P-phenylenediamine
Bijkersma-Pot, Laura

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Comment on ‘No major role for glutathione S-transferase gene polymorphisms in sensitization to para-phenylenediamine and other xenobiotics: a study of association and a meta-analysis’: reply from authors

L.M. Pot, B.Z. Alizadeh, D. Ahrenberg, P.-J. Coenraads, H. Snieder, B. Blömeke

1 Department of Dermatology, University Medical Center Groningen, University of Groningen, The Netherlands
2 Unit of Genetic Epidemiology & Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
3 Department of Environmental Toxicology, University Trier, Trier, Germany

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Comment

G. Westphal and A. Schnuch

Madam, The correspondence of Pot and colleagues ‘No major role for glutathione S-transferase gene polymorphisms in sensitization to para-phenylenediamine and other xenobiotics: a study of association and a meta-analysis’ may leave the impression that we had argued that glutathione S-transferase (GST) polymorphisms may be generally associated with contact allergy. In fact, we investigated GST polymorphisms in sensitization to mercury-containing compounds such as thiomersal (thimerosal), as thiomersal is exclusively detoxified via glutathione conjugation. We therefore compared thiomersal-sensitized individuals with healthy controls and individuals who were sensitized toward para-phenylenediamine. We found that GSTM1 confers a protective effect towards thiomersal and an additive effect concerning GSTT1. We observed no association in the case of para-phenylenediamine sensitization. The latter is consistent with the notion that the compound is not predominantly detoxified via the GST conjugation. We concluded that ‘Patients sensitized to thiomersal exhibited GSTM1-negative genotypes significantly more frequently than the control group. This seems to reveal a substance-specific association and not a general trait of contact allergic patients, as the more frequent occurrence of the GSTM1 deficiency was not seen in contact allergic patients sensitized against para-substituted-aryl compounds. Furthermore the GST allele frequencies in the “thiomersal-group” are not influenced by additional allergies other than phenylmercury or ammoniated mercury chloride. This further supports the concept that the investigation of enzyme polymorphisms may yield allergen-specific genetic markers for increased risk.’ We interpret this substance-specific finding as indirect affirmation of the hapten hypothesis. We hope that this clarification will help to avoid further misunderstandings.

References

3. Westphal GA, Schnuch A. Glutathione S-transferase as possible protective factors in contact sensitization: an indirect affirmation for the hapten theory. Contact Dermatitis 2010; 63 (Suppl. 1): 34.
Reply

Madam, We would like to thank Westphal and Schnuch for responding to our letter, ‘No major role for glutathione S-transferase gene polymorphisms in sensitization to para-phenylenediamine and other xenobiotics: a study of association and a meta-analysis’. As described in their paper, we have acknowledged the fact that Westphal et al. referred to the substrate specificity of thiomersal (thimerosal) for glutathione S-transferase (GST) enzymes. However, both papers used in our meta-analysis also describe the possible role of oxidative stress in sensitization to the studied xenobiotics. Wang et al. suggested that poor GSTT1 activity reduced the protection from reactive oxygen species (ROS) damage and therefore contributed to the occurrence of allergic contact dermatitis to chromate. In addition, Westphal et al. mentioned the lack of complete understanding of thiomersal allergy and discussed the possibility that the toxicity of thiomersal could have been indirectly related to – among other things – oxidative stress. Moreover, a recently published paper addressed the induction of ROS and CD86 by thiomersal- and mercury analogue-treated monocyte-derived dendritic cells. In general, reduced protection against and subsequent exposure to ROS has been related to contact dermatitis. With the linkage of metabolism of the particular allergens to ROS, and the general linkage of ROS to contact sensitization, we believe that the performed meta-analysis is defensible and justifiable. Nevertheless, as mentioned in our paper, the differences found in the meta-analysis can be partially explained by the fact that detoxification of the different xenobiotics is dependent on additional factors and cannot be attributed solely to the examined GST genes. This might, as addressed in Westphal and Schnuch’s response, particularly be the case for para-phenylenediamine. On the other hand, looking in closer detail actually reveals that results from our study are not that different from those of Westphal et al. They did not find a significant association of the GSTT1 deletion polymorphism with sensitization and only found a relatively moderate odds ratio for GSTM1 deficiency (odds ratio 2.0, 95% confidence interval 1.2–3.4, n = 60 cases), while studying the GST model substrate thiomersal. This suggests that for substrates presumably solely metabolized by GSTs, the effect of GST polymorphisms on sensitization is small. From a substrate specificity perspective, one would then expect that xenobiotics which are not a model substrate and are not solely detoxified by GSTs have an even lower, or no association, as was shown in our study. Hence, we still support our conclusion that common genetic polymorphisms in GSTs seem not to play a major role in predisposition to sensitization.
References


