February 23 , 2011
Case Western Reserve University
Cleveland, OH

Autism Research : Recent Advances + Future Directions

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VP, Scientific Affairs

One Strong

Our Mission

"Change the future for all who struggle with autism spectrum disorders."

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About Us: Our Impact (2005-2010)

- Enhanced awareness around the world (WAAD)

- Combating Autism Act of 2006 (~$920 million for research, surveillance, awareness and early identification)

- Insurance coverage in 23 states; >20 more on the way

- Over $142 million committed to research funding to date:

  - First prevalence studies (Korea, India, Ireland, Mexico, Taiwan)

  - Identification of genetic risk factors

  - Early diagnosis (from ~4-5 yr to ~2-3 yr)

  - Intensive early intervention (<24 mos)

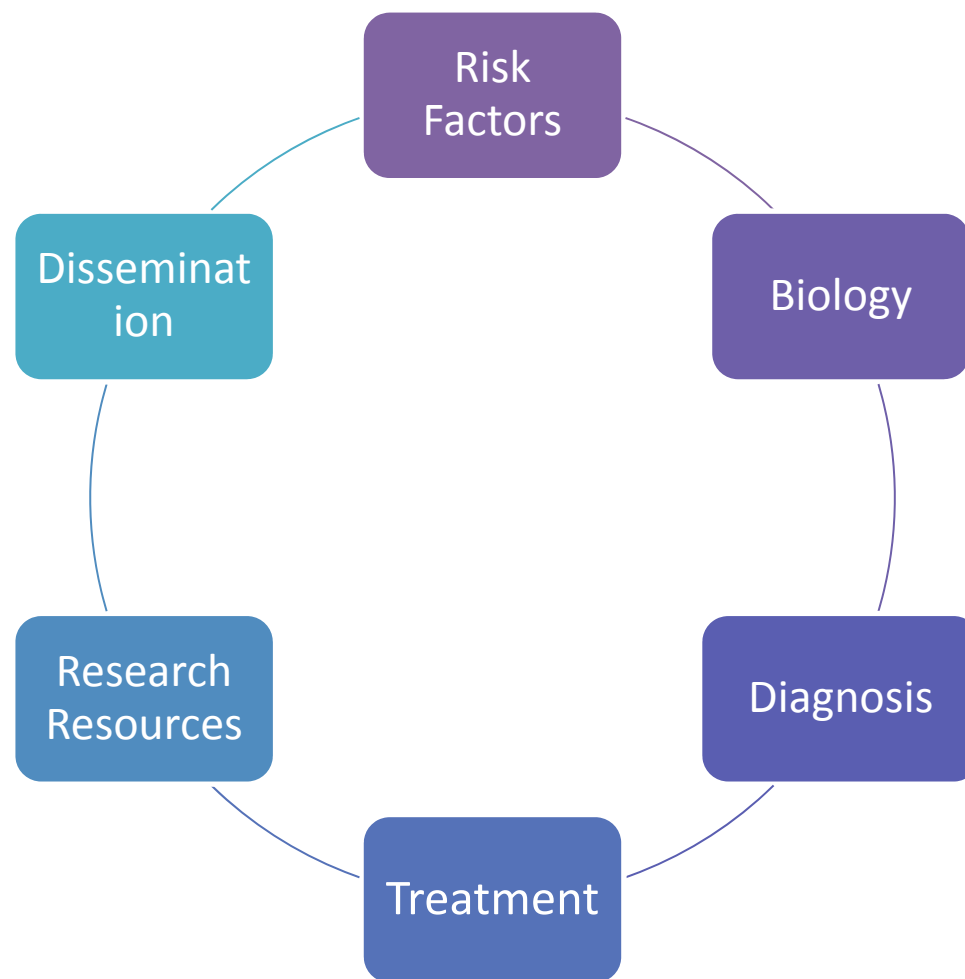 - American Academy of Pediatrics autism clinical guidelines

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Our Goals

- *Accelerate* the pace of science
- Promote *collaboration* and data-sharing worldwide
- Create *resources* to facilitate research
- Build *relationships* to leverage resources
- Fund *training programs* for scientists
- Stimulate *novel ideas* and new directions
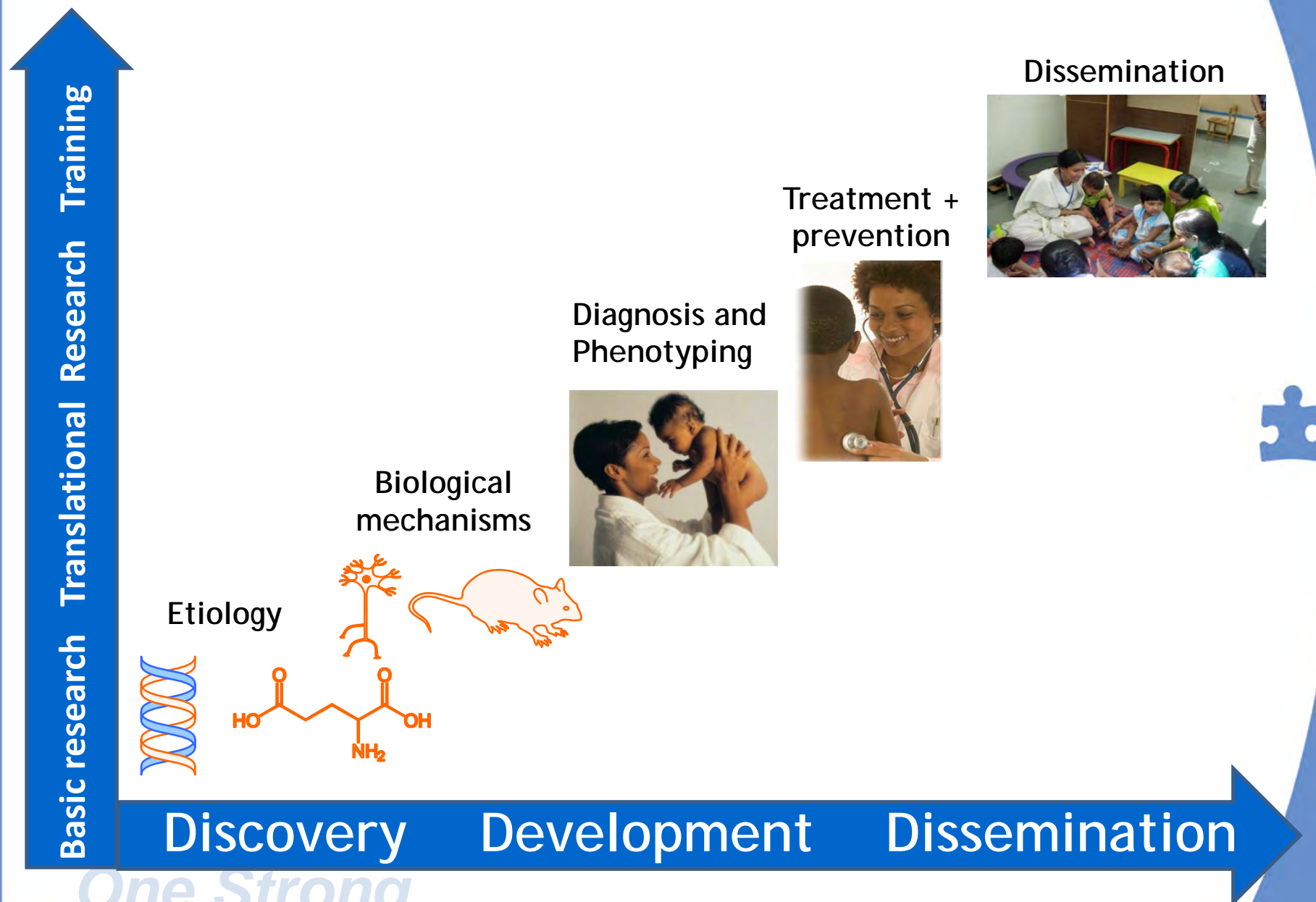- Translate research into real world *solutions*

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Research Portfolios

A Continuum of Solutions

Basic research   Translational Research   Training

Discovery   Development   Dissemination

Etiology

Biological mechanisms

Diagnosis and Phenotyping

Treatment + prevention

Dissemination

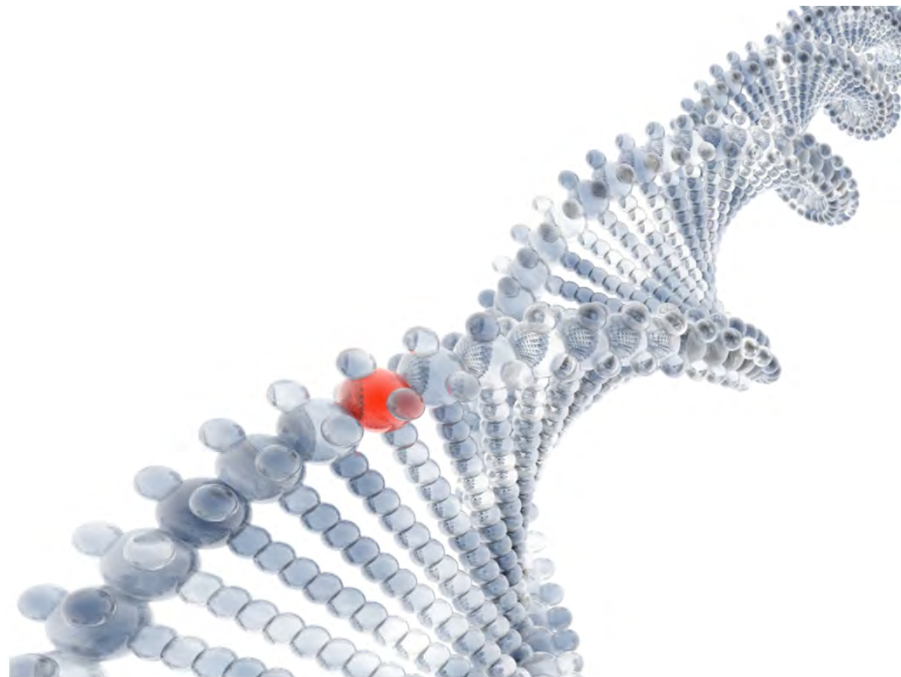One Strong

Courtesy: G. Dawson

Research Portfolio

Etiology (Risk Factors)

Genetics, Environmental Sciences, Epidemiology

Recent Highlights

Genome-wide Association Study (GWAS); Copy Number Variants (CNV)
Pre-maturity; parental age
CDC/ADDM prevalence

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Research Portfolio

Etiology (Risk Factors)

Genetics, Environmental Sciences, Epidemiology

Looking Forward

Genetic screening/risk assessment
GxE: Epigenome
New prevalence data (e.g., CDC/ADDM, Korea, Mexico, Taiwan)

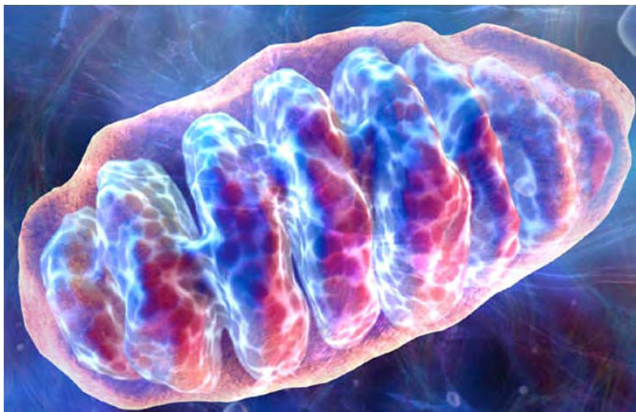*One Strong*

Research Portfolio

Biology (Mechanisms)

Neuroscience, Molecular Biology, Immunology, etc.
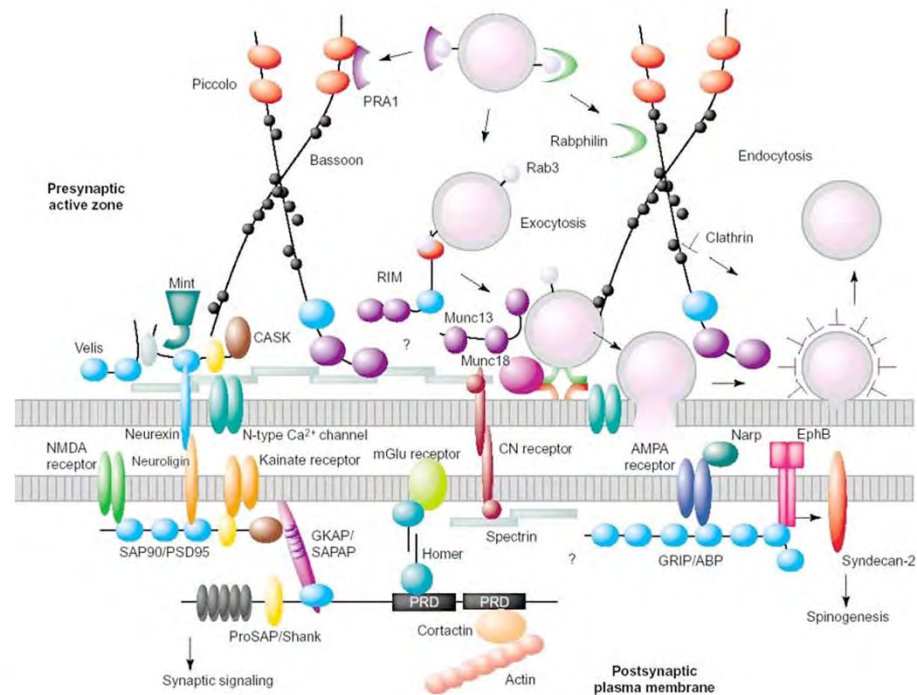
Recent Highlights

Converging pathways – Network imbalance
New mouse models
Mitochondria

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Research Portfolio
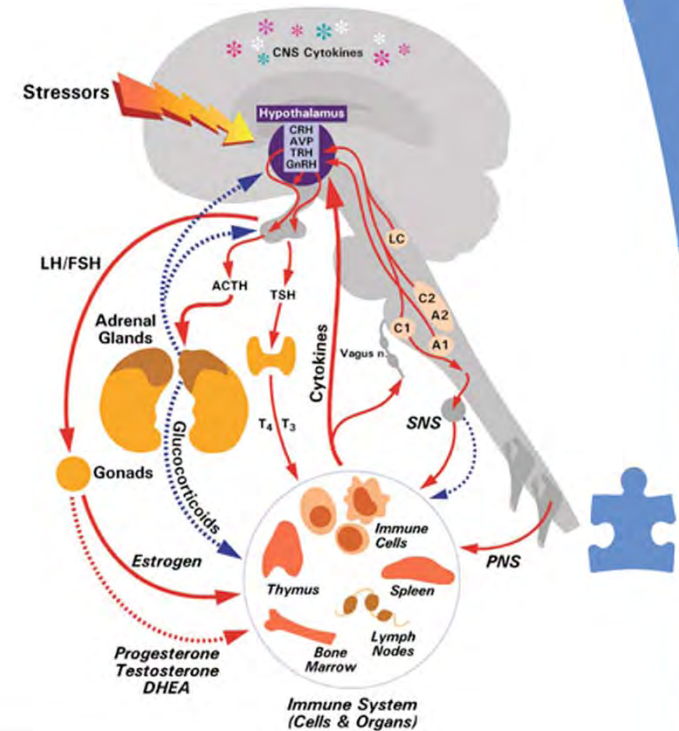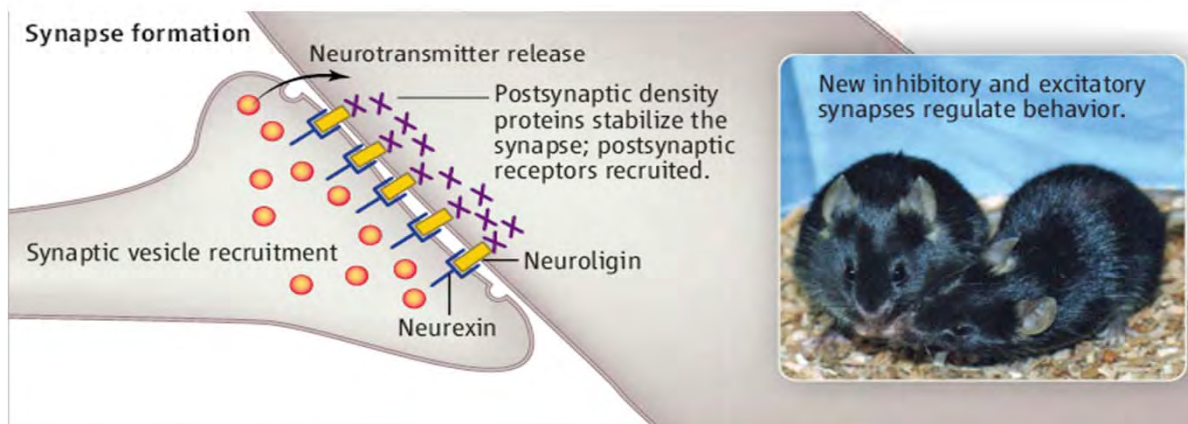
Biology (Mechanisms)

Neuroscience, Molecular Biology, Immunology, etc.

Looking Forward

More animal models
Immune system + brain development

New inhibitory and excitatory synapses regulate behavior.

Research Portfolio

Diagnosis

Behavioral, Biomarkers

Recent Highlights

Vocalization + risk (e.g. LENA)
BSRC recommendations in Pediatrics
Focused phenotyping

LENA™
Every Word Counts

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Research Portfolio

Diagnosis

Behavioral, Biomarkers

Looking Forward

More efficient instruments
BSRC Recurrence/Outcome report
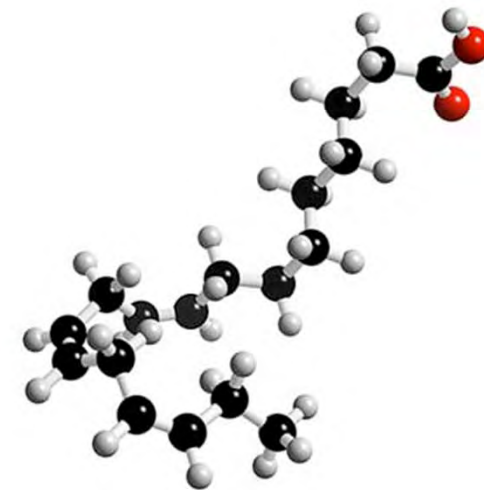Biomarkers? (epigenetic)

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Research Portfolio

Treatment

Behavioral, Pharmacological, CAM

Recent Highlights

Reversal of symptoms (Fragile X, Rett, TSC)
Parents-mediated intervention

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Research Portfolio

Treatment

Behavioral, Pharmacological, CAM

Looking Forward

Toddler Treatment Network research results
Drug development

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Research Portfolio

International/Dissemination

Awareness, Research, and Training/Services

Recent Highlights

World Autism Awareness Day
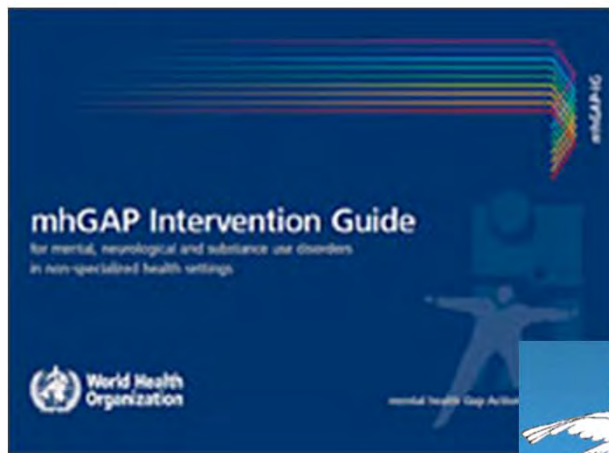Global Autism Public Health Initiative

Research Portfolio

International/Dissemination

Awareness, Research, and Training/Services

Looking forward

WHO mhGAP IG/Movement for Global Mental Health
Comparative effectiveness studies

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Research Portfolio

Clinical and Research Resources

Autism Treatment Network (ATN)

Autism Clinical Trials Network (ACTN)

Autism Genetic Resource Exchange (AGRE)

Autism Tissue Program (ATP/ATP-UK)

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Research Portfolio

Research Consortia + Networks

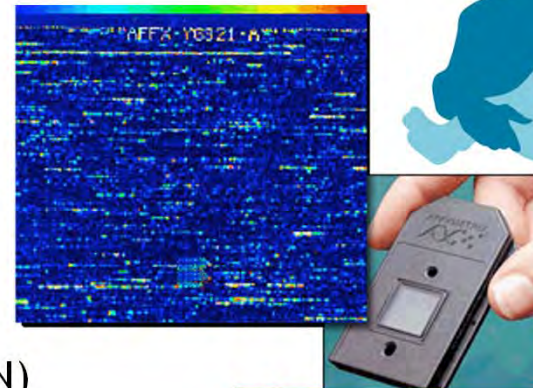Autism Genome Project (AGP)

Baby Siblings Research Network (BSRC)
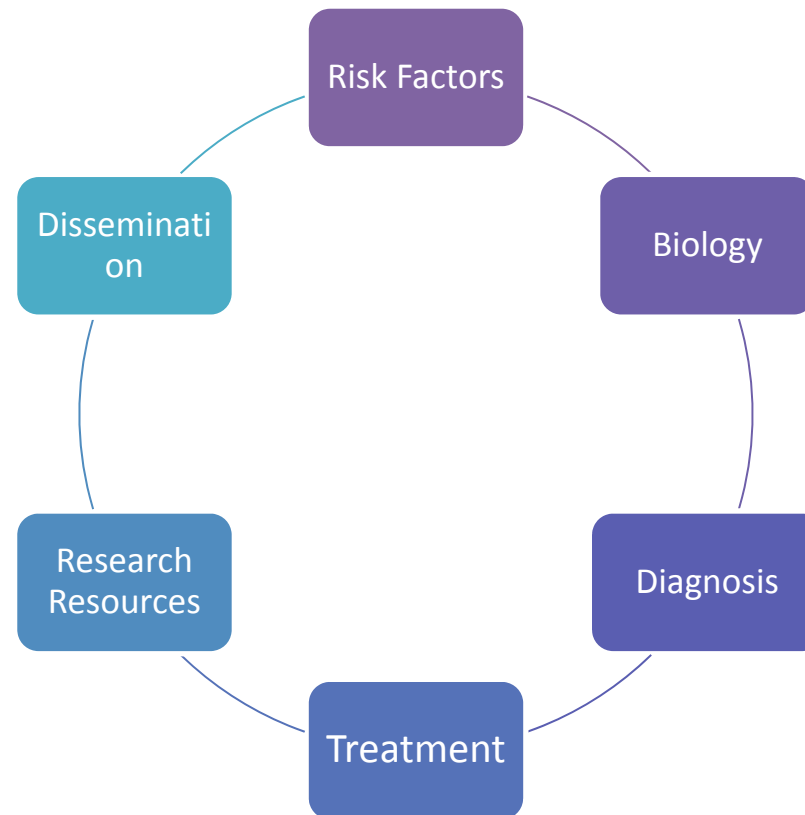
British Autism Study of Infant Siblings (BASIS)

International Autism Epidemiology Network (IAEN)

Autism Speaks Toddler Treatment Network (TTN)

Research Portfolio

With so many opportunities and finite resources, how do we prioritize?

Risk Factors

Biology

Diagnosis

Treatment

Research Resources

Dissemination

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Scientific Strategic Planning Process

Guided by our mission

| Analysis of funding priorities and outcomes of past funding | Assessment of current status of AS priorities, initiatives and funding | Input from outside "thought leaders" and parents | SAC Meeting to solicit their input | Presentation to the Board of Directors at December board meeting |
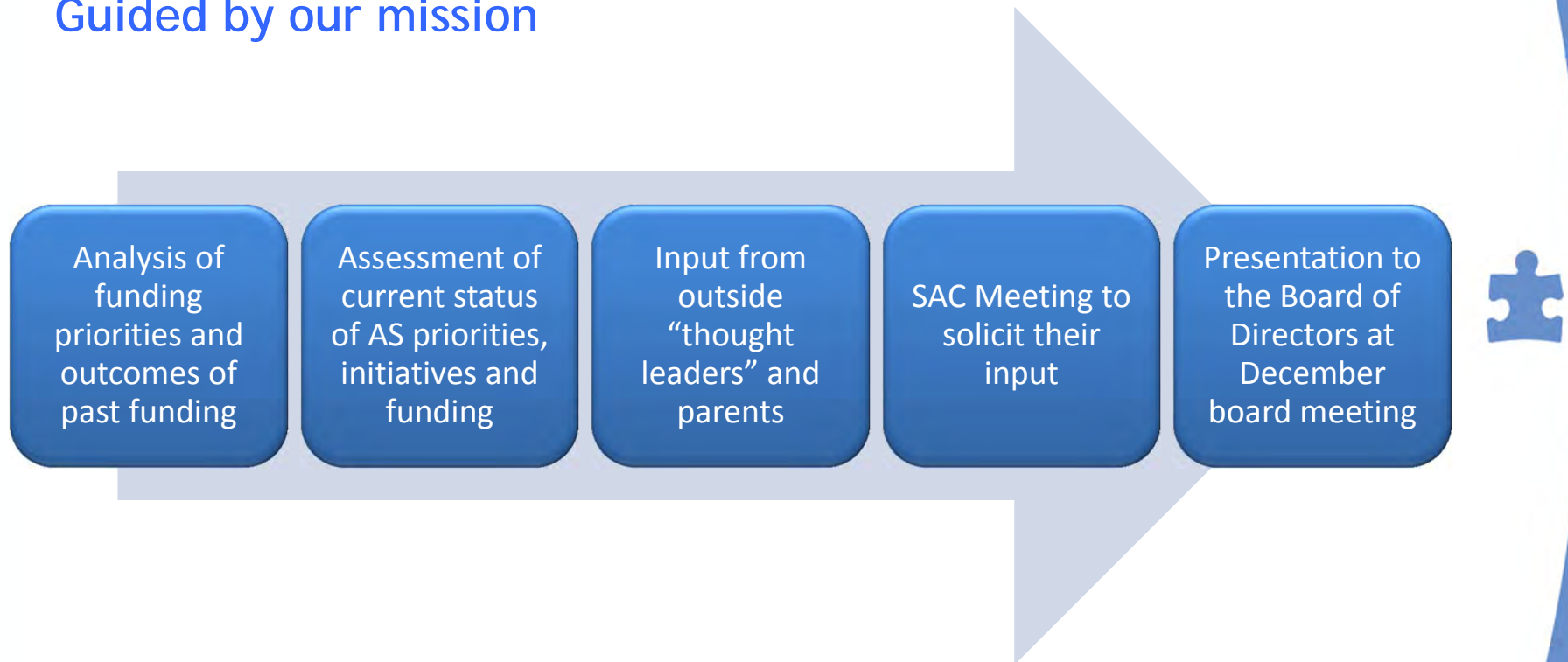
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Accelerating the Pace of Autism Research

Discovery → Development → Delivery

Translation from basic science to treatments

Translation of new knowledge into clinical/family service
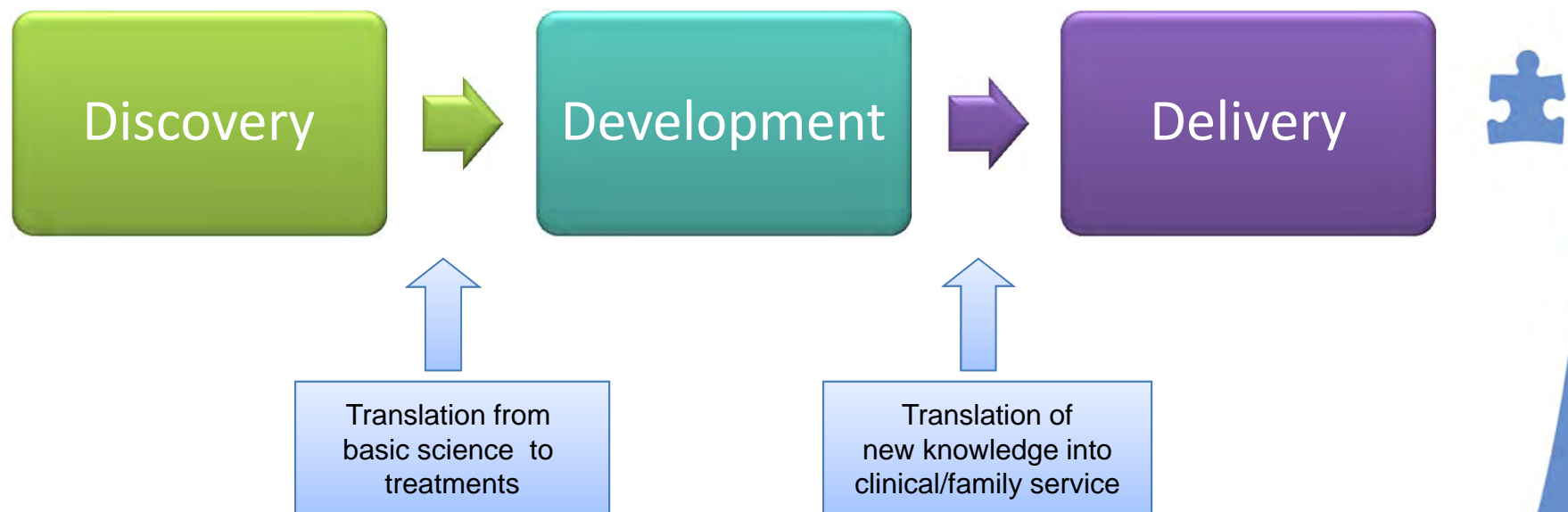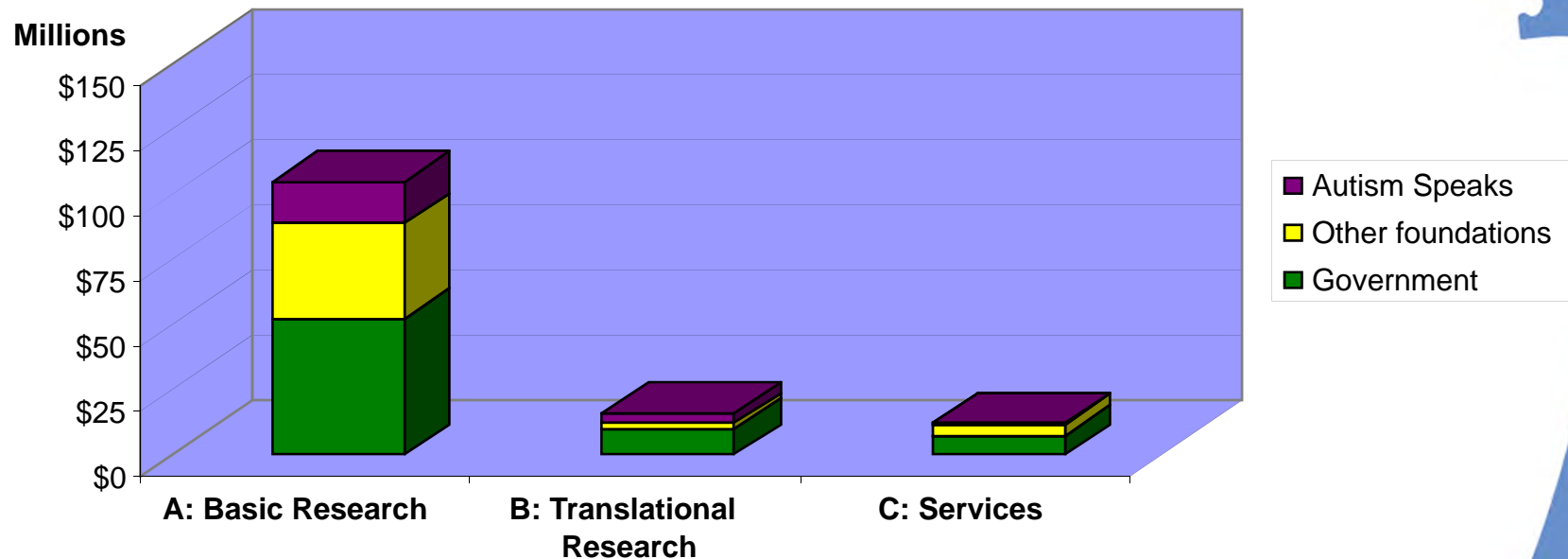
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Courtesy of S. Colamarino: Adapted from IOM Clinical Research Roundtable

2007 Total New Commitments to Autism
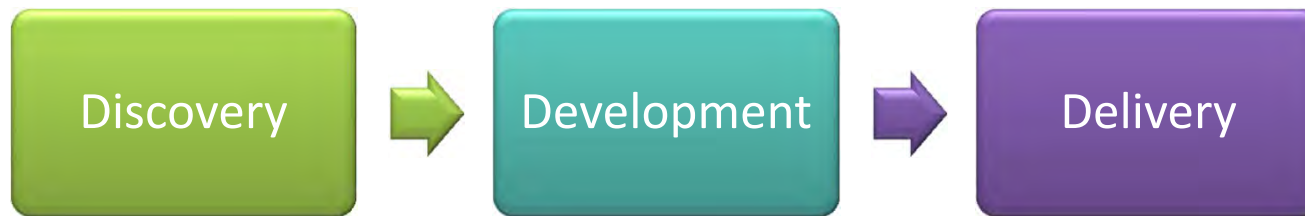
Courtesy: S. Colamarino

Translation: Program Example 1

Autism Genome Project (AGP)

"Consortium of Consortia"

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Autism Genome Project
Membership
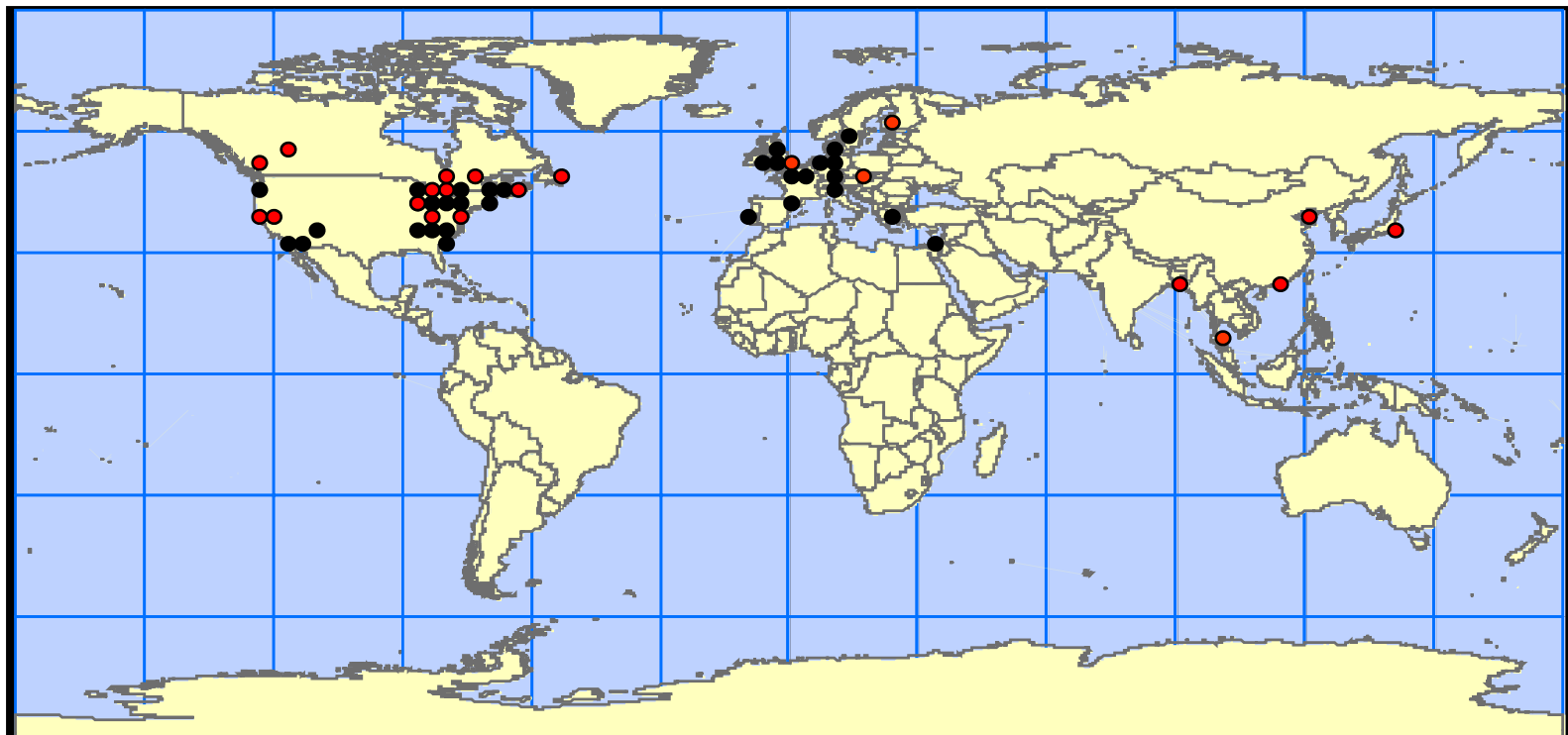
170 scientists in 57 academic centers & institutions in 19 countries

AGP Sites   Genome Canada Funded AGP extension sites

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Courtesy: S. Scherer

AGP Overview
(Current sites I)

- **CANADA:**
  - Toronto/Ontario (Scherer/Szatmari/Paterson)
- **USA:**
  - CHOP (Hakonarson)
  - Indiana (Nurnberger)
  - Miami (Pericak-Vance)
  - MSSM (Buxbaum)
  - Ohio (Vieland)
  - Pittsburgh (Devlin)
  - Pennsylvania (Schellenberg)

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AGP Overview
(Current sites II)

- **European Union:**

  - ➤ **France:** Paris (Betancur)
  - ➤ **Germany:** Heidelberg/Frankfurt (Klauck/Freitag)
  - ➤ **Ireland:** TCD & UCD (Gallagher/Gill/Ennis/Green)
  - ➤ **Italy:** Bologna & Pisa (Maestrini/Battaglia)
  - ➤ **Portugal:** (Vicente/Oliviera)
  - ➤ **UK:** Oxford & IMGSAC (inc. Newcastle) (Monaco/Bailey)*

- **Pending sites:**

  - ➤ Qatar, Japan, Italy, US (Johns Hopkins), Taiwan

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*PI in transition

AGP Overview

- **Vehicle for International Autism Research:**

  - Large Scale Consortium Activities
  - Phenotype Analysis (PAC) and Genomics Committee coordinated activities
  - Facilitation of smaller scale projects

- **Critical AGP Infrastructure + Assets**
  - Economy of Scale
  - Shared Resources
  - Centralized Consortium-wide database
  - Networking, synergy, and mentorship

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*Courtesy AGP

AGP Overview
(Phases)

- **Phase 1 (2004-2007):**

  - Linkage Analysis; CNV analysis

- **Phase 2 (2007-2010):**

  - Copy Number Variations (CNV)
  - Whole genome association (WGA)/CNV screen
  - Phenotype/ QTL analysis
  - Candidate genes from these analyses

- **Phase 3 (2011 -?)**

  - Likely to focus on translation and additional discovery

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2010 AGP Accomplishments

What:
- Identification of new autism risk genes based on copy number variants (CNV) – submicroscopic DNA insertions and deletions - found in the genome of individuals with autism

How:
- 1,000 cases vs. 1,300 controls
- Each genotyped with 1,000,000 SNP

Findings:
- Greater genic CNV burden in individuals with autism, especially in genes associated with autism and intellectual disabilities
- New genes: SHANK2, SYNGAP1, DLGAP2, PTCHD1, etc.; Synapse related, as well as new pathways (cell proliferation, projection/motility, and signaling).
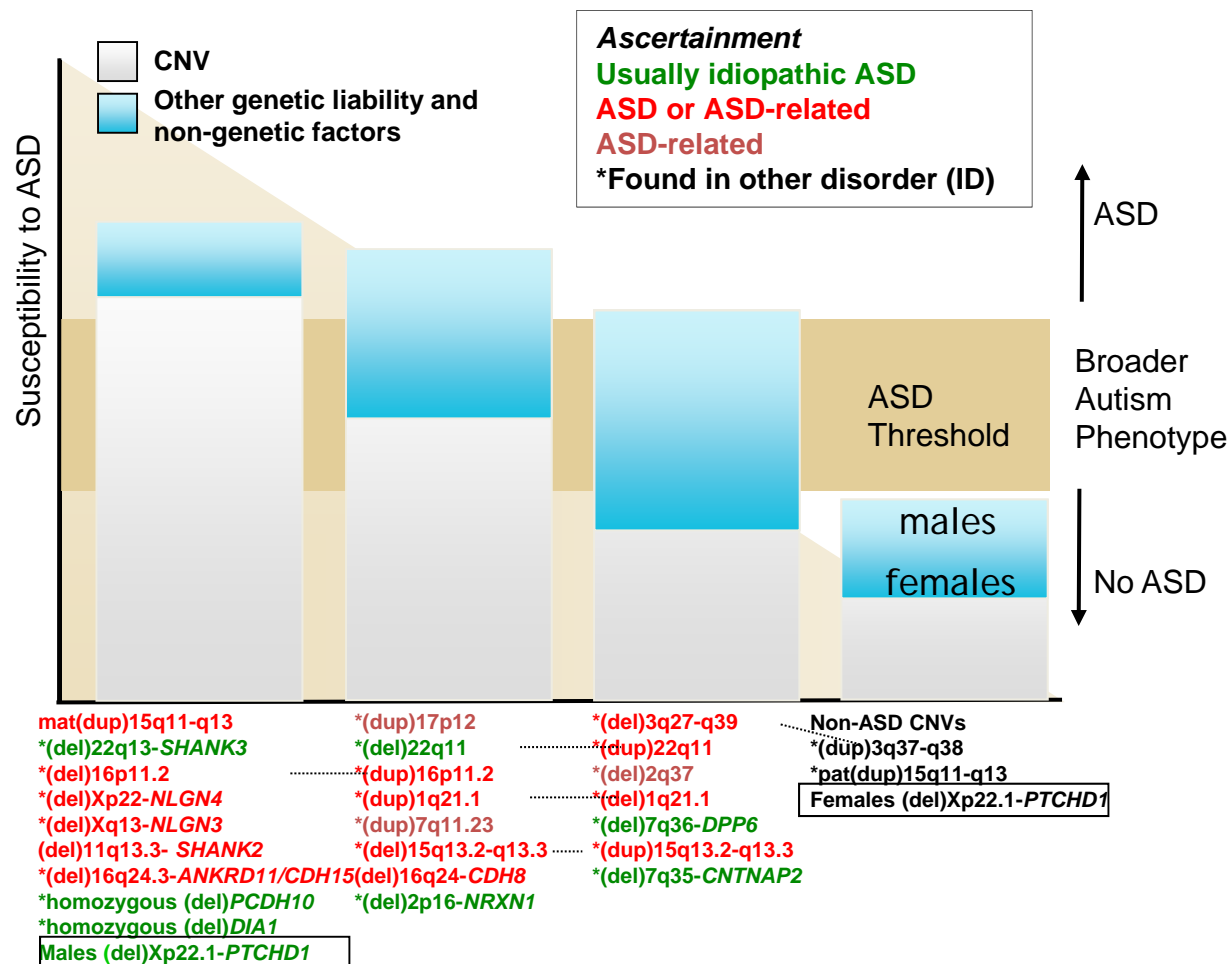
What does it mean for individuals and families?
- Rare variants/common disorder; risk assessment
- Novel therapeutic targets; personalized medicine

*Pinto et. al. "Functional impact of global rare copy number variation in autism spectrum disorder" Nature (2010)
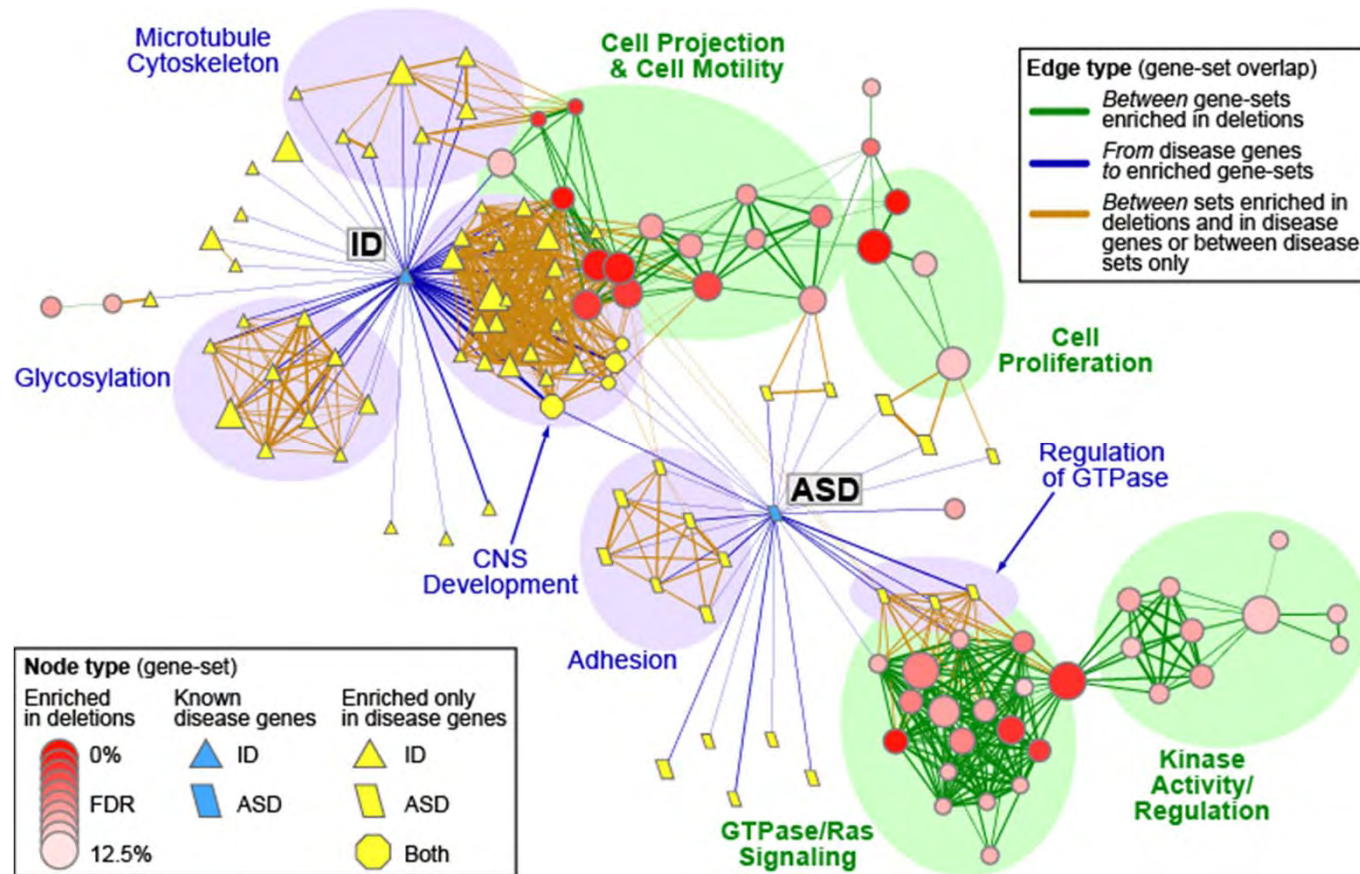
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Model of relative contribution of CNVs to ASD susceptibility

*Courtesy AGP

Functional Enrichment Gene-set Map for ASD

- ASD and ID risk genes may be linked in a connected pathway

- Rare mutations in developmental networks can expose otherwise buffered stochastic variation in gene expression leading to phenotypic variation

*Courtesy AGP

ASD CNVs/genes in Other Neuropsychiatric Disorders

#	Cytoband	Locus	Disorder[a]	References[b]
1	1q21.1	GPR89A	ASD, BD	2, 24
2	1q21.1	1q21.1 locus	ASD, SZ	6, 8, 17, 18
3	1q44	KIF26B	SZ, ADHD	3, 7, 12
4	2p16.3	NRXN1	ASD, SZ, BD	2, 5, 7, 9, 12, 15, 18, 20, 24
5	2p21	PLEKHH2	BD, ADHD	3, 24
6	2q22.1	SPOPL	SZ, ADHD	8, 24
7	2q32.1	CALCRL	BD, ADHD	3, 24
8	3p24.3	TBC1D5	SZ, BD	8, 24
9	3p26.1-p25.1	GRM7	BD, ADHD	3, 24
10	3p26-p25	CNTN6	BD, ADHD	3, 24
11	5p15.2	CTNND2	SZ, ADHD	3, 20
12	5p15.3	TPPP	ASD, SZ	2, 8
13	5p15.33	PLEKHG4B	SZ, BD	8, 24
14	6q25.2-q27	PARK2	ASD, BD, ADHD	3, 5, 24
15	7q11.22	AUTS2	ASD, ADHD	3, 5
16	7q31	IMMP2L	BD, ADHD	3, 24
17	7q35-q36	CNTNAP2	ASD, SZ, BD, ADHD	1, 3, 4, 14, 24
18	7q36.1	PRKAG2	ASD, SZ	19, 21
19	7q36.2	DPP6	ASD, ADHD	3, 9
20	8p22	NAT2	SZ, ADHD	3, 12
21	9p23-p24.3	PTPRD	BD, ADHD	3, 24
22	9q33.1	ASTN2	ASD, SZ, BD, ADHD	5, 12, 20, 24, 25
23	13q14.3-q21.1	PCDH9	ASD, BD	2, 9, 24
24	15q11.2-q12	GABRA5	ASD, SZ	2, 12
25	15q13.1	NDNL2	ASD, SZ	7, 13, 16,
26	15q21.1	DUOXA1	ASD, ADHD	3, 19
27	16p11.2	16p11.2 locus	ASD, SZ	9, 22, 21
28	16p13.3	A2BP1	ASD, BD, ADHD	3, 10, 11, 24
29	16q23.3-q24.1	WWOX	SZ, BD	13, 24
30	17p12	CDRT15	SZ, BD	8, 24
31	17p12	CDRT4	SZ, BD	8, 24
32	17p12	TEKT3	SZ, BD	8, 24
33	17p12	FAM18B2	SZ, BD	8, 24
34	17p12-p11.2	COX10	SZ, BD	8, 24
35	17p12-p11.2	PMP22	SZ, BD	8, 24
36	17p12-p11.2	HS3ST3B1	SZ, BD	8, 24
37	17q12	ZNHIT3	SZ, ADHD	3, 13
38	18p11.2	MC5R	BD, ADHD	3, 24
39	18p11.2	MC2R	BD, ADHD	3, 24
40	19p12	ZNF676	ASD, ADHD	2, 3
41	20p12	PAK7	ASD, SZ, ADHD	3, 5, 12
42	22q11.21	22q11.2 locus	ASD, SZ	5, 6, 8, 12, 13, 17, 18
43	22q12.3	LARGE	ASD, SZ, BD	19, 21, 24
44	Xp22.3; Yp11.3	IL3RA	SZ, BD	8, 24
45	Xp22.3; Yp11.3	ASMTL	SZ, BD	8, 24
46	Xp22.32; Yp11.3	SLC25A6	SZ, BD	8, 24
47	Xp22.33; Yp11.3	P2RY8	SZ, BD	8, 24

[a]Abbreviations: ASD, Autism Spectrum Disorder; ADHD, Attention Deficit Hyperactive Disorder; BD, Bipolar Disorder; SZ, Schizophrenia
[b]References: [1]Alarcon et al. 2008 [PMID:18179893]; [2]Bucan et al. 2009 [PMID:19557195]; [3]Elia et al. 2009 [PMID:19546859]; [4]Friedman et al. 2008 [PMID:17646849]; [5]Glessner et al. 2009 [PMID:19404257]; [6]ISC. 2008 [PMID:18668038]; [7]Kirov et al. 2008 [PMID:17989066]; [8]Kirov et al. 2009 [PMID:19181681]; [9]Marshall et al. 2008 [PMID:18252227]; [10]Martin et al. 2007 [PMID:17503474]; [11]Morrow et al. 2008 [PMID:18621663]; [12]Need et al. 2009 [PMID:19197363]; [13]Rodriguez-Santiago et al. 2009 [PMID:19528963]; [14]Rossi et al. 2008 [PMID:18675947]; [15]Rujescu et al. 2009 [PMID:18945720]; [16]Sebat et al. 2007

Unpublished with Ann Bassett, Russell Schachar, Paul Arnold and AGP collaborators
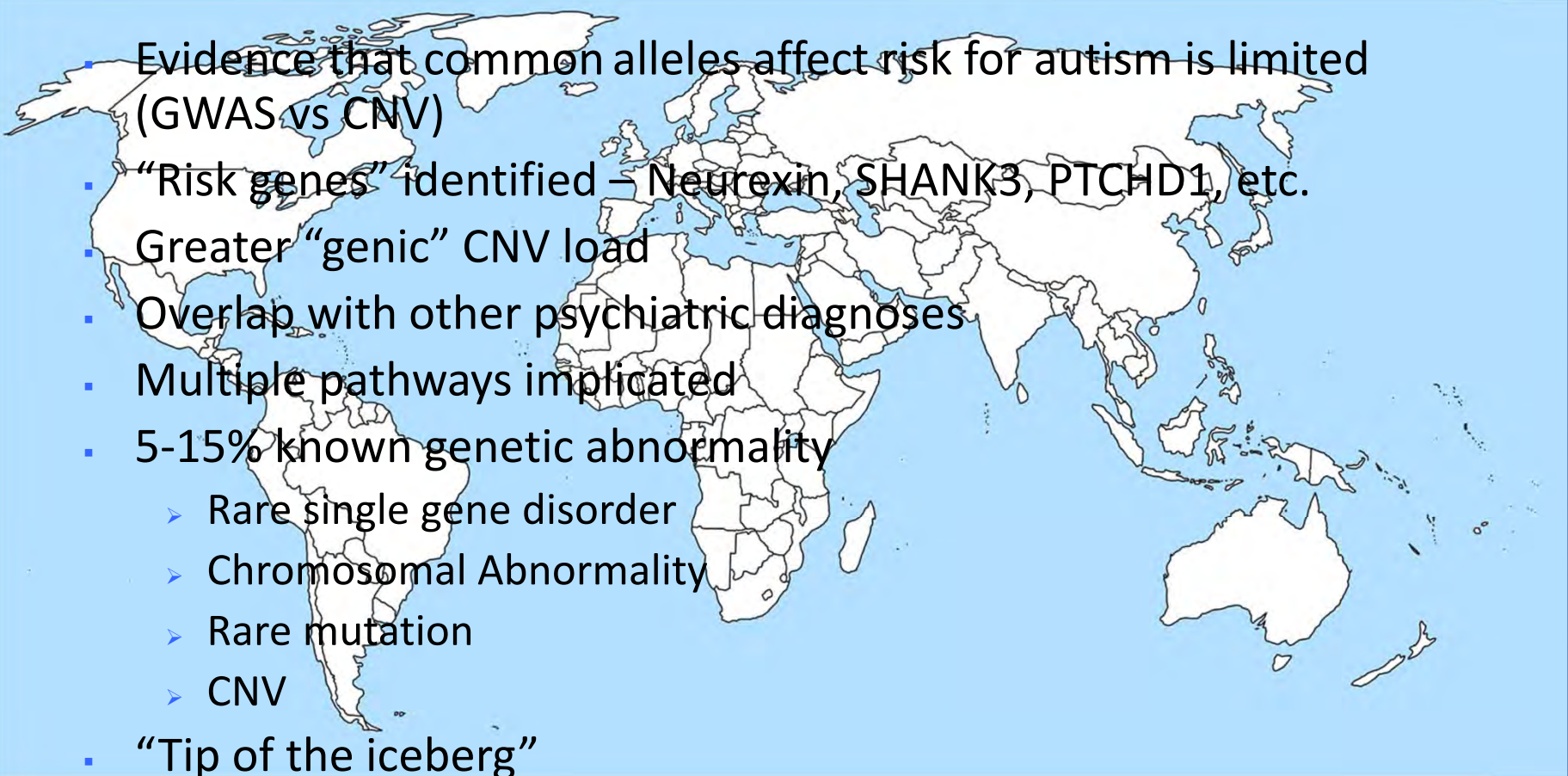
*Courtesy AGP

AGP Overview
(Main Findings)

- Evidence that common alleles affect risk for autism is limited (GWAS vs CNV)
- "Risk genes" identified – Neurexin, SHANK3, PTCHD1, etc.
- Greater "genic" CNV load
- Overlap with other psychiatric diagnoses
- Multiple pathways implicated
- 5-15% known genetic abnormality
  - Rare single gene disorder
  - Chromosomal Abnormality
  - Rare mutation
  - CNV
- "Tip of the iceberg"
  - More genetic abnormalities will be detected by sequencing

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Genetic Risk Factors for Autism: Translating Discoveries into Diagnostics

Organizers: Dr. Steve Scherer,
McLaughlin Centre, University of Toronto
Dr. Andy Shih, Autism Speaks
Dr. Geri Dawson, Autism Speaks

Local Organizational Contact:
Jenny Kaderali (416) 813-7654 x1574
jenny.kaderali@sickkids.ca

This symposium will serve as a forum to discuss the scientific, clinical, ethical, legal, policy and communication aspects of translating new Autism Spectrum Disorders (ASD) genetic discoveries into clinical screening and diagnostic tools for promoting the well-being of individuals and families with ASD.

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Treatment Informed by Genetics:
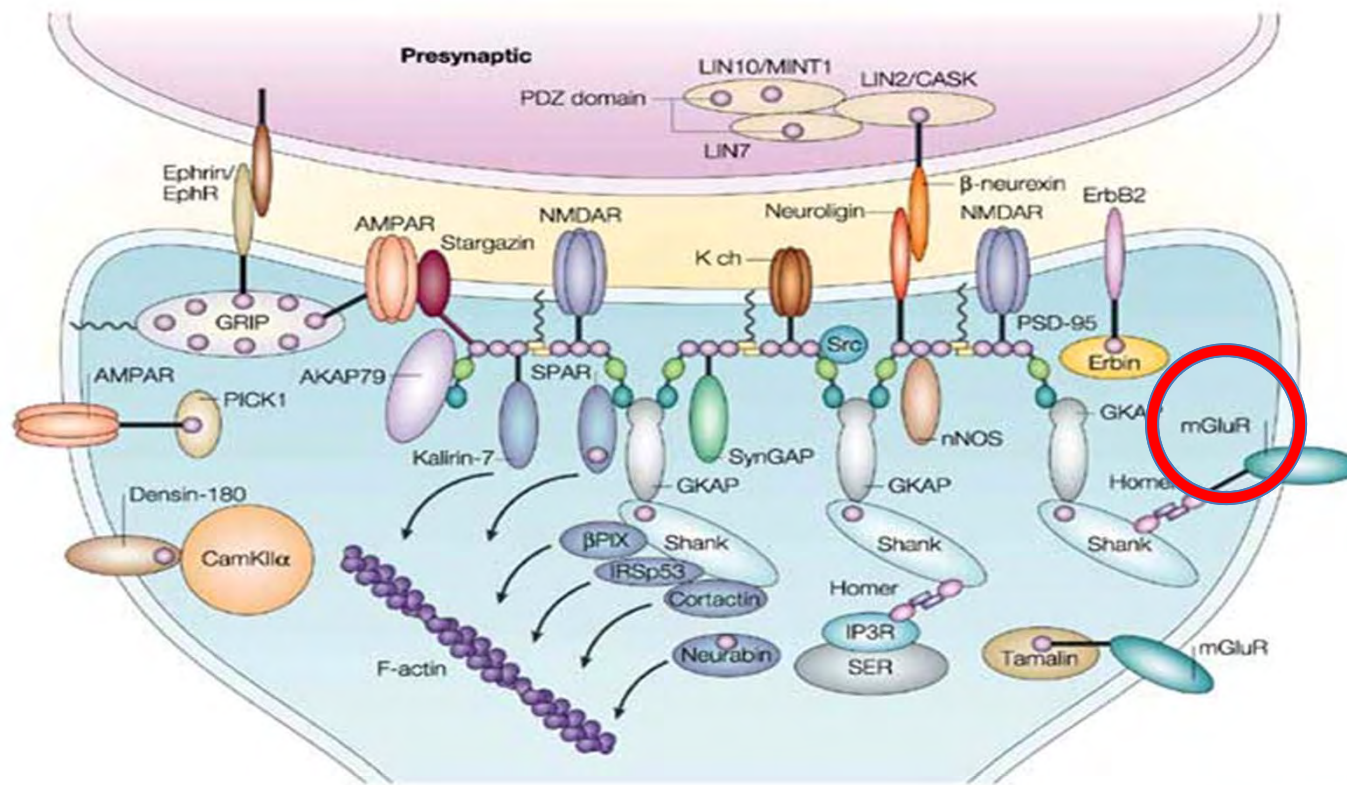
Fragile X Syndrome

FMRP's role in fragile X pathogenesis and treatment

Treatment Informed by Genetics:
Synaptic molecules

Nature Reviews | Neuroscience

Treatment Informed by Genetics:
Synaptic molecules
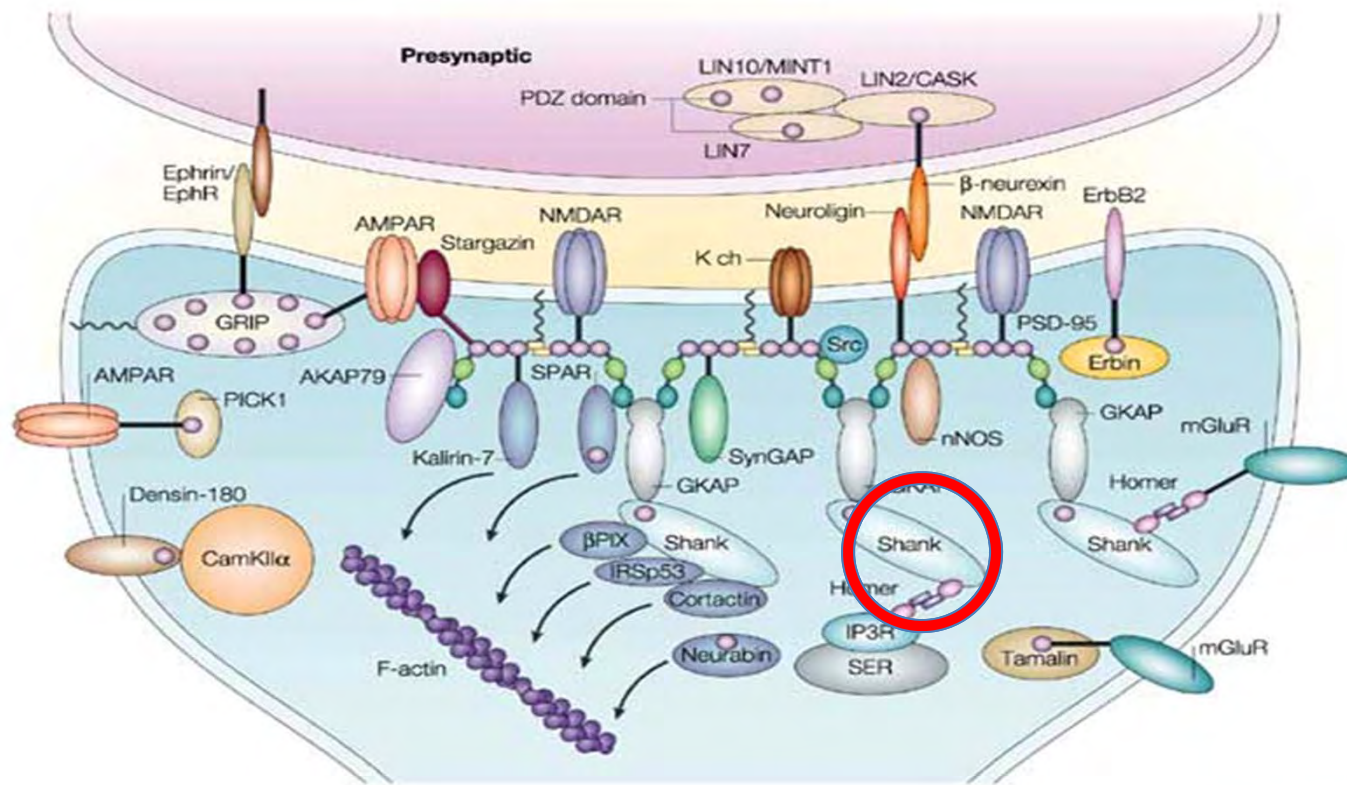
Nature Reviews | Neuroscience

LTP Induction and Maintenance Impaired in SHANK3 knockout mice
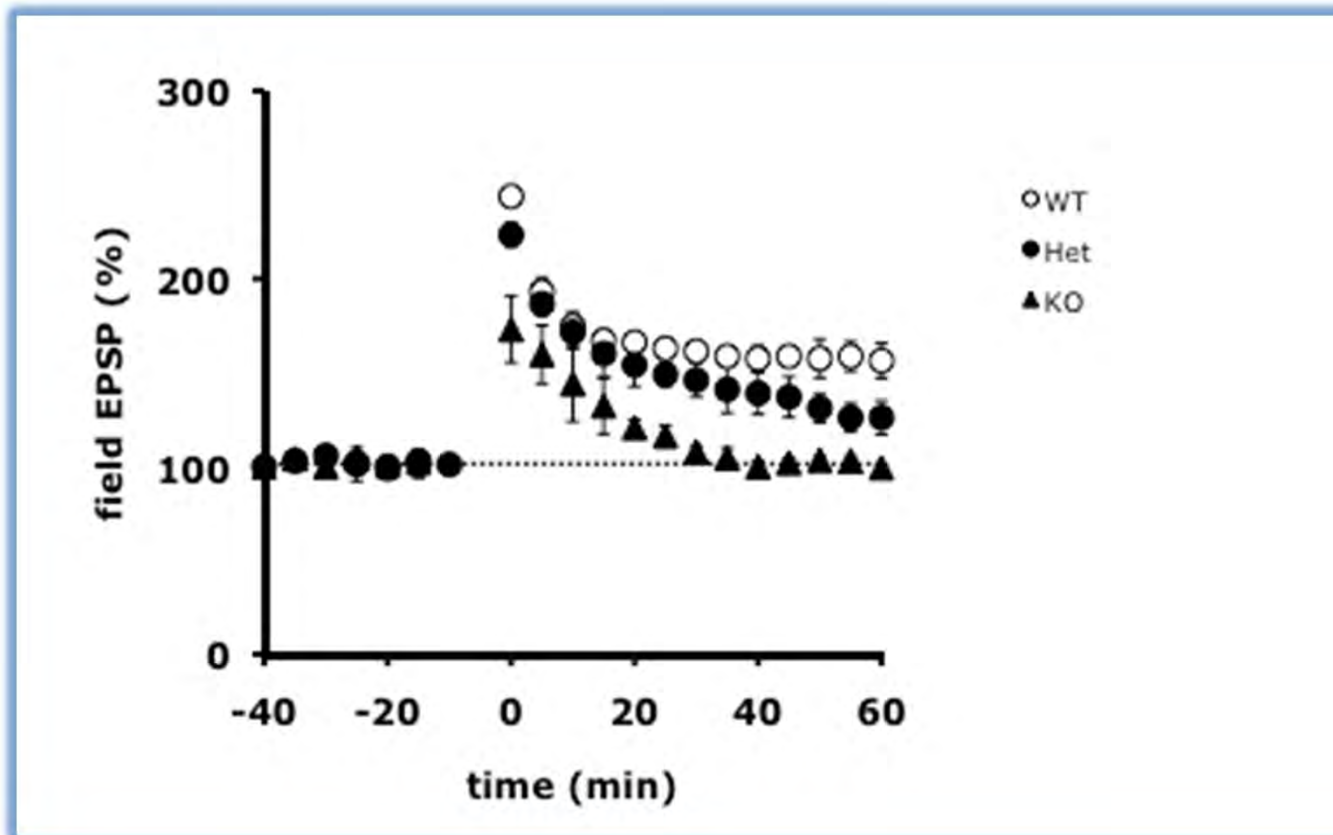
Both LTP induction and maintenance is impaired in Shank3 knockouts

Courtesy: Joseph Buxbaum

Effects of (1-3)IGF-1 treatment on LTP in SHANK3 knockout mice

(1–3)IGF-1 is administered daily via i.p. injections (0.01 mg/g body weight) starting at P13–15 and continued for 2 weeks for electrophysiological recordings.

Courtesy: Joseph Buxbaum

Autism Speaks
Translational Medicine Research Initiative

- Two meetings held in January 2011 (co-sponsored with Pfizer)

  - *Outcome measures for Clinical Trials with Individuals with ASD: Challenges and Opportunities*
  - *Translational Medicine Research in Autism: Challenges and Opportunities*
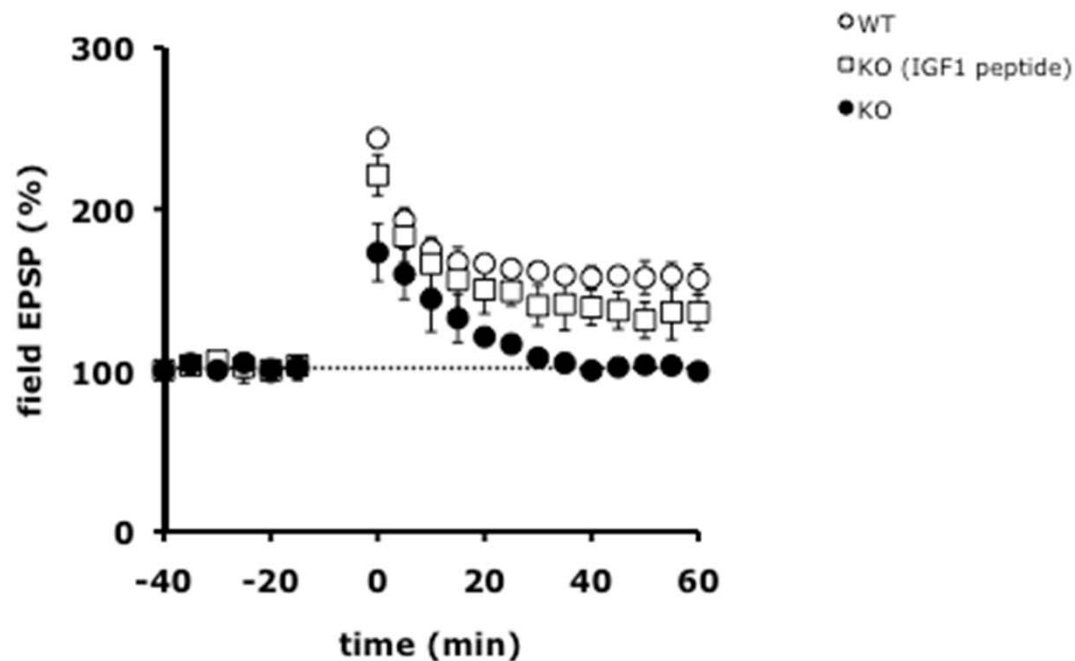
- Topics: Target identification, outcome measures, biomarkers, discovery strategy, trial design, "model disorders", co-morbid conditions, etc.

- Participants: Researchers, Pharma, biotech, NIH, FDA

- Hiring: VP of Translational Research

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Translational Program Example 2

Global Autism Public Health Initiative (GAPH)

Why International Efforts?

- To find and deliver answers to affected individuals and families around the world

- Unique opportunities to address key scientific questions and priorities in causes, diagnosis/treatment, and dissemination that are also relevant to priorities of the US

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Measuring the Global Autism Public Health Challenge

World Health Organization "Burden of Disease"

§ Prevalence
§ Functional impairment
§ Chronicity
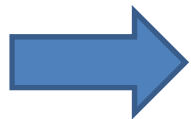§ Age of Onset
§ Cost

"Disability Adjusted Life Year" (DALY)

→ •Autism > Type 1 Diabetes, childhood leukemia, CF
•Costs to society in US: ~$35B/yr
•Costs to families are immeasurable

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Global Challenges to Progress

- Lack of public health statistics

- Lack of training and expertise

- Lack of public and professional awareness

- Stigma

- Lack of evidence-base

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Why International Efforts?

Key Scientific Questions and Opportunities

- Epidemiology: What can we learn about autism risk factors by comparing prevalence and incidence around the world?

- Environmental Sciences: Can we identify environmental risk factors (e.g. toxicants, diet, infectious agents, etc.) by comparing exposures across countries?

- Genetics: Are there population-specific genetic risk factors? (e.g. do Europeans and Africans have the same genetic risk factors?) Other populations (e.g. Middle East) offer unique opportunities for discovering autism risk genes.

- Diagnosis and treatment: How do culture and social norms impact recognition/diagnosis and treatment?

- Dissemination: What is the best way to implement and sustain best practices, even in places with limited resources and capacity?

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A Platform for Developing Solutions
Global Autism Public Health Initiative (GAPH)

An international advocacy and development effort to help partner countries to:

- Enhance awareness and understanding of autism

- Build capacity for research and service excellence; Facilitate collaboration

- Improve the quality of life for individuals with ASD and their families by disseminating best practices

GLOBAL AUTISM PUBLIC HEALTH *Initiative*

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GAPH and Autism Speaks scientific priorities
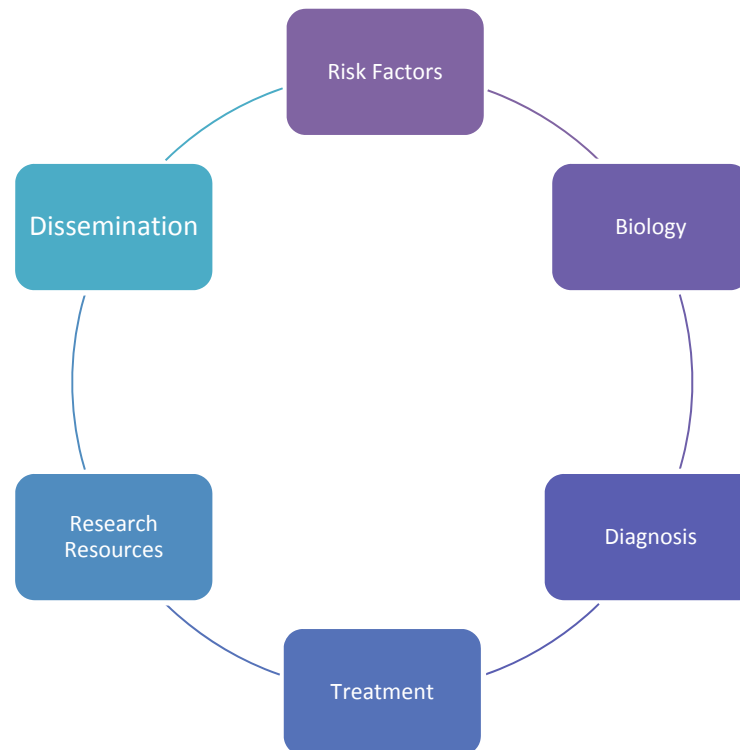
- Interfaces with all portfolios

- Addresses important knowledge/practice gaps: Translation and dissemination

- Aim to deliver near-term community impact/benefit

- Aim to facilitate systemic changes for sustainable or more permanent solutions

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GAPH Values

- Sense of urgency

- Scientific excellence

- Inclusive collaboration

- Benefits to individuals and families touched by autism

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GAPH Activities

Research:

- Epidemiology – Prevalence and incidence; risk factors

- Genetics – Risk factors in various populations (e.g., Middle East)

- Screening/Diagnosis – More efficient instruments and technologies

- Treatment – Community-based intervention

- Implementation/Dissemination – Best practices in different settings

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GAPH Activities

Development and Implementation:

Goal: *Deliver feasible, cost-effective, efficacious and sustainable service solutions in a variety of settings (Primary to tertiary/rural to urban)*

- Screening and diagnosis

- Treatment

- Monitoring and evaluation

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Key GAPH tactics for addressing challenges

- Prioritize and coordinate activities in awareness, research and service development

- Local ownership of efforts; Outside experts serve as advisors and facilitators. Priority set by local stakeholders (e.g. service development vs. awareness, epidemiology vs. genetics, etc.)

- Driven by collaboration with local government, professionals and families

- Adapt evidence-based solutions to accommodate cultural/social factors, and available resources and infrastructure

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Highlights of GAPH Accomplishments

- World Autism Awareness Day (2008)

- International Autism Epidemiology Network* (100+ researchers from >30 countries)

- Active in 23 countries worldwide (e.g., awareness, research, training)

- Screening and diagnostic instruments have been adapted in languages spoken by 1.75 billion people

- A standardize international training program for the use of screening and diagnostic instruments launched by UMACC, WPS, and Autism Speaks (e.g. NIMH collaboration in India)

- First ever epidemiology studies in Korea, Taiwan, Mexico, South Africa, and India

- Light it Up Blue!

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*co-developed with the CDC

World Autism Awareness Day

- One of only three UN sanctioned days
- Began in 2008 through a collaboration with Autism Speaks and the State of Qatar
- Is now celebrated every April 2 in over 60 countries on 6 continents

World Autism Awareness Day

World Autism Awareness Day

LIGHT IT UP BLUE — Start a conversation in your community to help raise awareness

- Light buildings in **blue** on April 1, 2010 – the eve of World Autism Awareness Day

GAPH 2010 Highlights

New countries:

Brazil
- National conference with key stakeholders
- Development of community consensus priorities (both professionals and families)
- Provide process and content support for the development and launch of **Autismo e Realidade**, a Sao Paulo-based foundation aimed to enhance autism awareness, research and services in Brazil

Serbia
- National conference with key stakeholders co-organized with UNDP and WHO
- Leadership-level engagement of MoH, MoE, MoL&SP, NGOs
- Aim to launch GAPH-Serbia in 2011

South Africa
- National conference with key stakeholders co-organized with KwaZulu Natal University
- National Advisory Committee established for the development of GAPH-SA

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GAPH 2010 Highlights

New partnership:

World Health Organization

✓Guidelines on treatment of child mental disorders including developmental disorders.

✓A model intervention package including a section on child mental disorders that will include interventions applicable for developmental disorders, including autism, for use in low and middle income countries.

✓Publication of evidence review on epidemiological data on autistic spectrum disorders.

✓Publication of research agenda on developmental disorders including autism.

✓Contribution to advocacy efforts on child mental disorders including developmental disorders among policy makers and countries.

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GAPH 2010 Highlights

New partnership:

International League Against Epilepsy

- Task Force formed

- Priorities:

1. Advancing and disseminating knowledge on the co-occurrence of autism spectrum disorders (ASD) and the epilepsies.

2. Promoting awareness, research, and training common to both epilepsy and autism.

3. Promoting better services and care for individuals with both epilepsy and autism

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GAPH 2011 Directions

New development strategy:

Regional development network leveraging existing GAPH relationships

Benefits: Cost-sharing (e.g., training), coordinated activities (awareness), facilitate dissemination of information and best practices

- *Southeast Europe Autism Network (SEAN):* Facilitated by ACF and MoH Albania. Launched December 2010 with MoH of Albania, Bosnia and Herzegovinia, Croatia, FYRKMacedonia, and Slovenia

- *Southeast Asia Autism Network (SAAN):* Facilitated by SEARO/WHO and the government of Bangladesh. To be launched Q3 2011. Initially targeting countries that have already expressed interests, including Thailand, India, Maldives, Bhutan, and Sri Lanka.
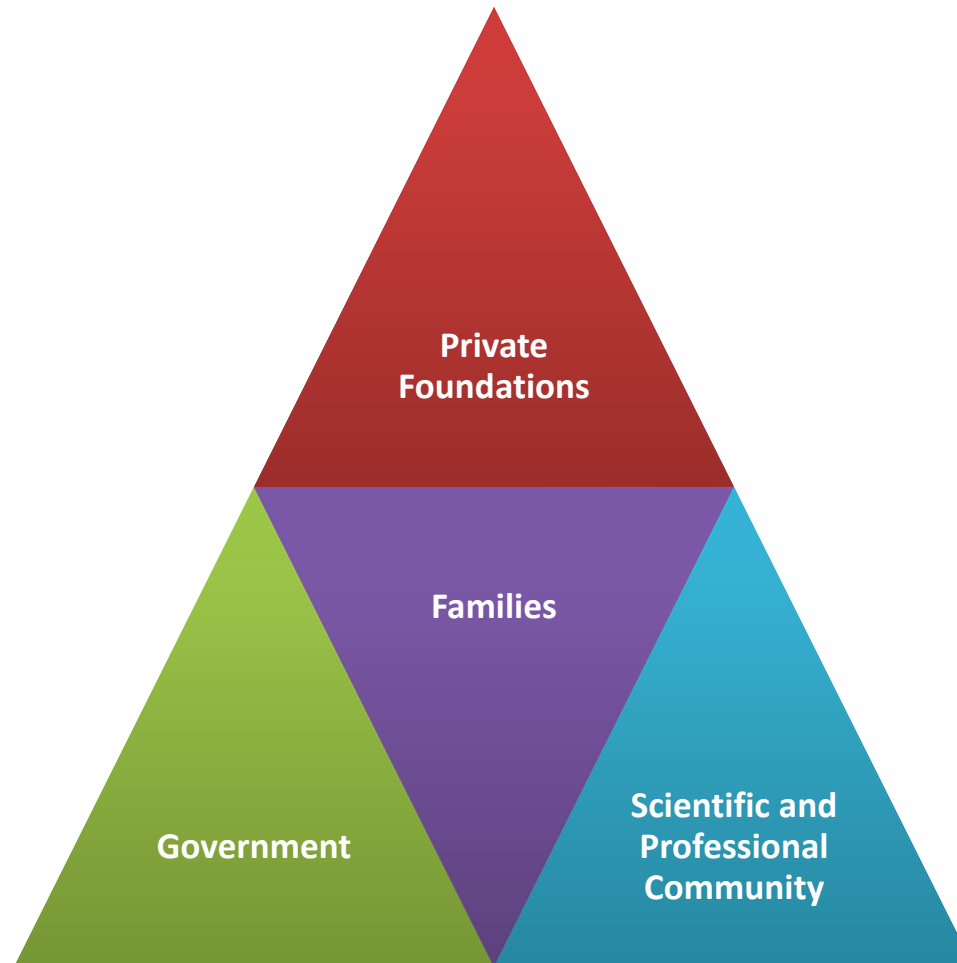
Emphasis:

- Developing evidence-base
- Evaluating performance and impact

One Strong

Together We Will Build a Better Tomorrow

Private Foundations

Families

Government

Scientific and Professional Community

Thank You!

One Strong