Autism: från genetik till möjlig behandling

Lars Westberg
University of Gothenburg
Institute of Neuroscience and Physiology
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Pharmacological therapies for the core symptoms of autism

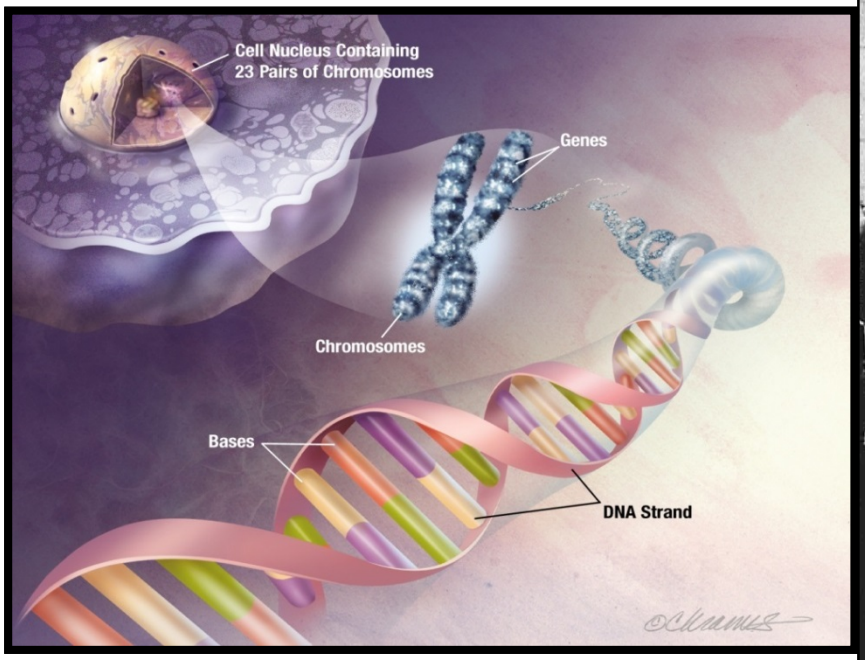
Skepticism towards the possibilities of drug treatment for autism

- Unkown patophysiology
- Caused by permanent and irreversible defects during early neurodevelopment

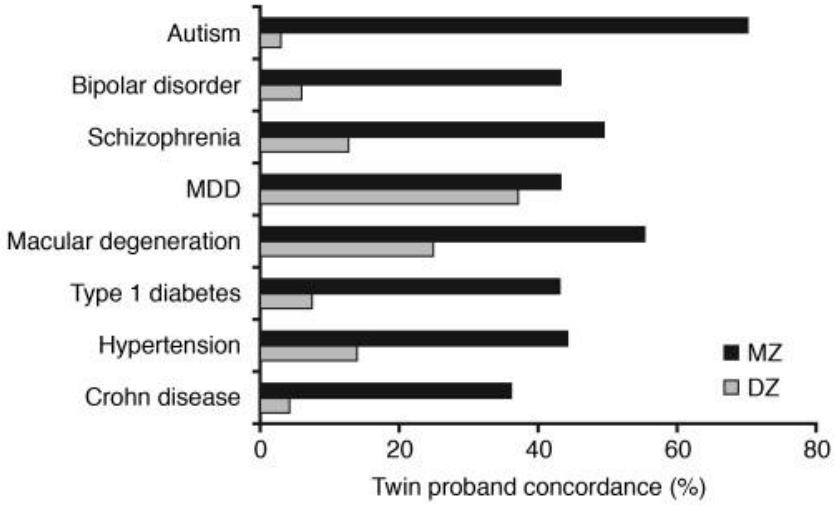
Three milestones during the last decade(s) changed the picture

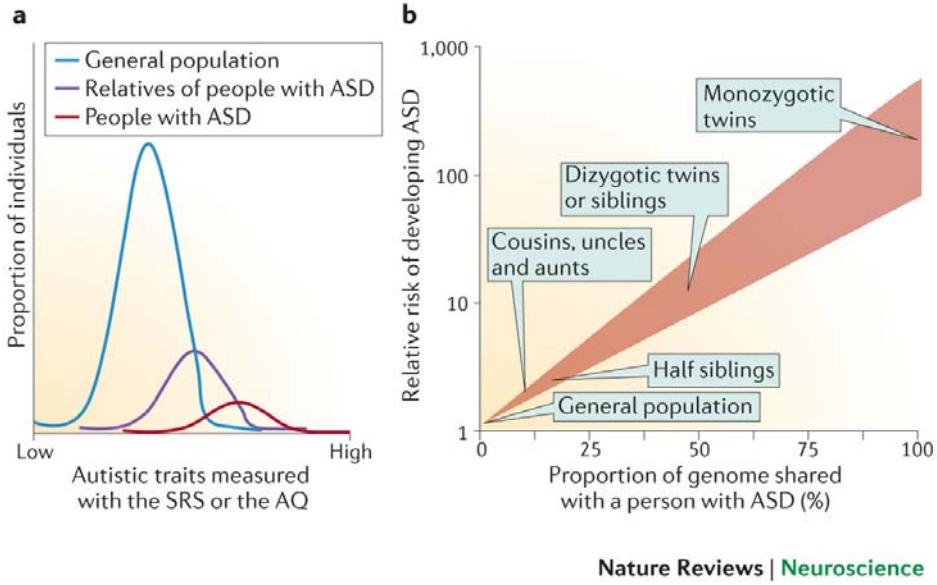
1) Human genetic studies: Identification of genes contributing to ASD.
2) Mouse models of autism: Neurodevelopmental defects are not necessarily permanent; maybe reversible
3) The identification of the ’social molecule’ oxytocin.

Human genetics



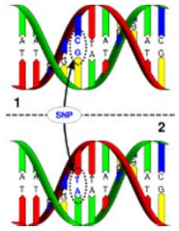
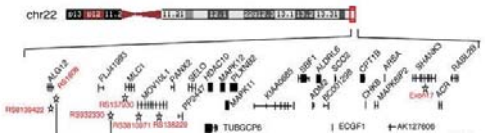
Genetics of autism





Nature Reviews | Neuroscience

Genetic variation: Summary

SNV  CNV  repeats 

- One individual carries about 3 million genetic variants.
- Genetic variation comprises: single-nucleotide variants (SNVs), tandem repeats, short insertions / deletions and copy-number variants (CNVs).
- The vast majority of these variants (>95%) are common variants (prevalence > 5%).
- Approximately 130,000 of the variants are rare variants (prevalence: 0.5–5%)
- Less than 1% of the variants are either unique to the individual or shared by a very small number of relatives.
- Any one individual carries, on average, 18–74 *de novo* SNVs in their genome, including 1–4 located in the exons of their genes .

Genes of autism

Monogenetic syndromes associated with high risk of ASD

- Fragile X syndrome – *FMR1*
- Rett syndrome - *MECP2*
- Tuberous sclerosis complex – *TSC1, TSC2*
- Neurofibromatosis – *NF1*

Cell, Vol. 65, 905–914, May 31, 1991, Copyright © 1991 by Cell Press

Identification of a Gene (*FMR-1*) Containing a CGG Repeat Coincident with a Breakpoint Cluster Region Exhibiting Length Variation in Fragile X Syndrome

Annemieke J. M. H. Verkerk,* Maura Pieretti,† James S. Sutcliffe,‡ Ying-Hui Fu,† Derek P. A. Kuhl,† Antonio Pizzuti,† Orly Reiner,† Stephen Richards,† Maureen F. Victoria,† Fuping Zhang,‡ Bert E. Eussen,* Gert-Jan B. van Ommen,§ Lau A. J. Blonden,§ Gregory J. Riggins,‡ Jane L. Chastain,‡ Catherine B. Kunst,‡ Hans Galjaard,* C. Thomas Caskey,† David L. Nelson,† Ben A. Oostra,‖ and Stephen T. Warren‡

al., 1986; Webb et al., 1986). Fragile X syndrome segregates as an X-linked dominant disorder with reduced penetrance, since either sex, when carrying the fragile X mutation, may exhibit mental deficiency. Sherman et al. (1984, 1985) have shown that approximately 30% of carrier females are penetrant and that 20% of males carrying the fragile X chromosome are phenotypically normal but may transmit the disorder and have fully penetrant grandsons. In addition to the mental retardation, which is variable in

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letter

Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2

Ruthie E. Amir[1], Ignatia B. Van den Veyver[2,3], Mimi Wan[5], Charles Q. Tran[3], Uta Francke[5,6] & Huda Y. Zoghbi[1,2,4]

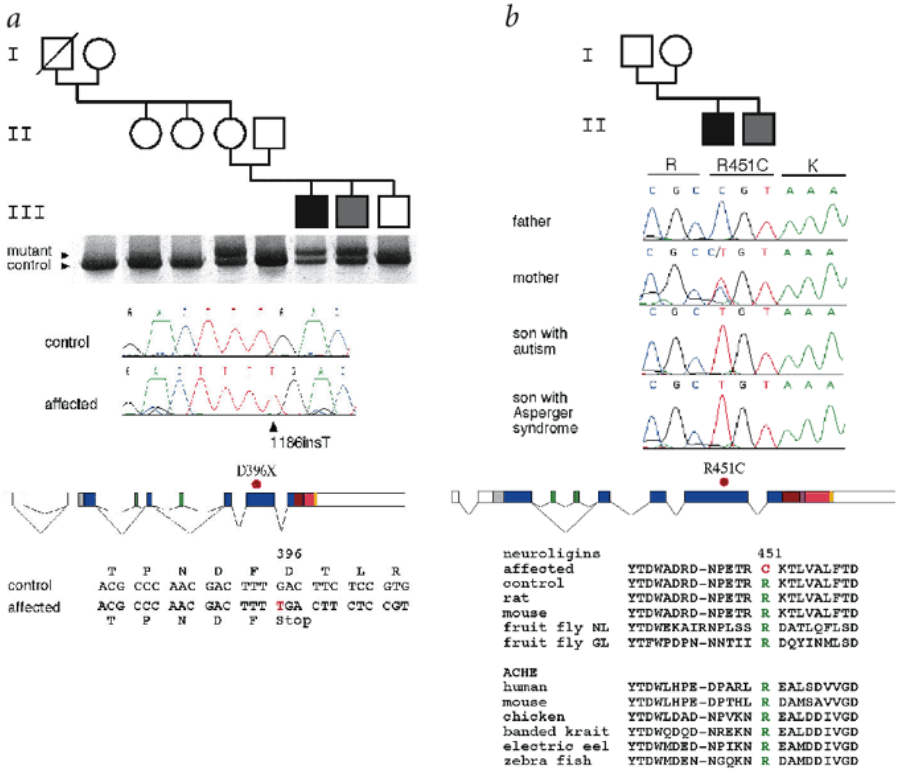
Rare mutations in autism

brief communications

Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism

Published online 31 March 2003; doi:10.1038/ng1136

Many studies have supported a genetic etiology for autism. Here we report mutations in two X-linked genes encoding neuroligins NLGN3 and NLGN4 in siblings with autism-spectrum disorders. These mutations affect cell-adhesion molecules localized at the synapse and suggest that a defect of synaptogenesis may predispose to autism.



Jamain S, Quach H, Betancur C, Råstam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, Bourgeron T: Nat Genet. 2003 May;34(1):27-9.

nature genetics

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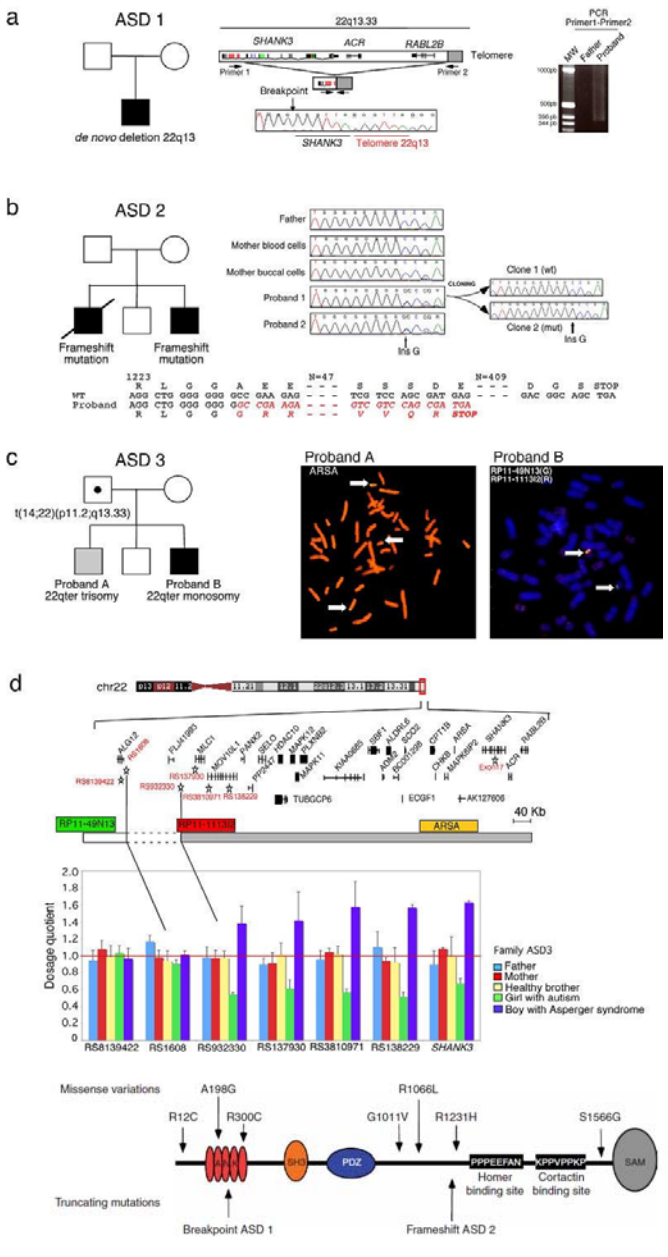
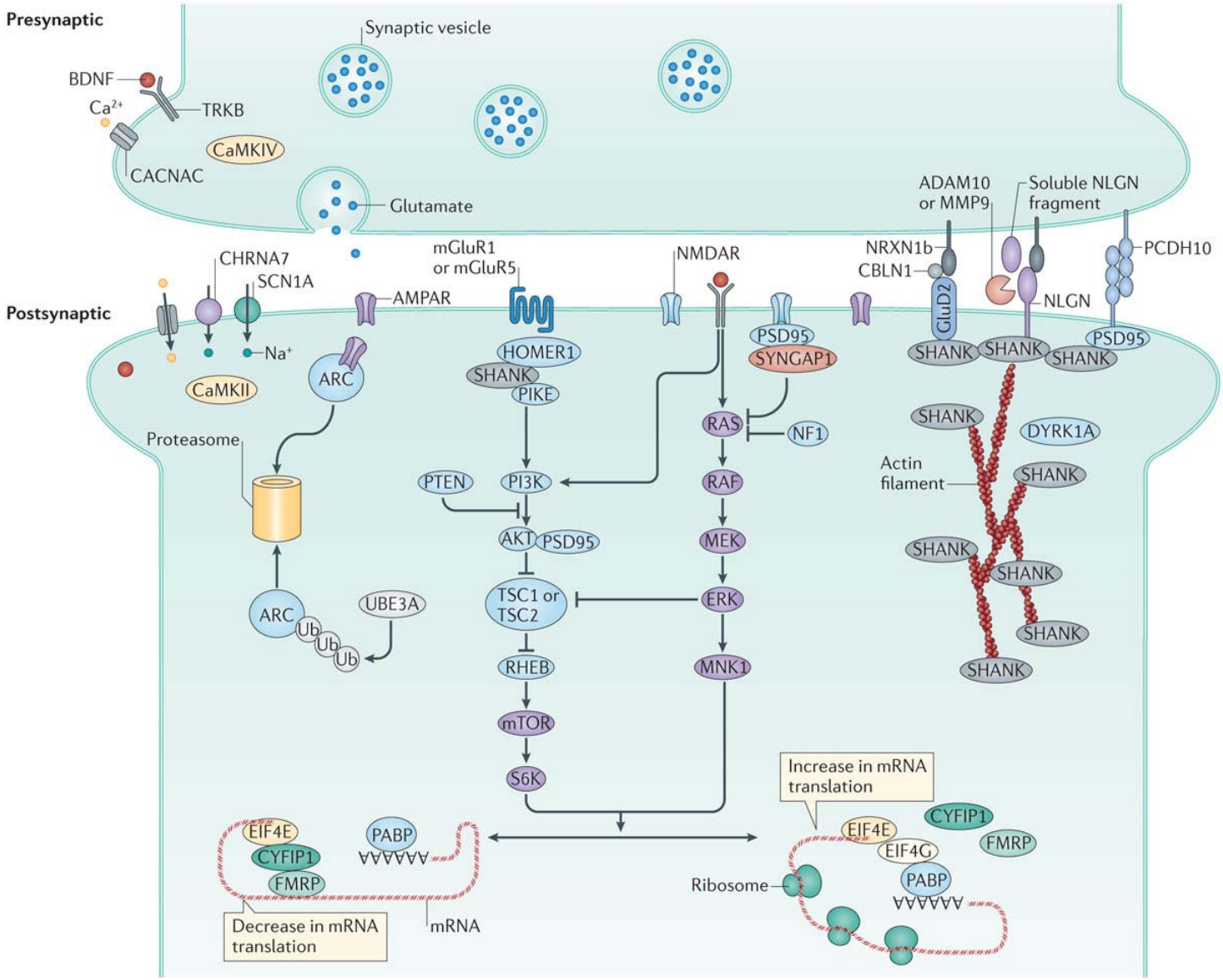
Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders

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]

SHANK3 (also known as ProSAP2) regulates the structural organization of dendritic spines and is a binding partner of neuroligins; genes encoding neuroligins are mutated in autism and Asperger syndrome. Here, we report that a mutation of a single copy of *SHANK3* on chromosome 22q13 can result in language and/or social communication disorders. These mutations concern only a small number of individuals, but they shed light on one gene dosage–sensitive synaptic pathway that is involved in autism spectrum disorders.



Genes of autism



Nature Reviews | Neuroscience

CNVs in autism

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 14, 2008 VOL. 358 NO. 7

Association between Microdeletion and Microduplication at 16p11.2 and Autism

Lauren A. Weiss, Ph.D., Yiping Shen, Ph.D., Joshua M. Korn, B.S., Dan E. Arking, Ph.D., David T. Miller, M.D., Ph.D., Ragnheidur Fossdal, B.Sc., Evald Saemundsen, B.A., Hreinn Stefansson, Ph.D., Manuel A.R. Ferreira, Ph.D., Todd Green, B.S., Orah S. Platt, M.D., Douglas M. Ruderfer, M.S., Christopher A. Walsh, M.D., Ph.D., David Altshuler, M.D., Ph.D., Aravinda Chakravarti, Ph.D., Rudolph E. Tanzi, Ph.D., Kari Stefansson, M.D., Ph.D., Susan L. Santangelo, Sc.D., James F. Gusella, Ph.D., Pamela Sklar, M.D., Ph.D., Bai-Lin Wu, M.Med., Ph.D., and Mark J. Daly, Ph.D., for the Autism Consortium

1. **A 500kb region of the short arm of the chromosome is either missing or duplicated in autism patients.**
2. **Now replicated in many studies – accounts for about 1% of autism patient.**
3. **Highly penetrant but not "autism-specific": Also found in patients with MR, Schizophrenia etc.**
4. **Contains about 25 genes, still not clear which are the most important.**

Major CNVs in autism

b Copy number variants

Location	Type	Size (kb)	Frequency in autism
16p11.2	Deletion	422	0.37%
7q11.23	Duplication	1,371	0.09%
15q11.2	Duplication	161	0.18%
15q11.2–13.1	Duplication	4,856	0.16%
15q13.2–13.3	Duplication	1,508	0.13%
16p11.2	Duplication	521	0.13%
15q13.2–13.3	Duplication and deletion	1,508	0.16%
16p11.2	Duplication and deletion	521	0.50%
22q11.21	Duplication and deletion	2,521	0.13%

Frequencies are based on a meta-analysis of studies with a combined sample of 3,816 cases with autism[37].

To date, several whole exome (WES) and whole genome sequencing studies (WGS) plus CNV analyses, have identified ASD genes:

- > 65 genes contain "likely gene disrupting" mutations: loss of function, and nonsense, splice site, damaging missense and frameshift indels in ASD patients

Neuron
Article

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,*]

Table 4. Integrating Small De Novo Deletions in TADA Identified 65 ASD Genes

dnLoF Count	FDR ≤ 0.01	0.01 < FDR ≤ 0.05	0.05 < FDR ≤ 0.1
≥2	*ADNP, ANK2,* ***ARID1B****, ASH1L,* ***CHD2****, CHD8, CUL3, DSCAM, DYRK1A, GRIN2B, KATNAL2, KDM5B,* ***KMT2C****, NCKAP1, POGZ, SCN2A, SUV420H1,* ***SYNGAP1****, TBR1,* ***TCF7L2****,* ***TNRC6B****, WAC*	*BCL11A, FOXP1, GIGYF1, ILF2, KDM6B, PHF2, RANBP17, SPAST, WDFY3*	*DIP2A, KMT2E*
1	***NRXN1****, PTEN,* ***SETD5****,* ***SHANK2****,* ***SHANK3****,* ***TRIP12***	*DNMT3A, GABRB3,* ***KAT2B****, MFRP, MYT1L, P2RX5*	*AKAP9, APH1A, CTTNBP2, ERBB2IP, ETFB, INTS6, IRF2BPL,* ***MBD5****, NAA15, NINL, OR52M1, PTK7, TRIO, USP45*
0	–	*MIB1, SLC6A1, ZNF559*	*ACHE, CAPN12,* ***NLGN3***

Genes with a small de novo deletion are in bold. FDR, false discovery rate.

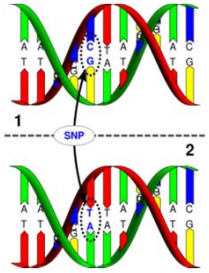
Convergence of pathways of autism

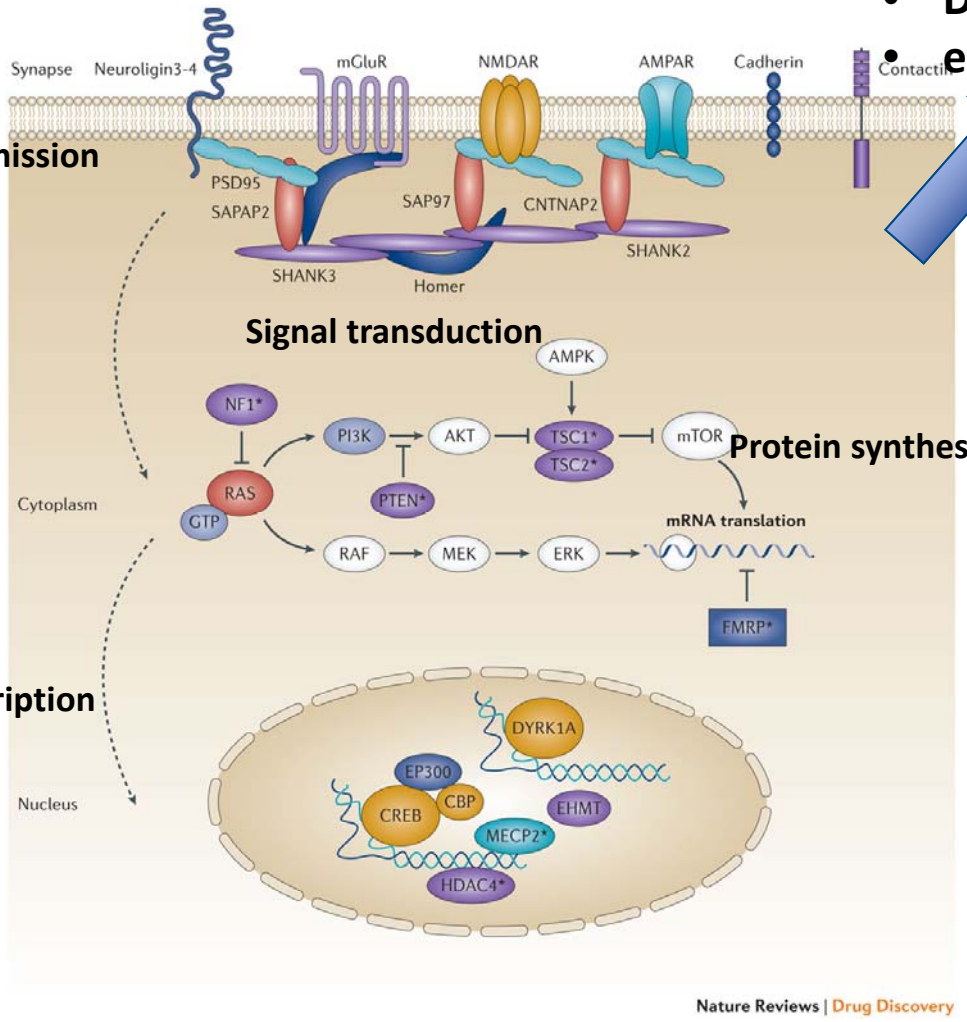
Synaptic homeostasis

- **Synaptogenes**
- **Axon guidance**
- **Dendritic growth**
- **etc**

Synaptic transmission

ASD genes





Common SNVs/SNPs in autism

LETTERS

nature genetics

Most genetic risk for autism reside

Trent Gaugler[1], Lambertus Klei[2], Stephan J Sanders[3,4], Corneliu
Milind Mahajan[8], Dina Manaa[8], Yudi Pawitan[9], Jennifer Reiche
Pamela Sklar[6–8,11,12], Oscar Svantesson[9], Abraham Reichenberg
Kathryn Roeder[1,14] & Joseph D Buxbaum[5,6,8,11,15,16]

ORIGINAL ARTICLE

The oxytocin receptor gene (*OXTR*) is associated with autism spectrum disorder: a meta-analysis

D LoParo and ID Waldman

The oxytocin receptor gene (*OXTR*) has been studied as a risk factor for autism spectrum disorder (ASD) owing to converging evidence from multiple levels of analysis that oxytocin (OXT) has an important role in the regulation of affiliative behavior and social bonding in both nonhuman mammals and humans. Inconsistency in the effect sizes of the *OXTR* variants included in association studies render it unclear whether *OXTR* is truly associated with ASD, and, if so, which *OXTR* single-nucleotide polymorphisms (SNPs) are associated. Thus, a meta-analytic review of extant studies is needed to determine whether *OXTR* shows association with ASD, and to elucidate which specific SNPs have a significant effect on ASD. The current meta-analysis of 16 *OXTR* SNPs included 3941 individuals with ASD from 11 independent samples, although analyses of each individual SNP included a subset of this total. We found significant associations between ASD and the SNPs rs7632287, rs237887, rs2268491 and rs2254298. *OXTR* was also significantly associated with ASD in a gene-based test. The current meta-analysis is the largest and most comprehensive investigation of the association of *OXTR* with ASD and the findings suggest directions for future studies of the etiology of ASD.

Molecular Psychiatry advance online publication, 5 August 2014; doi:10.1038/mp.2014.77

Psychoneuroendocrinology 68 (2016) 1–5

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Short communication

Further investigations of the relation between polymorphisms in sex steroid related genes and autistic-like traits

Anna Zettergren[a,b,*], Sara Karlsson[a], Daniel Hovey[a], Lina Jonsson[a], Jonas Melke[a], Henrik Anckarsäter[c], Paul Lichtenstein[d], Sebastian Lundström[c,e], Lars Westberg[a]

[a] Institute of Neuroscience and Physiology, Department of Pharmacology, University of Gothenburg, Sweden
[b] Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, University of Gothenburg, Sweden
[c] Institute of Neuroscience and Physiology, Centre of Ethics, Law and Mental Health (CELAM), University of Gothenburg, Sweden
[d] Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden
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ABSTRACT

Autism spectrum disorders (ASDs) are more prevalent in boys than in girls, indicating that high levels of testosterone during early development may be a risk factor. Evidence for this hypothesis comes from studies showing associations between fetal testosterone levels, as well as indirect measures of prenatal androgenization, and ASDs and autistic-like traits (ALTs). In a recent study we reported associations between ALTs and single nucleotide polymorphisms (SNPs) in the genes encoding estrogen receptor 1 (*ESR1*), steroid-5-alpha-reductase, type 2 (*SRD5A2*) and sex hormone-binding globulin (*SHBG*) in a subset ($n = 1771$) from the Child and Adolescent Twin Study in Sweden (CATSS). The aim of the present study was to try to replicate these findings in an additional, larger, sample of individuals from the CATSS ($n = 10,654$), as well as to analyze additional SNPs of functional importance in *SHBG* and *SRD5A2*. No associations between the previously associated SNPs in the genes *ESR1* and *SRD5A2* and ALTs could be seen in the large replication sample. Still, our results show that two non-linked SNPs (rs6259 and rs9901675) at the *SHBG* gene locus might be of importance for language impairment problems in boys. The results of the present study do not point toward a major role for the investigated SNPs in the genes *ESR1* and *SRD5A2* in ALTs, but a possible influence of genetic variation in *SHBG*, especially for language impairment problems in boys, cannot be ruled out.

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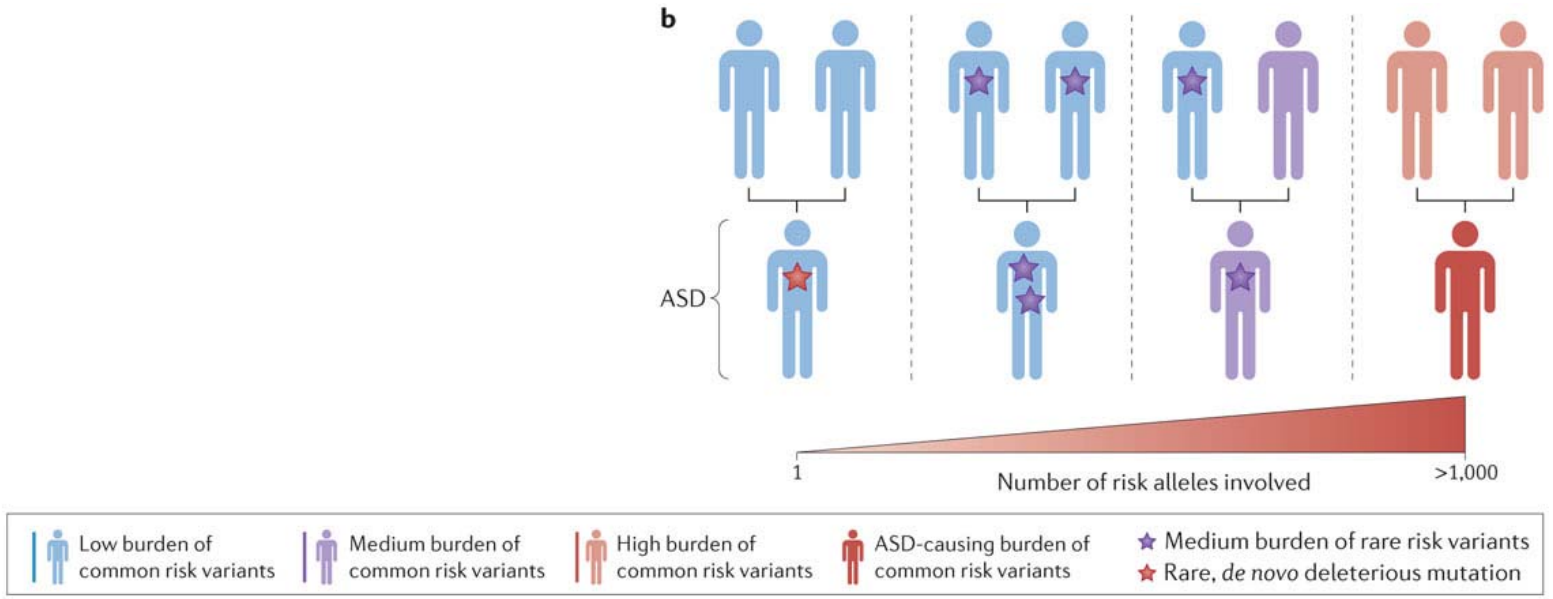
’Multiple-hit-model’

An interplay between rare mutations and genetic background.



Bourgeron, Nature Reviews Neuroscience 2015

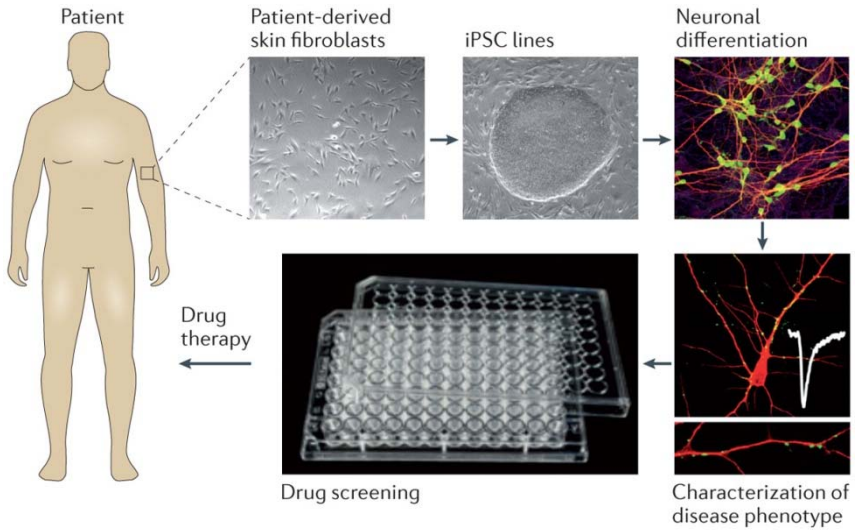
Genetics of autism: Summary

- Common, rare and *de novo* mutations all contribute to the genetic risk of ASD.
- None of the genes identified so far accounts for more of 1% of all cases of ASD.
- The number of genes responsible for 'monogenic' forms of ASD is estimated to be more than 400.
- Monogenic forms of the disorder account for 10–20% of all ASD cases.
- Monogenic autosomal recessive forms of ASD could account for an additional 3–6% of the cases.
- Today, karyotypes, CNV analysis and exome sequencing can detect a genetic cause for ASD in almost 25% of the cases.
- The genetic contribution to ASD may be shaped by a combination of rare deleterious variants and a myriad of low-risk alleles - common SNPs. The interplay between rare deleterious variants and common low-risk alleles will therefore influence the phenotypic diversity observed in the population.

Translation from genetics to molecular pathway and neuronal mechanisms

Animal models

Induced Pluripotent Stemcells (iPSCs)



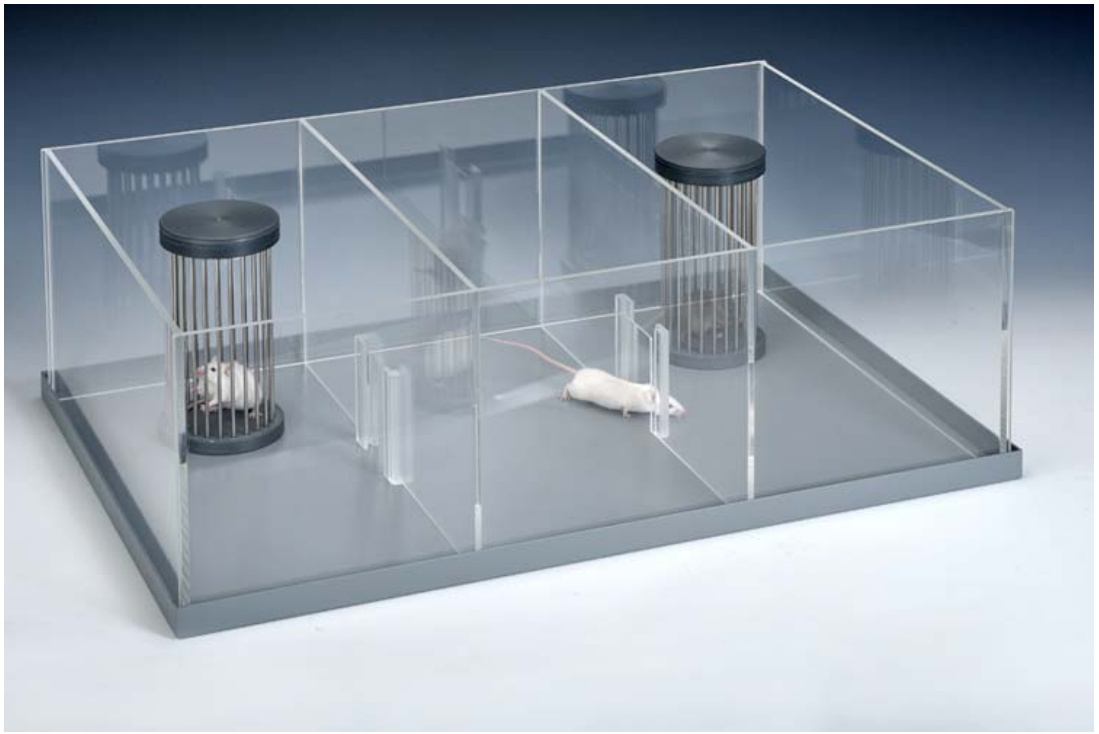
Nature Reviews | Drug Discovery

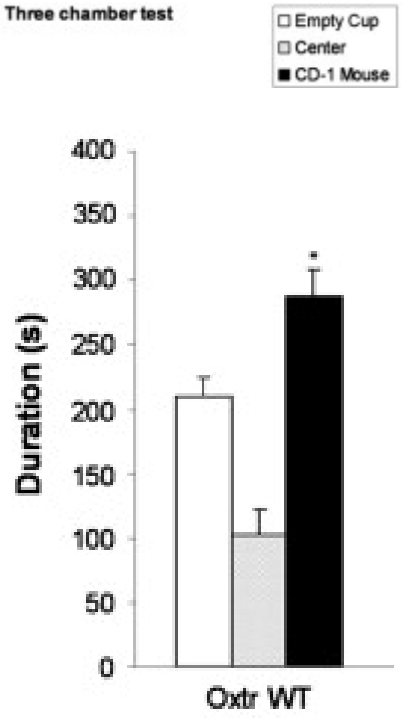
Autism in mice

Social deficits

Sociability

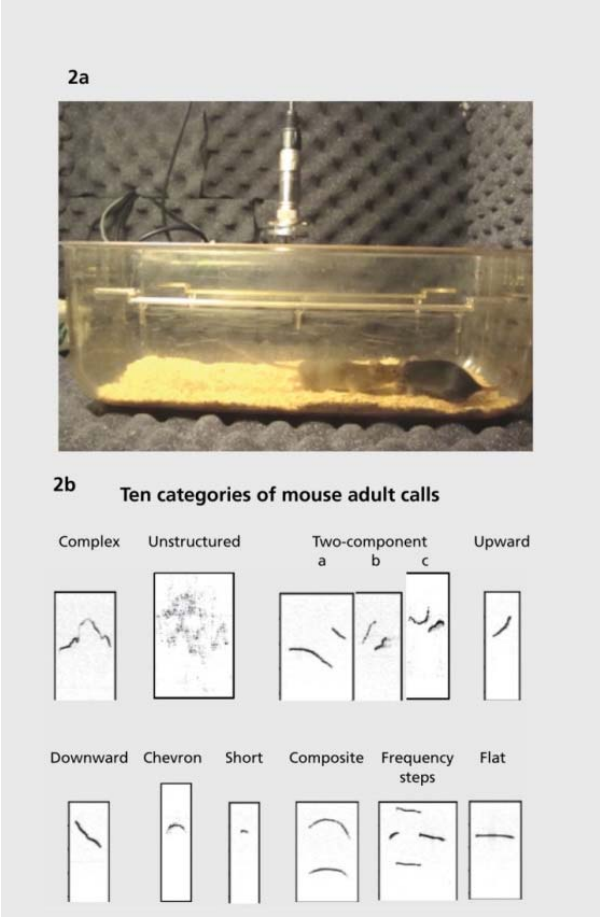
Preference for social novelty





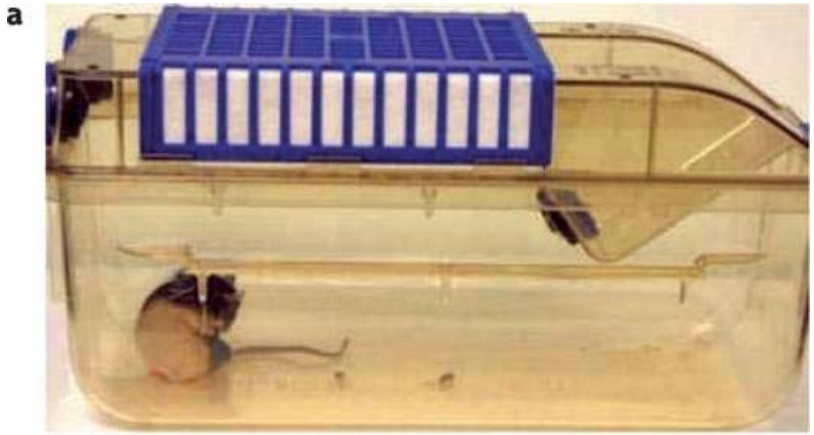
Social communication

Ultrasonic vocalisations



Restricted and repetitive behaviors

Self-grooming



Phentotypes in mouse models of autism

Table 5 Phenotypic similarities between mutant mouse models of the genes of interest

Mutant mouse models → / *Phenotypes ↓*	Cntnap2	Nlgn1	Nlgn2	Nlgn3	Nlgn4	Nrxn1α	Pten	Shank1	Shank2	Shank3
Spine density	—					—	↑	↓	↓	↓
Dendritic arborization	↓			↑			↑			↑
LTP		↓		↑			↑	—	↑	↓
mGluR-dependent LTD				↓			↓	—	—	—
Social interaction	↓	↓	—	↓	↓	—	↓	—	↓	↓
Communication	↓		↓	↓	↓			↓	↓	↓
Repetitive behavior	↑	↑	—	↑	—	↑	↑	—	↑	↑

↑ = Increase ↓ = Impairment/decrease — = No change

Reversibility of neurodevelopment

Possible to reverse symptoms and brain abnormalities caused by 'autism-genes'?

A simple model may explain both the Xa versus Xi and the gene versus intergenic differential methylation we observed: Constantly inactive regions, such as gene-poor regions and the entire Xi, may be more prone to loss of methylation maintenance (even if originally highly methylated). The resulting methylation decrease, for the entire Xi and for Xa intergenic regions, would thus highlight Xa gene body–specific methylation. At the same time, promoter CpG islands, which are protected from methylation on Xa, would remain more methylated on Xi.

In contrast to the widely held view that X chromosome allele–specific methylation is restricted to CpG islands on the inactive X, our global allele-specific methylation analyses uncovered extensive methylation specifically affecting transcribable regions (gene bodies) on the active X whether it is in the male or the female. One aspect of sex chromosome dosage compensation is the require-

Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

Jacky Guy,[1] Jian Gan,[2] Jim Selfridge,[1] Stuart Cobb,[2] Adrian Bird[1]*

Rett syndrome is an autism spectrum disorder caused by mosaic expression of mutant copies of the X-linked *MECP2* gene in neurons. However, neurons do not die, which suggests that this is not a neurodegenerative disorder. An important question for future therapeutic approaches to this and related disorders concerns phenotypic reversibility. Can viable but defective neurons be repaired, or is the damage done during development without normal MeCP2 irrevocable? Using a mouse model, we demonstrate robust phenotypic reversal, as activation of MeCP2 expression leads to striking loss of advanced neurological symptoms in both immature and mature adult animals.

Mutations in the X-linked *MECP2* gene are the primary cause of Rett syndrome (RTT), a severe autism spectrum disorder with delayed onset that affects 1 in 10,000 girls (*1*). *MECP2* mutations are also found in patients with other neurological conditions, including learning disability, neonatal encephalopathy, autism, and X-linked mental

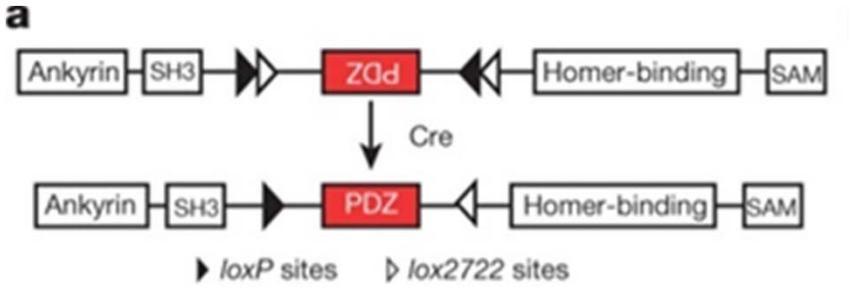
LETTER

doi:10.1038/nature16971

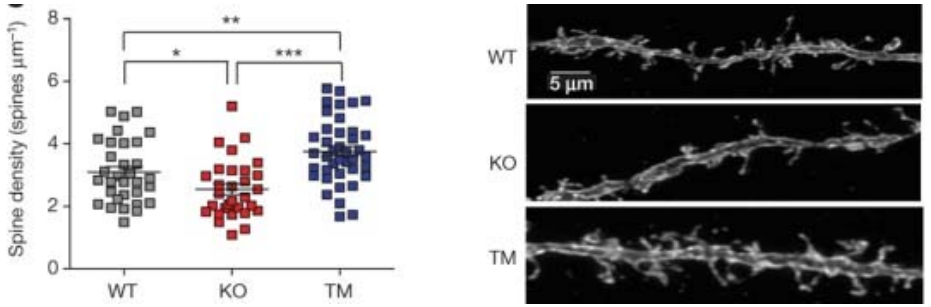
Adult restoration of *Shank3* expression rescues selective autistic-like phenotypes

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]

Conditional knock-in mouse model allows re-expression of SHANK3 in adulthood



Adult *Shank3* re-expression increased the spine density in the striatum



LETTER

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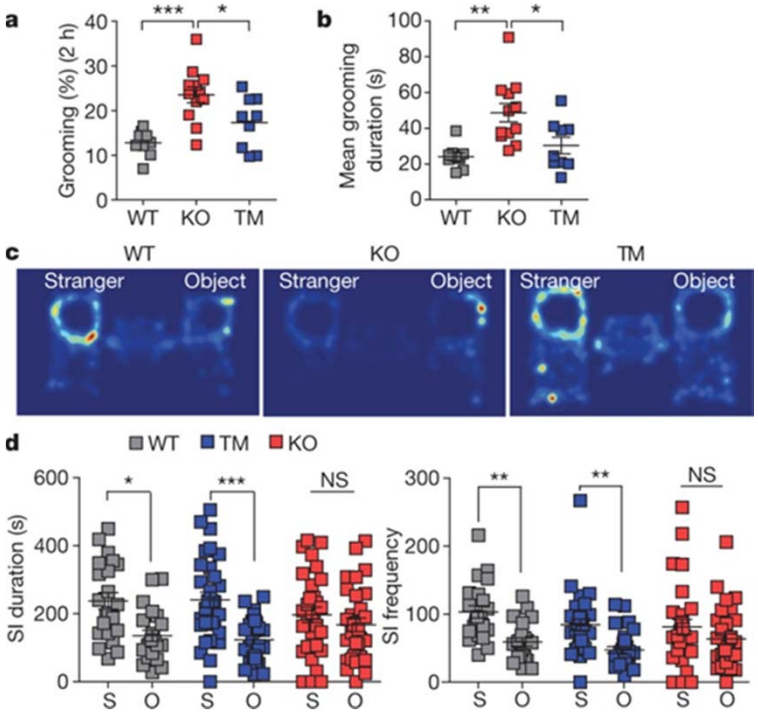
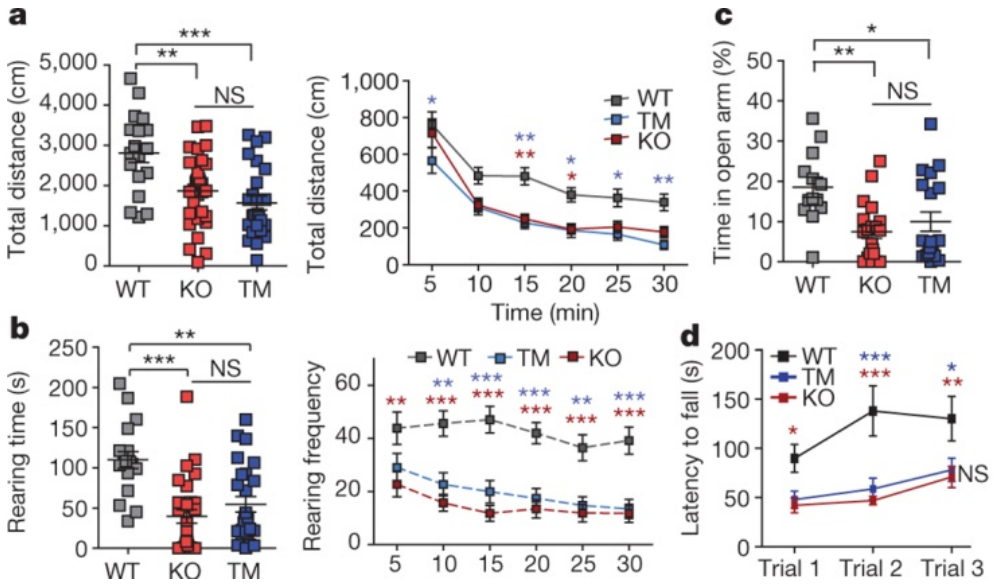
Yuan Mei[1]*, Patricia Monteiro[1,2,3]*, Yang Zhou[1], Jin-Ah Kim[1], Xian Gao[1,4], Zhanyan Fu[1,3] & Guoping Feng[1,3]

Adult *Shank3* expression rescued repetitive grooming and social interaction



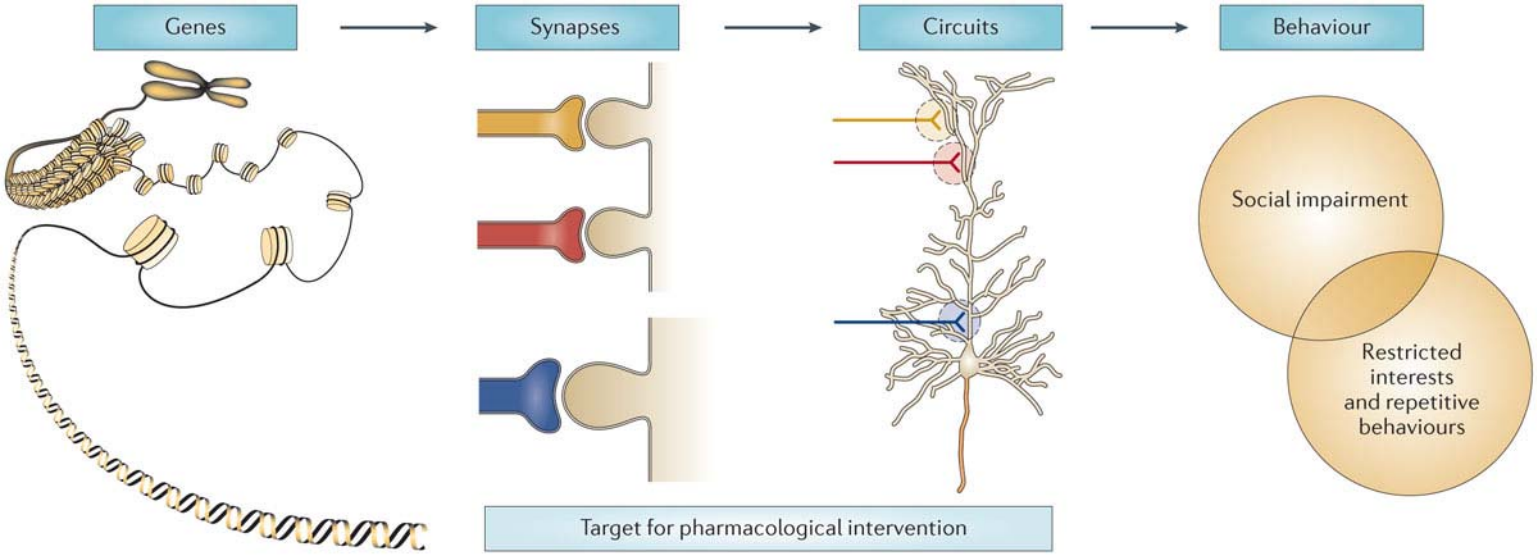
Restoring *Shank3* expression in adulthood did not rescue anxiety and rotarod deficits



Pharmacology of autism

- **Causal treatment - From mouse to human**
- **Symptomatic treatment**

Causal treatment - From mouse to human



Nature Reviews | Drug Discovery

Causal treatment - From mouse to human

Science

REPORTS

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10.1126/science.aad5487 (2016).

CLK2 inhibition ameliorates autistic features associated with SHANK3 deficiency

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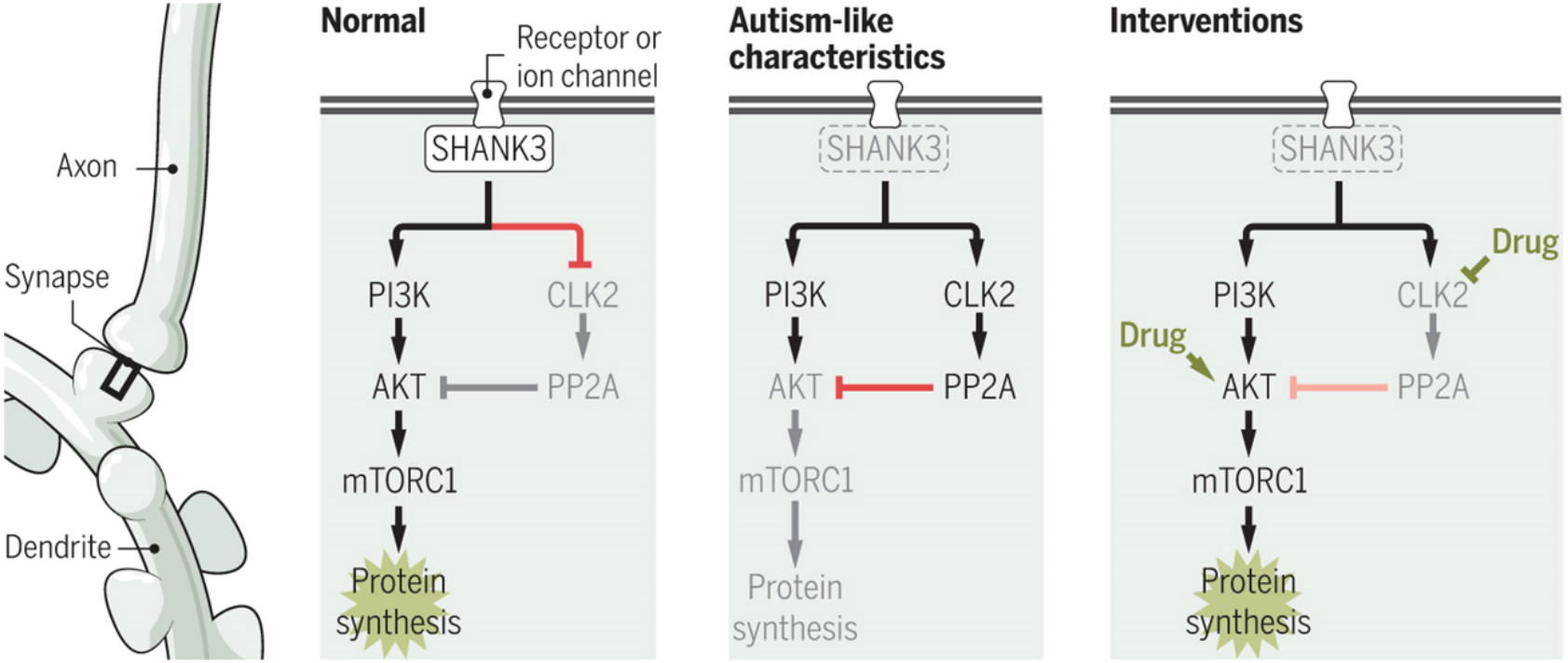
Axon
Synapse
Dendrite
Normal
Receptor or ion channel
SHANK3
PI3K
CLK2
AKT
PP2A
mTORC1
Protein synthesis
Autism-like characteristics
SHANK3
PI3K
CLK2
AKT
PP2A
mTORC1
Protein synthesis
Interventions
SHANK3
Drug
PI3K
CLK2
Drug
AKT
PP2A
mTORC1
Protein synthesis

Neuron
Report

SAHLGRENSKA AKADEMIN

Correction of Fragile X Syndrome in Mice

Gül Dölen,[1,2] Emily Osterweil,[1] B.S. Shankaranarayana Rao,[3] Gordon B. Smith,[1] Benjamin D. Auerbach,[1] Sumantra Chattarji,[4] and Mark F. Bear[1,*]
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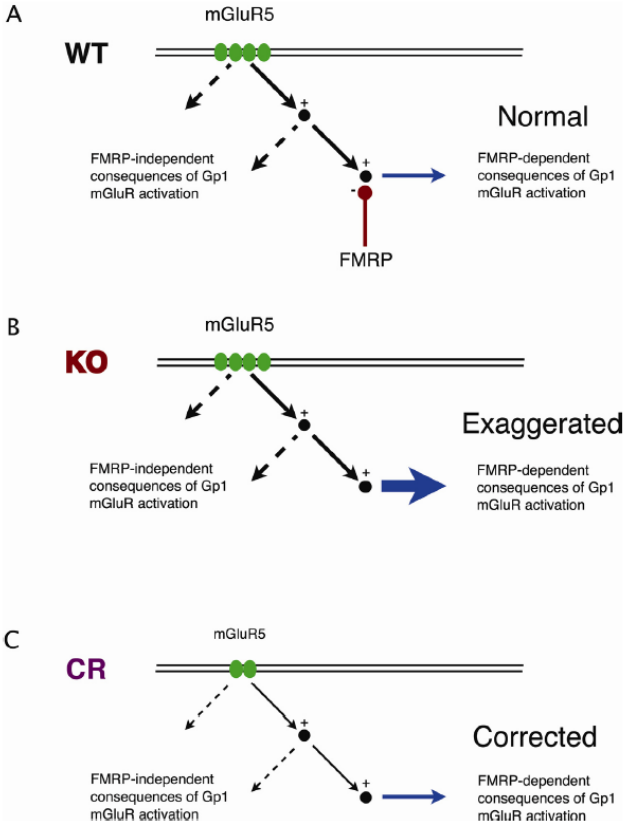
DOI 10.1016/j.neuron.2007.12.001

SUMMARY

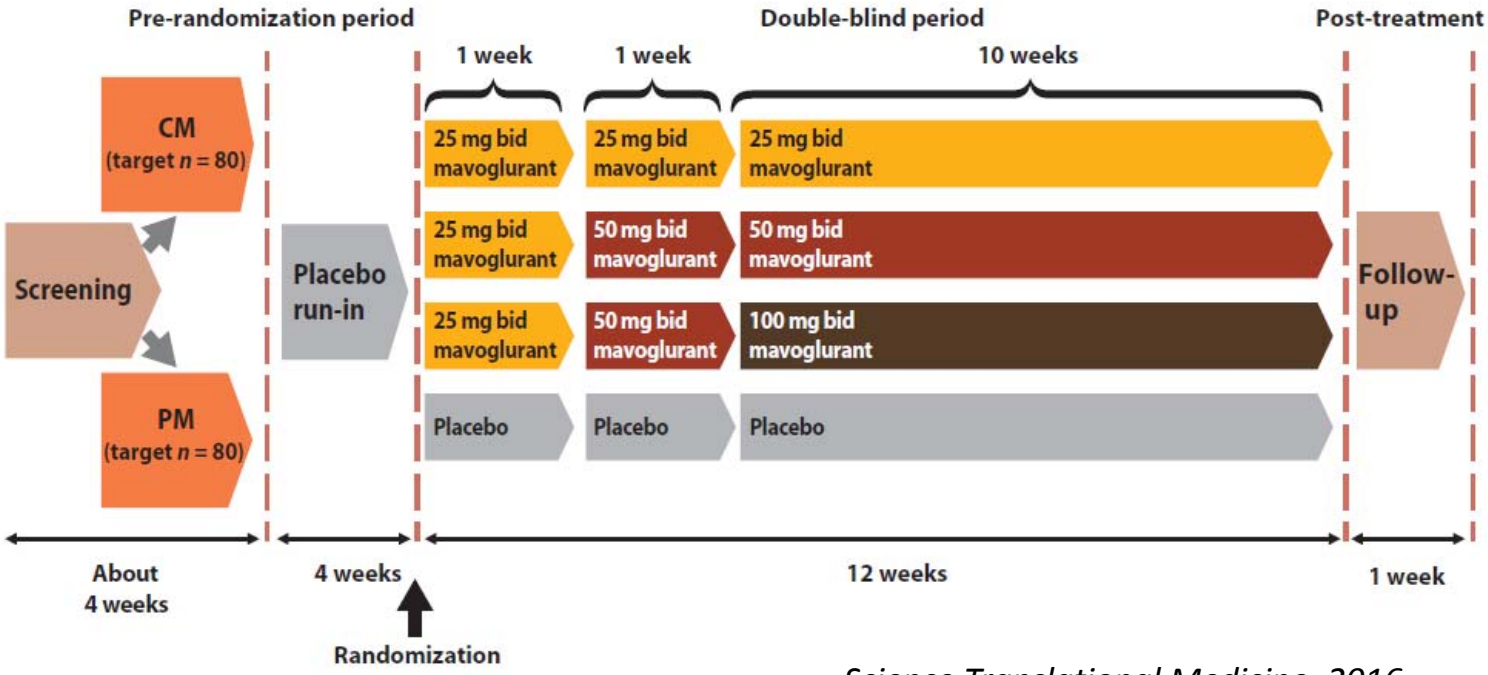
Fragile X syndrome (FXS) is the most common form of heritable mental retardation and the leading identified cause of autism. FXS is caused by transcriptional silencing of the *FMR1* gene that encodes the fragile X mental retardation protein (FMRP), but the pathogenesis of the disease is unknown. According to one proposal, many psychiatric and neurological symptoms of FXS result from unchecked activation of mGluR5, a metabotropic glutamate receptor. To test this idea we generated *Fmr1* mutant mice with a 50% reduction in mGluR5 expression and studied a range of phenotypes with relevance to the human disorder. Our results demonstrate that mGluR5 contributes significantly to the pathogenesis of the disease, a finding that has significant therapeutic implications for fragile X and related developmental disorders.



FRAGILE X SYNDROME

Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials

Elizabeth Berry-Kravis,[1]* Vincent Des Portes,[2,3]* Randi Hagerman,[4] Sébastien Jacquemont,[5,6] Perrine Charles,[7] Jeannie Visootsak,[8] Marc Brinkman,[9] Karin Rerat,[10] Barbara Koumaras,[11] Liansheng Zhu,[12] Gottfried Maria Barth,[13] Thomas Jaecklin,[14] George Apostol,[14] Florian von Raison[14†]



Science Translational Medicine, 2016

Fig. 1. Study design.

FRAGILE X SYNDROME

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Complete methylation

Partial methylation

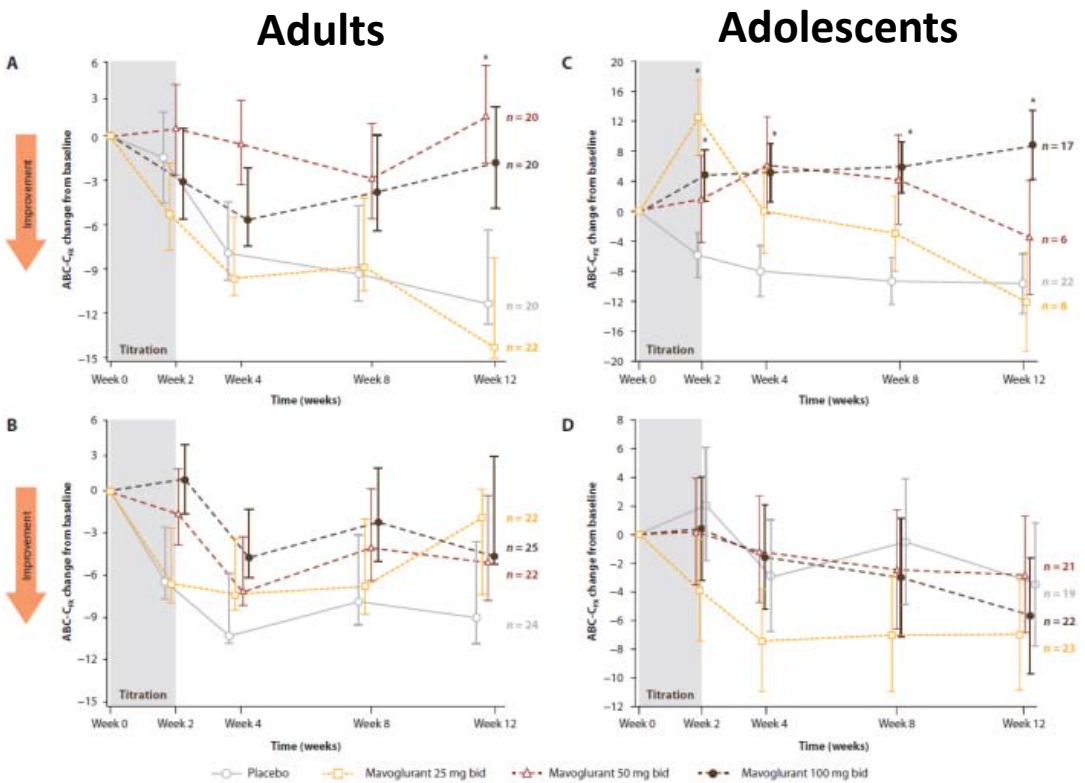

Fig. 3. ABC-C$_{FX}$ least square (LS) mean change from baseline (after placebo run-in). (**A**) CM stratum in adult population. (**B**) PM stratum in adult population. (**C**) CM stratum in adolescent population. (**D**) PM stratum in adolescent population. *, statistical significance at 5% level. (A) 50 mg bid, week 12: $P = 0.018$; (C) 100 mg bid, week 2: $P = 0.022$; week 4: $P = 0.013$; week 8: $P = 0.002$; week 12: $P = 0.004$; 25 mg bid, week 2: $P = 0.003$. Data presented as LS means (±SEM).

GÖTEBORGS UNIVERSITET

RESEARCH ARTICLE

FRAGILE X SYNDROME

Effects of STX209 (Arbaclofen) on Neurobehavioral Function in Children and Adults with Fragile X Syndrome: A Randomized, Controlled, Phase 2 Trial

Elizabeth M. Berry-Kravis,[1] David Hessl,[2] Barbara Rathmell,[3] Peter Zarevics,[3] Maryann Cherubini,[3] Karen Walton-Bowen,[3] Yi Mu,[4] Danh V. Nguyen,[4] Joseph Gonzalez-Heydrich,[5] Paul P. Wang,[3]* Randall L. Carpenter,[3] Mark F. Bear,[6] Randi J. Hagerman[7]

Research on animal models of fragile X syndrome suggests that STX209, a γ-aminobutyric acid type B ($GABA_B$) agonist, might improve neurobehavioral function in affected patients. We evaluated whether STX209 improves behavioral symptoms of fragile X syndrome in a randomized, double-blind, placebo-controlled crossover study in 63 subjects (55 male), ages 6 to 39 years, with a full mutation in the *FMR1* gene (>200 CGG triplet repeats). We found no difference from placebo on the primary endpoint, the Aberrant Behavior Checklist—Irritability (ABC-I) subscale. In the other analyses specified in the protocol, improvement was seen on the visual analog scale ratings of parent-nominated problem behaviors, with positive trends on multiple global measures. Post hoc analysis with the ABC—Social Avoidance scale, a newly validated scale for the assessment of fragile X syndrome, showed a significant beneficial treatment effect in the full study population. A post hoc subgroup of 27 subjects with more severe social impairment showed improvements on the Vineland II–Socialization raw score, on the ABC—Social Avoidance scale, and on all global measures. STX209 was well tolerated, with 8% incidences of sedation and of headache as the most frequent side effects. In this exploratory study, STX209 did not show a benefit on irritability in fragile X syndrome. Nonetheless, our results suggest that $GABA_B$ agonists have potential to improve social function and behavior in patients with fragile X syndrome.

Science Translational Medicine, 2012

Remarks on Clincial trials

- Possible to translate results from mice to human?
- Choice of treatment group
- Target engagement
- Selection of outcome measures
- The impact of the placebo effect

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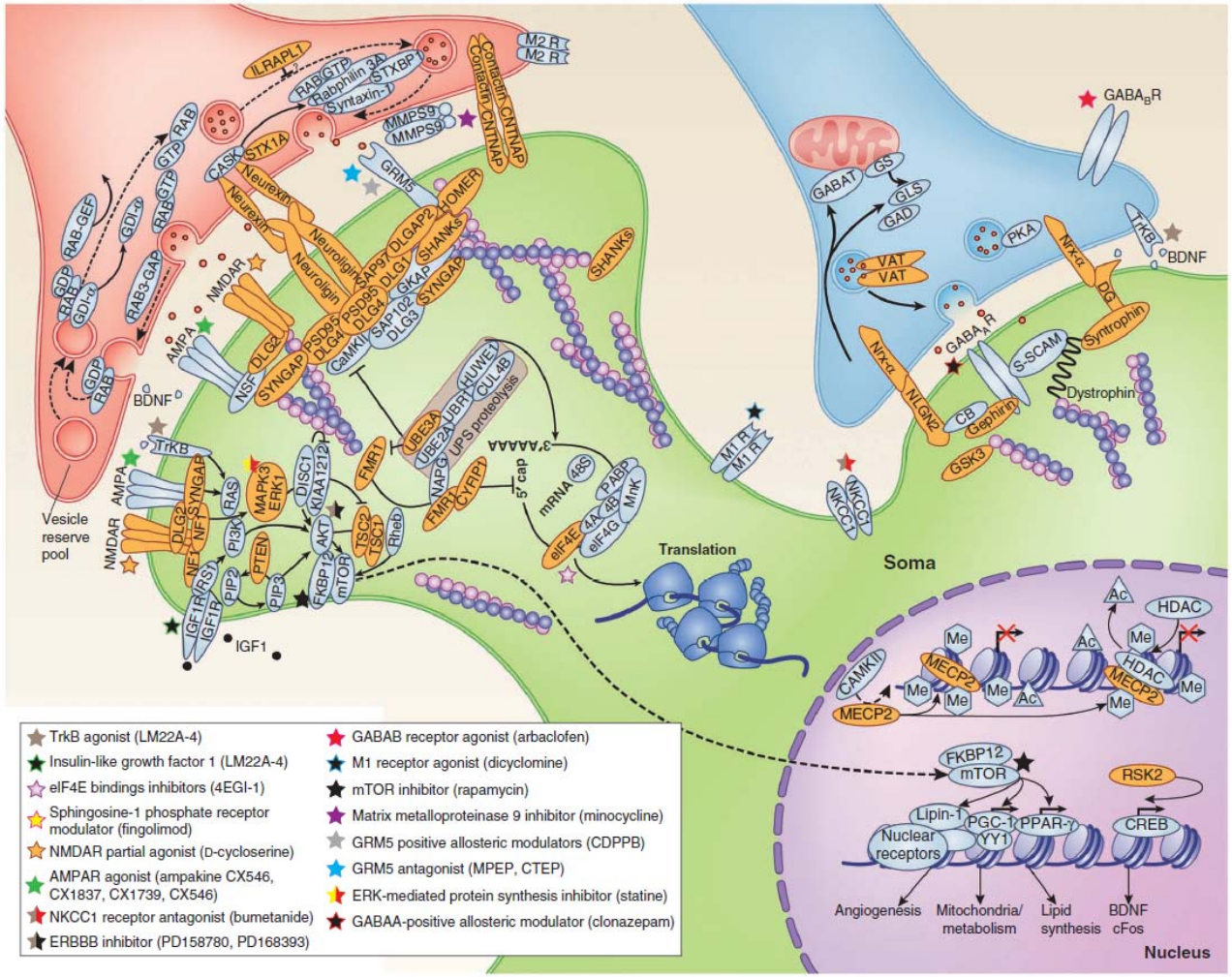
Pharmacological treatments under development

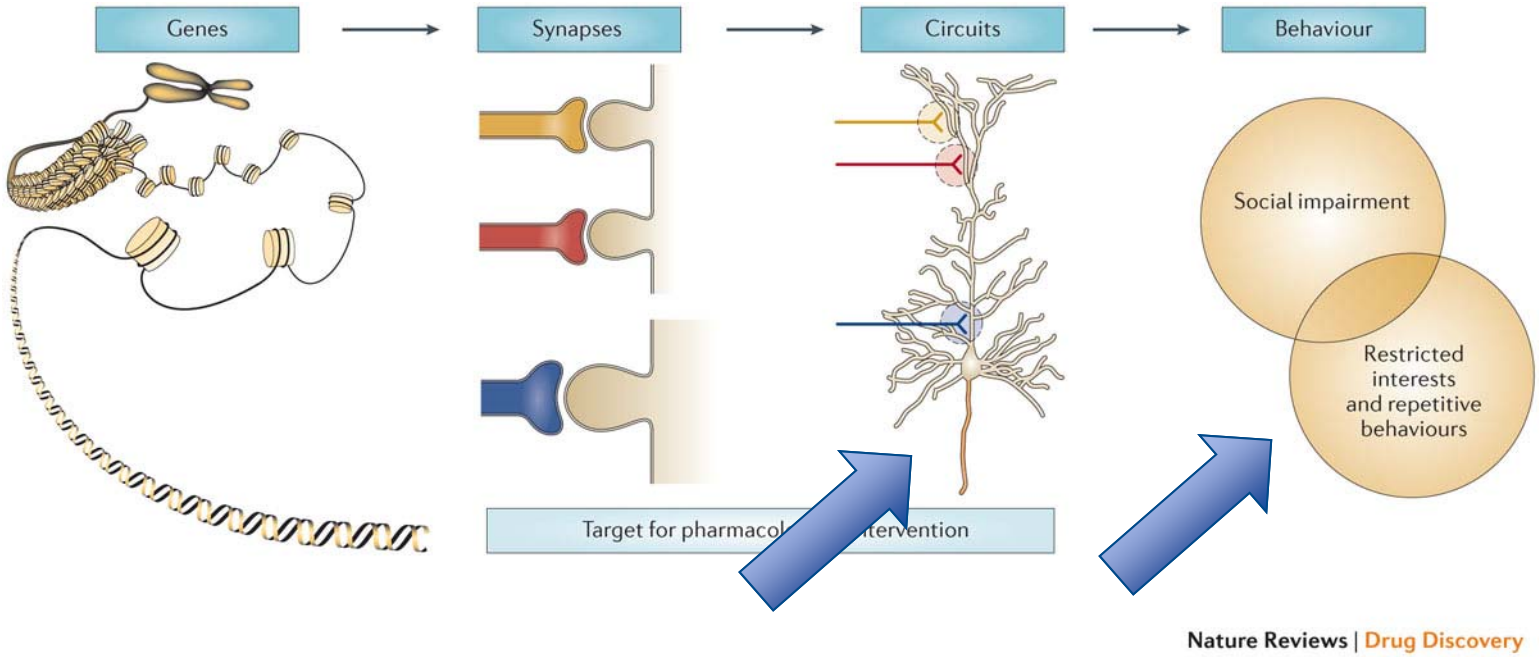


Autism – Products under Development by Companies

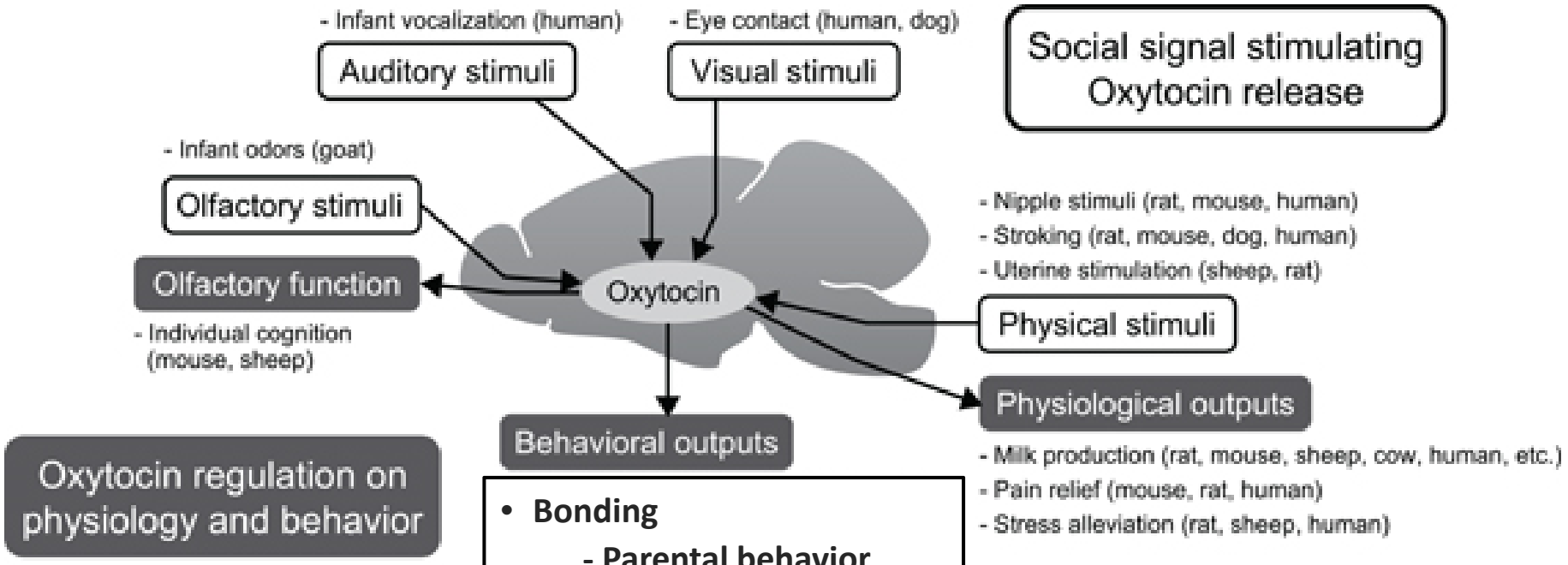
Products under Development by Companies, H2 2015				
Product Name	Company	Indication Name	Stage of Development	Territory
CM-AT	Curemark, LLC	Autism	Pre-Registration	United States
aripiprazole	Otsuka Holdings Co., Ltd.	Autism	Phase III	Japan
lurasidone hydrochloride	Sumitomo Dainippon Pharma Co., Ltd.	Autism	Phase III	Global
(dextromethorphan hydrobromide + quinidine sulfate)	Otsuka Holdings Co., Ltd.	Autism	Phase II	Global
memantine hydrochloride	Merz Pharma GmbH & Co. KgaA	Autism	Phase II	Global
RG-7314	F. Hoffmann-La Roche Ltd.	Autism	Phase II	Global
ITI-007	Intra-Cellular Therapies, Inc.	Autism	Phase I	Global
oxytocin	Optinose US Inc.	Autism	Phase I	Global
RO-5285119	F. Hoffmann-La Roche Ltd.	Autism	Phase I	Global
Stem Cell Therapy for Multiple Sclerosis, Rheumatoid Arthritis, Autism and Bronchopulmonary Dysplasia	Translational Biosciences	Autism	Phase I	Global
acamprosate calcium	Confluence Pharmaceuticals LLC	Autism	Preclinical	Global
ADX-71441	Addex Therapeutics Ltd	Autism	Preclinical	Global
ADX-88178	Addex Therapeutics Ltd	Autism	Preclinical	Global
aripiprazole	Aequus Pharmaceuticals Inc.	Autism	Preclinical	Global
carbetocin	Retrophin Inc.	Autism	Preclinical	Global
CN-2097	Ardane Therapeutics, Inc	Autism	Preclinical	Global
Source: Global Markets Direct				

Products under Development by Companies, H2 2015 (Contd..1)				
Product Name	Company	Indication Name	Stage of Development	Territory
Stem Cell Therapy for Neurodegenerative Disorders	BrainStorm Cell Therapeutics Inc.	Autism	Preclinical	Global
HTL-14242	Heptares Therapeutics Limited	Autism	Preclinical	Global
KM-391	Cellceutix Corporation	Autism	Preclinical	Global
MD-1103	MedDay	Autism	Preclinical	Global
Small Molecule to Modulate GABRA5 Receptor for CNS Disorders	AgeneBio Inc.	Autism	Preclinical	Global
Small Molecule to Target GPR63 for Autism	Omeros Corporation	Autism	Preclinical	Global
Small Molecules to Agonize GABAA-Beta 2 Receptor for Epilepsy and Autism	BioCrea GmbH	Autism	Preclinical	Global
Drug for Autism	Berg Pharma, LLC	Autism	Discovery	Global
Small Molecule to Agonize GABAA Receptor Subunit Alpha-5 for Autism	Saniona AB	Autism	Discovery	Global
Small Molecules to Antagonize NMDA2A for Central Nervous System Disorders	Mnemosyne Pharmaceuticals, Inc.	Autism	Discovery	Global
Small Molecules to Inhibit Translation Initiation Factor-4E for Cancer and Autism	Egenix, Inc.	Autism	Discovery	Global
Small Molecules to Target Oxytocin for Autism and Anxiety Disorders	Epigenetix Inc	Autism	Discovery	Global
RP-5063	Reviva Pharmaceuticals Inc.	Autism	Unknown	Global
Source: Global Markets Direct				

Symptomatic treatment



Oxytocin


- Infant vocalization (human)
Auditory stimuli
- Eye contact (human, dog)
Visual stimuli
Social signal stimulating Oxytocin release
- Infant odors (goat)
Olfactory stimuli
Olfactory function
- Individual cognition (mouse, sheep)
Oxytocin
- Nipple stimuli (rat, mouse, human)
- Stroking (rat, mouse, dog, human)
- Uterine stimulation (sheep, rat)
Physical stimuli
Physiological outputs
- Milk production (rat, mouse, sheep, cow, human, etc.)
- Pain relief (mouse, rat, human)
- Stress alleviation (rat, sheep, human)
Behavioral outputs
Oxytocin regulation on physiology and behavior
• Bonding
- Parental behavior
- Pair-bonding behavior
• Social cognition
- Social recognition
• Aggression
• Anxiolysis

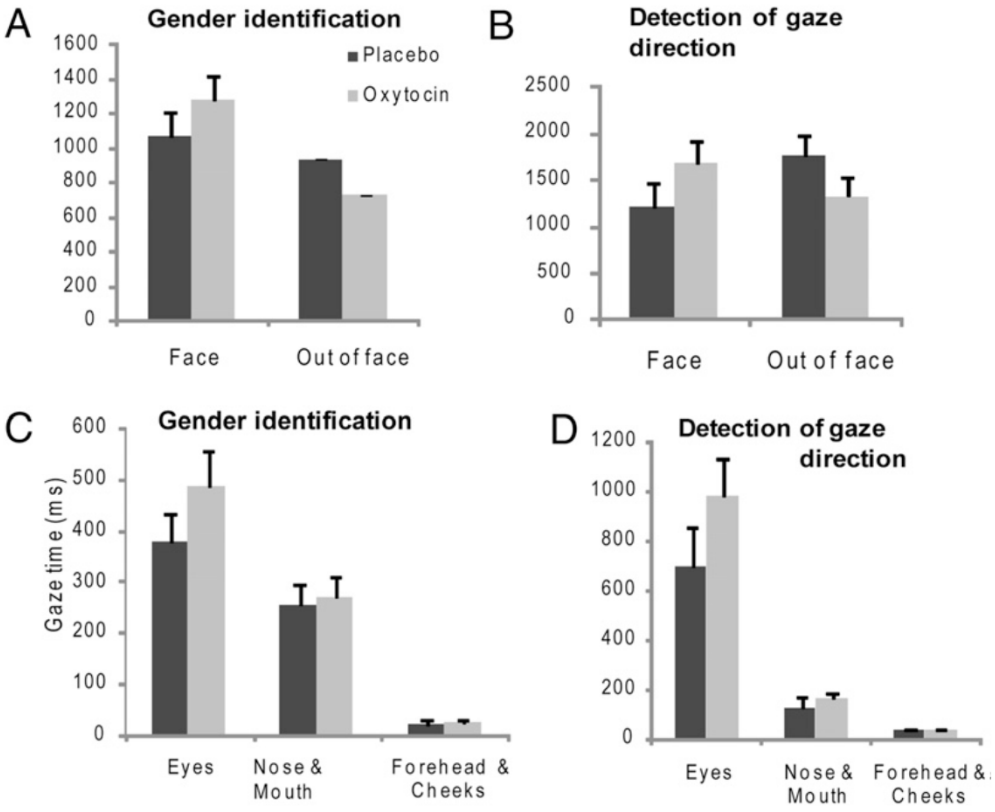
Thus, oxytocin seems to influence different human social behaviors.

How?

- **Reduce anxiety**
- **Increase social motivation**
- **Increase salience of social cues - social attention**

Oxytocin treatment and autism

- symptom relief
- increased eye gazing
- improved emotion recognition
- etc



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Auyeung B *et al*, Transl Psychiatry. 5:e507 (2015)

Oxytocin treatment in autism

- Single dose intranasal spray improves social awareness and use of appropriate social aproach behaviors in context, appropriate use of of eye contact, gestures, and understanding and recognition of facial expression – in individuals with and without autism.
- Promising, but contradictory, results from 'clinical trials' of continous oxytocin treatment on diagnostic symptoms of autism.
- Combination of oxytocin and behavioral therapy should be evalutated in patients.
- Development of alternative treatment strategies is on-going e.g. by increasing endogenous oxytocin by melanocortin receptor agonist melanotan-II, in animal models.
- Are subgroups of patients more responsive to oxytocin and others?

Concluding Remarks

- Autism can probably be caused by altered synaptic function / synaptic homeostasis probably causing imbalance between excitation (glutamate) and inhibition (GABA) of relevant neural circuits.
- Studies in mice suggest that neurodevelopmental events and autism-like symptom may be reversible in adulthood.
- Several drug targets have beed identified in mice studies, which are and should be evaluated.
- Several drugs are under development.
- Oxytocin may turn out to be helpful in improving social fucntioning in autism patients.

Future directions

- Genetic subgroups with respect to rare mutations should be evaluated to symptoms and treatment response.
- Identification of the common variants

- Genome-wide studies of huge samples of patients and controls
- Identification of sub-groups of patients, and their genetics.
- Investigating the genetics of endophenotypes of ASD e.g. eye-tracking measures during social attention

- Evaluation of other animal models e.g. zebrafish; maybe having better validity than mice, and allows drug screening.

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Research Group

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Postdocs: Jenny Landin, Susanne Henningsson

Students: Laura Hosta

Collaborators

CATSS: Paul Lichtenstein,KI; Henrik Anckarsäter, Sebastian Lundström, GU

TCHAD: Paul Lichtenstein, KI

MultiEmo: Petri Laukka, Håkan Fischer, SU

iTwin: Terje Falck-Ytter, KI, UU

Oxytocin study: Siri Leknes, Oslo University

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