

Tau Mutations as a Novel Risk Factor for Cancer - Response

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We do not exclude that different *MAPT* mutations might (or might not) exert differential effects on cancer development. Most of *MAPT* missense mutations cause a reduced microtubule polymerization² and some of them, including the P301L, have been shown to lead to microtubules instability³. Not only these alterations can impact the mitotic spindle dynamics, causing chromosomal mis-segregation, but also tau's function as DNA chaperone might be impaired, leading to DNA damage. It is of course possible that some missense mutations might more or less predispose an individual to developing cancer based on the affected amino-acid(s). As for *MAPT* exon 10 splicing mutations, they usually increase the 4R tau isoforms, which can cause an excessive microtubule stabilization⁴, whilst 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.

Deuschländer and colleagues reported of a large family carrying the N279K *MAPT* mutation, which affects exon 10 splicing and does not influence microtubule polymerization². Deuschländer 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), whilst the *MAPT* mutations identified in the remainder 39/63 mutations carriers were not specified.

In our study we reported 1 family carrying the N279K *MAPT* mutation with 2 cancer-affected subjects. Deuschländer and colleagues did not find evidence of cancer in their N279K family. If on one hand, it may be the case that their particular family might carry some unknown protective factors, genetic or of other nature, on the other, assessments on potential links between the N279K *MAPT* mutation and cancer will need to be evaluated in more N279K families. Additionally, we also described 2 families carrying the IVS10+16C>T *MAPT* splicing mutation, 1 having one cancer-affected subject and the other none.

Deuschländer and colleagues cite a paper demonstrating that *MAPT* mutations cause aneuploidy in neurons and glia, where the N279K *MAPT* mutation was also analyzed. However, further details were not included as only aggregated data from different missense mutations are shown⁵. It is important to note that, while aneuploidy can cause neurodegeneration, it can be linked to cancer in non-neural tissues⁶.

We suggest the P301L missense change as the most evident *MAPT* mutation showing a link between mutated tau and cancer, as 7 out of 8 families had cancer affected subjects⁶. The influence on microtubule polymerization and dynamics is well documented^{2,3}. We hope that other families carrying *MAPT* missense mutations will be studied, to expand on our understanding of the connection between tau and cancer. Further efforts are needed to investigate cancer risk modifiers as well as to validate findings of cancer risk in association with the position of the mutated amino-acid, as in the case of work carried out for other cancer susceptibility genes.

References

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