Author's response to reviews

Title: Genetic modifiers of Hb E / beta 0 thalassemia identified by a two-stage genome-wide association study

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Version: 3 Date: 28 January 2010

Author's response to reviews: see over
Dear Dr. Zauner:

We are re-submitting our manuscript# 1541535174284682 (Genetic modifiers of Hb E / 6 \( \beta \) thalassemia identified by a two-stage genome-wide association study) which hopefully addresses the reviewers’ remaining concerns. Please find our point by point response to these concerns below.

1. The comments: "significant findings were not replicated in independent samples" has not been answered.

We have included a statement acknowledging that these findings have not been replicated on page 15 with the following statement "As these findings are novel, they have not been replicated in an independent sample. Replication of these associations for either disease severity or HbF is necessary."

2. Also, please make the distinction between the known and novel findings in the remaining text, not only in the introduction.

We italicized the SNPs previously shown to be associated with disease severity in Ma et al., in Clinical Genetics in table 3. There were five such SNPs, a fact that has been noted in page 10-11 of the results; “These included SNPs in the \( \beta \)-globin gene cluster on chromosome 11 previously reported to be associated with HbF levels in other samples, including the \( Xmn1 \) polymorphism 158 bp upstream from the G\( \gamma \) gene and the \( HincII \) site in the \( \psi \beta \)-globin gene. Five of these SNPs were previously reported to be associated with disease severity in this sample by by Ma et al. [19] (see table 3).”

3. Table 3: What I mean is %variance explained by SNPs for quantitative HbF% not case-control status. Please also include standard errors of the betas.

Two columns have been added to table 3, one showing the SE of the beta estimate for HbF% and one showing the % variation in HbF% explained by each SNP, as calculated by dividing the type III sum of squares for each SNP from the adjusted model by the corrected total sum of squares.

4. Please insert/incorporate the relevant responses to the reviewers in the manuscript. Some replies have not been incorporated in the manuscript.

The following responses have been included in the paper:
Page 10, 1\(^{st}\) paragraph: The mean age in the severe group was lower than the mild groups, mostly because severe patients are identified at younger age. The difference in severity between males and females has no known biological explanation and likely represents random variation, an issue which we correct by adjustment.

Page 10: \(Xmn1\) is correlated with rs3759074 at \( r^2 = .92 \) and with rs3886223 at \( r^2 = .46 \).

Sincerely,
Richard Sherva