

-----Original Message-----

From: XXX YYY<xxx@yyy.zzz>

Sent: Fri, May 31, 2013 at 12:27 AM

To: Managing Editor

Subject: Re: Request for final decision for manuscript number 2013/OR/4731

The key review points in the review are: As a result of genetic analysis, it was found that in a small percentage (5-12%) of ROP patients from several different ethnic backgrounds three of the four FEVR causing genes encoding Norrin (NDP), frizzled 4 (FZD4) and low density lipoprotein receptor protein 5 (LRP5) are mutated. Mutations were not reported to date in the fourth FEVR causing gene (TSPAN 12) encoding a member of the tetraspanin family. The above studies imply that some of the Wnt signaling pathway genes (NDP, FZD4 and LRP5) play a role in the development of advanced ROP. Future studies must address the functional significance of each mutation and large-scale analysis using a mixed population of ROP patients to understand the true roles of genetic and epigenetic impact on the progression of ROP. The availability of animal models may provide opportunities for the development of novel therapeutic approaches to prevent or treat this pediatric blinding disorder.

Drs Noriyuki Azuma and Filipa Flor de Lima, and Wei-Chi Wu all gave 9 score for the manuscript (3 expert reviewers from Japan, Taiwan and Portugal). [Drs .....(Sentence deleted to hide personal communication)]

1. I advise the introduction to start like this: In addition to prematurity and environmental factors, there is a strong genetic predisposition to retinopathy of prematurity (Genetic Susceptibility to Retinopathy of Prematurity. Matthew J. Bizzarro, Naveed Hussain, Baldevin Jonsson, Rui Feng, Laura R. Ment, Jeffrey R. Gruen, Heping Zhang, Vineet Bhandari. *Pediatrics* 2006; 118:1858 -1863)
2. I advise a conclusion like this: "Recent research with candidate gene approach, higher concordance rate in monozygotic twins and other clinical and experimental animal studies, suggest a strong genetic predisposition to ROP besides environmental factors such as prematurity. Three genes, which are involved in the Wnt signaling pathway, are mutated in both FEVR and in a small percentage of ROP disorder. However, none of the genetic factors identified thus far in ROP, account for a substantial number of patient population. Future studies involving genomics, bioinformatics and proteomics may provide a better understanding of the pathophysiology and management of ROP (J Biomed Sci. 2010 Genetic susceptibility to advanced retinopathy of prematurity (ROP) by the same author Shastry BS) and please add this reference also: Retinopathy of prematurity: is genetic predisposition an important risk factor? Kwinta, Przemko; Pietrzyk, Jacek J. *Expert Review of Ophthalmology* Volume 2, Number 2, April 2007, pp. 275-283(9).

I reviewed the paper and the reviewers comment and made my own contribution because I want to have the paper include more relevant references.

I fully agree that this paper is for publication and I agree with score of 9.

**Editor's Details:**

Prof. Ahmad M Mansour

Department of Ophthalmology, American University of Beirut, Lebanon

**Note: Modification was done in this email ONLY to hide the identity.**