Author's response to reviews

Title: Novel GALT variations and mutation spectrum in the Korean population with decreased galactose-1-phosphate uridyltransferase activity

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BMC Medical Genetics

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Title: Novel mutations of the $GALT$ gene and mutation spectrum in the Korean population with decreased galactose-1-phosphate uridylyltransferase activity

Dear Editor,

Thank you very much for your comments and feedbacks. We agree that the manuscript could be clarified as reviewers’ suggestion. We did our best to enhance the quality of this study in terms of scientific merit and readability by addressing all concerns and incorporating all suggestions raised by you and the two reviewers. We have described our responses below. We tracked our changes to depict what and how we amended the paper. The changes in the revised manuscript were highlighted in yellow.

We hope that the revised manuscript will better meet the requirements of the *BMC Medical Genetics* for publication. Thanks again for the constructive review of paper.

Sincerely yours,

Hyung-Doo Park, M.D., Ph.D. on behalf of all authors
Responses to comments

Referee(s)' Comments to Author:

Reviewer 1 (Anna Marabotti)

1) Background, page 3: In my opinion, reference 3 (Coss et al 2013), that is referred to a very precise population, is not pertinent with the presentation of general long-term complications that are common to galactosemic people worldwide. I’d suggest to replace current reference 3 with Waisbren et al., J Inherit Metab Dis 2012 (PMID: 21779791)

Reply: The authors agree with the reviewer’s opinion and replaced reference 3 in the manuscript submitted previously with Waisbren et al., J Inherit Metab Dis 2012 (PMID: 21779791) in the revised manuscript on ‘Background’ section.

2) Methods: can Authors include information, if known, about compliance of patients to galactose-free diet?

Reply: Unfortunately, this was a retrospective study and the detailed information about compliance of patients to galactose-free diet was mostly unavailable. We hope that long-term follow up about compliance of patients to galactose-free diet will be performed in future and would be helpful for patients with classic galactosemia.

3) Results, paragraph “Mutation spectrum of the GALT gene in Korean patients”, page 8: please correct the mistake in the code c.940A<G.
Reply: The authors corrected the mistake in the revised manuscript.

4) Discussion, page 9: the Authors state that “Our study also revealed that measurement of GALT enzyme activity was not enough to predict the genotypes and to make a decision for treatment in some patients”. I think that the lack of correlation between genotype and phenotype in classic galactosemia is already well known, therefore this study does not reveal any new data on this point. Authors should amend this sentence accordingly.

Reply: The authors agree with the reviewer’s opinion and the sentence has been revised accordingly with corresponding references in the revised manuscript.

In addition, we added two references as follows: the paper of Tyfield et al., Hum Mutat. 1999 (PMID: 10408771) which refers to the considerable genetic heterogeneity and phenotypic heterogeneity that is observed in galactosemia and the paper of Mohamed Jama et al., J Mol Diagn 2007 (PMID: 17884932) which refers to a combination of known mutations and genetic variants that modify enzyme levels which could be the reason of the lack of correlation between genotype and phenotype.

5) Discussion, page 11: the Authors make the hypothesis that the prevalence of classic galactosemia is increasing in the Korean population, on the basis of the results of newborn screening before 2006 and in 2012. However, this difference could be due to a different panel of population screened, or to different methods used more recently with respect to old methods, or to other variables that they take into account e.g. to discuss the different prevalence of classic galactosemia among different countries. Can Authors rule out these hypotheses before suggesting that the prevalence of classic galactosemia is strikingly
increasing in Korea?

Reply: The authors agree with the reviewer’s opinion that it could not be ruled out the differences in prevalence between 2006 and 2012 which could be due to a different panel of population screened, or to different methods used more recently with respect to old methods, or to other variables that they take into account the increasing. In Korea, the accreditation and inspection program by the Planned Population Federation of Korea for the proper quality control and quality assurance of clinical laboratory performing newborn screening for galactosemia has been settled since 2008 which could also affect the increasing prevalence. The authors added a discussion on this point in the revised manuscript.

6) Table 1, page 19: please explain the meaning of superscript “d” near mutations p.Asn314Asp referred to cases 5 and 6, that is not present in the legend. Maybe this is a mistake? (the symbol should be “§”, as in cases 11, 12 and 13?)

Reply: The authors corrected the mistake in the revised Table 1.

Reviewer 2 (Kent Lai)

Overall, it is an interesting and informative manuscript. The authors did an excellent job in the writing; very easy to understand and good use of the English language. A major concern for this paper lies on the lack of expression studies of the three nucleotide changes in the GALT gene. Although the clinical data and the use of computer modeling programs predicted that these changes are detrimental, these results are by no means definitive, especially due to the wide range of GALT activity in the normal controls. Since there are only a handful of
"mutations", this reviewer believes that the authors should make an effort to express these variant GALT genes to see if the nucleotide changes are truly detrimental. Without definitive proofs, it is too early to claim that these changes are mutations. Also, the inclusion of expression studies will improve the overall quality of the paper.

Reply: The authors agree with the editor’s and the reviewer’s opinion to improve the quality of the paper by assessing if the novel missense variations are real mutations by expression studies. Unfortunately, this study is retrospective and patients’ nucleic acid was not available in most cases for assessment of the pathogenicity of novel variations. The authors clearly stated that the variants we found cannot be defined detrimental mutations as reviewer’s suggestion, and the word “mutation” which indicated novel variants were revised to “likely pathogenic variation” in the revised manuscript.

EDITOR'S COMMENTS

"Authors should be informed about one of the reviewer’s advice to improve the quality of the paper by assessing if the novel missense variations are real mutations by expression studies. However, if they do not agree in performing further experiments, they should clearly state that the variants they found cannot be defined detrimental mutations and rather emphasize the other result of their study, i.e. that the Asian GALT mutations seem clearly different from the European mutations."

Reply: The authors agree with the editor’s and the reviewer’s opinion to improve the quality of the paper by assessing if the nucleotide changes are real mutations by expression studies. Unfortunately, this study is retrospective and patients’ nucleic acid was not available in most cases for assessment of the pathogenicity of exonic or
intrinsic variations. The authors clearly stated that the variants we found cannot be defined detrimental mutations as suggested and the word “mutation” which indicated novel variants were revised to “likely pathogenic variation” in the revised manuscript. The authors also added a discussion to emphasize that the Asian GALT mutations seemed different from European mutations by adding corresponding references studied in other Asian populations such as Chinese (Cheung et al., 1999 J Paediatr Child Health) and Japanese (Hirokawa et al., 1999 Eur J Hum Genet and Ashino et al., 1995 Hum Mutat).