Author’s response to reviews

Title: Mitochondrial neurogastrointestinal encephalopathy as a mimic of Crohn's disease: a case report

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Author’s response to reviews:

Dear Editor,

Thank you for your review of our manuscript and associated suggestions. We have made changes to the manuscript to address the points raised by reviewer 2 as follows:

Reviewer 2’s comment:

The report is well written and informative since it affects the diagnosis of Crohn's disease in a rare Mendelian disorder and potentially the response to azathioprin. It adds to the current literature in particular Garone et al. Brain. 2011. In addition to the case report, that authors searched the UK IBD Genetics Consortium dataset of 2513 patients with Crohn's disease for MNGIE variants. This is an important strategy but the authors need to provide a proper analysis since the sequencing performed in the Luo et al. Nat Genetics 2017 paper was not designed to detect ultrarare variants - what is the coverage of the gene sequencing in this region? What is the power to detect one heterozygous mutation with the available coverage and the call algorithm used? What is the power to detect two heterozygous mutations? Is this sufficient to exclude variants?

Addition made to manuscript (page 4, lines 92-97):
The previously reported whole genome sequencing of Crohn’s disease produced median coverage 4x genome-wide. At this sequencing depth it is not possible to exclude ultra-rare variants in TYMP in the 2513 patients who were analysed. This would require high coverage sequencing. Their absence does, however, make it unlikely that TYMP variation is a significant cause of Crohn’s disease or that MNGIE phenocopying Crohn’s disease is a common problem.

We fully acknowledge that the low coverage sequencing was not designed to detect ultra-rare variants and have made this clear by inserting a short passage into the manuscript to reflect this.

We look forward to further correspondence. Many thanks.