New Findings in Autism

Joseph D. Buxbaum, MSc, PhD
The Seaver Autism Center for Research and Treatment
New York, USA

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Disclosure: Mount Sinai and JDB have a shared patent on the use of IGF-1 in PMS/22q13DS

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We greatly appreciate the support of –
Autism Science Foundation; Autism Speaks; NIH; Seaver Foundation; Simons Foundation
All the participating families; and our known and anonymous private donors.

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Two views on developmental disorders

Top down – Behavior

Bottom up – Causes

- 1. Developmental disorders are frequently *behaviorally* defined
  - For example, autism is defined by:
    - Deficits in social interaction and the social use of language
    - Presence of stereotypical mannerism and/or proscribed interests
- 2. Developmental disorders can be *caused* by genetic or environmental insults
  - For example, autism is highly genetic

Hypothesis: As we learn more about the causes of autism this will lead to better treatments

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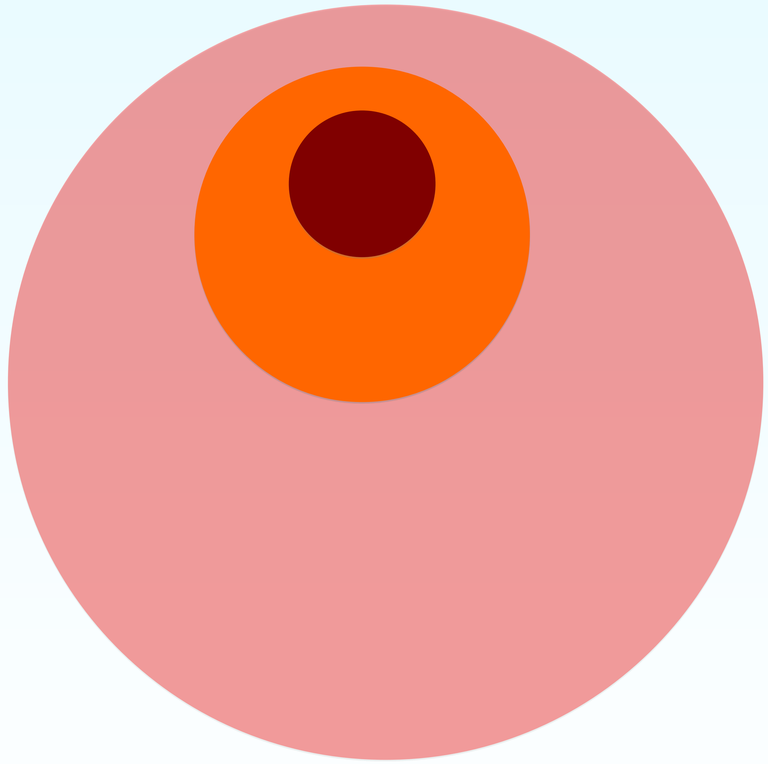
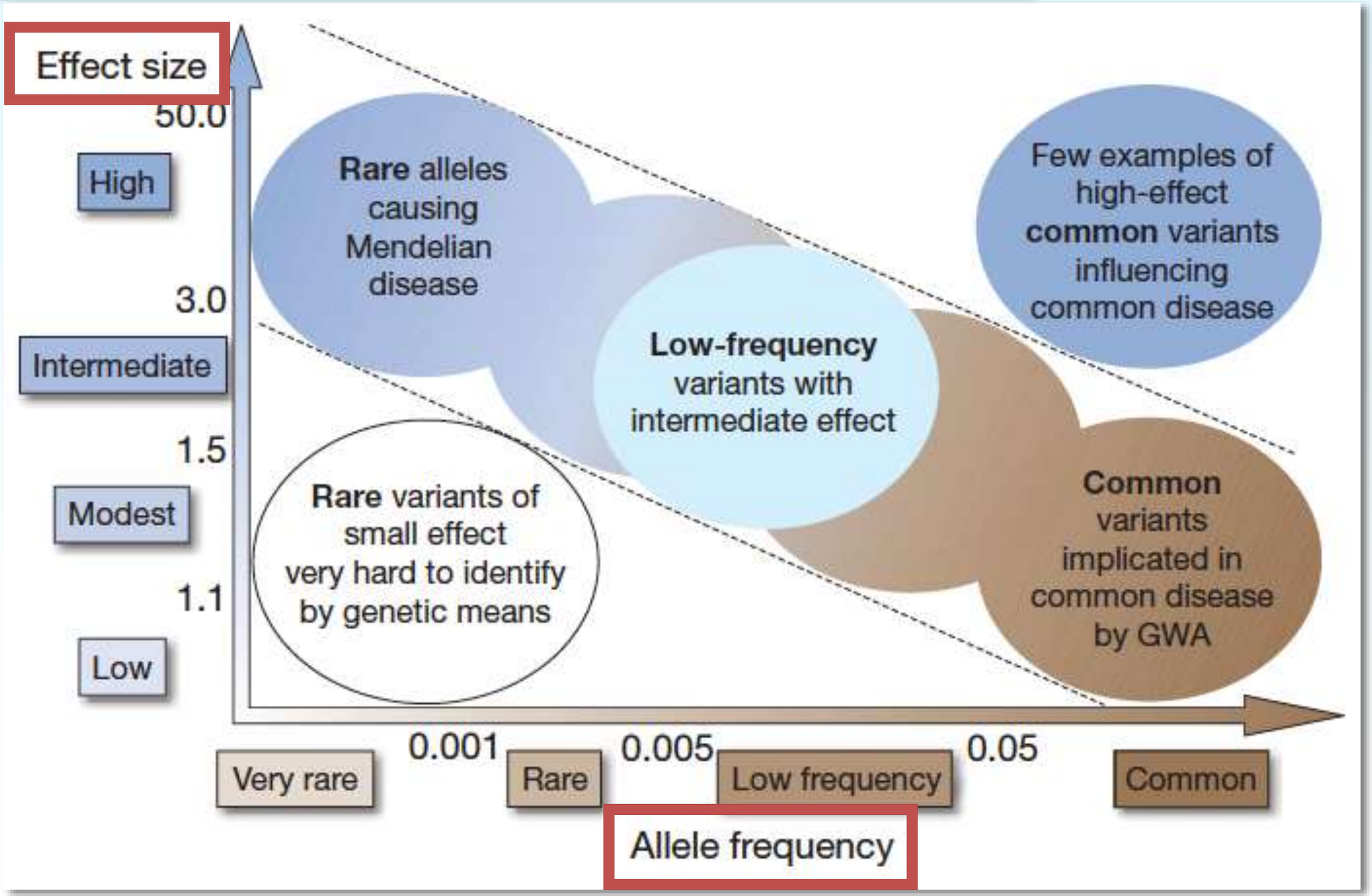
Impact of discovering an etiology for a development disorder

- Benefit to patient
  - More informed care
  - Soon? - Personalized medicine
- Benefit to family
  - Information about clinical course
  - Information about recurrence
  - Family and advocacy groups
- Benefit to society
  - Clinical information on a population level
  - Understanding of mechanisms
  - New targets for medicine
  - Model systems
  - New medicines



Finding the missing heritability of complex diseases

Teri A. Manolio[1], Francis S. Collins[2], Nancy J. Cox[3], David B. Goldstein[4], Lucia A. Hindorff[5], David J. Hunter[6], Mark I. McCarthy[7], Erin M. Ramos[5], Lon R. Cardon[8], Aravinda Chakravarti[9], Judy H. Cho[10], Alan E. Guttmacher[1], Augustine Kong[11], Leonid Kruglyak[12], Elaine Mardis[13], Charles N. Rotimi[14], Montgomery Slatkin[15], David Valle[9], Alice S. Whittemore[16], Michael Boehnke[17], Andrew G. Clark[18], Evan E. Eichler[19], Greg Gibson[20], Jonathan L. Haines[21], Trudy F. C. Mackay[22], Steven A. McCarroll[23] & Peter M. Visscher[24]



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]

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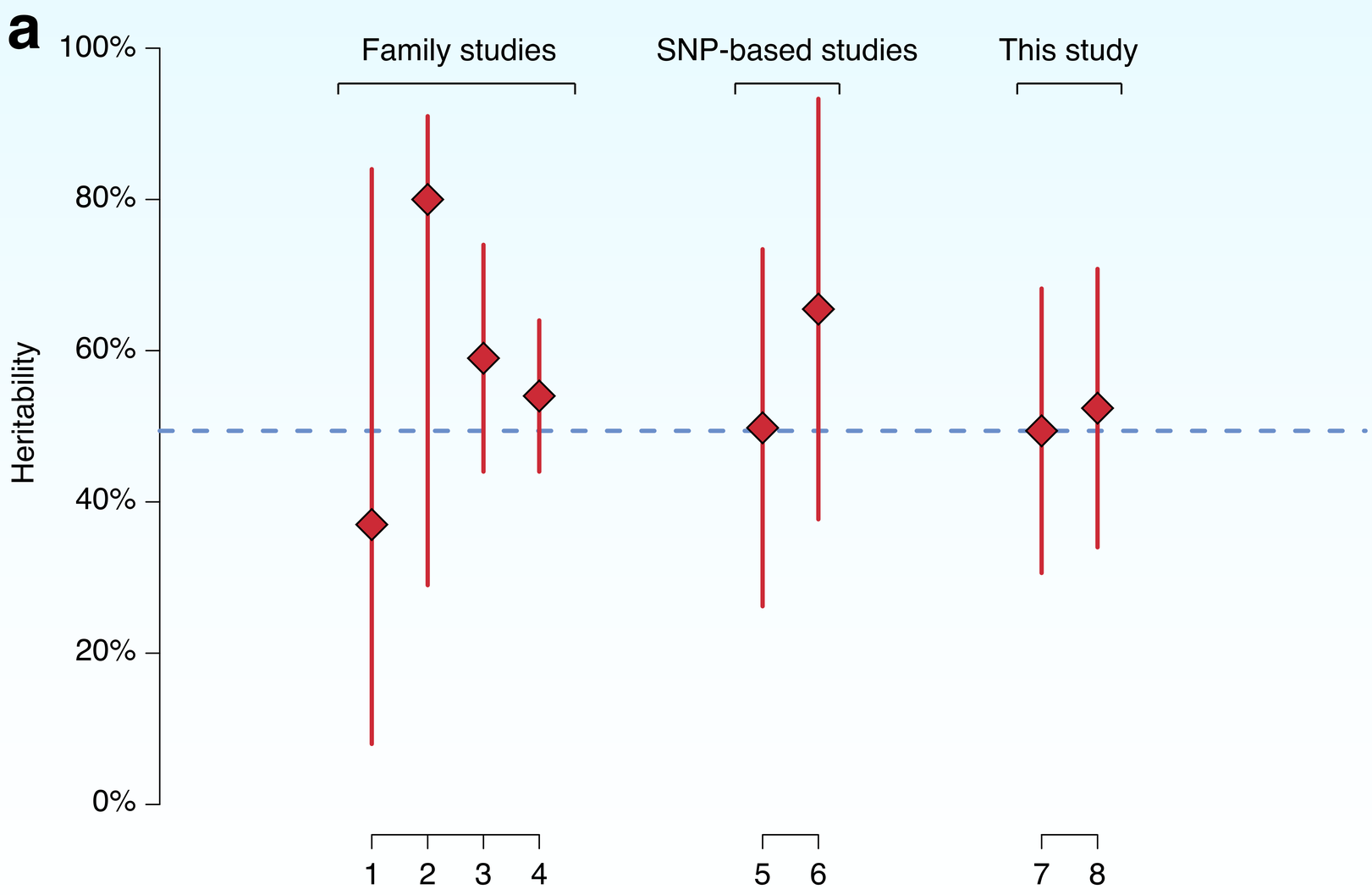

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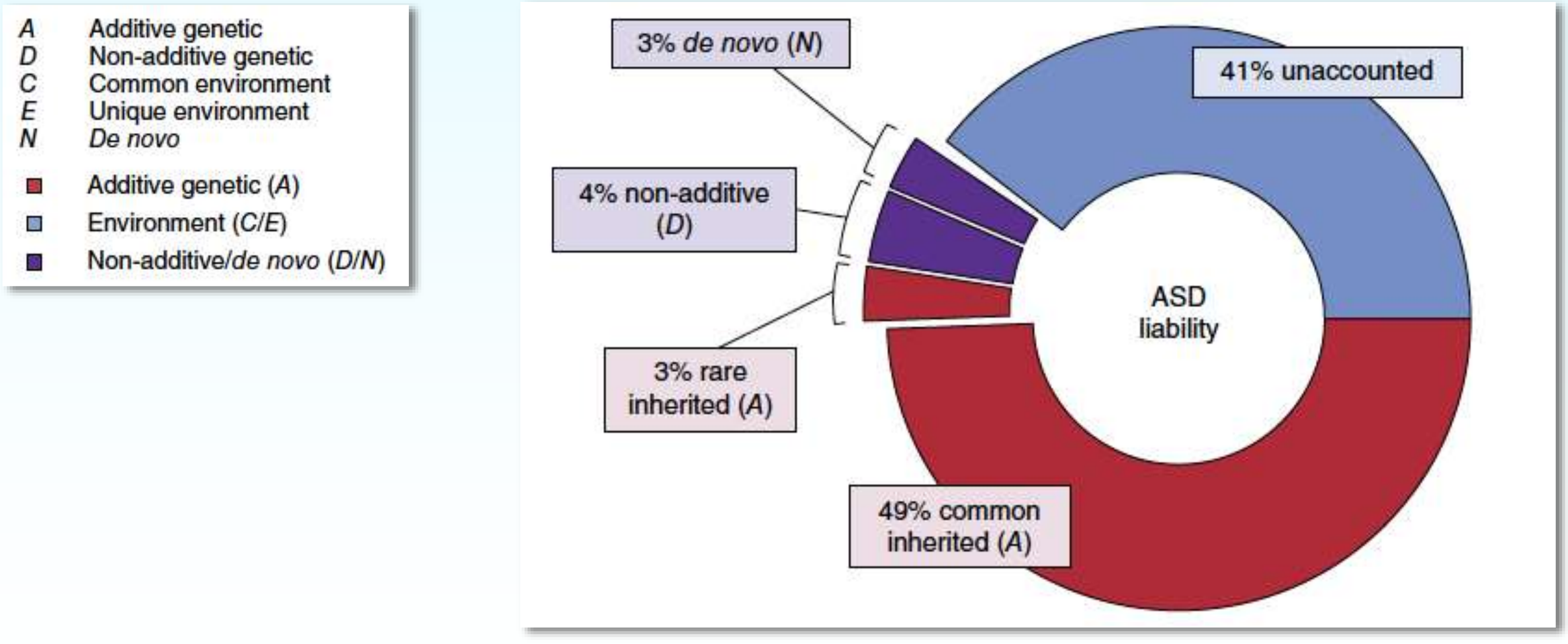

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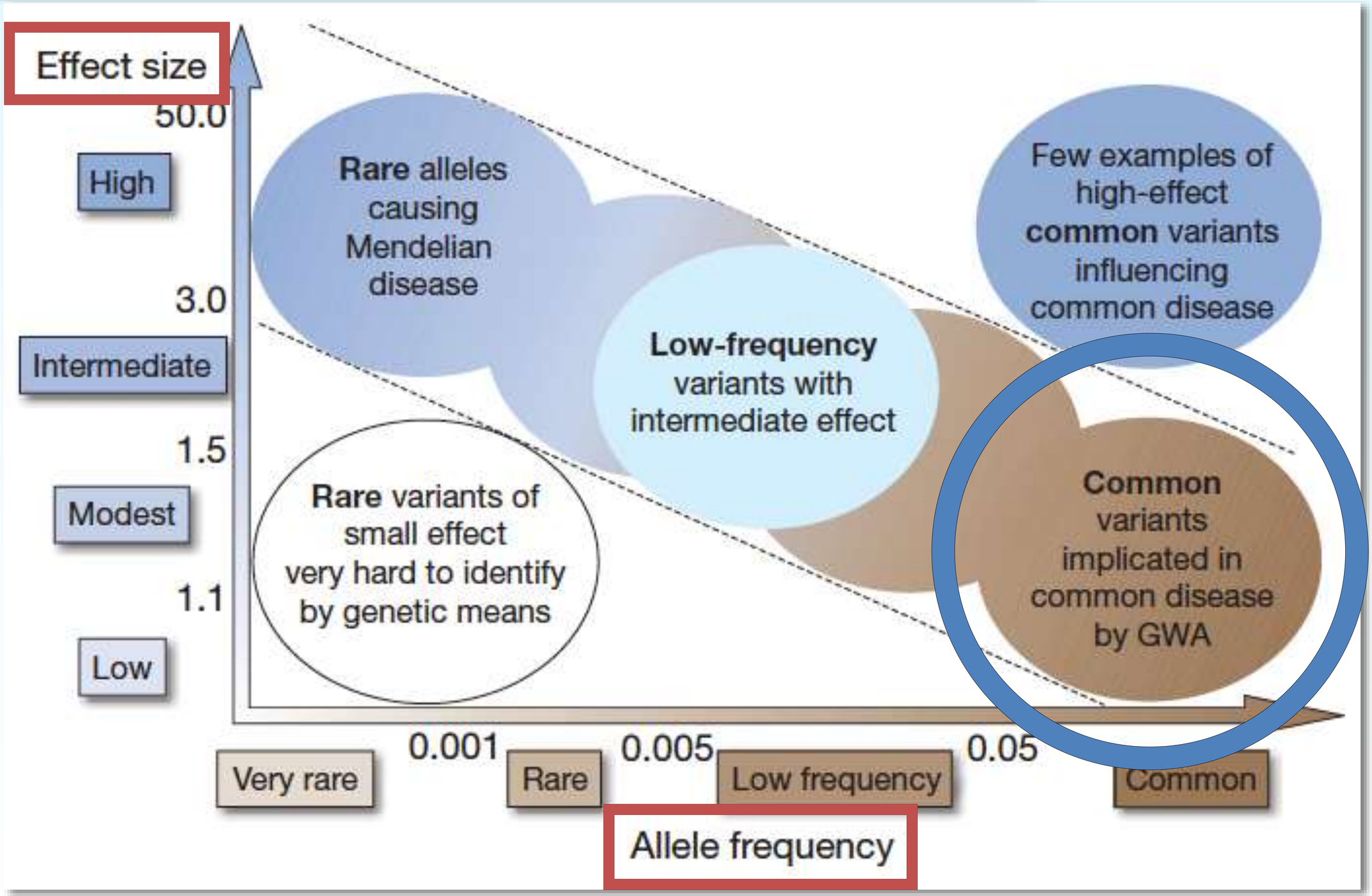

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

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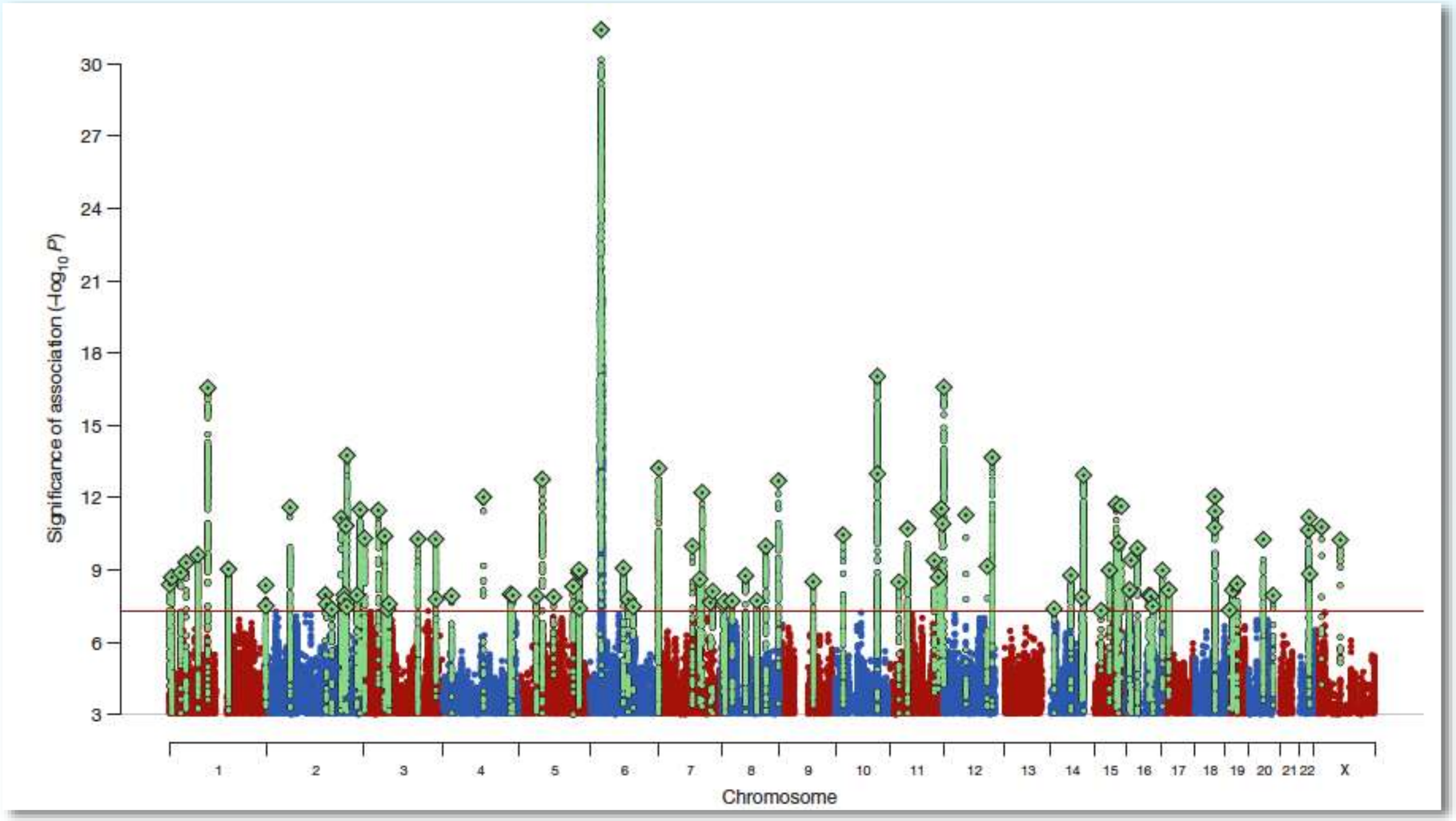

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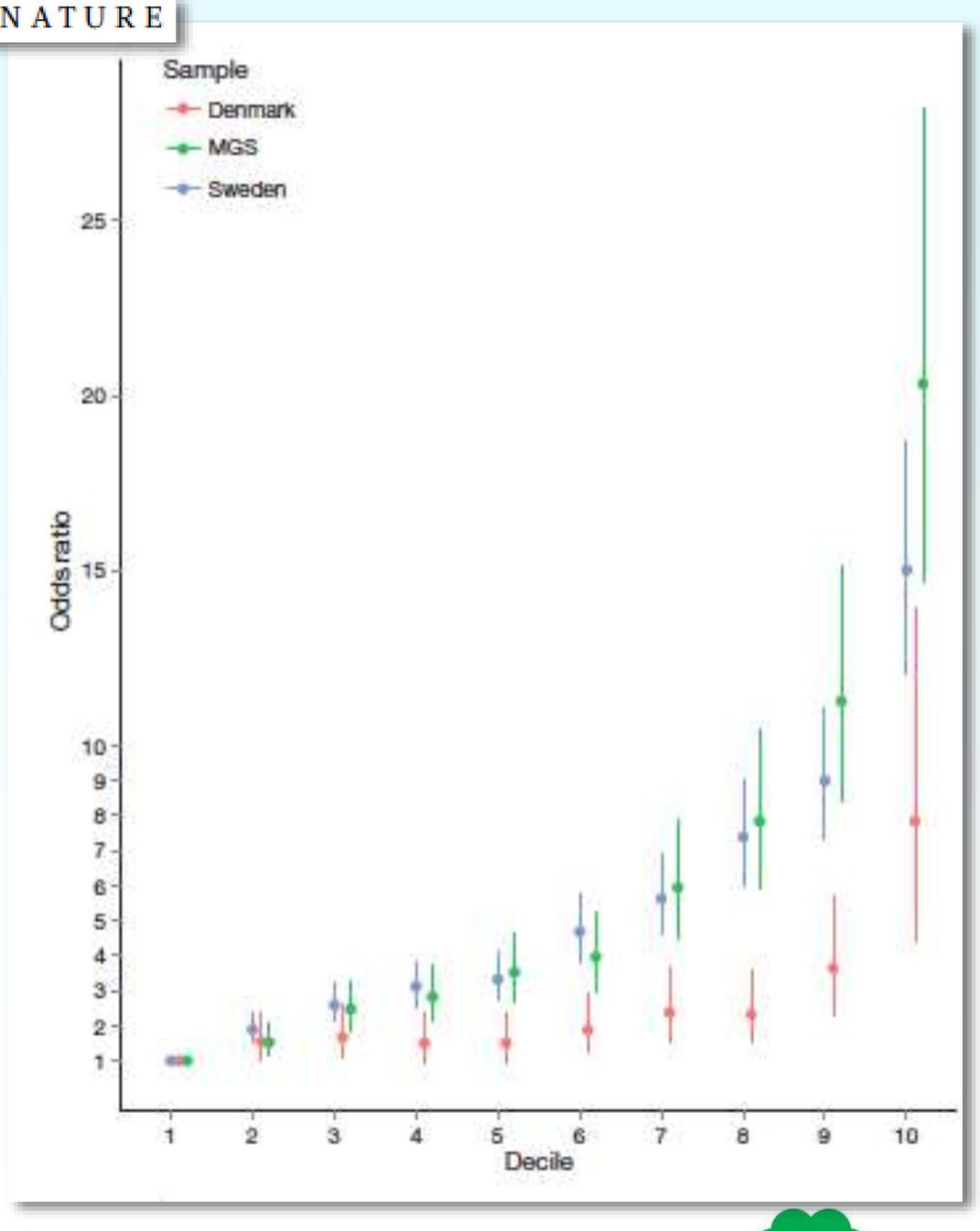

Individuals with few risk SNPs

Individuals with many risk SNPs

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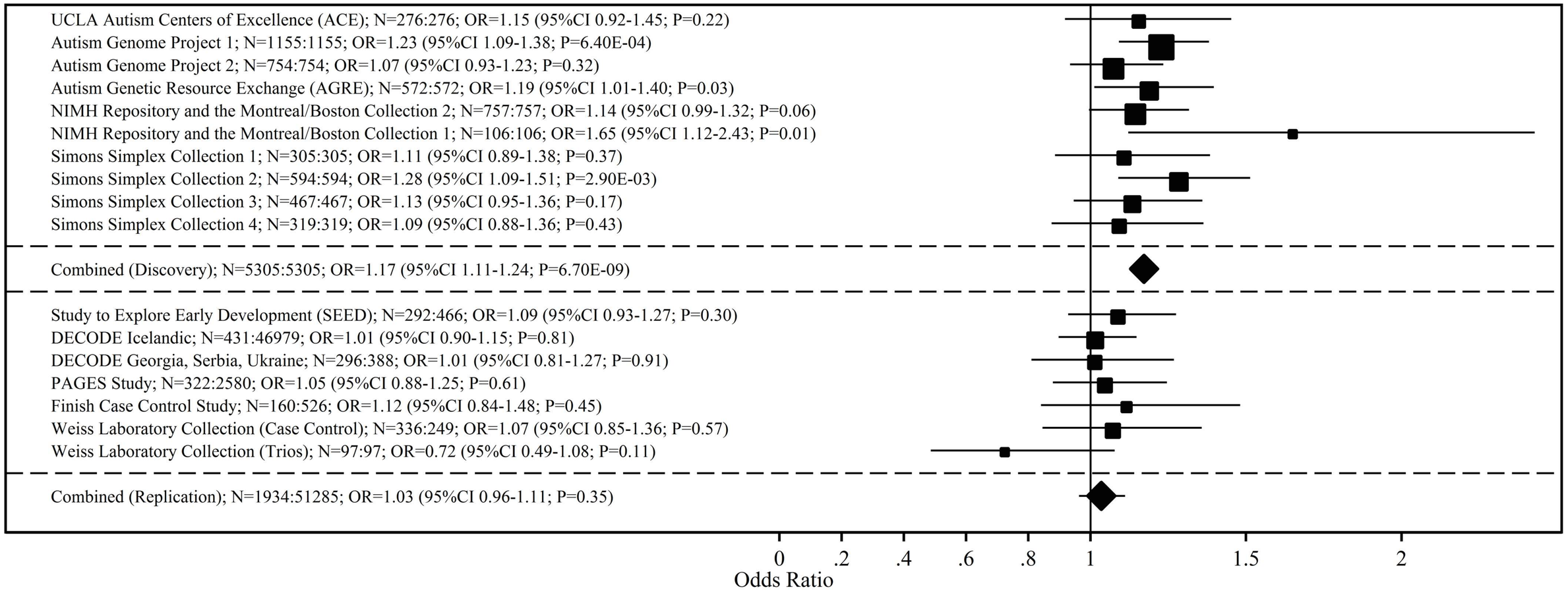
PGC-ASD study



First unequivocal GWAS signal in ASD – Ric Anney et al

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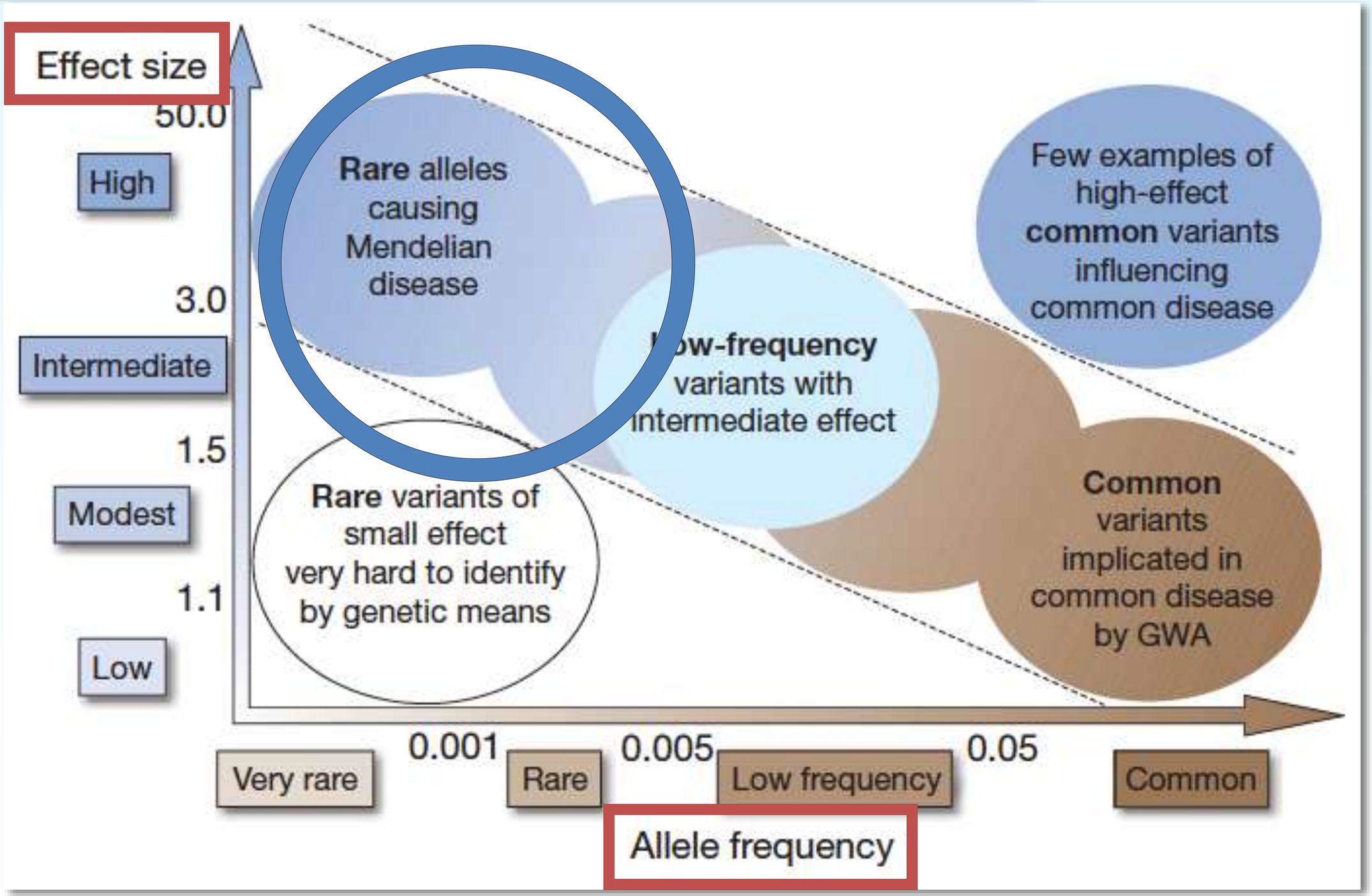

Toward Fulfilling the Promise of Molecular Medicine in Fragile X Syndrome

Dilja D. Krueger and Mark F. Bear

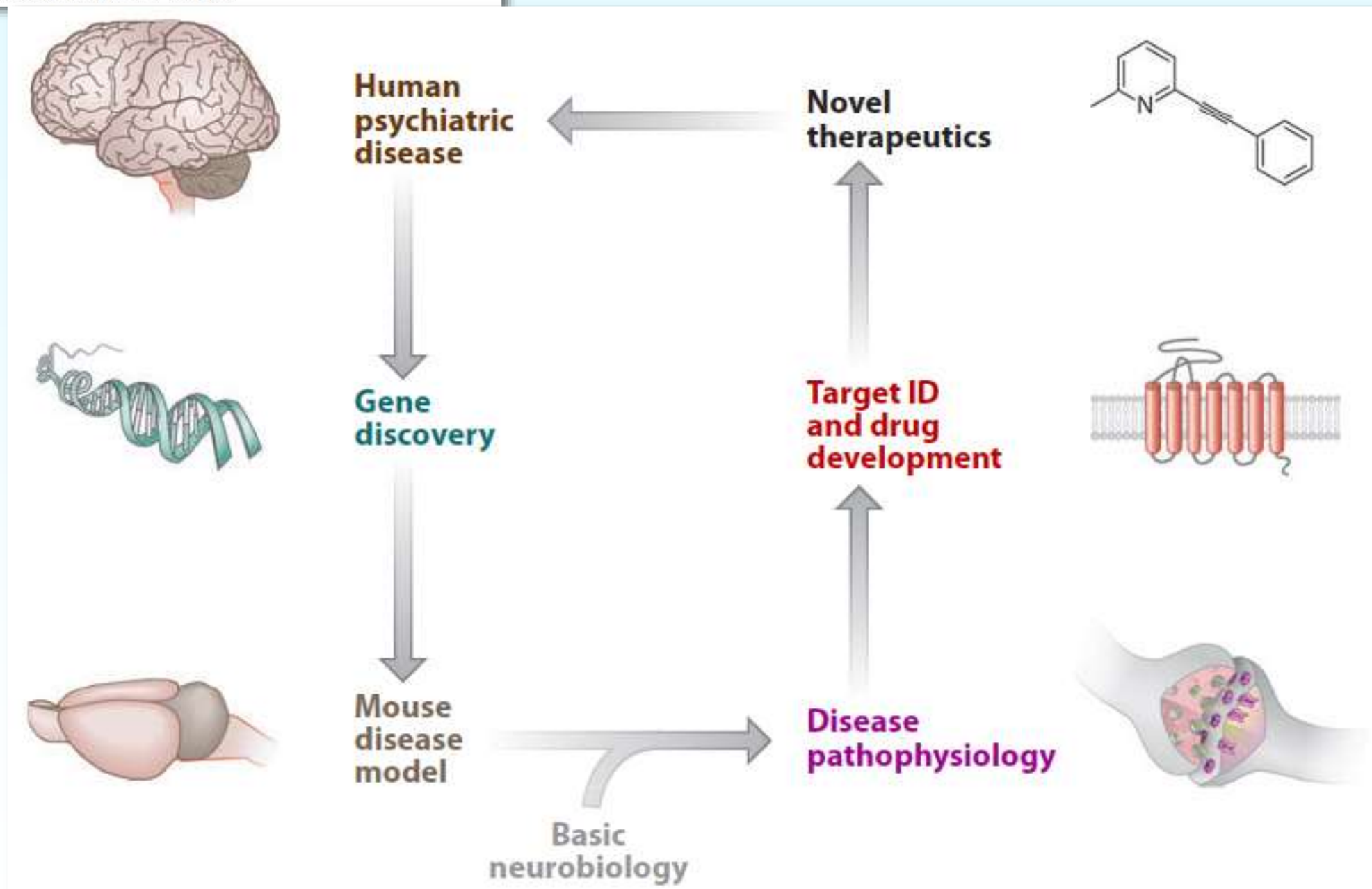

Figure 1

The promise of molecular medicine in psychiatric and neurodevelopmental disorders (see sidebar "The Promise of Molecular Medicine in Brain Disorders" for explanation).

ASC

ARTICLE

doi:10.1038/nature13772

Synaptic, transcriptional and chromatin genes disrupted in autism

A list of authors and their affiliations appears at the end of the paper

SSC

ARTICLE

doi:10.1038/nature13908

The contribution of *de novo* coding mutations to autism spectrum disorder

Ivan Iossifov[1]*, Brian J. O'Roak[2,3]*, Stephan J. Sanders[4,5]*, Michael Ronemus[1]*, Niklas Krumm[2], Dan Levy[1], Holly A. Stessman[2], Kali T. Witherspoon[2], Laura Vives[2], Karynne E. Patterson[2], Joshua D. Smith[2], Bryan Paeper[2], Deborah A. Nickerson[2], Jeanselle Dea[4], Shan Dong[5,6], Luis E. Gonzalez[7], Jeffrey D. Mandell[4], Shrikant M. Mane[8], Michael T. Murtha[7], Catherine A. Sullivan[7], Michael F. Walker[4], Zainulabedin Waqar[7], Liping Wei[6,9], A. Jeremy Willsey[4,5], Boris Yamrom[1], Yoon-ha Lee[1], Ewa Grabowska[1,10], Ertugrul Dalkic[1,11], Zihua Wang[1], Steven Marks[1], Peter Andrews[1], Anthony Leotta[1], Jude Kendall[1], Inessa Hakker[1], Julie Rosenbaum[1], Beicong Ma[1], Linda Rodgers[1], Jennifer Troge[1], Giuseppe Narzisi[1,10], Seungtai Yoon[1], Michael C. Schatz[1], Kenny Ye[12], W. Richard McCombie[1], Jay Shendure[2], Evan E. Eichler[2,13], Matthew W. State[4,5,7,14] & Michael Wigler[1]

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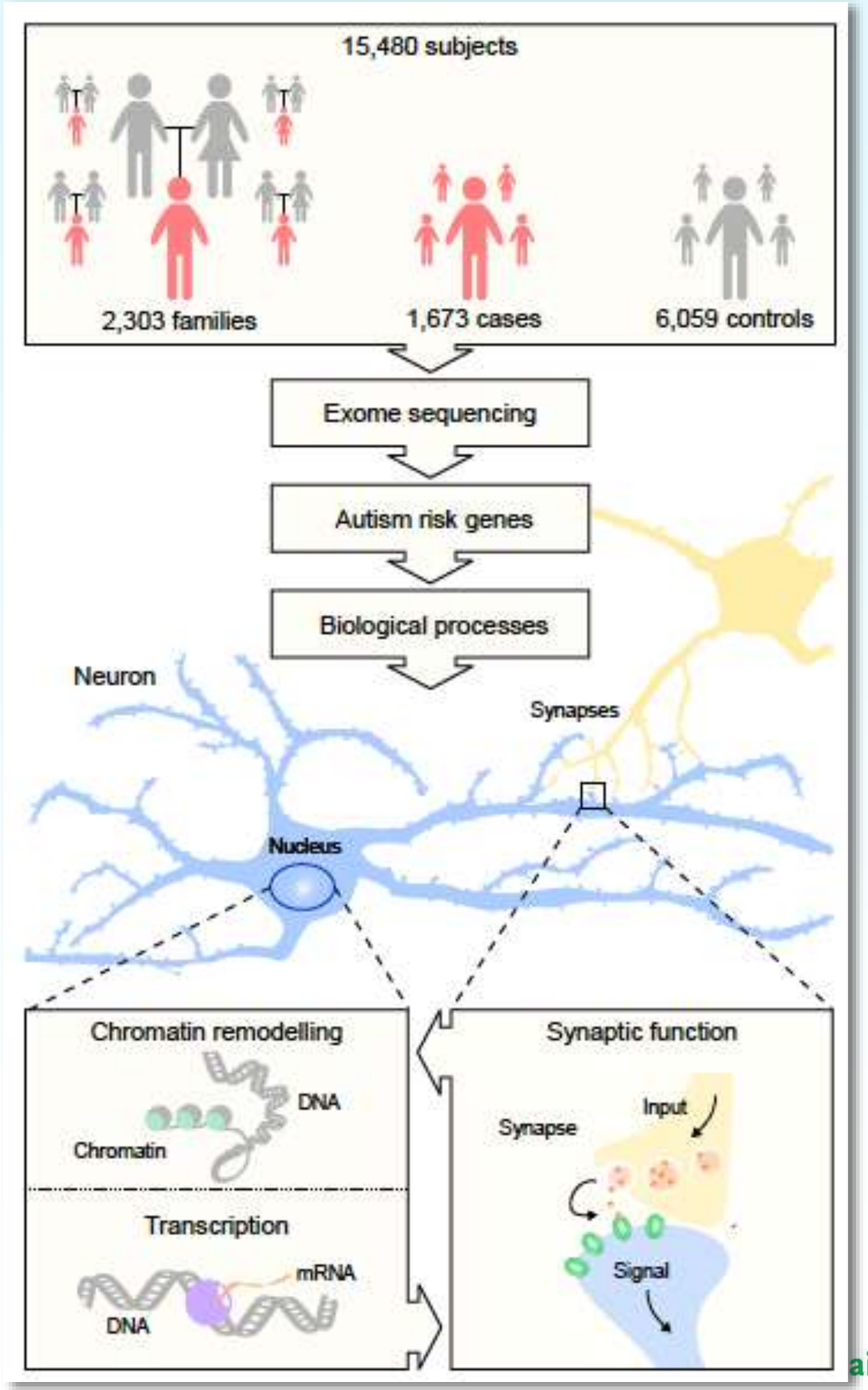
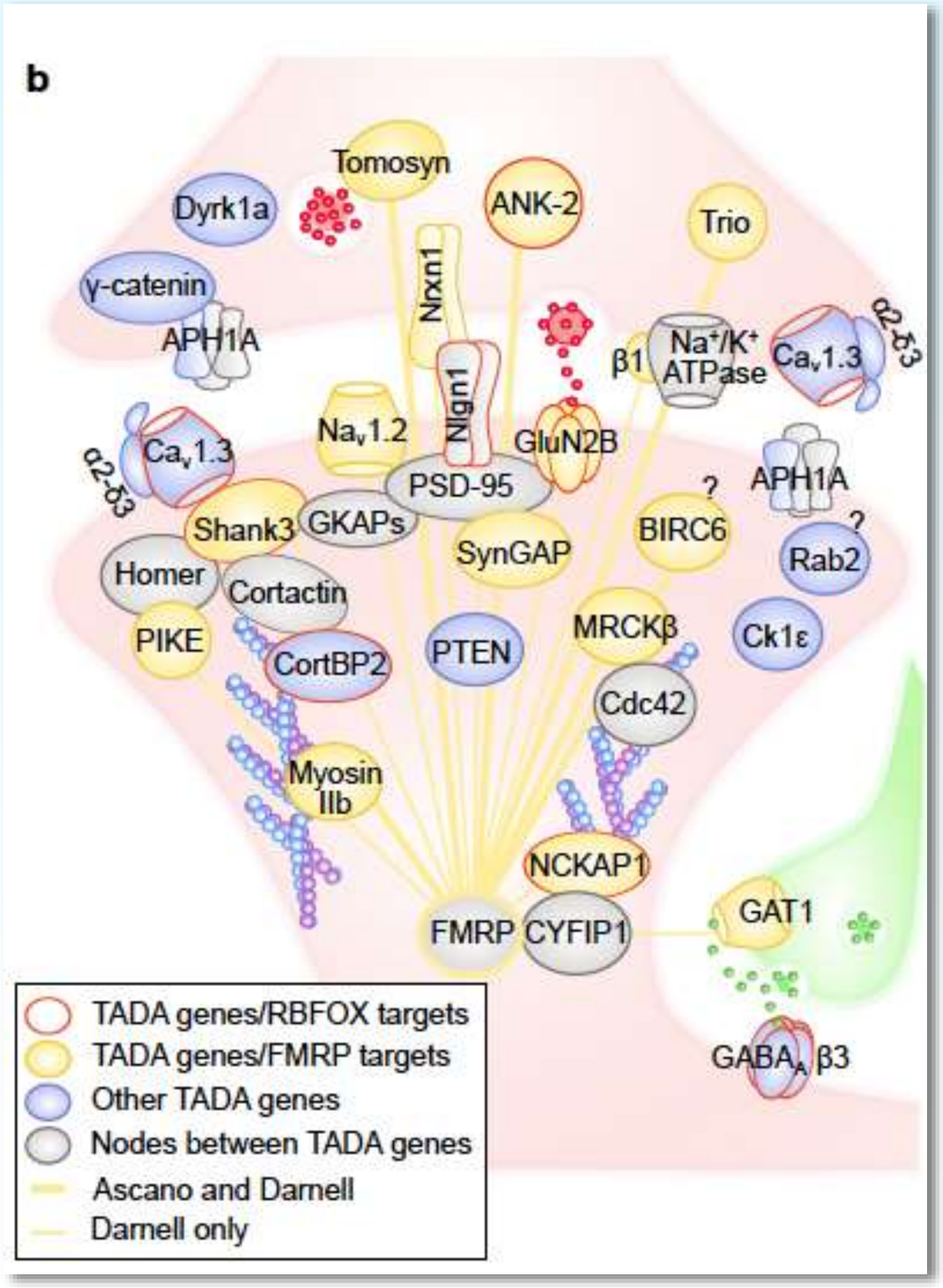
Buxbaum, Daly, Devlin, Roeder, and State, PI

ASC 1 - Summary



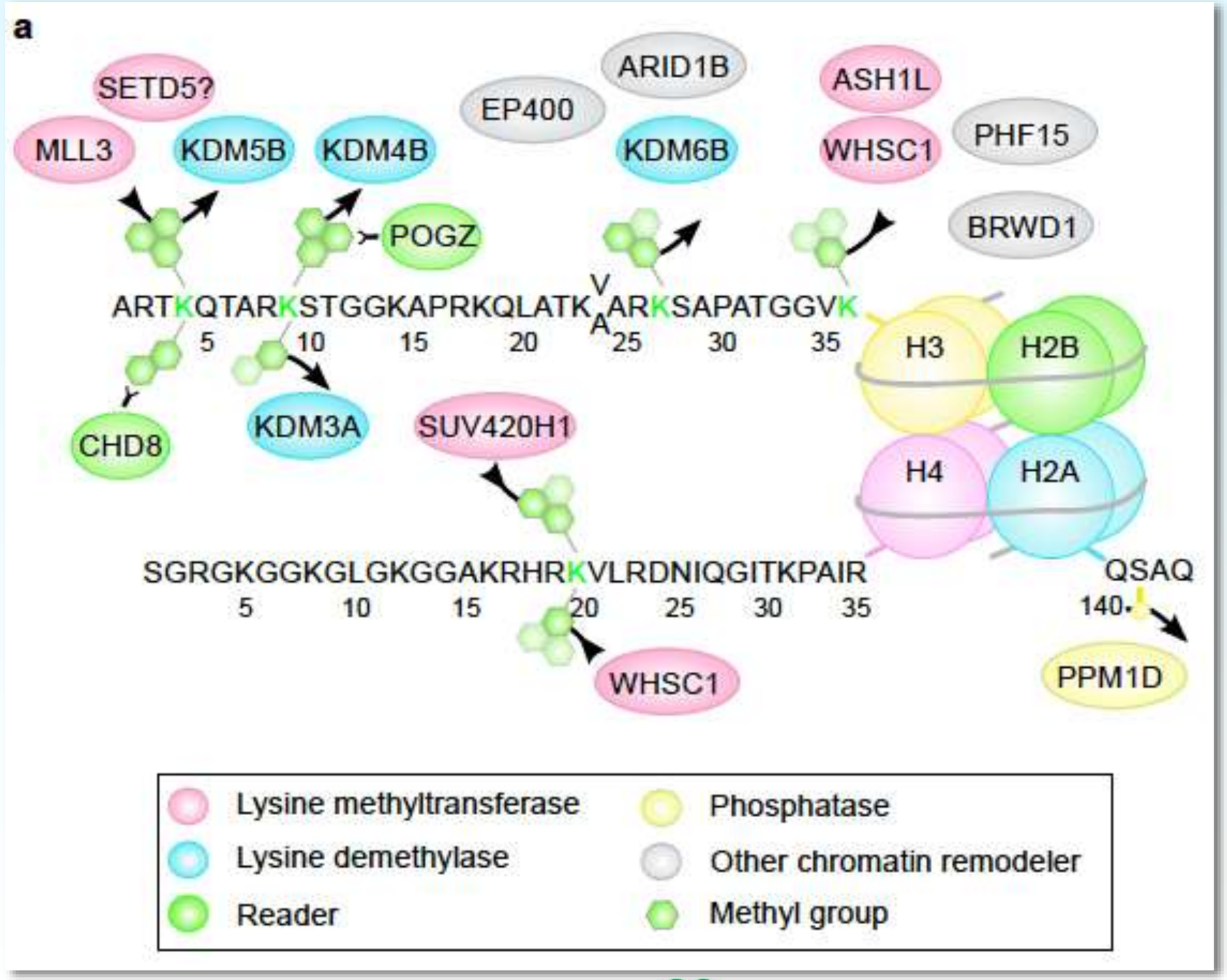
ASC – Study 1

Many of the ASC genes are synaptic



ASC – Study 1

Many of the ASC genes are involved in chromatin remodelling



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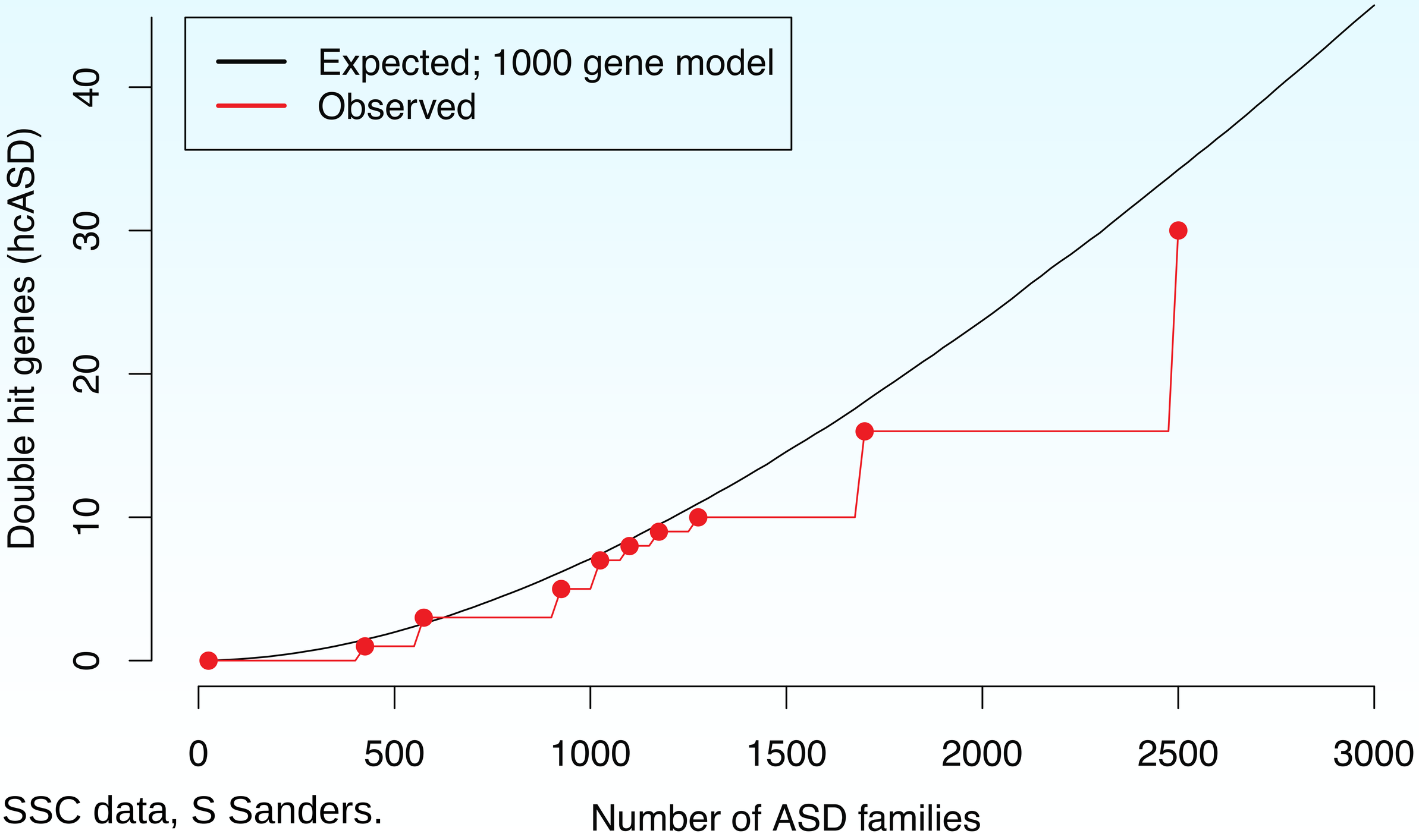
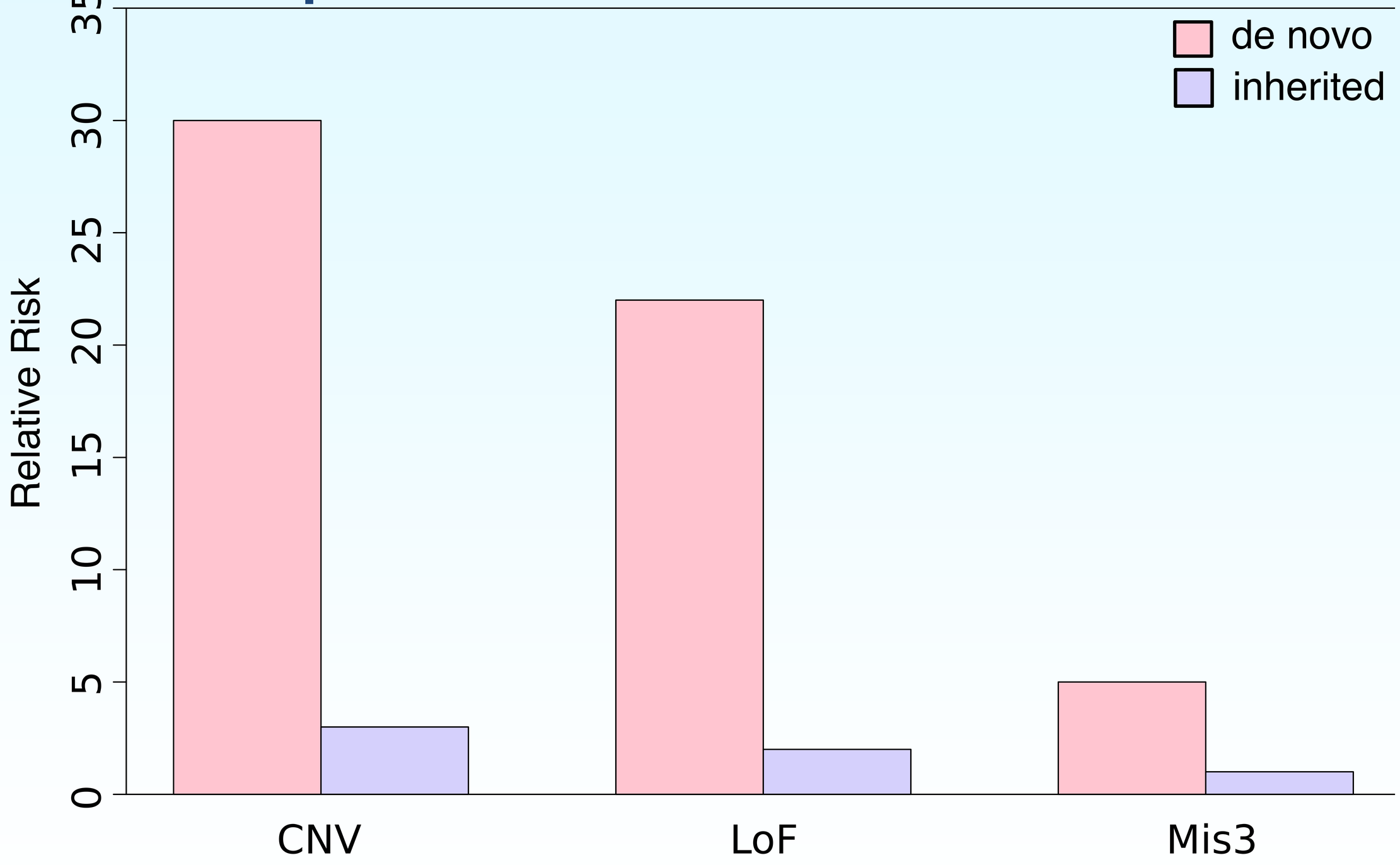
Multiple hit de novo LoF genes



SSC data, S Sanders.

Comparison of Relative Risks



Slide from K Roeder

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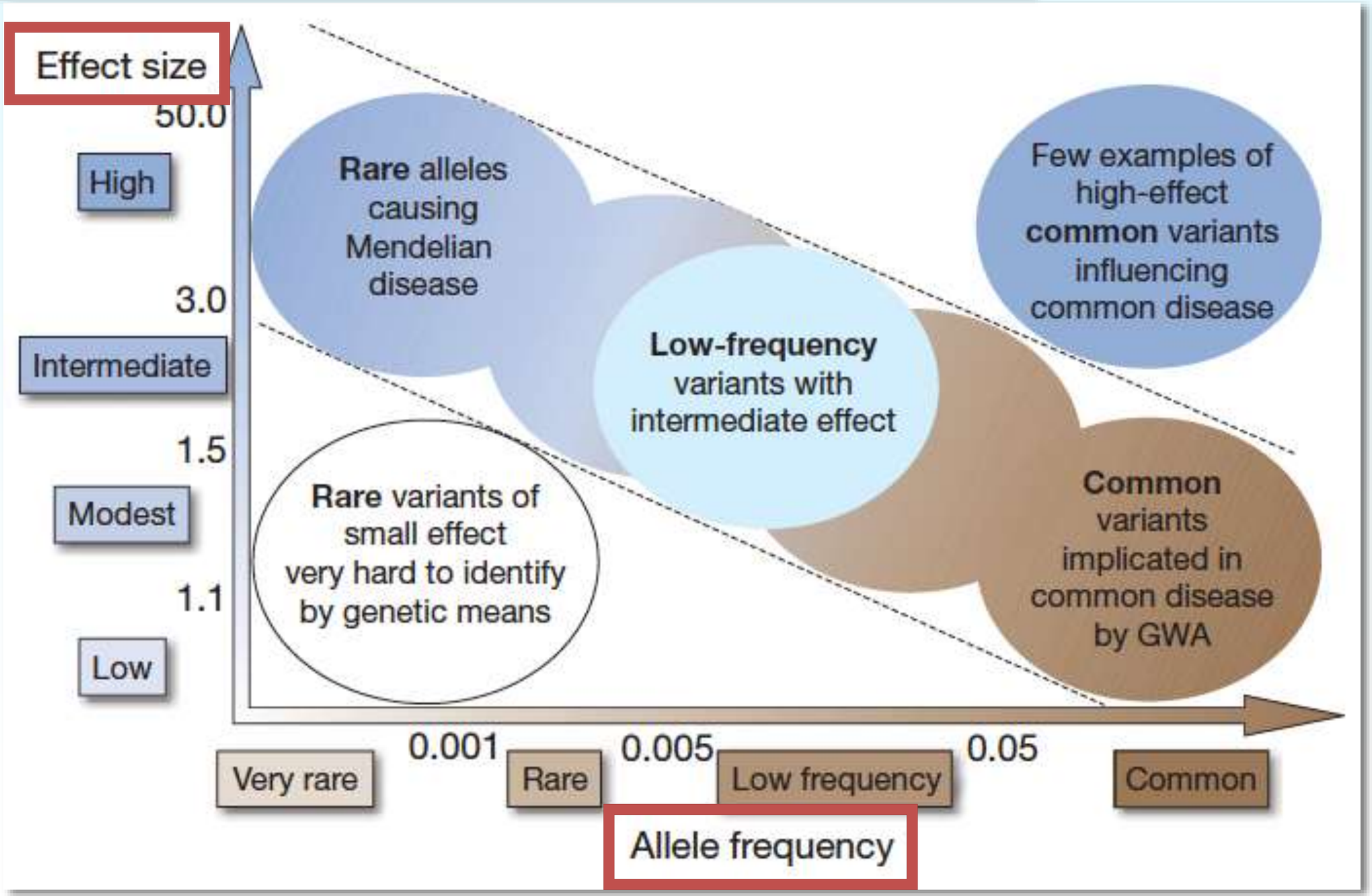

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"In the SSC sample, structured to enrich for *de novo* CNV and LoF mutations, their contribution to the variance in liability is 2.6. Yet *de novo* events can have a large impact on liability and 14% of subjects carry such mutations: roughly 80% of subjects that are carriers of a *de novo* CNV would not be affected if they were not carriers; likewise, for carriers of *de novo* LoF mutations, 57% would not be affected."

In many/most cases, autism results from the interaction of common and rare genetic variation

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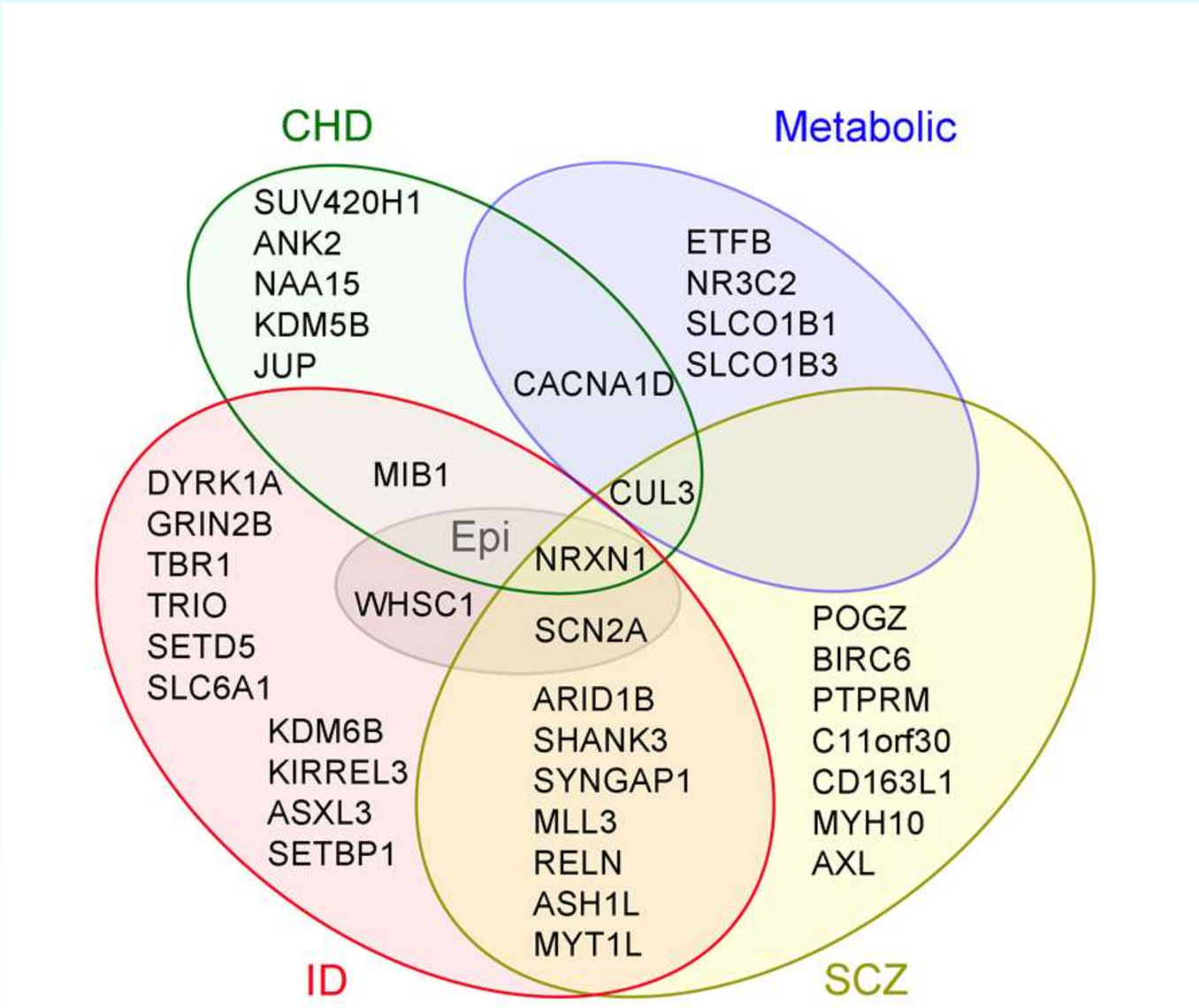
ASC – Study 1



Many of the ASC genes have been implicated in other disorders

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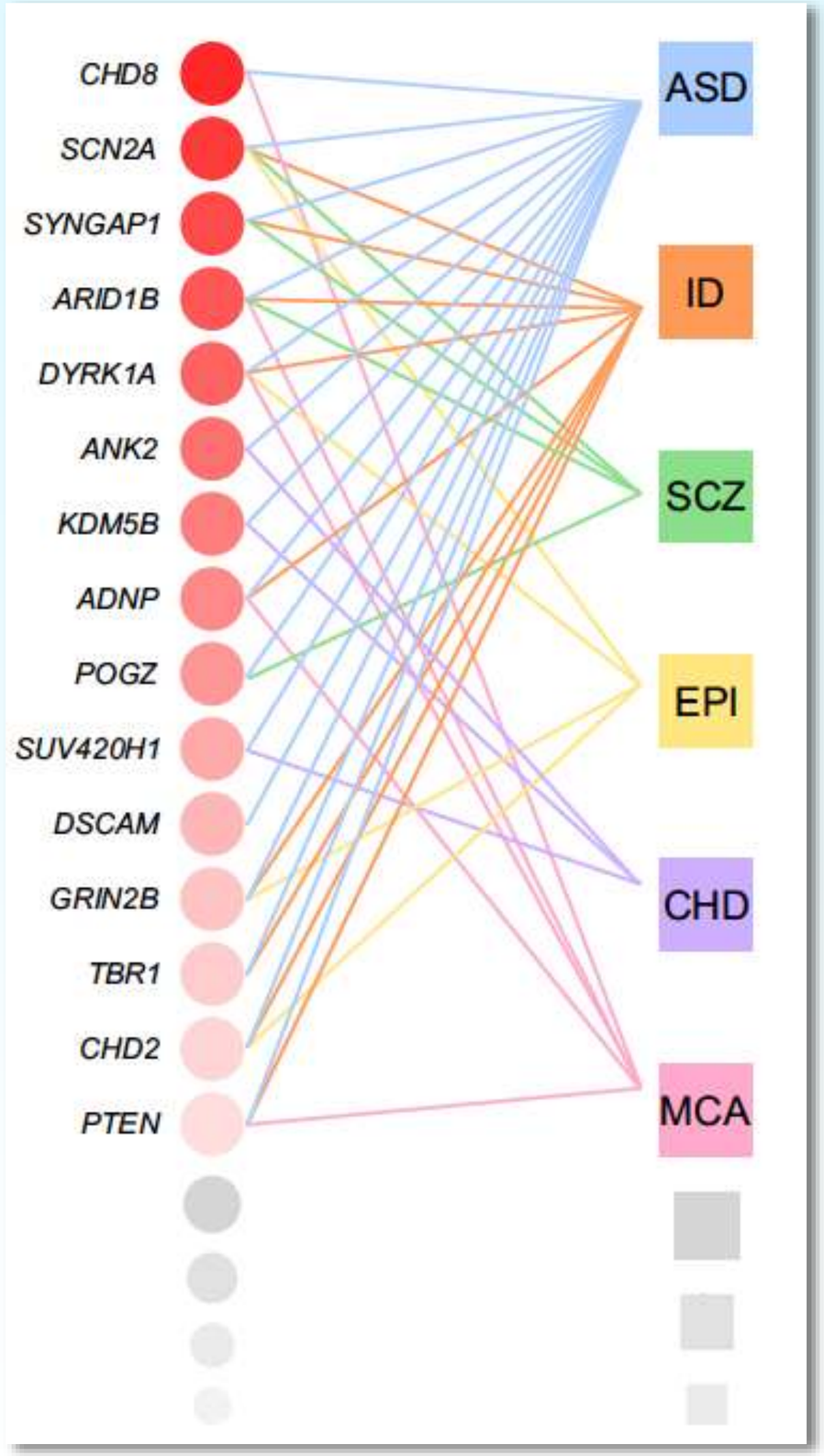
Commentary

Biological Psychiatry

DSM-5 and Psychiatric Genetics— Round Hole, Meet Square Peg

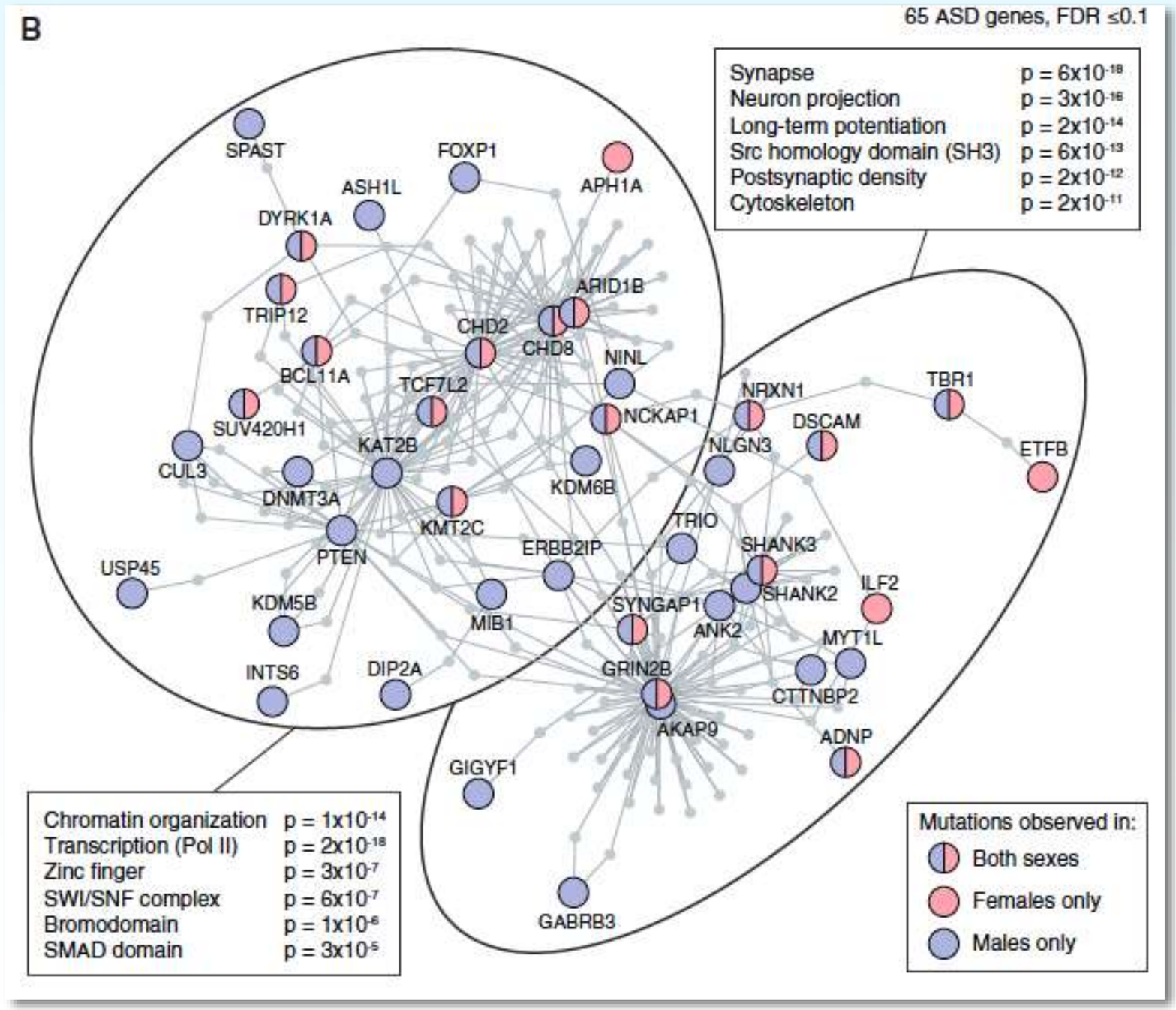


Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci

Stephan J. Sanders,[1,*] Xin He,[2] A. Jeremy Willsey,[1] A. Gulhan Ercan-Sencicek,[3] Kaitlin E. Samocha,[4,5,6] A. Ercument Cicek,[7,8] Michael T. Murtha,[3] Vanessa H. Bal,[1] Somer L. Bishop,[1] Shan Dong,[9] Arthur P. Goldberg,[10,11] Cai Jinlu,[10,11] John F. Keaney III,[12] Lambertus Klei,[13] Jeffrey D. Mandell,[1] Daniel Moreno-De-Luca,[14] Christopher S. Poultney,[10,11] Elise B. Robinson,[4,5] Louw Smith,[1] Tor Solli-Nowlan,[15] Mack Y. Su,[16] Nicole A. Teran,[17] Michael F. Walker,[1] Donna M. Werling,[1] Arthur L. Beaudet,[18] Rita M. Cantor,[19] Eric Fombonne,[20] Daniel H. Geschwind,[21] Dorothy E. Grice,[11] Catherine Lord,[22] Jennifer K. Lowe,[21] Shrikant M. Mane,[23] Donna M. Martin,[24] Eric M. Morrow,[25] Michael E. Talkowski,[26] James S. Sutcliffe,[27] Christopher A. Walsh,[28] Timothy W. Yu,[28] Autism Sequencing Consortium, David H. Ledbetter,[29] Christa Lese Martin,[29] Edwin H. Cook,[30] Joseph D. Buxbaum,[10,11] Mark J. Daly,[4,5] Bernie Devlin,[13] Kathryn Roeder,[7,31] and Matthew W. State[1,*]

Neuron 87, 1215–1233, September 23, 2015

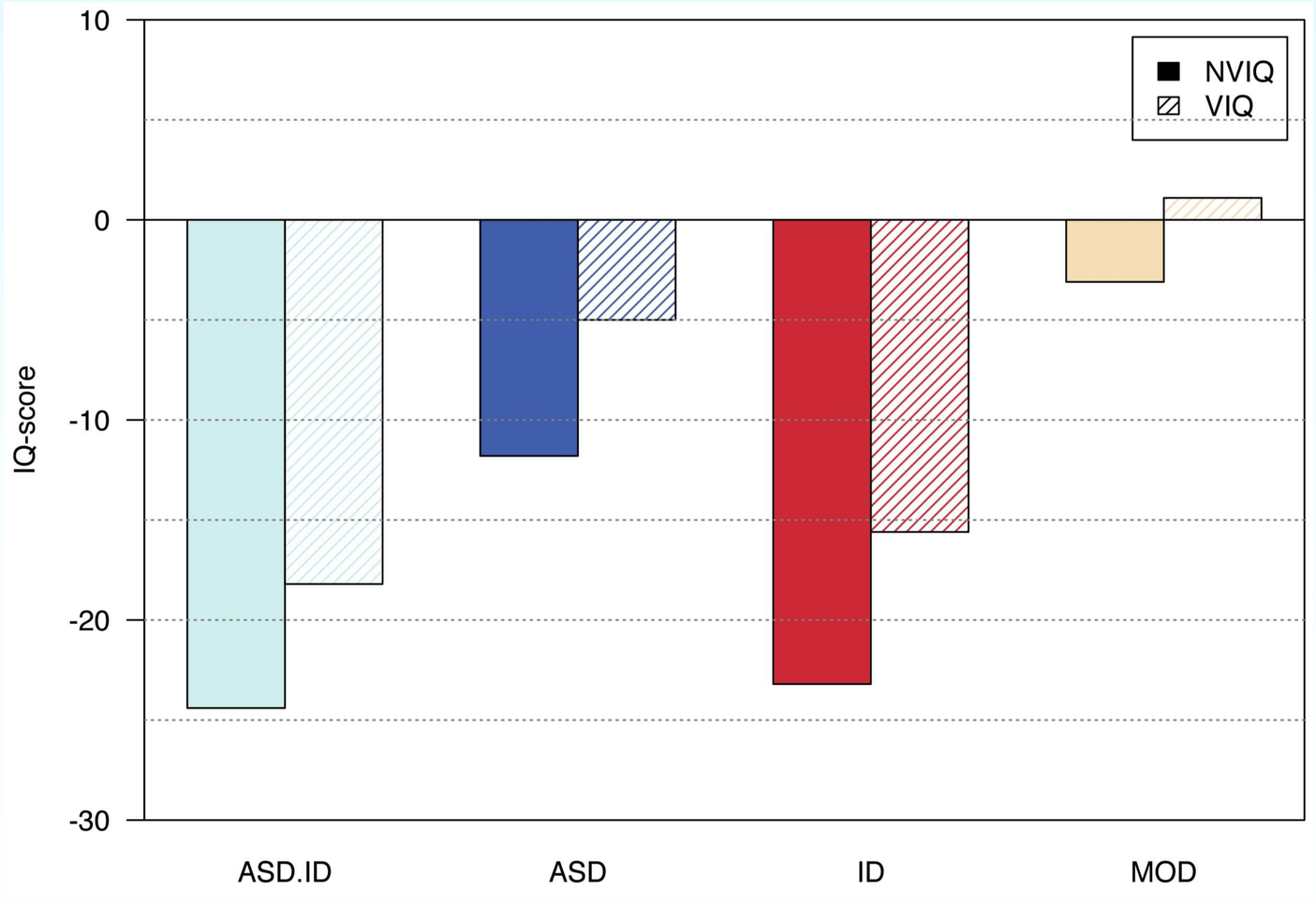
ASC+SSC



Combining autism and intellectual disability exome data yields insight into both disorders

Ercument Cicek, Lambertus Klei, Silvia De Rubeis, Joseph Buxbaum, Kathryn Roeder, Bernie Devlin, DDD (Jeff Barrett, Matthew Hurles, …), ASC, *unpublished*

ASC+DDD



For the first time we are showing *specificity* of autism and NDD genes

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PMS –

“IT’S NOT WHAT YOU THINK” ®

- PMS (or Phelan McDermid Syndrome) is a genetic disorder that often presents with autism
- PMS is caused by mutations in the gene **SHANK3**

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OPEN ACCESS Freely available online

PLOS | GENETICS

Meta-analysis of *SHANK* Mutations in Autism Spectrum Disorders: A Gradient of Severity in Cognitive Impairments

Claire S. Leblond[1,2,3], Caroline Nava[4,5,6], Anne Polge[7], Julie Gauthier[8], Guillaume Huguet[1,2,3], Serge Lumbroso[7], Fabienne Giuliano[9], Coline Stordeur[1,2,3,10], Christel Depienne[4,5,6], Kevin Mouzat[7], Dalila Pinto[11], Jennifer Howe[12], Nathalie Lemière[1,2,3], Christelle M. Durand[1,2,3], Jessica Guibert[1,2,3], Elodie Ey[1,2,3], Roberto Toro[1,2,3], Hugo Peyre[13], Alexandre Mathieu[1,2,3], Frédérique Amsellem[1,10,14], Maria Rastam[15], I. Carina Gillberg[16], Gudrun A. Rappold[17], Richard Holt[18], Anthony P. Monaco[18], Elena Maestrini[19], Pilar Galan[20], Delphine Heron[21,22,23], Aurélia Jacquette[21,22], Alexandra Afenjar[21,22,23], Agnès Rastetter[4,5,6], Alexis Brice[4,5,6], Françoise Devillard[24], Brigitte Assouline[25], Fanny Laffargue[26], James Lespinasse[27], Jean Chiesa[28], François Rivier[29,30], Dominique Bonneau[31,32], Beatrice Regnault[33], Diana Zelenika[34], Marc Delepine[34], Mark Lathrop[34], Damien Sanlaville[35], Caroline Schluth-Bolard[35], Patrick Edery[35], Laurence Perrin[36], Anne Claude Tabet[36], Michael J. Schmeisser[37], Tobias M. Boeckers[37], Mary Coleman[38], Daisuke Sato[12], Peter Szatmari[12], Stephen W. Scherer[12], Guy A. Rouleau[39], Catalina Betancur[5,40,41], Marion Leboyer[14,42,43,44], Christopher Gillberg[16,45], Richard Delorme[1,2,3,10,14☯], Thomas Bourgeron[1,2,3,14,☯*]

Abstract

SHANK genes code for scaffold proteins located at the post-synaptic density of glutamatergic synapses. In neurons, *SHANK2* and *SHANK3* have a positive effect on the induction and maturation of dendritic spines, whereas *SHANK1* induces the enlargement of spine heads. Mutations in *SHANK* genes have been associated with autism spectrum disorders (ASD), but their prevalence and clinical relevance remain to be determined. Here, we performed a new screen and a meta-analysis of *SHANK* copy-number and coding-sequence variants in ASD. Copy-number variants were analyzed in 5,657 patients and 19,163 controls, coding-sequence variants were ascertained in 760 to 2,147 patients and 492 to 1,090 controls (depending on the gene), and, individuals carrying *de novo* or truncating *SHANK* mutations underwent an extensive clinical investigation. Copy-number variants and truncating mutations in *SHANK* genes were present in ~1% of patients with ASD: mutations in *SHANK1* were rare (0.04%) and present in males with normal IQ and autism; mutations in *SHANK2* were present in 0.17% of patients with ASD and mild intellectual disability; mutations in *SHANK3* were present in 0.69% of patients with ASD and up to 2.12% of the cases with moderate to profound intellectual disability. In summary, mutations of the *SHANK* genes were detected in the whole spectrum of autism with a gradient of severity in cognitive impairment. Given the rare frequency of *SHANK1* and *SHANK2* deleterious mutations, the clinical relevance of these genes remains to be ascertained. In contrast, the frequency and the penetrance of *SHANK3* mutations in individuals with ASD and intellectual disability—more than 1 in 50—warrant its consideration for mutation screening in clinical practice.

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]

	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.

Population of the USA ~320 million

Rate of PMS is *minimally* ~1/10,000

320,000,000/10,000 = 32,000

AN ESTIMATED 32,000 INDIVIDUALS IN USA WITH PMS

For comparison -
Rett syndrome occurs in 1 in 10,000-20,000 births
Fragile X syndrome occurs in 1 in 5000-6000 births (1 in 2500-4000 males)

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Impact of discovering an etiology for a development disorder

- Benefit to patient
  - More informed care
  - Soon? - Personalized medicine
- Benefit to family
  - Information about clinical course
  - Information about recurrence
  - Family and advocacy groups
- Benefit to society
  - Clinical information on a population level
  - Understanding of mechanisms
  - New targets for medicine
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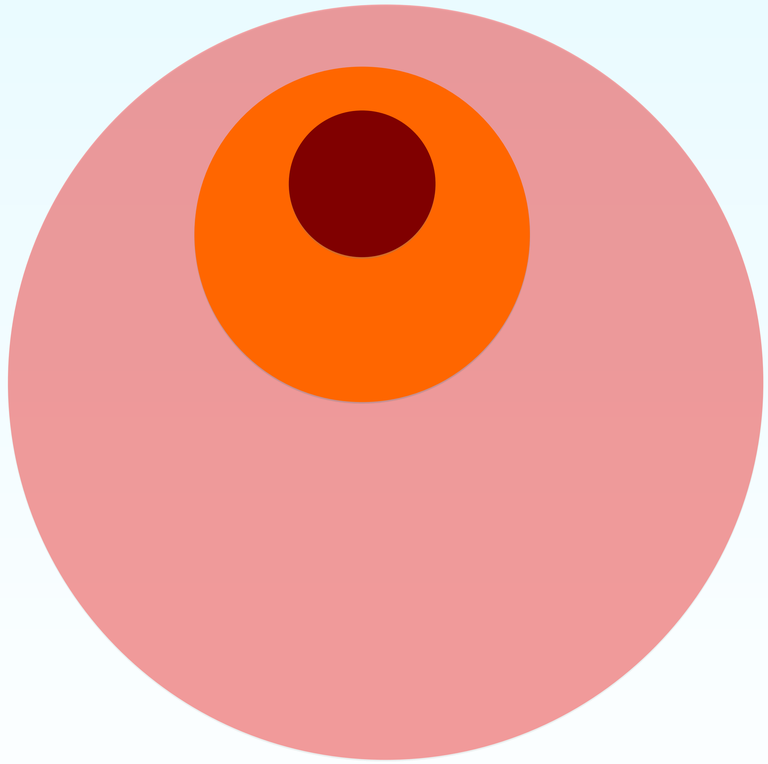
  - New medicines



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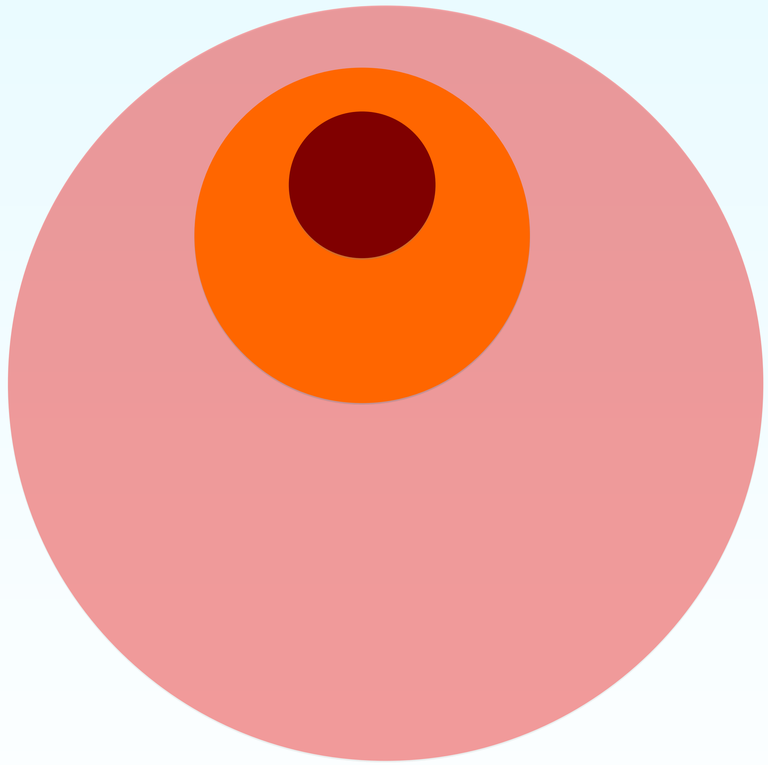
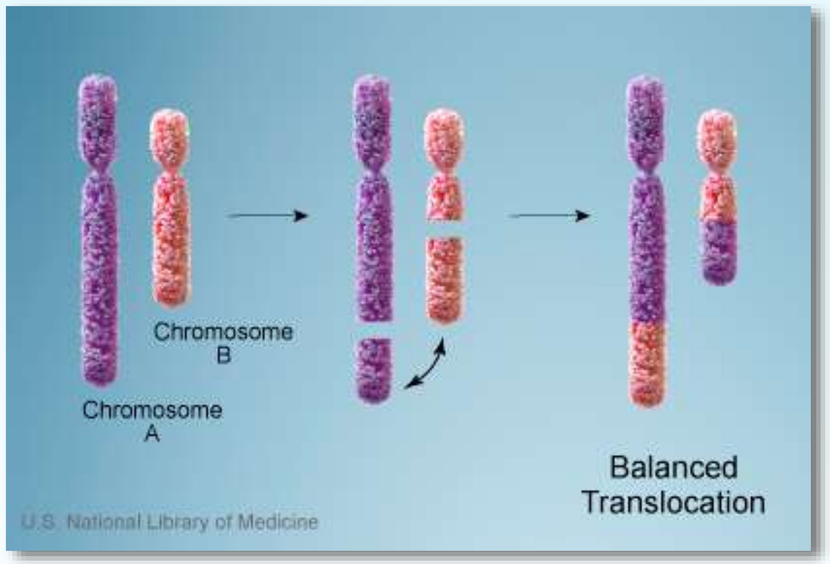
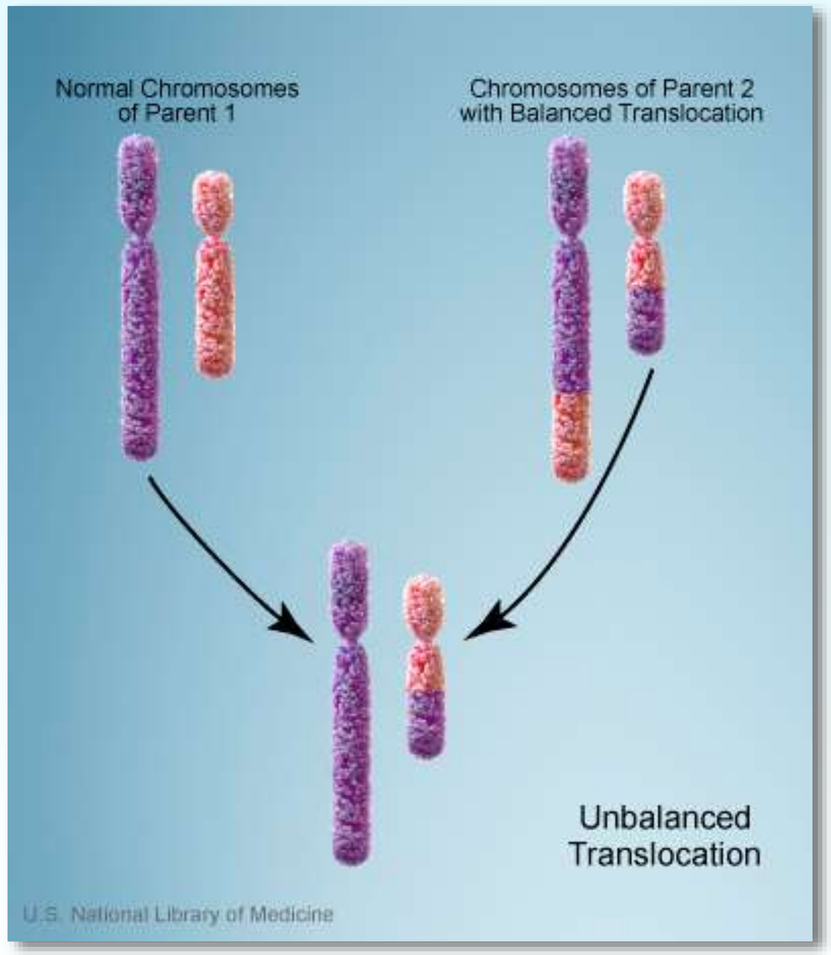
  - Model systems
  - New medicines



About 25% of PMS comes from a parent with a balanced translocation





This means that each child in such a family has a 50% chance of having PMS

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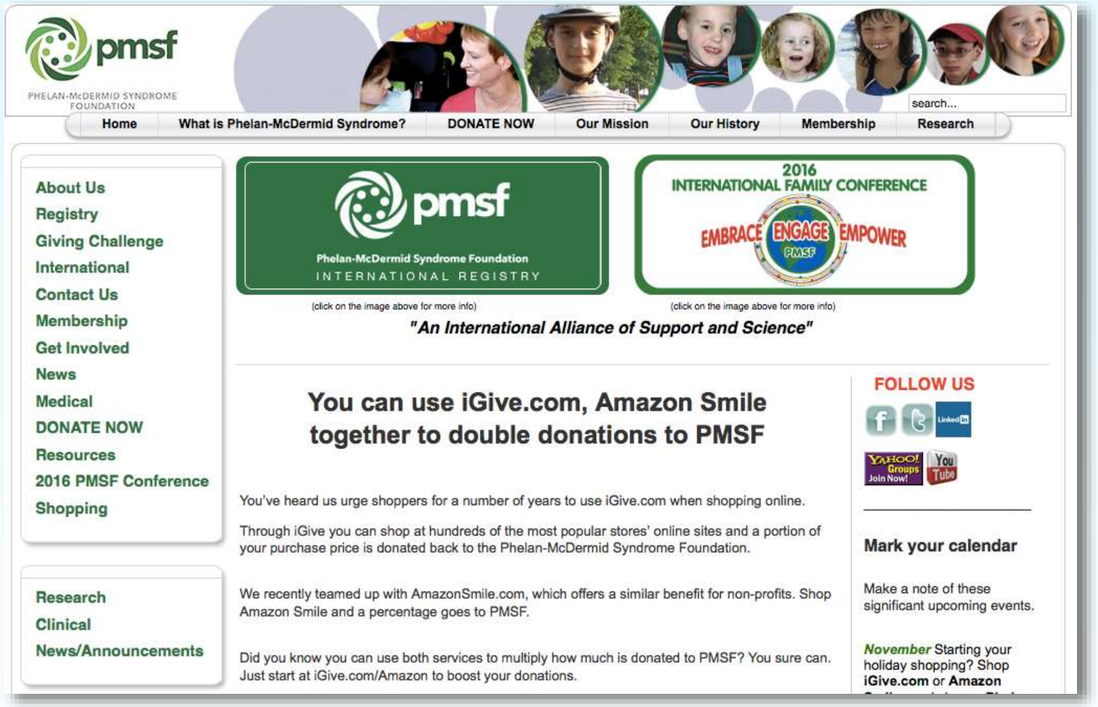
Phelan-McDermid Syndrome Foundation



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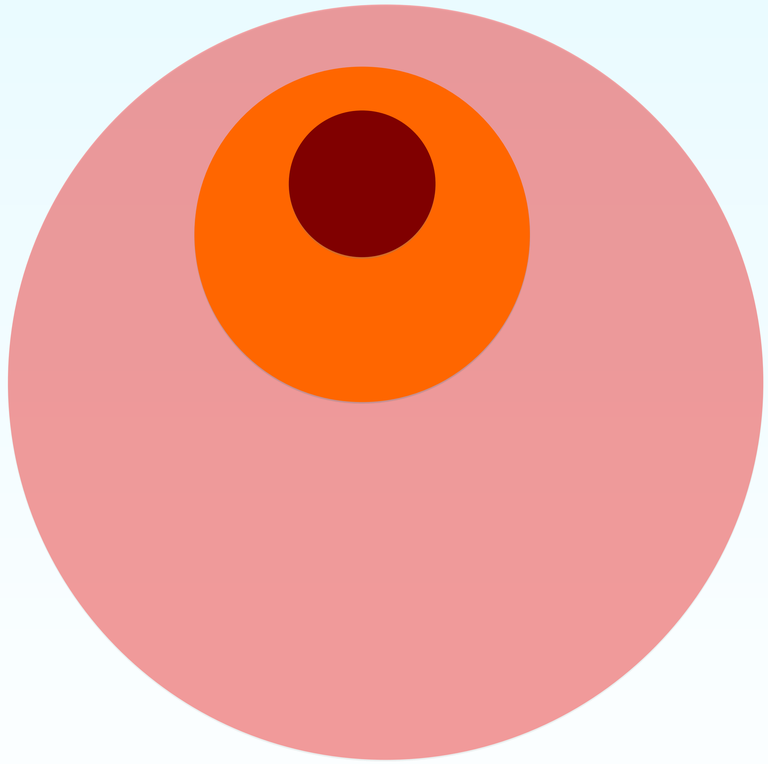
Impact of discovering an etiology for a development disorder

- Benefit to patient
  - More informed care
  - Soon? - Personalized medicine
- Benefit to family
  - Information about clinical course
  - Information about recurrence
  - Family and advocacy groups
- Benefit to society
  - Clinical information on a population level
  - Understanding of mechanisms
  - New targets for medicine
  - Model systems
  - New medicines

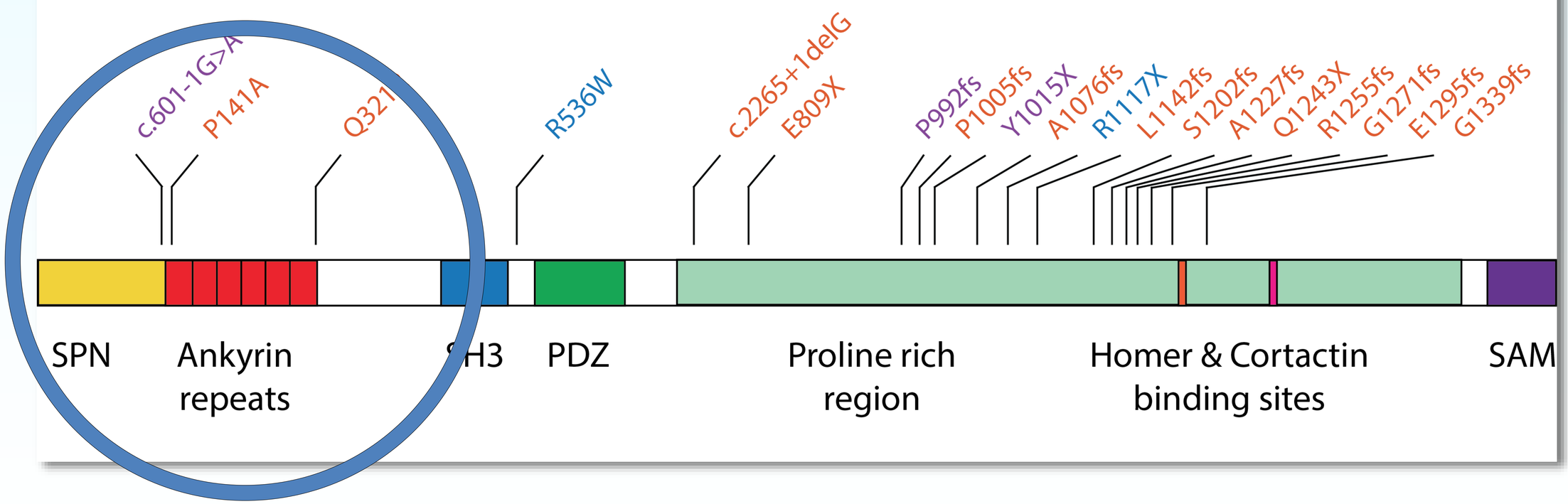


High-risk mutations in SHANK3

ASD n = 14/2147 (0.7%)

SCZ n = 2/185 (1%)

ID n = 3/435 (0.7%)



From cohort studies

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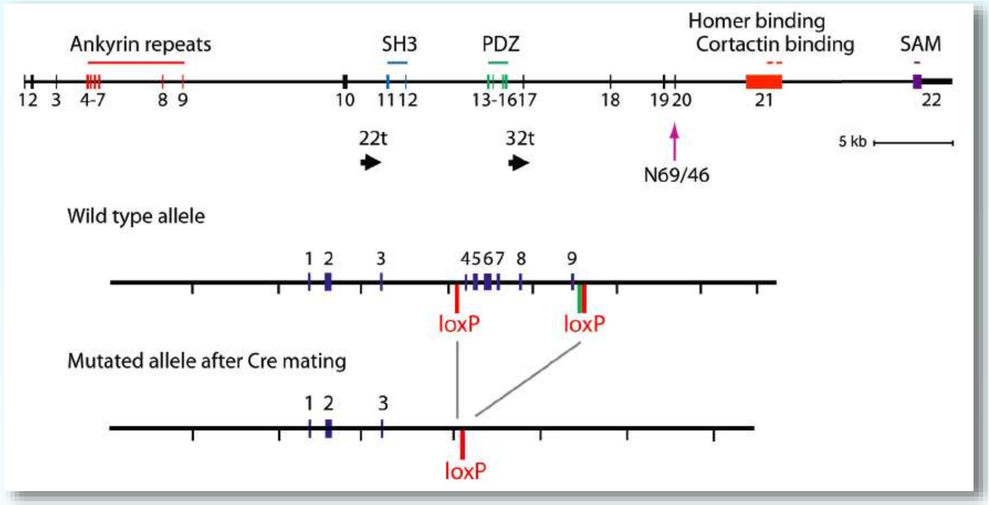
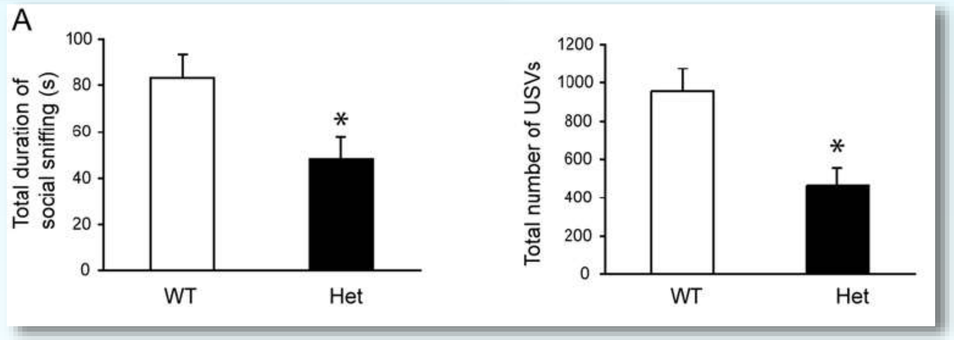
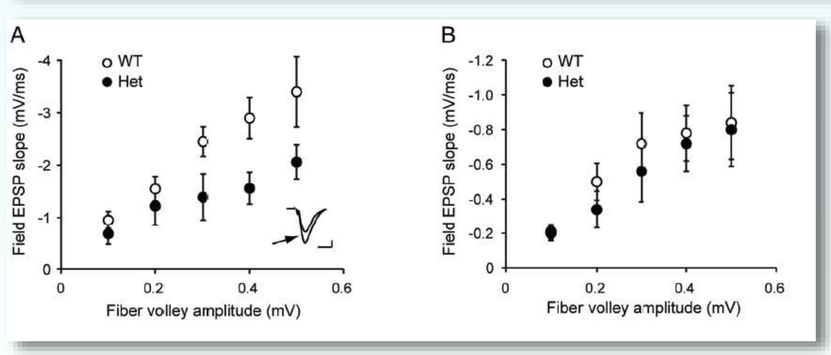
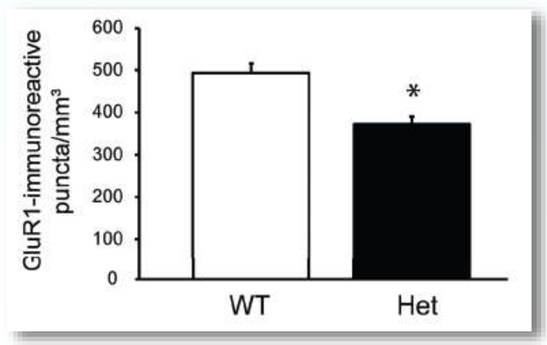
Haploinsufficiency of the autism-associated *Shank3* gene leads to deficits in synaptic function, social interaction, and social communication

Ozlem Bozdagi[1,2†], Takeshi Sakurai[1,2†], Danae Papapetrou[3], Xiaobin Wang[4], Dara L Dickstein[3], Nagahide Takahashi[2], Yuji Kajiwara[2], Mu Yang[6], Adam M Katz[6], Maria Luisa Scattoni[6,7], Mark J Harris[6], Roheeni Saxena[6], Jill L Silverman[6], Jacqueline N Crawley[6], Qiang Zhou[4,8], Patrick R Hof[3], Joseph D Buxbaum[1,2,3,5*]









Heterozygous Shank3 knockout mice show behavioral abnormalities (including social and motor deficits), and evodence for immature glutamatergic synapses.

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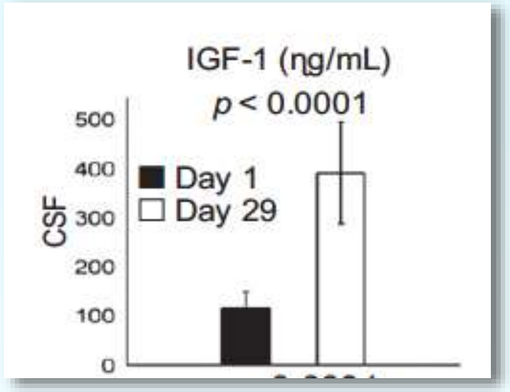
Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome

Omar S. Khwaja[a,b,1], Eugenia Ho[a,c,1], Katherine V. Barnes[a], Heather M. O'Leary[a], Luis M. Pereira[d], Yaron Finkelstein[e,f], Charles A. Nelson III[g], Vanessa Vogel-Farley[g], Geneva DeGregorio[g], Ingrid A. Holm[h,i], Umakanth Khatwa[j], Kush Kapur[a,k], Mark E. Alexander[j,l], Deirdre M. Finnegan[a], Nicole G. Cantwell[a], Alexandra C. Walco[a], Leonard Rappaport[g], Matt Gregas[a,k], Raina N. Fichorova[m], Michael W. Shannon[f,i,2], Mriganka Sur[n], and Walter E. Kaufmann[a,3]



IGF-1 enters the CNS, is safe, and improves apnea measures and anxiety and mood in Rett syndrome.

Breathing indices	Pre-MAD	Post-MAD	Pre-OLE	Post-OLE	Pre-MAD to Post-OLE
Apnea index (mean ± SE)	10.11 ± 19.34	5.11 ± 9.68	4.67 ± 6.81	3.00 ± 5.72	−7.12 ± 4.58
Student's *t P*	–	–	–	–	0.159
Wilcoxon signed rank *P*	–	–	–	–	0.094
RI model *P*	–	–	–	–	0.018
Hyperventilation index (mean ± SE)	3.55 ± 6.71	3.00 ± 6.59	6.44 ± 16.86	3.66 ± 8.97	0.12 ± 0.93
Student's *t P*	–	–	–	–	0.908
Wilcoxon signed rank *P*	–	–	–	–	0.875
RI model *P*	–	–	–	–	0.963

Measure	V1 mean	V5 mean	Mean difference	Mean difference SE	Student's *t P*	Wilcoxon signed rank *P*
Behavioral subtotal (MBA)	24.00	19.88	−4.11	1.11	0.006	0.016
Passive/unengaged (CA)	0.33	0.00	−0.33	0.17	0.081	0.250
Intermittent laughter (CA)	0.33	0.00	−0.33	0.17	0.081	0.250
Fear/anxiety subtotal (RSBQ)	3.55	2.77	−0.79	0.66	0.274	0.281
Spells of laughter at night (RSBQ)	0.77	0.44	−0.33	0.17	0.081	0.250
Social avoidance subtotal (ADAMS)	4.55	3.11	−1.44	0.84	0.122	0.109

V1, visit 1 of OLE; V5, visit 5 of OLE.

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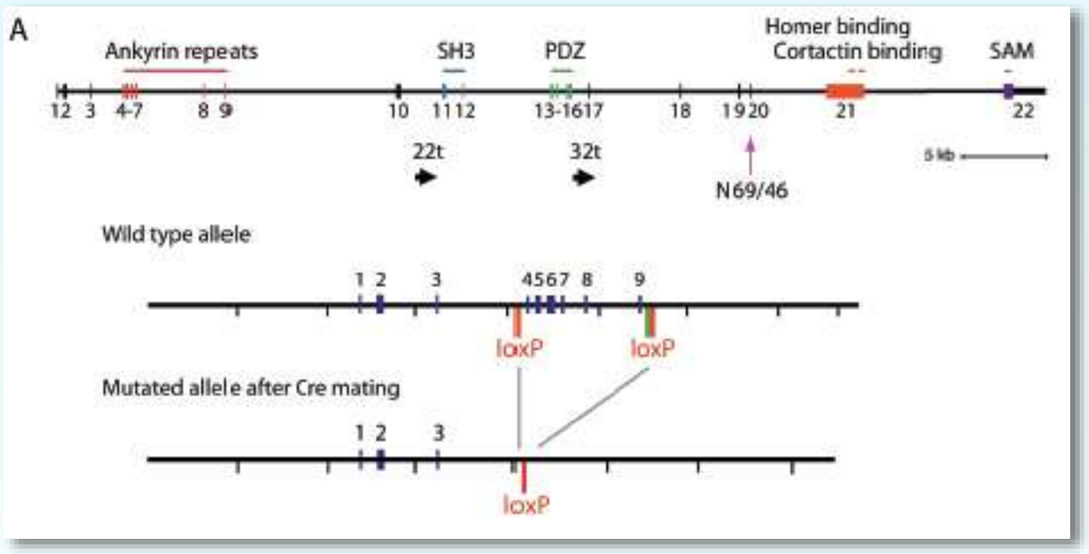
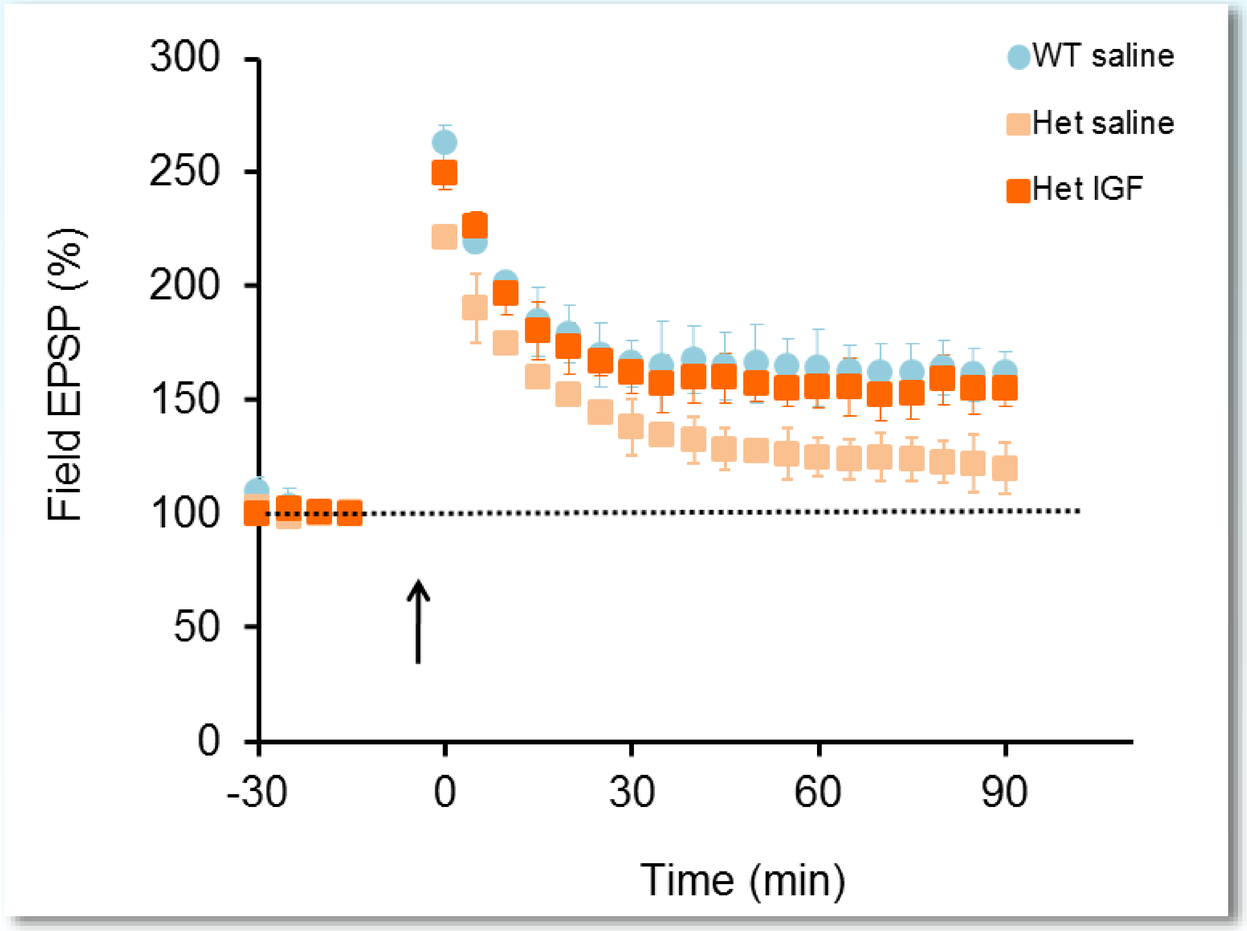
Insulin-like growth factor-1 rescues synaptic and motor deficits in a mouse model of autism and developmental delay

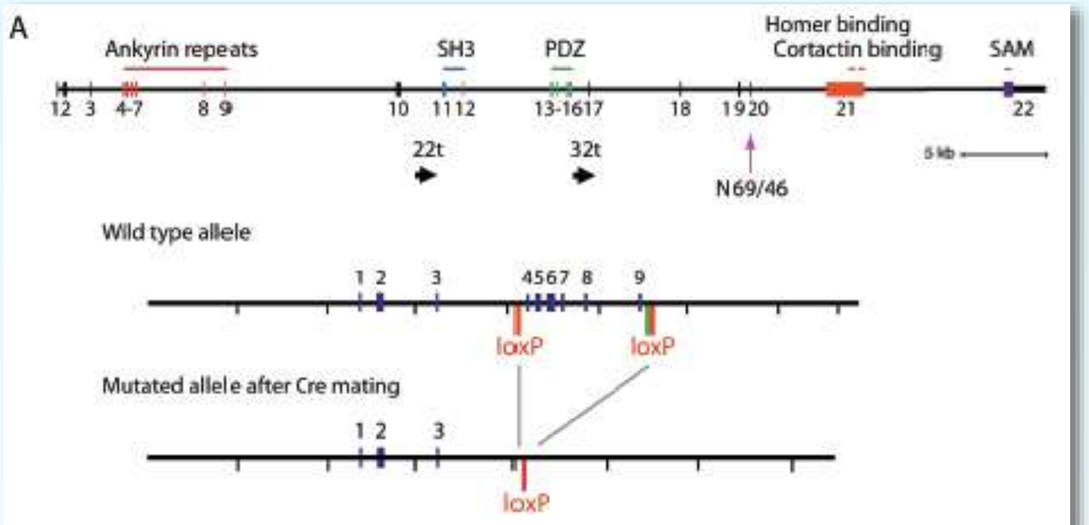
Ozlem Bozdagi[1,2], Teresa Tavassoli[1,2] and Joseph D Buxbaum[1,2,3,4,5,6*]

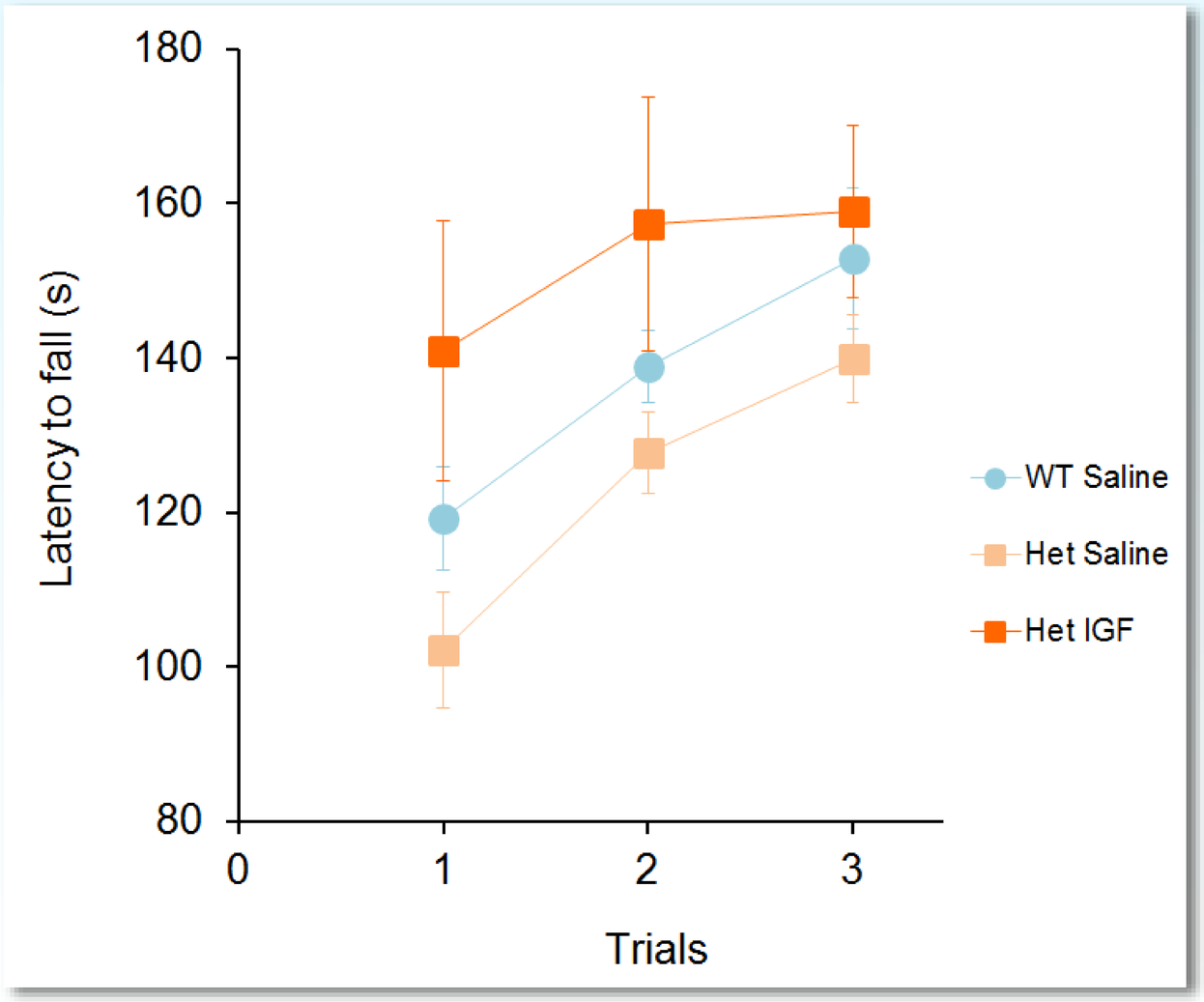




Insulin-like growth factor-1 rescues synaptic and motor deficits in a mouse model of autism and developmental delay

Ozlem Bozdagi[1,2], Teresa Tavassoli[1,2] and Joseph D Buxbaum[1,2,3,4,5,6*]





A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

Alexander Kolevzon[1,2,3,4,5,10*], Lauren Bush[1,4,10], A Ting Wang[1,2,4,6,10], Danielle Halpern[1,4,10], Yitzchak Frank[1,4,5,7,10], David Grodberg[1,4,10], Robert Rapaport[5,9,10], Teresa Tavassoli[1,4,10], William Chaplin[11], Latha Soorya[12] and Joseph D Buxbaum[1,2,3,4,6,8,10]

Kolevzon *et al. Molecular Autism* 2014, **5**:54
http://www.molecularautism.com/content/5/1/54

What is next for IGF-1 in PMS?

- Rare Disease Clinical Research Network
  - Currently 6 PMS sites in the USA
    - Mount Sinai (**Prof. Alex Kolevzon**), Rush, BCH, NIH, UTSW, Stanford
- Knowledge-sharing and collaboration with European sites
  - EU-AIMS
  - Spain, France, Germany, etc
- In discussion with Ipsen for reduced cost IGF-1
- NIH funding for additional subjects for IGF-1 trial
  - Adding novel biomarkers in this 2nd study
- Autism Science Foundation had provided pilot support for IGF-1 in idiopathic autism

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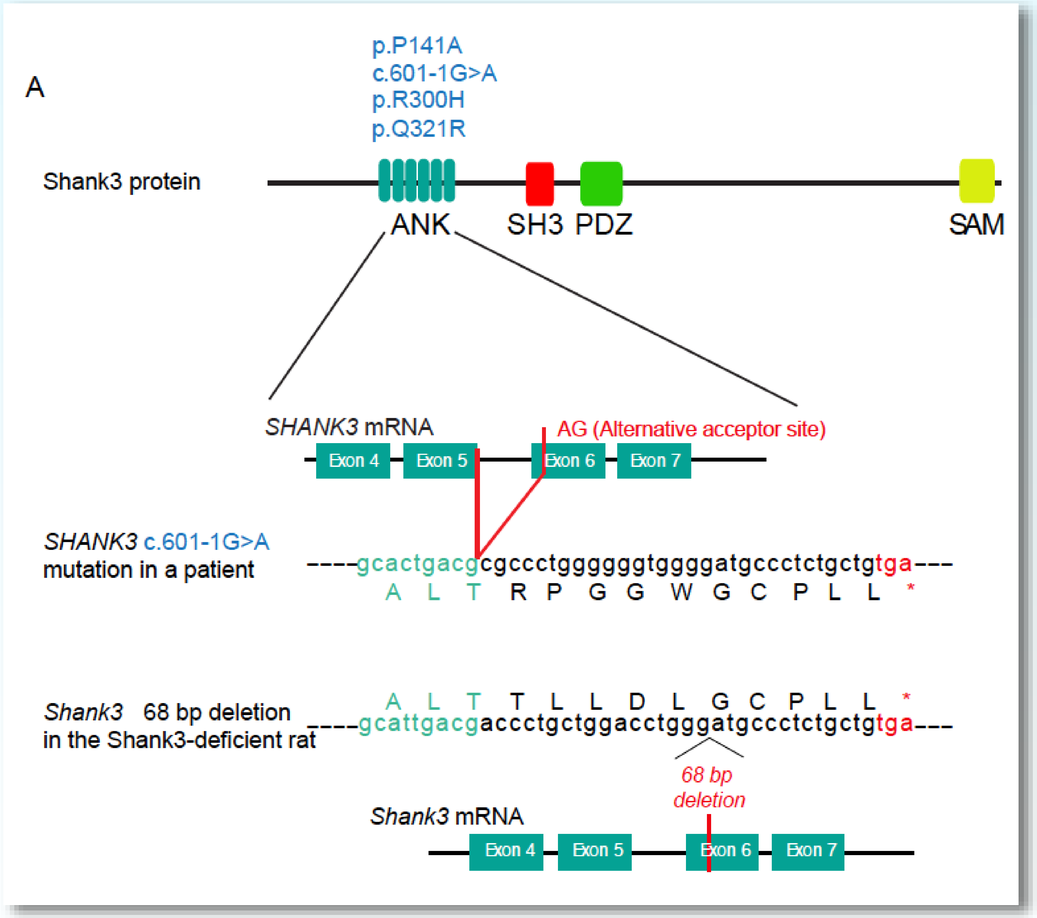
The *Shank3*-deficient rat,
a novel genetically modified rat model for autism

Hala Harony-Nicolas

Oxytocin reverses social deficits in the Shank3-deficient rat, a novel genetically modified rat model for autism

- Why rats?
  - They have a substantially larger brain
  - The brain regions anatomy and connectivity are better identified in rats
    - The rat mPFC is considered to be homologous in function to PFC in human
      - The precise cytoarchitecture, connectivity, and function of the rat mPFC has been worked out in better detail
  - Broad array of behavioral and physiological analyses possible
  - A primary choice of pharmaceutical industry for studying pharmacokinetic properties of novel drug



Dr. Paulina Rychenova and Bill Gibson

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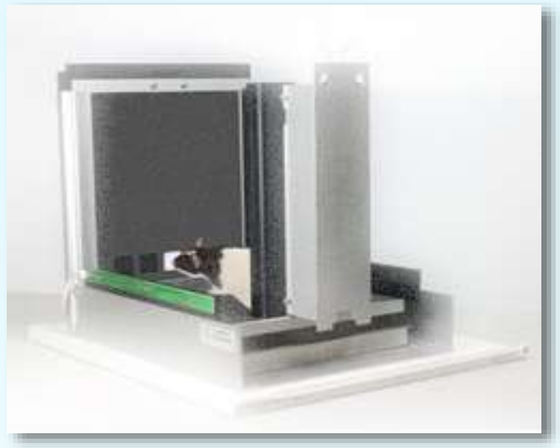
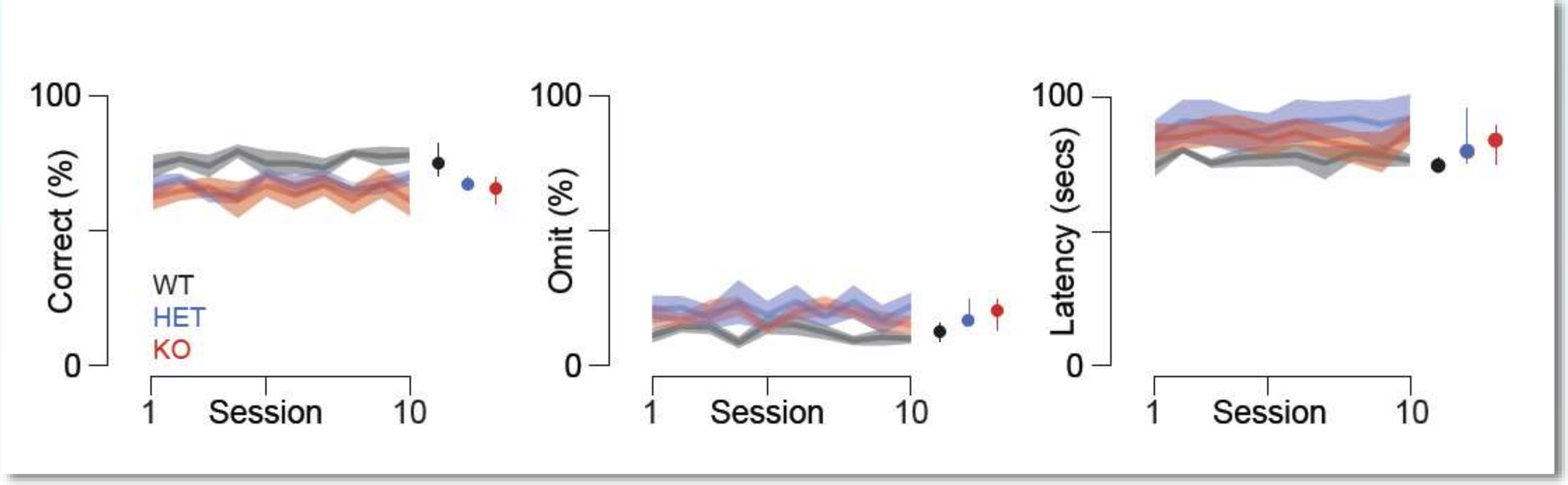
Attentional deficits in Shank3-deficient rats





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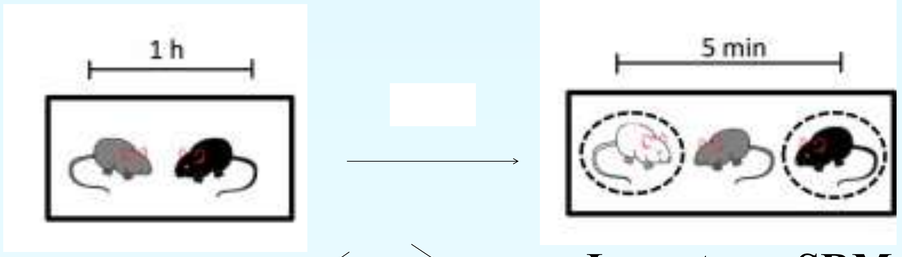
Social recognition memory (SRM) deficits in Shank3-deficient rats

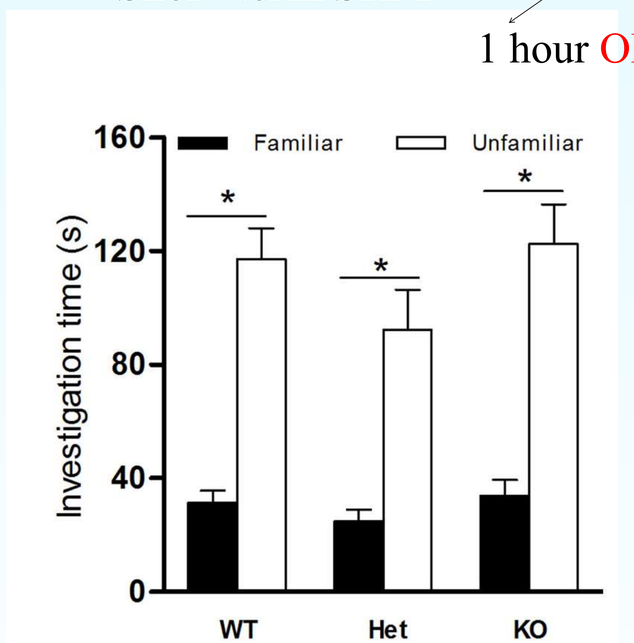
Social discrimination test

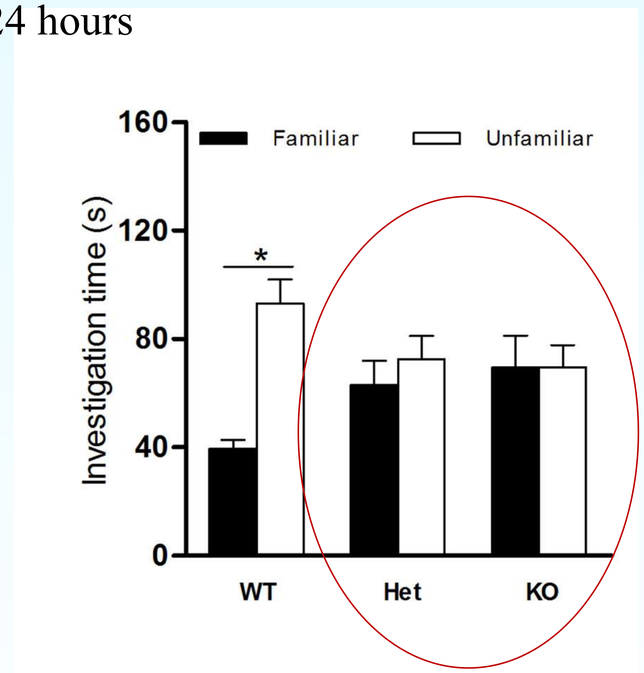


Short-term SRM

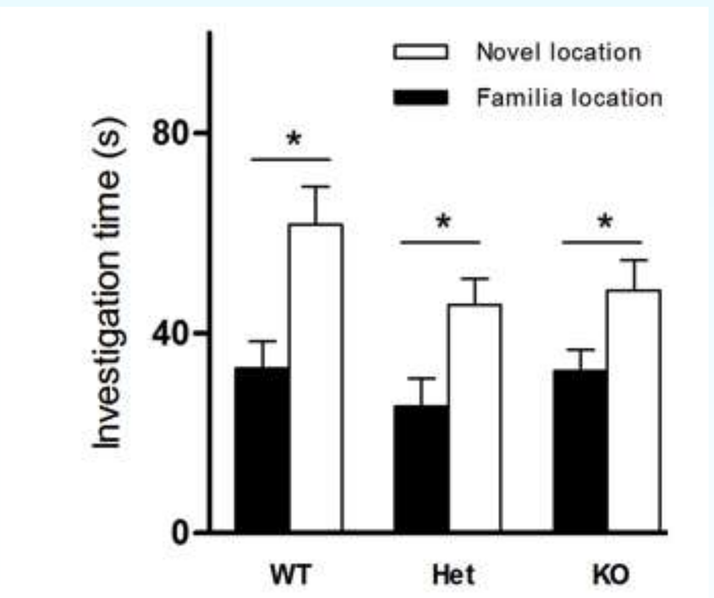
Long-term SRM

1 hour OR 24 hours





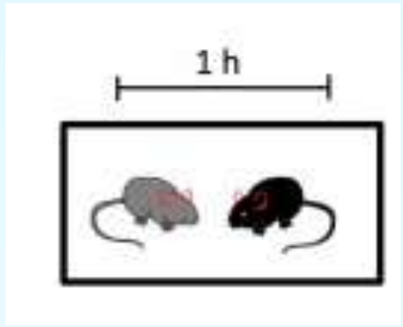
Long-term object location dependent memory



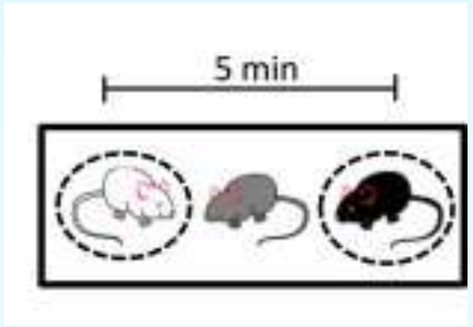
Shank3-deficient rats display impaired long but not short-term SRM

Effects of oxytocin on SRM

10 min

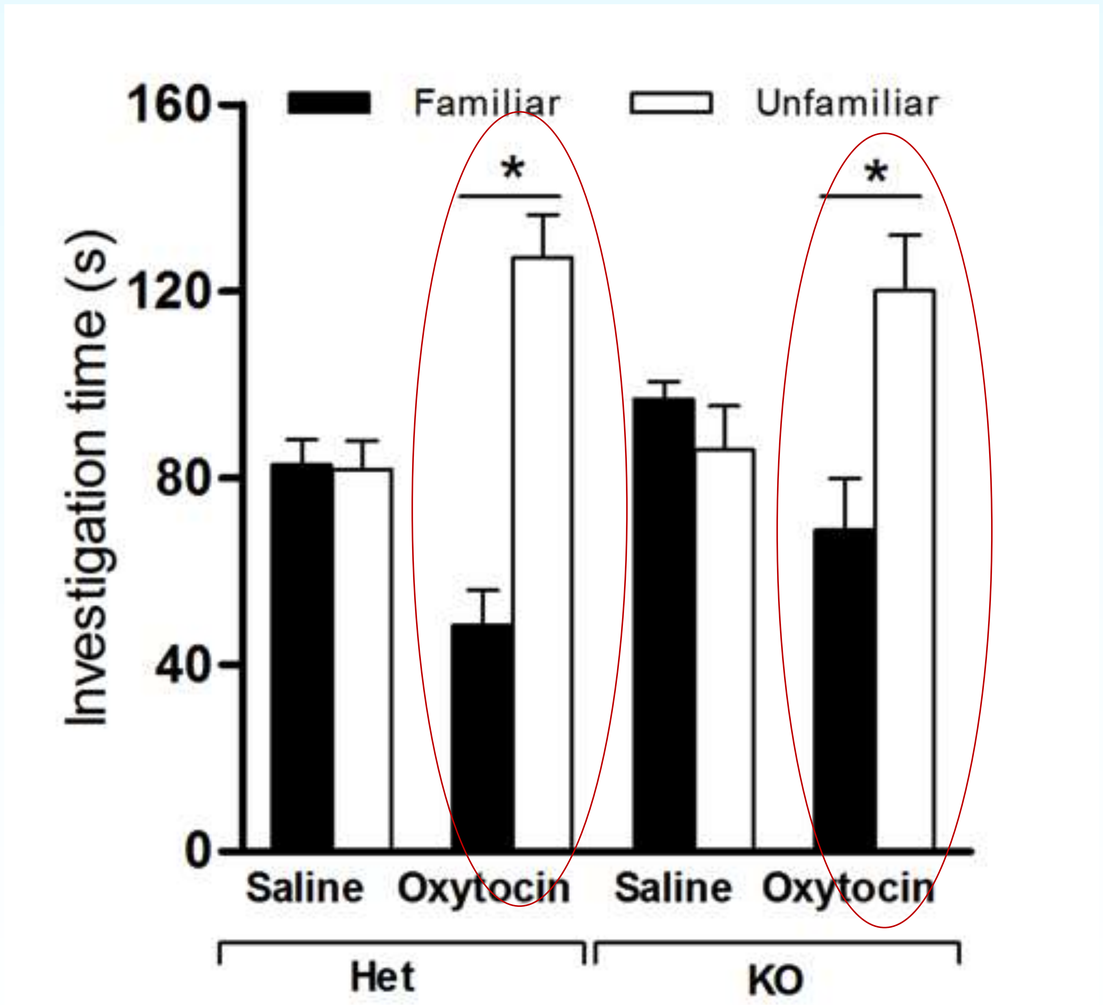


24 h



Oxytocin intracerebroventricular injection

In addition to its well-known role in modulating mammalian social behaviors, there is a specific role for oxytocin in the acquisition of SRM (Gur et al., *Biological psychiatry* 2014; Ferguson *et a*l., *Nature Genetics* 2000).



Oxytocin reverses the long term social recognition memory deficits observed in the *Shank3*-deficient rats

Oxytocin in PMS

Prof. Alex Kolevon and the Seaver Center have FDA approval for a clinical trial for this study

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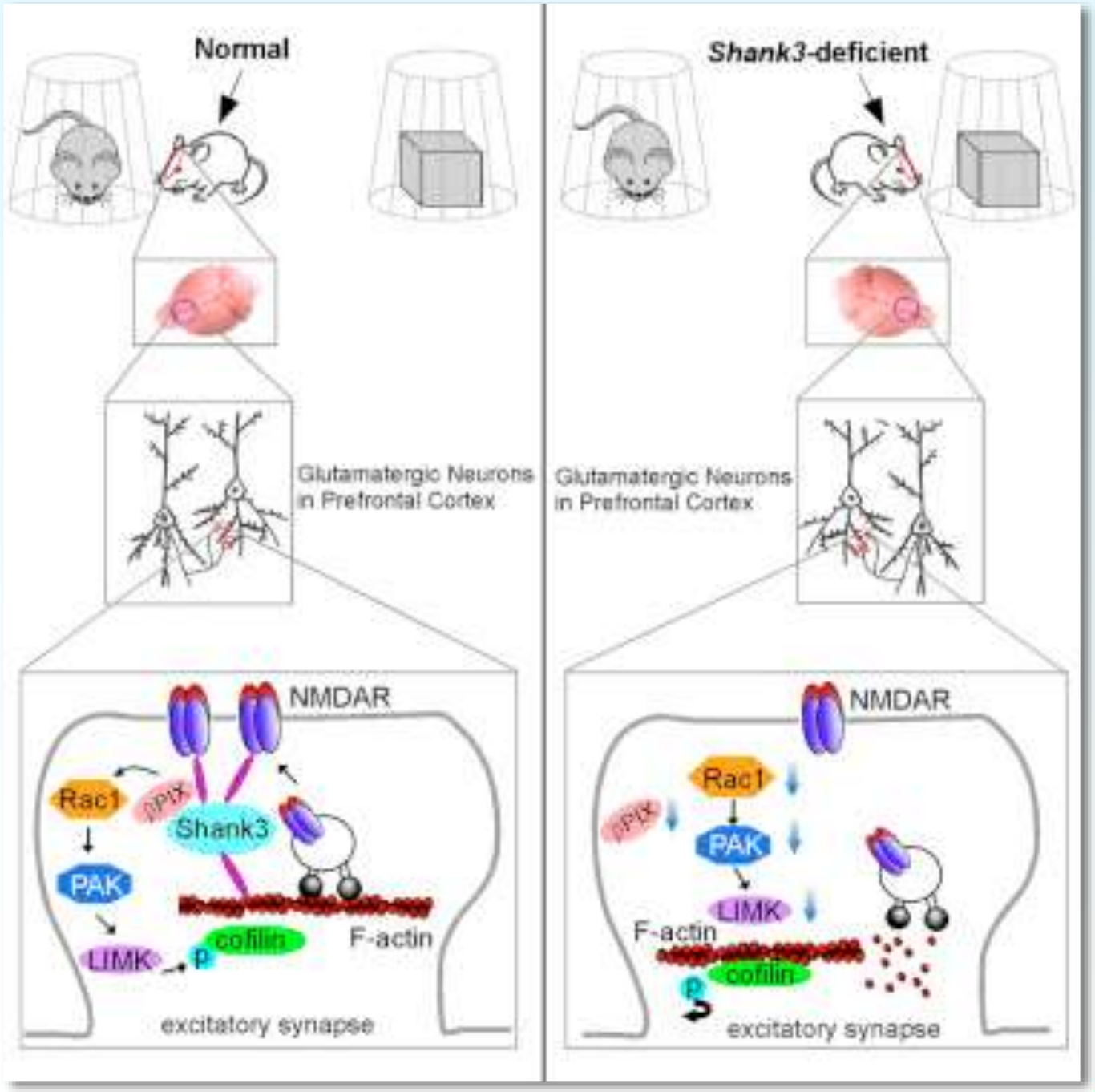
Autism-like Deficits in *Shank3*-Deficient Mice Are Rescued by Targeting Actin Regulators

Lara J. Duffney,[1,4] Ping Zhong,[1,4] Jing Wei,[1,4] Emmanuel Matas,[1] Jia Cheng,[1] Luye Qin,[1] Kaijie Ma,[1] David M. Dietz,[2] Yuji Kajiwara,[3] Joseph D. Buxbaum,[3] and Zhen Yan[1,*]



Highlights

- *Shank3* deficiency induces ASD-like behavioral deficits and NMDAR hypofunction in PFC
- *Shank3* deficiency leads to reduced synaptic F-actin and altered actin regulators in PFC
- Inhibiting cofilin rescues behavioral and synaptic deficits in *Shank3*-deficient mice
- Manipulating cortical Rac1 or PAK controls the manifestation of ASD-like phenotypes

In Brief

Shank3 haploinsufficiency is an autism risk factor. Duffney et al. reveal that *Shank3* deficiency causes the diminished synaptic actin filaments and NMDA receptors in prefrontal cortex. Targeting key actin regulators, including cofilin, Rac1, and PAK, rescues the autism-like behavioral and synaptic deficits, which provides a strategy for autism treatment.

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Conclusions

- There are many autism genes
- These genes are associated with a very broad spectrum of relative risk
- Additive effects likely explain most cases
- Genes map to synaptic, chromatin, and transcriptional pathways
- Many-to-many relationships appear to be true for many/most? autism genes and neurodevelopmental phenotypes
- However, careful studies can begin to tease these things apart
- There are many examples of genes leading to novel clinical trials in autism and developmental delay syndromes
- **Over the next few years we will begin to learn which of these approaches is having beneficial effects on disability in autism**

More information

- The Seaver Autism Center
  - www.seaverautismcenter.org
  - Annual research summary
    - http://issuu.com/johndavey/docs/seaver-annualupdate-2014-15
  - Participating
    - theseavercenter@mssm.edu
- The ASC
  - https://genome.emory.edu/ASC/
- Participating in autism research through an ASC site
  - Contact Jessica Brownfeld
    - Jessica.Brownfeld@mssm.edu

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The ASC continues to sequence new samples – please join us!

ASD trios, ID trios, and epilepsy trios (even OCD and Tourette trios)

Samples in First Publication

14654 samples
(includes 2303 trios)

ARRA ASC case-control (Daly) - 799 samples (427 cases, 372 controls

ARRA ASC case-control (Sabo) - 933 samples (444 cases, 489 controls)

ARRA ASC trios (Schellenberg) - 141 samples (47 trios)

ARRA ASC trios (Sutcliffe) - 131 samples (44 trios)

Boston Autism Consortium (Daly) - 676 samples (209 trios)

Central Valley of Costa Rica (Buxbaum) - 529 samples (177 trios)

Finland (Palotie) - 153 samples (51 trios)

Germany (Freitag & Chiocchetti) - 1040 samples (353 trios)

Middle Eastern (Walsh) - 733 samples (255 trios)

PAGES Swedish cases (Buxbaum & Hultman) - 435 samples (435 controls)

Seaver Autism Center (Kolevzon) - 230 samples (72 trios)

Simons Simplex Collection (State, Eichler, Wigler) - 2475 samples (825 trios)

Swedish controls (Purcell, Daly, Sklar & Hultman) - 2526 samples (2526 controls)

TASC (Buxbaum) - 613 samples (203 trios)

UK 10K trios (Barrett) - 201 samples (67 trios)

UK 10K case-control (Barrett) - 3039 samples (367 cases, 2672 controls)

Current Data Freeze

21287 Samples (including):

1. 9397 SSC samples

2. Samples from first publication

3. 3783 Newly Sequenced Samples
(includes 1130 trios or quads)

Japan (Aleksic) - 199 samples (65 trios/quads)

Spain (Parellada) - 438 samples (145 trios/quads)

PAGES (Sweden) - 280 samples (116 parents/164 cases)

Mt. Sinai Seaver (Buxbaum) trios - 54 samples (18 trios)

U Penn (Minshew) trios - 113 samples (37 trios/quads)

TASC-LCL DNA - 1958 samples (650 cases/1268 parents/29 sibs)

TASC-WB DNA - 99 samples (1 case/92 parents/6 sibs)

Utah (Coon) - 555 samples (185 cases/370 parents = 185 complete trios)

Portugal (Barbosa) - 87 samples (29 Trios)

Ongoing or Planned Sequencing

Data back this year

1705 samples
(includes 272 trios or quads)

Japan (Branko Aleksic) - 487 samples (188 ASD & 299 Controls)

PAGES (Sweden) - 278 samples (134 cases and 144 controls - includes 40 parents & 12 complete trios)

U Pitt (Minshew) - 481 samples (175 cases, 306 controls - includes 112 complete trios & 4 complete quads)

TASC-LCL (AGRE) - 247 samples (includes 62 trios, 12 quads, 1 quint)

TASC-WB DNA - 4 samples (4 cases)

Mt. Sinai Seaver (Buxbaum) trios - 34 samples (10 trios/quads)

Portugal (Barbosa) - 174 samples (58 complete trios)

Sites being recruited

5514 samples
(includes 1723 trios)

Hong Kong (Chung) – 350 samples (25 trios, 275 cases)

Italy (Persico) – 1947 samples (649 trios)

Brazil (dos Santos e Passos-Bueno) – 2256 samples (752 trios)

Argentina (Vanini Sesarini) – 292 samples (74 trios, 70 cases)

Ohio (Herman) – 669 samples (223 trios)

Additional samples being contributed by member sites, including PAGES, Germany, Mt. Sinai Seaver, Portugal, Turin Italy.

To be sequenced this year

1082 samples
(includes 294 trios or quads)

PAGES (Sweden) - 80 samples (69 cases, 11 parents)

UC Davis (Tassone) - 743 samples (420 parents, 5 aff sibs, 105 unaff sibs, including 210 complete trios/quads)

Miami (Pericak-Vance) - 108 samples (36 trios)

Turin Italy (Brusco) - 151 samples (48 trios & 7 cases)

TARGET

5000 samples per year,
for the next 5 years.

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Thank you for your attention!

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