Understanding ASD in the 21st Century

The Hospital for Sick Children
University of Toronto

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Professor of Psychiatry & Neurology
Director NIH Autism Center of Excellence

March 5, 2010
We wish to honor those individuals and families who have believed in research and been committed to participating again and again.
Behaviorally Defined Syndromes

3 Core Symptoms
Associated Symptoms: sensory, motor
Co-morbid Conditions: intellectual disability, ADHD, seizures, regulation disorders
Behaviorally Based Interpretations of Brain Dysfunction Dominated the 20th C

- Social impairment is pathognomonic & inferred to be the cause of syndrome - social primacy
- Alternative: No primary core deficits found - no unifying core deficits - each sign independent (dimensional approach) & independent genes
- Pitfall: expectation that brain acts according to behavioral principles - failure to seek out neurological mechanisms & principles that govern presentation & expression of neurodevelopmental disorders
New Findings Demand New Account
### Table 1 | ASD-related syndromes

<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>
</tr>
<tr>
<td>Smith–Lemli–Optiz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
</tr>
<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>
</tr>
<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>Gene</th>
<th>Syndrome or mutation(s)</th>
<th>Replicated association</th>
<th>Analysis of variant</th>
<th>Mouse model</th>
<th>Other evidence</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DISC1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ITGB3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AHI1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>EN2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>NRXN1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<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>
</tr>
<tr>
<td>CACNA1C</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
<td>3</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>CADPS2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>DHCR7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1; hypocholesterolaemia in a proportion of probands</td>
<td>4</td>
</tr>
<tr>
<td>FMR1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN4X</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<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>
<td>5</td>
</tr>
<tr>
<td>UBE3A</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>5</td>
</tr>
<tr>
<td>RELN</td>
<td>2</td>
<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>
Cortical activation & synchronization during sentence comprehension in HFA subjects

Marcel Just
Vlad Cherkassky
Tim Keller
Nancy Minshew

Just et al. 2004, Brain 127: 1811-1821
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order
Functional Underconnectivity: fMRI of the Tower of London

Marcel Just
Nancy Minshew
Tim Keller
Vlad Cherkassky
Rajesh Kana

Just et al., 2006 [Epub ahead of print], Cereb Cortex
Group differences in functional connectivity

Control group

Group with autism

Functional connectivity (z)

ROI pairs

LPOG:RPOG
LPOG:RT
RIFG:RIPL
ROCG:RST
RLDPF:RIPS
LDLPF:CLIPS
LRL:RIPS
LIPS:RSFG
RIPS:RSFG
RIFG:RIPS
LDLPF:RIPS
RHECHL:RHP
LIFG:RIPS
RCBELL:RIPS
WORK ORDER: Connect pieces

Equal opportunity- same job description for everyone
Define A Pathophysiologic Sequence For ASD

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome
First: Astute Clinical Observations

Sir Michael Rutter, 2008
Key Features of Autism

1. Impaired social reciprocity
2. Impaired social communication
3. Repetitive, stereotyped interests & behavior
4. Onset in first 2-3 years of life

Q: Is the constellation inherent in a cohesive syndrome or is it an artifact of diagnostic practice?

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
Some Key Clinical Features of Autism

1. Marked male preponderance (3-4:1) BUT this applies to most neurodevelopmental disorders
2. Association with intellectual impairment BUT IQ range extends from severely impaired to superior
3. Association with epilepsy in 25-33% with onset in adolescence
4. Association with increased head circumference

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
1. Spontaneous Mutations: Increased rate of “de novo” copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Opened door to two genetic mechanisms: inherited gene mutations and spontaneous copy number mutations - instability in replication of DNA.

2. Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice.

Some Biological Features of Autism

1. Raised serum serotonin in 30% but nonspecific
2. No consistent or marked response to psychotropics
3. Very limited generalization of responses to psychological interventions
4. Brain imaging: no localized abnormality, rather an impaired integration across systems
5. No consistent neuropathological pattern except findings suggest prenatal origin

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
1. Spontaneous Mutations: Increased rate of "de novo" copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Opened door to two genetic mechanisms: inherited gene mutations and spontaneous copy number mutations - instability in replication of DNA.

2. Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice.

1. Association with some diagnosable medical condition in at least 10% of cases
2. Strongest association with tuberous sclerosis but largely a function of location of tubers, low IQ and epilepsy
3. Definite, but weak association with fragile X anomaly

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
Some Genetic & Related Features

1. Marked increase in familial risk (50x)
2. Heritability circa 90%, 3-12 genes involved
3. Increased rate of chromosomal anomalies (but diagnostically nonspecific)
4. Increased rate of congenital anomalies but apart from ch 15, nonspecific
5. Association with increased parental age
6. Increase in copy number variations

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
Is autism a synapse-opathy?
Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit.

The constellation & mode of presentation reflect the underlying brain mechanism and its location.

Vascular, infectious, traumatic, autoimmune, developmental-maturational-degenerative are types of mechanisms.
Developmental Neurobiologic Processes

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration**
- Neuronal organization***
- Myelination
## Discriminant Function Analysis: Domains Without Deficits

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Letter Cancellation; Number Cancellation</td>
<td>66.70</td>
<td>0.33</td>
</tr>
<tr>
<td>Sensory Perception</td>
<td>Finger Tip Writing; Luria-Nebraska Sharp/Dull Tactile Scale item</td>
<td>64.40</td>
<td>0.29</td>
</tr>
<tr>
<td>Simple Language</td>
<td>K-TEA Reading; K-TEA Spelling WRMT-R Attack; Controlled Oral Word Association</td>
<td>71.20</td>
<td>0.42&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Simple Memory</td>
<td>CVLT Trial 1</td>
<td>65.20</td>
<td>0.30</td>
</tr>
<tr>
<td>Visuo-Spatial</td>
<td>WAIS-R Block Design</td>
<td>56.10</td>
<td>0.12</td>
</tr>
</tbody>
</table>

<sup>1</sup>Kappa below .40 indicates poor agreement beyond chance

<sup>2</sup>Significant *Kappa* reflects superior performance by autistic subjects

<sup>3</sup>Based on 33 individually age, IQ, gender matched pairs of subjects
### Discriminant Function Analysis¹: Domains With Deficits

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Grooved Pegboard; Trail Making A</td>
<td>75.80</td>
<td>0.52</td>
</tr>
<tr>
<td>Complex Language</td>
<td>K-TEA Reading Comprehension; Verbal Absurdities; Token Test</td>
<td>72.70</td>
<td>0.45</td>
</tr>
<tr>
<td>Complex Memory</td>
<td>Nonverbal Selective Reminding-Consistent Long Term Retrieval; WMS-R Story Recall-Delayed Recall; Rey-Osterrieth Figure-Delayed Recall</td>
<td>77.30</td>
<td>0.55</td>
</tr>
<tr>
<td>Reasoning</td>
<td>20 Questions; Picture Absurdities; Trail Making B</td>
<td>75.8</td>
<td>0.52</td>
</tr>
</tbody>
</table>

¹Based on 33 individually matched pairs of autistic & control subjects (Neuropsychologic Functioning in Autism: Profile of a Complex Information Processing Disorder, JINS, 3:303-316, 1997)
The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

<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>
</tr>
<tr>
<td>• Rule-learning</td>
<td>• Face Recognition</td>
</tr>
<tr>
<td>• Visuospatial processing</td>
<td></td>
</tr>
</tbody>
</table>
What Does The Profile Mean?

- Simpler abilities intact or enhanced

- Information processing capacity limited—integrative processing & higher order cognitive abilities disproportionately impaired

Inference: higher order brain circuitry is under developed- over-reliance on lower order visual circuitry to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
Autism is the result of alterations in how the brain processes information, which alter how the mind sees the world.
Brain Affected Broadly in ASD

From the beginning
Many domains, not one
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

This strategy is proving invaluable in bringing new insights to autism

What Are Infant Siblings Teaching Us About Autism in Infants? Rogers, 2009
Developmental Characteristics of Infant Sibs: Onset > 6 mos; Motor & Balance

- No developmental differences at 6 mos
- Developmental differences at 12 mos on standardized tests- a developmental deceleration
- Gap widens between 12 & 24 months and beyond
- Differences in fine and gross motor- early
- Less mouthing of objects-less vocalizations
- Truncal instability when sitting- early
Developmental Characteristics of Infant Sibs: Sensory-Repetitive-Visual Regard

- Repetitive behaviors: unusual visual regard and 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 temperamental 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
Developmental Characteristics of Infant Sibs: Social Realm

- No social signs at 6 months don’t predate other sx
- Delays in verbal and nonverbal language at 12 months but not earlier
- Best predictor of response to name at 14 mos- child’s self initiated and spontaneous gaze shifts from toy to parent- joint attention- this is a social impairment
Lack of behavioral markers at 6 months; earliest differences are subtle, involve a few behaviors or small differences

Socially normal at 6 months

Onset: not early or regressive but rather slower or faster mounting of symptoms- a deceleration of development: core symptoms present at 12 mos and grow more severe over time

“Associated symptoms” are integral-irritability, sensory responsivity, activity level, poor gross motor development
“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 2. 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 linearmodel centered at 12 months).
What is happening in the BRAIN in infant sibs?

Onset of acceleration of brain growth at 9-12 months-coincident with onset of symptoms.

Brain growth in ASD is inverse of Retts syndrome.
Brain disturbances produce a constellation of neurologic signs & symptoms.

The constellation & mode of presentation reflect the underlying brain mechanism and its location.

Impairments present when the time in development comes for that skill to appear.
Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration**
- Neuronal organization***
- Myelination
**TABLE 2-24 Organization**

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

15-1/2 wks          22 wks                23 wks             ~25 wks

27 weeks           Full term brain               Adult
Figure 2-43 Camera lucida composite drawings of neurons in the visual (calcarine) cortex of human infants of 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

A  One month old

B  Six month old

C  24 month old
Social impairment

- OFC – Orbitofrontal cortex
- ACC – Anterior cingulate cortex
- FG – Fusiform gyrus
- STS – Superior temporal sulcus
- A – Amygdala
- IFG – Inferior frontal gyrus
- PFC – Posterior parietal cortex

Communication deficits

- IFG – Inferior frontal gyrus
- (Broca’s area)
- STS – Superior temporal sulcus
- SMA – Supplementary motor area
- BG – Basal ganglia
- SN – Substantia nigra
- Th – Thalamus
- PN – Pontine nuclei

Repetitive behaviors

- OFC – Orbitofrontal cortex
- ACC – Anterior cingulate cortex
- BG – Basal ganglia
- Th – Thalamus

TRENDS in Neurosciences
BRAIN Affected BROADLY in ASD

Cortical-Cortical Connections
Cortical-amygdala
Cortical-striate
Growth dysregulation at other critical ages
A Disorder of Brain Connectivity: al Profile Results From

Underconnectivity of cortical networks
Excessive local connections
How Does the Brain Classify Words?
Results of Recent fMRI Studies

- Encoding by the brain is distributed—involves multiple brain regions—leads to flexibility
- Each word encoded according to four attributes in adults:
  - Eating
  - Shelter
  - Manipulation
  - Number of characters in word
- Vital to design of early interventions
Share common signaling pathways involved in connecting neurons together
Mechanisms are basis of new intervention
Made Possible By Large Scale Collaboration: The Autism Genome Project (AGP)

• Large-scale, collaborative genetics research project
• To identify genetic factors underlying autism
• Involves researchers from over 50 centres in the USA, Europe, and Canada
• AGP members published more than 200 peer-reviewed manuscripts on autism since 2003

www.autismgenome.org
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.

Tend to have one thing in common: are involved in determining where and how brain cells (neurons) are connected and talk to each other.
Axonal Pathfinding & Targeting:
-- Cadherins
-- LRRs

Synaptic Targeting & Function:
-- Neurexins/Neuroligins

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
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</tr>
<tr>
<td>22q deletion</td>
<td><em>SHANK3</em></td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td><em>CNTNAP2</em></td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td><em>FMR1</em></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>
</tr>
<tr>
<td>Smith–Lemli–Optiz syndrome</td>
<td><em>DHCR7</em></td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td><em>MECP2</em></td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td><em>CACNA1C</em></td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
</tr>
<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>Gene</th>
<th>Syndrome or mutation(s)</th>
<th>Replicated association</th>
<th>Analysis of variant</th>
<th>Mouse model</th>
<th>Other evidence</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DISC1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ITGB3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AHI1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>EN2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>NRXN1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<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>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CACNA1C</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
<td>3</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>CADPS2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
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<tr>
<td>DHCR7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1: hypocholesterolaemia in a proportion of probands</td>
<td>4</td>
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<tr>
<td>FMR1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN4X</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</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>
</tr>
<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>
</tr>
<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>
<td>5</td>
</tr>
<tr>
<td>UBE3A</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1: expression is dysregulated in pervasive developmental disorders</td>
<td>5</td>
</tr>
<tr>
<td>RELN</td>
<td>2</td>
<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>
1. Genes whose products affect **axonal targeting and pathfinding** i.e. getting neurons connected in the right way

**Cadherins** and **leucine-rich repeat proteins** which are cell surface proteins expressed in neuronal processes - thought to be important for establishing connections between cells in the developing brain
2. Those that affect **synaptic functioning**:

*Neurexins and neuroligins* bind each other across the synapse (i.e. glue neurons together) and mediate signaling across the synapse, and affect the properties of neural networks by specifying synaptic functions (i.e. excitatory versus inhibitory).
3. Those that appear to affect **dendritic function**: 

**Shank** family of synaptic proteins function as molecular scaffolds at the post synaptic density and promote the maturation and enlargement of dendritic spines.
Axonal Pathfinding & Targeting:
-- Cadherins
-- LRRs

Synaptic Targeting & Function:
-- Neurexins/Neuroligins

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
A Molecular Pathophysiology Emerges

- 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
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.
A cognitive rehabilitation intervention for remediating neurocognitive and social-cognitive deficits developed by Hogarty and colleagues (2004, 2006).

Neurocognitive Training
- Computer-based training in attention, memory, and problem-solving.
- 1 hour/week
- 60 hours total

Social-Cognitive Group Therapy
- Training in perspective-taking, gistfulness, non-verbal communication, emotion perception, and much, much more.
- 1.5 hours/week
- 45 sessions

Goals of CET

I. Foster Higher Thinking By Becoming:

- Gistful vs. Concrete
- An Active Thinker vs. Passive Receiver of Information
- Cognitively Flexible vs. Following Rigid Rules
- More Spontaneous vs. Rehearsed
- More of an Initiator vs. Doing Nothing
II. Help to develop:
- Social Wisdom (norms and rules of behavior)
- Context Appraisal (what is going on)
- Perspective Taking (how others feel, think and respond)
- Foresightfulness (If I do this ..., then ...)
- Empathy and Support (being reciprocal)
- Social Comfort
Process of CET

- 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)
Progress Comes From Participation

We wish to honor those individuals and families who have believed in research and been committed to participating again and again.