The Present and Future of Biomedical Research on Autism

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What causes autism?
There are likely to be many causes of autism and many types of autism?

AutismS not Autism
What causes autism?

Genes
G₁, G₂, G₃, ..., Gₙ

Environment
Factor₁, Factor₂, ..., Factorₙ

Autism Type A
Autism Type B
Autism Type C

Recent genetic findings
Defined mutations, genetic syndromes and de novo copy number variation probably account for about 10–20% of cases, with none of these known causes accounting for more than 1–2%.

None of the molecules or syndromes currently linked to the ASDs has been proven to selectively cause autism.

Abrahams and Geschwind., Nature Reviews Genetics, 2008
ASD-related syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s) associated with the syndrome</th>
<th>Proportion of patients with the syndrome that have an ASD</th>
<th>Proportion of patients with an ASD that have the syndrome</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q duplication</td>
<td>Unknown</td>
<td>High</td>
<td>1–2%</td>
<td>101</td>
</tr>
<tr>
<td>Angelman syndrome</td>
<td>UBE3A (and others)</td>
<td>&gt;40%</td>
<td>Rare</td>
<td>102, 103</td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTNAP2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
</tr>
<tr>
<td>Fragile-X syndrome</td>
<td>FMR1</td>
<td>25% of males; 6% of females</td>
<td>1–2%</td>
<td>105</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
</tr>
<tr>
<td>Potocki-Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>DHCPR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
</tr>
</tbody>
</table>

Abrahams and Geschwind, Nature Reviews Genetics, 2008

Copy Number Variation

Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat,⁶itative, B. Lakshmi,⁶ Dheeraj Malhotra,³ Jennifer Troge,⁶ Christa Lese-Martin,² Tom Walsh,¹ Boris Yamrom,² Seungtae Yoon,² Alex Kranzitz,² Jade Randall,² Anthony Loetta,² Deepa Pol,¹ Ray Zhang,² Yoon-Ha Lee,¹ James Hicks,¹ Sarah J. Spencer,¹ Annette T. Lee,² Kajsa Puesa,¹ Terho Lehtimäki,¹ David Ledbetter,² Peter K. Gregersen,¹ Joel Bregman,¹ James S. Sutcliffe,² Vaidshri Jhanaputra,³ Wendy Chung,² Dorothy Warburton,¹ Mary-Claire King,¹ David Skuse,³ Daniel H. Geschwind,² T. Conrad Gilliam,¹ Kenny Yu,¹ Michael Wigler¹∗

We tested the hypothesis that de novo copy number variation (CNV) is associated with autism spectrum disorders (ASDs). We performed comparative genome hybridization (CGH) on the genomic DNA of patients and unaffected subjects to detect copy number variants not present in their respective parents. Candidate genomic regions were validated by higher-resolution CGH, paternity testing, cytogenetics, fluorescence in situ hybridization, and microsatellite genotyping. Confirmed de novo CNVs were significantly associated with autism (P < 0.0002). Such CNVs were identified in 12 out of 128 (10%) of patients with sporadic autism. In 2 out of 77 (2.6%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls. Most de novo CNVs were smaller than microsatropic resolution. Affected genomic regions were highly heterogeneous and included mutations of single genes. These findings establish de novo germline mutation as a more significant risk factor for ASD than previously recognized.

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Brain Pathology

The trajectory of brain development, rather than the end product, may be the most distinguishing feature of the neuropathology of autism.

What is the evidence for a role of the amygdala in autism?
Autism MRI Study Design
Male subjects (n=98), age 7.5-18.5 years

Diagnostic tests: ADOS, ADIR, IQ

Diagnostic groups:
  - Low Functioning Autism (n=17)
  - High Functioning Autism (n=25)
  - Asperger Syndrome (n=25)
  - Normal Control (n=25)

Excluded: seizure disorder, Fragile X
Imaging: 1.5T at UC Davis & 3T at Stanford University
Analyze software package

Summary of Amygdala Growth

![Chart showing amygdala growth comparison between control and autism groups. The chart indicates a 40% increase in volume for the autism group compared to control.](chart.png)
Conclusions

The amygdala is pathological in autism.

Which behavioral impairments might result from amygdala pathology?

The Amygdala

- Fear Responses
- Social Behavior
- Reward Association
- Memory Modulation
The Amygdala is a Protection Device

- Inhibits behavior to allow time for evaluation.
- Evaluates environmental stimuli (both inanimate objects and other organisms) for possible danger.
  
  If danger is detected, orchestrates other brain regions to produce appropriate responses.

Hypothesis

Why look at the immune system?

- A healthy immune system is necessary for normal development of the nervous system.
- There is ongoing communication between these two systems throughout life.
Detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders

Sharifa Wills a,b, Marisel Cabanalit a,c, Jeff Bennett a,d, Paul Ashwood c,a,d,e,
David G. Amaral a,b,f, Judy Van de Water a,g,h

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b Department of Psychiatry and Behavioral Sciences, Center for Neuroscience, California National Primate Research Center, University of California, Davis, CA 95616, USA
c Department of Medical Microbiology and Immunology, University of California at Davis, CA 95616, USA
d The MIND Institute, University of California at Davis, CA 95616, USA
e MIND Institute, Center for Children’s Environmental Health, University of California, Davis, CA 95616, USA

THE ROLE OF MATERNAL ANTIBODIES TO FETAL BRAIN IN AUTISM

Autism: Maternally derived antibodies specific for fetal brain proteins

Daniel Braunschweig a,g,h, Paul Ashwood b,g,h, Paula Krakowiak c,g,h, Irvae Hertz-Picciotto c,g,h,
Robin Hansen b,g,h, Lisa A. Croen a, Isaac N. Pessah f,g,h, Judy Van de Water b,g,h,n
An Immunological Model of Autism in the Nonhuman Primate

Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism

Loren A. Martin, Paul Ashwood, Daniel Braunschweig, Maricel Cabanlit, Judy Van de Water, David G. Amaral