

# Overview of Genetics of Behavioral Disorders in Children: Autism Spectrum Disorders as a Case Study

Abha R. Gupta, MD, PhD

Developmental-Behavioral Pediatrics

Department of Pediatrics and Child Study Center



# DSM-5 criteria for Autism Spectrum Disorder

- A. Persistent deficits in social communication and social interaction across multiple contexts
- B. Restricted, repetitive patterns of behavior, interests, or activities
- C. Symptoms must be present in the early developmental period.
- D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- E. Not better explained by intellectual disability or global developmental delay

# Autism Spectrum Disorder (ASD)

- Prevalence:
  - 0.6/100 (Fombonne 2005)
  - 1.47/100 (CDC 2014)
- No known cure, limited treatment
- Pathophysiology largely unknown
- Strong evidence for genetics

# Evidence for genetic basis of ASD

Sibling recurrence risk: 18.7% (Ozonoff *et al* 2011)

Twin studies (Bailey *et al* 1995, Hallmayer *et al* 2011)

- Identical twins share an ASD diagnosis more frequently than fraternal twins
- Identical twins do not always share an ASD diagnosis

10% of cases also have a genetic syndrome

- Fragile X
- Tuberous sclerosis

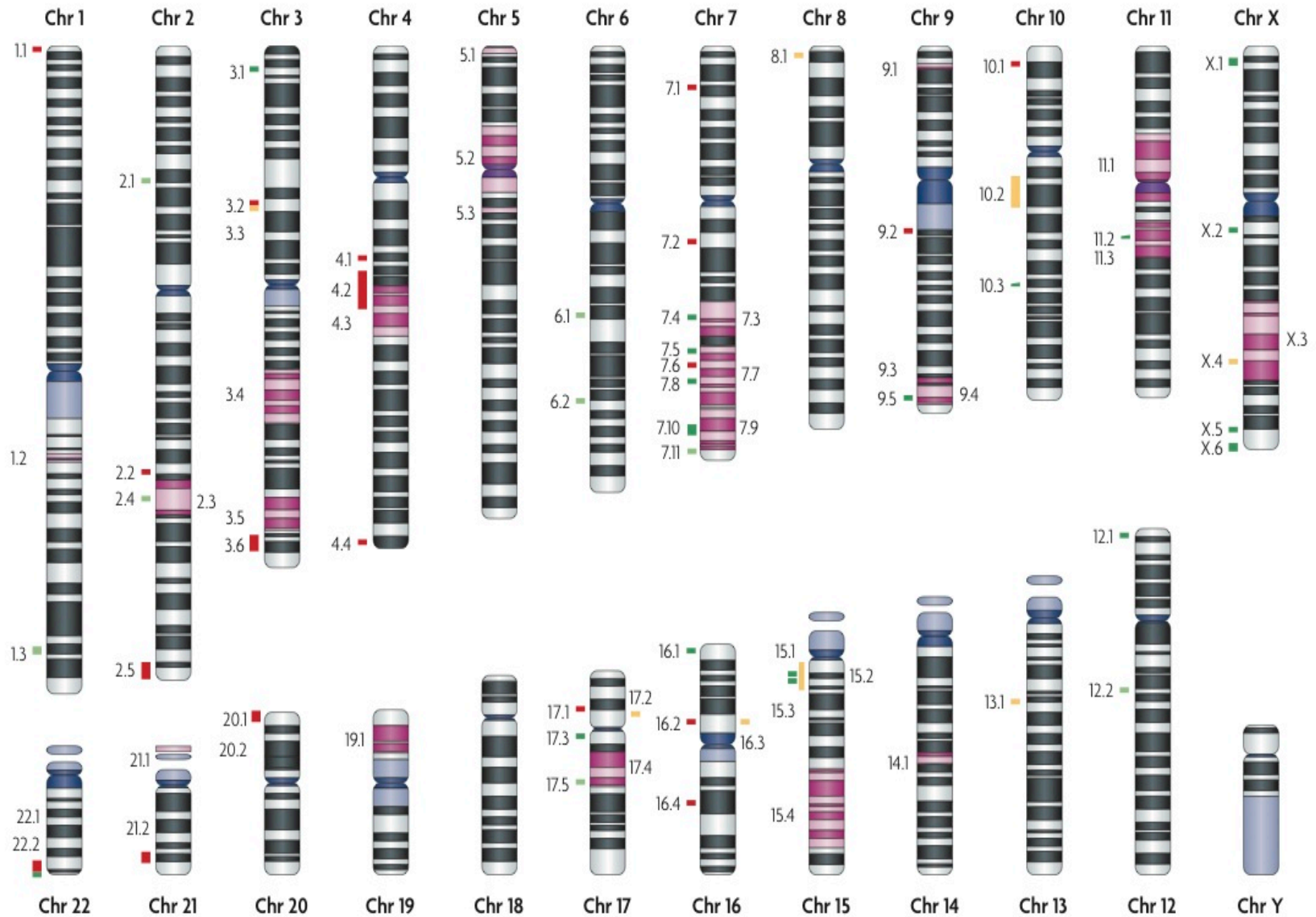
# Genetics of ASDs

ASDs are complex disorders with:

- Wide clinical variability
- Multiple causal factors
- A great deal of genetic heterogeneity

There is no one gene for autism, not even a few.  
There are likely hundreds.

# Chromosomal regions implicated in ASD

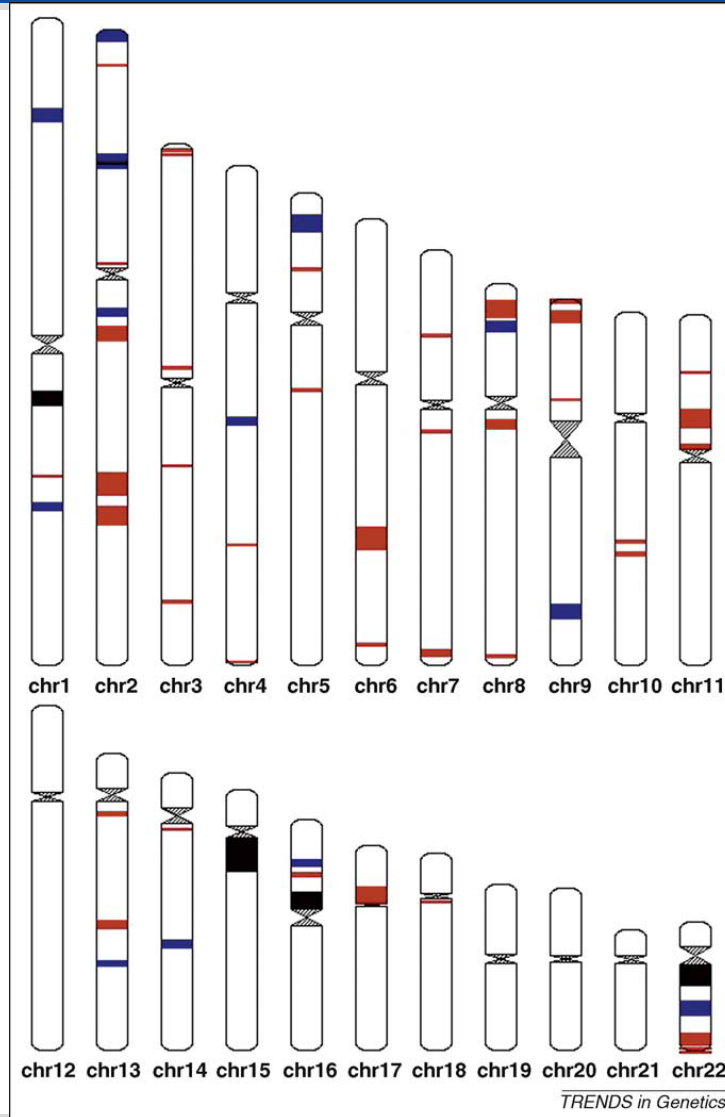


# ASD and schizophrenia

Red: ASD

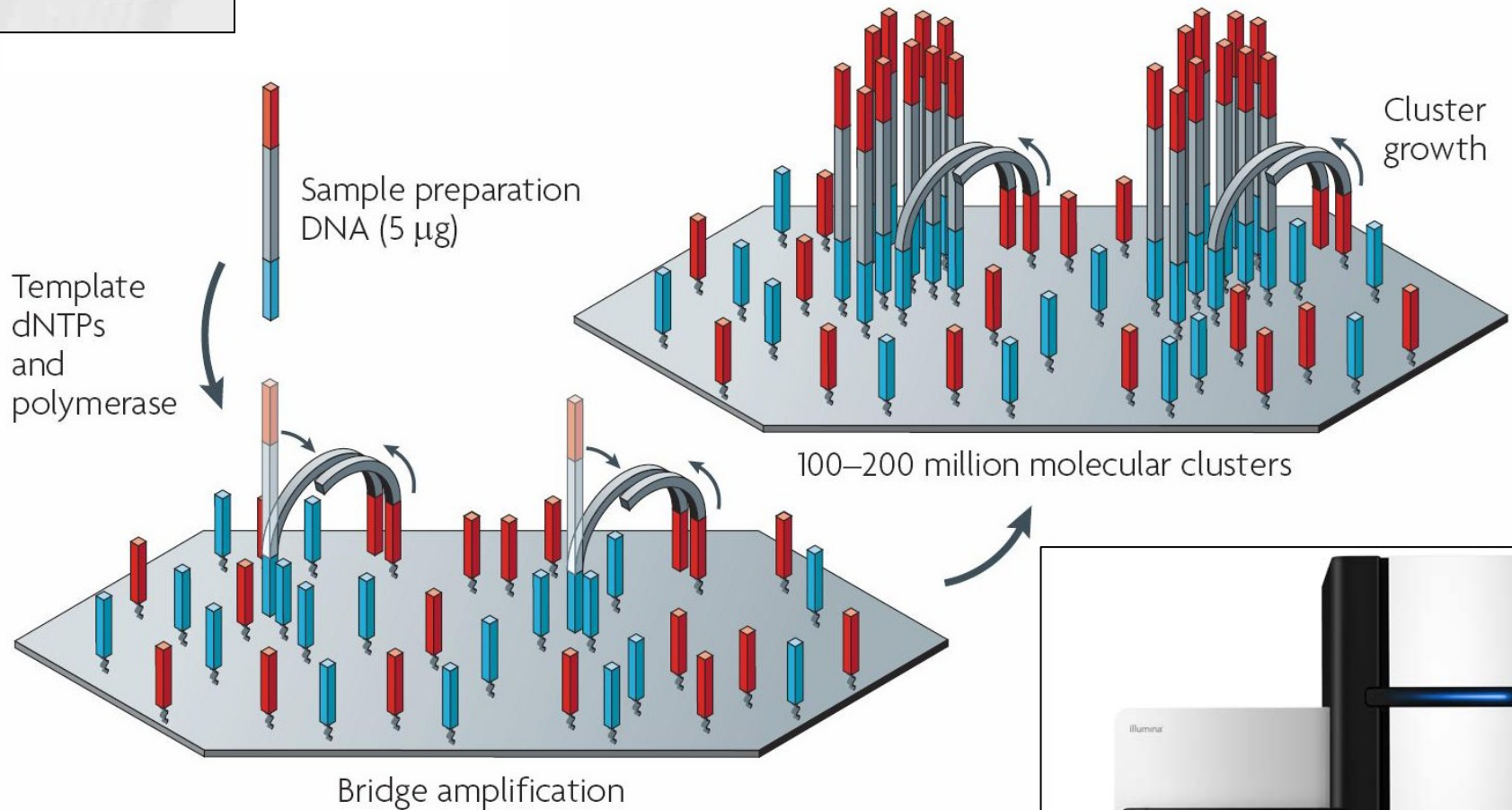
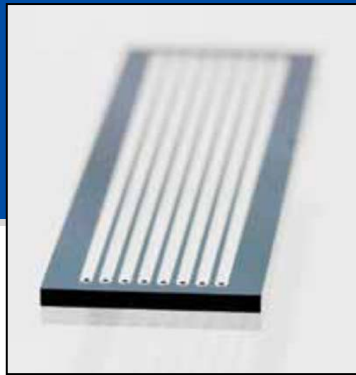
Blue: schizophrenia

Black: both



Merikangas *et al* 2009

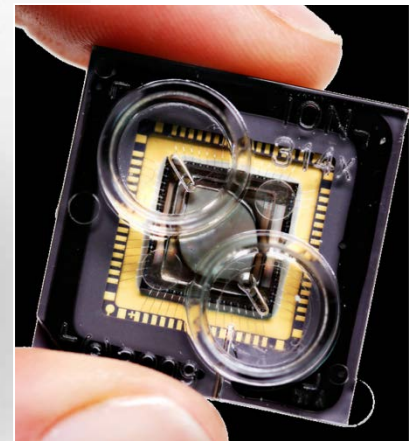
# Whole-exome sequencing



Metzker 2010

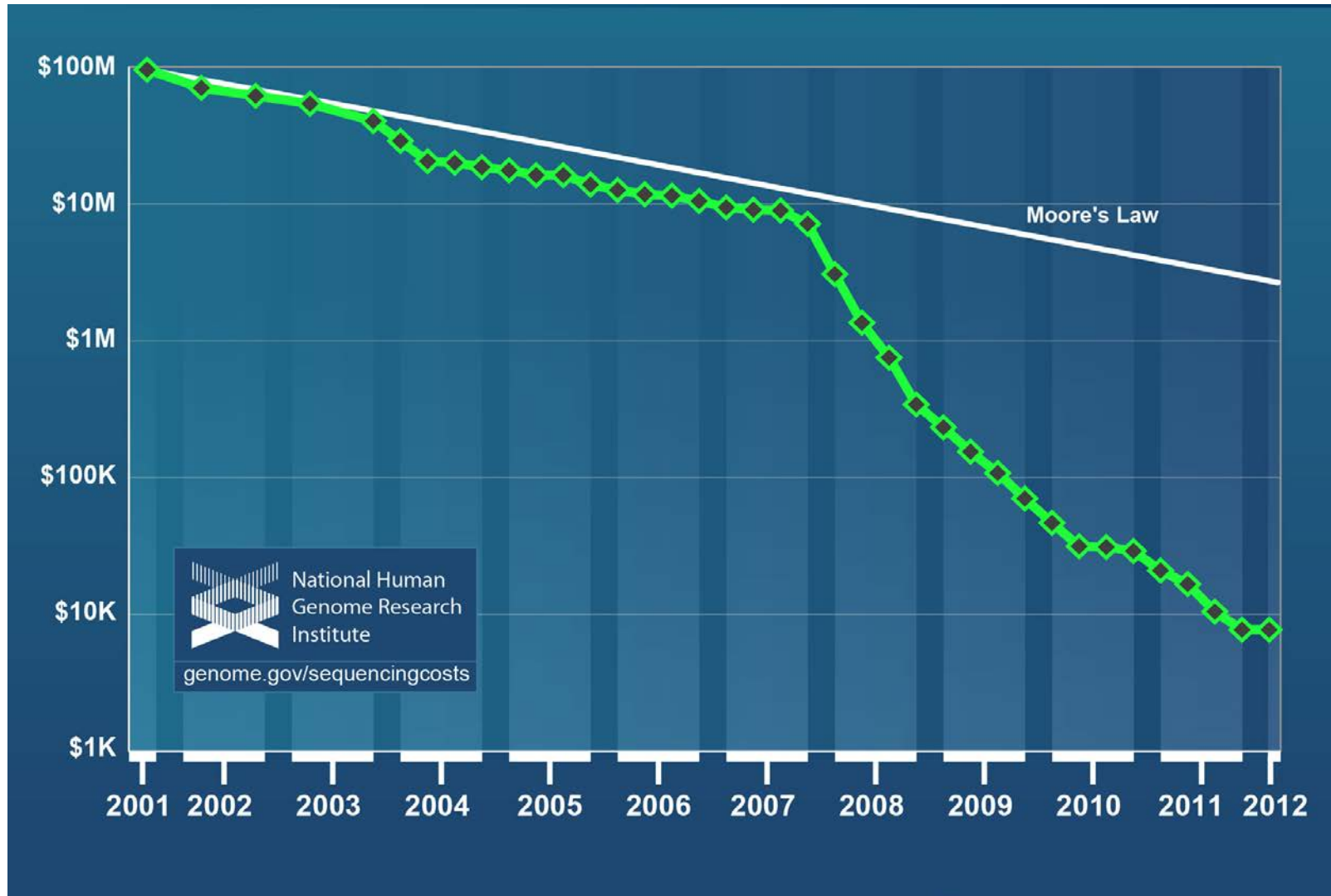


# Whole-genome sequencing

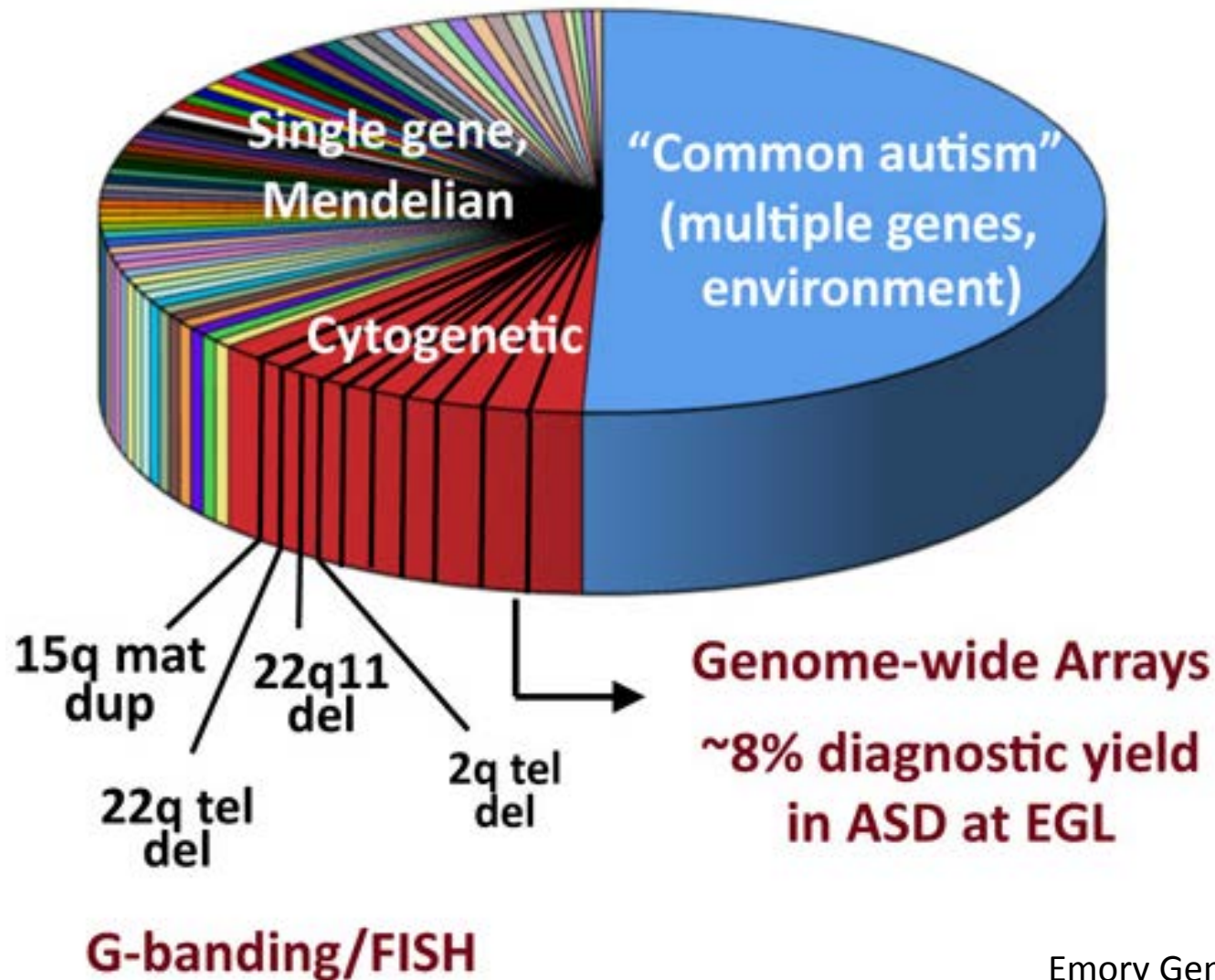


Ion Proton

# Cost per human genome

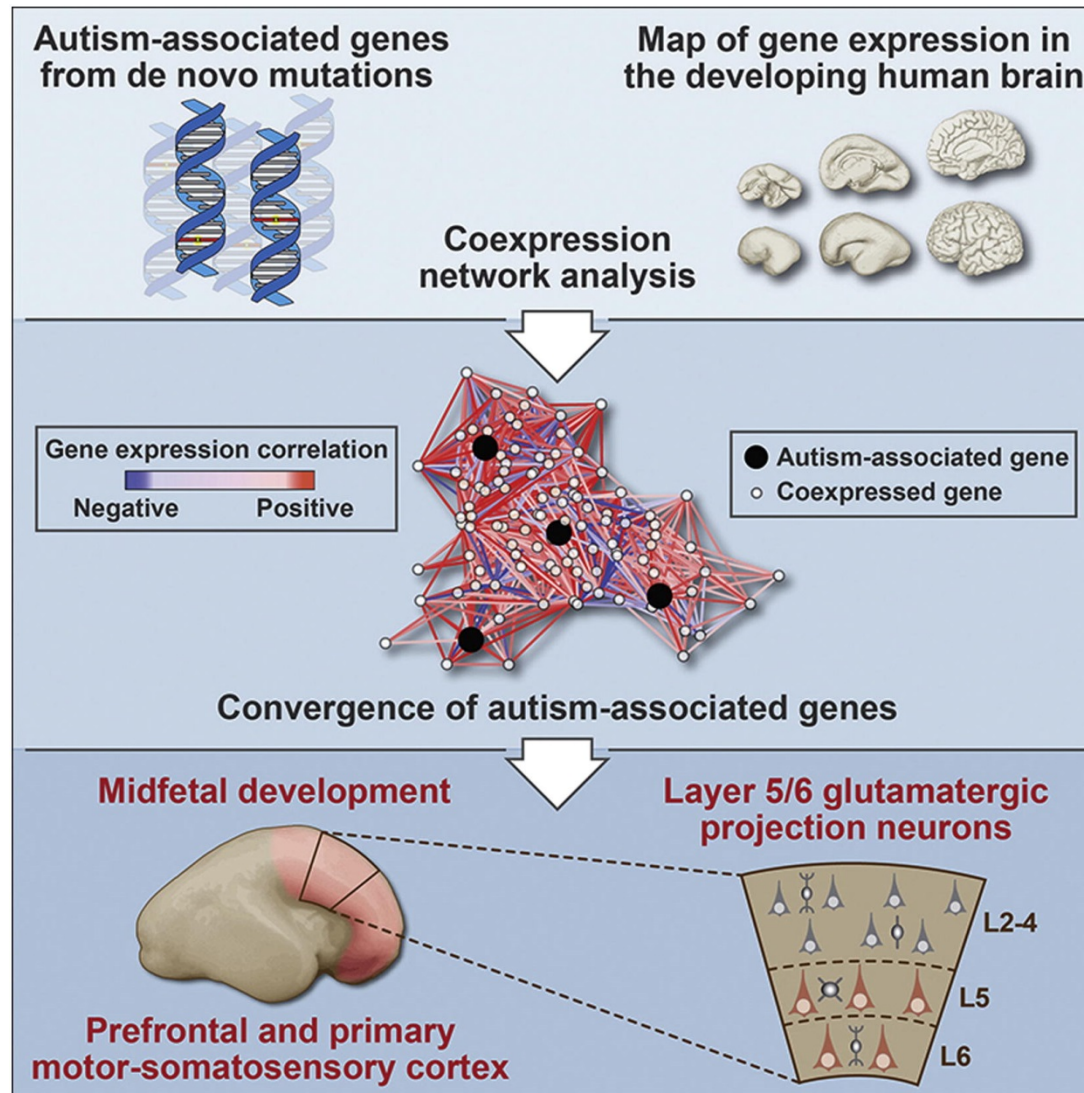


# Genetic architecture of ASD



Emory Genetics Laboratory

# Gene co-expression analysis



Willsey *et al* 2013



# Commercial autism gene panel

## Genes Included on the Panel

This panel sequences 62 individual autosomal and X-linked genes. These genes were selected to represent the most common single gene etiologies associated with a syndrome that includes autism as a significant clinical feature.

AP1S2	FOXP2	PHF6
ARX	GABRB3	PNKP
ATRX	HOXA1	PQBP1
AVPR1A	HPRT1	PTCHD1
BDNF	KDM5C	PTEN
BRAF	L1CAM	PTPN11
CACNA1C	MBD5	RAB39B
CASK	MECP2	RAI1
CDKL5	MED12	RELN
CHD7	MEF2C	SCN1A
CNTNAP2	MET	SHANK3
VPS13B	MID1	SLC2A1
CREBBP	NHS	SLC6A4
DHCR7	NIPBL	SLC9A6
DMD	NLGN3	SMC1A
EHMT1	NLGN4X	TCF4
FGD1	NRXN1	TSC1
FMR1	NSD1	TSC2
FOLR1	OPHN1	UBE3A
FOXG1	PAFAH1B1	ZEB2
FOXP1	PCDH19	



## CONTACT INFORMATION

JoAnne Babb, Molecular Diagnostic Sample Coordinator  
jbabb@ggc.org  
1-800-473-9411 (toll free) or 864-941-8147

Kellie King, MS, Laboratory Representative  
kking@ggc.org  
1-800-473-9411 (toll free) or 864-388-1055

Julie Jones, Ph.D., Director of Molecular Diagnostic Laboratory  
juliejones@ggc.org  
1-800-473-9411 (toll free) or 864-388-1049

*This brochure is published by Greenwood Genetic Center, a nonprofit institute organized to provide clinical genetic services and laboratory testing, to develop educational programs and materials, and to conduct research in the field of medical genetics.*

## Next Generation Sequencing

## Syndromic Autism 62-gene Panel



Information for Healthcare Providers

# Genes to pathophysiology to treatment

## Rett syndrome and *MECP2*

- Mutations in *MECP2* cause most cases of Rett syndrome.
- *MECP2* controls the expression of other genes.
- Patients show abnormal neurons but not neuronal death: Can viable but defective neurons be repaired?
- Mutant mice lacking *MECP2* develop neurological symptoms.
- Reactivation of *MECP2* in adult mutant mice reversed symptoms (Guy *et al* 2007).
- Absence of *MECP2* doesn't irreversibly damage neurons.

# Genes to pathophysiology to treatment

## Fragile X syndrome (FXS) and *FMR1*

- Loss of *FMR1* causes FXS.
- *FMR1* controls the expression of other genes.
- Pathophysiology involves hyperactivity of a glutamate receptor.
- Mutant mice lacking *FMR1* develop neurological symptoms.
- Reducing activity of the glutamate receptor rescued symptoms (Dolen *et al* 2007).
- R-baclofen corrects deficits (Henderson *et al* 2012).

# Genes to pathophysiology to treatment

## Tuberous sclerosis (TS) and *TSC*

- Mutations in *TSC1* and *TSC2* cause TS.
- Pathophysiology involves a signaling pathway in the hippocampus (mammalian target of rapamycin).
- Mutant mice lacking 1 copy of *TSC2* show cognitive deficits. Treatment of adult mutant mice with rapamycin improved behavioral deficits (Ehninger *et al* 2008).
- Mutant mice lacking 1 or 2 copies of *TSC1* in cerebellum show decreased neuronal activity, abnormal social interaction, and repetitive behavior. Treatment with rapamycin prevented deficits (Tsai *et al* 2012).



# Future directions

- Increase study populations by ten-fold
- Whole-genome sequencing: regulatory elements
- Pathway analysis
- Epigenetics
- Biomarkers: neuroimaging, eye tracking
- Genetic overlap between neuropsychiatric disorders
- Functional analysis of variants: bridging genetics and neuroscience
  - *In vitro* and *in vivo* studies
  - Postmortem brain tissue, induced pluripotent stem cells, animal systems

Thank you for your attention!