Author's response to reviews

Title: New Jersey Center for Tourette Syndrome Sharing Repository: Methods and Sample Description

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Author's response to reviews: see over
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Anastasios Koutsos, PhD.
Senior Assistant Editor
BMC-series journals

Reference MS #: 1425713254196704 - New Jersey Center for Tourette Syndrome Sharing Repository: Methods and Sample Description

Dear Dr. Koutsos,

Thank you for your careful consideration of our manuscript (MS# 1425713254196704) entitled “New Jersey Center for Tourette Syndrome Sharing Repository: Methods and Sample Description”. We greatly appreciate your helpful comments, as well as those of the reviewers. Below is our response to the concerns of the reviewers. Each comment is addressed individually below, and the locations of the corresponding changes in the text are indicated.

We hope that our responses and revisions have made the paper acceptable for publication in BMC Medical Genomics, and look forward to your response.

Sincerely,

Gary A. Heiman, Ph.D.
Assistant Research Professor
Rutgers University
Response to Reviewer comments

EDITOR’S COMMENTS
Please note that the format requirements differ between BMC Genomics and BMC Medical Genomics. Therefore, as your manuscript was originally submitted in BMC Genomics and was transferred to BMC Medical Genomics, could you please go through the list of changes provided below and revise your manuscript accordingly?

We have re-formatted the manuscript to correspond with the “database articles” format requirements of BMC Medical Genomics as stipulated on the webpage: [http://www.biomedcentral.com/bmcmedgenomics/ifora/?txt_jou_id=2050&txt_mst_id=1008](http://www.biomedcentral.com/bmcmedgenomics/ifora/?txt_jou_id=2050&txt_mst_id=1008).

REVIEWER #1:
1. The term “uneven neuropsychological profile” is somewhat vague. Authors may want to be more specific.

   We have clarified this (1st paragraph of background).

2. The “need for large replication samples”, while true cannot be an explanation for the failure to identify replicable susceptibility alleles

   We have revised this sentence (second paragraph of background).

3. Chronic Tics is not an associated disorder; would use DSM IV terms here, when referring to disorders

   We have revised the sentence accordingly (last paragraph of the Background section).

4. I suspect HIPAA refers to Health Insurance Portability and Accountability Act? This should be written out.

   We have written out Health Insurance Portability and Accountability Act (section Subjects and methods).

5. Why only recruit strict TS (P4; how can that be known in the stage of recruitment?) and not also other tic disorders? Related to this: it is somewhat confusing that the presence of any tic disorder is being assessed (P5). When TS turns out not be present, but CMT is present, would patients be excluded from the repository? Or not?

   We agree with the reviewer that excluding probands with CMT is too restrictive. In the time since the original submission of this manuscript, we have refined our inclusion criteria to include probands with definite DSM-IV TS or Chronic Motor or Vocal Tic Disorder. During the recruitment call, probands (or their legal guardian) are asked about symptoms and if a clinician has diagnosed the proband. Probands that screen positive are
asked to participate. Only subjects that meet the minimum inclusion criteria (as stated above) are included in the repository. We have revised the section “Subjects and methods” accordingly.

6. Please specify what is being meant be an atypical presentation?

*We have clarified atypical presentation (page 6) by adding examples.*

7. It is important to state on which diagnostic assessments PDD/ASD diagnoses are being based. Use of ADI/ADOS?

*The detailed symptom self- (or Parent-) report questionnaire and semi-structured interview focused on the primary diagnoses of interest -- tic disorder, OC symptoms, trichotillomania, and ADD symptoms. If, in the course of the developmental/medical history, the subject or parent reported other current or lifetime diagnoses, these were briefly queried and noted. The clinician flagged these potentially relevant co-morbid conditions (e.g., as in the case of Autism spectrum). However, we would make no representation that our diagnostic assessment of these secondary diagnoses was of the same level of detail or completeness as was that of the primary diagnoses. We have clarified this in the manuscript on the bottom of page 6.*

**REVIEWER #2**

**MAJOR REVISIONS**

While the samples available in the repository currently are a good starting point for genetic studies, it is very desirable that the number of samples continue to grow. The increasing likelihood of genetic heterogeneity and the role of many loci of relatively small effect in the etiology of GTS may necessitate the collection of much larger sample sizes than have been attained thus far by existing studies in order to achieve the power needed to identify relevant causative factors.

*We agree with the reviewer and have updated the repository numbers to the current level (section: “Sample Description”).*

1. It would be useful if the authors could provide a sentence or two about whether the sponsors have a targeted goal for a particular number of affected individuals or types of pedigree structures for the repository and the estimate of the time frame for achieving it.

*We are gathering DNA, cell lines and clinical information from approximately 1000 persons who either seem to have Tourette disorder or are related to someone with Tourette disorder. We have added this to the section, “Sample Description.”*

2. Also, if there are discussions underway with other organizations (such as other regional Tourette syndrome associations) to expand the geographical areas in which
participants are being recruited for the repository, then a sentence or two added to the paper would be useful.

_We are currently assembling a team of clinicians and researchers with the goal to submit a grant for multi-site collaboration in order to substantially the increase the sample. We have added this to the section, “Sample Description.”_

3 If there are any firm plans for extension or other new aspects of the repository the authors should provide a short paragraph about them.

_There are no other plans._

MINOR REVISIONS FOR THE AUTHORS TO RESPOND TO AS THEY THINK BEST

1. The fourth sentence under section “4. Availability and requirements” needs recasting to be clearer. Perhaps just adding the words “on the” to make “based qualifications” read as “based on the qualifications” would be one way of clarifying the meaning and flow if that is what the authors intended.

_We have made this change (fourth sentence under section “4. Availability and requirements)._ 

2. As the repository resources get increasing use in the future, one of the issues that could develop is in regard to the reliability of the diagnostic assessments. I accept that an experienced clinician made the diagnoses in the repository based on the standard criteria referenced. In the future a followup project that could be sponsored by the supporting organization might be for a panel of diagnosticians to review the available material and assign diagnoses independently. Then these diagnostic results could be made available to subsequent accessors of the repository in a form that would include a reliability score. Some individual participants will be borderline or harder to diagnose for various reasons. It will be useful to future researchers to take this information into account. I would urge the sponsoring organizations to support such a subproject and perhaps encourage researchers to seek funding for accomplishing it. Only if the authors can relate firm existing plans with respect to reliability of diagnoses, would I ask them to include a short description in the manuscript about such future plans.

_The reliability of diagnosis is an important, but complex issue. We are administering widely-used instruments (e.g., YGTSS) but currently only utilize one experienced clinician to evaluate the subjects. As we develop the proposal to a multi-site study, we include procedures to maintain the highest reliability possible._