MILESTONES IN AUTISM RESEARCH: CLUES TO THE FUTURE OF TREATMENT

Autism Europe 2013
Budapest, Hungary

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Transformative Advances: Science Advancing *Treatment & Services*

- All manifestations as a single syndrome
- Multiple cortical systems basis links clinical syndrome to genetics and neurobiology
- Hundreds of genes reduced to a small number of molecular signaling pathways
- Signaling pathways lead to biologic treatments
- Environmental associations are antenatal
- Biggest “E” effect is intervention.
- Shared gene and neural basis across psychiatric disorders suggests that system based treatments will cross diagnostic boundaries
Clinical Manifestations: Chance Association, Artifact or Shared Biology?

3 Core Symptoms
Associated symptoms: sensory, motor
Co-morbid Conditions: intellectual disability, ADHD, seizures, mood problems, long list of behavior issues

Typically resulted in many diagnoses per patient. In a syndrome, the constellation is explained by the cause, which is at the neurobiologic level.
Infant Sib Studies: Multiple Systems Affected Simultaneously

• “Associated symptoms” like motor and sensory & “co-morbid disorders” such as hyperactivity, mood lability, intellectual disability, poor motor development emerge together with “core” symptoms in 2nd year.

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

Rogers et al, 2009
“Decades of research have clearly implicated genes that regulate how brain cells and networks develop and interconnect.”

Neuronal organization refers to development of complex circuitry underlying the higher order abilities that are most uniquely human. Multiple _cortical_ systems disorder is a match.
Connecting Genes To Brain Development to Neural Systems To Treatments

• Organogenesis
• Neuronal proliferation?
• Neuronal migration*
• Neuronal organization**
• Glial proliferation?
• Myelination

* Implicated in ASD

**Dendrite Morphology/Function**
- SHANK3/SHANK2
- Reelin
- DLGAP2

**Synaptic CAMs**
- Neurexins/Neuroligins
- Cadherings
- CNTN4
- CNTNAP2
- SYNGAP1
Changes in prefrontal axons may disrupt the network in autism.

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Abstract

Neural communication is disrupted in autism by unknown mechanisms. Here, we examined whether in autism there are changes in axons, which are the conduit for neural communication. We investigated single axons and their ultrastructure in the white matter of postmortem human brain tissue below the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and lateral prefrontal cortex (LPFC), which are associated with attention, social interactions, and emotions, and have been consistently implicated in the pathology of autism. Area-specific changes below ACC (area 32) included a decrease in the largest axons that communicate over long distances. In addition, below ACC there was overexpression of the growth-associated protein 43 kDa accompanied by excessive number of thin axons that link neighboring areas. In OFC (area 11), axons had decreased myelin thickness. Axon features below LPFC (area 46) appeared to be unaffected, but the altered white matter composition below ACC and OFC changed the relationships among all prefrontal areas examined, and could indirectly affect LPFC function. These findings provide a mechanism for disconnection of long-distance pathways, excessive connections between neighboring areas, and inefficiency in pathways for emotions, and may help explain why individuals with autism do not adequately shift attention, engage in repetitive behavior, and avoid social interactions. These changes below specific prefrontal areas appear to be linked through a cascade of developmental events affecting axon growth and guidance, and suggest targeting the associated signaling pathways for therapeutic interventions in autism.
Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting.

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Abstract

There is increasing evidence that autism spectrum disorders (ASDs) can arise from rare highly penetrant mutations and genomic imbalances. The rare nature of these variants, and the often differing orbits of clinical and research geneticists, can make it difficult to fully appreciate the extent to which we have made progress in understanding the genetic etiology of autism. In fact, there is a persistent view in the autism research community that there are only a modest number of autism loci known. We carried out an exhaustive review of the clinical genetics and research genetics literature in an attempt to collate all genes and recurrent genomic imbalances that have been implicated in the etiology of ASD. We provide data on 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behavior. These genes and loci have all been causally implicated in intellectual disability, indicating that these two neurodevelopmental disorders share common genetic bases. A genetic overlap between ASD and epilepsy is also apparent in many cases. Taken together, these findings clearly show that autism is not a single clinical entity but a behavioral manifestation of tens or perhaps hundreds of genetic and genomic disorders. Increased recognition of the etiological heterogeneity of ASD will greatly expand the number of target genes for neurobiological investigations and thereby provide additional avenues for the development of pathway-based pharmacotherapy. Finally, the data provide strong support for high-resolution DNA microarrays as well as whole-exome and whole-genome sequencing as critical approaches for identifying the genetic causes of ASDs.
Behavioral Profiles of Mouse Models for Autism Spectrum Disorders

Elodie Ey, Claire S. Leblond, and Thomas Bourgeron

Autism spectrum disorders (ASD) are characterized by impairments in reciprocal social communication, and stereotyped verbal and nonverbal behaviors. In approximately 10–25% of the affected individuals, a genetic mutation associated with the condition can be identified. Recently, mutations altering synapse formation, cellular/synaptic growth rate and regulation of excitatory and inhibitory currents were identified in patients with intellectual disability, typical autism, Asperger syndrome or neurological syndromes associated with autistic traits. Following these genetic findings, mouse models carrying mutations similar to those identified in patients have been generated. These models offer the opportunity to investigate in vivo the physiological and behavioral consequences of the mutations. Here, we review the existing data on the phenotypes of mice carrying mutations in genes associated with ASD including neuroligin, neurexin and Shank mutant mice as well as the Fmr1, Mecp2, Ube3a, Nf1, Pten and Tsc1/Tsc2 mutant mice. The diversity and complexity of the phenotype of these mouse models reflect the broad range of phenotypes observed in patients with ASD. Remarkably, results from therapeutic approaches (e.g., modulation of gene expression, administration of pharmacological and nonpharmacological substances, enriched environment) are encouraging since some behavioral alterations could be reversed even when treatment was performed on adult mice. These ongoing studies should therefore increase our understanding of the biological alterations associated with ASD as well as the development of knowledge-based treatments.
Modifying Behavioral Phenotypes in *Fmr1*KO Mice: Genetic Background Differences Reveal Autistic-Like Responses


Fragile X syndrome (FXS) is the most common inherited form of intellectual disability in humans. In addition to cognitive impairment, patients may exhibit hyperactivity, attention deficits, social difficulties and anxiety, and autistic-like behaviors. The degree to which patients display these behaviors varies considerably and is influenced by family history, suggesting that genetic modifiers play a role in the expression of behaviors in FXS. Several studies have examined behavior in a mouse model of FXS in which the *Fmr1* gene has been ablated. Most of those studies were done in *Fmr1* knockout mice on a pure C57BL/6 or FVB strain background. To gain a better understanding of the effects of genetic background on behaviors resulting from the loss of *Fmr1* gene expression, we generated F1 hybrid lines from female *Fmr1* heterozygous mice on a pure C57BL/6J background bred with male *Fmr1* wild-type (WT) mice of various background strains (A/J, DBA/2J, FVB/NJ, 129S1/SvImJ and CD-1). Male *Fmr1* knockout and WT littermates from each line were examined in an extensive behavioral test battery. Results clearly indicate that multiple behavioral responses are dependent on genetic background, including autistic-like traits that are present on limited genetic backgrounds. This approach has allowed us to identify improved models for different behavioral symptoms present in FXS including autistic-like traits.
Genes Lead to Cellular Signaling Pathways That Lead to New Biologic Treatments Critical to Treatment of Severe Cases

• Clinically, there are **two worlds of autism.** One world is that of the less severe cases for whom various neurocognitive rehabilitation strategies are changing outcome. The second world is that of the severe cases where treatments are not working.
Mammalian target of rapamycin (mTOR) inhibition: potential for antiseizure, antiepileptogenic, and epileptostatic therapy.

Ryther RC, Wong M.

New epilepsy treatments are needed that not only inhibit seizures symptomatically (antiseizure) but also prevent the development of epilepsy (antiepileptogenic). The mammalian target of rapamycin (mTOR) pathway may mediate mechanisms of epileptogenesis and serve as a rational therapeutic target. mTOR inhibitors have antiepileptogenic and antiseizure effects in animal models of the genetic disease, tuberous sclerosis complex. The mTOR pathway is also implicated in epileptogenesis in animal models of acquired epilepsy and infantile spasms, although the effects of mTOR inhibitors are variable depending on the specific conditions and model. Furthermore, beneficial effects on seizures are lost when treatment is withdrawn, suggesting that mTOR inhibitors are "epileptostatic" in only stalling epilepsy progression during treatment. Clinical studies of rapamycin in human epilepsy are limited, but suggest that mTOR inhibitors at least have antiseizure effects in tuberous sclerosis patients. Further studies are needed to assess the full potential of mTOR inhibitors for epilepsy treatment.
Autistic-like social behaviour in Shank2-mutant mice improved by restoring NMDA receptor function.


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Abstract
Autism spectrum disorder (ASD) is a group of conditions characterized by impaired social interaction and communication, and restricted and repetitive behaviours. ASD is a highly heritable disorder involving various genetic determinants. Shank2 (also known as ProSAP1) is a multi-domain scaffolding protein and signalling adaptor enriched at excitatory neuronal synapses, and mutations in the human SHANK2 gene have recently been associated with ASD and intellectual disability. Although ASD-associated genes are being increasingly identified and studied using various approaches, including mouse genetics, further efforts are required to delineate important causal mechanisms with the potential for therapeutic application. Here we show that Shank2-mutant (Shank2(-/-)) mice carrying a mutation identical to the ASD-associated microdeletion in the human SHANK2 gene exhibit ASD-like behaviours including reduced social interaction, reduced social communication by ultrasonic vocalizations, and repetitive jumping. These mice show a marked decrease in NMDA (N-methyl-D-aspartate) glutamate receptor (NMDAR) function. Direct stimulation of NMDARs with D-cycloserine, a partial agonist of NMDARs, normalizes NMDAR function and improves social interaction in Shank2(-/-) mice. Furthermore, treatment of Shank2(-/-) mice with a positive allosteric modulator of metabotropic glutamate receptor 5 (mGluR5), which enhances NMDAR function via mGluR5 activation, also normalizes NMDAR function and markedly enhances social interaction. These results suggest that reduced NMDAR function may contribute to the development of ASD-like phenotypes in Shank2(-/-) mice, and mGluR modulation of NMDARs offers a potential strategy to treat ASD.
Most psychiatric disorders are moderately to highly heritable. The degree to which genetic variation is unique to individual disorders or shared across disorders is unclear. To examine shared genetic etiology, we use genome-wide genotype data from the Psychiatric Genomics Consortium (PGC) for cases and controls in schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD). We apply univariate and bivariate methods for the estimation of genetic variation within and covariation between disorders. SNPs explained 17-29% of the variance in liability. The genetic correlation calculated using common SNPs was high between schizophrenia and bipolar disorder (0.68 ± 0.04 s.e.), moderate between schizophrenia and major depressive disorder (0.43 ± 0.06 s.e.), bipolar disorder and major depressive disorder (0.47 ± 0.06 s.e.), and ADHD and major depressive disorder (0.32 ± 0.07 s.e.), low between schizophrenia and ASD (0.16 ± 0.06 s.e.) and non-significant for other pairs of disorders as well as between psychiatric disorders and the negative control of Crohn's disease. This empirical evidence of shared genetic etiology for psychiatric disorders can inform nosology and encourages the investigation of common pathophysiologicals for related disorders.
Environmental Effects in Causation Are Intra-uterine: Seeing the Power of Science to Change Outcomes

- Toxicologic studies of traffic & pesticides report associations with exposures during pregnancy and early postnatal period (Volk et al, 2013)
- Scott et al. 2013 conclude that environmental effects in ASD are antenatal (Scott et al, 2013)
- These findings have cleared the way to consider brain plasticity and the power of postnatal treatments to change courses
The Biggest “E” Effect in ASD is Behavioral and Cognitive Interventions

• Lots of evidence that human environmental influences of parents and school programs are strong and positive
• These treatments change the brain
• Think about “E” effects in a new way
• Think about neuroplasticity across the life span
Is He Being Bad? Social and Language Brain Networks during Social Judgment in Children with Autism

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Abstract

Individuals with autism often violate social rules and have lower accuracy in identifying and explaining inappropriate social behavior. Twelve children with autism (AD) and thirteen children with typical development (TD) participated in this fMRI study of the neurofunctional basis of social judgment. Participants indicated in which of two pictures a boy was being bad (Social condition) or which of two pictures was outdoors (Physical condition). In the within-group Social–Physical comparison, TD children used components of mentalizing and language networks (bilateral inferior frontal gyrus (IFG), bilateral medial prefrontal cortex (mPFC), and bilateral posterior superior temporal sulcus (pSTS)), whereas AD children used a network that was primarily right IFG and bilateral pSTS, suggesting reduced use of social and language networks during this social judgment task. A direct group comparison on the Social–Physical contrast showed that the TD group had greater mPFC, bilateral IFG, and left superior temporal pole activity than the AD group. No regions were more active in the AD group than in the group with TD in this comparison. Both groups successfully performed the task, which required minimal language. The groups also performed similarly on eyetracking measures, indicating that the activation results probably reflect the use of a more basic strategy by the autism group rather than performance disparities. Even though language was unnecessary, the children with TD recruited language areas during the social task, suggesting automatic encoding of their knowledge into language; however, this was not the case for the children with autism. These findings support behavioral research indicating that, whereas children with autism may recognize socially inappropriate behavior, they have difficulty using spoken language to explain why it is inappropriate. The fMRI results indicate that AD children may not automatically use language to encode their social understanding, making expression and generalization of this knowledge more difficult.
Going Forward

• Finding a neural systems based definition of symptoms & developing systems-based Rx
• Anticipation that neurocognitive and biologic treatments for ASD will also be applicable to disorders with overlapping symptoms
• More consideration of how to think about situations in order to see changes in behavior and more success AND more consideration about how to develop automatic processing skills