Seventy years since Kanner’s account, what do we think causes autism in 2013?

24th September 2013
Karolinska Institutet
Dr Angelica Ronald
Genes Environment Lifespan laboratory, Centre for Brain and Cognitive Development, Birkbeck, University of London
70 years ago…

b.1943  b.1947  b.1943  b.1941
He often spun the forms around. . . the whole performance was very repetitious. He never used language as a means of communicating with people. . . . He did not respond to being called and did not look at his mother when she spoke to him.’

(Kanner 1943, p 237, describing boy with early infantile autism)
ASD

Social-communication

Restricted Repetitive behaviours and interests

American Psychiatric Association (2013)
Outline

1. An Etiological Continuum
2. Female Risk
3. The Fractionable Autism Triad
4. Clues from Comorbidity
## Risk Factors

**Genetic**
- Common variants
- Copy number variants
- Rare mutations
- De novo mutations
- Genetic syndromes

**Environmental**
- Obstetric complications
- Prenatal maternal stress
Risk Factors

Genetic
- Common variants
- Copy number variants
- Rare mutations
- De novo mutations
- Genetic syndromes

Environmental
- Obstetric complications
- Prenatal maternal stress

Parental age

Methylation
Monozygotic (MZ) twins: share all DNA code

Dizygotic (DZ) twins: share on average 50% of their DNA code

Both genes and environment play a role

MZ = Monozygotic twins
DZ = Dizygotic twins

Concordances for ASD from Lichtenstein et al (2010)

Review articles:

Posthuma & Polderman (2013). What have we learned from recent twin studies about the etiology of neurodevelopmental disorders? *Current Opinion in Neurology*, 26, 11-21.
Etiology of autistic traits

The etiology of autistic traits does not differ across the distribution of severity

Robinson et al (2011) Archives of General Psychiatry
The relationship between autistic traits and autism

- Genetic link between autism and autistic traits
- Same environmental risk factors for autism and autistic traits e.g. birth complications

Lundstrom et al (2012) *Archives of General Psychiatry*
Robinson et al (2011) *Archives of General Psychiatry*
Ronald et al (2010) *Child Development*
Ronald et al (2011) *Frontiers in Developmental Psychology*
The relationship between autistic traits and autism

- Characteristics of autism in general population (see original work by S. Baron-Cohen, D. V. M. Bishop, J. N. Constantino, D. H. Skuse)

- Family members show elevated autistic traits (e.g. Bishop et al., 2006; Bolton et al., 1994)

- Specific aberrant cortical structure similar for autism and autistic traits (Wallace et al 2012 Journal of Neuroscience)
Understanding nonshared environment from differences in monozygotic twins

Ronald et al (2010) *Child Development*
Wong et al (2013) *Molecular Psychiatry*

... and the forthcoming RATSS study!
Autism and Birth Complications

Cause or Consequence?
Differences within MZ pairs discordant for birth problems

Ronald et al (2010) *Child Development*  
N = 63 pairs
Autism and Epigenetics

An Environmental Risk?
**ASD MZ Twin Samples**

- Childhood Autism Spectrum Test (CAST)
- ASD diagnoses assigned using Diagnostic Wellbeing Assessment (DAWBA)
- Whole blood DNA and RNA (controlled for blood cell counts) at age 15, buccal DNA age 5, 12, 15
- Parental DNA

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>No of MZ twin-pairs</th>
<th>No of Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MZ twins discordant for:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed ASD</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Social Autistic Symptoms</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Non-social Autistic Symptoms</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Communicative Impairments</td>
<td>8</td>
<td>16</td>
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<tr>
<td><strong>MZ twins concordant for:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed ASD</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Low CAST scores (controls)</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

Slides from Chloe Wong

TOTAL 48 96
Distinctive patterns of DNA methylation associated with both autism diagnosis and related behaviour traits, and increasing severity of symptoms

Wong et al (2013) Molecular Psychiatry
ASD MZ Twin Study

ORIGINAL ARTICLE

Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits

CCY Wong¹, EL Meaburn¹,², A Ronald¹,², TS Price¹,³, AR Jeffries¹, LC Schalkwyk¹, R Plomin¹ and J Mill¹,⁴

Wong et al (2013) Molecular Psychiatry
An Etiological Continuum

• Autism spectrum disorders show high heritability

• Nonshared environment is significant but vital to assess its role independently of genetic influences

• Autism and autistic traits appear to lie on a quantitative phenotypic and etiological continuum
Outline

1. An Etiological Continuum
2. Female Risk
3. The Fractionable Autism Triad
4. Clues from Comorbidity
Female Risk
Is there evidence for different phenotypic presentations in girls with ASD?
## Sample Characteristics

### Table 1. Participant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>ASD Girls (N=17)</th>
<th>ASD Boys (N=17)</th>
<th>TD Girls (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CA</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M \ (SD)$</td>
<td>15.07 (2.70)</td>
<td>14.21 (2.25)</td>
<td>10.30 (.64)</td>
</tr>
<tr>
<td>Range</td>
<td>(7.70-18.90)</td>
<td>(7.70-19.10)</td>
<td>(9.10-11.70)</td>
</tr>
<tr>
<td><strong>Full IQ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M \ (SD)$</td>
<td>63.00 (8.10)</td>
<td>68.88 (11.85)</td>
<td>91.88(11.60)</td>
</tr>
<tr>
<td>Proportion Low IQ ≥ 70</td>
<td>82.40%</td>
<td>58.80%</td>
<td>0%</td>
</tr>
<tr>
<td>Proportion High IQ &lt; 70</td>
<td>17.60%</td>
<td>41.20%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Range</td>
<td>(52.00-82.00)</td>
<td>(52.00-96.00)</td>
<td>(55-108)</td>
</tr>
<tr>
<td><strong>MA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mdn</td>
<td>9.44</td>
<td>9.83</td>
<td>9.39</td>
</tr>
<tr>
<td>Range</td>
<td>(4.26-13.05)</td>
<td>(5.27-12.98)</td>
<td>(8.43-11.52)</td>
</tr>
</tbody>
</table>

Note: CA = Chronological age; MA = Mental Age;<sup>a</sup> CA data available for $N = 71$ (27 girls with ASD, 27 boys with ASD, 17 TD girls).

Nguyen & Ronald (Submitted)
Results

No significant sex differences on autism symptoms, sensory over-responsivity, or behaviour problems

Nguyen & Ronald (Submitted)
Do females with ASD have a greater burden of risk factors?


Commentary: Werling & Geschwind (2013). *Proceedings of the National Academy of Sciences*
### Increase in risk to siblings of female probands

![Graph showing increase in risk to siblings of female probands.

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>TEDS</th>
<th>CATSS</th>
<th>Combined Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Non-Probands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n(TEDS)= 3,444</td>
<td>-0.06</td>
<td>-0.05</td>
<td>-0.07</td>
</tr>
<tr>
<td>n(CATSS)=5,340</td>
<td>† P&lt;0.0001</td>
<td>† P&lt;0.0001</td>
<td>† P&lt;0.0001</td>
</tr>
<tr>
<td>Male Probands</td>
<td>0.42</td>
<td>0.34</td>
<td>0.37</td>
</tr>
<tr>
<td>n(TEDS)= 262</td>
<td>‡ P=0.002</td>
<td>‡ P=0.024</td>
<td>† P&lt;0.0001</td>
</tr>
<tr>
<td>n(CATSS)=470</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Probands</td>
<td>0.78</td>
<td>0.55</td>
<td>0.64</td>
</tr>
<tr>
<td>n(TEDS)= 136</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n(CATSS)=230</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Robinson et al (2013). *Proceedings of the National Academy of Sciences*

Commentary: Werling & Geschwind (2013). *Proceedings of the National Academy of Sciences*
Autism in females

Commentary: Werling & Geschwind (2013). Proceedings of the National Academy of Sciences
Outline

1. An Etiological Continuum
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Bivariate twin model

\[
\begin{align*}
C & \rightarrow \text{Trait 1} \\
C & \rightarrow \text{Trait 2} \\
E & \rightarrow \text{Trait 1} \\
E & \rightarrow \text{Trait 2} \\
A & \rightarrow \text{Trait 1} \\
A & \rightarrow \text{Trait 2} \\
C & \rightarrow \text{Trait 1} \\
C & \rightarrow \text{Trait 2} \\
E & \rightarrow \text{Trait 1} \\
E & \rightarrow \text{Trait 2}
\end{align*}
\]
Genetic correlation ($r_g$)
Genetic correlation ($r_g$)

If $r_g = 0$, there are no common genetic influences across two traits.
If $r_g = 1$, all the genes influencing the two traits are completely overlapping. At the genetic level, these two things are the same.
Genetic correlation ($r_g$)

$r_g = 0.5$, some genes are overlapping between the two traits, and some are specific to each
Nonshared environmental correlation ($r_e$)

$r_e = 0.5$, some environments are overlapping between the two traits, and some are specific to each
Autistic symptoms may have different causes

- $r_{ph} = \text{phenotypic correlation}$
- $r_{g} = \text{genetic correlation}$

Diagram:

- Social
- Communication
- Restricted Repetitive Behaviours & Interests

Correlation:

- $r_{ph} = ?$
- $r_{g} = ?$
Weak links between autistic traits

Modest genetic overlap between different autistic traits

Ronald et al (2006a, b) *Journal of the American Academy of Child & Adolescent Psychiatry*
Fractionable Autism Triad Hypothesis

Robinson et al (2012) *Behavior Genetics*
Commentary: Mandy & Skuse (2008) *J Child Psychol Psychiatry*
Outline

1. An Etiological Continuum
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4. Clues from Comorbidity
Comorbidity in ASD

- 70% have at least one comorbid disorder
- 40% have two or more comorbid disorders

Twin studies on co-occurring psychopathology

Social-communication

- Internalising traits
- ADHD
- Language problems

Restricted Repetitive behaviours and interests

- Tic disorder
- Low cognitive ability/learning disorders
- Psychopathic tendencies
- Clumsiness
- Developmental coordination disorder

See reviews by Ronald & Hoekstra (2011); Posthuma & Polderman (2013)
Autism and ADHD
Twin study on ASD and ADHD comorbidity

• 6107 twin pairs
• Mean age 7.88 years (SD=.53)
• Parent and teacher report

Autistic traits  
ADHD behaviours

\[ r = 0.40 - 0.54 \text{ (all } p < 0.001) \]

Childhood Asperger Syndrome Test  
(Scott et al., 2002)

Diagnostic and Well Being Assessment  
(Goodman et al., 2000)

Conners DSM-IV symptom scales  
(Conners et al., 1998)
Substantial genetic overlap with ADHD in 8-year-olds

Traits in the population

Categorical diagnoses

Male/female

Genes that influence ADHD but not ASD behaviours

Genes that influence ASD but not ADHD behaviours

Genes that are common to both ASD and ADHD
Converging evidence for overlap in genetic influences

- **Age 2** (parent report): $r_g = .27$  
  Ronald et al., 2010

- **Age 8** (parent/teacher): $r_g = .54-.57$  
  Ronald et al., 2008

- **Age 12** (parent report): $r_g = .23-.41$  
  Taylor et al., 2013

- **Age 18-33** (self report): $r_g = .72$  
  Reiersen et al., 2008

See also Lundstrom et al., 2011 and Polderman et al., 2013
Evidence for overlap in environmental influences

<table>
<thead>
<tr>
<th>Age</th>
<th>ASD</th>
<th>ADHD</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td><strong>Ronald et al., 2010</strong></td>
</tr>
<tr>
<td>(parent report)</td>
<td>r_e = -0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td><strong>Ronald et al., 2008</strong></td>
</tr>
<tr>
<td>(parent/teacher report)</td>
<td>r_e = 0.16-0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td><strong>Taylor et al., 2013</strong></td>
</tr>
<tr>
<td>(self report)</td>
<td>r_e = 0.16-0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-33</td>
<td></td>
<td></td>
<td><strong>Reiersen et al., 2008</strong></td>
</tr>
<tr>
<td>(self report)</td>
<td>r_e = 0.26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See also Lundstrom et al., 2011 and Polderman et al., 2013
But what about specific symptoms?
Ronald, Larsson, Anckarsäter & Lichtenstein (Under review)
Ronald, Larsson, Anckarsäter & Lichtenstein (Under review)
But what about development?
Autistic traits and ADHD traits: Longitudinal relationship?

Taylor et al (2013) Psychological Medicine
Autistic traits and ADHD traits: Longitudinal relationship?

Taylor et al (2013) Psychological Medicine
ASD + ADHD: Why?

• Family studies -- shared familial influences (Mulligan et al., 2008; Nijmeijer et al., 2009)

• Twin studies -- overlapping genetic and environmental influences (Constantino et al., 2003; Reiersen et al., 2008; Ronald et al., 2008, Ronald et al., 2010; Lundstrom et al., 2011; Polderman et al., 2013)

• Models support the conceptual distinction of ASD and ADHD, while also showing significant symptom-specific etiological influences

• ASD and ADHD traits influence each other across development (Taylor et al., 2013)
Large-scale genetic study identifying pleiotropic genes

GWAS, genome-wide association study

Calcium channel signalling genes

**Figure S9.** Functional relationship between 21 calcium channel activity genes that showed significant association with 5 disorders at $p < 10^{-5}$ in the primary meta analysis (http://string-db.org)\(^{13}\). The network view summarizes the network of predicted associations for a particular group of proteins. The network nodes are proteins. The edges represent the predicted functional associations, supported by the existence of the seven types of evidence.

1. Genes and environment influence risk for autism and evidence supports an etiological continuum with autistic traits

2. New empirical evidence supports a female protective effect against autism

3. Different symptoms within autism appear to have different causal pathways

4. Behaviour genetic research on comorbidity informs our understanding about the causes of autism
Autism

Everyone else
The Autisms

e.g. Abrahams & Geschwind (2008)
e.g. Ronald et al (2006, 2010)
e.g. Robinson et al (2013)
Autism

Sleep problems

ADHD

Depression

Anxiety

e.g. Ronald et al (2008); Lundstrom et al (2011)
Autism

Everyone else

e.g. Ronald et al (2006); Lundstrom et al (2011)
1943-2013
1943-2013
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Collaborators:
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Dr Henrik Larsson
Professor Paul Lichtenstein
Dr Emma Meaburn
Professor Jon Mill
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Professor Robert Plomin
Dr Elise Robinson
Dr Kim Saudino
Dr Leo Schalkwyk
Professor Emily Simonoff
Mr Mark Taylor
Professor Andrew Whitehouse
Dr Chloe Wong

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Thank you

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