Right temporal variant frontotemporal dementia and primary lateral sclerosis associated with dual *C9orf72* and *SQSTM1* mutations

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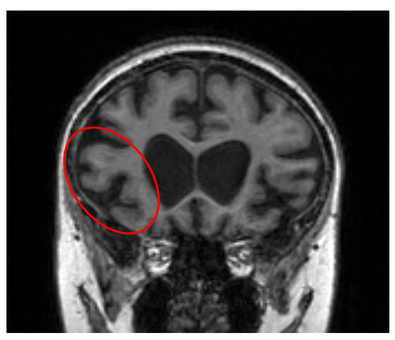
Background

- The chromosome 9 open reading frame 72 (*C9orf72*) hexanucleotide repeat expansion is the most common genetic mutation identified in familial frontotemporal dementia (FTD) and motor neuron disease (MND) [1]. FTD patients with this mutation typically have behavioural variant FTD (bvFTD) and symmetrical, often subtle, brain atrophy on neuroimaging [1,2]. MND patients typically have the ALS variant; other variants such as primary lateral sclerosis (PLS) are very rarely seen [3]. Right temporal variant FTD (RT-FTD) causes prominent right temporal lobe atrophy, behavioural change, prosopagnosia and impairment of semantic knowledge [4]. Rarely it can be associated with MND (RT-FTD-MND), but no genetic cause has previously been described for this syndrome [5].
- Mutations in sequestosome 1 (*SQSTM1*), which encodes the protein p62, were originally identified in patients with Paget's disease of the bone [6]. Recently, *SQSTM1* mutations have been identified in patients with FTD [7-11], ALS [12-16] and FTD/ALS [7,8,11]. Dual mutation cases, possessing both the *C9orf72* expansion and a *SQSTM1* mutation have recently been described in patients with either FTD [9,17], ALS [14], or FTD/ALS [11].
- We present details of the clinical, neuroimaging and neuropsychological phenotype of a patient who developed clinical features of combined RT-FTD and the PLS variant of MND, and possessed a novel combination of two mutations: the *C9orf72* expansion and a *SQSTM1* p.Glu396fs mutation.

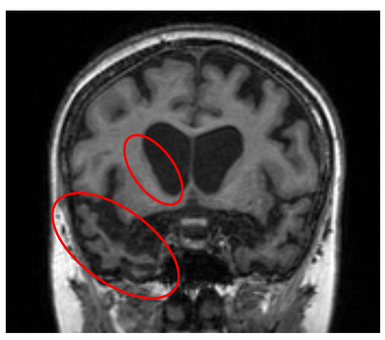
Clinical Details and Investigations

- A 67 year old, right-handed female presented with 7 years of progressive behavioural change followed by 4 years of progressive semantic impairment and prosopagnosia. She had also developed falls and difficulty walking due to left leg stiffness and ankle clonus over the previous 18 months. There were no upper limb or bulbar symptoms at presentation. Her father had had MND, with onset at 62 years, dying at 64. There was no other relevant history. Her behavioural changes included: apathy, loss of empathy, lack of appreciation of sarcasm, hoarding facial creams, obsession with her facial appearance and Sudoku puzzles, excessive handwashing, flitting unexplained chronic pains and rigid routines and eating habits. She had difficulty recognising neighbours. She also had semantic impairment, with difficulty naming people and objects, and deteriorating spelling and reading. There were no reported memory or visuoperceptual difficulties.
- On initial examination her MMSE score was 27/30 and she had reduced verbal fluency, concrete proverb interpretation, significant word-finding difficulties and poor recognition of famous faces, with intact posterior cortical function. Cranial nerves were normal. She had bilaterally increased upper and lower limb tone, ankle clonus and pathologically brisk reflexes, worse on the left. She had mild left-sided pyramidal weakness but no muscle wasting or fasciculations. At initial presentation she dragged her left leg and required use of a walking stick. She was seen twice over the next seven months and exhibited rapidly deteriorating progressive cognitive and motor decline. She was using a wheelchair 4 months after initial presentation and 3 months later became bed-bound, dysphagic, and almost completely mute.
- Nerve conduction studies and electromyography (EMG) were normal on two occasions (performed once at her local neurological centre and again 4 months later at our centre). Routine bloods were normal. Non-volumetric MRI brain and cervical spine imaging performed locally showed prominent right temporal lobe atrophy and no evidence of cervical spinal disease. Volumetric MRI brain performed at our centre 6 months later showed neuroimaging abnormalities as seen below. This patient had clinical features consistent with RT-FTD (early behavioural change and prosopagnosia followed by semantic impairment) and progressive, asymmetrical upper motor neuron signs consistent with the PLS variant of MND.
- Due to her family history of MND, a blood sample was sent for DNA testing. This revealed a pathogenic heterozygous *C9orf72* hexanucleotide repeat expansion. Further genetic analysis using a next generation sequencing dementia panel [18] revealed an additional heterozygous *SQSTM1* p.Glu396fs nonsense mutation. There were no mutations in any other known FTD- or MND-associated genes and no personal or family history of Paget's disease.

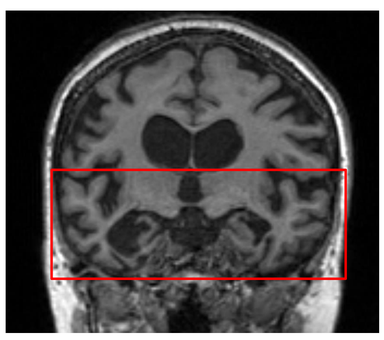
Anterior



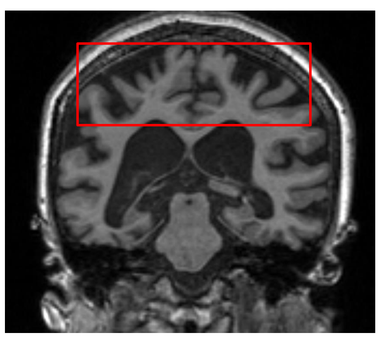
Bilateral but asymmetrical frontal lobe atrophy, affecting inferior and superior frontal gyri and anterior cingulate cortex, more severe on the right. Significant expansion of anterior horns of lateral ventricles.



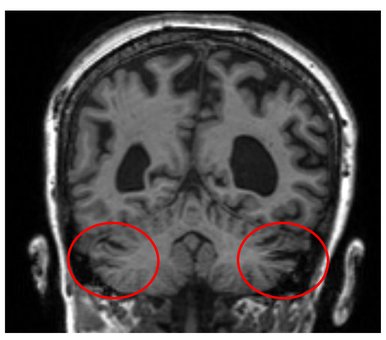
Bilateral but markedly asymmetrical significant anterior temporal lobe atrophy, much worse on the right. Very marked bilateral caudate nucleus atrophy, also more severe on the right.



Bilateral but markedly asymmetrical atrophy of temporal lobes, worse on right. Significant atrophy of hippocampus, amygdala, fusiform and inferior temporal gyrus, and atrophy of the insula and inferior frontal gyrus. Bilateral thalamic atrophy and enlargement of the third ventricle.



More widespread cerebral atrophy extending posteriorly to affect parietal cortex bilaterally, with significant enlargement of the lateral ventricles.



Marked and selective bilateral atrophy of lobule VIIa-Crus I in the superior-posterior region of the cerebellum (typically seen in *C9orf72* expansion cases)

Posterior

Neuropsychology

- Two initial neuropsychology assessments, performed locally and then repeated at our centre 6 months later, demonstrated progressive semantic impairment, executive dysfunction and impaired facial recognition, with intact posterior cortical function. Further neuropsychology testing 5 months later (shown below) demonstrated a reduction in MMSE score to 24/30 and further cognitive decline in multiple domains, with progression to involve calculation.

Test	Subset	Raw score	Percentile score	
Wechsler Abbreviated Scale of Intelligence (WASI)	Verbal	Vocabulary 17/80 Similarities 8/48	**<1st** **<1st**	**IQ = 58**
	Performance	Block design 16/71 Matrix reasoning 7/32	**5-25th** **5-25th**	**IQ = 80**
Recognition Memory Test	Faces	23/50	**<5th**	
	Words	20/50	**<5th**	
WMS-R Digit Span	Forwards	6/12	**25-50th**	
	Backwards	4/12	**5-25th**	
Graded Naming Test	n/a	1/30	**<1st**	
British Picture Vocabulary Scale	n/a	82/150	**<1st**	
Graded Difficulty Arithmetic Test	Total	3/24	**1-5th**	
D-KEFS Color-Word Interference Test	Colour naming	78 seconds	**<1st**	
	Word naming	41 seconds	**<1st**	
	Ink colour naming	129 seconds	**<1st**	
Verbal Fluency	F words in 1 minute	4	**<1st**	
Category Fluency	Animals in 1 minute	3	**<1st**	
Trail Making Test	Part A	53 seconds	**5-25th**	
	Part B	207 seconds	**5-25th**	
WAIS-R Digit Symbol	n/a	25/93	**1-5th**	

Discussion

- To our knowledge, this is the first reported case of an underlying gene mutation in a patient with RT-FTD-MND. It is also the first reported case of a dual *C9orf72/SQSTM1* mutation in a patient with clinical features of PLS. Previously reported dual mutation cases either had clinical bvFTD alone [9,17], the ALS variant of MND alone [14] or clinical features of FTD/ALS [11].
- Although the *SQSTM1* p.Glu396fs mutation has been reported in patients with bvFTD alone [9,17], our case describes a novel association of this particular mutation with FTD/MND, and a novel concurrence of the *SQSTM1* p.Glu396fs mutation with the *C9orf72* expansion. This adds to the phenotypic picture associated with *SQSTM1* mutations and to an expanding list of different *SQSTM1* mutations identified in patients with dual *C9orf72/SQSTM1* mutations and FTD or MND. See the **Summary Table** below for details.
- Our patient had an asymmetrical, right-sided brain atrophy pattern, which has been previously described in FTD patients with other *SQSTM1* mutations [7,8,19]. However, she also had bilateral parietal, thalamic and cerebellar atrophy, as seen in FTD patients with the *C9orf72* expansion [2]. This supports the view that mutations in different genes are associated with distinct neuroimaging phenotypes.
- Patients presenting with atypical variants of FTD or MND, or FTD/MND, should have a thorough family history taken for neurodegenerative disease. A personal or family history of Paget's disease should also be explored, given its link to mutations in the FTD- and MND-associated *SQSTM1* and *VCP* genes.
- Given increasing discovery of cases with dual mutations in several FTD- or MND- associated genes, patients with atypical clinical presentations or neuroimaging features should be considered for genetic testing with a 'dementia panel' that looks for mutations in multiple neurodegenerative disease associated genes [18], as well as being tested for the *C9orf72* expansion.

Summary Table

FTD gene mutation	Age at onset of FTD (years)	Disease duration of FTD (years)	Clinical presentation	Neuroimaging phenotype	Neuropathology	Behavioural & psychiatric features	Language & cognitive impairment	Extrapyramidal or other features	Motor neuron disease features
***C9orf72* expansion**	Mean: 50 Range: 21-83	Mean: 8-9 Range: 1-22	BvFTD +/- MND (ALS variant) or MND alone; less commonly nfvPPA	Symmetrical, diffuse, often subtle atrophy. Subcortical i.e. thalamic, cerebellar & posterior cortical atrophy	FTLD-TDP Type A or Type B Prominent p62 positive, TDP-43 negative inclusions in cerebellar & hippocampal granule cell layer. Dipeptide repeat inclusions are co-localised with p62	Apathy, disinhibition, less sweet tooth, more complex unusual repetitive behaviours Psychosis and anxiety common; odd delusions or visual/auditory/tactile hallucinations	Less common, few have nfvPPA/ svPPA Early episodic memory impairment, apraxia & dyscalculia	Common (30%); symmetrical akinetic-rigid syndrome +/- postural or rest tremor; gait disturbance Few cases with cerebellar ataxia	Common in bvFTD>PPA cases Typically ALS (bulbar onset in >40%); PLS and PMA are rare
***SQSTM1* mutations**	Mean: 60 Range: 41-78	Mean: 10.2 Range: 2-29	FTD/MND, MND alone or bvFTD alone; +/- Paget's disease of bone	Symmetrical frontotemporal atrophy in some Others have asymmetrical atrophy of right-perisylvian region, or of right inferior frontal, medial orbitofrontal regions, precentral gyrus & anterior insula	FTLD-TDP Type A or B Prominent neuronal cytoplasmic & glial TDP-43 positive inclusions in frontal & temporal cortices. p62 positive inclusions co-localised with TDP-43. No dipeptide repeat pathology	BvFTD or RT-FTD (prosopagnosia & semantic impairment); prominent apathy, paranoia, hoarding, unexplained pain & bulimia also described	One case of atypical apraxia of speech; otherwise unusual. Visuoconstructional apraxia described	Parkinsonism seen early or late Paget's disease of bone (alone or with FTD or MND)	FTD/MND and MND more common than bvFTD alone; MND is usually ALS variant, often bulbar onset
***C9orf72/SQSTM1* dual mutations** **FTD alone** [**refs**]: p.Arg212Cys [9,17]; p.Ala16Val [9]; p.Gly219Val [9] **ALS alone:** p.Pro392Leu [14] **FTD/ALS:** p.Pro392Leu [11] **FTD/PLS:** (p.Glu396fs; our case)	Limited data Range: 57-60	Limited data Range: 2-8	Limited data bvFTD alone, MND alone or bvFTD/ALS +/- Paget's disease Our case had RT-FTD-PLS without known Paget's disease	Limited data Our FTD/PLS case with *C9orf72*/p.Glu396fs dual mutation had asymmetrical temporal atrophy worse on right & subcortical, parietal & cerebellar atrophy *C9orf72*/p.Arg212Cys mutation case had symmetrical frontotemporal atrophy *C9orf72*/p.Pro392Leu mutation case had mild cortico-subcortical atrophy worse on left	Limited data FTLD-TDP Type A with *C9orf72*/p.Arg212Cys dual mutation Dipeptide repeat pathology predominates p62 inclusions in hippocampal pyramidal cell layer & cerebellum co-localised with TDP-43	bvFTD with prominent disinhibition, perseveration and apathy; aggression reported Our case had prominent apathy, lack of empathy, rigid routines & eating habits, unexplained flitting pain, unusual obsessions & repetitive handwashing	Paucity of speech, echolalia, pallilalia; dysarthria if ALS develops Our case had profound semantic impairment & prosopagnosia	Late parkinsonism (akinetic-rigid syndrome) described in a bvFTD case with *C9orf72*/p.Arg212Cys mutation Paget's disease of bone (+/- FTD) in 2 cases	One bvFTD case had clinical ALS but a normal EMG; an isolated MND case had classical ALS without cognitive impairment Our case had RT-FTD-PLS and two normal EMGs

References & Acknowledgements

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