

Reviewer's report

Title: A survey of self-reported chemical-related sensitivity is associated with gene variants of drug metabolizing enzymes

Version: 1 **Date:** 14 April 2006

Reviewer: Gail McKeown-Eyssen

Reviewer's report:

General

This paper provides useful information on the association between genes involved in drug-metabolizing enzymes and reported sensitivity to chemicals. There are few investigations of these issues so the paper makes a useful contribution to the field.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

As the authors point out, a major challenge to progress in the field is the lack of a generally accepted case definition of multiple chemical sensitivity (MCS). Indeed, a single name for the condition has not even been agreed. For this reason it is especially important that cases be carefully described, in order to facilitate comparisons between studies, and to permit findings to be applied to appropriate groups of patients. In this investigation, cases were people who scored above the median on a score of reported sensitivity to selected chemicals. So far as I am aware, the validity and reproducibility of this scale have not been published. The authors state that these properties were studied in a sample of 20 study participants who also completed the validated questionnaire developed by Miller et al. Despite the small size of the sample, it would be most helpful if a comparison of the sensitivity and specificity of the new scale were provided in relation to Miller's work. It would also be helpful if the authors could provide information on features of any of the previous 7 case definitions which have been proposed (eg. such as whether symptoms were acquired after a specific health even, as required by Cullen).

As part of the characterization of cases, the authors should describe in more detail the nature of the medical practice from which they were drawn, and, if possible, for what diagnoses the patients attended the practice, as well as how participants compared with those sampled but who did not participate. Any relevant characteristics which would allow the reader to understand the whether or not study participants who were classified as cases likely satisfied any of the seven published case definitions for chemical sensitivity would be extremely useful, as would information establishing that the control subjects were really free of sensitivities.

Because genetic variants differ across populations, it would be very helpful to have any information on the background of the Caucasian study subjects which might potential confound the case-control comparisons. For example, how was Caucasian defined (eg. number of Caucasian grandparents etc)? Was place of birth distributed equally between the groups?

The genes studied in this investigation are well chosen and two of the genes, GSTT1 and GSTM1 have not previously been studied in the context of MCS. The findings are clearly displayed and appropriately discussed.

Interpretation of the findings related to NAT2 is more challenging because, although variants of the

same gene were previously associated with MCS (McKeown-Eyssen et al), the associations in the two studies are in opposite directions. The present paper finds that slow acetylation is associated with increased risk, while McKeown-Eyssen et al found that fast acetylators were at increased risk. It is essential for understanding of MCS that reasons for these discrepant results be investigated and discussed as thoroughly as possible.

A first difference between the studies is the case definition employed, and it is for this reason that detailed description of study subjects requested above is particularly important.

A second major difference is that McKeown-Eyssen's study was confined to women, while the present results are for both sexes combined. It would therefore be extremely helpful if the authors would present a secondary analysis of the NAT2 results after stratification by sex. While this would reduce the sample size, it would provide insight into whether sex modifies the association of NAT2 to MCS, and might lead to understanding of the discrepant findings.

Finally, the present study considered NAT2 phenotypes in two basic categories, slow or fast acetylators. McKeown-Eyssen et al also considered an intermediate category of acetylation. It would be helpful if the investigators would examine the same phenotype distribution as reported by McKeown-Eyssen, so that details of differences in the findings can be fully appreciated. However, to understand the effect of this categorisation in more detail, I have taken the distribution of genotypes published in McKeown-Eyssen and calculated crude odds ratios for the same categories as used in the present paper. The Canadian data still suggest that fast acetylators are at increased risk (OR=1.38), so difference in the method of classifying the genotypes does not appear to account entirely for the different findings.

It would be most helpful to the understanding of the relationship between NAT2 and MCS if the authors would repeat their analyses for the women in their study, so that comparable information for the same sexes would be available from Germany and Canada. A thorough discussion of the similarities and differences between the women included in the studies would be of great assistance in leading to an understanding of the roles of genes in MCS, and whether international differences in genotype frequency can account for differences in findings. The discussion should consider these issues in as much depth as possible.

In summary, this paper makes a most useful contribution to the understanding of biology underlying MCS, a poorly understood and controversial condition. In addition to the data currently presented in their paper, the authors have available to them data on men and women separately which should shed light on differences in international findings. Inclusion of data on women, together with a deeper exploration of the gene frequencies which underlie the observations, will ensure that international differences in findings can be as completely understood as possible.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The written style of this paper is excellent, but there are several small infelicities of English usage that could be corrected.

Cover page: The usual expression is that someone died 'suddenly' not 'surprisingly'. It is sad that this occurred and dedication of the paper is most appropriate.

Page 4, lines 18/19: 'However, since it is discussed controversial if gene variants.....' should read 'However, since it is controversial whether gene variants...'

Page 6, lines 5/6: 'The lack of a generally accepted case definition for chemical hypersensitivity has prolonged progress...' should read 'The lack of a generally accepted case definition for chemical hypersensitivity has delayed progress...'

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.