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Analysis of C9orf72 repeat expansions in a large international cohort of dementia with Lewy bodies

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Abstract

C9orf72 repeat expansions are a common cause of amyotrophic lateral sclerosis and frontotemporal dementia. To date, no large-scale study of dementia with Lewy bodies (DLB) has been undertaken to assess the role of *C9orf72* repeat expansions in the disease. Here, we investigated the prevalence of *C9orf72* repeat expansions in a large cohort of DLB cases and identified no pathogenic repeat expansions in neuropathologically or clinically defined cases, showing that *C9orf72* repeat expansions are not causally associated with DLB.

Keywords

C9orf72; Dementia with Lewy bodies (DLB); Genetic screen

1. Introduction

Hexanucleotide repeat expansions (HREs) in a noncoding region of *C9orf72* are recognized as the most common genetic cause of familial and sporadic amyotrophic lateral sclerosis, frontotemporal dementia (FTD), amyotrophic lateral sclerosis-FTD, and Huntington disease phenocopies (Beck et al., 2013; Boeve et al., 2012; Hensman Moss et al., 2014; Majounie et al., 2012c; Simon-Sanchez et al., 2012; van der Zee et al., 2013).

A normal repeat expansion shows 1 to 23 GGGGCC repeats located between exons 1a and 1b of *C9orf72* (DeJesus-Hernandez et al., 2011; Renton et al., 2011). HREs identified in several neurodegenerative syndromes were found to range from 500 to 4400 repeats, but on a repeat-primed polymerase chain reaction (PCR), more than 32 repeats are often considered a pathogenic genotype (Beck et al., 2013).

C9orf72 HREs have been identified in nonmotor neurodegenerative phenotypes including Alzheimer's disease (AD) at frequencies of ~1% (Beck et al., 2013; Harms et al., 2013; Kohli et al., 2013; Majounie et al., 2012b), although conflicting reports exist in the literature (Rollinson et al., 2012; Xi et al., 2012).

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Disclosure statement

Ronald C. Petersen reports consultancies with Roche, Inc, Merck, Inc, Genentech, Inc, Biogen, Inc, and Eli Lilly. Brad F. Boeve reports GE Healthcare, FORUM Pharmaceuticals, and C2N Diagnostics as research support and advisory board member of the Tau Consortium. The remaining authors report no competing interests.

Dementia with Lewy bodies (DLB) accounts for 15%–25% of all dementia cases (Heidebrink, 2002). Its core features encompass cognitive impairment, fluctuating attention, parkinsonism, and recurrent visual hallucinations (Weisman and McKeith, 2007). Neuropathological diagnosis of DLB is achieved when the presence of Lewy bodies is confirmed in the cortex and the brainstem (McKeith et al., 2005). Little is known about the genetics of DLB, although molecular studies seem to point toward genetic overlaps with other neurodegenerative diseases, mainly with AD and Parkinson's disease (PD) (Bras et al., 2014; Guerreiro et al., 2016; Keogh et al., 2016; Meeus et al., 2012).

So far, the *C9orf72* repeat expansion has only been genotyped in small cohorts of ~100 DLB cases or less (Geiger et al., 2016; Lesage et al., 2013; Robinson et al., 2014; Snowden et al., 2012; Yeh et al., 2013). We have recently shown in a large cohort that *C9orf72* repeat expansions are not a common cause of DLB in pathologically diagnosed cases (Guerreiro et al., 2015). Here, we expand on these findings using a cohort of 1524 DLB cases.

2. Material and methods

Samples consisted of an international cohort of 1398 neuropathologically diagnosed DLB cases and 126 clinically diagnosed DLB cases (Supplementary Table 1). DNA was extracted from brain tissue for the neuropathologically diagnosed samples and from blood for the clinical diagnosed samples using standard procedures. We performed repeat-primed PCR according to Renton et al. (2011). Genotypes were assessed using Peak Scanner v2.0 (Applied Biosystems) with repeat expansions displaying a characteristic saw tooth pattern with a 6 base pair periodicity on analysis.

3. Results

Repeat mean number was 5.17 (± 4.30 standard deviation) ranging from 1 to 58. All except 5 samples presented less than 23 repeats in the repeat-primed PCR (Supplementary Fig. 1). Two neuropathologically diagnosed DLB samples showed 32 repeats and 1 showed 33 repeats; and 2 clinically diagnosed samples exhibited 33 and 58 repeats. These last 2 samples had been previously analyzed as part of the cohort published by Snowden et al. (2012).

4. Discussion

This is the first study genotyping the *C9orf72* HREs in a large cohort of mainly neuropathologically diagnosed DLB samples. Within the neuropathologically defined DLB cases, we did not find any HREs above the typical threshold for pathogenicity (~32 repeats). This is concordant with previous studies that found no repeat expansions in 34 clinically diagnosed cases of a Taiwanese cohort or in 111 pathological DLB cases (Geiger et al., 2016; Yeh et al., 2013). Snowden et al. (2012) found 2 cases with HREs greater than 30 repeats in a study that was comprised of 102 “probable DLB” blood samples. When the same group restricted their analysis to include only pathologically diagnosed samples, no pathogenic repeat expansions were identified (Robinson et al., 2014).

DLB is considered to be part of a spectrum between AD and PD (Weisman and McKeith, 2007) where large *C9orf72* HREs are not frequent. In AD, it was suggested that pathogenic repeat expansions may only be associated with late onset AD (Kohli et al., 2013) or that amnesic FTD (which is easily misdiagnosed as AD) could be responsible for the low frequencies observed for AD (Majounie et al., 2012b). In PD, there is no evidence for a role of *C9orf72* pathogenic repeat expansions (Majounie et al., 2012a; Xi et al., 2012).

Clinical symptoms in DLB can vary substantially from patient to patient and some can even overlap with less typical forms of FTD (Claassen et al., 2008), which could account for the pathogenic repeat expansions found in misdiagnosed DLB clinical cases. Furthermore, recent data suggest that the threshold for pathogenicity of HREs should be higher than the initially proposed 30 repeats (Xi et al., 2015).

In our cohort of neuropathologically diagnosed DLB samples, we found 3 cases with likely benign 32 and 33 repeats. Excluding the clinically diagnosed cases, we found no evidence of pathogenic repeat expansions. Even including the clinically diagnosed cohort, no extended repeat expansions were identified; with the longest allele exhibiting 58 repeats.

Our study shows that *C9orf72* pathogenic repeat expansions are not a common cause of DLB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.neurobiolaging.2016.08.023>.

References

- Beck J, Poulter M, Hensman D, Rohrer JD, Mahoney CJ, Adamson G, Campbell T, Uphill J, Borg A, Fratta P, Orrell RW, Malaspina A, Rowe J, Brown J, Hodges J, Sidle K, Polke JM, Houlden H, Schott JM, Fox NC, Rossor MN, Tabrizi SJ, Isaacs AM, Hardy J, Warren JD, Collinge J, Mead S. Large C9orf72 hexanucleotide repeat expansions are seen in multiple neurodegenerative syndromes

and are more frequent than expected in the UK population. *Am J Hum Genet.* 2013; 92(3):345–353. DOI: 10.1016/j.ajhg.2013.01.011 [PubMed: 23434116]

- Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, Pedraza O, Vemuri P, Jones D, Lowe V, Murray ME, Dickson DW, Josephs KA, Rush BK, Machulda MM, Fields JA, Ferman TJ, Baker M, Rutherford NJ, Adamson J, Wszolek ZK, Adeli A, Savica R, Boot B, Kuntz KM, Gavriloa R, Reeves A, Whitwell J, Kantarci K, Jack CR Jr, Parisi JE, Lucas JA, Petersen RC, Rademakers R. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. *Brain.* 2012; 135(Pt 3):765–783. DOI: 10.1093/brain/aws004 [PubMed: 22366793]
- Bras J, Guerreiro R, Darwent L, Parkkinen L, Ansorge O, Escott-Price V, Hernandez DG, Nalls MA, Clark LN, Honig LS, Marder K, Van Der Flier WM, Lemstra A, Scheltens P, Rogaeva E, St George-Hyslop P, Londos E, Zetterberg H, Ortega-Cubero S, Pastor P, Ferman TJ, Graff-Radford NR, Ross OA, Barber I, Braae A, Brown K, Morgan K, Maetzler W, Berg D, Troakes C, Al-Sarraj S, Lashley T, Compta Y, Revesz T, Lees A, Cairns N, Halliday GM, Mann D, Pickering-Brown S, Dickson DW, Singleton A, Hardy J. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. *Hum Mol Genet.* 2014; 23(23):6139–6146. DOI: 10.1093/hmg/ddu334 [PubMed: 24973356]
- Claassen DO, Parisi JE, Giannini C, Boeve BF, Dickson DW, Josephs KA. Frontotemporal dementia mimicking dementia with Lewy bodies. *Cogn Behav Neurol.* 2008; 21(3):157–163. DOI: 10.1097/WNN.0b013e3181864a09 [PubMed: 18797258]
- DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman H, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron.* 2011; 72(2):245–256. DOI: 10.1016/j.neuron.2011.09.011 [PubMed: 21944778]
- Geiger JT, Arthur KC, Dawson TM, Rosenthal LS, Pantelyat A, Albert M, Hillis AE, Crain B, Pletnikova O, Troncoso JC, Scholz SW. C9orf72 Hexanucleotide Repeat Analysis in Cases with Pathologically Confirmed Dementia with Lewy Bodies. *Neurodegener Dis.* 2016; 16(5–6):370–372. DOI: 10.1159/000445872 [PubMed: 27241037]
- Guerreiro R, Escott-Price V, Darwent L, Parkkinen L, Ansorge O, Hernandez DG, Nalls MA, Clark L, Honig L, Marder K, van der Flier W, Holstege H, Louwersheimer E, Lemstra A, Scheltens P, Rogaeva E, St George-Hyslop P, Londos E, Zetterberg H, Ortega-Cubero S, Pastor P, Ferman TJ, Graff-Radford NR, Ross OA, Barber I, Braae A, Brown K, Morgan K, Maetzler W, Berg D, Troakes C, Al-Sarraj S, Lashley T, Compta Y, Revesz T, Lees A, Cairns NJ, Halliday GM, Mann D, Pickering-Brown S, Powell J, Lunnon K, Lupton MK, International Parkinson's Disease Genomics, C. Dickson D, Hardy J, Singleton A, Bras J. Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases. *Neurobiol Aging.* 2016; 38:214 e217–214 e210. DOI: 10.1016/j.neurobiolaging.2015.10.028
- Guerreiro R, Kun-Rodrigues C, Darwent L, Orme T, Parkkinen L, Ansorge O, Clark L, Honig L, Marder K, van der Flier W, Lemstra A, Scheltens P, Rogaeva E, St George-Hyslop P, Londos E, Zetterberg H, Ortega-Cubero S, Pastor P, Barber I, Braae A, Brown K, Morgan K, Maetzler W, Berg D, Troakes C, Al-Sarraj S, Lashley T, Compta Y, Van Deerlin VM, Trojanowski JQ, Clarimon J, Lesage S, Galasko D, Masliah E, Tienari PJ, Revesz T, Lees A, Ferman TJ, Graff-Radford NR, Ross OA, Dickson D, Escott-Price V, Cairns N, Halliday G, Mann D, Pickering-Brown S, Singleton A, Hardy J, Bras J. C9ORF72 in a Large International Cohort of Neuropathologically diagnosed Dementia with Lewy Bodies Cases. *Am J Neurodegener Dis.* 2015; 4(Suppl 1):1–178. [PubMed: 26389015]
- Harms M, Benitez BA, Cairns N, Cooper B, Cooper P, Mayo K, Carrell D, Faber K, Williamson J, Bird T, Diaz-Arrastia R, Foroud TM, Boeve BF, Graff-Radford NR, Mayeux R, Chakraverty S, Goate AM, Cruchaga C, Consortium N.-L.N.F.S. C9orf72 hexanucleotide repeat expansions in clinical Alzheimer disease. *JAMA Neurol.* 2013; 70(6):736–741. DOI: 10.1001/2013.jamaneurol.537 [PubMed: 23588422]
- Heidebrink JL. Is dementia with Lewy bodies the second most common cause of dementia? *J Geriatr Psychiatry Neurol.* 2002; 15(4):182–187. [PubMed: 12489913]

- Hensman Moss DJ, Poulter M, Beck J, Hehir J, Polke JM, Campbell T, Adamson G, Mudanohwo E, McColgan P, Haworth A, Wild EJ, Sweeney MG, Houlden H, Mead S, Tabrizi SJ. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. *Neurology*. 2014; 82(4):292–299. DOI: 10.1212/WNL.000000000000061 [PubMed: 24363131]
- Keogh MJ, Kurzawa-Akanbi M, Griffin H, Douroudis K, Ayers KL, Hussein RI, Hudson G, Pyle A, Cordell HJ, Attems J, McKeith IG, O'Brien JT, Burn DJ, Morris CM, Thomas AJ, Chinnery PF. Exome sequencing in dementia with Lewy bodies. *Transl Psychiatry*. 2016; 6:e728.doi: 10.1038/tp.2015.220 [PubMed: 26836416]
- Kohli MA, John-Williams K, Rajbhandary R, Naj A, Whitehead P, Hamilton K, Carney RM, Wright C, Crocco E, Gwirtzman HE, Lang R, Beecham G, Martin ER, Gilbert J, Benatar M, Small GW, Mash D, Byrd G, Haines JL, Pericak-Vance MA, Zuchner S. Repeat expansions in the C9ORF72 gene contribute to Alzheimer's disease in Caucasians. *Neurobiol Aging*. 2013; 34(5):1519 e1515–1512. DOI: 10.1016/j.neurobiolaging.2012.10.003
- Lesage S, Le Ber I, Condroyer C, Broussolle E, Gabelle A, Thobois S, Pasquier F, Mondon K, Dion PA, Rochefort D, Rouleau GA, Durr A, Brice A, French Parkinson's Disease Genetics Study, G. C9orf72 repeat expansions are a rare genetic cause of parkinsonism. *Brain*. 2013; 136(Pt 2):385–391. DOI: 10.1093/brain/aws357 [PubMed: 23413259]
- Majounie E, Abramzon Y, Renton AE, Keller MF, Traynor BJ, Singleton AB. Large C9orf72 repeat expansions are not a common cause of Parkinson's disease. *Neurobiol Aging*. 2012a; 33(10):2527 e2521–2522. DOI: 10.1016/j.neurobiolaging.2012.05.007
- Majounie E, Abramzon Y, Renton AE, Perry R, Bassett SS, Pletnikova O, Troncoso JC, Hardy J, Singleton AB, Traynor BJ. Repeat expansion in C9ORF72 in Alzheimer's disease. *N Engl J Med*. 2012b; 366(3):283–284. DOI: 10.1056/NEJMc1113592 [PubMed: 22216764]
- Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, Chio A, Restagno G, Nicolaou N, Simon-Sanchez J, van Swieten JC, Abramzon Y, Johnson JO, Sendtner M, Pamphlett R, Orrell RW, Mead S, Sidle KC, Houlden H, Rohrer JD, Morrison KE, Pall H, Talbot K, Ansorge O, Chromosome, A.L.S.F.T.D.C., French research network on, F.F.A., Consortium, I. Hernandez DG, Arepalli S, Sabatelli M, Mora G, Corbo M, Giannini F, Calvo A, Englund E, Borghero G, Floris GL, Remes AM, Laaksovirta H, McCluskey L, Trojanowski JQ, Van Deerlin VM, Schellenberg GD, Nalls MA, Drory VE, Lu CS, Yeh TH, Ishiura H, Takahashi Y, Tsuji S, Le Ber I, Brice A, Drepper C, Williams N, Kirby J, Shaw P, Hardy J, Tienari PJ, Heutink P, Morris HR, Pickering-Brown S, Traynor BJ. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol*. 2012c; 11(4):323–330. DOI: 10.1016/S1474-4422(12)70043-1 [PubMed: 22406228]
- McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londo E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M, Consortium on, D.L.B. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005; 65(12):1863–1872. DOI: 10.1212/01.wnl.0000187889.17253.b1 [PubMed: 16237129]
- Meeus B, Verstraeten A, Crosiers D, Engelborghs S, Van den Broeck M, Mattheijssens M, Peeters K, Corsmit E, Elinck E, Pickut B, Vandenberghe R, Cras P, De Deyn PP, Van Broeckhoven C, Theuns J. DLB and PDD: a role for mutations in dementia and Parkinson disease genes? *Neurobiol Aging*. 2012; 33(3):629 e625–629 e618. DOI: 10.1016/j.neurobiolaging.2011.10.014
- Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes AM, Kaganovich A, Scholz SW, Duckworth J, Ding J, Harmer DW, Hernandez DG, Johnson JO, Mok K, Ryten M, Trabzuni D, Guerreiro RJ, Orrell RW, Neal J, Murray A, Pearson J, Jansen IE, Sondervan D, Seelaar H, Blake D, Young K, Halliwell N, Callister JB, Toulson G, Richardson S, Gerhard A, Snowden J, Mann D, Neary D, Nalls MA, Peuralinna T, Jansson L, Isoviita VM, Kaivorinne AL, Holtta-Vuori M, Ikonen E, Sulkava R, Benatar M, Wu J, Chio A, Restagno G, Borghero G, Sabatelli M, Consortium I. Heckerman D, Rogaeva E, Zinman L, Rothstein JD, Sendtner M, Drepper C, Eichler EE, Alkan C, Abdullaev Z, Pack SD, Dutra A, Pak E, Hardy J, Singleton A, Williams NM, Heutink P, Pickering-Brown S, Morris HR, Tienari PJ, Traynor BJ. A

- hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011; 72(2):257–268. DOI: 10.1016/j.neuron.2011.09.010 [PubMed: 21944779]
- Robinson A, Davidson Y, Snowden JS, Mann DM. C9ORF72 in dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*. 2014; 85(12):1435–1436. DOI: 10.1136/jnnp-2014-307622 [PubMed: 24648039]
- Rollinson S, Halliwell N, Young K, Callister JB, Toulson G, Gibbons L, Davidson YS, Robinson AC, Gerhard A, Richardson A, Neary D, Snowden J, Mann DM, Pickering-Brown SM. Analysis of the hexanucleotide repeat in C9ORF72 in Alzheimer's disease. *Neurobiol Aging*. 2012; 33(8):1846 e1845–1846. DOI: 10.1016/j.neurobiolaging.2012.01.109
- Simon-Sanchez J, Dopper EG, Cohn-Hokke PE, Hukema RK, Nicolaou N, Seelaar H, de Graaf JR, de Koning I, van Schoor NM, Deeg DJ, Smits M, Raaphorst J, van den Berg LH, Schelhaas HJ, De Die-Smulders CE, Majoor-Krakauer D, Rozemuller AJ, Willemsen R, Pijnenburg YA, Heutink P, van Swieten JC. The clinical and pathological phenotype of C9ORF72 hexanucleotide repeat expansions. *Brain*. 2012; 135(Pt 3):723–735. DOI: 10.1093/brain/awr353 [PubMed: 22300876]
- Snowden JS, Rollinson S, Lafon C, Harris J, Thompson J, Richardson AM, Jones M, Gerhard A, Neary D, Mann DM, Pickering-Brown S. Psychosis, C9ORF72 and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*. 2012; 83(10):1031–1032. DOI: 10.1136/jnnp-2012-303032 [PubMed: 22832738]
- van der Zee J, Gijssels 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, Pernecky R, Diehl-Schmid J, de Mendonca A, Miltenberger-Miltenyi G, Pereira S, Pimentel J, Nacmias B, Bagnoli S, Sorbi S, Graff C, Chiang HH, Westerlund M, Sanchez-Valle R, Llado A, Gelpi E, Santana I, Almeida MR, Santiago B, Frisoni G, Zanetti O, Bonvicini C, Synofzik M, Maetzler W, Vom Hagen JM, Schols L, Heneka MT, Jessen F, Matej R, Parobkova E, Kovacs GG, Strobel T, Sarafov S, Tournev I, Jordanova A, Danek A, Arzberger T, Fabrizi GM, Testi S, Salmon E, Santens P, Martin JJ, Cras P, Vandenberghe R, De Deyn PP, Cruts M, Van Broeckhoven C, van der Zee J, Gijssels I, Dillen L, Van Langenhove T, Theuns J, Philtjens S, Sleegers K, Baumer V, Maes G, Corsmit E, Cruts M, Van Broeckhoven C, van der Zee J, Gijssels I, Dillen L, Van Langenhove T, Philtjens S, Theuns J, Sleegers K, Baumer V, Maes G, Cruts M, Van Broeckhoven C, Engelborghs S, De Deyn PP, Cras P, Engelborghs S, De Deyn PP, Vandenbulcke M, Vandenbulcke M, Borroni B, Padovani A, Archetti S, Pernecky R, Diehl-Schmid J, Synofzik M, Maetzler W, Muller Vom Hagen J, Schols L, Synofzik M, Maetzler W, Muller Vom Hagen J, Schols L, Heneka MT, Jessen F, Ramirez A, Kurzwelley D, Sachtleben C, Mairer W, de Mendonca A, Miltenberger-Miltenyi G, Pereira S, Firmo C, Pimentel J, Sanchez-Valle R, Llado A, Antonell A, Molinuevo J, Gelpi E, Graff C, Chiang HH, Westerlund M, Graff C, Kinhult Stahlbom A, Thonberg H, Nennesmo I, Borjesson-Hanson A, Nacmias B, Bagnoli S, Sorbi S, Bessi V, Piaceri I, Santana I, Santiago B, Santana I, Helena Ribeiro M, Rosario Almeida M, Oliveira C, Massano J, Garret C, Pires P, Frisoni G, Zanetti O, Bonvicini C, Sarafov S, Tournev I, Jordanova A, Tournev I, Kovacs GG, Strobel T, Heneka MT, Jessen F, Ramirez A, Kurzwelley D, Sachtleben C, Mairer W, Jessen F, Matej R, Parobkova E, Danel A, Arzberger T, Maria Fabrizi G, Testi S, Ferrari S, Cavallaro T, Salmon E, Santens P, Cras P, European Early-Onset Dementia, C. A pan-European study of the C9orf72 repeat associated with FTLN: geographic prevalence, genomic instability, and intermediate repeats. *Hum Mutat*. 2013; 34(2):363–373. DOI: 10.1002/humu.22244 [PubMed: 23111906]
- Weisman D, McKeith I. Dementia with Lewy bodies. *Semin Neurol*. 2007; 27(1):42–47. DOI: 10.1055/s-2006-956754 [PubMed: 17226740]
- Xi Z, Zhang M, Bruni AC, Maletta RG, Colao R, Fratta P, Polke JM, Sweeney MG, Mudanohwo E, Nacmias B, Sorbi S, Tartaglia MC, Rainero I, Rubino E, Pinessi L, Galimberti D, Surace EI, McGoldrick P, McKeever P, Moreno D, Sato C, Liang Y, Keith J, Zinman L, Robertson J, Rogaeva E. The C9orf72 repeat expansion itself is methylated in ALS and FTLN patients. *Acta Neuropathol*. 2015; 129(5):715–727. DOI: 10.1007/s00401-015-1401-8 [PubMed: 25716178]
- Xi Z, Zinman L, Grinberg Y, Moreno D, Sato C, Bilbao JM, Ghani M, Hernandez I, Ruiz A, Boada M, Moron FJ, Lang AE, Marras C, Bruni A, Colao R, Maletta RG, Puccio G, Rainero I, Pinessi L, Galimberti D, Morrison KE, Moorby C, Stockton JD, Masellis M, Black SE, Hazrati LN, Liang Y, van Haersma de With J, Fornazzari L, Villagra R, Rojas-Garcia R, Clarimon J, Mayeux R, Robertson J, St George-Hyslop P, Rogaeva E. Investigation of c9orf72 in 4 neurodegenerative

disorders. *Arch Neurol.* 2012; 69(12):1583–1590. DOI: 10.1001/archneurol.2012.2016 [PubMed: 22964832]

Yeh TH, Lai SC, Weng YH, Kuo HC, Wu-Chou YH, Huang CL, Chen RS, Chang HC, Traynor B, Lu CS. Screening for C9orf72 repeat expansions in parkinsonian syndromes. *Neurobiol Aging.* 2013; 34(4):1311 e1313–1314. DOI: 10.1016/j.neurobiolaging.2012.09.002

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