ASD: Research to Practice in the 21st Century

Lindamood Bell Annual Conference

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We wish to honor those individuals and families who have believed in research and been committed to participating again and again.
What does ‘cause’ mean?

Etiology: originating trigger
Pathophysiology: mechanisms
Functional analysis of behavior: in the present time
Why is understanding cause important?

Defining etiology means prevention (e.g., fetal rubella, untreated PKU, counseling) & knowledge of a group of cases

Defining pathophysiology means enabling development of more effective treatments because they target specific mechanisms and/or etiologies closer to the actual or root cause.
A Connected Sequence of Mechanisms From DNA to Behavior

Abnormal Genetic Coding for Brain Development

Disturbance in Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome
Autism is the result of alterations in how the brain processes information, which alters how the mind sees, thinks and feels at conscious & non-conscious levels.
These alterations in information processing are the result of altered development of the connections of cortical brain cells (neurons) that form cortical networks that perform higher order functions.
15-20 genes or chromosomal syndromes discovered to be associated with about 20% of ASD cases-about 1-3% of cases each.

These genes all direct development of connections among cortical neurons.
Discovery of these genes led to identification of molecular mechanisms which led to use of a drug to prevent the development of ASD in tuberous sclerosis.
Understanding the mechanisms causing alterations in thinking and feeling has led to new neurocognitive interventions designed to promote secondary growth of brain connections and conscious knowledge and wisdom.
Understanding these mechanisms has also led to more accurate functional analysis of behavior and more effective behavioral approaches.
Understanding these mechanisms is leading to reconceptualization of the syndrome and diagnostic with integration of core symptoms, associated symptoms and co-morbid symptoms into manifestations of a common pathophysiology.
Technology has enabled & accelerated progress

- Technology has a mathematical basis
- Gains based on math are exponential, not linear (1:1)
- Future advances will occur rapidly

(BBC, 2010)
Autism: From the 20\textsuperscript{th} to the 21\textsuperscript{st} century

New Findings Demanded New Account

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New Understanding of Etiology & Cause

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New Mechanisms Discovered

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New Treatments
Brain growth dysregulation

1. Indicative of disturbances in brain developmental mechanisms
2. Widespread but selective brain involvement: 3 core symptoms not enough
3. Gray matter (brain cell bodies) and white matter (brain cell extensions for connections) = neurons, cortical
Other Signs of Disturbances in Developmental Neurobiologic Mechanisms?

Yes. Golgi stains of brain cells show truncated dendritic tree.
And then there was functional underconnectivity of brain networks…

Began with a mathematical observation:
Synchronization & collaboration among cortical regions to perform higher level tasks
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Reliably lower cortical connectivity in autism during sentence comprehension task
Group differences in functional connectivity

Control group

Group with autism

Functional connectivity (z)

ROI pairs

And then there was further refinement of underconnectivity in ASD:

- Corticocortical underconnectivity
- Underconnectivity with frontal cortex
- Anterior-posterior asynchrony
- Enhanced local posterior connections— even language tasks processed by visual system rather than language system; previously characterized as verbal-performance disparity
- Extended to amygdala, striatum...default network
- Local neighborhoods to distributed networks
And then there were genes for autism

And they were all involved in a few aspects of the development of brain connections
Dendrite Morphology/Function
SHANK3/SHANK2
Reelin
DLGAP2

Axonal Outgrowth/Pathfinding
Slit/LRRs
Reelin
Tau Kinases
Cadherins
SYNGAP1

Synaptic CAMs
Neurexins/Neuroligins
Cadherings
CNTN4
CNTNAP2
SYNGAP1

Many Mostly Rare Genes Found In ASD

- No single or even few genes implicated. Rather, numerous candidates with a modest at best increased risk for autism. Like ingredients in a cake mix.

- Tend to have one thing in common: are involved in determining where and how brain cells (neurons) are connected and talk to each other.
Genes involved in autism code for development of connections between neurons

Disorders of:
- Axonal outgrowth & pathfinding
- Synapse formation & maintenance

Cause of autism is now being defined in terms of these mechanisms.
And then there was a new genetic mechanism: copy number variation
New Genetic Findings

- CNVs associated with autism are scattered across chromosomes - explains nonspecific association of autism with chromosomal syndromes
- Common mechanisms across etiologies resulted in syndromic vs non-syndromic instead of primary vs secondary case distinctions
Copy Number Variation or CNV

- More common in families with 1 affected child than in families with $\geq 2$ affected children
- Genes found in autism, also found in schizophrenia, anxiety disorder, & ADHD
- Variable penetrance + genetic background affects gene expression
Circle From Behavior to DNA Complete

Proof of concept:
Consistent mechanism across levels
Scientific plausibility supported
Application to treatment in mice & humans
Identification of Genes Reveals Molecular Mechanisms of ASD
Model showing possible interaction of FMRP with the mTORC1 complex. In wild-type mice, FMRP represses PIKE or other endogenous activator of PI3K/Akt signaling and thereby exerts a negative regulatory effect on mTOR signaling. Activation of group I mGluRs by the agonist DHPG promotes formation of an mGluR-Homer-PIKE complex, which engages PI3K/Akt signaling (Rong et al., 2003). PI3K/Akt in turn stimulates mTOR signaling, initiation of translation of synaptic proteins in dendrites, and mGluR-LTD. In FMRP-deficient mice, the positive effector (PIKE) is upregulated and mTOR signaling is overactivated and DHPG insensitive, leading to aberrant synthesis of synaptic proteins and exaggerated protein synthesis-independent mGluR-LTD. The PI3K inhibitor LY294002 reduces p-mTOR to wild-type levels and restores DHPG sensitivity.
Further Validation of these Concepts
Began with: home video movies showed symptoms of autism long before diagnosis

Key Q: What are the first behavioral characteristics that predict the development of autism?

Method: study of infants with an older sibling diagnosed with autism
Development of “Infant Sibs” in 1st Year: Social & Communication Realm

- No social signs at 6 months
- Social signs don’t predate other sx
- Delays in verbal and nonverbal language at 12 months but not earlier
“Infant Sibs” 1st Signs: Sensory Responses-Repetitive Motor-Visual Regard

- Unusual visual regard & repetitive waving of arms and hands at 12 and 18 mos
- Sensory-related behaviors: under and over responsiveness at 12 months but not 6 mos
- Social emotional: no temperament differences at 6 mos, over time temperamentally more difficult with more intense distress and more time fixating on objects; accompany- don’t predate- sx
- At 24 months, emotional and behavioral self-dysregulation distinguished infant sibs dx ASD
Implications: All features evolve from same pathophysiology

- “Associated symptoms” are integral-irritability, altered sensory responses, poor regulation of activity & emotion; “dysregulatory” manifestations
- Poor gross motor development included
- Intellectual Disability clearly integral
Conclusions From Infant Sibling Findings

“These findings do not support the view that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously.”

“Children’s developmental rates are decelerating markedly in a 12 month period, with IQs dropping from average to below 50 for some children.”

Sally Rogers, 2009
Figure: Occipital–frontal (OFC) Z score measurements (N 195) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linear model centered at 12 months).
What is happening to the brain while development of infant sibs goes off track?

- Onset of acceleration of brain growth at 9-12 months in most - coincident with onset of symptoms - then plateaus
- Brain growth in ASD is inverse of Retts syndrome.
Behaviorally Defined Syndrome With No Known Connection Between “Core”, “Associated” “Comorbid”

FROM: 3 Core Symptoms +
- Associated Symptoms: sensory, motor
- Co-morbid Conditions: intellectual disability, ADHD, seizures, regulation disorders

TO: whatever mechanism causes one causes all; organizing or explanatory principles arise from original events
Brain disturbances produce a constellation of neurologic signs & symptoms: symptoms/signs equally important

Impairments present when the time in development comes for that skill to appear

The constellation & mode of presentation reflect the underlying brain mechanism and its location
Brain Developmental Disturbances in ASD Involve Well Known Aspects of Brain Development

- Neuronal organization - most cases
- Neuronal migration - severe seizures
- Neuronal proliferation - extreme premies
What is going on during brain development?
Normal Developmental Neurobiologic Events

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration**
- Neuronal organization***
- Myelination
<table>
<thead>
<tr>
<th>TABLE 2-24  Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak Time Period</strong></td>
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<tr>
<td>5 months’ gestation-years postnatal</td>
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<tr>
<td><strong>Major Events</strong></td>
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<tr>
<td>Subplate neurons: establishment and differentiation</td>
</tr>
<tr>
<td>Lamination: alignment, orientation, and layering of cortical plate neurons</td>
</tr>
<tr>
<td>Neurite outgrowth: dendritic and axonal ramifications</td>
</tr>
<tr>
<td>Synaptogenesis</td>
</tr>
<tr>
<td>Cell death and selective elimination of neuronal processes and of synapses</td>
</tr>
<tr>
<td>Glial proliferation and differentiation</td>
</tr>
</tbody>
</table>
How the Brain Develops

15-1/2 wks          22 wks                23 wks             ~25 wks
27 weeks           Full term brain               Adult
Camera Lucida composite drawings of neurons in the visual (calcarine) cortex of human infants indicated gestational ages. Note the appearance and elaboration of basilar dendrites and the tangential spread of apical dendrites, as well as the accompanying maturation of the visual evoked response (top). (Courtesy of Dr. Dominick Purpura).
How the Brain Develops
Brain Affected Broadly But Selectively in ASD

The selectivity reflects the role these genes and developmental neurobiologic mechanisms play in cortical systems development.

This is the common underlying biological basis among the symptoms. The many symptoms don’t co-occur by chance.
“Cognition” Affected Broadly in ASD

From the beginning
Many domains, not one
<table>
<thead>
<tr>
<th>Intact or Enhanced</th>
<th>Cognitive Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Complex Sensory</td>
</tr>
<tr>
<td>Sensory Perception</td>
<td>Complex Motor</td>
</tr>
<tr>
<td>Elementary Motor</td>
<td>Complex Memory</td>
</tr>
<tr>
<td>Simple Memory</td>
<td>Complex Language</td>
</tr>
<tr>
<td>Formal Language</td>
<td>Concept-formation</td>
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<tr>
<td>Rule-learning</td>
<td>Face Recognition</td>
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<tr>
<td>Visuospatial</td>
<td></td>
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<tr>
<td>processing</td>
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</table>
ASD “Cognitive” Profile

- Elementary abilities intact or enhanced
- Information processing capacity limited
- Integrative processing disproportionately impaired
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
Identification of Genes Leads to Definition of Molecular Mechanisms
Defining molecular mechanisms empowers a new world of interventions

mTor inhibitor Rapamycin to prevent development of seizures, intellectual disability and ASD in infants and toddlers diagnosed with TSC gene tuberous sclerosis; clinical trials in progress
Model showing possible interaction of FMRP with the mTORC1 complex. In wild-type mice, FMRP represses PIKE or other endogenous activator of PI3K/Akt signaling and thereby exerts a negative regulatory effect on mTOR signaling. Activation of group I mGluRs by the agonist DHPG promotes formation of an mGluR-Homer-PIKE complex, which engages PI3K/Akt signaling (Rong et al., 2003). PI3K/Akt in turn stimulates mTOR signaling, initiation of translation of synaptic proteins in dendrites, and mGluR-LTD. In FMRP-deficient mice, the positive effector (PIKE) is upregulated and mTOR signaling is overactivated and DHPG insensitive, leading to aberrant synthesis of synaptic proteins and exaggerated protein synthesis-independent mGluR-LTD. The PI3K inhibitor LY294002 reduces p-mTOR to wild-type levels and restores DHPG sensitivity.
Implications of Connectivity Disturbances For Intervention
Altering cortical connectivity: remediation-induced changes in the white matter of poor readers

Keller TA, Just MA

Neuroimaging studies using diffusion tensor imaging (DTI) have revealed regions of cerebral white matter with decreased microstructural organization (lower fractional anisotropy or FA) among poor readers. We examined whether 100 hr of intensive remedial instruction affected the white matter of 8- to 10-year-old poor readers. Prior to instruction, poor readers had significantly lower FA than good readers in a region of the left anterior centrum semiovale. The instruction resulted in a change in white matter (significantly increased FA), and in the very same region. The FA increase was correlated with a decrease in radial diffusivity (but not with a change in axial diffusivity), suggesting that myelination had increased. Furthermore, the FA increase was correlated with improvement in phonological decoding ability, clarifying the cognitive locus of the effect. The results demonstrate the capability of a behavioral intervention to bring about a positive change in cortico-cortical white matter tracts.
Implications of “Cognitive Profile” For New Interventions
Cognitive Enhancement Therapy:
• Developed to treat individuals with schizophrenia
• Based on established neuro-rehabilitation principles
  • Efficacy demonstrated in two NIMH trials
  • Improved cognition and daily life function
• Prevented brain shrinking & even increased brain
• Active ingredients: processing speed & metacognition particularly social-emotional perspective taking
Cognitive Enhancement Therapy (CET)  
A Neurocognitive Intervention For Adults

- Starts with basic socialization and attention training in pairs (3mo to 6mo)
- Moves to small group-based social-cognitive training (6mo to 18mo)
- Simultaneously moves to executive function and problem-solving training (6mo to 18mo)
- All provided in the context of meaningful functional goals (e.g., work, school, girlfriend)
Findings From First Open Trial:

- Every participant: $\geq 1$ cognitive domain at $< 1\%$
  - IQ scores 100-150
- At 9 month point: significant improvements in processing speed, working memory, some evidence generalization
  - 100% retention; 80% attendance over winter
  - good satisfaction rating
- 18 month point: October 2011
- Begin single blind CER study w/ Enhanced Supportive Therapy, & pre-post-imaging,
  - Test new maintenance therapy
Implications of “Cognitive Profile” For New Interventions:
Implications of "Cognitive Profile" For Novel Intervention:

• Greeble Training as a method of training multi-dimensional integration of information
  • Visual processing: proxy for high level processing
• Greebles: proxy for novel objects & category development
• Questions: Can they learn greebles? Does this improve face processing? Does it improve high level processing in other domains? Does it enhance systems connectivity?
Intervention to Enhance Face Recognition and Brain Plasticity in Autism

Perceptual Bias to Focus on Local Elements

Especially Difficult for Recognition of Individual Faces

Atypical Development of Face-Related Cortex

Whole is more than sum of parts!

Toddler viewer with autism: focus on non-essential inanimate details

Aversion to Faces?

Greeble Intervention – Learning to Integrate the Elements
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Aversion to Faces?

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Greeble Intervention – Learning to Integrate the Elements
Identification of Genes Leads to Definition of Molecular Mechanisms:

- Use mTOR inhibitor to treat gene disorders resulting from enhanced activity of this pathway - PTEN, tuberous sclerosis
  - Tuberous sclerosis: most cases spontaneous mutations
    - TSC 1 and TSC 2 genes
  - TSC (complex): mental retardation, epilepsy, ASD
  - Other organ involvement: heart & kidney tumors
  - 40-60% meet ADI ADOS criteria for ASD as children
Model showing possible interaction of FMRP with the mTORC1 complex. In wild-type mice, FMRP represses PIKE or other endogenous activator of PI3K/Akt signaling and thereby exerts a negative regulatory effect on mTOR signaling. Activation of group I mGluRs by the agonist DHPG promotes formation of an mGluR-Homer-PIKE complex, which engages PI3K/Akt signaling (Rong et al., 2003). PI3K/Akt in turn stimulates mTOR signaling, initiation of translation of synaptic proteins in dendrites, and mGluR-LTD. In FMRP-deficient mice, the positive effector (PIKE) is upregulated and mTOR signaling is overactivated and DHPG insensitive, leading to aberrant synthesis of synaptic proteins and exaggerated protein synthesis-independent mGluR-LTD. The PI3K inhibitor LY294002 reduces p-mTOR to wild-type levels and restores DHPG sensitivity.
Rapamycin treatment reduces anxiety, improves social activity, and controls seizures. In the open-field test, rapamycin (Rapa)-treated Pten mutant mice showed no significant difference from rapamycin-treated controls, whereas vehicle-treated Pten mutants showed statistically significant decrease in center time compared with vehicle-treated control mice.
Rapamycin injection progressively reduces seizure duration and frequency of *Pten* mutant mice. *n* = 6 mice per group. *p* < 0.05 compared between vehicle- and rapamycin-treated mutants. Data are mean ± SEM and were analyzed by ANOVA, followed by post hoc t test.
We wish to honor those individuals and families who have believed in research and been committed to participating again and again.

Progress Comes From Participation
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s) associated with the syndrome</th>
<th>Proportion of patients with the syndrome that have an ASD</th>
<th>Proportion of patients with an ASD that have the syndrome</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q duplication — Angelman syndrome</td>
<td>UBE3A (and others)</td>
<td>&gt;40%</td>
<td>1–2%</td>
<td>101–103</td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTNAP2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>25% of males; 6% of females</td>
<td>1–2%</td>
<td>105</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
</tr>
<tr>
<td>Potocki–Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
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<tr>
<td>Smith–Lemli–Optiz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
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<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
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<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
</tr>
</tbody>
</table>

The rates quoted in the table depend on the population that is being evaluated. For example, rates are higher in individuals from simplex families compared with multiplex families, and are higher in dysmorphic and mental retardation populations compared with idiopathic populations. *High* is used for syndromes in which no good estimates exist (that is, only a handful of individuals with the syndrome in question have been identified). It should also be noted that none of the studies cited here indicates that assessment for the autism spectrum disorder (ASD) was performed blind to a patient’s primary diagnosis. An expanded version of the table with additional variables can be found in [Supplementary Information S1](#) (table). CACNA1C, calcium channel voltage-dependent L type alpha 1C subunit; CNTNAP2, contactin associated protein-like 2; DHCR7, 7-dehydrocholesterol reductase; FMR1, fragile X mental retardation 1; MECP2, methyl CpG binding protein 2; SHANK3, SH3 and multiple ankyrin repeat domains 3; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2; UBE3A, ubiquitin protein ligase E3A.
<table>
<thead>
<tr>
<th><strong>Gene</strong></th>
<th><strong>Syndrome or mutation(s)</strong></th>
<th><strong>Replicated association</strong></th>
<th><strong>Analysis of variant</strong></th>
<th><strong>Mouse model</strong></th>
<th><strong>Other evidence</strong></th>
<th><strong>Total score</strong></th>
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<td><strong>Promising</strong></td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<td>GRIK2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1: homozygous mutation results in non-syndromic mental retardation</td>
<td>2</td>
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<tr>
<td>NRXN1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>SLC25A12</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1: associated with neurite outgrowth, expression is upregulated in ASD brain</td>
<td>2</td>
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<tr>
<td><strong>Probable</strong></td>
<td></td>
<td></td>
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<tr>
<td>CACNA1C</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>CNTNAP2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<td>MET</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1: expression reduced in brains of cases versus controls</td>
<td>3</td>
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<td>OXTR</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1: expression reduced in blood of cases versus controls</td>
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</tr>
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<td>SHANK3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1: modulates glutamate-dependent reconfiguration of dendritic spines</td>
<td>3</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1: clinical benefit from inhibitors, variation linked to gray-matter volume</td>
<td>3</td>
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<td>CADPS2</td>
<td>2</td>
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<td>DHCR7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1: hypocholesterolaemia in a proportion of probands</td>
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<td>FMR1</td>
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<td>NLGN3</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>NLGN4X</td>
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<td>0</td>
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<td>1</td>
<td>0</td>
<td>4</td>
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<td>PTEN</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1: mutations result in abnormal structure and function of the synapse</td>
<td>4</td>
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<tr>
<td>TSC2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1: regulates dendrite morphology and function of glutamatergic synapses</td>
<td>4</td>
</tr>
<tr>
<td>GABRB3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1: expression is dysregulated in pervasive developmental disorders</td>
<td>4</td>
</tr>
<tr>
<td>MECP2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1: MECP2 deficiency causes reduced expression of UBE3A and GABRB3</td>
<td>5</td>
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<tr>
<td>TSC1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1: regulates dendrite morphology and function of glutamatergic synapses</td>
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<tr>
<td>UBE3A</td>
<td>2</td>
<td>0</td>
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<td>1: expression is dysregulated in pervasive developmental disorders</td>
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<td>RELN</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1: levels reduced in brains of cases versus controls</td>
<td>6</td>
</tr>
</tbody>
</table>