

How can the clinical manifestations of autism shed light on environmental etiologies?

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What is autism?

§ Developmental Disorder

- § Must onset before age 3 years

- § Development affects symptom expression

- § Symptoms exacerbated/alleviated by development

§ One of several Pervasive Developmental Disorders or Autism Spectrum Disorders

- § **Autism**

- § Pervasive Developmental Disorder – Not Otherwise Specified

- § Asperger Syndrome

- § (Rett Disorder)

- § (Childhood Disintegrative Disorder)

Autism is characterized by:

- § **Deficits in Social Interactions (2 or more)**
 - § Impairment in use of nonverbal behaviors
 - § Failure to develop peer relationships
 - § Lack of spontaneous seeking to share enjoyment, etc
 - § Lack of social or emotional reciprocity
- § **Communication deficits (verbal & nonverbal) (1 or more)**
 - § Delayed/lack of spoken language
 - § Inability to converse with others
 - § Stereotyped and repetitive or idiosyncratic language
 - § Lack of make-believe or social imitative play
- § **Fixated interests and/or repetitive behaviors (1 or more)**
 - § Preoccupation with one or more restricted interests
 - § Inflexible adherence to specific nonfunctional routines
 - § Stereotyped and repetitive motor mannerisms
 - § Persistent preoccupation with parts of objects

Social Deficits in Autism

Typical Child – Joint Attention

VIDEO EXAMPLE

Social Deficits in Autism

Child with Autism – Joint Attention

VIDEO EXAMPLE

Communication Deficits in Autism
Typical child – Making needs known
and sharing joy/interest with others

VIDEO EXAMPLE

Communication Deficits in Autism Child with Autism – Same Task

VIDEO EXAMPLE

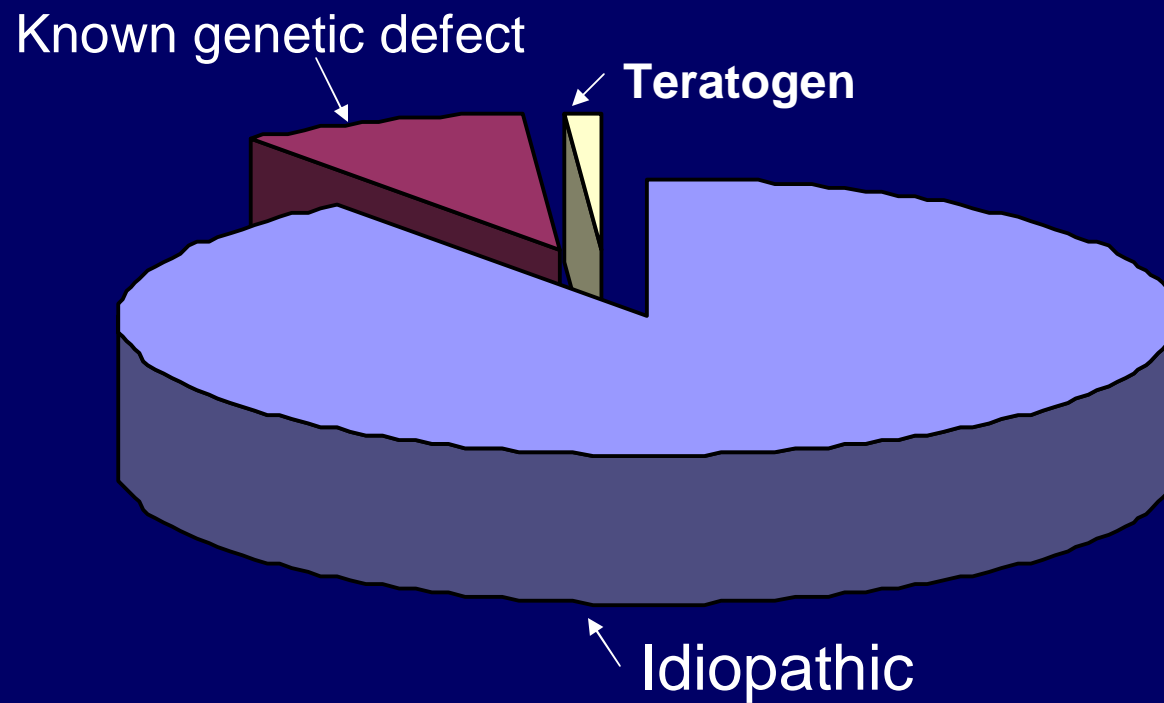
Social Deficits in Autism, and Fixated Interests/Repetitive Behaviors

VIDEO EXAMPLE

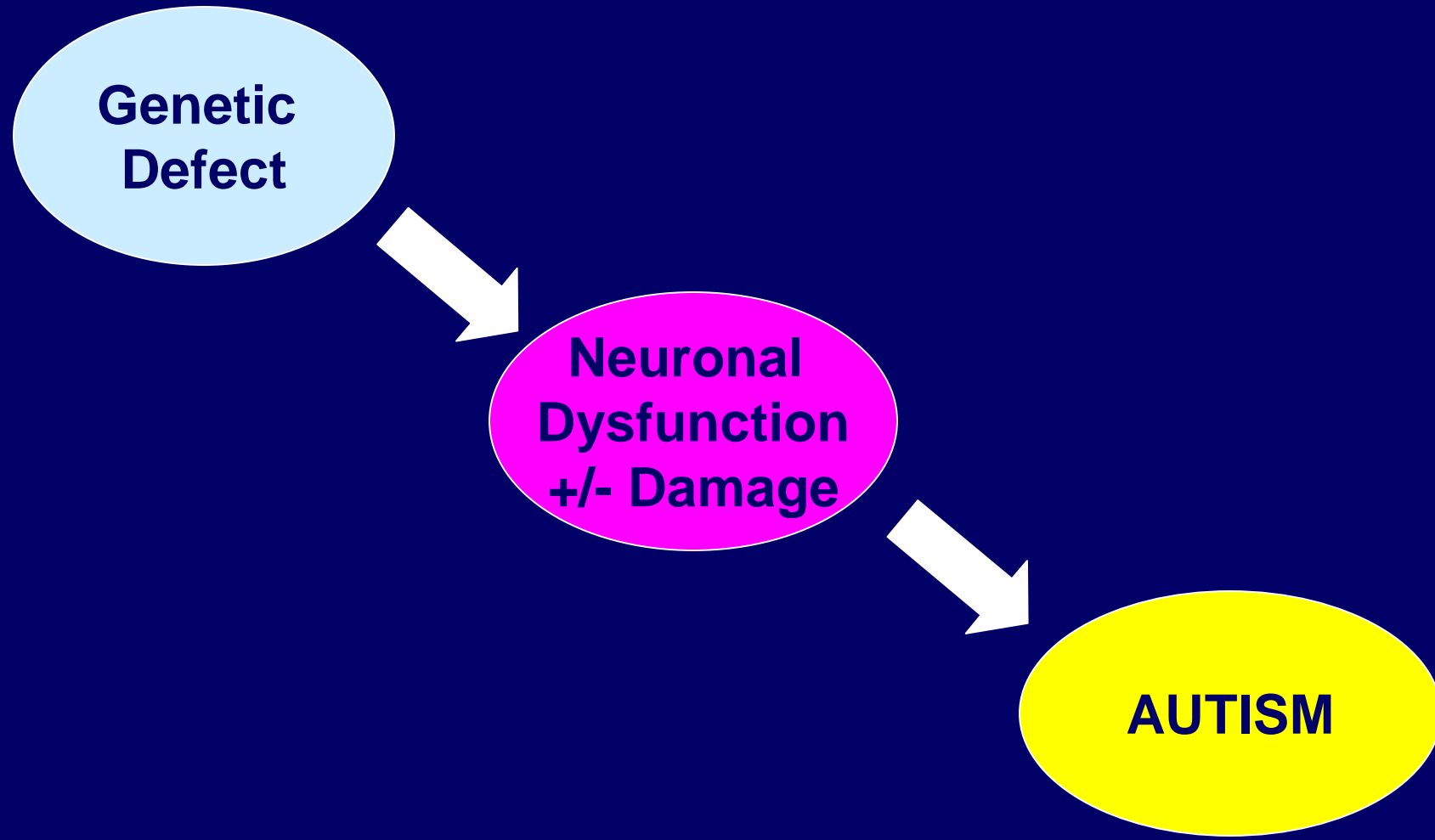
Fixated Interests/Repetitive Behaviors

VIDEO EXAMPLE

Causes of Autism



Pathogenesis of Autism

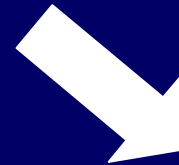
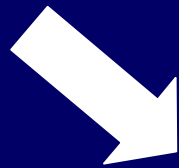


Pathogenesis of Autism

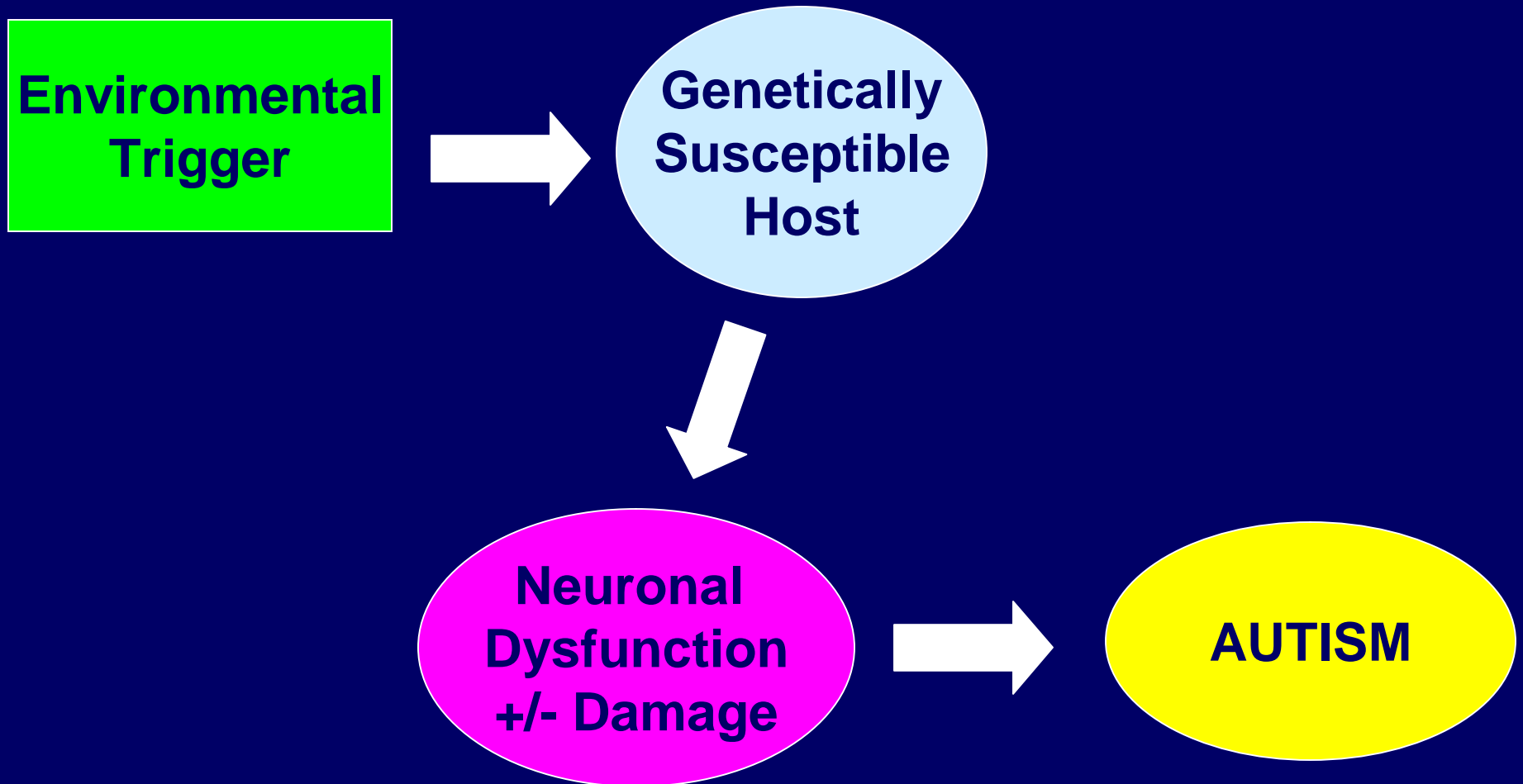
**Environmental
Trigger
(Teratogen)**

**Neuronal
Dysfunction
+/- Damage**

AUTISM



Pathogenesis of Autism



Potential Environmental Triggers

- § Toxicants
- § Infectious agents
- § Household exposures
- § Food, dietary supplements and vitamins/minerals
- § Drugs, medications and herbal remedies
- § Other medical interventions
- § Technological advances
- § Countless others encountered by mom, dad & child

Clinical Clues to Environmental Etiologies

- § Association with teratogenic agents
- § Reported prevalence is increasing
- § 12 – 18 months age at onset
- § Medical co-morbidities
- § Response to treatments
- § Other observations
- § REGRESSIVE SUBTYPE

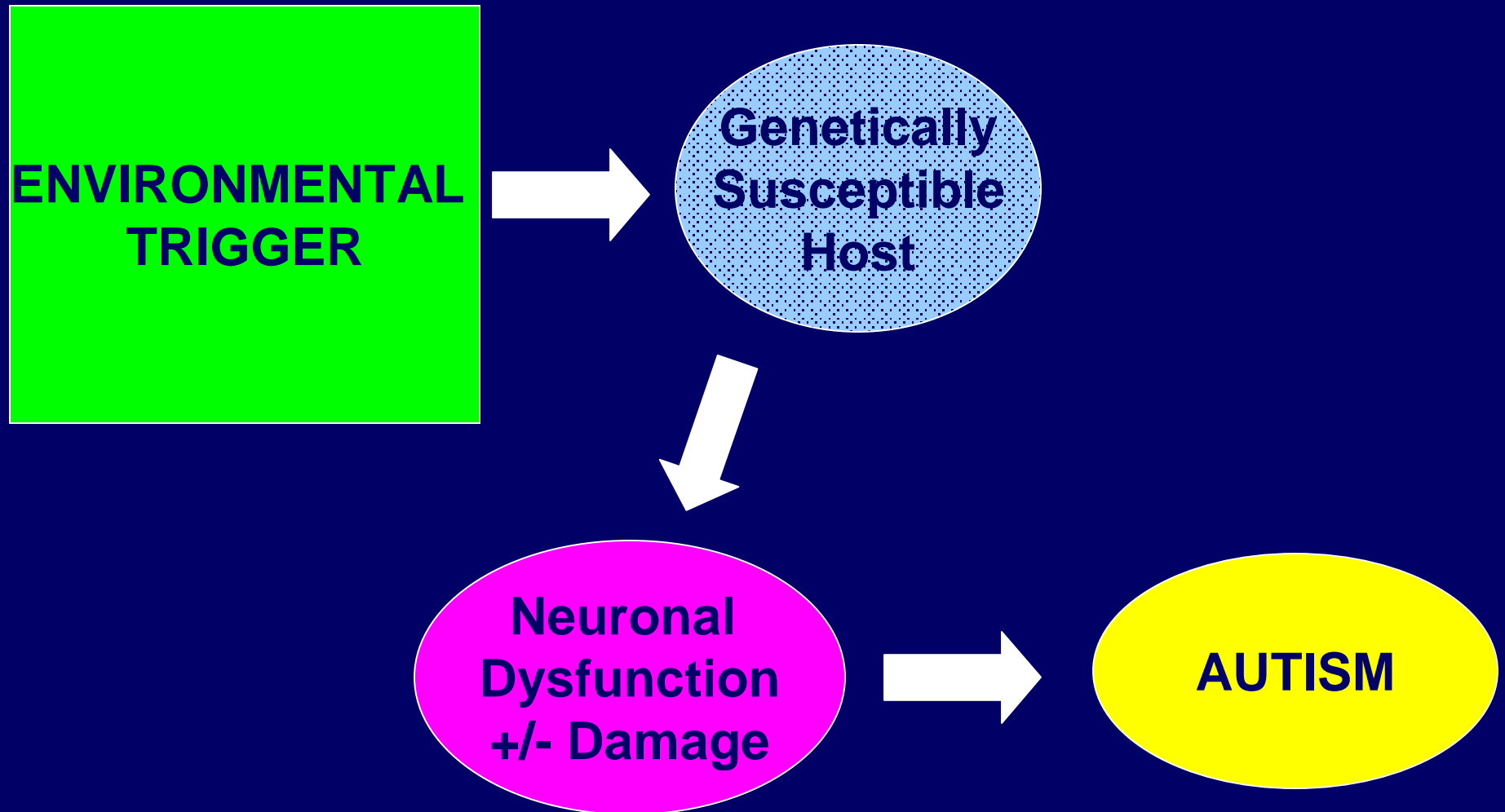
Clinical Clues: Regressive Subtype

- § Normal development until 12 – 30 months age and then loss of language and social skills
- § 15-50% of autism has regressive features (rate depends on definition of regression)
- § Reported prognosis for regressive autism is poor
- § Regression can be acute or slow and subtle
- § Videotapes often show that development wasn't completely normal before regression occurred, but obvious loss of acquired skills.

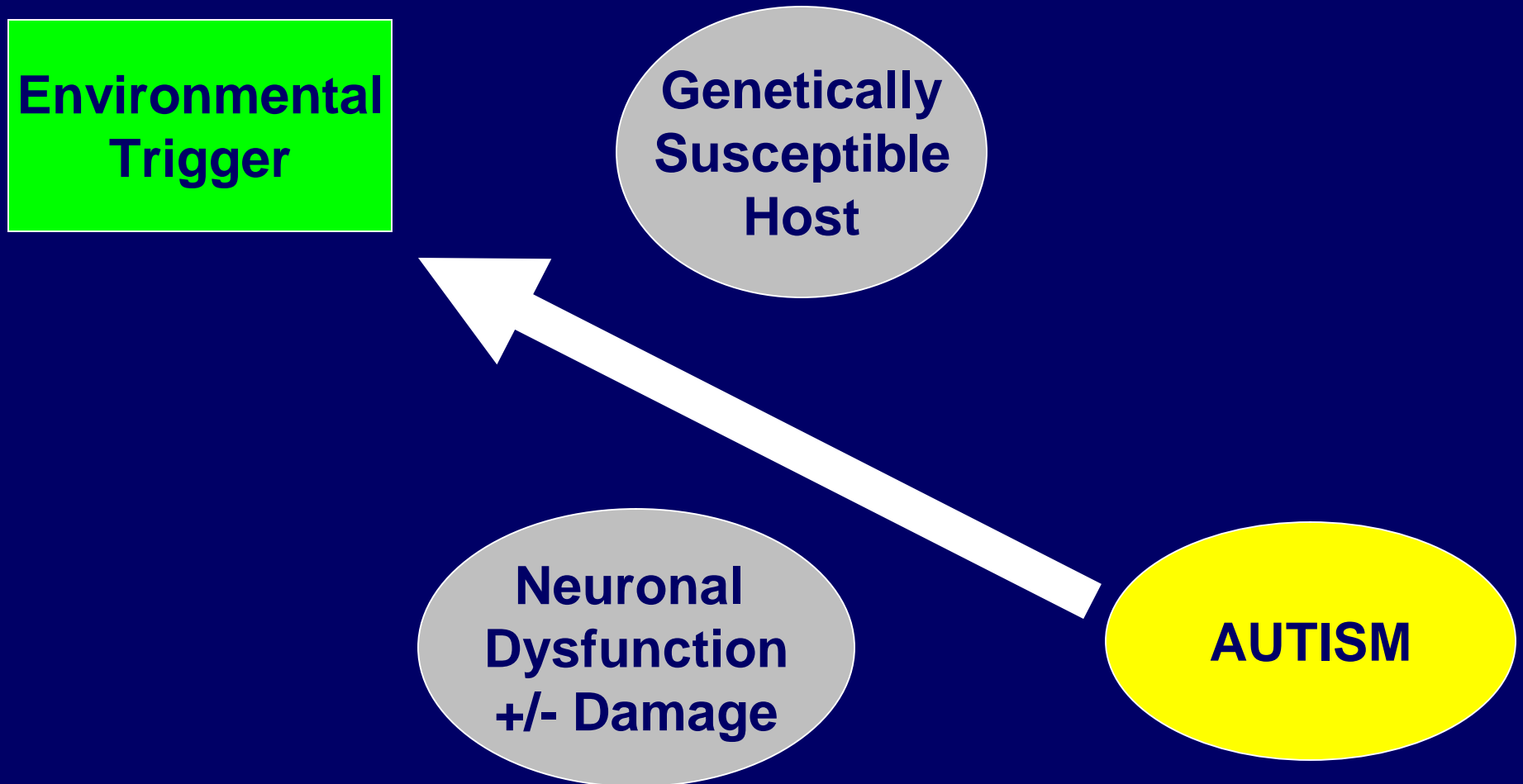
REGRESSIVE AUTISM

3 VIDEO EXAMPLES

Pathogenesis of (Regressive)Autism



How do we trace back from the clinical picture to the environmental trigger?



What do we need clinically to find these environmental factors?

- Standardized definition of autism and related disorders
- Brain pathology – what happened where & when?
- Incidence data from populations with disparate risk factors (same diagnostic criteria for each time/place)
- Systematic evaluation of anecdotal case reports (n=1)
- Randomized controlled trials of novel therapeutics (Reliable, valid, developmentally-appropriate, and change-sensitive outcome measures)
- Identification of clinically meaningful subtypes
 - Onset and clinical presentation
 - Associated symptoms and clinical course
 - Medical and behavioral comorbidities
 - Sensitive and specific biological/behavioral markers

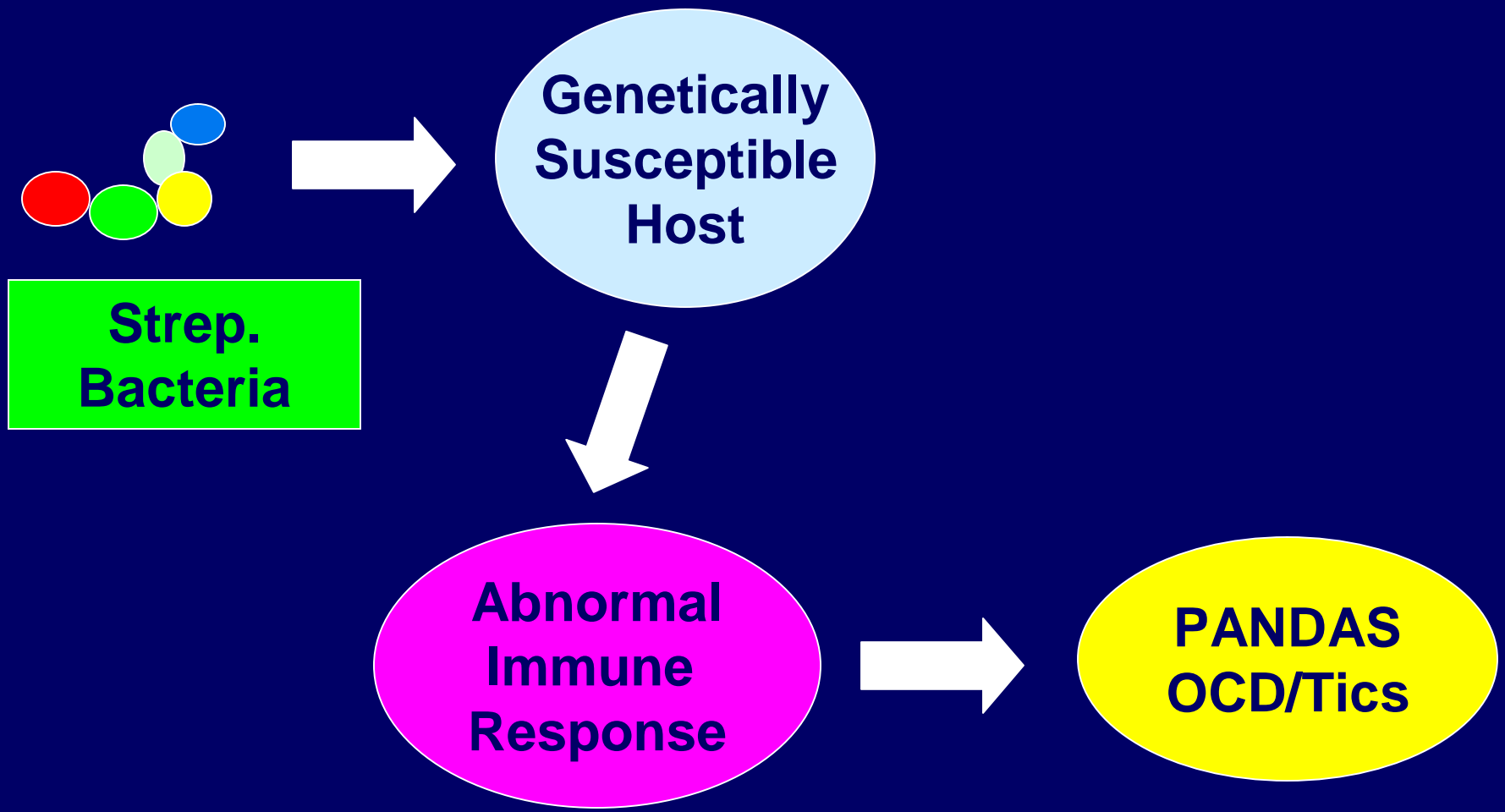
Tracking Environmental Triggers

A Lesson from OCD

The PANDAS Subgroup

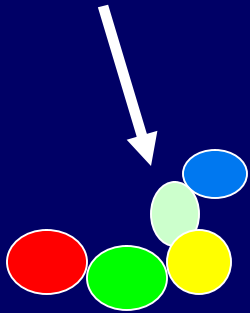
- § Acute onset, episodic course, onset at 5 – 8 yrs, boys outnumber girls 3:1
- § Comorbid tics, ADHD, and separation anxiety
- § When acutely ill – developmental regression, social isolation/aggressiveness, emotional lability, sensory defensiveness, sleep difficulties, enuresis & daytime urgency, and choreiform movements (95%)
- § Clinical similarities to Sydenham chorea (neurologic manifestation of rheumatic fever)
- § Temporal association with Strep infections (Strep throat and scarlet fever)

The PANDAS Subgroup: From Clinical Observations to Cause and Cure



PANDAS Research: From Clinical Observations to Cause & Cure

**ANTIBIOTIC
PROPHYLAXIS**



**Strep.
Bacteria**

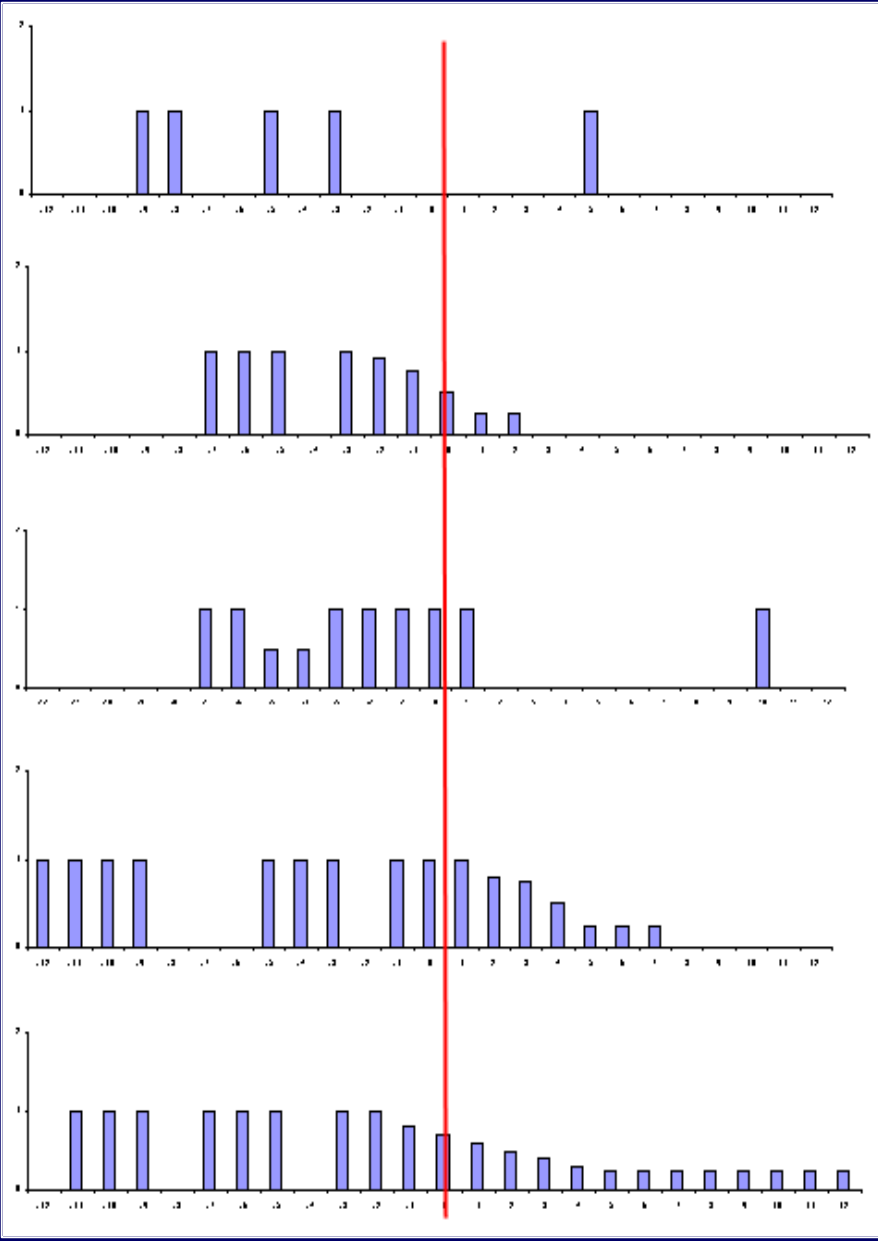
**Genetically
Susceptible
Host**

**Abnormal
Immune
Response**

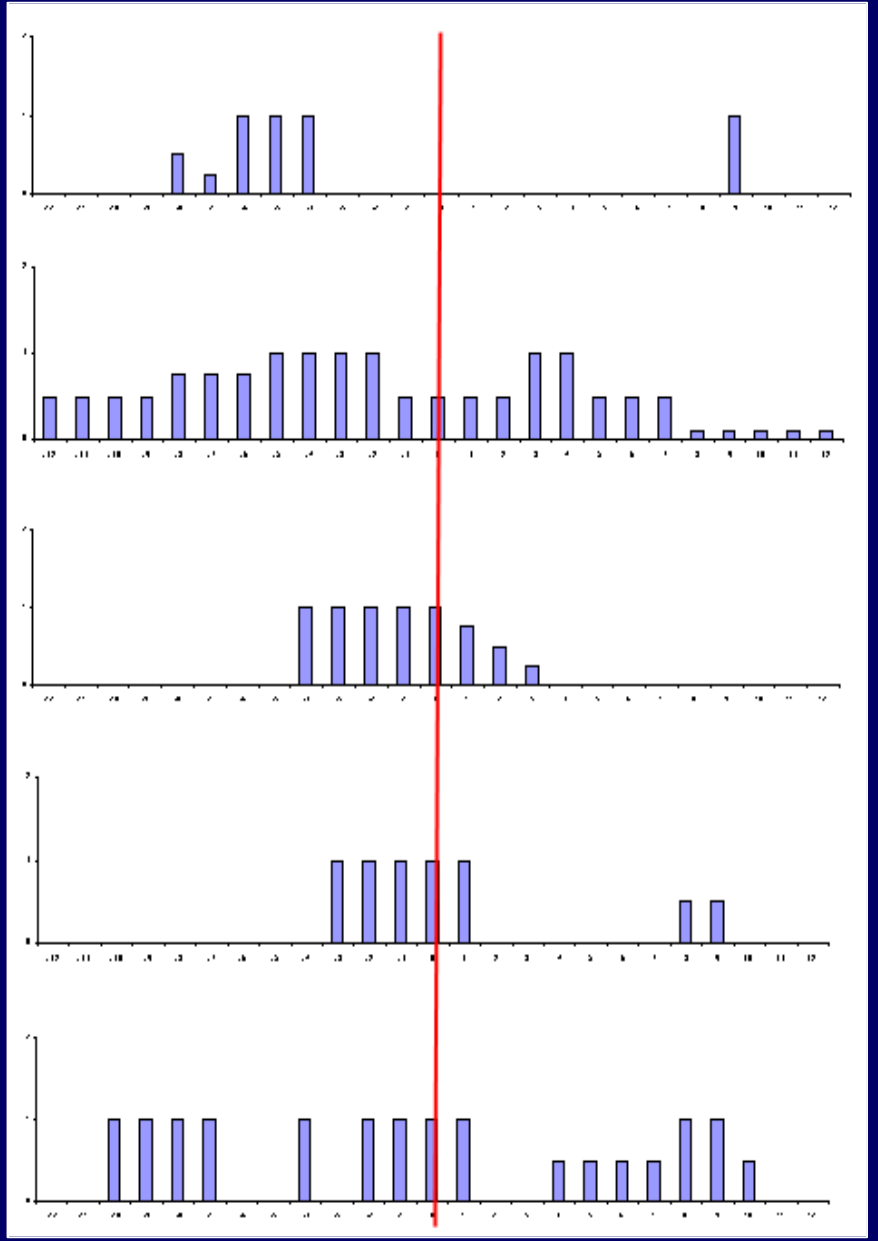
**PANDAS
OCD/Tics**



PENICILLIN

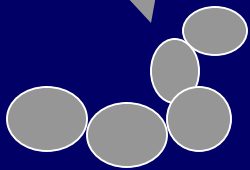


AZITHROMYCIN



PANDAS Research: From Clinical Observations to Cause & Cure

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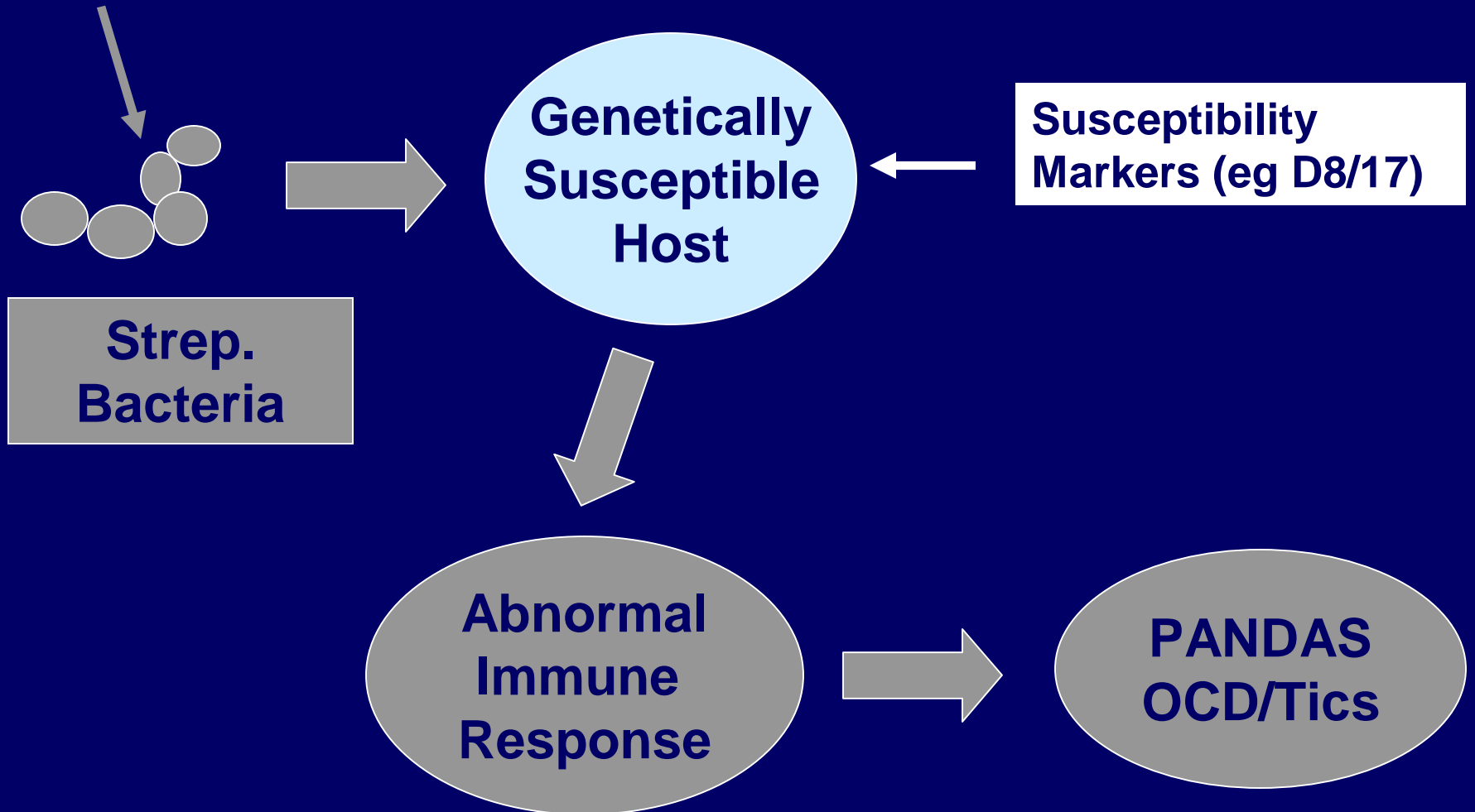
**Strep.
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**Genetically
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**Susceptibility
Markers (eg D8/17)**

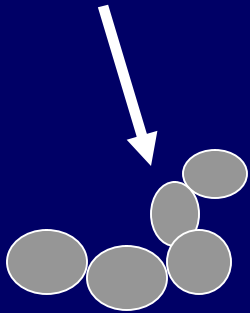
**Abnormal
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**PANDAS
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PANDAS Research: From Clinical Observations to Cause & Cure

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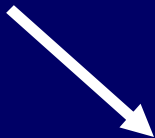


**Genetically
Susceptible
Host**

**BIOMARKERS
(E.g., D8/17)**

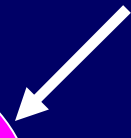


**Immunomodulatory
Therapy**



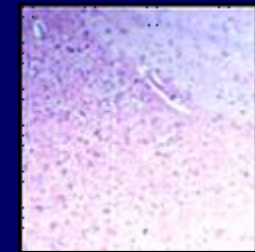
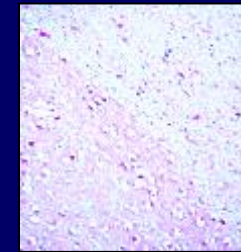
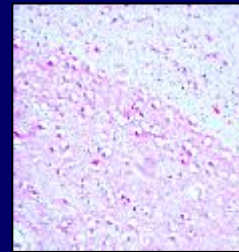
**Abnormal
Immune
Response**

**Disease Marker
(Antibody titers)**



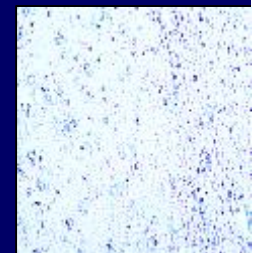
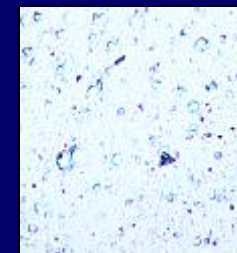
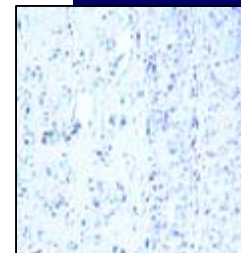
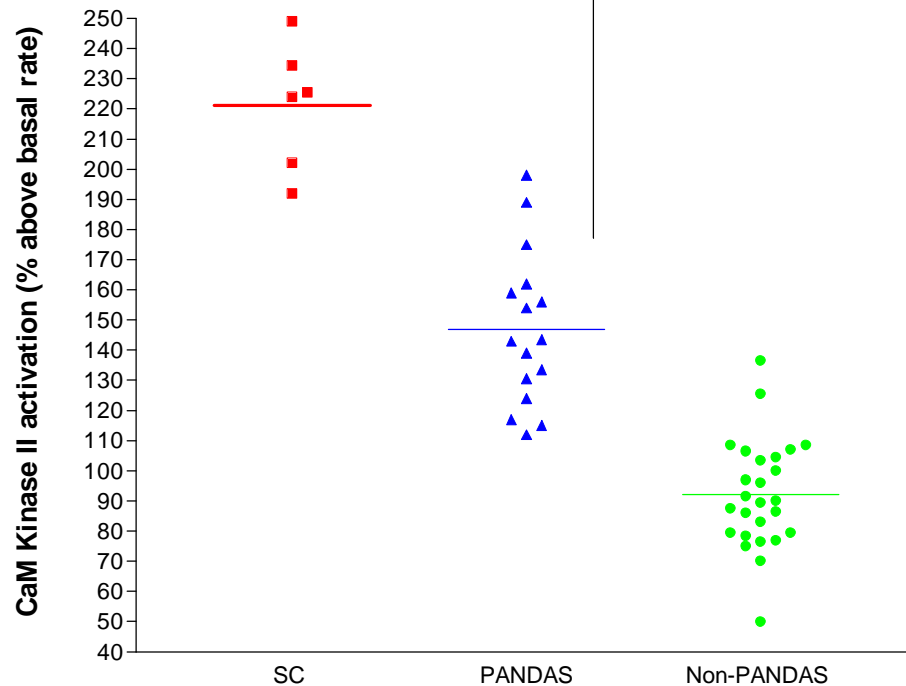
**PANDAS
OCD/Tics**

Cross-reactive Antibodies in Sydenham's & PANDAS



PANDAS

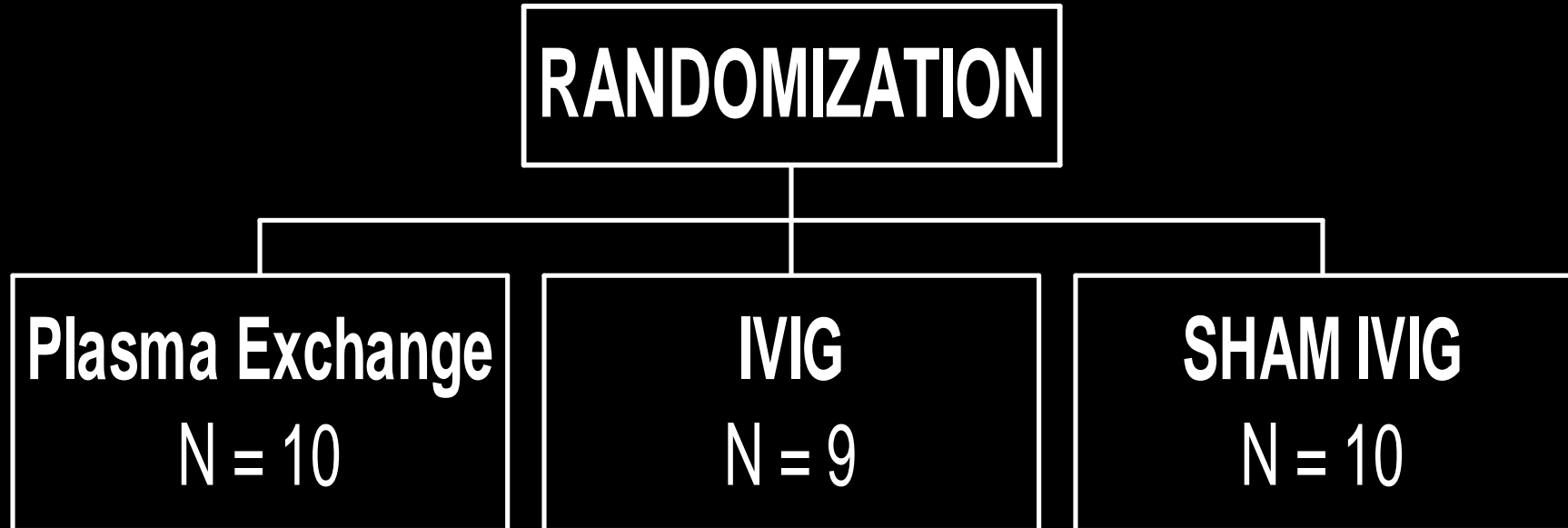
SC



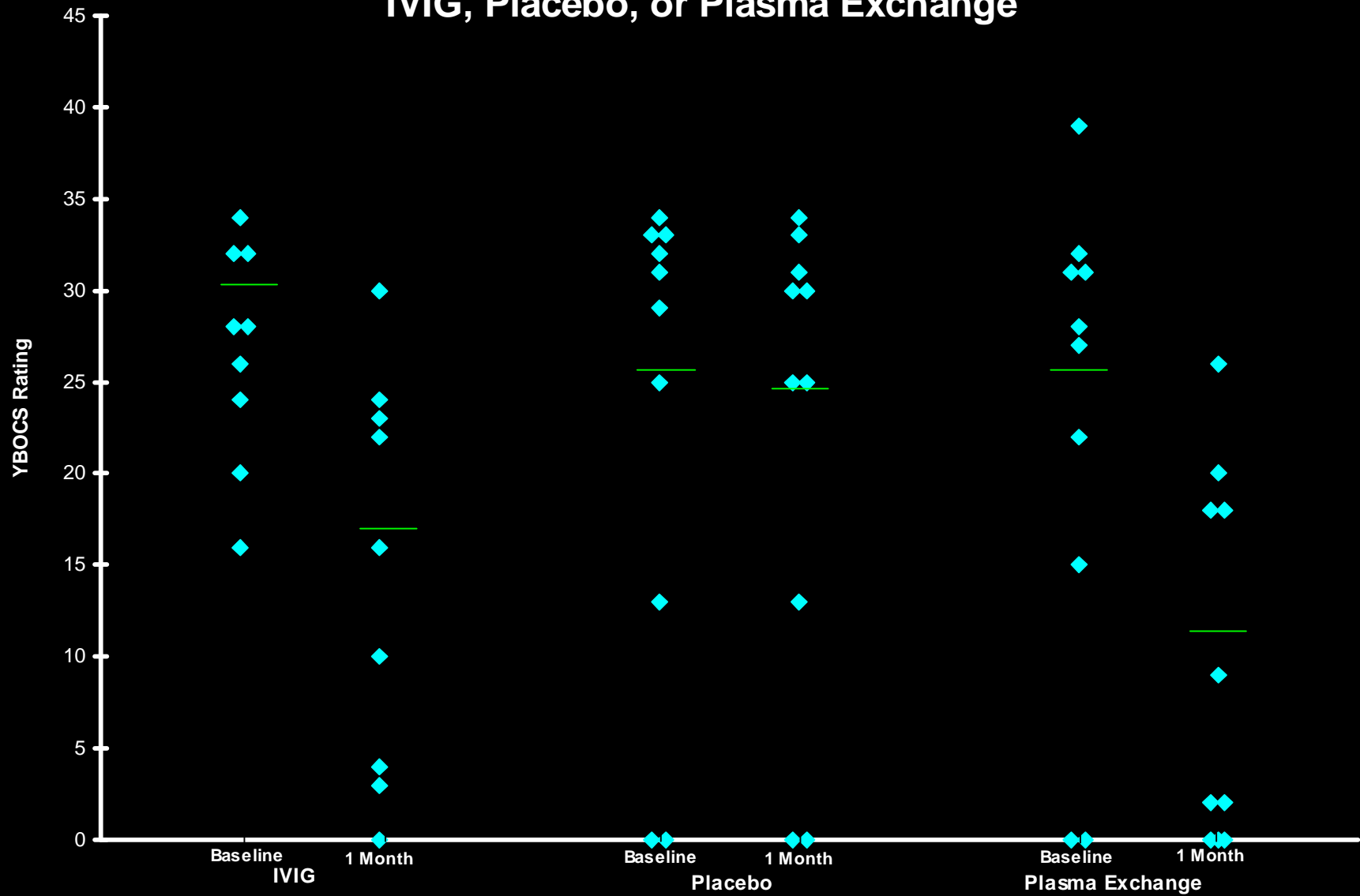
Controls

Can be used as
diagnostic tests

Immunomodulatory Treatment Trial Plasma Exchange vs. IVIG vs. Placebo

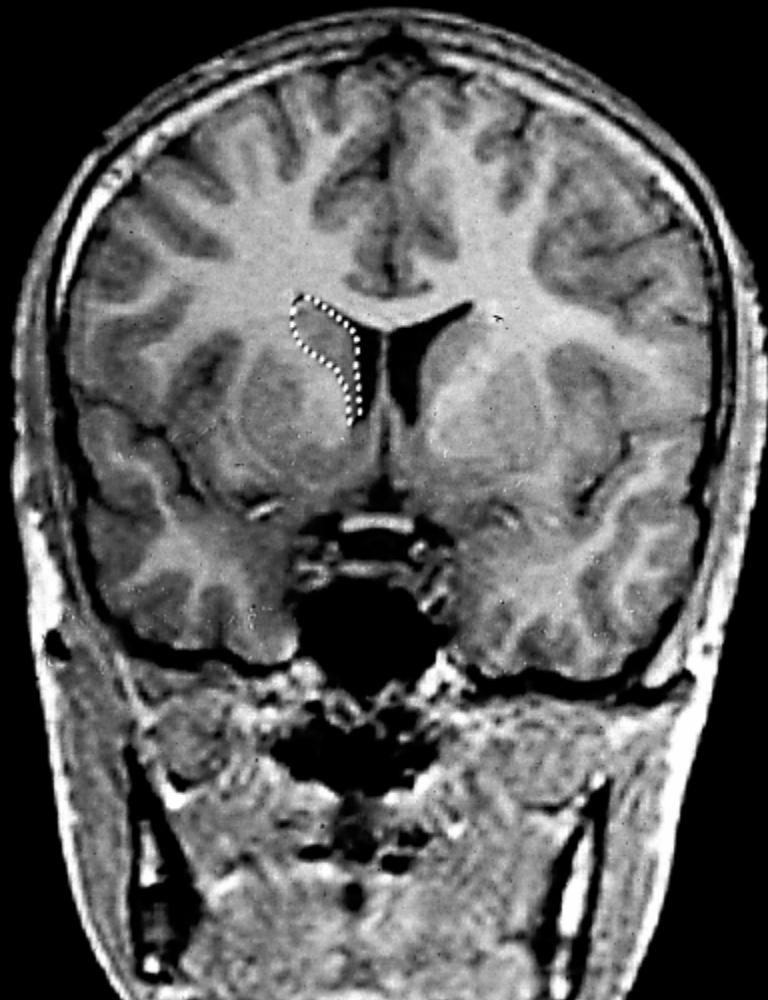


Change in OCD Severity 1 Month Following Treatment With IVIG, Placebo, or Plasma Exchange



Caudate Size in 14 y.o. Patient with OCD

BEFORE TREATMENT



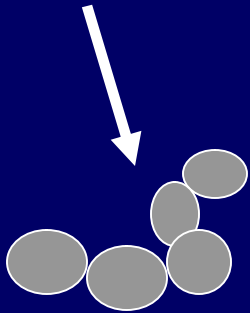
AFTER TREATMENT



SWEDO & GIEDD.

PANDAS Research: From Clinical Observations to Cause & Cure

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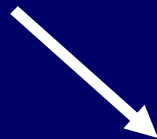
**Susceptibility
Markers (eg D8/17)**



**Disease Marker
(Antibody titers)**



**Immunomodulatory
Therapy**



**Abnormal
Immune
Response**



**NO PANDAS
NO OCD/Tics**

Autism Research: Moving from Clinical Observations to Cause & Cure

