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A Calcium Channel Alpha2delta Subunit Theory of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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A Calcium Channel $\alpha 2\delta$ Subunit Theory of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating disease whose etiology is currently unknown. This paper presents a novel theory in which ALS is caused by an impairment of the $\alpha 2\delta$ subunit of voltage-gated calcium channels (VGCCs), most likely due to autoimmune targeting. I show how the impairment mechanistically induces chronic calcium, which in turn explains the major clinical, epidemiological, and pathological evidence known about the disease. The same theory explains the major variant of frontotemporal dementia (FTD) that greatly overlaps with ALS.

Keywords: ALS; FTD; high threshold voltage-gated calcium channel; a2d subunit

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal disease involving the degeneration of motor neurons (MTNs) [1,2]. Most patients exhibit sporadic ALS (sALS), whose etiology is not known, while 10% of the patients show a familial form (fALS) that involves identified genetic mutations. In both variants, approved treatments only have a marginal benefit, and death occurs a few years after diagnosis. There is substantial overlap between ALS and frontotemporal dementia (FTD), especially its behavioral variant (FTDbv), which is associated with TDP43 [3].

Beyond a few initial hypotheses [4], there is currently no theory that addresses the major facts of sALS, fALS or FTD. Here I present a new theory of ALS and FTDbv that explains their etiology, pathophysiology, and clinical symptoms. The main thesis is that sALS is caused by an impairment of the $\alpha 2\delta$ (a2d) subunit of high voltage-activated voltage-gated calcium channels (H-VGCCs), most likely due to autoimmune targeting. This results in chronically higher calcium entry throughout life, which eventually yields toxicity that causes the disease symptoms, cellular stress and degeneration. The mutations associated with fALS also induce chronic calcium, with similar downstream consequences.

Section 2 provides general background on VGCCs and the a2d subunit, including its role in synapse development, signaling, and maintenance. Section 3 explains the reasons for suspecting a2d, and presents an account of the specific calcium and a2d impairment in ALS. Section 4 details evidence supporting the theory, including calcium dysregulation in ALS, the explanatory power of chronic calcium for the facts known about ALS, a2d evidence, and insulin-related evidence. Section 5 discusses autoimmunity in ALS, and Section 6 discusses FTD.

2. Voltage-Gated Calcium Channels (VGCCs)

2.1. General Background

The family of VGCCs includes high voltage-activated VGCCs (H-VGCC) and the low voltage-activated T-type VGCC, which is not involved in ALS. H-VGCCs are comprised of a pore alpha1 (a1) subunit, an auxiliary beta subunit, and an auxiliary a2d subunit [5–8]. Each of these has several gene variants and some have alternative splicing variants. H-VGCCs include L-VGCC (L-type, Cav1), P/Q-VGCC (Cav2.1), N-VGCC (Cav2.2), and R-VGCC (Cav2.3). H-VGCCs are activated in relatively depolarized membrane potentials and support transmitter release and sustained execution.

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Cav1.1 is expressed in skeletal muscle, where it promotes voltage sensing, calcium outflux from the sarcoplasmic reticulum, and excitation-contraction coupling. Cav1.2 is expressed in neurons, the cardiovascular system, pancreas beta cells, adrenal chromaffin cells [9], and skin [10]. Cav1.3 is expressed in metabolism and valence areas, including the extended amygdala, hypothalamus nuclei, and brainstem [11]. Cav2.1 is expressed in neurons, including MTN axons (presynaptically) and cerebellar Purkinje cells. Cav2.2 is highly expressed throughout the brain during development, with high cortex and hippocampus expression remaining in adulthood [12]. Cav2.3 is expressed in neurons, cardiac and smooth muscle, and beta cells [7]. L-VGCC-like channels are expressed in immune cells, including B cells and T cells [13–17].

2.2. The a2d Subunits

The a2d subunit is present in L-VGCC, P/Q-VGCC, and N-VGCC [6]. There are four a2d genes, a2d1-4. The subunit is generated by a single gene whose product is cleaved into two disulfide-bonded polypeptides. This cleavage is essential for its function [18]. The subunit is extracellular, glycosylated, and GPI-anchored at the membrane [19].

With respect to distribution, a2d1 is widely expressed in the brain, mainly in excitatory neurons, including in the hippocampus, hypothalamus, the insula, olfactory areas, and dorsal root ganglia [20,21]. It is less strongly expressed in frontal areas. It is expressed in skeletal muscle [22], the heart, smooth muscle [6] and pancreatic beta cells, where it is the main a2d subunit [23]. a2d2 is mainly expressed in inhibitory neurons and in the cerebellum [20]. It is also expressed in immune T cells [17]. a2d3 is expressed in MTNs and caudate-putamen (i.e., the motor system) [20,21], and also in the retina [24]. a2d4 is limited to the retina [25].

2.3. Physiological roles of a2d

Both of the auxiliary H-VGCC subunits, beta and a2d, promote VGCC trafficking to the plasma membrane [26]. A specific role of the a2d subunit is to promote channel anchoring in stable membrane sites, including neural synapses [27]. There is unequivocal evidence that a2d promotes synapse formation, maintenance and neurotransmission [28–35]. a2d supports high amplitude synaptic calcium entry, both via VGCC activation and via association with NMDA receptors and promotion of their surface trafficking [36–38]. The subunit supports anchoring of VGCC in lipid rafts [19,39,40], and synaptic adhesion [41–44]. These roles are highly preserved: invertebrate a2d homologs are expressed at the neuromuscular junction (NMJ), where they are involved in synaptogenesis and presynaptic morphology [45,46].

We particularly emphasize the role of a2d within the larger plasticity picture of adhesion molecules such as neuroligin/neurexin and LRRTM. Such proteins connect pre- and postsynaptic sites to improve synapse stability and signaling [47]. The a2d subunit participates with these proteins in trans-synaptic nanocolumns that are connected to the cytoskeleton and restrict the spatial propagation of neurotransmitters, allowing strong and rapid downstream signaling [47].

3. Proposed Calcium & a2d Impairment in ALS

3.1. Motivation

3.2. Calcium Evidence

The involvement of high calcium and calcium channels in ALS pathology is well-known and supported by overwhelming evidence given in Section 4. The present paper is the first to propose a causal role for a2d impairment. There are several reasons to focus on a2d as the main culprit in ALS, summarized here.

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3.3. Suspect by Subcellular Location

The role of a2d is to support synapses, and synaptic impairment at the NMJ is the major pathological feature in ALS [48–52], with axon degeneration preceding MTN death.

3.4. Suspect by Membrane Location

a2d is located extracellularly, making it accessible to antibodies, immune cells, and other circulating factors. The beta subunits are intracellular, and the a1 subunits are transmembrane proteins.

3.5. Suspect by Elimination

The antibody evidence listed in Section 4 clearly demonstrates autoimmune targeting of H-VGCCs in ALS. However, it does not point to any specific channel or protein, with positive results regarding the involvement of L-, P/Q-, and N-VGCCs, which have different a1 subunits. This lack of specificity with respect to a1 seems to point to the target being the a2d and/or the beta subunits (although Section 5 explains why this argument actually does not rule out the L-VGCC a1 subunit). However, the target could also be a region of genetic overlap between several a1 subunits. Naturally, there may also be several disease variants, each targeting a different subunit.

3.6. Calcium Part of the Theory

My account of calcium in ALS is as follows. Usually starting in early life, most likely as a result of a channelopathy or autoimmune targeting, H-VGCCs calcium metabolism is excessively active in ALS. This high basal activity provides ALS patients with physical and mental strength that are commonly higher than in other people (e.g., ALS is known to be associated with sports).

Calcium can induce toxicity, and this is eventually what it does in ALS. At some point in life, some of the tissues expressing H-VGCC start showing decreased function. There are three major such tissues, MTNs, skeletal muscle (SKM), and insulin-releasing pancreas beta cells (in FTD, it is specific areas of the brain). Cardiorespiration is also damaged, as seen by the most common death cause.

As is the case for many biological agents, healthy calcium signaling involves strong (high amplitude) influx that is rapidly terminated and cleared via negative feedback (negFB) mechanisms [53–56]. In addition, healthy signaling occurs in restricted nanodomains where the Ca^{2+} signal is boosted [57]. In ALS, due to calcium channel subunit impairment, at disease onset we have the opposite situation, prolonged and weaker signaling. This is what the term **chronic** commonly refers to. Thus, our premise is that ALS involves strong cellular calcium that at some point turns to be chronic and toxic.

3.7. a2d Part of the Theory

How does a2d impairment cause excessive calcium throughout life, which turns into chronic calcium at disease onset? The main role of a2d is to anchor the channel at stable membrane sites where it supports signaling nanodomains. Without a functioning a2d, the beta subunit still supports channel trafficking, but it is not anchored properly at the membrane. Without nanodomains, more calcium enters the cell.

Moreover, it is reasonable to assume that part of the action of a2d is to exert negative feedback on channel transcription and trafficking, because stable anchoring at the membrane is the last step needed for channel formation. Without a functioning a2d, the number of a1 subunits would be larger, which induces larger calcium entry.

A simple complementary mechanims whereby reduced a2d function can yield chronicity is by increasing the channel's lateral mobility [58], which can decouple it from the synapse and yield similar consequences as reduced negative feedback.

Which a2d? As there are four a2d genes, a theory that points to a2d needs to address their respective roles in the disease. There are at least three possible hypotheses. First, each a2d could give

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rise to a different disease. a2d3, which is expressed in skeletal muscle and MTNs, would be responsible for ALS; a2d1, with its cortical expression, would be the target in FTD; a2d2, with its cerebellum expression, would be involved in some variants of autoimmune cerebellum ataxia (some of which are known to attack VGCCs) [59]; and a2d4 might be involved in some autoimmune retinal diseases (see below). A problem with this (too) elegant proposal is that beta cell impairment is fundamental to ALS (see Section 4), and beta cells mainly express a2d1.

Another hypothesis is that the main culprit in ALS is a2d1, since it is strongly expressed in the tissues most affected in ALS (the motor system, brain, and beta cells). Yet another possibility is that all a2d subunits can be affected, since they possess considerable genetic overlap.

At present, all of these hypotheses are possible, since there is insufficient evidence to arbitrate between them. The last two seem more likely than the first for ALS, but the role of a2d2 and a2d4 in the first hypothesis may be valid.

In summary, impaired a2d function can induce chronically higher calcium entry into cells throughout life. At some point, this results in calcium toxicity that yields degeneration and death.

4. ALS Evidence

4.1. Calcium

4.2. Serum, Ig, CSF Evidence

There is overwhelming direct and indirect evidence that patient antibodies, serum, and CSF interact with calcium channels in ALS. A thorough search found 36 papers [60–95].

In 18 of these papers, the interaction directly involved increased calcium. Patient antibodies and sera induce the following effects: (most of these results are MTNs) increased P-VGCC currents (and open time) in cerebellum Purkinje cells [67], extracellular calcium-dependent cell death in MTN-neuroblastoma hybrid cell line (VCS4.1), prevented by N- or P-VGCC (but not L-VGCC) antagonists [68], increased calcium and vesicle number in spinal MTNs [72], increased Ca^{2+} currents in a hybrid MTN VCS4.1 cells [71], increased extracellular calcium entry via VGCCs leading to higher intracellular calcium in hybrid MTN VCS4.1 cells [77], increased Ca^{2+} influx via P/Q-VGCC, N-VGCC (only weakly via L-VGCC) in cortical synaptosomes [81], development of L-VGCC (but not P/Q-VGCC-)-induced transmitter release in the neuromuscular junction (NMJ) [84], increased presynaptic Ca^{2+} in MTNs, along with golgi patholgoy and increased golgi Ca^{2+} [82], faster H-VGCC current activation in MTNs [85], MTN degeneration and significantly increased number of Ca^{2+}-containing golgi, mitochondria, and rough endoplasmic reticulum (ER) [86], potentiation of transmitter release from MTN via influx through N-VGCC [88], necrosis, MTN degeneration, swelling and Ca^{2+} of golgi endoplasmic reticulum, mitochondria [87], increased muscle miniature end-plate potential frequency, NMJ ACh release, which are significantly decreased in P/Q-VGCC (but not N-VGCC) KO [89], intracellular Ca^{2+} release in astrocytes via IP3 (intracellular stores) [91], high rather than oscillating L-VGCC-mediated intracellular Ca^{2+} in mouse islets (in ALS patients with type 2 diabetes) [92], MTN degeneration, inclusion-like IgG accumulation, increased intracellular Ca^{2+} [93], increased number of synaptic and Ca^{2+} elevation in MTN terminals [94], and increased cytoplasmic calcium, cell death in mice MTNs [95] (the last two results are with serum of patients with identified mutations).

In 8 of the 36 papers, the interaction resulted in directly decreased Ca^{2+}. This includes decreased charge movement, peak calcium current, and slower channel inactivation in skeletal muscle L-VGCCs [63], decreased mean skeletal muscle L-VGCC open time with stabilization to a smaller amplitude [65], decreased peak L-VGCC current with increased tail current deactivation rate in mammalian skeletal muscle fibers [66], decreased charge movement and peak L-VGCC currents in isolated muscle fibers [70], depressed inward Ba^{2+}-mediated (high threshold) VGCC currents in rat cerebellum granule culture [69], suppressed intracellular Ca^{2+} increase via P/Q-VGCCs (but not N-, L-VGCC) influx in

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cultured neurons [74], decreased H-VGCC peak and faster and more hyperpolarized inactivation in mice DRG neurons [76], and inhibition of L-VGCC-mediated dopamine release [79].

In 8 of the 36 papers, the reported results indirectly support increased calcium, including increased NMJ presynaptic ACh release frequency following 4 hour and 4-12 week incubation [60,61], increased NMJ miniature end-plate potential frequency (resting quantal ACh release) [62], enhanced excitatory transmission in hippocampus culture via presynaptic glutamate release [75], increased CSF glutamate [78], increased NMJ spontaneous transmitter release and quantal content, with similar effects produced by caffeine via Ca^{2+} [80], increased spontaneous NMJ ACh release in 3/4 cases [83] (this paper also reported decreased spontaneous NMJ ACh release in some cases, indirectly supporting decreased calcium), and endoplasmic reticulum stress in spinal MTNs [90] (this result is with sALS CSF). These results only provide indirect support, because although increased neurotransmitter release can stem from increased calcium, it can also be due to other reasons.

The presence of VGCC antibodies was reported in several papers, including antibodies to L-VGCC [64,70,83] and P-, Q-, and N-VGCC [73]. Patient IgGs were found to be present in MTN axon terminals [96].

Many of these results were done in the same lab (Appel), but more than half of them were done by unrelated labs, over more than two decades. A technical argument was raised against the initial wave of these results [97], but it has been refuted [87].

It should be emphasized that this evidence is from ALS patients, not from animal models, which are not valid for sALS (according to the present paper).

4.3. Direct MTN Evidence

There is direct and indirect evidence for calcium involvement in ALS beyond calcium-related antibody/serum effects. Calcium is significantly increased in patient muscle nerve terminals [98].

4.4. Drug Evidence

Taking VGCC blockers or ACE inhibitors (which decrease intracellular Ca^{2+} [99]) against hypertension is associated with decreased ALS risk [100–102].

4.5. Genetic Evidence

MTNs induced from pluripotent stem cells of patients with all major fALS-associated genes (C9orf72, SOD1, TDP43, FUS) show higher Ca^{2+} (basal and transients) [103]. In SOD1 mutants, increased MTN calcium and sodium persistent inward currents is early postnatal change [104].

4.6. Other Tissue

It can be argued that a general H-VGCC impairment cannot be the core cause of ALS, because this would cause a much wider impairment than the MTN one seen in ALS. However, ALS patients actually do show wide impairment, which overlaps the distribution of H-VGCCs. In addition to MTNs and skeletal muscle issues, ALS patients show cognitive deficits [105,106], cardiorespiratory and cardiovascular damage [107–112], skin neuropathy [113–115], pain in all disease stages, sometimes before motor symptoms [116], impaired insulin secretion [117,118], Purkinje cell damage [119], and immune system dysregulation (excessive inflammation coupled with inefficient immune responses) [120]. The affected tissues are precisely those with high H-VGCC expression. In addition, calcium is significantly increased in patient blood lymphocytes [121].

The beta cell evidence is especially relevant. Like the calcium evidence, both increased and decreased insulin release have been reported [117]. The decrease is of early phase secretion [118].

The question why MTNs are more sensitive than the other tissues is discussed below.

In summary, there is overwhelming evidence for calcium dysregulation in ALS, pointing to chronic calcium.

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4.7. Explanatory Power for ALS Facts

Studying the sALS literature, several major pathological phenomena can be identified: muscle use problems, muscle wasting, muscle spasms (fasciculation, twitches) (the three main clinical symptoms); symptom appearance with aging (the main epidemiological datum); degeneration of spinal or bulbar (but not ocular) MTNs (the main pathological datum); aggregation of the TDP43 protein [122], oxidativestress [123–129], and mitochondria dysfunction [130] (the main cellular data); hypermetabolism in motor areas [131] (the main imaging datum); and toxicity of patient serum/Ig/CSF (much of it related to calcium, as detailed above).

Chronic intracellular calcium can explain all of these data points. It can cause muscle spasms because intracellular Ca^{2+} elevation is what induces muscle contractions [132]. Hypermetabolism is identified using PET via increased glucose uptake capacity. Chronic calcium would yield a chronic activation of calcium pumps (PMCA, SERCA), which consume ATP [133]. Relative ATP deficiency activates AMPK, which increases Glut4 translocation to the cell surface [134] and thus glucose uptake capacity. Increased activated AMPK is indeed present in patient MTNs [135,136]. Chronically high ATP consumption can also account for muscle wasting (see also insulin discussion below).

Chronic calcium induces oxidativestress (mainly H2O2), mitochondria permeability pore opening, and ER stress [137–142]. oxidativestress and H2O2 induce and are enhanced by the cellular stress responses, including the unfolded protein and heat shock responses, and can lead to apoptosis [143–145]. TDP43 is a major protein recruited by cellular stress responses [122]. Cellular stress and oxidativestress (specifically H2O2) induce TDP43 aggregation, and its localization in stress granules [146–151]. TDP43 is strongly related to ALS, both due to intracellular aggregates in almost all patients [152,153] and to mutations in 10% of fALS patients [122]. In our view, it is not causal in sALS, since the parsimonious account of its aggregation is chronic activation by stress responses. Chronic cellular stress eventually activates the death arms of cellular stress responses [154,155], explaining MTN degeneration and muscle use problems.

The late onset age of ALS can be explained by the fact that normal aging involves increased calcium currents [156,157] and reduced calcium buffering [158], making aged cells more susceptible to abnormal Ca^{2+} [1].

The specific vulnerability of non-ocular MTNs in ALS has been explained by the fact that these MTNs express very low levels of calcium binding proteins [159,160] (although there are also conflicting results [161]). Eye movements and the cerebellum might be relatively preserved because the level of these proteins in oculomotor neurons and Pukinje cells are 5-6 and 15 times higher, respectively [160,162]. Moreover, sensitive MTNs (tongue) express 3 fold higher levels of H-VGCC currents than ocular MTNs [163]. In addition, MTNs have long axons and high energy requirements, making them more sensitive to chronic ATP consumption and oxidativestress.

High pre-onset physical activity is strongly associated with increased ALS risk [164–170] (although there are also neutral results [171,172]). High calcium increases muscle contraction capacity and performance, explaining this datum.

In summary, chronic calcium is toxic to cells and can account for the salient data of ALS.

4.8. a2d

There is some evidence for the a2d hypothesis. It is small compared to the strong evidence implicating H-VGCCs, but sufficient for lending credibility to the theory.

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[1] A more specific mechanism for disease onset is impaired insulin signaling (see below), which also occurs with aging.

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4.9. Patient IgG interacts with a2d, with the predicted effects

There is one direct evidence supporting the hypothesis. In a study with ALS patients comorbid with type 2 diabetes (DB2), in 60% of the patients, serum induced high rather than oscillating L-VGCC-mediated intracellular Ca^{2+} in mouse pancreas beta cells. The ALS-DB2 serum induced 2.4x higher basal insulin release, and somewhat lower glucose-stimulated insulin secretion than DB2 serum. Crucially, this was shown to be mediated by IgG targeting the a2d1 subunit [92]. IgGs from ALS patients not diagnosed with DB2 were not tested.

Thus, patient IgG contains a2d1 antibodies, and these induce effects that are similar to those induced by chronic calcium (increased release with a smaller amplitude).

4.10. a2d is Decreased in ALS

The a2d1 subunit was shown to be significantly decreased in patient MTNs (8 vs. 3 controls) and in familial iPSCs-derived MTNs (24 vs. 18) [173]. However, the same project reported similar results for a large number of other proteins.

4.11. a2d Suppression Increases Risk

Gabapentin and pregabalin are a2d ligands that disrupt channel function and are routinely used for treating epilepsy and pain. Suppression of a2d should enhance the a2d impairment present in ALS and exacerbate the state of ALS patients. Indeed, a regional census study in Italy found that usage of antiepileptic drugs 5-6 years prior to ALS diagnosis was associated with increased ALS risk [174]. In about half of these patients, the drug was gabapentin.

4.12. a2d Suppression Accelerates Symptoms

Respiration problems are a hallmark of ALS. In a clinical trial of gabapentin in ALS, it exacerbated patient condition by accelerating respiration (forced vital capacity) decline [175]. Gabapentin therapy can also induce recurrent hypoventilation and respiratory failure in non-ALS patients [176,177].

4.13. a2d Suppression is Associated with Motor Diseases

Gabapentin can induce severe myopathy and other muscle problems (myositis, rhabdomyolysis) [178–184]. It can also induce myoclonus (twitches, spasms, fasciculations), a core feature of ALS [185–188].

Myasthenia gravis (MG) is an autoimmune disease involving antibodies targeting the NMJ (mainly nicotinic receptors) [189]. There is some evidence that gabapentin may be harmful in MG [190], showing that suppression of a2d can be involved in NMJ damage.

4.14. Animal Models

Mice with a2d2 mutations display impaired motor performance [191]. Two non-lethal a2d knockout mouse models have been reported, with a2d1 KOs showing no apparent motor deficits [192], and a2d4 KOs being hyperactive [25]. The latter model shows again that a2d impairment can result in increased physical activity, but a2d4 is not expressed in relevant tissue in humans. The former model does not support the a2d hypothesis, but it does not refute it either. Mice do not exhibit the neurodegenerative diseases associated with aging in humans, so the a2d1 model might be a model of pre- but not post-onset human ALS.

4.15. Insulin

The fact that a paper presenting a theory of ALS contains a section on insulin may be surprising, since insulin is not mentioned at all in neurology textbooks and general ALS reviews [1,2,193], and is mentioned very little even in focused reviews of metabolism in ALS [194,195].

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In my view, insulin is fundamental to the disease [117]. Not only is insulin function impaired by the causal processes of ALS, it is this impairment that serves as a major trigger of disease symptoms. Here I summarize results from a companion paper focusing on insulin in ALS [117], and add new evidence specific to calcium channels and cholesterol.

4.16. Insulin Impairment

There is a large body of evidence from glucose tolerance tests showing that insulin secretion and/or signaling are impaired in ALS. However, this is usually not detected: although some ALS patients are diagnosed with diabetes (DB), most of them are not, because patient glucose levels are inside the normal range. My explanation for this is that chronic calcium induces excessive insulin-independent glucose uptake (IIGU) that masks the insulin problem. As detailed above, chronic calcium can explain the ALS hypermetabolism results via excessive ATP consumption, activated AMPK, and Glut4 membrane translocation, resulting in increased glucose uptake capacity that compensates for reduced insulin. Moreover, intracellular calcium directly induces IIGU, even at amounts below the muscle contraction threshold.

4.17. Insulin and ALS Processes

Insulin and the detrimental processes taking place in ALS mutually oppose each other. Insulin promotes the growth mode of cellular stress responses, and opposes their death mode. It promotes protein synthesis, opposes degeneration, and reduces excessive H2O2 and intracellular calcium. Conversely, the harmful modes of cellular stress responses induce insulin resistance [117].

4.18. Insulin and Diabetes

Early diabetes (usually type 1 (DB1)) is associated with increased risk for ALS, which we explain in two complementary ways. First, the VGCC impairment that causes ALS also damages beta cells, and this can manifest as early DB. Second, the lifelong impairment in insulin shown in DB1 is difficult to control even with modern medicine, yielding an earlier onset in people with ALS. In the former, the two diseases have the same core cause, while in the latter, insulin deficiency increases risk. Indeed, DB1 patients and mouse models exhibit early MTN loss and impaired muscle function [196–198].

Late diabetes (type 2 (DB2)) is associated with decreased ALS risk, which seems to contradict our view that insulin impairment is the trigger for disease symptoms. However, DB2 involves elevated levels of blood insulin, and many patients are given insulin-based treatment. The theory here predicts insulin to be protective, and indeed, there is epidemiological evidence showing that taking insulin-based drugs reduces ALS risk [117]. DB2 also involves higher blood glucose, which was recently shown to be associated with lower TDP43 pathology in normal aging [199].

4.19. Trajectories

Insulin and body mass index (BMI) trajectories are detailed in the companion paper [117].

4.20. Calcium

Insulin's beneficial effect on acute (non-chronic) calcium signaling is detailed in the companion paper [117]. For example, insulin rapidly activates Akt, ERK1/2, and CaMKII [200,201]. Crucially, L-VGCC or CaMKII inhibitors significantly decrease insulin-stimulated glucose uptake in SKM [202]. As long as insulin release is OK, it manages to cover up for the ALS problem. As it starts deteriorating, disease symptoms erupt.

4.21. Cholesterol

Insulin is a major factor in cholesterol synthesis via the Akt/mTOR/SREBP axis [203,204]. Cholesterol is in turn an essential component of lipid rafts, which are crucial for synaptic receptors,

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including nicotinic receptors at the NMJ [205,206], and for cytoskeleton health during both axonal growth and neurite maintenance [207,208]. Indeed, ALS patients show cholesterol dysregulation [209,210]. However, cholesterol does not seem to be a major factor in the disease, in light of the quite small effect exerted by statins [211]. Insulin's protective effect occurs via calcium metabolism much more than with lipid metabolism.

5. Autoimmunity

In addition to the calcium-related antibody evidence cited above, it has long been recognized that ALS shows elevated circulating immune complexes [212–214] and spinal cord infiltration by T cells [215]. More recently, reduced numbers of regulatory T cells cells were shown to correlate with disease progression [216,217]. Impaired blood-spinal and blood-brain barriers in ALS were reported [218]. Thus, the immune system is clearly active in ALS [120,219], and immune T cells express a2d, in T cells [17].

Immune involvement in a neurodegeneration disease is not surprising, since degenerating cells recruit immune (and glia) cells. Here I present the case for autoimmune reactivity being actually causal in ALS.

5.1. Calcium-Related Antibodies

The strongest body of evidence for autoimmunity is the one detailed above with respect to the presence and effect of patient antibodies interacting with calcium channels. While such antibodies can result from degeneration or injury that are due to other reasons (e.g., an inherent born VGCC abnormality, or traumatic brain injury, which is indeed associated with increased ALS risk [166,167, 220]), autoimmunity trivially explains their existence. Moreover, the physically fit lifetime phenotype of ALS supports an early event rather than a relatively late injury.

5.2. Immune Complement

The classical pathway of complement activation is by antigen-antibody complexes [221], and the complement terminal pathway induces neurodegeneration and cell death. Among the four IgG subclasses, only IgG1 and IgG3 bind complement effectively [222], and IgG3 is the subclass of 1B50-1, an a2d1 antibody [223]. There is substantial evidence for classical complement activation in ALS [212,213,224–227], including in spinal cord and motor end-plates [228–230]. Activation in motor end-plates includes ones that are still innervated [230].

Complement provides strong evidence to an active antibody-mediated process that contributes to or is responsible for NMJ deinnervation, and the antibodies are of the type that can target a2d.

5.3. Association with Autoimmune Diseases

General support for ALS being related to autoimmunity (but not specifically to a2d) comes from its disproportional pre-onset association with autoimmune diseases, including in an all-England study [231], an all-Sweden study [232], a large Netherlands study [233], and the FDA adverse event reporting system [234].

5.4. Association with Myasthenia Gravis (MG)

As mentioned above, MG is an autoimmune disease that targets nicotinic receptors in the NMJ [189]. ALS in associated with MG beyond chance levels [235–237]. A possible scenario here is that the NMJ impairment in MG triggers the autoimmune reaction against VGCCs, inducing ALS symptoms.

5.5. Muscular Autoimmune Diseases Targeting VGCCs

There are several autoimmune diseases that target VGCCs. The most relevant one is Lambert-Eaton myasthenic syndrome (LEMS), which is a neuromuscular disease. LEMS involves

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antibodies against the a1, beta or a2d subunits of P/Q-VGCC, but not antibodies to a2d alone [238]. Thus, an autoimmune disease that targets a2d can be expected, but has not been found yet.

5.6. NMJ Exposure

Above, we explained the specific vulnerability of non-ocular MTNs in ALS via reduced calcium buffering and increased VGCC currents. A simpler account is that the NMJ lies outside the blood-brain barrier, exposing it to circulating antibodies and immune cells.

5.7. Ocular MTNs

The well known ocular immune privilege [239] can be argued to provide another explanation for the relative protection of ocular MTNs, supporting autoimmunity in ALS. However, this account is not that convincing, given that ocular MTNs are damaged in the autoimmune diseases LEMS and MG [189].

The retina strongly expresses a2d4 [25] and also some a2d3 [24]. It can be speculated that these are the targets in the minority of LEMS and MG patients that do not exhibit the antibodies usually associated with these diseases. However, I am not aware of any evidence supporting this idea.

5.8. Adaptive Immune Trajectories in ALS

If ALS is caused by autoimmunity, both active adaptive immune cells and antibodies should be detected, which is indeed the case. However, there is a factor that complicates the situation: immune cells themselves, including B and T cells, express L-VGCCs or L-VGCC-like channels [13,15,240,241]. In particular, L-VGCCs are crucial for B cell proliferation and their transition into plasma cells, which are the ones secreting antibodies [14,242–244]. Plasma cells also express L-VGCCs [241], and a2d2 is essential for the proper function of Th2 T cells [17]. This means that an immune reaction against H-VGCCs could target immune cells themselves, eventually resulting in decreasing antibody and lymphocyte levels.

This observation supports the theory instead of opposing it, since it can explain why serum/Ig-VGCC interaction was not identified in all ALS patients.

There is some evidence supporting this model. IgG levels were reported to be normal at early disease stages, and strongly decrease with disease progression, along with CD4 T cell activation [245]. IgG levels were significantly higher in male patients than in controls, but negatively correlated with disease severity and duration [225]. Serum circulating immune complexes, mainly composed of IgG, were significantly elevated on diagnosis, but decreased to control levels at the 2nd visit (although IgG remained high) [214]. A recent meta-analysis found that lower IgG is associated with early- vs. late-onset patients, indicating that disease severity negatively correlates with IgG levels [226]. In addition, B cells were reported to be completely absent from spinal cord infiltrates [246], and lymphocytes were markedly decreased in early stage ALS [247].

In summary, there is some support for autoimmunity being causal in ALS, but most of the evidence is also consistent with immunity being recruited by other causal factors, e.g., genetic mutations or injury.

6. frontotemporal Dementia (FTD)

6.1. Background

FTD has substantial overlap with ALS. 40% of FTD patients show MTN dsyfunction [248], and 50% of ALS patients show FTD symptoms, with many meeting diagnosis criteria [249]. FTD has two main variants, tau-positive and tau-negative, and the tau-negative variant involves pathological TDP43 as in ALS [152,153]. As in ALS, most TDP43 inclusions colocate with stress granules [250].

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There are also FTD variants distinguished by symptoms (e.g., with certain types of language damage). For simplicity, I will focus on the TDP43 variant (roughly FTDbv) here.

FTD is classified as a dementia because it eventually involves degeneration and memory loss. However, it is very different from other dementias. Symptoms manifest as executive dysfunction, apathy, behavioral disinhibition, hypereating, and lack of empathy, with relative sparing of episodic memory [251,252].

6.2. Theory

Due to the tight link with ALS, our starting point is that the underlying cause is similar, a VGCC impairment. As in ALS, we need to ask whether there are neurons that are particularly vulnerable, and why. It turns out that the von-economo neurons (VENs) in the insula and ACC are specifically vulnerable [253,254], and that their anatomical and molecular profile [255] is very similar to that of MTNS: they have large axons and low expression of calcium buffer proteins [256]. Thus, **in both ALS and FTD, the main damage is in neurons that are more sensitive to calcium overload**.

To complete the picture, we need to show that VEN impairment can explain the major FTD symptoms. It has been shown that lesions of the anterior insula (but not ACC) impair the capacity of identifying others' pain [257], explaining the lack of empathy and the behavioral disinhibition in FTD. Feeling your own pain is known to be essential for empathy for others' pain [258], and gray matter loss in the right insula and anterior temporal cortex is associated with blunted pain in FTD [259]. Relatedly, the anterior insula is the major site of interoceptive heart inputs to the brain, with blunted heart reactivity to emotional stimuli in FTDbv [260].

As in ALS, there is a link between the appearance of symptoms and low insulin-induced glucose uptake. Regardless of FTD, self control is known to be lowest when brain glucose is low [261]. The symptoms of insulin-induced Hypoglycemia are well-known and include rudeness, violence, abnormal sexual behavior, exhiliration, asociality, perseveration, impulsivity, slowness, speech difficulties, and even hallucinations [262]. Hypereating and sweet craving in FTD can simply be explained by the brain sensing a deficiency in insulin-induced glucose uptake. Further supporting metabolism involvement, excessive eating is correlated to hypothalamus atrophy [263,264].

FTD apathy can be explained via blunted facial EMG responses due to right insula damage [265].

Insula lesions yield swallowing problems, which may directly explain swallowing problems in many ALS patients (in addition to the classical accounts) [266].

6.3. Glucose Evidence

In addition to the evidence cited above with respect to the damage in FTD focusing on frontal areas and VENs, there is a large body of evidence showing 'hypometabolism' in FTD in these areas [267,268]. This is generally shown using FDG-PET, where decreased PET ligand binding is interpreted as hypometabolism. However, what decreased PET ligand binding shows is reduced expression of glucose transporters, which implies higher utilization (ligand binding can also show higher occupancy, which has the same effect due to negative feedback). Thus, it is not that the vulnerable areas utilize less glucose, they in fact uptake more glucose. This we explain exactly as in ALS – chronic activation of VGCCs induces excessive insulin-independent glucose uptake, where glucose is not used for protein synthesis and anti-oxidant defenses, promoting degeneration.

Insulin is involved in these results. FTD involves increased fasting insulin, HOMA-IR (indicating insulin resistance), triglycerides, and lower HDL [269]. DB type 2 occurs in 39% vs. 23% in controls [270]. C-peptide, indicating insulin, is increased, with 5y earlier onset with higher levels [271]. Note that higher C-peptide is associated with regional cortical thinning in cognitively healthy people [272].

There are other indications of hypoglycemia, including dysregulation of CRH, ACTH, and cortisol [273]. A coarse trend was found where CSF glucose was lower and with a lower standard deviation than all other groups tested [274].

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6.4. Calcium Evidence

As in ALS, FTD shows calcium pathology. The calcium binding protein calbindinD28 is dramatically decreased in frontal cortex in patients with both ALS and FTD [275]. Patients CSF is toxic to mouse spinal GABA and calbindinD28 neurons [276].

Interestingly, the brain distribution of L-VGCC (Cav1.2) includes valence (amygdala) and motor areas, but not the hippocampus [11], supporting our account of the difference between FTD and dementias involving episodic memory.

Serum calcium binding proteins (9, 10) are decreased in FTD [277]. FTD patients show significantly increased serum calcium [278]. iPSCs from FTD-tau patients also show dysregulated Ca^{2+} elevation after electrical stimulation [279]. There is Ca^{2+} damage with oxidativestress biomarkers [280]. In one case, P/Q-VGCC, and N-VGCC antibodies caused FTD symptoms in a patient with rheumatoid arthritis and thyroid history [281].

6.5. Autoimmunity Evidence

FTD shows a wide range of antibodies compared to other dementias [282]. In 41/175 (23%) of patients, serum has anti-GluA3 antibodies [283]. FTD shows blood-brain barrier dysfunction, with significantly higher CSF IgGs. This shows more in ALS-FTD than ALS and is associated with worse prognosis [284]. FTD patients had about 25% more autoimmune diseases than controls (lowest in FTD with C9orf72 mutation) [285].

6.6. Additional VEN and Areal Evidence

In FTD patients, loss of VENs and of GABA theta subunit-expressing pyramidal neurons is associated with TDP43 and FUS pathology [286]. Frontoinsular VENs and fork cells show early, disproportionate TDP43 aggregation, correlating with symptom severity and empathy loss [287].

Obviously, VENs are not the only vulnerable neurons. All frontal areas around them show early atrophy, including ACC, mPFC [288], insula, orbital frontal cortex [289], bilateral inferior frontal gyrus, temporal pole, and the rest of the insula [290].

We also note that aging and high BMI involve hypoperfusion specifically in the insula and limbic brainstem, respectively [291]. Diabetes predicts brain hypoperfusion only in the insula, with higher brain hypoperfusion in insula in diabetes vs. obesity [291]. Thus, the insula is specifically vulnerable to gluocse metabolism possibly even without calcium impairment. Hypoglycemia events double dementia risk, and vice versa [292].

7. Discussion

In this paper I presented the first complete theory of ALS and FTD, a theory that explains their etiology and pathology. The theory has three components. First, the fundamental problem is in H-VGCCs. Second, the specific subunit that is most likely involved in most (or all) cases is a2d (although we did leave open which of a2d1-a2d4 are more involved). Third, the source of the problem could be genetic or autoimmune-induced.

7.1. TDP43

A large part of the research done in ALS focuses on the TDP43 protein. In my view, it is not a core cause of the disease, since TDP43 aggregates simply indicate chronic metabolic cellular stress. I think that it is a mistake to focus so much research priority on TDP43 instead of on more fundamental topics.

7.2. Calcium

I think that the centrality of calcium in ALS would be easily accepted by the readers, due to the fact that calcium dysregulation has been so thoroughly demonstrated [293,294]. The challenge with calcium in ALS has turned out to be the identification of the specific subunit(s) involved, due to

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contradictory results produced by the early set of papers. The present paper is the first to raise the idea that the a2d subunit is the core one. This makes sense for a large number of reasons detailed above. (Naturally, other subunits can also trigger the detrimental processes described here in various constellations.)

We should remember that the a2d subunit is cleaved, folded, glycosylated, GPI-anchored in lipid rafts, and uses disulfide bonds. It seems that antibodies only bind it in this state, causing null results in experiments with denatured proteins. This is an empirical issue to be resolved, and it trivially explains some negative results.

7.3. Autoimmunity

We have presented the case that the a2d impairment in ALS stems from autoimmunity. It should be emphasized that it is possible that it stems from some genetic (or epigenetic) cause. At present, there is no evidence supporting this direction, but given that mutations in many relevant genes are strongly associated with ALS (fALS), this is a possibility that needs to be examined.

ALS cells are stronger than normal throughout life, because they enjoy more calcium. At some point, calcium gets chronic and toxic, and this self-amplifying process rapidly damages cells, eventually killing them. This model holds for MTNs, beta cells, skeletal muscle cells, and possibly immune cells. The turning point commonly (but surely not always) occurs when insulin function is reduced to such an extent that it cannot support the ATP, anti-oxidativestress, and protein synthesis requirements of the affected cells.

These results are consistent with a model in which antibodies target immune cell VGCCs throughout life, without noticeable damage (or maybe even improving their reactivity). At some point cells cannot contain this state, setting in motion a detrimental process that does not depend on antibodies anymore. Chronic calcium is self-amplifying (since it involves the suppression of negFB), and perfectly fits the properties of such a detrimental process.

7.4. Insulin

As explained above, the collapse of insulin signaling is a strong candidate for what actually triggers the eruption of the disease. At present, this view is not shared by anybody (in fact, it is actively disputed by many people I have contacted). It is not clear to me why physicians assume that if patient blood glucose levels are at the normal range, this indicates healthy insulin function. About half of cellular glucose uptake is insulin-independent, and it is known to be triggered by calcium. This excessive calcium masks the insulin problem in ALS, and can easily be identified via the initial stages of the OGTT, which can show decreased insulin secretion. The OGTT is a common and easy test and should be administered to all ALS patients.

7.5. FTD

FTD is a simple parallel of ALS in which the vulnerable cells are prefrontal VENs and their neighbors, which have properties similar to MTNs. I have shown how this simple model can naturally explain the various FTD symptoms, including lack of empathy and disinhibition.

7.6. Theory Predictions

As far as I know, the basic experiment to support or refute the a2d direction has not been conducted. No study has reported testing ALS IgGs against the a2d subunit (any of them) alone. Studies widely report testing against the a1 subunit, but not against the auxiliary subunits.

The most relevant reported result is Shi et al [92]. They studied ALS patients with DB2, showing that in 60% of them IgGs target the a2d1 subunit when it is expressed in cells. It should not be too difficult to extend this result to the general sALS population.

I believe that insulin treatment may be disease-modifying in ALS if started early enough, and this is one of my theory predictions.

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7.7. Treatment

In addition to insulin, the theory implies that available immune-based therapies might be beneficial in sALS, since they directly target the disease's causal processes. For example, spectacular results have been recently achieved with CAR T therapy targeting B cells (CD19) against lupus [295]. However, it could be that the damage in ALS has already been done and that B cells are already deficient.

It may be thought that gabapentin and pregabalin, L-VGCC blockers, could help. However, gabapentin impairs a2d membrane trafficking [296].

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1. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. Nature Reviews Disease Primers. 2017;3(1):1-19.
2. Leigh N, Sreedharan J, Wijesekera L. Motor neuron disease: Amyotrophic lateral sclerosis. In: Neuroscience in the 21st Century: From Basic to Clinical, Second Edition. Springer New York; 2016. p. 3799-841.
3. Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. CNS drugs. 2010;24:375-98.
4. Van Den Bosch L. Amyotrophic lateral sclerosis: mechanisms and therapeutic strategies. In: Disease-Modifying Targets in Neurodegenerative Disorders. Elsevier; 2017. p. 277-96.
5. Catterall WA. Voltage-gated calcium channels. Cold Spring Harbor perspectives in biology. 2011;3(8):a003947.
6. Dolphin AC. Voltage-gated calcium channels and their auxiliary subunits: physiology and pathophysiology and pharmacology. The Journal of physiology. 2016;594(19):5369-90.
7. Striessnig J, Pinggera A, Kaur G, Bock G, Tuluc P. L-type Ca2+ channels in heart and brain. Wiley Interdisciplinary Reviews: Membrane Transport and Signaling. 2014;3(2):15-38.
8. Geisler S, Schöpf CL, Obermair GJ. Emerging evidence for specific neuronal functions of auxiliary calcium channel $\alpha 2\delta$ subunits. General physiology and biophysics. 2015;34(2):105.
9. Gandía L, Mayorgas I, Michelena P, Cuchillo I, de Pascual R, Abad F, et al. Human adrenal chromaffin cell calcium channels: drastic current facilitation in cell clusters, but not in isolated cells. Pflügers Archiv. 1998;436(5):696-704.
10. Lee SE, Lee SH. Skin barrier and calcium. Annals of dermatology. 2018;30(3):265-75.
11. Hetzenauer A, Sinnegger-Brauns M, Striessnig J, Singewald N. Brain activation pattern induced by stimulation of L-type Ca2+-channels: contribution of Cav1.3 and Cav1.2 isoforms. Neuroscience. 2006;139(3):1005-15.
12. Pilch KS, Ramgoolam KH, Dolphin AC. Involvement of CaV2.2 channels and $\alpha 2\delta$-1 in hippocampal homeostatic synaptic plasticity. bioRxiv. 2022.
13. Akha AAS, Willmott NJ, Brickley K, Dolphin AC, Galione A, Hunt SV. Anti-Ig-induced Calcium Influx in Rat B Lymphocytes Mediated by cGMP through a Dihydropyridine-sensitive Channel. Journal of Biological Chemistry. 1996;271(13):7297-300.
14. Hoek KL, Antony P, Lowe J, Shinners N, Sarmah B, Wente SR, et al. Transitional B cell fate is associated with developmental stage-specific regulation of diacylglycerol and calcium signaling upon B cell receptor engagement. The Journal of Immunology. 2006;177(8):5405-13.
15. Grafton G, Stokes L, Toellner KM, Gordon J. A non-voltage-gated calcium channel with L-type characteristics activated by B cell receptor ligation. Biochemical pharmacology. 2003;66(10):2001-9.
16. Pelletier L, Moreau M. Cav1 channels is also a story of non excitable cells: Application to calcium signalling in two different non related models. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2021;1868(6):118996.
17. Rosa N, Triffaux E, Robert V, Mars M, Klein M, Bouchaud G, et al. The β and $\alpha 2\delta$ auxiliary subunits of voltage-gated calcium channel 1 (Cav1) are required for TH2 lymphocyte function and acute allergic airway inflammation. Journal of Allergy and Clinical Immunology. 2018;142(3):892-903.

 doi:10.20944/preprints202410.0704.v1

18. Kadurin I, Ferron L, Rothwell SW, Meyer JO, Douglas LR, Bauer CS, et al. Proteolytic maturation of $\alpha 2\delta$ represents a checkpoint for activation and neuronal trafficking of latent calcium channels. Elife. 2016;5:e21143.
19. Davies A, Kadurin I, Alvarez-Laviada A, Douglas L, Nieto-Rostro M, Bauer CS, et al. The $\alpha 2\delta$ subunits of voltage-gated calcium channels form GPI-anchored proteins, a posttranslational modification essential for function. Proceedings of the National Academy of Sciences. 2010;107(4):1654-9.
20. Cole RL, Lechner SM, Williams ME, Prodanovich P, Bleicher L, Varney MA, et al. Differential distribution of voltage-gated calcium channel alpha-2 delta ($\alpha 2\delta$) subunit mRNA-containing cells in the rat central nervous system and the dorsal root ganglia. Journal of Comparative Neurology. 2005;491(3):246-69.
21. Taylor C, Garrido R. Immunostaining of rat brain, spinal cord, sensory neurons and skeletal muscle for calcium channel alpha2-delta ($\alpha 2$-δ) type 1 protein. Neuroscience. 2008;155(2):510-21.
22. Obermair GJ, Kugler G, Baumgartner S, Tuluc P, Grabner M, Flucher BE. The Ca2+ channel $\alpha 2\delta$-1 subunit determines Ca2+ current kinetics in skeletal muscle but not targeting of α1S or excitation-contraction coupling. Journal of Biological Chemistry. 2005;280(3):2229-37.
23. Mastrolia V, Flucher SM, Obermair GJ, Drach M, Hofer H, Renström E, et al. Loss of $\alpha 2\delta$-1 calcium channel subunit function increases the susceptibility for diabetes. Diabetes. 2017;66(4):897-907.
24. Pérez de Sevilla Müller L, Sargoy A, Fernández-Sánchez L, Rodriguez A, Liu J, Cuenca N, et al. Expression and cellular localization of the voltage-gated calcium channel $\alpha 2\delta 3$ in the rodent retina. Journal of Comparative Neurology. 2015;523(10):1443-60.
25. Klomp A, Omichi R, Iwasa Y, Smith RJ, Usachev YM, Russo AF, et al. The voltage-gated Ca2+ channel subunit $\alpha 2\delta$-4 regulates locomotor behavior and sensorimotor gating in mice. PloS one. 2022;17(3):e0263197.
26. Ferron L, Koshti S, Zamponi GW. The life cycle of voltage-gated Ca2+ channels in neurons: an update on the trafficking of neuronal calcium channels. Neuronal signaling. 2021;5(1).
27. Cassidy JS, Ferron L, Kadurin I, Pratt WS, Dolphin AC. Functional exofacially tagged N-type calcium channels elucidate the interaction with auxiliary $\alpha 2\delta$-1 subunits. Proceedings of the National Academy of Sciences. 2014;111(24):8979-84.
28. Hoppa MB, Lana B, Margas W, Dolphin AC, Ryan TA. $\alpha 2\delta$ expression sets presynaptic calcium channel abundance and release probability. Nature. 2012;486(7401):122-5.
29. Risher WC, Kim N, Koh S, Choi JE, Mitev P, Spence EF, et al. Thrombospondin receptor $\alpha 2\delta$-1 promotes synaptogenesis and spinogenesis via postsynaptic Rac1. Journal of Cell Biology. 2018;217(10):3747-65.
30. Tedeschi A, Dupraz S, Laskowski CJ, Xue J, Ulas T, Beyer M, et al. The calcium channel subunit Alpha2delta2 suppresses axon regeneration in the adult CNS. Neuron. 2016;92(2):419-34.
31. Schöpf CL, Ablinger C, Geisler SM, Stanika RI, Campiglio M, Kaufmann WA, et al. Presynaptic $\alpha 2\delta$ subunits are key organizers of glutamatergic synapses. Proceedings of the National Academy of Sciences. 2021;118(14):e1920827118.
32. Wang Y, Fehlhaber KE, Sarria I, Cao Y, Ingram NT, Guerrero-Given D, et al. The auxiliary calcium channel subunit $\alpha 2\delta$4 is required for axonal elaboration, synaptic transmission, and wiring of rod photoreceptors. Neuron. 2017;93(6):1359-74.
33. Kadurin I, Alvarez-Laviada A, Ng SFJ, Walker-Gray R, D'Arco M, Fadel MG, et al. Calcium currents are enhanced by $\alpha 2\delta$-1 lacking its membrane anchor. Journal of Biological Chemistry. 2012;287(40):33554-66.
34. Bernstein GM, Jones OT. Kinetics of internalization and degradation of N-type voltage-gated calcium channels: Role of the $\alpha 2/\delta$ subunit. Cell calcium. 2007;41(1):27-40.
35. Rougier JS, Albesa M, Syam N, Halet G, Abriel H, Viard P. Ubiquitin-specific protease USP2-45 acts as a molecular switch to promote α 2 δ-1-induced downregulation of Cav 1.2 channels. Pflügers Archiv-European Journal of Physiology. 2015;467:1919-29.
36. Chen J, Li L, Chen SR, Chen H, Xie JD, Sirrieh RE, et al. The $\alpha 2\delta$-1-NMDA receptor complex is critically involved in neuropathic pain development and gabapentin therapeutic actions. Cell reports. 2018;22(9):2307-21.
37. Zhou JJ, Li DP, Chen SR, Luo Y, Pan HL. The $\alpha 2\delta$-1–NMDA receptor coupling is essential for corticostriatal long-term potentiation and is involved in learning and memory. Journal of Biological Chemistry. 2018;293(50):19354-64.

 doi:10.20944/preprints202410.0704.v1

38. Savalli N, Pantazis A, Sigg D, Weiss JN, Neely A, Olcese R. The $\alpha 2\delta$-1 subunit remodels CaV1.2 voltage sensors and allows Ca2+ influx at physiological membrane potentials. Journal of General Physiology. 2016;148(2):147-59.
39. Robinson P, Etheridge S, Song L, Armenise P, Jones OT, Fitzgerald EM. Formation of N-type (Cav2.2) voltage-gated calcium channel membrane microdomains: lipid raft association and clustering. Cell calcium. 2010;48(4):183-94.
40. Davies A, Douglas L, Hendrich J, Wratten J, Van Minh AT, Foucault I, et al. The calcium channel $\alpha 2\delta$-2 subunit partitions with CaV2.1 into lipid rafts in cerebellum: implications for localization and function. Journal of Neuroscience. 2006;26(34):8748-57.
41. García K, Nabhani T, García J. The calcium channel $\alpha 2/\delta 1$ subunit is involved in extracellular signalling. The Journal of physiology. 2008;586(3):727-38.
42. Fell B, Eckrich S, Blum K, Eckrich T, Hecker D, Obermair GJ, et al. $\alpha 2\delta 2$ controls the function and trans-synaptic coupling of Cav1.3 channels in mouse inner hair cells and is essential for normal hearing. Journal of Neuroscience. 2016;36(43):11024-36.
43. Canti C, Nieto-Rostro M, Foucault I, Heblich F, Wratten J, Richards M, et al. The metal-ion-dependent adhesion site in the Von Willebrand factor-A domain of $\alpha 2\delta$ subunits is key to trafficking voltage-gated Ca2+ channels. Proceedings of the National Academy of Sciences. 2005;102(32):11230-5.
44. Brockhaus J, Schreitmüller M, Repetto D, Klatt O, Reissner C, Elmslie K, et al. α-Neurexins together with $\alpha 2\delta$-1 auxiliary subunits regulate Ca2+ influx through Cav2.1 channels. Journal of Neuroscience. 2018;38(38):8277-94.
45. Caylor RC, Jin Y, Ackley BD. The Caenorhabditis elegans voltage-gated calcium channel subunits UNC-2 and UNC-36 and the calcium-dependent kinase UNC-43/CaMKII regulate neuromuscular junction morphology. Neural Development. 2013;8(1):1-13.
46. Kurshan PT, Oztan A, Schwarz TL. Presynaptic $\alpha 2\delta$-3 is required for synaptic morphogenesis independent of its Ca2+-channel functions. Nature neuroscience. 2009;12(11):1415-23.
47. Biederer T, Kaeser PS, Blanpied TA. Transcellular nanoalignment of synaptic function. Neuron. 2017;96(3):680-96.
48. Dennys EH, Norris FH. Amyotrophic lateral sclerosis: impairment of neuromuscular transmission. Archives of neurology. 1979;36(4):202-5.
49. Maselli RA, Wollman RL, Leung C, Distad B, Palombi S, Richman DP, et al. Neuromuscular transmission in amyotrophic lateral sclerosis. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 1993;16(11):1193-203.
50. Bruneteau G, Bauché S, Gonzalez de Aguilar JL, Brochier G, Mandjee N, Tanguy ML, et al. Endplate denervation correlates with Nogo-A muscle expression in amyotrophic lateral sclerosis patients. Annals of clinical and translational neurology. 2015;2(4):362-72.
51. Dadon-Nachum M, Melamed E, Offen D. The "dying-back" phenomenon of motor neurons in ALS. Journal of Molecular Neuroscience. 2011;43(3):470-7.
52. Loeffler JP, Picchiarelli G, Dupuis L, Gonzalez De Aguilar JL. The role of skeletal muscle in amyotrophic lateral sclerosis. Brain Pathology. 2016;26(2):227-36.
53. Penniston J, Enyedi A. Modulation of the plasma membrane Ca2+ pump. The Journal of membrane biology. 1998;165(2):101-9.
54. Iacobucci GJ, Popescu GK. Ca2+-dependent inactivation of GluN2A and GluN2B NMDA receptors occurs by a common kinetic mechanism. Biophysical journal. 2020;118(4):798-812.
55. Ben-Johny M, Yue DT. Calmodulin regulation (calmodulation) of voltage-gated calcium channels. Journal of General Physiology. 2014;143(6):679-92.
56. Liang H, DeMaria CD, Erickson MG, Mori MX, Alseikhan BA, Yue DT. Unified mechanisms of Ca2+ regulation across the Ca2+ channel family. Neuron. 2003;39(6):951-60.
57. Tadross MR, Tsien RW, Yue DT. Ca2+ channel nanodomains boost local Ca2+ amplitude. Proceedings of the National Academy of Sciences. 2013;110(39):15794-9.
58. Heine M, Heck J, Ciuraszkiewicz A, Bikbaev A. Dynamic compartmentalization of calcium channel signalling in neurons. Neuropharmacology. 2020;169:107556.
59. Loehrer PA, Zieger L, Simon OJ. Update on paraneoplastic cerebellar degeneration. Brain Sciences. 2021;11(11):1414.

 doi:10.20944/preprints202410.0704.v1

60. Uchitel OD, Appel SH, Crawford F, Sczcupak L. Immunoglobulins from amyotrophic lateral sclerosis patients enhance spontaneous transmitter release from motor-nerve terminals. Proceedings of the National Academy of Sciences. 1988;85(19):7371-4.
61. Uchitel OD, Scornik F, Protti D, Fumberg C, Alvarez V, Appel SH. Long-term neuromuscular dysfunction produced by passive transfer of amyotrophic lateral sclerosis immunoglobulins. Neurology. 1992;42(11):2175-5.
62. Appel SH, Engelhardt JI, Garcia J, Stefani E. Immunoglobulins from animal models of motor neuron disease and from human amyotrophic lateral sclerosis patients passively transfer physiological abnormalities to the neuromuscular junction. Proceedings of the National Academy of Sciences. 1991;88(2):647-51.
63. Stefani E. Calcium current and charge movement of mammalian muscle: action of amyotrophic lateral sclerosis immunoglobulins. The Journal of Physiology. 1991;444(1):723-42.
64. Smith RG, Hamilton S, Hofmann F, Schneider T, Nastainczyk W, Birnbaumer L, et al. Serum antibodies to L-type calcium channels in patients with amyotrophic lateral sclerosis. New England Journal of Medicine. 1992;327(24):1721-8.
65. Magnelli V, Sawada T, Delbono O, Smith RG, Appel SH, Stefani E. The action of amyotrophic lateral sclerosis immunoglobulins on mammalian single skeletal muscle Ca2+ channels. The Journal of Physiology. 1993;461(1):103-18.
66. Delbono O, Magnelli V, Sawada T, Smith RG, Appel SH, Stefani E. Fab fragments from amyotrophic lateral sclerosis IgG affect calcium channels of skeletal muscle. American Journal of Physiology-Cell Physiology. 1993;264(3):C537-43.
67. Llinas R, Sugimori M, Cherksey B, Smith RG, Delbono O, Stefani E, et al. IgG from amyotrophic lateral sclerosis patients increases current through P-type calcium channels in mammalian cerebellar Purkinje cells and in isolated channel protein in lipid bilayer. Proceedings of the National Academy of Sciences. 1993;90(24):11743-7.
68. Smith RG, Alexianu ME, Crawford G, Nyormoi O, Stefani E, Appel SH. Cytotoxicity of immunoglobulins from amyotrophic lateral sclerosis patients on a hybrid motoneuron cell line. Proceedings of the National Academy of Sciences. 1994;91(8):3393-7.
69. Zhainazarov A, Annunziata P, Toneatto S, Cherubini E, Nistri A. Serum fractions from amyotrophic lateral sclerosis patients depress voltage-activated Ca2+ currents of rat cerebellar granule cells in culture. Neuroscience letters. 1994;172(1-2):111-4.
70. Kimura F, Smith RG, Delbono O, Nyormoi O, Schneider T, Nastainczyk W, et al. Amyotrophic lateral sclerosis patient antibodies label Ca2+ channel $\alpha 1$ subunit. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1994;35(2):164-71.
71. Mosier DR, Baldelli P, Delbono O, Smith RG, Alexianu ME, Appel SH, et al. Amyotrophic lateral sclerosis immunoglobulins increase Ca2+ currents in a motoneuron cell line. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1995;37(1):102-9.
72. Engelhardt JI, Siklós L, Kőműves L, Smith RG, Appel SH. Antibodies to calcium channels from ALS patients passively transferred to mice selectively increase intracellular calcium and induce ultrastructural changes in motoneurons. Synapse. 1995;20(3):185-99.
73. Lennon VA, Kryzer TJ, Griesmann GE, O'Suilleabhain PE, Windebank AJ, Woppmann A, et al. Calcium-channel antibodies in the Lambert–Eaton syndrome and other paraneoplastic syndromes. New England Journal of Medicine. 1995;332(22):1467-75.
74. Andjus PR, Khiroug L, Nistri A, Cherubini E. ALS IgGs suppress $Ca2+_i$ rise through P/Q-type calcium channels in central neurones in culture. Neuroreport. 1996;7(12):1914-6.
75. Andjus PR, Stevic-Marinkovic Z, Cherubim E. Immunoglobulins from motoneurone disease patients enhance glutamate release from rat hippocampal neurones in culture. The Journal of Physiology. 1997;504(1):103-12.
76. Yan HD, Lim W, Lee KW, Kim J. Sera from amyotrophic lateral sclerosis patients reduce high-voltage activated Ca2+ currents in mice dorsal root ganglion neurons. Neuroscience letters. 1997;235(1-2):69-72.
77. Colom LV, Alexianu ME, Mosier DR, Smith RG, Appel SH. Amyotrophic lateral sclerosis immunoglobulins increase intracellular calcium in a motoneuron cell line. Experimental neurology. 1997;146(2):354-60.
78. La Bella V, Goodman JC, Appel SH. Increased CSF glutamate following injection of ALS immunoglobulins. Neurology. 1997;48(5):1270-2.

 doi:10.20944/preprints202410.0704.v1

79. Offen D, Halevi S, Orion D, Mosberg R, Stern-Goldberg H, Melamed E, et al. Antibodies from ALS patients inhibit dopamine release mediated by L-type calcium channels. Neurology. 1998;51(4):1100-3.
80. O'Shaughnessy TJ, Yan H, Kim J, Middlekauff EH, Lee KW, Phillips LH, et al. Amyotrophic lateral sclerosis: serum factors enhance spontaneous and evoked transmitter release at the neuromuscular junction. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 1998;21(1):81-90.
81. Grassi C, Martire M, Altobelli D, Azzena G, Preziosi P. Characterization of Ca2+-channels responsible for K+-evoked [3H] noradrenaline release from rat brain cortex synaptosomes and their response to amyotrophic lateral sclerosis IgGs. Experimental neurology. 1999;159(2):520-7.
82. Pullen A, Humphreys P. Ultrastructural analysis of spinal motoneurones from mice treated with IgG from ALS patients, healthy individuals, or disease controls. Journal of the neurological sciences. 2000;180(1-2):35-45.
83. Muchnik S, Losavio A, De Lorenzo S. Effect of amyotrophic lateral sclerosis serum on calcium channels related to spontaneous acetylcholine release. Clinical neurophysiology. 2002;113(7):1066-71.
84. Fratantoni SA, Weisz G, Pardal AM, Reisin RC, Uchitel OD. Amyotrophic lateral sclerosis IgG-treated neuromuscular junctions develop sensitivity to L-type calcium channel blocker. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2000;23(4):543-50.
85. Carter JR, Mynlieff M. Amyotrophic lateral sclerosis patient IgG alters voltage dependence of Ca2+ channels in dissociated rat motoneurons. Neuroscience letters. 2003;353(3):221-5.
86. Pullen A, Demestre M, Howard R, Orrell R. Passive transfer of purified IgG from patients with amyotrophic lateral sclerosis to mice results in degeneration of motor neurons accompanied by Ca2+ enhancement. Acta neuropathologica. 2004;107(1):35-46.
87. Demestre M, Howard R, Orrell R, Pullen A. Serine proteases purified from sera of patients with amyotrophic lateral sclerosis (ALS) induce contrasting cytopathology in murine motoneurones to IgG. Neuropathology and applied neurobiology. 2006;32(2):141-56.
88. Pagani MR, Reisin RC, Uchitel OD. Calcium signaling pathways mediating synaptic potentiation triggered by amyotrophic lateral sclerosis IgG in motor nerve terminals. Journal of Neuroscience. 2006;26(10):2661-72.
89. Gonzalez LE, Kotler ML, Vattino LG, Conti E, Reisin RC, Mulatz KJ, et al. Amyotrophic lateral sclerosis-immunoglobulins selectively interact with neuromuscular junctions expressing P/Q-type calcium channels. Journal of neurochemistry. 2011;119(4):826-38.
90. Vijayalakshmi K, Alladi PA, Ghosh S, Prasanna V, Sagar B, Nalini A, et al. Evidence of endoplasmic reticular stress in the spinal motor neurons exposed to CSF from sporadic amyotrophic lateral sclerosis patients. Neurobiology of disease. 2011;41(3):695-705.
91. Milošević M, Stenovec M, Kreft M, Petrušić V, Stević Z, Trkov S, et al. Immunoglobulins G from patients with sporadic amyotrophic lateral sclerosis affects cytosolic Ca2+ homeostasis in cultured rat astrocytes. Cell Calcium. 2013;54(1):17-25.
92. Shi Y, Park KS, Kim SH, Yu J, Zhao K, Yu L, et al. IgGs from patients with amyotrophic lateral sclerosis and diabetes target CaVα2δ1 subunits impairing islet cell function and survival. Proceedings of the National Academy of Sciences. 2019;116(52):26816-22.
93. Obál I, Nógrádi B, Meszlényi V, Patai R, Ricken G, Kovacs GG, et al. Experimental motor neuron disease induced in mice with long-term repeated intraperitoneal injections of serum from ALS patients. International journal of molecular sciences. 2019;20(10):2573.
94. Meszlényi V, Patai R, Polgár TF, Nógrádi B, Körmöczy L, Kristóf R, et al. Passive Transfer of Sera from ALS Patients with Identified Mutations Evokes an Increased Synaptic Vesicle Number and Elevation of Calcium Levels in Motor Axon Terminals, Similar to Sera from Sporadic Patients. International Journal of Molecular Sciences. 2020;21(15):5566.
95. Polgár TF, Meszlényi V, Nógrádi B, Körmöczy L, Spisák K, Tripolszki K, et al. Passive Transfer of Blood Sera from ALS Patients with Identified Mutations Results in Elevated Motoneuronal Calcium Level and Loss of Motor Neurons in the Spinal Cord of Mice. International journal of molecular sciences. 2021;22(18):9994.
96. Engelhardt J, Soós J, Obál I, Vigh L, Siklós L. Subcellular localization of IgG from the sera of ALS patients in the nervous system. Acta Neurologica Scandinavica. 2005;112(2):126-33.
97. Nyormoi O. Proteolytic activity in amyotrophic lateral sclerosis IgG preparations. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1996;40(5):701-6.

 doi:10.20944/preprints202410.0704.v1

98. Siklós L, Engelhardt J, Harati Y, Smith RG, Joó F, Appel SH. Ultrastructural evidence for altered calcium in motor nerve terminals in amyotrophc lateral sclerosis. Annals of neurology. 1996;39(2):203-16.
99. Bader M. Tissue renin-angiotensin-aldosterone systems: Targets for pharmacological therapy. Annual review of pharmacology and toxicology. 2010;50:439-65.
100. Pfeiffer RM, Mayer B, Kuncl RW, Check DP, Cahoon EK, Rivera DR, et al. Identifying potential targets for prevention and treatment of amyotrophic lateral sclerosis based on a screen of medicare prescription drugs. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2020;21(3-4):235-45.
101. Hu N, Ji H. Medications on hypertension, hyperlipidemia, diabetes, and risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. Neurological Sciences. 2022:1-11.
102. Lin FC, Tsai CP, Lee JKW, Wu MT, Lee CTC. Angiotensin-converting enzyme inhibitors and amyotrophic lateral sclerosis risk: a total population–based case-control study. JAMA neurology. 2015;72(1):40-8.
103. Bursch F, Kalmbach N, Naujock M, Staege S, Eggenschwiler R, Abo-Rady M, et al. Altered calcium dynamics and glutamate receptor properties in iPSC-derived motor neurons from ALS patients with C9orf72, FUS, SOD1 or TDP43 mutations. Human Molecular Genetics. 2019;28(17):2835-50.
104. Quinlan K, Schuster J, Fu R, Siddique T, Heckman C. Altered postnatal maturation of electrical properties in spinal motoneurons in a mouse model of amyotrophic lateral sclerosis. The Journal of physiology. 2011;589(9):2245-60.
105. Ringholz G, Appel SH, Bradshaw M, Cooke N, Mosnik D, Schulz P. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology. 2005;65(4):586-90.
106. McCombe P, Wray N, Henderson R. Extra-motor abnormalities in amyotrophic lateral sclerosis: another layer of heterogeneity. Expert review of neurotherapeutics. 2017;17(6):561-77.
107. Corcia P, Pradat PF, Salachas F, Bruneteau G, le Forestier N, Seilhean D, et al. Causes of death in a post-mortem series of ALS patients. Amyotrophic lateral sclerosis: official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2008;9(1):59-62.
108. Rosenbohm A, Schmid B, Buckert D, Rottbauer W, Kassubek J, Ludolph AC, et al. Cardiac findings in amyotrophic lateral sclerosis: a magnetic resonance imaging study. Frontiers in Neurology. 2017;8:479.
109. Timmins HC, Saw W, Cheah BC, Lin CS, Vucic S, Ahmed RM, et al. Cardiometabolic health and risk of amyotrophic lateral sclerosis. Muscle & Nerve. 2017;56(4):721-5.
110. Mach L, Konecny T, Helanova K, Jaffe AS, Sorenson EJ, Somers VK, et al. Elevation of cardiac troponin T in patients with amyotrophic lateral sclerosis. Acta Neurologica Belgica. 2016;116:557-64.
111. Kläppe U, Chamoun S, Shen Q, Finn A, Evertsson B, Zetterberg H, et al. Cardiac troponin T is elevated and increases longitudinally in ALS patients. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2022;23(1-2):58-65.
112. Gdynia H, Kurt A, Endruhn S, Ludolph A, Sperfeld A. Cardiomyopathy in motor neuron diseases. Journal of Neurology, Neurosurgery & Psychiatry. 2006;77(5):671-3.
113. Weis J, Katona I, Müller-Newen G, Sommer C, Necula G, Hendrich C, et al. Small-fiber neuropathy in patients with ALS. Neurology. 2011;76(23):2024-9.
114. Dalla Bella E, Lombardi R, Porretta-Serapiglia C, Ciano C, Gellera C, Pensato V, et al. Amyotrophic lateral sclerosis causes small fiber pathology. European journal of neurology. 2016;23(2):416-20.
115. Nolano M, Provitera V, Manganelli F, Iodice R, Caporaso G, Stancanelli A, et al. Non-motor involvement in amyotrophic lateral sclerosis: new insight from nerve and vessel analysis in skin biopsy. Neuropathology and Applied Neurobiology. 2017;43(2):119-32.
116. Chiò A, Mora G, Lauria G. Pain in amyotrophic lateral sclerosis. The Lancet Neurology. 2017;16(2):144-57.
117. Rappoport A. Insulin in Amyotrophic Lateral Sclerosis: Impairment, Tests and Treatment; 2023. https://www.preprints.org/manuscript/202212.0297/v3, DOI=10.20944/preprints202212.0297.v3.
118. Araki K, Araki A, Honda D, Izumoto T, Hashizume A, Hijikata Y, et al. TDP-43 regulates early-phase insulin secretion via CaV1.2-mediated exocytosis in islets. The Journal of clinical investigation. 2019;129(9):3578-93.
119. Coan G, Mitchell CS. An assessment of possible neuropathology and clinical relationships in 46 sporadic amyotrophic lateral sclerosis patient autopsies. Neurodegenerative Diseases. 2015;15(5):301-12.
120. Béland LC, Markovinovic A, Jakovac H, De Marchi F, Bilic E, Mazzini L, et al. Immunity in amyotrophic lateral sclerosis: Blurred lines between excessive inflammation and inefficient immune responses. Brain Communications. 2020;2(2):fcaa124.

121. Curti D, Malaspina A, Facchetti G, Camana C, Mazzini L, Tosca P, et al. Amyotrophic lateral sclerosis: oxidative energy metabolism and calcium homeostasis in peripheral blood lymphocytes. Neurology. 1996;47(4):1060-4.
122. Prasad A, Bharathi V, Sivalingam V, Girdhar A, Patel BK. Molecular mechanisms of TDP-43 misfolding and pathology in amyotrophic lateral sclerosis. Frontiers in molecular neuroscience. 2019;12:25.
123. Barber SC, Shaw PJ. Oxidative stress in ALS: key role in motor neuron injury and therapeutic target. Free Radical Biology and Medicine. 2010;48(5):629-41.
124. Ferrante RJ, Browne SE, Shinobu LA, Bowling AC, Baik MJ, MacGarvey U, et al. Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis. Journal of neurochemistry. 1997;69(5):2064-74.
125. Smith RG, Henry YK, Mattson MP, Appel SH. Presence of 4-hydroxynonenal in cerebrospinal fluid of patients with sporadic amyotrophic lateral sclerosis. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1998;44(4):696-9.
126. Pedersen WA, Fu W, Keller JN, Markesbery WR, Appel S, Smith RG, et al. Protein modification by the lipid peroxidation product 4-hydroxynonenal in the spinal cords of amyotrophic lateral sclerosis patients. Annals of neurology. 1998;44(5):819-24.
127. Mitsumoto H, Santella RM, Liu X, Bogdanov M, Zipprich J, Wu HC, et al. Oxidative stress biomarkers in sporadic ALS. Amyotrophic Lateral Sclerosis. 2008;9(3):177-83.
128. Blasco H, Veyrat-Durebex C, Bocca C, Patin F, Vourc'h P, Kouassi Nzoughet J, et al. Lipidomics reveals cerebrospinal-fluid signatures of ALS. Scientific reports. 2017;7(1):1-10.
129. Simpson E, Henry Y, Henkel J, Smith R, Appel SH. Increased lipid peroxidation in sera of ALS patients: a potential biomarker of disease burden. Neurology. 2004;62(10):1758-65.
130. Carrì MT, D'Ambrosi N, Cozzolino M. Pathways to mitochondrial dysfunction in ALS pathogenesis. Biochemical and biophysical research communications. 2017;483(4):1187-93.
131. Dupuis L, Pradat PF, Ludolph AC, Loeffler JP. Energy metabolism in amyotrophic lateral sclerosis. The Lancet Neurology. 2011;10(1):75-82.
132. Mukund K, Subramaniam S. Skeletal muscle: A review of molecular structure and function, in health and disease. Wiley Interdisciplinary Reviews: Systems Biology and Medicine. 2020;12(1):e1462.
133. Smith IC, Bombardier E, Vigna C, Tupling AR. ATP consumption by sarcoplasmic reticulum Ca2+ pumps accounts for 40-50% of resting metabolic rate in mouse fast and slow twitch skeletal muscle. PloS one. 2013;8(7):e68924.
134. Osler ME, Zierath JR. Minireview: adenosine 5'-monophosphate-activated protein kinase regulation of fatty acid oxidation in skeletal muscle. Endocrinology. 2008;149(3):935-41.
135. Liu YJ, Ju TC, Chen HM, Jang YS, Lee LM, Lai HL, et al. Activation of AMP-activated protein kinase α1 mediates mislocalization of TDP-43 in amyotrophic lateral sclerosis. Human molecular genetics. 2015;24(3):787-801.
136. Liu YJ, Lee LM, Lai HL, Chern Y. Aberrant activation of AMP-activated protein kinase contributes to the abnormal distribution of HuR in amyotrophic lateral sclerosis. FEBS letters. 2015;589(4):432-9.
137. Takeyama N, Miki S, Hirakawa A, Tanaka T. Role of the mitochondrial permeability transition and cytochrome C release in hydrogen peroxide-induced apoptosis. Experimental cell research. 2002;274(1):16-24.
138. Marchi S, Vitto VAM, Patergnani S, Pinton P. High mitochondrial Ca2+ content increases cancer cell proliferation upon inhibition of mitochondrial permeability transition pore (mPTP). Cell Cycle. 2019;18(8):914-6.
139. Hansson MJ, Månsson R, Morota S, Uchino H, Kallur T, Sumi T, et al. Calcium-induced generation of reactive oxygen species in brain mitochondria is mediated by permeability transition. Free Radical Biology and Medicine. 2008;45(3):284-94.
140. Baumgartner HK, Gerasimenko JV, Thorne C, Ferdek P, Pozzan T, Tepikin AV, et al. Calcium elevation in mitochondria is the main Ca2+ requirement for mitochondrial permeability transition pore (mPTP) opening. Journal of Biological Chemistry. 2009;284(31):20796-803.
141. Butler MR, Ma H, Yang F, Belcher J, Le YZ, Mikoshiba K, et al. Endoplasmic reticulum (ER) Ca2+-channel activity contributes to ER stress and cone death in cyclic nucleotide-gated channel deficiency. Journal of Biological Chemistry. 2017;292(27):11189-205.

 doi:10.20944/preprints202410.0704.v1

142. Connolly NM, Prehn JH. The metabolic response to excitotoxicity–lessons from single-cell imaging. Journal of bioenergetics and biomembranes. 2015;47(1-2):75-88.
143. Marinho HS, Real C, Cyrne L, Soares H, Antunes F. Hydrogen peroxide sensing, signaling and regulation of transcription factors. Redox biology. 2014;2:535-62.
144. Tan Y, Ichikawa T, Li J, Si Q, Yang H, Chen X, et al. Diabetic downregulation of Nrf2 activity via ERK contributes to oxidative stress–induced insulin resistance in cardiac cells in vitro and in vivo. Diabetes. 2011;60(2):625-33.
145. Ahn SG, Thiele DJ. Redox regulation of mammalian heat shock factor 1 is essential for Hsp gene activation and protection from stress. Genes & development. 2003;17(4):516-28.
146. Ayala V, Granado-Serrano AB, Cacabelos D, Naudí A, Ilieva EV, Boada J, et al. Cell stress induces TDP-43 pathological changes associated with ERK1/2 dysfunction: implications in ALS. Acta neuropathologica. 2011;122(3):259-70.
147. Cohen TJ, Hwang AW, Unger T, Trojanowski JQ, Lee VM. Redox signalling directly regulates TDP-43 via cysteine oxidation and disulphide cross-linking. The EMBO journal. 2012;31(5):1241-52.
148. Colombrita C, Zennaro E, Fallini C, Weber M, Sommacal A, Buratti E, et al. TDP-43 is recruited to stress granules in conditions of oxidative insult. Journal of neurochemistry. 2009;111(4):1051-61.
149. Chang HY, Hou SC, Way TD, Wong CH, Wang IF. Heat-shock protein dysregulation is associated with functional and pathological TDP-43 aggregation. Nature communications. 2013;4(1):1-11.
150. Zuo X, Zhou J, Li Y, Wu K, Chen Z, Luo Z, et al. TDP-43 aggregation induced by oxidative stress causes global mitochondrial imbalance in ALS. Nature structural & molecular biology. 2021;28(2):132-42.
151. Xu WC, Liang JZ, Li C, He ZX, Yuan HY, Huang BY, et al. Pathological hydrogen peroxide triggers the fibrillization of wild-type SOD1 via sulfenic acid modification of Cys-111. Cell death & disease. 2018;9(2):1-17.
152. Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, et al. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochemical and biophysical research communications. 2006;351(3):602-11.
153. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006;314(5796):130-3.
154. Hetz C, Zhang K, Kaufman RJ. Mechanisms, regulation and functions of the unfolded protein response. Nature reviews Molecular cell biology. 2020;21(8):421-38.
155. Kültz D. Molecular and evolutionary basis of the cellular stress response. Annual review of physiology. 2005;67(1):225-57.
156. Núñez-Santana FL, Oh MM, Antion MD, Lee A, Hell JW, Disterhoft JF. Surface L-type Ca2+ channel expression levels are increased in aged hippocampus. Aging Cell. 2014;13(1):111-20.
157. Moore SJ, Murphy GG. The role of L-type calcium channels in neuronal excitability and aging. Neurobiology of learning and memory. 2020;173:107230.
158. Kumar A, Bodhinathan K, Foster TC. Susceptibility to calcium dysregulation during brain aging. Frontiers in aging neuroscience. 2009:2.
159. Reiner A, Medina L, Figueredo-Cardenas G, Anfinson S. Brainstem motoneuron pools that are selectively resistant in amyotrophic lateral sclerosis are preferentially enriched in parvalbumin: evidence from monkey brainstem for a calcium-mediated mechanism in sporadic ALS. Experimental neurology. 1995;131(2):239-50.
160. Vanselow BK, Keller BU. Calcium dynamics and buffering in oculomotor neurones from mouse that are particularly resistant during amyotrophic lateral sclerosis (ALS)-related motoneurone disease. The Journal of physiology. 2000;525(Pt 2):433.
161. Laslo P, Lipski J, Nicholson LF, Miles GB, Funk GD. Calcium binding proteins in motoneurons at low and high risk for degeneration in ALS. Neuroreport. 2000;11(15):3305-8.
162. von Lewinski F, Keller BU. Ca2+, mitochondria and selective motoneuron vulnerability: implications for ALS. Trends in neurosciences. 2005;28(9):494-500.
163. Miles GB, Lipski J, Lorier AR, Laslo P, Funk GD. Differential expression of voltage-activated calcium channels in III and XII motoneurones during development in the rat. European Journal of Neuroscience. 2004;20(4):903-13.

 doi:10.20944/preprints202410.0704.v1

164. Harwood CA, Westgate K, Gunstone S, Brage S, Wareham NJ, McDermott CJ, et al. Long-term physical activity: an exogenous risk factor for sporadic amyotrophic lateral sclerosis? Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2016;17(5-6):377-84.
165. Visser AE, Rooney JP, D'Ovidio F, Westeneng HJ, Vermeulen RC, Beghi E, et al. Multicentre, cross-cultural, population-based, case–control study of physical activity as risk factor for amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(8):797-803.
166. Filippini T, Fiore M, Tesauro M, Malagoli C, Consonni M, Violi F, et al. Clinical and lifestyle factors and risk of amyotrophic lateral sclerosis: A population-based case-control study. International journal of environmental research and public health. 2020;17(3):857.
167. Chen GX, Douwes J, van den Berg LH, Glass B, McLean D, 't Mannetje AM. Sports and trauma as risk factors for Motor Neurone Disease: New Zealand case–control study. Acta Neurologica Scandinavica. 2022;145(6):770-85.
168. Daneshvar DH, Mez J, Alosco ML, Baucom ZH, Mahar I, Baugh CM, et al. Incidence of and mortality from amyotrophic lateral sclerosis in National Football League athletes. JAMA network open. 2021;4(12):e2138801-1.
169. Fang F, Hållmarker U, James S, Ingre C, Michaëlsson K, Ahlbom A, et al. Amyotrophic lateral sclerosis among cross-country skiers in Sweden. European journal of epidemiology. 2016;31(3):247-53.
170. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. Neurology. 2002;59(5):773-5.
171. Korner S, Kammeyer J, Zapf A, Kuzma-Kozakiewicz M, Piotrkiewicz M, Kuraszkiewicz B, et al. Influence of environment and lifestyle on incidence and progress of amyotrophic lateral sclerosis in a German ALS population. Aging and disease. 2019;10(2):205.
172. Rosenbohm A, Peter R, Dorst J, Kassubek J, Rothenbacher D, Nagel G, et al. Life course of physical activity and risk and prognosis of amyotrophic lateral sclerosis in a German ALS registry. Neurology. 2021;97(19):e1955-63.
173. Mamoor S. Differential expression of CACNA2D1 in amyotrophic lateral sclerosis; 2022. https://osf.io/mnxup, DOI=10.31219/osf.io/mnxup.
174. D'Ovidio F, d'Errico A, Farina E, Calvo A, Costa G, Chiò A. Amyotrophic lateral sclerosis incidence and previous prescriptions of drugs for the nervous system. Neuroepidemiology. 2016;47(1):59-66.
175. Miller R, Gelinas D, Dronsky V, Mendoza M, Barohn R, Bryan W, et al. Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. Neurology. 2001;56(7):843-8.
176. Recurrent hypoventilation and respiratory failure during gabapentin therapy. Journal of the American Geriatrics Society. 2001;49(4):498.
177. Pérez RC, Lechuga MG, Alvarez MML, Albisu AA. Gabapentin-induced central hypoventilation. Medicina clinica. 2007;128(13):519.
178. Tuccori M, Lombardo G, Lapi F, Vannacci A, Blandizzi C, Tacca MD. Gabapentin-induced severe myopathy. Annals of Pharmacotherapy. 2007;41(7-8):1301-5.
179. Lipson J, Lavoie S, Zimmerman D. Gabapentin-induced myopathy in 2 patients on short daily hemodialysis. American Journal of Kidney Diseases. 2005;45(6):e100-4.
180. Siniscalchi A, Mintzer S, De Sarro G, Gallelli L. Myotoxicity Induced by Antiepileptic Drugs: Could be a Rare but Serious Adverse Event? Psychopharmacology Bulletin. 2021;51(4):105-16.
181. Ghosh S, Villan S, Al Yazeedi W. Gabapentin-induced myositis in a patient with spinal cord injury–a case report. Qatar Medical Journal. 2020;2020(2):30.
182. Coupal TM, Chang DR, Pennycooke K, Ouellette HA, Munk PL. Radiologic findings in gabapentin-induced myositis. Journal of Radiology Case Reports. 2017;11(4):30.
183. Choi MS, Jeon H, Kim HS, Jang BH, Lee YH, Park HS, et al. A case of gabapentin-induced rhabdomyolysis requiring renal replacement therapy. Hemodialysis International. 2017;21(1):E4-8.
184. Bilgir O, Çalan M, Bilgir F, Kebapçilar L, Yüksel A, Yildiz Y, et al. Gabapentin-induced rhabdomyolysis in a patient with diabetic neuropathy. Internal Medicine. 2009;48(12):1085-7.
185. Desai A, Kherallah Y, Szabo C, Marawar R. Gabapentin or pregabalin induced myoclonus: A case series and literature review. Journal of Clinical Neuroscience. 2019;61:225-34.
186. Kaufman KR, Parikh A, Chan L, Bridgeman M, Shah M. Myoclonus in renal failure: two cases of gabapentin toxicity. Epilepsy & Behavior Case Reports. 2014;2:8-10.

 doi:10.20944/preprints202410.0704.v1

187. Shea Yf, Mok MMy, Chang RSk. Gabapentin-induced myoclonus in an elderly with end-stage renal failure. J Formos Med Assoc. 2014;113(9):660-1.
188. Guddati A, Zafar Z, Cheng J, Mohan S. Treatment of gabapentin-induced myoclonus with continuous renal replacement therapy. Indian Journal of Nephrology. 2012;22(1):59.
189. Verschuuren JJ, Palace J, Murai H, Tannemaat MR, Kaminski HJ, Bril V. Advances and ongoing research in the treatment of autoimmune neuromuscular junction disorders. The Lancet Neurology. 2022;21(2):189-202.
190. Boneva N, Brenner T, Argov Z. Gabapentin may be hazardous in myasthenia gravis. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2000;23(8):1204-8.
191. Barclay J, Balaguero N, Mione M, Ackerman SL, Letts VA, Brodbeck J, et al. Ducky mouse phenotype of epilepsy and ataxia is associated with mutations in the Cacna2d2 gene and decreased calcium channel current in cerebellar Purkinje cells. Journal of Neuroscience. 2001;21(16):6095-104.
192. Fuller-Bicer GA, Varadi G, Koch SE, Ishii M, Bodi I, Kadeer N, et al. Targeted disruption of the voltage-dependent calcium channel $\alpha 2/\delta$-1-subunit. American Journal of Physiology-Heart and Circulatory Physiology. 2009;297(1):H117-24.
193. Jankovic J, Mazziotta J, Pomeroy S, Newman N. Bradley and daroff's neurology in clinical practice, 8th edition. Elsevier; 2021.
194. Guillot SJ, Bolborea M, Dupuis L. Dysregulation of energy homeostasis in amyotrophic lateral sclerosis. Current Opinion in Neurology. 2021;34(5):773-80.
195. D'Amico E, Grosso G, Nieves JW, Zanghì A, Factor-Litvak P, Mitsumoto H. Metabolic abnormalities, dietary risk factors and nutritional management in amyotrophic lateral sclerosis. Nutrients. 2021;13(7):2273.
196. Toth C, Hebert V, Gougeon C, Virtanen H, Mah JK, Pacaud D. Motor unit number estimations are smaller in children with type 1 diabetes mellitus: A case–cohort study. Muscle & Nerve. 2014;50(4):593-8.
197. Maratova K, Soucek O, Matyskova J, Hlavka Z, Petruzelkova L, Obermannova B, et al. Muscle functions and bone strength are impaired in adolescents with type 1 diabetes. Bone. 2018;106:22-7.
198. Muramatsu K, Niwa M, Tamaki T, Ikutomo M, Masu Y, Hasegawa T, et al. Effect of streptozotocin-induced diabetes on motoneurons and muscle spindles in rats. Neuroscience Research. 2017;115:21-8.
199. Oveisgharan S, Capuano AW, Nag S, Agrawal S, Barnes LL, Bennett DA, et al. Association of hemoglobin A1C with TDP-43 pathology in community-based elders. Neurology. 2021;96(22):e2694-703.
200. Illario M, Monaco S, Cavallo AL, Esposito I, Formisano P, D'Andrea L, et al. Calcium-calmodulin-dependent kinase II (CaMKII) mediates insulin-stimulated proliferation and glucose uptake. Cellular signalling. 2009;21(5):786-92.
201. Monaco S, Illario M, Rusciano MR, Gragnaniello G, Di Spigna G, Leggiero E, et al. Insulin stimulates fibroblast proliferation through calcium-calmodulin-dependent kinase II. Cell Cycle. 2009;8(13):2024-30.
202. Wright D, Fick C, Olesen J, Lim K, Barnes B, Craig B. A role for calcium/calmodulin kinase in insulin stimulated glucose transport. Life sciences. 2004;74(7):815-25.
203. Suzuki R, Lee K, Jing E, Biddinger SB, McDonald JG, Montine TJ, et al. Diabetes and insulin in regulation of brain cholesterol metabolism. Cell metabolism. 2010;12(6):567-79.
204. Shimano H, Sato R. SREBP-regulated lipid metabolism: convergent physiology–divergent pathophysiology. Nat Rev Endocrinol. 2017;13(12):710.
205. Willmann R, Pun S, Stallmach L, Sadasivam G, Santos AF, Caroni P, et al. Cholesterol and lipid microdomains stabilize the postsynapse at the neuromuscular junction. The EMBO journal. 2006;25(17):4050-60.
206. Baenziger JE, Domville JA, Therien JD. The role of cholesterol in the activation of nicotinic acetylcholine receptors. In: Current topics in membranes. vol. 80. Elsevier; 2017. p. 95-137.
207. Head BP, Patel HH, Insel PA. Interaction of membrane/lipid rafts with the cytoskeleton: impact on signaling and function: membrane/lipid rafts, mediators of cytoskeletal arrangement and cell signaling. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2014;1838(2):532-45.
208. Whitehead SN, Gangaraju S, Aylsworth A, Hou ST. Membrane raft disruption results in neuritic retraction prior to neuronal death in cortical neurons. Bioscience trends. 2012;6(4):183-91.
209. Wuolikainen A, Acimovic J, Lövgren-Sandblom A, Parini P, Andersen PM, Björkhem I. Cholesterol, oxysterol, triglyceride, and coenzyme Q homeostasis in ALS. Evidence against the hypothesis that elevated 27-hydroxycholesterol is a pathogenic factor. PloS one. 2014;9(11):e113619.
210. Dodge JC, Jensen EH, Yu J, Sardi SP, Bialas AR, Taksir TV, et al. Neutral lipid cacostasis contributes to disease pathogenesis in amyotrophic lateral sclerosis. Journal of Neuroscience. 2020;40(47):9137-47.

 doi:10.20944/preprints202410.0704.v1

211. Schumacher J, Peter R, Nagel G, Rothenbacher D, Rosenbohm A, Ludolph A, et al. Statins, diabetes mellitus and prognosis of amyotrophic lateral sclerosis: data from 501 patients of a population-based registry in southwest Germany. European journal of neurology. 2020;27(8):1405-14.
212. Apostolski S, Nikolić J, Bugarski-Prokopljević C, Miletić V, Pavlović S, Filipović S. Serum and CSF immunological findings in ALS. Acta neurologica scandinavica. 1991;83(2):96-8.
213. Oldstone M, Perrin L, Wilson C, Norris Jr F. Evidence for immune-complex formation in patients with amyotrophic lateral sclerosis. The Lancet. 1976;308(7978):169-72.
214. Saleh IA, Zesiewicz T, Xie Y, Sullivan KL, Miller AM, Kuzmin-Nichols N, et al. Evaluation of humoral immune response in adaptive immunity in ALS patients during disease progression. Journal of neuroimmunology. 2009;215(1-2):96-101.
215. Engelhardt JI, Tajti J, Appel SH. Lymphocytic infiltrates in the spinal cord in amyotrophic lateral sclerosis. Archives of neurology. 1993;50(1):30-6.
216. Beers DR, Zhao W, Wang J, Zhang X, Wen S, Neal D, et al. ALS patients' regulatory T lymphocytes are dysfunctional, and correlate with disease progression rate and severity. JCI insight. 2017;2(5).
217. Sheean RK, McKay FC, Cretney E, Bye CR, Perera ND, Tomas D, et al. Association of regulatory T-cell expansion with progression of amyotrophic lateral sclerosis: a study of humans and a transgenic mouse model. JAMA neurology. 2018;75(6):681-9.
218. Garbuzova-Davis S, Hernandez-Ontiveros DG, Rodrigues MC, Haller E, Frisina-Deyo A, Mirtyl S, et al. Impaired blood–brain/spinal cord barrier in ALS patients. Brain research. 2012;1469:114-28.
219. Beers DR, Appel SH. Immune dysregulation in amyotrophic lateral sclerosis: mechanisms and emerging therapies. The Lancet Neurology. 2019;18(2):211-20.
220. Feddermann-Demont N, Junge A, Weber KP, Weller M, Dvořák J, Tarnutzer AA. Prevalence of potential sports-associated risk factors in Swiss amyotrophic lateral sclerosis patients. Brain and behavior. 2017;7(4):e00630.
221. Kanmogne M, Klein RS. Neuroprotective versus neuroinflammatory roles of complement: From development to disease. Trends in neurosciences. 2021;44(2):97-109.
222. Morgan G, Levinsky R. Clinical significance of IgG subclass deficiency. Archives of disease in childhood. 1988;63(7):771.
223. Sui X, Geng JH, Li YH, Zhu GY, Wang WH. Calcium channel $\alpha 2\delta 1$ subunit (CACNA2D1) enhances radioresistance in cancer stem-like cells in non-small cell lung cancer cell lines. Cancer Management and Research. 2018;10:5009.
224. Kawamata T, Akiyama H, Yamada T, McGeer P. Immunologic reactions in amyotrophic lateral sclerosis brain and spinal cord tissue. The American journal of pathology. 1992;140(3):691.
225. Chen X, Feng W, Huang R, Guo X, Chen Y, Zheng Z, et al. Evidence for peripheral immune activation in amyotrophic lateral sclerosis. Journal of the Neurological Sciences. 2014;347(1-2):90-5.
226. Wang M, Liu Z, Du J, Yuan Y, Jiao B, Zhang X, et al. Evaluation of Peripheral Immune Activation in Amyotrophic Lateral Sclerosis. Frontiers in neurology. 2021:1028.
227. Kjældgaard AL, Pilely K, Olsen KS, Lauritsen AØ, Pedersen SW, Svenstrup K, et al. Complement profiles in patients with amyotrophic lateral sclerosis: A prospective observational cohort study. Journal of Inflammation Research. 2021;14:1043.
228. Donnenfeld H, Kascsak R, Bartfeld H. Deposits of IgG and C3 in the spinal cord and motor cortex of ALS patients. Journal of neuroimmunology. 1984;6(1):51-7.
229. Sta M, Sylva-Steenland R, Casula M, De Jong J, Troost D, Aronica E, et al. Innate and adaptive immunity in amyotrophic lateral sclerosis: evidence of complement activation. Neurobiology of disease. 2011;42(3):211-20.
230. Bahia El Idrissi N, Bosch S, Ramaglia V, Aronica E, Baas F, Troost D. Complement activation at the motor end-plates in amyotrophic lateral sclerosis. Journal of neuroinflammation. 2016;13(1):1-12.
231. Turner MR, Goldacre R, Ramagopalan S, Talbot K, Goldacre MJ. Autoimmune disease preceding amyotrophic lateral sclerosis: an epidemiologic study. Neurology. 2013;81(14):1222-5.
232. Cui C, Longinetti E, Larsson H, Andersson J, Pawitan Y, Piehl F, et al. Associations between autoimmune diseases and amyotrophic lateral sclerosis: a register-based study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2021;22(3-4):211-9.
233. Seelen M, van Doormaal PT, Visser AE, Huisman MH, Roozekrans MH, de Jong SW, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. Journal of neurology. 2014;261(10):1949-56.

 doi:10.20944/preprints202410.0704.v1

234. Gaimari A, Fusaroli M, Raschi E, Baldin E, Vignatelli L, Nonino F, et al. Amyotrophic Lateral Sclerosis as an Adverse Drug Reaction: A Disproportionality Analysis of the Food and Drug Administration Adverse Event Reporting System. Drug Safety. 2022:1-11.
235. Gotaas HT, Skeie GO, Gilhus NE. Myasthenia gravis and amyotrophic lateral sclerosis: A pathogenic overlap. Neuromuscular Disorders. 2016;26(6):337-41.
236. del Mar Amador M, Vandenberghe N, Berhoune N, Camdessanché JP, Gronier S, Delmont E, et al. Unusual association of amyotrophic lateral sclerosis and myasthenia gravis: a dysregulation of the adaptive immune system? Neuromuscular Disorders. 2016;26(6):342-6.
237. de Pasqua S, Cavallieri F, D'Angelo R, Salvi F, Fini N, D'Alessandro R, et al. Amyotrophic lateral sclerosis and myasthenia gravis: association or chance occurrence? Neurological Sciences. 2017;38:441-4.
238. Hajela RK, Huntoon KM, Atchison WD. Lambert–Eaton syndrome antibodies target multiple subunits of voltage-gated Ca2+ channels. Muscle & nerve. 2015;51(2):176-84.
239. Zhou R, Caspi RR. Ocular immune privilege. F1000 biology reports. 2010;2.
240. Badou A, Jha MK, Matza D, Flavell RA. Emerging roles of L-type voltage-gated and other calcium channels in T lymphocytes. Frontiers in immunology. 2013;4:243.
241. McRory JE, Hamid J, Doering CJ, Garcia E, Parker R, Hamming K, et al. The CACNA1F gene encodes an L-type calcium channel with unique biophysical properties and tissue distribution. Journal of Neuroscience. 2004;24(7):1707-18.
242. Davenport B, Li Y, Heizer JW, Schmitz C, Perraud AL. Signature channels of excitability no more: L-type channels in immune cells. Frontiers in immunology. 2015;6:375.
243. Zhang JY, Zhang PP, Zhou WP, Yu JY, Yao ZH, Chu JF, et al. L-type Cav1.2 calcium channel-α-1C regulates response to rituximab in diffuse large B-cell lymphoma. Clinical Cancer Research. 2019;25(13):4168-78.
244. Hemon P, Renaudineau Y, Debant M, Le Goux N, Mukherjee S, Brooks W, et al. Calcium signaling: from normal B cell development to tolerance breakdown and autoimmunity. Clinical Reviews in Allergy & Immunology. 2017;53:141-65.
245. Zhang R, Gascon R, Miller RG, Gelinas DF, Mass J, Hadlock K, et al. Evidence for systemic immune system alterations in sporadic amyotrophic lateral sclerosis (sALS). Journal of neuroimmunology. 2005;159(1-2):215-24.
246. Troost D, Van den Oord J, JONG JVD. Immunohistochemical characterization of the inflammatory infiltrate in amyotrophic lateral sclerosis. Neuropathology and applied neurobiology. 1990;16(5):401-10.
247. Provinciali L, Laurenzi M, Vesprini L, Giovagnoli A, Bartocci C, Montroni M, et al. Immunity assessment in the early stages of amyotrophic lateral sclerosis: a study of virus antibodies and lymphocyte subsets. Acta neurologica scandinavica. 1988;78(6):449-54.
248. Burrell JR, Kiernan MC, Vucic S, Hodges JR. Motor neuron dysfunction in frontotemporal dementia. Brain. 2011;134(9):2582-94.
249. Lomen-Hoerth C, Murphy J, Langmore S, Kramer J, Olney R, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? Neurology. 2003;60(7):1094-7.
250. Liu-Yesucevitz L, Bilgutay A, Zhang YJ, Vanderwyde T, Citro A, Mehta T, et al. Tar DNA binding protein-43 (TDP-43) associates with stress granules: analysis of cultured cells and pathological brain tissue. PloS one. 2010;5(10):e13250.
251. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(9):2456-77.
252. Schroeter ML, Vogt B, Frisch S, Becker G, Seese A, Barthel H, et al. Dissociating behavioral disorders in early dementia-an FDG-PET study. Psychiatry Research: Neuroimaging. 2011;194(3):235-44.
253. Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, et al. Early frontotemporal dementia targets neurons unique to apes and humans. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2006;60(6):660-7.
254. Kim EJ, Sidhu M, Gaus SE, Huang EJ, Hof PR, Miller BL, et al. Selective frontoinsular von Economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. Cerebral cortex. 2012;22(2):251-9.
255. Pineda SS, Lee H, Fitzwalter BE, Mohammadi S, Pregent LJ, Gardashli ME, et al. Single-cell profiling of the human primary motor cortex in ALS and FTLD. bioRxiv. 2021.
256. Nimchinsky EA, Vogt BA, Morrison JH, Hof PR. Spindle neurons of the human anterior cingulate cortex. Journal of Comparative Neurology. 1995;355(1):27-37.

 doi:10.20944/preprints202410.0704.v1

257. Gu X, Gao Z, Wang X, Liu X, Knight RT, Hof PR, et al. Anterior insular cortex is necessary for empathetic pain perception. Brain. 2012;135(9):2726-35.
258. Rutgen M, Seidel EM, Silani G, Riecansky I, Hummer A, Windischberger C, et al. Placebo analgesia and its opioidergic regulation suggest that empathy for pain is grounded in self pain. Proceedings of the National Academy of Sciences. 2015;112(41):E5638-46.
259. Fletcher PD, Downey LE, Golden HL, Clark CN, Slattery CF, Paterson RW, et al. Pain and temperature processing in dementia: a clinical and neuroanatomical analysis. Brain. 2015;138(11):3360-72.
260. Marshall CR, Hardy CJ, Allen M, Russell LL, Clark CN, Bond RL, et al. Cardiac responses to viewing facial emotion differentiate frontotemporal dementias. Annals of clinical and translational neurology. 2018;5(6):687-96.
261. Gailliot MT, Baumeister RF. The physiology of willpower: Linking blood glucose to self-control. Personality and social psychology review. 2007;11(4):303-27.
262. Adlersberg D, Dolger H. Medico-legal problems of hypoglycemic reactions in diabetes. Annals of Internal Medicine. 1939;12(11):1804-15.
263. Piguet O, Petersén Å, Yin Ka Lam B, Gabery S, Murphy K, Hodges JR, et al. Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. Annals of neurology. 2011;69(2):312-9.
264. Bocchetta M, Gordon E, Manning E, Barnes J, Cash DM, Espak M, et al. Detailed volumetric analysis of the hypothalamus in behavioral variant frontotemporal dementia. Journal of Neurology. 2015;262(12):2635-42.
265. Kumfor F, Hazelton JL, Rushby JA, Hodges JR, Piguet O. Facial expressiveness and physiological arousal in frontotemporal dementia: Phenotypic clinical profiles and neural correlates. Cognitive, Affective, & Behavioral Neuroscience. 2019;19:197-210.
266. Im I, Jun JP, Hwang S, Ko MH. Swallowing outcomes in patients with subcortical stroke associated with lesions of the caudate nucleus and insula. Journal of International Medical Research. 2018;46(9):3552-62.
267. Morbelli S, Ferrara M, Fiz F, Dessi B, Arnaldi D, Picco A, et al. Mapping brain morphological and functional conversion patterns in predementia late-onset bvFTD. European journal of nuclear medicine and molecular imaging. 2016;43(7):1337-47.
268. Fukai M, Hirosawa T, Kikuchi M, Hino S, Kitamura T, Ouchi Y, et al. Different patterns of glucose hypometabolism underlie functional decline in frontotemporal dementia and Alzheimer's disease: FDG-PET study. Neuropsychiatry. 2018;8(2):441-7.
269. Ahmed RM, MacMillan M, Bartley L, Halliday GM, Kiernan MC, Hodges JR, et al. Systemic metabolism in frontotemporal dementia. Neurology. 2014;83(20):1812-8.
270. Golimstok A, Cámpora N, Rojas JI, Fernandez MC, Elizondo C, Soriano E, et al. Cardiovascular risk factors and frontotemporal dementia: a case–control study. Translational neurodegeneration. 2014;3(1):1-6.
271. Zanardini R, Benussi L, Fostinelli S, Saraceno C, Ciani M, Borroni B, et al. Serum C-Peptide, Visfatin, resistin, and ghrelin are altered in sporadic and GRN-Associated frontotemporal lobar degeneration. Journal of Alzheimer's Disease. 2018;61(3):1053-60.
272. Yoon C, Kang M, Shin H, Jeon S, Yang JJ, Kim S, et al. Higher C-peptide levels are associated with regional cortical thinning in 1093 cognitively normal subjects. European Journal of Neurology. 2014;21(10):1318-e81.
273. Woolley JD, Khan BK, Natesan A, Karydas A, Dallman M, Havel P, et al. Satiety-related hormonal dysregulation in behavioral variant frontotemporal dementia. Neurology. 2014;82(6):512-20.
274. Jensen CS, Gleerup HS, Musaeus CS, Hasselbalch SG, Høgh P, Waldemar G, et al. Cerebrospinal fluid glucose is not altered in patients with dementia. Clinical Biochemistry. 2023;112:1-5.
275. Ferrer I, Tuñón T, Serrano M, Casas R, Alcantara S, Zujar M, et al. Calbindin D-28k and parvalbumin immunoreactivity in the frontal cortex in patients with frontal lobe dementia of non-Alzheimer type associated with amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 1993;56(3):257-61.
276. Spalloni A, Caioli S, Bonomi E, Zona C, Buratti E, Alberici A, et al. Cerebrospinal fluid from frontotemporal dementia patients is toxic to neurons. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2021;1867(6):166122.
277. Katzeff JS, Bright F, Lo K, Kril JJ, Connolly A, Crossett B, et al. Altered serum protein levels in frontotemporal dementia and amyotrophic lateral sclerosis indicate calcium and immunity dysregulation. Scientific reports. 2020;10(1):1-12.

278. Phan K, He Y, Pickford R, Bhatia S, Katzeff JS, Hodges JR, et al. Uncovering pathophysiological changes in frontotemporal dementia using serum lipids. Scientific Reports. 2020;10(1):1-13.
279. Imamura K, Sahara N, Kanaan NM, Tsukita K, Kondo T, Kutoku Y, et al. Calcium dysregulation contributes to neurodegeneration in FTLD patient iPSC-derived neurons. Scientific reports. 2016;6(1):1-10.
280. Palluzzi F, Ferrari R, Graziano F, Novelli V, Rossi G, Galimberti D, et al. A novel network analysis approach reveals DNA damage, oxidative stress and calcium/cAMP homeostasis-associated biomarkers in frontotemporal dementia. PLoS one. 2017;12(10):e0185797.
281. Younes K, Lepow LA, Estrada C, Schulz PE. Auto-antibodies against P/Q-and N-type voltage-dependent calcium channels mimicking frontotemporal dementia. SAGE Open Medical Case Reports. 2018;6:2050313X17750928.
282. Arshad F, Varghese F, Paplikar A, Gangadhar Y, Ramakrishnan S, Chaudhuri JR, et al. Role of Autoantibodies in Neurodegenerative Dementia: An Emerging Association. Dementia and Geriatric Cognitive Disorders. 2021;50(2):153-60.
283. Borroni B, Stanic J, Verpelli C, Mellone M, Bonomi E, Alberici A, et al. Anti-AMPA GluA3 antibodies in Frontotemporal dementia: a new molecular target. Scientific reports. 2017;7(1):1-10.
284. Li JY, Cai ZY, Sun XH, Shen DC, Yang XZ, Liu MS, et al. Blood–brain barrier dysfunction and myelin basic protein in survival of amyotrophic lateral sclerosis with or without frontotemporal dementia. Neurological Sciences. 2022;43:3201-10.
285. Katisko K, Solje E, Koivisto AM, Krüger J, Kinnunen T, Hartikainen P, et al. Prevalence of immunological diseases in a Finnish frontotemporal lobar degeneration cohort with the C9orf72 repeat expansion carriers and non-carriers. Journal of Neuroimmunology. 2018;321:29-35.
286. Gami-Patel P, Scarioni M, Bouwman FH, Boon BD, van Swieten JC, Brain Bank N, et al. The severity of behavioural symptoms in FTD is linked to the loss of GABRQ-expressing VENs and pyramidal neurons. Neuropathology and applied neurobiology. 2022;48(4):e12798.
287. Nana AL, Sidhu M, Gaus SE, Hwang JHL, Li L, Park Y, et al. Neurons selectively targeted in frontotemporal dementia reveal early stage TDP-43 pathobiology. Acta neuropathologica. 2019;137(1):27-46.
288. Boccardi M, Sabattoli F, Laakso MP, Testa C, Rossi R, Beltramello A, et al. Frontotemporal dementia as a neural system disease. Neurobiology of aging. 2005;26(1):37-44.
289. Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Archives of neurology. 2008;65(2):249-55.
290. Wang Y, Shen D, Hou B, Sun X, Yang X, Gao J, et al. Brain structural and perfusion changes in amyotrophic lateral sclerosis-frontotemporal dementia patients with cognitive and motor onset: a preliminary study. Brain Imaging and Behavior. 2022:1-11.
291. Képes Z, Nagy F, Budai Á, Barna S, Esze R, Somodi S, et al. Age, BMI and diabetes as independent predictors of brain hypoperfusion. Nuclear Medicine Review. 2021;24(1):11-5.
292. Yaffe K, Falvey CM, Hamilton N, Harris TB, Simonsick EM, Strotmeyer ES, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA internal medicine. 2013;173(14):1300-6.
293. Appel SH, Beers D, Siklos L, Engelhardt JI, Mosier DR. Calcium: the darth vader of ALS. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2001;2(1):47-54.
294. Patai R, Nógrádi B, Engelhardt JI, Siklós L. Calcium in the pathomechanism of amyotrophic lateral sclerosis–Taking center stage? Biochemical and biophysical research communications. 2017;483(4):1031-9.
295. Mackensen A, Müller F, Mougiakakos D, Böltz S, Wilhelm A, Aigner M, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nature Medicine. 2022:1-9.
296. Hendrich J, Van Minh AT, Heblich F, Nieto-Rostro M, Watschinger K, Striessnig J, et al. Pharmacological disruption of calcium channel trafficking by the $\alpha 2\delta$ ligand gabapentin. Proceedings of the National Academy of Sciences. 2008;105(9):3628-33.