Author’s response to reviews

Title: MDM2 SNP309 is associated with high grade node positive breast tumours and is in linkage disequilibrium with a novel MDM2 intron 1 polymorphism

Authors:

Fiona EM Paulin (f.e.m.paulin@dundee.ac.uk)
Mary O’Neill (m.a.oneill@dundee.ac.uk)
Gillian McGregor (g.mcgregor@dundee.ac.uk)
Andrew Cassidy (a.j.cassidy@dundee.ac.uk)
Alison Ashfield (alison.ashfield@nhs.net)
Clinton W Ali (clintonali22@btinternet.com)
Alastair J Munro (a.j.munro@dundee.ac.uk)
Lee Baker (l.baker@dundee.ac.uk)
Colin A Purdie (colin.purdie@nhs.net)
David P Lane (d.p.lane@dundee.ac.uk)
Alastair M Thompson (a.m.thompson@dundee.ac.uk)

Version: 2 Date: 10 April 2008

Author’s response to reviews: see over
Dear Sirs,

We would be grateful if you could consider this manuscript for publication.

In this manuscript we investigated polymorphisms within intron 1 of MDM2. Unlike previous publications, we sequenced across the region and in addition to the well characterised SNP309 (G>T) we identified three other SNPs; 344T>A, 285G>C and 443G>T. SNP 344T>A has been reported previously but not studied, and the latter two SNPs, to our knowledge, represent novel polymorphisms. Moreover, SNP285 was found to be in linkage disequilibrium with 309G which could have implications on all earlier reports of SNP309. Furthermore, the 285C/C, 309G/G double homozygous genotype was only observed in the breast cancer cohort, implying a potential role in breast cancer pathogenesis.

Accurate sequencing of this region is of particular importance as within the materials and methods section of a recent publication a statement was made to indicate that in a previous publication, 32 out of 113 samples had been incorrectly genotyped with respect to SNP309, and 22 out of 113 samples were duplicates. This therefore meant that the original conclusion that SNP309 was associated with a low apoptotic frequency is no longer valid. While this is stated within the materials and methods section of the second paper, and no formal retraction has been published, it would also imply that the influence of SNP309 is much more complex than originally hypothesised. Potentially SNP285 could play such a role.

We also examined SNP309 in relation to clinicopathological parameters and found that the 309G/G genotype was associated with high grade, node positive tumours and thus poorer prognosis: novel findings in the breast cancer field. However, we did not observe an association between genotype and age of breast cancer diagnosis even when patients were stratified by a combination of menopausal and estrogen receptor status. Comparing previous studies we highlight that there appear to be great differences in ER positivity dependent on race and ethnicity, which, in part, may explain the discrepant nature of the literature.

As BMC Cancer is widely read, we feel that the membership would be interested in this current study which substantially adds to our knowledge about SNP309 and provides potential explanations for inconsistencies within the literature. Furthermore, it highlights the need to examine published data very carefully. We therefore hope that BMC Cancer will consider this manuscript for publication.

Yours faithfully,
Fiona Paulin.

References