

Supplementary data:

Genome-wide analyses as part of the international FTLT-DTP whole genome sequencing consortium reveals novel disease risk factors and increases support for immune dysfunction in FTLT

Cyril Pottier, PhD¹, Yingxue Ren, PhD², Ralph B. Perkerson III, MSc¹, Matt Baker, BSc¹, Gregory D. Jenkins, MSc³, Marka van Blitterswijk, MD, PhD¹, Mariely DeJesus-Hernandez, BSc¹, Jeroen G. J. van Rooij, BSc⁴, Melissa E. Murray, PhD¹, Elizabeth Christopher, MBA¹, Shannon K. McDonnell, MSc³, Zachary Fogarty³, Anthony Batzler, BSc³, Shulan Tian, PhD³, Cristina T. Vicente, PhD¹, Billie Matchett, BSc¹, Anna M. Karydas⁵, Ging-Yuek Robin Hsiung, MD⁶, Harro Seelaar, MD, PhD⁴, Merel O. Mol, MD⁴, Elizabeth C. Finger, MD⁷, Caroline Graff, MD^{8, 9}, Linn Öijerstedt, MD^{8, 9}, Manuela Neumann, MD^{10, 11}, Peter Heutink, PhD^{10, 12}, Matthis Synofzik, MD^{10, 12}, Carlo Wilke, MD^{10, 12}, Johannes Prudlo, MD^{10, 13}, Patrizia Rizzu, PhD¹⁰, Javier Simon-Sanchez, PhD^{10, 12}, Dieter Edbauer, MD^{14, 15}, Sigrun Roeber, MD¹⁶, Janine Diehl-Schmid, MD¹⁷, Bret M. Evers, MD, PhD¹⁸, Andrew King, FRCPath^{19, 20}, M-Marsel Mesulam, MD²¹, Sandra Weintraub, PhD^{21, 22}, Changiz Geula, PhD²¹, Kevin F. Bieniek, PhD^{1, 23}, Leonard Petrucelli, PhD¹, Geoffrey L. Ahern, MD, PhD²⁴, Eric M. Reiman, MD²⁵, Bryan K. Woodruff, MD²⁶, Richard J. Caselli, MD²⁶, Edward D. Huey, MD²⁷, Martin R. Farlow, MD²⁸, Jordan Grafman, PhD²⁹, Simon Mead, FRCPath, PhD³⁰, Lea T. Grinberg, MD^{5, 31}, Salvatore Spina, MD, PhD⁵, Murray Grossman, MD³², David J. Irwin, MD³², Edward B. Lee, MD, PhD³³, EunRan Suh, PhD³³, Julie Snowden, PhD³⁴, David Mann, PhD³⁵, Nilufer Ertekin-Taner, MD, PhD^{1, 36}, Ryan J. Uitti, MD³⁶, Zbigniew K. Wszolek, MD³⁶, Keith A. Josephs, MD³⁷, Joseph E. Parisi, MD³⁷, David S. Knopman, MD³⁷, Ronald C. Petersen, MD³⁷, John R. Hodges, FRCPath³⁸, Olivier Piguet, PhD³⁹, Ethan G. Geier⁵, Jennifer S. Yokoyama⁵, Robert A. Rissman, PhD^{40, 41}, Ekaterina Rogaeva, PhD⁴², Julia Keith, MD^{43, 44}, Lorne Zinman, MD⁴³, Maria Carmela Tartaglia, MD^{42, 45}, Nigel J. Cairns, PhD⁴⁶, Carlos Cruchaga, PhD⁴⁷, Bernardino Ghetti, MD⁴⁸, Julia Kofler, MD⁴⁹, Oscar L Lopez, MD^{50, 24}, Thomas G. Beach, MD, PhD⁵¹, Thomas Arzberger, MD^{52, 14, 16}, Jochen Herms, MD^{14, 16}, Lawrence S. Honig, MD, PhD⁵³, Jean Paul Vonsattel, MD⁵⁴, Glenda M. Halliday, PhD^{38, 55}, John B. Kwok, PhD^{38, 55}, Charles L. White, III, MD¹⁸, Marla Gearing, PhD⁵⁶, Jonathan Glass, MD⁵⁶, Sara Rollinson, PhD⁵⁷, Stuart Pickering-Brown, PhD⁵⁷, Jonathan D. Rohrer, MD, PhD⁵⁸, John Q. Trojanowski, MD, PhD³³, Vivianna Van Deerlin, MD, PhD³³, Eileen H. Bigio, MD²¹, Claire Troakes, PhD¹⁹, Safa Al-Sarraj, FRCPath^{19, 20}, Yan Asmann, PhD², Bruce L. Miller, MD⁵, Neill R. Graff-Radford, MBBCh³⁶, Bradley F. Boeve, MD³⁷, William W. Seeley, MD^{5, 31}, Ian R. A. Mackenzie, MD⁵⁹, John C. van Swieten, MD, PhD⁴, Dennis W. Dickson, MD¹, Joanna M. Biernacka, PhD³ and Rosa Rademakers, PhD^{1#}

Corresponding author:

Rosa Rademakers, Ph.D.

Department of Neuroscience, Mayo Clinic, Jacksonville

4500 San Pablo Road, Jacksonville, FL 32224

Phone: (904) 953-6279

Fax: (904) 953-7370

E-mail: Rademakers.rosa@mayo.edu

1. Department of Neuroscience, Mayo Clinic, Jacksonville, FL
2. Department of Health Sciences Research, Mayo Clinic, Jacksonville, FL
3. Department of Health Sciences Research, Mayo Clinic, Rochester, MN
4. Department of Neurology, Erasmus Medical Center, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands
5. Department of Neurology, University of California, Memory and Aging Center, San Francisco, CA, USA
6. Division of Neurology, Department of Medicine, University of British Columbia, Vancouver BC, Canada V6T 2B5
7. Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON N6A 2E2 Canada
8. Department NVS, Division of Neurogeriatrics, Karolinska Institutet, Visionsgatan 4, J10:20 171 64, Solna, Sweden
9. Theme Aging, Unit for hereditary dementias, Karolinska University Hospital-Solna, Sweden
10. German Center for Neurodegenerative Diseases (DZNE), 18147 Rostock, Germany
11. Department of Neuropathology, University of Tübingen, 72076 Tübingen, Germany
12. Hertie Institute for Clinical Brain Research, University of Tübingen, 72076 Tübingen, Germany
13. Department of Neurology, Rostock University Medical Center, 18147 Rostock, Germany
14. German Center for Neurodegenerative Diseases (DZNE), Feodor-Lynen-Str 17, D-81377 Munich, Germany
15. Munich Cluster of Systems Neurology (SyNergy), Feodor-Lynen-Str 17, 81377 Munich, Germany
16. Center for Neuropathology and Prion Research, Ludwig-Maximilians-University Munich, Germany, Feodor-Lynen-Straße 23, D-81377 Munich
17. Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany
18. Division of Neuropathology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9073 USA

19. London Neurodegenerative Diseases Brain Bank; Department of Basic and Clinical Neuroscience; Institute of Psychiatry, Psychology and Neuroscience; King's College London, SE5 8AF, UK
20. Department of Clinical Neuropathology, King's College Hospital NHS Foundation Trust, London, SE5 9RS, UK
21. Northwestern University Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Chicago, 60611, USA
22. Department of Psychiatry and Behavioral Sciences and Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611
23. Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Science Center San Antonio, San Antonio, Texas 78229
24. Department of Neurology, University of Arizona Health Sciences Center, 1501 North Campbell Avenue, Tucson, AZ 85724-5023
25. Banner Alzheimer's Institute, Phoenix, AZ 85006
26. Department of Neurology, Mayo Clinic Arizona, Scottsdale, AZ, 85259, USA
27. Departments of Psychiatry and Neurology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, 630 West 168th St P&S Box 16, New York, NY 10032
28. Indiana University School of Medicine, 355 West 16th Street, GH 4700 Neurology, Indianapolis, IN 46202
29. Department of Physical Medicine & Rehabilitation, Neurology, Cognitive Neurology and Alzheimer's Center, Department of Psychiatry, Feinberg School of Medicine, Northwestern University, 355 E Erie Street, Chicago, Illinois 60611-5146
30. MRC Prion Unit at University College London, Institute of Prion Diseases, London, UK
31. Department of Pathology, University of California, Memory and Aging Center, San Francisco, CA, USA
32. Penn Frontotemporal Degeneration Center, Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104 USA
33. Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104 USA
34. Cerebral Function Unit, Greater Manchester Neurosciences Centre, Salford Royal Hospital, Salford, UK
35. Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Salford Royal Hospital, Salford, UK

36. Department of Neurology, Mayo Clinic, Jacksonville, FL
37. Department of Neurology, Mayo Clinic, Rochester, MN
38. The University of Sydney, Central Clinical School and Brain & Mind Centre, Sydney, 2050;
39. The University of Sydney, School of Psychology and Brain & Mind Centre, Sydney, 2050, AUSTRALIA
40. Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093
41. Veterans Affairs San Diego Healthcare System, San Diego, CA 92161
42. Krembil Discovery Tower, Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, 60 Leonard Av, 4th Floor - 4KD481; Toronto, Ontario, Canada, M5T 0S8
43. Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5, Canada
44. Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON M5S 1A1, Canada
45. Krembil Neuroscience Center, Movement Disorder's Clinic, Toronto Western Hospital, 399 Bathurst street, ON, Canada, M5T 2S8
46. Department of Neurology, Knight Alzheimer Disease Research Center, Washington University School of Medicine, Saint Louis, Missouri 63108, USA
47. Department of Psychiatry, Knight Alzheimer Disease Research Center, Washington University School of Medicine, Saint Louis, Missouri 63108, USA
48. Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, 635 Barnhill Drive, MS A138, Indianapolis, IN 46202
49. Department of Pathology, University of Pittsburgh, Pittsburgh, PA 15213
50. Department of Neurology, University of Pittsburgh, Pittsburgh, PA 15213
51. Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, 85351, USA
52. Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilians-University Munich, Germany, Nussbaumstraße 7, D-80336 Munich,
53. Department of Neurology, Taub Institute, and GH Sergievsky Center, Columbia University Irving Medical Center, 630 West 168th St (P& S Unit 16), New York, NY 10032, USA
54. Department of Pathology and Taub Institute, Columbia University Irving Medical Center, 630 West 168th St, New York, NY 10032, USA
55. UNSW Medicine & NeuRA, Randwick, 2031 Australia

56. Department of Pathology and Laboratory Medicine and Department of Neurology, Emory University, Atlanta, GA 30322, USA

57. Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, University of Manchester, UK

58. Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK

59. Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada V5Z 1M9

SUPPLEMENTARY DATA

LEGEND ELECTRONIC DATA

Online Resource 2. Variants identified in the known FTLD genes. All rare variants identified via whole genome-sequencing in the known FTLD genes are presented and classified according to the ACMG guidelines.

Online Resource 3. Gene-based association analysis with rare variants results. Each gene is presented along with its total number of variants in FTLD-TDP patients (Total variant alleles patients), controls (Total variant alleles controls) and the number of variants included in the test (Number of markers in test). P values are presented with adjustment for sex and four PCs, and only adjusted for sex. Spreadsheet 1 (Nominally sig LOF) represents the genes with LOF variants. Spreadsheet 2 (LOF3vs0) provides the genes carrying rare LOF in at least 3 FTLD-TDP patients and not in controls. Spreadsheet 3 (Nominally sig LOFandmissense) represents the genes with LOF variants and coding changes predicted to be pathogenic by SIFT and Polyphen2. Spreadsheet 4 (LOFmissense3vs0) provides the genes carrying rare LOF and missense predicted pathogenic by SIFT and Polyphen2 in at least 3 FTLD-TDP patients and not in controls.

Online Resource 4. Similarity analyses between the known FTLD genes and genes identified via burden tests. Each gene is presented along with its prioritized rank, an overall p-value after FDR correction (Overall pValue) and the detail of each similarity queried by the ToppGene algorithm. Spreadsheet 1 (LOF) represents Toppgenes results for the genes with LOF variants in at least 3 FTLD-TDP patients and not in controls. Spreadsheet 2 (LOF and missense) represents Toppgenes results for the genes with LOF variants and coding changes predicted to be pathogenic by SIFT and Polyphen2 in at least 3 FTLD-TDP patients and not in controls.

Supplementary Table 1. Overview of FTLN-TDP patients with genetic causes updated after whole genome sequencing. The number of FTLN-TDP patients per site is presented and includes: patients without mutations, patients carrying mutations in the major FTLN-TDP genes (*GRN*, *C9ORF72*, *TBK1*) and patients carrying mutations in other genes (*OPTN*, *VCP*, *TARDBP*, *CHCHD10*, *SQSTM1*, *UBQLN2*, *hnRNPA1*, *hnRNPA2B1*, *CSF1R*, *FUS*, *CHMP2B*, *LRRK2*, and *TIA1*).

| Site | Number of FTLN-TDP | Non mutation carriers | Caucasian | | | Other genes |
|--|--------------------|------------------------------|------------------------------|------------------------------|----------------------------|----------------------------|
| | | | <i>GRN</i> | <i>C9ORF72</i> | <i>TBK1</i> | |
| Banner Sun Health Research Institute | 29 | 20 | 6 | 3 | 0 | 0 |
| Columbia University | 25 | 20 | 2 | 3 | 0 | 0 |
| Emory University | 48 | 25 | 6 | 13 | 0 | 1 |
| Erasmus University | 93 | 63 | 5 | 22 | 0 | 2 |
| German Center for Neurodegenerative Diseases | 24 | 14 | 2 | 7 | 1 | 0 |
| Indiana University | 32 | 14 | 13 | 4 | 1 | 0 |
| Karolinska University | 44 | 18 | 4 | 20 | 1 | 1 |
| King's College London | 50 | 39 | 3 | 6 | 1 | 0 |
| Ludwig-Maximilians-University Munich | 40 | 15 | 4 | 16 | 2 | 3 |
| Mayo Clinic Jacksonville/Rochester | 207 | 125 | 27 | 51 | 2 | 2 |
| Northwestern University | 69 | 43 | 16 | 8 | 1 | 1 |
| University College London | 54 | 28 | 13 | 13 | 0 | 0 |
| University of British Columbia | 72 | 30 | 9 | 26 | 1 | 0 |
| University of California San Diego | 15 | 10 | 2 | 3 | 0 | 0 |
| University of New South Wales | 47 | 16 | 9 | 20 | 0 | 2 |
| University of Pennsylvania | 95 | 41 | 17 | 29 | 3 | 2 |
| University of San Francisco | 101 | 62 | 10 | 22 | 2 | 1 |
| University of Toronto | 18 | 11 | 1 | 5 | 0 | 1 |
| University of Pittsburgh Medical Center | 20 | 14 | 2 | 3 | 1 | 0 |
| University Texas Southwestern Medical Center | 41 | 27 | 5 | 9 | 0 | 0 |
| Washington University School of Medicine | 24 | 17 | 2 | 4 | 0 | 0 |
| University of Western Ontario | 6 | 2 | 0 | 2 | 1 | 0 |
| TOTAL | 1154 | 654 (57.7%) | 158 (13.9%) | 289 (25.5%) | 17 (1.5%) | 16 (1.4%) |

Supplementary Table 2. Overview of FTLN-TDP patients and controls included in the discovery and replication stage after quality controls.

| Site | Discovery | | Replication | |
|--|-----------------------------|--------------------|-----------------------------|--------------------|
| | Number of FTLN-TDP patients | Number of controls | Number of FTLN-TDP patients | Number of controls |
| Banner Sun Health Research Institute | 13 | 0 | 2 | 0 |
| Columbia University | 20 | 0 | 0 | 0 |
| Emory University | 25 | 0 | 2 | 0 |
| Erasmus University | 40 | 0 | 1 | 0 |
| German Center for Neurodegenerative Diseases | 10 | 0 | 0 | 0 |
| Indiana University | 13 | 0 | 1 | 13 |
| Karolinska University | 9 | 0 | 0 | 0 |
| King's College London | 39 | 0 | 1 | 0 |
| Ludwig-Maximilians-University Munich | 17 | 0 | 0 | 0 |
| Mayo Clinic Jacksonville/Rochester | 124 | 838 | 7 | 1288 |
| Northwestern University | 23 | 0 | 17 | 38 |
| University College London | 12 | 0 | 10 | 0 |
| University of British Columbia | 20 | 0 | 15 | 0 |
| University of California San Diego | 6 | 0 | 2 | 10 |
| University of Manchester | 0 | 0 | 30 | 0 |
| University of New South Wales | 14 | 0 | 7 | 0 |
| University of Pennsylvania | 29 | 0 | 0 | 0 |
| University of San Francisco | 44 | 0 | 20 | 304 |
| University of Toronto | 10 | 0 | 0 | 0 |
| University of Pittsburgh Medical Center | 14 | 0 | 0 | 0 |
| University Texas Southwestern Medical Center | 22 | 0 | 3 | 0 |
| Washington University School of Medicine | 10 | 0 | 1 | 0 |
| University of Western Ontario | 3 | 0 | 0 | 0 |
| TOTAL | 517 | 838 | 119 | 1653 |

Supplementary Table 3. Candidate loci identified in genome-wide association analyses of the overall FTLD-TDP or FTLD-TDP pathological strata.

Each locus is presented with its most significant SNP along with its position, the closest gene (Locus Name), its minor allele frequency in controls and patients

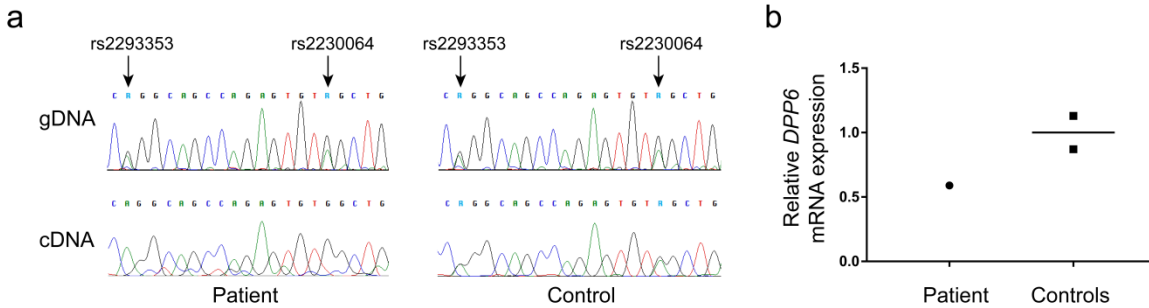
(MAF Controls/Patients), its odds ratio (OR) and pvalue.

| SNP ID | Position | Locus Name | MAF Controls/ Patients | All FTLD-TDP vs controls | | FTLD-TDP type A vs controls | | FTLD-TDP type B vs controls | | FTLD-TDP type C vs controls | |
|-------------|----------------|---------------------------------------|------------------------------|-----------------------------|----------|--------------------------------|----------|--------------------------------|----------|--------------------------------|----------|
| | | | | OR | pvalue | OR | pvalue | OR | pvalue | OR | pvalue |
| rs59810358 | chr1:25055747 | <i>MIR4425</i> | 0.15/0.17 | 1.38 | 4.94e-03 | 1.29 | 1.43e-01 | 1.12 | 5.01e-01 | 2.09 | 9.42e-06 |
| rs200527740 | chr1:61764008 | <i>INADL</i> | 0.07/0.08 | 1.42 | 2.64e-02 | 0.93 | 7.87e-01 | 1.04 | 8.77e-01 | 2.73 | 2.70e-06 |
| rs138835186 | chr1:173334272 | <i>LOC100506023</i> | 0.00/0.01 | 4.58 | 1.38e-03 | 1.74 | 4.45e-01 | 2.61 | 1.54e-01 | 11.21 | 3.89e-06 |
| rs61831315 | chr1:186126654 | <i>HMCN1</i> | 0.05/0.04 | 0.31 | 4.28e-06 | 0.26 | 2.44e-03 | 0.33 | 3.70e-03 | 0.22 | 2.18e-03 |
| rs6676599 | chr1:206711310 | <i>MAPKAPK2</i> | 0.19/0.21 | 1.41 | 1.09e-03 | 2.01 | 6.98e-06 | 1.31 | 7.05e-02 | 1.10 | 5.70e-01 |
| rs472856 | chr1:214936242 | <i>KCNK2</i> | 0.21/0.23 | 1.29 | 1.14e-02 | 1.01 | 9.65e-01 | 1.86 | 7.10e-06 | 1.09 | 5.95e-01 |
| rs34447323 | chr1:232974879 | <i>NTPCR</i> | 0.06/0.07 | 1.43 | 2.76e-02 | 2.59 | 8.18e-06 | 1.20 | 4.56e-01 | 0.80 | 4.85e-01 |
| | chr1:245753541 | <i>SMYD3</i> | 0.07/0.09 | 1.54 | 3.32e-03 | 1.59 | 3.62e-02 | 0.99 | 9.59e-01 | 2.40 | 7.29e-06 |
| rs2003298 | chr2:10946024 | <i>KCNF1</i> | 0.33/0.35 | 1.23 | 2.17e-02 | 0.99 | 9.38e-01 | 1.77 | 6.75e-06 | 1.05 | 7.21e-01 |
| rs4325802 | chr2:48717394 | <i>LHCGR;</i> <i>STON1-GTF2A1L</i> | 0.08/0.09 | 1.49 | 8.06e-03 | 1.23 | 3.87e-01 | 1.38 | 1.46e-01 | 2.64 | 6.19e-06 |
| rs76291845 | chr2:111131781 | <i>BCL2L11</i> | 0.01/0.01 | 2.78 | 3.61e-03 | 5.83 | 8.39e-06 | 1.29 | 6.41e-01 | 0.87 | 8.41e-01 |
| rs143339003 | chr2:142622395 | <i>KYNU</i> | 0.01/0.02 | 2.26 | 1.20e-02 | 5.09 | 6.80e-06 | 1.00 | 9.97e-01 | 0.33 | 2.85e-01 |
| rs78370899 | chr2:214695123 | <i>BARD1</i> | 0.00/0.01 | 6.38 | 1.19e-04 | 10.93 | 7.80e-06 | 2.41 | 2.57e-01 | 3.87 | 8.36e-02 |
| rs11712238 | chr3:82726692 | <i>GBE1</i> | 0.12/0.13 | 1.44 | 3.35e-03 | 1.43 | 4.96e-02 | 1.10 | 6.12e-01 | 2.25 | 3.49e-06 |
| rs34572606 | chr3:104580495 | <i>ALCAM</i> | 0.09/0.10 | 1.44 | 7.37e-03 | 0.83 | 4.38e-01 | 2.48 | 8.86e-08 | 1.16 | 5.25e-01 |
| rs13098438 | chr3:107115462 | <i>LINC00882</i> | 0.02/0.03 | 2.18 | 1.59e-03 | 1.64 | 2.06e-01 | 3.87 | 6.47e-06 | 0.87 | 7.81e-01 |
| rs397957892 | chr3:140089009 | <i>CLSTN2</i> | 0.09/0.10 | 1.43 | 6.68e-03 | 2.29 | 2.03e-06 | 1.14 | 5.30e-01 | 1.10 | 6.85e-01 |
| rs114146294 | chr3:162019418 | <i>LINC01192</i> | 0.02/0.02 | 2.43 | 1.79e-03 | 2.36 | 2.64e-02 | 0.82 | 7.13e-01 | 4.89 | 6.69e-06 |
| rs138512547 | chr3:194634939 | <i>TMEM44</i> | 0.02/0.03 | 2.01 | 4.47e-03 | 0.77 | 6.22e-01 | 1.50 | 2.79e-01 | 4.10 | 1.88e-06 |
| rs9818987 | chr3:194681701 | <i>FAM43A</i> | 0.36/0.33 | 0.66 | 8.49e-06 | 0.64 | 2.00e-03 | 0.67 | 3.04e-03 | 0.66 | 6.00e-03 |
| rs7683451 | chr4:22370936 | <i>ADGRA3</i> | 0.25/0.27 | 1.36 | 1.13e-03 | 0.93 | 6.22e-01 | 1.86 | 3.59e-06 | 1.34 | 5.18e-02 |
| rs62319305 | chr4:129302471 | <i>C4orf33</i> | 0.02/0.03 | 1.75 | 2.45e-02 | 0.99 | 9.83e-01 | 1.27 | 5.44e-01 | 4.06 | 8.39e-06 |
| rs78753485 | chr4:135810669 | <i>LINC00613</i> | 0.01/0.02 | 3.85 | 1.37e-04 | 2.29 | 1.36e-01 | 6.76 | 1.26e-06 | 2.35 | 1.28e-01 |

| | | | | | | | | | | | |
|-------------|-----------------|--|-----------|------|----------|-------|----------|------|----------|-------|----------|
| rs201446533 | chr4:159457218 | <i>RAPGEF2</i> | 0.06/0.06 | 1.53 | 1.32e-02 | 1.15 | 6.17e-01 | 0.87 | 6.28e-01 | 2.74 | 4.57e-06 |
| rs61707463 | chr4:169787358 | <i>C4orf27;</i> <i>LOC100506085</i> | 0.02/0.03 | 3.58 | 1.60e-06 | 3.08 | 3.01e-03 | 4.38 | 6.42e-06 | 2.79 | 1.02e-02 |
| rs11132244 | chr4:184422579 | <i>IRF2</i> | 0.30/0.27 | 0.64 | 9.17e-06 | 0.56 | 3.39e-04 | 0.72 | 2.16e-02 | 0.67 | 1.25e-02 |
| rs149734180 | chr5:24135712 | <i>C5orf17</i> | 0.02/0.02 | 1.98 | 1.43e-02 | 4.21 | 7.77e-06 | 0.59 | 3.31e-01 | 1.21 | 6.85e-01 |
| rs35422123 | chr5:34517139 | <i>RAI14</i> | 0.02/0.03 | 2.36 | 2.44e-04 | 1.00 | 9.91e-01 | 4.00 | 9.64e-07 | 2.21 | 2.73e-02 |
| rs35122968 | chr6:32714422 | <i>HLA-DQA2</i> | 0.06/0.08 | 2.07 | 2.33e-06 | 1.65 | 3.28e-02 | 2.50 | 9.68e-06 | 2.28 | 4.34e-04 |
| rs34422230 | chr6:32809218 | <i>HLA-DOB</i> | 0.03/0.05 | 2.31 | 3.80e-05 | 2.00 | 1.71e-02 | 3.34 | 1.86e-06 | 1.87 | 5.37e-02 |
| rs116655107 | chr6:44178162 | <i>CAPN11</i> | 0.02/0.03 | 2.45 | 1.16e-04 | 4.13 | 2.28e-06 | 1.40 | 3.44e-01 | 1.89 | 7.98e-02 |
| rs148211665 | chr6:49401592 | <i>MUT</i> | 0.01/0.02 | 3.26 | 7.26e-04 | 6.33 | 4.27e-06 | 2.68 | 6.31e-02 | 1.45 | 5.83e-01 |
| rs2781832 | chr6:74582646 | <i>LOC101928516</i> | 0.02/0.03 | 2.33 | 8.70e-04 | 1.46 | 3.51e-01 | 1.49 | 2.89e-01 | 4.51 | 2.97e-06 |
| rs11751521 | chr6:166505657 | <i>RPS6KA2</i> | 0.02/0.03 | 2.51 | 1.39e-04 | 2.84 | 1.13e-03 | 3.79 | 6.94e-06 | 1.13 | 7.83e-01 |
| rs6463679 | chr7:7305371 | <i>LOC101927354</i> | 0.34/0.37 | 1.49 | 4.39e-06 | 1.43 | 6.27e-03 | 1.45 | 2.69e-03 | 1.62 | 3.25e-04 |
| rs10231788 | chr7:47912542 | <i>PKD1L1</i> | 0.38/0.37 | 0.75 | 1.70e-03 | 0.52 | 7.68e-06 | 0.77 | 4.47e-02 | 0.97 | 8.37e-01 |
| rs2465481 | chr7:80134858 | <i>GNAI1</i> | 0.45/0.47 | 1.18 | 5.69e-02 | 1.94 | 2.72e-06 | 1.02 | 8.96e-01 | 1.05 | 7.49e-01 |
| rs117924488 | chr7:87788671 | <i>RUNDC3B</i> | 0.00/0.01 | 3.52 | 4.09e-03 | 0.38 | 4.10e-01 | 9.16 | 1.42e-06 | 1.89 | 3.68e-01 |
| rs10267171 | chr7:110723284 | <i>IMMP2L</i> | 0.19/0.21 | 1.61 | 6.53e-06 | 1.68 | 7.23e-04 | 1.73 | 2.33e-04 | 1.45 | 2.67e-02 |
| rs118113626 | chr7:154194746 | <i>DPP6</i> | 0.05/0.07 | 2.48 | 4.88e-08 | 2.80 | 5.93e-06 | 2.42 | 5.79e-05 | 2.17 | 1.63e-03 |
| rs4726389 | chr7:154225769 | <i>DPP6</i> | 0.05/0.07 | 2.45 | 4.63e-08 | 2.55 | 5.42e-05 | 2.65 | 5.52e-06 | 2.09 | 2.96e-03 |
| rs10109928 | chr8:10459514 | <i>LINC0001</i> | 0.03/0.04 | 2.32 | 1.88e-04 | 1.20 | 6.55e-01 | 2.56 | 1.25e-03 | 3.89 | 7.64e-06 |
| rs537967198 | chr8:13856936 | <i>SGCZ</i> | 0.02/0.03 | 2.60 | 1.44e-04 | 4.57 | 2.87e-06 | 2.59 | 4.62e-03 | 1.42 | 4.58e-01 |
| rs34441160 | chr8:95289791 | <i>C8orf37-AS1</i> | 0.07/0.08 | 1.63 | 1.13e-03 | 1.08 | 7.61e-01 | 2.36 | 9.13e-06 | 1.36 | 1.81e-01 |
| rs6468704 | chr8:99982161 | <i>RGS22</i> | 0.18/0.20 | 1.45 | 5.50e-04 | 1.12 | 4.74e-01 | 2.03 | 1.87e-06 | 1.30 | 1.14e-01 |
| rs2597335 | chr8:132411836 | <i>KCNQ3</i> | 0.36/0.34 | 0.78 | 8.21e-03 | 0.88 | 3.77e-01 | 0.97 | 8.05e-01 | 0.48 | 7.57e-06 |
| rs150427844 | chr8:139148204 | <i>COL22A1</i> | 0.00/0.01 | 3.66 | 5.97e-03 | 1.19 | 8.48e-01 | 2.02 | 3.08e-01 | 11.50 | 4.53e-06 |
| rs560900477 | chr8:142388515 | <i>TSNARE1</i> | 0.01/0.02 | 2.31 | 6.06e-03 | 5.24 | 3.43e-06 | 0.73 | 6.26e-01 | 1.24 | 7.04e-01 |
| rs143407351 | chr9:87397602 | <i>DAPK1</i> | 0.01/0.02 | 2.72 | 2.93e-04 | 1.63 | 2.88e-01 | 4.32 | 5.52e-06 | 2.19 | 6.88e-02 |
| rs553772563 | chr9:118093612 | <i>TLR4</i> | 0.00/0.01 | 7.19 | 1.22e-04 | 18.17 | 1.19e-06 | 2.25 | 3.50e-01 | 6.59 | 6.10e-03 |
| rs35323587 | chr9:135084306 | <i>OLFM1</i> | 0.12/0.15 | 1.78 | 1.50e-06 | 1.88 | 2.27e-04 | 1.74 | 9.47e-04 | 1.81 | 9.83e-04 |
| rs10762302 | chr10:69619172 | <i>C10orf35</i> | 0.40/0.38 | 0.83 | 3.74e-02 | 0.93 | 6.14e-01 | 1.03 | 8.44e-01 | 0.49 | 5.36e-06 |
| rs846611 | chr10:76791758 | <i>KCNMA1</i> | 0.04/0.05 | 1.87 | 8.84e-04 | 1.57 | 1.19e-01 | 1.22 | 4.94e-01 | 3.01 | 8.81e-06 |
| rs61870346 | chr10:125065282 | <i>CTBP2</i> | 0.02/0.03 | 2.63 | 3.64e-05 | 1.65 | 1.75e-01 | 3.83 | 3.29e-06 | 1.50 | 3.16e-01 |
| rs60078451 | chr11:1457322 | <i>BRSK2</i> | 0.05/0.07 | 1.92 | 1.46e-04 | 1.07 | 8.24e-01 | 2.75 | 5.77e-06 | 2.02 | 5.25e-03 |
| rs78934618 | chr11:2215067 | <i>ASCL2</i> | 0.02/0.03 | 2.18 | 1.67e-03 | 1.29 | 5.68e-01 | 1.97 | 5.39e-02 | 4.15 | 5.27e-06 |
| rs117197016 | chr11:87490779 | <i>TMEM135</i> | 0.01/0.01 | 2.24 | 2.39e-02 | 0.47 | 3.49e-01 | 0.51 | 3.78e-01 | 6.07 | 4.49e-06 |
| rs112301159 | chr11:94786566 | <i>AMOTL1</i> | 0.00/0.01 | 4.44 | 5.09e-03 | 2.47 | 3.28e-01 | 2.00 | 4.16e-01 | 13.35 | 7.35e-06 |

| | | | | | | | | | | | |
|-------------|-----------------|---------------------|-----------|------|----------|------|----------|-------|----------|------|----------|
| rs148048968 | chr12:15166523 | <i>RERG</i> | 0.22/0.19 | 0.59 | 7.35e-06 | 0.49 | 2.45e-04 | 0.58 | 1.43e-03 | 0.74 | 1.05e-01 |
| rs11064952 | chr12:119894382 | <i>CIT</i> | 0.01/0.02 | 3.39 | 1.81e-04 | 3.26 | 1.50e-02 | 6.25 | 1.88e-06 | 2.72 | 5.26e-02 |
| rs76586200 | chr12:130670602 | <i>STX2</i> | 0.01/0.01 | 3.28 | 1.78e-03 | 6.75 | 9.24e-06 | 2.78 | 6.68e-02 | 1.47 | 5.66e-01 |
| rs79079778 | chr13:32665173 | <i>PDS5B</i> | 0.00/0.01 | 4.09 | 2.22e-03 | 0.85 | 8.84e-01 | 10.63 | 8.16e-07 | 0.92 | 9.41e-01 |
| . | chr13:75544760 | <i>COMMD6</i> | 0.01/0.01 | 2.32 | 2.79e-02 | 1.88 | 2.91e-01 | na | na | 7.15 | 6.04e-06 |
| rs56232509 | chr14:32354422 | <i>AKAP6</i> | 0.08/0.09 | 1.58 | 2.00e-03 | 0.95 | 8.49e-01 | 2.42 | 3.63e-06 | 1.52 | 7.09e-02 |
| rs1198035 | chr14:81972701 | <i>LINC01467</i> | 0.30/0.32 | 1.48 | 2.81e-05 | 1.87 | 7.69e-06 | 1.53 | 1.41e-03 | 1.27 | 1.08e-01 |
| rs147183330 | chr14:87538376 | <i>GALC</i> | 0.02/0.04 | 2.46 | 1.11e-04 | 3.96 | 2.80e-06 | 1.92 | 4.39e-02 | 1.92 | 6.44e-02 |
| rs145502725 | chr15:25138308 | <i>PWARI</i> | 0.01/0.01 | 4.98 | 1.70e-04 | 3.95 | 2.93e-02 | 2.50 | 1.53e-01 | 8.72 | 8.16e-06 |
| rs4240777 | chr15:85946519 | <i>MIR548AP</i> | 0.31/0.35 | 1.51 | 4.97e-06 | 1.45 | 6.22e-03 | 1.47 | 2.30e-03 | 1.52 | 3.14e-03 |
| rs6496125 | chr15:95592748 | <i>LINC00924</i> | 0.09/0.10 | 1.55 | 1.55e-03 | 1.26 | 2.84e-01 | 1.29 | 2.06e-01 | 2.66 | 2.27e-07 |
| rs117434909 | chr16:15716617 | <i>MYH11;NDE1</i> | 0.02/0.02 | 2.42 | 2.62e-03 | 4.92 | 7.85e-06 | 1.07 | 9.04e-01 | 2.16 | 9.29e-02 |
| rs79805801 | chr16:79600738 | <i>MAF</i> | 0.01/0.01 | 4.30 | 2.95e-04 | 3.04 | 5.09e-02 | 8.30 | 3.21e-06 | 2.46 | 1.91e-01 |
| rs16940783 | chr16:86303304 | <i>LOC146513</i> | 0.07/0.08 | 1.59 | 2.34e-03 | 1.23 | 3.85e-01 | 1.47 | 7.52e-02 | 2.59 | 9.73e-06 |
| rs200162587 | chr17:2713612 | <i>CLUH</i> | 0.03/0.04 | 2.23 | 1.67e-04 | 1.82 | 5.43e-02 | 3.31 | 6.78e-06 | 2.01 | 2.40e-02 |
| rs708383 | chr17:44360386 | <i>FAM171A2</i> | 0.37/0.39 | 1.27 | 5.38e-03 | 1.97 | 1.69e-07 | 0.99 | 9.32e-01 | 0.94 | 6.80e-01 |
| rs1032914 | chr18:77787710 | <i>LINC01029</i> | 0.38/0.39 | 1.26 | 7.48e-03 | 1.24 | 1.10e-01 | 0.98 | 8.95e-01 | 1.86 | 8.78e-06 |
| rs118107613 | chr19:3020644 | <i>MIR1268A</i> | 0.02/0.02 | 2.04 | 1.62e-02 | 0.73 | 6.22e-01 | 1.50 | 3.63e-01 | 4.85 | 5.62e-06 |
| rs3952538 | chr19:15878713 | <i>CYP4F2</i> | 0.01/0.02 | 5.29 | 7.71e-06 | 5.39 | 1.21e-03 | 4.46 | 2.78e-03 | 8.88 | 3.85e-06 |
| rs12973192 | chr19:17642430 | <i>UNC13A</i> | 0.37/0.40 | 1.48 | 3.44e-06 | 1.35 | 1.90e-02 | 1.95 | 4.67e-08 | 1.10 | 4.94e-01 |
| rs35471514 | chr19:55544212 | <i>SBK3</i> | 0.03/0.03 | 1.96 | 3.00e-03 | 3.69 | 3.21e-06 | 1.22 | 5.80e-01 | 1.17 | 6.89e-01 |
| rs117883823 | chr20:37186204 | <i>RPN2</i> | 0.01/0.02 | 2.28 | 1.27e-02 | 0.55 | 4.39e-01 | 1.94 | 1.61e-01 | 5.61 | 6.73e-06 |
| rs6072689 | chr20:42341450 | <i>PTPRT</i> | 0.31/0.28 | 0.67 | 4.41e-05 | 0.77 | 7.38e-02 | 0.49 | 3.45e-06 | 0.73 | 4.15e-02 |
| rs56290045 | chr20:60462610 | <i>LOC101928048</i> | 0.02/0.02 | 2.53 | 7.39e-04 | 1.74 | 1.99e-01 | 1.47 | 3.74e-01 | 5.66 | 1.94e-07 |

Supplementary Figure 1. mRNA expression of *DPP6* in the LOF mutation carrier. **a)** *DPP6* complementary DNA (cDNA) and genomic DNA (gDNA) was used as template to perform PCR and sequencing analysis of a fragment containing the LOF mutation c.1345+1G>T and two known common variants: rs2293353 and rs2230064 in the FTLTD-TDP patient carrying the *DPP6* splice site mutation and a control. Based on gDNA sequencing, both our carrier and the selected control are heterozygous for rs2293353 and rs2230064. At the cDNA level, sequence chromatograms show the absence of the rare alleles of rs2293353 and rs2230064 in the *DPP6* LOF mutation carrier, suggesting degradation of the mutant allele by nonsense mediated decay. **b)** Relative mRNA expression of *DPP6* in cortex is presented after normalization to *GAPDH* and *MAP2*. The patient carrying the LOF mutation has reduced expression of *DPP6* mRNA as compared to two pathologically normal controls.



Supplementary Figure 2. TBK1 immunity related pathway and LOF variants identified in FTLD-TDP. The TBK1 pathway is shown along with the number of LOF variants identified through WGS in patients (red) and in controls (blue). LOF variants were identified in *TBK1*, *TRIM21*, *IRF3*, *IRF7*, *IRF8*, *DHX58* and *NOD2*. Following activation through the detection of DNA/RNA viruses, viral proteins or LPS, by different sensors, adaptor proteins are recruited (TRIF, MAVs, STING) to activate TBK1. Activated TBK1 then phosphorylates IRF3/8/7 triggering their nuclear translocation and activation of IFN gene expression. NEMO can also be activated triggering the NFκB pathway (p50/p65).

