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Functional Linear Models Extensions Uncover Pleiotropic Effects of Chronic Pain Phenotypes

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Functional linear models extensions uncover pleiotropic effects of chronic pain phenotypes

**Background & Motivation**

Growing scientific evidence suggests that intricate interactions of genetic risk factors with environmental exposures play a major role in the development of chronic pain conditions. In studies of relative contribution of an individual’s genetic composition to the perception of pain, the general characteristics of pain sensitivity are typically measured by a wide range of different, yet possibly etiologically related pain phenotypes.

Testing each of these pain-perception traits individually is subject to problems of multiple testing and low statistical power. Furthermore, pain-related traits may share common etiology and comprise binary, categorical, and quantitative measurements.

In the current study, we propose a novel statistical approach for simultaneous testing of multiple correlated phenotypes, including quantitative binary, categorical or a combination thereof, with the flexibility of adjusting for other covariates, to explore whether variation within the coding sequence of the gene encoding the P2X7 receptor (P2X7R) affects chronic pain sensitivity in humans.

**Materials**

P2RX7 encodes an ionotropic purinergic receptor central to the pro-inflammatory response; its genetic variation has been recently connected to chronic pain. Previously published results suggest an association between P2RX7 genotype and the amount of allodynia and chronic pain in mice and in humans (Sorge et al. (2012)).

Fibromyalgia and chronic pelvic pain are central sensitivity syndromes and may share genetic etiology. To test whether chronic pelvic pain sensitivity and fibromyalgia are associated with P2RX7, we obtained information over 53 single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) \( \geq 0.05 \) in a cohort of 2,703 subjects from the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) project. Covariates included gender, OPPERA site, case/control status of temporomandibular disorder (TMD), and the first three principal component analysis vectors accounting for variability due to ancestry.

<table>
<thead>
<tr>
<th>Male (n = 1,034)</th>
<th>Female (n = 1,669)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent TMD Cases</td>
<td>19.8%</td>
</tr>
<tr>
<td>Percent Chronic Pelvic Pain</td>
<td>0.8%</td>
</tr>
<tr>
<td>Percent Fibromyalgia</td>
<td>0.9%</td>
</tr>
<tr>
<td>OPPERA Site</td>
<td></td>
</tr>
<tr>
<td>Florida</td>
<td>25.5%</td>
</tr>
<tr>
<td>Maryland</td>
<td>27.7%</td>
</tr>
<tr>
<td>North Carolina</td>
<td>23.0%</td>
</tr>
<tr>
<td>New York</td>
<td>23.7%</td>
</tr>
</tbody>
</table>

**Methods**

The ‘Flipping’ Algorithm

Prior to the analysis, we implemented the ‘flipping’ algorithm that minimizes the number of 0-2 (or 2-0) patterns in genetic data (with SNP coding based on minor allele frequency). The result of association analyses that do not make a priori assumptions about the direction and the magnitude of effects should not be affected by ‘flipping’, but the power of our statistical analysis is enhanced (Vsevolozhskaya et al. (2014)).

**Results**

We tested for an association between 53 SNP variations in P2RX7 that were identified among 2,703 participants in the OPPERA study and two pleiotropic chronic pain conditions – chronic pelvis pain and fibromyalgia. Additional covariates included gender, OPPERA site, TMD case/control status, and the first three principal components. The P-value for association between two chronic pain conditions and P2RX7 was 0.197. Next, we proceeded to investigating the functional effects of the two chronic pain phenotypes. Functional effects, \( \hat{\beta}(t) \), allow to unveil a more nuanced blueprint of how phenotype effects may vary within a genetic region. Specifically, \( \hat{\beta}(t) \) – a functional interpret – estimates smooth baseline allelic dosage over multiple SNPs in the population (highlighted in Fig. 1).

Fig. 2 shows estimated effects of the chronic pelvis pain phenotype, i.e., estimated deviations from the baseline allelic dosage, with the 90% point-wise confidence intervals. The area around rs7958311 represents the highest hit with the strongest association with chronic pelvic pain. The direction of the effect suggests that carriers of rs7958311 may have a higher risk of chronic pelvic pain (note: rs7958311 minor allele frequency coding was ‘flipped’). rs7958311 is a part of the haploblock, containing gain-of-function variants rs208294, rs1718119, and rs3751143 that may comprise a pain protective haplotype.