Reviewer's report

Title: Somatic mitochondrial DNA mutations in cancer escape purifying selection and high pathogenicity mutations lead to the oncocytic phenotype: pathogenicity analysis of reported somatic mtDNA mutations in tumors.

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Reviewer: Laura Greaves

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This study describes the predicted pathogenicity of mitochondrial DNA (mtDNA) mutations in a very specific subset of tumours, oncocytic tumours, compared to non-oncocytic tumours and population variants. The relevance of mtDNA mutations in cancer is a contentious area and the authors have specifically investigated oncocytic tumours as these tumours exhibit a mitochondrial phenotype. They show, using well-validated mutation prediction software, that mtDNA mutations in tumours escape purifying selection seen in populations and in particular that pathogenic mtDNA mutations may lead to the oncocytic phenotype. It is a sound, well-thought out study which employs a number of essential quality control methods which are often lacking in such studies.

Minor essential revisions

1) On page 12 they state ‘Only complex IV, which is represented by just a single mtDNA encoded gene...’ - complex IV has 3 mtDNA encoded genes, this needs to be corrected

2) Although outside of the capabilities of the pathogenicity prediction software employed here, it would be interesting to know how many of the oncocytic and non-oncocytic tumours contained tRNA and rRNA mutations, as they are commonly found in solid tumours. Although predicting the pathogenicity of such mutations is difficult, these mutations are often seen in ageing tissues associated with mitochondrial dysfunction and are also common causes of mtDNA disease – you might expect them to be more frequent in the oncocytic tumours. It would be nice to have a brief comment or a comparison of the frequencies in the two tumour types.

3) Are there any data to suggest that mtDNA mutations accumulate in normal ageing tissues which develop oncocytic tumours? Pre-existing age-related mtDNA mutations may determine whether a tumour develops an oncocytic phenotype following cellular transformation.

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.

**Declaration of competing interests:**

I declare that I have no competing interests