The Quadruple Aim: Working Together, Achieving Success

RANDALL C ZERNZACH MD, COL, USAF, MC

27 January 2011
## Contactin 4 as a Possible Autism Susceptibility Locus

**Author(s):**

Wright Patterson Medical Center, Wright Patterson AFB, OH, 45433

**Supplementary Notes:**

Presented at the 2011 Military Health System Conference, January 24-27, National Harbor, Maryland

**Security Classification:**

- Report: Unclassified
- Abstract: Unclassified
- This Page: Unclassified

**Limitation of Abstract:** Same as Report (SAR)

<table>
<thead>
<tr>
<th>Report Date</th>
<th>Report Type</th>
<th>Dates Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 JAN 2011</td>
<td></td>
<td>00-00-2011 to 00-00-2011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution/Availability Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved for public release; distribution unlimited</td>
</tr>
</tbody>
</table>

**Abstract:**

[Abstract content]

<table>
<thead>
<tr>
<th>Subject Terms</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Security Classification</th>
<th>Limitation of Abstract</th>
<th>Number of Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclassified</td>
<td>Same as Report (SAR)</td>
<td>13</td>
</tr>
</tbody>
</table>

**Notes:**

- Approved for public release; distribution unlimited.
Autism is the most common neurodevelopmental disorder in the US

- Deficits in communication and social interaction skills with onset < 3 yrs
- Restricted interests and stereotypic and/or repetitive behaviors

- Up to 90% of the risk is genetic, although underlying causes remain unknown in > 80% of cases; extremely heterogeneous
To determine whether Contactin 4 (CNTN4) is an autism susceptibility gene using a carefully phenotyped local registry of autism families (CORA*) with DNA samples collected at Nationwide Children’s Hospital and WPAFB

* Central Ohio Registry for Autism
BACKGROUND: CORA

– Recruit 250-300 carefully phenotyped probands with ASD + family members
– For each proband; complete medical history, PE, pedigree, and appropriate psychological and genetic testing
– DNA and permanent cell lines prepared and stored on all family members
– Store relevant data in password protected database (SQL) constructed for this project
BACKGROUND: CNTN4

- Synapse protein; other CNTNs and CNTNAPs implicated in autism by deletions, rare mutations, and other genetic studies
- Maps to 3p26; deletions in this region associated with MR+/-autism, rare normals
- Index family with 4 yo male with severe autism (non-verbal IQ 109; ADOS 19); female sib with mixed language disorder; ~500 kb deletion in male, sister, and nl mother at 5’ end of CNTN4 on 3p26 (non-coding)
METHODS: Sequencing of CNTN4

- Sequenced 22 coding exons of CNTN4 in 87 CORA ASD affecteds (75 families)
  - 70 Males (80%); 74 Caucasian (84%)
  - Dx: autism 53 (61%), ASD 34 (39%)
  - ADOS in 76%; ADI-R in 51%
  - 68% of probands had genetics eval
- Sequenced same from 107 controls (52M/55F)
RESULTS

- 4 distinct missense variants identified in ASD cohort
  - All inherited from an unaffected parent (2Mat, 2Pat)
  - Variant found in 1 out of 2 sibs with a neurodevelopmental phenotype; not found in 1 normal sib
- 1 missense variant identified in a control
- All variants conserved thru evolution and predicted to adversely affect protein structure
CONCLUSIONS & LIMITATIONS

– Identified coding variants in 4/75 unrelated ASD patients (5.3%) and 1/107 controls (0.9%) p=0.16

– Hypothesize CNTN4 may function as an ASD susceptibility locus in combination with other genetic and/or environmental factors

– Need to study large numbers of additional affecteds and controls
ACKNOWLEDGEMENTS

**Wright-Patterson AFB**
Col Randall Zernzach  
Lt Col Craig Boreman

**NCH Genetics**
Gail Herman*  
Elizabeth Varga  
David Cunningham  
Kim McBride  
Cathy Cottrell  
Natalie Bir  
Carlos Alvarez

**NCH Autism Center**
Eric Butter  
Karen Ratliff-Schaub  
Johnna Evans

**NCH Genetics Labs**
Julie Gastier-Foster  
Devon Lamb-Thrush

**Kansas City**
Samuel Bouyain

**Funding**: USAF DoD/NIH Grants/Cooperative Agreements
CONTACTIN 4 AS A POSSIBLE AUTISM SUSCEPTIBILITY LOCUS
Autism Spectrum Disorder - ASD

- Declared a national public health crisis
  - Nationwide 1 in 110 children have an ASD
  - In the military 1 in 88 children have an ASD
- Autistic children in military families are especially impacted
- Early identification and intervention can dramatically improve functioning, social skills, and quality of life
- Strong genetic component
Over 75 Loci Implicated in ASD

Abrahams and Geschwind 2008
Define endophenotypes
  – Analysis of more homogenous subgroups

Large scale collaborative studies
  – Common risk variants
  – Copy number variation
  – Epigenetics