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# Recent Progress in the genomics of autism spectrum disorders

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Matthew W. State MD, PhD
Professor and Chairman,
Department of Psychiatry

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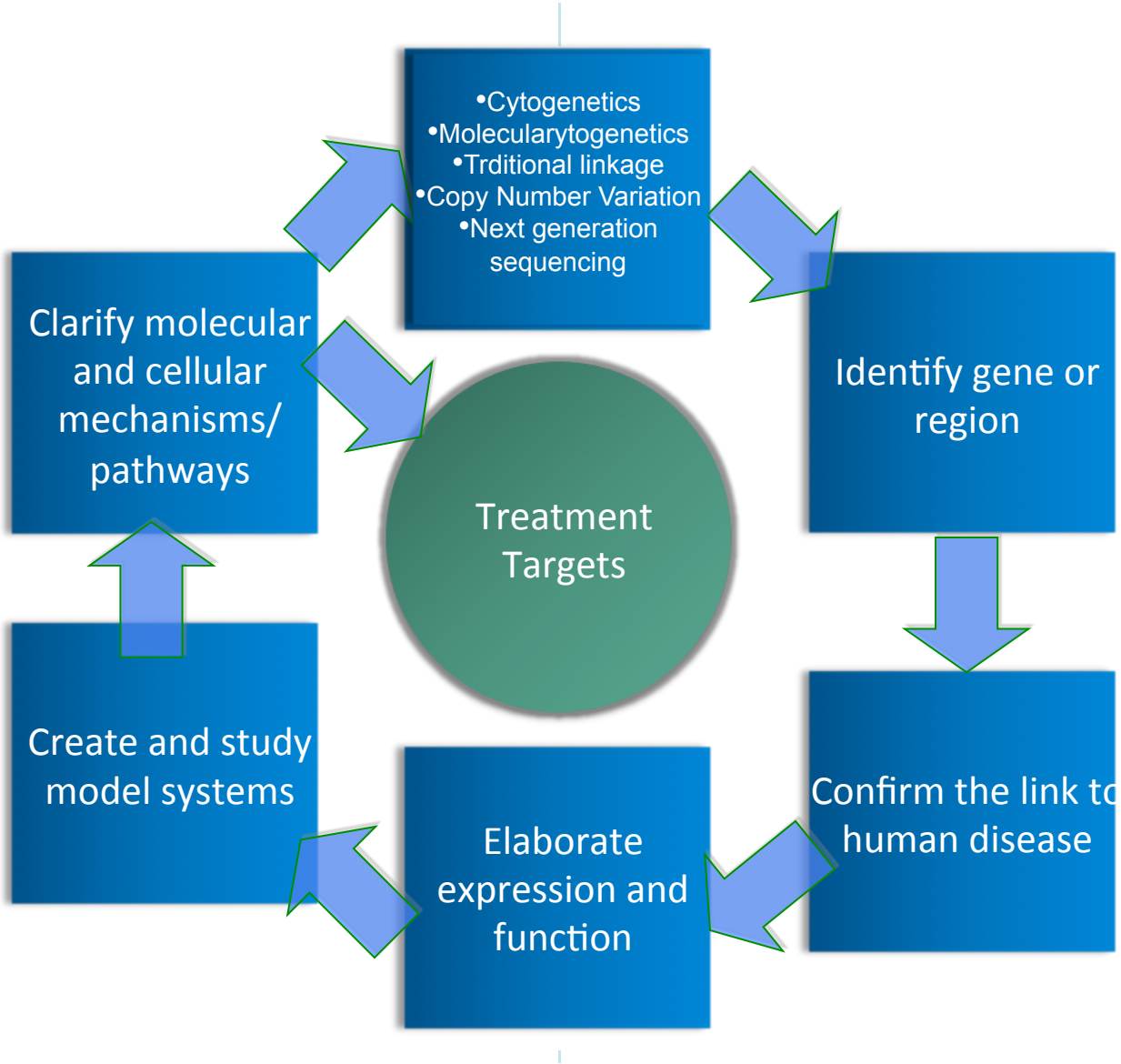
# Autism Spectrum Disorders

- Fundamental impairment in reciprocal social interaction, language development and restricted interests/repetitive behaviors
- Onset in early childhood
- Limited treatment options; nothing for core social deficits
- Lack of understanding of basic pathophysiological mechanisms is a major obstacle
- Gene discovery can be a critical first step on the path to solving this


•Cytogenetics
•Molecularytogenetics
•Trditional linkage
•Copy Number Variation
•Next generation sequencing
Identify gene or region
Confirm the link to human disease
Elaborate expression and function
Create and study model systems
Clarify molecular and cellular mechanisms/ pathways
Treatment Targets

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# Genetics 101

- Any two individuals are ~ 99% identical
- We are interested in the 1% difference
- These variations are the basis of the genetic contribution to risk
- “Gene discovery” is “variation discovery”

- Genetic variation can be common or rare in the population
  - common variation tends to have small effects and
  - rare variation tends to have big effects
- Genetic variation can involve the sequence of the DNA
  - Single Nucleotide Variants (SNVs; aka “point mutations”)
- Genetic variation can involve the structure of the DNA:
  - loses or gains = deletions or duplications.
  - Copy Number Variation (CNVs)
- Variation can be passed from generation to generation (transmitted) or new
  - Variation can occur in the parental germ-line/De novo in the child

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# Genetics of ASD

- Generally described as the most heritable NP disorder
- Few families with apparent Mendelian transmission
- Genetically complex, phenotypically heterogeneous group of disorders
- Lots of early emphasis on variation that is common in the genome (paralleling most early psychiatric genetics work)
- Candidate gene approaches; no clear results – similar to other areas of medicine
- Genome wide association studies (GWAS): powerful gene discovery approach in many common disorders --no replicating loci in ASD ~N=3000 cases

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# Genetics of ASD

- Important but infrequent and sporadic findings of rare coding mutations in genes coding synaptic proteins (NLGN4X, SHANK2, SHANK3)
- Growing appreciation of the overlap of ASD with monogenic syndromes (Fragile X, NF)
- First hint of a systematic approach to gene discovery in early copy number variation studies
  - Increased burden of de novo variation in simplex families (Sebat et al Science 2007)
  - Recurrent de novo CNVs; 16p11.2 (Weiss et al NEJM 2008; Kumar et al Hum Mol Genet 2008; Marshall et al Am J Hum Genet 2008)
  - Modest increase in burden (amount in cases v controls) of CNVs (Pinto et al Nature 2010)

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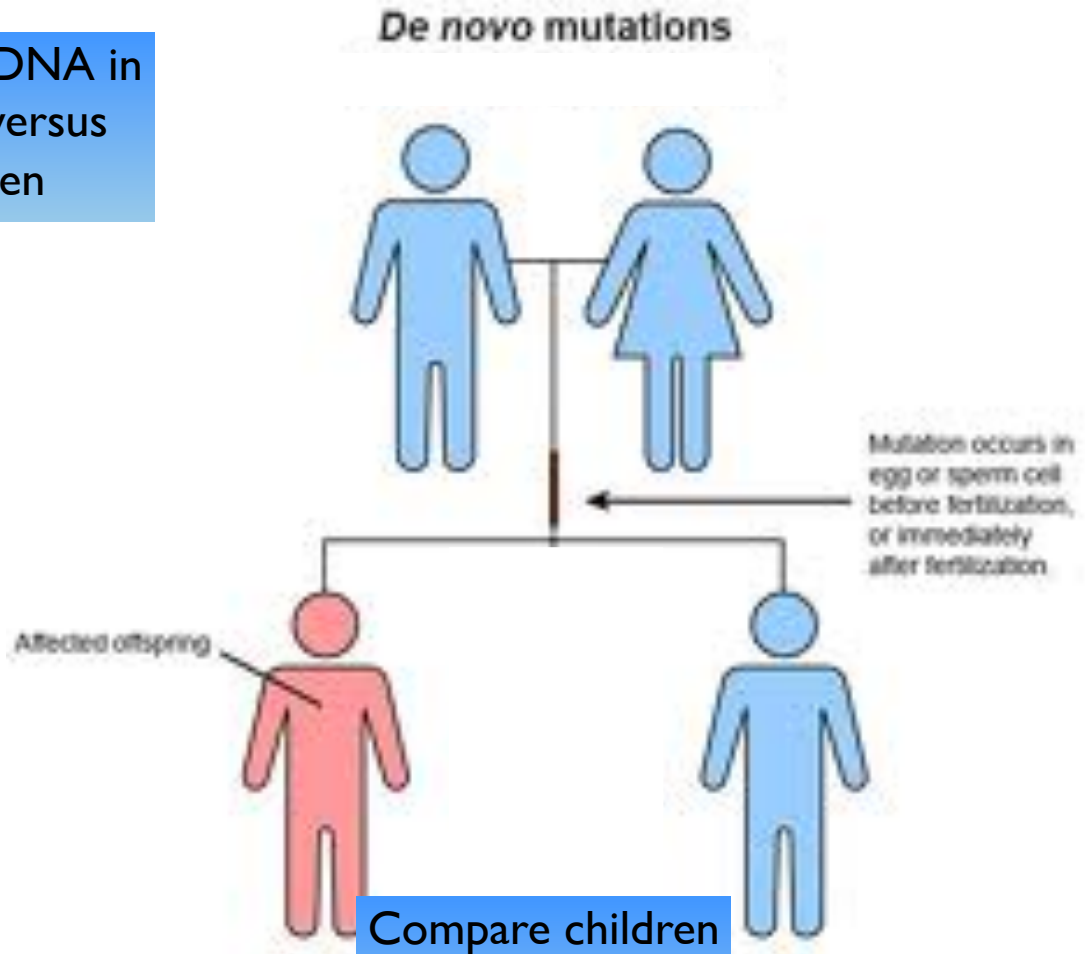
# Simons Simplex Collection

Compare DNA in parents versus children




Compare children in same family

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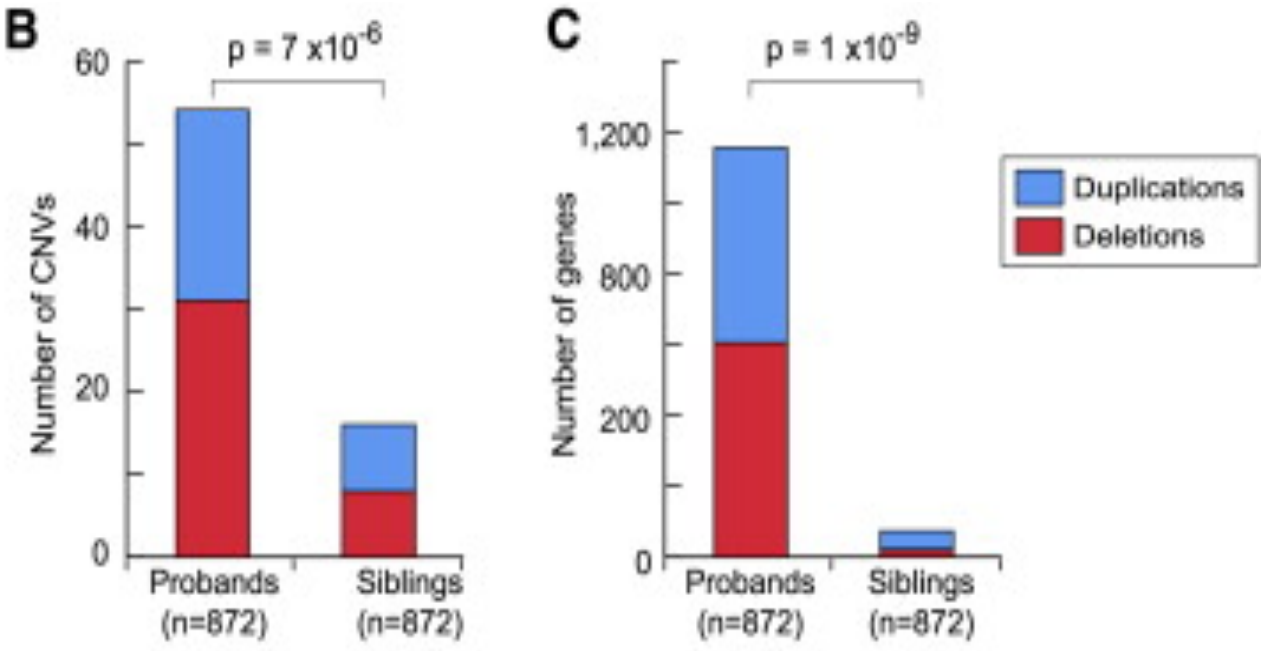
## Number of de novo CNVs

## Number of genes found within de novo CNVs




Large risks: 5x-16x increase
N=~1000 matched pairs

Sanders et al *Neuron* 2011

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# ASD (including 7q duplications)

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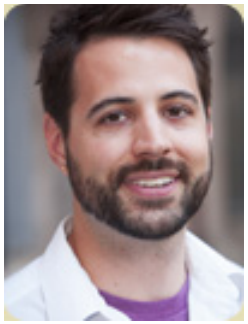
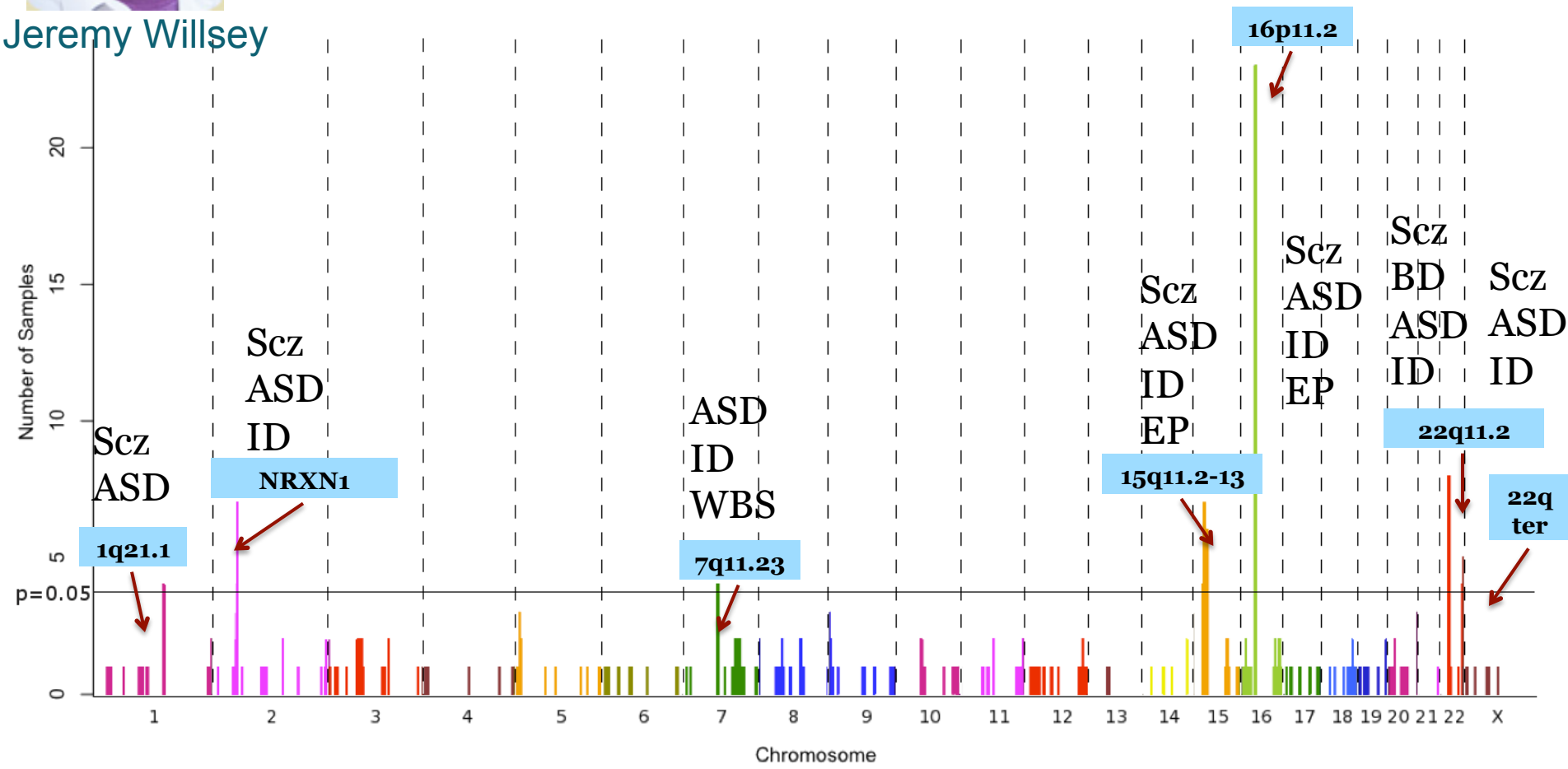
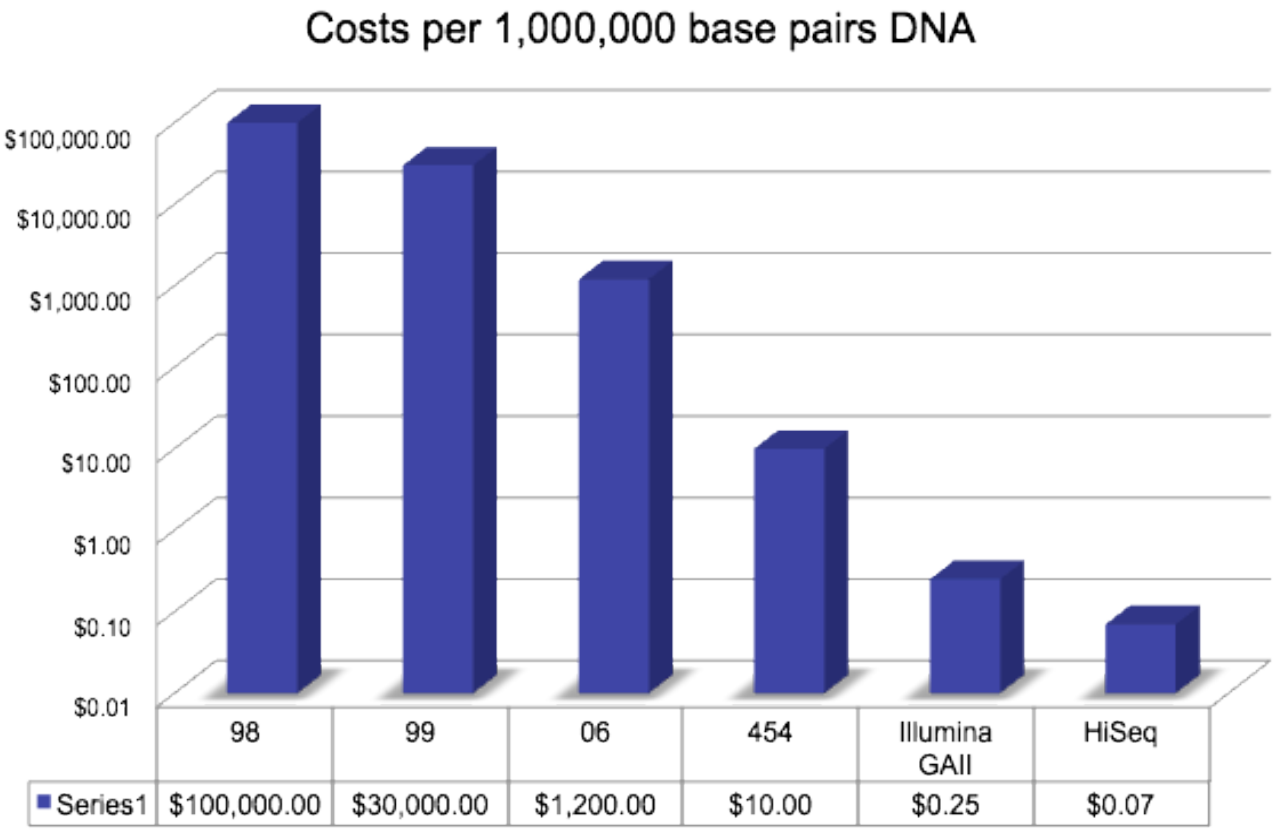
# 7q deletions



Jeremy Willsey




Willsey et al, unpublished


Costs per 1,000,000 base pairs DNA
$100,000.00
$10,000.00
$1,000.00
$100.00
$10.00
$1.00
$0.10
$0.01
98
99
06
454
Illumina GAII
HiSeq
Series1
$100,000.00
$30,000.00
$1,200.00
$10.00
$0.25
$0.07

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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], Nicholas J. Carriero[5], Kyle A. M
Kathryn Roeder[9], Daniel H. Ges

LETTER

doi:10.1038/nature11011

## 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], Zu
Lora Lewis[6], Yi Ha
Menachem Fromer
Jack R. Wimbish[14],
Joseph D. Buxbaur
James S. Sutcliffe[10]

LETTER

doi:10.1038/nature10989

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

Brian J. O'Roak[1], Laura
Joshua D. Smith[1], Emil
Elhanan Borenstein[1,3,]

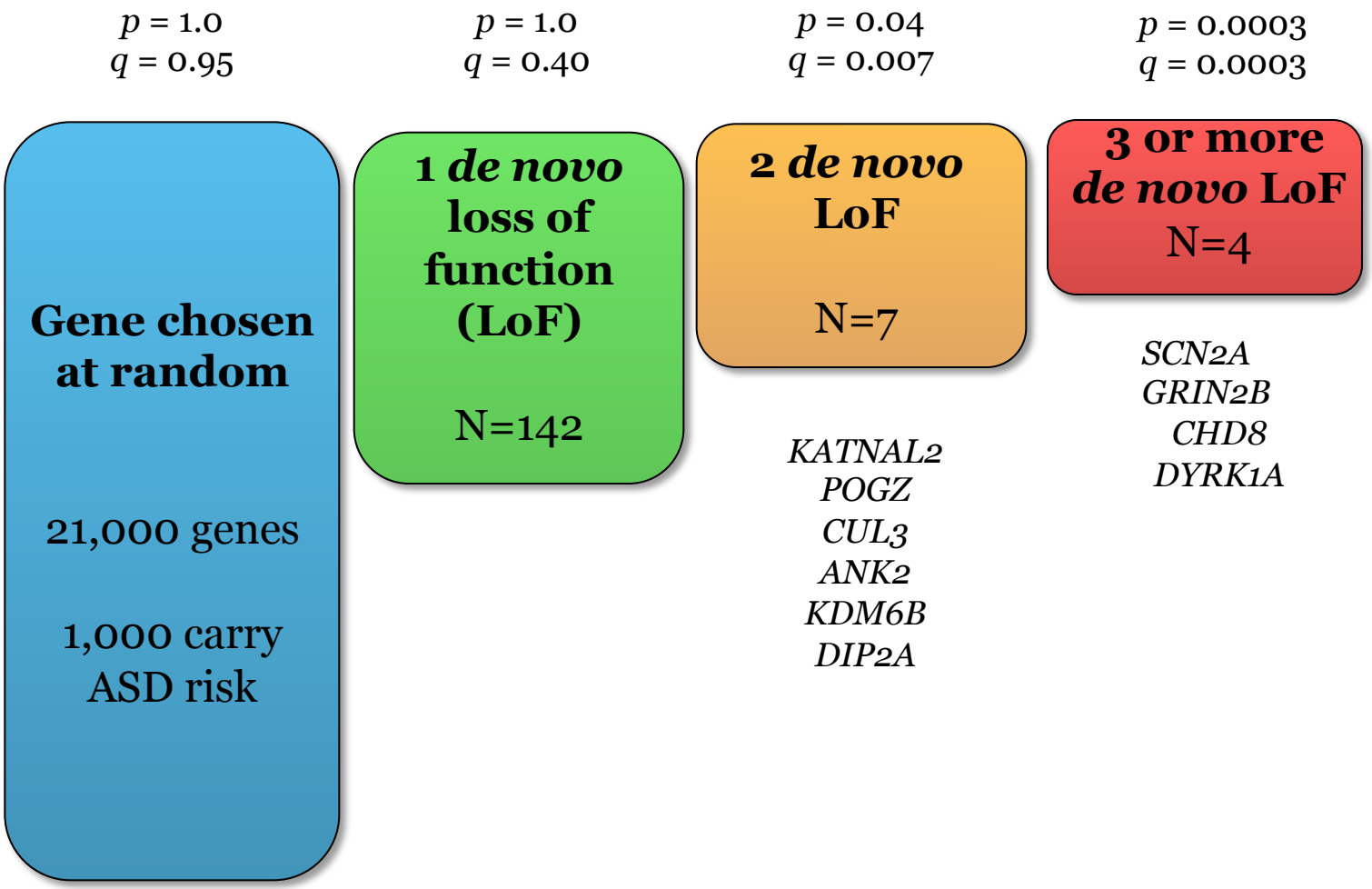
Neuron
Article

Cell PRESS

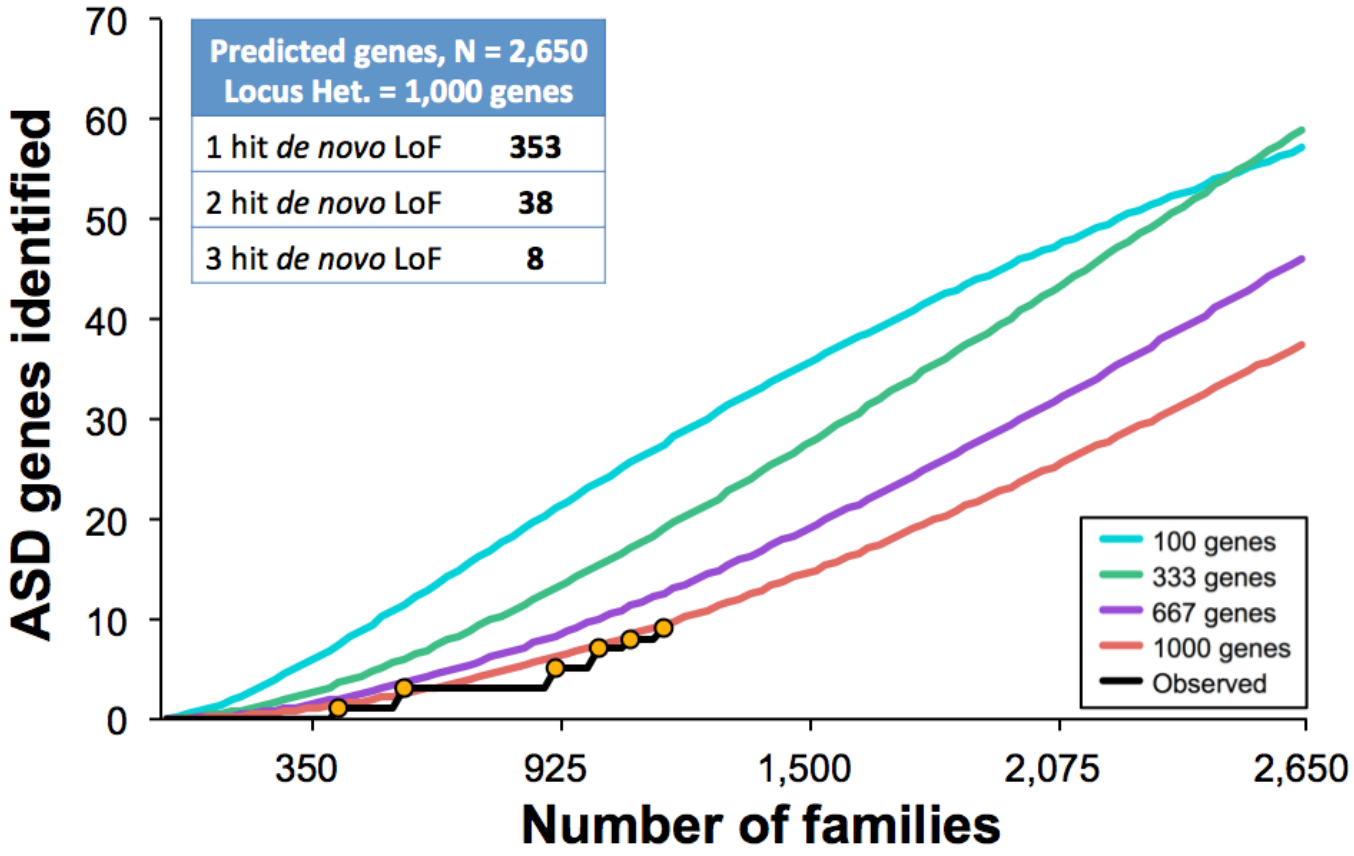
## De Novo Gene Disruptions in Children on the Autistic Spectrum

Ivan Iossifov,[1,6] Michael Ronemus,[1,6] Dan Levy,[1] Zihua Wang,[1] Inessa Hakker,[1] Julie Rosenbaum,[1] Boris Yamrom,[1] Yoon-ha Lee,[1] Giuseppe Narzisi,[1] Anthony Leotta,[1] Jude Kendall,[1] Ewa Grabowska,[1] Beicong Ma,[1] Steven Marks,[1] Linda Rodgers,[1] Asya Stepansky,[1] Jennifer Troge,[1] Peter Andrews,[1] Mitchell Bekritsky,[1] Kith Pradhan,[1] Elena Ghiban,[1] Melissa Kramer,[1] Jennifer Parla,[1] Ryan Demeter,[2] Lucinda L. Fulton,[2] Robert S. Fulton,[2] Vincent J. Magrini,[2] Kenny Ye,[3] Jennifer C. Darnell,[4] Robert B. Darnell,[4,5] Elaine R. Mardis,[2] Richard K. Wilson,[2] Michael C. Schatz,[1] W. Richard McCombie,[1] and Michael Wigler[1,*]
[1]Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA

Sanders et al *Nature* 2012

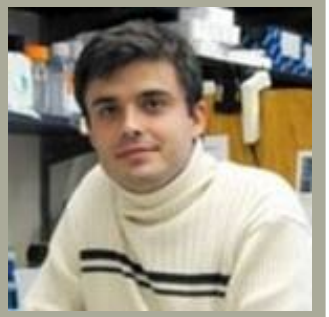

p = 1.0
q = 0.95
Gene chosen at random
21,000 genes
1,000 carry ASD risk
p = 1.0
q = 0.40
1 de novo loss of function (LoF)
N=142
p = 0.04
q = 0.007
2 de novo LoF
N=7
KATNAL2
POGZ
CUL3
ANK2
KDM6B
DIP2A
p = 0.0003
q = 0.0003
3 or more de novo LoF
N=4
SCN2A
GRIN2B
CHD8
DYRK1A

# 2 hit LoF consistent with 1,000 gene model




Sanders et al Nature 2012

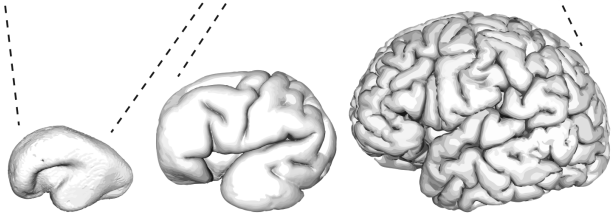
- When we started, the genetic architecture of ASD was largely speculation. We now know:
  - hundreds of CNVs perhaps 1000 genes
  - CNVs carry significant risk in ~5%-10% of cases
  - CNV risks for ASD are not specific
  - De novo SNVs in another(?) 15%
  - Increasing de novo SNV rate w paternal age
- Via the study of de novo mutation, there is a systematic path forward for gene discovery
- Clear association of *SCN2A, CHD8, GRIN2B, DYRK1A*
- How to manage the complexity: heterogeneity, phenotypic diversity and pleiotropy?
  - Pull on the thread and get all of biology
  - Can we determine when and where to look?



**A** Spatiotemporal human brain transcriptome

| Periods 1 & 2 | | |
|---|---|---|
| FC | PC | TC |
| OC | HIP | VF |
| MGE | LGE | CGE |
| DIE | DTH | URL |

| Periods 3-15 | | | |
|---|---|---|---|
| OFC | DFC | VFC | MFC |
| M1C | S1C | IPC | A1C |
| STC | ITC | V1C | HIP |
| AMY | STR | MD | CBC |

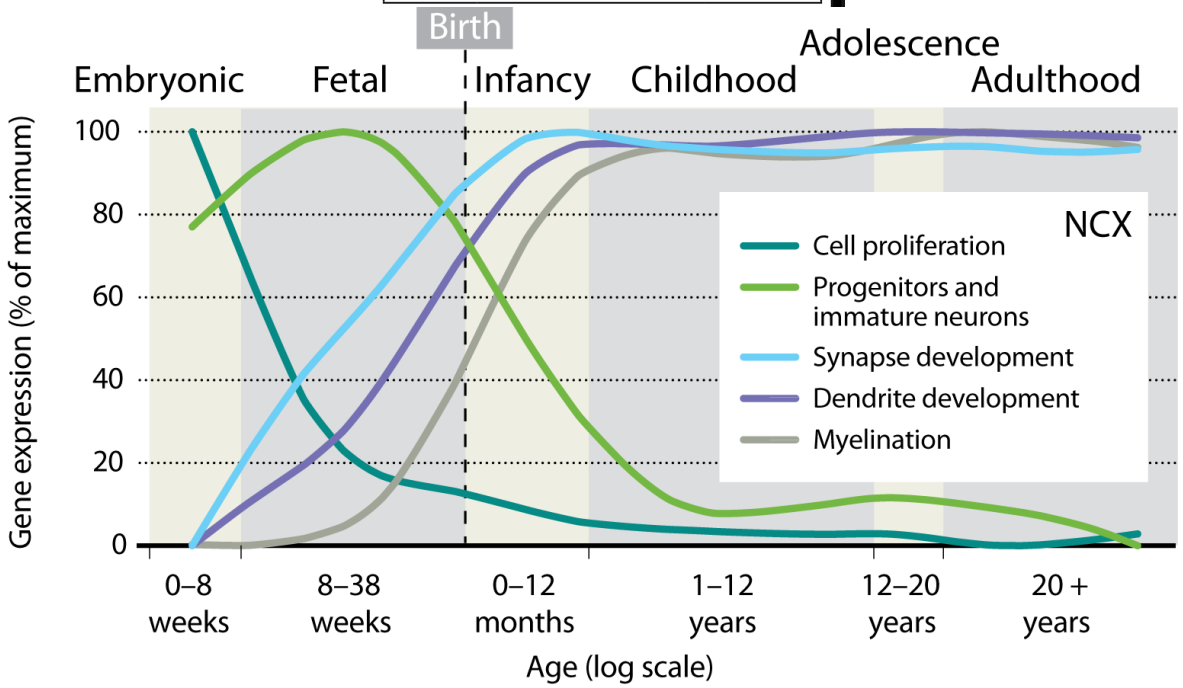


15 periods of development

**B**

| Period | Description | Age |
|---|---|---|
| 1 | Embryonic | 4-8 PCW |
| 2 | Early fetal | 8-10 PCW |
| 3 | Early fetal | 10-13 PCW |
| 4 | Early mid-fetal | 13-16 PCW |
| 5 | Early mid-fetal | 16-19 PCW |
| 6 | Late mid-fetal | 19-24 PCW |
| 7 | Late fetal | 24-38 PCW |
| 8 | Neonatal & early infancy | 0-6 M |
| 9 | Late infancy | 6-12 M |
| 10 | Early childhood | 1-6 Y |
| 11 | Middle and late childhood | 6-12 Y |
| 12 | Adolescence | 12-20 Y |
| 13 | Young adulthood | 20-40 Y |
| 14 | Middle adulthood | 40-60 Y |
| 15 | Late adulthood | 60Y+ |

*PCW, post-conceptional weeks; M, postnatal months; Y, postnatal years.*



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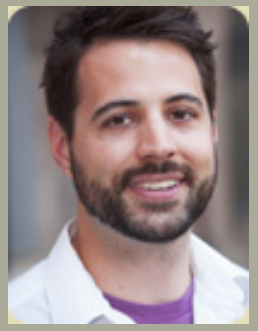
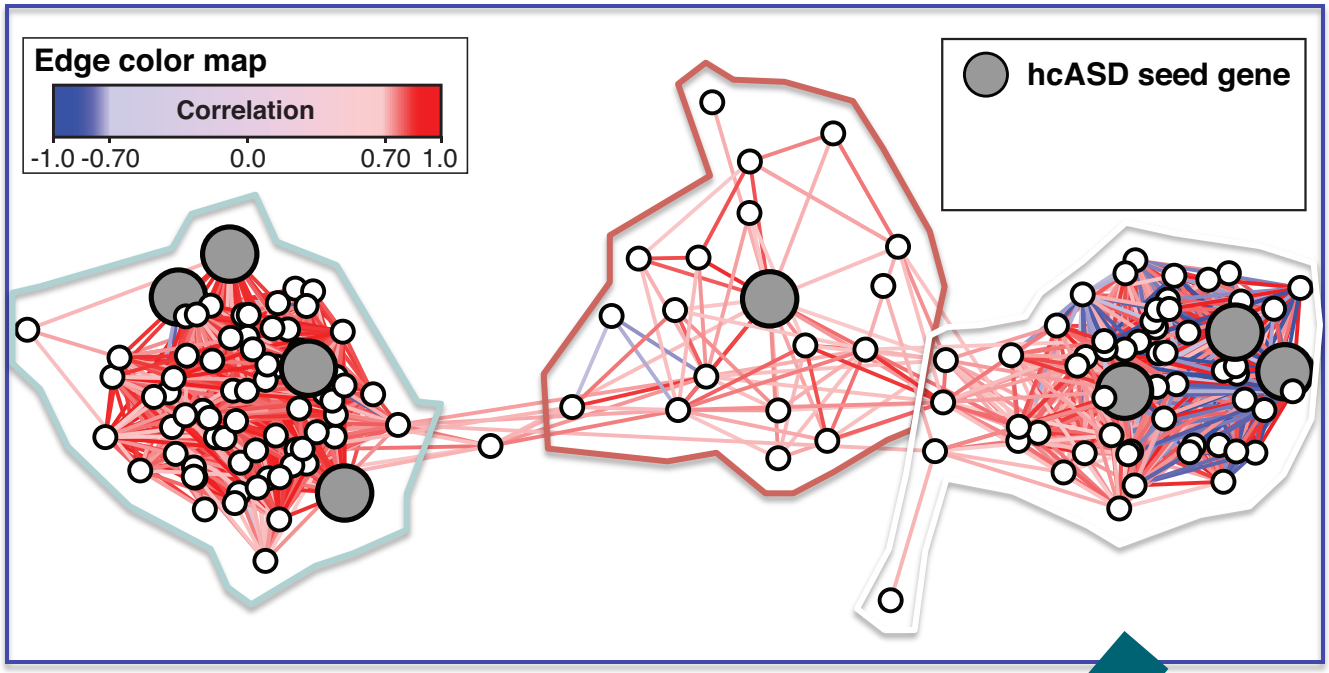
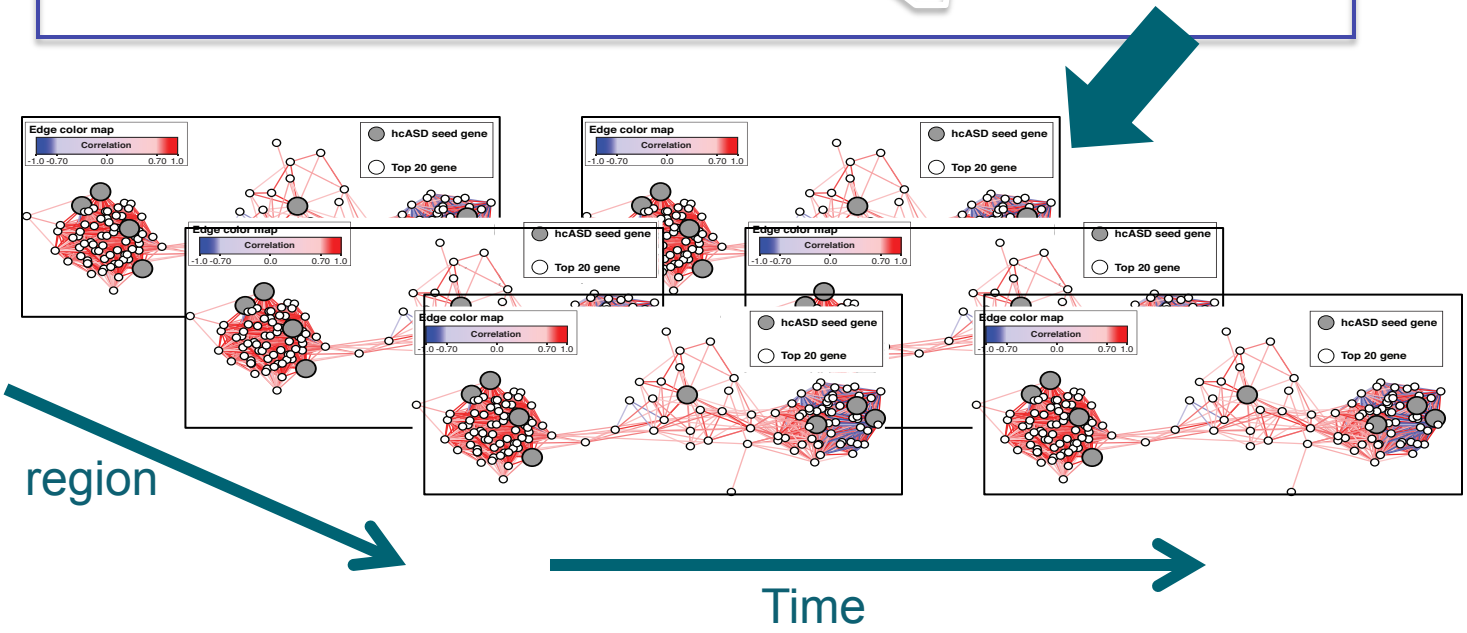


Jeremy Willsey

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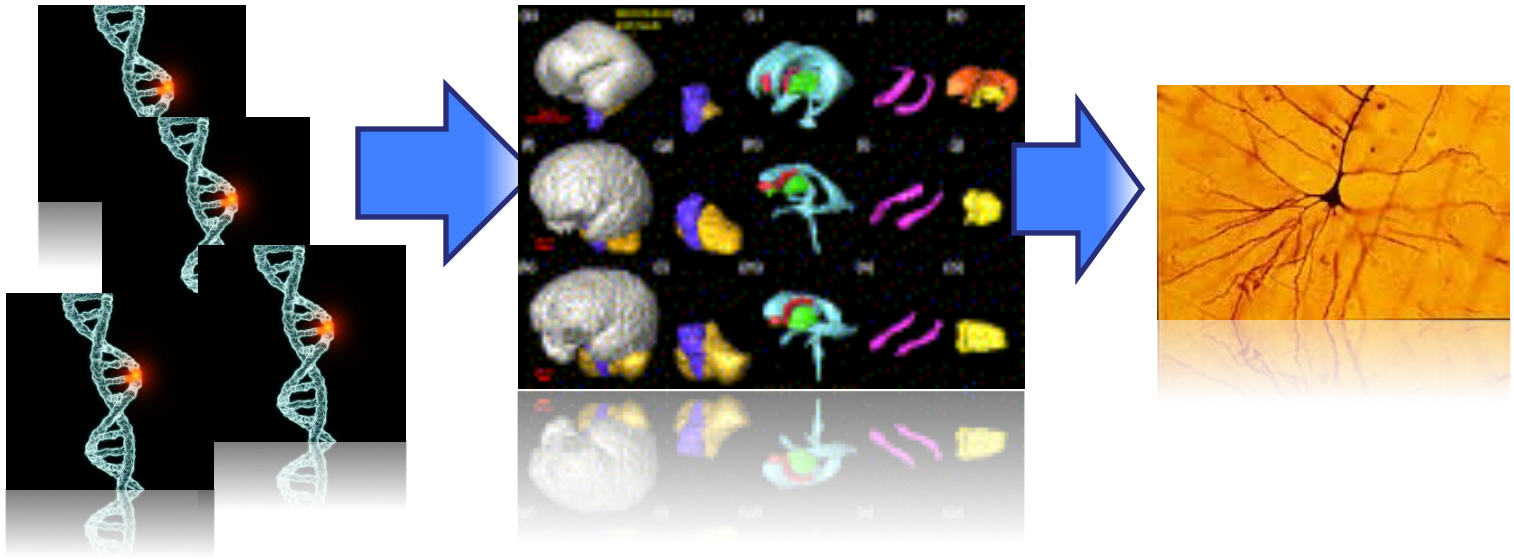

- Sea change in the genetics of ASD
- Systematic gene discovery can offer a foothold into biology
- Parallel advances in neurobiology and systems biology provide unprecedented traction
- The key to moving toward the development of novel and more effective treatments.

- Eric Morrow (Brown)
  - Dilber Gamsiz
- Jim Sutcliffe (Vanderbilt)
  - Brian Yaspan
  - Suzanne Thomson
  - Sabata Lund
- Ed Cook (UIC)
  - Lea Davis
  - Suma Jacob
- Bernie Devlin (Pittsburgh)
- Kathryn Roeder
  - Lambertus Klei
  - Su Chu
- Donna Martin (UMich)
- Dorothy Grice (Columbia)
- Dan Geschwind (UCLA)
  - Rui Luo
  - Jenni Lowe
  - Yuan Tian
- Rita Cantor (UCLA)

Ake Lu

- Chris Walsh (Boston Childrens')

Tim Yu

- Matt State (Yale/UCSF)

Stephan Sanders

Michael Murtha

Gulhan Erca

Abha Gupta

- Jay Tischfield and Andy Brooks (Rutgers)
- David Ledbetter (Geisinger )
- Christa Martin (Emory)

Daniel Moreno-De Luca

- Eric Fombonne (McGill)
- Cathy Lord (Cornell)
- Art Beaudet (Baylor)

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State lab
Stephan Sanders
Michael T. Murtha
Abha R. Gupta
John D. Murdoch
Melanie J. Raubeson
A. Jeremy Willsey
A. Gulhan Ercan-Sencicek
Nicholas M. DiLullo
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Gordon T. Ober
Nicole A. Teran
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Kyle A. Meyer

Richard P. Lifton
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Jason L. Stein

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SFARI: Simons Foundation Autism Research Initiative (www.sfari.org)