

2011 and 2012 publications related to “Question 2” of the IACC strategic plan

This is a collection of articles on topics relevant to updating Question 2 of the IACC strategic plan. It is a starting point for collecting references and updating the text for Question 2. This list is nowhere near exhaustive, and is not ranked in any way. For the strategic plan update, only advances published in 2011 and 2012 should be included. Note that Question 3, which covers genetic and environmental causes of autism, is closely related to Question 2.

Please refer to the 2011 version of the IACC strategic plan: <http://iacc.hhs.gov/strategic-plan/2011/understand.shtml>

Question 2 is “How can I understand autism?” The sub-questions are

- “What is happening early in development?”
- “Are there known biological differences that help explain ASD symptoms?” and
- “Can subgroups of people with ASD help us understand the etiology of ASD symptoms?”

For the 2012 update, the committee will be adding new sections on

- “What Is New in This Research Area, and What Have We Learned This Past Year?”
- “What Gap Areas Have Emerged Since Last Year?” and
- “What Progress Is Being Made in Fulfilling Objectives?”

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BIOMARKERS

49. Transl Psychiatry. 2012 Mar 13;2:e91. doi: 10.1038/tp.2012.19.

A novel blood-based biomarker for detection of autism spectrum disorders.

Momeni N, Bergquist J, Brudin L, Behnia F, Sivberg B, Joghataei MT, Persson BL.

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Autism spectrum disorders (ASD) are classified as neurological developmental disorders. Several studies have been carried out to find a candidate biomarker linked to the development of these disorders, but up to date no reliable biomarker is available. Mass spectrometry techniques have been used for protein profiling of blood plasma of children with such disorders in order to identify proteins/peptides that may be used as biomarkers for detection of the disorders. Three differentially expressed peptides with mass-charge (m/z) values of 2020 ± 1 , 1864 ± 1 and 1978 ± 1 Da in the heparin plasma of children with ASD that were significantly changed as compared with the peptide pattern of the non-ASD control group are reported here. This novel set of biomarkers allows for a reliable blood-based diagnostic tool that may be used in diagnosis and potentially, in prognosis of ASD.

PMCID: PMC3309533

PMID: 22832856 [PubMed - in process]

MOLECULAR BASIS

Transcriptomic analysis of autistic brain reveals convergent molecular pathways [POSTED 2011 ADVANCE] – Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH. Nature. 2011 May 25;474(7351):380-4. [PMID: 21614001]

A study found surprising consistency in molecular changes seen in the brains of people with autism across the spectrum, suggesting a common biological basis that may span multiple subtypes. Researchers analyzed postmortem brain tissue and found atypical patterns of gene expression common to many of the individuals with ASD. These findings may provide clues about how autism changes the brain at the molecular level, and lead to new avenues for developing treatments. In the study researchers focused on gene expression – the way information from the gene is used in the synthesis of functional gene products, often proteins. These proteins then perform specific tasks in the cell. In brains affected by autism, genes involved in neuron function and communication were expressed at much lower levels than in typically developing individuals, and the expression of genes involved in certain immune functions was abnormally high. The authors note that many of these genes are active during fetal development, supporting the theory that abnormal brain development may start very early in the womb. The findings also provide evidence that molecular changes in neuron function and communication are probably a cause of autism, rather than a result of the disorder. To identify common patterns of gene expression among people with autism, the researchers compared the frontal and temporal lobes of the brain – the frontal lobe is responsible for higher-level thinking including judgment

and social response, while the temporal lobe plays a key role in hearing and language and is also involved in sensory integration. They found that more than 500 genes were expressed at different levels in the frontal and temporal lobes of typically developing individuals, as would be expected in separate brain regions with differing functions. However, there was almost no difference in the levels of gene expression between the two regions in the brains of those with ASD. This blurring suggests a failure to differentiate regions in early brain development.

50. J Neurosci. 2012 Jul 18;32(29):10021-34.

MeCP2 is critical for maintaining mature neuronal networks and global brain anatomy during late stages of postnatal brain development and in the mature adult brain.

Nguyen MV, Du F, Felice CA, Shan X, Nigam A, Mandel G, Robinson JK, Ballas N.

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Mutations in the X-linked gene, methyl-CpG binding protein 2 (Mecp2), underlie a wide range of neuropsychiatric disorders, most commonly, Rett Syndrome (RTT), a severe autism spectrum disorder that affects approximately one in 10,000 female live births. Because mutations in the Mecp2 gene occur in the germ cells with onset of neurological symptoms occurring in early childhood, the role of MeCP2 has been ascribed to brain maturation at a specific developmental window. Here, we show similar kinetics of onset and progression of RTT-like symptoms in mice, including lethality, if MeCP2 is removed postnatally during the developmental stage that coincides with RTT onset, or adult stage. For the first time, we show that brains that lose MeCP2 at these two different stages are actively shrinking, resulting in higher than normal neuronal cell density. Furthermore, we show that mature dendritic arbors of pyramidal neurons are severely retracted and dendritic spine density is dramatically reduced. In addition, hippocampal astrocytes have significantly less complex ramified processes. These changes accompany a striking reduction in the levels of several synaptic proteins, including CaMKII α/β , AMPA, and NMDA receptors, and the synaptic vesicle proteins Vglut and Synapsin, which represent critical modifiers of synaptic function and dendritic arbor structure. Importantly, the mRNA levels of these synaptic proteins remains unchanged, suggesting that MeCP2 likely regulates these synaptic proteins post-transcriptionally, directly or indirectly. Our data suggest a crucial role for MeCP2 in post-transcriptional regulation of critical synaptic proteins involved in maintaining mature neuronal networks during late stages of postnatal brain development.

PMID: 22815516 [PubMed - in process]

82. Cell. 2012 May 11;149(4):899-911.

Species-dependent posttranscriptional regulation of NOS1 by FMRP in the developing cerebral cortex.

Kwan KY, Lam MM, Johnson MB, Dube U, Shim S, Rašin MR, Sousa AM, Fertuzinhos S, Chen JG, Arellano JI, Chan DW, Pletikos M, Vasung L, Rowitch DH, Huang EJ, Schwartz ML, Willemsen R, Oostra BA, Rakic P, Heffer M, Kostović I, Judaš M, Sestan N.

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Fragile X syndrome (FXS), the leading monogenic cause of intellectual disability and autism, results from loss of function of the RNA-binding protein FMRP. Here, we show that FMRP regulates translation of neuronal nitric oxide synthase 1 (NOS1) in the developing human neocortex. Whereas NOS1 mRNA is widely expressed, NOS1 protein is transiently coexpressed with FMRP during early synaptogenesis in layer- and region-specific pyramidal neurons. These include midfetal layer 5 subcortically projecting neurons arranged into alternating columns in the prospective Broca's area and orofacial motor cortex. Human NOS1 translation is activated by FMRP via interactions with coding region binding motifs absent from mouse *Nos1* mRNA, which is expressed in mouse pyramidal neurons, but not efficiently translated. Correspondingly, neocortical NOS1 protein levels are severely reduced in developing human FXS cases, but not FMRP-deficient mice. Thus, alterations in FMRP posttranscriptional regulation of NOS1 in developing neocortical circuits may contribute to cognitive dysfunction in FXS.

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PMCID: PMC3351852 [Available on 2013/5/11]

PMID: 22579290 [PubMed - indexed for MEDLINE]

38. Hum Mol Genet. 2012 Aug 23. [Epub ahead of print]

Inherited genetic variants in autism-related CNTNAP2 show perturbed trafficking and ATF6 activation.

Falivelli G, De Jaco A, Favaloro FL, Kim H, Wilson J, Dubi N, Ellisman MH, Abrahams BS, Taylor P, Comolletti D.

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Although genetic variations in several genes encoding for synaptic adhesion proteins have been found to be associated with autism spectrum disorders, one of the most consistently replicated genes has been CNTNAP2, encoding for contactin-associated protein-like 2 (CASPR2), a multidomain transmembrane protein of the neurexin superfamily. Using immunofluorescence confocal microscopy and complementary biochemical techniques, we compared wild-type CASPR2 to 12 point

mutations identified in individuals with autism. In contrast to the wild-type protein, localized to the cell surface, some of the mutants show altered cellular disposition. In particular, CASPR2-D1129H is largely retained in the endoplasmic reticulum (ER) in HEK-293 cells and in hippocampal neurons. BiP/Grp78, Calnexin and ERp57, key ER chaperones, appear to be responsible for retention of this mutant and activation of one signaling pathway of the unfolded protein response (UPR). The presence of this mutation also lowers expression and activates proteosomal degradation. A frame-shift mutation that causes a form of syndromic epilepsy (CASPR2-1253*), results in a secreted protein with seemingly normal folding and oligomerization. Taken together, these data indicate that CASPR2-D1129H has severe trafficking abnormalities and CASPR2-1253* is a secreted soluble protein, suggesting that the structural or signaling functions of the membrane tethered form are lost. Our data support a complex genetic architecture in which multiple distinct risk factors interact with others to shape autism risk and presentation.

PMID: 22872700 [PubMed - as supplied by publisher]

7. PLoS One. 2012;7(9):e44736. Epub 2012 Sep 12.

Brain transcriptional and epigenetic associations with autism. [QUESTION 3?]

Ginsberg MR, Rubin RA, Falcone T, Ting AH, Natowicz MR.

Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio, United States of America.

BACKGROUND: Autism is a common neurodevelopmental syndrome. Numerous rare genetic etiologies are reported; most cases are idiopathic.

METHODOLOGY/PRINCIPAL FINDINGS: To uncover important gene dysregulation in autism we analyzed carefully selected idiopathic autistic and control cerebellar and BA19 (occipital) brain tissues using high resolution whole genome gene expression and whole genome DNA methylation microarrays. No changes in DNA methylation were identified in autistic brain but gene expression abnormalities in two areas of metabolism were apparent: down-regulation of genes of mitochondrial oxidative phosphorylation and of protein translation. We also found associations between specific behavioral domains of autism and specific brain gene expression modules related to myelin/myelination, inflammation/immune response and purinergic signaling.

CONCLUSIONS/SIGNIFICANCE: This work highlights two largely unrecognized molecular pathophysiological themes in autism and suggests differing molecular bases for autism behavioral endophenotypes.

PMCID: PMC3440365

PMID: 22984548 [PubMed - in process]

66. J Neurosci. 2012 Jun 20;32(25):8663-77.

Disrupted ERK signaling during cortical development leads to abnormal progenitor proliferation, neuronal and network excitability and behavior, modeling human neuro-cardio-facial-cutaneous and related syndromes.

Pucilowska J, Puzerey PA, Karlo JC, Galán RF, Landreth GE.

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Genetic disorders arising from copy number variations in the ERK (extracellular signal-regulated kinase) MAP (mitogen-activated protein) kinases or mutations in their upstream regulators that result in neuro-cardio-facial-cutaneous syndromes are associated with developmental abnormalities, cognitive deficits, and autism. We developed murine models of these disorders by deleting the ERKs at the beginning of neurogenesis and report disrupted cortical progenitor generation and proliferation, which leads to altered cytoarchitecture of the postnatal brain in a gene-dose-dependent manner. We show that these changes are due to ERK-dependent dysregulation of cyclin D1 and p27(Kip1), resulting in cell cycle elongation, favoring neurogenic over self-renewing divisions. The precocious neurogenesis causes premature progenitor pool depletion, altering the number and distribution of pyramidal neurons. Importantly, loss of ERK2 alters the intrinsic excitability of cortical neurons and contributes to perturbations in global network activity. These changes are associated with elevated anxiety and impaired working and hippocampal-dependent memory in these mice. This study provides a novel mechanistic insight into the basis of cortical malformation which may provide a potential link to cognitive deficits in individuals with altered ERK activity.

PMID: 22723706 [PubMed - indexed for MEDLINE]

81. Nature. 2012 May 16;485(7398):363-7. doi: 10.1038/nature11091.

KCTD13 is a major driver of mirrored neuroanatomical phenotypes of the 16p11.2 copy number variant.

Golzio C, Willer J, Talkowski ME, Oh EC, Taniguchi Y, Jacquemont S, Raymond A, Sun M, Sawa A, Gusella JF, Kamiya A, Beckmann JS, Katsanis N.

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Comment in

Nature. 2012 May 17;485(7398):318-9.

Copy number variants (CNVs) are major contributors to genetic disorders. We have dissected a region of the 16p11.2 chromosome--which encompasses 29 genes--that confers susceptibility to neurocognitive defects when deleted or duplicated. Overexpression of each human transcript in zebrafish embryos identified KCTD13 as

the sole message capable of inducing the microcephaly phenotype associated with the 16p11.2 duplication, whereas suppression of the same locus yielded the macrocephalic phenotype associated with the 16p11.2 deletion, capturing the mirror phenotypes of humans. Analyses of zebrafish and mouse embryos suggest that microcephaly is caused by decreased proliferation of neuronal progenitors with concomitant increase in apoptosis in the developing brain, whereas macrocephaly arises by increased proliferation and no changes in apoptosis. A role for KCTD13 dosage changes is consistent with autism in both a recently reported family with a reduced 16p11.2 deletion and a subject reported here with a complex 16p11.2 rearrangement involving de novo structural alteration of KCTD13. Our data suggest that KCTD13 is a major driver for the neurodevelopmental phenotypes associated with the 16p11.2 CNV, reinforce the idea that one or a small number of transcripts within a CNV can underpin clinical phenotypes, and offer an efficient route to identifying dosage-sensitive loci.

PMCID: PMC3366115 [Available on 2012/11/16]

PMID: 22596160 [PubMed - indexed for MEDLINE]

85. J Neurosci. 2012 Apr 25;32(17):5880-90.

Pten deletion in adult hippocampal neural stem/progenitor cells causes cellular abnormalities and alters neurogenesis.

Amiri A, Cho W, Zhou J, Birnbaum SG, Sinton CM, McKay RM, Parada LF.

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Adult neurogenesis persists throughout life in restricted brain regions in mammals and is affected by various physiological and pathological conditions. The tumor suppressor gene Pten is involved in adult neurogenesis and is mutated in a subset of autism patients with macrocephaly; however, the link between the role of PTEN in adult neurogenesis and the etiology of autism has not been studied before. Moreover, the role of hippocampus, one of the brain regions where adult neurogenesis occurs, in development of autism is not clear. Here, we show that ablating Pten in adult neural stem cells in the subgranular zone of hippocampal dentate gyrus results in higher proliferation rate and accelerated differentiation of the stem/progenitor cells, leading to depletion of the neural stem cell pool and increased differentiation toward the astrocytic lineage at later stages. Pten-deleted stem/progenitor cells develop into hypertrophied neurons with abnormal polarity. Additionally, Pten mutant mice have macrocephaly and exhibit impairment in social interactions and seizure activity. Our data reveal a novel function for PTEN in adult hippocampal neurogenesis and indicate a role in the pathogenesis of abnormal social behaviors.

PMID: 22539849 [PubMed - indexed for MEDLINE]

86. Sci Transl Med. 2012 Apr 25;4(131):131ra51.

Negative allosteric modulation of the mGluR5 receptor reduces repetitive behaviors and rescues social deficits in mouse models of autism.

Silverman JL, Smith DG, Rizzo SJ, Karras MN, Turner SM, Tolu SS, Bryce DK, Smith DL, Fonseca K, Ring RH, Crawley JN.

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Comment in

Sci Transl Med. 2012 Apr 25;4(131):131fs9.

Nat Rev Drug Discov. 2012 Jun;11(6):440-1.

Neurodevelopmental disorders such as autism and fragile X syndrome were long thought to be medically untreatable, on the assumption that brain dysfunctions were immutably hardwired before diagnosis. Recent revelations that many cases of autism are caused by mutations in genes that control the ongoing formation and maturation of synapses have challenged this dogma. Antagonists of metabotropic glutamate receptor subtype 5 (mGluR5), which modulate excitatory neurotransmission, are in clinical trials for fragile X syndrome, a major genetic cause of intellectual disabilities. About 30% of patients with fragile X syndrome meet the diagnostic criteria for autism. Reasoning by analogy, we considered the mGluR5 receptor as a potential target for intervention in autism. We used BTBR T+tf/J (BTBR) mice, an established model with robust behavioral phenotypes relevant to the three diagnostic behavioral symptoms of autism--unusual social interactions, impaired communication, and repetitive behaviors--to probe the efficacy of a selective negative allosteric modulator of the mGluR5 receptor, GRN-529. GRN-529 reduced repetitive behaviors in three cohorts of BTBR mice at doses that did not induce sedation in control assays of open field locomotion. In addition, the same nonsedating doses reduced the spontaneous stereotyped jumping that characterizes a second inbred strain of mice, C58/J. Further, GRN-529 partially reversed the striking lack of sociability in BTBR mice on some parameters of social approach and reciprocal social interactions. These findings raise the possibility that a single targeted pharmacological intervention may alleviate multiple diagnostic behavioral symptoms of autism.

PMID: 22539775 [PubMed - indexed for MEDLINE]

18. Neuron. 2012 Sep 6;75(5):904-15.

Autism-Associated Promoter Variant in MET Impacts Functional and Structural Brain Networks.

Rudie JD, Hernandez LM, Brown JA, Beck-Pancer D, Colich NL, Gorrindo P, Thompson PM, Geschwind DH, Bookheimer SY, Levitt P, Dapretto M.

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As genes that confer increased risk for autism spectrum disorder (ASD) are identified, a crucial next step is to determine how these risk factors impact brain structure and function and contribute to disorder heterogeneity. With three converging lines of evidence, we show that a common, functional ASD risk variant in the Met Receptor Tyrosine Kinase (MET) gene is a potent modulator of key social brain circuitry in children and adolescents with and without ASD. MET risk genotype predicted atypical fMRI activation and deactivation patterns to social stimuli (i.e., emotional faces), as well as reduced functional and structural connectivity in temporo-parietal regions known to have high MET expression, particularly within the default mode network. Notably, these effects were more pronounced in individuals with ASD. These findings highlight how genetic stratification may reduce heterogeneity and help elucidate the biological basis of complex neuropsychiatric disorders such as ASD.

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PMID: 22958829 [PubMed - in process]

Pharmacogenomics J. 2012 Oct;12(5):368-71. doi: 10.1038/tpj.2011.23. Epub 2011 Jun 7.

Gene expression in blood is associated with risperidone response in children with autism spectrum disorders.

Lit L, Sharp FR, Bertoglio K, Stamova B, Ander BP, Sossong AD, Hendren RL.

Source

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Abstract

Children with autism spectrum disorders (ASDs) often have severe behavioral problems. Not all children with these problems respond to atypical antipsychotic medications; therefore, we investigated whether peripheral blood gene expression before treatment with risperidone, an atypical antipsychotic, was associated with improvements in severe behavioral disturbances 8 weeks following risperidone treatment in 42 ASD subjects (age 112.7 ± 51.2 months). Exon expression levels in blood before risperidone treatment were compared with pre-post risperidone change in Aberrant Behavior Checklist-Irritability (ABC-I) scores. Expression of exons within five genes was correlated with change in ABC-I scores across all risperidone-treated subjects: GBP6, RABL5, RNF213, NFKBID and RNF40 ($\alpha < 0.001$). RNF40 is located at 16p11.2, a region implicated in autism and schizophrenia. Thus, these genes expressed before treatment were associated with subsequent clinical response. Future studies will be needed to confirm these results and determine whether this expression profile is associated with risperidone response in other disorders, or alternative antipsychotic response within ASD.

PMID: 21647175 [PubMed - in process] PMCID: PMC3175502 [Available on 2013/4/1]

SENSORY PROCESSING

Pediatr Res. 2011 May;69(5 Pt 2):48R-54R.

Sensory processing in autism: a review of neurophysiologic findings. [REVIEW]

Marco EJ, Hinkley LB, Hill SS, Nagarajan SS.

Source

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Abstract

Atypical sensory-based behaviors are a ubiquitous feature of autism spectrum disorders (ASDs). In this article, we review the neural underpinnings of sensory processing in autism by reviewing the literature on neurophysiological responses to auditory, tactile, and visual stimuli in autistic individuals. We review studies of unimodal sensory processing and multisensory integration that use a variety of neuroimaging techniques, including electroencephalography (EEG), magnetoencephalography (MEG), and functional MRI. We then explore the impact of covert and overt attention on sensory processing. With additional characterization, neurophysiologic profiles of sensory processing in ASD may serve as valuable biomarkers for diagnosis and monitoring of therapeutic interventions for autism and reveal potential strategies and target brain regions for therapeutic interventions.

PMID: 21289533 [PubMed - indexed for MEDLINE] PMCID: PMC3086654 Free PMC Article

8. PLoS One. 2012;7(9):e44084. Epub 2012 Sep 12.

Auditory processing in high-functioning adolescents with autism spectrum disorder.

Depape AM, Hall GB, Tillmann B, Trainor LJ.

Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Ontario, Canada.

Autism Spectrum Disorder (ASD) is a pervasive developmental disorder including abnormalities in perceptual processing. We measure perception in a battery of tests across speech (filtering, phoneme categorization, multisensory integration) and music (pitch memory, meter categorization, harmonic priming). We found that compared to controls, the ASD group showed poorer filtering, less audio-visual integration, less specialization for native phonemic and metrical categories, and a higher instance of absolute pitch. No group differences were found in harmonic priming. Our results are discussed in a developmental framework where culture-specific knowledge acquired early compared to late in development is most impaired, perhaps because of early-accelerated brain growth in ASD. These results suggest that early auditory remediation is needed for good communication and social functioning.

PMCID: PMC3440400

PMID: 22984462 [PubMed - in process]

45. Res Dev Disabil. 2012 Nov;33(6):2255-64. Epub 2012 Jul 24.

Differential brain responses to cries of infants with autistic disorder and typical development: An fMRI study.

Venuti P, Caria A, Esposito G, De Pisapia N, Bornstein MH, de Falco S.

Department of Cognitive Science and Education, University of Trento, Trento, Italy.

This study used fMRI to measure brain activity during adult processing of cries of infants with autistic disorder (AD) compared to cries of typically developing (TD) infants. Using whole brain analysis, we found that cries of infants with AD compared to those of TD infants elicited enhanced activity in brain regions associated with verbal and prosodic processing, perhaps because altered acoustic patterns of AD cries render them especially difficult to interpret, and increased activity in brain regions associated with emotional processing, indicating that AD cries also elicit more negative feelings and may be perceived as more aversive and/or arousing. Perceived distress engendered by AD cries related to increased activation in brain regions associated with emotional processing. This study supports the hypothesis that cry is an early and meaningful anomaly displayed by children with AD. It could be that cries associated with AD alter parent-child interactions much earlier than the time that reliable AD diagnosis normally occurs.

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PMID: 22835685 [PubMed - in process]

48. J Autism Dev Disord. 2012 Jul 26. [Epub ahead of print]

The Relationship between Sensory Sensitivity and Autistic Traits in the General Population.

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Individuals with Autism Spectrum Disorders (ASDs) tend to have sensory processing difficulties (Baranek et al. in J Child Psychol Psychiatry 47:591-601, 2006). These difficulties include over- and under-responsiveness to sensory stimuli, and problems modulating sensory input (Ben-Sasson et al. in J Autism Dev Disorders 39:1-11, 2009). As those with ASD exist at the extreme end of a continuum of autistic traits that is also evident in the general population, we investigated the link between ASD and sensory sensitivity in the general population by administering two questionnaires online to 212 adult participants. Results showed a highly significant positive correlation ($r = .775$, $p < .001$) between number of autistic traits and the frequency of sensory processing problems. These data suggest a strong link between sensory processing and autistic traits in the general population, which in turn potentially implicates sensory processing problems in social interaction difficulties.

PMID: 22832890 [PubMed - as supplied by publisher]

BRAIN STRUCTURE

3. J Intellect Disabil Res. 2012 Sep 24. doi: 10.1111/j.1365-2788.2012.01599.x.
[Epub ahead of print]

Fractional anisotropy distributions in 2- to 6-year-old children with autism.

Cascio C, Gribbin M, Gouttard S, Smith RG, Jomier M, Field S, Graves M, Hazlett HC, Muller K, Gerig G, Piven J.

Psychiatry and Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, Tennessee, USA Department of Biostatistics, Human Genome Sciences, Rockville, Maryland, USA Department of Computer Science, University of Utah, Salt Lake City, Utah, USA Psychiatry/Carolina Institute for Developmental Disabilities, University of North Carolina, Chapel Hill, North Carolina, USA Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina, USA Frank Porter Graham Child Development Institute, Chapel Hill, North Carolina, USA Department of Epidemiology and Health Policy Research, University of Florida, Gainesville, Florida, USA.

Background Increasing evidence suggests that autism is a disorder of distributed neural networks that may exhibit abnormal developmental trajectories. Characterisation of white matter early in the developmental course of the disorder is critical to understanding these aberrant trajectories. **Methods** A cross-sectional study of 2- to 6-year-old children with autism was conducted using diffusion tensor imaging combined with a novel statistical approach employing fractional anisotropy distributions. Fifty-eight children aged 18-79 months were imaged: 33 were diagnosed with autism, 8 with general developmental delay, and 17 were typically developing. Fractional anisotropy values within global white matter, cortical lobes and the cerebellum were measured and transformed to random F distributions for each subject. Each distribution of values for a region was summarised by estimating δ , the estimated mean and standard deviation of the approximating F for each distribution. **Results** The estimated δ parameter, δ , was significantly decreased in individuals with autism compared to the combined control group. This was true in all cortical lobes, as well as in the cerebellum, but differences were most robust in the temporal lobe. Predicted developmental trajectories of across the age range in the sample showed patterns that partially distinguished the groups. Exploratory analyses suggested that the variability, rather than the central tendency, component of was the driving force behind these results. **Conclusions** While preliminary, our results suggest white matter in young children with autism may be abnormally homogeneous, which may reflect poorly organised or differentiated pathways, particularly in the temporal lobe, which is important for social and emotional cognition.

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PMID: 22998325 [PubMed - as supplied by publisher]

27. J Am Acad Child Adolesc Psychiatry. 2012 Sep;51(9):921-33. Epub 2012 Aug 1.
Trajectories of early brain volume development in fragile x syndrome and autism.

Hazlett HC, Poe MD, Lightbody AA, Styner M, Macfall JR, Reiss AL, Piven J.

University of North Carolina (UNC) at Chapel Hill and the Carolina Institute for Developmental Disabilities.

OBJECTIVE: To examine patterns of early brain growth in young children with fragile X syndrome (FXS) compared with a comparison group (controls) and a group with idiopathic autism.

METHOD: The study included 53 boys 18 to 42 months of age with FXS, 68 boys with idiopathic autism (autism spectrum disorder), and a comparison group of 50 typically developing and developmentally delayed controls. Structural brain volumes were examined using magnetic resonance imaging across two time points, at 2 to 3 and again at 4 to 5 years of age, and total brain volumes and regional (lobar) tissue volumes were examined. In addition, a selected group of subcortical structures implicated in the behavioral features of FXS (e.g., basal ganglia, hippocampus, amygdala) was studied.

RESULTS: Children with FXS had larger global brain volumes compared with controls but were not different than children with idiopathic autism, and the rate of brain growth from 2 to 5 years of age paralleled that seen in controls. In contrast to children with idiopathic autism who had generalized cortical lobe enlargement, children with FXS showed specific enlargement in the temporal lobe white matter, cerebellar gray matter, and caudate nucleus, but a significantly smaller amygdala.

CONCLUSIONS: This structural longitudinal magnetic resonance imaging study of preschoolers with FXS observed generalized brain overgrowth in children with FXS compared with controls, evident at age 2 and maintained across ages 4 to 5. In addition, different patterns of brain growth that distinguished boys with FXS from boys with idiopathic autism were found.

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PMCID: PMC3428739 [Available on 2013/9/1]

PMID: 22917205 [PubMed - in process]

28. Neurology. 2012 Sep 18;79(12):1244-51. Epub 2012 Aug 22.
Peritrigonal and temporo-occipital heterotopia with corpus callosum and cerebellar dysgenesis.

Pisano T, Barkovich AJ, Leventer RJ, Squier W, Scheffer IE, Parrini E, Blaser S, Marini C, Robertson S, Tortorella G, Rosenow F, Thomas P, McGillivray G, Andermann E, Andermann F, Berkovic SF, Dobyns WB, Guerrini R.

Correspondence & reprint requests to Dr. Guerrini: r.guerrini@meyer.it.

OBJECTIVE: To describe a homogeneous subtype of periventricular nodular heterotopia (PNH) as part of a newly defined malformation complex.
METHODS: Observational study including review of brain MRI and clinical findings of a cohort of 50 patients with PNH in the temporo-occipital horns and trigones, mutation analysis of the FLNA gene, and anatomopathologic study of a fetal brain.
RESULTS: There were 28 females and 22 males. All were sporadic with the exception of an affected mother and son. Epilepsy occurred in 62%, cerebellar signs in 56%, cognitive impairment in 56%, and autism in 12%. Seventy percent were referred within the 3rd year of life. Imaging revealed a normal cerebral cortex in 76% and abnormal cortical folding in 24%. In all patients the hippocampi were under-rotated and in 10% they merged with the heterotopia. Cerebellar dysgenesis was observed in 84% and a hypoplastic corpus callosum in 60%. There was no gender bias or uneven gender distribution of clinical and anatomic severity. No mutations of FLNA occurred in 33 individuals examined. Heterotopia in the fetal brain revealed cytoarchitectonic characteristics similar to those associated with FLNA mutations; cortical pathology was not typical of polymicrogyria. Cerebellar involvement was more severe and the hippocampi appeared simple and under-rotated.
CONCLUSIONS: This series delineates a malformation complex in which PNH in the trigones and occipito-temporal horns is associated with hippocampal, corpus callosum, and cerebellar dysgenesis. This subtype of PNH is distinct from classic PNH caused by FLNA mutations.

PMID: 22914838 [PubMed - in process]

5. Eur Arch Psychiatry Clin Neurosci. 2012 Sep 18. [Epub ahead of print]

Magnetic resonance spectroscopy study of the glutamatergic system in adolescent males with high-functioning autistic disorder: a pilot study at 4T.

Joshi G, Biederman J, Wozniak J, Goldin RL, Crowley D, Furtak S, Lukas SE, Gönenc A.

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The pilot study aimed at examining the neural glutamatergic activity in autism. Seven adolescent males (mean age: 14 ± 1.8 ; age range: 12-17 years) with intact intellectual capacity (mean IQ: 108 ± 14.26 ; IQ range: 85-127) suffering from autistic disorder and an equal number of age- and sex-matched healthy controls underwent a two-dimensional magnetic resonance spectroscopy scan at 4T. Results indicated significantly high glutamate (Glu) levels in the anterior cingulate cortex of autistic disorder versus control subjects (paired t test $p = 0.01$) and

a trend for lower Glu in the right medial temporal lobe, which was not statistically different between the groups (paired t test $p = 0.06$). These preliminary findings support the glutamatergic dysregulation hypothesis in autism and need to be replicated in a larger sample.

PMID: 22986449 [PubMed - as supplied by publisher]

34. Proc IEEE Int Symp Biomed Imaging. 2012:542-545.

DISCOVERY OF GENES THAT AFFECT HUMAN BRAIN CONNECTIVITY: A GENOME-WIDE ANALYSIS OF THE CONNECTOME.

Jahanshad N, Hibar DP, Ryles A, Toga AW, McMahon KL, de Zubicaray GI, Hansell NK, Montgomery GW, Martin NG, Wright MJ, Thompson PM.

Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Los Angeles, CA.

Human brain connectivity is disrupted in a wide range of disorders - from Alzheimer's disease to autism - but little is known about which specific genes affect it. Here we conducted a genome-wide association for connectivity matrices that capture information on the density of fiber connections between 70 brain regions. We scanned a large twin cohort (N=366) with 4-Tesla high angular resolution diffusion imaging (105-gradient HARDI). Using whole brain HARDI tractography, we extracted a relatively sparse 70×70 matrix representing fiber density between all pairs of cortical regions automatically labeled in co-registered anatomical scans. Additive genetic factors accounted for 1-58% of the variance in connectivity between 90 (of 122) tested nodes. We discovered genome-wide significant associations between variants and connectivity. GWAS permutations at various levels of heritability, and split-sample replication, validated our genetic findings. The resulting genes may offer new leads for mechanisms influencing aberrant connectivity and neurodegeneration.

PMCID: PMC3420975 [Available on 2013/1/1]

PMID: 22903411 [PubMed]

35. Brain Res. 2012 Aug 10. pii: S0006-8993(12)01268-1. doi:

10.1016/j.brainres.2012.07.056. [Epub ahead of print]

Age-related abnormalities in white matter microstructure in autism spectrum disorders.

Kleinmans NM, Pauley G, Richards T, Neuhaus E, Martin N, Corrigan NM, Shaw DW, Estes A, Dager SR.

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Abnormalities in structural and functional connectivity have been reported in autism spectrum disorders (ASD) across a wide age range. However, developmental changes in white matter microstructure are poorly understood. We used a cross-sectional design to determine whether white matter abnormalities measured using diffusion tensor imaging (DTI) were present in adolescents and adults with ASD and whether age-related changes in white matter microstructure differed between ASD and typically developing (TD) individuals. Participants included 28 individuals with ASD and 33 TD controls matched on age and IQ and assessed at one time point. Widespread decreased fractional anisotropy (FA), and increased radial diffusivity (RaD) and mean diffusivity (MD) were observed in the ASD group compared to the TD group. In addition, significant group-by-age interactions were observed in FA, RaD, and MD in all major tracts except the brain stem, indicating that age-related changes in white matter microstructure differed between the groups. We propose that white matter microstructural changes in ASD may reflect myelination and/or other structural differences including differences in axonal density/arborization. In addition, we suggest that white matter microstructural impairments may be normalizing during young adulthood in ASD. Future longitudinal studies that include a wider range of ages and more extensive clinical characterization will be critical for further uncovering the neurodevelopmental processes unfolding during this dynamic time in development.

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53. Brain Struct Funct. 2012 Jul 10. [Epub ahead of print]

Changes in grey matter development in autism spectrum disorder.

Greimel E, Nehr Korn B, Schulte-Rüther M, Fink GR, Nickl-Jockschat T, Herpertz-Dahlmann B, Konrad K, Eickhoff SB.

Child Neuropsychology Section, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of the RWTH Aachen, Aachen, Germany, Ellen.Greimel@med.uni-muenchen.de.

Results on grey matter (GM) structural alterations in autism spectrum disorder (ASD) are inconclusive. Moreover, little is known about age effects on brain-structure abnormalities in ASD beyond childhood. Here, we aimed to examine regional GM volumes in a large sample of children, adolescents, and adults with ASD. Magnetic resonance imaging scans were obtained in 47 male ASD subjects and 51 matched healthy controls aged 8-50 years. We used whole-brain voxel-based morphometry to first assess group differences in regional GM volume across age. Moreover, taking a cross-sectional approach, group differences in age effects on regional GM volume were investigated. Compared to controls, ASD subjects showed reduced GM volumes in the anterior cingulate cortex, posterior superior temporal sulcus, and middle temporal gyrus. Investigation of group differences in age effects on regional GM volume revealed complex, region-specific alterations in ASD. While GM volumes in the amygdala, temporoparietal junction, septal nucleus

and middle cingulate cortex increased in a negative quadratic fashion in both groups, data indicated that GM volume curves in ASD subjects were shifted to the left along the age axis. Moreover, while GM volume in the right precentral gyrus decreased linearly with age in ASD individuals, GM volume development in controls followed a U-shaped pattern. Based on a large sample, our voxel-based morphometry results on group differences in regional GM volumes help to resolve inconclusive findings from previous studies in ASD. Results on age-related changes of regional GM volumes suggest that ASD is characterized by complex alterations in lifetime trajectories of several brain regions that underpin social-cognitive and motor functions.

PMID: 22777602 [PubMed - as supplied by publisher]

87. Ann N Y Acad Sci. 2012 Apr;1252:332-7. doi: 10.1111/j.1749-6632.2012.06446.x.

Atypical hemispheric asymmetry in the arcuate fasciculus of completely nonverbal children with autism.

Wan CY, Marchina S, Norton A, Schlaug G.

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Despite the fact that as many as 25% of the children diagnosed with autism spectrum disorders are nonverbal, surprisingly little research has been conducted on this population. In particular, the mechanisms that underlie their absence of speech remain unknown. Using diffusion tensor imaging, we compared the structure of a language-related white matter tract (the arcuate fasciculus, AF) in five completely nonverbal children with autism to that of typically developing children. We found that, as a group, the nonverbal children did not show the expected left-right AF asymmetry--rather, four of the five nonverbal children actually showed the reversed pattern. It is possible that this unusual pattern of asymmetry may underlie some of the severe language deficits commonly found in autism, particularly in children whose speech fails to develop. Furthermore, novel interventions (such as auditory-motor mapping training) designed to engage brain regions that are connected via the AF may have important clinical potential for facilitating expressive language in nonverbal children with autism.

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PMID: 22524376 [PubMed - indexed for MEDLINE]

NEUROPATHOLOGY

9. Science. 2012 Sep 14;337(6100):1301-3.

Neuroscience. The emerging biology of autism spectrum disorders. [A GOOD REVIEW]

State MW, Šestan N.

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PMID: 22984058 [PubMed - indexed for MEDLINE]

REGRESSION

Prevalence and Onset of Regression within Autism Spectrum Disorders: A Meta-analytic Review.

Barger BD, Campbell JM, McDonough JD.

J Autism Dev Disord. 2012 Aug 2. [Epub ahead of print]

Rates and onset of regression were meta-analyzed from 85 articles representing 29,035 participants with autism spectrum disorders (ASD). Overall prevalence rate for regression was 32.1, 95 % CI [29.5, 34.8] occurring at mean of 1.78 years, 95 % CI [1.67, 1.89]. Regression prevalence rates differed according to four types of regression: language regression, 24.9 %; language/social regression, 38.1 %; mixed regression, 32.5 %; and unspecified regression, 39.1 %. Regression prevalence also differed according to sampling method: population-based prevalence was 21.8 %, clinic-based prevalence was 33.6 %, and parent survey-based prevalence was 40.8 %. Risk of regression was equal for males and females, but higher for individuals diagnosed with autism versus another ASD. Later age of regression onset was predicted by older age of child.

73. Pediatr Neurol. 2012 Jul;47(1):65-7.

Levetiracetam-induced reversible autistic regression. [ALSO EPILEPSY]

Camacho A, Espín JC, Nuñez N, Simón R.

Section of Pediatric Neurology, Department of Neurology, Hospital Universitario 12 de Octubre, Madrid, Spain. acamachosalas@yahoo.es

Levetiracetam is a commonly prescribed antiepileptic drug, and is generally well tolerated, but can eventually cause behavioral disturbances. These disturbances seem more frequent in children and in patients with a previous psychiatric history. We report on reversible autistic regression induced by levetiracetam in a 6-year-old girl with spastic cerebral palsy, mild cognitive deficiency, and focal epilepsy. She was diagnosed with pervasive developmental disorder, and demonstrated mild to moderate impairment in pragmatic language and interactions with peers. After the introduction of levetiracetam, she developed stereotypies,

and her social and communicative skills deteriorated severely. She also exhibited mood lability. When the medication was discontinued, a dramatic response occurred, with a complete resolution of new abnormal findings. Levetiracetam can provoke unusual behavioral adverse effects in certain patients who are biologically more vulnerable.

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PMID: 22704022 [PubMed - in process]

NEURAL SYSTEMS/CIRCUITRY

21. Psychiatry Res. 2012 Sep 1. [Epub ahead of print]

Decreased leftward bias of prefrontal activity in autism spectrum disorder revealed by functional near-infrared spectroscopy.

Tamura R, Kitamura H, Endo T, Abe R, Someya T.

Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Niigata Psychiatric Center, Niigata, Japan.

Hemodynamic responses in rostral prefrontal cortex (RoPFC) were measured by functional near-infrared spectroscopy. Although performance level was equal, autistic patients showed a decrease in leftward bias of the balance between right and left RoPFC activity when compared with typically developing children when anatomical imitation was contrasted with mirror-image imitation.

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12. Soc Cogn Affect Neurosci. 2012 Sep 13. [Epub ahead of print]

Functional Brain Networks and White Matter Underlying Theory-of-Mind in Autism.

Kana RK, Libero LE, Hu CP, Deshpande HR, Colburn JS.

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Human beings constantly engage in attributing causal explanations to one's own and to others' actions, and theory-of-mind (ToM) is critical in making such inferences. Although children learn causal attribution early in development, children with autism spectrum disorders (ASD) are known to have impairments in the development of intentional causality. This fMRI and DTI study investigated the neural correlates of physical and intentional causal attribution in people with ASD. In the fMRI scanner, 15 adolescents and adults with ASD and 15 age-and-IQ-matched typically developing peers made causal judgments about comic

strips presented randomly in an event-related design. All participants showed robust activation in bilateral posterior superior temporal sulcus (pSTS) at the temporoparietal junction (TPJ) in response to intentional causality. Participants with ASD showed lower activation in TPJ, right inferior frontal gyrus, and left premotor cortex. Significantly weaker functional connectivity was also found in the ASD group between TPJ and motor areas during intentional causality. DTI data revealed significantly reduced fractional anisotropy in ASD participants in white matter underlying the temporal lobe. In addition to underscoring the role of TPJ in ToM, this study found an interaction between motor simulation and mentalizing systems in intentional causal attribution and its possible discord in autism.

PMID: 22977198 [PubMed - as supplied by publisher]

61. Eur J Neurosci. 2012 Sep;36(6):2782-2788. doi: 10.1111/j.1460-9568.2012.08172.x. Epub 2012 Jun 28.

Abnormal modulation of corticospinal excitability in adults with Asperger's syndrome.

Oberman L, Eldaief M, Fecteau S, Ifert-Miller F, Tormos JM, Pascual-Leone A.

Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
Department of Rehabilitation, Faculty of Medicine, Laval University, Quebec, QC, Canada
Institut Universitari de Neurorehabilitació Guttmann, Universitat Autònoma de Barcelona, Badalona, Spain
Harvard-Thorndike Clinical Research Center, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA.

Most candidate genes and genetic abnormalities linked to autism spectrum disorders (ASD) are thought to play a role in developmental and experience-dependent plasticity. As a possible index of plasticity, we assessed the modulation of motor corticospinal excitability in individuals with Asperger's syndrome (AS) using transcranial magnetic stimulation (TMS). We measured the modulatory effects of theta-burst stimulation (TBS) on motor evoked potentials (MEPs) induced by single-pulse TMS in individuals with AS as compared with age-, gender- and IQ-matched neurotypical controls. The effect of TBS lasted significantly longer in the AS group. The duration of the TBS-induced modulation alone enabled the reliable classification of a second study cohort of subjects as AS or neurotypical. The alteration in the modulation of corticospinal excitability in AS is thought to reflect aberrant mechanisms of plasticity, and might provide a valuable future diagnostic biomarker for the disease and ultimately offer a target for novel therapeutic interventions.

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75. Autism. 2012 Jun 14. [Epub ahead of print]

White matter and development in children with an autism spectrum disorder.

Mak-Fan KM, Morris D, Vidal J, Anagnostou E, Roberts W, Taylor MJ.

University of Toronto, Canada and Hospital for Sick Children, Toronto, Canada.

Recent research suggests that brain development follows an abnormal trajectory in children with autism spectrum disorders (ASD). The current study examined changes in diffusivity with age within defined white matter tracts in a group of typically developing children and a group of children with an ASD, aged 6 to 14 years. Age by group interactions were observed for frontal, long distant, interhemispheric and posterior tracts, for longitudinal, radial and mean diffusivity, but not for fractional anisotropy. In all cases, these measures of diffusivity decreased with age in the typically developing group, but showed little or no change in the ASD group. This supports the hypothesis of an abnormal developmental trajectory of white matter in this population, which could have profound effects on the development of neural connectivity and contribute to atypical cognitive development in children with ASD.

PMID: 22700988 [PubMed - as supplied by publisher]

UNDERSTANDING SUBTYPES OF AUTISM, INCLUDING SYNDROMIC AUTISM

Mutations causing syndromic autism define an axis of synaptic pathophysiology [2011 POSTED ADVANCE] – Auerbach BD, Osterweil EK, Bear MF. Nature. 2011 Nov 23;480(7375):63-8. [PMID: 22113615]

New research reveals that two genetic forms of autism, fragile X syndrome and tuberous sclerosis, are actually caused by opposite malfunctions – while fragile X is caused by overproduction of proteins at the synapse, tuberous sclerosis is caused by underproduction. Interestingly, while the causes of fragile X and tuberous sclerosis are distinctly different, both disorders often result in intellectual disability and autism spectrum disorder. Researchers made the discovery while studying mGluR5 (Metabotropic glutamate receptor 5), a receptor on the surface of neurons that is key in aiding communication at the synapse – the junction between neurons. During normal signaling, the mGluR5 receptor binds to the neurotransmitter glutamate after it is released across the synapse, resulting in the production of new synaptic proteins. Fragile X protein (FMRP) halts protein synthesis to ensure that the appropriate amount is produced – in fragile X syndrome, changes to the gene that controls FMRP allow synaptic proteins to continue production unchecked, resulting in too much protein. Researchers have previously shown that introducing a substance to block mGluR5 reverses some of the symptoms of fragile X, and human drug trials are currently underway. Armed with an understanding of the underlying causes of fragile X, researchers in this study examined mice with tuberous sclerosis mutations and discovered something surprising. In this case, the disorder was caused by the opposite malfunction – too little protein synthesis at the synapse, which could be treated with a drug stimulating mGluR5. Further, when the researchers bred the two mice together, many of their autistic features went away. The findings of the study indicate that proper brain function can only occur within a narrow range of mGluR5 protein

synthesis – changes in either direction lead to syndromes with similar behavioral symptoms. This also suggests that drug treatments for autism spectrum disorder will need to be individually tailored, as conditions that appear similar may have quite different underlying causes.

Protein interactome reveals converging molecular pathways [2011 POSTED ADVANCE] –

Sakai Y, Shaw CA, Dawson BC, Dugas DV, Al-Mohtaseb Z, Hill DE, Zoghbi HY. *Sci. Transl. Med.* 2011 Jun 8;3(86):86ra49. [PMID: 21653829]

A recent study sheds light on how a variety of different mutations in genes that seemingly have little in common can each result in the symptoms of autism. To answer this question, researchers developed a molecular map of protein networks or "interactome" to identify how proteins associated with ASD interact with hundreds of other proteins. Researchers used genes known to be associated with syndromic autism as a starting point for building the interactome. Syndromic autism occurs as part of a broader genetic disorder such as fragile X, Angelman syndrome, and Rett syndrome – understanding protein interactions with syndromic autism may give insight into idiopathic autism, or autism with no known cause. Using 26 genes associated with syndromic autism, researchers hypothesized that the seemingly dissimilar genes might interact with shared partners in common molecular pathways, leading to the symptoms of autism. Indeed, researchers identified a complex network of 539 proteins that interacted with the autism-related proteins, successfully demonstrating that all of the proteins linked to autism are connected by interactions with common partners. The interactome confirmed previously suspected gene relationships and several new pairings, such as the connection between SHANK3 and TSC1, which share 21 common protein partners. Researchers then performed a microarray analysis on 288 individuals with idiopathic autism in a search for genes within the interactome. They identified three novel copy number variations – chromosomal deletions and duplications – on genes found in the network, demonstrating that the interactome may help to identify new genes related to ASD and understand complicated genetic variation.

Shared Synaptic Pathophysiology in Syndromic and Nonsyndromic Rodent Models of Autism

Stéphane J. Baudouin, Julien Gaudias, Stefan Gerharz, Laetitia Hatstatt, Kuikui Zhou, Pradeep Punnakkal, Kenji F. Tanaka, Will Spooren, Rene Hen, Chris I. De Zeeuw, Kaspar Vogt, and Peter Scheiffele
Science 1224159 Published online 13 September 2012 [DOI:10.1126/science.1224159]

The genetic heterogeneity of autism poses a major challenge for identifying mechanism-based treatments. A number of rare mutations are associated with autism, and it is unclear whether these result in common neuronal alterations. Monogenic syndromes, such as fragile X, include autism as one of their multifaceted symptoms and have revealed specific defects in synaptic plasticity. We discovered an unexpected convergence of synaptic pathophysiology in a nonsyndromic form of autism with those in fragile X syndrome. Neuroligin-3 knockout mice (a model for nonsyndromic autism) exhibited disrupted hetero-synaptic competition and perturbed metabotropic glutamate receptor-dependent synaptic plasticity, a hallmark of fragile X. These phenotypes could be rescued by re-expression of neuroligin-3 in juvenile mice, highlighting the possibility for reverting neuronal circuit alterations in autism after completion of development.

1. *Sci Transl Med.* 2012 Sep 19;4(152):152ra128.

Reversal of Disease-Related Pathologies in the Fragile X Mouse Model by Selective Activation of GABAB Receptors with Arbaclofen.

Henderson C, Wijetunge L, Kinoshita MN, Shumway M, Hammond RS, Postma FR, Brynczka C, Rush R, Thomas A, Paylor R, Warren ST, Vanderklish PW, Kind PC, Carpenter RL, Bear MF, Healy AM.

Seaside Therapeutics Inc., Cambridge, MA 02139, USA.

Fragile X syndrome (FXS), the most common inherited cause of intellectual disability and autism, results from the transcriptional silencing of FMR1 and loss of the mRNA translational repressor protein fragile X mental retardation protein (FMRP). Patients with FXS exhibit changes in neuronal dendritic spine morphology, a pathology associated with altered synaptic function. Studies in the mouse model of fragile X have shown that loss of FMRP causes excessive synaptic protein synthesis, which results in synaptic dysfunction and altered spine morphology. We tested whether the pharmacologic activation of the γ -aminobutyric acid type B (GABA(B)) receptor could correct or reverse these phenotypes in Fmr1-knockout mice. Basal protein synthesis, which is elevated in the hippocampus of Fmr1-knockout mice, was corrected by the in vitro application of the selective GABA(B) receptor agonist STX209 (arbaclofen, R-baclofen). STX209 also reduced to wild-type values the elevated AMPA receptor internalization in Fmr1-knockout cultured neurons, a known functional consequence of increased protein synthesis. Acute administration of STX209 in vivo, at doses that modify behavior, decreased mRNA translation in the cortex of Fmr1-knockout mice. Finally, the chronic administration of STX209 in juvenile mice corrected the increased spine density in Fmr1-knockout mice without affecting spine density in wild-type mice. Thus, activation of the GABA(B) receptor with STX209 corrected synaptic abnormalities considered central to fragile X pathophysiology, a finding that suggests that STX209 may be a potentially effective therapy to treat the core symptoms of FXS.

PMID: 22993295 [PubMed - in process]

10. Science. 2012 Sep 13. [Epub ahead of print]

Shared Synaptic Pathophysiology in Syndromic and Nonsyndromic Rodent Models of Autism.

Baudouin SJ, Gaudias J, Gerharz S, Hatstatt L, Zhou K, Punnakkal P, Tanaka KF, Spooren W, Hen R, De Zeeuw CI, Vogt K, Scheiffele P.

Biozentrum of the University of Basel, Switzerland.

The genetic heterogeneity of autism poses a major challenge for identifying mechanism-based treatments. A number of rare mutations are associated with autism, and it is unclear whether these result in common neuronal alterations. Monogenic syndromes, such as fragile X, include autism as one of their multifaceted symptoms and have revealed specific defects in synaptic plasticity. We discovered an unexpected convergence of synaptic pathophysiology in a

nonsyndromic form of autism with those in fragile X syndrome. Neuroligin-3 knockout mice (a model for nonsyndromic autism) exhibited disrupted hetero-synaptic competition and perturbed metabotropic glutamate receptor-dependent synaptic plasticity, a hallmark of fragile X. These phenotypes could be rescued by re-expression of neuroligin-3 in juvenile mice, highlighting the possibility for reverting neuronal circuit alterations in autism after completion of development.

PMID: 22983708 [PubMed - as supplied by publisher]

13. J Intellect Disabil Res. 2012 Sep 14. doi: 10.1111/j.1365-2788.2012.01609.x. [Epub ahead of print]

Early identification of autism in fragile X syndrome: a review.

McCary LM, Roberts JE.

Department of Psychology, University of South Carolina, Columbia, SC, USA.

Fragile X syndrome (FXS) is the leading genetic cause of autism, accounting for approximately 5% of autism cases with as many as 50% of individuals with FXS meeting DSM-IV-TR criteria for autistic disorder. Both FXS and idiopathic autism (IA) are attributed to genetic causes; however, FXS is an identified single gene disorder whereas autism is a complex disorder with multiple potential causes, some of which have been identified. Studies in IA have focused on the prospective longitudinal examination of infant siblings of children with autism as a target group due to their high risk of developing the disorder. We propose that this same model be applied to the study of infants with FXS. There is a lack of research focusing on the early development of autism within FXS and debate in the literature regarding how to best conceptualise this co-morbidity or whether it should be considered a co-morbid condition at all. Studying the emergence and stability of autism in infants with FXS has multiple benefits such as clarifying the underlying mechanisms of the development of autism in FXS and solidifying similarities and differences between co-morbid FXS with autism and IA. Infant research in both IA and FXS are discussed as well as conclusions and implications for practice and future research.

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PMID: 22974167 [PubMed - as supplied by publisher]

14. J Neurosci. 2012 Sep 12;32(37):12841-7.

MeCP2 Phosphorylation Is Required for Modulating Synaptic Scaling through mGluR5. [MOLECULAR BASIS ALSO]

Zhong X, Li H, Chang Q.

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MeCP2 (methyl CpG binding protein 2) is a key player in recognizing methylated DNA and interpreting the epigenetic information encoded in different DNA methylation patterns. The functional significance of MeCP2 to the mammalian nervous system is highlighted by the discovery that mutations in the MECP2 gene cause Rett syndrome (RTT), a devastating neurological disease that shares many features with autism. Synaptic scaling is a form of non-Hebbian homeostatic plasticity that allows neurons to regulate overall excitability in response to changes in network neuronal activity levels. While it is known that neuronal activity can induce phosphorylation of MeCP2 and that MeCP2 can regulate synaptic scaling, the molecular link between MeCP2 phosphorylation and synaptic scaling remains undefined. We show here that MeCP2 phosphorylation is specifically required for bicuculline-induced synaptic scaling down in mouse hippocampal neurons and this phenotype is mediated by mGluR5 (metabotropic glutamate receptor 5). Our results reveal an important function of MeCP2 in regulating neuronal homeostasis and may eventually help us understand how MECP2 mutations cause RTT.

PMID: 22973007 [PubMed - in process]

15. N Engl J Med. 2012 Sep 12. [Epub ahead of print]

Phenotypic Heterogeneity of Genomic Disorders and Rare Copy-Number Variants. [QUESTION 3?]

Girirajan S, Rosenfeld JA, Coe BP, Parikh S, Friedman N, Goldstein A, Filipink RA, McConnell JS, Angle B, Meschino WS, Nezarati MM, Asamoah A, Jackson KE, Gowans GC, Martin JA, Carmany EP, Stockton DW, Schnur RE, Penney LS, Martin DM, Raskin S, Leppig K, These H, Smith R, Aberg E, Niyazov DM, Escobar LF, El-Khechen D, Johnson KD, Lebel RR, Siefkas K, Ball S, Shur N, McGuire M, Brasington CK, Spence JE, Martin LS, Clericuzio C, Ballif BC, Shaffer LG, Eichler EE.

The authors' affiliations are listed in the Appendix.

Background Some copy-number variants are associated with genomic disorders with extreme phenotypic heterogeneity. The cause of this variation is unknown, which presents challenges in genetic diagnosis, counseling, and management. **Methods** We analyzed the genomes of 2312 children known to carry a copy-number variant associated with intellectual disability and congenital abnormalities, using array comparative genomic hybridization. **Results** Among the affected children, 10.1% carried a second large copy-number variant in addition to the primary genetic lesion. We identified seven genomic disorders, each defined by a specific copy-number variant, in which the affected children were more likely to carry multiple copy-number variants than were controls. We found that syndromic

disorders could be distinguished from those with extreme phenotypic heterogeneity on the basis of the total number of copy-number variants and whether the variants are inherited or de novo. Children who carried two large copy-number variants of unknown clinical significance were eight times as likely to have developmental delay as were controls (odds ratio, 8.16; 95% confidence interval, 5.33 to 13.07; $P=2.11 \times 10^{-38}$). Among affected children, inherited copy-number variants tended to co-occur with a second-site large copy-number variant (Spearman correlation coefficient, 0.66; $P < 0.001$). Boys were more likely than girls to have disorders of phenotypic heterogeneity ($P < 0.001$), and mothers were more likely than fathers to transmit second-site copy-number variants to their offspring ($P = 0.02$). Conclusions Multiple, large copy-number variants, including those of unknown pathogenic significance, compound to result in a severe clinical presentation, and secondary copy-number variants are preferentially transmitted from maternal carriers. (Funded by the Simons Foundation Autism Research Initiative and the National Institutes of Health.).

PMID: 22970919 [PubMed - as supplied by publisher]

32. BMC Med Genet. 2012 Aug 21;13(1):75. [Epub ahead of print]

A case report of Chinese brothers with inherited MECP2-containing duplication: autism and intellectual disability, but not seizures or respiratory infections.

Xu X, Xu Q, Zhang Y, Zhang X, Cheng T, Wu B, Ding Y, Lu P, Zheng J, Zhang M, Qiu Z, Yu X.

ABSTRACT: BACKGROUND: Autistic spectrum disorders (ASDs) are a family of neurodevelopmental disorders with strong genetic components. Recent studies have shown that copy number variations in dosage sensitive genes can contribute significantly to these disorders. One such gene is the transcription factor MECP2, whose loss of function in females results in Rett syndrome, while its duplication in males results in developmental delay and autism. **CASE PRESENTATION:** Here, we identified a Chinese family with two brothers both inheriting a 2.2 Mb MECP2-containing duplication (151,369,305 -- 153,589,577) from their mother. In addition, both brothers also had a 213.7 kb duplication on Chromosome 2, inherited from their father. The older brother also carried a 48.4 kb duplication on Chromosome 2 inherited from the mother, and a 8.2 kb deletion at 11q13.5 inherited from the father. Based on the published literature, MECP2 is the most autism-associated gene among the identified CNVs. Consistently, the boys displayed clinical features in common with other patients carrying MECP2 duplications, including intellectual disability, autism, lack of speech, slight hypotonia and unsteadiness of movement. They also had slight dysmorphic features including a depressed nose bridge, large ears and midface hypoplasia. Interestingly, they did not exhibit other clinical features commonly observed in American-European patients with MECP2 duplication, including recurrent respiratory infections and epilepsy. **CONCLUSIONS:** To our knowledge, this is the first identification and characterization of Chinese Han patients with

MECP2-containing duplications. Further cases are required to determine if the above described clinical differences are due to individual variations or related to the genetic background of the patients.

PMID: 22909152 [PubMed - as supplied by publisher]

36. Eur J Hum Genet. 2012 Aug 15. doi: 10.1038/ejhg.2012.175. [Epub ahead of print]
Prevalence of SHANK3 variants in patients with different subtypes of autism spectrum disorders. [QUESTION 3?]

Boccuto L, Lauri M, Sarasua SM, Skinner CD, Buccella D, Dwivedi A, Orteschi D, Collins JS, Zollino M, Visconti P, Dupont B, Tiziano D, Schroer RJ, Neri G, Stevenson RE, Gurrieri F, Schwartz CE.

1] Greenwood Genetic Center, Greenwood, SC, USA [2] Istituto di Genetica Medica, Università Cattolica del S. Cuore, Rome, Italy.

Autism spectrum disorders (ASDs) include three main conditions: autistic disorder (AD), pervasive developmental disorder, not otherwise specified (PDD-NOS), and Asperger syndrome. It has been shown that many genes associated with ASDs are involved in the neuroligin-neurexin interaction at the glutamate synapse: NLGN3, NLGN4, NRXN1, CNTNAP2, and SHANK3. We screened this last gene in two cohorts of ASD patients (133 patients from US and 88 from Italy). We found 5/221 (2.3%) cases with pathogenic alterations: a 106 kb deletion encompassing the SHANK3 gene, two frameshift mutations leading to premature stop codons, a missense mutation (p.Pro141Ala), and a splicing mutation (c.1820-4 G>A). Additionally, in 17 patients (7.7%) we detected a c.1304+48C>T transition affecting a methylated cytosine in a CpG island. This variant is reported as SNP rs76224556 and was found in both US and Italian controls, but it results significantly more frequent in our cases than in the control cohorts. The variant is also significantly more common among PDD-NOS cases than in AD cases. We also screened this gene in an independent replication cohort of 104 US patients with ASDs, in which we found a missense mutation (p.Ala1468Ser) in 1 patient (0.9%), and in 8 patients (7.7%) we detected the c.1304+48C>T transition. While SHANK3 variants are present in any ASD subtype, the SNP rs76224556 appears to be significantly associated with PDD-NOS cases. This represents the first evidence of a genotype-phenotype correlation in ASDs and highlights the importance of a detailed clinical-neuropsychiatric evaluation for the effective genetic screening of ASD patients. European Journal of Human Genetics advance online publication, 15 August 2012; doi:10.1038/ejhg.2012.175.

PMID: 22892527 [PubMed - as supplied by publisher]

39. Stem Cells. 2012 Oct;30(10):2128-39. doi: 10.1002/stem.1180.
Disease Modeling Using Embryonic Stem Cells: MeCP2 Regulates Nuclear Size and RNA Synthesis in Neurons.

Yazdani M, Deogracias R, Guy J, Poot RA, Bird A, Barde YA.

Biozentrum, University of Basel, Basel, Switzerland.

Mutations in the gene encoding the methyl-CpG-binding protein MECP2 are the major cause of Rett syndrome, an autism spectrum disorder mainly affecting young females. MeCP2 is an abundant chromatin-associated protein, but how and when its absence begins to alter brain function is still far from clear. Using a stem cell-based system allowing the synchronous differentiation of neuronal progenitors, we found that in the absence of MeCP2, the size of neuronal nuclei fails to increase at normal rates during differentiation. This is accompanied by a marked decrease in the rate of ribonucleotide incorporation, indicating an early role of MeCP2 in regulating total gene transcription, not restricted to selected mRNAs. We also found that the levels of brain-derived neurotrophic factor (BDNF) were decreased in mutant neurons, while those of the presynaptic protein synaptophysin increased at similar rates in wild-type and mutant neurons. By contrast, nuclear size, transcription rates, and BDNF levels remained unchanged in astrocytes lacking MeCP2. Re-expressing MeCP2 in mutant neurons rescued the nuclear size phenotype as well as BDNF levels. These results reveal a new role of MeCP2 in regulating overall RNA synthesis in neurons during the course of their maturation, in line with recent findings indicating a reduced nucleolar size in neurons of the developing brain of mice lacking *Mecp2*. *STEM Cells* 2012;30:2128-2139.

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PMID: 22865604 [PubMed - in process]

59. *Am J Med Genet A*. 2012 Aug;158A(8):1841-7. doi: 10.1002/ajmg.a.34014. Epub 2012 Jun 27.

Investigation of autistic features among individuals with mild to moderate Cornelia de Lange syndrome.

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Cornelia de Lange syndrome (CdLS) is a congenital disorder characterized by distinctive facial features, growth retardation, limb abnormalities, intellectual disability, and behavioral problems. Autism has been reported to occur frequently in CdLS, but the frequency of autism in individuals with the milder CdLS phenotype is not well studied. We investigated autistic features by using a screening tool and a diagnostic interview in 49 individuals with the mild to moderate phenotype from a CdLS research database at the Children's Hospital of Philadelphia. The Social Communication Questionnaire (SCQ), a screening instrument for autistic disorder, was completed for all individuals. For individuals who screened positive and a subset of those that screened negative,

the Autism Diagnostic Interview-Revised (ADI-R) was administered. Autistic symptom severity was not significantly different by gender, age groups, and genotypes. There was a significant correlation between higher levels of adaptive functioning and lower scores of autistic symptoms. The estimated prevalence of significant autistic features by ADI-R criteria was 43% in our cohort of individuals with the mild to moderate CdLS phenotype, which suggests that prevalence of autistic disorder may be higher than previously described among individuals with mild to moderate phenotype of CdLS. Clinicians who take care of individuals with CdLS should have a high index of suspicion for autistic features, and refer for further evaluation when these features are present in order to expedite appropriate intervention.

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PMID: 22740374 [PubMed - in process]

60. Mol Autism. 2012 Jun 27;3(1):5.

High-functioning autism spectrum disorder and fragile X syndrome: report of two affected sisters.

Chaste P, Betancur C, Gérard-Blanluet M, Bargiacchi A, Kuzbari S, Drunat S, Leboyer M, Bourgeron T, Delorme R.

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richard.delorme@rdb.aphp.fr.

ABSTRACT:BACKGROUND: Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability (ID), as well as the most frequent monogenic cause of autism spectrum disorder (ASD). Men with FXS exhibit ID, often associated with autistic features, whereas women heterozygous for the full mutation are typically less severely affected; about half have a normal or borderline intelligence quotient (IQ). Previous findings have shown a strong association between ID and ASD in both men and women with FXS. We describe here the case of two sisters with ASD and FXS but without ID. One of the sisters presented with high-functioning autism, the other one with pervasive developmental disorder not otherwise specified and low normal IQ.

METHODS: The methylation status of the mutated FMR1 alleles was examined by Southern blot and methylation-sensitive polymerase chain reaction. The X-chromosome inactivation was determined by analyzing the methylation status of the androgen receptor at Xq12.

RESULTS: Both sisters carried a full mutation in the FMR1 gene, with complete methylation and random X chromosome inactivation. We present the phenotype of the two sisters and other family members.

CONCLUSIONS: These findings suggest that autistic behaviors and cognitive impairment can manifest as independent traits in FXS. Mutations in FMR1, known to cause syndromic autism, may also contribute to the etiology of high-functioning, non-syndromic ASD, particularly in women. Thus, screening for FXS in patients with ASD should not be limited to those with comorbid ID.

PMCID: PMC3444384

PMID: 22738402 [PubMed - in process]

71. Mov Disord. 2012 Jul;27(8):1060-2. doi: 10.1002/mds.25057. Epub 2012 Jun 18.

Hand stereotypies distinguish Rett syndrome from autism disorder.

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BACKGROUND: Rett syndrome (RTT) and autism disorder (AD) are 2 neurodevelopmental disorders of early life that share phenotypic features, one being hand stereotypies. Distinguishing RTT from AD often represents a challenge, and given their distinct long-term prognoses, this issue may have far-reaching implications. With the advances in genetic testing, the contribution of clinical manifestations in distinguishing RTT from AD has been overlooked.

METHODS: A comparison of hand stereotypies in 20 children with RTT and 20 with AD was performed using detailed analyses of videotaped standardized observations.

RESULTS: Striking differences are observed between RTT and AD children. In RTT, hand stereotypies are predominantly complex, continuous, localized to the body midline, and involving mouthing. Conversely, in AD children, hand stereotypies are simple, bilateral, intermittent, and often involving objects.

CONCLUSIONS: These results provide important clinical signs useful to the differential diagnosis of RTT versus AD, especially when genetic testing for RTT is not an option.

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PMID: 22711266 [PubMed - in process]

96. J Neuropathol Exp Neurol. 2012 May;71(5):382-97.

Differences between the pattern of developmental abnormalities in autism associated with duplications 15q11.2-q13 and idiopathic autism.

Wegiel J, Schanen NC, Cook EH, Sigman M, Brown WT, Kuchna I, Nowicki K, Wegiel J, Imaki H, Ma SY, Marchi E, Wierzba-Bobrowicz T, Chauhan A, Chauhan V, Cohen IL, London E, Flory M, Lach B, Wisniewski T.

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The purposes of this study were to identify differences in patterns of developmental abnormalities between the brains of individuals with autism of unknown etiology and those of individuals with duplications of chromosome 15q11.2-q13 (dup[15]) and autism and to identify alterations that may contribute to seizures and sudden death in the latter. Brains of 9 subjects with dup(15), 10

with idiopathic autism, and 7 controls were examined. In the dup(15) cohort, 7 subjects (78%) had autism, 7 (78%) had seizures, and 6 (67%) had experienced sudden unexplained death. Subjects with dup(15) autism were microcephalic, with mean brain weights 300 g less (1,177 g) than those of subjects with idiopathic autism (1,477 g; $p < 0.001$). Heterotopias in the alveus, CA4, and dentate gyrus and dysplasia in the dentate gyrus were detected in 89% of dup(15) autism cases but in only 10% of idiopathic autism cases ($p < 0.001$). By contrast, cerebral cortex dysplasia was detected in 50% of subjects with idiopathic autism and in no dup(15) autism cases ($p < 0.04$). The different spectrum and higher prevalence of developmental neuropathologic findings in the dup(15) cohort than in cases with idiopathic autism may contribute to the high risk of early onset of seizures and sudden death.

PMID: 22487857 [PubMed - indexed for MEDLINE]

Sci Transl Med. 2012 Sep 19;4(152):152ra127.

Effects of STX209 (Arbaclofen) on Neurobehavioral Function in Children and Adults with Fragile X Syndrome: A Randomized, Controlled, Phase 2 Trial.

Berry-Kravis EM, Hessel D, Rathmell B, Zarevics P, Cherubini M, Walton-Bowen K, Mu Y, Nguyen DV, Gonzalez-Heydrich J, Wang PP, Carpenter RL, Bear MF, Hagerman RJ.

Source

Departments of Pediatrics, Neurological Sciences, and Biochemistry, Rush University Medical Center, Chicago, IL 60612, USA.

Abstract

Research on animal models of fragile X syndrome suggests that STX209, a γ -aminobutyric acid type B (GABA(B)) agonist, might improve neurobehavioral function in affected patients. We evaluated whether STX209 improves behavioral symptoms of fragile X syndrome in a randomized, double-blind, placebo-controlled crossover study in 63 subjects (55 male), ages 6 to 39 years, with a full mutation in the FMR1 gene (>200 CGG triplet repeats). We found no difference from placebo on the primary endpoint, the Aberrant Behavior Checklist-Irritability (ABC-I) subscale. In the other analyses specified in the protocol, improvement was seen on the visual analog scale ratings of parent-nominated problem behaviors, with positive trends on multiple global measures. Post hoc analysis with the ABC-Social Avoidance scale, a newly validated scale for the assessment of fragile X syndrome, showed a significant beneficial treatment effect in the full study population. A post hoc subgroup of 27 subjects with more severe social impairment showed improvements on the Vineland II-Socialization raw score, on the ABC-Social Avoidance scale, and on all global measures. STX209 was well tolerated, with 8% incidences of sedation and of headache as the most frequent side effects. In this exploratory study, STX209 did not show a benefit on irritability in fragile X syndrome. Nonetheless, our results suggest that GABA(B) agonists have potential to improve social function and behavior in patients with fragile X syndrome.

PMID: 22993294 [PubMed - in process]

IMMUNOLOGY/AUTOIMMUNE

19. J Neuroimmunol. 2012 Aug 27. [Epub ahead of print]

Maternal autism-associated IgG antibodies delay development and produce anxiety in a mouse gestational transfer model.

Braunschweig D, Golub MS, Koenig CM, Qi L, Pessah IN, Van de Water J, Berman RF.

Division of Rheumatology/Allergy and Clinical Immunology, University of California, Davis, 451 E. Health Sciences Drive, Suite 6510 GBSF, Davis, CA 95616 USA; The M.I.N.D. Institute, University of California, Davis, Davis, CA 95616, USA; NIEHS Center for Children's Environmental Health, University of California, Davis, Davis, CA 95616, USA.

A murine passive transfer model system was employed to ascertain the effects of gestational exposure to a single, intravenous dose of purified, brain-reactive IgG antibodies from individual mothers of children with autism (MAU) or mothers with typically developing children (MTD). Growth and behavioral outcomes in offspring were measured from postnatal days 8 to 65 in each group. Comparisons revealed alterations in early growth trajectories, significantly impaired motor and sensory development, and increased anxiety. This report demonstrates for the first time the effects of a single, low dose gestational exposure of IgG derived from individual MAU on their offspring's physical and social development.

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PMID: 22951357 [PubMed - as supplied by publisher]

22. Autism Res Treat. 2012;2012:190930. Epub 2012 Jun 19.

Prenatal and Postnatal Epigenetic Programming: Implications for GI, Immune, and Neuronal Function in Autism. [QUESTION 3?, NOT A REVIEW]

Waly MI, Hornig M, Trivedi M, Hodgson N, Kini R, Ohta A, Deth R.

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Although autism is first and foremost a disorder of the central nervous system, comorbid dysfunction of the gastrointestinal (GI) and immune systems is common, suggesting that all three systems may be affected by common molecular mechanisms. Substantial systemic deficits in the antioxidant glutathione and its precursor, cysteine, have been documented in autism in association with oxidative stress and impaired methylation. DNA and histone methylation provide epigenetic regulation of gene expression during prenatal and postnatal development. Prenatal epigenetic programming (PrEP) can be affected by the maternal metabolic and nutritional environment, whereas postnatal epigenetic programming (PEP) importantly depends upon nutritional support provided through the GI tract. Cysteine absorption from the GI tract is a crucial determinant of antioxidant capacity, and systemic deficits of glutathione and cysteine in autism are likely to reflect impaired cysteine absorption. Excitatory amino acid transporter 3 (EAAT3) provides cysteine uptake for GI epithelial, neuronal, and immune cells, and its activity is decreased during oxidative stress. Based upon these observations, we propose that neurodevelopmental, GI, and immune aspects of autism each reflect

manifestations of inadequate antioxidant capacity, secondary to impaired cysteine uptake by the GI tract. Genetic and environmental factors that adversely affect antioxidant capacity can disrupt PrEP and/or PEP, increasing vulnerability to autism.

PMCID: PMC3420412

PMID: 22934169 [PubMed]

23. *Methods Mol Biol.* 2012;934:219-40.

Autism spectrum disorders: from immunity to behavior. [REVIEW]

Careaga M, Ashwood P.

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Autism spectrum disorders (ASD) are complex and heterogeneous with a spectrum of diverse symptoms. Mounting evidence from a number of disciplines suggests a link between immune function and ASD. Although the causes of ASD have yet to be identified, genetic studies have uncovered a host of candidate genes relating to immune regulation that are altered in ASD, while epidemiological studies have shown a relationship with maternal immune disturbances during pregnancy and ASD. Moreover, decades of research have identified numerous systemic and cellular immune abnormalities in individuals with ASD and their families. These include changes in immune cell number, differences in cytokine and chemokine production, and alterations of cellular function at rest and in response to immunological challenge. Many of these changes in immune responses are associated with increasing impairment in behaviors that are core features of ASD. Despite this evidence, much remains to be understood about the precise mechanism by which the immune system alters neurodevelopment and to what extent it is involved in the pathogenesis of ASD. With estimates of ASD as high as 1% of children, ASD is a major public health issue. Improvements in our understanding of the interactions between the nervous and immune system during early neurodevelopment and how this interaction is different in ASD will have important therapeutic implications with wide ranging benefits.

PMID: 22933149 [PubMed - in process]

31. *Dev Neurobiol.* 2012 Oct;72(10):1327-34. doi: 10.1002/dneu.22052. Epub 2012 Sep 4.

Maternal and fetal antibrain antibodies in development and disease. [REVIEW]

Fox E, Amaral D, Van de Water J.

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Recent evidence has emerged indicating that the maternal immune response can have a substantial deleterious impact on prenatal development (Croen et al., [2008]: *Biol Psychiatry* 64:583-588). The maternal immune response is largely sequestered

from the fetus. Maternal antibodies, specifically immunoglobulin G (IgG), are passed to the fetus to provide passive immunity throughout much of pregnancy. However, both protective and pathogenic autoantibodies have equal access to the fetus (Goines and Van de Water [2010]: *Curr Opin Neurol* 23:111-117). If the mother has an underlying autoimmune disease or has reactivity to fetal antigens, autoantibodies produced before or during pregnancy can target tissues in the developing fetus. One such tissue is the fetal brain. The blood brainbarrier (BBB) is developing during the fetal period allowing maternal antibodies to have direct access to the brain during gestation (Diamond et al. [2009]: *Nat Rev Immunol*; Braunschweig et al. [2011]; *Neurotoxicology* 29:226-231). It has been proposed that brain injury by circulating brain-specific maternal autoantibodies might underlie multiple congenital, developmental disorders (Lee et al. [2009]: *Nat Med* 15:91-96). In this review, we will discuss the current state of research in the area of maternal autoantibodies and the development of autism. © 2012 Wiley Periodicals, Inc. *Develop Neurobiol*, 2012.

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PMID: 22911883 [PubMed - in process]

37. *Neuron Glia Biol.* 2012 Jul 6:1-9. [Epub ahead of print]

Evidence of microglial activation in autism and its possible role in brain underconnectivity. [REVIEW]

Rodriguez JI, Kern JK.

Stop Calling It Autism, Fort Worth, TX, USA.

Evidence indicates that children with autism spectrum disorder (ASD) suffer from an ongoing neuroinflammatory process in different regions of the brain involving microglial activation. When microglia remain activated for an extended period, the production of mediators is sustained longer than usual and this increase in mediators contributes to loss of synaptic connections and neuronal cell death. Microglial activation can then result in a loss of connections or underconnectivity. Underconnectivity is reported in many studies in autism. One way to control neuroinflammation is to reduce or inhibit microglial activation. It is plausible that by reducing brain inflammation and microglial activation, the neurodestructive effects of chronic inflammation could be reduced and allow for improved developmental outcomes. Future studies that examine treatments that may reduce microglial activation and neuroinflammation, and ultimately help to mitigate symptoms in ASD, are warranted.

PMID: 22874006 [PubMed - as supplied by publisher]

Annu Rev Neurosci. 2012;35:369-89.

The complement system: an unexpected role in synaptic pruning during development and disease.

Stephan AH, Barres BA, Stevens B.

Source

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Abstract

An unexpected role for the classical complement cascade in the elimination of central nervous system (CNS) synapses has recently been discovered. Complement proteins are localized to developing CNS synapses during periods of active synapse elimination and are required for normal brain wiring. The function of complement proteins in the brain appears analogous to their function in the immune system: clearance of cellular material that has been tagged for elimination. Similarly, synapses tagged with complement proteins may be eliminated by microglial cells expressing complement receptors. In addition, developing astrocytes release signals that induce the expression of complement components in the CNS. In the mature brain, early synapse loss is a hallmark of several neurodegenerative diseases. Complement proteins are profoundly upregulated in many CNS diseases prior to signs of neuron loss, suggesting a reactivation of similar developmental mechanisms of complement-mediated synapse elimination potentially driving disease progression.

PMID: 22715882 [PubMed - in process]

Neuron. 2012 May 24;74(4):691-705.

Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner.

Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, Ransohoff RM, Greenberg ME, Barres BA, Stevens B.

Source

Department of Neurology, F.M. Kirby Neurobiology Center, Children's Hospital, Harvard Medical School, Boston, MA 02115, USA.

Abstract

Microglia are the resident CNS immune cells and active surveyors of the extracellular environment. While past work has focused on the role of these cells during disease, recent imaging studies reveal dynamic interactions between microglia and synaptic elements in the healthy brain. Despite these intriguing observations, the precise function of microglia at remodeling synapses and the mechanisms that underlie microglia-synapse interactions remain elusive. In the current study, we demonstrate a role for microglia in activity-dependent synaptic pruning in the postnatal retinogeniculate system. We show that microglia engulf presynaptic inputs during peak retinogeniculate pruning and that engulfment is dependent upon neural activity and the microglia-specific phagocytic signaling pathway, complement receptor 3(CR3)/C3. Furthermore, disrupting microglia-specific CR3/C3 signaling resulted in sustained deficits in synaptic connectivity. These results define a role for microglia during postnatal development and identify underlying mechanisms by which microglia engulf and remodel developing synapses.

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Comment in

Complement-mediated microglial clearance of developing retinal ganglion cell axons. [Neuron. 2012]

PMID: 22632727 [PubMed - indexed for MEDLINE]

40. J Neuroimmunol. 2012 Oct 15;251(1-2):94-102. Epub 2012 Jul 31.

Decreased levels of total immunoglobulin in children with autism are not a result of B cell dysfunction.

Heuer LS, Rose M, Ashwood P, Van de Water J.

Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis, USA; The M.I.N.D. Institute, University of California at Davis, USA; NIEHS Center for Children's Environmental Health, University of California, Davis, Davis, CA 95616, USA.

Autism spectrum disorders are a heterogeneous group of behaviorally defined disorders having complex etiologies. We previously reported a direct correlation between lower plasma levels of the immunoglobulins (Ig) IgG and IgM and increased severity of behavioral symptoms in children with autism. Our current objective was to determine if these reduced plasma levels of IgG and IgM are the result of defective B cell development, activation, or function. Results suggest no differences in the B cell parameters measured, indicating that decreased Ig in autism is not a result of B cell dysfunction and other immune cells might be involved.

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PMCID: PMC3432686 [Available on 2013/10/15]

PMID: 22854260 [PubMed - in process]

47. Transl Psychiatry. 2012 Apr 3;2:e98. doi: 10.1038/tp.2012.24.

Effects of maternal immune activation on gene expression patterns in the fetal brain.

Garbett KA, Hsiao EY, Kálmán S, Patterson PH, Mirnics K.

Department of Psychiatry, Vanderbilt University, Nashville, TN 37203, USA.

We are exploring the mechanisms underlying how maternal infection increases the risk for schizophrenia and autism in the offspring. Several mouse models of maternal immune activation (MIA) were used to examine the immediate effects of MIA induced by influenza virus, poly(I:C) and interleukin IL-6 on the fetal brain transcriptome. Our results indicate that all three MIA treatments lead to strong and common gene expression changes in the embryonic brain. Most notably, there is an acute and transient upregulation of the α , β and γ crystallin gene family. Furthermore, levels of crystallin gene expression are correlated with the severity of MIA as assessed by placental weight. The overall gene expression changes suggest that the response to MIA is a neuroprotective attempt by the developing brain to counteract environmental stress, but at a cost of disrupting typical neuronal differentiation and axonal growth. We propose that this cascade of events might parallel the mechanisms by which environmental insults contribute to the risk of neurodevelopmental disorders such as schizophrenia and autism.

PMCID: PMC3337077

PMID: 22832908 [PubMed - in process]

51. Proc Natl Acad Sci U S A. 2012 Jul 31;109(31):12776-81. Epub 2012 Jul 16.

Modeling an autism risk factor in mice leads to permanent immune dysregulation.

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Increasing evidence highlights a role for the immune system in the pathogenesis of autism spectrum disorder (ASD), as immune dysregulation is observed in the brain, periphery, and gastrointestinal tract of ASD individuals. Furthermore, maternal infection (maternal immune activation, MIA) is a risk factor for ASD. Modeling this risk factor in mice yields offspring with the cardinal behavioral and neuropathological symptoms of human ASD. In this study, we find that offspring of immune-activated mothers display altered immune profiles and function, characterized by a systemic deficit in CD4(+) TCR β (+) Foxp3(+) CD25(+) T regulatory cells, increased IL-6 and IL-17 production by CD4(+) T cells, and elevated levels of peripheral Gr-1(+) cells. In addition, hematopoietic stem cells from MIA offspring exhibit altered myeloid lineage potential and differentiation. Interestingly, repopulating irradiated control mice with bone marrow derived from MIA offspring does not confer MIA-related immunological deficits, implicating the peripheral environmental context in long-term programming of immune dysfunction. Furthermore, behaviorally abnormal MIA offspring that have been irradiated and transplanted with immunologically normal bone marrow from either MIA or control offspring no longer exhibit deficits in stereotyped/repetitive and anxiety-like behaviors, suggesting that immune abnormalities in MIA offspring can contribute to ASD-related behaviors. These studies support a link between cellular immune dysregulation and ASD-related behavioral deficits in a mouse model of an autism risk factor.

PMCID: PMC3411999 [Available on 2013/1/31]

PMID: 22802640 [PubMed - in process]

52. Transl Psychiatry. 2012 Jul 10;2:e134. doi: 10.1038/tp.2012.61.

Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain.

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Despite increasing evidence of oxidative stress in the pathophysiology of autism, most studies have not evaluated biomarkers within specific brain regions, and the functional consequences of oxidative stress remain relatively understudied. We examined frozen samples from the cerebellum and temporal cortex (Brodmann area 22 (BA22)) from individuals with autism and unaffected controls (n=15 and n=12 per group, respectively). Biomarkers of oxidative stress, including reduced

glutathione (GSH), oxidized glutathione (GSSG) and glutathione redox/antioxidant capacity (GSH/GSSG), were measured. Biomarkers of oxidative protein damage (3-nitrotyrosine; 3-NT) and oxidative DNA damage (8-oxo-deoxyguanosine; 8-oxo-dG) were also assessed. Functional indicators of oxidative stress included relative levels of 3-chlorotyrosine (3-CT), an established biomarker of a chronic inflammatory response, and aconitase activity, a biomarker of mitochondrial superoxide production. Consistent with previous studies on plasma and immune cells, GSH and GSH/GSSG were significantly decreased in both autism cerebellum ($P<0.01$) and BA22 ($P<0.01$). There was a significant increase in 3-NT in the autism cerebellum and BA22 ($P<0.01$). Similarly, 8-oxo-dG was significantly increased in autism cerebellum and BA22 ($P<0.01$ and $P=0.01$, respectively), and was inversely correlated with GSH/GSSG in the cerebellum ($P<0.01$). There was a significant increase in 3-CT levels in both brain regions ($P<0.01$), whereas aconitase activity was significantly decreased in autism cerebellum ($P<0.01$), and was negatively correlated with GSH/GSSG ($P=0.01$). Together, these results indicate that decreased GSH/GSSG redox/antioxidant capacity and increased oxidative stress in the autism brain may have functional consequence in terms of a chronic inflammatory response, increased mitochondrial superoxide production, and oxidative protein and DNA damage.

PMCID: PMC3410618

PMID: 22781167 [PubMed - in process]

70. *Neuron Glia Biol.* 2011 Feb;7(1):85-97. Epub 2012 Apr 30.

Does microglial dysfunction play a role in autism and Rett syndrome? [REVIEW]

Maezawa I, Calafiore M, Wulff H, Jin LW.

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Autism spectrum disorders (ASDs) including classic autism is a group of complex developmental disabilities with core deficits of impaired social interactions, communication difficulties and repetitive behaviors. Although the neurobiology of ASDs has attracted much attention in the last two decades, the role of microglia has been ignored. Existing data are focused on their recognized role in neuroinflammation, which only covers a small part of the pathological repertoire of microglia. This review highlights recent findings on the broader roles of microglia, including their active surveillance of brain microenvironments and regulation of synaptic connectivity, maturation of brain circuitry and neurogenesis. Emerging evidence suggests that microglia respond to pre- and postnatal environmental stimuli through epigenetic interface to change gene expression, thus acting as effectors of experience-dependent synaptic plasticity. Impairments of these microglial functions could substantially contribute to several major etiological factors of autism, such as environmental toxins and cortical underconnectivity. Our recent study on Rett syndrome, a syndromic autistic disorder, provides an example that intrinsic microglial dysfunction due to genetic and epigenetic aberrations could detrimentally affect the

developmental trajectory without evoking neuroinflammation. We propose that ASDs provide excellent opportunities to study the influence of microglia on neurodevelopment, and this knowledge could lead to novel therapies.

PMID: 22717189 [PubMed - in process]

97. Nature. 2012 Mar 18;484(7392):105-9. doi: 10.1038/nature10907.

Wild-type microglia arrest pathology in a mouse model of Rett syndrome.

Derecki NC, Cronk JC, Lu Z, Xu E, Abbott SB, Guyenet PG, Kipnis J.

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Comment in

Nat Rev Neurol. 2012;8(5):239.

Rett syndrome is an X-linked autism spectrum disorder. The disease is characterized in most cases by mutation of the MECP2 gene, which encodes a methyl-CpG-binding protein. Although MECP2 is expressed in many tissues, the disease is generally attributed to a primary neuronal dysfunction. However, as shown recently, glia, specifically astrocytes, also contribute to Rett pathophysiology. Here we examine the role of another form of glia, microglia, in a murine model of Rett syndrome. Transplantation of wild-type bone marrow into irradiation-conditioned Mecp2-null hosts resulted in engraftment of brain parenchyma by bone-marrow-derived myeloid cells of microglial phenotype, and arrest of disease development. However, when cranial irradiation was blocked by lead shield, and microglial engraftment was prevented, disease was not arrested. Similarly, targeted expression of MECP2 in myeloid cells, driven by Lysm(cre) on an Mecp2-null background, markedly attenuated disease symptoms. Thus, through multiple approaches, wild-type Mecp2-expressing microglia within the context of an Mecp2-null male mouse arrested numerous facets of disease pathology: lifespan was increased, breathing patterns were normalized, apnoeas were reduced, body weight was increased to near that of wild type, and locomotor activity was improved. Mecp2(+/-) females also showed significant improvements as a result of wild-type microglial engraftment. These benefits mediated by wild-type microglia, however, were diminished when phagocytic activity was inhibited pharmacologically by using annexin V to block phosphatidylserine residues on apoptotic targets, thus preventing recognition and engulfment by tissue-resident phagocytes. These results suggest the importance of microglial phagocytic activity in Rett syndrome. Our data implicate microglia as major players in the pathophysiology of this devastating disorder, and suggest that bone marrow transplantation might offer a feasible therapeutic approach for it.

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PMID: 22425995 [PubMed - indexed for MEDLINE]

J Neuroimmunol. 2012 Aug 20. [Epub ahead of print]

Neonatal levels of cytokines and risk of autism spectrum disorders: An exploratory register-based historic birth cohort study utilizing the Danish Newborn Screening Biobank. [ALSO BIOBANKING]

Abdallah MW, Larsen N, Mortensen EL, Atladóttir HO, Nørgaard-Pedersen B, Bonefeld-Jørgensen EC, Grove J, Hougaard DM.

Source

Abstract

The aim of the study was to analyze cytokine profiles in neonatal dried blood samples (n-DBSS) retrieved from The Danish Newborn Screening Biobank of children developing Autism Spectrum Disorders (ASD) later in life and controls. Samples of 359 ASD cases and 741 controls were analyzed using Luminex xMAP technology and clinical data were retrieved from nationwide registers. Findings showed that children developing ASD were more likely to have decreased levels of both T helper-1(Th-1)-like cytokines (i.e. IFN- γ) and Th-2like cytokines (i.e. IL-4, IL-10) which may suggest a depressed or hypoactive immune cell activity during neonatal period in ASD

EPILEPSY

Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits [POSTED 2011 ADVANCE] – Peñagarikano O, Abrahams BS, Herman EI, Winden KD, Gdalyahu A, Dong H, Sonnenblick LI, Gruver R, Almajano J, Bragin A, Golshani P, Trachtenberg JT, Peles E, Geschwind DH. Cell. 2011 Sep 30;147(1):235-46. [PMID: 21962519]

A new mouse model of autism, created by eliminating a gene strongly associated with the disorder in humans, shows promise for understanding the biology that underlies ASD and testing new treatments. By eliminating the CNTNAP2 gene (contactin associated protein-like 2), researchers were able to create mice with behaviors that closely mimicked those of its human counterparts – the mice exhibited repetitive behaviors, abnormal social interactions, and irregular vocalizations, in addition to experiencing seizures and hyperactivity. CNTNAP2 is thought to play an important role in the development of language, and variants of the gene have been linked to an increased risk of autism and epilepsy. Prior to experiencing seizures, the mice showed signs of abnormal brain circuit development – researchers observed irregularities in communication between neurons and their migration within the brain. These observations complement earlier studies suggesting that children with autism carrying a CNTNAP2 variant have a "disjointed brain." The frontal lobe is poorly connected with the rest of the brain but shows an overconnection with itself, resulting in poor communication with other brain regions. Notably, the mice in the study responded positively to risperidone, an antipsychotic medication approved by the FDA to treat symptoms of irritability and aggression associated with ASD. While their social interactions did not improve – risperidone has not been shown to improve social function in humans – there was a marked improvement in repetitive grooming and a decrease in hyperactivity. Creating an animal model of autism that closely resembles the symptoms and behaviors in humans may be an important tool in understanding neural development in autism and developing new treatments.

Mutations in BCKD-kinase Lead to a Potentially Treatable Form of Autism with Epilepsy

Gaia Novarino, Paul El-Fishawy, Hulya Kayserili, Nagwa A. Meguid, Eric M. Scott, Jana Schroth, Jennifer L. Silhavy, Majdi Kara, Rehab O. Khalil, Tawfeg Ben-Omran, A. Gulhan Ercan-Sencicek, Adel F. Hashish, Stephan J. Sanders, Abha R. Gupta, Hebatalla S. Hashem, Dietrich Matern, Stacey Gabriel, Larry Sweetman, Yasmeen Rahimi, Robert A. Harris, Matthew W. State, and Joseph G. Gleeson
Science 1224631 Published online 6 September 2012 [DOI:10.1126/science.1224631]

Autism spectrum disorders are a genetically heterogeneous constellation of syndromes characterized by impairments in reciprocal social interaction. Available somatic treatments have limited efficacy. We have identified inactivating mutations in the gene BCKDK (Branched Chain Ketoacid Dehydrogenase Kinase) in consanguineous families with autism, epilepsy, and intellectual disability. The encoded protein is responsible for phosphorylation-mediated inactivation of the E1- α subunit of branched chain ketoacid dehydrogenase (BCKDH). Patients with homozygous BCKDK mutations display reductions in BCKDK mRNA and protein, E1- α phosphorylation, and plasma branched chain amino acids. Bckdk knockout mice show abnormal brain amino acid profiles and neurobehavioral deficits that respond to dietary supplementation. Thus, autism presenting with intellectual disability and epilepsy caused by BCKDK mutations represents a potentially treatable syndrome.

GASTROINTESTINAL

2. Autism. 2012 Sep 17. [Epub ahead of print]

Diseases of the gastrointestinal tract in individuals diagnosed as children with atypical autism: A Danish register study based on hospital diagnoses.

Mouridsen SE, Isager T, Rich B.

Bispebjerg University Hospital, Denmark.

The purpose of this study is to compare the prevalence and types of diseases (International Classification of Mental and Behavioural Disorders, 10th Edition codes K20-K93) relating to the gastrointestinal tract in a clinical sample of 89 individuals diagnosed as children with atypical autism/pervasive developmental disorder not otherwise specified with 258 controls from the general population. All participants were screened through the nationwide Danish National Hospital Register. The average observation time was 32.9 years, and mean age at the end of the observation period was 48.5 years. Among the 89 cases with atypical autism, a total of 22 (24.7%) were registered with at least one diagnosis of any disease of the gastrointestinal tract, against 47 of 258 (18.2%) in the comparison group ($p = 0.22$; odds ratio = 1.5; 95% confidence interval = 0.8-2.6). Without reaching statistical significance, the rate of diseases of the gastrointestinal tract was particularly high (odds ratio = 1.2) in those with intelligence quotient < 70. Overall, people with atypical autism had about the same frequency of gastric, intestinal and hepatic diseases as had controls.

PMID: 22987890 [PubMed - as supplied by publisher]

4. Autism Res. 2012 Sep 20. doi: 10.1002/aur.1253. [Epub ahead of print]

Molecular Characterisation of Gastrointestinal Microbiota of Children With Autism (With and Without Gastrointestinal Dysfunction) and Their Neurotypical Siblings.

Gondalia SV, Palombo EA, Knowles SR, Cox SB, Meyer D, Austin DW.

Swinburne Autism Bio-Research Initiative (SABRI), Faculty of Life and Social Sciences, Swinburne University of Technology, Hawthorn, Victoria, Australia.

Many children with autism spectrum disorders (ASDs) suffer from gastrointestinal problems such as diarrhoea, constipation and abdominal pain. This has stimulated investigations into possible abnormalities of intestinal microbiota in autistic patients. Therefore, we designed this study to identify differences (and/or similarities) in the microbiota of children with autism (without gastrointestinal dysfunction: n = 23; with gastrointestinal dysfunction: n = 28) and their neurotypical siblings (n = 53) who share a similar environment using bacterial tag-encoded FLX amplicon pyrosequencing. Regardless of the diagnosis and sociodemographic characteristics, overall, Firmicutes (70%), Bacteroidetes (20%) and Proteobacteria (4%) were the most dominant phyla in samples. Results did not indicate clinically meaningful differences between groups. The data do not support the hypothesis that the gastrointestinal microbiota of children with ASD plays a role in the symptomatology of ASD. Other explanations for the gastrointestinal dysfunction in this population should be considered including elevated anxiety and self-restricted diets. *Autism Res* 2012, ••: ••-••. © 2012 International Society for Autism Research, Wiley Periodicals, Inc.

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PMID: 22997101 [PubMed - as supplied by publisher]

41. *J Abnorm Child Psychol.* 2012 Aug 1. [Epub ahead of print]

Anxiety, Sensory Over-Responsivity, and Gastrointestinal Problems in Children with Autism Spectrum Disorders.

Mazurek MO, Vasa RA, Kalb LG, Kanne SM, Rosenberg D, Keefer A, Murray DS, Freedman B, Lowery LA.

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Children with autism spectrum disorders (ASD) experience high rates of anxiety, sensory processing problems, and gastrointestinal (GI) problems; however, the associations among these symptoms in children with ASD have not been previously examined. The current study examined bivariate and multivariate relations among anxiety, sensory over-responsivity, and chronic GI problems in a sample of 2,973 children with ASD enrolled in the Autism Treatment Network (ages 2-17 years, 81.6 % male). Twenty-four percent of the sample experienced at least one type of chronic GI problem (constipation, abdominal pain, bloating, diarrhea, and/or nausea lasting three or more months). Children with each type of GI problem had significantly higher rates of both anxiety and sensory over-responsivity. Sensory over-responsivity and anxiety were highly associated, and each provided unique contributions to the prediction of chronic GI problems in logistic regression analyses. The results indicate that anxiety, sensory over-responsivity and GI problems are possibly interrelated phenomenon for children with ASD, and may have common underlying mechanisms.

PMID: 22850932 [PubMed - as supplied by publisher]

GENDER/SEX

11. Med Hypotheses. 2012 Sep 11. pii: S0306-9877(12)00382-9. doi: 10.1016/j.mehy.2012.08.015. [Epub ahead of print]

Are there two different neural pathways for gender differences in autism spectrum disorders? - A pilot study.

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Many studies have described sex differences in the prevalence of autism spectrum disorders (ASD) which was diagnosed four times more often in boys than in girls. However, there is no unified conclusion about why gender differences exist in ASD. Several theories attempt to elaborate why ASD in boys is more prevalent than that in girls including extreme male brain, failure of accurate diagnosis, endocrinologic mechanism effecting brain development and genetics explanation. Based on previous studies we hypothesize that there may be two different neural pathways existed in boys and girls with ASD. Using de novo copy number variations (CNVs) from boys and girls with ASD, we tested the genes contained in de novo CNVs from boys and girls with ASD by a web database. Two significant different neural pathways were identified. It indicated that a different combination of genes in the neural pathways may be responsible for sex difference of ASD. Then it is favorable to the judgment of the prognosis and influence on the treatment.

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44. J Am Acad Child Adolesc Psychiatry. 2012 Aug;51(8):788-97. Epub 2012 Jun 26.

How different are girls and boys above and below the diagnostic threshold for autism spectrum disorders?

Dworzynski K, Ronald A, Bolton P, Happé F.

National Clinical Guideline Centre, Royal College of Physicians.

OBJECTIVE: This study aimed to explore sex differences in autistic traits in relation to diagnosis, to elucidate factors that might differentially impact whether girls versus boys meet diagnostic criteria for autism or a related autism spectrum disorder (ASD).

METHOD: Data from a large population-based sample of children were examined. Girls and boys (aged 10-12 years) meeting diagnostic criteria for an ASD were compared with those failing to meet diagnostic criteria despite very high scores

on a trait measure of ASD, the Childhood Autism Spectrum Test (CAST). Information about behavioral difficulties as reported by teachers, and early estimates of intellectual functioning, were compared.

RESULTS: Girls, but not boys, meeting diagnostic criteria for ASD showed significantly more additional problems (low intellectual level, behavioral difficulties) than peers with similarly high CAST scores who did not meet diagnostic criteria.

CONCLUSIONS: These data suggest that, in the absence of additional intellectual or behavioral problems, girls are less likely than boys to meet diagnostic criteria for ASD at equivalently high levels of autistic-like traits. This might reflect gender bias in diagnosis or genuinely better adaptation/compensation in girls.

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74. PLoS One. 2012;7(6):e38355. Epub 2012 Jun 12.

Sex differences and autism: brain function during verbal fluency and mental rotation.

Beacher FD, Radulescu E, Minati L, Baron-Cohen S, Lombardo MV, Lai MC, Walker A, Howard D, Gray MA, Harrison NA, Critchley HD.

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Autism spectrum conditions (ASC) affect more males than females. This suggests that the neurobiology of autism: 1) may overlap with mechanisms underlying typical sex-differentiation or 2) alternately reflect sex-specificity in how autism is expressed in males and females. Here we used functional magnetic resonance imaging (fMRI) to test these alternate hypotheses. Fifteen men and fourteen women with Asperger syndrome (AS), and sixteen typically developing men and sixteen typically developing women underwent fMRI during performance of mental rotation and verbal fluency tasks. All groups performed the tasks equally well. On the verbal fluency task, despite equivalent task-performance, both males and females with AS showed enhanced activation of left occipitoparietal and inferior prefrontal activity compared to controls. During mental rotation, there was a significant diagnosis-by-sex interaction across occipital, temporal, parietal, middle frontal regions, with greater activation in AS males and typical females compared to AS females and typical males. These findings suggest a complex relationship between autism and sex that is differentially expressed in verbal and visuospatial domains.

PMCID: PMC3373504

PMID: 22701630 [PubMed - in process]

USE of BIOSPECIMENS AND IPSCS

54. Trends Mol Med. 2012 Aug;18(8):463-71. Epub 2012 Jul 6.

Cellular reprogramming: a novel tool for investigating autism spectrum disorders. [REVIEW]

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in reciprocal social interaction and communication, as well as the manifestation of stereotyped behaviors. Despite much effort, ASDs are not yet fully understood. Advanced genetics and genomics technologies have recently identified novel ASD genes, and approaches using genetically engineered murine models or postmortem human brain have facilitated understanding ASD. Reprogramming somatic cells into induced pluripotent stem cells (iPSCs) provides unprecedented opportunities in generating human disease models. Here, we present an overview of applying iPSCs in developing cellular models for understanding ASD. We also discuss future perspectives in the use of iPSCs as a source of cell therapy and as a screening platform for identifying small molecules with efficacy for alleviating ASD.

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PMID: 22771169 [PubMed - in process]

69. Curr Opin Neurobiol. 2012 Jun 18. [Epub ahead of print]

Modeling neurodevelopmental disorders using human neurons. [REVIEW]

Chailangkarn T, Acab A, Muotri AR.

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The cellular and molecular mechanisms of neurodevelopmental conditions such as autism spectrum disorders have been studied intensively for decades. The unavailability of live patient neurons for research, however, has represented a major obstacle in the elucidation of the disease etiologies. Recently, the development of induced pluripotent stem cell (iPSC) technology allows for the generation of human neurons from somatic cells of patients. We review ongoing studies using iPSCs as an approach to model neurodevelopmental disorders, the promise and caveats of this technique and its potential for drug screening. The reproducible findings of relevant phenotypes in Rett syndrome iPSC-derived neurons suggest that iPSC technology offers a novel and unique opportunity for the understanding of and the development of therapeutics for other autism spectrum disorders.

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100. Mol Psychiatry. 2012 Jan 10. doi: 10.1038/mp.2011.180. [Epub ahead of print]
Rett syndrome induced pluripotent stem cell-derived neurons reveal novel Neurophysiological alterations.

Farra N, Zhang WB, Pasceri P, Eubanks JH, Salter MW, Ellis J.

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Rett syndrome (RTT) is a neurodevelopmental autism spectrum disorder caused by mutations in the methyl-CpG-binding protein 2 (MECP2) gene. Here, we describe the first characterization and neuronal differentiation of induced pluripotent stem (iPS) cells derived from *Mecp2*-deficient mice. Fully reprogrammed wild-type (WT) and heterozygous female iPS cells express endogenous pluripotency markers, reactivate the X-chromosome and differentiate into the three germ layers. We directed iPS cells to produce glutamatergic neurons, which generated action potentials and formed functional excitatory synapses. iPS cell-derived neurons from heterozygous *Mecp2*(308) mice showed defects in the generation of evoked action potentials and glutamatergic synaptic transmission, as previously reported in brain slices. Further, we examined electrophysiology features not yet studied with the RTT iPS cell system and discovered that MeCP2-deficient neurons fired fewer action potentials, and displayed decreased action potential amplitude, diminished peak inward currents and higher input resistance relative to WT iPS-derived neurons. Deficiencies in action potential firing and inward currents suggest that disturbed Na(+) channel function may contribute to the dysfunctional RTT neuronal network. These phenotypes were additionally confirmed in neurons derived from independent WT and hemizygous mutant iPS cell lines, indicating that these reproducible deficits are attributable to MeCP2 deficiency. Taken together, these results demonstrate that neuronally differentiated MeCP2-deficient iPS cells recapitulate deficits observed previously in primary neurons, and these identified phenotypes further illustrate the requirement of MeCP2 in neuronal development and/or in the maintenance of normal function. By validating the use of iPS cells to delineate mechanisms underlying RTT pathogenesis, we identify deficiencies that can be targeted for in vitro translational screens. Molecular Psychiatry advance online publication, 10 January 2012; doi:10.1038/mp.2011.180.

PMID: 22230884 [PubMed - as supplied by publisher]

24. Nat Cell Biol. 2012 Sep;14(9):911-23. doi: 10.1038/ncb2566. Epub 2012 Aug 26.

CDKL5 ensures excitatory synapse stability by reinforcing NGL-1-PSD95 interaction in the postsynaptic compartment and is impaired in patient iPSC-derived neurons.

Ricciardi S, Ungaro F, Hambrock M, Rademacher N, Stefanelli G, Brambilla D, Sessa A, Magagnotti C, Bachi A, Giarda E, Verpelli C, Kilstrup-Nielsen C, Sala C, Kalscheuer VM, Broccoli V.

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Mutations of the cyclin-dependent kinase-like 5 (CDKL5) and netrin-G1 (NTNG1) genes cause a severe neurodevelopmental disorder with clinical features that are closely related to Rett syndrome, including intellectual disability, early-onset intractable epilepsy and autism. We report here that CDKL5 is localized at excitatory synapses and contributes to correct dendritic spine structure and synapse activity. To exert this role, CDKL5 binds and phosphorylates the cell adhesion molecule NGL-1. This phosphorylation event ensures a stable association between NGL-1 and PSD95. Accordingly, phospho-mutant NGL-1 is unable to induce synaptic contacts whereas its phospho-mimetic form binds PSD95 more efficiently and partially rescues the CDKL5-specific spine defects. Interestingly, similarly to rodent neurons, iPSC-derived neurons from patients with CDKL5 mutations exhibit aberrant dendritic spines, thus suggesting a common function of CDKL5 in mice and humans.

PMID: 22922712 [PubMed - in process]