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Somatic mutations in melanoma and non-melanoma skin cancers: exome sequence-based study

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Skin cancer represents the most common human malignancy worldwide, with over a million cases detected each year, and is, therefore, a significant global public health problem. In this study we aimed to search for potential driver mutations associated with different skin cancers' initiation and progression, using next-generation sequencing. We investigated different skin tumors, including melanocytic and keratinocytic lesions. Overall, the study included over 600 neoplastic skin lesions. Tumors and corresponding blood tissues were subjected to whole-exome sequencing.

Based on exome sequencing of primary melanomas, we report frequent novel somatic UV-signature mutations in a bidirectional promoter of diphthamide biosynthesis 3 (*DPH3)* and oxidoreductase NAD-binding domain containing 1 (*OXNAD1)* genes, adjacent and within a binding motif for E-twenty six (Ets) transcription factors. Follow-up screening of different skin lesions showed that the *DPH3* promoter mutations were present in melanocytic nevi, melanoma, seborrheic keratoses, basal cell carcinoma of skin and squamous cell carcinoma of skin. The mutations were shown to increase promoter activity in both *DPH3* and *OXNAD1* orientations. The present study is the first report on the mutational landscape of melanocytic nevi, based on whole-exome sequencing. We report multiple somatic alterations, including missense and nonsense mutations in several cancer census genes. The average mutation rate in melanocytic nevi is comparable to those of malignant tumors, and the mutation pattern is a hallmark of UV-induced mutagenesis, as previously reported in different skin cancers. We also performed the first whole-exome sequencing on a seborrheic keratosis lesion and report a high mutation burden, which is at the lower end of the mutation burden in squamous cell carcinoma of skin but comparable to many other malignant tumors. The vast majority of somatic alterations appeared to be typical UV-signature mutations, and most mutations were present with high allele frequency, which is consistent with the reported clonal nature of seborrheic keratosis. Follow-up screening revealed four genes with recurrent mutations, apart from those previously reported.

Describing tumor mutational landscape is crucial to reveal mechanisms of carcinogenesis and develop new therapeutic strategies. Particularly, *DPH3* promoter mutations are among the first frequent alterations reported within the non-coding regulatory sequences in human cancers. Their high recurrence and specificity suggest a potential role in carcinogenesis. The mutations' functionality and prevalence in other cancer types merit further investigation.