Author's response to reviews

Title: Association of HLA-B*5801 Allele and Allopurinol -Induced Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis

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Version: 2 Date: 16 June 2011

Author's response to reviews: see over
June 9, 2011

Dear Editors:

On behalf of all the authors, I would like to resubmit our manuscript entitled: ‘Association of HLA-B*5801 Allele and Allopurinol -Induced Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis’ to be considered as an original research article for publication in your journal. This study found a strong and significant association between HLA-B*5801 and allopurinol-induced SJS/TEN. Therefore, HLA-B*5801 allele screening may be considered in patients who will be treated with allopurinol.

At the end of letter, we have revised our manuscript and responded point-by-point to each issue raised by the reviewers.

This paper has not been published previously and is not under consideration elsewhere. The authors are responsible for the reported research, and have participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript, and have approved the manuscript as submitted. The data, models, and methodology used in the research are proprietary. The authors report no conflicts of interest.

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Thank you for considering this paper for publication.

Sincerely,

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On behalf of all authors
Response to reviewers

Reviewer #1
This study is a meta-analysis of the association of HLA-B*5801 and allopurinol-induced SJS/TEN. It has been shown in several studies that there are some association between HLA-B*5801 and allopurinol-induced SJS/TEN. Association between HLA-B allele and drug-induced SJS/TEN has also been reported with carbamazepine. Moreover, marked ethnic different in this association has been demonstrated. This review mentioned that there was no ethnic different in the association among HLA-B*5801 and allopurinol-induced SJS/TEN. Major Compulsory Revisions

Comment #1
The major defect of this study is that the data that included in the study is not up to date. The review stopped at October 2009. Why the authors do not review the recent studies of these association. Several recent reports on this association in several ethnic have been published.

Answer: We followed the reviewer’s advice and updated our searching until June 2011. We found 2 additional studies which have been included in our analysis. We have inserted the updated period of searching time in the method section as shown below.

We performed systematic searches on the following databases: MEDLINE, PreMEDLINE, Cochrane library, International Pharmaceutical Abstracts (IPA), Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), World Health Organization (WHO) International Clinical Trial Registry, and ClinicalTrials.gov from its inception until June 2011.

Based on the new searching performed, we have identified 2 studies (Kang et al and Jung et al) which have been included in our meta-analysis. These two studies provide more information in Korean population and the findings are consistent with other studies, allowing combining the results without heterogeneity problem. We have revised our manuscript by adding more information in several parts as summarized below.

1) Changes in the result section
2) Changes in the figures
3) Changes in the tables section

Changes in the result section
The changes in result section were underlined and in bold.
Table 3 summarizes the results of all comparisons. All studies demonstrated a statistically significant association between HLA-B*5801 and allopurinol-induced SJS/TEN. In the primary analyses, SJS/TEN cases were significantly more likely to carry HLA-B*5801 allele compared with both matched-control (OR 96.60, 95%CI 24.49-381.00, p<0.001) and population-control (OR 79.28, 95%CI 41.51-151.35, p<0.001) (Figure 2). There was no apparent publication bias as revealed by Begg’s and Egger’s test (Egger’s test for bias, p=0.732 and Begg’s test for bias p=0.602). No statistically significant heterogeneity was found based on I-squared ($I^2=0.0\%$) and Q-statistics ($p=0.482$ for matched-control and $p=0.751$ for population-control).

Changes in the figures
The studies that were added in the forest plot were Kang et al 2011 and Jung et al 2011.

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Matched-control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hung SI (2005)</td>
<td>242.27 (14.11, 4158.77)</td>
<td>23.30</td>
</tr>
<tr>
<td>Kang H (2011)</td>
<td>34.00 (3.25, 358.12)</td>
<td>34.13</td>
</tr>
<tr>
<td>Jung J (2011)</td>
<td>47.17 (2.23, 999.15)</td>
<td>20.20</td>
</tr>
<tr>
<td>Total ($I^2=0.0%, p=0.482$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Population-control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hung SI (2006)</td>
<td>164.28 (3.52, 2833.82)</td>
<td>5.16</td>
</tr>
<tr>
<td>Kaniwa N (2008)</td>
<td>64.11 (120.8, 242.41)</td>
<td>13.69</td>
</tr>
<tr>
<td>Lonjou C (2008)</td>
<td>101.45 (44.96, 228.82)</td>
<td>68.18</td>
</tr>
<tr>
<td>Kang H (2011)</td>
<td>26.89 (3.17, 282.78)</td>
<td>8.57</td>
</tr>
<tr>
<td>Jung J (2011)</td>
<td>36.84 (1.70, 756.81)</td>
<td>4.60</td>
</tr>
<tr>
<td>Total ($I^2=0.0%, p=0.751$)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Changes in the tables section
The changes in tables were underlined and in bold.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>SJS/TE Cases&lt;sup&gt;a&lt;/sup&gt; (n)</th>
<th>Controls Matched (n)</th>
<th>Population (n)</th>
<th>Data Collection SJS/TEN Cases</th>
<th>Controls</th>
<th>Specific Requirement for Case Allopurinol Exposure&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Matching Criteria</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung SI [10]</td>
<td>2005</td>
<td>Case-control</td>
<td>21</td>
<td>135</td>
<td>93&lt;sup&gt;e&lt;/sup&gt;</td>
<td>R</td>
<td>R</td>
<td>Yes</td>
<td>Drug, hospital</td>
<td>7</td>
</tr>
<tr>
<td>Kaniwa N [11]</td>
<td>2008</td>
<td>Case-population control&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10</td>
<td>-</td>
<td>493&lt;sup&gt;e&lt;/sup&gt;</td>
<td>R</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Lonjou C [12]</td>
<td>2008</td>
<td>Case-population control&lt;sup&gt;d&lt;/sup&gt;</td>
<td>31</td>
<td>-</td>
<td>1822&lt;sup&gt;f&lt;/sup&gt;</td>
<td>R (N = 70), P (N = 80)</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Tassaneeyakul W [13]</td>
<td>2009</td>
<td>Case-control&lt;sup&gt;e&lt;/sup&gt;</td>
<td>27</td>
<td>54</td>
<td>-</td>
<td>R</td>
<td>R</td>
<td>Yes</td>
<td>Drug, hospital</td>
<td>7</td>
</tr>
<tr>
<td>Kang HR [14]</td>
<td>2011</td>
<td>Case-control&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5</td>
<td>57</td>
<td>485&lt;sup&gt;h&lt;/sup&gt;</td>
<td>R</td>
<td>R</td>
<td>Yes</td>
<td>Drug, hospital</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviation: R=retrospective, P=prospective, NOS = Newcastle-Ottawa Scale, NR = not report
<sup>a</sup>Only patients that received drugs of interest (Allopurinol) were included.
<sup>b</sup>Including: maximum time to develop adverse drug reaction (ADR) from drug initiation [10, 12, 13], improvement of symptom upon drug discontinuation [10, 13], and exclusion of patients without symptoms upon re-exposure [10].
<sup>c</sup>Healthy subjects randomly selected from a biobank under nationwide population study, in which 3312 Han Chinese descendants were recruited based on the geographic distribution across Taiwan. There was no self-report of adverse drug events by any of the population control.
<sup>d</sup>Using population based as control group.
<sup>e</sup>Data of healthy Japanese reported by Tanaka H, et al. [20].
<sup>g</sup>Author described the study as cross-sectional case-control study.
<sup>h</sup>Using allele frequency from the general population of Korea.
Table 2 Patients’ demographic information

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>% Male</th>
<th>Mean age, yr (range)</th>
<th>Ethnicity</th>
<th>Country</th>
<th>Allopurinol Dose, mg/day (range)</th>
<th>Actual Duration of Allopurinol Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung SI [10]</td>
<td>2005</td>
<td>52.4</td>
<td>62.4 (25-91)</td>
<td>Han</td>
<td>Taiwan</td>
<td>100 (50-300)</td>
<td>26 d (1-56 d)</td>
</tr>
<tr>
<td>Lonjou C [12]</td>
<td>2008</td>
<td>58.1</td>
<td>55.0 (21-83)</td>
<td>Mixed</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tassaneeyakul W</td>
<td>2009</td>
<td>55.6</td>
<td>65.0 (38-81)</td>
<td>Thai</td>
<td>Thailand</td>
<td>NR</td>
<td>14 d (3-50 d)</td>
</tr>
<tr>
<td>Kang HR [14]</td>
<td>2011</td>
<td>60.0</td>
<td>50.0 (42-80)</td>
<td>Korean</td>
<td>Korea</td>
<td>200 (100-300)</td>
<td>29.1 m (6-72 m)</td>
</tr>
</tbody>
</table>

Abbreviations: SJS = Stevens-Johnson Syndrome, TEN = Toxic Epidermal Necrolysis; NR=No Report; NA=Not Applicable; d=day(s); m=month(s)

a The percent male of matched-controls (% male in population controls is 55.91).

b Mean age in matched-controls (mean age in population controls is 53.9 (22-91)).

c Including Asian, South American, African, and European.

d The values from matched-controls group.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>HLA-B*5801 Positive/Total</th>
<th>Odds Ratio (OR)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SJS/TEN Cases</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Matched-control</td>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td>Jung JW [15]</td>
<td>2011</td>
<td>2/2</td>
<td>41/432</td>
<td>47.17</td>
</tr>
<tr>
<td>Pooled OR</td>
<td></td>
<td>96.60</td>
<td></td>
<td>24.49-381.00</td>
</tr>
<tr>
<td>Population-control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lonjou C [12]</td>
<td>2008</td>
<td>19/31</td>
<td>28/1822</td>
<td>101.45</td>
</tr>
<tr>
<td>Pooled OR</td>
<td></td>
<td>79.28</td>
<td></td>
<td>41.53-151.35</td>
</tr>
</tbody>
</table>

Abbreviations: SJS = Stevens-Johnson Syndrome, TEN = Toxic Epidermal Necrolysis; OR = Odds Ratio
Comment #2
Discussion part is too long, authors specify several strengths of their research work which may not be necessary to here.

Answer: We agreed that the discussion was slightly long. We read through them and found that those strengths are important and need to be discussed. However, to shorten the length of our manuscript, we have removed some elaborating parts out as shown below.

The sentences there were removed were underlined and in bold.

Several strengths of our research work deserve more discussion. First, our study is the first one including all kinds of studies determining association of HLA-B*5801 and SJS/TEN development. Three studies conducted conventional matched case-control, while the other 2 studies used population data from another source as control. Only one study conducted retrospective cohort design. Despite the differences of sources of control and its selection, the results are consistent across different studies. Second, all SJS/TEN cases were in accordance with the consensus definition [16-18]. These stringent inclusion criteria lowered the risk of misclassification, resulting in increased reliability of our research findings. Third, our meta-analysis adopted the Newcastle-Ottawa scale [19] as a tool to evaluate quality of all case control studies. The Newcastle-Ottawa approach has been reported in several articles to have a good validity for assessing the observational study [25-28]. The average quality score of 5 represented a good quality of overall evidence.

In addition, we have removed some parts of discussion related to mechanism of allopurinol-induced SJS/TEN. (The underlined and bold fonts are removed)

There are numerous genetic polymorphisms of HLA that are implicated for predisposing individuals to particular diseases or undesirable responses to drug therapy. For example, HLA-DRB1*0401 and HLA-DRB*0404 are associated with rheumatoid arthritis [31]. Interestingly, HLA-A3, HLA-B52 and some others are found to involve in the development of intolerance of non-steroidal anti-inflammatory drugs (NSAIDs) [32]. The exact mechanism of HLA polymorphism-induced diseases are still under extensive investigation. However, despite high prevalence of HLA-B*5801 in some populations (Asian, Han Chinese and Thai) [33], the incidences of SJS/TEN in these populations owing to allopurinol are relatively low [13, 34]. Thus, cellular & molecular machinery may be responsible for this discrepancy.

Furthermore, we have removed some parts of discussion related to the implication of our findings (The underlined and bold fonts are removed).
Nevertheless, a cost-effectiveness and/or pharmacoeconomic analysis is required to further aid clinicians and policy makers whether HLA-B*5801 genetic test should be adopted in clinical practice.

From our results, a genotypic testing of the HLA-B allele may have a benefit to the patients before receiving the drug. Knowing the HLA-B allele status of allopurinol users may guide clinicians in determining the optimal choice in order to lower the likelihood of allopurinol-induced SJS/TEN. In addition, a specific study for investigating the underlying mechanism of the allopurinol-induced TEN/SJS is warranted.

Given the extent of the potential benefits, HLA-B*5801 allele screening may be considered prior to the initiation of allopurinol. To aid efficient resource allocation, a cost-effectiveness study of this genetic screening is warranted.

We incorporated the issue mentioned above in one paragraph at the end of discussion section as showed below.

The implications of our research findings are more likely significant among population with high prevalence of HLA-B*5801. Based on the strong association of the presence of HLA-B*5801 alleles and SJS/TEN, it is presumed that the attributable risk of SJS/TEN due to the existence of this gene is larger among those with the gene. Allele frequency was reported as high as 6-8% among Southeast Asian population and <1% among Western European population [8, 45]. From our results, a genotypic testing of the HLA-B allele may have a benefit to the patients before receiving the drug; particularly in high risk population (e.g. Asian). Knowing the HLA-B allele status of allopurinol users may guide clinicians in determining the optimal choice in order to lower the likelihood of allopurinol-induced SJS/TEN. Presumably these events are avoidable; it might be prudent to consider whether such genetic test should be adopted into routine practice in high-risk population. In order to convince the policy makers to support such genetic testing, a formal cost-effectiveness analysis is warranted.

Comment #3
The reason why is no ethnic different in the association between HLA-B*5801 and allopurinol like carbamazepine and HLA-B*1502 need to be discussed.

Answer: We have inserted a discussion about the reason of those different associations.

Interestingly, HLA-B*5801 has a more pronounced effect on allopurinol-induced SJS/TEN compared to those found in the case of HLA-B*1502 and CBZ-induced SJS/TEN. In the latter case, the incidence may be associated with other contributing factors (i.e. other genes) to trigger the adverse drug reaction, whereas those factors may play less role in initiating SJS/TEN in case of HLA-
B*580. A study in Japan [46] reported that CBZ-induced SJS/TEN was associated with HLA-B*1511, a member of HLA-B75 type that also includes HLA-B*1502, HLA-B*1508, HLA-B*1515, HLA-B*1521, HLA-B*1530, and HLA-B*1531. These suggested that not only HLA-B*1502 but also other HLA-B75 members are risk factors for CBZ-induced SJS/TEN. By comparison, the strong association between HLA-B*5801 and allopurinol-induced SJS/TEN has been validated in different populations and may be a universal phenomenon since it has been identified in all Chinese, Japanese, Thai, Korean and European patients [10-15].

Comment #4
This association is not limited to only SJS/TEN, it also association with DRESS induced by allopurinol, is it worth to mention in this study.

Answer: We have inserted a brief discussion on the fact that DRESS induced by allopurinol is not in the scope of our study. Below is the paragraph inserted in the discussion section.

Our study is also only limited to the investigation of the association between HLA-B*5801 and allopurinol-induced SJS/TEN. In fact, there has been a number of studies reporting a potential association of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and HLA-B*5801 [10, 47]. The interpretation of our findings should be limited to SJS/TEN cases and not be generalizable to other severe cutaneous adverse reactions (SCARs).

Reviewer #2

With the manuscript entitled “Association of HLA-B*5801 Allele and Allopurinol-Induced Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis” the authors reviewed several earlier studies performed in this field. My questions and comments to the manuscript are the following:

Comment #5
Background:
When reporting the incidence of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the authors refer to one retrospective study performed two decades ago in Singapore and a review paper not focusing on the calculation of incidence. However, there have been reports on prospective registries leading to reliable incidence rates for SJS and TEN such as Rzany et al, J Clin Epidemiol, 1996 and Mockenhaupt, Norgauer, ACI, 2002. The latter publication also provides demographic data including mortality.
We followed the reviewer’s suggestion by incorporating information from the references and rewriting the text as shown below.

**Original version**
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe manifestations of cutaneous hypersensitivity reactions affecting 0.4-1.2 and 1-6 persons per million population each year, respectively [1, 2]. Despite the low incidence, the mortality rate has been estimated at 5% for SJS and 30% for TEN [2].

**Revised version**
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe manifestations of cutaneous hypersensitivity reactions affecting approximately 0.4 to 6 persons per million populations each year [1-3]. Despite the low incidence, the mortality rate has been estimated at 5% for SJS and 30-50% for TEN [2, 4, 5].

**Inserted references**

**Comment #6**
When speaking about medications with a risk to induce SJS/TEN, the authors refer to Halevy et al 2008. However, this paper mainly reports on allopurinol which is actually the only uric acid lowering agent with a risk for SJS/TEN, but not on other medication. The reference for the multinational case-control-study the authors are mentioning is missing: Mockenhaupt et al, J Invest Dermatol, 2008.

Answer: We followed the reviewer’s suggestion by removing the citation of Halevy out as it focused only allopurinol. We used the suggested reference (Mockenhaupt) instead as it is the multinational case-control study as cited below.

Iatrogenic causes that have been firmly correlated with both SJS and TEN syndromes include: antiepileptic drugs, antibiotics, and uric acid lowering agents [2, 5]. A multinational case-control study recently reported that allopurinol, a xanthine oxidase inhibitor commonly used to treat hyperuricemia and gouty arthritis, was the most frequent drug associated with SJS and TEN [7].
Inserted references


Comment #7
Methods:
The criteria for case classification are based on a consensus definition published by an international group of dermatologists in 1993. Actually, the authors refer to this publication, but they do not provide all authors. Roujeau was one of the co-authors of this publication, but nevertheless the criteria should not be referred to as “Roujeau’s criteria”, but as the consensus definition. In reference 11, Roujeau only summarizes the information of the earlier original publication of Bastuji-Garin et al.

Answer: We followed the reviewer’s suggestion by changing “Roujeau’s criteria” to “consensus definition” and cited the references (references number 16-18).


Comment #8
Results:
The authors are speaking about “Japan Severe Adverse Reaction (JSAR) research group. If I understood the Japanese colleagues correctly in their presentation at international meetings, they call their group “JSCAR”.

Answer: We agree with the reviewer and do recheck the correct abbreviation. Therefore, we made corrections by replacing the term “JSAR” to “JSCAR”.

Comment #9

~ 11 ~
I find it difficult to consider a meta-analysis of four studies a scientific breakthrough. In contrast, I am afraid that rather clear findings of these four studies are somewhat diluted by the results of the meta-analysis.

Answer: Meta-analysis is a technique used to synthesize overall findings of existing literature. Our research work was conducted with accordance to standard systematic review approach; studies were identified and evaluated systematically. Furthermore, all available scientific papers related to this are included. At the end, data were available and very consistent, indicating the suitability for meta-analysis. We believe that presenting the finding of each study and the combined results (synthesized through meta-analytic technique) will give a better picture of overall findings with stronger evidence than presenting each of them individually.

Comment #10
Discussion:
The first sentence of the discussion should simply be deleted.

Answer: We followed the reviewer’s suggestion by removing the sentence from the “Discussion” section.

The sentences there were removed were underlined and in bold.

To the best of our knowledge, this report is the first meta-analysis conducted to determine the association between HLA-B*5801 allele and the risk of SJS/TEN among patients receiving allopurinol. Our findings indicate that HLA-B*5801 allele is significantly associated with increased risk of developing SJS/TEN in patients using allopurinol.

Comment #11
The authors report about “several strengths” of their study, but what about the pitfalls?

Answer: We have not directly listed out the pitfalls in our study. However, we described them as limitations and concerns in discussion section. The first one was that the findings need to be interpreted with caution despite the lack of publication bias revealed from statistical test. (This issue is addressed in the paragraph starting with “Despite the absence of statistical significance”). The second one is the fact that we cannot conclude that having HLA-B*5801 is the only factor related to risks of SJS/TEN development. (This issue is addressed in the paragraph starting “One interesting debate ongoing regarding association between HLA-B*5801”).

The last limitation in our study was that we addressed only SJS/TEN cases. Cases with DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) were previously reported to be potentially associated with HLA-B*5801. We have
inserted the discussion about this issue in the discussion section as well. *(This issue is addressed in the paragraph starting “Our study is also only limited to the investigation”)*

**Comment #12**

Is it really helpful to combine results of a 100% allele frequency of HLA-B*5801 and allopurinol-induced SJS/TEN in Han-Chinese and 55% of allele frequency in Europeans?

**Answer:**

In this study, we aim to identify the association between HLA-B*5801 and allopurinol-induced SJS using meta-analysis. Although the genetic differences of HLA-B*5801 across populations are documented; however, the results of our sensitivity analyses showed no heterogeneity among the studies. We found that the association remains existed with the consistent magnitude regardless of population with varying allele frequency. *(The summary odds ratio was 74.18 (95% CI; 26.95-204.14) and 101.45 (95% CI; 44.98 -228.82) for Asian and non-Asian populations, respectively.)* However, this issue is further discussed in our discussion section.

We added a sentence into the manuscript to explain our results obtained from the sensitivity analysis and heterogeneity. The sentence which was inserted was shown below in bold and underlined.

*Meta-analysis is not only pooling studies’ findings, but this analysis can also determine heterogeneity occurred among the selected studies. The results from our sensitivity analysis demonstrated no significant heterogeneity among populations despite differences in their allele frequency between Asian and non-Asian. Thus, it is justified to perform such analysis despite similarity in the trend of results from the chosen reports. Our findings revealed that despite some differences in several characteristics (e.g. race, sources and selection of control), the association is still consistent and suitable for pooling using meta-analytic technique [29].*

**Comment #13**

On page 15 of their manuscript the authors suggest different hypotheses related to the pathomechanism of SJS/TEN. However, it has to be clearly stated that this is hypothetic and not proven.

**Answer:**

We made some changes in our manuscript to clearly indicate that our discussion in this particular issue is hypothetical. There might be other responsible factors contributing to this effect (as shown in the newly edited text below).
We have inserted a sentence and some key words in the following paragraph. They were shown in Bold and underlined texts.

**Despite several postulated mechanisms for the association of HLA-B*5801 and allopurinol-induced SJS/TEN, thus far, there is no definitive proven mechanism. Nonetheless, an immunologic mechanism might play a role in SJS/TEN development** [31-33].

**Comment #14**

The authors suggest that genotype testing of the HLA-B allele may be beneficial for patients before receiving the drug. This had already been known for Han-Chinese populations before receiving allopurinol (or carbamazepine) but I doubt the benefit for patients of European decent due to low allele frequency and only 55% HLA-B*5801 expression in allopurinol-induced cases of SJS/TEN.

**Answer:** We realize about the reviewer’s concern upon the benefit of the genetic screening in populations with lowered susceptibility (e.g. non-Asian populations), therefore, we added several sentences into our revised manuscript to specifically indicate that Asian populations would benefit more if the genetic screening policy and test are applied.

This issue is addressed in the paragraph in “Discussion section”. The inserted sentences were shown in Bold and underlined texts.

*The implications of our research findings are more likely significant among population with high prevalence of HLA-B*5801. Based on the strong association of the presence of HLA-B*5801 alleles and SJS/TEN, it is presumed that the attributable risk of SJS/TEN due to the existence of this gene is larger among those with the gene. Allele frequency was reported as high as 6-8% among Southeast Asian population and <1% among Western European population [8, 45]. From our results, a genotypic testing of the HLA-B allele may have a benefit to the patients before receiving the drug; particularly in high risk population (e.g. Asian). Knowing the HLA-B allele status of allopurinol users may guide clinicians in determining the optimal choice in order to lower the likelihood of allopurinol-induced SJS/TEN. Presumably these events are avoidable; it might be prudent to consider whether such genetic test should be adopted into routine practice in high-risk population. In order to convince the policy makers to support such genetic testing, a formal cost-effectiveness analysis is warranted.*