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Letter to the Editor

Cancer Research

Tau Mutations as a Novel Risk Factor for Cancer—Letter

Angela B. Deutschländer[1], Bradley F. Boeve[2], Howard J. Rosen[3], Adam L. Boxer[3], and Zbigniew K. Wszolek[1], on behalf of the LEFFTDS Consortium

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.

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LEFFTDS Consortium

Danielle Brushaber[1], Giovanni Coppola[2], Bradford Dickerson[3], Jamie Fong[4], Tatiana Foroud[5], Leah Forsberg[1], Ralitza Gavrilova[1], Nupur Ghoshal[6], Jill Goldman[7], Jon Graff-Radford[1], Neill Graff-Radford[8], Murray Grossman[9], Hilary W. Heuer[4], Ging-Yuek R. Hsiung[10], Edward D. Huey[7], David Irwin[9], David Jones[1], Kejal Kantarci[1], Anna Karydas[4], David Knopman[1], John Kornak[4], Joel Kramer[4], Walter Kremers[1], Walter Kukull[11], Maria Lapid[1], Diane Lucente[3], Ian Mackenzie[10], Scott McGinnis[3], Bruce Miller[4], Len Petrucelli[8], Rosa Rademakers[8], Eliana M. Ramos[2], Katherine Rankin[4], Katya Rascovsky[9], Les Shaw[9], Jeremy Syrjanen[1], Joanne Taylor[4], Arthur Toga[12], John Trojanowski[9], Sandra Weintraub[13], and Bonnie Wong[3]

[1]Mayo Clinic, Rochester, Minnesota.
[2]University of California, Los Angeles (UCLA), Los Angeles, California.
[3]Harvard University/MGH, Boston, Massachusetts.
[4]University of California, San Francisco (UCSF), San Francisco, California.
[5]National Cell Repository for Alzheimer's Disease (NCRAD), Indiana University, Indianapolis, Indianapolis
[6]Washington University, St. Louis, Missouri.
[7]Columbia University, New York, New York.
[8]Mayo Clinic, Jacksonville, Florida.
[9]University of Pennsylvania, Philadelphia, Philadelphia.
[10]University of British Columbia, Vancouver, British Columbia, Canada.
[11]National Alzheimer Coordinating Center (NACC), University of Washington, Seattle, Washington.
[12]Laboratory of Neuroimaging (LONI), USC, Los Angeles, California.
[13]Northwestern University, Chicago, Illinois.

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[1]Department of Neurology, Mayo Clinic, Jacksonville, Florida. [2]Department of Neurology, Mayo Clinic, Rochester, Minnesota. [3]Department of Neurology, University of California San Francisco, San Francisco, California.

Corresponding Author: Angela B. Deutschländer, Mayo Clinic Florida, 4500 San Pablo Road S, Jacksonville, 32224 FL. Phone: 904-953-2000; Fax: 904-953-6036; E-mail: Deutschlander.angela@mayo.edu

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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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