ADHD and Neurogenetic Syndromes

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MOLECULAR BIOLOGY

BEHAVIORAL PHENOTYPE ABNORMALITIES

- CANDIDATE GENES
- GENE PRODUCTS
- ADVANCES IN DIAGNOSIS
- MULTIDISCIPLINARY INTEREST
ADHD and Neurogenetic syndromes

- The most common neurodevelopmental disorder in childhood
- Estimated prevalence is 3-9%
- No single etiology → multifactorial hypothesis
Pre-perinatal Risk Factors for ADHD

[Cigarette Exposure]

[Alcohol Exposure]

[Drug Exposure]

[LBW]

[Socioeconomic Status]

[Maternal Age at Birth]

[Parental IQ]

[Parenteral ADHD]

[Parenteral CD]

OR

[Spencer et al, 2002]
ADHD and Neurogenetic syndromes

Familiar Twin Adoption studies

Familiarity of ADHD

The importance of Genetic Factors
Heritability of ADHD

[Heritability graph showing data from various studies on the heritability of ADHD, Panic Disorder, Schizophrenia, and Height.]

[Faraone et al, 2005]
GENETIC POLYMORPHISMS

- GIT1
- SNAP-25
- Gβ5
- COMT
- DBH
- DIRAS2
- DRD4
- MAOA
- DAT1
- LPHN3
- 5HTT
- Val66Met BDNF

ADHD SYMPTOMS
CANDIDATE GENES

regulating

dopamine
norepinephrine
serotonin
gamma-aminobutyric acid
neurosteroids
A Family Based Association Study of DRD4, DAT1, and 5HTT and Continuous Traits of Attention-Deficit Hyperactivity Disorder

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ADHD and Neurogenetic Syndromes

- Tuberous Sclerosis
- Neurofibromatosis type I
- VeloCardioFacial syndrome (del22q11.2)
- Fragile X
- Williams syndrome
- Sexual aneuploidies
Tuberous Sclerosis Complex

TSC1: 9q
TSC2: 16p

- Hypomelanotic macules
- Epilepsy
- Subependymal nodules
- Renal AMLs
- Facial angiofibromas
- Retinal hamartoma
- Shagreen patch
- Forehead plaque
- Liver AMLs
- Periungual fibromas

0 - 2 years
2 - 5 years
5 - 9 years
0 - 14 years
14 - 16 years
Tuberous Sclerosis Complex

**TSC1** gene on chromosome 9q34 (Hamartin)

**TSC2** gene on chromosome 16p13 (Tuberin)

- Altered neurotransmission
- Synaptic modifications
- White matter abnormalities

Epilepsy

Autism

Cognitive impairment
BEHAVIORAL PHENOTYPE IN TSC

ADHD has been reported as being more frequent than in the general population, ranging from about 30% to 60%.

Hyperactive subtype is the most common.

ADHD is more frequent in TSC children with seizures and/or strategically located cortical tubers.
Genetic Linkage of Attention-Deficit/Hyperactivity Disorder on Chromosome 16p13, in a Region Implicated in Autism

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Neurofibromatosis type 1

- Two or more of the following features:
  1. Six or more café-au-lait spots
  2. Two or more neurofibroma of any type or one or more plexiform neurofibromas
  3. Freckling in the axillary or inguinal region
  4. Optic glioma (tumor of the optic pathway)
  5. Two or more Lisch nodules
  6. A distinctive osseous lesion
  7. A first-degree relative with NF I
Deficits in visuospatial and visuoperceptual

Deficits in executive functioning, sustained and switching attention

ADHD is present in one-third of NF1 children, prevalently of inattentive type

In a study of cognitive assessments of 81 children with NF1 ages 8-16 years, sustained attention difficulties were reported in 63% of children with NF1, with 38% fulfilling the diagnostic criteria for ADHD.

[Hyman et al, 2005]
Neurofibromatosis I

NF1 gene: 17q11.2

neurofibromine
Signaling Pathways For Learning and Memory

Glutamate Receptors
- NMDA
- AMPA

Post-Synaptic Membrane
- CaMKII
- CaMKIV
- PKC
- Ca++

GRB
- Ras
- Raf
- MEK
- MAPK
- RSK2
- PKA
- cAMP
- Adenylate Cyclase

Growth Factors
- Ach
- Serotonin

Glutamate
- Dopamine
- Norepinephrine

Nucleus
- Thyroid Receptor
- CREB
- CBP
- TIC
- mRNA

Transcription
UBO’s  
(Unidentified Bright Objects)
UB0’s in NF1
Unidentified Bright Objects

- Aree di iperintensità di segnale visibili alla RMN encefalo con e senza mdc, presenti nel 60-70% pz NF1
  - Aree di edema intramielinico
  - Localizzati prevalentemente a livello di sistema cortico-striatale talamo cervelletto e tronco
Localizzazione degli UBO’s

CORTECCIA PRE-FRONTALE
 (Controllo impulsività
 Attenzione)

CAUDATO
 (Controllo impulsività)

PUTAMEN
 (Attenzione Divisa, controllo impulsività)

CORTECCIA FRONTALE
 (Pianificazione, fluenza verbale e percezione visuo-spaziale)

GIRO DEL CINGOLO
 (Controllo impulsività, Memoria)

TALAMO
 (Percezione visuo-spaziale, Attenzione divisa, Memoria)
Division of Child Neurology “Tor Vergata” University

Distribution Criteria NFI
ADHD in Neurofibromatosis type 1

19 bambini

[Galasso et al 2004]
ADHD in Neurofibromatosis type 1

- UBO-
  - ADHD-
    - 0%
  - ADHD+
    - 100%

- UBO+
  - ADHD-
    - 20%
  - ADHD+
    - 80%

- UBO+ ADHD-
  - 45%

- UBO+ ADHD+
  - 55%
Velo-Cardio-Facial/DiGeorge syndrome

- The most common microdeletion syndrome due to del22q11.2
- 1: 4000
- Very heterogeneous phenotype
- Palatal abnormalities 70%
- Cardiovascular anomalies 75%
- Typical gestalt
Velo-Cardio-Facial syndrome
(FISH analysis)
Velo-Cardio-Facial syndrome

- All patients have learning difficulties
- IQ in borderline range/MR of various degrees
- 35%-55% ADHD (Inattentive type)
- 8%-43% ODD
- 25% Schizophrenia

In VCFS patients a prefrontal-parietal network dysfunction has been described

[Antshel et al, 2005]
VCFS and COMT polymorphisms

- The impact of Val158Met polymorphism (rs4680) of COMT on executive functions in VCFS patients is still unclear.

- Recent studies failed to find an association between this polymorphism and nonsyndromic ADHD, hypothesizing an involvement of other functional COMT haplotypes.

[Halleland et al, 2009]  
[Gizer et al, 2009]
Williams syndrome
Deletion of 7q11.23

- Distinctive facial appearance
- Cardiac abnormalities (SAS)
- Short stature
- Peculiar behavioral phenotype

- Mental retardation (75% mild)
- Learning difficulties (95%)
- Visual-spatial deficit
The most prevalent psychiatric diagnosis in WS is ADHD (64.7%).

68.8% of WS children met criteria for predominantly Inattentive Type, 27.3% for Combined Type, and 3.9% had predominantly Hyperactive-Impulsive Type of ADHD.

[Leyfer et al., 2006]
Williams syndrome
(FISH analysis)
The deletion of *LIMK1* in ko mice lead to an altered actin-based regulation of spines and growth cones, and to changes in hippocampal LTP and NMDA receptor functions.

Moreover, *LIMK1* ko mice showed hyperactivity and impaired spatial learning.

The telomeric part of WS region encompasses the *LIMK1* gene, which encodes a cytoplasmic protein kinase. 

*LIMK1* is thought to be involved in the establishment and maintenance of normal spine morphology.

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Moreover, *LIMK1* ko mice showed hyperactivity and impaired spatial learning.

[Schubert et al, 2009]

[LIMK1](http://example.com) gene, which encodes a cytoplasmic protein kinase

[Schratt et al, 2006]
Fragile X syndrome
Fragile X syndrome

Behavioral Phenotype

- Autistic behavior
- Motor delay
- Speech delay
- Deficit in visuo-motor skills, short-term memory
54 to 59% of boys with FXS met diagnostic behavioral criteria for ADHD

ADHD-inattentive type only (31.5%), ADHD-hyperactive type only (7.4%), or ADHD-combined type (14.8%) based on parent or teacher reports
FMRP protein in FXS

The absence of FMRP leads to dysregulation of many genes, with consequent alterations in neurotransmission and synaptic connections.

Structural imaging studies of individuals with the full mutation show an enlargement of
- Hippocampus
- Amygdala
- Caudate nucleus
- Thalamus

and a reduction in size of
- Cerebellar vermis
- Superior temporal gyrus

Involvement in the regulation of memory, learning, sensory processing, motor behavior

[Sullivan et al, 2006]
[Hessl et al, 2004]
Fragile X syndrome

Backes et al, 2003
SEXUAL ANEUPLOIDIES

Turner Syndrome

Klinefelter Syndrome

Nonviable

Male

XXX

Female (triple X)

Female (Turner syndrome)

Male (Klinefelter syndrome)

Nonviable

XXX

X0

XY

Male

Sperm

Female

Eggs

0

Nondisjunction

0Y

0X

Female

Eggs

0Y
ORGANIZATIONAL EFFECTS:
differences in neuron number, nuclear volume, dendritic length, neuronal membrane organization, synaptic formation, neuronal connectivity and neuropeptide receptor

ACTIVATIONAL EFFECTS:
synthesis and secretion of neuropeptides, changes in receptor number and function, dendritic morphology and number of synaptic inputs
Turner syndrome

Short stature
Gonadal dysgenesis
Typical phenotype
Cardiac and renal abnormalities
Other anomalies
ADHD and Turner Syndrome

- 18-fold increase in the prevalence of ADHD in girls with TS (24%) compared with girls in the general population, and a 4.8-fold increase when compared with both genders in the general population (5%)

Fronto-parietal and frontostriatal networks' abnormalities

[Russel et al, 2006]  
[Haberecht et al, 2001]
KLINEFELTER Syndrome

Klinefelter HF, Reifenstein EC, Albright F

“Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism and increased secretion of follicle-stimulating hormone.”
J Clinical Endocrinol Metab 1942

- Typical appearance
- Hypogonadism - Infertility
- Gynecomastia
- Learning disabilities
ADHD, Klinefelter Syndrome and variants

- In 51 KS patients aged 6–19 years, ADHD was diagnosed in 63% of cases [Bruining et al, 2009]
- In XXY Y KS the rate of ADHD is 72% [Tartaglia et al, 2008]

A combined effect of genes and hormones probably influences brain development and functions, conditioning the behavioral phenotype

- In a study of 29 ADHD young males, blood levels of dehydroepiandrosterone (DHEA) and its principal metabolite dehydroepiandrosterone sulfate (DHEAS) were inversely correlated with the severity of hyperactivity
- Moreover, a 3-month treatment of ADHD with methylphenidate produced not only an improvement of ADHD symptoms, but also an increase in serum levels of DHEAS and DHEA [Strous et al, 2001]
ADHD in Neurogenetic syndromes

- Hyperactivity and attention deficit in children with mental retardation
- Is ADHD specific of the syndrome? Or does it depend on mental retardation?
- The real frequency of ADHD in specific syndromes and its genetic correlations

A better understanding of the etiology of ADHD
Thank you for your attention