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LETTER

Role of DFNA5 in hearing loss and cancer – a comment on Rakusic et al

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Dear editor

We would like to comment on the paper published by Rakusic et al about sudden bilateral hearing loss in gastric cancer as the only symptom of disease.[1] The authors state that "Inactivated *DFNA5*, otherwise described in hereditary bilateral deafness, perhaps favors the development of deafness in patients with gastric cancer".[1] We believe this conclusion is erroneous. Although DFNA5 has been implicated in both hearing loss and cancer, the underlying molecular mechanisms are different and completely opposite (Figure 1).

In 1998, we identified the first *DFNA5* mutation in a Dutch family, as a cause for a specific form of progressive, sensorineural, and non-syndromic hearing loss.[2] This type of hearing loss is inherited in an autosomal dominant manner. Afterward, other families were reported with hearing loss due to *DFNA5* mutations.[3–8] Although all these *DFNA5* mutations are different on DNA level, they all result in skipping of exon 8 on mRNA level, and have an identical effect on the protein.[9]

The *DFNA5* mutation leading to hearing loss is thought to be an activating, gain of function mutation. As the DFNA5 protein has an apoptosis inducing capacity, the effect is expected to be an increase in apoptosis, possibly leading to hearing loss by apoptosis of cells crucial for hearing, such as cochlear hair cells (Figure 1).[10]

Since 1998, a number of papers on DFNA5 have been published, pointing toward an involvement in cancer.[9-20] Here the molecular mechanism is different. *DFNA5* becomes inactivated through DNA promotor methylation. Because of the inactivation, DFNA5 loses its capacity to induce apoptosis and most likely contributes to tumorigenesis in this manner (Figure 1).

In conclusion, a very specific gain of function mutation in *DFNA5* leads to hearing loss, while inactivation of *DFNA5* on the epigenetic level (DNA methylation) plays a role in cancer. Therefore, in our opinion, the observed sudden bilateral deafness in the 60-year-old woman is not caused by inactivation of *DFNA5*. Akino et al showed that *DFNA5* is methylated in 52% of primary gastric cancers and

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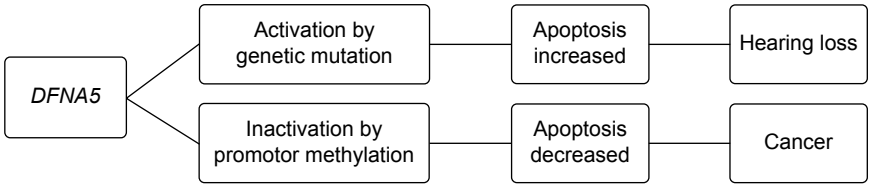

Figure 1 Possible mechanism of DFNA5 in hearing loss and cancer.

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was correlated with positivity for Epstein–Barr virus and the absence of metastasis.[14] In patients with metastasized gastric cancer the incidence of *DFNA5* methylation was 16.7% (2/12).[14] The observation that *DFNA5* is inactivated in this woman is thus not exceptional and in agreement with the literature. However, as described above, inactivation of *DFNA5* is very unlikely to be the cause of the observed hearing loss.

Disclosure

The authors have no conflict of interest to disclose in this correspondence.

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Authors' reply

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Dear editor

We are pleased that our article has caused so much interest and especially we appreciate comments by Croes et al who are devoted to research of *DFNA5* gene.

Following alignment analysis of DFNA5 coding region and our primers used in quantitative reverse transcription polymerase chain reaction we noticed that reverse primer hybridized to the nucleotide sequence within exon 8. This could be the explanation why we obtained undetectable levels of *DFNA5* on transcription level and prove that in this patient mutation in coding region and consequently exon 8 skipping, caused observed bilateral deafness. However our aim is to more precisely determine changes in coding region as well as in promoter region of *DFNA5* gene which is a possible cause of gastric cancer.

Our intention was to describe a very unusual clinical presentation of gastric cancer. Patient's family history was negative for hearing impairment. Within 3 weeks she was completely deaf. Due to the uncommon symptom we questioned the potential link between hearing loss and cancer. *DFNA5* analysis was made as an attempt to explain the connection.

DFNA5 is very interesting because in one gene there are two changes, hypermethylation and mutation, in two relatively remote places that lead to the opposite effects – activation and deactivation. Activation leads to deafness and deactivation to cancer. The Cancer Genome Atlas Research Network divided gastric cancers into four subtypes; Epstein–Barr virus-positive, microsatellite instability-positive, genomically stable and chromosomally unstable.[1] Although contrary to previous hypothesis,[2] from a clinical point of view it could be speculated that hypermethylation of promoter region leads to gastric cancer and causes chromosome instability with de novo mutation of *DFNA5* gene. It remains possible that mutation became clinically apparent due to dramatic onset of hearing loss but because of the small number of patients it is impossible to prove.

Many aberrantly methylated genes are reported[3] as well as *DFNA5*.[3,4] Even though the role of DFNA5 in hereditary hearing loss as well as in carcinogenesis is well described,[3] there is still a gap in knowledge to explain the mechanism of these two events occurring in the same patient. Is there any association? DNA methylation is now a topic of interest.

Many questions still remain unanswered. What about DFNA5 in normal gastric mucosa? What is the pathological finding of n. VIII (Statoacoustic nerve was unfortunately not analyzed on autopsy)? Is there Epstein–Barr virus in tumor tissue? Is there any hypermethylation of promotor region? In families with hereditary DFNA5 associated hearing loss are there any data about cancer incidence? But it is beyond the scope of our article.

Disclosure

The authors have no conflicts of interest to disclose in this correspondence.

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