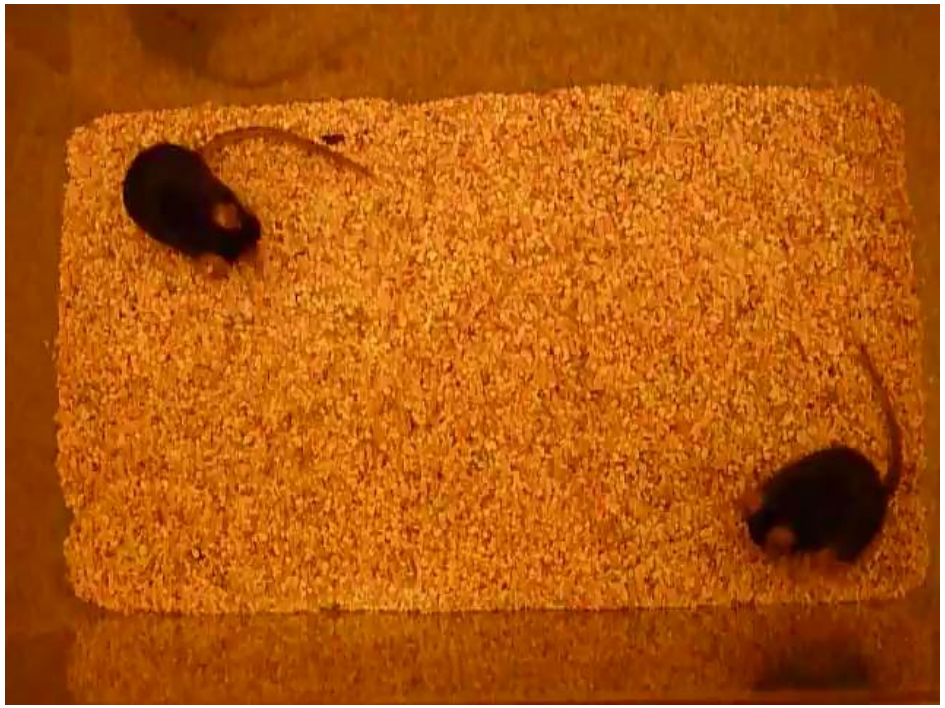
Citation: Holy TE, Guo Z (2005) Ultrasonic songs of male mice. PLoS Biol 3(12): e386.

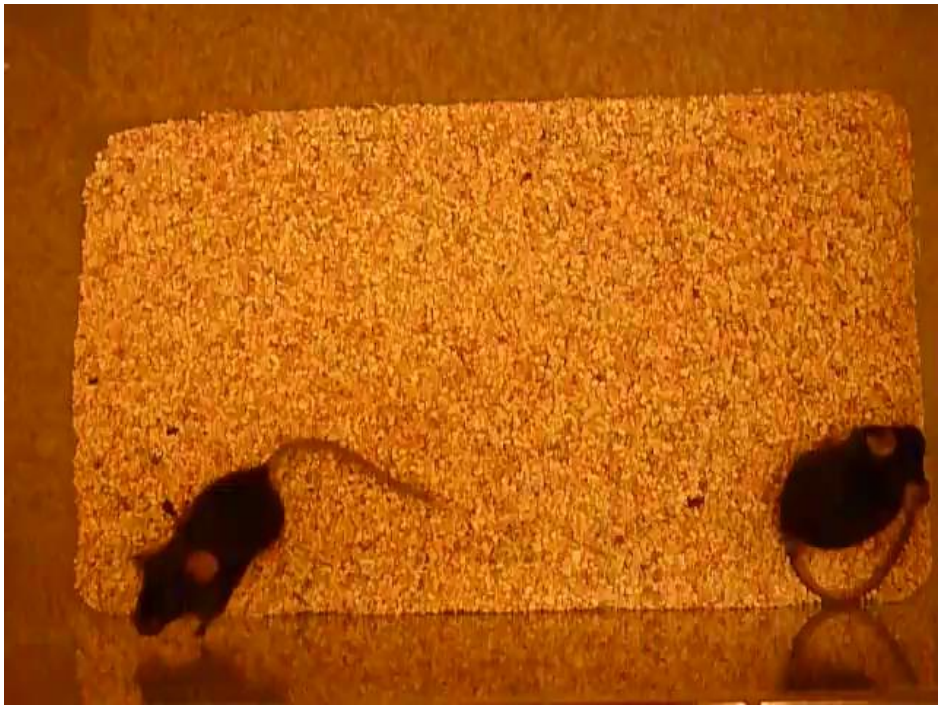
Mice with CNTNAP/.CASPR2 mutations show:

- reduced USV
- reduced sociability
- increased repetitive behaviors
- increase hyperactivity
- increase sensory hypersensitivity

(Penagarikano et al. *Cell* 2011)

CNTNAP2 mouse knockout
Treatment with Oxytocin



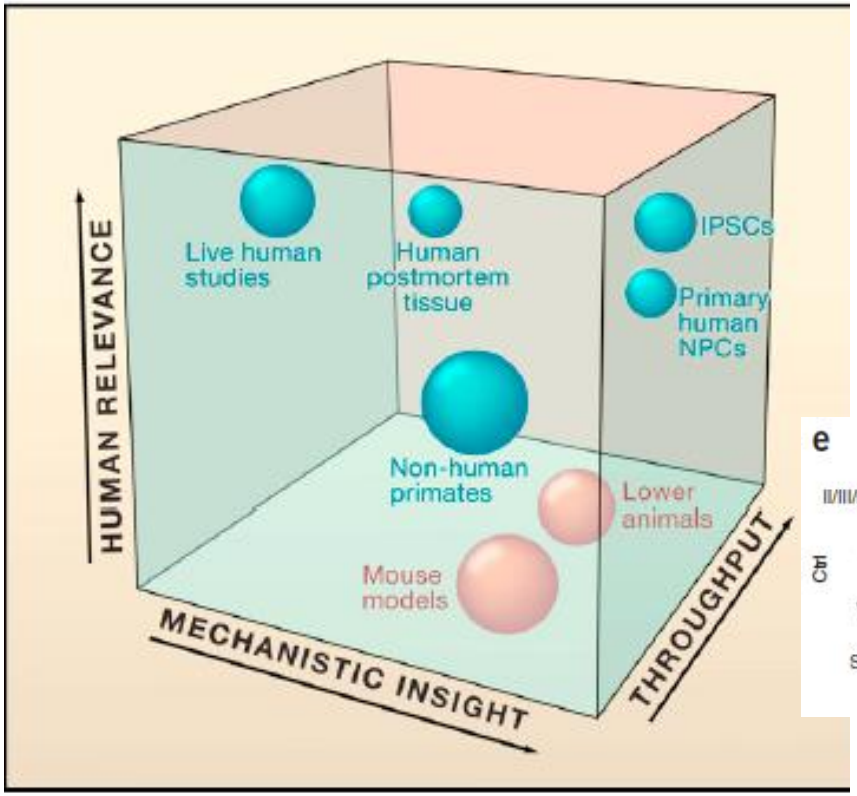


Olga Penagarinkaro, PhD

Opportunities:

- Understand mechanism at synapse, cell, circuit level
- Predictive validity – use mouse for in vivo screening

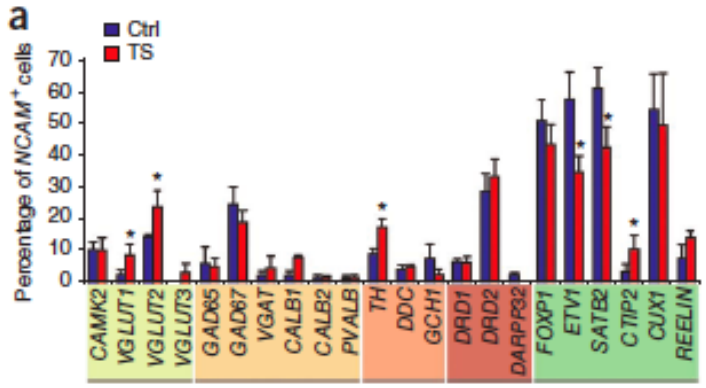
How do we develop therapeutics?



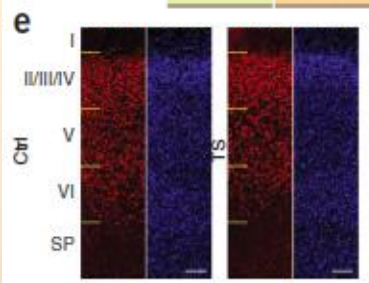
The Human Brain in a Dish: The Promise of iPSC-Derived Neurons

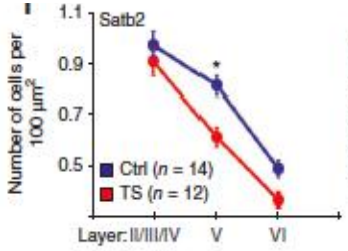
Cell

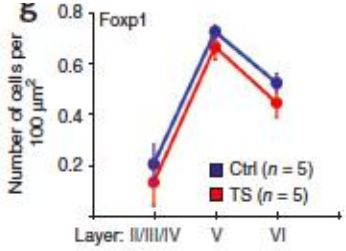
Ricardo Dolmetsch[1,*] and Daniel H. Geschwind[2,*]

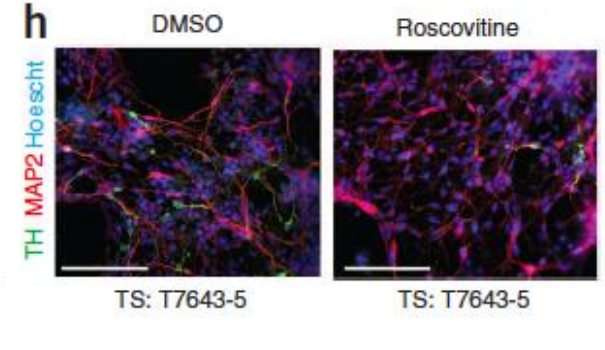


Pasca et al.
Nature Medicine
2011

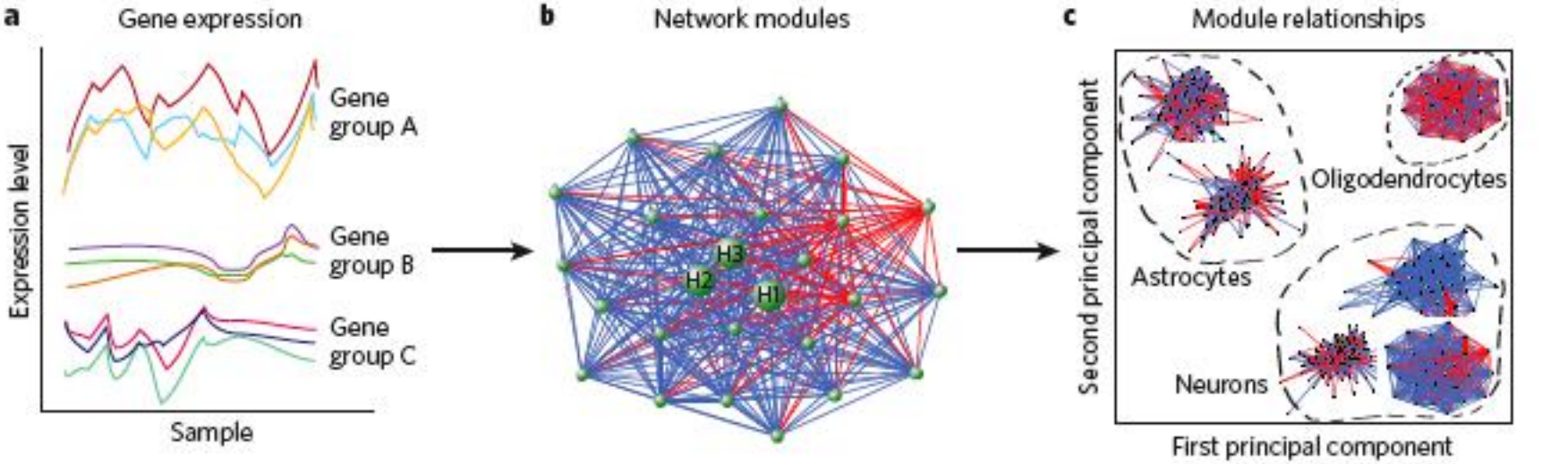








Using Network Biology to Provide an Integrated View (WGCNA; Zhang and Horvath 2005)



GESCHWIND AND KONOPKA NATURE 2009

Network structure is robust and reproducible (it is real: Horvath et al. *PNAS* 2006; Oldham et al. *Nat Neurosci* 2008; Winden et al. 2009 *Mol Sys Biol*; Miller et al. P*NAS* 2010).

A gene's network position is biologically meaningful

We can identify groups of co-expressed genes called modules that correspond to key elements of biological function (Oldham et al. 2006; Oldham et al. 2008; Winden et al. 2009).

And within modules, we can identify the most central, "hub" genes (Horvath et al. 2006; Oldham et al. 2008, Winden et al. 2009).

This structure serves as a basis for identification of biological meaningful insights

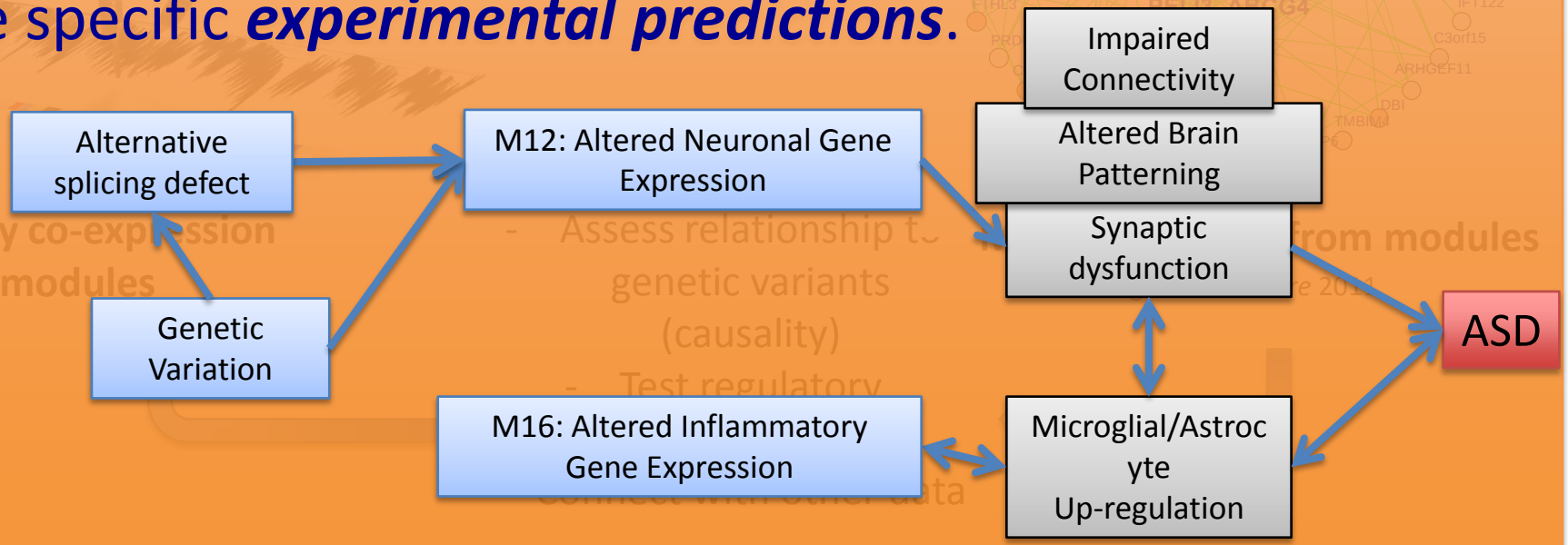
- Comparative network analysis – modules
- Comparative network analysis - gene connectivity
- Guilt by association—functional annotation

Network Analysis to Network Inference

Dissect functional relationships of thousands of genes to a few modules.

Can relate ***complex*** genetic and phenotypic variables to these modules.

Make specific ***experimental predictions***.



Disease complexity and heterogeneity: some lessons

Challenge

- Heterogeneity
  - Genetic
  - Phenotypic
- Etiological overlap
  - Sz, ADHD, ASD, epilepsy
- Multiple levels of dysfunction lead to abnormal behavior and cognition
  - –connecting genetic variation to targetable mechanisms.

Solution

- Large sample sizes needed for power to detect genetic variation.
  - Importance of community resources (not consortia)
  - Data sharing (high quality)
- Cross disorder study
  - Measure appropriate phenotypes
  - Data repositories that work
- Integrative or systems biology approaches are needed
  - Convergent approaches
    - True collaborative research
    - Multidisciplinary
    - Analysis vs. Data Generation

What we have learned from ASD genetics

- Successes
  - Many genetic causes of autism spectrum disorders (ASD) have been identified.
    - This has been fueled by large scale shared patient resources for research that are readily available.
    - True collaboration and multidisciplinary approaches
  - This knowledge greatly facilitates development of multiple model systems and drug development (based on monogenic forms).
- Challenges
  - ASD is an example of extreme genetic/etiologic heterogeneity.
  - Disease etiologies don’t obey diagnostic boundaries
  - Future: EMR based genetics (scale, and cross disorder).
  - Model validity needs to be carefully assessed.
  - Will therapy developed for one form of ASD be relevant to others?

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