



 I do not intend to discuss any unapproved or investigative use of commercial products or devices. What is the Cause of Autism?

- Background
- Genetic Contributions
- Where is the Lesion?
- Neurochemistry
- Immune Factors

Diverse Autistic Symptoms Makes Search for Biomarkers Difficult

Core Symptoms

- Poor Eye Contact
- Impaired Social Reciprocity
- Impaired Communication
 Insomnia
- Echolalia
- Need for Sameness
- Stereotypies

Associated Symptoms

- ADHD symptoms
- Irritability
- Anxiety
- Intellectual Disability

Heterogeneity Complicates Research

- Range of Autistic Severity
- Range of Intellectual Ability
- Possible differences among phenotypic subtypes
 - Autistic disorder (autism)
 - Asperger's disorder
 - PDD NOS (atypical autism)
- Might heterogeneity lead to missed findings?

Autistic Regression 25-30% of children with autism Loss of language and/or social at 15-30 months Doesn't necessarily imply environmental "hit" Possible links

- Gastrointestinal symptoms
- Autoimmunity
- Sleep
- Epileptiform activity on EEG

Werner & Dawson (2005) Arch Gen Psychiatry Valicenti-McDermott et al (2008) Pediatr Neurol Giannotti et al (2008) J Aut Dev Disord



Genetic Syndromes Associated with Autism					
Syndrome	Gene(s) associated with the syndrome	Proportion of patients with the syndrome that have an ASD	Proportion of patients with an ASD that have the syndrome		
15q duplication — Angelman syndrome	UBE3A (and others)	>40%	1-2%		
16p11 deletion	Unknown	High	-1%		
22q deletion	SHANK3	High	1%		
			-		

K3 H KAP2 -; 2! alloci 2! nosome -{ on 17p11	High -70% 25% of males; 6% of females 25% -90%	1% Rare L-2% Rare Unknown
AP2	-70% 25% of males; 6% of females 25% -90%	Rare 1–2% Rare Unknown
2: alloci 2: nosome on 17p11	25% of males; 6% of females 25% -90%	1–2% Rare Unknown
alloci 2: nosome -: on 17p11	-90%	Rare Unknown
nosome	-90%	Unknown
07 50	50%	Kare
′2 Al ∍y	All individuals have Rett yndrome	0.5%
IA1C 60	50-80%	Unknown
	20%	-1%
•	vA1C 6 and TSC2 2	syndrome VA1C 60–80% and TSC2 20%













Autism and Temporal Lobes

- Increase in autism in tuberous sclerosis when tubers are present in temporal lobes
- Multiple case reports of acquired autism secondary to herpes simplex encephalitis which primarily affects temporal lobes

Bolton et al (2002) *Brain* Ghaziuddin et al (2002) *Eur Child Adolesc Psychiatry*







Neurochemistry of Autism

- 5-HT
- GLU
- GABA
- OXYTOCIN
- MELATONIN







5-HT challenge studies

- Acute Tryptophan Depletion
- TRYP is essential AA for 5-HT production
- Administration of TRYP-free AA mixture results in significant reduction of 5-HT in plasma and 5-HIAA in CSF in 5 hours
- 11/17 adults with autism worse with TRYP depletion vs. 0/17 worse with sham depletion

McDougle et al (1996) Arch Gen Psychiatry



Serotonin Transporter Gene (SLC6A4)

- Encodes 5-HT Transporter
- Conflicting findings regarding association with autism
 - Long variant
 - Short variant
 - No association
- Possible association between autism subtypes (rigid compulsive behavior)
- Possible association with cortical gray matter volume























Number of Families in Each Group with a Specific Autoimmune Disease				
	PDD (n=101)	Autoimmune (n=101)	Healthy (n=101)	
Rheumatic Fever	23	10	6	
Hypothyroidism/ Hashimoto's	36	11	14	
PDD > Controls (p < .05				
Sweeten et al (2	003) Pediatrics			







What is the Underlying Cause of Autism?

- Autism is clearly genetic
 - Multiple genes acting together
 - Epigenetics (changes in gene expression)
 - Increased identification of specific genetic syndrome associated with autism
- Environmental contributions may also be important
 - Complex interactions with genes and neurodevelopment
- fMRI reveals abnormalities in fusiform face area and amygdala

What is the Underlying Cause of Autism?

- 5-HT abnormalities
 - Peripheral blood
 - PET
 - Challenge Studies
- Emerging evidence of glutamatergic and oxytocin abnormalities
- Immune system activation may also play a role

Lack of Singular Neurobiology

- Heterogeneity of "the autisms"
- Complexity of neurodevelopmental disorders
- Innate challenges of research
 - Low prevalence of ASDs
 - Age of onset
 - Communication and cognitive limitations
 - Importance of choosing suitable controls to account for specificity of findings

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