“Understanding How the Mind & Brain Think in Autism”

Sharon Regional Behavioral Health Services
April 23, 2010

Nancy Minshew, MD
Director, NIH Autism Center of Excellence
Professor Psychiatry & Neurology
University of Pittsburgh USA
Clinical Syndrome

Diagnostic Systems
- Quick Impressions
- Diagnostic Criteria
- Individual Symptoms
- Diagnostic Instruments
- Individuals With Autism
Pervasive Developmental Disorders (DSM-IV)  
*Autism Spectrum Disorders (Informal)

DSM-IV (1994): Pervasive Developmental Disorders

- *Autistic Disorder
- *Asperger’s Disorder
- *Pervasive Developmental Disorder NOS
- Childhood Disintegrative Disorder
- Rett’s Disorder

Group may vary widely depending on diagnostic instruments used-ADI-R &/or ADOS- & other exclusions; therefore findings may vary widely. Clinicians vary in their practices.
By What Name? Autism Spectrum Disorders

- Autistic Disorder
- Asperger’s Disorder
- Pervasive Developmental Disorder Not Otherwise Specified

Accurate distinctions between these outside a research setting unlikely. Need a functional definition in social, language, adaptive and problem behavior domains instead.
Autism Spectrum Disorder, DSM-V
Coming 2014

- ASD, not PDD
- Continue to be behaviorally based
- No separate category for cases due to underlying conditions such as tuberous sclerosis, fragile-x syndrome, NF, PTEN, metabolic disorders, etc
Estimates of Expressive Language Level at Age 9 in Children Dxd With Autism at Age 3

Studies of Chicago & North Carolina:

- 39.6 – 40.9% speak in complex sentences
- 28.9 – 35.3% speak in sentences, but not fluent
- 10.5-16.8% have words but not sentences
- 14.3-14.4 have no or few consistent words
Autism Spectrum Disorders
Same Disorder Wide Range Severity

- Spoken language as rough index of severity
- No evidence that divisions of a clinical syndrome based on severity alone have any validity
- Variability or heterogeneity is the rule
- Superimposed on a core of common impaired higher order functions
Recognizing Verbal Individuals With ASD

- Strange or odd: reflects social impairment
- Monotone voice: usually too loud
- Little to no facial expression or one constant
- Upset by change, rituals for doing things in set ways; scripts for saying things
- Obsessions- with collecting stuff or a topic; super memory for facts or attention to small details
- Clumsy, awkward
Other Distinguishing & Important Features

- No hallucinations
- Onset in first three years
- Socially emotionally very young: naïve, child-like
- Very poor perspective taking if any
- Poor face & emotion recognition
- Gullible
- Very few strategies for problem solving, not flexible
Asperger’s Disorder vs Autistic Disorder

- Fewer symptoms than for Autistic Disorder
- Absence of delayed & disordered language development now and before 5 years
- Often precocious language development
- Actual application of diagnosis: highly variable with poor distinction between HFA, AS, PDDNOS
Quick Diagnosis of ASD in LFA

- **Intermediate severity**: few interactions; alone; echolalic or few stereotyped sentences; self-stimulatory behavior; difficulty with change; sensory issues; likes parts of objects not whole

- **Most severe**: no interactions, no language, no comprehension, no prosody, no face expression, no adaptive behavior- out of proportion to IQ; direct care staff can tell who has autism vs non-autistic MR- they are highly familiar with IQ expectations
Diagnostic criteria for 299.00
Autistic Disorder

A total of six (or more) items from 1, 2, and 3, with at least two from 1, and one each from 2 and 3. *(on the following 3 slides)*

A. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:
   - social interaction
   - language as used in social communication, or
   - symbolic or imaginative play
Diagnostic criteria for 299.00
Autistic Disorder (cont’d)

- Qualitative Impairment in Social Interaction
  - Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
  - Failure to develop peer relationships appropriate to developmental level
  - A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
  - Lack of social or emotional reciprocity
Diagnostic criteria for 299.00
Autistic Disorder (cont’d)

- Qualitative Impairment in Communication
  - Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
  - In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
  - Stereotyped and repetitive use of language or idiosyncratic language
  - Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
Diagnostic criteria for 299.00  
Autistic Disorder (cont’d)

- Restricted Repetitive and Stereotyped Patterns of Behavior, Interests, and Activities:
  - Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
  - Apparently inflexible adherence to specific, nonfunctional routines or rituals.
  - Stereotyped and repetitive motor mannerism (e.g., hand or finger flapping or twisting, or complex whole-body movements).
  - Persistent preoccupation with parts of objects
Behavioral Expression of Social Deficit

- **Most severe:** no response to any social overture & no attempt to initiate social contact with others

- **Intermediate:** a few unvarying stereotyped ways of initiating contact, contact initiated solely for needs; not sustained; no understanding of social etiquette between people or in groups

- **Less severe:** interactions consist of monologues, extended scripts that sound original but aren't, or are dependent on others’ questions; inadvertently offensive to others but also naive and gullible; can’t chit chat
Language & Communication Deficits

- **Most severe**: global aphasia & aprosodia (loss or impaired ability to speak or understand language); mute
- **Intermediate**: echolalic with no comprehension → a few echoed sentences used functionally to indicate needs → a few stereotyped sentences used rote with extremely limited comprehension; short scripts; talks but not to you
- **Less severe**: grammatically correct sentences but deficits in comprehension of idioms, metaphors, and stories; talk about obsessions; monologues; long scripts; unending questions; cannot chit-chat; conversation not reciprocal
- **Bottom line**: expression is greater than comprehension
Expression of Impairment in Play

- **Most severe:** complete lack of interest in toys
- **Intermediate:** interest in smell, taste, or texture of objects; preoccupation with the parts of toys (spins wheels, lines up; carries around): nonfunctional or atypical play
- **Less severe:** functional play sequences but play is stereotyped; may precisely imitate video or TV; preoccupied with game shows, letter-word games, computer, video games- advantage due to piecemeal processing & rule based
Restricted & Repetitive Behavior: Expression of Local-Global Cognitive Deficit

- **Most severe:** self-stimulatory behavior disproportionate to IQ, oblivious to world

- **Intermediate:** interest in elementary features but not whole, tantrums with change, rituals for doing things, controlling of what others do and say

- **Less severe:** tolerant of ordinary changes, narrow range of interests that are preoccupations or obsessions with a focus on details, poor concept formation, problem solving; inflexibility; rule and fact based; no common sense or insight
Social Emotional Immaturity: Disturbance in Affective Contact Not Included in DSM

- Capacity to experience, comprehend, and regulate emotions at a basic and cognitive level is severely impaired and unrecognized despite frequent abnormal imaging abnormalities of the amygdala, an emotion structure of the brain.

- Most verbal ASD adults are socially-emotionally 12-18 months to 4-5 years of age. Failure to recognize this in treatment worsens behavior.
Autism Diagnostic Interview-R (research): documents key features of early presentation (ages 4-5) and current manifestations, and other important historical information

Autism Diagnostic Observation Schedule-G (research reliability): direct observation and interaction with an individual to observe social-communication and imaginative elements of ASD

Toddler versions
"My ability to function in the world & develop social relationships has been learned solely through my intellect...and use of my visualization skills. I have learned by rote how to act in different situations. Using my visualization ability, I observe myself from a distance in each situation. I call this my "little scientist in the corner"... I take note of the details that make up the situations just like a scientist observes an experiment. All that data gets put on my computer hard drive memory..."
Dr. Temple Grandin

“For some of us with ASDs, the emotional-relatedness physical or biochemical circuitry is missing- no matter how hard we try, it’s a bridge that may never be built because some of the basic building materials are missing.”

“Romantic relationships have a level of social complexity that I still don’t understand today and I consciously choose not to participate in them. My way of thinking and functioning does not describe everyone on the spectrum.”
Temple Grandin’s Perspective

“I experience the emotion of love, but it’s not the same that most neurotypical people do. Does that mean my love is less valuable than what other people feel?”

“Some people with autism don’t understand or experience any sort of emotional attachment or romantic love. I would speculate that autism involves an atypical development of the ...reward systems.”
“On June 2, 1975, I was very angry. The bottom of my stomach felt as if I had swallowed a dumbbell: I spent much of my childhood and teenage years dealing with that emotion and getting to know it intimately.”

“My autism brought me much misery and unhappiness, and in essence robbed me of a childhood. I was born with a pervasive fear that never seemed to diminish, so I spent most of my earliest years devising ways to lessen the unrelenting terror, if not get rid of the chronic dread completely. To that end, I tried to find ways to look at and take in the world that would make sense to me and
“..be less overwhelming, while at the same time, provide a measure of comfort, control, balance, and security- all of which were missing from my life. Isolating and manipulating objects while tuning out people; fixating on repetitive motions; asking the same questions over and over; developing stereotypical movements, arbitrary rules and rigid thinking; and focusing to an extreme degree on one item or event to the exclusion of every else were among the ways I found some control and security, while temporarily sidestepping my fears.”
Autism: A Disorder of Affective Contact:  
Part 2 of Brain Behavior Definitions

- Capacity to experience, understand & regulate emotions fundamentally impaired and not widely appreciated

- Many verbal ASD individuals socially-emotionally as young as 12-18 months to 3-5 years of age- causes major symptoms, needs remediation

- Studies of amygdala-cortical interactions and connectivity related to social motivation, frustration management, in progress, need to understand basis to guide treatment

Social Emotional Immaturity: Also Not in DSM
What Causes Autism?

At What Level?
Between Molecule & Behavior?
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-in instability in replication of DNA.

The Top 10 of 2007 (cont’d.)

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome
Other Caveats About ASDs: Medical Causes

- In 75-80% of ASD cases, there is no identifiable cause for behavioral syndrome besides ASD.

- About 15-20% have an identified genetic syndrome (syndromic autism) or gene mutation (non-syndromic autism) as causal. Most common are fragile-x syndrome, tuberous sclerosis and chromosome 15q deletion syndrome. Individually each genetic cause is rare.
Verify That Every Child With ASD Has Had:
There Should Be No Second Children With:

- Physical exam for Tuberous Sclerosis
- Genetics test for Fragile X, chromosomes, microarray
- A newborn screen for metabolic diseases (blood spot at birth, state-mandated)
How the Mind & Brain in Autism Thinks & Feels
Autism is the result of alterations in how the brain processes information that alters how the mind sees the world.
Why is that important to you?

It is the cornerstone of treatment.
It is the footprint of the cause.
Neurologists’ characterize all impaired AND all intact abilities to identify common characteristics (information processing) that reflect their shared dependence on a common underlying cause (altered brain connectivity).

This approach was particularly beneficial in autism because both were part of the abnormal profile that defines behavior.
The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

**Intact or Enhanced**
- Attention
- Sensory Perception
- Elementary Motor
- Simple Memory
- Formal Language
- Rule-learning
- Visuospatial processing

**Cognitive Weaknesses**
- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition
What Are the Shared Underlying Features: Information Processing, Brain Connectivity

- Simpler abilities are intact or enhanced
- Information processing capacity is limited - integrative processing & higher order cognitive abilities are disproportionately impaired
- Inference: higher order brain circuitry is under developed - they are reliant on lower order circuitry particularly visual circuitry to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
Jim was admitted for possible mania. He was agitated and had been sending money to television evangelists and became preoccupied with sin and being good, which he talked about constantly. The psychiatrists attempted daily to PERSUADE him to try lithium but he refused. His reason was that he took lithium on June 4, 1978 and he got a stomachache. He went to the clinic and a scene ensued. Staff yelled at him. No amount of REASONING worked to change his mind, until he was told and SHOWN there were now two forms of lithium - one was pink and one was blue. He took the bad blue before, but this time he would take the good pink. He immediately agreed to the medication. The deterioration in his behavior was the result of losing his job for asking a woman a question about her clothing, which was interpreted as sexual harassment. All structure was gone from his life. Socially-emotionally he was three years old. He was not reciprocal in conversation. He talked, the doctors talked.
Bill is a young adult with autism who decided to take figure skating lessons. His mother drove to the rink several times a week. After a while, she decided to skate while he had his lesson. Bill performed his routine, but people learned to stay out of his way. He went where his program required him to go regardless of others. One day his mother forgot to note where Bill was and he ran her over, knocking her unconscious. The emergency team was called and she was given first aide and taken to the hospital. The next day she asked Bill why he did not come to her assistance, since he was an Eagle Scout with a first aide badge. He replied “It expired.”
# Effect of dual task on memory span and tracking performance

<table>
<thead>
<tr>
<th>People with autism (n = 16)</th>
<th>Digit recall</th>
<th>Tracking performance</th>
<th>Mu score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>single</td>
<td>dual</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>86.19</td>
<td>48.13</td>
<td>52.75</td>
</tr>
<tr>
<td>SD</td>
<td>7.55</td>
<td>16.77</td>
<td>10.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controls (n = 16)</th>
<th>Digit recall</th>
<th>Tracking performance</th>
<th>Mu score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>87.25</td>
<td>86.88</td>
<td>54.06</td>
</tr>
<tr>
<td>SD</td>
<td>4.81</td>
<td>7.58</td>
<td>14.61</td>
</tr>
</tbody>
</table>

Digit recall is expressed as a percentage of correct sequences.

Dual task performance deficit in autism;
*(but matched performance in single task conditions)*

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry
Cross-Sectional Study of Postural Control

- 5-47 years of age HFA, normal IQ; n=61, c=47
- Delayed onset of maturation of postural control
- Fail to achieve adult levels
- Due to impaired sensory integration - vestibular, visual, labyrinth; suggests under-connectivity
- Not cerebellar, not motor
The neuropsychologic profile and postural control findings define deficits considerably beyond the DSM triad, suggesting a more brain-wide though still selective disturbance in information processing and its neuronal architecture—fitting a disorder of neuronal organization.

Williams et al. 2006, 12: 279-298
Pathophysiologic Sequence of Neurodevelopmental Disorders

Abnormalities in Genetic Code for Brain Development
  ↓
Abnormal Mechanisms of Brain Development
  ↓
Structural and Functional Abnormalities of Brain
  ↓
Cognitive & Neurological Abnormalities
  ↓
Behavioral Syndrome
Abilities that adults take for granted that normally develop in infancy and toddlerhood:

For example:

- Our abilities to recognize faces and emotional expressions
- Our abilities to understand the difference between basic categories in the world—cats, dogs, lions …
Concept Formation Deficits: Search for More Fundamental Cognitive Mechanisms

- Motor concept learning
- Memory dependent on strategies
- Story creation or theme identification
- Face recognition
- Face affect recognition
- Strategy formation, problem solving
A Mechanism For Rapid Automatic Processing

- Non-conscious
- Not verbally mediated
- Flexible
Infants are born with automatic mechanisms that allow them to form Prototypical Representations of Information.
Which of these is the best example of a dog?
Which of the following two faces looks more familiar to you?
Correlation of ratings by Controls vs. Autistics: $r = -.06$
The way individuals with autism come to learn about both the world and people is different from individuals who do not have autism.

There are core differences in the way they learn categorical information and acquire “expertise”

Gasgeb, Strauss, & Minshew. Child Dev 2006; 77: 1717-1729
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.

Pathophysiologic Sequence of Neurodevelopmental Disorders

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome
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.
Pathophysiologic Sequence of Neurodevelopmental Disorders

Abnormalities in Genetic Code for Brain Development

↓

Abnormal Mechanisms of Brain Development

↓

Structural and Functional Abnormalities of Brain

↓

Cognitive & Neurological Abnormalities

↓

Behavioral Syndrome
What Are Infant Siblings Teaching Us About Autism in Infants?

Rogers, 2009
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
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
Repetitive behaviors: unusual visual regard and waving of arms and hands, 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-regulation distinguished infant sibs later 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
Developmental Characteristics of Infant Sibs: Overview Thus Far: Surprises

- 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
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.
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 linear model centered at 12 months).
What is happening in the brain in infant sibs?

How do neurologists analyze this presentation and this broad profile of impairments and enhanced abilities?
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
Disease Processes

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins
- Developmental processes
**TABLE 2-24  Organization**

<table>
<thead>
<tr>
<th>Peak Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 months’ gestation–years postnatal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Events</th>
</tr>
</thead>
<tbody>
<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 Composition Drawing of neurons in the visual (calcarine) cortex of human infants of indicated gestational ages.

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
How the Brain Develops

A  One month old
I
II
III
IV
V
VI

B  Six month old

C  24 month old


Minicolumnar pathology in autism
MF Casanova, MD; DP Buxhoeveden, PHD; AE Switala; & E Roy, PhD
Developmental Processes

- Organogenesis
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
Neuronal organization refers to the events in brain development that result in the abilities that are most unique to humans.

- Neuronal organizational events include the development of neuronal processes, dendritic arborizations, synaptogenesis, and the rich interconnections between neurons.
Pathophysiologic Sequence of Neurodevelopmental Disorders

Abnormalities in Genetic Code for Brain Development

↓

Abnormal Mechanisms of Brain Development

↓

Structural and Functional Abnormalities of Brain

↓

Cognitive & Neurological Abnormalities

↓

Behavioral Syndrome
Axonal Pathfinding & Targeting:
-- Cadherins
-- LRRs

Synaptic Targeting & Function:
-- Neurexins/Neuroligins

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
<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><strong>Promising</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>AH11</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><strong>Probable</strong></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>
</tr>
<tr>
<td>DHCRI</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>
<tr>
<td>Syndrome</td>
<td>Gene(s) associated with the syndrome</td>
<td>Proportion of patients with the syndrome that have an ASD</td>
<td>Proportion of patients with an ASD that have the syndrome</td>
<td>Refs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15q duplication — Angelman syndrome</td>
<td>UBE3A (and others)</td>
<td>&gt;40%</td>
<td>1–2%</td>
<td>101–103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTNAP2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potocki–Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith–Lemli–Optiz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
<td></td>
<td></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 (map position)</th>
<th>Relevant findings</th>
<th>Replication of results</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1A (12q14–12q15)</td>
<td>A positional candidate for ASD and important in rodent social behaviour. Interacts with OXTR. Association with affection status ($p = 0.004$) and a quantitative trait — Vineland Subscale Score ($p = 0.007$)</td>
<td>No replication</td>
<td>147</td>
</tr>
<tr>
<td>CNTNAP2 (7q35)</td>
<td>A positional candidate gene with observed mutations. mRNA distribution markedly different in human versus rodent species. Association with affection status ($p = 2 \times 10^{-3}$) and a quantitative trait — age at first word ($p = 0.05$)</td>
<td>Independent replication</td>
<td>37–41</td>
</tr>
<tr>
<td>DISC1 (1q42)</td>
<td>A key gene in psychiatric disorders and functionally linked to neuregulin signalling. Associated with ASD in a Finnish isolate by family-based association ($p = 0.0007$) and a case–control analysis ($p = 9 \times 10^{-9}$)</td>
<td>No replication</td>
<td>122</td>
</tr>
<tr>
<td>EN2 (7q36)</td>
<td>A positional candidate that is linked to cerebellar abnormalities in mutant mice. SNP and haplotype-based associations to affection in multiple cohorts ($p = 5 \times 10^{-5}$, 0.001 and 0.04)</td>
<td>Independent replication</td>
<td>129,130</td>
</tr>
<tr>
<td>GABRB3 (15q11–15q12)</td>
<td>A positional candidate: dysregulated in Rett syndrome. Angelman syndrome and autism brain[^23]. Association with autism in multiple cohorts ($p = 0.0014$ and 0.0011)</td>
<td>Independent replication</td>
<td>25,114, 115</td>
</tr>
<tr>
<td>GRIK2 (6q21)</td>
<td>A positional candidate that is linked to neuregulin signalling by PSD95. A rare homozygous mutation in an Iranian pedigree results in non-syndromic mental retardation. Association with autism in Caucasian ($p = 0.0002$) and Chinese populations ($p = 0.01$)</td>
<td>Independent replication</td>
<td>144,145</td>
</tr>
<tr>
<td>ITGB3 (17q21)</td>
<td>Positional candidate involved in regulation of serotonin. Evidence for functional interaction with SLC6A4. Association with whole-blood serotonin levels in multiple populations ($p = 0.01$ and 0.0055) and autism ($p = 0.00076$)</td>
<td>Serotonin QTL replicated</td>
<td>136,137</td>
</tr>
<tr>
<td>MET (7q31)</td>
<td>Positional candidate and reduced expression in brains of cases versus controls. Association between promoter variant and affection status in two large family-based cohorts ($p = 0.0005$ and 0.001) and a case–control analysis ($p = 0.001$). A function difference was observed between the two alleles of the associated variant</td>
<td>Internal replication</td>
<td>70,123</td>
</tr>
<tr>
<td>OXTR (3p25)</td>
<td>Important in rodent social behaviour, reduced in blood of cases versus controls and interacts with AVPR1A. Association with affection status ($p = 0.0094$ and $5 \times 10^{-3}$) and a quantitative trait — intelligence quotient ($p = 0.0002$)</td>
<td>Association with affection status has been replicated</td>
<td>127,128</td>
</tr>
<tr>
<td>RELN (7q22)</td>
<td>Positional candidate and identification of rare variants among cases. Expression levels are reduced in brains of cases versus controls. Association with affection status by case–control analyses ($p = 0.001$) and family-based analyses ($p = 0.001$ and 0.002)</td>
<td>Independent replication</td>
<td>117–121</td>
</tr>
<tr>
<td>SLC25A12 (2q24)</td>
<td>A positional candidate that is related to neurite outgrowth and is upregulated in the prefrontal cortex of autistic subjects. Association between affection status and both single SNPs ($p = 0.0094$ and 0.02) and haplotypes ($p = 5 \times 10^{-3}$ and 0.03)</td>
<td>Independent replication</td>
<td>124,126</td>
</tr>
<tr>
<td>SLC6A4 (17q11)</td>
<td>A positional candidate that is involved in the regulation of serotonin. Variation in SLC6A4 is linked to grey matter volume in the cortex. Evidence for functional interaction with ITGB3. Some clinical benefit is seen with SLC6A4 inhibitors. Association between promoter variant and both affection status ($p = 0.007$ and 0.007) and cortical grey matter volume ($p = 0.004$). Rare variants transmitted to cases at greater than expected frequency</td>
<td>Replicated, although complex and controversial</td>
<td>131–134</td>
</tr>
</tbody>
</table>
Websites

- CeFAR  www.pittautismresearch.org
- PA Dept. of Public Welfare:
  http://www.youtube.com/watch?v=uH3HWYOh-pk
- Autism Gateway:  www.autismgateway.com