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Letter to the Editor

Two mutations, one family: C9orf72 and SQSTM1 in neurodegenerative diseases

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Dear Editor,

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with minimally known etiology. The disease is phenotypically associated with frontotemporal dementia, FTD [1,2] presenting as ALS-FTD. C9orf72 has been associated with ALS and FTD, and the manifestation of either disease is partially dependent on the number of repeat expansions [3]. Genetic investigations in ALS have also identified the SQSTM1 mutation to be associated with the disease [1,4]. SQSTM1 encodes the SQSTM1/p62 a cargo protein that assists in the assembly of autophagosomes, and mutations implies impaired autophagy and toxic buildup of intracellular substances as proposed mechanisms in ALS-FTD in the C9orf72 pathway [5]. SQSTM1 is also a genetic mutation that is implicated in the pathogenesis in Paget's disease, and is only newly observed in ALS patients [4]. In mice, a decreased expression of C9orf72 shows an increase in the aggregation of SQSTM1, and the ensuing cellular dysfunction is mediated by toxic build-up of ATXN2 intermediate repeats [6]. Almeida et al. explored the connections between the two mutations, Paget's Bone Disease, and FTD. They found that FTD could be caused by both genes and it is possible that the expressivity of each gene's mutation could potentially influence the severity of disease [7]. Here, we present a case of a patient with ALS-FTD shown to carry both SQSTM1 and C9orf72 mutations, both showing autosomal dominant inheritance with incomplete penetrance.

2. Methods

Medical records of the patient and all family members who received care were reviewed for any reported neuromuscular or cognitive impairment. Neurodegenerative diagnostic criteria included in the grouping of neurodegeneration found in medical records were: variations of clinically documented dementia (early onset Alzheimer's disease (AD), advanced AD, FTD) and ALS. These designations were taken from pathology reports.

2.1. Case presentation

P_0 presented to a neurologist for progressive left leg weakness, foot drop, and multiple falls over a period of 6 months at the age of 63. He had developed hypertension, mild essential tremor, depression, and anxiety. He smoked one pack per day and rarely consumed alcohol. His older brother was a patient of the neurology clinic and had been diagnosed with ALS at the age of 48. Magnetic resonance imaging (MRI) of brain with and without contrast showed a generalized atrophy, nonspecific small white matter hyperintensities, and no other abnormalities. Electromyography (EMG) and nerve conduction studies (NCS), showed evidence of a severe generalized axonal peripheral neuropathy predominantly affecting the axons of motor nerves. A limited EMG suggested a superimposed left L1-S5 radiculopathy, as demonstrated by moderate spontaneous activity of the left tibialis anterior and mild spontaneous activity of both the left gastrocnemius and left paraspinal muscles at L5 and S1. Six months later, another EMG/NCS was done of the bilateral upper extremities and showed active denervation throughout muscle groups of the arms, forearms, and mid-thoracic paraspinal muscles. Also noted were diffuse chronic denervation changes, including the tongue and orbicularis oris. Over the next few months, his symptoms progressed to include dysarthria, drooling, and progressive bilateral leg weakness. His behavior became more disinhibited and he lacked the ability to plan. Eventually this cognitive decline progressed to a point where he required the assistance of a caretaker.

An ALS genetic panel was ordered, and the patient had the following gene mutations: hexanucleotide C9orf72 and SQSTM1. His C9orf72 mutation (mRNA, NM_001256054.2) had a repeat expansion > 35 GGGGCC repeats. His SQSTM1 gene mutation (NM_003900.4) included the variant p.K238E, with an expansion 712A > G, with no evidence of Paget's disease or the mutation p.P392L.

Notable findings include P_0 father and five of nine of his father's siblings having a documented neurodegenerative disease, shown in Fig. 1. Pathology records upon death were not available for three paternal family members. There were no neurodegenerative diseases described in P_0's maternal family medical records.

P_0's health continued to deteriorate over the next year, until he finally succumbed to ALS. His brother had lived with ALS for approximately 6 years. He died at the age of 52. The other family members have also died, with the exception of their sister.

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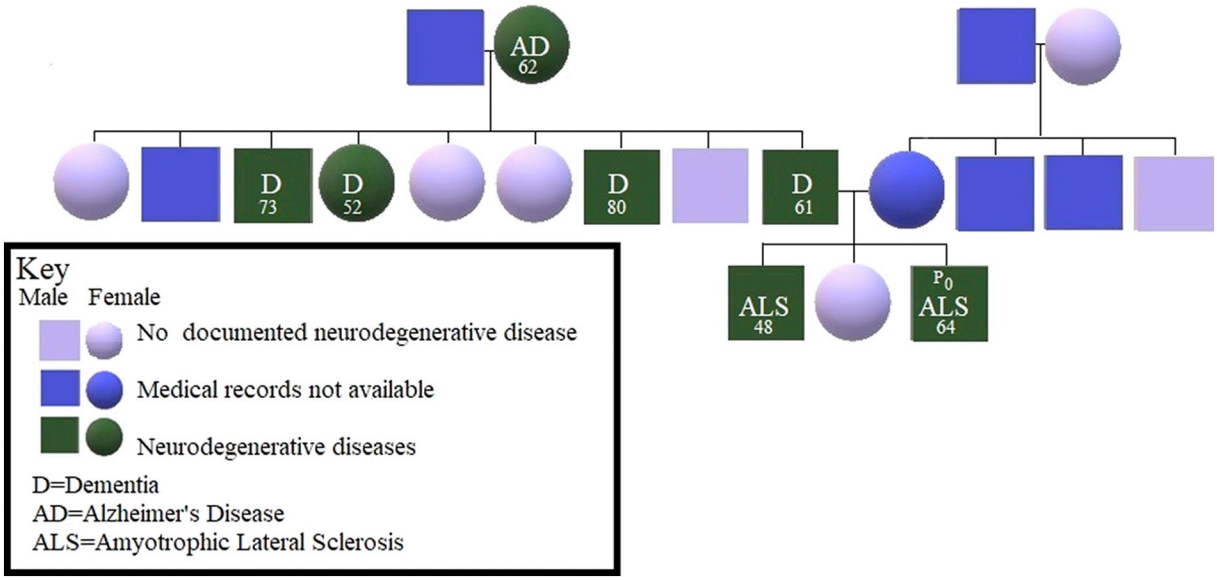

Fig. 1. Genogram of ALS-FTD Patient, P_0. All patients are deceased, with the exception of P_0's sister. The numbers below the letter are the age of onset for the neurodegenerative patients.

2.2. Discussion/conclusion

The presented patient P_0 was confirmed to carry both C9orf72 and SQSTM1 mutations which, to date, have yet to be described in the same family of patients. It is unclear to what degree the SQSTM1 and C9orf72 mutations contribute to the expression of the ALS-FTD phenotype in P_0, but it has been shown via mouse model and ALS/FTD patient's induced pluripotent stem cells, that the loss of function of C9ORF72 leads to the susceptibility neurodegenerative damage and glutamate receptor injury [8]. SQSTM1 may be related to the dampened or loss of expression of oxidative response genes [9]. In retrospect, the non-specific white matter changes initially reported on the Brain MRI of P_0 may, on careful inspection, reflect the more patterned white matter changes reportedly associated with C9orf72 [10]. It is possible that the combined effects of the two mutations result in full penetrance of ALS-FTD spectrum, despite historical understanding that neither mutation alone demonstrates complete penetrance [5]. This multi-genetic effect may explain, in part, the extent of disease involvement among the paternal lineage.

The present case exemplifies the complex genetics of ALS-FTD syndrome complex, and it lends support to the fact that ALS and FTD may, in fact, be variations of similar disease processes. Furthermore, the identification of these two mutations has significant implications for progeny, and genetic counseling for them is indicated. We must continue to define the complex interplay between various genetic mutations associated with neurodegenerative diseases to better understand the nuanced phenotypes.

Consent

The patient was consented for medical record access before cognitive decline/death. IRB approval was given to use family members medical records posthumously.

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References

[1] I. Le Ber, et al., SQSTM1 mutations in French patients with frontotemporal dementia or frontotemporal dementia with amyotrophic lateral sclerosis, JAMA Neurol. 70 (11) (2013) 1403–1410, https://doi.org/10.1001/jamaneurol.2013.3849 (PubMed PMID: 24042580; PMCID: PMC4199096).
[2] R.M. Liscic, Als and Ftd: insights into the disease mechanisms and therapeutic targets, Eur. J. Pharmacol. (2017), https://doi.org/10.1016/j.ejphar.2017.10.012 (PubMed PMID: 29031901).
[3] A. Ratti, et al., C9ORF72 repeat expansion in a large Italian ALS cohort: evidence of a founder effect, Neurobiol. Aging 33 (10) (2012), https://doi.org/10.1016/j.neurobiolaging.2012.06.008 2528 e7-14. (PubMed PMID: 22766072).
[4] E. Rubino, et al., SQSTM1 mutations in frontotemporal lobar degeneration and amyotrophic lateral sclerosis, Neurology. 79 (15) (2012) 1556–1562, https://doi.org/10.1212/WNL.0b013e31826e25df (PubMed PMID: 22972638; PMCID: PMC3655323).
[5] A.L. Hogan, et al., Expression of ALS/FTD-linked mutant CCNF in zebrafish leads to increased cell death in the spinal cord and an aberrant motor phenotype, Hum. Mol. Genet. 26 (14) (2017) 2616–2626, https://doi.org/10.1093/hmg/ddx136 (PubMed PMID: 28444311).
[6] C. Corbier, C. Sellier, C9ORF72 is a GDP/GTP exchange factor for Rab8 and Rab39 and regulates autophagy, Small GTPases 8 (3) (2017) 181–186, https://doi.org/10.1080/21541248.2016.1212688 (PubMed PMID: 27494456; PMCID: PMC5584738).
[7] M.R. Almeida, et al., Characterization of an FTLD-PDB family with the coexistence of SQSTM1 mutation and hexanucleotide (G(4)C(2)) repeat expansion in C9orf72 gene, Neurobiol. Aging 40 (2016) 191 e1–e8, https://doi.org/10.1016/j.neurobiolaging.2015.12.015 (PubMed PMID: 26839080).
[8] Y. Shi, et al., Haploinsufficiency leads to neurodegeneration in C9ORF72 ALS/FTD human induced motor neurons, Nat. Med. 24 (3) (2018) 313–325, https://doi.org/10.1038/nm.4490 (PubMed PMID: 29400714; PMCID: PMC6112156).
[9] A. Goode, S. Rea, M. Sultana, B. Shaw, M.S. Searle, R. Layfield, et al., ALS-FTLD associated mutations of SQSTM1 impact on Keap1-Nrf2 signalling, Mol. Cell. Neurosci. 76 (2016) 52–58, https://doi.org/10.1016/j.mcn.2016.08.004 (PubMed PMID: 27554286; PMCID: PMC5062946).
[10] J.M. Papma, et al., Cognition and gray and white matter characteristics of presymptomatic C9orf72 repeat expansion, Neurology. 89 (12) (2017) 1256–1264 Epub 2017/09/01 https://doi.org/10.1212/wnl.0000000000004393 (PubMed PMID: 28855404).

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