Mount Sinai

Seaver Autism Center for Research and Treatment

Gene mutations in autism and associated neurodevelopmental disorders

Joseph D. Buxbaum, PhD, Director,
The Seaver Autism Center for Research and Treatment

Disclosures: Mount Sinai and JDB have a shared patent on the use of IGF-1 in PMDS; JDB is on the SAB of Coronis Neuroscience (no compensation, but options if the company goes public; E(X) < 100USD); Coronis is developing treatments for ADNP.

Rare Disease Day 2019

seaver autism center for research & treatment @ mount sinai

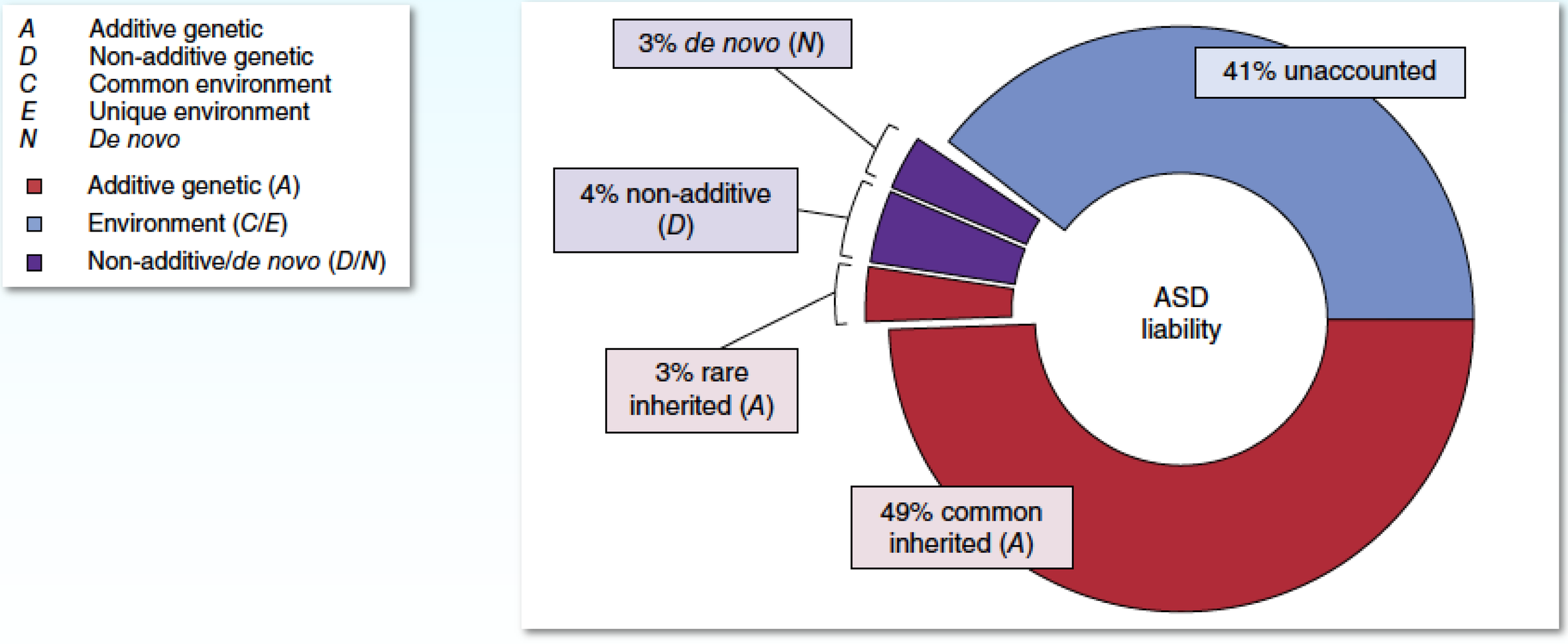
Mizuyaf NDD syndrome

- The cause is unambiguous and uncontested
- There is an easy and accurate test for this syndrome
- There is very high conversion
  - If the test is positive there is 80-100% likelihood that the syndrome will manifest
- There are cell and animal models with highest construct validity
  - Translational biomarkers have been developed
- There is good preclinical evidence that reversing the causal deficit will lead to improvements, even if given later in life
- Unbiased estimates of prevalence place it at ~1:15,000 live births
  - Orphan designation, but not vanishingly rare
- Very engaged family foundation with registries of patients
- Expert sites are doing extensive phenotyping and can identify key clinical endpoints
- FDA is very supportive
  - Works with families; More flexible about endpoints/indications; PRV is likely
- If a drug is successful, there is reasonable path for the same drug to also get an indication in related disorders

Most genetic risk for autism resides with common variation

Trent Gaugler[1], Lambertus Klei[2], Stephan J Sanders[3,4], Corneliu A Bodea[1], Arthur P Goldberg[5–7], Ann B Lee[1], Milind Mahajan[8], Dina Manaa[8], Yudi Pawitan[9], Jennifer Reichert[5,6], Stephan Ripke[10], Sven Sandin[9], Pamela Sklar[6–8,11,12], Oscar Svantesson[9], Abraham Reichenberg[5,6,13], Christina M Hultman[9], Bernie Devlin[2], Kathryn Roeder[1,14] & Joseph D Buxbaum[5,6,8,11,15,16]

NATURE GENETICS VOLUME 46 | NUMBER 8 | AUGUST 2014



The Autism Sequencing Consortium-2 (ASC2) exome working group


Anders Borglum


Joseph Buxbaum


Ercument Cicek


David Cutler


Mark Daly


Bernie Devlin


Jakob Grove


Kathryn Roeder


Behrang Mahjani

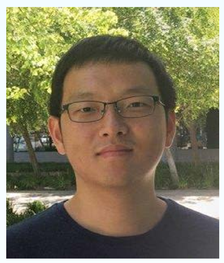

Stephan Sanders


Matt State


Mike Talkowski

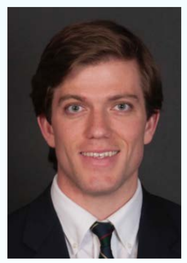

Jack Kosmicki


Kyle Satterstrom


Joon An


Harrison Brand


Michael Breen

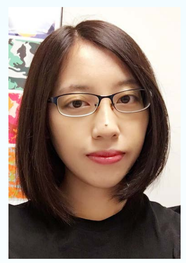

Ryan Collins


Silvia De Rubeis


Minshi Peng


Brooke Sheppard

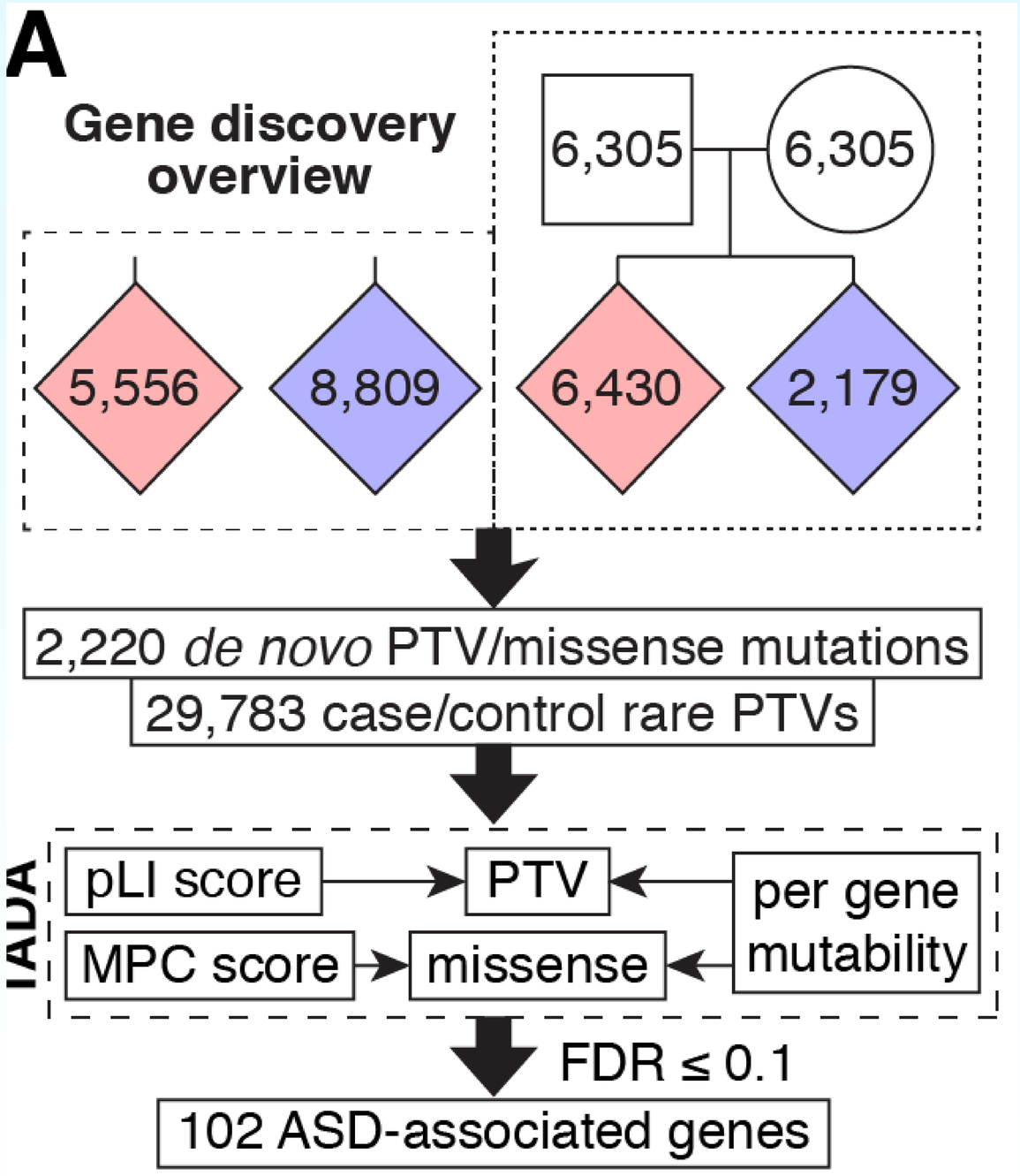

Jiebiao Wang


Xinyi Xu

… plus the entire ASC

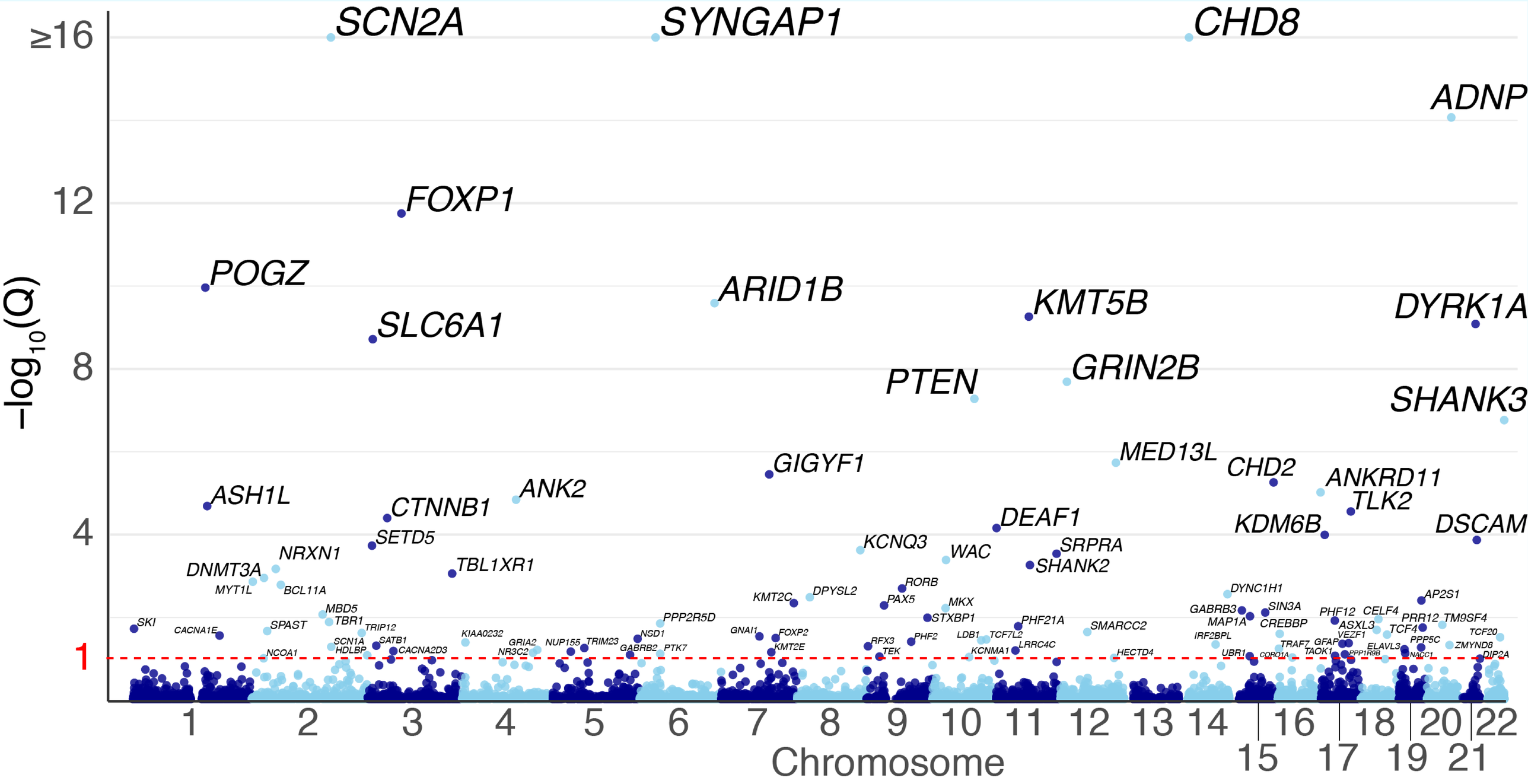
seaver autism center for research & treatment @ mount sinai

ASC2 (n~36,000)



seaver autism center for research & treatment @ mount sinai

ASC2 (n~36,000)



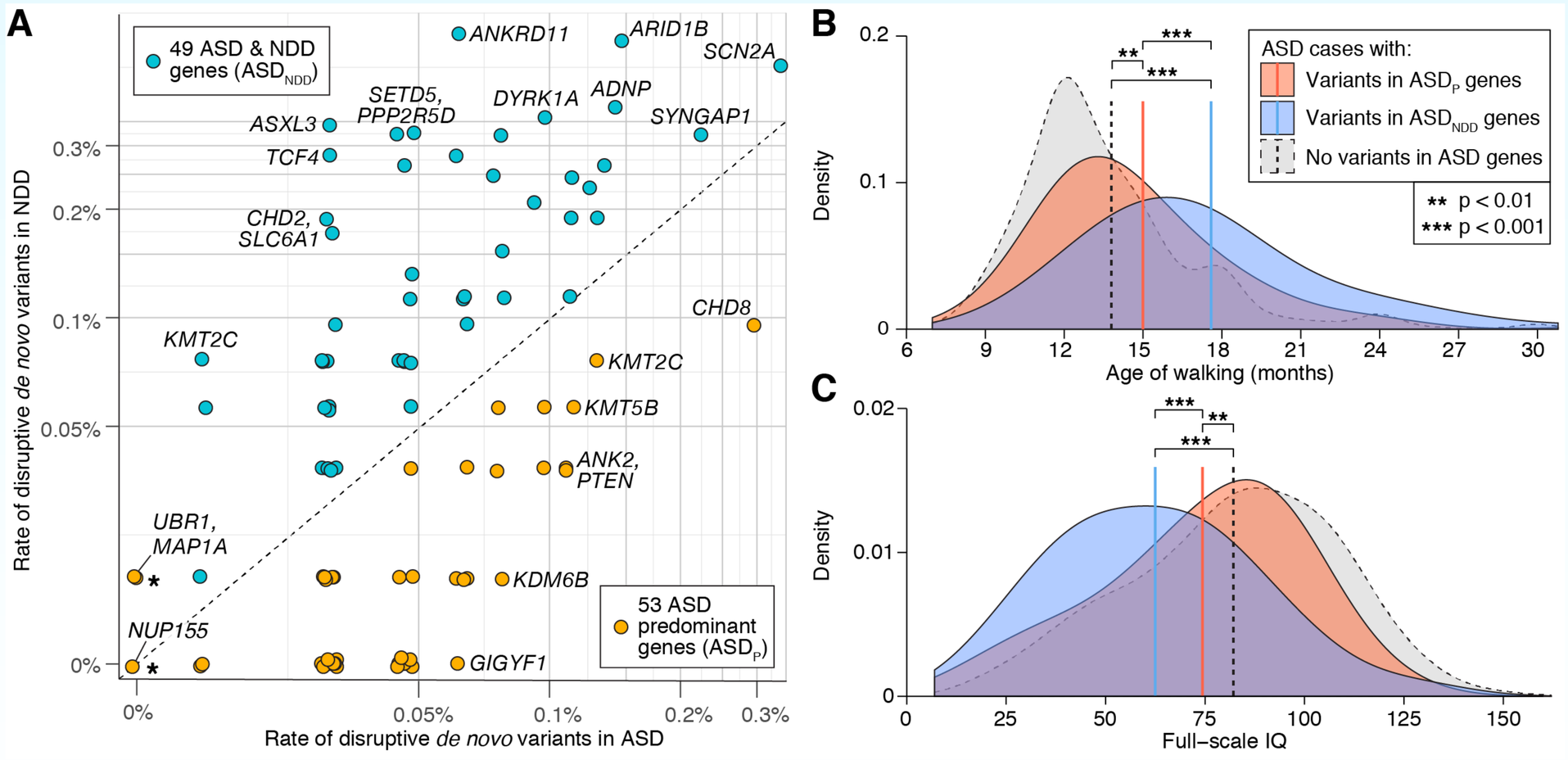
seaver autism center for research & treatment @ mount sinai

Large-scale discovery of novel genetic causes of developmental disorders

The Deciphering Developmental Disorders Study*

ASD vs NDD:

Social cognition vs general cognition?



seaver autism center for research & treatment @ mount sinai

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

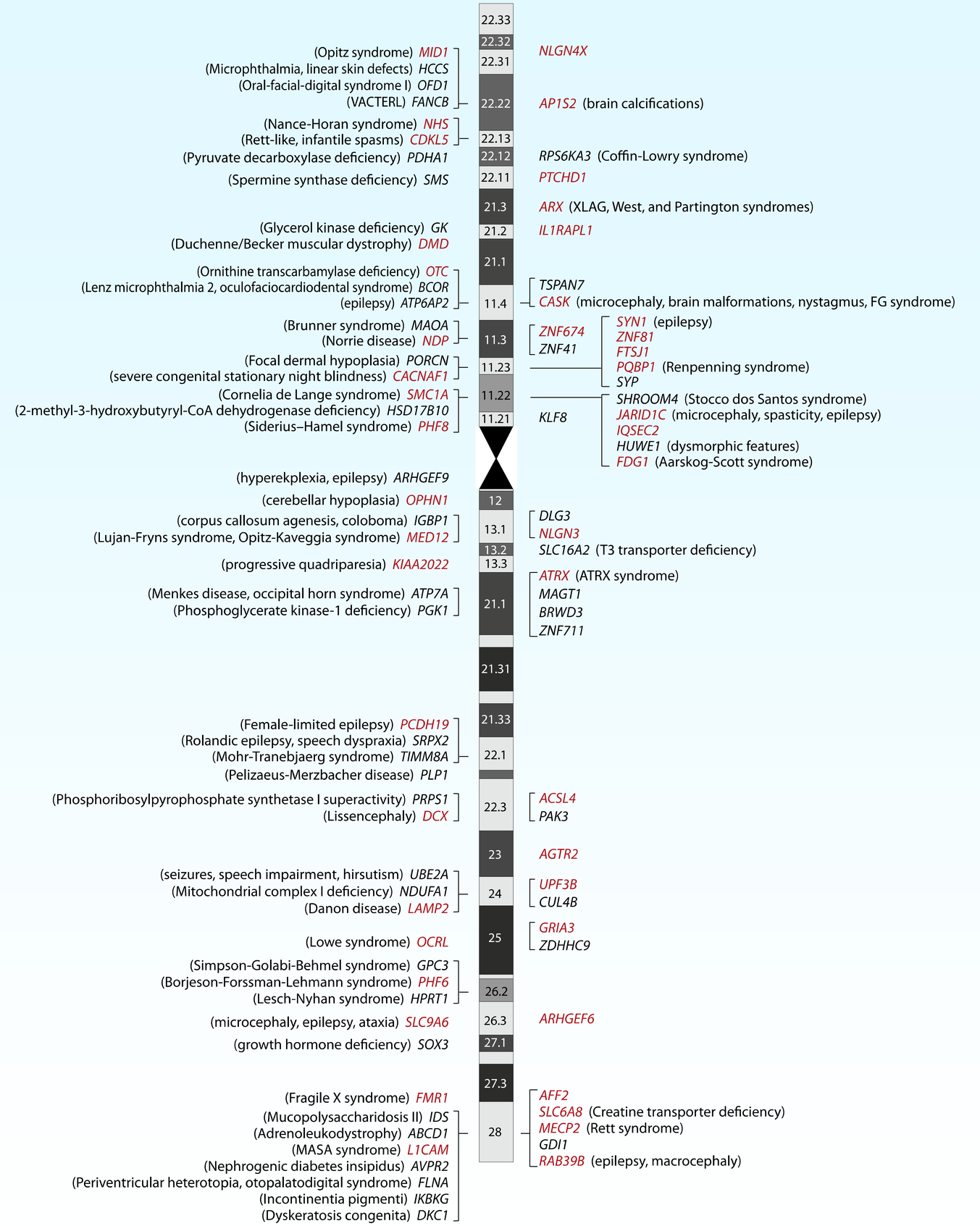
BRAIN RESEARCH

Review

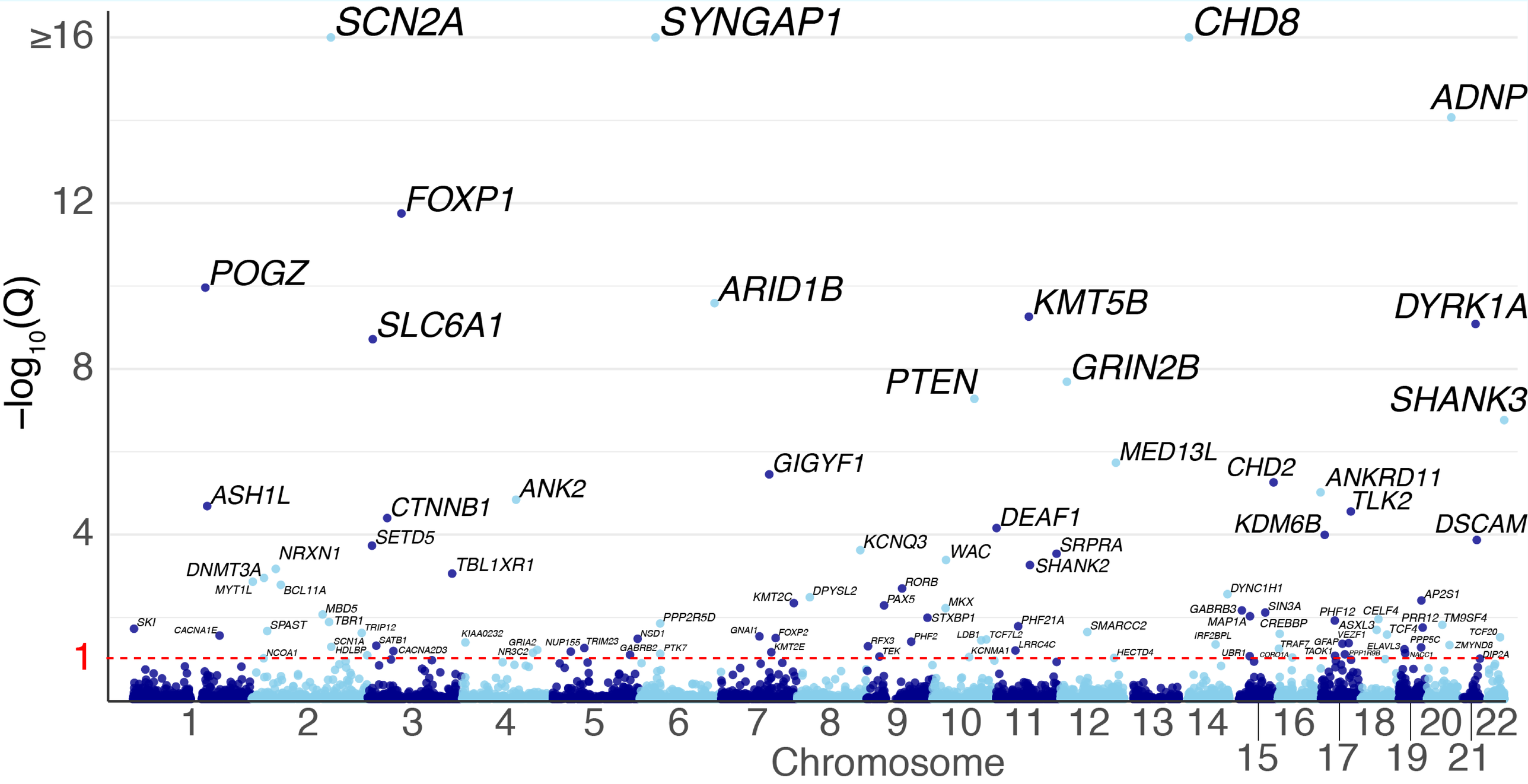
Etiological heterogeneity in autism spectrum disorders: More than 100 genetic and genomic disorders and still counting

Catalina Betancur

INSERM, U952, Paris, France
CNRS, UMR 7224, Paris, France
UPMC Univ Paris 06, Paris, France



ASC2 (n~36,000)

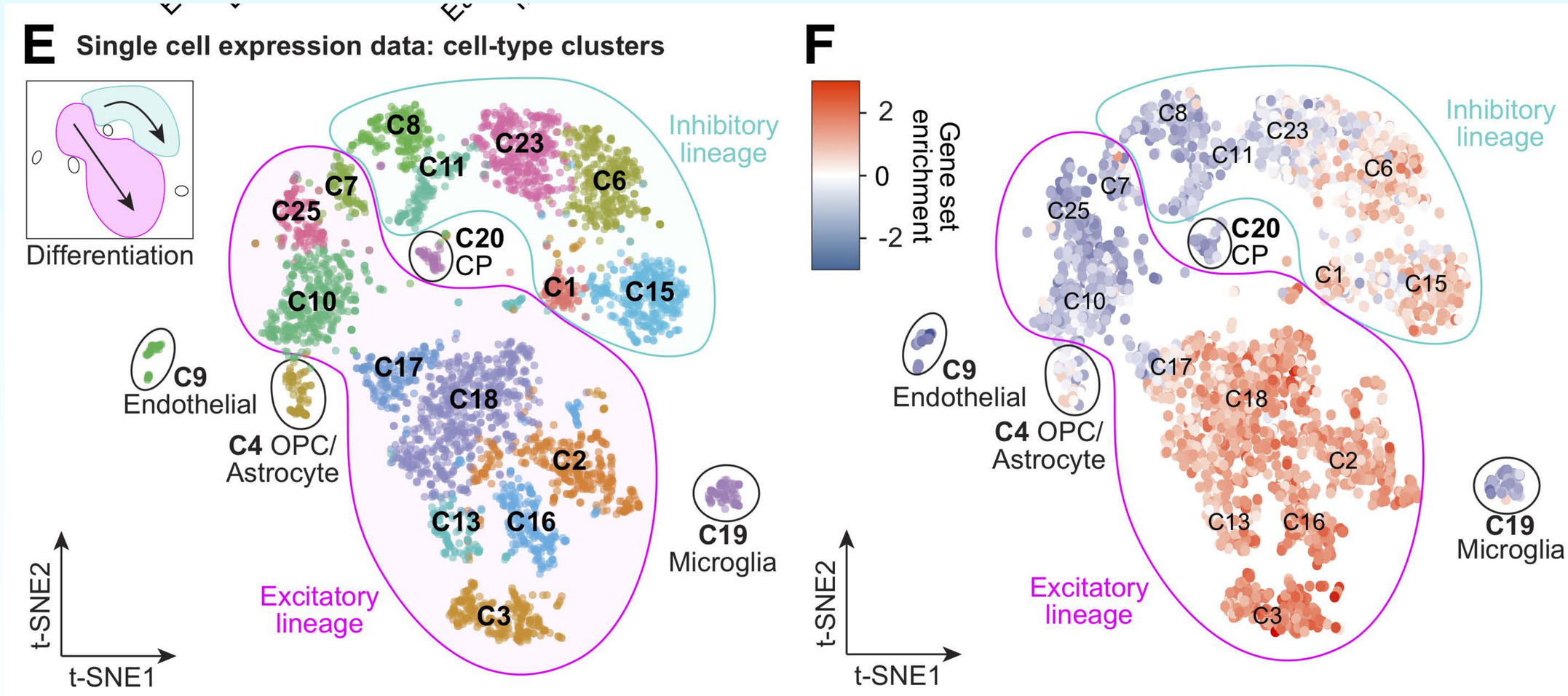


seaver autism center for research & treatment @ mount sinai

ASD/DD/ID gene mutations identified via **HTS**

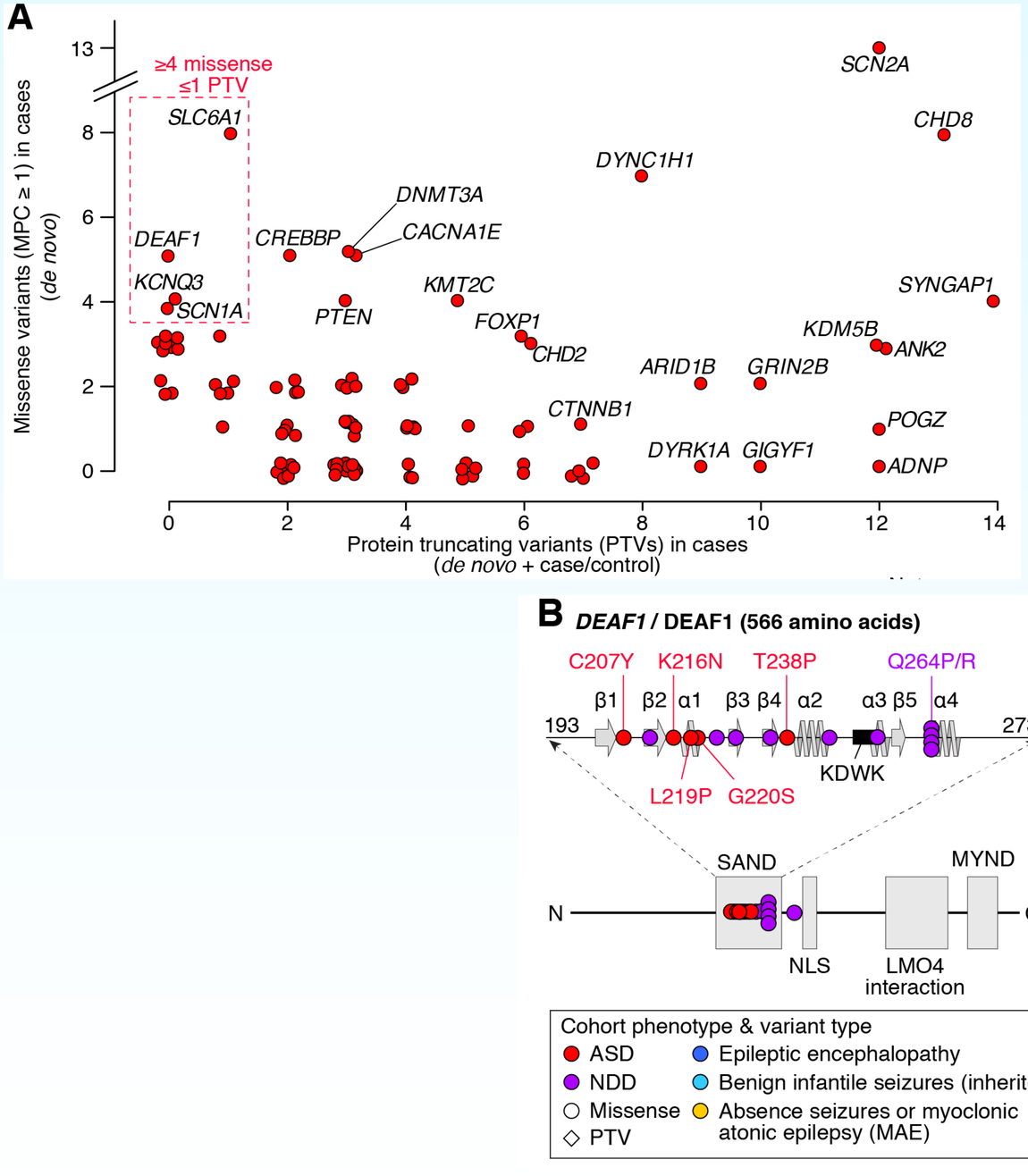
- Not a single pathway by any stretch of the imagination
  - Precision medicine is critical
- Overwhelmingly dominant
  - We are most powered for de novo mutations, which are generally dominant
  - Second allele that can be manipulated
- Primarily LoF
  - But we know the genetic mechanism for many of the recurrent genes)
- Can show a U-shaped curve
- However, tend to be very severe
- In certain cases, it has been shown that late re-expression has benefit
  - Also, behavioral therapies have some efficacy even later in disease
- Top genes are “fairly” common
- Top genes are highly penetrant

ASC – No single pathway



seaver autism center for research & treatment @ mount sinai

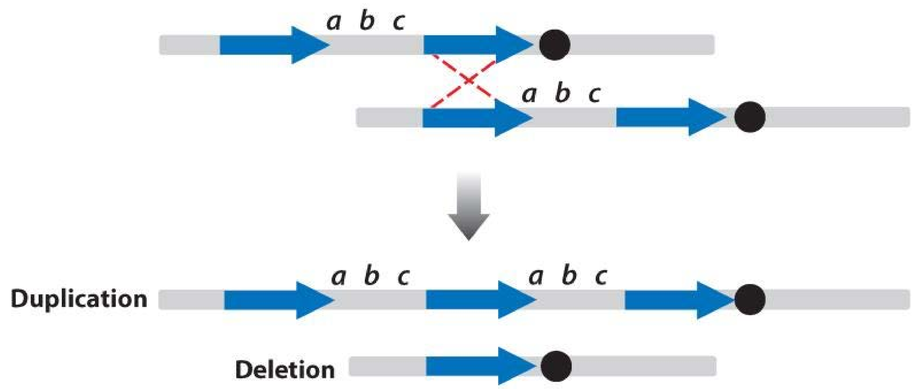
ASC - Primarily LoF



seaver autism center for research & treatment @ mount sinai

U-shaped curve

Figure 1

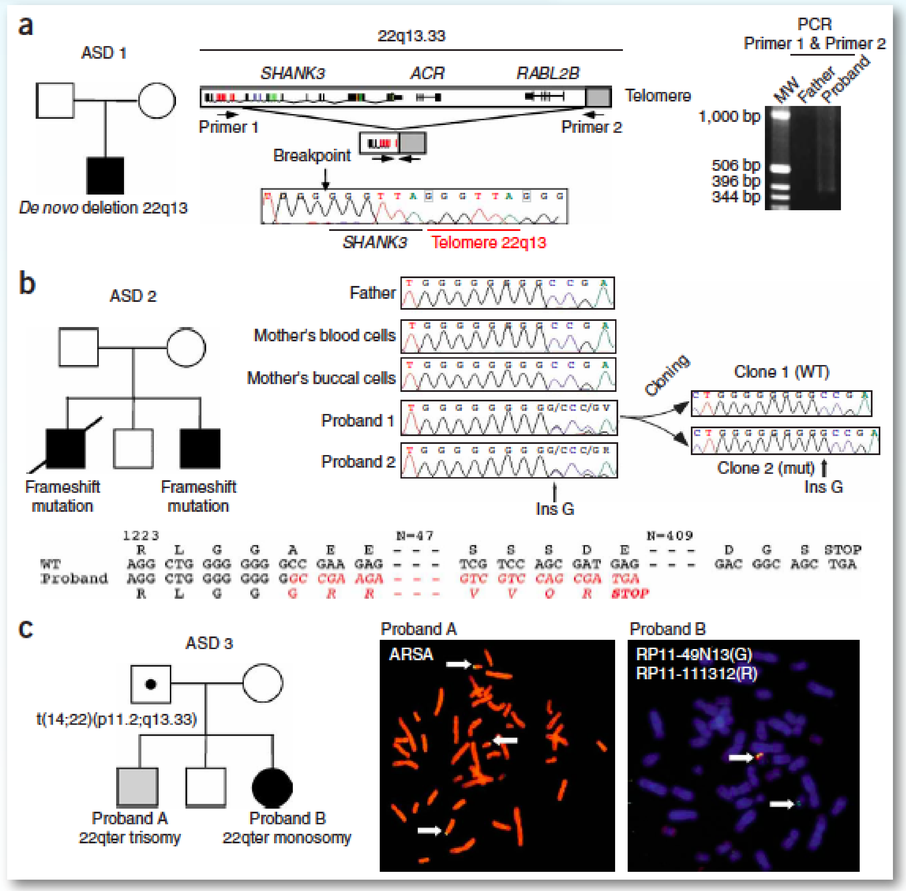


- 22q11.2
  - Del: Digeorge Syndrome, Velocardiofacial Syndrome; anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), autism; higher rates of schizophrenia.
  - Dup: Severe congenital anomalies and developmental delays, autism.
- 7q11.23
  - Del: Williams Syndrome
  - Dup: Developmental delay, intellectual disability, autism, speech-language delays
- 17p11.2
  - Del: Smith-Magenis Syndrome; global developmental delay, moderate intellectual disability, autism
  - Dup: Potocki-Lupski syndrome; language delay, moderate intellectual disability, autism.
- 16p11.2
  - Del: mild intellectual disability, language delay, autism
  - Dup: mild intellectual disability, autism.

Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders

Christelle M Durand[1], Catalina Betancur[2], Tobias M Boeckers[3], Juergen Bockmann[3], Pauline Chaste[1], Fabien Fauchereau[1,4], Gudrun Nygren[5], Maria Rastam[5], I Carina Gillberg[5], Henrik Anckarsäter[5], Eili Sponheim[6], Hany Goubran-Botros[1], Richard Delorme[1], Nadia Chabane[7], Marie-Christine Mouren-Simeoni[7], Philippe de Mas[8], Eric Bieth[8], Bernadette Rogé[9], Delphine Héron[10], Lydie Burglen[11], Christopher Gillberg[5,12], Marion Leboyer[2,13] & Thomas Bourgeron[1,4]

NATURE GENETICS VOLUME 39 | NUMBER 1 | JANUARY 2007



Tend to be very severe

Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and *SHANK3* deficiency

Latha Soorya[1,2,13], Alexander Kolevzon[1,2,3*], Jessica Zweifach[1], Teresa Lim[2], Yuriy Dobry[2], Lily Schwartz[1], Yitzchak Frank[1,2,3,4], A Ting Wang[1,2,5], Guiqing Cai[1,2,6], Elena Parkhomenko[1,2], Danielle Halpern[1,2], David Grodberg[1,2], Benjamin Angarita[2], Judith P Willner[3,6], Amy Yang[3,6], Roberto Canitano[1,14], William Chaplin[8], Catalina Betancur[9,10,11] and Joseph D Buxbaum[1,2,5,6,7,12]

Soorya *et al. Molecular Autism* 2013, 4:18

	N	%
Consensus ASD diagnosis (n = 32)		
Autism	24	75
Autism spectrum	3	9.4
Not ASD	5	15.6
Nonverbal IQ classification (n = 30)		
Average (IQ 100–110)	1	3.3
Mild intellectual disability (IQ 50–55 to 70)	3	10
Moderate intellectual disability (IQ 35–40 to 50–55)	3	10
Severe intellectual disability (IQ 20–25 to 35–40)	7	23.3
Profound intellectual disability (IQ <20-25)	16	53.3

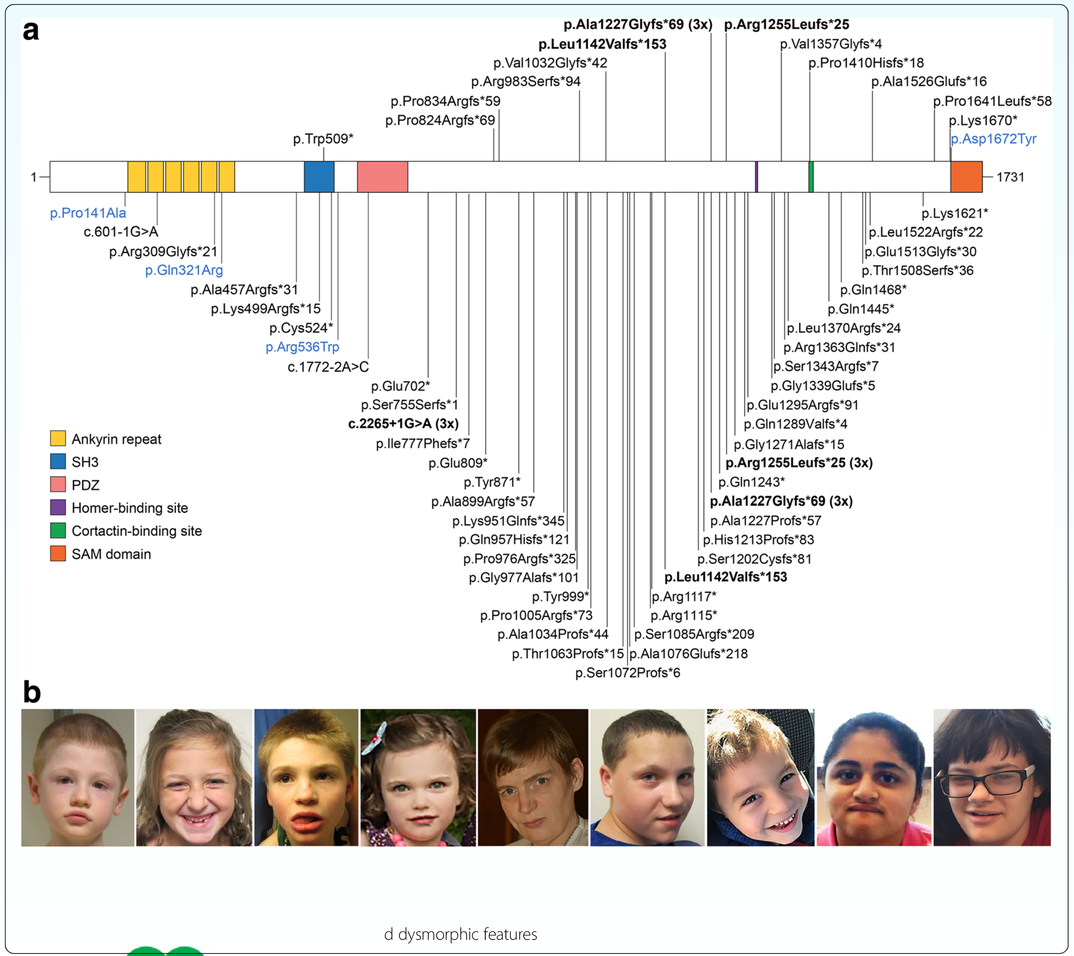
ASD, autism spectrum disorder; IQ, intelligence quotient.

beis *et al. Molecular Autism* (2018) 9:31
https://doi.org/10.1186/s13229-018-0205-9

RESEARCH Open Access

Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by *SHANK3* point mutations

Silvia De Rubeis[1,21], Paige M. Siper[1,21], Allison Durkin[1], Jordana Weissman[1], François Muratet[1,2], Danielle Halpern[1,2], Maria del Pilar Trelles[1,2], Yitzchak Frank[1,3], Reymundo Lozano[1,2,4,5], A. Ting Wang[1,2], J. Lloyd Holder Jr[6], Catalina Betancur[7*], Joseph D. Buxbaum[1,2,5,8,9,10*] and Alexander Kolevzon[1,2,4,10*]

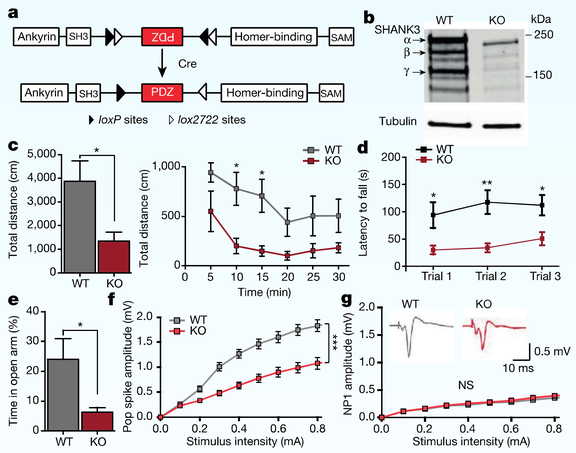


seaver autism center for research & treatment @ mount sinai

Re-expression of SHANK3

Adult restoration of *Shank3* expression rescues selective autistic-like phenotypes

Yuan Mei[1]*, Patricia Monteiro[1,2,3]*, Yang Zhou[1], Jin-Ah Kim[1], Xian Gao[1,4], Zhanyan Fu[1,3] & Guoping Feng[1,3]



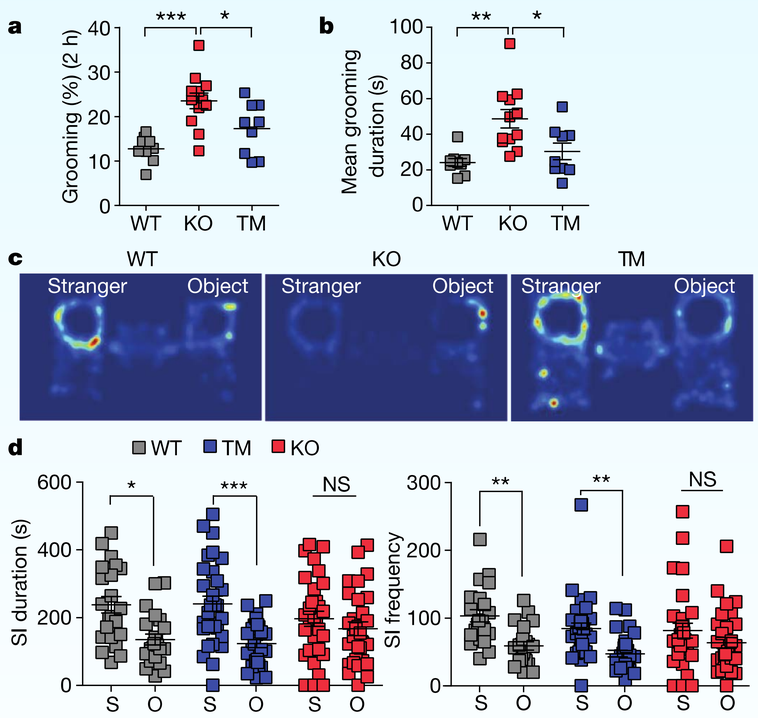


Figure 3 | Adult *Shank3* expression rescued repetitive grooming and social interaction. **a**, **b**, Significantly reduced repetitive grooming behaviour in TM compared to KO mice. **c**, Representative heat maps from the social interaction test for all groups. **d**, Unlike WT mice, KO mice showed no preference for social interaction (SI) with a stranger (S) mouse rather than a novel object (O); this behaviour is rescued in the TM group. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ (one-way repeated measures ANOVA with Bonferroni post-hoc test (**a**, **b**, **d**, left), Kruskal–Wallis test with Dunn's multiple comparison test owing to non-normal distribution (**d**, right)). Data are mean ± s.e.m. (**a** and **b**: $n = 9$ WT, $n = 9$ TM and $n = 12$ KO mice; **d**: $n = 22$ WT, $n = 30$ TM and $n = 30$ KO mice).

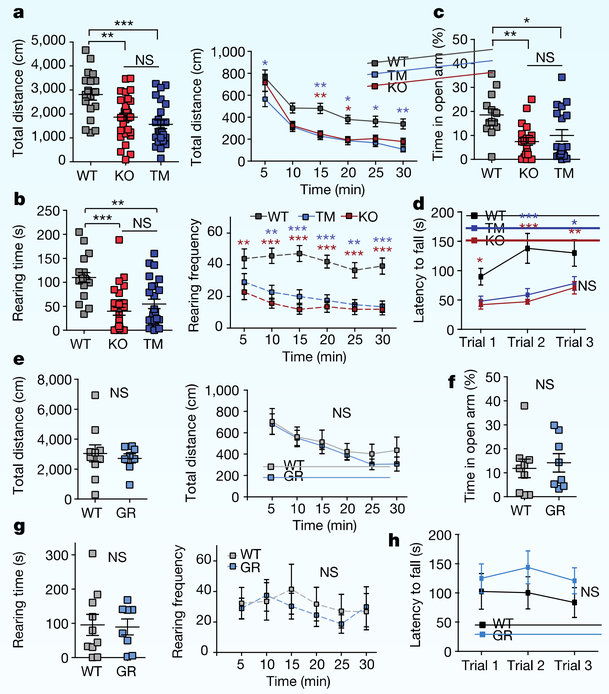
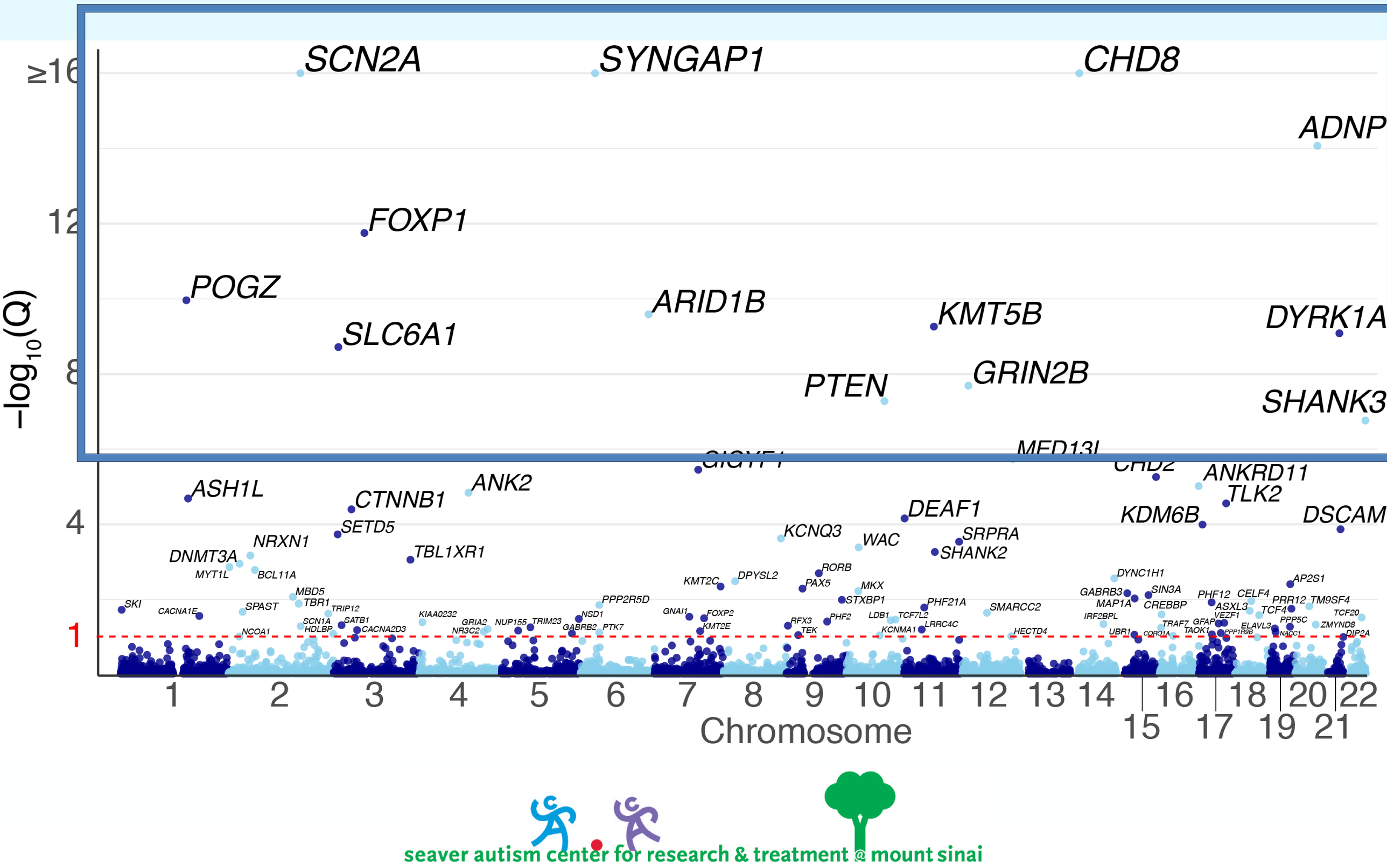


Figure 4 | Restoring *Shank3* expression in adulthood did not rescue anxiety and rotarod deficits. **a**, **b**, Open-field tests indicated that SHANK3 re-expression in adults (TM) does not rescue reduced locomotion and reduced rearing (axiogenic behaviour) in KO mice. NS, not significant. **c**, KO mice spend less time exploring the open arm during the elevated zero maze test; this behaviour is also not rescued in TM group. **d**, Motor coordination measurement from rotarod is not rescued in TM group. **e**–**h**, Germline rescued (GR) $Shank3^{fx/fx}$ mice show that all above parameters for open-field, elevated zero maze and rotarod tests can be rescued if *Shank3* expression is restored at the germ-cell stage. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ (one-way ANOVA (**a**, left, **c**), Kruskal–Wallis test with Dunn's multiple comparisons (**b**, left), two-tailed *t*-test (**e**, left, **f**, **g**, left); two-way repeated measures ANOVA with Bonferroni post-hoc test (**a**, right, **b**, right, **d**, **e**, right, **g**, right, **h**). Data are mean ± s.e.m. (**a**–**c**: $n = 18$ WT, $n = 25$ TM and $n = 27$ KO mice; **d**: $n = 13$ WT, $n = 19$ TM and $n = 21$ KO mice; **e**–**h**: $n = 10$ WT and $n = 8$ GR mice).

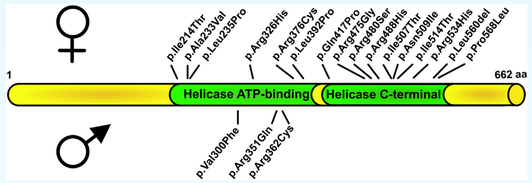
ASC2 (n~36,000)



seaver autism center for research & treatment @ mount sinai

Mutations in top genes are “relatively” common

Mutations in *DDX3X* Are a Common Cause of Unexplained Intellectual Disability with Gender-Specific Effects on Wnt Signaling



substitutions found in affected males are all located within the helicase ATP-binding domain.

DDX3X
  1-3% of ID in girls;
SHANK3
  0.5% of ASD; 0.5% of ID
ANDP
  0.2% of ASD; higher in ID?
Etc

1:15,000-1:20,000

SHANK3 haploinsufficiency: a “common” but underdiagnosed highly penetrant monogenic cause of autism spectrum disorders

Catalina Betancur[1,2,3*] and Joseph D Buxbaum[4]

Table 1 22q13.3 deletions involving *SHANK3* identified through microarray analyses in autism spectrum disorder samples

Study	Subjects	22q13.3 deletions
Sebat *et al.* [5]	165	1 *de novo*
Moessner *et al.* [6]	400	2 *de novo* [a]
Weiss *et al.* [7]	299 [b]	0
van der Zwaag *et al.* [8]	105	0
Guilmatre *et al.* [9]	260	2 *de novo*
Qiao *et al.* [10]	100	0
Schaefer *et al.* [11]	68	0
Pinto *et al.* [12] + Autism Genome Project (manuscript in preparation)	2,446	3 *de novo* [c]
Shen *et al.* [13]	848	0
Rosenfeld *et al.* [14]	1,461	4 (2 *de novo*, 2 unknown)
Bremer *et al.* [15]	223	1 *de novo*
Sanders *et al.* [16]	1,124	0
Wisniowiecka-Kowalnik *et al.* [17]	145	0
Girirajan *et al.* [18]	243	0
Total	**7,887**	**13 (0.16%)**

Table 2 *De novo SHANK3* mutations identified through large-scale screening of autism spectrum disorder samples

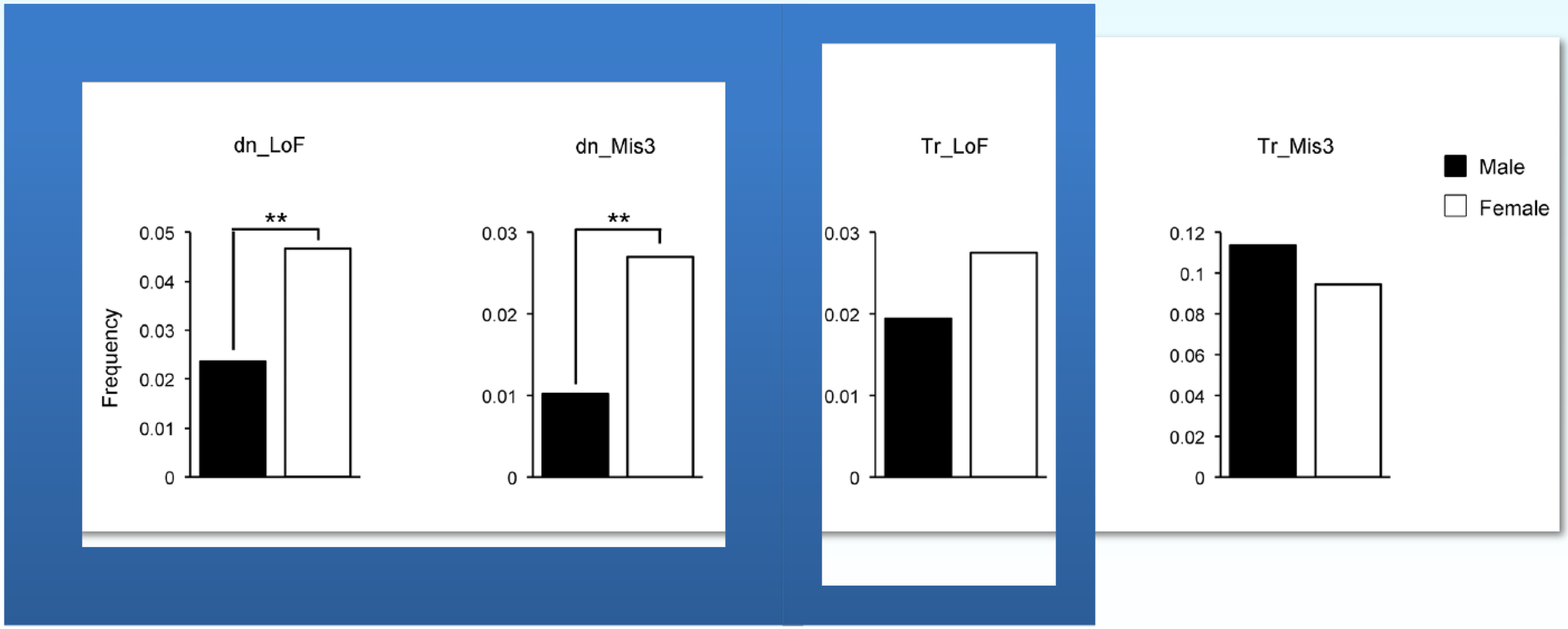
Study	Subjects	Mutations	Nucleotide[a]	Protein[b]	Exon/intron
Durand *et al.* [2]	227	1	g.51159940-51159941insG	p.A1227fs	exon 21
Moessner *et al.* [6]	400	1	g.51121844A>G	p.Q321R	exon 8
Gauthier *et al.* [22]	427	1	g.51153476delG	(splice site deletion)	intron 19
Schaaf *et al.* [23]	339	0			
Boccuto *et al.* [24]	221	2	g.51117094C>G	p.P141A	exon 4
			g.51160144delG	p.E1295fs	exon 21
Total	**1,614**	**5 (0.31%)**			

seaver autism center for research & treatment @ mount sinai

ASC – Top genes are highly penetrant

Synaptic, transcriptional and chromatin genes disrupted in autism

13 NOVEMBER 2014 | VOL 515 | NATURE | 209



OR 20-70

OR ~ 5

seaver autism center for research & treatment @ mount sinai

ASD/DD/ID gene mutations identified via **HTS**

- Not a single pathway by any stretch of the imagination
  - Precision medicine is critical
- Overwhelmingly dominant
  - We are most powered for de novo mutations, which are generally dominant
  - Second allele that can be manipulated
- Primarily LoF
  - But we know the genetic mechanism for many of the recurrent genes)
- Can show a U-shaped curve
- However, tend to be very severe
- In certain cases, it has been shown that late re-expression has benefit
  - Also, behavioral therapies have some efficacy even later in disease
- Top genes are “fairly” common
- Top genes are highly penetrant

PMS/SHANK3 NDD syndrome

- The cause is unambiguous and uncontested – SHANK3 loss
- There is an easy and accurate test for this syndrome – genetic test
- There is very high conversion – ”fully” penetrant
  - If the test is positive there is 80-100% likelihood that the syndrome will manifest
- There are cell and animal models with highest construct validity
  - Translational biomarkers have been developed – EEG etc
- There is good preclinical evidence that reversing the causal deficit will lead to improvements, even if given later in life – mouse models
- Unbiased estimates of prevalence place it at ~1:15,000 live births
  - Orphan designation, but not vanishingly rare – good objective data
- Very engaged family foundation with registries of patients - PMSF
- Expert sites are doing extensive phenotyping and can identify key clinical endpoints – RDCRN
- FDA is expected to be very supportive
  - Works with families; More flexible about endpoints/indications; PRV is likely
- If a drug is successful, there is reasonable path for the same drug to also get an indication in related disorders – SHANK2?, EEG biomarker

Mizuyaf syndrome

- There is no syndrome called Mizuyaf syndrome
  - (Mizuyaf is Hebrew for ‘forged’)
- However, there are at dozens of NDD syndromes with many of these properties
  - And the fraction with most of them will increase with more experimentation

Seaver Autism Center - Drug Discovery and Development

	Molecular Target	Human Neurons	GM Rodent Models	Patients
Expertise	• Lead site for international Autism Sequencing Consortium (ASC) n~38,000 • Knowledge of top genes • Knowledge of primary molecular targets	• Molecular results from neural cells • Multiple protocols to create induced neurons • Known cellular phenotype	• Phenotypes of relevant models • Behavioral endpoints • Translatable biomarkers	• Lead site for ASC • Phenotype of patients • Clinical endpoints • Clinical trials • Multi-site trials
Resources	• Biochemical and molecular biological assays	• CRISPR-Cas9 generated stem cells • Patient-derived stem cells	• Mouse and rat models	• Prospectively assessed patient groups • Multi-site studies • Assess 150-200 new families per year
DDD Pipeline	• DNA, RNA, protein and pathway based, targeted therapeutics *and/or* • Agnostic, high-throughput screens	• Develop robust cellular phenotype assays to screen libraries and test lead compounds • Use phenotype assays for go/no-go decisions	• Identify relevant phenotypes to use as in vivo validation of lead compounds • Use phenotype assays for go/no-go decisions	• Clinical trials

ADNP; DDX3X; FOXP1; SHANK3

seaver autism center for research & treatment @ mount sinai

Thank you!

seaver autism center for research & treatment @ mount sinai