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Letter to the Editor

Before D-loop Variants and mtDNA Copy Number can be Recommended as Diagnostic and Prognostic Biomarlers for BSCC, Corresponding Studies are Required

Short title: D-loop variants and mtDNA copy number in BSCC

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Abstract

We read with interest the article by Sayal et al. on an 81-year-old man with basal cell squamous cell carcinoma (BSCC) in the mouth (left upper gingiva), in whom cell-free mtDNA analysis of saliva revealed an increased mtDNA copy number and the D-loop variant D310 [1]. It was concluded that cell-free mtDNA in saliva can be used for cancer detection and that an increased mtDNA copy number may be an indicator of early stages of head and neck cancer [1]. The study is noteworthy, but some points should be discussed.

Keywords: basaloid squamous cell carcinoma, mtDNA copy number, D-loop, heteroplasmy rate, outcome

Introduction:

Letter to the Editor

We read with interest the article by Sayal et al. on an 81-year-old man with basal cell squamous cell carcinoma (BSCC) in the mouth (left upper gingiva), in whom cell-free mtDNA analysis of saliva revealed an increased mtDNA copy number and the D-loop variant D310 [1]. It was concluded that cell-free mtDNA in saliva can be used for cancer detection and that an increased mtDNA copy number may be an indicator of early stages of head and neck cancer [1]. The study is noteworthy, but some points should be discussed.

The first point is that the increase in mtDNA copy number is unusual and was not adequately explained [1]. Normally, the mtDNA copy number is reduced in malignant tumors [2] and also decreases with age. How can the increase in mtDNA copy number be explained? Is it conceivable that the increased mtDNA copy number was due to the increased energy requirements of tumor cells and that the increased replication rate of tumor cells requires increased energy output from their mitochondria? BSCC is known to be characterized by a high mutation rate [1]. In an earlier study, the increased mtDNA copy number in patients with CADASIL was attributed to reduced methylation of the D-loop [3]. An increased mtDNA copy number also promotes the progression of malignancy [4]. An increased mtDNA copy number has also been associated with a poor prognosis in renal cell carcinoma [5]. Increased oxidative stress can also increase mtDNA copy number. A reduced mtDNA copy number on the contrary has been associated with vascular calcification. At least certain D-loop variants are known to correlate with lifespan [6].

The second point is that the index study examined only a single patient, which limits the significance of the results [1]. More comprehensive studies with larger study cohorts and large control groups are needed to assess whether mtDNA copy number and D-loop variants can be reliably used as diagnostic biomarkers for the detection of head and neck malignancies in adults.

The third point is that the patient had undergone therapy with pingyangmycin and radiation therapy [1]. Were there any indications that the cancer therapy was responsible for the increased mtDNA copy number and not the primary tumor itself? With regard to the effect of drugs on mtDNA copy number and the occurrence of mtDNA variants, we should be aware of the current medication of the index patients in addition to the cancer treatment.

The fourth point is that no family history was reported and that no results of mtDNA analysis in first-degree relatives, especially the mother, were reported [1]. To rule out whether or not the detected variant was inherited, genetic testing of the mother should be performed. Although the D-loop variant rarely causes mitochondrial disorders, it is imperative to rule out the possibility that a first-degree relative carried the B310 variant or suffered from a mitochondrial disorder.

The fifth point is that the genetic tests were only performed once [1]. Repeated genetic testing is essential to assess whether the mtDNA copy number has changed over time and whether the D-loop variants increase as the disease progresses. This is particularly important as the patient has developed metastasis of the right parotid gland.

Finally, no heteroplasmy rates of the B310 variant were reported [1]. Since the phenotype depends not only on the mtDNA copy number and D-loop variants, but also on the heteroplasmy rates and haplotype, these parameters are crucial for assessing their impact on disease progression and outcome.

In summary, before a general conclusion can be drawn about the validity of increased mtDNA copy number and the presence of D-loop variants in patients with BSCC, prospective studies with larger homogeneous groups of these patients at different stages of the disease are needed. Before mtDNA copy number or D-loop variants can be recommended as diagnostic, prognostic, or outcome biomarkers for BSCC, appropriate studies are needed.

Declarations

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Consent to participation: not applicable

Consent for publication: not applicable

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Completing interests: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contribution: JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval.

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