

## Tau Mutations as a Novel Risk Factor for Cancer—Letter

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Rossi and colleagues (2018) recently reported an increased cancer frequency in 15 families with frontotemporal lobar degeneration (FTLD) and mutations in the microtubule-associated protein tau (*MAPT*) gene (15% of 162 subjects of *MAPT* FTLD kindreds; 9% of 717 controls; ref. 1). They concluded that *MAPT* mutations raise the risk for cancer nearly fourfold (multivariate Cox proportional hazard model: HR = 3.72); some mutations may be less cancer predisposing than others (e.g., due to differential microtubule-binding capacity or DNA chaperone ability of mutated tau). The *MAPT* P301L mutation leads to increased tau phosphorylation and reduces microtubule polymerization. Microtubules are critical for mitotic spindle formation. The *MAPT* N279K mutation affects exon 10 splicing, resulting in increased 4R tau (2). Both mutations result in increased aneuploidy and apoptosis of neuronal and glia cells (3).

The "Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects" (LEFFTDS) study is a multicenter study of symptomatic and asymptomatic subjects of families with *MAPT*, granulin precursor (*GRN*), or *C9orf72* mutations, conducted in accordance with the Declaration of Helsinki and approved by Institutional Review Boards of all sites. Written informed consent was obtained from all participants. Currently, 294 LEFFTDS subjects have data available on cancer and mutation status (50.6 ± 14.0 years, 155 f; 170/294 mutation carriers: 51.0 ± 14.4 years, 89 f). Sixty-three subjects (45.8 ± 13.2 years, 33 f) have *MAPT* mutations (N279K: *n* = 5; P301L: *n* = 19); 1/63 reported possible cancer (melanoma). Forty-four subjects (57.7 ± 3.5 years, 19 f) have *GRN* mutations; 2 of 44 reported cancer (prostate and colon). Sixty-three subjects (51.6 ± 14.4 years, 37 f) have the *C9orf72* repeat expansion; 8 of 63 reported cancer (colon, nonmelanoma skin carcinoma, melanoma, and breast cancer). Finally, 124 subjects from families with *MAPT* (*n* = 41), *GRN* (*n* = 40), or *C9orf72* (*n* = 43) mutations (50.0 ± 13.3 years, 66 f) had no mutation in these genes; 10 of 124 reported cancer (CLL, breast, *C9orf72* kindreds; colon, skin, ovarian, breast, thyroid, *GRN* kindreds; 1 report of breast cancer, *MAPT* kindred). Thus, we found the lowest cancer risk in *MAPT* mutation carriers.

Furthermore, we are not aware of a single report of cancer in a large American family with pallido-ponto-nigral degeneration (PPND) due to the N279K *MAPT* mutation. This

family (*n* = 332 individuals; 65 N279K *MAPT* mutation carriers; 60 symptomatic) has been closely followed since 1987; the phenotype consists of rapidly progressive parkinsonism and frontotemporal dementia (4). Our letter thus reports mainly on individuals harboring the *MAPT* N279K mutation (PPND family), whereas Rossi and colleagues (2018) included eight families with *MAPT* P301L mutations. Differential *MAPT* mutations may contribute differentially to cancer risk.

## Disclosure of Potential Conflicts of Interest.

A.B. Deuschländer reports receiving a commercial research grant from Allergan Educational Grant. H.J. Rosen reports receiving a commercial research grant from Biogen Pharmaceuticals and is a consultant/advisory board member for Ionis Pharmaceuticals and Wave Pharmaceuticals. A.L. Boxer reports receiving a commercial research grant from Genentech, Roche, Biogen, BMS, Lilly and has ownership interest (including stocks and patents) in Alector, Aeton Therapeutics. He is a consultant/advisory board member for Abbvie, Arkuda, Merck, Novartis, Samumed, Toyama, UCB, Asceneuro, and Wave. No potential conflicts of interest were disclosed by the other authors.

## LEFFTDS Consortium

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## Acknowledgments

The LEFFTDS study is supported by the following NIH grants: U01 AG045390-01A1, U54 NS092089, U24 AG021886, U01 AG016976, and P50 NS072187 (to B. Boeve, H. Rosen, A. Boxer, and Z.K. Wszolek).

Received August 15, 2018; revised September 17, 2018; accepted September 17, 2018; published first October 29, 2018.

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doi: 10.1158/0008-5472.CAN-18-2313

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Deutschländer et al.

## References

1. Rossi G, Redaelli V, Contiero P, Fabiano S, Tagliabue G, Perego P, et al. Tau mutations serve as a novel risk factor for cancer. *Cancer Res* 2018;78:3731–39.
2. Caneus J, Granic A, Rademakers R, Dickson DW, Coughlan CM, Chial HJ, et al. Mitotic defects lead to neuronal aneuploidy and apoptosis in frontotemporal lobar degeneration caused by MAPT mutations. *Mol Biol Cell* 2018;29:575–86.
3. Rossi G, Tagliavini F. Frontotemporal lobar degeneration: old knowledge and new insight into the pathogenetic mechanisms of tau mutations. *Front Aging Neurosci* 2015;7:192.
4. Wszolek ZK, Pfeiffer RF, Bhatt MH, Schelper RL, Cordes M, Snow BJ, et al. Rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration. *Ann Neurol* 1992; 32:312–20.

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*Cancer Res* 2018;78:6523-6524. Published OnlineFirst October 29, 2018.

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