Velocardiofacial Syndrome: Effects of Haploinsufficiency of the COMT gene on Brain Function

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DSM-Based Psychiatric Research

Disorders defined by DSM/ICD (i.e., phenomenology):

- Symptoms and signs
- Cognitive deficits
Should Our Understanding of the Brain Start with DSM-Defined Disorders?

Risk Factor A
Risk Factor B
Risk Factor C
Risk Factor D
Risk Factor E
Risk Factor F
Risk Factor G
Risk Factor H

"Diagnosis"

Neural Pathways
Behavioral Neurogenetics

An interdisciplinary research paradigm that uses neurogenetic conditions as models for understanding psychiatric disorders

- Fragile X Syndrome
- Velo-Cardio-Facial Syndrome
- Williams Syndrome
- Prader-Willi Syndrome

Brain Disorders

• Behavior
• Psychiatric symptoms
• Cognition
What is Schizophrenia Really?

Risk Factor A

Risk Factor B

Risk Factor C

Risk Factor D

Risk Factor E

Risk Factor F

Risk Factor G

Risk Factor H

Neural Pathways

Schizophrenia

22q11 deletion
Velo-Cardio-Facial / DiGeorge / 22q11.2 Deletion Syndrome

A Model For Understanding Etiological and Pathophysiologicaal Pathways Leading to Schizophrenia
Velo-Cardio-Facial / DiGeorge Syndrome

- Typical facial features
- Cleft anomalies
- Congenital cardiac anomalies
- Immunological deficiencies
- Hypocalcemia
VCFS & DiGeorge Syndrome are Caused by a Microdeletion in Chromosome 22

Fig. 1. Deletions of 22q11 associated with the DiGeorge phenotype. The positions of reported microdeletions in the 22q11 locus: (a) typical deleted region (TDR) of 3 Mb; (b) 1.5 Mb deletion; (c--i) atypical deletions. The organization of candidate genes in the 22q11 locus is shown.
Prevalence

• 1:2,000 – 1:4,000 live births
• The most common known microdeletion syndrome
Cognitive Deficits in VCFS

- Borderline intelligence
- Performance IQ < verbal IQ (in children)
- Verbal IQ < Performance IQ (adults)
- Relative strength in reading, writing and spelling
- Deficits in mathematics and visuospatial perception
Common Psychiatric Disorders in VCFS

- ADHD 40%
- Anxiety disorders 50%
- Psychotic disorders 30%
- Depressive disorders 20%
VCFS and Schizophrenia

- 30% of subjects with VCFS develop psychosis by early adulthood (Murphy 1999).
- The psychotic disorder is clinically similar to ‘idiopathic’ schizophrenia (Bassett 2003).
- VCFS is the most common identifiable genetic risk factor to schizophrenia.
Volumetric Findings in Children with VCFS

- 11% reduction in overall brain volume
- Relatively preserved prefrontal volume
- Decreased parietal lobe volume
- Decreased posterior fossa volumes (e.g., cerebellar vermis)
- Enlarged amygdala

Eliez 2000, 2002; Kates 2001, 2006; Simon 2005
Cortical Thickness in VCFS

Decreased cortical thickness in VCFS compared to controls:
- Parieto-occipital cortex
- Lateral occipital gyrus
- Inferior frontal gyrus

{Bearden, Cerebral Cortex 2007; 17:1889-98}
Candidate Genes for Neuropsychiatric disorders from the 22q11.2 Region

Fig. 1. Deletions of 22q11 associated with the DiGeorge phenotype. The positions of reported microdeletions in the 22q11 locus: (a) typical deleted region (TDR) of 3 Mb; (b) 1.5 Mb deletion; (c—i) atypical deletions. The organization of candidate genes in the 22q11 locus is shown.
Catechol-O-methyltransferase (COMT) Val158 Met affects catabolism of catecholamine neurotransmitters. High activity is associated with the Val-Val genotype, while Low activity is associated with the Met-Met genotype. Zalsman et al.
All subjects with VCFS carry only one copy of the COMT gene.

Catecholamine

COMT Val158 Met

High activity

Low activity
Prefrontal Cognitive Function and Prefrontal Dopamine Levels: The Inverted U-Shape Curve

Goldman-Rackish
COMT Genotype and the Inverted U-Shape Curve in non-VCFS Subjects
COMT Genotype and the Inverted U-Shape Curve in VCFS Subjects
The Stanford Longitudinal Study

• 30 children with VCFS and 23 matched IQ controls were evaluated first at the age of 13 years and reevaluated at 18 years.
• At time 1 none of the subjects had a psychotic disorder.
• At time 2, seven subjects (30%) developed a psychotic disorder

Gothelf et al. Nat Neuroscience, 2005;11:1500-2
Longitudinal Effects of COMT Genotype on Change in VIQ in VCFS

Greater Reduction Met > Val:

- VIQ
- Expressive language abilities on CELF-III.
- Prefrontal grey matter volume
COMT Genotype and Psychosis in VCFS
Psychiatric Symptoms Predicting Psychosis in VCFS

Time 1

- COMT Met
- Subthreshold Psychotic Sx
- Anxiety Disorder or Sx (OCD)
- Lower VIQ

Time 2

Psychotic Disorder And Symptoms \( (R^2=61\%) \)

Treat with Atypical antipsychotics?

Longitudinal Changes in White Matter Volume During Adolescence

- At baseline cranial white matter was reduced by 17% in VCFS compared to normals
- During adolescence white matter increased more in VCFS
- ‘Catch-up’ of white matter deficits

Gothelf et al. Schiz Res 2007; 96: 72-81
Longitudinal Changes in Superior Temporal Gyrus During Adolescence

- Decreased grey matter reduction in superior temporal gyrus
- Delayed cortical maturation
Longitudinal Changes in Amygdala Volume During Adolescence

- Reduction in amygdala volume
**COMT Genotype and PFC Activation in non-VCFS subjects**

Val/Val > Met/Met activation:
- In DLPFC during N-Back test (Egan, PNAS 2001; 98:6917)
- In ACC during attentional control task (Blasi, J Neurosci 2005; 25:5038)
COMT Genotype and PFC Activation in VCFS subjects
**Go/NoGo Behavioral Scores**

<table>
<thead>
<tr>
<th></th>
<th>VCFS (n=13)</th>
<th>Typicals (n=14)</th>
<th>Developmental Delay (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>17.8 (3.5)</td>
<td>17.2 (3.4)</td>
<td>18.1 (4.8)</td>
</tr>
<tr>
<td><strong>Males/Females</strong></td>
<td>8/5</td>
<td>7/7</td>
<td>4/5</td>
</tr>
<tr>
<td><strong>Full-scale IQ</strong>*</td>
<td>74.5 (18.9)</td>
<td>122.2 (12.8)</td>
<td>61.2 (10.1)</td>
</tr>
<tr>
<td><strong>False alarms rate</strong></td>
<td>13.2 (12.1)</td>
<td>8.4 (5.1)</td>
<td>15.3 (14.7)</td>
</tr>
<tr>
<td><strong>RT to No Go errors</strong></td>
<td>411.8 (127.3)</td>
<td>417.7 (139.9)</td>
<td>532.8 (210.2)</td>
</tr>
</tbody>
</table>

*Typical Controls > VCFS and Developmentally Delayed Controls*
Greater Parietal activation in VCFS vs. controls during the Go/NoGo condition

Greater activation in VCFS compared to typically developing (TD) and developmentally disabled (DD) controls in superior & inferior parietal lobules

Greater ACC Activation \((Met > Val)\) in VCFS While Performing Go/NoGo task

- ROI analyses restricted to BA 9/46 and 24/32
- BA24 (Tal: -4, 5, 31) 
P<0.05 corrected 
Cluster size = 54 voxels

- VCFS Met carriers compensate for an inhibitory deficit by additional recruitment of prefrontal regions.
Association of COMT Met with ADHD and OCD in VCFS (an Israeli Sample)

Rate of psychiatric disorders (n = 55):
- ADHD - 42%
- OCD - 25%
- SZ/Szaff - 9%

Peripheral DA markers in Response to AMPT in VCFS Met Carriers

- Higher levels of dopamine and lower levels of HVA in urine and plasma of adults with VCFS compared to controls

Boot, Neuropsychopharmacology 2007, in press
VCFS Met carriers compared to controls:

- Elicited significantly smaller mismatch negativity (MMN) amplitudes for both tone (duration) and speech (voicing) deviants.
- Performed more poorly on tests expressive language and verbal working memory tasks.

Baker, Biol Psychiatry 2005; 58:23-31
Effect of COMT Genotype on Brain Morphology

Kates, Neuropsych Genet 2006; 141:274-80

Van Amelsvoort, Psychol Med 2008; 38:89-100
COMT Met/Val Genotype in VCFS: Additional Findings

• No association between the COMT genotype and executive functioning and working memory (Kates 2006; Van Amelsvoort 2008; Glaser 2006)

• Association of the COMT Val allele with worse cognitive functioning in children with VCFS (Bearden 2004)

• No association of COMT genotype with schizophrenia but Met carriers performed worse on frontal cognitive tests, communication, and social functioning measures (Bassett 2007)
Possible Explanations for Inconsistencies in Results

- The neuropsychiatric risk is associated with haplotype (G-A-A) within the COMT gene.
Possible Explanations for Inconsistencies in Results

- Interactions with other genes from the 22q11.2 deletion region (e.g. PRODH)
  - VCFS subjects with COMT Met + Hyperprolinemia had 2.8 increased risk for psychosis (Raux 2007)
- Interaction with other genes outside the 22q11.2 deletion region (e.g. BDNF)
- Interaction with gender
- Difference in samples’ age range (children vs. adults) and cross-sectional vs. longitudinal design
  - Met carriers are doing better during childhood and deteriorate during adolescence following the increase in prefrontal dopamine levels
Theoretical Model of Developmental Psychopathology in VCFS

22q11.2 Deletion

COMT (Met)

Other Genes (e.g., PRODH & non-deleted genotype)

Environment

Brain Dev & Fxn (PFC, DA)

Prodromal Symptoms

Psychosis & Anxiety

Cognition & Language

Kates et al Am J Psychiatry 2007:
Collaborators

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