"Current Scientists’ Perspectives of Autism”

Medical Genetics
Children’s Hospital of Pittsburgh

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Nancy Minshew, MD
Director, NIH Autism Center of Excellence
University of Pittsburgh
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”
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.

Medical Associations

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

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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”
The Top 10 of 2007

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Structural Variation of Chromosomes in Autism Spectrum Disorder


Structural variation (copy number variation [CNV] including deletion and duplication, translocation, inversion) of chromosomes has been identified in some individuals with autism spectrum disorder (ASD), but the full etiologic role is unknown. We performed genome-wide assessment for structural abnormalities in 427 unrelated ASD cases via single-nucleotide polymorphism microarrays and karyotyping. With microarrays, we discovered 277 unbalanced CNVs in 44% of ASD families not present in 500 controls (and re-examined in another 1152 controls). Karyotyping detected additional balanced changes. Although most variants were inherited, we found a total of 27 cases with de novo alterations, and in three (11%) of these individuals, two or more new variants were observed. De novo CNVs were found in ~7% and ~2% of idiopathic families having one child, or two or more ASD siblings, respectively. We also detected 13 loci with recurrent/overlapping CNV in unrelated cases, and at these sites, deletions and duplications affecting the same gene(s) in different individuals and sometimes in asymptomatic carriers were also found. Notwithstanding complexities, our results further implicate the SHANK3-NLGN4-NRXN1 postsynaptic density genes and also identify novel loci at DPP6-DPP10-PCDH19 (synapse complex), ANKR1D1, DPYD, PTCHD1, 15q24, among others, for a role in ASD susceptibility. Our most compelling result discovered CNV at 16p11.2 (p = 0.002) (with characteristics of a genomic disorder) at ~1% frequency. Some of the ASD regions were also common to mental retardation loci. Structural variants were found in sufficiently high frequency influencing ASD to suggest that cytogenetic and microarray analyses be considered in routine clinical workup.

Introduction

Autism (MIM 209850) is a neurodevelopmental disorder that manifests in the first three years of life. The group of pervasive developmental disorders (PDDs), also termed autism spectrum disorders (ASDs), includes autism as well as PDD-not otherwise specified (PDD-NOS) and Asperger's disorder. The three core characteristics of the ASDs are impairments of reciprocal social interactions, problems in common with fragile X (MIM 300624) and Rett syndrome (MIM 312750), tuberous sclerosis (MIM 191100), and other medical genetic conditions. Heritability estimates for ASDs, as determined from twin and family studies, are ~90%, and linkage scans have mapped candidate risk loci. Based on a recent systematic review, cytogenetically detectable chromosome abnormalities are found in 7.4% (129/1749) of ASD cases with a range from 0% to 54%. The highest occurrence of events is observed in syndromic
1. Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice
3. Autism Genome Project (AGP): largest genetics consortium, launched in 2004, largest study ever conducted to find the genes associated with risk of developing autism. 50 academic and research institutions from 19 countries, pooled resources and used DNA microarray to scan the human genome for genetic causes of autism; first analyses made public in 2007. Nature Genetics 2007. Chromo 2, 7, and 11 plus linkage signals only present in girls, identification of a specific candidate gene neurexin, associated with copy number variation
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.

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The Top 10 of 2007 (cont’d)

4. First drug approved by FDA to treat symptoms associated w/ autism; Risperdal

5. PTEN conditional knock out mice display enlarged brains and social behavioral deficits: PTEN interacts with several proteins in a signaling cascade that are tied to tuberous sclerosis and neurofibromatosis. 17% of individuals with autism & macrocephaly had PTEN gene. KO mice raises rescue possibilities.
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The Top 10 of 2007 (cont’d)

6. Mouse models of genes associated with autism in humans: neuroligin-3 gene mouse model: mouse has deficits in social behaviors and an increased ability for spatial learning.

7. Functional connectivity: neural deficits not in a single structure but in wiring that networks that connect different parts of brain.
The Top 10 of 2007 (cont’d)

8. Discovery of rare families with SHANK3 gene mutations added further evidence to synaptic dysfunction hypothesis. Codes for synapse formation & maintenance. It also interacts with neuroligins and neurolexins.

9. Lack of response to name at one year is one of earliest signs of autism; signs of autism can be identified at 14 mos in half of cases.

10. Parental age (paternal or maternal or both) is related to but not necessarily the cause of increased risk of autism.
A genetic variant that disrupts MET transcription is associated with autism


Departments of *Pediatrics and Medical Anatomy and Physiology and **Behavioral Genetics, Centre for Research on Human Development, and **Behavioral Genetics, Centre for Research on Human Development, University of Miami, Miami, FL, USA. *Institute of Biomedical Sciences, University of Miami, Miami, FL, USA. **Institute of Biomedical Sciences, University of Miami, Miami, FL, USA. ***Institute of Biomedical Sciences, University of Miami, Miami, FL, USA. ****Institute of Biomedical Sciences, University of Miami, Miami, FL, USA.

There is strong evidence for a genetic predisposition to autism and an intense interest in understanding the role of genetic factors in the development of autism spectrum disorder (ASD). The role of genetic variants in the regulation of the MET receptor tyrosine kinase (MET), a member of the epidermal growth factor receptor family, has been suggested as a potential candidate for autism susceptibility. In the present study, we used a transgenic mouse model to investigate the role of MET in the development of behavior and cognition relevant to autism spectrum disorder. We found that MET expression was decreased in the cortex, hippocampus, and striatum of transgenic animals compared to wild-type controls. These results support the hypothesis that MET dysregulation may contribute to the development of behavior and cognitive abnormalities seen in autism spectrum disorder. The findings also highlight the potential utility of targeting MET in the treatment of autism spectrum disorder.
Transforming Findings

1. Autism as a disorder of complex information processing
2. Autism as a disorder of connectivity
3. Autism as a disorder of dysregulated growth of the cerebral hemispheres-gray and white matter but not cc
4. CNV in simplex; synapse-related genes in simplex & multiplex families
Conclusions

1. HGF promotes a generalized increase in growth and branching in both basal and apical dendrites in layer 2 pyramidal cortical neurons.
2. Acts through MET receptor expressed by these neurons.
3. Both expressed in cortical plate by E14:
   - HGF layers 4 and 5
   - MET layers 2, 3, 4, and 5
Conclusions

1. Genes involved in autism vulnerability are likely to be involved in multiple biologic processes both within and outside of the CNS.

2. Neuropathologic abnormalities observed in autistic individuals are consistent with many of the processes involving MET/HGF.
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 stability in replication of DNA.

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Pathophysiologic sequence of a neurodevelopmental disorder

- Abnormalities in Genetic Code for Brain Development
  - Abnormal Mechanisms of Brain Development
    - Structural and Functional Abnormalities of Brain
      - Cognitive & Neurologic Abnormalities
        - Behavioral Syndrome
Official Category in DSM-IV: Pervasive Developmental Disorder

- Autistic Disorder
- Asperger’s Disorder
- Pervasive Developmental Disorder Not Otherwise Specified
- Childhood Disintegrative Disorder (onset: 4-12 yr)
- Rett’s Disorder
Informal Category Not in DSM-IV: 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, and adaptive abilities and problem behaviors instead.
Recognizing ASD in Able More Individuals

- Strange or odd: reflects social impairment
- Monotone voice: usually too loud
- Little to no facial expression
- 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
Recognizing ASD in Those More Affected

- **Intermediate severity:** echolalic, few scripted stereotyped sentences; socially isolated; self-stimulatory behavior; difficulty with change; sensory issues
- **Most severe:** no language, no comprehension, no prosody, 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
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.
Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit.

Multi-organ involvement is the rule in non-acquired neurologic disorders- because affected genes are in every cell in the body.
Neurologists’ approach to investigating brain dysfunction is to characterize all impaired abilities AND all intact abilities to define common principles or characteristics of the underlying disease process.
Identifying the Cognitive & Neurologic Basis of Autism: Beginning with the Right Questions
# The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

<table>
<thead>
<tr>
<th>Intact or Enhanced</th>
<th>Cognitive Weaknesses</th>
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<td>Attention</td>
<td>Complex Sensory</td>
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<td>Sensory Perception</td>
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<td>Elementary Motor</td>
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<td>Formal Language</td>
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<td>Face Recognition</td>
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<td>Visuospatial processing</td>
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What Does The Profile Mean About Neurologic Function & Neural Circuitry?

- Simpler processing & abilities are intact/enhanced
- Information processing capacity is limited-integrative processing & higher order cognitive abilities are disproportionately impacted

Inference: higher order circuitry is under developed-they are reliant on lower order circuitry & basic cognitive abilities to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
Brain activation during sentence comprehension in autism In Brain, 2004

Autism group has less activation in **Broca’s area**
• (a sentence integration area)
than the control group and more in **Wernicke’s area**
• (a word processing area)
Results are consistent with poorer comprehension of complex sentences, coupled with good word reading (spelling bee champs)
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Functional Connectivity
The activation in two cortical areas can be less synchronized (upper panel) or more synchronized (lower panel) for different people.
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

ROI pairs


Functional connectivity (z)
Cognitively the problem is with prototype formation and *automatic processes* as opposed to conscious, verbally mediated reasoning.
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 …
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?
Gender Categorization
5- to 7-Year-Old Children

Strauss, M.S. et al., Child Development (under revision)

* p < .05
Gender Categorization
13- to 17- Year Old Teenagers

Typical Hair  Typical Cap  Atypical Hair  Atypical Cap

Control  Autism

* p < .05
What are the brain systems involved in representing the actions and intentions of other people?

Pelphrey et al. (2003) *Journal of Neuroscience*

Carter & Pelphrey (2007) *Social Neuroscience*
Incongruent > Congruent

Neurotypical

Autism

All Eye Movements

Incongruent > Congruent

Pelphrey et al. (2005) Brain
Pelphrey et al. (2002); *Journal of Autism and Developmental Disorders*