VANDERBILT KENNEDY CENTER
FOR RESEARCH ON HUMAN DEVELOPMENT

Recent Discoveries in Autism and other Neurodevelopmental Disorders

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Director, Vanderbilt Kennedy Center
Annette Schaffer Eskind Chair
Professor of Pharmacology

Translating Research to Practice – IDDRCs Set the Agenda

Nature (gene) ~~versus~~ Nurture (environment)

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Research Informs The Way That We Intervene

TIME

IN PARTNERSHIP WITH CNN

Science & Health

Does Watching TV Cause Autism?

Viewpoint: Childhood vaccines, toxins, genes and now television watching? The alarming rise in autism rates is one of the biggest mysteries of modern medicine, but it's irresponsible to blame one factor without hard scientific proof

By CLAUDIA WALLIS

Waldman, Nicholson, Adilov
Cornell and Indiana University-Purdue

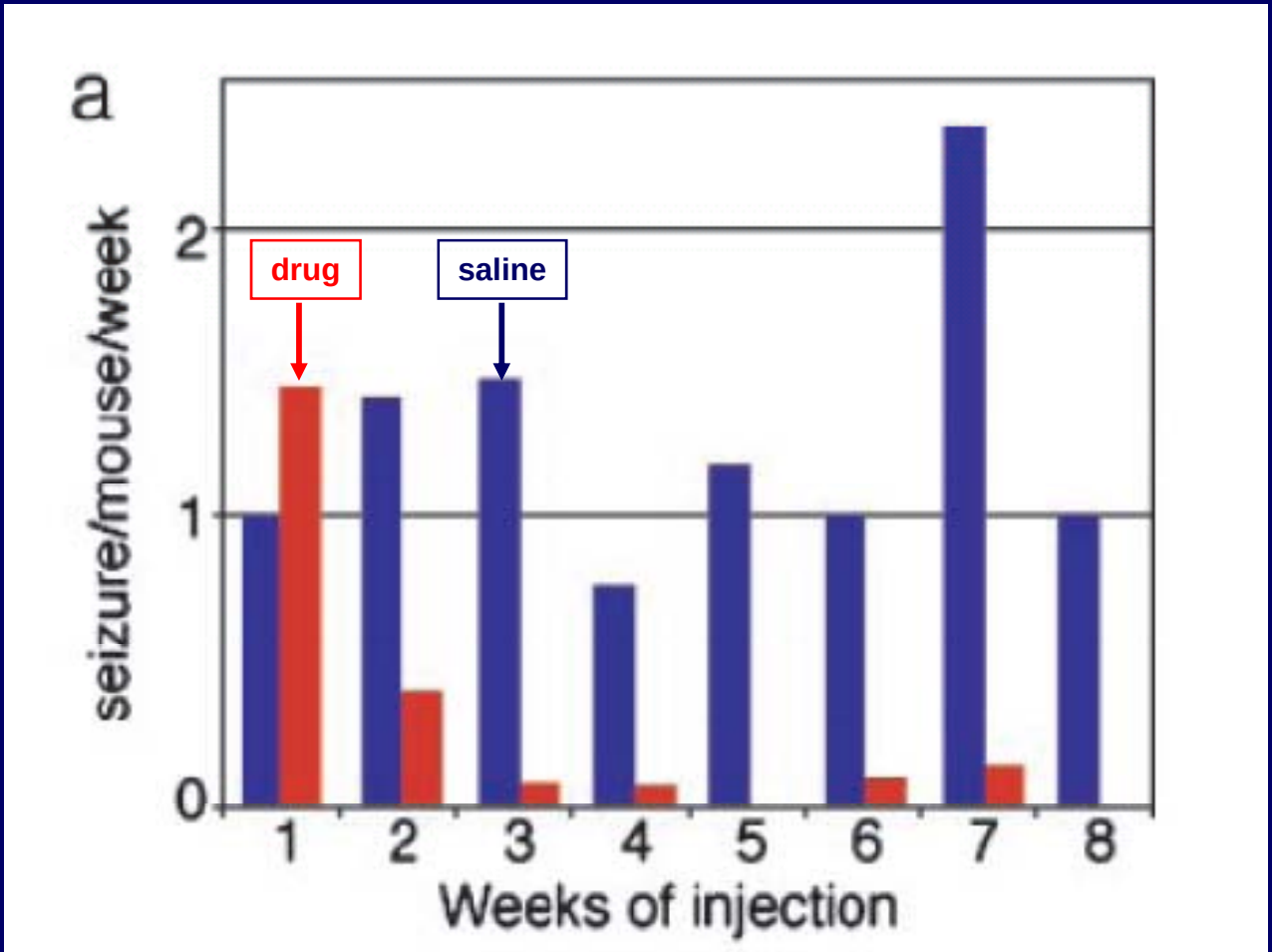
Genetic syndromes (typically rare)… discoveries that are not just academic exercises

- Fragile X (FRM1)***
- Rett Syndrome (MeCP2)+++++
- Angelman Syndrome (Ube3a)+++++
- Tuberous Sclerosis (TSC1,2)***
- Timothy Syndrome ($Ca_v1.2$)
- Smith-Lemli Opitz (Dhcr7)+++++
- Neurofibromatosis (NF1, NF2)***

Gene discoveries have led to strategies to prevent or even reverse clinical syndromes in animal models

……..and now clinical trials are underway

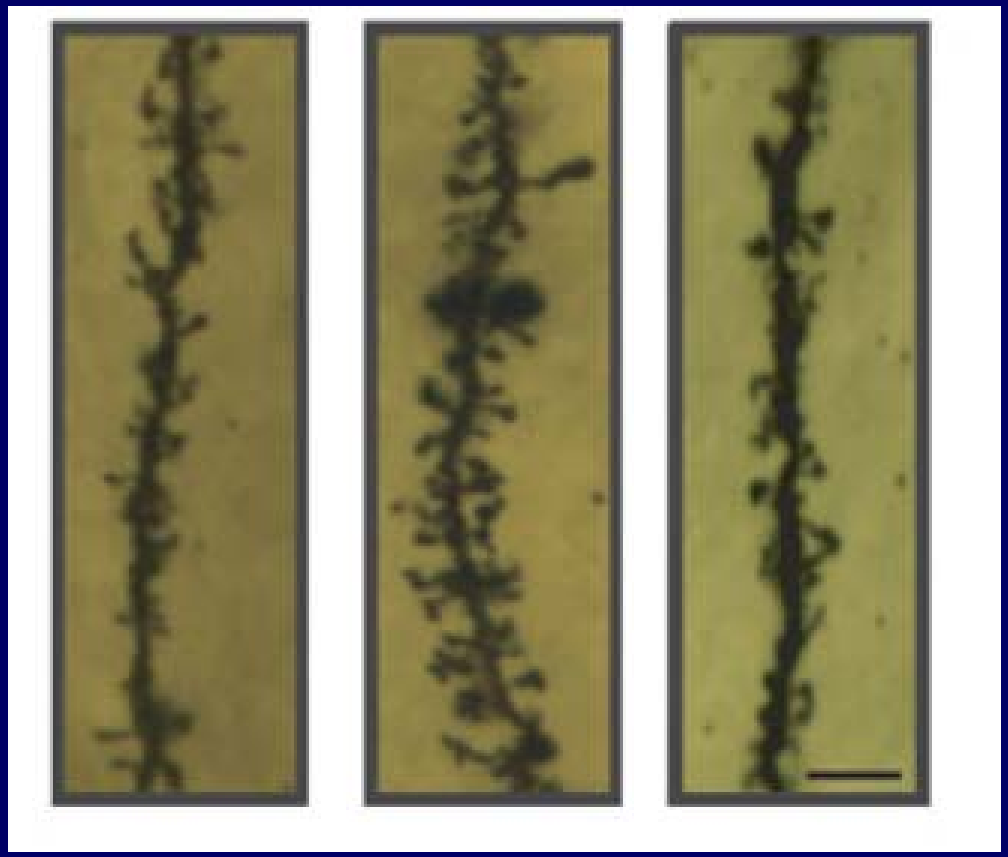
Drug eliminates seizures in Tuberous Sclerosis Model



Kwon et al 2003 PNAS

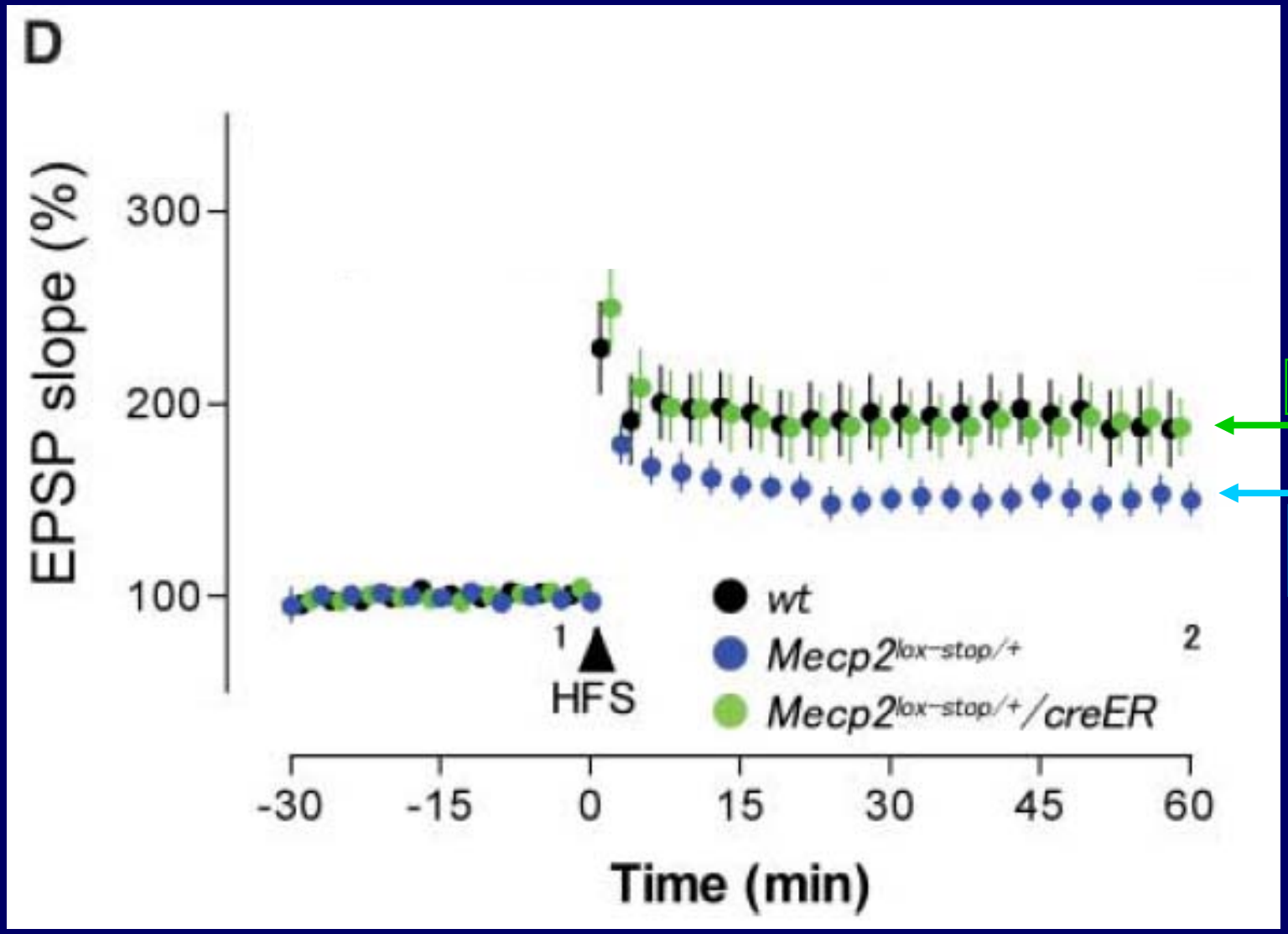
Drug Corrects Brain Architecture Due to Fragile X Mutation

Typical Fragile X Rescue



Dolen et al 2005, Neuron

Reversing Cognitive Impairment in Adult Mice with Rett Syndrome

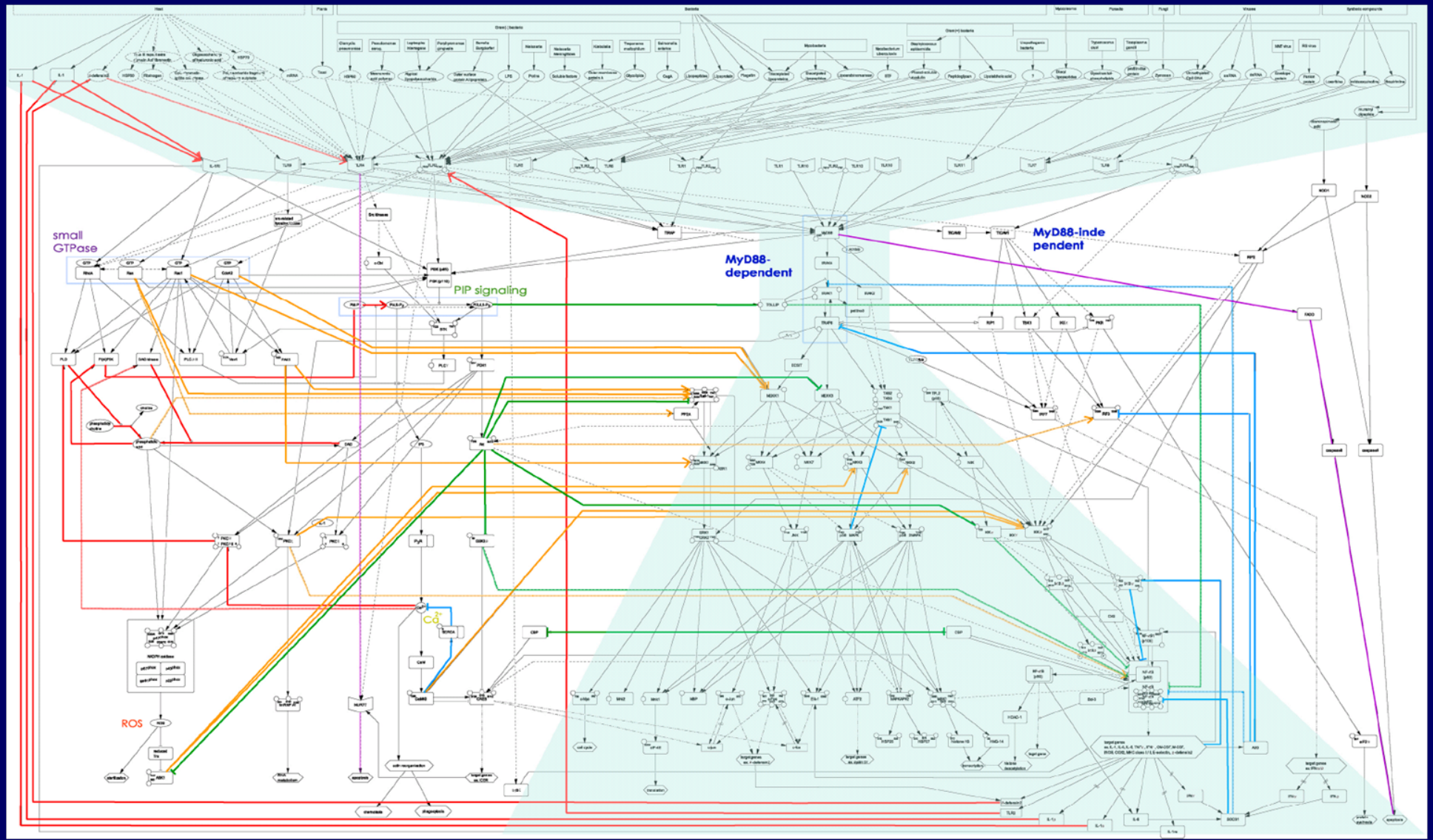


learning

deficit in learning

Guy et al, 2007, Science

Discoveries about rare disorders have led the way to a new understanding of brain and molecular architecture



Look familiar?

What is the hope for understanding the causes and coming up with the best treatments for more common disorders?

The Autisms are Common (1 in 90 boys; 1 in 150 overall)…

…….and complex

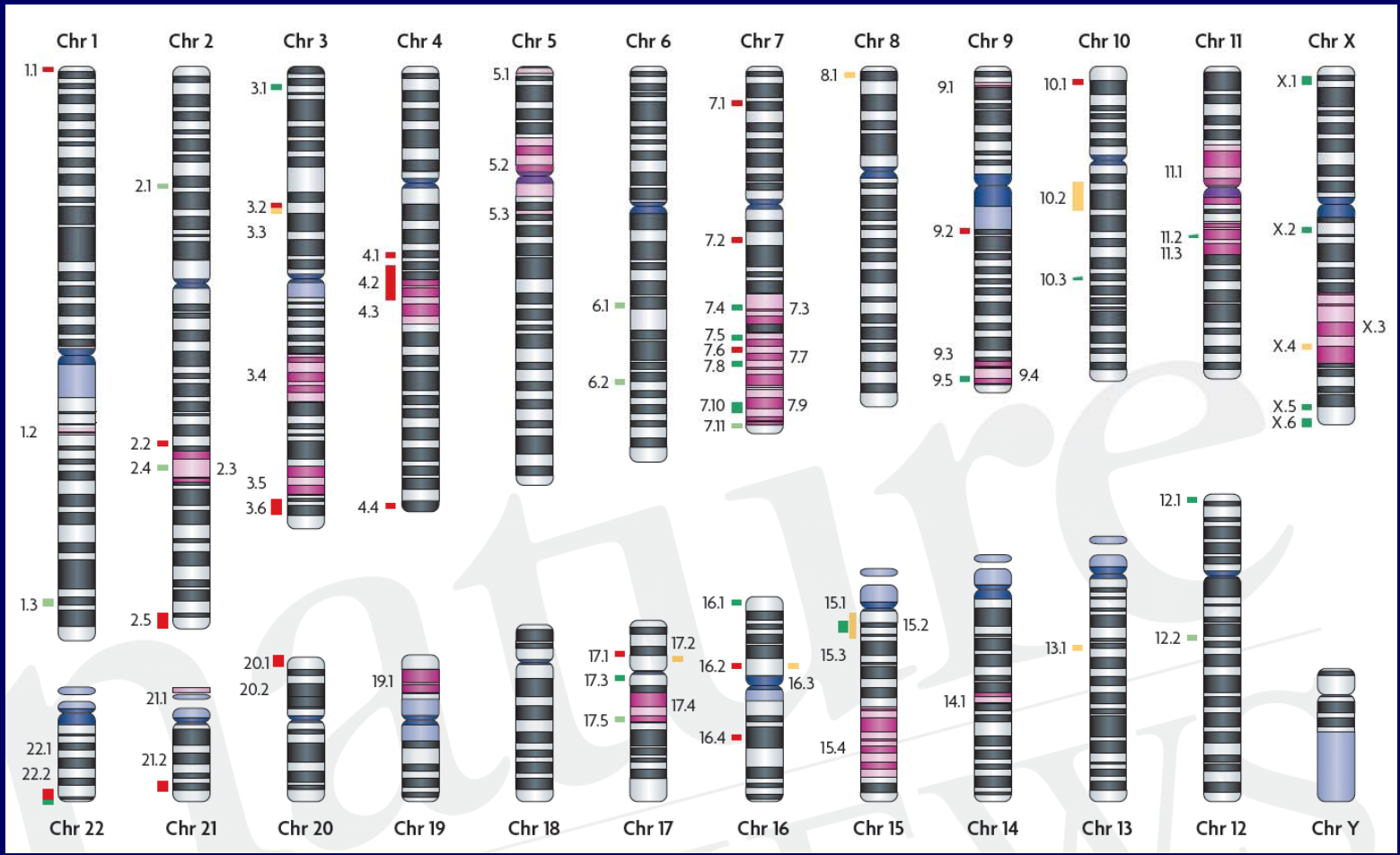
- Heterogeneity in core symptoms

- Major differences in developmental course

- Variation in co-occurring conditions
  (e.g. anxiety, thought disorder, aggression, self-injury, epilepsy, sleep, gastro-intestinal, immune)

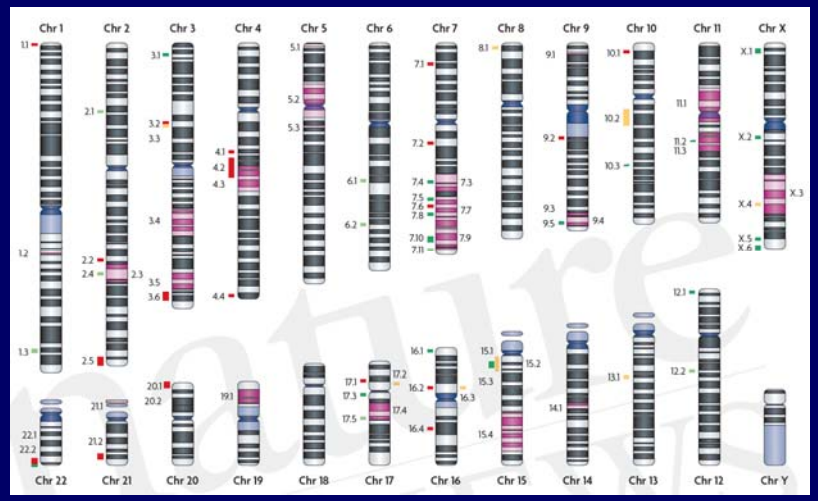
- Wide range in responsiveness to treatments

Risk for the autisms may lie with dozens of genes <u>and</u> environmental factors



Abrahams and Geschwin, 2008 Nature Review Genetics

Discoveries Driven by Genome Consortia of Dozens of Collaborative Scientists, Many at <u>IDDRCs</u>



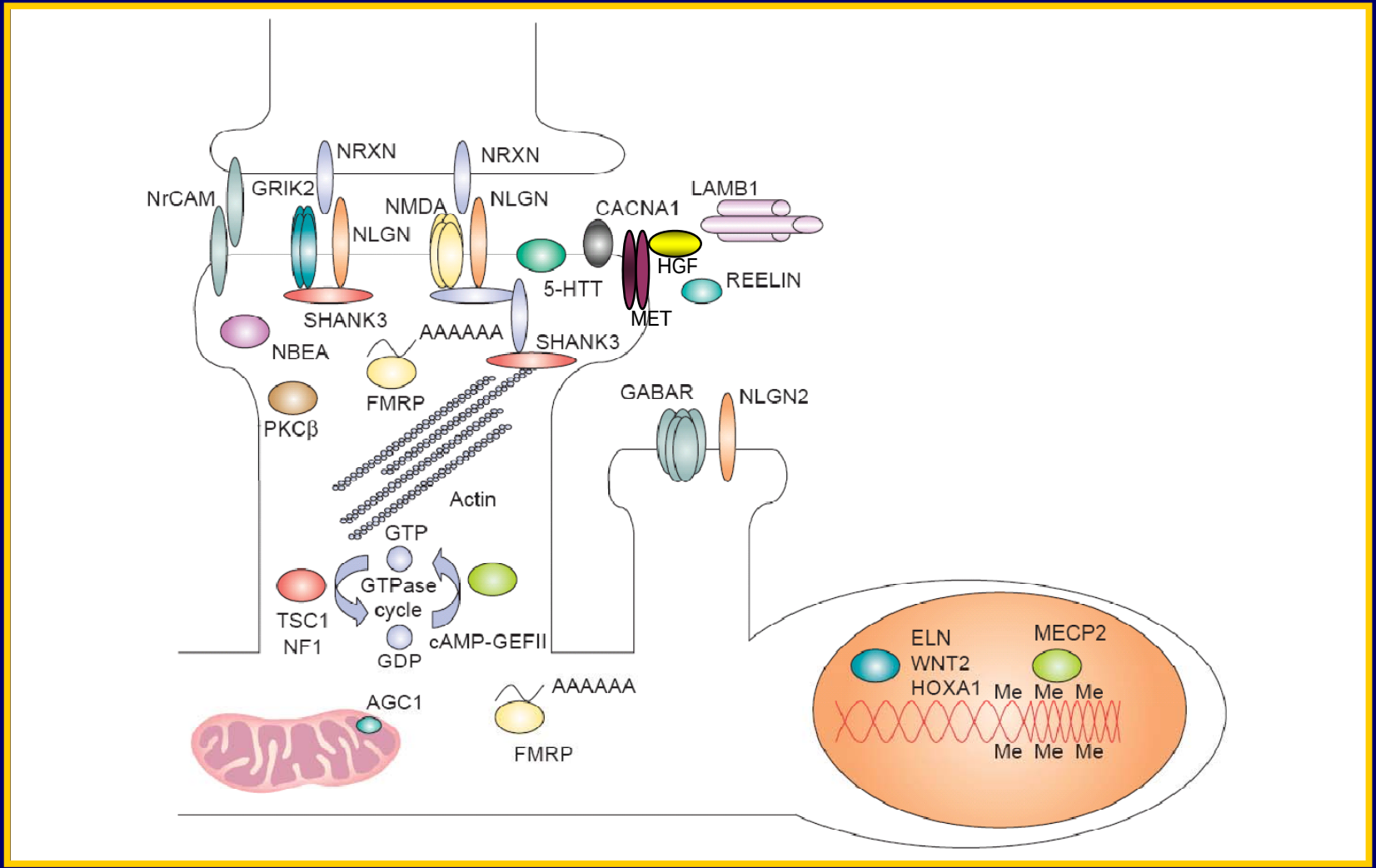
AGRE

Simons Simplex

AGP

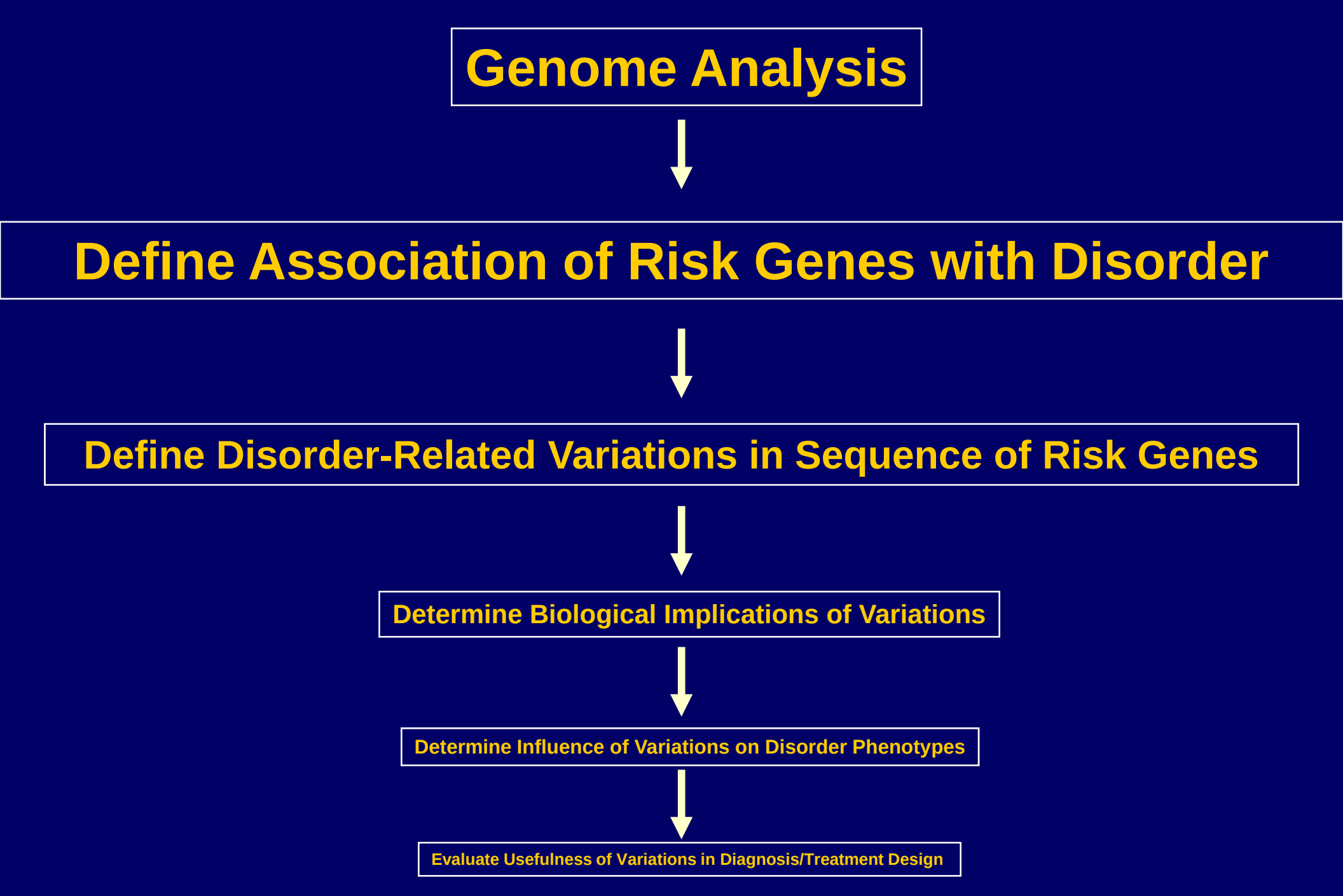
Boston Autism Consortium

Genetic Risk Involves Networks that Control Architecture and Communication – the Synapse



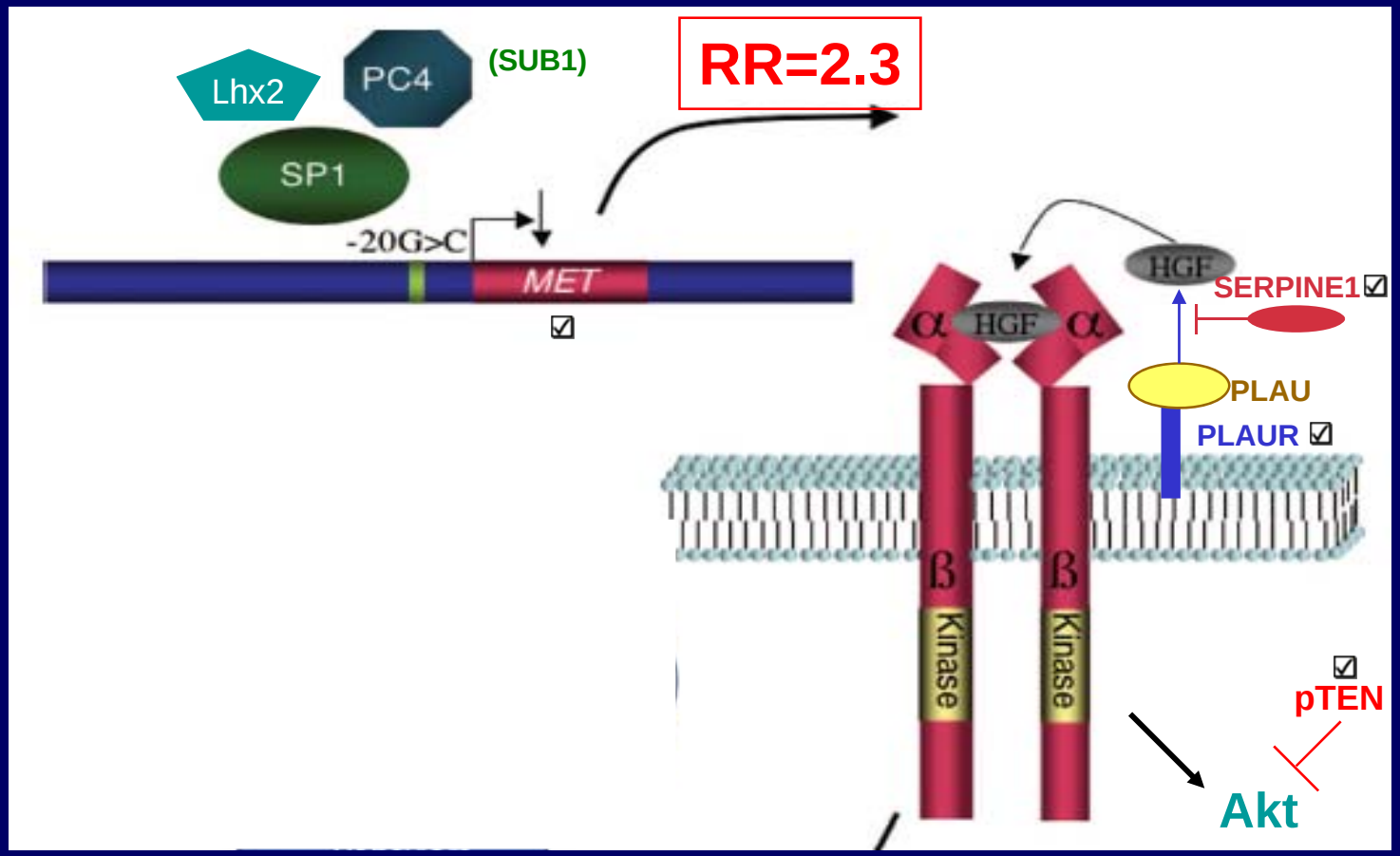
Contributions to Atypical Brain Architecture and Chemistry in the autisms

- How much of the risk is due to direct impact of gene mutations on brain development?
- How much of the risk is due to direct impact of gene mutations on parallel developing organ systems (e.g. brain & gut/immune)?
- How much of the risk is due to genetically established sensitivities to environmental factors?
- How much of the <u>heterogeneity</u> of clinical symptoms of children with ASD are influenced through an interplay of genetic and environmental factors?


Genome Analysis
Define Association of Risk Genes with Disorder
Define Disorder-Related Variations in Sequence of Risk Genes
Determine Biological Implications of Variations
Determine Influence of Variations on Disorder Phenotypes
Evaluate Usefulness of Variations in Diagnosis/Treatment Design

IDDRC approach - Use a basic understanding of development/clinical medicine to design studies of integrative ASD systems genetics

Genetic Findings in the Met/PI3K Signaling Pathway



Adapted from State. 2006. *PNAS*

IDDRC Leading the Way:
Cozzarrelli Prize for Outstanding Biomedical Science Paper

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February 15, 2007

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Genetic studies can help us identify unique types of autisms for better diagnosis and treatments.

– a side to the autisms about which many in health care, policy and the public do not know

autism © 2003
SAGE Publications
and The National
Autistic Society
Vol 7(2) 165–171; 032484
1362-3613(200306)7:2

Prevalence of chronic gastrointestinal symptoms in children with autism and autistic spectrum disorders

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Cincinnati Children's Hospital, USA

PEDIATRICS

Constipation With Acquired Megarectum in Children With Autism

Nadeem Afzal, Simon Murch, Kumran Thirrupathy, Leslie Berger, Andrew Fagbemi and Robert Heuschkel

Pediatrics 2003;112;939-942

0196-206X/06/2702-0128
DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS
Vol. 27, No. 2, April 2006
Printed in U.S.A.

Frequency of Gastrointestinal Symptoms in Children with Autistic Spectrum Disorders and Association with Family History of Autoimmune Disease

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ORIGINAL ARTICLES
THE JOURNAL OF PEDIATRICS
NOVEMBER 1999

Gastrointestinal abnormalities in children with autistic disorder

Karoly Horvath, MD, PhD, John C. Papadimitriou, MD, PhD, Anna Rabsztyn, Cinthia Drachenberg, MD, and J. Tyson Tildon, PhD

BMJ

Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database

Corri Black, James A Kaye and Hershel Jick

BMJ 2002;325;419-421
doi:10.1136/bmj.325.7361.419

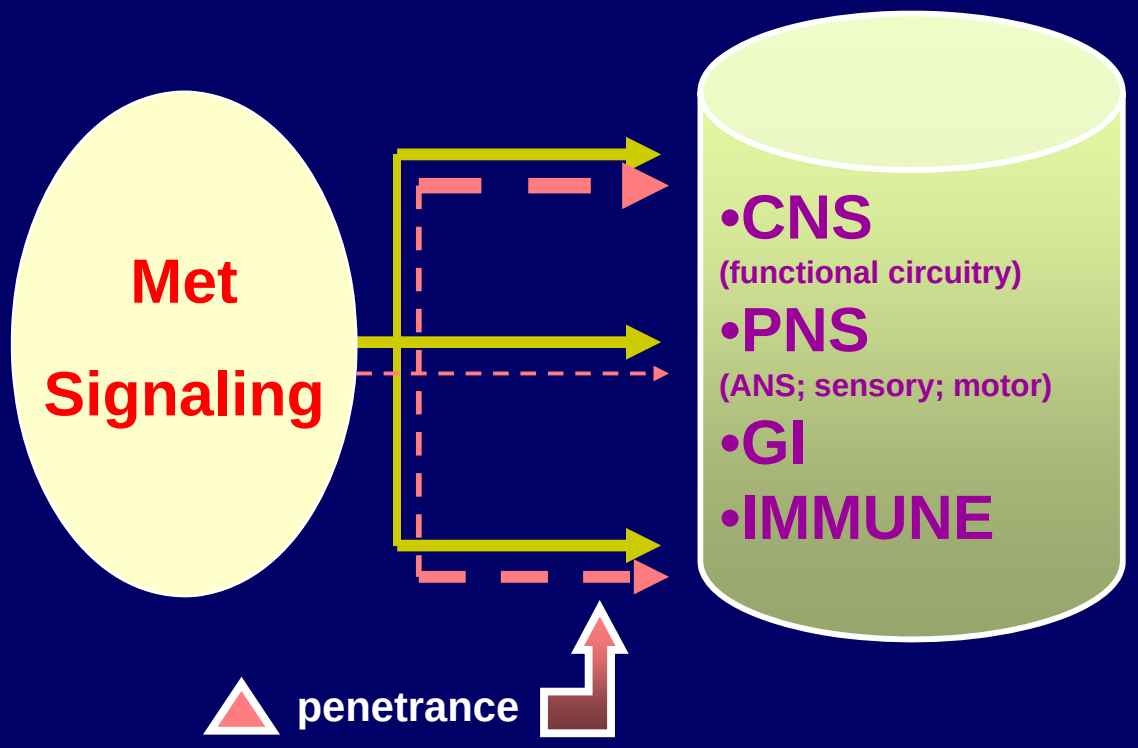
Journal of Autism and Developmental Disorders, Vol. 35, No. 6, December 2005 (© 2005)
DOI 10.1007/s10803-005-0019-4

Gastrointestinal Factors in Autistic Disorder: A Critical Review

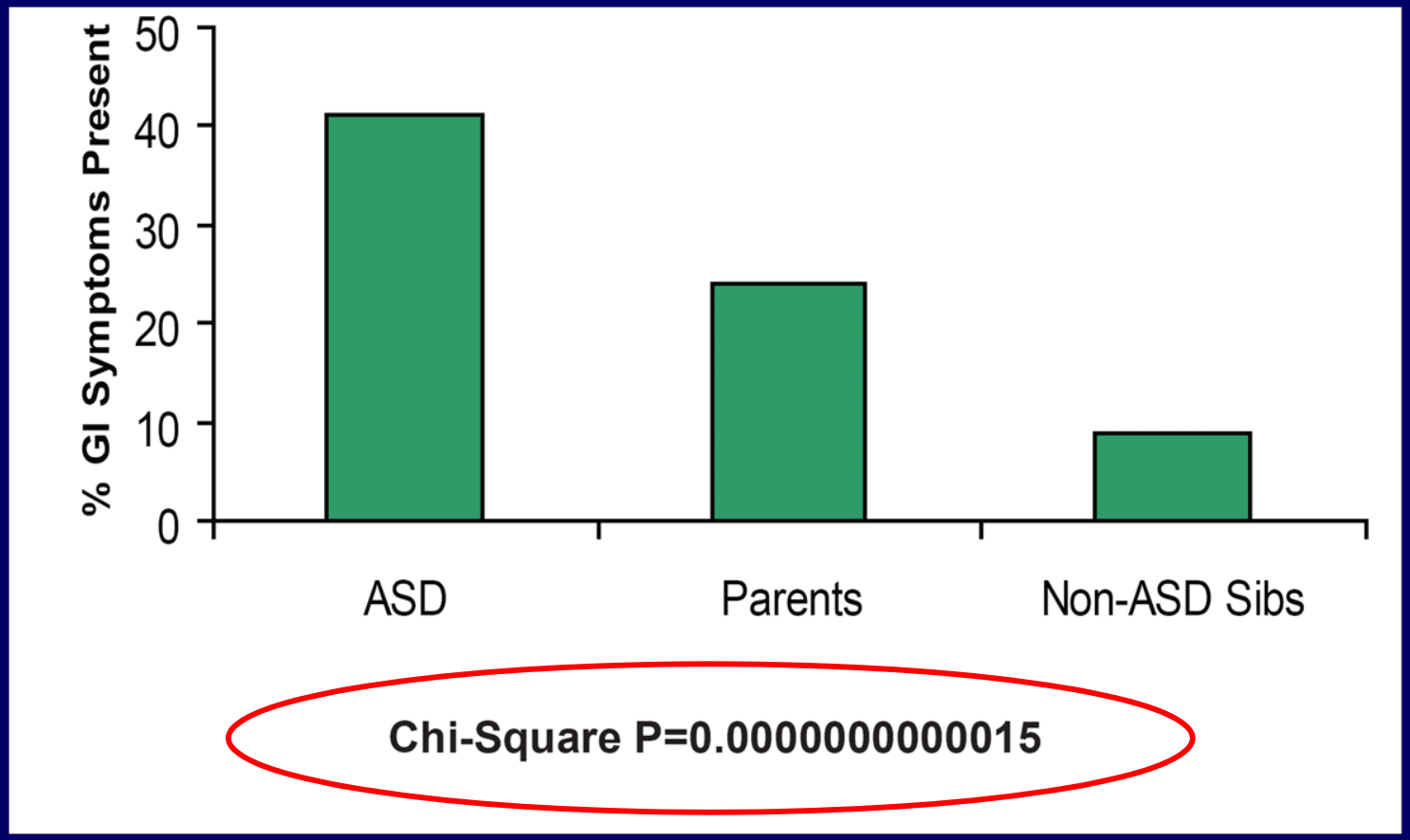
Craig A. Erickson,[1–3] Kimberly A. Stigler,[1,3] Mark R. Corkins,[2,3] David J. Posey,[1,3] Joseph F. Fitzgerald,[2,3] and Christopher J. McDougle[1–4]

Tahara et al J Pharm Exp Ther 307 (2003)

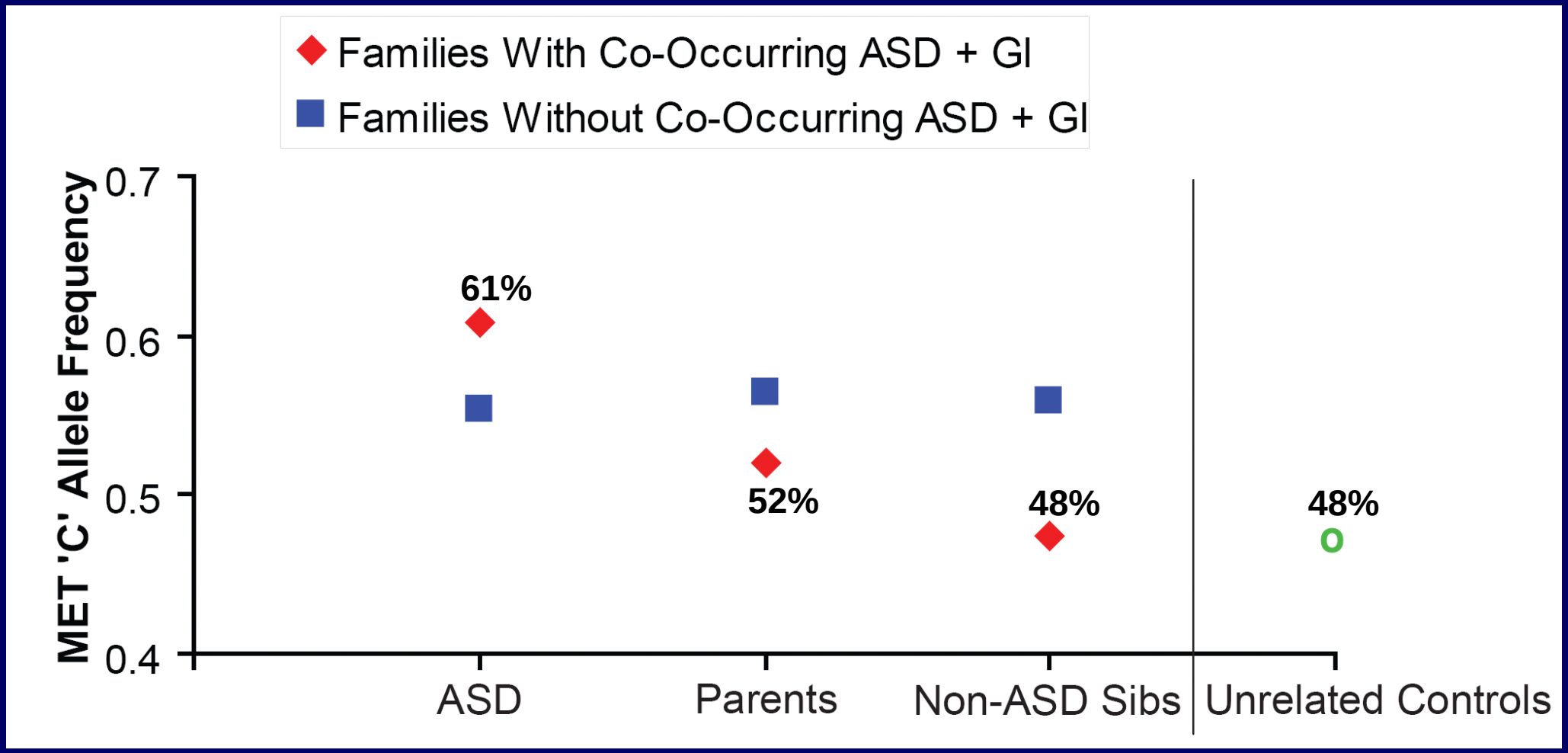
Gene Networks Are Functionally Diverse - Parallel Developmental Influences



Presence of GI symptoms in genetic sample of 214 families



MET risk 'C' allele is over-represented in co-occurring ASD + GI



Why does this discovery matter?

Billions of dollars annually that are currently being spent by families can be channeled to treatments that make sense based on the science.

- How much of the risk is due to direct impact of mutations on brain development?

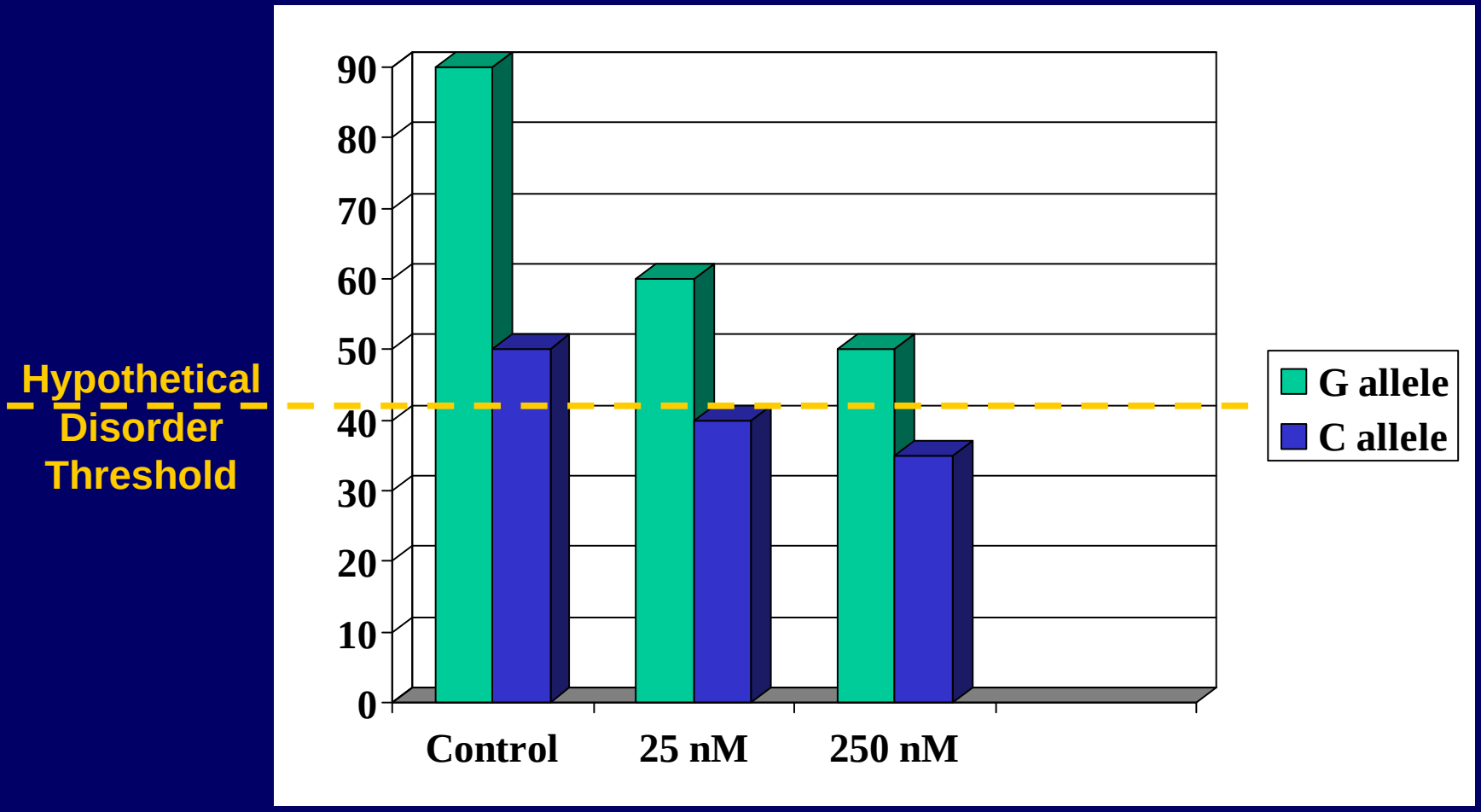
- How much of the risk is due to direct impact of mutations on peripheral functions that influence brain development?

- **How much of the risk is due to genetically established sensitivities to environmental perturbations?**

- How much of the phenotypic heterogeneity of individuals with ASD are influenced combinatorially through genetic and/or environmental factors?

Genetic Vulnerability & Environmental Risk

Benzo-a-pyrene Impact on *MET* Gene Transcription



[BaP]

Campbell, Hood and Levitt, unpublished

NY Times - CLAUDIA DREIFUS - A Conversation With Arno Motulsky Father of Pharmacogenomics
APR. 29, 2008
A Genetics Pioneer Sees a Bright Future, Cautiously

"Q. WHAT'S THE POINT OF KNOWING THIS?
A. It's exciting to learn that because of heredity, different people can see the same thing differently. I think this may prove useful in studying more complex brain functions. If this were 20 years ago, I'd focus on neurogenetics. What's going on in the brain, that's the last frontier."

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We are moving from *'what it isn't'* to *'what it is'* !!!!