Phenotype to phenotype correlations

Using new data mining techniques to find associations with IQ and other clinical features.

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Machine Learning

Dr. Alan Holland of Cork, Ireland
Data Mining

- Machine Learning
- Development of algorithms allowing computers to alter behavior based on data.
- Recognition of complex patterns not readily apparent with manual observation.
Data Mining Applications

- The Super Market Loyalty Card:
  - Large numbers of customers
  - Large numbers of products
  - Use of Data Mining to predict future trends in purchases.

http://knowledge.wpcarey.asu.edu/article.cfm?articleid=1451
Data Mining in VCFS

- Large number of patients
- Frequently occurring categorical phenotypes

- Decision trees
  - Computer generated model of the best way to get to a given phenotype
  - Yes/No responses
Decision Trees

VERTEBRAL_ARTERY_LOOPS_KINKS = yes: yes (115.23/3.8)
VERTEBRAL_ARTERY_LOOPS_KINKS = no
  | VPI/HYPERNASALITY = yes
  |   | ABERRANT_R_SUBCLAVIAN = yes: yes (12.32/0.15)
  |   | ABERRANT_R_SUBCLAVIAN = no
  | IAA_TYPE_B = yes: yes (4.81/0.33)
  | IAA_TYPE_B = no
  |   | SENSORINEURAL_HEARING_LOSS = yes: yes (6.66/0.69)
  |   | SENSORINEURAL_HEARING_LOSS = no
  |   | GENERALIZED_ANXIETY_DISORDER = yes: no (9.99/2.57)
  |   | GENERALIZED_ANXIETY_DISORDER = no
  |       | PDA = yes: yes (4.2/0.3)
  |       | PDA = no
  |       |   | PROMINENT_NASAL_BRIDGE = yes
  |       |   |     | ADD/ADHD = yes: yes (6.68/0.72)
  |       |   |     | ADD/ADHD = no
  |       |   |     | CHRONIC_OTITIS.MEDIA = yes: no (6.14/1.96)
  |       |   |     | CHRONIC_OTITIS.MEDIA = no: yes (6.96/1.65)
  |       |   | PROMINENT_NASAL_BRIDGE = no: no (7.12/1.83)
VPI/HYPERNASALITY = no
  | ABSENT/HYPOPLASTIC_ADENOID = yes: yes (2.81/0.12)
  | ABSENT/HYPOPLASTIC_ADENOID = no: no (19.07/2.14)
Decision Trees

- VPI
- ADD/ADHD
- Chronic otitis media
- Reynaud’s phenomenon
- Scoliosis
- Spinal Anomalies
- Psychosis
- Low IQ
- Laryngeal web
- Low platelet counts
- And more...
Results

- Craniofacial
  - VPI
  - Chronic OM
  - ADD/ADHD
  - Attached ear lobes
  - Overfolded helices
  - Bulbus nasal tip
  - Broad nasal bridge
  - Small ears

- Autoimmune
  - Reynaud’s phenomenon
  - Scoliosis
  - Spinal anomalies
  - Rough skin on hands
  - Thrombocytopenia
  - Hypocalcemia/hypoparathyroidism
  - Frequent URI

- Psychiatric/Learning
  - ADD/ADHD
  - IQ
Chronic Otitis Media

• COM: 57.2% of our population
• Associated craniofacial findings:
  – Prominent nasal bridge
  – Attached lobules (VPI is also associated with attached lobules)
  – Bulbous nasal tip
  – Small ears
• Relationship with rotation of the cranial base and formation of the ear canal, middle ear space and eustachian tube?
ADD/ADHD and Chronic Otitis Media

Sample of 250 patients, (p=0.0001).
ADD/ADHD: 29.6% of our population
COM: 57.2% of our population

39.1% (n=56) of patients with COM also have ADD/ADHD
16.8% (n=18) without COM have ADD/ADHD

75.6% (n=56) of patients with ADD/ADHD also have COM
49.4% (n=87) without ADD/ADHD have COM
ADD/ADHD and COM

• Primary malformation affecting both development of the brain and the middle ear?

• COM related to transient hearing deficiencies, speech/language differences and behavioral consequences?
  – ADD/ADHD in VCFS is most often of the inattention (not hyperactive) type
### Is COM associated with attention difficulties?

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts et al. 2004</td>
<td>• Metanalysis of 11 studies, ages 1-5</td>
</tr>
<tr>
<td></td>
<td>• No significant difference in receptive language, expressive language,</td>
</tr>
<tr>
<td></td>
<td>receptive vocabulary, syntax.</td>
</tr>
<tr>
<td>Cross et al. 2010</td>
<td>• Prospective study</td>
</tr>
<tr>
<td></td>
<td>• 698 children assessed for middle ear effusion at ages 0-3; attention</td>
</tr>
<tr>
<td></td>
<td>and behavior between ages 2-7.</td>
</tr>
<tr>
<td></td>
<td>• No significant correlation between duration of MEE and behavior</td>
</tr>
<tr>
<td></td>
<td>problems or attention</td>
</tr>
</tbody>
</table>
Ruben, RJ. 1997 and 1999
- COM early in life (ages 0-9)
- Poorer performance in variety of linguistic tasks at all ages 1-9.

Asbjornsen et al. 2000 and 2005
- Dichotic listening studies, avg. age of 9, show subtle lasting differences in perceiving messages given against background noise,
- Focusing attention on one stimulus to cause the other to become background noise
- Despite normal hearing assessed by standard audiometric studies.

Silva at al. 1982
- New Zealand children at age 5 w/ bilateral OME compared to w/o blt. OME.
- More dependent
- Shorter attention spans
- Weaker goal orientation
- More restless, fidgety, destructive, unpopular and disobedient

Bennett at al. 2001
- Followed above New Zealand children evaluated for OME btw ages 5-9 into the teen years (11-18). Based on parent and teacher reports:
  - More inattentive behavior
  - More hyperactivity
  - Lower IQ
  - Many other behavioral problems

Timmerman et al. 2007
- 160 children ages 4-7 with COM, compared to control group of 2779 NHIS-participating children.
  Parent strengths and difficulties questionnaire (SDQ) showed most significant difference in overall difficulties and hyperactive-inattentive behaviors.
• Is this a causal relationship?

• Does intervention with myringotomy and tube placement alter the association with ADD/ADHD?

• These questions are as of yet unanswered.
IQ and Congenital Heart Disease

• Decision Tree:
  – Variety of cardiac findings...

• Normal cardiovascular system (n=51): mean IQ= 74.31, abnormal cardiovascular system (n=83): mean IQ= 69.25 (p=0.029).

• Not all congenital heart disease...

• Not all cyanotic congenital heart disease...
# Cyanotic Heart Disease

<table>
<thead>
<tr>
<th>Congenital Heart Condition</th>
<th>Association with IQ</th>
<th>Number P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interrupted Aortic Arch Type B</td>
<td>No significant association</td>
<td>n=12 ( p=0.95 )</td>
</tr>
<tr>
<td>Pulmonary atresia or stenosis</td>
<td>No significant association</td>
<td>n=13 ( p=0.39 )</td>
</tr>
<tr>
<td>Tetrology of Fallot</td>
<td>Significantly associated</td>
<td>n=15 ( p=&lt;0.0001 )</td>
</tr>
<tr>
<td>VSD</td>
<td>Significantly associated</td>
<td>n=38 ( p=0.0003 )</td>
</tr>
</tbody>
</table>

Comparing effect of VSD vs. TOF on IQ: no significant difference in effect of one or the other on IQ
IQ and Congenital Heart Disease

• Effect of early cyanosis/degree of cyanosis?

• Effect of surgery v. no surgery?
  – Early work suggests no significant difference.

• Why some heart conditions and not others?
  – Genetic components?
  – Subtle physiologic difference in effects of forms of CHD?
Reynaud’s Phenomenon:

• Small vessel vasospasm of the fingers, toes, nose, and ear tips in response to cold temperatures and strong emotional stimuli.

• Strongly associated with autoimmune disease.

• This finding is present in 20% of our population (n=44).

• Sample size: 182-218

http://en.wikipedia.org/wiki/Raynaud%27s_phenomenon
<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>+ phenotype who also have Reynaud’s</th>
<th>- phenotype who also have Reynaud’s</th>
<th>Number</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent URI</td>
<td>45%</td>
<td>8%</td>
<td>N=29</td>
<td>Fisher’s p=0.0001</td>
</tr>
<tr>
<td>Chronic Otitis Media</td>
<td>29%</td>
<td>11%</td>
<td>N=34</td>
<td>Fisher’s p=0.0003</td>
</tr>
<tr>
<td>Rough skin on the hands/feet</td>
<td>27%</td>
<td>6%</td>
<td>N=15</td>
<td>P=0.0002</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33%</td>
<td>10%</td>
<td>N=5</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>30%</td>
<td>16%</td>
<td>N=13</td>
<td>P=0.04</td>
</tr>
</tbody>
</table>
- **Scoliosis:** present in 25% of our population.
- **Sample size 196-222.**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>+ Phenotype and also have Scoliosis</th>
<th>- Phenotype and also have Scoliosis</th>
<th>Number P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral vocal cord paresis</td>
<td>40%</td>
<td>9%</td>
<td>N=14 P=0.00002</td>
</tr>
<tr>
<td>Hypocalcemia/hypo parathyroidism</td>
<td>40%</td>
<td>13%</td>
<td>N=12 P=0.0002</td>
</tr>
<tr>
<td>Enamel hypoplasia</td>
<td>32%</td>
<td>17%</td>
<td>N=12 P=0.035</td>
</tr>
<tr>
<td>Rough skin on hands/feet</td>
<td>29%</td>
<td>13%</td>
<td>N=18 P=0.008</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>44%</td>
<td>22%</td>
<td>N=8 P=0.012</td>
</tr>
<tr>
<td>Reynaud’s phenomenon</td>
<td>33%</td>
<td>18%</td>
<td>N=13 P=0.04</td>
</tr>
</tbody>
</table>
Interpretation of Data

- Correlation not equal to causation.
- If there is a cause and effect relationship... Which way does it go?
- Clinical implications...
Bibliography


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