

Genetics of Childhood Neuropsychiatric Disorders : Hope for a New Understanding

Dan Geschwind MD PhD

Professor of Neurology, Psychiatry and
Human Genetics

Director, Program in Neurogenetics

Director of UCLA CART UCLA School of Medicine

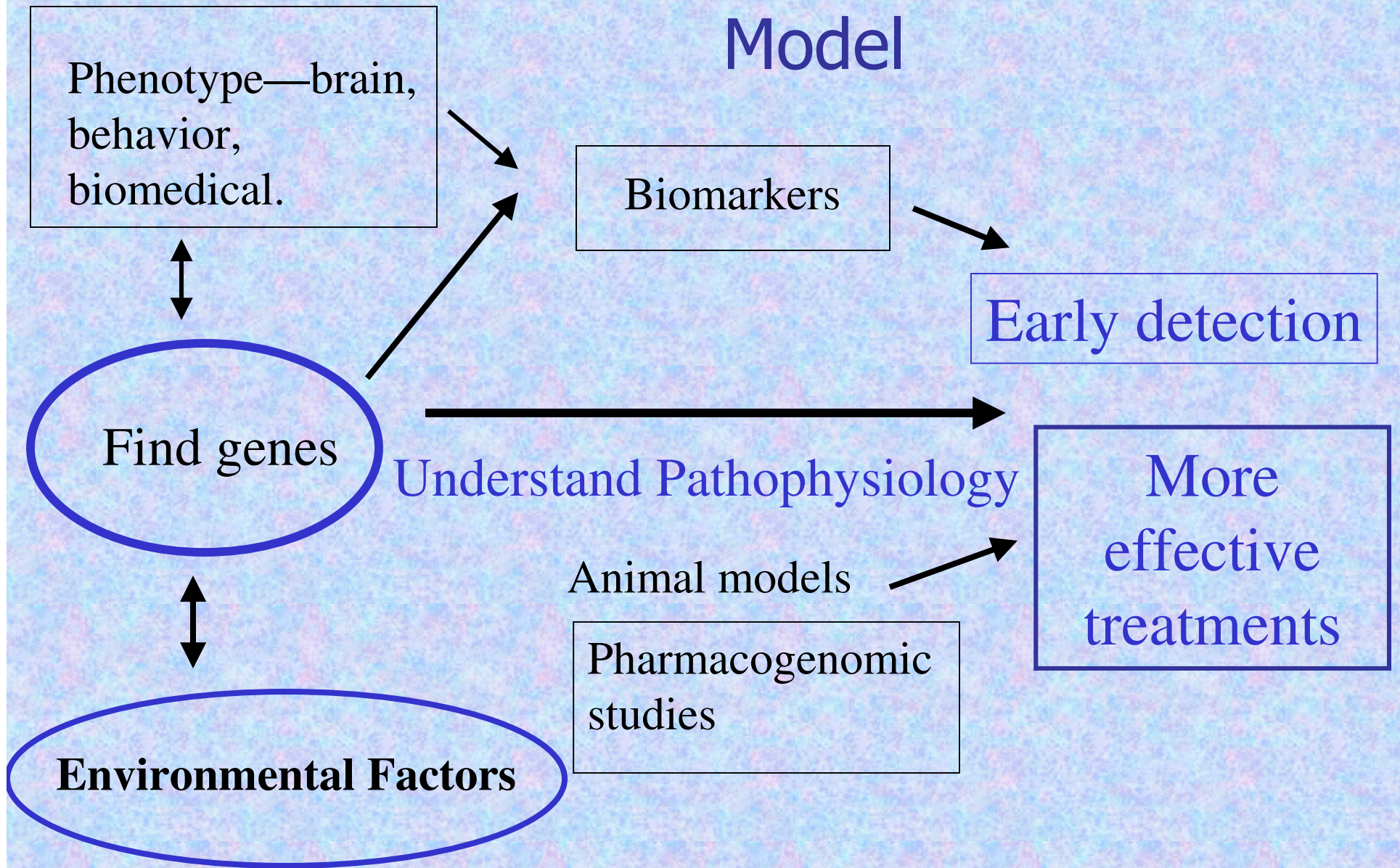




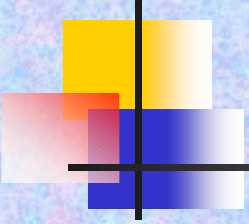
How does genetics help us?

- n Genetics is a set of powerful methods whose goal is to further our biological understanding of and treatment of disease.
- n We can use these methods to further our understanding of any disease that has a heritable component.
- n Genetics permits causality assessment in humans
- n The use of genetics does not undermine potential environmental contributions. Rather, it enhances our ability to detect such effects.

Genetic Research Model



Evidence for high genetic risk for Idiopathic autism

- 
- n MZ twins (80%) are much more likely to share autism than DZ twins (25%).
 - n On average, siblings of autistic children have a 10% chance of having autistic disorder, or a 25 to 50-fold risk to develop autism compared with the general population.
 - n The SRR is larger than OCD, schizophrenia, dyslexia ADHD, and other "common" diseases with significant genetic components, but overall heritability estimates based on twin data are not that different.
 - n Heritability = 0.7-0.9
 - n And, the DZ/sibling ratio suggests shared environment

Implications of Knowing Genetic Causes of Disease

- n Knowing the mutational basis of the disorder has significant implications for treatment and recurrence risk.
 - n *de novo* mutations vs. heritable (environment?)
 - n Mendelian vs. non-mendelian
- n Knowing the mutational basis of the disorder has potentially significant implications for prevention.
 - n Gene - environment interactions.
 - n Mechanism of mutation may be preventable (paternal age).

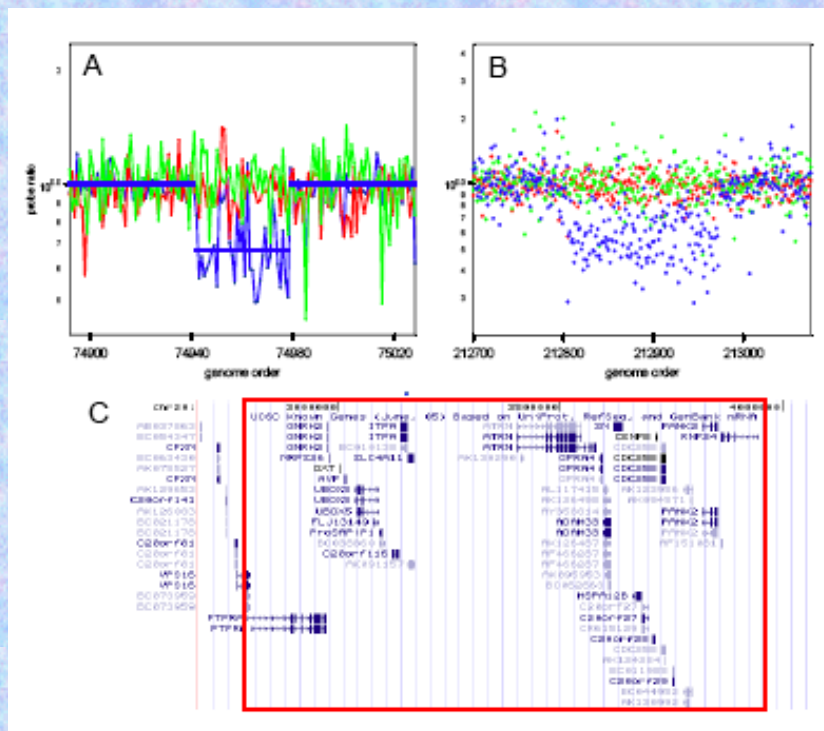
www.sciencemag.org SCIENCE

Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat,^{1*} B. Lakshmi,¹ Dheeraj Malhotra,¹ Christa Lese-Martin,² Jennifer Troge,¹ Tom Walsh,³ Boris Yamrom,¹ Seungtai Yoon,¹ Alex Krasnitz,¹ Jude Kendall,¹ Anthony Leotta,¹ Deepa Pai,¹ Ray Zhang,¹ Yoon-Ha Lee,¹ James Hicks,¹ Sarah J Spence,⁴ Annette T. Lee,⁵ Kaija Puura,⁶ Terho Lehtimäki,⁷ David Ledbetter,² Peter K. Gregersen,⁵ Joel Bregman,⁸ James S. Sutcliffe,⁹ Vaidehi Jobanputra,¹⁰ Wendy Chung,¹⁰ Dorothy Warburton,¹⁰ Mary-Claire King,³ David Skuse,¹¹ Daniel H. Geschwind,¹² T. Conrad Gilliam,¹³ Kenny Ye,¹⁴ Michael Wigler^{1*}

(10–14), including patients with syndromic forms of autism (15). Yet, the association of spontaneous CNVs in idiopathic autism has not been systematically investigated. Thus, a large-scale study of genome copy number variation in ASD was needed. We have performed high-resolution genomic microarray analysis on a sample of 264 families to determine the rate of de novo copy number mutation in unaffected and affected children.

Our study focused on a sample of 264 families, including 118 “simplex” families containing a single child with autism, 47 “multiplex” families with multiple affected siblings, and 99 control families with no diagnoses of autism.



DeNovo CNV found in:

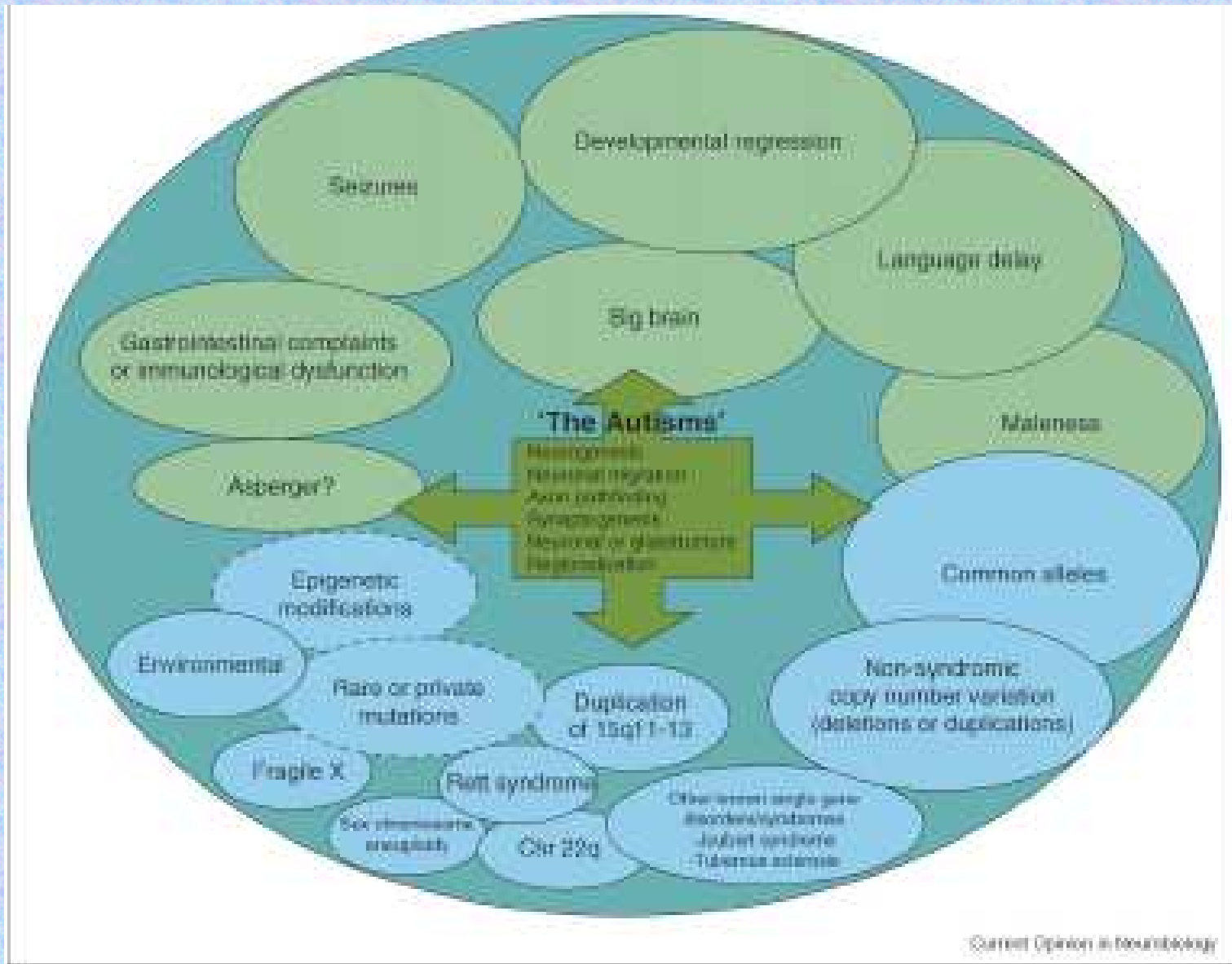
- n 3% of familial cases and
- n 10% of simplex cases
- n 1% of controls (all dups)

The genetics of autism: known syndromes

- n 5-10% have chromosomal abnormalities
 - n Fragile X (1%) and Rett are rarer?
 - n Sex chromosome (1%)
- n Other genetic syndromes and copy number variants (TS, Joubert):
 - n most common is 15q duplication (1-2%)
 - n 16p dup/del (1-2%)
- n Majority of cases will be due to complex genetics
 - n models estimate 3-15 genes



The Autisms



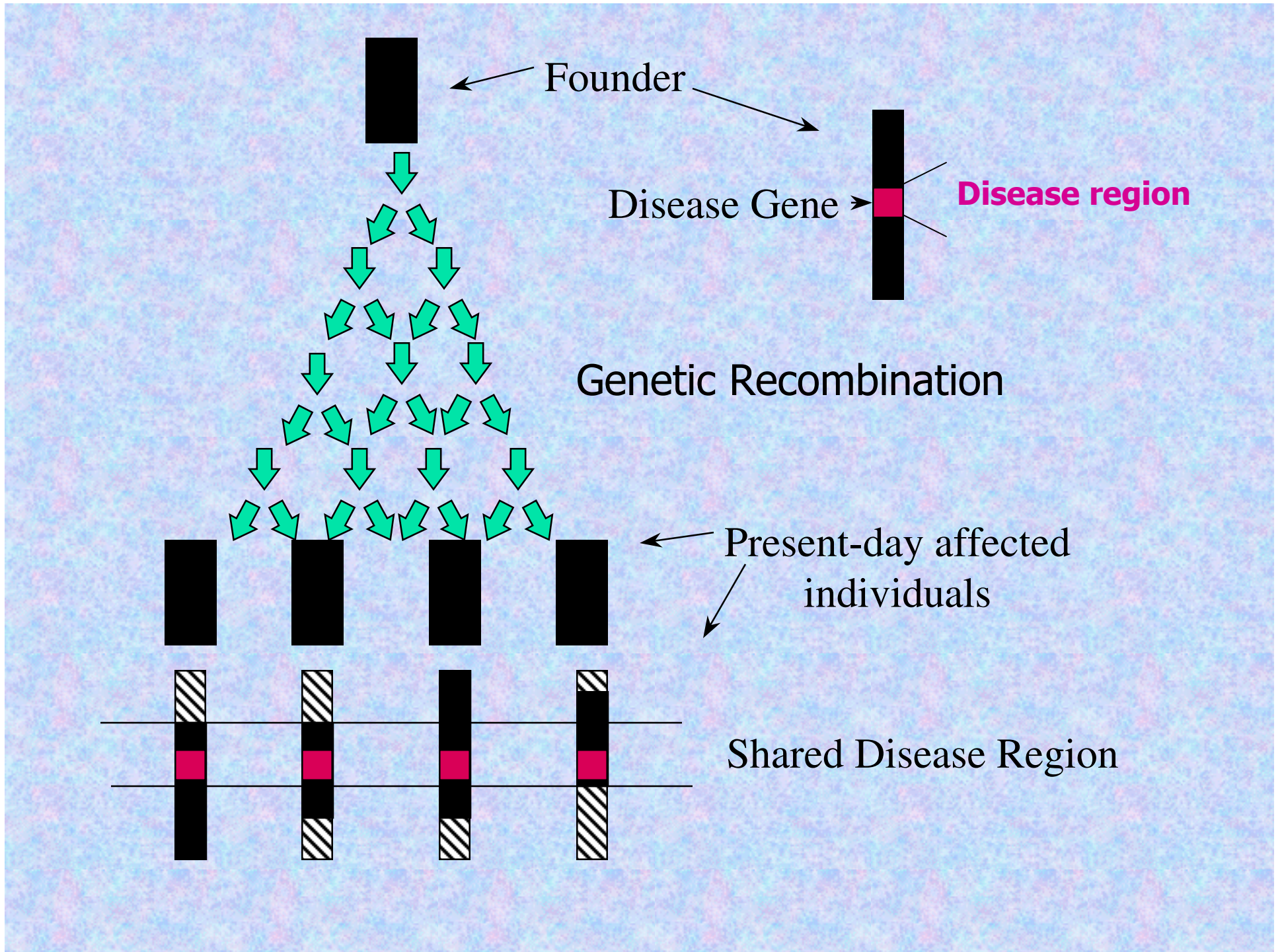
Geschwind and Levitt, 2007

Genetic architecture and practical matters

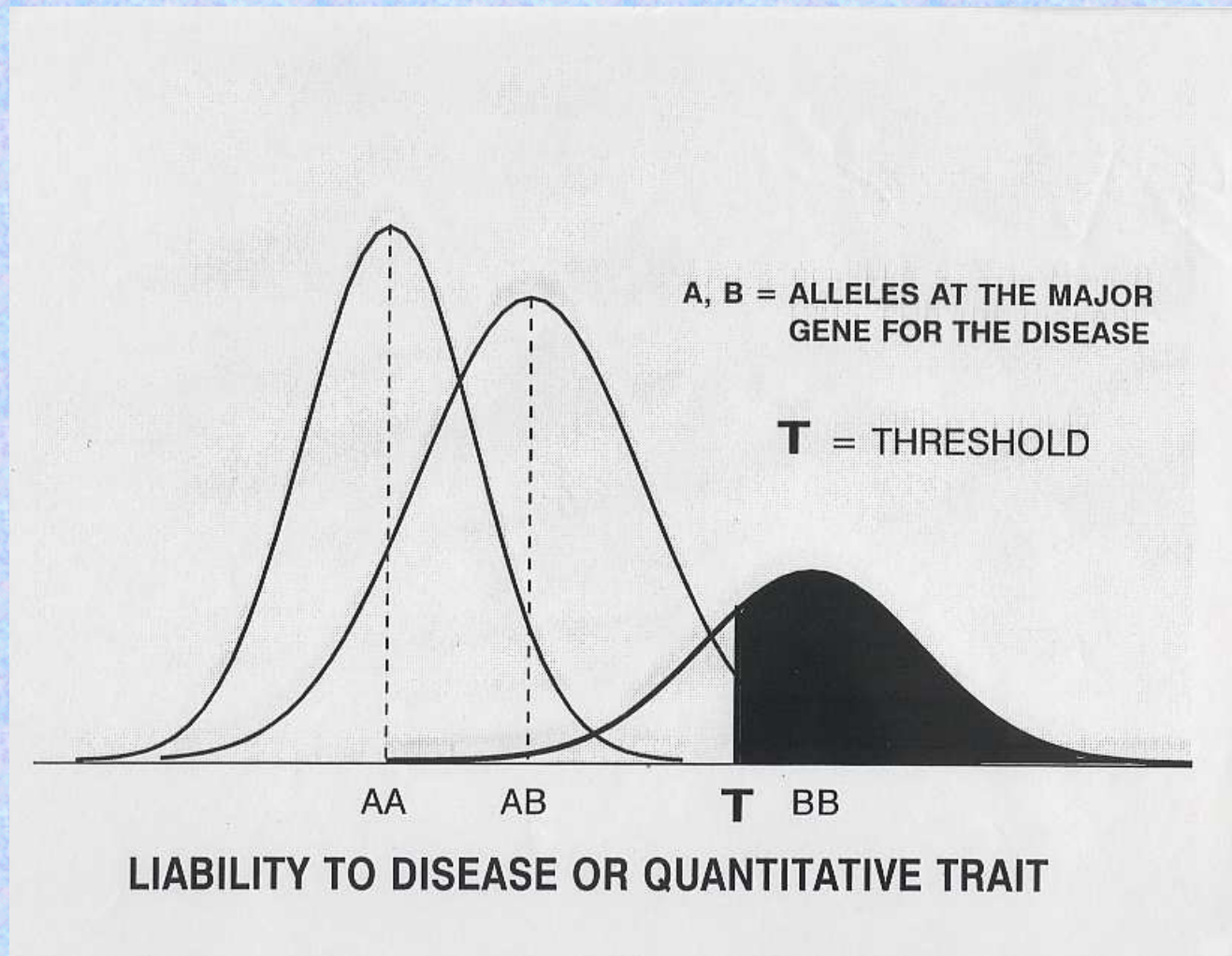
- n To what extent are childhood neuropsychiatric disorders due to genetic, but non-heritable etiologies?
 - n De novo events mutations?
 - n Epigenetics?
- n This is likely to be related to severity (intellectual disability?).
- n Most common, less severe disorders will have a significant contribution from common genetic variants.

Common Diseases are Complex

- n Many genes contribute to the phenotype.
- n Multiple genes act together (polygenic) or with the environment (multifactorial).
- n Common variants may contribute. Each gene contributes a portion of the risk.
- n Environmental influences may be significant.
- n Variable expression (ie. Language delay, MR).
- n Variable penetrance (not all carriers of a risk allele display phenotype).
- n Disease status may be a quantitative, ?arbitrary? cut-off (QTL).



Multigenetic/Complex diseases



Solutions to complex genetics: endophenotypes

Am. J. Hum. Genet. 70:60-71, 2002

Evidence for a Language Quantitative Trait Locus on Chromosome 7q in Multiplex Autism Families

Maricela Alarcón,^{1,2} Rita M. Cantor,³ Jianjun Liu,⁴ T. Conrad Gilliam,^{4,5} the Autism Genetic Resource Exchange Consortium,⁶ and Daniel H. Geschwind^{1,2}

¹Center for Neurobehavioral Genetics and Neuropsychiatric Research Institute, ²Department of Neurology, and ³Departments of Human Genetics and Pediatrics, UCLA School of Medicine, Los Angeles; and ⁴Columbia Genome Center and ⁵Departments of Psychiatry and Genetics and Development, Columbia University, New York

Autism is a syndrome that has several genetic regions. The Autism Genetic Resource Exchange Consortium (AGRE) genotyped for 335 SNPs in a linkage analysis, with a significant [Z] 2.98; same region supported by a putative autism endophenotype.

Article

A Quantitative Trait Locus Analysis of Social Responsiveness in Multiplex Autism Families

Jacqueline A. Duvall, B.S.

Ake Lu, Ph.D.

Rita M. Cantor, Ph.D.

Richard D. Todd, M.D., Ph.D.

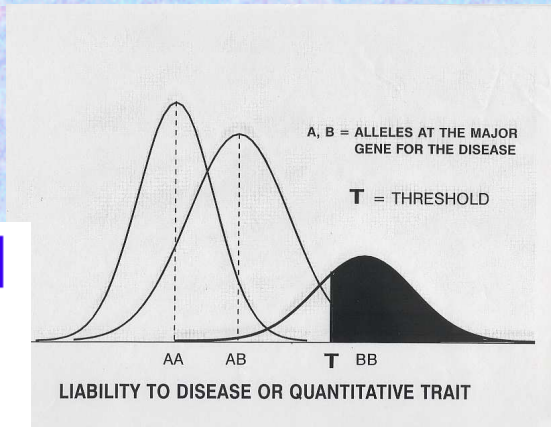
John N. Constantino, M.D.

Daniel H. Geschwind, M.D.

Objective: Autism is a complex genetic disorder with a highly heterogeneous phenotype defined by repetitive behaviors, language deficits, and problems with reciprocal social interactions. The authors present the first genome-wide scan for a social endophenotype in autism using the Social Responsiveness Scale, which pro-

vides a quantitative measure of autistic genetic risk factors; the cohort was stratified by the sex of affected individuals.

Results: The quantitative Social Responsiveness Scale genome scan identified two loci on chromosomes 11 and 17, with the highest score on chromosome 11 ($z = 3.22$). In contrast, no linkage signals



Human Molecular Genetics, 2007, Vol. 16, No. ? 1-17
doi:10.1093/hmg/ddm116
Advance Access published on xxx

Genome-wide expression profiling of lymphoblastoid cell lines distinguishes different forms of autism and reveals shared pathways

Yuhei Nishimura^{1,2,3}, Christa L. Martin⁷, Araceli Vazquez Lopez², Sarah J. Spence^{1,4,5}, Ana Isabel Alvarez-Retuerto⁴, Marian Sigman^{4,6}, Corinna Steindler^{8,9}, Sandra Pellegrini^{8,9}, N. Carolyn Schanen^{8,9}, Stephen T. Warren⁷ and Daniel H. Geschwind^{1,2,3,4,*}



Size and Scale of Study

- n Need large collection of families
- n Need to screen a large number of genes
- n Requires large collaborative efforts of many scientists and physicians
- n The more families and genes scanned, the more costly.
- n *But, genetics provides a direct and virtually certain method for getting to a molecular understanding of such disorders.*

Create a Large, Open Resource

Autism Genetic Resource Exchange

- n An open resource shared with the scientific community
- n More than 750 families.
- n 10k SNP Genome Scan and fine mapping data
- n Phenotype data:
 - n ADI-R, ADOS
 - n basic cognitive and language testing
 - n physical/neuro exams
 - n medical histories
- n Karyotyping/molecular cytogenetics



AGRE ACCESS: Application Data Download Program Information Pedigree Catalog Reference

AGRE
Autism Genetic Resource Exchange

SEARCH

The Autism Genetic Resource Exchange (AGRE) is the world's first collaborative gene bank for autism, sponsored by Cure Autism Now

Update:
New Data Available For Download
Pedigrees of 586 Families

Please take the [AGRE Researcher Survey](#)

- About AGRE Program
- Family Participation
- AGRE Research News
- Contact AGRE Program
- Site Map/Index

Autism Genetic Resource Exchange (AGRE)
A collaborative genebank to speed the pace of research to find the genes and ultimately the cure for autism. A resource established by Cure Autism Now, a non-profit foundation.

AGRE provides biomaterials and an unprecedented resource of phenotype and genotype information that is freely available for analysis by members of the scientific community.
[obtain access](#)

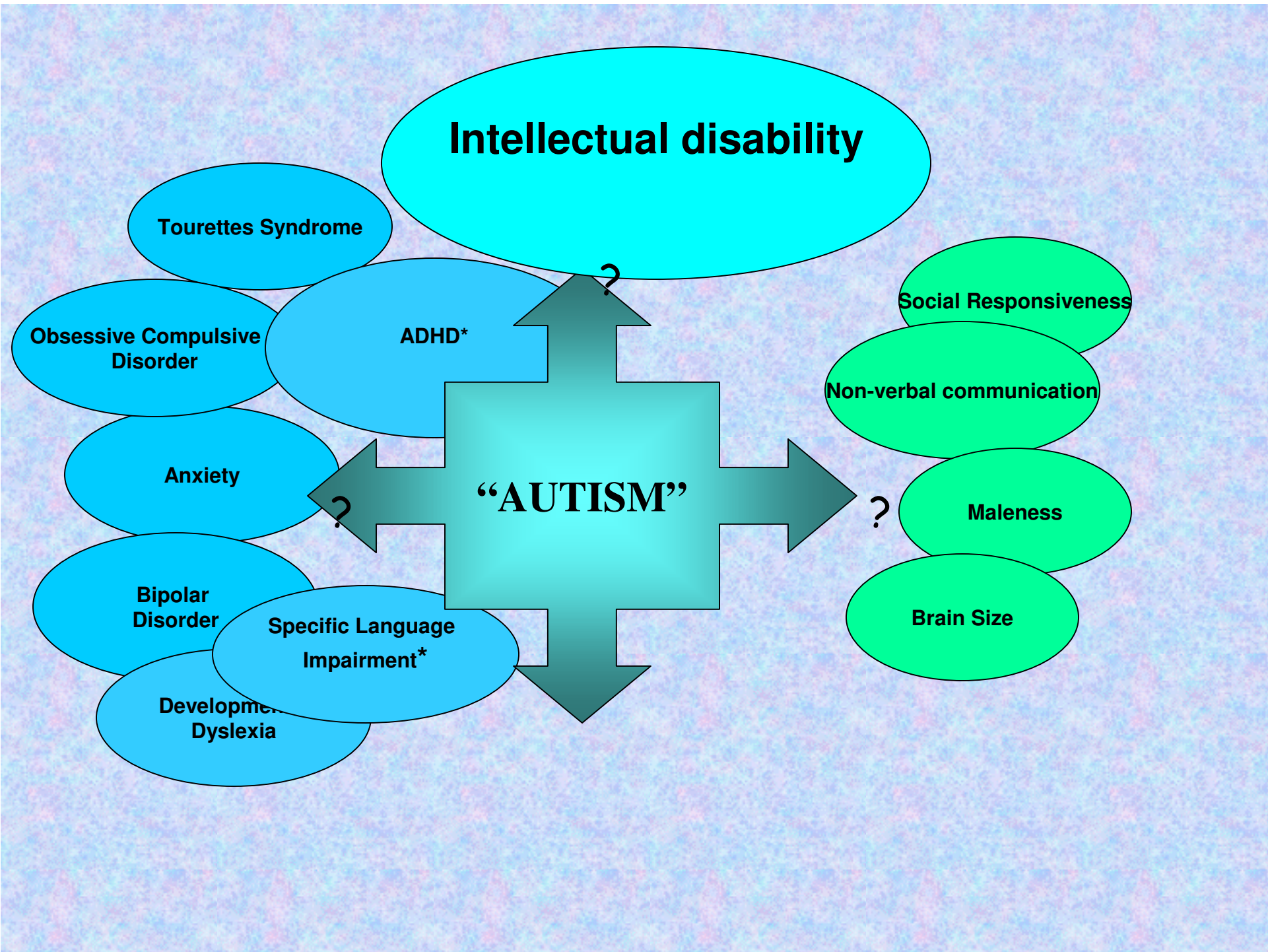
[AGRE Frequently Asked Questions](#)
Answers to common questions about AGRE.

[ISAAC User Guide:](#)
A step-by-step guide for downloading phenotype data from ISAAC.

[GENOTYPE DATA:](#)
Whole Genome Scan and Finemapping data on **356** families. Candidate Gene and Loci Data contributed by Dr. Buxbaum
NEW! Candidate SNP Genotyping data contributed by Dr. Sutcliffe
NEW! Finemapping data on Chr.5 and Chr.17 contributed by Dr. Nelson

[PHENOTYPE DATA:](#)
ADI-R, ADOS, Raven, and Handedness testing results with all interview data points and computer scored algorithm results are available for download.
Medical histories, Physical Neurological exam data, Peabody scores, and Vineland scores are also available.

cure
Autism
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Genome-wide analyses of human perisylvian cerebral cortical patterning

PNAS Early Edition | 1 of 6

B. S. Abrahams, D. Tentler, J. V. Perederiy, M. C. Oldham, G. Coppola, and D. H. Geschwind*

Program In Neurogenetics and Neurobehavioral Genetics Neurology Department and Semel Institute for Neuroscience and Behavior, David Geffen School of Medicine, University of California, Los Angeles, CA 90095-1769

Edited by Jon H. Kaas, Var

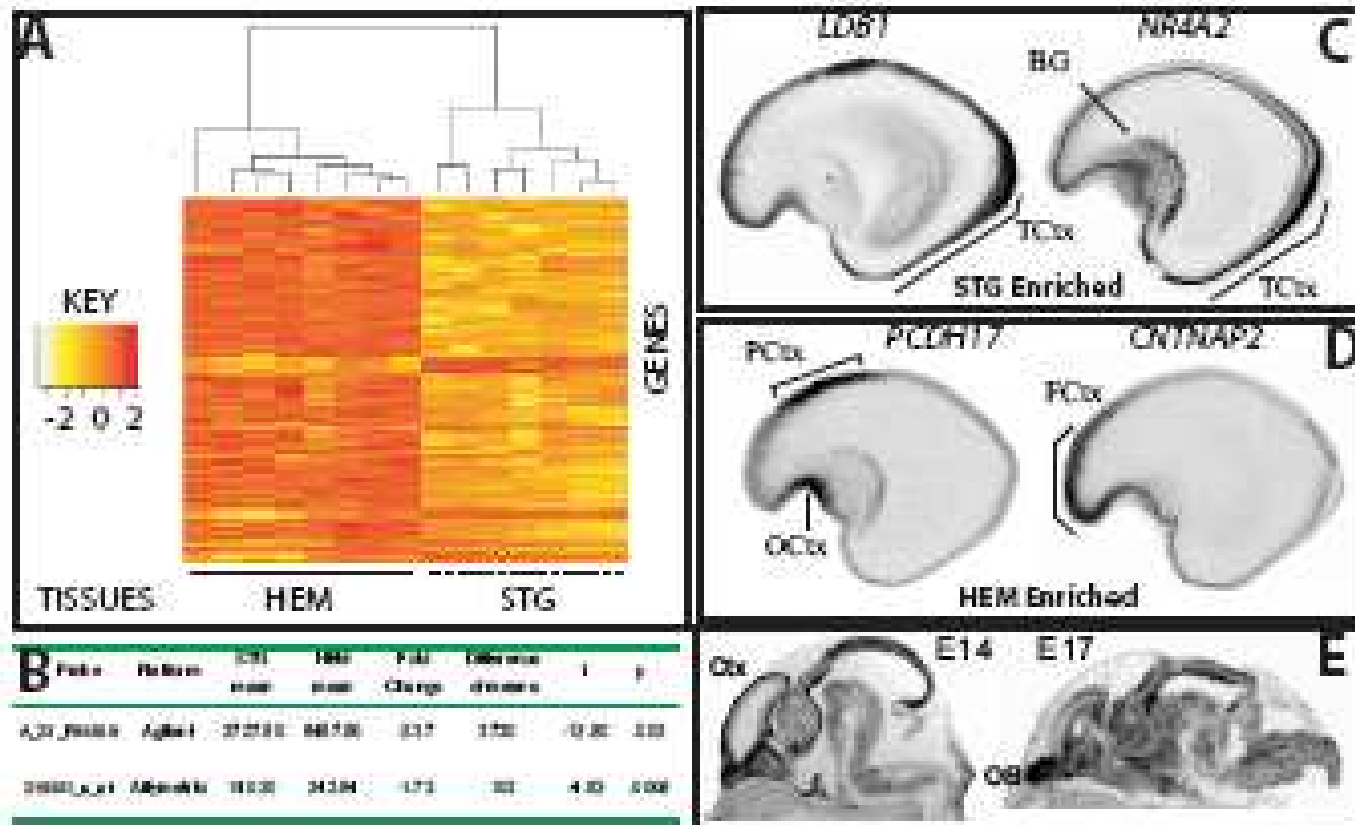
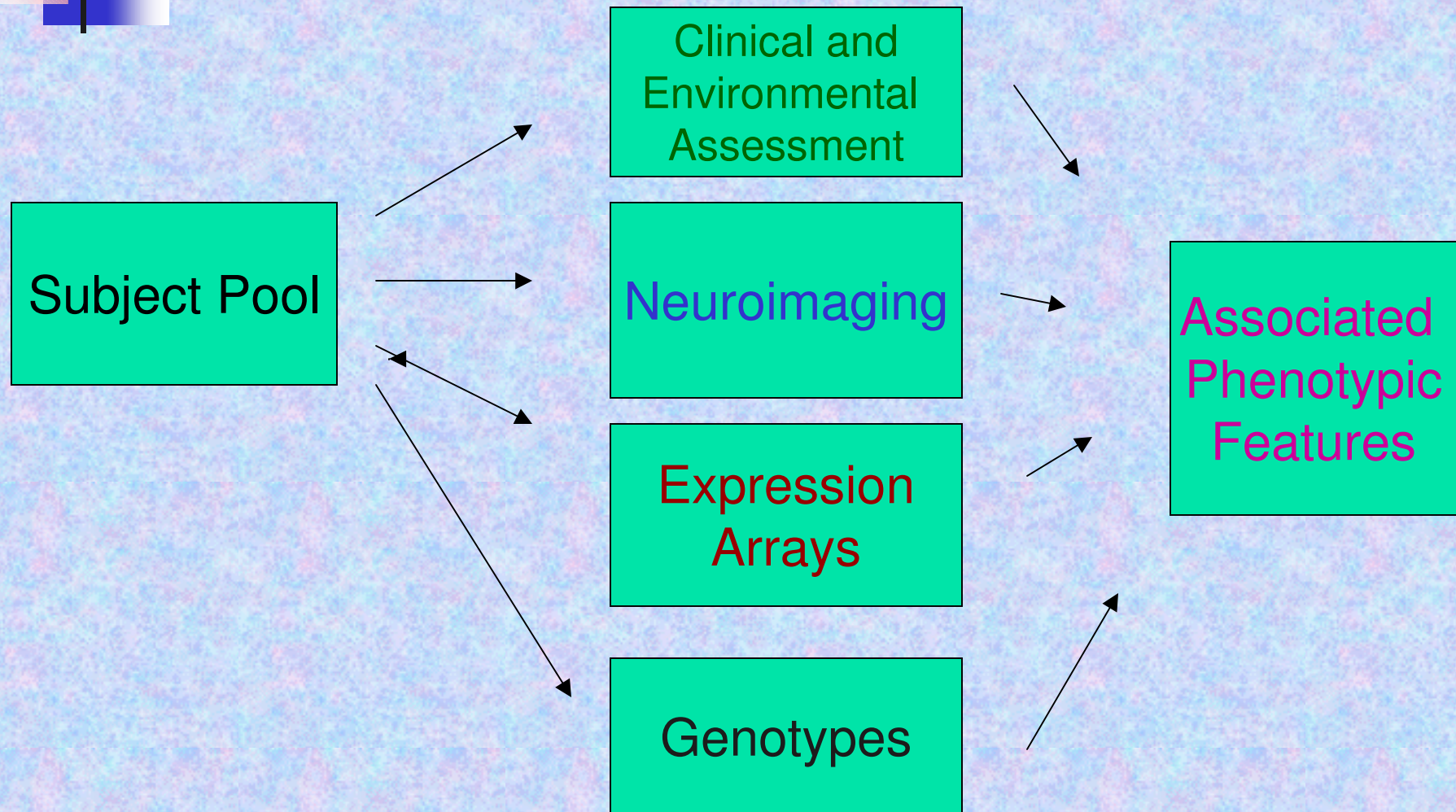


Fig2. Functional Genomic Analysis of Peri-sylvian Brain Patterning. (A) Unsupervised hierarchical clustering discriminates between superior temporal gyrus (STG) and whole cerebral hemisphere (HEM) by regional differences in gene expression. (B) Agilent and Affymetrix arrays independently identify *CNTNAP2* as differentially expressed between STG and HEM. (C and D) In situ hybridization confirms differential expression between STG and HEM. (E) Marked differences in *CNTNAP2* expression exist between mouse and human at similar developmental stages highlight enrichment in highly evolved human frontal regions.

To know what a given genotype means
we will need to have comprehensive
phenotype information



Summary

- n Genetics offers a means to understand etiology (causality) of childhood neuropsychiatric disease.
- n Genetic mechanisms are likely to be manifold. Thus, multiple approaches are warranted.
- n The impact of knowing genetic etiologies is broad, and includes improved knowledge of environmental factors, treatment and normal human variation.
- n Integration of genetic knowledge with other disciplines, and careful exploration of phenotype and trajectory will be crucial.
- n Planning and resources are needed with emphasis on large scale, collaborative efforts.