Six New Things About Autism That Will Influence the Future

CARD Conference

January 12, 2013

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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.
No one likes change.
Panic & grumbling ensue.
Understanding changes views.
Why Do We Have To Give Up DSM-IV?

**Autistic Disorder: DSM-IV**

- 3 Core Symptoms
- Associated symptoms: sensory, motor
- Co-morbid Conditions: intellectual disability, ADHD, seizures, mood problems, long list of behavior issues (Pg. 71-72 TR version)

Not a clinically or biologically valid conceptualization and no longer functional; families and professionals are confused by it.
The DSM-IV Clinical Construct is Invalid

Lessons Learned From Infants At Risk for ASD
Began with: home video movies showed symptoms of autism long before diagnosis

Now, examine development carefully, from infancy, in infant sibs of children with ASD

20% will have an ASD (Ozonoff et al., 2011) and another 30% will have milder delays (Landa et al., 2007; Messinger et al., under review)

Key Q: What are the first behavioral characteristics predictive of autism?
Earliest Signs of ASD in Infant Sibs: Before 6 mos: Motor & Balance (Sensory)

- Head lag in pull-to-sit at 6 mos and delays in postural control notable by 3-4 months (Flanagan, Landa, Bauman, 2012; Bhat, Galloway, Landa, 2012)

- Deficits result in less mouthing of objects, less vocalizing, and less opportunity for learning object concepts

- Delays in the more global indices of fine and gross motor skills are also early
Sensory-related behaviors: under and over responsiveness by 12 months but not at 6 mos

Repetitive behaviors: unusual waving of arms and hands and unusual visual regard by 12 mos

Social emotional: no temperamental differences at 6 mos; over time, temperamentally more difficult with more intense distress and more time fixating on objects;

“Developmental rates decelerate markedly after 12 months with IQs dropping from average to below 50 for some children.”
At 24 months, poor emotion and behavioral self-regulation distinguished infant sibs later dx ASD

The above manifestations accompany- don’t predate “core” sx

“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.”

Sally Rogers, 2009
The Biologic Constructs Underlying DSM-IV Are Also Invalid

Common genes across neuropsychiatric disorders that have overlapping behavioral manifestations
Modified from Kooy 2010
Figure 2. Genes Disrupted by Chromosomal Abnormalities Confer Risk across Diagnostic Groups

All genes disrupted by a BCA and analyzed in the CNV analyses are shown. Although all genes are implicated in ASD or NDD by BCA disruption in this study, some loci also represented single-gene contributors to previously recognized genomic disorder (GD) regions (three microdeletion syndromes, two terminal deletion syndromes, and one duplication syndrome). There were also genes discovered in ASD or NDD in this study that had been previously linked to adolescent- or adult-onset neuropsychiatric disorders (NPD) by common variation association studies. The asterisk (*) denotes a gene not previously implicated in ASD or NDD (category 3). See also Table 1 and Table S2 for CNV and GWAS support for each locus.
Emotion Dysregulation in Bipolar Disorder, ASD, & Schizophrenia Linked to Dysfunction in Same Brain Circuitry

Suggests that common tools can be developed that target behavior regardless of diagnosis- has lead to dimensional focus in diagnosis and treatment.
AMY-ACC-DLPFC are core regions of neural network of identification and regulation of emotion

Role in mood/affect regulation:

- **Amygdala (AMY)**. Critical to sensing and assessing emotionally-salient stimuli.
- **Anterior cingulate cortex** (subgenual ACC; BA 25): integrates information about emotional salience (bottom-up) with cognitive control and motivational states (top-down).
- **Dorsolateral prefrontal cortex**: cognitive assessment of emotional salience (cortical top-down regulation)

*Phillips et al, Mol Psy, 2008*
Thong 2. DSM-5: A Monumental Effort

Started 2005
World-wide work of many
A $20 Million investment by APA
DSM is, above all, a manual to be used by clinicians, and changes made for DSM-5 must be implementable in routine specialty practices.

Make revisions that will lead to better clinical diagnostic practice.

Revisions should be guided by research evidence.
Revisions are designed to lead to:

- Earlier diagnosis
- Earlier treatment
- More accurate treatment
- Prevention of later complications
12 DSM-5 Work Groups

- ADHD & Disruptive Behavior Disorders
- Anxiety, Obsessive-Compulsive Spectrum, Post-traumatic, and Dissociative Disorders
- Disorders in Childhood and Adolescence
- Eating Disorders Mood Disorders
- Neurocognitive Disorders
- Neurodevelopmental Disorders
DSM-5 Work Groups, Cont’d

- Personality and Personality Disorders
- Psychotic Disorders
- Sexual and Gender-Identity Disorders
- Sleep-Wake Disorders
- Somatic Distress Disorders
- Substance-Related Disorders
6 Cross-Cutting Study Groups

- Diagnostic Spectra Study Group
- Life Span Developmental Approach Study Group
- Gender and Cross-Cultural Study Group
- Psychiatric/General Medical Interface Study Group
- Impairment Assessment and Instruments Study Group
- Diagnostic Assessment Instruments Study Group
Country Representation of Approved Nominees

- United States, 123
- Europe, 22
  - Denmark, 1
  - France, 1
  - Germany, 3
  - Italy, 1
  - Netherlands, 6
  - Sweden, 1
  - Switzerland, 1
  - UK, 8
- South Africa, 1
- Latin America, 3
- Western Pacific, 4
- Canada, 8

Race and Ethnicity of Approved Nominees

- White (non-Hispanic), 131
- Hispanic, 12
- African American, 7
- Asian, 10
- Native American, 1

Gender Representation of Approved Nominees

- Male, 112
- Female, 49
Revised DSM Chapter Structure:

Put Disorders That Have Common Biology and Genes Together To Inform Clinicians of Related Disorders and Key Differential Diagnoses
DSM-5: Criteria that reflect syndrome breadth & heterogeneity

- Add developmental dimension - life span view of disorders
- Add measurements of distress, disability, and severity
- “Living document”
Proposed Major Revisions to Criteria Format:

♦ DSM-5 could benefit from offering explicit criteria for both categories and dimensions (not or)

♦ For any psychiatric disorder, a number of aspects could be conceptualized and assessed dimensionally

♦ Behavioral dimensions can capture co-occurring disorders & sub-threshold symptoms

Future DSM-5 Developments

DSM-5 will go electronic:

- **adding links** to key supporting documents/evidence/descriptions and
- **electronic communications** between patients and clinicians
Based on growing understanding of underlying mechanisms at all levels between gene and behavior
The Multiple Meanings of Cause-
The Multiple Levels of Mechanisms

Etiology
Pathophysiology
Cause of a Current behavior- Functional analysis
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.

Abnormalities in Genetic Code for Brain Development

⇒

Abnormal Mechanisms of Brain Development

⇒

Structural and Functional Abnormalities of Brain

⇒

Cognitive, Affective & Neurological Abnormalities

⇒

Behavioral Syndrome
Aspects of Brain Development

- Organogenesis
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
Thing 3. Genetic Discoveries in ASD

Reflect the growth in technology
Which is now exponential
Exciting times for genetics of Autism Spectrum Disorders

Adapted from Betancur (2011, Brain Res. 1380:42-77)
Copy Number Variations (CNVs)
The Awakening to Small DNA Alterations

Small (micro-) deletions or duplications of DNA distributed involving all chromosomes, inherited or spontaneous, occurring constantly.
Another New Genetic Mechanism Discovered

Fragmentation of chromosomes during replication and scrambled recombination of pieces - a new cause of microscopic duplications and deletions. Many more gene alterations linked to ASD.
Making Sense of Lots of Genes in ASD

Determining the functional relationships among genes. If it looks complex, it is and so is ASD and the path ahead.
Figure 5. Network Analysis of Genes Implicated in Autism or Neurodevelopment in This Study

A large network of genes disrupted by BCAs in this study are connected by first-, second-, or higher-order interactions. No networks were significantly enriched for genes disrupted by BCAs after correction for multiple comparisons, though a number of loci have limited functional annotation available or remain of unknown function. See also Figure S4.
Conclusions

- Understand much about the genetic architecture of autism; will understand much more very soon.
- More genes and more potential drug targets
- Momentum for discovery is huge and due to
  — Pooling data
  — Funding
- 5 years from now gene discovery in ASD will become passé: translation will be the key for ASD in the near future!
What will come of genetic discoveries?

Diagnosis at a genetic level

Biologic (brain) treatments resulting from identification of altered signaling pathways
Infant DNA Tests Speed Diagnosis of Rare Diseases

By GINA KOLATA

From the day she was born, the girl had seizure after seizure. Doctors at Children’s Mercy Hospital in Kansas City, Mo., frantically tried to keep her alive. Weeks passed and every medication failed. Finally, her family decided to let their baby go, and the medical devices were withdrawn. She was 5 weeks old.

Her doctors suspected a genetic disorder, and as it happened the hospital had just begun a study of a new technique for quickly analyzing the DNA of newborns, zeroing in on mutations that can cause disease.

This new method, published on Wednesday in the magazine Science Translational Medicine, is a proof of concept — a demonstration in four babies that it is possible to quickly scan a baby’s entire DNA and pinpoint a disease-causing mutation in a couple of days instead of the more typical weeks or months. The study’s investigators said the test could be one of the first practical fruits of the revolution in sequencing an individual’s entire DNA.

For the baby with seizures, her doctors provided a sample of her blood. The analysis took only 50 hours and provided an answer. The baby had a mortal gene mutation so rare that it had been reported just once before.
ORIGINAL ARTICLE

Predicting the diagnosis of autism spectrum disorder using gene pathway analysis

E Skafidas¹, R Testa²,³, D Zantomio⁴, G Chana⁵, IP Everall⁵ and C Pantelis²,⁵
Autism spectrum disorder (ASD) depends on a clinical interview with no biomarkers to aid diagnosis. The current investigation interrogated single-nucleotide polymorphisms (SNPs) of individuals with ASD from the Autism Genetic Resource Exchange (AGRE) database. SNPs were mapped to Kyoto Encyclopedia of Genes and Genomes (KEGG)-derived pathways to identify affected cellular processes and develop a diagnostic test. This test was then applied to two independent samples from the Simons Foundation Autism Research Initiative (SFARI) and Wellcome Trust 1958 normal birth cohort (WTBC) for validation. Using AGRE SNP data from a Central European (CEU) cohort, we created a genetic diagnostic classifier consisting of 237 SNPs in 146 genes that correctly predicted ASD diagnosis in 85.6% of CEU cases. This classifier also predicted 84.3% of cases in an ethnically related Tuscan cohort; however, prediction was less accurate (56.4%) in a genetically dissimilar Han Chinese cohort (HAN). Eight SNPs in three genes (KCNMB4, GNAO1, GRM5) had the largest effect in the classifier with some acting as vulnerability SNPs, whereas others were protective. Prediction accuracy diminished as the number of SNPs analyzed in the model was decreased. Our diagnostic classifier correctly predicted ASD diagnosis with an accuracy of 71.7% in CEU individuals from the SFARI (ASD) and WTBC (controls) validation data sets. In conclusion, we have developed an accurate diagnostic test for a genetically homogeneous group to aid in early detection of ASD. While SNPs differ across ethnic groups, our pathway approach identified cellular processes common to ASD across ethnicities. Our results have wide implications for detection, intervention and prevention of ASD.
Thing 4. Gene Expression: Molecular Signaling Pathways in the Brain

Door to Biologic Treatments for ASD
Figure 3 | A functional map of ASD. Enrichment results were mapped as a network of gene sets (nodes) related by mutual overlap (edges), where the colour (red, blue or yellow) indicates the class of gene set. Node size is proportional to the total number of genes in each set and edge thickness represents the number of overlapping genes between sets. a, Gene sets enriched for deletions are shown (red) with enrichment significance (FDR q-value) represented as a node colour gradient. Groups of functionally related gene sets are circled and labelled (groups, filled green circles; subgroups, dashed line). b, An expanded enrichment map shows the relationship between gene sets enriched in deletions (a) and sets of known ASD/intellectual disability genes. Node colour hue represents the class of gene set (that is, enriched in deletions, red; known disease genes (ASD and/or intellectual disability (ID) genes), blue; enriched only in disease genes, yellow). Edge colour represents the overlap between gene sets enriched in deletions (green), from disease genes to enriched sets (blue), and between sets enriched in deletions and in disease genes or between disease gene sets only (orange). The major functional groups are highlighted by filled circles (enriched in deletions, green; enriched in ASD/intellectual disability, blue).
Thing 5. ASD Genes Also Lead to Identification of Altered Developmental Neurobiologic Mechanisms
Components of Brain Development

- Organogenesis
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
Clinical Clues to Altered Brain Developmental Mechanisms
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).
Most Likely Disrupted Brain Development Mechanisms in ASD

Neuronal Organizational Events

Synapse formation/maintenance
Axonal outgrowth/pathfinding
Development of cortical organization
Is autism a synapse-opathy?
Some early and recent identified genes converge on synapse

- **TSC1/TSC2** (Gillberg et al., 1994, Fombonne et al. 1997)
- **PTEN** (Goffin et al., 2001, Butler et al. 2005)
- **FMR1** (Kielinen et al., 2004, Clifford et al. 2007)
- **NLGN4/NLGN3** (Jamain et al 2003; Thomas et al 1999)
- **CNTN4** (Fernandez et al 2004 and 2008; Roohi et al 2009, Wang et al 2009)
- **SHANK3/SHANK2** (Durand et al 2007; Berkel et al 2010, Pinto 2010)
- **NRXN1** (Szatmari et al. 2007; Kim et al 2008)

Cartoon of
Excitatory synapse

State, *Neuron* 2010
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).
Axonal Model

• Preliminary reading of AGP GWAS analyses showed CNVs and association of SNP alleles with autism that are proximate to genes of interest more than would be expected by chance in:
  – synaptic CAMS
  – Leucine rich repeat (LRR) protein genes
  – various mediators of axonal microtubule stabilization

• These are all known to mediate axonal outgrowth, stability, and targeting.

**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
3-8% of Extreme Premies (26-28 weeks) Develop Cerebral Palsy and ASD

Neuronal Proliferation & Migration
Neurons born next to ventricles are damaged when migrating to cortex
By a germinal matric hemorrhage.
Documented by post mortem studies
And we can measure these differences in ever more elegant detail. Can then target for treatment & monitor responses.
“Biology gives you a brain. Life turns it into a mind.” Jeffrey Eugenides

Scientists have discovered that the brain is even more beautifully organized than they had imagined.

Neurons in the brain zip messages to one another along long white fibers called axons. Previously, scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called “diffusion tensor MRI” that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid.

BY LAURA HELMUTH
Neurons in the brain zip messages to one another along long white fibers called axons. Previously scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called “diffusion tensor MRI” that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid. For instance, the red axons in the image converge on the purple pathway at a 90-degree angle. Axons are interwoven like “the warp and weft of a fabric,” the researchers say, with the pattern bent along the brain’s convolutions. “It’s really pretty, all the little loops and folds,” Wedeen says.
The technique Wedeen and colleagues use is called "diffusion spectrum MRI," a variation on an existing technique. By monitoring how water moves along axons and at what angle these brain fibers cross one another, the researchers found a surprisingly geometric pattern. The three-dimensional grid is visible in this detail from a rhesus monkey brain.
This image from a rhesus monkey shows the larger-scale structure of the grid of axons as they swoop and swirl through the convolutions of the primate's brain.
Images used from:

- **Animal Brains, More Beautiful Than You Could Ever Imagine**
- More than just eye candy, these images are teaching scientists new insights into how the brain is organized
- By Laura Helmuth
- *Smithsonian* magazine, July-August 2012

Disruption of Connectivity within Neural Systems

Neuronal Level

Structural Connections

Functional Connections

Inducing Plasticity