Author’s response to reviews

Title: The analysis of APOL1 genetic variation and haplotype diversity provided by 1000 Genomes project

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Author’s response to reviews:

RE: BNEP-D-16-00676

Dear Editors and Reviewers,

We would like to thank you and reviewers for your very valuable comments and suggestions. We have carefully read the comments and suggestions, and responded them point-by-point. The changes have been highlighted using track changes. We also tried to correct the spelling mistakes and improve the English Writing. We hope it would be suitable for publication in your journal. At the following, the points mentioned by the reviewers will be discussed.

Thank you for your consideration.

Yours sincerely

Guisen Li

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Reviewer#1

General comments

1. As it is mentioned in the introduction that the association of ApoL1 can increased risk of multiple kinds of kidney diseases mainly in African Americans, specifically kidney diseases including focal segmental glomerulosclerosis (FSGS), hypertensive nephropathy (HTN), human immunodeficiency virus associated nephropathy (HIVAN), etc. but there are some other diseases that can increase the risk of kidney diseases due to CKD, ESRD, Systemic lupus erythematosus, artherosclerosis, PLA2R-positive membranous glomerulopathy, cancer and type2 diabetes that can cause severity as well as mortality of the patient. (if in the highlighted regions it should mentioned the it will be more informative)

Response: Thanks for your comments, we agreed with it completely. We have added those information in Paragraph 3 of Introduction Section.

2. In this context there is no information regarding the association or role of APOL1 in viral, bacterial and other parasitological diseases (except trypansomiasis) which are associated with APOL1 and increase risk of kidney disease.

Response: Thank you for your kind suggestions. We have added the discussion about the relationship between APOL1 gene and human immunodeficiency virus. Please see changes in Paragraph 3 of Introduction Section.

3. APOL1 can also play protective in renal cell carcinoma, but there is no such discussion whether the different kinds of population show this behavior or not.

Response: Thank you for your kind suggestions. We carefully checked all publications, there only one literature but didn’t report the difference in the effects of APOL1 gene mutation on renal cell carcinoma in different kinds of population. It was a very good suggestion and would be explored in the future. We cite this literature in Paragraph 3 of Introduction Section.

4. There is no such information regarding the effects of APOL1 variants on phenotypes beyond the kidney, in addition to their role in innate immunity as per the 1000 genome analysis. The association of MYH9 with non-diabetic nephropathies are not narrated in the discussion part.

Response: Thank you for the nice suggestions. In this article, we are mainly exploring the predictive effect of the haplotypes of APOL1, but the specific mechanism of these haplotypes in renal diseases and immune diseases is not clear. Researches have shown that APOL1 is significantly associated with ESKD than all previously reported SNPs in MYH9, so we only focus on the correlation between APOL1 gene and kidney diseases in this paper.

5. In his manuscript the role of G1 is bit elaborated whereas the role of G2 is not, as per an African study, published in BMC genetics (Matasha et al 2015), the role of G2 in increase of cardiovascular disease including stroke and kidney complication.
Response: Thank you for the nice suggestions. APOL1 risk variant G2 is a two codons deletion (haplotype rs71785313; 6-bp in frame deletion, ΔN388Y389). There no frequency information about G2 in 1000 Genomic Database, so we didn’t analyze the role of G2 in the haplotype of different populations.

6. Gender specific analysis of different age group of different population those are at risk in the population should be provided.

Response: Thank you for your kind suggestions. Age information of the sample was not available in the 1000 genome database, in addition, our main focus is the distribution of the haplotypes in different regions of APOL1 in different populations.

Specific comments:

Introduction:

1. 7th number line: APOL1 present in plasma...could be...APOL1 is present in plasma and mainly associated.

2. 32 lines: The CDS encoded...APOL gene family, three functions........ and SRA-interacting domain. could be written as The CDS encoded APOL1....... family. There are three functional domains; pore forming domain (PFD), membrane-addressing domain (MAD) and SRA-interacting domain.

3. 34th & 35th line: Part of the signal peptide encoded by...exon 4 could be written as... Part of the signal peptide is encoded by exons 2, exon 3 and exon 4.

Method section:

1. Line no 7: All we analyzed....... Phase 3 could be modified as we analyzed all the SNPs data of APOL1 are from 1000 Genomes Phase 3.

2. 16th line—SNP could be SNPs

3. Lne no 53: triallelic alleles according NCBI .... the 1000. could be written as triallelic alleles according to NCBI and Ensembl, which be properly corrected as per the 1000...

4. Table numbering and figure numbering is confusing...like Table S4, S5 and figure S3, S7... Numbering of figure and table should be properly done...

Result:

1. Line no. 19: In all eight haplotypes...... the frequencies of seven haplotypes were could be written as... out of the eight haplotype the frequencies of seven haplotypes were significantly.
Response: Thank you for your kind suggestions. We have changed all the specific comments one by one, and we highlighted all changes in the revised manuscript. In addition, we asked a native English-speaking staff to modify the English expression.

Reviewer#2

Brinda Rana (Reviewer 2): Peng and Li describe the haplotype diversity of the APOL1 gene in 4 populations included in the 1000 Genomes Project. The study uses extant data from this project. It is always handy for investigators pursuing a genetic association study on a particular gene to have a paper such this which describes haplotypes in different ethnic groups. Thus, the results are valuable to the scientific community. The authors chose BMC Nephrology because of some previous reports linking the APOL1 gene and kidney function, however, that is the extent of the relationship of the paper with Nephrology. Perhaps another genetic or molecular evolution journal would be more appropriate with additional analysis such as phylogenetic analysis in populations. There are also numerous language errors which include some grammatical errors, but mostly misplaced articles.

Response: We are very grateful to the reviewer for your careful review and suggestions. Population-based genetic studies have identified lots of kidney diseases which had increased genetic risk of developing and progressing. The prevalence of CKD is increasing worldwide with apparently racial diversity, genetic factors played an important role in the development of CKD. The two variants (G1 and G2) of APOL1 has been shown to be associated with an increased susceptibility of multiple kinds of kidney diseases, particularly in African Americans, such as FSGS, hypertensive nephropathy, HIVAN, etc. Haplotype analysis can help researchers to determine the diseases susceptible genes, and can make a better understanding about the diseases and the patients genotype. So, our study based on the haplotype frequency distribution of APOL1 will help researchers to study the relationship between APOL1 gene variation and susceptibility to renal disease in different populations.