Team 3: Physical Health/Functioning

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Genetic Disposition and Patient-reported Quality of Life Outcomes
Rochester, MN, February 26 – 28, 2009
Self-rated Physical Health/Functioning Background

- MOS SF tools – physical limitations (PF10) subscale
- PROMIS – item bank for domain of physical function
- IRT used to reduce the MOS data
- Physical function and self-rated health status demonstrated predictors of mortality
Self–rated Physical Health and Overall Quality of Life

- Constructs are almost independent
- Patient may have high perceived physical-well being and yet have deficits in mental well-being that cause a compromised overall QOL
Question 1

Which potential biological pathways have been considered and/or shown to describe a possible genetic disposition for perceived or self-rated physical health or functioning?
Figure 1. Graphic presentation of the most parsimonious model explaining the genetic and environmental effects in self-rated health, disease severity, maximal walking speed, and depressive symptoms. The numbers in the figure show the standardized coefficients, standard errors given in parentheses. The proportion of variance accounted for by additive genetic effects (A), shared environmental effects (C), nonadditive genetic effects (D), or nonshared environmental effects (E) can be obtained by squaring the respective standardized coefficient.
Heritability over time of self-rated health is stable

Figure 1. Cholesky path model depicting common and unique factors for genetic and environmental sources of variance for self-rated health measured at four consecutive points in time. The figure is simplified and contains only one of the twins in the pair. A = genetic factors; a = genetic loadings; E = nonshared environmental factors; e = nonshared environmental loadings; C = shared environmental factors; c = shared environmental loadings.
Age and Sex Differences in Genetic and Environmental Factors for Self-Rated Health: A Twin Study

Pia Svedberg,1 Paul Lichtenstein,1 and Nancy L. Pedersen1,2

Figure 1. A univariate path model for genetic analysis with twin data. Additive genetic (A), shared environmental (C), and nonshared environmental (E) influences on the measured variable are shown for both members of a twin pair. $R_g =$ genetic correlation for opposite-sexed twins.
Other Models

• Romeis five-point assessment of health, 44% of variability due to genetic factors

• Multiple regression models
Physical Health Measures Versus Self-perceived Health

- Lot of work done on genetic mechanisms of physical health measures
- Johnson: metabolic efficiency and adaptation to stress
- Linkage between perceived health and intelligence indicate that mechanisms for intelligence may be the same ones for physical health
Question 2

Which *genes* and *genetic variants* have been considered and/or shown to have a potential association with perceived or self-rated physical health or functioning?
Separating Genetic Influences on Physiological and Self-reported Health

• Lippi: meta-analysis of all papers that include “sports” and “genetics”

• Hypothetical mechanisms posed for each aspect of the phenotypes including the domain of self-perceived health

• Rankinen summarizes the potential genes related to physical performance: blueprint for PROs
Self-Rated Health in a Longitudinal Perspective: A 9-Year Follow-Up Twin Study

Pia Svedberg, Margaret Gatz, Paul Lichtenstein, Sven Sandin, and Nancy L. Pedersen

<table>
<thead>
<tr>
<th>Item</th>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How would you rate your general health status?</td>
<td>1 = bad</td>
</tr>
<tr>
<td>2. How would you rate your general health status</td>
<td>2 = reasonable</td>
</tr>
<tr>
<td>compared to 5 years ago?</td>
<td>3 = good</td>
</tr>
<tr>
<td>3. How would you rate your health status</td>
<td>1 = worse</td>
</tr>
<tr>
<td>compared to others in your age group?</td>
<td>2 = about the same</td>
</tr>
<tr>
<td>4. Do you think your health prevents you</td>
<td>3 = better</td>
</tr>
<tr>
<td>from doing things you would like to do?</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Items were standardized to a mean of 0 and a standard deviation of 1 before they were summed. In Questionnaire 2, 3, and 4 (1987, 1990, 1993) the items were standardized with the weights from the Questionnaire 1 (1984) items.*
Rankinen summarizes the potential genes related to physical performance. 

Our Research

- DPYD, MTHFR, TYMS play a role in cellular health
- May have a role in self-perceived health
Goldman (1984) found presence of the epsilon 4 allele of the APOE gene was predictive of self-reported health in national Taiwan survey of people over 54
Stress Response Genes

- Heat shock protein HSP70 genes
- HSPA1A, HSPA1B, HSPA1L present within the MHC region on chromosome 6 has been related to the concept of stress response
- -110A>C polymorphism in heat shock genes HSP70-1 related to poor self-related health (Singh, Front Biosci, 2007)
Question 3

What datasets are available to explore the association of genes and perceived or self-rated physical health or functioning?
NCCTG Datasets

• Multiple clinical trials with blood and PROs to answer all sorts of questions ($$)

• Large lung cancer registry

• Large Barrett’s esophagus registry

• Large GI, IC databases
RTOG Datasets

- Multiple clinical trials – radiotherapy
- Do census of other cooperative groups for datasets?
Northwestern University

- NUGENE project
  - PROMIS measures
  - Specific genetic variables, potential for GWAS
  - Type II diabetes
Question 4

How would you design a new prospective study to explore the association of genes and perceived or self-rated physical health or functioning?
GWAS or Specific?

• Long list of potential genes as candidates, almost as efficient to do them all?

• Assess patients perceived health (for example) with cancer diagnosis throughout disease process to assess the role of these genetics variables in the longitudinal self-reported physical health using the SF36 physical scale and/or MDASI physical symptom items
Table 1  Evaluation of Putative Endophenotypes for Major Depression

<table>
<thead>
<tr>
<th>Psychopathological endophenotypes</th>
<th>Specificity</th>
<th>State-independence</th>
<th>Heritability</th>
<th>Familial association</th>
<th>Cosegregation</th>
<th>Plausibility</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood (mood bias)</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>6</td>
</tr>
<tr>
<td>Anhedonia (impaired reward function)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>9</td>
</tr>
<tr>
<td>Impaired learning and memory</td>
<td>±</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Direction of appetite change</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>4</td>
</tr>
<tr>
<td>Diurnal variation</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>6</td>
</tr>
<tr>
<td>Exec. cogn. function (response speed)</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>Psychomotor change</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>Increased stress sensitivity</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>9</td>
</tr>
</tbody>
</table>

| Biological endophenotypes        |             |                     |              |                      |               |              |       |
| REM sleep abnormalities          | ±           | +                   | +            | ++                   | +             | ++          | 7     |
| Increased amygdala activity      | ++          | +                   | 0            | 0                    | 0             | +++         | 6     |
| Decreased subgenual PFC activity | +           | +                   | 0            | 0                    | 0             | +++         | 5     |
| Left ACC volume reduction        | +           | ++                  | 0            | ++                   | 0             | ++          | 7     |
| Hippocampal volume reduction     | –           | ++                  | +            | +                    | 0             | ++          | 6     |
| Reduced 5-HT_{1A} receptor BP    | +           | ++                  | +            | 0                    | 0             | +++         | 7     |
| Tryptophan depletion             | +++         | +++                 | ++           | ++                   | ++            | +++         | 14    |
| Catecholamine depletion          | +           | +++                 | 0            | 0                    | 0             | +++         | 7     |
| dex/CRH test                     | ±           | +                   | ++           | ++                   | +             | +++         | 11    |
| CRH dysfunction                  | +           | +                   | +            | 0                    | 0             | +++         | 6     |

*–, one or more studies did not support this finding (with no positive studies), or the majority of studies do not support this finding; ±, equal number of studies support this finding and do not support this finding; +, at least one study supports this finding and no studies do not support this finding, or the majority of studies support this finding; ++, two or more studies support this finding, and no studies do not support this finding; +++ three or more studies support this finding, and no studies do not support this finding; 0, data not available.