Reviewer’s report

Title: Autoantibody against transient receptor potential M1 cation channels of retinal ON bipolar cells in paraneoplastic vitelliform retinopathy

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Reviewer: Anuradha Dhingra

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The manuscript by Wang et al presents a case report on paraneoplastic vitelliform retinopathy associated with metastatic cutaneous melanoma. This is the first case report showing association of paraneoplastic vitelliform retinopathy to TRPM1, a protein normally expressed in melanocytes and in retinal ON bipolar cells. The authors present histological, immunocytochemical, and ultrastructural characterization of the retina from autopsied eyes of a paraneoplastic vitelliform retinopathy patient and show that outer plexiform layer (OPL) and inner nuclear layers of retina are most affected with severe disintegration of many bipolar cells and synaptic contacts. In agreement with reduced OPL thickness, the TRPM1 immunostaining indicated loss of ON bipolar dendritic tips. Furthermore, the authors also show infiltration of TRPM1 positive metastatic melanoma cells in the lungs.

In retina, TRPM1 serves as a non-selective cation channel and is responsible for the light ON response and previous studies have shown that certain melanoma associated retinopathy patients develop auto-antibodies against TRPM1. The current study helps with advancing our understanding of underlying disease mechanisms in paraneoplastic vitelliform retinopathy.

Essential Minor revisions:

1. General: The relevance of TRPM1 positive cells in the lung is not clear. Especially in light of the prognostic relationship between TRPM1 downregulation with melanoma aggressiveness (ref 17-19), one would expect TRPM1 levels to go down in metastasis and this should be addressed. For example, is the expression of TRPM1 in the metastatic melanoma suggestive of certain type of melanoma?

2. In conclusions second sentence: “The immunohistochemical data provide direct evidence….. metastatic melanoma cells in paraneoplastic vitelliform retinopathy.” As patient’s serum was not used to test for TRPM1 auto-antibodies, the term ‘direct’ may be misleading here. Therefore, this sentence should be rephrased.

Discretionary Revisions:

1. In background 3rd paragraph: “In addition, several groups have found …. stationary night blindness [25, 26].” Another paper in the same year by Li et al (Am J Hum Genet. 2009) should also be cited.
“TRPM1 is also...dendritic tips [20, 21]” The references in this sentence [20, 21] were the first to suggest that TRPM1 is present in bipolar cells based on appaloosa horse model and RNA in situ data. The protein expression in bipolar cells was shown by later studies and should also be cited here.

2. Figures: Images in Fig 1 appear to have relatively more lesions than Fig 2. Is it just a chance (ie regional difference) and if so, a comment on this would be helpful.

3. In Figure 1-3, it would help to provide a scale bar.

**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' below