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Review

Genetic Variants and Heat Shock Proteins: Unraveling Their Interplay in Neurodegenerative Sclerosis—A Comprehensive Review

Jacqueline Soares Barros Bittar [1], Caroline Christine Pincela da Costa [1], Nayane Soares de Lima [1], Angela Adamski da Silva Reis [1,2] and Rodrigo da Silva Santos [1,2,*]

[1] Neurogenetics Research Center, Institute of Biological Sciences (ICB II), Federal University of Goiás (UFG), Goiânia 74690-900, Goiás, Brazil; jacqueline_bittar@egresso.ufg.br (J.S.B.B.); carolinechristine@discente.ufg.br (C.C.P.d.C.); nayanelima@discente.ufg.br (N.S.d.L.); angela@ufg.br (A.A.d.S.R.)

[2] Department of Biochemistry and Molecular Biology, Institute of Biological Sciences (ICB II), Federal University of Goiás (UFG), Goiânia 74690-900, Goiás, Brazil

* Correspondence: rdssantos@ufg.br

Abstract

Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) are multifactorial and progressive neurodegenerative diseases (ND), which cause a functional capacity decline. Both diseases etiology remains unclear. They may have a hereditary genetic architecture, but they can also be due to a combination of genetic and environmental factors. Heat shock proteins (HSPs) play a crucial role in protein quality control, avoiding protein dysfunction and, consequently, cell apoptosis, which are well-known pathogenic mechanisms of ND. There are studies about chaperones physiology. However, research on their pathophysiology is scarce. Especially when it comes to their associated dysfunctions with Single nucleotide variants (SNV) on HSPs in ND. Thus, this review aimed to examine the role of genetic variants in genes encoding HSPs and their contribution to the pathophysiology of these sclerosis. We performed a qualitative and descriptive literature review, searching by the indexed terms "amyotrophic lateral sclerosis," "genetic variants," "heat shock proteins," "Hsp40", "Hsp70", Hsp90", "DNAJC7", "multiple sclerosis," "neurodegenerative diseases," "protein quality control", and "SNV" in the PubMed/NCBI, EMBASE and SciELo databases. Results described by a qualitative synthesis of the most significant studies. Despite the existence of studies with genetic variants in HSPs in patients with ND, we realize in this review the need for more specific research on this topic to demonstrate a significance as to the responsibility for deleterious effects in the modification in genes HSPs linked to sclerosis.

Keywords: amyotrophic lateral sclerosis; chaperones; genetics variants; multiple sclerosis; neurodegenerative diseases; protein quality control; sclerosis

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1. Introduction

Neurodegenerative diseases (NDs) are functional disorders driven by protein misfolding, leading to the accumulation of intracellular or extracellular aggregates that ultimately result in neuronal death [1]. They are characterized by a progressive loss of neuronal function, often associated with the deposition of misfolded mutant proteins that alter the physicochemical properties of the brain and peripheral organs [2]. Consequently,

protein misfolding within the central nervous system (CNS) is a common hallmark of NDs [3]. These disorders primarily affect older individuals, and their prevalence is steadily increasing due to the global rise in life expectancy [1].

NDs include a subclass known as motor neuron diseases (MNDs), which are characterized by motor impairments associated with varying degrees of muscle atrophy and/or spasticity. These alterations result from dysfunction or loss of motor neurons (MNs). The regulation of skeletal muscle contraction and relaxation relies on MNs, including lower motor neurons located in the bulbar region and spinal cord, as well as upper motor neurons in the cerebral cortex [4]. The protein quality control system (PQC) is made by specific families of proteins, which have the function of removing defective proteins, maintaining their perfect homeostasis. Pathogenic variants interfere with normal RNA production and can cause protein dysfunction during the formation of skeletal muscle fibers and glial cells, resulting in aberrant protein and subsequent MNs degeneration. These dysfunctions can be due to loss of function (LOF) or production of aberrant and neurotoxic proteins—gain of function (GOF). The consequences are an imbalance in protein homeostasis and damage to nerve cells, resulting in cell death [5].

Amyotrophic lateral sclerosis (ALS) is an MND that presents degeneration in the motor neurons of the brain and spinal cord and other neuronal cells [5]. The clinical symptoms may appear in the bulbar region, involving muscle speech, mastication, and swallowing; and limb onset, affecting upper or lower limbs [6]. It causes severe disability and eventually death from ventilatory failure. Clinically, it is characterized by progressive and rapid muscle weakness, spasticity, and atrophy leading to the inevitable muscle paralysis and patient's death in a mean period of 2 to 5 years after diagnosis [7,8], which is performed through electroneuromyography and imaging tests to exclude mimicking diseases. There are patients who survive longer, around 10–20 years, depending on the diagnosis [8]. The diagnosis of ALS is established mainly by the El Escorial criteria, determined by the World Federation of Neurology [9].

The average age of onset is between 50 and 60 years [6]. Most diagnosed cases (~90%) are classified as sporadic (sALS), while approximately 10% are familial (fALS). From a biochemical perspective, studies have demonstrated that excessive oxidative stress, mitochondrial dysfunction, aberrant protein metabolism, impaired axonal transport, and the accumulation of misfolded proteins all contribute to disease pathogenesis [7,10]. In recent years, over 40 mutations associated with ALS have been linked to the accumulation of toxic misfolded proteins, which form protein aggregates—hallmarks of the disease—that ultimately lead to neurodegeneration [11].

In contrast, Multiple Sclerosis (MS) is an ND; however, it is not classified within the subclass of MNDs. MS is an autoimmune disorder of the CNS that periodically targets specific regions of the brain and spinal cord, leading to inflammation, demyelination, gliosis, and neuronal loss. Common symptoms include weakness, numbness, visual disturbances, and tingling pain, although their presentation and severity can vary greatly among patients [8,12]. Evidence indicates that environmental and lifestyle factors—such as smoking, low vitamin D levels, Epstein–Barr virus infection, and childhood obesity—contribute to the onset of the disease. Unlike ALS, which is frequently associated with early mortality, MS is not typically considered a fatal condition. Nonetheless, epidemiological data indicate that individuals diagnosed with this disease exhibit a reduced life expectancy. It is evidenced in a study carried out in Canada, which estimated approximately 6 to 10 years shorter than that of the general population [13]. The diagnosis of MS is based on clinical evaluation, imaging studies, and laboratory tests to confirm neuronal demyelination [14]. Magnetic resonance imaging (MRI) is a crucial paraclinical test for establishing an accurate and early diagnosis of MS [15].

Although the two diseases are distinct neurodegenerative pathologies, they both share relevant diagnostic and epidemiological challenges. A meta-analysis conducted in by Xu et al. [16] reported a global prevalence and incidence of ALS of 4.42 cases per 100,000 individuals and 1.59 cases per 100,000 individuals per year, respectively. The study also showed that ALS is more frequent in males, with incidence increasing with age [16]. In Brazil, epidemiological data on ALS are scarce. A nationwide compilation published in 1998 estimated a prevalence of 0.9–1.5 cases per 100,000 individuals and an incidence of 0.4 cases per 100,000 individuals per year [17]. More recently, research conducted by Moura et al. [18] (2004–2013) using death certificate data reported an age-adjusted mortality rate ranging from 0.61 to 0.89 per 100,000 person-years [18].

The two diseases also differ in their global prevalence. In the case of MS, approximately 2.8 million individuals worldwide are affected [19]. It is more commonly associated with young women, occurring at roughly twice the rate observed in men. The annual incidence in women is approximately 3.6 cases per 100,000 inhabitants, compared to 2.0 cases per 100,000 in men [12,20,21]. According to data from the Multiple Sclerosis International Federation (MSIF), the global prevalence of MS was estimated in 2020 at approximately 36 cases per 100,000 population. The Atlas of MS provides detailed prevalence data for most countries (Figure 1) [19]. In Brazil, the prevalence of MS is 8.69 persons/100,000 inhabitants [22].

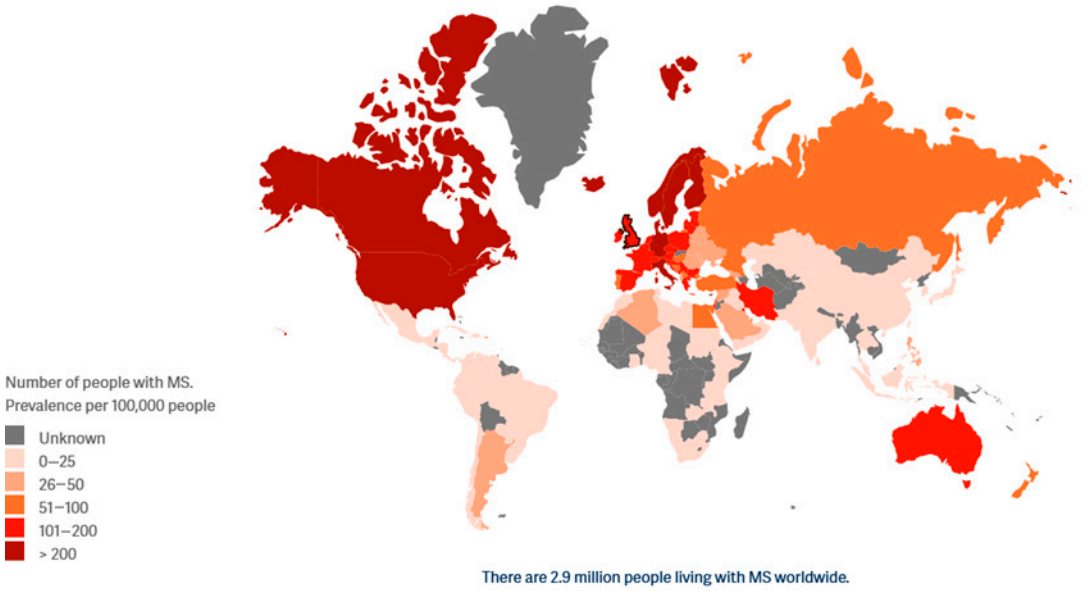

Figure 1. Number of people with Multiple sclerosis in the world. Atlas of MS, from The Multiple Sclerosis International Federation, 2020 [19].

It is essential to note that ALS and MS, although distinct in etiology and pathogenesis, share some relevant pathophysiological mechanisms, including neuroinflammation, oxidative stress, and the accumulation of misfolded proteins, which justify the interest in studying these diseases in the context of the chaperone system. ALS is a progressive neurodegenerative disease characterized by the selective loss of upper and lower motor neurons, leading to muscle weakness, spasticity, atrophy, and respiratory failure [23]. It is characterized by the accumulation of mutant proteins such as SOD1, TDP-43, FUS, and C9orf72, which form cytotoxic aggregates that compromise cellular homeostasis and overload the capacity of molecular chaperones. In ALS, dysfunction of the chaperone system, especially the HSP70 and DNAJ families, has been associated with failure in protein quality control and the induction of apoptotic pathways [1,24].

On the other hand, MS is an inflammatory autoimmune condition of the CNS, characterized by demyelination, infiltration of autoreactive immune cells, and lesion formation that culminates in axonal damage [25]. In neuronal tissues affected by MS, there is an exacerbated presence of chaperones such as HSP70, HSP90, and αB-crystallin (HspB5), which can have protective or pro-inflammatory effects depending on the dynamics involved. It should be noted that the dysregulated expression of chaperones in the CNS, associated with the chronic inflammatory process, as well as oxidative stress, may contribute to the autoimmune pattern present in MS [24].

Both ALS and MS are rare, multifactorial, and progressive NDs that lead to a decline in functional capacity, exerting a substantial impact on the quality of life of patients and their caregivers. Their etiology involves a complex interplay between environmental factors and genetic variations [14]. The etiology of each disease remains unclear. Although ALS and MS present distinct clinical symptoms (Table 1), these differences can still complicate the diagnostic process. A major limitation to achieving an accurate prognosis is the absence of effective treatment options. Nevertheless, rehabilitation remains a commonly employed strategy to alleviate symptoms in both conditions [11,25].

Table 1. Similarities and differences between symptoms in ALS and MS.

Symptoms	Amyotrophic Lateral Sclerosis (ALS)	Multiple Sclerosis (MS)	Key Differences
Muscle Weakness	Present, primarily in the upper and lower limbs.	Can occur, typically associated with motor function loss.	Common in both, but with different underlying causes.
Walking Difficulties	Common due to progressive muscle weakness.	Can occur due to coordination and balance loss.	ALS causes progressive muscle weakness, while MS may affect balance.
Spasticity	Present, with progressive muscle stiffness.	May occur, but is not a predominant symptom.	More pronounced in ALS.
Fatigue	Present, but not a central symptom.	Common, particularly during relapses.	Fatigue is more prevalent in MS.
Speech Impairments	Progressive difficulty speaking due to paralysis of speech muscles.	May occur due to loss of coordination, but it is not common.	Common in ALS, rare in MS.
Vision Problems	Not a common symptom.	Visual issues, such as optic neuritis, are common during relapses.	Clear distinction between the conditions.
Swallowing Difficulties	Common due to weakness in muscles responsible for swallowing.	May occur in advanced stages of the disease.	More early and severe in ALS.
Pain	Less frequent but may occur due to spasticity.	Can be intense, especially during relapses affecting peripheral nerves.	Neuropathic pain is more common in MS.
Disease Stages	Progressive and irreversible.	May have relapses and remissions, with stable phases between attacks.	ALS is progressive without remission phases.

Adapted from: Deeb O.; Nabulsi M., 2020 [8].

Regarding pharmacotherapy, these conditions differ markedly in their response to treatment. MS responds to corticosteroids, which help control inflammation and alleviate symptoms. By comparison, ALS treatments such as riluzole and edaravone generally extend survival by only a few months [3,5,11]. Although ongoing research has advanced the understanding of ALS, a definitive cure remains elusive, underscoring the urgent need

for novel therapeutic strategies. Recent advances in ALS treatment have highlighted several promising approaches, which includes the use of miRNAs for gene regulation via the RNA-induced silencing complex (RISC), RNA interference (RNAi) for mRNA silencing, stem cell therapies to replace damaged cells, and gene therapy targeting epigenetic modifications like histone modifications, miRNAs, and DNA methylation [26].

Although the etiology of both diseases remains unclear and their symptoms differ, they may still be confused, complicating diagnosis, prognosis, and the development of effective treatments [8]. Both conditions exhibit features of sclerosis; however, they respond differently to available therapies (Table 2).

Table 2. Pharmacotherapy for Multiple sclerosis (MS) and Amyotrophic lateral sclerosis (ALS).

Drug/Therapy	ALS	MS	Mechanism of Action	Limitations
Riluzole	Approved	Not used for MS	Inhibiting the excitatory glutamate that contributes to neuron injury	Prolongs survival for few months
Edaravone	Approved	Not used for MS	Reduce and neutralizes oxidative stress in neurons and global cells	There is still a very limited experience of this medication
Glucocorticoids Corticosteroids	Not used for ALS	Approved	Blocks lymphocyte activation and immune cell entry into CNS	Diabetes; Hypertension, Osteoporosis
Mitoxantrone	Not used for ALS	Approved	Immunosuppressive; Immunomodulatory	Risk of infection; leukopenia; Gonadotoxicity Bladder cancer
Cyclophosphamide	Not used for ALS	Approved	Immunosuppressive; Immunomodulatory	Risk of infection; leukopenia; Gonadotoxicity Bladder cancer
Beta-Interferon	Not used for ALS	Approved	Inhibition of T-cells activation and proliferation apoptosis	Lipoatrophy and risk of site infection; Complication in Thyroid disease
Glatiramer Acetate (Copaxone)	Not used for ALS	Approved	No precise mechanism of action, but it is assumed to be as Interferon	A few beneficial effects in RRMS and PMS
Fingolimod Siponimod	Not used for ALS	Approved	Suppresses immune attacks on nerves reducing further damage	Fingolimod cause cardiac and ophthalmological adverse events
Teriflunomide	Not used for ALS	Approved	Inhibition T cells	Elevated liver enzymes
Dimethyl fumarate	Not used for ALS	Approved	Inhibition pro-inflammatory Nrf2 [1]	Lymphopenia
Ocrelizumab Naalizumab Alemtuzumab	Not used for ALS	Approved	Monoclonal antibodies	Herpes infection

[1] Nrf2: Factor erythroid 2-related factor 2. Adapted from: Deeb O.; Nabulsi M., 2020 [8].

In the context of ALS and MS, understanding the cellular mechanisms involved in neurodegenerations is essential to elucidating how complex biological processes can influence the pathogenesis of both. Thus, HSPs, a group of chaperone proteins, stand out.

These interact with other proteins to prevent misfolding, assisting in their stabilization and enabling them to acquire their native conformation. Therefore, they perform an important quality control function when monitoring and maintaining the native conformation of the proteins during their folding [27]. They prevent the formation of protein aggregates, thereby avoiding functional loss and subsequent cell apoptosis, which are well-established pathogenic mechanisms in ND [28]. These dysfunctions contribute to an increase in conformational disorders, particularly within the endoplasmic reticulum, where defective proteins may be retained for eventual degradation by the ubiquitin-proteasome system (UPS) or via autophagy, processes facilitated by HSPs [29].

Numerous publications have addressed the role of HSPs in ND. However, few have described the dysfunctions of these chaperones associated with genetic variations in the literature. HSPs play a crucial role in maintaining protein homeostasis by assisting in the refolding of misfolded proteins and facilitating the degradation of irreparably damaged proteins. In MS, HSPs, such as HSPA (Hsp70), modulate immune responses, while in ALS, HSPs are involved in protein quality control, particularly in motor neurons, where the accumulation of misfolded proteins like SOD1 and TDP-43 is a hallmark of the disease [1,25].

New computational approaches, such as genome-wide association studies (GWAS), have significantly advanced the understanding of correlations between rare and pathogenic variants, enabling the discovery of novel genes and their genetic variations. Recent studies by the International Multiple Sclerosis Genetics Consortium (IMSGC) using GWAS identified approximately 233 variants associated with MS [30,31]. In ALS, the combination of GWAS with a novel tool known as RefMap identified 690 risk genes, supported by the epigenetic signatures of motor neurons (MNs) [32].

This review examines the role of heat shock proteins (HSPs) and their functions in PQC within the neurodynamics of the central nervous system (CNS), as well as their involvement when genetic variants occur in genes associated with sclerosis, particularly in the presence of single nucleotide variants (SNVs). We applied descriptive qualitative research, conducted as a narrative literature review. This approach enables the inclusion of recent studies on the topic and their findings, potentially encompassing diverse perspectives. Such integration fosters new insights into the subject and supports the consolidation of knowledge [33–35]. Following bibliographic analysis and selection through title and abstract screening, studies relevant to the topic of interest were included in this review.

2. Protein Quality Control (PQC)

The senescence process is associated with complications in maintaining proteostasis mechanisms, in addition to impairing the activation of protective mechanisms common to cells, which makes it difficult to perpetuate the status quo of the cell. Aging determines factors that cause cellular stress and can culminate in the deregulation of protein machinery, leading to the production of defective protein products. In response, the body uses PQC to prevent further cellular damage, aiming to assist in the folding or "marking" of defective protein products and subsequently directing them to some degradation pathway, either ubiquitin–proteasome system (UPS) or autophagy [29].

In order to maintain cellular proteostasis, a complex consisting of approximately 1400 proteins is involved, including chaperones, their co-chaperones, and their regulators, as well as proteins responsible for defending against oxidative stress and those belonging to the protein degradation machinery (UPS and autophagic machinery). To maintain proteostasis, it is crucial that the cell properly refolds misfolded proteins, when possible, or promotes their degradation. It is important to note that some proteins, when misfolded, culminate in neuropathological processes contributing to the development of NDs [29].

Additionally, HSPs are overexpressed and, at the same time, activate degradative pathways that remove defective proteins, thereby preventing them from exerting harmful effects [5,36]. Their primary function is to assist in the proper folding of other proteins through different mechanisms of action, thus preventing imbalances in proteostasis, or protein homeostasis. This process occurs at distinct stages of protein biogenesis, including translation, folding, processing, and degradation via the UPS or autophagy [37].

Autophagy is an important mechanism for neural homeostasis, avoiding cell death (Figure 2). In ALS, dysfunctional autophagy plays a central role in disease progression and leads to the accumulation of toxic protein aggregates. The mitophagy failure results in the buildup of damaged mitochondria, further exacerbating cellular stress. Additionally, reticulophagy dysfunction contributes to endoplasmic reticulum (ER) stress, disrupting protein folding and cellular homeostasis. These processes, in conjunction with excitotoxicity—the over-activation of neurons by excessive glutamate—initiate inflammation, increasing oxidative stress and further impairing cellular function. The accumulation of calcium in the cytoplasm and mitochondria amplifies mitochondrial damage, further compromising cellular integrity. Ultimately, these disruptions culminate in cellular apoptosis and neuronal death, driving the neurodegenerative process in ALS [11].

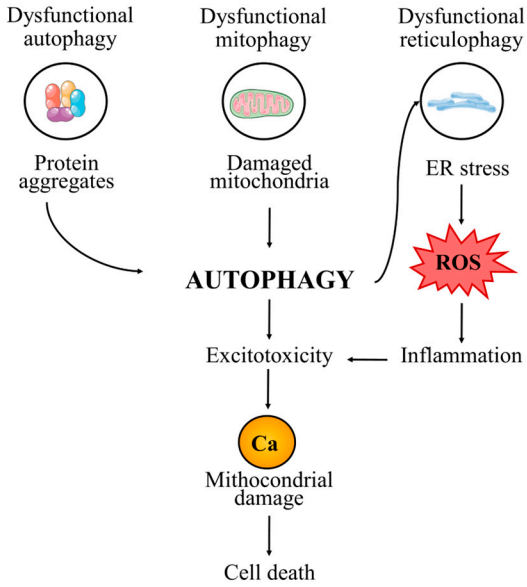

Figure 2. Interconnected pathogenic mechanisms in ALS: the role of autophagy. The interrelationship between dysfunctional autophagy and other pathogenic mechanisms in ALS. Dysfunctional autophagy, including protein aggregates, mitophagy, and reticulophagy, leads to the accumulation of protein aggregates, damaged mitochondria, and endoplasmic reticulum (ER) stress, respectively. These dysfunctions promote the production of reactive oxygen species (ROS), contributing to excitotoxicity and inflammation. The buildup of calcium (Ca) exacerbates mitochondrial damage, ultimately leading to cell death, a key process in ALS pathogenesis.

Thus, the PQC system maintains balanced proteostasis during protein production by correcting misfolded proteins or directing irreparably damaged ones to degradation pathways [36]. Chaperones may be required at various stages of this process, particularly during the formation of high molecular weight native proteins [37].

3. Heat Shock Protein

The term "chaperone," originally from the French "chaperon" (meaning "lady-in-waiting"), was first used in 14th-century England and later adapted by the French. In cell biology, it now refers to proteins involved in the quality control of other proteins [38,39].

In the middle of 1962, the functions of chaperones in response to thermal shock were already being studied. The first research took place with *Drosophila* conducted by researcher Ferricio Ritossa. It was noticed that, after thermal stimuli, the insect's salivary chromosomes increased in response to cellular stress [40]. This phenomenon is known as the heat shock response (HSR). Other researchers working with this same current of thought, when they injected denatured proteins in *Drosophila* or *Escherichia coli* or oocytes of *Xenopus laevis*, they noticed an increase in the expression of HSP, which are also involved in the process of responses to cellular stress. Another piece of evidence that stood out was that exposure to heat at different temperatures activated the HSPs genes transiently, characterizing the group with a self-regulating role. Therefore, HSPs are responsible for mediating protein homeostasis and maintaining the correct folding and translocation of proteins in normal conditions and under stress [7,41–43].

The most common class of chaperones is HSPs, also known as stress proteins, which are the focus of this review. They are initially identified as proteins that respond to thermal stress or other forms of protein toxicity. Their classification is based on molecular weight and function. These proteins range from 17 kDa to over 100 kDa, and HSPs' classification divides them into the following families: Hsp110; Hsp90; Hsp70; Hsp60/10 (chaperonins); TRic-chaperonin; Chaperonin-like; Hsp40 (co-chaperones); and Hspsmall (small chaperones) [44]. The families of Hsp40, Hsp70, and Hsp90 are the most found in the CNS, and they are objects of this study [7,44].

HSP's have an important role in the cellular homeostasis of the proteins, preventing native proteins from aggregating or becoming dysfunctional in cellular stress situations. HSP's increase to protect cells in environmental chances or situations that cause a protein denaturation reaction. Thus, it controls the proper function of the protein machinery [45]. They can be intracellular or extracellular chaperones. Generally, act in a specific subcellular region, as chaperones localized in endoplasmic reticulum, in mitochondria, in the lysosomes, and/or cytoplasm [5] (Table 1). However, this review placed significantly greater emphasis on intracellular stress-induced chaperones, especially the HSPA (Hsp70), HSPC (Hsp90), DNAJC (Hsp40), localized in nucleus/cytosol, and their importance in ALS and MS.

Another important aspect addressed in this review is the updated nomenclature for HSPs. Sequencing the human genome and computational gene annotations revealed that different family members often had multiple names for the same gene. To resolve this, the HUGO Gene Nomenclature Committee (HGNC) standardized HSP classifications and incorporated them into the National Center for Biotechnology Information (NCBI) Entrez Gene database, facilitating their primary identification in bioinformatics resources. Table 3 summarizes the HSP families, their previous nomenclature, the newly proposed names, as well as the cellular localization of the proteins and their functions as chaperones [7,46].

Table 3. Families of Heat shock protein (HSP) with their suggestive new guidelines, number of human genes identified, where they are predominant, and the most principal functions.

HSP Families	New Nomenclature	Members Genes (Humans)	Predominant Location	Functions	Others References
Hspsmall	HSPB	11	Nucleus/Cytosol/ Cytoskeleton/Cillium Golgi Apparatus (GA)	Assist the autophagy process; mitophagy; neuroprotection and prevents protein, inhibition of cell death; reduced oxidative damage.	[1,47,48]

Table 3. *Cont.*

HSP Families	New Nomenclature	Members Genes (Humans)	Predominant Location	Functions	Others References
Hsp60 Hsp10 Chaperonin	HSPD1 HSPE1	1 1	Mitochondria Cytosol Extracellular	Folding of newly formed proteins; refolding denatured proteins in the mitochondria	[49–51]
Hsp70	HSPA	13	Cytosol, Lysossomes, Mitochondria; Endoplasmasmic Reticulum; Microsomes	Selective Autophagy; folding of newly formed proteins; prevention of aggregation; unfolding of misfolded proteins	[52,53]
Hsp90	HSPC	5	Cytosol; Endoplasmasmic Reticulum; Mitochondria	Prevent protein aggregation; accelerates the final formation of the mature protein	[44,54]
Hsp110	HSPH	4	Cytosol; Endoplasmasmic Reticulum	Solubilization of protein aggregates; helps the folding with nucleotide exchange factors (NEF)	[50]
TRic chaperonins	CCT	9	Cytosol	An essential role in folding newly synthesized cytosolic proteins and preventing protein aggregation; activation heat shock transcription factors (HSFs)	[50,55]
Chaperonin-like	MKKS BBS6 BBS10 BBS12	3	Cilia; centrosome/basal body functions.	Basal body functions	[7]
Hsp40	DNAJA	4	Nucleus/Mitochondria/ ER/Cytosol/Membrane	Recruits' protein clients for HSPA; stimulate ATP hydrolysis for HSPA; assist the stability of the peptide chaperone complex; helps the folding with NEF; reduce the aggregation of SOD1G93A; Neuron-specific DNAJB2a aids in refolding and solubilizing mutant TDP-43; reduces and prevents aggregation of alpha-synuclein and "tau" protein	[1,44]
	DNAJB	14	Nucleus/Cytosol Membrane/ER		
	DNAJC	30	Nucleus/Cytosol/ER/ Membrane/ Mitochondria/GA		

Evolution of HSP Nomenclature—A representation of the standardized nomenclature for HSP families as proposed by the HUGO Gene Nomenclature Committee (HGNC). The figure illustrates the transition from the old nomenclature to the suggested new guidelines, providing insights into the number of human genes identified, predominant protein locations, and crucial chaperone functions.

3.1. Heat Shock Protein Intracellular (CI) and Extracellular (CE)

Chaperones can be located intracellular (CI) and extracellular (CE). In the space inside the cells have been identified in mammals, 332 genes encoding 88 chaperones and 244 co-chaperones. The function in both species is similar, except that CE cannot perform the correct folding of misfolded proteins, because the amount of extracellular ATP is reduced, acting as a holdase. CE stabilizes dysfunctional proteins by directing them to

the intracellular space for further degradation. They can perform degradation through the plasminogen activation pathway. It also assists in the regulation of complement and proteins of the innate immune system [36]. Despite the evidence that chaperones engage in cooperation with the protein customers in their perfect folding, they also exert other functions as described in the articles cited in this study.

3.2. Modulation Carried out by HSPs as the Protein Quality Control

HSPs are expressed at low levels in most eukaryotic cells but are induced by cellular stress such as increased temperature, radiation, exposure to chemicals, oxidative stress, and various physiological and pathological stimuli. They also stimulate the production of pro-inflammatory cytokines and promote dendritic cells [32]. Cellular aging or its disorder, caused by multiple factors, is also responsible for the formation of misfolded proteins, which means proteins that have reached a non-native, often cytotoxic, or non-functional conformation. These accumulate in three different forms: protein inclusions, amorphous aggregates, and amyloid fibrils that form polymorphic oligomers. These pathogenic structures can be enhanced by genetic variants and specific post-translational modifications, which are found in neuropathological inclusions in neurons of ND [54].

The proteostasis imbalance by the factors listed stimulates the heat shock response (HSR), which is a pathway for ubiquitous cytoprotective signaling that activates the heat shock transcription factor (HSF-1). They are specific DNA-binding proteins that have the function of activating or repressing genes coding HSPs. Therefore, HSF-1 is considered the major regulator of PQC expression in response to proteotoxic stress conditions. The HSPA + HSPC + DNAJ complex regulates the extent to which HSF-1 remains active, inhibiting it when no longer needed [55].

To understand how chaperones work in the PQC, it is necessary to explain the two specific categories classified based on their energy dependence. The "Foldase mechanisms,"—this category depends on the hydrolysis of ATP for the coordination and release of client protein, in the folding process. Moreover, it assists the transition of non-native client conformations to their native conformations. This category includes HSPA and HSPC. On the other hand, the "Holdase mechanisms" are ATP-independent, and they usually prevent protein aggregation by tightly holding onto and sequestering their client proteins in a non-native state. Only HSPB is in this category because it does not have an ATPase function. It captures free unfolded proteins and maintains them in soluble forms. A higher cellular concentration of holdases is important in cells with slow or absent growth because the holdases are the source of energy for these cells. Therefore, they are essential in differentiated neurons that do not divide [54,56].

In addition to the categories, it is necessary to understand the binding domains between client proteins and chaperones. In general, chaperone functions are defined in two terminal domains—the nucleotide-binding domain (NBD) that interacts with co-chaperones and the substrate binding domain (SBD) which binds the hydrophobic patches reducing protein disjunction interactions (Figure 3) [7].

HSPH (Hsp100) has 4 human isoforms, the same architecture as Hsp70 with two domains (NBD and SBD). It functions as a nucleotides exchange factor (NEF) during the action of HSPA, since it is ATP-dependent, but its concentration is low in the CNS [7].

HSPC (Hsp90) has 5 isoforms and is composed of three domains: the N-terminal domain is responsible for nucleotide exchange; the Middle domain is responsible for recognizing the client proteins and triggers hydrolysis of ATP and the C-terminal domain is an important site for the dimerization. This family requires ATP hydrolysis and structural rearrangement to reconfigure abnormally folded proteins to their normal states [7]. Co-chaperones carry out this process including DNAJ proteins [45]. The HSPC chaperones

are important regulators of the protein folding process in all eukaryotic cells, preventing protein aggregation. Its concentration in the body varies from 1 to 2%, but in situations of cellular stress, it increases up to 6%. Like other HSPs, they can be regulated by HSF1 or post-translational modification (PTM), as phosphorylation, acetylation, S-nitrolysation, and oxidation [57]. The examples of some important proteins in which HSPC regulates correct folding and maturation: steroid hormone receptors, protein kinases, transcription factors, and E3 ubiquitin ligases [58].

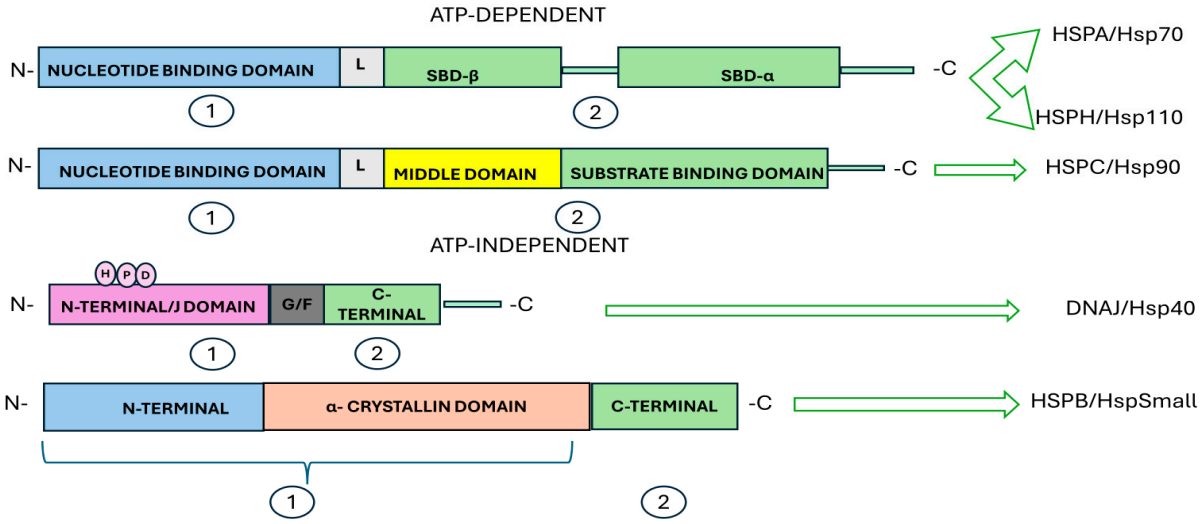

Figure 3. Functional Domains in Families of HSPs—Geometric representation of the main domains in each family of HSPs. Types of domains in each family of HSPs. Presentation in the geometric form of the main HSPs domains. HSPA and HSPH have two domains: NBD and SBD linked by a folding connection; HSPC has three domains: NBD (number 1), SBD (number 2), and Middle domain. It also presents a flexible connection linking the domains. DNAJ has two domains with the J domain having formed by histidine, proline, and aspartate, which help bind to the HSPA/Hsp70 NBD. HSPB has two domains: α-Crystallin composed of one hundred amino acids flanked by N and C terminals of diverse sizes. Adapted figure [7].

HSPA (Hsp70) has 13 human isoforms, it is dependent-ATP with two domains and two regions in its structure. It consists of a conserved ATPase domain; a middle region with protease-sensitive sites; a peptide binding domain (NBD), which controls the interaction with the client protein; and a C-terminal substrate-binding domain (SBD) to bind co-chaperones and other HSPs [7]. This domain identifies the hydrophobic regions in the client during the initial stages of its folding. SBD is divided into two subdomains: alpha and beta. The first works as if it were a lid, which opens by trapping the client protein that connects to the NBD, known as the second subdomain (SBD-β). This occurs when ATP binds to NBD, the ATP is hydrolyzed, and the lid closes. Another chaperone, nucleotide exchange factors (NEF) bind to the NBD to accelerate the release of ADP by promoting the opening of the SBD-alfa and the client protein accordingly being released. This process is known as the chaperone cycle and occurs in the presence of DNAJ [58,59]. Under normal conditions, they participate in the correct folding of the proteins that are formed, but also under stress conditions, preventing protein aggregation and misfolding in the proteostasis [7]. Considering the most common processes involving ND, it becomes necessary to understand its cycle (Figure 4).

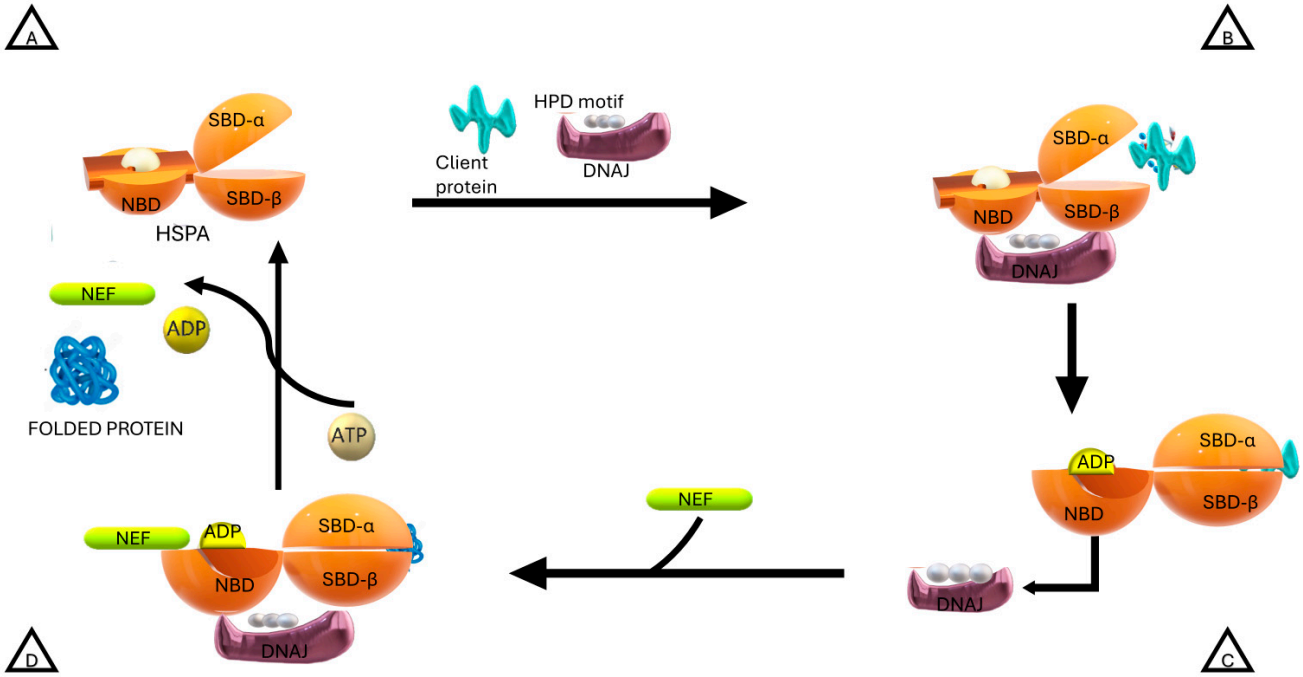

Figure 4. HSPA Cycle (Hsp70) with Co-chaperone DNAJ. Schematic representation of HSPA (Hsp70) cycle with co-chaperone DNAJ. Color members: HSPA-orange; DNAJ-purple; tripeptide motif (HPD) DNAJ-white. The cycle begins at (A) with HSPA in the ATP-bound state, featuring its Substrate-Binding Domain (SBD) in an open, low-affinity conformation. (B) The co-chaperone DNAJ (Hsp40) delivers an unfolded client protein to the SBD and stimulates ATP hydrolysis. (C) The hydrolysis of ATP to ADP induces a conformational change that closes the SBD over the client protein, trapping it with high affinity. (D) The Nucleotide Exchange Factor (NEF) binds to the Nucleotide-Binding Domain (NBD), causing the release of ADP. The subsequent binding of a new ATP molecule resets the cycle, opening the SBD and releasing the client protein, allowing it to attain its native conformation.

HSPD/E (Hsp60) known as chaperonins share a double ring-like structure forming a symmetrical football complex. They are crucial in protein folding and unfolding. However, little is known about its structure and physicochemical properties [52,53].

DNAJ (Hsp40), also known as the J domain. It is a specific type of molecular chaperone involved in PCQ. Humans have identified 49 genes in eukaryotic cells [44]. This family is divided into three classes, which are described in Table 3. DNAJA, which has a cysteine in the zinc finger region linked by the intermediate J domain of regions rich in glycine and phenylalanine. DNAJB differs from DNAJA, because it has no cysteine-rich region linked to the J domain. DNAJC contains only the J domain, but they perform several quality control functions and are unique in the process of assisting proteins HSPA [44]. DNAJ is responsible for recruiting Hsp70 and stimulating its hydrolysis, given that it is an ATP-dependent chaperone. This allows it to close its binding domain around an unfolded polypeptide chain [59]. It has three domains: N-terminal J-domain site (containing ~70 amino acids) that consists of four alpha-helices and a histidine, proline, and aspartic acid (HPD motif), which is located between helices II and III [44,60]. This site is responsible for stimulating Hsp70 nucleotide exchange, a short region that allows the protein to have a strong level of flexibility and a C-terminal domain. J domain protein family channels client protein to Hsp70 vitalizing its ATPase activity and leaving this complex. After, the breakdown of Hsp70 to its apo-form by a NEF liberating ADP from it occurs. The NBD stays free to engage ATP, leading the α-helical open and releasing clients [7].

DNAJC7 is highly expressed in the brain [44], consistent with its proposed neuroprotective role [28]. In its formation, it has two tetratricopeptide (TPR) domains that interact

with HSPA and HSPC proteins. They play an important role in modulating the flow of HSPA and HSPC substrates, contributing to the control of proteins such as glucocorticoids and progesterone receptors. In addition, DNAJC7 TPR domains are shared with other proteins, such as the co-chaperones HOP, responsible for HSPA and HSPC organizing protein, to facilitate substrate transfer [44].

HSPB (Hspsmall) has 11 human isoforms that are independent of ATP. Like Hsp90, it possesses two domains, one of which is known as α-crystallin or the oligomeric "holdase". α-Crystallin is a member of the small heat-shock protein (sHSP) family and consists of two subunits, αA and αB. Both αA- and αB-crystallin act as chaperones and anti-apoptotic proteins. The α-crystallin domain plays a crucial role in protein refolding, helping to retain misfolded polypeptides, preventing protein aggregation. It can also correctly refold this protein or degrade them under stress conditions, eliminating from the cell (antioxidant and anti-apoptotic actions) [1,7]. Another important function of chaperones refers to the process of autophagy assisted by them, which can be considered another way of acting in PQC [61].

3.3. System of Protein Degradation Involving HSPs

The protein degradation system, known as autophagy, also functions as a PQC. It can occur in three ways that differ from each other by internalization process proteins when phagocytized by lysosomes: (i) macroautophagy, also known as autophagy; (ii) chaperone-mediated autophagy (CMA); (iii) microautophagy [61]. This study will address the two most researched pathways and where there is participation of HSP.

3.3.1. Chaperone-Assisted Selective Autophagy

Chaperone-assisted selective autophagy (CASA) is one of the macroautophagy processes for degrading proteins. It is a protein complex, originally described in muscle cells, formed by chaperones (HSPA8 and HSPB8), co-chaperones (BAG-3), and UPS ligase proteins (STUB/CHIP) [62,63]. The HSPs recognize client protein (substrate) when poorly folded or aged and bind to them with the aid of BAG-3, to the ATPase domain, and are responsible for the release of the substrate. The BAG3 has a tryptophan-tryptophan domain (WW) which binds to the HSPA and prefers proteins rich in proline. In the next stage, the protein complex suffers ubiquitination by STUB1/CHIP (ligase ubiquitin), which interacts with the autophagic receptor sequestosome 1 (SQSTM1), through a specific domain known as ubiquitin-associated (UBA). Even now, the expansion of the isolation membrane (phagophore) occurs, and the autophagosome is formed, which will be encompassed by the lysosome, ending the protein complex by the CASA pathway (Figure 5) [61].

The CASA mechanism has a neuroprotective effect. Evidence shows that mutations in genes linked to ND phenotypes stimulate increased expression of HSPs and their co-chaperones, accelerating the degradation of aberrant proteins by the ubiquitination system. Regarding the pathology of ALS, it is associated with already known genes such as *C9orf72*, *SOD1*, *TARDBP*, and *FUS*. However, most ALS cases are characterized by the aggregation of fragmented particles of varying kDa of the aberrant protein TDP-43 in the cytoplasm. These fragments can be found at 35 kDa and 25 kDa, with the most common being known as TDP-25. The chaperones involved in the CASA complex are overexpressed through the HSR stimulus and the degrading actions are initiated, reducing the insoluble particles in the MN and myoblast. This mechanism prevents cell toxicity. Therefore, the CASA complex is beneficial in MN and myoblasts, evidencing its importance for the PQC system in human health [64].

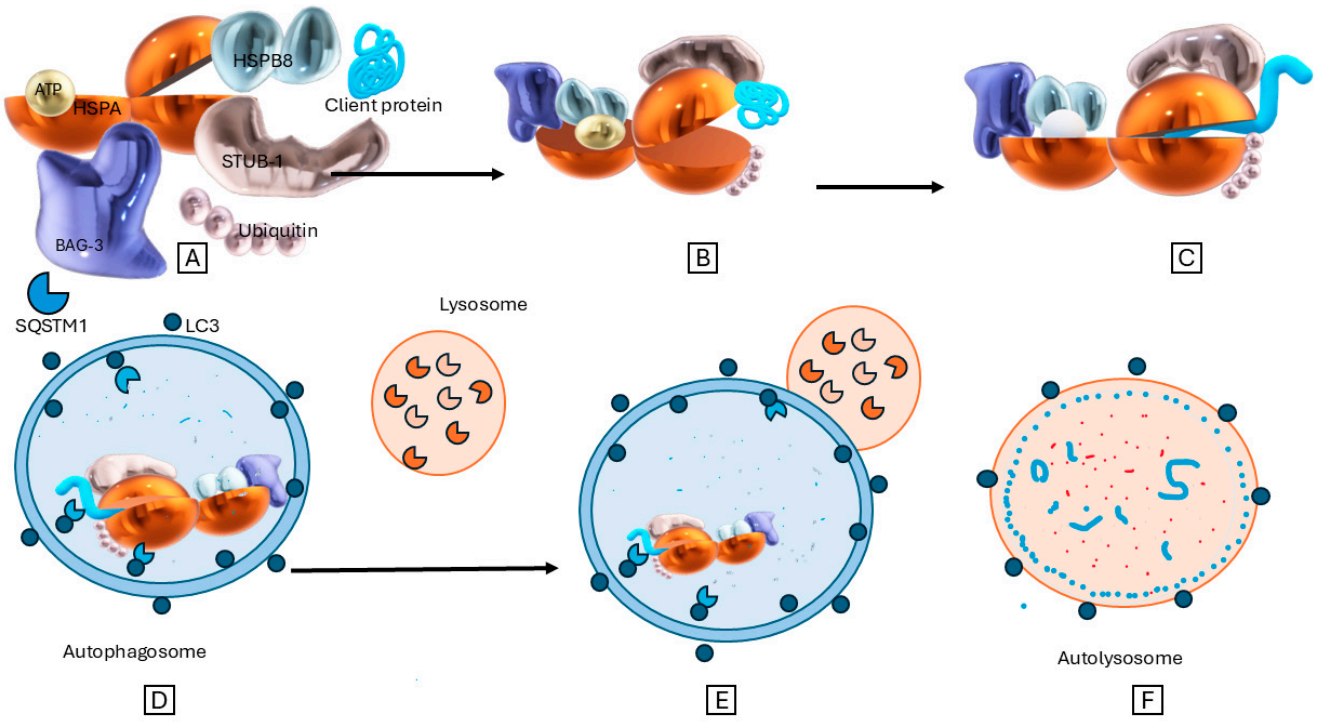

Figure 5. Schematic representation of the CASA complex. Schematic representation of the Chaperone-assisted selective autophagy (CASA) complex formed by Chaperones: HSPA and HSPB8; cochaperone: BAG-3 and the Ubiquitin-ligase: STUB1. SQSTM1: autophagy receptor. LC3: decorated phagophore. (**A**) CASA complex members; (**B**) CASA members recognize and remove client protein in the cell cytoplasm; (**C**) Client protein that can be damaged or misfolded protein undergoes ubiquitination and becomes a linear form. (**D**) Engulfment of the client protein and CASA Complex into a phagophore membrane with the aid of SQSTM1 and LC3, creating the autophagosome. (**E**) Fusion autophagosome and lysosome. (**F**) ending the degradation.

In relation to MS by action of the CASA complex, the mechanism can be beneficial when the reduction in oxidative stress and inflammatory disorders occurs. However, autophagy can activate the production of immunoreactive cells triggering exacerbated inflammatory reactions. In a case–control study conducted (1/1) with 186 individuals showed results pointed to genetic variation in the genes that encode the proteins of the CASA complex, affecting the autophagy process [65].

3.3.2. Chaperone-Mediated Autophagy (CMA)

CMA is another pathway of protein degradation with the involvement of HSPA8, which differs from CASA because it does not involve the formation of autophagosomes (vesicles). The client protein complex and chaperone are associated with a lysosome 2A (LAMP-2A), that is translocated into the lysosome. The degradation happens this way, the protein must have in its formation a specific combination of five amino acids (motif-KFERQ), demonstrating the specificity of this route [66]. In this process, ATP-dependent HSPAs participate with other chaperones, but the most found are HIP, HSP90, HSP40, HOP, and BAG-1 (Figure 6) [67].

As well as the CASA pathway, there is evidence that its overexpression happens in response to genotoxicity, it maintains the stability of the genome and protein balance, and is involved neuronal protection against oxidative stress. Therefore, important PQC functions are performed by the CMA. Both pathways play a significant role in regulating metabolism, transcription, DNA repair, and cell cycle, regulating many aging-associated human diseases, such as neurodegenerative, cancer, and metabolic disorders. When further investigated,

it is possible to know the still obscure mechanisms when they relate to these diseases, especially sclerosis, and to find viable alternatives for more effective treatments [68].

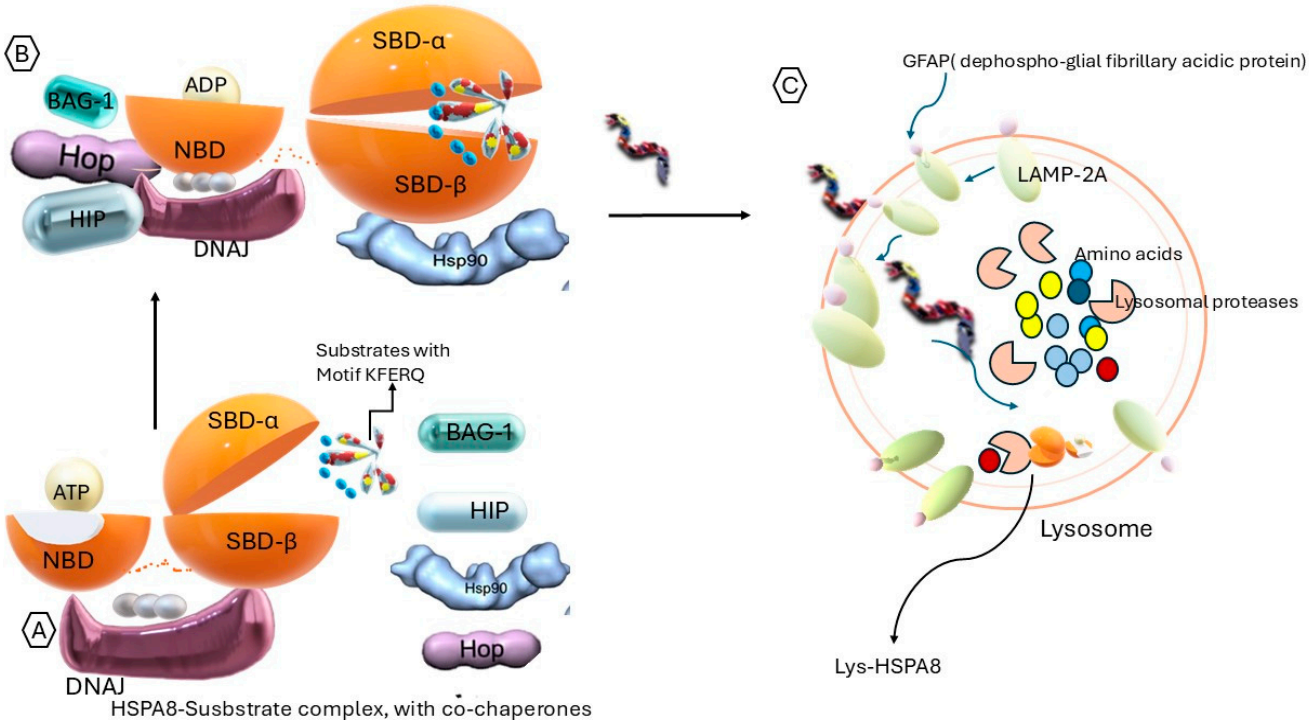

Figure 6. Schematic representation of Client Protein Degradation via CMA. Schematic representation of client protein degradation via Chaperone-mediated autophagy (CMA). Color members: HSPA—orange; DNAJ—purple; HSPC/Hsp90—blue; co-chaperone HOP: light purple; co-chaperone BAG1: green capsule; co-chaperone HIP: blue capsule. The process begins in the cytosol (**A**,**B**), where the HSPA8 chaperone complex, along with co-chaperones (e.g., DNAJ, HIP, Hop), recognizes and binds to substrate proteins containing the KFERQ lysosomal targeting motif. The formation of this complex is dependent on ATP hydrolysis. (**C**) The HSPA8-substrate complex is then targeted to the lysosome, where the substrate interacts with the membrane receptor LAMP-2A. Following unfolding, the protein is translocated into the lysosomal lumen, a process aided by the intralysosomal HSPA8 (Lys-HSPA8). Inside the lysosome, the protein is finally degraded by proteases into its constituent amino acids.

Evidence of association with CMA dysfunctions is few; however, in the article's review, a study was found showing that HSPA was reduced in lymphomonocytes of sporadic patients with ALS. This contributes to the accumulation of TDP-43 because a mutation in KFERQ-like in the TDP-43 coding gene stopped its degradation and increased its accumulation, leading to cell toxicity in the MNs [69].

Studies associating autophagy with chaperones and MS were not found in the research bases used. However, increased autophagy and neuropathologic symptoms of MS are associated with the autoimmune response of the disease. There are published studies showing that the expression of genes involved in the autophagy process is associated with mitochondrial dysfunction [65].

4. Complex of HSPA, HSPC, and Their Co-Chaperones in Neurodegenerative Sclerosis

The complex of the HSPA and HSPC with its co-chaperones DNAJ or HSPH, when overexpressed, increases the resistance of cells to stress, suppressing possible degenerative phenotypes, involved in NDs [60]. These complexes are considered sentinels because they are in constant vigilance in all parts of the body. They work to prevent cellular

damage and ensure quality control of the proteostasis network (PN). This process comprises adequate protein synthesis, from folding, maturation, and protein degradation in their distinct stages [70]. The chaperones are the most important PN molecules because they are responsible for the protein's conformational structure [1].

The time promotes alterations in cells due to an aging natural process [55,71]. Consequently, it causes a loss of balance PN that adds to the reduction in the production of HSPA, HSPC, and their co-chaperones. This dysfunction leads to increased protein aggregation, favoring the development of various conformational diseases. These changes are influenced by external and environmental factors as well as oxidative stress. Combined with genetic variations, which encode defective and dysfunctional proteins, they ultimately result in toxicity or cell death [71].

The mutant protein expression is associated with LOF and depletion of chaperone capacity. In pathologies involving mutant proteins such as TDP-43, FUS, and C9orf72, the HSPB1 interacts with low complexity (LC) regions. Especially with TDP-43, it plays a role in the disassembly of proteotoxic droplets, facilitating their transition into a liquid state [1]. TDP-43, an RNA/DNA-binding protein, is found in the aggregate of the motor neurons' cytoplasm in 97% of patients with ALS. HSPB1 depletion was identified in the spinal motor neurons of patients with ALS containing TDP43 aggregates [72].

In studies involving HSPA, HSPC, DNAJC7, and ALS, it was evidenced that this complex, when it suffers a mutation in the gene *DNAJC7*, causes prejudgment of RNA and vesicular trafficking processing, and it suppresses transposons, contributing to cell toxicity and neurodegeneration. Thus, it will not be the recognition of the TPR domain, because HSPA and HSPC need this domain for their complete cycle to occur, stimulating holdase and, therefore, peptide binding. They will not bind correctly, leading to an accumulation of misfolded proteins [28,30,73,74].

There is evidence that variants in other isoforms of *DNAJ* may be involved in the neuropathological pathways of diseases such as neurodegeneration [44]. For example, an action involving DNAJB2 encoded by a gene with the same name, which, together with HSPA, is a potent anti-aggregation for the TDP-43. But a mutation in *DNAJB2* showed a reduction in co-chaperone function by increasing aggregates of the TDP-43 protein [75].

HSPA after different forms of stress is overexpressed to mediate cytoprotective functions. It also triggers immune responses that promote immune recognition of antigens, including myelin autoantigens. This is because HSR is stimulated by increasing the production of the HSPA1A isoform in the peripheral blood mononuclear cells (PBMCs). This process was evidenced in patients with MS, while in the control group, this increase did not happen [76].

Another recent article had an objective to analyze the protective function of the following genes and their proteins with the same identification: BDNF, NT4/5, SIRT1, HSPA, and HSPB. The researchers used confirmed patients with MS as a case group, compared to healthy controls. The result showed that the level of gene expression and the concentration of proteins encoded by them, in the case group, were reduced in the first three genes. While in HSPs, they were significantly increased [77], but more studies are needed on this theme. Even though genetic variants in HSPs have been identified in patients with these pathologies and their different forms of manifestation. The exact influence of these factors on the pathophysiology of ALS and MS remains unclear, but research has shown its neuroprotective function [43,44].

4.1. Pathogenic Genetic Variants and Amyotrophic Lateral Sclerosis

ALS is a multifactorial genetic disease that has several genetic variants involved with the phenotype of the disease, and many of them are expressed significantly in the genotype.

The most common examples of significant genetic variants are *FUS*, *TARDBP*, *SOD1*, and *C9orf72*, whose damage to protein conformations impairs the cellular homeostasis mechanisms, leading to neuronal loss [1]. There are other rare genetic variants linked to ALS beyond the genes mentioned; they were discovered by GWAS, and some of them are associated with LOF, as described in Table 4.

Table 4. Rare genes linked to ALS and dysfunctions caused by variants.

Mutated Gene	Probable Dysfunctions	References
VAPB; CHMP2B; VCP	Affects the formation of autophagosomes.	[11,78]
SQSTM1; OPTN; UBQLN2; VAPB	Impairs the formation of autophagosomes and ubiquitination.	[11,78]
DCTN + FUS CHMP2B;	Impairs the retrograde transport of autolysosomes, Stops the formation of autolysosomes.	[11,78]
NEK1 + C21orf2 or NEK1 + VAPB	DNA damage repairs are not complete, and the maintenance of the cytoskeletal system is not impaired.	[79]
TBK1 + OPTN + SQSTM1 TBK1 + FUS TBK1 + TARDBP TBK1 + C9orf72	Impairs the autophagy, mitophagy process, and innate immunity	[79]
CCNF; TUBA4A; VCP; ALS2	Cytoskeletal dysfunction	[79]
UBQLN2; SPG11; KIF5A; PFN1	Dysfunction in RNA processing	[79]
DNAJC7(TPR2)	Impaired processing of RNA, vesicular traffic, and transposons suppression contribute to cell toxicity, and inhibit downstream of TDP-43 clearance. Folding error of polypeptides, aggregation aberrant protein.	[28,44,73,74]

Rare Genes Associated with ALS—A comprehensive overview of rare genes linked to ALS, a multifactorial genetic disease.

The genes that encode DNAJ chaperones, as *DNAJC7*, have been most described in recent articles, when it comes to HSPs and sclerosis [28,44,73,74,80–85].

The largest whole-exome sequencing (WES) study was performed with the *DNAJC7* gene, from the Hsp40 family, in the European community. Initially, it was conducted with 11,703 subjects (3864 cases and 7839 controls), and the researchers identified six rare protein truncation variants. Two other studies, one from Israel and another from the United Kingdom, increased the number of samples analyzed. Thus, the total of ALS patients evaluated increased to 5095, and the controls increased to 28,910. In this new sampling, six different protein truncation variants were obtained in eight individuals with ALS. In addition, the authors noted that multiple independent variants may be harbored in the same gene associated with the same disease. Also, the association of *SOD1*, *NEK1*, and *FUS* in ALS. A highly restricted Hsp40 gene, *DNAJC7*, was found. To follow up on the results of the research, the investigators replicated the truncating variants of DNAJC7 proteins in an independent cohort of ALS and validated the functionality of the protein, realizing that the loss of *DNAJC7* may be a new genetic risk factor for ALS [28].

Studies performed in Asian cohorts demonstrated that the frequency of rare *DNAJC7* variants was less than 1%; however, most of them were not considered pathogenic by the adopted pathogenicity validation requirements [73,74,81–84]. Miyazaki et al. [86] evidenced that serum levels of Hsp70 and Hsp90 were significantly higher in ALS patients. They examined HSP27, HSP70, and HSP90 in 58 patients diagnosed with ALS and in 85 healthy controls. The results were significantly higher in patients for HSP70 and HSP90, but for HSP2,7, there was no difference between the control and case [85]. However, the results

published by Rooney et al. [85], about serological investigation by immunoenzymatic assay of HSPA, HSPC, and DNAJC7 proteins, in three European cohorts, demonstrated the opposite. This study showed that there was no association between the risk of the disease and the survival of patients with the serum HSPs concentrations in samples of healthy controls, from the statistical point of view [86].

Other research, in a Japanese cohort composed of 804 patients with sporadic ALS, were screened via exome analysis and found six (0.87%) rare missense variants [(p.Asp21Ala/D21A); (p.Gly98Val/G98V); (p.Met165Ile/M165I); (Thr302Met/T302M) (p.Thr341Pro/T341P); (p.Tyr344Cys/Y344C)], and one splice-site variant (c.1447 + 2T > C) of the *DNAJC7* gene. The variants are located near the Tetratricopeptide repeat 2 domain (TPR-2), which is critical for co-chaperone recognition of HSPA and HSPC. Mutations in this region may impair chaperone function. In the 191 control subjects, these variants were not found. In silico analysis revealed that the identified variants are highly pathogenic. The gene variants were not reported in the Japanese public database. The authors suggested that the variants are rare [73].

In the Chinese population, three studies also investigated this gene. He et al. [74] found three (0.4%) ALS patients with a *DNAJC7* mutation (R156K; N369T; R156X), in the cohort composed of 730 sporadic ALS and 2500 unaffected controls. However, these variants in burden analysis showed no enrichment of rare *DNAJC7* variants [74]. The results were found similar in the research of Wang et al. [84]. The authors analyzed Whole-Exome sequencing, and only four (0.19%) variants were considered pathogenic [c.235C > T/p.R79W); (c.647G > A/p.R216Q); (c.899G > A/p.R300Q); (c.1279A > T/p.K427X)]. Thus, burden analysis has no enrichment of rare variants [84]. Sun et al. [81] also analyzed a Chinese cohort consisting of 326 patients with sporadic ALS, 16 with familial ALS, 6 ALS patients presenting with concomitant frontotemporal dementia (FTD), and 2445 healthy controls. They have not evidenced a pathogenic variant of *DNAJC7* in the Chinese ALS cohort [81]. In another study in an Asian cohort, Taiwan, where 325 ALS patients were analyzed by PCR amplification and Sanger sequencing, only one (0.3%) pathogenic variant (p.Q134Rfs*6) was found. Concerning this variant, tests were carried out to predict its pathogenicity and to verify the loss of function protein, with positive results. It is not found in the Taiwan biobank database [82]. This underscores the need for further studies involving diverse cohorts worldwide to ensure comprehensive evaluation and validation.

4.2. Pathogenic Genetic Variants and Multiple Sclerosis

In MS, serum antibodies against some Hsp (small) increase during disease relapses, while α, β-crystallin expression in brain lesions indicates remission phase initiation [87].

HSPA1A, *HSPA1B*, and *HSP-HOM*, located on chromosome 6 (6p21.3), are genes that encode the Hsp70 protein and are in the Major Histocompatibility Complex (MHC). The allele HLA DRB *1501 * is the most frequent with the susceptibility of MS. In primary studies involving chaperones, there were no records of pathogenic variants in HSP genes associated with MS. Its overexpression, when there is demyelination of myelin sheaths, has been the target for studies on possible therapeutic targets since they trigger pro-inflammatory and immunoregulatory types of autoimmune diseases [76].

In the analysis of the reviewed articles, it was noticed that the chaperones are involved in research using them as likely pharmacological receptors, especially the HSPB. This conclusion is because they play a strong protective role when performing their PQC functions. In this way, these studies can enable a new direction for the treatment of ND [1,4].

5. Approaches Therapeutic in Neurodegenerative Diseases, ALS, and MS

There are no therapies to cure ND, just to reduce acute exacerbations of symptoms by controlling them. Early diagnosis of the disease and adherence to drug therapy can try to stabilize the progression by delaying definitive disability or even death. For MS, up to 2019, different drugs have been approved. Among them, the group of steroids (glucocorticoids) that are the most used are immunosuppressants, immunomodulators, and drugs that make up modifying therapies for the disease (DMTs). Thereafter, it acts on the immune system, preventing more myelin from being damaged; however, remyelination is not possible [8].

The principles that guide the use of drugs are the possible therapeutic targets of the neurotransmitter system. However, in ND pathogenesis, they find themselves disorganized. Regarding ALS, there are two drugs approved for use in the world: Riluzole and Edaravone. A third, which is the combination of sodium phenylbutyrate and taurursodiol, has been approved by the US Food and Drug Administration (FDA) but has its use restricted in a few countries [3].

Research with Antisense oligonucleotides (ASO) has been performed for the treatment of ALS; however, for cases where neurotoxicity by GOF with mutations in *SOD1*, *FUS*, *C9or72*, and *ATXN2* [79–81,88]. ASOs are small sequences of DNA that can reduce the expression of a target gene at the post-transcriptional level, making them attractive for neutralizing mutant or toxic gene products [80]. Further studies are in the clinical trials phase, such as the induced pluripotent stem cells (PCSi) from cells of ALS patients. However, the tests are performed for mutations in the *SOD1* gene [79]. The CRISPR/Cas9 technique has been the target of studies in search of a more promising gene therapy using viral vectors associated with mutant and wild alleles [79,80,89].

Scientific studies have shown the potential of HSPs as a therapeutic target because they perform a cytoprotective function depending on the context for which they are required. The modulation capacity that they have with upregulation or downregulation favors discussions of their use as biomarkers or target receptors for the treatment of ND, but nothing has been approved for therapeutic use [90].

6. ARBs and New Therapeutic Targets for Multiple Sclerosis

Recent studies have highlighted the potential role of Angiotensin Receptor Blockers (ARBs) in modulating the immune response in MS. The renin–angiotensin system (RAS), traditionally associated with blood pressure regulation, has been implicated in autoimmune inflammation within the central nervous system. Research indicates that ARBs, by inhibiting the angiotensin II type 1 receptor (AT1R), can reduce the migration of antigen-presenting cells (APCs) and the expression of pro-inflammatory chemokines, thereby ameliorating disease progression in experimental models of MS [91].

Further investigations have demonstrated that ARBs, such as losartan, can influence the expression of AT1R in glial cells, including astrocytes and microglia, within the inflamed central nervous system. Moreover, ARBs has shown decreased expression of pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, IFN-γ, and IL-17, and increased expression of anti-inflammatory cytokines, such as IL-10 and TGF-β [92], although its effects remain contradictory [93]. This modulation suggests that ARBs may exert their effects through direct actions on glial cells, independent of blood pressure regulation, offering a novel therapeutic avenue for MS [94].

In the clinical context, the combination of ARBs with other disease-modifying therapies has also been explored. The use of ARBs and angiotensin-converting enzyme inhibitors in conjunction with interferon beta-1b in patients with relapsing-remitting MS showed a trend toward increased relapse rates in the ARB group. However, these findings highlight

the necessity for further research to clarify the clinical implications of ARB use in MS therapy [95].

The development of novel ARBs, such as bisartans, which feature dual anionic tetrazole moieties, has opened new possibilities for MS treatment. These compounds demonstrate enhanced binding affinities to ACE2 and the spike protein complex, suggesting potential antiviral properties. Although primarily investigated in the context of COVID-19, the multifunctional nature of bisartans warrants consideration for their application in MS, particularly in modulating immune responses and neuroinflammation [96].

Additionally, the structural studies of myelin basic protein (MBP) peptides, particularly concerning their binding to MHC II molecules, provide important information into how immune modulation might be achieved. The work by Mantzourani et al. [94] explores the structural requirements for MBP binding to MHC II and the subsequent T-cell receptor recognition, offering a valuable framework for understanding the immune processes in MS and the potential role of ARBs in altering these immune responses [97]. The modulation of the RAS through ARBs presents a promising therapeutic strategy for MS. While experimental models have shown beneficial effects, clinical studies yield mixed results, necessitating further investigation. The development of novel ARBs with enhanced properties may offer additional avenues for therapeutic intervention in MS, potentially improving patient outcomes through targeted modulation of immune and inflammatory pathways.

7. Discussion

For the scoping of scientific curiosity to identify possible SNVs in HSPs, different searches were performed. The most important articles were selected, and several were cited in the databases chosen for research. However, the PubMed database contributed more to the work. Using the following descriptors: “Single nucleotide variant,” “Amyotrophic lateral sclerosis”, and “HSP”, no article was found. When modifying the last descriptor by “Hsp70” and “Hsp90”, the research was not satisfactory. However, when searching randomly for a specific mutant gene of ALS, especially involving the autophagy process, few articles have been described.

Similarly, the same descriptors were used for ALS modifying the word by Multiple sclerosis, and no article was found. Then, the term “Single Nucleotide” was removed, and even then, no articles were found either.

The type of most articles found were Review and the primary works were scarce, concerning the functional process of the chaperones. Studies on variants in genes linked to HSPs were little. The recent ones addressed the variant in the *DNAC7* gene, but only in ALS. Other variants addressed are implicated with mutations of other genes involved in the sclerosis pathophysiology.

There are recent manuscripts, from different cohorts around the world, discussing the *DNAJC7* gene as being possibly responsible for ALS pathology phenotypes, but with a low percentage of frequency, characterizing the rarity of the variant [28,74,81–84].

Regarding mutated variants in genes encoding HSP, one protein that has recently attracted research interest is DNAJC7 and its association with ALS risk. Some studies analyzing case–control cohorts in Asian populations have reported statistically significant findings, making it unclear whether the variant is truly pathogenic and directly linked to ALS [28,73,74,81–83]. In contrast, recent proteomic studies, such as the one by Imam et al. [97], have shifted focus toward alternative biomarkers in ALS, identifying 44 proteins related to skeletal muscle structure and function, with a notable absence of HSPs in patient biofluids, suggesting a new direction for understanding ALS pathogenesis and treatment possibilities [95].

It was noticed in the reviews that HSPs increase a lot when there is the production of defective proteins; this happens because they have the function of controlling and preventing non-conformational proteins from remaining inside the cells. But they can also be inhibited when a mutation modifies the binding domains, and they cannot perform the quality control function or do not recognize the binding site.

8. Conclusions

The articles reviewed have shown that HSPs are involved in protein dysfunctions associating them with quality control. However, they have not shown robust publications that demonstrate genetic variants in their coding genes to the point of characterizing statistical significance that confirms the pathogenicity of the few variants found. Thus, further studies are needed on patients. It is important to emphasize that research conducted on different cohorts across various regions provides greater contributions to new discoveries. This approach increases the likelihood of identifying new paradigms regarding the influence of rare variants in the etiology of ALS.

Whereas in the etiology of ND, there is a rupture of the native conformation proteins, changing its three-dimensional form, understanding of the functioning, and regulation of HSPs in proteostasis has become quite promising in relation to research with pharmacological treatments using chaperones.

In this context, investment in scientific research and its advocates is crucial to determine whether mutations in HSP-encoding genes confer pathogenic properties. Thus, it may be responsible for the phenotypic characteristics of the disease, but more studies will be necessary about the genotyping of these chaperones.

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