Which of these is not like the other? Null hypotheses for biologically informed multilocus profile scores (BIMPS)

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Background

Biologically informed multilocus profile scores (BIMPS):
- Combine variants previously shown to influence a system into a score of genetic influence
- Ex¹:

![Graph showing multilocus profile scores](image)

- Traditionally have used noncompetitive tests of significance (ex: null hypothesis is of no effect)

HPA-Axis:
- Regulates the body’s response to stress
- Stress a strong predictor of psychopathology
- May moderate the relationship between genetic predisposition to psychopathology and actual diagnostic outcomes

Aim: To develop and present a method for competitively testing BIMPS against alternate genotypic scores of no specific biological import, using a novel HPA-axis profile as a test system.

Basic Methods

Participants: Young adult volunteers who completed the Duke Neurogenetics Study (PI: Hariri) and had usable fMRI, genetic, and self-report data (n=334) were included in analyses.

Threat Task: Emotion-specific face blocks expressing fear, anger, neutral, or surprise (Panel A) interleaved with a sensorimotor control task (Panel B).

![Threat Task images](image)

Imaging parameters and analyses: 3T fMRI scanner. Single subject contrasts for amygdala reactivity (i.e., Panel A > Panel B) were entered into second-level one-sample t-tests thresholded at p < 0.05, FWE, with an extent threshold of 10 voxels within the right centromedial amygdala region of interest.

Childhood adversity: Measured via self-report on the Childhood Trauma Questionnaire.²

Statistical analyses:

<table>
<thead>
<tr>
<th>HPA axis profile</th>
<th>childhood adversity</th>
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<tbody>
<tr>
<td></td>
<td>amygdala reactivity</td>
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</table>

Profile Score

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Risk Allele(s)</th>
<th>MAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FKBP5</td>
<td>rs1360780</td>
<td>T</td>
<td>0.310</td>
</tr>
<tr>
<td>CRHBP</td>
<td>rs10473984</td>
<td>T</td>
<td>0.068</td>
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<tr>
<td>CRHR1</td>
<td>rs110402</td>
<td>G</td>
<td>0.414</td>
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<tr>
<td>MR</td>
<td>rs2070951/rs5522</td>
<td>TC and CT</td>
<td>0.399</td>
</tr>
</tbody>
</table>

Max between-variant $r^2$: 0.060

Competitive Testing

1. Using PLINK, selected only autosomal SNPs for testing.
2. Pruned the SNP database to include only those SNPs with MAF > 0.05 and pairwise $r^2 < 0.10$ to approximate conditions of original analysis.
3. Randomly selected 4 of the remaining SNPs and summed the number of minor alleles for each subject to form a "profile score."
4. Performed a moderation analyses of the interactive effects of the "profile score" and childhood trauma on centromedial amygdala reactivity to the threat task.
5. Repeated steps 3-4 a total of 10,000 times to obtain an empirical p distribution.
6. Compared the t-value of the original profile score analysis to the empirical distribution to assess competitive significance.

Results

With noncompetitive testing, p=0.023.
With competitive testing, p=0.056.

original t-value: 2.281

Conclusion

In this analysis, an HPA axis BIMPS predicted statistically significant variance relative to a null hypothesis of no effect in a self-contained test of significance. Specifically, individuals with a BIMPS reflective of increased HPA axis activation and reduced negative feedback were characterized by elevated amygdala reactivity if they experienced elevated early life adversity.

However, the interaction effect was reduced to a trend when compared to the summation of randomly selected alleles in a competitive test of significance. The method proposed here as an alternative to null hypothesis testing, competitive permutation testing, assesses whether a hypothesized profile outperforms a random set of SNPs. Such competitive testing is necessary to protect against potential false positive results derived from profile approaches.

References

References:

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