Autistic disorder

- a mental disorder diagnosed within the first 3 years of life
- a severe neurodevelopmental disorder characterised by:
  1. typically no period of normal development
  2. moderate retardation in 75% of cases  IQ 35-50
  3. more variable: hyperactivity, under- or over-sensitivity to sensory stimuli, impulsivity, aggression, self-injury
- only small % go on to live independently as adults

Commonly used screening tools:
Childhood Autism Rating Scale (CARS) - similar to DSMIV Autism Behavioral Checklist (ABC) – does not exclude other developmental problems, gives false positive rate of 46%
Prevalence

- autistic disorder: 3-6 in 10,000  (0.045%)
- autism spectrum disorders: 1 in 300  (0.3%)

4 : 1  boys:girls

500% increase in diagnosed cases 1991-97
- increased awareness, changing diagnostic criteria, not new environmental causes

% phenocopies estimated to be very low

- originally thought to have environmental cause
  - no reported cases of autistic children having autistic parents
  - risk to siblings “only” 3 -10%

Twin and family studies

- all consistent, indicate strong genetic component
  - first degree relative risk = 3 – 10%

Concordances

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Autistic disorder</th>
<th>Recent studies</th>
<th>Cognitive/social deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ twins</td>
<td>36%</td>
<td>70%</td>
<td>92%</td>
</tr>
<tr>
<td>DZ twins</td>
<td>0%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>siblings</td>
<td>3%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>unrelated</td>
<td>0.05%</td>
<td>0.05%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

tetragonic correlations

- total population screening, systematic standardized methods of diagnosis, screening out of other conditions
- ONLY idiopathic autism
Conclusions

- Autism is almost completely genetically determined
- Multivariate analysis: different genetic influences exist for the 3 types of symptoms (social, communications, restricted interests) + supported by cognitive and brain data [Happe, Ronald, Plomin, 2006]
- Heritability 80 - 90%
- No evidence for shared environment
- Very small non-shared environment component
- Complex, quantitative inheritance — many genes, interactions
- Any environmental factors likely work by interacting with susceptible genotypes

Known causes of autism spectrum disorders:
  - ~5% have chromosomal anomaly (duplications of Angelman region, chr 15)
  - ~10% have Mendelian condition (fragile X, tuberous sclerosis)

85% have unknown genetic cause (idiopathic autism)
  - Several candidate DNA regions from whole genome scans: chromosome 7q

**ADHD - attention-deficit hyperactivity disorder**

Most predictive characteristics:
1. 
2. 
3.

DSMIII-R single category  DSMIV 3 categories
ADHD I primarily inattentive
ADHD H/I primarily hyperactive/impulsive
ADHD C combined type

Prevalence: 6 - 7% at elementary school age
  5 : 1 boys : girls
  - Continues into adolescence, 1/3 cases → adulthood
  - Frequently comorbid with CD, ODD
  - Increased risk for substance abuse, dependence
Family and adoption studies

Recent large US study: ADHD combined type
familial tendency: 25% first degree relative risk
5% prevalence

adoption studies: biological parent/offspring resemblance is much greater than adoptive parent/offspring

Twin studies
• consistent results even with different measurement methods and heterogeneity of phenotype

Concordances 20 twin studies
MZ = 51% DZ = 33% Prevalence = 5%
heritability ~ 76% no shared e
Using quantitative measure:
same sex, 13 year-old twins, hyperactivity ratings:

<table>
<thead>
<tr>
<th></th>
<th>Rated by</th>
<th>Mother</th>
<th>Father</th>
<th>Teacher</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ twins</td>
<td>0.68</td>
<td>0.48</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>DZ twins</td>
<td>-0.08</td>
<td>0.21</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

mother's ratings show contrast effects
genetic overlap between inattentive & hyperactive symptoms

Conclusions:
• clear genetic influence
• heritability ~70% range = 50 – 90% depending on measurement
• non-additive gene effects
• little evidence for shared environment

environmental risk factors identified in some studies: parental alcohol dependence, maternal smoking, maternal drinking during pregnancy, very low birth weight

mouse model: knock-out of dopamine transporter gene, chr 9 shows extreme hyperactivity

DRD4, DAT1 + other loci implicated in humans

Adolescent conduct disorder (CD)

• general disregard for rights & property of others
  - destruction of property, theft
  - aggressive behavior fighting, bullying
  - disobedience, lying, deceit, running away from home

Prevalence: 14 -20% boys > girls

CD is one of the most prevalent childhood disorders
most common reasons for psychiatric referral
strongest predictors of adult psychopathology
alcohol & drug dependence depression anxiety disorders anti-social personality disorder

Latent trait analysis: ADHD/CD – genetic correlation with CD, differences produced by e
Older studies in text book
McGuffin (1985) juvenile delinquency
Twin concordances: MZ = 87% DZ = 72%
Twin correlations for quantitative measures:

- CBCL by mother
- Rutter scale by mother

<table>
<thead>
<tr>
<th></th>
<th>MZ boys</th>
<th></th>
<th>DZ boys</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>boys</td>
<td>0.47</td>
<td>0.73</td>
<td>0.40</td>
<td>0.50</td>
</tr>
<tr>
<td>girls</td>
<td>0.56</td>
<td>0.70</td>
<td>0.38</td>
<td>0.55</td>
</tr>
<tr>
<td>opposite sex</td>
<td>0.49</td>
<td>0.32</td>
<td></td>
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</tr>
</tbody>
</table>

- modest/low genetic influence, heritability higher in girls
- sex differences for Rutter scale ratings
- large non-shared and shared environment

Problems identified in study methodology:
- sample ascertainment
- age distribution
- method of assessment

- Heterogeneity

Large environmental component - role of family emphasized
- ineffective and/or harsh parenting, poor supervision, lack of discipline, parental conflict, separation, divorce
- all identified as risk factors for CD
- but could these reflect parental psychopathology?
Recent studies

2682 twin pairs community-based sample DSMII-R
Australian Twin Registry Male prevalence = 20%
Female prevalence = 3%

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Concordance</th>
<th>Tetrachoric r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male MZ</td>
<td>396</td>
<td>0.53</td>
<td>0.70</td>
</tr>
<tr>
<td>MZ</td>
<td>231</td>
<td>0.37</td>
<td>0.37</td>
</tr>
<tr>
<td>Female MZ</td>
<td>930</td>
<td>0.30</td>
<td>0.68</td>
</tr>
<tr>
<td>DZ</td>
<td>533</td>
<td>0.18</td>
<td>0.48</td>
</tr>
<tr>
<td>Opposite sex</td>
<td>592</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>- male proband</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>- female proband</td>
<td></td>
<td>0.45</td>
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</tr>
</tbody>
</table>

- larger genetic influence
- shared environment < 30%
- sex differences in prevalence rates but not influences

Peer influence

• previously identified as part of environmental influence
• but,

Genes for ‘bad behavior’?

• mediation of gene influence is likely to be via personality attributes, cognitive style

Comorbidity with ADHD

CD probands 30-50% also have ADHD
ADHD probands 50% show CD/antisocial symptoms
latent trait analysis – type of multivariate analysis capable of revealing underlying influences, here = genetic influence
DRD4 7-repeat(long) allele associated with ADHD and comorbid CD