SFARI

Simons Foundation Autism Research Initiative

Annual Science Meeting

Washington, DC

September 12 – 14, 2010

MEETING AGENDA

SUNDAY, SEPTEMBER 12

2:00-5:00 Registration

5:00-7:00 **introductions;** All SFARI Investigators give a brief (one-rr of their SFARI-supported research.

7:00-7:45 Hors d'oeuvres and cocktails

7:46-9:46 Dinner & Evening Program
Welcome: **Jim Simons**
Remarks: **Gerry Fischbach**
Keynote Address: **Richard Litton, Human Hypertension: General-Population Therapeutics**

MONDAY, SEPTEMBER 13

7:30-8:30 Breakfast

Session #1: Cognition and Behavior
Session Moderator: **Kevin Pelphrey**

8:30-9:00 **Ami Klin / Warren Jones**

9:00-9:30 **Joseph Piven**

9:30-10:00 **Randy Buckner**

10:00-10:30 Break

10:30-11:00 **Rebecca Saxe**

11:00-11:30 **Marlene Behrmann**

11:30-12:00 Open Discussion

12:00-1:10 Lunch

Session #2: Gene Discovery and Expression Part I
Session Moderator: **Lauren Weiss**

1:10-1:40 **Mike Wigler**

1:40-2:10 **Matt State**

2:10-2:40 **Evan Eichler**

2:40-3:10 Break

Session #3: Gene Discovery and Expression Part II
Session Moderator: **Huda Zoghbi**

3:10-3:30 **Stephen Warren**

3:30-3:50 **Isaac Kohane**

3:50-4:10 **Barbara Wold**

4:10-4:30 Break

4:30-4:50 **Eric Courchesne**

4:50-5:10 **Dan Arking**

5:10-5:30 **Dan Geschwind**

5:30-6:00 Open Discussion

7:30-8:00 Hors d'oeuvres and cocktails

8:00-9:30 Dinner & Evening Program
Introduction: **Marilyn Simons**
"Bye" A movie by **Anthony Morrison**
Remarks: **Catherine Lord**

TUESDAY, SEPTEMBER 14TH

7:30-8:30	Breakfast
	Session # 4: Molecular Mechanisms / Synaptic Biology Part I Session Moderator: **Bernardo Sabatini**
8:0-8:50	**Guoping Feng**
8:60-9:10	**Ricardo Dolmetsch**
9:10-9:30	**Hazel Sive**
9:30-9:50	Break
9:50-10:10	**Maria Karayiorgou**
10:10-10:30	**Ben Philpot**
10:30-11:00	Open Discussion and Break
	Session # 5: Molecular Mechanisms / Synaptic Biology Part II Session Moderator: **Gerry Fischbach**
11:00-11:30	**Luis:Parada**
11:30-12:00	**Thomas Südhof**
12:00-12:45	**Eric Kandel, The Long and Short of Autism Research 2010**
1:00	Lunch & Departure

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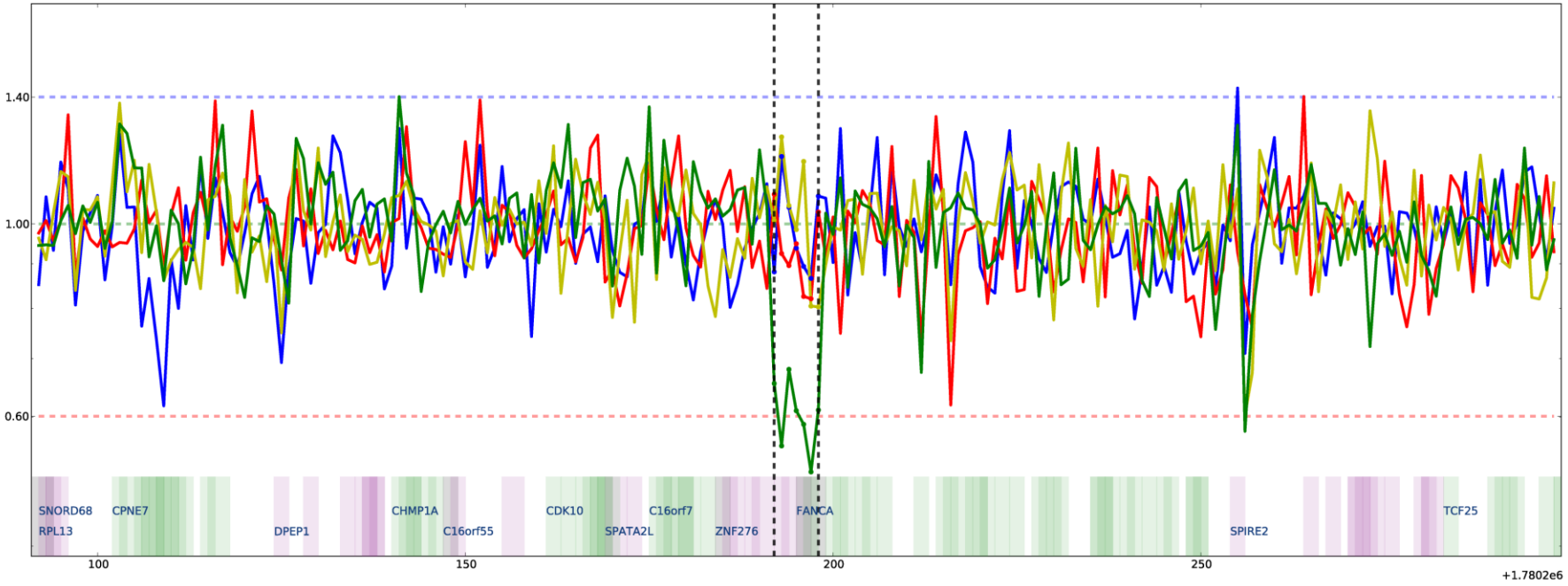

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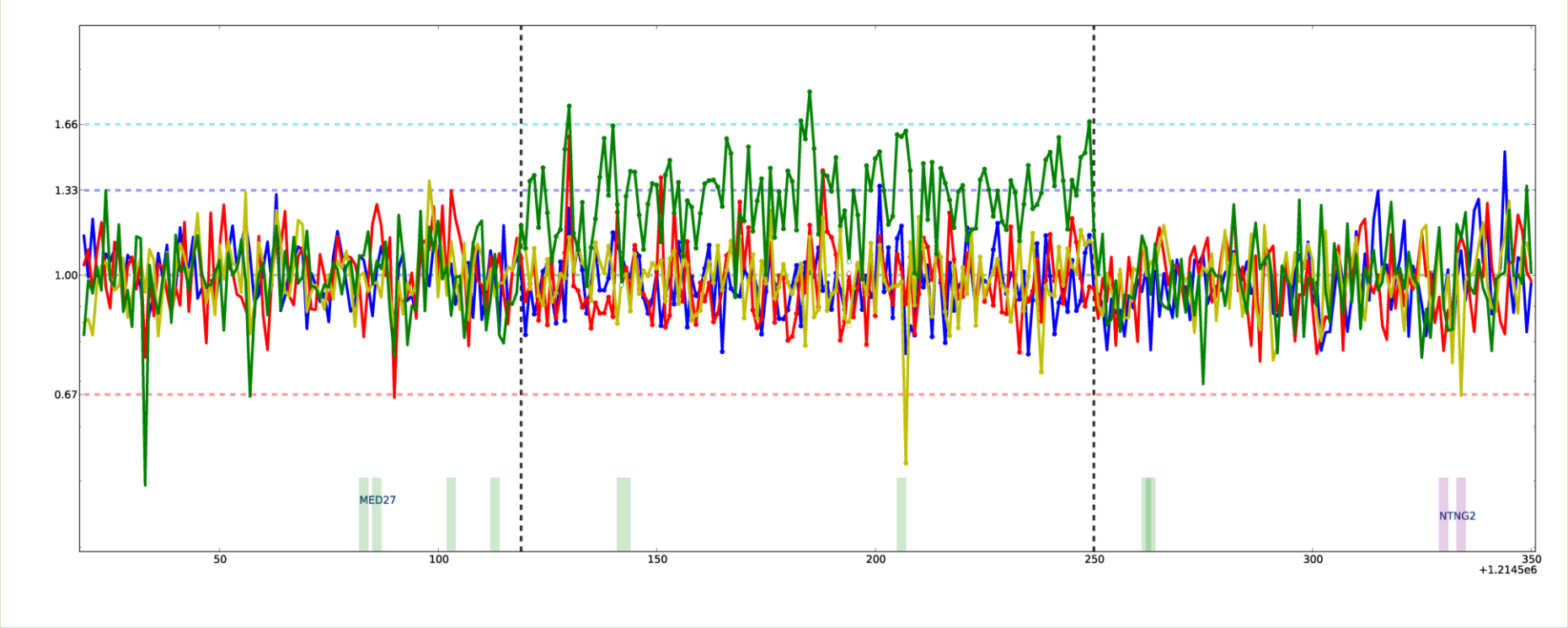
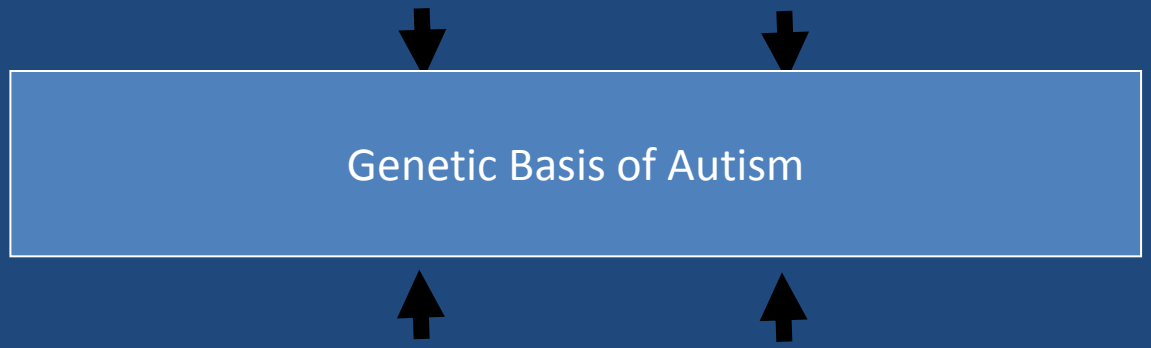


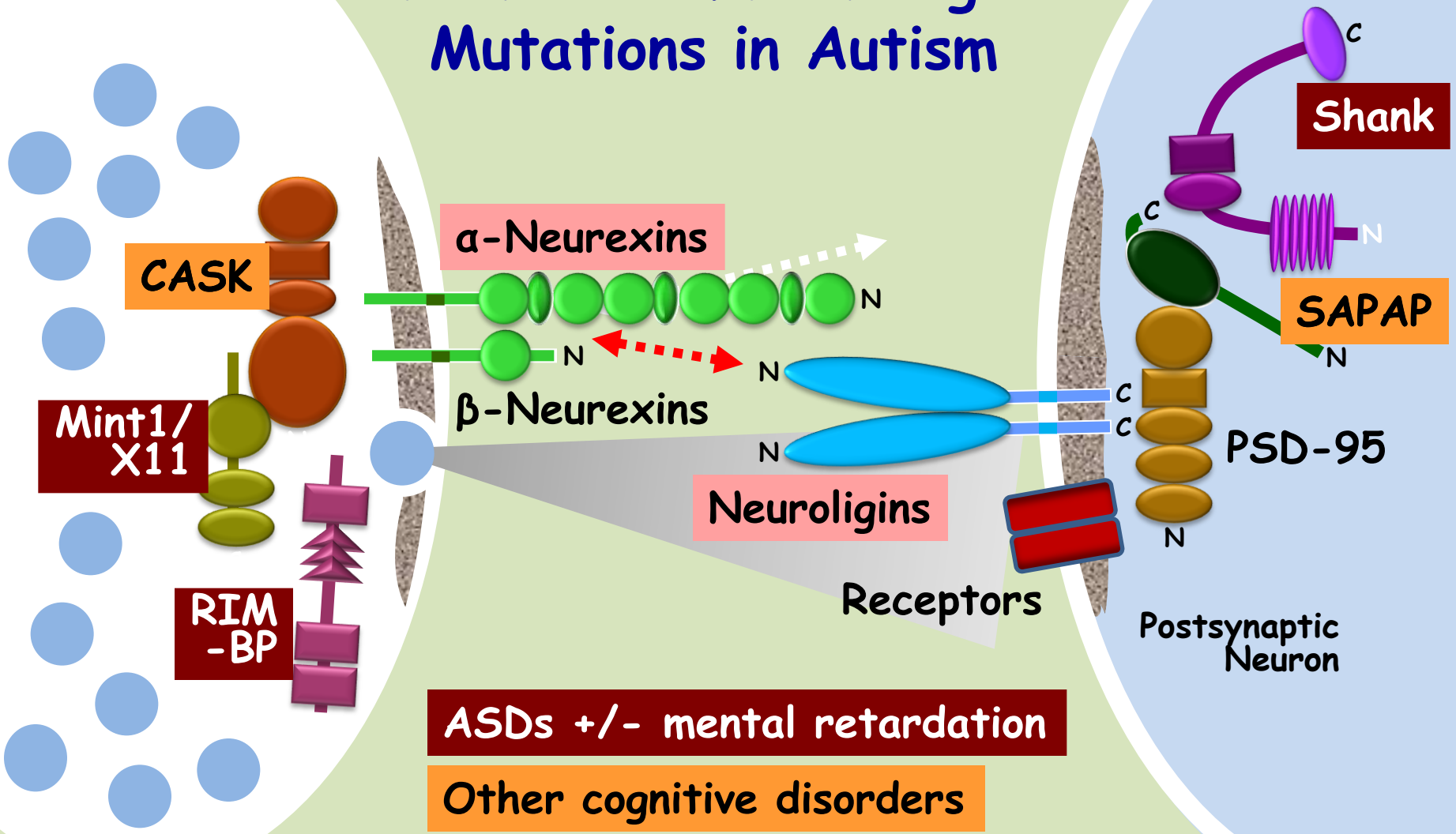
Gene Discovery – Copy Number Variants (CNVs)
E. Eichler

- Large CNVs (>200 kbp) ~10%
- Smaller CNVs (1 kbp—200 kbp)
  - Gene disruptive CNVs ~10%



- Exome de novo disruptive
- Exome inherited rare

Neurexin & Neuroligin Mutations in Autism

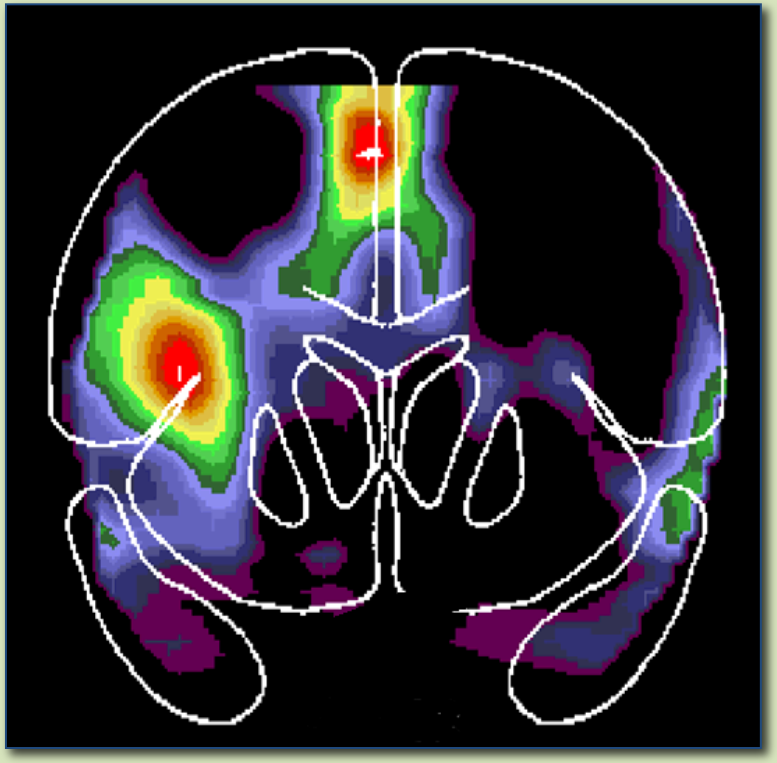


ASDs +/- mental retardation

Other cognitive disorders

Neurexins & neuroligins define a potential synaptic pathway in ASD pathogenesis

Markers of Functional Specialization: Asymmetry (R. Buckner)



BRAIN RESEARCH 1221 (2008) 115–125

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Research Report

Atypical functional lateralization of language in autism spectrum disorders

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ARTICLE INFO

Article history:
Accepted 29 April 2008
Available online 14 May 2008

Keywords:
fMRI
Asymmetry
Letter fluency
Category fluency
Frontal lobe

ABSTRACT

Impaired language is a prominent behavioral marker of autism spectrum disorders (ASD), but its neurobiological underpinnings are incompletely understood. We studied letter and category fluency in 14 high functioning ASD individuals and 14 age-matched controls. Each fluency condition was compared to self-paced repetition of the word "nothing." Responses were recorded to monitor performance. In letter fluency, the ASD group had significantly greater activation than controls in the right frontal and right superior temporal lobes. Between-group differences were not observed in left prefrontal cortex. By examining functional asymmetry in frontal cortex, we found that the ASD group had significantly reduced lateralization of activation patterns in letter fluency compared to the controls. In category fluency, no between-group differences in lateralization were found, in light of greater bilateral activation in controls. These findings indicate reduced hemispheric differentiation for certain verbal fluency tasks in ASD, consistent with some previous evidence of atypical functional and structural asymmetries in autism. Abnormal functional organization may contribute to the language impairment seen in ASD.

1. Introduction

Atypical language development is a prominent behavioral marker of autism spectrum disorders (ASD). In young autistic children, language deficits are among the most salient overt symptoms. Lack of spoken language by 2 years of age is often the first indicator to impel parents to seek professional advice (De Giacomo and Fombonne, 1998) or to be recognized as a significant risk factor by pediatricians. The timing of language acquisition is a key predictor of functional outcome; acquisition of useful speech by 5–6 years of age has been associated with better educational and functional attainment in adulthood (Howlin et al., 2000).

The severity of language deficits in individuals with ASD varies markedly. Approximately half of all individuals with autistic disorder remain nonverbal throughout life, while other individuals may develop fluent language and extensive vocabularies (Volkmar et al., 2000). However, even in high

Challenges

Very little is known about diversity in systems-level brain architecture.

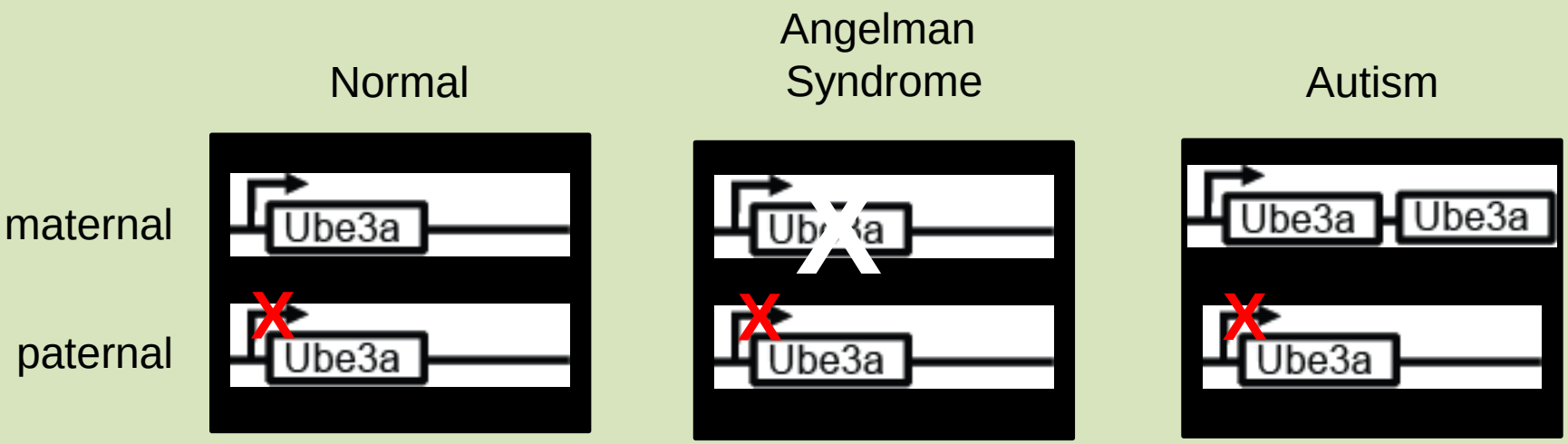
What is normal and what is atypical is unclear.

Genetic influences emerge from rare variants or may exert small effects necessitating large samples for many forms of discovery.

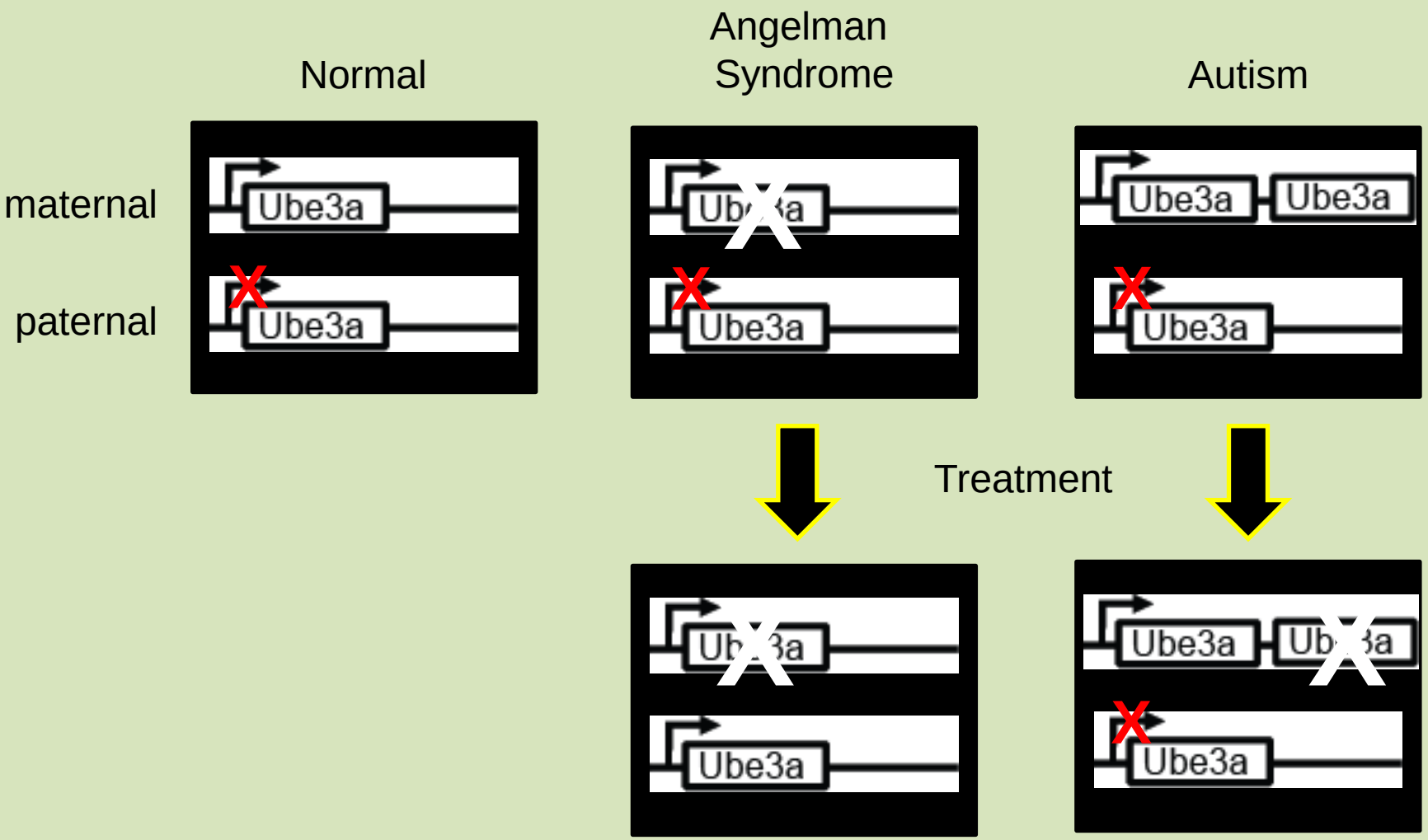
Need an approach to explore diversity across normal individuals.

- Robust within individuals.
- Amenable to collection of large samples.
- Provides a foundation for genetic explorations.
- Can be connected to behavior.
- Extendable to ASD and related groups.

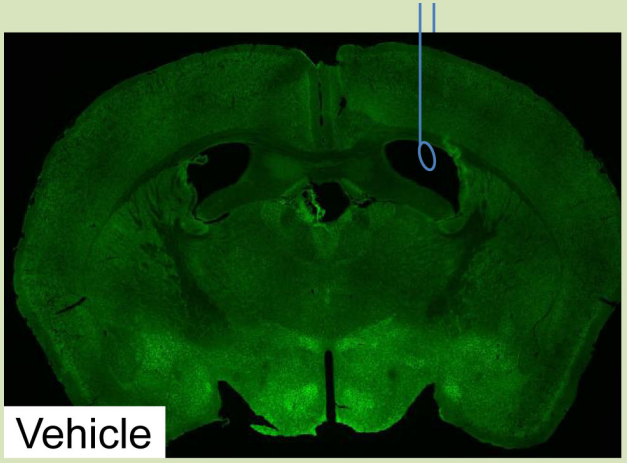
Paternal imprinting of Ube3a (B. Philpot)

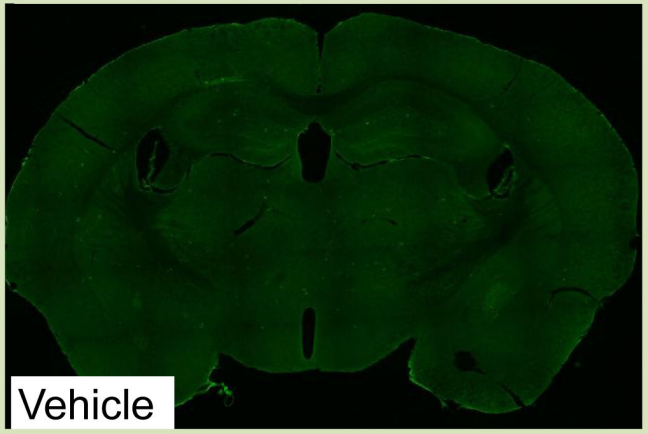


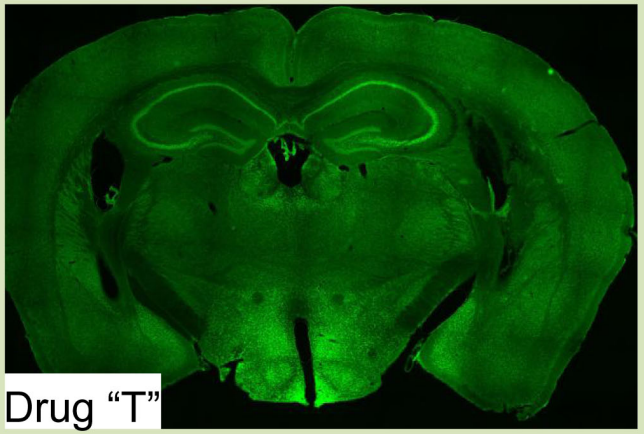
Therapeutic Strategy



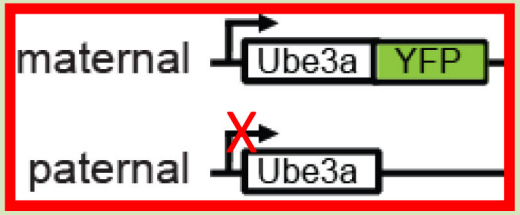
Unsilencing of paternal Ube3a throughout brain



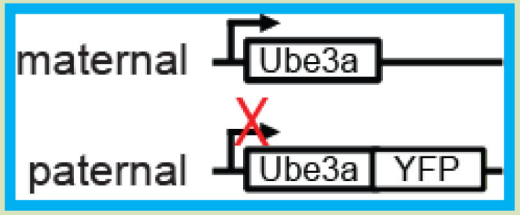




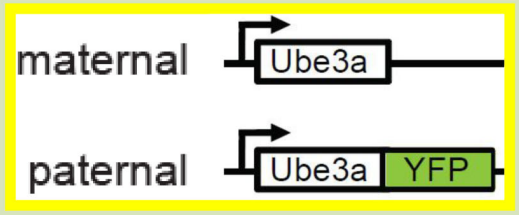
Maternal Ube3a-YFP



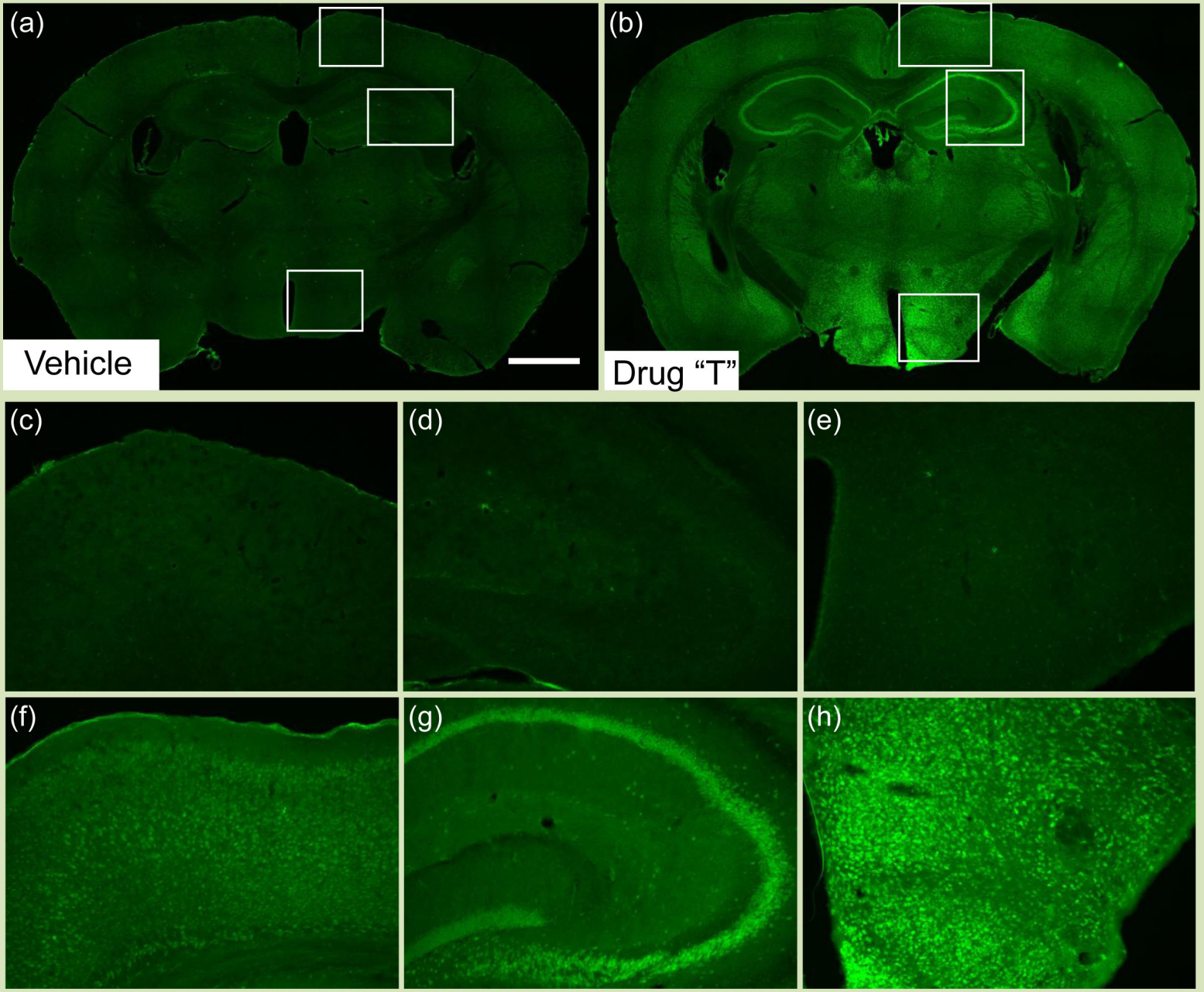
Paternal Ube3a-YFP

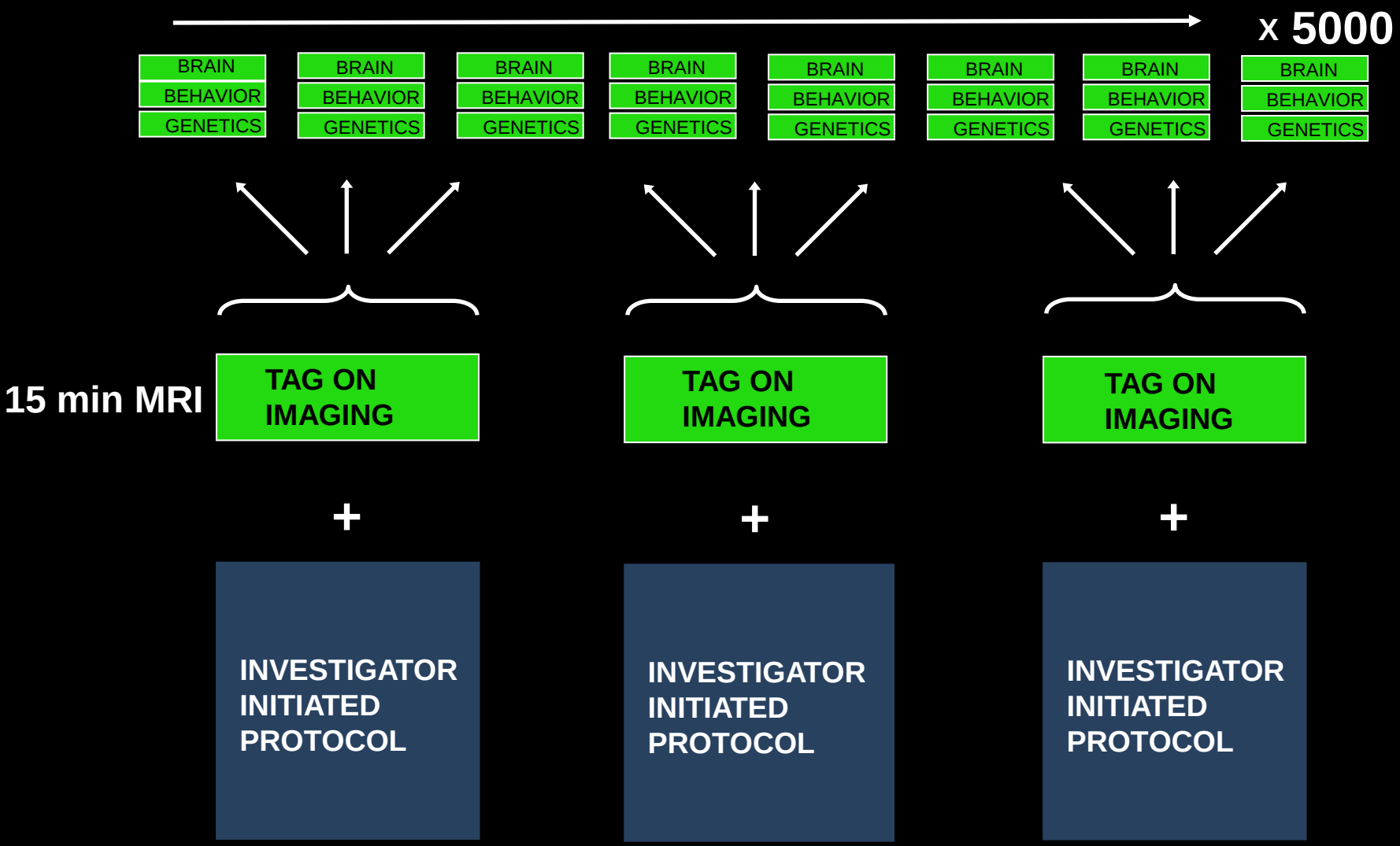


Paternal Ube3a-YFP



Unsilencing of paternal Ube3a throughout brain

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BRAIN
BEHAVIOR
GENETICS
15 min MRI
TAG ON IMAGING
TAG ON IMAGING
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INVESTIGATOR INITIATED PROTOCOL
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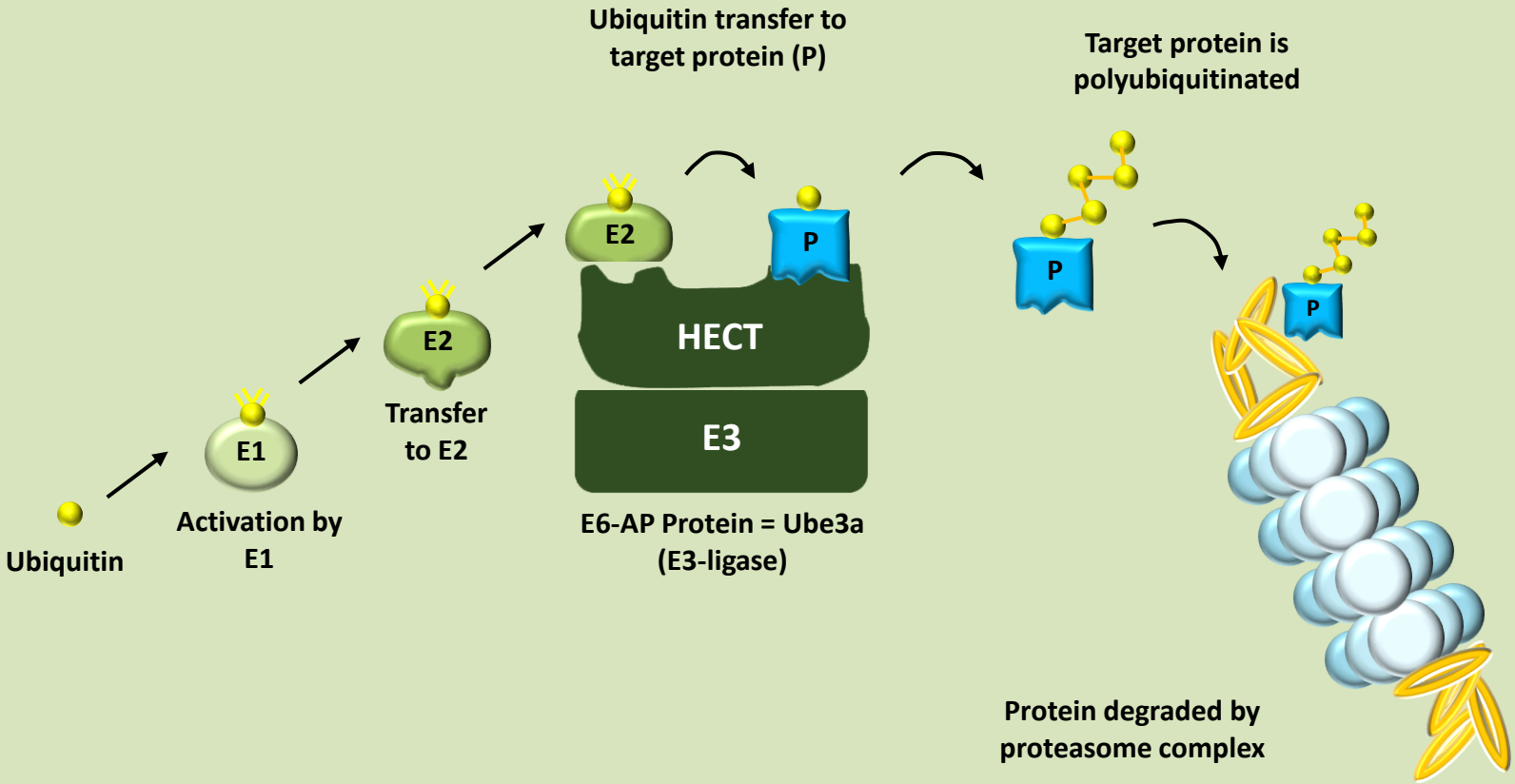
Function of Ube3a



modified from Dan, 2008

Ube3a in Autism Spectrum Disorders

- Deletions or mutations of *UBE3A* underlie Angelman syndrome, a severe mental retardation and autism spectrum disorder

  (Wagstaff and Beaudet labs, 1997; Peters et al., 2004)

- Maternal duplication of the 15q11-13 region, spanning the *UBE3A* gene, is one of the most identifiable genetic causes of autism

  (Cook et al., 1997; Schroer et al., 1998; Glessner et al., 2009)

- *UBE3A* is required for experience-driven plasticity during critical periods

  (Yashiro et al., 2009; Sato and Stryker, 2010)

Lesson #3: Two-Hit CNV Model of Disease

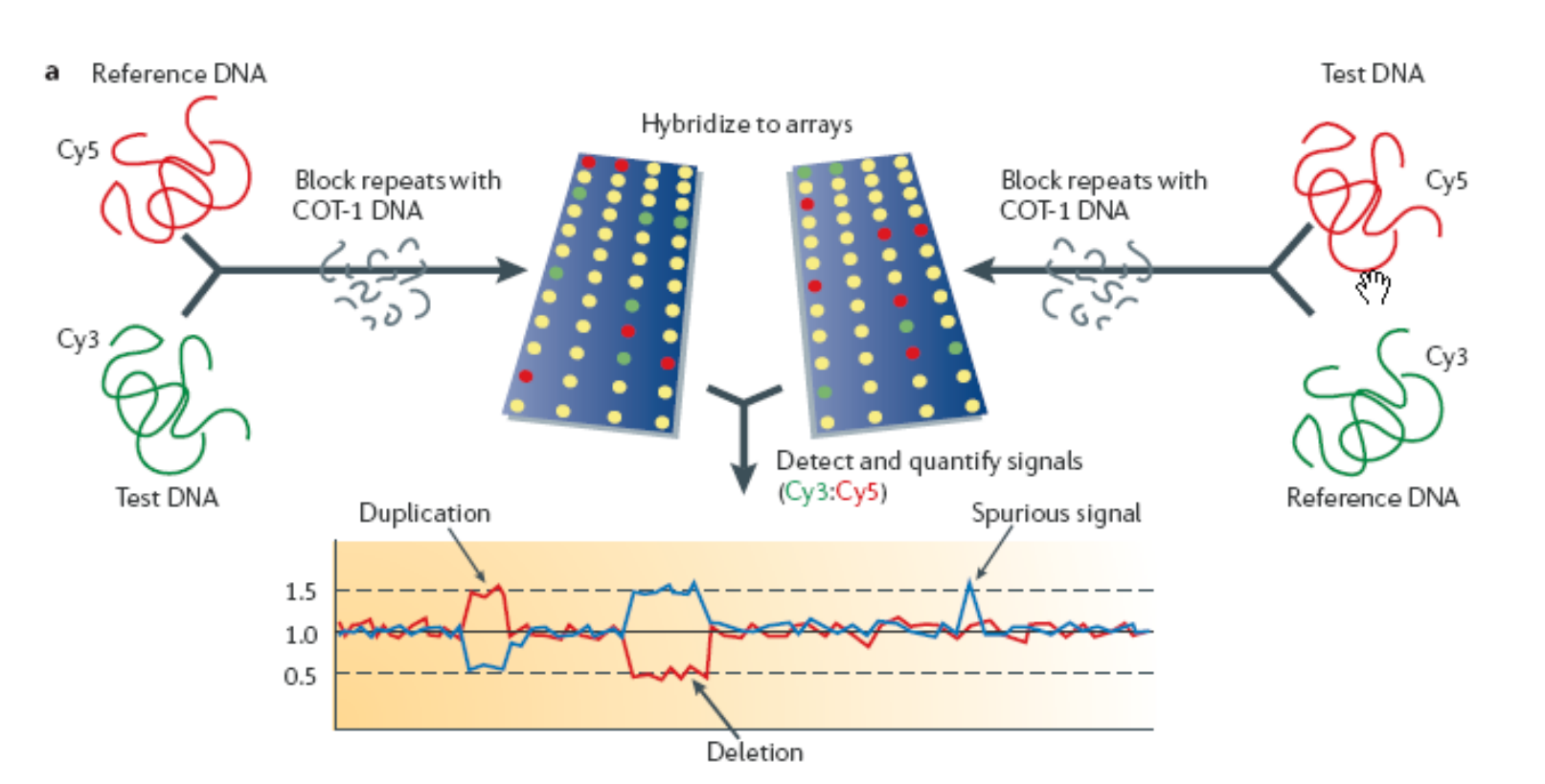
Disorder	Cases (n)	Total cases	Incidence (%)	*de novo* (%)	Second hits	Second hit (%)	*p*-value
Smith-Magenis syndrome	25	20,647	0.12	100%	0	0%	
17q21.31 syndrome	29	20,647	0.14	100%	0	0%	
Williams syndrome	60	20,647	0.29	100%	3	5%	0.52
DiGeorge syndrome	113	20,647	0.54	76.4%	8	7%	0.17
15q13.3 deletion	66	20,647	0.32	24%	6	9.1%	0.1
16p11.2 deletion	91	20,647	0.44	76.4%	9	9.9%	0.03
22q11.2 duplication		26,176	0.37	22.5%	11	11.3%	0.011
1q21.1 deletion		25,866	0.37	33%	11	11.2%	0.01
16p12.1 deletion		21,127	0.19	4.76%	9	21.9%	0.0002
Controls[1]	471	5285			21	4.4%	
Controls (unconditioned)2		5285			21	0.39%	

1For comparison, controls were conditioned to have at least one large CNV (>500 kbp) and then the number of second hits in these cases were counted. 2controls were not (conditioned)2 for first hit. This gives an estimate of two hits in the general population compared to affected individuals

Summary
(E. Eichler 9/2010)

- Large CNVs (~500 kbp) account for ~11% of SSC–inheritance assessment suggests that 1/3 rd are *de novo.*
- Refinement of 17 targeted regions identifies candidate smaller CNVs in 13.8% of samples eg. CDH8 and ACACA
- New hotspots emerging eg. 15q25 highlighting specific genes *IMMP2L, ATXBP1, CTNNA3 (*1-2% of patients)
- Exome sequencing on 17 trios—reveals de novo and inherited mutations in strong candidates (FOXP1, GRIN2B, CNTNAP2, SHANK2).

Copy Number Variants



General Strategy