SOF Analysis Plan Submission Form

Date: Jan 5, 2010

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Other investigators who will be working on this analysis: Marc Hochberg

Analysis Plan Title: Association of COMT polymorphism and hip pain in SOF

Data sets to be used: visits 1, 2, 5, and 6

Primary variables to be used in the analysis: See analysis plan

Do you plan to submit an abstract based on these results? ☐ YES x ☐ NO
If YES, when is the abstract due?

Who will perform the analyses?
☐ Coordinating Center
x ☐ Other local analyst, please specify:

Please attach a 1-2 page description of your analysis plan. Please include the following:

1) Short background/rationale for addressing the research question
2) Brief description of statistical methods
3) Mock tables

E-mail this completed form (as an attachment) to Dana Kriesel (dkriesel@sfcc-cpmc.net).
SOF Analysis Plan #635

SOF Analysis plan: COMT polymorphism and hip pain in SOF

First author: Tuhina Neogi
SOF Sponsor: Nancy Lane
Additional SOF co-authors: Michael Nevitt

Research Questions:
1. Is the Val-158-Met polymorphism of the \textit{COMT} gene associated with hip pain? Is this polymorphism associated with osteoarthritis-related hip pain?
2. Are other \textit{COMT} SNPs or \textit{COMT} haplotypes associated with hip pain?

Background/Rationale:
Hip osteoarthritis (OA) is a prevalent disease among older adults, with some estimates indicating 27% of persons aged $\geq 45$ having evidence of OA.\textsuperscript{1} The primary clinical manifestation of hip OA is that of pain and functional limitation, accounting for a significant health care burden.\textsuperscript{2} It has generally been accepted that there is only a modest association between radiographic features of OA and joint pain, particularly for milder disease.

Interindividual differences in pain sensitivity may add to the discrepancy between radiographic findings and pain ratings. Genetic predisposition,\textsuperscript{3, 4} prior experience,\textsuperscript{5, 6} expectations about analgesic treatment,\textsuperscript{7, 8} current mood,\textsuperscript{9} and social and cultural environment\textsuperscript{10-12} all contribute to a person’s response to pain. Unless such factors are also taken into account, these factors will confound any structure-symptom association studies. Thus, it is important to determine what role such factors play. We therefore would like to explore some potential genetic associations with hip pain, which may partly explain the apparent discordance between hip pain symptoms and radiographic features of OA. We propose focusing on polymorphisms that have already been studied in other settings and appear to be promising in their association with pain.

Although there are a number of association studies linking genetic variations and mutations to an increased risk for hand, hip, and knee OA,\textsuperscript{13-16} these associations may not account for discrepancies in the experience of pain. However, there are genetic determinants of pain sensitivity that may, at least partially, explain these differences. A polymorphism of the estrogen receptor $\alpha$ gene is associated with an increased risk for moderate or severe pain in female patients with temporomandibular disease.\textsuperscript{17} The risk of developing painful temporomandibular disease depends furthermore on haplotype variants of the gene encoding \textit{catechol-O-methyltransferase} (\textit{COMT}), an enzyme that regulates catecholamine and enkephalin levels.\textsuperscript{18} More recently, the Val158Met functional polymorphism of \textit{COMT} has been associated with hip OA-related pain.\textsuperscript{19} We recently found that this same functional polymorphism was associated with knee pain among those with and without OA (unpublished; ACR abstract 2009: \textit{Arthritis Rheum}. 2009;60(10):S236). As well, \textit{COMT} transcription may be regulated by estrogen,\textsuperscript{20, 21} thereby providing a potential biologic reason why more females suffer from OA pain. Another link may be related to aromatase inhibitors used in the treatment of breast cancer which can modulate both estrogen and COMT and have been associated with a heretofore unexplained musculoskeletal pain syndrome, as well as other hormone-depleting therapies.\textsuperscript{22, 23}

\textit{COMT} haplotypes are also associated with differences in mechanical and thermal pain thresholds of healthy individuals,\textsuperscript{24} indicating that genetic variants may determine both overall pain sensitivity and the susceptibility to develop chronic pain in a disease. Twin studies also suggest genetic factors contribute to the risk for low back pain and neck pain.\textsuperscript{25, 26}
Differences in pain sensitivity and the response to analgesic treatment have been linked to gender, race and ethnicity, further indicating that overall pain sensitivity may be in part genetically determined. It is, however, necessary to take into account that these differences may be influenced by and reflect shared psychosocial and cultural factors, and disparities in the access to health care.

The Study of Osteoporotic Fractures affords a unique opportunity to address the question of genetic polymorphisms and their relation to hip pain, and specifically hip OA-related pain, due to its large community-based sample and x-ray studies of hips. In this proposal, we seek to replicate the findings of the Rotterdam Study’s original discovery findings of an association of the Val158Met functional polymorphism of COMT with hip OA-related pain. Such replication would also support the findings of an association of this COMT polymorphism with knee OA-related pain in the Health ABC Study.

Responses to reviewers:
Reviewer 1:
1. The primary COMT SNP studied in the two prior studies that we would like to replicate is the Val158Met (rs4680) polymorphism. As there are other COMT SNPs, we will also created haplotypes as used in Ref 18.

2. Because we are replicating original discovery findings, we will not be using a GWAS approach. Thus we will be focusing on the previously studied SNP rather than how well the density of the gene COMT is “covered” in terms of number of SNPs.

3. In the OA literature, findings focused on a single SNP do get published (e.g. for GDF-5, FRZB).

4. We can certainly consider NSAID or other pain medication use as potential confounders in these analyses.

Reviewer 2:
1. COMT genotyping has been performed and is available in the genetic dataset.
Variables to be used in main analysis

| Main predictors (2 main predictors to be used in separate sets of analyses): | COMT polymorphisms:  
Val158Met (rs4680)  
Other COMT polymorphisms: create haplotypes as used in\textsuperscript{18} |
| --- | --- |
| Outcome variables: | Hip Symptoms:  
EHIP (ever had hip pain lasting at least 1 month): visit 1  
SHIP (since last visit): visit 2, 4, 5  
HP8PNL/HP8PNR (past 8 yrs, ever had pain lasting at least 1 month, either hip): visit 5 |
| Covariates: | Demographics:  
Age, sex  
Anthropometry:  
BMI (or height, weight if BMI unavailable)  
Hip x-ray features (at any time: visit 1 or 5):  
Radiographic Hip OA (RHOA): Modified Croft $\geq 2$ or presence of total hip replacement  
Degree of Hip OA involvement: JSN 0-4, OST 0-3  
CES-D (if available)  
NSAIDs/other pain meds |

Analysis plan:

1. Assess robustness of data: call rate, Hardy-Weinburg equilibrium, population stratification

2. Person-based analyses:
   - categorize individuals as having hip pain Y/N (one or both hips); different definitions will be explored, but options may include: persons who say yes to HP8PNL/R or EHIP (less stringent def’n); persons who say yes to SHIP at all 3 visits (more stringent definition)
   - determine prevalence of each polymorphism by pain category
   - compute ORs using logistic regression, adjusting for important potential confounders
   - repeat analyses in sex-specific manner

3. Secondary analyses:
   - stratified by presence/absence of RHOA
   - sensitivity analyses with different definitions of pain
   - sensitivity analyses with # of hips that have pain (dose-response)
   - sensitivity analyses adjusting for degree of hip OA involvement
## Mock Tables

### Table 1: Participant Characteristics

<p>| | |</p>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>BMI</td>
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<tr>
<td>Race</td>
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<tr>
<td>Presence of hip pain:</td>
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<tr>
<td>One hip</td>
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<tr>
<td>Both hips</td>
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<tr>
<td>Frequency of COMT Val158Met polymorphism</td>
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<tr>
<td>Frequency of other COMT polymorphisms</td>
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<tr>
<td>Frequency of COMT haplotypes</td>
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<td>Proportion of hips with OA</td>
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</tbody>
</table>

### Table 2: Main Results

<table>
<thead>
<tr>
<th></th>
<th>Persons with hip pain (N=xxx)</th>
<th>Persons without hip pain (N=xxx)</th>
<th>Crude and Adj OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Val158Met polymorphism:</td>
<td>Frequency</td>
<td>Frequency</td>
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<tr>
<td>Whole sample</td>
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<td>RHOA sample</td>
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<tr>
<td>Aromatase cytochrome polymorphisms:</td>
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<td>Whole sample</td>
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<td>RHOA sample</td>
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*adjusted for age, sex, BMI
References


