Understanding the role of somatic mutations in TARDBP in FTLD-TDP type C

Vanshika Bidhan (1,2), Sarah Wynants (1,2), Toon Swings (3), Marleen Van den Broeck (1,2), Jeroen van Rooij (4), Merel O Mol (4), Safa Al-Sarraj (5,6), Istvan Bodi (5,6), Andrew King (5,6), Claire Troakes (5), Jolien Schaeverbeke (7,8), Dietmar R Thal (8,9), Rik Vandenberghe (7,10), Mathieu Vandenbulcke (11,12), Aivi T Nguyen (13), Reichard R Ross (13), Julia Kofler (14), Oscar Lopez (15), Charles L White, III (16), Bradley F Boeve (17), Neill R Graff-Radford (17), Keith A Josephs (18), Ronald C Petersen (18), Melissa E Murray (19), Dennis W Dickson (19), Harro Seelaar (4), John C Van Swieten (4), Wouter De Coster (1,2), Rosa Rademakers (1,2,19)

(1) Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium
(2) VIB Center for Molecular Neurology, VIB, Antwerp, Belgium
(3) VIB Technology Watch, Technology Innovation Lab, VIB, Leuven, Belgium
(4) Alzheimer Center, Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands
(5) Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
(6) King's College Hospital NHS Foundation Trust, London, UK
(7) Laboratory for Cognitive Neurology, Department of Neurosciences, Leuven Brain Institute, KU Leuven, Leuven, Belgium
(8) Laboratory for Neuropathology, Department of Imaging and Pathology, and Leuven Brain Institute, KU-Leuven, Leuven, Belgium
(9) Department of Pathology, University Hospital Leuven (UZ Leuven), Leuven, Belgium
(10) Department of Neurology, University Hospital Leuven (UZ Leuven), Leuven, Belgium
(11) Department of Geriatric Psychiatry, University Hospital Leuven (UZ Leuven), Leuven, Belgium
(12) Laboratory for Neuropsychiatry, Department of Neurosciences, Leuven Brain Institute, KU Leuven, Leuven, Belgium
(13) Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
(14) Department of Pathology, University of Pittsburgh, Pittsburg, PA, USA
(15) Department of Neurology, University of Pittsburgh, Pittsburg, PA, USA
(16) University of Texas Southwestern Medical Center, Dallas, TX, USA
(17) Department of Neurology, Mayo Clinic, Jacksonville, FL, USA
(18) Department of Neurology, Mayo Clinic, Rochester, MN, USA
(19) Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

State of art: Somatic mutations in TARDBP have been reported at the bulk-level in FTLD-TDP type C, a subtype of FTLD characterized by TDP-43 pathology and most often a sporadic occurrence. Systematic identification, replication and validation of somatic TARDBP variants using single-cell methods, however, has not been performed.

Methodology: We performed single-nuclei targeted DNA sequencing of neurons derived from the superior temporal gyrus of FTLD-TDP type C cases (n=53) and controls (n=36) using the

Mission Bio Tapestri platform. Samples were pooled in sets of 5. We investigated the somatic variants in TARDBP and compared their burden in a case-control setting.

Results: We first developed a deconvolution strategy leveraging germline variants to assign neuronal nuclei to each individual, resulting in 32,188 nuclei from cases and 5174 nuclei from controls. We identified 2247 somatic TARDBP single nucleotide variants, occurring at a very low frequency and affecting every codon of the gene. Interestingly, we observed a higher burden of non-synonymous TARDBP variants in cases than in controls. Based on careful selection criteria, we also identified non-synonymous variants which are over-represented or exclusively present in cases.

Conclusion: We detected a high level of very rare TARDBP somatic variants in neuronal nuclei in both cases and controls. Our work shows that single nuclei amplicon sequencing offers a novel opportunity to identify rare somatic variants in disease. The identification of variants unique or overrepresented in cases suggests their potential involvement in FTLD-TDP type C, however further analyses and validation is ongoing.