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ESPS Peer-review Report
Name of Journal: World Journal of Medical Genetics
ESPS Manuscript NO: 4391
Title: Genetic alterations in head and neck squamous cell carcinoma: the next-gen sequencing era
Reviewer code: 00505382
Science editor: Song, Xiu-Xia
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

This review aims to address the current knowledge of genetic changes associated with HNSCC tumor progression. The authors start by describing the role of TP53 mutations. Here they correctly point out the major role of this tumor suppressor in HNSCC. Although it is not possible to cite every relevant paper, some relevant references appear missing. E. g. when the authors state that "…, a truncating TP53 mutation is associated with a worse overall survival and progression-free survival." They refer to the 2011 clinical study by Lindenbergh-van der Plas et al., whereas another study published in 2005 (Mandic et al., Reduced cisplatin sensitivity of head and neck squamous cell carcinoma cell lines correlates with mutations affecting the COOH-terminal nuclear localization signal of p53. Clin Cancer Res. 2005) was not mentioned. In the latter in vitro study, it was shown that HNSCC cell lines with C-terminal truncating TP53 mutations are significantly more resistant to cisplatin-treatment. The authors also point out the important role of high risk HPV in HNSCC cancer, which has major implications for treatment and prognosis of the patient. Here they discuss the mechanism of action of the two viral proteins E6 and E7 and their influence on p53 and RB. Similarly, they highlight the role of p16 that is frequently used as a surrogate marker of HPV infection. They further point out the recently discovered role of NOTCH1 that is found mutated in a substantial portion of HNSCC patients. Importantly, the major and central role of EGFR in HNSCC disease is pointed out and the efficacy of therapeutics such as cetuximab is critically discussed.

Furthermore, the authors address the role of the Ras and PI3K pathways in HNSCC progression. After pointing out the role of epigenetic changes in gene silencing or activation the authors conclude that Next Generation Sequencing is a valuable tool to characterize the mutation pattern in HNSCC tumors, which could aid to the treatment concept of personalized medicine. The length of the

manuscript appears appropriate, considering it to be a short review. The two figures only show general pathways that can be found in several text books. The authors should try to more specifically adapt the figures to the context of the paper. In general, the manuscript is clearly written, however, it is recommended, that the manuscript is thoroughly proofread since it has several orthographical errors. After correction, the manuscript could be suitable for publication in WJMG.