Cancer Research

Tau Mutations as a Novel Risk Factor for Cancer—Response

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We thank Deutschländer and colleagues (1) for their interest in our work and for providing us with the opportunity to expand on concepts included in our original article.

We do not exclude that some *MAPT* mutations may have a little or no effect on cancer development. Most of *MAPT* missense mutations cause a reduced microtubule polymerization (2) and some of them, including the P301L, have been demonstrated to produce overly dynamic microtubules (3). These alterations can impact on the mitotic spindle dynamics, causing chromosome missegregation. Furthermore, the DNA chaperone ability also may be impaired by a mutated protein, leading to DNA damage. It is of course possible that, due to their position in the protein or the feature of the specific amino acids, some missense mutations may be less cancer predisposing than others.

As for *MAPT* exon 10 splicing mutations, they usually increase the 4R tau isoforms, which can cause excessive microtubule stabilization (4), whereas DNA binding may not be affected by an excess of wild-type protein. Thus, otherwise than in the case of missense mutations, splicing mutations may not affect the microtubule dynamics of the mitotic spindle and/or the DNA-binding ability of tau, thus not causing abnormal chromosome segregation or DNA damage, that are processes that may lead to cancer.

Deutschländer and colleagues reported on a large family carrying the N279K *MAPT* mutation, which affects exon 10 splicing and does not influence microtubule polymerization (2). Deutschländer and colleagues did not find evidence of cancer development. They also indicated a rather low cancer incidence in their cohort of FTD families carrying a *MAPT* mutation, yet it did not appear clear what *MAPT* mutations occurred in their 63 subjects, as only 5 subjects with N279K and 19 with P301L *MAPT* mutations were reported (24/63), whereas the *MAPT* mutations identified in the remainder 39 of 63 mutations carriers were not specified.

In our study, we reported a cohort with 1 family carrying the N279K *MAPT* mutation who had 2 cancer-affected subjects. A single family comprises too small a number of subjects to conclude that the mutation is linked to cancer, and the data of Deutschländer and colleagues may support the view that there is not a causal effect. Alternatively, their particular family might carry some unknown protective factors, genetic or of other nature. We had also 2 families carrying the IVS10+16C>T *MAPT* splicing mutation, one having 1 cancer-affected subject and the other none, thus being *per se* not conclusive.

Deutschländer and colleagues cited an article demonstrating that *MAPT* mutations cause aneuploidy in neurons and glia, where the N279K *MAPT* mutation was analyzed but not reported in detail, as only aggregated data from different missense mutations are shown (5). Although aneuploidy can cause neurodegeneration, it can be linked to cancer in nonneural tissues (6).

We think that the P301L is the most evident *MAPT* mutation showing a link between mutated tau and cancer, as 7 of 8 families had cancer-affected subjects (6). The influence on microtubule polymerization and dynamics is well documented (2, 3). We hope that other families carrying, in particular, *MAPT* missense mutations will be studied to strengthen the connection between tau and cancer. Further effort is needed to investigate cancer risk modifiers as well as to validate findings of cancer risk by mutation position, resembling the work carried out for well-known cancer susceptibility genes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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