Neurobiology of Aging 69 (2018) 293.e9–293.e11

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Negative results

No supportive evidence for *TIA1* gene mutations in a European cohort of ALS-FTD spectrum patients

Yalda Baradaran-Heravi [a,b], Lubina Dillen [a,b], Hung Phuoc Nguyen [a,b], Sara Van Mossevelde [a,b,c], Jonathan Baets [b,c,d], Peter De Jonghe [b,c,d], Sebastiaan Engelborghs [b,e], Peter P. De Deyn [b,e], Mathieu Vandenbulcke [f,g], Rik Vandenberghe [f,h], Philip Van Damme [h,i,j], Patrick Cras [b,c], Eric Salmon [k], Matthis Synofzik [l,m], Peter Heutink [l,n], Carlo Wilke [l,m], Javier Simon-Sanchez [l,m], Ricard Rojas-Garcia [o], Janina Turon-Sans [o], Alberto Lleó [p], Ignacio Illán-Gala [p], Jordi Clarimón [p], Barbara Borroni [q], Alessandro Padovani [q], Pau Pastor [r,s], Monica Diez-Fairen [r,s], Miquel Aguilar [r,s], Ellen Gelpi [t], Raquel Sanchez-Valle [u], Sergi Borrego-Ecija [u], Radoslav Matej [v,w], Eva Parobkova [v,w], Benedetta Nacmias [x], Sandro Sorbi [x,y], Silvia Bagnoli [x], Alexandre de Mendonça [z], Catarina Ferreira [z], Matthew J. Fraidakis [aa], Janine Diehl-Schmid [bb], Panagiotis Alexopoulos [bb], Maria Rosário Almeida [cc], Isabel Santana [cc], Christine Van Broeckhoven [a,b,*], Julie van der Zee [a,b,**], on behalf of the BELNEU Consortium[1] and the EU EOD Consortium[2]

[a] *Neurodegenerative Brain Diseases Group, VIB-UAntwerp Center for Molecular Neurology, Antwerp, Belgium*
[b] *Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium*
[c] *Department of Neurology, Antwerp University Hospital (UZA), Edegem, Belgium*
[d] *Neurogenetics Group, VIB-UAntwerp Center for Molecular Neurology, Antwerp, Belgium*
[e] *Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA), Middelheim and Hoge Beuken, Antwerp, Belgium*
[f] *Department of Neurosciences, Faculty of Medicine, KU Leuven, Leuven, Belgium*
[g] *Department of Old Age Psychiatry and Memory Clinic, University Hospitals Leuven, Leuven, Belgium*
[h] *Department of Neurology, University Hospitals Leuven, Leuven, Belgium*
[i] *Department of Neurosciences, Faculty of Medicine, KU Leuven, Leuven, Belgium*
[j] *Laboratory of Neurobiology, Center for Brain and Disease Research, VIB, Leuven, Belgium*
[k] *Cyclotron Research Centre, University of Liege and Memory Clinic, CHU Liege, Belgium*
[l] *Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany*
[m] *Neurodegeneration, German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany*
[n] *Genome Biology of Neurodegenerative Diseases, German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany*
[o] *Department of Neurology, Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain and Center for Networked Biomedical Research into Rare Diseases (CIBERER)*
[p] *Department of Neurology, Memory Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain and Center for Networked Biomedical Research into Neurodegenerative Disorders (CIBERNED)*
[q] *Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Italy*
[r] *Fundació per la Recerca Biomèdica i Social Mútua de Terrassa, Terrassa, Barcelona, Spain*
[s] *Memory Disorders Unit, Department of Neurology, University Hospital Mutua de Terrassa, Terrassa, Barcelona, Spain*
[t] *Neurological Tissue Bank of the Biobanc, Hospital Clínic, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[u] *Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Department, Hospital Clínic, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[v] *Department of Pathology and Molecular Medicine, Thomayer Hospital, Prague, Czech Republic*
[w] *Department of Pathology, Third Medical Faculty, Charles University, Prague, Czech Republic*
[x] *Department of Neuroscience, Psychology, Drug Research and Child Health - University of Florence, Florence, Italy*
[y] *IRCCS Don Gnocchi, Florence, Italy*

* Corresponding author at: Neurodegenerative Brain Diseases Group – VIB-UAntwerp Center for Molecular Neurology, University of Antwerp - CDE, Universiteitsplein 1, 2610 Antwerp, Belgium. Tel.: +32 3 265 1101; fax: +32 3 265 8410.
** Corresponding author at: Neurodegenerative Brain Diseases Group – VIB-UAntwerp Center for Molecular Neurology, University of Antwerp - CDE, Universiteitsplein 1, 2610 Antwerp, Belgium. Tel.: +32 3 265 1032; fax: +32 3 265 8410.

E-mail addresses: christine.vanbroeckhoven@uantwerpen.vib.be (C. Van Broeckhoven), julie.vanderzee@uantwerpen.vib.be (J. van der Zee).

https://doi.org/10.1016/j.neurobiolaging.2018.05.005

[z] Faculty of Medicine, University of Lisbon, Portugal
[aa] NeuroRARE Centre for Rare and Genetic Neurological & Neuromuscular Diseases & Neurogenetics, Athens, Greece
[bb] Department of Psychiatry and Psychotherapy, Technische Universität München, München, Germany
[cc] Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal

ARTICLE INFO

Article history:
Received 22 March 2018
Accepted 5 May 2018
Available online 23 May 2018

Keywords:
Amyotrophic lateral sclerosis (ALS)
Frontotemporal dementia (FTD)
TAR DNA-Binding protein 43 (TDP-43)
T cell–restricted intracellular antigen-1 gene (*TIA1*)

ABSTRACT

We evaluated the genetic contribution of the T cell–restricted intracellular antigen-1 gene (*TIA1*) in a European cohort of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) patients. Exonic resequencing of *TIA1* in 1120 patients (693 FTD, 341 ALS, 86 FTD-ALS) and 1039 controls identified in total 5 rare heterozygous missense variants, affecting the *TIA1* low-complexity domain (LCD). Only 1 missense variant, p.Met290Thr, identified in a familial FTD patient with disease onset at 64 years, was absent from controls yet received a combined annotation-dependent depletion score of 11.42. By contrast, 3 of the 4 variants also detected in unaffected controls, p.Val294Glu, p.Gln318Arg, and p.Ala381Thr, had combined annotation-dependent depletion scores greater than 20. Our findings in a large European patient-control series indicate that variants in *TIA1* are not a common cause of ALS and FTD. The observation of recurring *TIA1* missense variants in unaffected individuals lead us to conclude that the exact genetic contribution of *TIA1* to ALS and FTD pathogenesis remains to be further elucidated.

1. Introduction

Exome sequencing in an unresolved European amyotrophic lateral sclerosis (ALS)–frontotemporal dementia (FTD) family with transactive response DNA-binding protein-43 (TDP-43) brain pathology identified a co-segregation missense mutation in the low-complexity domain (LCD) of the T cell–restricted intracellular antigen-1 gene (*TIA1*), affecting stress granule dynamics (Mackenzie et al., 2017). Subsequent genetic screening revealed 6 additional rare missense mutations affecting the LCD in 3 unrelated ALS and 2 ALS-FTD patients, all absent from controls, giving an overall mutation frequency of ~2% familial ALS and <0.5% sporadic ALS (Mackenzie et al., 2017). Aiming to replicate the reported genetic association of *TIA1* with ALS and ALS-FTD, we set up a genetic screen of *TIA1* in a European case-control series of ALS-FTD spectrum patients, also including pure FTD patients.

2. Materials and methods

We sequenced the entire *TIA1* coding region (exons 1–13) in a total of 1120 patients and 1039 controls originating from different European countries (detailed methodology description and ethical assurance provided in Supplementary Material). The patient cohorts were recruited in the framework of the Belgian Neurology (BELNEU) Consortium, the European Early-Onset Dementia (EU EOD) Consortium, and the Tübingen FTD Exome series, as described (Blauwendraat et al., 2017; van der Zee et al., 2013; van der Zee et al., 2017). DNA and medical/demographic information was included on all patients, comprising 693 patients diagnosed with FTD, 341 patients with ALS, and 86 patients with concomitant FTD and ALS (FTD-ALS).

3. Results

We identified a total of 5 rare (minor allele frequency [MAF] <1%) heterozygous missense variants, with only 1 variant (p.Met290Thr) absent from the control cohort (Fig. 1, and Supplementary Material Table S1). All 5 missense variants mapped to the conserved *TIA1* LCD region (exons 11–13).

The p.Met290Thr (rs116707801) was present in an Italian familial FTD patient (age at onset 64 years, age at death 67 years). In ExAC NFE, this variant is counted 3 times in 66,732 alleles and has a combined annotation-dependent depletion (CADD) score of 11.42. The second missense variant identified in patients, p.Val294Glu (rs769199100), was present in an isolated Italian ALS patient (onset age 39 years). It was reported only once in 66,732 alleles of the ExAC NFE data set and received a CADD score of 20.9. However, we also observed the p.Val294Glu variant in one of our 1039 control individuals, also from Italian origin (age at inclusion 58 years). Furthermore, we detected a heterozygous missense variant p.Ala381Thr (rs768554955) in another Italian control individual (age at inclusion 70 years). The p.Ala381Thr variant was observed once in 66,740 alleles in ExAC NFE (MAF 0.001%) with a CADD score of 22.4.

In addition to these rare coding variants, we detected 2 recurring missense variants with ExAC NFE MAFs just below 1%. The p.Gln318Arg (rs115611153) variant was present in 15 patients and 29 controls. Despite its recurrent presence in unaffected individuals, it was scored among the 1% most deleterious variants in the genome, with a CADD score of 23.5. The p.Asn357Ser (rs116621885) variant was present in 14 patient and 18 controls, and had a CADD score of 14.25.

No further low-frequency or common variants were detected.

4. Discussion

We evaluated the genetic contribution of *TIA1* in 693 FTD, 341 ALS, and 86 ALS-FTD patients, including 80 patients with

[1] Belgian Neurology (BELNEU) Consortium: The following neurologist of the BELNEU Consortium have contributed to the clinical and pathological phenotyping and follow-up of the Belgian patient cohorts: Johan Goeman, Dirk Nuytten (Hospital Network Antwerp, Antwerp); Anne Sieben, Jan L. De Bleecker, Patrick Santens (University Hospital Ghent, Ghent); Jan Versijpt, Alex Michotte (University Hospital Brussels, Brussels); Adrian Ivanoiu (Saint-Luc University Hospital, Brussels); Olivier Deryck, Bruno Bergmans (General Hospital Sint-Jan Brugge, Bruges); Christiana Willems, Nina De Klippel (General Hospital Jessa, Hasselt); Dirk Peeters (General Hospital Groeninge Kortrijk).

[2] European Early-Onset Dementia (EU EOD) Consortium: The following members of the EU EOD Consortium have contributed to the clinical and pathological phenotyping and follow-up of the patients at their site that were included in the EU EOD Cohort: Silvana Archetti (Biotechnology Laboratory, Department of Diagnostics, Brescia Hospital, Italy); Elisa Bonomi (Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Italy); Irene Piaceri (Department of Neuroscience, Psychology, Drug Research and Child Health - University of Florence, Florence, Italy); Camilla Ferrari (IRCCS Don Gnocchi, Florence, Italy); Frederico Simões do Couto, Ana Verdelho, Gabriel Miltenberger-Miltényi (Faculty of Medicine, University of Lisbon, Lisbon, Portugal).

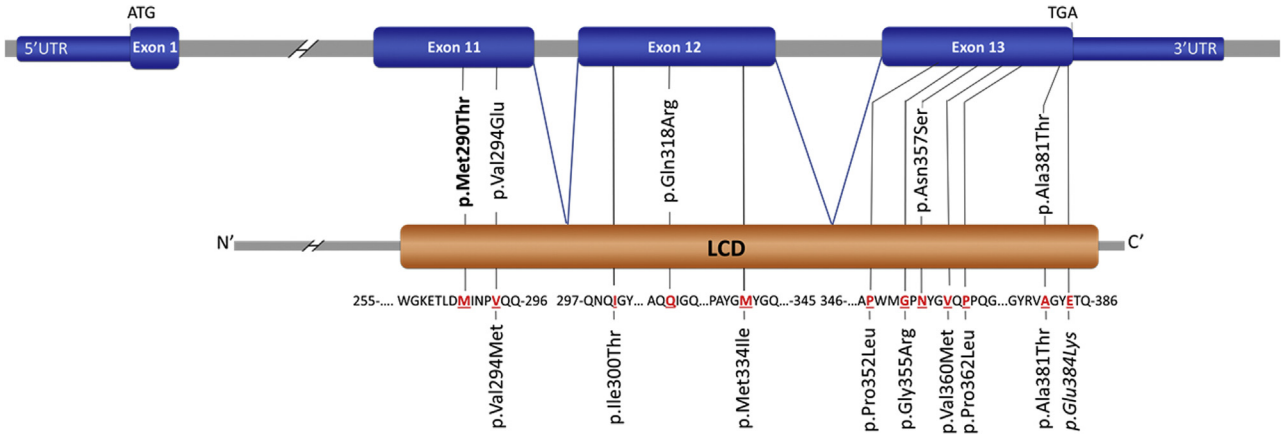

Fig. 1. Schematic representation of *TIA1* gene structure and protein with identified coding variants. Illustrated are the genomic region of *TIA1* exon 11-13 encoding for the low complexity domain (LCD). Variants identified in the present study are listed on top of the LCD structure; bold: patient-specific variant detected in a FTD patient, others: variants also detected in control individuals. Below the LCD structure, amino acid residues encoded by the respective exons and previously reported variants in ALS or ALS-FTD patients (Mackenzie et al., 2017; Yuan et al., 2017), as well as the Glu384Lys mutation identified in Welander distal myopathy (in *italics*) (Klar et al., 2013).

pathology-confirmed TDP-43 pathology. In line with Mackenzie et al., we did not identify any variants outside the LCD region. Only 1 variant was present in patients only, the other 4 were also observed in unaffected controls.

The patient-specific variant p.Met290Thr was observed in 1 male familial FTD patient of 693 FTDs (0.14%) and absent from a well-characterized control cohort of 1039 individuals. The CADD score however was significantly less than 20, indicating it is less likely to have a deleterious effect on protein function and explain the disease phenotype of the patient. In the absence of supportive co-segregation and functional evidence, we propose to classify this variant as variant of uncertain significance. We identified a female sporadic ALS patient with early disease onset of 34 years with a p.Val294Glu variant classified as deleterious by a CADD score of 20.9. However, we also detected the same variant in 1 male control individual of 58 years old. Of interest is that a different amino acid change at the same codon position (p.Val294Met, CADD score 22.3) was reported in an ALS patient by Mackenzie et al. and proposed it to be pathogenic (Mackenzie et al., 2017). We detected an additional missense variant, suggested to be pathogenic by Mackenzie et al. (p.Ala381Thr, CADD score 22.4), in one of our investigated controls with inclusion age of 70 years. In total, 3 of the 4 missense variants identified in unaffected control subjects had a CADD score >20, including the p.Gln318Arg variant present in 29 of our tested controls (CADD score 23.5).

Despite ours and others' ambiguous genetic observations (Van Der Spek et al., 2017), we acknowledge that *TIA1* is a promising functional candidate gene for TDP-related ALS and FTD.

Similar to other ALS and ALS-FTD genes, it encodes an RNA-binding protein that assembles into stress granules. Mutant *TIA1* was shown to alter these stress granule dynamics and, by this, promote TDP-43 accumulation and aggregation (Mackenzie et al., 2017).

Our findings in a large European patient-control cohort indicate that variants in *TIA1* are not a common cause of ALS and FTD. Furthermore, the observation of recurring *TIA1* LCD missense variants in unaffected individuals, including variants with estimated CADD scores >20, together with the lack of significant co-segregation in informative families, lead us to conclude that it is too early to attribute *TIA1* genetic variation to ALS or FTD risk.

Disclosure statement

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.05.005.

References

Blauwendraat, C., Wilke, C., Simon-Sanchez, J., Jansen, I.E., Reifschneider, A., Capell, A., Haass, C., Castillo-Lizardo, M., Biskup, S., Maetzler, W., Rizzu, P., Heutink, P., Synofzik, M., 2017. The wide genetic landscape of clinical frontotemporal dementia: systematic combined sequencing of 121 consecutive subjects. Genet. Med. 20, 240–249.

Klar, J., Sobol, M., Melberg, A., Mabert, K., Ameur, A., Johansson, A.C., Feuk, L., Entesarian, M., Orlen, H., Casar-Borota, O., Dahl, N., 2013. Welander distal myopathy caused by an ancient founder mutation in TIA1 associated with perturbed splicing. Hum. Mutat. 34, 572–577.

Mackenzie, I.R., Nicholson, A.M., Sarkar, M., Messing, J., Purice, M.D., Pottier, C., Annu, K., Baker, M., Perkerson, R.B., Kurti, A., Matchett, B.J., Mittag, T., Temirov, J., Hsiung, G.R., Krieger, C., Murray, M.E., Kato, M., Fryer, J.D., Petrucelli, L., Zinman, L., Weintraub, S., Mesulam, M., Keith, J., Zivkovic, S.A., Hirsch-Reinshagen, V., Roos, R.P., Zuchner, S., Graff-Radford, N.R., Petersen, R.C., Caselli, R.J., Wszolek, Z.K., Finger, E., Lippa, C., Lacomis, D., Stewart, H., Dickson, D.W., Kim, H.J., Rogaeva, E., Bigio, E., Boylan, K.B., Taylor, J.P., Rademakers, R., 2017. TIA1 mutations in amyotrophic lateral sclerosis and frontotemporal dementia promote Phase Separation and alter stress granule dynamics. Neuron. 95, 808–816.e9.

Van Der Spek, R.A., van Rheenen, W., Pulit, S.L., Kenna, K.P., Ticozzi, N., Kooyman, M., McLaughlin, R.L., Moisse, M., van Eijk, K.R., van Vugt, J., Andersen, P., Nazli Basak, A., Blair, I., De Carvalho, M., Chio, A., Corcia, P., Couratier, P., Drory, V.E., Glass, J.D., Hardiman, O., Mora, J.S., Morrison, K.E., Mitne-Neto, M., Robberecht, W., Shaw, P.J., Panades, M.P., van Damme, P., Silani, V., Gotkine, M., Weber, M., Van Es, M.A., Landers, J.E., Al-Chalabi, A., Van Den Berg, L.H., Veldink, J.H. Project Mine Als Sequencing, C., 2017. Reconsidering the causality of TIA1 Mutations in ALS. Amyotroph. Lateral Scler. Frontotemporal Degener. 19, 1–3.

van der Zee, J., Gijselinck, I., Dillen, L., Van Langenhove, T., Theuns, J., Engelborghs, S., Philtjens, S., Vandenbulcke, M., Sleegers, K., Sieben, A., Baumer, V., Maes, G., Corsmit, E., Borroni, B., Padovani, A., Archetti, S., Perneczky, R., Diehl-Schmid, J., de Mendonca, A., Miltenberger-Miltenyi, G., Pereira, S., Pimentel, J., Nacmias, B., Bagnoli, S., Sorbi, S., Graff, C., Chiang, H.H., Westerlund, M., Sanchez-Valle, R., Llado, A., Gelpi, E., Santana, I., Almeida, M.R., Santiago, B., Frisoni, G., Zanetti, O., Bonvicini, C., Synofzik, M., Maetzler, W., vom Hagen, J.M., Schols, L., Heneka, M.T., Jessen, F., Matej, R., Parobkova, E., Kovacs, G.G., Strobel, T., Sarafov, S., Tournev, I., Jordanova, A., Danek, A., Arzberger, T., Fabrizi, G.M., Testi, S., Salmon, E., Santens, P., Martin, J.J., Cras, P., Vandenberghe, R., De Deyn, P.P., Cruts, M., Van Broeckhoven, C. on behalf of the BELNEU Consortium and the EU EOD Consortium, 2013. A Pan-European Study of the C9orf72 Repeat associated with FTLD: geographic prevalence, genomic Instability, and intermediate repeats. Hum. Mutat. 34, 363–373.

van der Zee, J., Gijselinck, I., Van Mossevelde, S., Perrone, F., Dillen, L., Heeman, B., Bäumer, V., Engelborghs, S., De Bleecker, J., Baets, J., Gelpi, E., Rojas-García, R., Clarimón, J., Lleó, A., Diehl-Schmid, J., Alexopoulos, P., Perneczky, R., Synofzik, M., Just, J., Schöls, L., Graff, C., Thonberg, H., Borroni, B., Padovani, A., Jordanova, A., Sarafov, S., Tournev, I., de Mendonça, A., Miltenberger-Miltényi, G., Simões do Couto, F., Ramirez, A., Jessen, F., Heneka, M.T., Gómez-Tortosa, E., Danek, A., Cras, P., Vandenberghe, R., De Jonghe, P., De Deyn, P.P., Sleegers, K., Cruts, M., Van Broeckhoven, C. on behalf of the BELNEU Consortium and the EU EOD Consortium, 2017. TBK1 Mutation Spectrum in an Extended European Patient Cohort with Frontotemporal Dementia and Amyotrophic Lateral Sclerosis. Hum. Mutat. 38, 297–309.

Yuan, Z., Jiao, B., Hou, L., Xiao, T., Liu, X., Wang, J., Xu, J., Zhou, L., Yan, X., Tang, B., Shen, L., 2017. Mutation analysis of the TIA1 gene in Chinese patients with amyotrophic lateral sclerosis and frontotemporal dementia. Neurobiol. Aging. 64, 160.e9–160.e12.