Table 1
Frequencies of ALS patients with *C9orf72* and *SOD1* mutations in different countries

Study	Population	*C9orf72*			*SOD1*	
		Familial ALS	Sporadic ALS	Mean AAO (range), years	Familial ALS	Sporadic ALS
This study, 2012	Japanese (JaCALS)	0% (0/11)	0.4% (2/552)	64.7 (57–72)	NA	NA
Akimoto et al. (2011)	Japanese (JaCALS)	NA	NA	NA	NA	1.6% (4/255)
DeJesus-Hernandez et al. (2011)	Mixed[a]	23.5% (8/34)	4.1% (8/195)***	54.5 (41–72)	11.8% (4/34)	0% (0/195)
Renton et al. (2011)	Finish	46.4% (52/112)**	21.0% (61/290)***	53 (30–71)	NA	NA
Gijselinck et al. (2012)	Flanders-Belgian	46.7% (7/15)*	4.9% (6/122)***	54.5 (38–64)	0% (0/16)	0% (0/125)
Stewart et al. (2012)	Unknown[b]	27.4% (17/62)	3.6% (6/169)**	58.2 (39–82)	Total 8.2% (19/231)	
Byrne et al. (2012)	Ireland	40.8% (20/49)*	4.9% (19/386)***	56.3 (NA)	Total 0% (0/191)	
Cooper-Knock et al. (2012)	Northern England	42.9% (27/63)*	7.0% (35/500)***	57.3 (27–74)	Total 2.5% (14/563)	
Chiò et al. (2012)	Italian	37.5% (45/120)*	NA	59.0 (NA-80)	0% (0/141)	NA
	Sardinian	57.1% (12/21)**	NA	60.4 (NA)	NA	NA
	German	22.0% (9/41)	NA	56.4 (NA)	NA	NA
Majounie et al. (2012)	England	45.9% (45/98)**	6.8% (62/916)***	NA	NA	NA
	German	21.7% (15/69)	5.2% (22/421)***	NA	NA	NA
	Italian	37.8% (34/90)*	4.1% (19/465)***	NA	NA	NA
	Sardinian	57.9% (11/19)**	7.8% (10/129)***	NA	NA	NA
	USA White	US total 36.2% (59/163)*	5.4% (48/890)***	NA	NA	NA
	USA Hispanic		8.3% (6/72)***	NA	NA	NA
	USA Black		4.1% (2/49)	NA	NA	NA
	Australian	NA	5.3% (14/263)***	NA	NA	NA
	Israeli	21.4% (3/14)	NA	NA	NA	NA
	Indian	NA	0% (0/31)	NA	NA	NA
	Asian	5.0% (1/20)	0% (0/238)	NA	NA	NA
	Pacific islander/Guam	NA	0% (0/90)	NA	NA	NA
Sabatelli et al. (2012)	Italian	NA	3.7% (60/1624)***	58.6 (49–65)	NA	NA
	Sardinian	NA	6.8% (9/133)***	62.9 (58–63)	NA	NA

Key: AAO, age at onset; ALS, amyotrophic lateral sclerosis; JaCALS, Japanese Consortium of Amyotrophic Lateral Sclerosis Research; NA, not available.
[a] Mixed included 229 ALS patients from Mayo Clinic, Florida: White (212), Asian (1), Pacific Islander (1), and Black or African American (15).
[b] Unknown included 231 ALS patients from the ALS Clinic of Vancouver Coastal Health and the University of British Columbia (Vancouver General Hospital and GF Strong Rehabilitation Centre sites).
* $p < 0.05$, compared with our results (2-tailed, Yates's χ^2 test).
** $p < 0.01$, compared with our results (2-tailed, Yates's χ^2 test).
***$p < 0.001$ compared with our results (2-tailed, Yates's χ^2 test).

3.2.4. Subject B-II (family B)

Subject B-II, a sibling of Patient B-I, had a *C9orf72* mutation but did not have symptoms of dementia or motor neuron disease until age 76 (Fig. 1).

4. Discussion

We began this study considering patients without family histories of ALS to be SALS because our cohort included only family histories of ALS but not FTD or PPA. Although it may be difficult to describe the real frequency in SALS because 1 of the SALS patients had a family member who developed PPA, the frequencies of the *C9orf72* mutation in Japanese patients were 0.4% (2/552) in SALS and 0% (0/11) in FALS according to this classification. In contrast, the frequencies of the *C9orf72* mutation fall within the ranges of 21%–57% in FALS and 3%–21% in SALS in Western populations (Table 1), and the *C9orf72* mutation has been reported as the most common genetic cause of FALS and SALS in Western populations (Byrne et al., 2012; Chiò et al., 2012; Cooper-Knock et al., 2012; DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012; Majounie et al., 2012; Renton et al., 2011; Sabatelli et al., 2012; Stewart et al., 2012). However, the *C9orf72* mutation in this study was not more frequent than the *SOD1* mutation in Japanese SALS patients (0.4% and 1.6%, Table 1) (Akimoto et al., 2011). Considering these data, the *C9orf72* mutation is more common than the *SOD1* mutation in Western populations but not in Japan, suggesting different genetic backgrounds. Our results may explain the association study of rs2814707 on 9p21.2, which was reported to be the most significantly associated SNP with SALS in Caucasian but not in Japanese and Chinese populations (Iida et al., 2011). A recent report revealed that the rate of expansion in Asian FALS and SALS was 5% (1/20) and 0% (0/238), respectively (Majounie et al., 2012). An analysis of the SNPs on chromosome 9p revealed that all 4 subjects with the *C9orf72* mutation and another Japanese subject from the previously mentioned report (Majounie et al., 2012) share a shorter region of the risk haplotype

than Western populations. Thus, the haplotype bearing the *C9orf72* mutation was only shared in a narrow region between Western and Asian populations, suggesting that the *C9orf72* mutation may be an old mutation in human migration history from Western to East Asia. This mutation was estimated to be approximately 1500 years old (Majounie et al., 2012).

Bulbar onset and cognitive impairment have been reported to be more common in ALS patients with the *C9orf72* repeat expansion (Chiò et al., 2012; Cooper-Knock et al., 2012; DeJesus-Hernandez et al., 2011; Sabatelli et al., 2012; Stewart et al., 2012). We did not find any patients with bulbar onset, but we identified 2 patients with dementia. Although the age at onset has been known to be lower in SALS patients with the *C9orf72* mutation than in those without this mutation (Sabatelli et al., 2012), our patients exhibited a relatively older age at onset (Table 1).

Although apparently sporadic patients with *C9orf72* mutation have been detected worldwide (Byrne et al., 2012; Cooper-Knock et al., 2012; Sabatelli et al., 2012), it was not known whether this phenomenon was due to incomplete penetrance or to spontaneous expansion of the GGGGCC hexanucleotide repeat from a nonpathogenic parental form (ie, a de novo expansion). In this study, we found a 76-year-old healthy individual with a *C9orf72* mutation (Subject B-II), as described in previous studies (Majounie et al., 2012; Renton et al., 2011). This discovery suggests not de novo expansion but incomplete penetrance, which explains the existence of apparently sporadic patients with the *C9orf72* mutation. Although it has been reported that the penetrance of the *C9orf72* mutation is almost full by 80 years by Kaplan–Meier analysis of 603 mutant gene carriers and 5 neurologically healthy individuals, further studies of family members of patients with the *C9orf72* mutation will be required to calculate the true penetrance and to improve genetic counseling.

Finally, we found a PPA patient with the *C9orf72* mutation after detecting the mutation in a SALS patient, suggesting the importance of collecting information regarding whether SALS patients have a family history of dementia or aphasia. Therefore, the possibility of *C9orf72* mutation should be investigated when clinicians meet with SALS patients after determining their family histories of FTD or PPA. Furthermore, our data supported Byrne and colleagues' suggestion that a family history of FTD should also be included in the revised definition of FALS (Byrne et al., 2012).

Disclosure statement

All of the authors disclose no conflicts of interest. The study was approved by the ethical committees of the participating centers. All participants gave written informed consent.

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Appendix A. Members of the Japanese Consortium for Amyotrophic Lateral Sclerosis Research (JaCALS)

Dr. Mitsuya Morita, Dr. Imaharu Nakano (Division of Neurology, Department of Internal Medicine, Jichi Medical University); Dr. Masashi Aoki (Department of Neurology, Tohoku University School of Medicine); Dr. Koichi Mizoguchi (Department of Neurology, Shizuoka Institute of Epilepsy and Neurological Disorders); Dr. Kazuko Hasegawa (Division of Neurology, National Hospital Organization, Sagamihara National Hospital); Dr. Akihiro Kawata (Department of Neurology, Tokyo Metropolitan Neurological Hospital); Dr. Ikuko Aiba (Department of Neurology, National Hospital Organization Higashinagoya National Hospital); Dr. Takashi Imai (Division of Neurology, National Hospital Organization, Miyagi National Hospital); Dr. Koichi Okamoto (Department of Neurology, Gunma University Graduate School of Medicine); Dr. Koji Abe (Department of Neurology, Okayama University Graduate School of Medicine); and Dr. Hirohisa Watanabe, Dr. Mizuki Ito, Dr. Jo Senda (Department of Neurology, Nagoya University Graduate School of Medicine).

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2012.05.011.

References

Akimoto, C., Morita, M., Atsuta, N., Sobue, G., Nakano, I., 2011. High-Resolution Melting (HRM) Analysis of the Cu/Zn Superoxide Dismutase (SOD1) Gene in Japanese Sporadic Amyotrophic Lateral Sclerosis (SALS) Patients. Neurol. Res. Int. 2011, 165415.

Brooks, B.R., Miller, R.G., Swash, M., Munsat, T.L., 2000. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Other Mot. Neuron Disord. 1, 293–299.

Byrne, S., Elamin, M., Bede, P., Shatunov, A., Walsh, C., Corr, B., Heverin, M., Jordan, N., Kenna, K., Lynch, C., McLaughlin, R.L., Iyer, P.M., O'Brien, C., Phukan, J., Wynne, B., Bokde, A.L., Bradley, D.G., Pender, N., Al-Chalabi, A., Hardiman, O., 2012. Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study. Lancet Neurol. 11, 232–240.

Chiò, A., Borghero, G., Restagno, G., Mora, G., Drepper, C., Traynor, B.J., Sendtner, M., Brunetti, M., Ossola, I., Calvo, A., Pugliatti, M., Sotgiu, M.A., Murru, M.R., Marrosu, M.G., Marrosu, F., Marinou, K., Mandrioli, J., Sola, P., Caponnetto, C., Mancardi, G., Mandich, P., La Bella, V., Spataro, R., Conte, A., Monsurrò, M.R., Tedeschi, G., Pisano, F., Bartolomei, I., Salvi, F., Lauria Pinter, G., Simone, I., Logroscino, G., Gambardella, A., Quattrone, A., Lunetta, C., Volanti, P., Zollino, M., Penco, S., Battistini, S., Renton, A.E., Majounie, E., Abramzon, Y., Conforti, F.L., Giannini, F., Corbo, M., Sabatelli, M., ITALSGEN consortium, 2012. Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of C9ORF72. Brain 135, 784–793.

Cooper-Knock, J., Hewitt, C., Highley, J.R., Brockington, A., Milano, A., Man, S., Martindale, J., Hartley, J., Walsh, T., Gelsthorpe, C., Baxter, L., Forster, G., Fox, M., Bury, J., Mok, K., McDermott, C.J., Traynor, B.J., Kirby, J., Wharton, S.B., Ince, P.G., Hardy, J., Shaw, P.J., 2012. Clinico-pathological features in amyotrophic lateral sclerosis with expansions in C9ORF72. Brain 135, 751–764.

DeJesus-Hernandez, M., Mackenzie, I.R., Boeve, B.F., Boxer, A.L., Baker, M., Rutherford, N.J., Nicholson, A.M., Finch, N.A., Flynn, H., Adamson, J., Kouri, N., Wojtas, A., Sengdy, P., Hsiung, G.Y., Karydas, A., Seeley, W.W., Josephs, K.A., Coppola, G., Geschwind, D.H., Wszolek, Z.K., Feldman, H., Knopman, D.S., Petersen, R.C., Miller, B.L., Dickson, D.W., Boylan, K.B., Graff-Radford, N.R., Rademakers, R., 2011. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. Neuron 72, 245–256.

Deng, H.X., Chen, W., Hong, S.T., Boycott, K.M., Gorrie, G.H., Siddique, N., Yang, Y., Fecto, F., Shi, Y., Zhai, H., Jiang, H., Hirano, M., Rampersaud, E., Jansen, G.H., Donkervoort, S., Bigio, E.H., Brooks, B.R., Ajroud, K., Sufit, R.L., Haines, J.L., Mugnaini, E., Pericak-Vance, M.A., Siddique, T., 2011. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature 477, 211–215.

Gijselinck, I., Van Langenhove, T., van der Zee, J., Sleegers, K., Philtjens, S., Kleinberger, G., Janssens, J., Bettens, K., Van Cauwenberghe, C., Pereson, S., Engelborghs, S., Sieben, A., De Jonghe, P., Vandenberghe, R., Santens, P., De Bleecker, J., Maes, G., Bäumer, V., Dillen, L., Joris, G., Cuijt, I., Corsmit, E., Elinck, E., Van Dongen, J., Vermeulen, S., Van den Broeck, M., Vaerenberg, C., Mattheijssens, M., Peeters, K., Robberecht, W., Cras, P., Martin, J.J., De Deyn, P.P., Cruts, M., Van Broeckhoven, C., 2012. A C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. Lancet Neurol. 11, 54–65.

Iida, A., Takahashi, A., Deng, M., Zhang, Y., Wang, J., Atsuta, N., Tanaka, F., Kamei, T., Sano, M., Oshima, S., Tokuda, T., Morita, M., Akimoto, C., Nakajima, M., Kubo, M., Kamatani, N., Nakano, I., Sobue, G., Nakamura, Y., Fan, D., Ikegawa, S., 2011. Replication analysis of SNPs on 9p21.2 and 19p13.3 with amyotrophic lateral sclerosis in East Asians. Neurobiol. Aging 32, e713–e754.

International HapMap Consortium, 2003. The International HapMap Project. Nature 426, 789–796.

Laaksovirta, H., Peuralinna, T., Schymick, J.C., Scholz, S.W., Lai, S.L., Myllykangas, L., Sulkava, R., Jansson, L., Hernandez, D.G., Gibbs, J.R., Nalls, M.A., Heckerman, D., Tienari, P.J., Traynor, B.J., 2010. Chromosome 9p21 in amyotrophic lateral sclerosis in Finland: a genome-wide association study. Lancet Neurol. 9, 978–985.

Lomen-Hoerth, C., Anderson, T., Miller, B., 2002. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. Neurology 59, 1077–1079.

Majounie, E., Renton, A.E., Mok, K., Dopper, E.G., Waite, A., Rollinson, S., Chiò, A., Restagno, G., Nicolaou, N., Simon-Sanchez, J., van Swieten, J.C., Abramzon, Y., Johnson, J.O., Sendtner, M., Pamphlett, R., Orrell, R.W., Mead, S., Sidle, K.C., Houlden, H., Rohrer, J.D., Morrison, K.E., Pall, H., Talbot, K., Ansorge, O., Hernandez, D.G., Arepalli, S., Sabatelli, M., Mora, G., Corbo, M., Giannini, F., Calvo, A., Englund, E., Borghero, G., Floris, G.L., Remes, A.M., Laaksovirta, H., McCluskey, L., Trojanowski, J.Q., Van Deerlin, V.M., Schellenberg, G.D., Nalls, M.A., Drory, V.E., Lu, C.S., Yeh, T.H., Ishiura, H., Takahashi, Y., Tsuji, S., Le Ber, I., Brice, A., Drepper, C., Williams, N., Kirby, J., Shaw, P., Hardy, J., Tienari, P.J., Heutink, P., Morris, H.R., Pickering-Brown, S., Traynor, B.J., Chromosome 9-ALS/FTD Consortium; French research network on FTLD/FTLD/ALS; ITALSGEN Consortium, 2012. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 11, 323–330.

Mok, K., Traynor, B.J., Schymick, J., Tienari, P.J., Laaksovirta, H., Peuralinna, T., Myllykangas, L., Chiò, A., Shatunov, A., Boeve, B.F., Boxer, A.L., DeJesus-Hernandez, M., Mackenzie, I.R., Waite, A., Williams, N., Morris, H.R., Simon-Sanchez, J., van Swieten, J.C., Heutink, P., Restagno, G., Mora, G., Morrison, K.E., Shaw, P.J., Rollinson, P.S., Al-Chalabi, A., Rademakers, R., Pickering-Brown, S., Orrell, R.W., Nalls, M.A., Hardy, J., 2012. The chromosome 9 ALS and FTD locus is probably derived from a single founder. Neurobiol. Aging 33, e3–e8.

Neumann, M., Sampathu, D.M., Kwong, L.K., Truax, A.C., Micsenyi, M.C., Chou, T.T., Bruce, J., Schuck, T., Grossman, M., Clark, C.M., McCluskey, L.F., Miller, B.L., Masliah, E., Mackenzie, I.R., Feldman, H., Feiden, W., Kretzschmar, H.A., Trojanowski, J.Q., Lee, V.M., 2006. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314, 130–133.

Renton, A.E., Majounie, E., Waite, A., Simón-Sánchez, J., Rollinson, S., Gibbs, J.R., Schymick, J.C., Laaksovirta, H., van Swieten, J.C., Myllykangas, L., Kalimo, H., Paetau, A., Abramzon, Y., Remes, A.M., Kaganovich, A., Scholz, S.W., Duckworth, J., Ding, J., Harmer, D.W., Hernandez, D.G., Johnson, J.O., Mok, K., Ryten, M., Trabzuni, D., Guerreiro, R.J., Orrell, R.W., Neal, J., Murray, A., Pearson, J., Jansen, I.E., Sondervan, D., Seelaar, H., Blake, D., Young, K., Halliwell, N., Callister, J.B., Toulson, G., Richardson, A., Gerhard, A., Snowden, J., Mann, D., Neary, D., Nalls, M.A., Peuralinna, T., Jansson, L., Isoviita, V.M., Kaivorinne, A.L., Holtta-Vuori, M., Ikonen, E., Sulkava, R., Benatar, M., Wuu, J., Chiò, A., Restagno, G., Borghero, G., Sabatelli, M., Heckerman, D., Rogaeva, E., Zinman, L., Rothstein, J.D., Sendtner, M., Drepper, C., Eichler, E.E., Alkan, C., Abdullaev, Z., Pack, S.D., Dutra, A., Pak, E., Hardy, J., Singleton, A., Williams, N.M., Heutink, P., Pickering-Brown, S., Morris, H.R., Tienari, P.J., Traynor, B.J., ITALSGEN Consortium, 2011. A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. Neuron 72, 257–268.

Sabatelli, M., Conforti, F.L., Zollino, M., Mora, G., Monsurrò, M.R., Volanti, P., Marinou, K., Salvi, F., Corbo, M., Giannini, F., Battistini, S., Penco, S., Lunetta, C., Quattrone, A., Gambardella, A., Logroscino, G., Simone, I., Bartolomei, I., Pisano, F., Tedeschi, G., Conte, A., Spataro, R., La Bella, V., Caponnetto, C., Mancardi, G., Mandich, P., Sola, P., Mandrioli, J., Renton, A.E., Majounie, E., Abramzon, Y., Marrosu, F., Marrosu, M.G., Murru, M.R., Sotgiu, M.A., Pugliatti, M., Rodolico, C., ITALSGEN Consortium, Moglia, C., Calvo, A., Ossola, I., Brunetti, M., Traynor, B.J., Borghero, G., Restagno, G., Chiò, A., 2012. C9ORF72 hexanucleotide repeat expansions in the Italian sporadic ALS population. Neurobiol. Aging, 33, e15-e20.

Stewart, H., Rutherford, N.J., Briemberg, H., Krieger, C., Cashman, N., Fabros, M., Baker, M., Fok, A., DeJesus-Hernandez, M., Eisen, A., Rademakers, R., Mackenzie, I.R., 2012. Clinical and pathological features of amyotrophic lateral sclerosis caused by mutation in the C9ORF72 gene on chromosome 9p. Acta Neuropathol. 123, 409–417.

Ticozzi, N., Tiloca, C., Morelli, C., Colombrita, C., Poletti, B., Doretti, A., Maderna, L., Messina, S., Ratti, A., Silani, V., 2011. Genetics of familial Amyotrophic lateral sclerosis. Arch. Ital. Biol. 149, 65–82.

Valdmanis, P.N., Daoud, H., Dion, P.A., Rouleau, G.A., 2009. Recent advances in the genetics of amyotrophic lateral sclerosis. Curr. Neurol. Neurosci. Rep. 9, 198–205.