Nov 25, 2015

Dear Prof Qi:

Thank you and the reviewers for their thorough review and most valuable comments on our manuscript titled "Interactions between Traffic Air Pollution and Glutathione S-transferase Genes on Childhood Asthma" (NO: 22258). We have carefully answered all concerns of the reviewers, and some alterations (in red text) have been made according to the reviewers' suggestions. Please find the revised manuscript for your consideration for publication.

We would greatly appreciate the opportunity to consider any further changes if you require.

Sincerely Yours,

Yungling Leo Lee, MD, PhD
Corresponding Author

Reviewer Comments:

1. ***Curiosity: Are there studies on the prevalence of different genetic polymorphisms according to the different races?***

Yes, the International HapMap Project is collaborated different genetic data of different races. Allele frequencies of genetic polymorphisms according to the different races could be found from NCBI website (http://www.ncbi.nlm.nih.gov/).

2. ***I think that must be updated. In the article there is no reference in the last three years.***

Thank you very much for the valuable concerns. We updated some references within three years in INTRODUCTION and DISCUSSION. The references are as follows:

(1) **Sears MR**. Trends in the prevalence of asthma. *Chest* 2014; **145**: 219-225 [PMID: 24493506 DOI: 10.1378/chest.13-2059]

(2) **Masoli M**, Fabian D, Holt S, Beasley R. Global burden of asthma. *Global Initiative for Asthma (GINA)* 2004; http://www.ginasthma.org/local/uploads/files/GINABurdenReport_1.pdf (accessed Nov 17, 2015).

(3) **Su MW**, Tung KY, Liang PH, Tsai CH, Kuo NW, Lee YL. Gene-gene and gene-environmental interactions of childhood asthma: a multifactor dimension reduction approach. *PLoS One* 2012; **7**: e30694 [PMID: 22355322 DOI: 10.1371/journal.pone.0030694]

(4) **Nishimura KK**, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, Thyne S, Farber HJ, Serebrisky D, Kumar R, Brigino-Buenaventura E, Davis A, LeNoir MA, Meade K, Rodriguez-Cintron W, Avila PC, Borrell LN, Bibbins-Domingo K, Rodriguez-Santana JR, Sen S, Lurmann F, Balmes JR, Burchard EG. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. *Am J Respir Crit Care Med* 2013; **188**: 309-318 [PMID: 23750510 DOI: 10.1164/rccm.201302-0264OC]

(5) **Su MW**, Tsai CH, Tung KY, Hwang BF, Liang PH, Chiang BL, Yang YH, Lee YL. GSTP1 is a hub gene for gene-air pollution interactions on childhood asthma. *Allergy* 2013; **68**: 1614-1617 [PMID: 24117884 DOI: 10.1111/all.12298]

(6) **MacIntyre EA**, Brauer M, Melen E, Bauer CP, Bauer M, Berdel D, Bergstrom A, Brunekreef B, Chan-Yeung M, Klumper C, Fuertes E, Gehring U, Gref A, Heinrich J, Herbarth O, Kerkhof M, Koppelman GH, Kozyrskyj AL, Pershagen G, Postma DS, Thiering E, Tiesler CM, Carlsten C, Group TAGS. GSTP1 and TNF Gene variants and associations between air pollution and incident childhood asthma: the traffic, asthma and genetics (TAG) study. *Environ Health Perspect* 2014; **122**: 418-424 [PMID: 24465030 DOI: 10.1289/ehp.1307459]

In addition, we have added the following sentences “In a large birth cohort, children carrying *GSTP1* minor alleles may constitute a susceptible population at increased risk of asthma associated with NO2 exposure” in our revised DISCUSSION.

3. ***Relate to high levels of NO2 with late asthma but not with early (<0.5 years): Could you suggest a cumulative effect dose of NO2 is required to develop asthma?***

Thank you very much for the concern. We found significantly interactive effects on late-onset asthma, but not on early-onset asthma. Cumulative effect is one of the reasons. Another reason is might be different pathogenesis between early- and late-onset asthma. Nowadays, raising question is about non-allergic asthma with low eosinophil in airway [1] and late-onset asthma might be part of non-eosinophilic asthma. However, it is limited to explain in the current study because of our study design.

Reference:

1. Nakagome K, Matsushita S, Nagata M. Neutrophilic inflammation in severe asthma. *Int Arch Allergy Immunol* 2012; **158 Suppl 1**: 96-102