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EDITED BY

Jolanta Dorszewska,
Poznan University of Medical Sciences,
Poland

REVIEWED BY

Takahisa Kanekiyo,
Mayo Clinic Florida,
United States
Homira Behbahani,
Karolinska Institutet,
Sweden

*CORRESPONDENCE

Woojin Scott Kim
woojin.kim@sydney.edu.au

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ATP-binding cassette transporter expression is widely dysregulated in frontotemporal dementia with TDP-43 inclusions

Jared S. Katzeff, Hiu Chuen Lok, Surabhi Bhatia, YuHong Fu,
Glenda M. Halliday and Woojin Scott Kim*

Brain and Mind Centre & School of Medical Sciences, The University of Sydney, Sydney, NSW, Australia

The human brain is highly enriched in lipids and increasing evidence indicates that dysregulation of lipids in the brain is associated with neurodegeneration. ATP-binding cassette subfamily A (ABCA) transporters control the movement of lipids across cellular membranes and are implicated in a number of neurodegenerative diseases. However, very little is known about the role of ABCA transporters in frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), which is a common form of younger-onset dementia. We therefore undertook a comprehensive analysis of the expression of ABCA transporters (ABCA1–13) in five key brain regions (amygdala, inferior temporal cortex, superior frontal cortex, cerebellum and parietal cortex) in FTLD-TDP and controls. We found that the expression of ABCA2, ABCA3, ABCA4, ABCA7, ABCA9, ABCA10 and ABCA13 was significantly altered in FTLD-TDP in a region-specific manner. In addition, the expression of ABCA transporters correlated specifically to different neural markers and TARDBP. These results suggest substantial dysregulation of ABCA transporters and lipid metabolism in FTLD-TDP and these changes are associated with neuroinflammation.

KEYWORDS

frontotemporal dementia, ATP-binding cassette subfamily A, ABCA transporters, lipids, TDP-43, neurodegeneration

Introduction

ATP-binding cassette subfamily A (ABCA) consist of 12 members named ABCA1-13, with ABCA11 being a pseudogene. The primary role of ABCA transporters is transport of lipids, such as cholesterol and phospholipids, across cellular membranes (Piehler et al., 2012). ABCA transporters have been implicated in pathologies including ABCA1 in Tangier's disease (Brooks-Wilson et al., 1999), ABCA4 in Stargardt macular dystrophy (Allikmets et al., 1997) and ABCA12 in harlequin-type ichthyosis (Kelsell et al., 2005). The role of lipid transporters in the brain is important due to the high lipid content of the brain, with approximately 40% of grey matter and 65% of white matter consisting of lipids (O'Brien and Sampson, 1965). Dysregulation of ABCA transporters expression is associated with various neurodegenerative diseases (Katzeff

and Kim, 2021). ABCA1, ABCA2 and ABCA7 have been linked to Alzheimer's disease (AD). ABCA7 gene variants are the fourth highest genetic risk factor linked to late-onset AD (Hollingworth et al., 2011), while genetic variants of ABCA1 and ABCA2 are known risk modulators of AD (Mace et al., 2005; Lupton et al., 2014). As well as lipid dysregulation, the pathological role of ABCA7 is related to amyloid- β clearance and phagocytosis (Fu et al., 2016; Sakae et al., 2016).

Inclusions of TAR DNA-binding protein-43 (TDP-43) have been estimated to occur in 19–57% of AD cases (Amador-Ortiz et al., 2007; Josephs et al., 2014). However, the expression of ABCA transporters in other TDP-43 pathologies such as frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), which accounts for 32–54% of total FTLD cases, is currently unknown. FTLD-TDP is characterized by aberrant nucleocytoplasmic transport of TDP-43, which results in deposition of phosphorylated TDP-43 in the cytoplasm. Of interest, TDP-43, which is encoded by the *TARDBP* gene, has extensive functions including transcription, translation and mRNA trafficking, and alterations in its physiological functions are known to associate with mitochondrial dysfunction and neuroinflammation, the latter being increasingly recognized as a hallmark of FTLD-TDP pathology (Bevan-Jones et al., 2020).

The expression of ABCA transporters is known to modulate neuroinflammation, which has been shown to have a close association with protein aggregation in FTLD-TDP, as indicated by the presence of activated microglia in regions with TDP-43 pathology (Trageser et al., 2019). Indeed, it has been reported that microglia from ABCA1 knockout mice exhibit a heightened pro-inflammatory response (Karasinska et al., 2013). In addition, ABCA7 knockout or haploinsufficiency in AD hinders amyloid- β clearance, suggesting that ABCA7 expression has a neuroprotective role and modulates microglial responses in neurodegeneration (Fu et al., 2016; Aikawa et al., 2018).

In the current study, the transcriptional levels of all ABCA transporters, common neural cell markers and TARDBP were measured in brain regions progressively affected in FTLD-TDP. TARDBP was measured to determine if there was a correlation between TDP-43 pathology and dysregulation of ABCA transporter expression. Firstly, ABCA expression changes in FTLD-TDP compared to controls were determined, followed by correlating these expression changes with neural subtype makers and TARDBP expression.

Materials and methods

Human brain tissues

Fresh-frozen post-mortem brain tissue samples were obtained with consent from the Sydney Brain Bank and NSW Brain Tissue Resource Centre. All brain donors underwent standardized assessments in life and standardized neuropathological examination, and met current consensus diagnostic criteria for

FTLD-TDP (Cairns et al., 2007; Mackenzie et al., 2010) or no significant neuropathology (controls; Hyman et al., 2012; Montine et al., 2012). Tissue samples from the amygdala (earliest affected), inferior temporal and superior frontal cortices (next affected), cerebellum and finally parietal cortex (Rabinovici and Miller, 2010) of 10 FTLD-TDP sporadic cases (5 male, 5 female) and 11 controls (5 male, 6 female without neurological, psychiatric or neuropathological disease) were used in this study (Table 1). The 10 FTLD-TDP cases were previously confirmed as having TDP-43 pathology (Tan et al., 2013). The mean age of the two groups were 72.9 ± 13.0 and 79.5 ± 12.1 years, respectively. Ethics approval for the study was from the University of New South Wales Human Research Ethics (approval number: HC15789).

Protein extraction

Tris-buffered saline (TBS) and SDS-soluble proteins were serially extracted from 100 mg of fresh-frozen brain tissues, as previously described (Murphy et al., 2013). Briefly, tissues were homogenized in 10 volumes of TBS homogenization buffer (20 mM Tris, 150 mM NaCl, pH 7.4, 5 mM EDTA, 0.02% sodium azide) containing protease inhibitor cocktail (Roche) using Qiagen TissueLyser (3×30 s, 30 Hz cycles), followed by centrifugation at 100,000 g for 1 h at 4°C, with supernatant collected as TBS-soluble fraction. The pellet was resuspended in SDS solubilization buffer (TBS homogenization buffer containing 5% SDS) using 3×30 sec, 30 Hz cycles with

TABLE 1 Demographic information of cases used in this study.

ID	Case	Age	Sex	PMI (h)	Disease dura. (y)	Brain pathol.
1	FTLD	66	M	39	2	TDP-43
2	FTLD	62	M	15	3	TDP-43
3	FTLD	72	F	25	1	TDP-43
4	FTLD	61	M	37	2.5	TDP-43
5	FTLD	65	F	22	5	TDP-43
6	FTLD	84	F	17	8	TDP-43
7	FTLD	60	M	28	3	TDP-43
8	FTLD	99	F	13	14	TDP-43
9	FTLD	86	F	25	8	TDP-43
10	FTLD	74	M	20	7	TDP-43
11	Control	85	F	23	N/A	N/A
12	Control	79	M	8	N/A	N/A
13	Control	89	F	23	N/A	N/A
14	Control	101	F	9	N/A	N/A
15	Control	84	M	9	N/A	N/A
16	Control	93	F	15	N/A	N/A
17	Control	74	M	10	N/A	N/A
18	Control	63	M	24	N/A	N/A
19	Control	66	M	23	N/A	N/A
20	Control	74	F	20	N/A	N/A
21	Control	67	F	15	N/A	N/A

TissueLyser, and centrifuged at 100,000g for 30 min at 25°C, with supernatant collected as SDS-soluble fraction. Protein concentration was measured using a bicinchoninic acid assay (Pierce BCA Protein Assay Kit) following the manufacturer's instructions.

Western blotting

Western blotting was carried out as previously described (Phan et al., 2020). Protein lysates (10 µg) were heated with sample buffer (3.2% SDS, 32% glycerol, 0.16% bromophenol blue, 100 mM Tris-HCl, pH 6.8, 8% 2-mercaptoethanol). They were then electrophoresed on Criterion Stain-free 4–20% SDS-PAGE gels (Bio-Rad) and transferred onto nitrocellulose membranes at 100 volts for 30 min. The membranes were blocked with TBS containing 5% nonfat dry milk and probed overnight at 4°C with TDP-43 antibody (Proteintech, 10,782-2-AP, 1:2,000) and β-actin (Abcam, ab6276, 1:10,000). They were then washed three times in TBS containing 0.1% Tween 20 and incubated with horseradish peroxidase-conjugated secondary antibodies for 2 h at room temperature. Signals were detected using enhanced chemiluminescence and Gel Doc System (Bio-Rad).

Immunohistochemistry

Immunohistochemistry of FTLD-TDP superior frontal cortex was carried out as previously described (Phan et al., 2021). Briefly, formalin-fixed, paraffin-embedded sections (10 µm) were deparaffinized in xylene and rehydrated through graded ethanol, followed by antigen retrieval with citrate buffer (pH 6.0) using a pressure cooker (Aptum Bio Retriever 2,100, Aptum Biologics Ltd., United Kingdom) at a peak temperature of ~121°C and gradually cooling to room temperature. Endogenous peroxidase was blocked with 1% hydrogen peroxide in 50% ethanol. Sections were probed with TDP-43 antibody (Proteintech, 10,782-2-AP, 1:400) and NeuN antibody (Biolegend, SIG-39860, 1:100), washed with PBS and incubated with the corresponding secondary antibodies (Thermo Fisher Scientific, A-10042 and A-31571, 1:250) and 4',6-diamidino-2-phenylindole DAPI (Sigma-Aldrich, D9542, 1 mg/ml). The slides were treated with 70% Sudan Black for 30 min and 10 mM CuSO₄ in 50 mM ammonium acetate buffer (pH 5.0) to quench auto-fluorescence signals prior to cover-slipping with anti-fade fluorescence mounting medium (DAKO, S3023) and then sealed with nail polish. Negative controls (without primary antibodies or secondary antibodies) were performed for each immunohistochemistry run, and no signals were detected in each case.

Microscopy imaging

For immunohistochemistry, stained sections were scanned using an Olympus VS120 Slide Scanner with the same focus and

exposure settings. For immunofluorescence, multiple sections were examined and representative images were captured with a Nikon C2 confocal microscope and associated Nikon NIS Elements software (version 4.60). Images were adjusted for contrast and converted to TIFF format on Fiji software (ImageJ version 2.0.0-rc-69/1.52p).

RNA isolation, reverse transcription and quantitative PCR

RNA was isolated using TRI Reagent (Sigma, Castle Hill, NSW, Australia) following the manufacturer's protocol. All procedures were carried out using RNase-free reagents and consumables. Two micrograms of RNA were reverse transcribed into cDNA using Moloney-murine leukemia virus reverse transcriptase and random primers (Promega, Annandale, NSW, Australia) in a 20 µl reaction mixture. cDNA was then used as a template in quantitative PCR, using a Mastercycler ep realplex S (Eppendorf) and the fluorescent dye SYBR Green (Bio-Rad), following the manufacturer's protocol. Briefly, each reaction (20 µl) contained 1x RealMasterMix, 1x SYBR green, 5 pmoles of primers and 1 µl of template. Amplification was carried out with 40 cycles of 94°C for 15 s and 60°C for 1 min. Gene expression was normalized to the housekeeper genes β-actin, GAPDH and cyclophilin A. All primers used are listed in Table 2. A no-template control was included for each PCR amplification assay. The level of expression for each gene was calculated using the comparative threshold cycle (Ct) value method using the formula $2^{-\Delta\Delta Ct}$ (where $\Delta\Delta Ct = \Delta Ct \text{ sample} - \Delta Ct \text{ reference}$).

Statistical analysis

All statistical analyses were performed using SPSS statistical software (IBM, Chicago, IL, United States). A multivariate general linear model analysis covarying for age, sex and PMI was used to determine differences in ABCA, TARDBP and neural subtype mRNA expression in FTLD-TDP compared to controls, with *post hoc* statistical significance set at $p < 0.05$. Partial correlations co-varying for age, sex and PMI were used to determine if alterations in ABCA expression were associated with alterations in neural subtype and/or TARDBP mRNA expression with statistical significance set at $p < 0.05$.

Results

Expression of ABCA transporters in FTLD-TDP brain

Firstly, TDP-43 pathology in FTLD-TDP cases was confirmed by western blotting (Figure 1A) and immunohistochemistry (Figure 1B). To determine if ABCA transporter expression was

TABLE 2 Primer sequences.

Gene	Sequence (5'-3')	Product size (bp)
ABCA1	F: AACTCTACATCTCCCTTCCCG R: CTCCTGTCGCATGTCCTCC	123
ABCA2	F: AGTGCTCAGCCTTCGTACAG R: AGGCGGTACAGGATTTTGG	188
ABCA3	F: ACGGTCTGGAACCTTCTCT R: TGTGAGAAGGGATGTAGGCAA	187
ABCA4	F: CGCTCAGGCAGAACCATCAT R: TGAGCAGTAGAGCCTTCCCT	102
ABCA5	F: AGCCAAACAGCACATGTGGCGA R: AGACAGCCTCTGCCTCCTCCA	101
ABCA6	F: GCTTCATTTCTCCCACTTGTAT R: GCTGAATCTTGAGACCCATCA	102
ABCA7	F: CTAGCCGATGCCCGCACTGT R: GACGTCAGCAGCTCCGCGA	170
ABCA8	F: ACCTGGGACGGGTAGATACAT R: CCCAAGACCTCTTACCTGCC	130
ABCA9	F: TAGCCCTTTGCCTTCACTG R: TGCCATATTCAGCGGGCAA	195
ABCA10	F: GTTAAGCGTGAAAGGAGAGC R: GCGTCTTCGGGATTTGTTC	168
ABCA13	F: GCAGAGTTCTTGGGGGAAT R: CACTTCCAGTTCTTGGCCCT	115
β -ACTIN	F: GAATTCGCGCCACGGCTCTCCAGCT R: AAGCTTTTTCGTGGATGCCACAGGACT	163
CYCLOPHILIN A	F: AGGTTCTCTGCTTTCACAGA R: GTCTTGGCAGTGCAGATGAA	211
GAPDH	F: AATGAAGGGTCATTGATGG R: AAGGTGAAGGTCGGAGTCAA	108
GFAP	F: TCCTGGAACAGCAAACAAG R: CAGCCTCAGGTTGGTTTCAT	224
MAP2	F: TTGGTGCCGAGTGAGAAGA R: GTCTGGCAGTGGTTGGTTAA	99
TARDBP	F: AGCCAAGATGAGCCTTTGAGAA R: ACTGAGAGAAGAAGCTCCCGC	94
TMEM119	F: CTGGCCTTCTGCTGATGTTC R: TCACTCTGGTCCAGTACTTC	116
TPPP	F: GAGCAGCGAGGAGGCCGTT R: GCCTCGACACTGTGGGCGAC	105

Sequence of forward (F) and reverse (R) primers and product size is provided.

altered in FTLT-DTP, qPCR was performed to measure the overall relative expression of all ABCA genes in five brain regions, amygdala (affected early), inferior temporal cortex, superior frontal cortex, cerebellum and parietal cortex (affected late; Figure 2). ABCA2, ABCA3, ABCA4, ABCA7, ABCA9, ABCA10 and ABCA13 all demonstrated altered mRNA expression in specific regions of FTLT-DTP compared to controls. There were no significant changes to other transporters in any of the regions examined, while ABCA12 expression was undetectable in all five regions. ABCA2 was decreased 0.2-fold in the amygdala and

increased in the superior frontal cortex (4-fold) and cerebellum (1.8-fold). ABCA3 was elevated in the amygdala (1.2-fold), superior frontal cortex (2.1-fold) and the cerebellum (1.6-fold). ABCA4 was elevated in the amygdala (2.1-fold), the inferior temporal cortex (3.9-fold) and the parietal cortex (4.8-fold). ABCA7 was increased 4.9-fold in the superior frontal cortex. ABCA9 was lower in the inferior temporal cortex (0.4-fold) but 1.5-fold higher in both the superior frontal cortex and cerebellum. ABCA10 was increased 1.6-fold in the cerebellum only. ABCA13 was elevated in the inferior temporal cortex (7-fold), cerebellum (2.6-fold) and the parietal cortex (4.5-fold).

Expression of neural markers and TARDBP in FTLT-DTP brain

To quantify mRNA expression of neural subtype markers, qPCR was performed for markers for neurons (MAP2), microglia (TMEM119), oligodendrocytes (TPPP) and astrocytes (GFAP) in all five brain regions (Figure 3). Additionally, TARDBP was also measured to evaluate TDP-43 expression in these brain regions. TMEM119, GFAP and TARDBP showed significant region-specific altered expression in FTLT-DTP compared to controls (Figure 3). TMEM119 was increased in the amygdala (1.9-fold), the inferior temporal cortex (4.4-fold) and the parietal cortex (3.7-fold). GFAP was elevated in all brain regions examined: 1.9-fold in the amygdala, 3.6-fold in the inferior temporal cortex, 8.8-fold in the superior frontal cortex, 4.6-fold in the cerebellum and 1.9-fold in the parietal cortex. TARDBP was significantly increased in the inferior temporal cortex (2.2-fold) and the parietal cortex (2.5-fold) and decreased in the cerebellum (0.3-fold).

Correlations between ABCA transporters and neural markers

A partial correlation analysis covarying for age, sex and PMI was performed to determine if there was a relationship between ABCA transporters, TARDBP and neural subtype markers: immune related neural markers (TMEM119 and GFAP; Figure 4A) and non-immune related neural markers (MAP2 and TPPP; Figure 4B). While correlation analysis was performed for all ABCA transporters, only ABCA transporters that showed significant expression changes in FTLT-DTP in Figure 2 are discussed here. ABCA4 correlated positively with TMEM119 ($r=0.711$, $p<0.0001$; Figure 4A), TPPP ($r=0.285$, $p<0.01$) and TARDBP ($r=0.413$, $p<0.001$; Figure 4B). ABCA7 levels correlated positively with GFAP ($r=0.442$, $p<0.0001$; Figure 4A) and negatively with MAP2 ($r=-0.210$, $p<0.05$; Figure 4B). ABCA8 correlated positively to both GFAP ($r=0.442$, $p<0.0001$) and TMEM119 ($r=0.452$, $p<0.0001$; Figure 4A). ABCA9 correlated negatively with TMEM119 ($r=-0.303$, $p<0.002$; Figure 4A). There is a weak

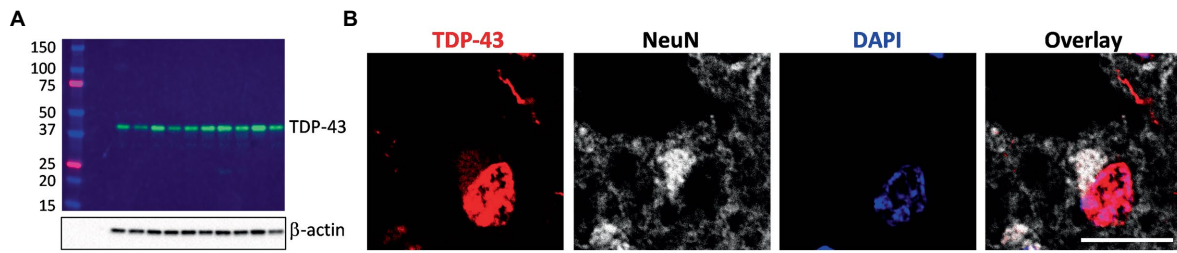


FIGURE 1
Verification of TDP-43 pathology in FTLD-TDP cases. (A) Western blotting of TDP-43 protein (43 kDa) in superior frontal cortex (SFC) in each FTLD-TDP (N=10) cases; β -actin as a loading control; protein ladder (kDa). (B) Immunohistochemistry of neurons in FTLD-TDP SFC stained with TDP-43 (red), NeuN (grey), and DAPI (blue). Scale bar=20 μ m.

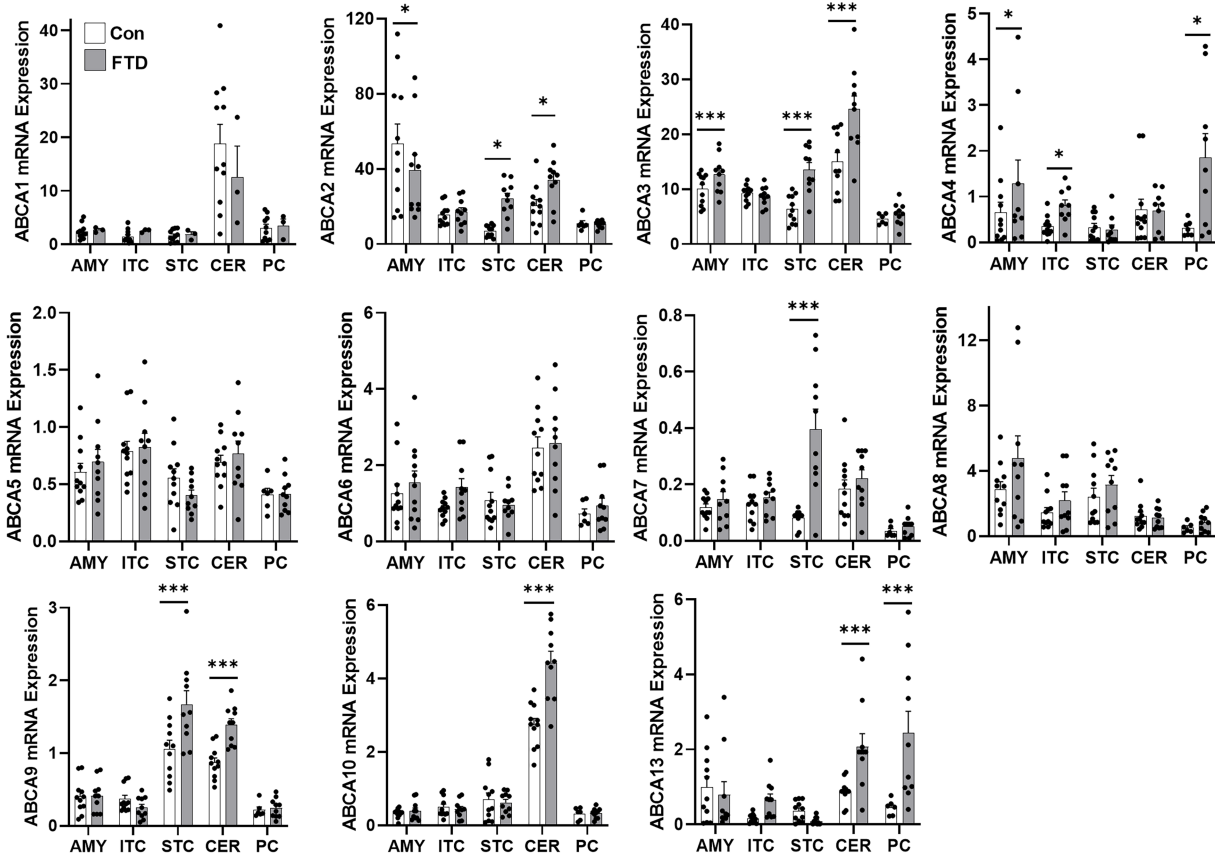


FIGURE 2
mRNA expression of ABCA transporters in FTLD-TDP and control brain. mRNA expression of ABCA transporters in amygdala (AMY), inferior temporal cortex (ITC), superior frontal cortex (SFC), cerebellum (CER) and parietal cortex (PC) in FTLD-TDP and control brain as measured by qPCR. Data represent mean and SE as error bars, * $p < 0.05$ and *** $p < 0.001$.

negative correlation between ABCA10 and TMEM119 ($r = -0.216, p < 0.05$; Figure 4A) and MAP2 ($r = -0.313, p = 0.001$; Figure 4B) and a weak positive correlation with TARDBP ($r = 0.278, p = 0.005$; Figure 4B). ABCA13 correlated strongly with TMEM119 ($r = 0.601, p < 0.001$; Figure 4A) and TARDBP ($r = 0.397, p < 0.001$; Figure 4B).

Discussion

ABCA transporters have been associated with numerous pathologies and are increasingly studied in relation to AD but there is limited knowledge on other neurodegenerative diseases, particularly those with TDP-43 pathology, such as FTLD-TDP. In

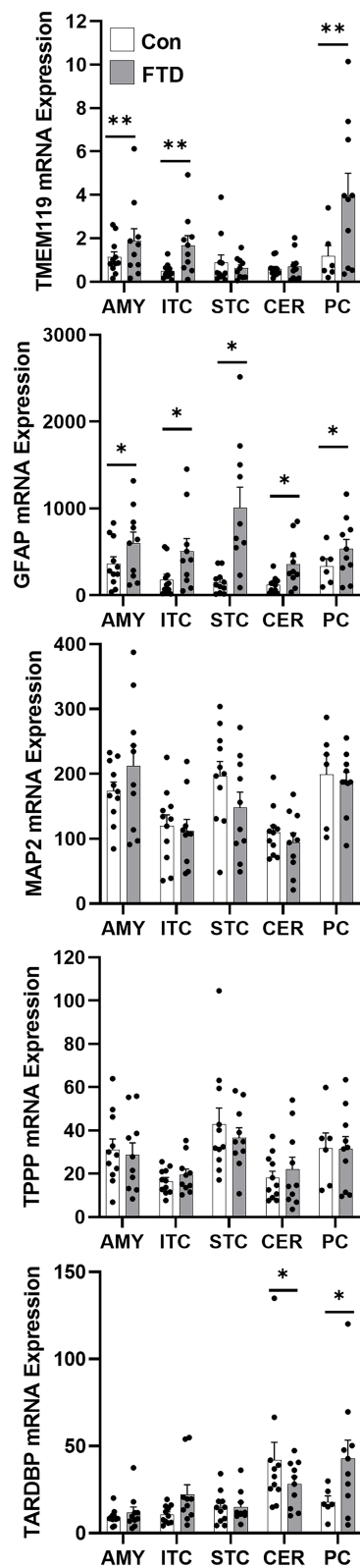
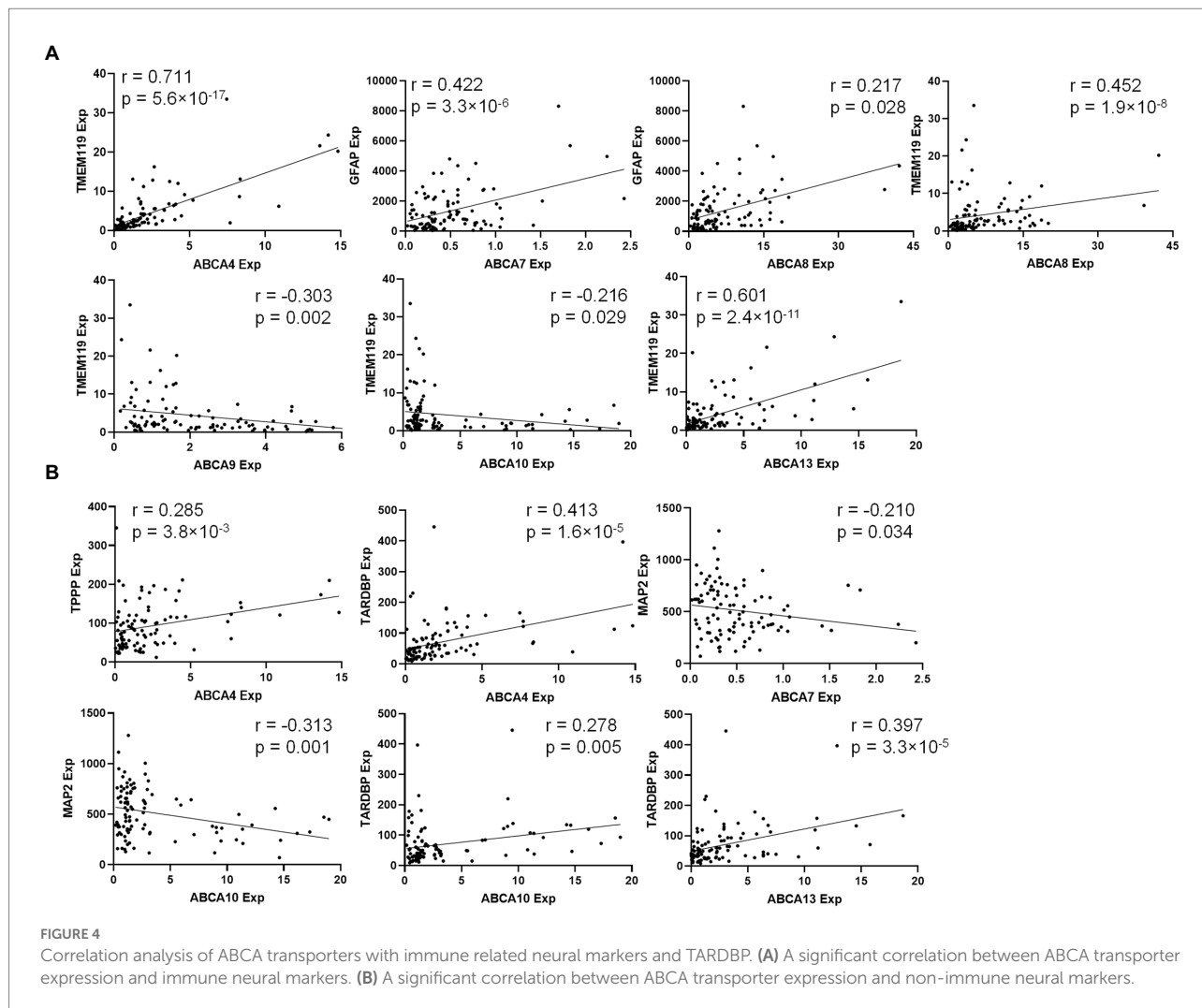


FIGURE 3

mRNA expression of TARDBP and neural markers in FTLD-TDP and control brain. mRNA expression of TARDBP and neural markers, TMEM119 (microglia), GFAP (astrocytes), MAP2 (neurons) and TPPP (oligodendrocytes) in amygdala (AMY), inferior temporal cortex (ITC), superior frontal cortex (SFC), cerebellum (CER) and parietal cortex (PC) in FTLD-TDP and control brain as measured by qPCR. Data represent mean and SE as error bars, * $p < 0.05$ and ** $p < 0.01$.



this study, we provide a comprehensive analysis of ABCA transporter expression in the human brain across multiple brain regions. We report changes in ABCA transporter expression in FTLT-TDP compared to controls, with these changes correlating with expression of neural subtype markers, particularly those relating to inflammation (GFAP and TMEM19). This suggests that ABCA transporters may play a role in neuroinflammation in FTLT-TDP. Considering neuroinflammation is increasingly recognized as a hallmark of FTLT-TDP, further understanding the involvement of ABCA transporter dysregulation in neuroinflammation could provide insights into the aetiology of FTLT-TDP.

The expression of ABCA transporters in the FTLT-TDP was vastly different to that of normal brains, with abundant lipid dysregulation indicated by the upregulation of many of these ABCA lipid transporters. Currently, lipid dysregulation has not been well investigated in FTLT-TDP with only some recent studies examining lipid changes in blood of patients with frontotemporal dementia (FTD; Kim et al., 2018; Murley et al., 2020; Phan et al., 2020). In a neuronal model of FTD tauopathy,

dysregulation of the lipid phosphatidylserine was shown to trigger microglial phagocytosis of affected neurons (Brelstaff et al., 2018).

The role of ABCA transporters in lipid dysregulation and neurodegeneration has been studied in greater detail in AD, where ABCA7 and ABCA2 have been implicated in the aetiology of AD. ABCA2 overexpression increases expression of genes associated with neurodegeneration and ABCA2 knockdown reduces amyloid- β production (Davis and Tew, 2018). Loss-of-function mutations in ABCA7 lead to impaired amyloid- β clearance and dysregulated macrophage phagocytosis (Aikawa et al., 2018). The maintenance of ABCA2 and ABCA7 protein levels is associated with cell protection by removal of toxic lipids (Chen et al., 2004; Lyssenko and Pratico, 2021), particularly neuronal ROS peroxidated lipid which is sequestered into glial lipid droplets, delaying neurotoxicity (Moulton et al., 2021). Our results show ABCA2 and ABCA7 upregulation in FTLT-TDP in a region-specific manner, with significant increases in ABCA7 expression in the superior frontal cortex (Figure 2), a region which usually sustains substantial tissue loss. We also show a strong positive association between ABCA7 and GFAP levels, an

astrocyte marker, consistent with the concept that the increase in ABCA7 is largely in glia that could assist with peroxidated lipid sequestration in astrocytes (Moulton et al., 2021). The elevated levels of ABCA2 and ABCA7 in FTL-D-TDP reported here could be critical to compensatory mechanisms. Interestingly, rare variants of the ABCA7 gene have been identified in two sporadic cases of FTD (Ciani et al., 2019) and a homozygous loss-of-function ABCA7 variant was also identified, suggesting ABCA7 as a candidate gene for monogenic FTD (Wagner et al., 2021). A partial deletion in the ABCA7 gene and a variant in the GRN gene has been found in a patient with semantic variant of primary progressive aphasia (Antonell et al., 2020), one of the clinical phenotypes associated with FTL-D-TDP. Loss-of-function mutations in ABCA7 are also prevalent in AD (Hollingworth et al., 2011; Steinberg et al., 2015) with evidence of TDP-43 positive neurofibrillary tangles and neuronal cytoplasmic inclusions in these cases (Van den Bossche et al., 2016) despite lower protein levels. This would be consistent with ABCA7 delaying neurotoxicity through glial mechanisms (Moulton et al., 2021), and that dysregulation of that mechanism and increases in ABCA2 induce neuronal TDP-43 deposition potentially through protein condensation phenomena (Vendruscolo, 2022). The regional selectivity in FTL-D-TDP warrants further research in concert with the regional involvement of ABCA transporters in glia and neurons in FTL-D-TDP.

In contrast, ABCA1, ABCA5 and ABCA8 levels were not significantly altered in FTL-D-TDP. Physiologically, ABCA1 plays a major role in cholesterol efflux and regulates intracellular cholesterol levels. ABCA1 is critical in physiological brain function where it loads newly synthesised cholesterol from astrocytes onto apoE/apoA-I to transport cholesterol to neurons and myelin (Zhao et al., 2017), a mechanism which does not appear to be disrupted in FTL-D-TDP. ABCA5 has also been implicated as a cholesterol efflux transporter (Fu et al., 2015) while ABCA8 may impact oligodendroglial functions (Bleasel et al., 2013). Our results show that the levels of ABCA8 positively correlated with increased astrocytic and microglial markers in FTL-D-TDP (Figure 4A). As loss of ABCA8 reduces oligodendroglial precursors and mature oligodendrocytes (Liu et al., 2022) and its expression in human prefrontal cortex associates with myelination (Kim et al., 2013), its positive association to increased astrocytic GFAP (most dominant in superior frontal cortex) may suggest additional compensation of cortical oligodendrocytes to FTL-D-TDP.

Our results also identify dysfunction of numerous ABCA transporters in FTL-D-TDP that have not previously been implicated in neurodegeneration. Very little is known about ABCA3, ABCA9 and ABCA10. ABCA3 has been pathologically linked to surfactant deficiency, a lung disorder relating to aberrant lipid transport that is fatal in newborns (Shulenin et al., 2004) while there is very little knowledge on the physiological and pathological functions of ABCA9 and ABCA10. ABCA4 is associated with autosomal recessive Stargardt macular dystrophy (Sun et al., 2000). It is thought to be primarily associated with the

retina with a murine model of Stargardt macular dystrophy that contained double knockout *Abca4*^{-/-} and *Rdh8*^{-/-} exhibiting reduced inflammation (Kohno et al., 2013). Some evidence suggest that structural changes to the brain are associated with Stargardt's disease. In one study, imaging analyses showed a significant grey matter loss bilaterally in the occipital cortices and in the fronto-orbital cortices, and reductions in fractional anisotropy in the supratentorial white matter regions (Olivo et al., 2015). ABCA13 is expressed on the photoreceptor outer segments and functions in the visual cycle. It facilitates the transport of retinylidene-phosphatidylethanolamine or phosphatidylethanolamine from the lumen to the cytoplasm of the disc membrane by acting as a flippase. In Stargardt macular dystrophy, the loss of this function led to disruption in the transport of these two molecules (Sun et al., 2000; Tsybovsky et al., 2010; Quazi et al., 2012).

Our results show that ABCA13 was the most dysregulated ABCA transporter globally in FTL-D-TDP. ABCA13 has been studied mainly in terms of mental conditions, such as schizophrenia, bipolar disorder or depression (Knight et al., 2009). It is downregulated in schizophrenia, bipolar disorder, major depression (Knight et al., 2009; Dwyer et al., 2011; Chen et al., 2017) and dementia with Lewy bodies (Rajkumar et al., 2019), and upregulated in glioblastoma (Drean et al., 2018) and adenocarcinoma (Araujo et al., 2016). In a recent study, ABCA13 was shown to be associated with synaptic function in autism spectrum disorder (Kimura et al., 2022). Its downregulation results in impaired protein subcellular localisation and cholesterol trafficking (Nakato et al., 2021). The downregulation of ABCA13 in these psychiatric conditions is in contrast to the upregulation of ABCA13 (and ABCA4) in FTL-D-TDP, implying different roles for these ABCA transporters in FTL-D-TDP. The expression level of both ABCA4 and ABCA13 strongly correlated with the microglial cell markers TMEM119 and to TARDBP expression, suggesting a potential role for these ABCA transporters in neuroinflammation in FTL-D-TDP. Since neuroinflammation is widely considered as a hallmark of neurodegenerative diseases and its role in the aetiology of FTL-D is of increasing interest (Bright et al., 2019), the relationship between neuroinflammation, TARDBP and ABCA4 and ABCA13 should be further examined to determine if these ABCA transporters exhibit neuroprotective or more neurotoxic roles. Interestingly, there have been recent reports of TDP-43 inhibition of cholesterol biosynthesis through the master regulator of cholesterol homeostasis, sterol regulatory element-binding protein 2 (Egawa et al., 2022), particularly in the ubiquitous oligodendrocytes harbouring TDP-3 inclusion pathology in FTL-D-TDP (Ho et al., 2021).

The strength of this current study is the comprehensive coverage of the expression of all members of the ABCA transporter family. This is important as most of the ABCA transporters have not been investigated in the context of FTL-D-TDP, let alone FTL-D-TDP brain, despite the fact that lipid dysregulation is intrinsically linked to neurodegeneration. Another strength of this

study is the analysis of multiple regions of the brain that encompasses different stages of FTLN-TDP. This is important as lipid dysregulation changes with disease progression that would impact the response of the ABCA transporters. This study could have been further strengthened with the addition of protein expression data, although reliable antibodies against most of the ABCA transporters are not available for human protein lysates. Also, further research is required to determine regional and cell-type specific changes in ABCA transporters and their effect on FTLN-TDP tissue changes.

We provide new data characterising the expression of ABCA transporters in five brain regions affected at different stages of FTLN-TDP, correlating changes in ABCA transporters with expression of TARDBP and cell subtype markers. Data suggestive of cell type specific increases in ABCA transporters in FTLN-TDP include ABCA7 in astrocytes and ABCA4 and ABCA13 in microglia, with these microglia increases associated with increased TARDBP expression. Regulation of these transporters in the cell types identified has not been previously determined, requiring further research. However, the identification of widespread dysregulation of particular ABCA transporters, some not previously linked to neurodegenerative diseases, implies new and important physiological roles of these transporters in association with FTLN-TDP.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JK carried out RNA extraction and qPCR, analyzed the data, and wrote the manuscript. HL provided expert advice and revised the manuscript. SB prepared tissue lysates and carried out western blotting. YF carried out immunohistochemical analysis. GH provided expert advice and revised the manuscript. WK

conceived, developed, and supervised the project, analyzed the data, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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