# Rare diseases: Insights from landscape analysis of current research, spotlighting amyotrophic lateral sclerosis, Huntington's disease, and myasthenia gravis

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## Abstract

Rare diseases are a diverse group of disorders that despite each individual condition's rarity, collectively affect a significant portion of the global population. Currently approximately 10,000 rare diseases exist globally, 80% of these diseases have been identified as of genetic origins. In this review, we examine data from the CAS Content Collection to summarize scientific progress in the area of rare diseases. We examine the publication landscape in the area in effort to provide insights into current advances and developments. We then discuss the evolution of key concepts in the field, genetic associations, as well as the major technologies and development pipelines of rare disease treatments.

We focus our attention on three specific rare diseases: (i) amyotrophic lateral sclerosis, a terminal neurodegenerative disease affecting the central nervous system resulting in progressive loss of motor neurons that control voluntary muscles; (ii) Huntington's disease, another terminal neurodegenerative disease that causes progressive degeneration of nerve cells in the brain, with a wide impact on a person's functional abilities; and (iii) myasthenia gravis, a chronic autoimmune synaptopathy leading to skeletal muscle weakness. While the pathogenesis of these rare diseases is being elucidated, there is neither a cure nor preventative treatment available, only symptomatic treatment. The objective of the paper is to provide a broad overview of the evolving landscape of current knowledge on rare diseases, to outline challenges, and evaluate growth opportunities, all with an aim to further efforts in solving the remaining challenges.

Key words: rare disease; amyotrophic lateral sclerosis; Huntington's disease; myasthenia gravis; gene; pathogenesis; neurodegeneration; autoimmunity

## 1. Introduction

Rare diseases, also known as orphan diseases, are a diverse group of disorders that, despite each individual condition's rarity, collectively affect a significant portion of the global population. The exact definition of a rare disease varies from country to country, but generally, a disease is considered rare when it affects a limited number of people within a specific region or population. The World Health Organization (WHO) defines a rare disease as one that strikes fewer than 65 per 100,000 people. [1] According to the National Organization of Rare Disorders of the USA, [2] a rare disorder is a disease or condition that affects fewer than 200,000 Americans (i.e., less than ~60 per 100,000). [3, 4] In the European Union, a rare disease is one that affects no more than 1 person in 2000 [5] (i.e., <50 per 100,000). According to Global Genes, a global non-profit advocacy organization for individuals fighting rare and genetic diseases [6], currently approximately 10,000 rare diseases exist globally, with new ones being continually discovered. About 80% of these diseases have been identified as of genetic origins [7], and they often manifest in diverse and unpredictable ways.

Despite their individual rarity, rare diseases collectively impact millions of individuals worldwide – approximately 4-6% of the worldwide population, equivalent to from 300 to over 400 million people. [1, 8, 9] These conditions often present unique challenges due to their unfamiliarity, limited treatment options, and the difficulties associated with diagnosis. One of the primary challenges associated with rare diseases is their diagnosis. Due to their rarity and often complex clinical presentations, rare diseases are frequently misdiagnosed or undiagnosed altogether. This diagnostic struggle can be emotionally and financially difficult for patients and their families, leading to delays in appropriate treatment and care.

Moreover, the limited understanding of many rare diseases poses significant obstacles to the development of effective therapies. With only a handful of patients available for clinical trials, research into these conditions is often underfunded and progresses at a slower pace compared to more common diseases. Consequently, individuals living with rare diseases may have few, if any, treatment options available to them. As rare diseases each individually affect a small number of individuals, they have been ‘orphaned’ by the pharmaceutical industry, which has promoted the use of the term ‘orphan disease’ when referring to these conditions. [1]

Another critical issue facing the rare disease community is the lack of specialized healthcare providers and support services. Many rare diseases require multidisciplinary care from experts in various medical specialties, but access to such expertise can be limited, particularly in rural or underserved areas. Globally, less than 10% of patients with rare diseases receive disease-specific treatment. [1]

However, recent years have seen a growing awareness of rare diseases, leading to increased efforts to address the unmet needs of those affected. Since most rare diseases are genetic in their etiology, systematic research on them starts with efforts to identify genetic variants causative for each particular disease, with links between genetic mutations and diseases identified. [10, 11] Advances in genomic sequencing technologies and precision medicine hold promise for improved diagnosis and targeted treatments for many rare diseases. Additionally, initiatives such as orphan drug legislation [12-14] and incentives for rare disease research [15-17] have motivated pharmaceutical companies to invest in the development of therapies for these often-neglected conditions.

In this paper, we examine data from the CAS Content Collection [18], the largest human-curated collection of published scientific information, and analyze the publication landscape of

recent research in order to provide insights into the scientific progress in the area of rare diseases. We discuss the evolution of key concepts in the field as well as the major technologies and the development pipelines of rare disease treatments. We focus our attention on three specific rare diseases to perform a deeper dive into the research outlook in order to identify and understand obscure connections in these topics, namely: (i) amyotrophic lateral sclerosis (ALS), a terminal neurodegenerative disease affecting the central nervous system (CNS) resulting in progressive loss of motor neurons that control voluntary muscles; (ii) Huntington's disease (HD), another terminal neurodegenerative disease that causes progressive degeneration of nerve cells in the brain, with a wide impact on a person's functional abilities; and (iii) myasthenia gravis (MG), a chronic autoimmune synaptopathy leading to skeletal muscle weakness.

The objective of the paper is to provide a broad overview of the evolving landscape of current knowledge on rare diseases, to outline challenges, and evaluate growth opportunities, all with an aim to further efforts in solving the problems that still plague the field. The novelty and merit of the article stem from the extensive, wide-ranging coverage of the most up-to-date scientific information accumulated in the CAS Content Collection, allowing unique, unmatched breadth of landscape analysis and in-depth insights. We hope this report can serve as a useful resource for understanding the current state of knowledge and the importance of raising awareness in the field of rare disease research and development.

## 2. Landscape analysis of rare diseases research: Publication and patent trends from the CAS Content Collection

In this section we present our findings from a comprehensive analysis of more than 530,000 publications (journals and patents) in the field of rare diseases sourced from the CAS Content Collection™. Our aim for this analysis was to identify interesting trends in the field such as – leading research organizations and scientific journals, as well as identify leading rare diseases in terms of commercial exploration. In addition, we have focused on three of the most voluminous (in terms of journal and patent publications) rare diseases – ALS, HD and MG. Finally, we leveraged CAS REGISTRY, the CAS substance collection, to identify substances across different substance classes co-occurring with the three chosen rare diseases.

To fully capture the field, our subject matter experts utilized more than >650 search terms to ensure both identification of relevant publications in the field as well as capture a wide breath of pertinent information. The last two decades have seen an increasing interest in rare diseases as shown by the steady increase in journal publications, with a marked and steep increase between 2019-2021. Patent publications on the other hand, have increased consistently but at a much more moderate pace (Figure 1).

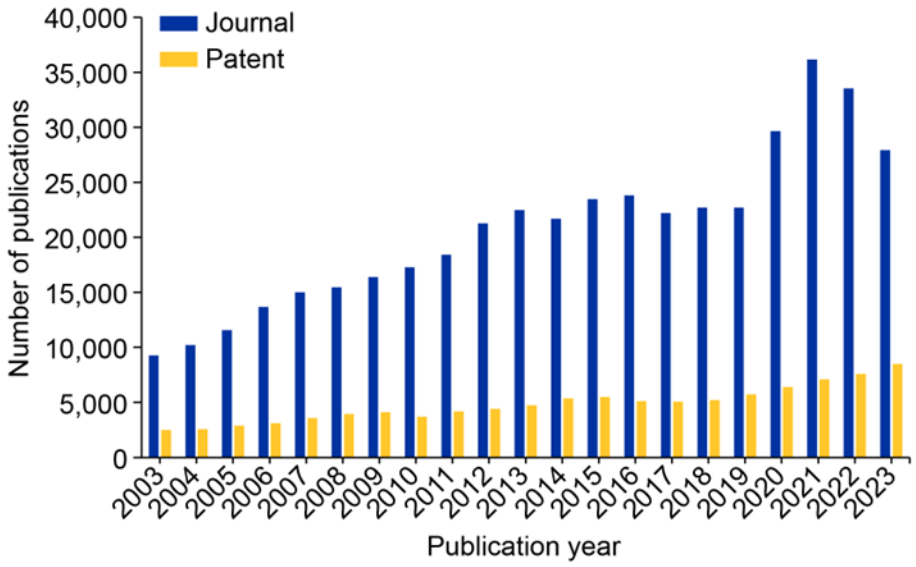


**Figure 1.** Publications in the field of rare diseases from the CAS Content Collection for the period 2003 to 2023.

To identify leading research organizations actively involved in publishing scientific content related to rare diseases, we first ranked them by the volume of journal articles followed by calculating the average number of citations per publication, a viable indicator of the scientific impact for published work. The top 100 research organizations in terms of number of journal articles were then ranked by the average number of citations per publication to give rise to the list in Figure 2. In terms of geographic distribution, ~67% of the leading 15 research institutions originated from the United States (USA). The remaining 35% consisted of research organizations from Canada (CAN) and the United Kingdom (GBR) accounting for 20% and 13%, respectively (Figure 2). Within the USA, key universities identified were University of Washington, University of Pennsylvania, Johns Hopkins University, University of California, Washington University, and University of Texas. Other important research organizations from the USA were Harvard Medical School, which ranked 1$^{st}$ among the leading 15 organizations, the US government run agency National Institute of Health (NIH), as well as the Mayo Clinic, and Baylor College of Medicine. Examples of recent journal articles published by researchers at Harvard Medical School include articles related to HD,[19, 20] MG,[21] ALS,[19, 20] as well rare tumors and cancers such as thymomas,[22] multiple myeloma,[21] and thyroid cancer.[23-25] Similarly, examples of research output from other leading US-based organizations revolve around rare diseases such as multiple sclerosis,[26, 27] ALS,[28-30] systemic lupus erythematosus (SLE),[31, 32] sickle cell anemia,[33, 34] among others and rare cancers such as hematological malignancies including multiple myeloma,[22] acute myeloid leukemia (AML),[35, 36] and non-Hodgkin's lymphoma.[37, 38] Research organizations originating in Canada and those originating in the United Kingdom (GBR) also appear to be directing research efforts towards rare diseases such as multiple sclerosis,[39-42] HD,[43-46] SLE,[47-50] and ALS,[51, 52] among others.

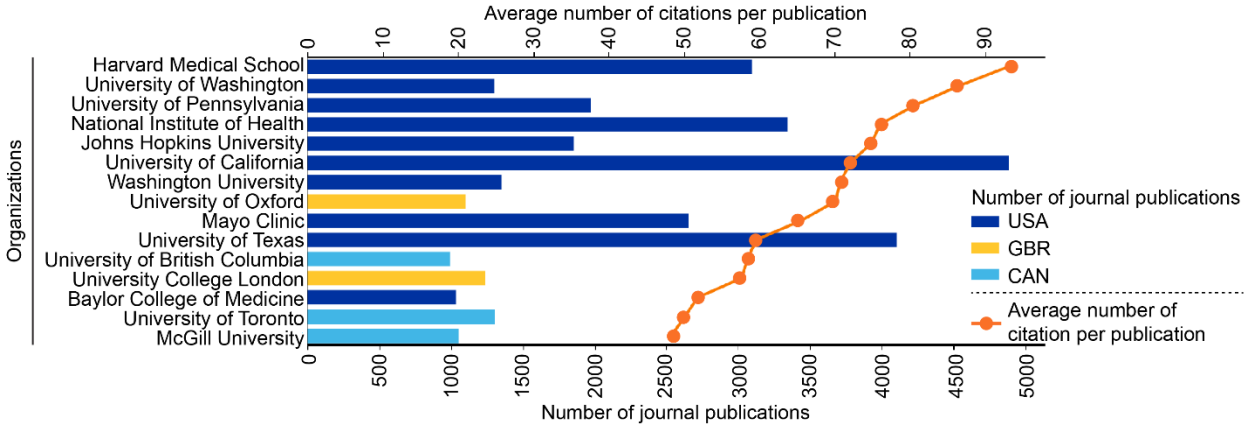


**Figure 2.** Leading research organizations in the field of rare diseases based on data from the CAS Content Collection for the period 2003 to 2023. Ranking was based on total number of journal publications and average number of citations per publication, an indicator of publication impact.

Using a similar methodology as described above, we identified leading scientific journals in the area of rare diseases – first by ranking journals by the volume of publications, followed by calculating average number of citations per publication, and finally by ranking them using the calculated average number of citations per publication. The leading scientific journals identified include the New England Journal of Medicine (*New Engl J Med*), Journal of Clinical Oncology (*J Clin Oncol*), and Proceedings of the National Academy of Sciences (*Pro Natl Acad Sci USA*), among others (Figure 3A). The scientific journal New England Journal of Medicine has half as many journal articles as the Proceedings of the National Academy of Sciences but two times the average number of citations per publication. When looked at from the lens of sheer volume of publications or number of citations a somewhat different group of scientific journals emerge. There is a moderate degree of overlap between the two lists (number of journal publications and number of citations) with scientific journals such as Blood, PLOS One, Proceedings of the National Academy of Sciences, Journal of Biological Chemistry (*J Biol Chem*), and Human Molecular Genetics (*Hum Mol Genet*) featuring in both lists (Figure 3B). However, the order of appearance differs, for instance, while the open-access journal PLOS One leads in terms of sheer number of publications (nearly 2X fold higher than the journal Blood, the 2$^{nd}$ leading journal), it is 3$^{rd}$ in terms of number of citations.

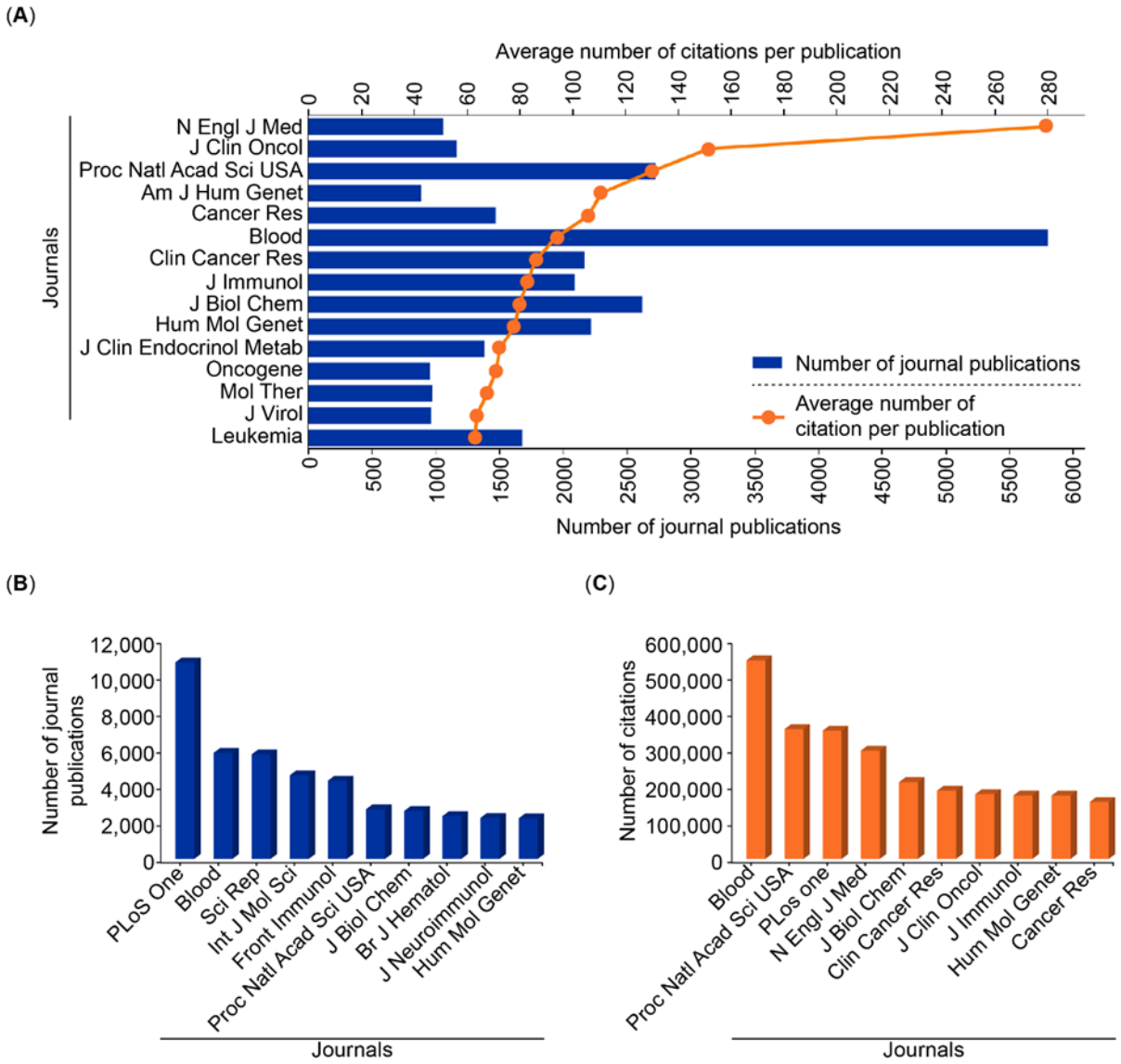


**Figure 3.** Leading research journals in the field of rare diseases based on data from the CAS Content Collection for the period 2003 to 2023. (**A**) Ranking was based on both total number of journal publications and average number of citations per publication, an indicator of publication impact. Leading research journals when ranking was based solely on total number of (**B**) journal publications and (**C**) citations.

A few highly cited journal articles published in the New England Journal of Medicine revolve around rare cancers such as melanoma,[53, 54] multiple myeloma,[55] and AML[53, 54] as well as other rare diseases such as SLE,[55] multiple sclerosis,[56, 57] and cystic fibrosis.[58] The 2019 article titled “Targeting huntingtin expression in patients with Huntington's disease”[59] by researchers in the United Kingdom and published in the New England Journal of Medicine described results of a Phase I/IIa trial for an oligonucleotide designed by Ionis Pharmaceuticals and F. Hoffmann–La Roche to inhibit mRNA of HTT, the main gene responsible for HD and has been cited more than 400 times. Another example of a highly cited article was “Neurotoxic reactive astrocytes are induced by activated microglia” published in 2017 in the journal Nature and described the role of A1 astrocytes in neuronal cell death and their abundance in HD, ALS, and other

neurodegenerative disorders.[60] Similar well-cited publications for MG include a review article published in the New England Journal of Medicine.[61]

Geographical distribution of patent assignees in the field of rare diseases indicates a high degree of overlap in leading countries or regions with 7 out of 10 being common between commercial as well as non-commercial entities – United States (USA), China (CHN), South Korea (KOR), France (FRA), Germany (DEU), Japan (JPN), Denmark (DEN) (Figure 4). Spain (ESP), Italy (ITA), and Belgium (BEL) appear to have greater non-commercial presence while the inverse appears to be true for the United Kingdom (GBR) and Israel (ISR). Overall, the USA contributes 31% and 40% to non-commercial and commercial patents, respectively, the highest by a country/region. This is followed by China (CHN) which appears to have a more comparable commercial and non-commercial contribution.

Among the non-commercial organizations, more than 65% of the leading organizations originate from the United States with the University of California leading overall (Figure 4A). The remaining consist of two research organizations each from South Korea (KOR) and China (CHN) with the L'Institut national de la santé et de la recherche médicale (INSERM) being the only French organization featuring in the top 15 non-commercial organizations. In recent years, these leading organizations appear to be involved in research across a variety of rare diseases such as SLE,[31] HD,[31] multiple sclerosis,[62-64] and the more obscure ones such as disabling pansclerotic morphea[65] and Von Hippel-Lindau disease.[66] Patents filed by researchers from the University of California in recent years (2015 onwards) cover a diverse group of ailments including developing small molecule inhibitors targeting various proteins and potentially useful in the treatment of ALS (WO2023086603,[67] WO2022104148[68]), using a SARS-Cov-2 pseudoviral delivery system for therapeutic transgene as potential treatment for HD (WO2022165538A1[69]), and development of GABA positive allosteric modulators (WO2018236955[70]) and peptide-based inhibitors for treatment of MG, (WO2018049053[71]).

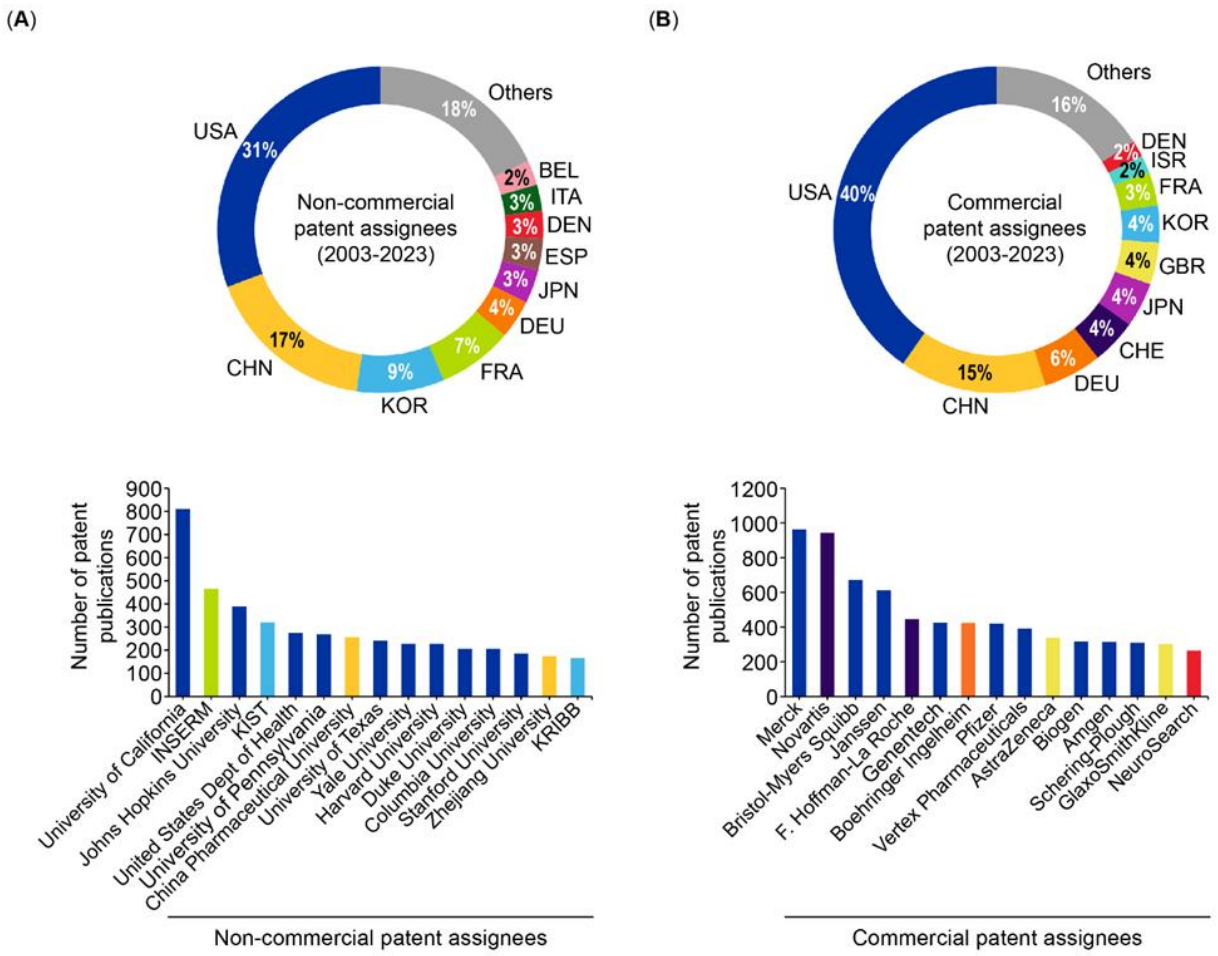


**Figure 4.** Leading organizations in the field of rare diseases based on patent publication data from the CAS Content Collection for the period 2003 to 2023. (**A)** Donut and (**B**) bar charts showing geographical distribution and leading organizations, respectively. Entities were separated into non-commercial and commercial organizations. Bars colored to correspond to countries or regions shown in the donut charts. Countries or regions represented by their standard three letter codes – United States (USA), China (CHN), South Korea (KOR), France (FRA), Germany (DEU), Japan (JPN), Spain (ESP), Denmark (DEN), Italy (ITA), Belgium (BEL), Switzerland (CHE), and United Kingdom (GBR).

Next, guided by our identification of leading commercial patent assignees we analyzed in greater detail patents by the top 6 companies (Figure 4B) to understand the spread of commercial interest across different rare diseases and shown as heat maps in Figure 5 and Supporting Information Figure S1 based on CAS indexing. Rare diseases such as multiple sclerosis,[72] SLE,[73] scleroderma, and HD appears to have high commercial interest across the six companies we chose to focus on as seen by the higher number of patent publications. In contrast, examples of rare diseases with apparent low commercial interest include iridocyclitis, familial Mediterranean fever,[74] Rett syndrome[75] and pseudoaldosteronism[76] (Figure 5). Similar heat map for rare cancers indicates that among these, kidney cancer,[77] thyroid cancer,[78] melanoma[79] and multiple myeloma,[80] a type of hematological malignancy, appears to a have number of patents filed by all six commercial companies. Examples of rare cancer that continue to be under explored commercially as exhibited by low patent publications include nasopharyngeal carcinoma,[81] blastic plasmacytoid dendritic cell cancer[82] and B-cell prolymphocytic leukemia[83, 84] among others (Supporting Information, Figure S1).

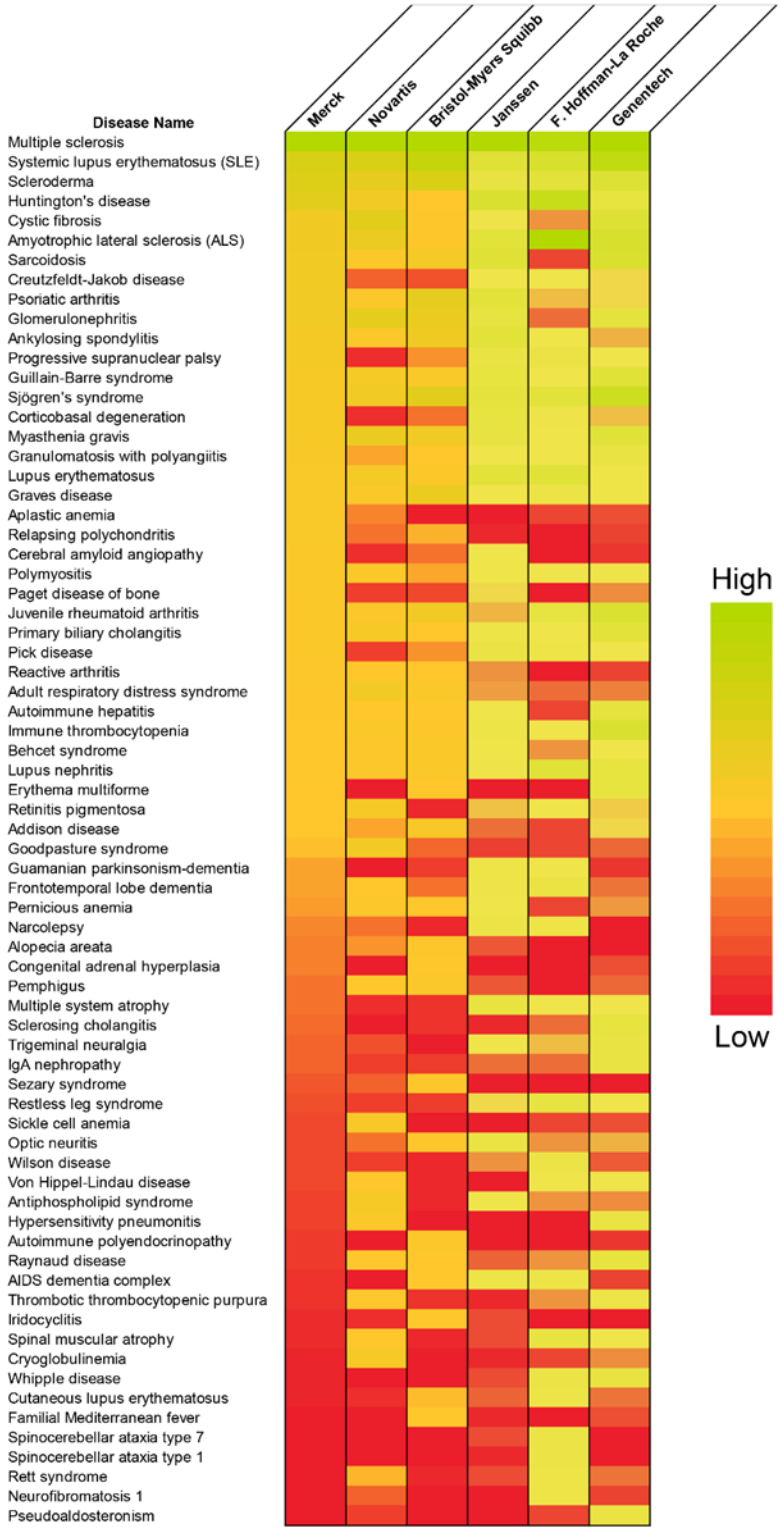


**Figure 5.** Heat map indicating number of patents filed by commercial organizations with respect to rare diseases. Patent assignees shown here are among the top 6 commercial patent assignees shown in Figure 4B. Data includes patent publications in the field of rare diseases from the CAS Content Collection for 2003-2023.

In our dataset we identified leading rare diseases and rare cancers based on the number of documents (journals and patents) associated with them using the robust data curation performed by CAS and are shown as a heat map in Figure 6 – ALS, HD, and MG all feature in the list. Other well-studied rare diseases include autoimmune diseases such as multiple sclerosis,[72] SLE,[73] scleroderma,[85] Sjögren's syndrome,[86] and inherited disorders such as cystic fibrosis[87] and sickle cell anemia.[88] Among the top 10 well-studied rare cancers, ~30% are hematological malignancies (or blood cancers) such as multiple myeloma,[80] non-Hodgkin's lymphoma,[89] and AML.[90] The list is also populated with rare cancers such as pheochromocytoma, type of neuroendocrine tumor[91]; cholangiocarcinoma, cancer of the bile duct,[92] and melanoma, a type of skin cancer.[79] Other examples of leading rare cancers include hepatocellular carcinoma,[93] a type of liver cancer, mesothelioma[94] which is cancer occurring in the tissue surrounding internal organs (mesothelium), and an aggressive form of brain cancer called glioblastoma.[95]

(**A**)

| | Disease | Number of journal publications (2003-2023) | Number of patent publications (2003-2023) |
|---|---|---|---|
| Non-cancer | Multiple sclerosis | 25511 | 22979 |
| | Systemic lupus erythematosus (SLE) | 22038 | 10584 |
| | Amyotrophic lateral sclerosis (ALS) | 12871 | 12042 |
| | Cystic fibrosis | 12213 | 6727 |
| | Huntington's disease | 8917 | 11484 |
| | Scleroderma | 6725 | 7567 |
| | Sickle cell anemia | 4816 | 2180 |
| | Sjögren's syndrome | 3157 | 5492 |
| | Myasthenia gravis | 2842 | 4716 |
| | Graft-versus-host reaction | 2654 | 4503 |

(**B**)

| | Disease | Number of journal publications (2003-2023) | Number of patent publications (2003-2023) |
|---|---|---|---|
| Cancer | Multiple myeloma | 23575 | 17303 |
| | Non-Hodgkin's lymphoma | 8510 | 8035 |
| | Acute myeloid leukemia | 5861 | 7534 |
| | Hodgkin disease | 5706 | 6809 |
| | Pheochromocytoma | 5667 | 1195 |
| | Cholangiocarcinoma | 5563 | 2309 |
| | Melanoma | 5224 | 15304 |
| | Hepatocellular carcinoma | 5110 | 6464 |
| | Mesothelioma | 4253 | 5326 |
| | Glioblastoma | 3964 | 7564 |

**Figure 6.** Heat map depicting number of journal and patent publications for leading rare diseases and rare cancers in our dataset of rare diseases. Data includes journal publications sourced/extracted from the CAS Content Collection for the period 2003-2023.

Having identified leading rare diseases and rare cancers in our dataset, we wanted to see how interest in these, and other rare diseases have played out over the last few years. To determine this, we plotted the relative increase in publications (journal and patent) for the period 2018-2022 normalized with respect to total publications for that period for each disease (Figure 7A). HD, ALS, and myasthenia gravis show a clear, steady, and consistent increase in publications over the 5-year period. This increase is perhaps most evident for myasthenia gravis with publications nearly doubling between 2018 and 2022. A few rare diseases such as scleroderma,[85] an autoimmune disease resulting in hardening of skin, Creutzfeld-Jakob disease,[96] an aggressive neurodegenerative disorder resulting in death and progressive supranuclear palsy,[97] neurodegenerative disorder affecting muscles and movement, show waning publications over the years. Sjögren's syndrome,[86] Graves' disease,[98] and juvenile rheumatoid arthritis[99] also show a downward trend in publications indicative of decrease in interest from the scientific community. Multiple sclerosis, SLE, sarcoidosis,[100] and Guillain-Barre syndrome,[101] all of which involve the body's immune system, show more or less consistent number of publications with minor fluctuations.

Calculating the patent-to-journal ratios for these diseases splits them more or less evenly – with 7 out of 14 analyzed rare diseases having a patent-to-journal ratio greater than 1, indicative of greater commercial interest. Out of the remaining 7, scleroderma has a patent-to-journal ratio of 1 while the rest six have a patent-to-journal ratio of less than 1 indicative of not as much commercial interest (Figure 7B). Out of the three rare diseases that we chose to focus on – HD and MG exhibit a patent-to-journal ratio greater than 1 by a modest extent. On the other hand, ALS has a patent-to-journal ratio of 0.7 indicating greater interest from the scientific community that is yet to translate to commercial prospects – this might also be attributable to the increased interest in ALS following the viral ice bucket phenomenon translating as increased journal publications as a result of increased funding. Among the 14 rare diseases analyzed, progressive supranuclear palsy and Graves disease lead in terms of having more than 4 times as many patents as journal publications (Figure 7B).

Similar analysis with respect to rare cancers reveals increase in publications across the board with all selected rare cancers showing clear, consistent, and rapid increase in publications (Supporting Information, Figure S2A). Of special note are Kaposi's sarcoma,[102] cancer affecting the lining of blood vessels and lymph nodes, glioblastoma,[95] cancer of the brain and/or spinal cord, and thyroid cancer[78] showing the greatest increase with publications more than doubling between 2019 and 2022 (Supporting Information, Figure S2A). The patent-to-journal ratios indicate seemingly high commercial interest for the selected/analyzed rare cancers with >70% exhibiting patent-to-journal ratios greater than 1 (Supporting Information, Figure S2B). The exceptions to this are multiple myeloma, esophagus cancer[103] and hepatocellular carcinoma,[93] a type of liver cancer, with low patent-to-journal ratios (Supporting Information, Figure S2B).

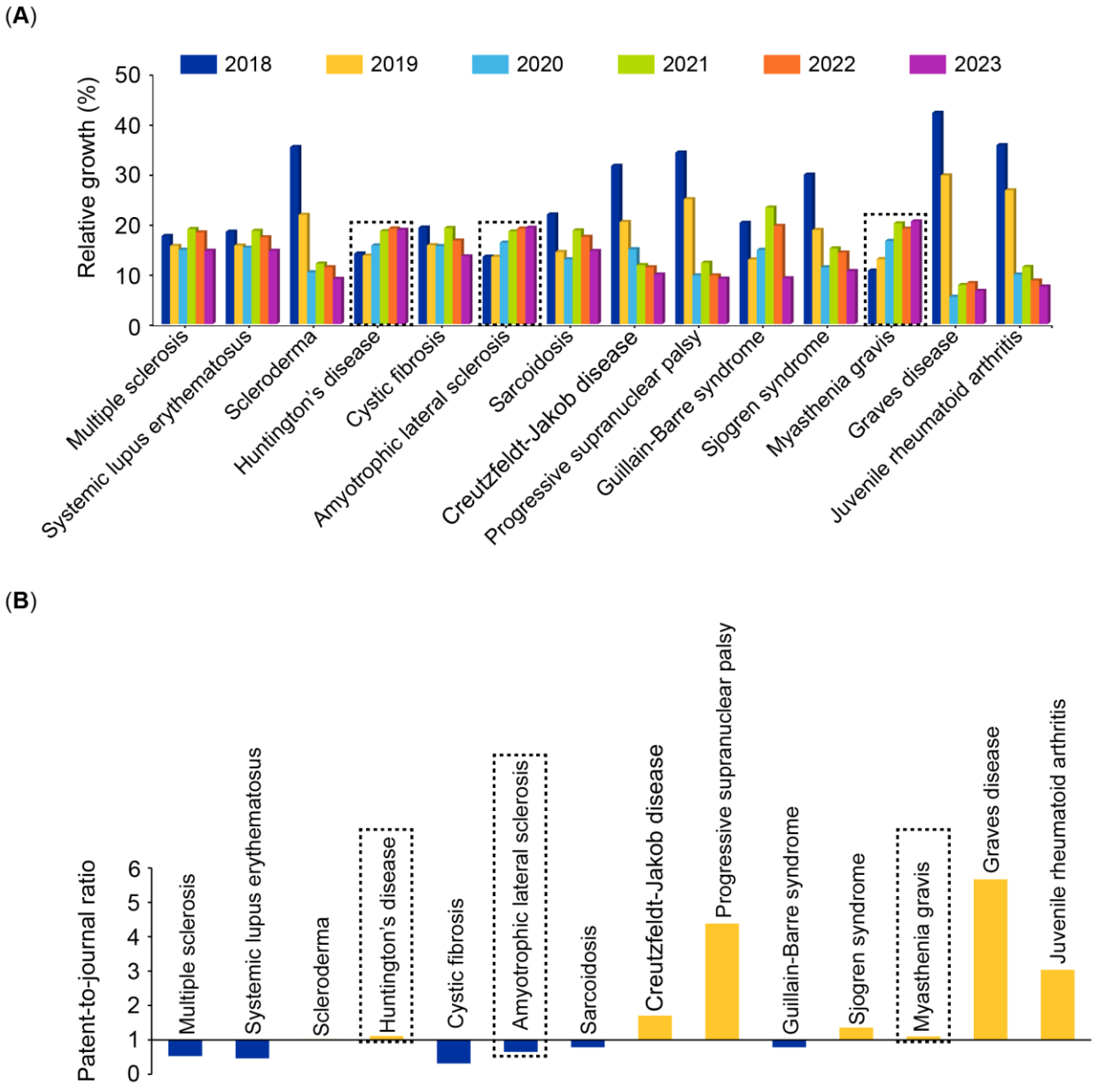


**Figure 7.** (**A**) Number of publications (journal and patent) and (**B**) patent-to-journal ratios for selected leading rare diseases in our dataset. Highlighted in dashed black boxes are the three rare diseases that we analyzed in detail. Data includes patent and journal publications sourced/extracted from the CAS Content Collection for the period 2018-2023 in the field of rare diseases.

# 3. Amyotrophic lateral sclerosis (ALS), Huntington's disease, myasthenia gravis

## Amyotrophic Lateral Sclerosis

*Overview*

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease or Lou Gehrig's disease, is a rare progressive neurodegenerative disorder affecting the nerve cells in the brain and spinal cord that control voluntary muscle movement.[104-109] Global estimates of ALS range from 1.9 per 100,000 to 6 per 100,000.[110-112] ALS shot to public attention because of the viral "ice bucket challenge" in 2014.[113] Though the exact impact of the viral challenge remains unknown[114-116] with opinions divided on whether the challenge truly had a real world impact, it is undeniable that it catapulted the disease to the public's attention. Individuals well-known in their respective fields have been afflicted by this disorder, perhaps one of the most famous ones being the theoretical physicist Stephen Hawking.[117]

ALS leads to the gradual degeneration and death of motor neurons, which are the nerve cells responsible for transmitting signals from the brain to the muscles.[118, 119] As motor neurons deteriorate, voluntary muscle control and movement are progressively impaired, leading to muscle weakness, twitching (fasciculations), stiffness, and eventually paralysis. The symptoms of ALS can vary widely among individuals and may initially affect different muscle groups. Common early symptoms include weakness in the hands, arms, legs, or muscles involved in speech, swallowing, or breathing. As the disease progresses, muscle weakness and atrophy spread to other parts of the body.[107] ALS can also affect the muscles involved in speech, swallowing, and breathing, leading to difficulties in speaking, chewing, swallowing (dysphagia), and breathing (respiratory compromise). Bulbar symptoms often contribute to significant disability and can pose life-threatening complications in advanced stages of the disease. In some cases, ALS may be associated with cognitive and behavioral changes, including difficulties with executive function, language, decision-making, and emotional regulation. This constellation of symptoms is referred to as frontotemporal dementia (FTD) or ALS-FTD, which represents a spectrum of overlapping neurodegenerative disorders.[118, 120-122]

ALS currently has no cure, and the underlying mechanisms driving the disease remain incompletely understood. Most cases of ALS are sporadic, meaning they occur without a clear family history, while a smaller percentage are inherited (familial ALS) due to genetic mutations. Several genes have been implicated in familial ALS, including C9orf72, SOD1, TARDBP, FUS, and others.[123-125]

Diagnosis of ALS is typically based on a thorough medical history, neurological examination, electromyography (EMG), nerve conduction studies, and exclusion of other possible causes of muscle weakness and motor dysfunction. Magnetic resonance imaging (MRI) and other imaging tests may also be used to rule out other conditions.[126, 127]

While there is no cure for ALS, various treatments and supportive interventions can help manage symptoms, improve quality of life, and prolong survival. These may include medications to alleviate muscle cramps, spasticity, or excessive saliva production, as well as physical therapy, occupational therapy, speech therapy, and assistive devices to maintain mobility and communication abilities.[128] In some cases, non-invasive ventilation or feeding tubes may be

necessary to support respiratory and nutritional needs. The US Food and Drug Administration (FDA) has approved a few medications for treating symptoms related to ALS[129, 130] including the benzothiazole Riluzole (Rilutek, Exservan, Tiglutik)[131, 132] in 1995, the antioxidant Edaravone (Radicava)[133] in 2017, and Sodium phenylbutyrate-Taurursodiol (Relyvrio)[134, 135], a combination of a histone deacetylase inhibitor and a bile acid, in 2022. Sadly, Relyvrio has been just reported to have failed Phase III trial.[136] The Phase 3b trial of Radicava has been also discontinued in 2023, as well as its extension study.[137, 138] The prognosis for ALS varies, with most individuals experiencing progressive disability over time. The rate of disease progression and life expectancy can vary widely among individuals, ranging from a few years to more than a decade from the onset of symptoms. Respiratory failure is the most common cause of death in ALS.[139-141]

*Pathogenesis of amyotrophic lateral sclerosis*

The pathogenesis of ALS is complex and involves a combination of genetic, environmental, and cellular factors. While the exact cause of ALS remains incompletely understood, several key mechanisms have been implicated in the degeneration of motor neurons characteristic of the disease.[122, 123, 142-145]

ALS primarily affects motor neurons, which are the nerve cells responsible for transmitting signals from the brain and spinal cord to the muscles, controlling voluntary muscle movement. The progressive degeneration and death of motor neurons lead to muscle weakness, atrophy, and eventual paralysis.[146, 147] Glutamate is the primary excitatory neurotransmitter in the CNS, including the motor neurons. In ALS, dysregulation of glutamate signaling occurs, leading to excessive levels of glutamate in the synaptic cleft. This excitotoxicity can damage motor neurons, contributing to their degeneration and death.[148-150] Motor neurons are particularly vulnerable to oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them with antioxidants. Oxidative stress can damage cellular structures, including proteins, lipids, and DNA, leading to motor neuron dysfunction and death.[151, 152] Abnormal protein aggregation is a hallmark feature of ALS pathology. Mutations in genes such as SOD1, TARDBP (encoding TDP-43), FUS, and C9orf72 can lead to the misfolding and aggregation of proteins within motor neurons and surrounding cells. These protein aggregates can disrupt cellular function and contribute to neurodegeneration.[153-156]

Mitochondria are the cellular organelles responsible for energy production and play a crucial role in maintaining neuronal function and viability. Dysfunction of mitochondria, including impaired energy metabolism and increased production of ROS, has been implicated in ALS pathogenesis, contributing to motor neuron degeneration.[157-159] In addition to motor neurons, non-neuronal cells such as astrocytes, microglia, and oligodendrocytes play important roles in ALS pathogenesis. Dysfunctional glial cells can contribute to neuroinflammation, excitotoxicity, and impaired neuronal support and repair mechanisms, further exacerbating motor neuron degeneration.[160-163] While most cases of ALS are sporadic, meaning they occur without a clear family history, approximately 5-10% of cases are familial and are associated with specific genetic mutations. Mutations in genes such as SOD1, TARDBP, FUS, and C9orf72 have been identified in familial ALS and can contribute to motor neuron dysfunction through various mechanisms.[164, 165] While the majority of ALS cases have no known cause, environmental factors such as exposure to toxins, heavy metals, pesticides, and traumatic brain injury have been suggested as potential risk factors for ALS. These factors may interact with genetic susceptibility to contribute to disease onset and progression.[166-168] Thus, ALS is likely a multifactorial disease involving

interactions between genetic susceptibility, environmental factors, and various cellular mechanisms leading to motor neuron degeneration and progressive muscle weakness and paralysis. The high heterogeneity of ALS and the failures of the efforts to find a singular cure have led some researchers to propose that it may not be a single disease, but rather a miscellany of overlapping conditions that share common characteristics, similarly to cancer. [169, 170] Further research is needed to fully elucidate the complex pathogenesis of ALS and identify effective therapeutic strategies for the treatment of this devastating neurodegenerative disorder.

*Genetic background of amyotrophic lateral sclerosis*

The genetic background of ALS is multifaceted, involving both familial and sporadic forms of the disease. While the majority of ALS cases are sporadic, meaning they occur without a clear family history, approximately 5-10% of cases are familial and have a known genetic component.[124, 125, 171-174]

Familial ALS (fALS) accounts for a small percentage of ALS cases and is characterized by a clear family history of the disease. In these cases, ALS is inherited in an autosomal dominant manner, meaning that a mutation in a single copy of a specific gene is sufficient to cause the disease. [175] Several genes have been implicated in familial ALS, including:

- SOD1 (Superoxide Dismutase 1): Mutations in the SOD1 gene were the first identified genetic cause of ALS. SOD1 encodes an enzyme involved in antioxidant defense, and mutations in this gene can lead to protein misfolding and aggregation, mitochondrial dysfunction, and motor neuron degeneration. [176-178]

- C9orf72 (Chromosome 9 Open Reading Frame 72): Expansion of a hexanucleotide repeat sequence (GGGGCC) within the C9orf72 gene is the most common genetic cause of ALS and frontotemporal dementia (FTD). The exact mechanism by which the repeat expansion leads to neurodegeneration is not fully understood but likely involves RNA toxicity, protein aggregation, and impaired nucleocytoplasmic transport.[123, 179-182]

- TARDBP (TAR DNA-Binding Protein): Mutations in the TARDBP gene, which encodes the TDP-43 protein involved in RNA processing and metabolism, have been identified in familial ALS cases. Abnormal accumulation of TDP-43 protein aggregates is a pathological hallmark of ALS.[183-185]

- FUS (Fused in Sarcoma): Mutations in the FUS gene, which encodes a DNA/RNA-binding protein involved in RNA processing and transport, have also been implicated in familial ALS. Like TDP-43, abnormal accumulation of FUS protein aggregates is observed in ALS.[186-188]

- Other Genes: Mutations in other genes, such as VCP (valosin-containing protein), OPTN (optineurin) and SQSTM1 (sequestosome 1) have been identified in rare familial ALS cases, although their contribution to disease pathogenesis is less well understood. [189-192]

Sporadic ALS (sALS) occurs in individuals with no family history of the disease and is thought to result from a combination of genetic susceptibility and environmental factors. While specific genetic mutations are less common in sALS compared to fALS cases, genome-wide association studies (GWAS) have identified common genetic variants associated with an increased risk of developing ALS. These variants are often found in genes involved in neuronal function, inflammation, and other biological pathways implicated in ALS pathogenesis.[193, 194]

Genes associated with ALS based on data from the CAS Content Collection are explored in Figure 8 to facilitate the identification of potential therapeutic targets and biological mechanisms underlying disease processes. Details about each of the identified genes can be found in Table 1. For a detailed methodology please refer to the Supporting Information.

ALS exhibits significant genetic heterogeneity, with different genetic mutations associated with distinct clinical phenotypes and disease progression. Additionally, genetic modifiers and environmental factors may influence the penetrance and expressivity of ALS-associated mutations, leading to variability in disease onset, severity, and progression among affected individuals.[124, 195, 196] Understanding the genetic basis of ALS is critical for elucidating disease mechanisms, identifying potential therapeutic targets, and developing personalized treatment approaches for individuals with ALS. Ongoing research efforts continue to uncover novel genetic risk factors and pathways underlying ALS pathogenesis, with the ultimate goal of improving outcomes for patients with this devastating neurodegenerative disorder.

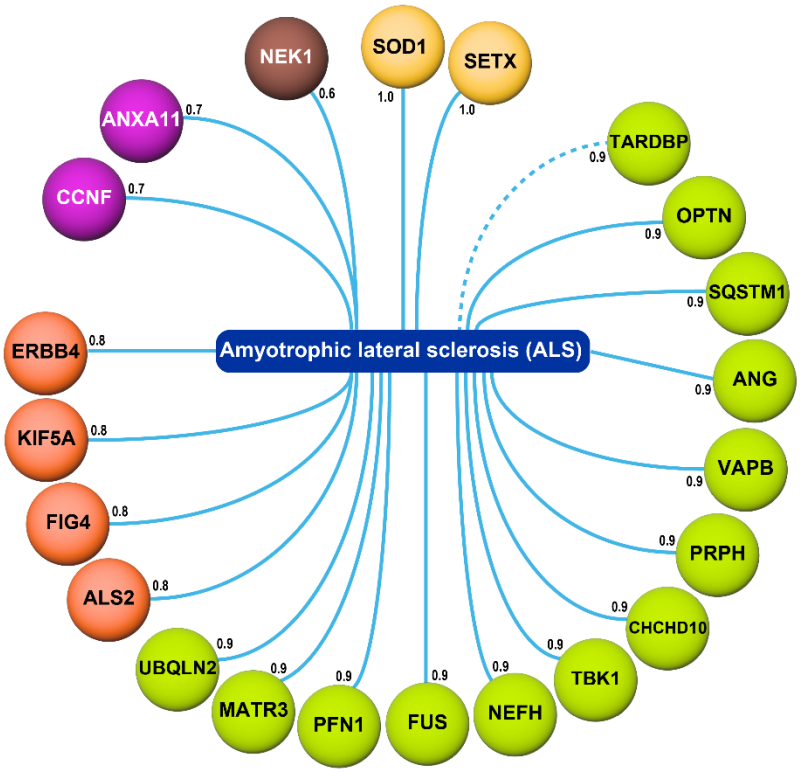


**Figure 8.** Genes associated with amyotrophic lateral sclerosis (ALS) based on data from the CAS Content Collection. Only genes with an association score of greater than 0.6 and with at least 10 records are shown here. Color corresponds to association score – yellow (1.0), green (0.9), orange (0.8), purple (0.7), and brown (0.6). The nature of the line indicates association source with dashed lines indicating a majority of records resulting from text mining.

**Table 1.** List of genes associated with amyotrophic lateral sclerosis (ALS), as shown in Figure 8, with the association type as causal or contributing.

| Gene | Association score | Protein | Expression profile, function and other diseases | Amyotrophic lateral sclerosis (ALS) |
|---|---|---|---|---|
| SOD1[197] | 1.0 | Superoxide dismutase 1 | An enzyme that scavenges superoxide radicals, superoxide dismutase 1 is crucial in converting ROS to molecular oxygen ($O_2$) and hydrogen peroxide ($H_2O_2$).[198, 199] Also referred to as copper-zinc superoxide dismutase (Cu/Zn SOD1, CuZn SOD1) due to the presence of a copper and Zn ion in the enzyme. [199] Superoxide dismutase are expressed in the neurons of CNS and are linked to neurological disorders.[200] | Mutations in superoxide dismutase 1 are thought to result in protein misfolding leading to ALS.[201, 202] In silico studies have tried to decipher changes in structure of mutant superoxide dismutase 1 resulting in "pathogenic conformational states" that might promote aggregation.[203] Researchers have also found a disulfide bond (C57-C146) to be critical for the normal functionality of superoxide dismutase 1.[204, 205] Research continues to be conducted to understand the exact effect of a mutation on protein structure using molecular modeling and simulation studies.[178] |
| SETX[206] | 1.0 | Senataxin | An enzyme classified as a superfamily 1B helicase, senataxin plays a critical role in resolving R-loops acting as a RNA:DNA helicase during DNA damage repair.[207] Mutations in SETX have been found in ataxia with oculomotor apraxia (AOA2). [208-211] | Mutations in senataxin have been linked to ALS4 (juvenile amyotrophic lateral sclerosis-4 with onset occurring before the age of 25[212]).[213, 214] These mutations are thought to interfere with senataxin's ability to regulate RNA polymerase II, control R loops, and binding to other protein partners among other things.[215, 216] |
| TARDBP[217] | 0.9 | Transactive response (TAR) DNA-binding Protein 43 kDa (TDP-43) | Protein composed of ~400 amino acid belonging to the heterogeneous nuclear ribonucleoprotein family.[218] TDP-43 is largely composed of 4 domains[219] and plays a role in RNA regulation.[218] Primarily a nuclear protein, TDP-43 shuttles between the nucleus and cytoplasm.[220] TDP-43 has been implicated in neurological disorders such as Alzheimer's,[221-224] Parkinson's [225] disease, | Mutations in TDP-43 have been observed in ALS.[229-232] These mutations can lead to formation of amyloid-like fibrils or cause TDP-43 to localize in the cytoplasm instead of the nucleus affecting RNA regulation.[220, 233] Recently researchers have determined that the aggregated forms of TDP-43 exhibit distinct folds depending on the type of disease (ALS [234] vs. type B FTLD-TDP |

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| | | | as well as frontotemporal dementia (FTD).[226-228] | [235]). A functional dimer, monomerization of TDP-43 has been shown to be important in ALS.[236] |
| OPTN[237] | 0.9 | Optineurin | A ~570 amino acid cytosolic protein that is expressed in a variety of tissues including the brain, heart, skeletal muscle, and eye among others.[238] Optineurin is involved in vesicular trafficking[239] and immune signaling.[240] Optineurin aggregates have been reported in Parkinson's disease[241] and its expression altered in a Parkinson's disease model.[242] Optineurin has a possible role in promoting aggregation of mutant huntingtin.[243] On the other hand, optineurin might have a beneficial role in Alzheimer's disease.[244] | Mutations in optineurin have been reported in ALS[245-250] with mutations affecting optineurin's ability to interact with mitochondria and affecting mitophagy.[238, 251] OPTN gene therapy is being explored as possible treatment option for ALS.[252] |
| SQSTM1[253] | 0.9 | Sequestosome 1 | Also referred to as p62, sequestosome 1 is a selective autophagy receptor.[254] Composed of multiple protein-protein interaction motifs, sequestosome 1 functions to eliminate misfolded and aggregated protein.[255] In addition, sequestosome 1 is important in aging and age-related diseases.[254] Besides ALS, SQSTM1 has been implicated in FTD[256-259] and Alzheimer's disease[260] among other neurological disorders. | Similar to the other genes listed in this table, mutations in sequestosome 1 have been identified in individuals suffering from ALS.[191, 192, 261, 262] For some mutations in sequestosome 1 its ability to bind to other protein binding partners is impaired leading to reduced autophagy.[263] Therefore, compounds enhancing autophagy may be a potential treatment strategy.[264] |
| ANG[265] | 0.9 | Angiogenin | As the name suggests, angiogenin is a small (~120 amino acid residues) protein that is crucial in angiogenesis (the formation of new blood vessels).[266, 267] Besides angiogenesis, other processes involving angiogenin include rRNA and mRNA transcription, tRNA metabolism[268] as well as playing a role in immune response.[269] Angiogenin belongs to the ribonuclease A superfamily. | Mutations in ANG, often loss-of-function, have been reported in ALS.[270, 271] Research is ongoing to determine the exact effect of reported/known ALS mutations on the structure and ribonuclease A activity of angiogenin.[272, 273] In a recent report, the role of angiogenin in ALS was shown to be more complex than was earlier thought.[274] |
| VAPB[275] | 0.9 | Vesicle-associated membrane protein (VAMP)-associated protein B and C (VAPB) | VAPB is a type IV membrane protein consisting of ~243 amino acids associated with the endoplasmic reticulum.[276] Known to interact with a wide variety of partners[277] | Mutations in VAPB have been detected in ALS patients.[281, 282] One mutation in particular appears to have been studied extensively in the context of ALS – a |

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| | | | often (but not always) via interaction between its MSP domain and a FFAT motif of the binding partner.[278] VAPB has been implicated in a number of neurological disorders including Alzheimer's and Parkinson's disease.[277] In addition, the role of VAPB in cancer is being actively studied.[279, 280] | Pro-to-Ser (P56S) mutation.[283-290] The P56S mutation appears to a toxic gain-of-function mutation and number of mechanisms have been proposed including affecting autophagy,[290] causing endoplasmic reticulum stress,[287, 289] changing the morphology of endoplasmic reticulum,[291] and diminishing VAPB's ability to mediate unfolded protein response.[283] Other mutations perhaps less well studied include P56H,[292] T46I,[293] V234I,[294] and a deletion mutant (ΔS160).[295] |
| PRPH[296] | 0.9 | Peripherin | A type III intermediate filament protein, which are part of the cytoskeleton (other members include desmin, vimentin and glial fibrillary acidic protein).[297] Unlike other type III intermediate filament proteins, peripherin is expressed primarily in the peripheral and CNS.[297, 298] Peripherin is thought to play a role in axonal growth.[299, 300] Researchers are exploring peripherin as potential biomarker for motor neuron diseases[301] and axonal damage.[302] | Upregulation of peripherin has been reported in ALS[303] with this upregulation proposed to have a detrimental effect as observed in mouse models.[304] Others have reported mutations in peripherin in ALS patients.[305] Peripherin splice variants prone to aggregation have also been reported.[303, 304] |
| CHCHD10[306] | 0.9 | Coiled-coil-helix-coiled-coil-helix domain containing protein 10 | A small protein (~149 amino acid residues) associated with the intermembrane space of mitochondria,[307] coiled-coil-helix-coiled-coil-helix domain containing protein 10 is also known as protein N27C7-4.[308] Like other members of the CHCHD-containing protein family, CHCH10 protein contain $(CX_9C)_2$ motifs.[307] Appears to play a role in mitochondrial structure and function.[307] Other diseases associated with CHCHD10 include late onset spinal motor neuronopathy[309] and mitochondrial myopathy.[310] | Mutations in CHCHD10 have been reported in ALS patients.[311-314] Overexpression of a mutant CHCHD10 was associated with abnormalities in mitochondria[312] and could underlie pathogenesis of ALS and FTD. |
| TBK1[315] | 0.9 | TANK binding kinase 1 | A serine/threonine protein kinase composed of ~729 amino acid residues, TBK1 plays a role in innate immunity, autophagy and | Among the many binding partners of TBK1 are optineurin and sequestosome 1/p62. Mutations in TBK1 have been |

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| | | | apoptosis among other cellular functions.[316] TBK1 binds to and interacts with a wide variety of protein partners utilizing different domains present in its structure.[316-318] Activation of TBK1 requires autophosphorylation at Ser172.[317, 319] Diseases that involve TBK1 include cancer[316, 320, 321] and autoimmune disorders[322, 323] with TBK1 inhibitors being explored as a viable strategy.[322, 324, 325] | reported in ALS[326-328] with mutations thought to interfere with autophagic function of TBK1[329] by affecting kinase activity.[330] Besides ALS, TBK1 mutations are also implicated in FTD.[331, 332] |
| NEFH[333] | 0.9 | Neurofilament heavy chain | Neurofilaments are heavily expressed in the central and peripheral nervous system.[334] They are made up of three subunits based on molecular weight, light, medium and heavy (NEFH).[335] They are also involved with cytoskeletal functions such as the regulation of axon diameter and growth.[336] Besides ALS, the other disease associated with NEFH includes Charcot-Marie-Tooth disease.[337-339] | Mutations in NEFH proteins have been reported to be associated with ALS such as those within the KSP repeat region of the tail domain.[340-342] Another study reports variants in NEFH associated with sALS such as the NEFH Ser787Arg.[343] |
| FUS[344] | 0.9 | Fused in sarcoma (FUS) RNA binding protein | A DNA/RNA binding protein, FUS is composed of ~506 amino acids.[345] FUS is expressed both in the nucleus and cytoplasm [345] and participates in a number of important cellular processes such as DNA repair[346] including mitochondrial DNA repair[347] and mRNA transport,t[347] among others. Some other names that FUS is known by include translocated in liposarcoma (TLS) and heterogeneous nuclear ribonucleoprotein P2 (HNRNPP2). Besides ALS, FUS has also been linked to FTD.[348, 349] | Mutations in the FUS gene have been linked to ALS over the last two decades.[187, 350-356] Some ALS-associated mutations have been found in the nuclear localization signal domain dampening the ability of FUS to bind transportin 1, a nuclear import receptor,[357] resulting in accumulation of mutant FUS in the cytoplasm.[358] An article published in 2018 describes FUS R495X ALS-associated mutation resulting in alterations in the mitochondria.[359] |
| PFN1[360] | 0.9 | Profilin 1 | Profilin 1 is a small actin binding protein composed of ~139 amino acid residues with a wide expression profile.[361] Profilin 1 helps in actin polymerization[362] by accelerating nucleotide exchange or by lowering actin concentration required to jump start polymerization.[361] Besides actin | Mutations in profilin have been observed in ALS[370-372] – aggregation of mutant profilin 1 often alongside TDP-43 is thought to be a contributing factor to ALS. Mutation in the phosphorylation site of profilin 1, important for actin polymerization, has also been |

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| | | | polymerization, profilin 1 appears to be important for a number of cellular processes including cell division[363] and membrane trafficking.[364, 365] In the last decade, profilin 1's role in cancer has investigated[366] with dysregulation of profilin 1 observed in breast cancer,[367] endometrial cancer,[368] as well as non-small cell lung cancer,[369] among others. | reported.[373] Molecular modeling and dynamic studies indicate that some mutations in profilin1 might affect the stability and functionality of the protein.[374] |
| MATR3[375] | 0.9 | Matrin 3 | A DNA/RNA binding nuclear protein, matrin 3 is composed of ~847 amino acid residues [376] organized into several domains such as RNA recognition motifs, zinc finger domain, and intrinsically disordered regions.[377, 378] The various functions that matrin 3 is involved in includes mRNA stabilization,[379] alternative splicing regulation,[380] DNA repair,[381] etc.[378] | Matrin 3 binds to and interacts with a number of different proteins including TDP-43 and FUS, which are also implicated in ALS.[378] Mutations in MATR3 has been detected in ALS patients.[382-386] |
| UBQLN2[387] | 0.9 | Ubiquilin 2 | A ubiquitin-like protein, ubiquilin 2 is an important component of the ubiquitin-proteosome system helping in the degradation of misfolded proteins.[388] The ubiquitin-like domain and ubiquitin-associated domains of ubiquilin 2 interact with the proteosome and the polyubiquitin chains on proteins, respectively. [389] | Mutations in UBQLN2 linked to ALS[390-392] possibly by hampering protein degradation by affecting its interaction with binding partners/other proteins.[393, 394] |
| ALS2[395] | 0.8 | Alsin | Composed of ~1657 amino acids arranged into four domains, alsin is a large protein that acts as a guanine nucleotide exchange factor for Rac1 and Rac5[396] and plays a role in membrane trafficking.[396, 397] Alsin expression has been observed in the CNS in mice[398] and studies with alsin knockdown and Rac1 mutants indicate that alsin-Rac1 signaling is important for axonal growth in motor neurons.[399] | Mutations in alsin have been detected in ALS patients.[400-403] Some ALS-associated mutations result in expression of short and long form of alsin lacking crucial domains, diminishing alsin's ability to effectively function as a guanine nucleotide exchange factor.[400] |
| FIG4[404] | 0.8 | Polyphosphoinositide phosphatase | Also known as SAC domain-containing protein 3 (Sac3) and is composed of ~907 amino acid residues.[405, 406] An enzyme, polyphosphoinositide phosphatase cleaves the phosphatase group from the 5-position of the inositol ring of phosphatidylinositol 3,5- | FIG4 mutations have been observed in ALS patients.[412-418] While the exact mechanism underlying ALS-associated disease mutations remains under investigation, evidence from FIG4's involvement in Charcot-Marie-Tooth |

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| | | | bisphosphate ($PI(3,5)P_2$).[406, 407] $PI(3,5)P_2$ is a lipid signaling molecule and thought to be important for development of the nervous system.[408] Mutation in FIG4 and deficiency of FIG4 are associated with Charcot-Marie-Tooth disease,[409] an inherited genetic condition affecting peripheral nerves,[410] and lysosomal storage disorder.[411] | disease indicates disruption of intracellular trafficking due to excessive vacuoles could be a possible reason.[419] [419] |
| KIF5A[420] | 0.8 | Kinesin family member 5A | Kinesin family member 5A belongs to the kinesin family of ATP-driven motor proteins.[421] Also referred to as kinesin-1, they are expressed in neurons[422] and are engaged in intracellular transport of protein complexes, mRNAs and others[423] as well as cell division.[424] Composed of ~1039 amino acid residues, kinesin family member 5A appears to be involved in trafficking of GABA receptors.[425] Under physiological conditions, kinesin family member 5A are autoinhibited [426] rendering them incapable of interacting with cargo and only upon binding of two partners – c-Jun N-terminal kinase–interacting protein 1 (JIP1) and fasciculation and elongation protein ζ1 (FEZ1) – is the autoinhibition lifted allowing kinesin family member 5A to carry out transport.[427] Besides ALS, expression levels of KIF5A appear to be altered in Alzheimer's disease[428, 429] and mutations in KIF5A appear to be associated with spastic paraplegia.[430-432] | In the last few years, there have been reports of KIF5A mutations observed in ALS patients.[385, 433-438] Recently, Baron et al.[439] elucidated the mechanism underlying an ALS-associated mutations in KIF5A – as per their explanation, the mutation rendered the autoinhibition of kinesin family member 5A ineffective resulting in increased mitochondrial transport. A research group from Tohoku university showed that an ALS-associated mutant of KIF5A had increased propensity to form aggregates.[440] Other ALS-associated mutations in KIF5A have also been identified.[441] |
| ERBB4[442] | 0.8 | Erb-b2 receptor tyrosine kinase 4 | A member of the epidermal growth factor receptor family, ErbB4 is a type of receptor tyrosine kinase.[443] Also referred to as HER4, ErbB4 is classified as a type I single transmembrane protein and is composed of ~1300 amino acid residues with a large extracellular and intracellular domain.[444] ErbB4 has been implicated in various types of cancer including breast, lung, and colorectal cancer, among others.[445, 446] | Mutations in ERBB4 have been reported in ALS patients.[447-450] ErbB4 binds to and interacts with a number of partners, one of which is neuregulin, small cell signaling protein molecules,[451] and undergo dimerization accompanied by autophosphorylation.[452] Mutations associated with ALS in the tyrosine kinase or C terminal domain of ErbB4 |

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| | | | | was accompanied by reduced autophosphorylation.[448] |
| CCNF[453] | 0.7 | Cyclin F [453] | Cyclins are proteins that regulate the activity of cyclin-dependent protein kinases (CDK).[454] Described first in 1994 by Bai et al,[454] cyclin F is composed of ~786 amino acid residues and is structurally similar to other cyclins (especially A and B) with a wide distribution profile. Cyclin F is a part of the Skp1–Cul1–F-box (SCF) E3 ubiquitin ligase complex and is involved in ubiquitination of proteins[455] with ubiquitinated protein eventually being degraded by the ubiquitin-proteasome system. Cyclin F has been implicated in cancer.[456-458] | Similar to other proteins important for autophagy such as TDP-43 and p62/ sequestosome 1, mutations in CCNF has been observed in and linked to ALS.[385, 459-462] Mutant CCNF results in abnormal ubiquitination, and this is thought to play a role in ALS.[459, 460] Another mechanism/pathway that may be important in ALS involves mutant cyclin F increasing the ATPase activity of valosin-containing protein eventually resulting in TDP-43 aggregation.[463] |
| ANXA11[464] | 0.7 | Annexin A11 | Annexin A11 is a ~504 amino acid residue long $Ca^{2+}$-dependent membrane protein that is wide expressed.[465] Annexin A11 is thought to be important for vesicle trafficking by aiding in stabilization of Sec31A, a component of the coat protein complex II.[466] In 2023, the full-length structure of annexin A11 was published[467] and is bound to help in understanding how disease causing mutations affect the protein. Annexin A11 appears to play a role in sarcoidosis, an inflammatory disorder.[465, 468] Another disease with possible annexin A11 involvement is immunoglobulin G4-related disease.[469, 470] | As with other genes noted here, mutations in ANXA11 have been reported in the context of ALS.[471-475] The various mechanisms by which mutant annexin A11 results in ALS included formation of insoluble aggregates, disruption of $Ca^{2+}$ homeostasis,[195, 476] and interference with RNA transport.[477] Structural studies of annexin A11 including crystal structure[478] have been reported that suggest possible effects of mutation on the structure and functionality of annexin A11.[479] |
| NEK1[480] | 0.6 | NIMA related kinase 1 | The never in mitosis A (NIMA)-related kinase 1 is a serine/threonine kinase.[480] It is highly expressed in neuronal and germ cells[481, 482] and plays a role in several cellular processes such as cell cycle regulation, cell death, cilia formation, and DNA damage response.[483, 484] NEK1 mutations appear to be associated with Mohr syndrome,[485] short rib-polydactyly syndrome, Majewski type,[486] and axial spondylometaphyseal dysplasia.[487] | Different NEK1 mutations have been discovered and associated with ALS in various cohorts.[488] Two main mutations, NEK1 loss-of-function variants and missense variants such as p.Arg261His have been discovered and are believed to be associated with ALS.[489-492] |

## Huntington's disease

*Overview*

Huntington's disease (HD), also known as Huntington's chorea, is a rare hereditary neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric symptoms (the term 'chorea' refers to the jerky, unpredictable movements of the muscles in the face, arms and legs that is a prevalent symptom of Huntington's disease).[493-499] The estimates are that the global prevalence of HD is ~2.7 per 100,000 persons.[500]

HD is caused by a mutation in the HTT gene, located on chromosome 4, which encodes the huntingtin protein. This mutation involves an expansion of a trinucleotide repeat sequence, known as CAG, within the gene. Individuals with HD inherit an expanded CAG repeat from one of their parents, leading to the production of a mutant huntingtin protein. The length of the CAG repeat is inversely correlated with the age of onset and severity of symptoms, with longer repeats generally associated with earlier onset and more severe disease. [501-504]

HD follows an autosomal dominant pattern of inheritance, meaning that a person who inherits a single copy of the mutant gene from one parent will develop the disease, regardless of whether the other parent carries the mutation. Each child of an affected individual has a 50% chance of inheriting the mutated gene.[505, 506] The mutant huntingtin protein disrupts normal cellular functions and leads to neuronal dysfunction and death, particularly in the basal ganglia and cerebral cortex of the brain. These regions are involved in movement control, cognition, and emotion regulation. Progressive degeneration of these brain areas results in the characteristic symptoms of HD, which typically worsen over time.[501, 507, 508]

The most prominent early symptoms of HD are often motor-related and may include involuntary movements called chorea, which are rapid, jerky, and random. Other motor symptoms can include dystonia (sustained muscle contractions causing twisting or repetitive movements), rigidity, bradykinesia (slowness of movement), and impaired coordination and balance.[509-511] HD also affects cognitive function, leading to impairments in memory, executive function, attention, and decision-making. As the disease progresses, individuals may experience difficulties with language, planning, problem-solving, and other cognitive tasks. [512, 513] Psychiatric symptoms are common in HD and can precede motor symptoms by several years. These can include depression, anxiety, irritability, apathy, impulsivity, and obsessive-compulsive behaviors. Psychiatric symptoms can significantly impact quality of life for individuals with HD and their caregivers.[514, 515] While most cases of HD typically manifest in adulthood, a small percentage of individuals develop symptoms during childhood or adolescence, known as juvenile-onset HD. Juvenile-onset HD tends to progress more rapidly and may have distinct clinical features compared to adult-onset HD.[493, 509, 516]

Currently, there is no cure for HD, and available treatments focus on managing symptoms and improving quality of life. Medications can help alleviate motor symptoms, psychiatric symptoms, and complications such as chorea and depression. Doctors utilize an arsenal of medications to help alleviate the symptoms of Huntington's disease including antipsychotics and antidepressants. Tetrabenazine (Xenazine)[517] and deutetrabenazine (Austedo)[518, 519] are two US FDA drugs approved in 2008 and 2017, respectively, for treating chorea in Huntington's disease. Physical therapy, speech therapy, and occupational therapy may also be beneficial in managing motor and functional impairments.[503, 520, 521] Genetic testing can confirm the diagnosis of HD in individuals with symptoms or a family history of the disease. Genetic counseling is recommended

for individuals considering testing to discuss the implications of the test results and the potential impact on themselves and their families.[509, 522] Ongoing research efforts aim to better understand the underlying mechanisms of HD and develop disease-modifying treatments. Clinical trials are underway to test potential therapies targeting the mutant huntingtin protein, neuroinflammation, and other pathways implicated in HD pathogenesis.[523-525] Despite the challenges posed by HD, advances in research and clinical care offer hope for improved treatments and ultimately a cure for this devastating neurodegenerative disorder.

*Pathogenesis of Huntington's disease*

The pathogenesis of Huntington's disease (HD) involves a complex interplay of genetic, molecular, and cellular mechanisms that ultimately lead to neurodegeneration in specific regions of the brain. [504, 526-528]

HD is caused by a mutation in the HTT gene, located on chromosome 4. This mutation involves an abnormal expansion of a trinucleotide repeat sequence, known as CAG, within the gene. The CAG repeat encodes a polyglutamine tract in the huntingtin protein. The mutant huntingtin protein (mHTT) has an expanded polyglutamine tract, which is toxic to neurons and disrupts normal cellular functions.[501, 509, 529] The expanded polyglutamine tract in mHTT leads to the misfolding and aggregation of the protein. These aggregates, known as inclusion bodies, accumulate within neurons and disrupt cellular processes. Protein aggregation is a hallmark feature of HD pathology and contributes to neuronal dysfunction and death.[530-532]

mHTT disrupts mitochondrial function, leading to impaired energy production, increased oxidative stress, and mitochondrial fragmentation. Mitochondrial dysfunction contributes to neuronal vulnerability and exacerbates neurodegeneration in HD.[533-535] Dysregulation of glutamate signaling and excitotoxicity play a role in HD pathogenesis. mHTT disrupts glutamate homeostasis, leading to excessive glutamate release and activation of NMDA receptors. Prolonged activation of NMDA receptors results in calcium influx, mitochondrial dysfunction, and neuronal damage.[536-539]

mHTT interferes with axonal transport, the process by which cellular components are transported along axons. Impaired axonal transport disrupts the delivery of essential proteins and organelles to synapses, leading to synaptic dysfunction and neuronal degeneration. [540-542] Neuroinflammatory processes contribute to HD pathogenesis and exacerbate neuronal damage. Activation of microglia and astrocytes, the resident immune cells of the CNS, leads to the release of pro-inflammatory cytokines, ROS, and other toxic molecules that contribute to neuronal dysfunction and death. [543-545]

mHTT disrupts gene transcription and expression, leading to widespread alterations in gene expression patterns in affected neurons. Transcriptional dysregulation affects multiple cellular pathways involved in neuronal function, survival, and plasticity, contributing to neurodegeneration in HD.[546-548] HD pathology affects synaptic function and plasticity, leading to impaired neurotransmission and synaptic loss. Synaptic dysfunction contributes to cognitive and motor impairments in HD and is an early feature of the disease.[549, 550] Certain neuronal populations, particularly those in the striatum and cerebral cortex, are selectively vulnerable to the toxic effects of mHTT. The striatum, which plays a crucial role in motor control and cognition, is severely affected in HD, leading to the characteristic motor and cognitive symptoms of the disease.[551-553]

*Genetic background of Huntington's disease*

The genetic background of Huntington's disease (HD) is primarily characterized by a mutation in the HTT gene, which is located on the short arm of chromosome 4 (4p16.3).[502, 506] The genetic mutation responsible for HD involves an abnormal expansion of a trinucleotide repeat sequence, known as CAG, within the HTT gene. The CAG repeat encodes a polyglutamine tract in the huntingtin protein. In individuals with HD, the CAG repeat is expanded beyond a certain threshold, resulting in an increased number of glutamine residues in the huntingtin protein.[526, 528, 554, 555]

HD follows an autosomal dominant pattern of inheritance, meaning that a person who inherits a single copy of the mutant HTT gene from one parent will develop the disease, regardless of whether the other parent carries the mutation. Each child of an affected individual has a 50% chance of inheriting the mutated gene. [502, 509] A notable feature of HD inheritance is anticipation, where the age of onset of symptoms tends to decrease and the severity of symptoms tends to increase in successive generations. This phenomenon is thought to be due to further expansion of the CAG repeat during transmission from one generation to the next. [556, 557] While the presence of an expanded CAG repeat in the HTT gene is necessary for the development of HD, the age of onset and severity of symptoms can vary widely among individuals with the mutation. Some individuals may carry the mutation but never develop symptoms (referred to as incomplete penetrance), while others may have an earlier onset and more severe disease. [558-560]

In addition to the CAG repeat expansion in the HTT gene, other genetic factors may influence the age of onset and progression of HD. Genetic modifiers, such as variations in other genes or non-genetic factors, may interact with the mutant HTT gene to modify disease onset, severity, and progression. Research into genetic modifiers may provide insights into the variability of HD phenotypes and identify potential targets for therapeutic intervention.[561-564]

While the role of HTT in HD is well-established [565-568], we wished to collate a comprehensive list of other genes that might play a role in the development of HD. Results from our are visualized in Figure 9. Besides HTT, other genes that might play a crucial role in the eitology of HD include BDNF, NPY, SIRT1, HAP1, PPARGC1A, JPH3, GRIN2B, CNTF, and IGF1. Details about each of the identified genes can be found in Table 2.

Genetic testing for the CAG repeat expansion in the HTT gene can confirm the diagnosis of HD in individuals with symptoms or a family history of the disease. Predictive genetic testing can also be offered to individuals who are at risk of inheriting the mutation but do not yet have symptoms. Genetic counseling is recommended for individuals considering testing to discuss the implications of the test results and the potential impact on themselves and their families.[569-571] Understanding the genetic basis of HD is essential for accurate diagnosis, genetic counseling, and the development of targeted treatments for this devastating neurodegenerative disorder.

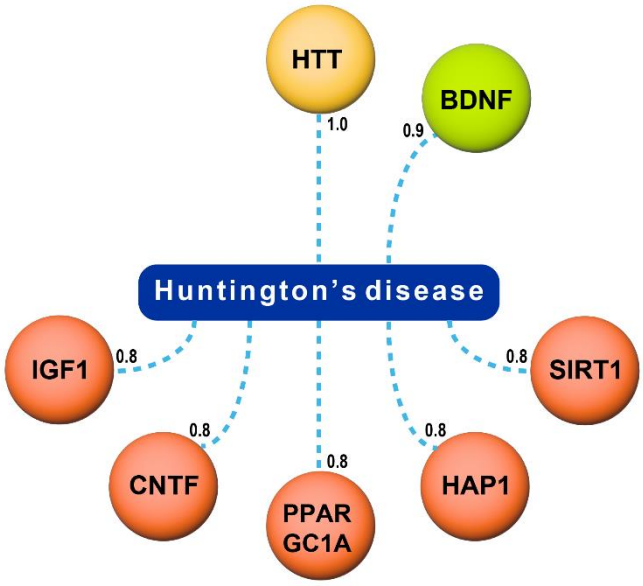


**Figure 9.** Genes associated with Huntington's disease (HD) based on data from the CAS Content Collection. Only genes with an association score of greater than 0.8 and with at least 10 records are shown here. Color corresponds to association score – yellow (1.0), green (0.9) and orange (0.8). The nature of the line indicates association source with dashed lines indicating a majority of records resulting from text mining.

**Table 2.** List of genes associated with Huntington's disease (HD), as shown in Figure 9, with the association type as causal or contributing.

| Gene | Association score | Protein | Expression profile, function and other diseases | Huntington's disease (HD) |
|---|---|---|---|---|
| BDNF[572] | 0.9 | Brain derived neurotrophic factor | Brain derived neurotrophic factor are small proteins expressed widely through various parts of the brain[573, 574] and important for synaptic plasticity.[574] Implicated in psychiatric illness.[575] | Reduction in levels of BDNF are observed in HD.[576, 577] Targeting BDNFs is also a potential therapeutic strategy in HD. [578, 579] Increasing BDNF levels are indirectly potentially beneficial in treating HD.[580, 581] There are conflicting reports about the utility of BDNF as a potential biomarker for HD.[582-584] |
| SIRT1[585] | 0.8 | Sirtuin 1 | Sirtuin is a type of deacetylase that is dependent on nicotinamide adenosine dinucleotide (NAD)[586] with a wide expression profile (brain as well as other organs such as kidney, liver, pancreas, spleen).[587] Sirtuin 1 appears to have a role in obesity [588], metabolic disorders including diabetes,[589, 590] as well as immune response.[591] | Sirtuin 1 appear to have a neuroprotective role in HD.[592, 593] Modulation of sirtuin 1 activity is being explored as viable therapeutic strategy[593-596] with arguments being made for sirtuin 1 activation [597] as well as inhibition.[598] Selisistat (CAS RN: 49843-98-3) was being developed as a small molecule inhibitor of sirtuin 1 for the treatment of HD.[599, 600] |
| HAP1[601] | 0.8 | Huntingtin associated protein 1 | Huntingtin associated protein 1 is expressed in various areas of the CNS including amygdala and hypothalamus among others. [602] HAP1 found to be important for trafficking of cellular components.[603, 604] HAP1 is also implicated in various neurodegenerative diseases such as Alzheimer's, Parkinson's as well as rare diseases such as ALS. [605] | HAP1 protein has been shown to interact with mutant huntingtin protein.[605] The HAP1-mHTT association impairs normal/physiological cellular trafficking carried out by HAP1 in conjunction with other proteins.[606, 607] There are contradictory studies indicating HAP1 has a bearing on age of onset.[608, 609] |
| PPARGC 1A[610] | 0.8 | Peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1 α (PGC-1α) | PGC-1α acts as a coactivator to PPARα and plays a role in mitochondrial energy metabolism.[611] PGC-1α has been studied in the context of physical fitness especially in athletes. [612-616] Recently, PGC-1α has been linked to Parkinson's disease. [617, 618] | Impaired levels of PGC-1α are observed in HD[619] with overexpression of PGC-1α allowing rescue in HD mice.[620] Mutant huntingtin protein is shown to inhibit PGC-1α expression.[621] Studies suggest that PGC-1α may have an impact on age of onset of HD.[622, 623] |

| | | | | |
|---|---|---|---|---|
| CNTF[624] | 0.8 | Ciliary neurotrophic factor | Ciliary neurotrophic factor is a cytokine belonging to the IL-6 family. [625] Expressed in Schwann cells as well as T cells. [626] The are also important for the survival of oligodendrocytes [627] and have been implicated in CNS diseases involving demyelination [628-630] as well as motor neuron disease. [631] | CNTF appears to have a neuroprotective role in HD.[632] Administration of CNTF has been explored as a potential treatment for HD with varying results.[633-636] |
| IGF1[637] | 0.8 | Insulin-like growth factor 1 | Also referred to as somatomedin C or somatomedin 1,[638] IGF1 is a small protein of 70 amino acid residues[639] secreted primarily by the liver.[640] Acts as a mediator of growth hormone and is critical in somatic growth.[640] Elevated IGF1 levels has been linked to rare disorders such as gigantism and acromegaly.[641] IGF1 has also been studied in the context of aging.[642, 643] | IGF1 has been associated with declining social cognition in HD[644] with IGF1 levels as potential indicators.[645] Targeting IGF1 has also been explored as a therapeutic strategy in HD with both IGF1 inhibitors[646] as well as administration of IGF1 itself having been studied.[647] |

## Myasthenia gravis

*Overview*

Myasthenia gravis (MG) is a rare chronic neuromuscular disorder characterized by weakness and rapid fatigue of voluntary muscles.[648-650] With the earliest accounts dating back to the late 1600s,[651] MG is described as an autoimmune disorder affecting neuromuscular junctions.[652] Thought to arise as a result of the body generating antibodies against the acetylcholine receptor (AChR) or muscle specific kinase,[652, 653] resulting in the immune system mistakenly attacking receptors on muscle cells, particularly at the neuromuscular junction where nerve impulses stimulate muscle contractions,[654-656] MG leads to muscle weakness and a host of other symptoms.[657, 658] During the Covid-19 pandemic, reports have emerged of onset of MG after SARS-Cov-2 infection. [659, 660] Global prevalence rates range from 150 to 200 cases per 1,000,000 people. The prevalence of MG in the United States is estimated at 14 to 20 cases per every 100,000 people or between 36,000 and 60,000 cases. In Europe, an estimated 56,000 to 123,000 individuals live with MG. [661, 662]

The hallmark symptom of MG is muscle weakness, which typically worsens with activity and improves with rest. This weakness can affect various muscles, including those controlling eye movements, facial expressions, chewing, swallowing, and breathing. Fatigue is also a common feature, with muscles becoming progressively weaker during periods of activity. Weakness in the muscles that control eye movements often leads to double vision or drooping of the eyelids (ptosis). Difficulty swallowing (dysphagia) can occur due to weakness in the muscles involved in chewing and swallowing. In severe cases, weakness of the muscles involved in breathing can lead to respiratory difficulties, which can be life-threatening. Symptoms of MG can vary widely among individuals and may fluctuate over time, making diagnosis challenging. [663-667]

Factors such as stress, illness, fatigue, or certain medications can exacerbate symptoms in people with MG. Diagnosis typically involves a thorough medical history, physical examination, blood tests to check for specific antibodies associated with MG, and specialized tests such as electromyography and nerve conduction studies. While there is no cure for MG, various treatments can help manage symptoms and improve quality of life. These may include medications such as acetylcholinesterase (AChE) inhibitors, immunosuppressants, and corticosteroids. [668-670] Some individuals may also benefit from procedures such as plasmapheresis or intravenous immunoglobulin therapy. In severe cases, surgical removal of the thymus gland (thymectomy) may be recommended. [671] With appropriate treatment, many people with MG can lead fulfilling lives. However, the course of the disease can be unpredictable, and long-term management often requires close monitoring and adjustments to treatment by developing a personalized treatment plan and receive ongoing support and care. [672-678]

*Pathogenesis of myasthenia gravis*

The pathogenesis of MG involves an autoimmune response targeting components of the neuromuscular junction (NMJ), where nerve impulses trigger muscle contractions. [662, 679] MG is primarily driven by an autoimmune response, where the body's immune system mistakenly identifies components of the NMJ as foreign and attacks them. The primary target of this autoimmune response is the AChRs on the muscle cell membrane. These receptors normally bind acetylcholine, a neurotransmitter released by motor neurons, to initiate muscle contractions.[652, 680, 681]

In MG, the immune system produces autoantibodies called anti-AChR antibodies. These antibodies bind to the AChR on the muscle cell membrane, leading to several effects: (i) some antibodies block the binding sites on the AChR, preventing acetylcholine from binding and initiating muscle contractions; (ii) other antibodies may cross-link adjacent AChR molecules, leading to internalization and degradation of the AChR complex, reducing the number of functional receptors on the muscle cell membrane; (iii) the binding of antibodies to AChR can also activate the complement system, a part of the immune system involved in inflammation and cell destruction. This further contributes to damage and dysfunction at the NMJ. [653, 682-684]

The presence of anti-AChR antibodies and complement activation disrupts neuromuscular transmission, leading to: (i) reduced signal transmission, since with fewer functional AChR available, the binding of acetylcholine released by motor neurons is impaired, resulting in weakened muscle contractions; (ii) endplate destruction, since chronic immune-mediated damage to the NMJ can lead to structural changes, including destruction of the postsynaptic membrane and alterations in the distribution of AChR. [685-687]

The thymus gland plays a role in the development of MG in some individuals. [688] It is commonly associated with thymic abnormalities, such as thymic hyperplasia or thymoma (a tumor of the thymus). The thymus is thought to contribute to the production of autoantibodies and the maturation of autoreactive T cells involved in the autoimmune response seen in MG. In general, the pathogenesis of MG involves a complex interplay between autoantibodies, complement activation, and immune-mediated damage at the neuromuscular junction, leading to impaired neuromuscular transmission and muscle weakness characteristic of the disease. [688-690]

*Genetic background of myasthenia gravis*

Myasthenia gravis has a complex genetic background, but it is not typically considered a purely genetic disorder like some other conditions. Instead, MG is primarily regarded as an autoimmune disease with genetic predispositions. While the exact cause of MG is unknown, there is evidence suggesting a genetic predisposition to the disease. Certain genetic variations or polymorphisms have been associated with an increased risk of developing MG. These variations are often related to genes involved in immune system function, such as genes encoding human leukocyte antigens (HLAs), specifically the HLA-B8 and HLA-DR3 alleles. [691-697]

MG can sometimes run in families, indicating a potential genetic component. [698] Family studies have shown that first-degree relatives of individuals with MG have a higher risk of developing the condition compared to the general population. However, the inheritance pattern is usually not straightforward, suggesting the involvement of multiple genetic and environmental factors. [698, 699]

Certain HLA alleles, particularly those within the major histocompatibility complex (MHC) region, have been consistently linked to an increased risk of MG. [700] For example, the HLA-DR3 allele has been associated with MG, especially in individuals with early-onset disease and thymic abnormalities. [696] However, HLA associations alone are not sufficient to explain the development of MG, indicating the involvement of other genetic and environmental factors. In addition to HLA alleles, studies have identified other genetic factors that may contribute to the risk of MG. These include genes involved in immune regulation, such as those encoding cytokines, chemokines, and components of the complement system. Variations in these genes may affect immune function and predispose individuals to autoimmune diseases like MG. [691, 701, 702]

Using data from the CAS Content Collection, we have put together genes known to have an association with MG (Figure 10). These genes include AGRN, LRP4, MUSK, and TTN and are explored in more detail in Table 3.

It is important to note that the development of MG likely involves complex interactions between genetic susceptibility factors and environmental triggers. [696] Environmental factors such as infections, medications, and hormonal changes may play a role in triggering the autoimmune response in genetically susceptible individuals. While genetic factors contribute to the susceptibility to MG, the disease's development is likely multifactorial, involving a combination of genetic predisposition, environmental triggers, and immune dysregulation. Further research is needed to elucidate the specific genetic mechanisms underlying MG and their interactions with environmental factors. [682, 703, 704]

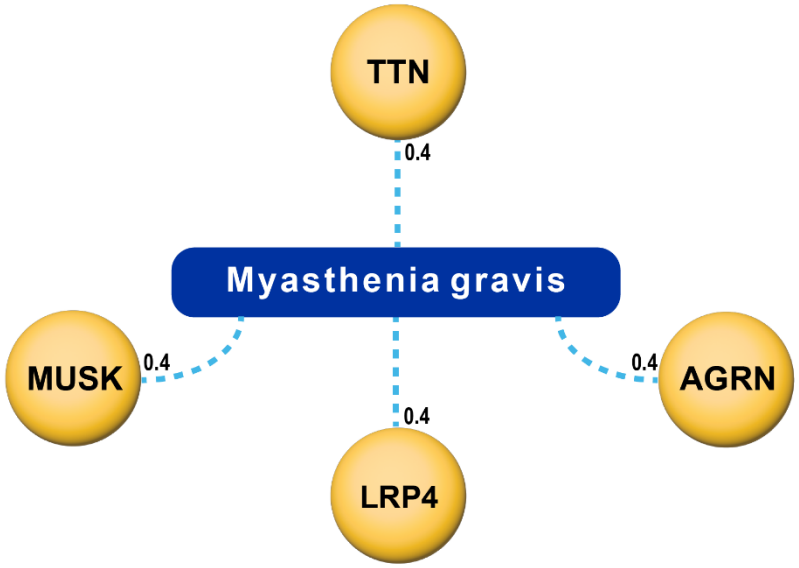


**Figure 10.** Genes associated with myasthenia gravis based on data from the CAS Content Collection. Only genes with an association score [705] greater than 0.4 and with at least 10 records are shown here. Color corresponds to association score with yellow corresponding to association scores of 0.4. The nature of the line indicates association source with dashed lines indicating a majority of records resulting from text mining.

**Table 3.** List of genes associated with myasthenia gravis (MG), as shown in Figure 10, with the association type as causal or contributing.

| Gene | Association score | Protein | Expression profile, function and other diseases | Myasthenia gravis (MG) |
|---|---|---|---|---|
| AGRN [706] | 0.4 | Agrin | Agrin is a glycosylated protein involved in activation of MuSK and the development of NMJs. [707] Two isoforms of agrin exist – neural agrin and muscle agrin. [707] Abnormalities in agrin have been observed in Alzheimer's [708, 709] and Parkinson's [710] diseases and agrin targeted therapy has also been suggested for treatment of cardiac injury. [711] Agrin's role in immune system has also been explored. [712] | Autoantibodies against agrin have been detected in individuals suffering from MG. [707, 713-715] Mice immunized with agrin generated agrin antibodies and exhibited reduced muscle weakness along with morphological changes in NMJs. [716] |
| LRP4 [717] | 0.4 | Low-density lipoprotein (LDL) receptor related protein 4 | LDL receptor related protein 4 is a receptor with a single transmembrane domain that binds to neural agrin and induces activation of MuSK leading to development of NMJs. [707] LRP4 has been implicated in neurological disorders. [718] | Similar to agrin, autoantibodies against LRP4 have been detected in individuals with MG [715, 719-721] – especially true of individuals suffering from double-seronegative myasthenia gravis. |
| MUSK [722] | 0.4 | Muscle associated receptor tyrosine kinase (MuSK) | The agrin-LRP4 complex binds to and activates MuSK, a receptor tyrosine kinase, which in turn interacts with other proteins (including docking-protein 7 and tumorous imaginal disc 1) to eventually cause clustering of acetylcholine receptors in the NMJs. [723, 724] Similar to agrin, MuSK is also a single transmembrane domain protein. [725] Involvement of MUSK has been studied in the context of muscle disorders including congenital myasthenic syndrome [726, 727] as well as fetal akinesia deformation sequence (FADs) [728, 729] a rare lethal disorder affecting infants. [730, 731] | MuSK-MG is a subtype of MG characterized by an acute onset [725, 732] and seemingly appear to be associated with worse outcomes than AChR antibody MG. [733] MuSK-MG tends to show greater prevalence among females [734] with recent studies published by researchers in China showing similar trends. [735, 736] Autoantibodies against MuSK prevent binding of LRP4 to MuSK disrupting NMJs. [737] |
| TTN [738] | 0.4 | Titin | Titin is one of the largest proteins in the human body and is composed of 27,000-34,000 amino acid residues. [739] Along with actin and myosin, titin is integral for muscle contraction. [740] Diseases arising due to mutations in the TTN gene are referred to as titanopathy and characterized by muscle weakness. [741-743] | Autoantibodies against titin have been reported in MG patients with thymoma. [744-746] |

## Landscape analysis of data on ALS, HD, and MG in CAS Content Collection

We focused our attention to the three rare diseases, ALS, HD, and MG, to perform a deeper dive into the publication landscape as reflected in the CAS Content Collection, in order to identify and understand indistinct connections and correlations in these areas.

## Documents yearly growth and geographic distribution

A look at journal and patent publication trends specific to the three diseases in focus indicates the following:

- Publications related to ALS show a steady incline over the last two decades with journal publications increasing by over 20% and the patent publications – by the impressive ~70% over 2019 to 2022 (Figure 11A).
- Growth in journal publications related to HD exhibit an upward trend increasing consistently till 2012, followed by a few years of pleateauing and growth in the period 2019-2021. Patent publications grow consistently after 2018 (Figure 11B).
- For MG, journal publications exhibit slow but generally consistent growth.Patent publications on the other hand appear to grow consistently after 2018, after years of pleateauing (Figure 11C).
- For all three diseases journal publications outnumber the patent publications.
- Comparison of geographical distribution of patent assignees in the three diseases areas indicate a high degree of overlap, with countries such as the United States (USA), China (CHN), South Korea (KOR), Japan (JPN), Germany (DEU), Switzerland (CHE), the United Kingdom (GBR), and France (FRA) being common amongst the three. Denmark (DEN) shows up in the top 10 countries or regions for patent assignees in ALS and HD while Israel (ISR) features in the top 10 for ALS and MG (Figure 11D-F).

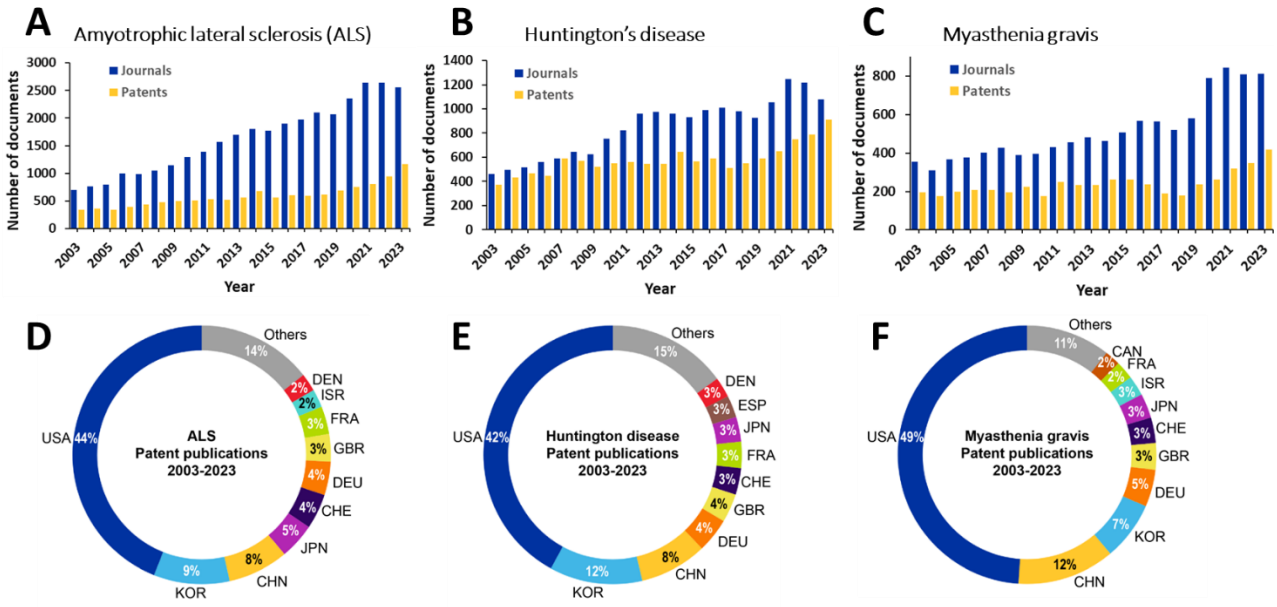


**Figure 11.** Publications for specific rare diseases: (A) amyotrophic lateral sclerosis (ALS), (B) Huntington's disease (HD) and (C) myasthenia gravis (MG). Donut graphs showing geographical distribution of patent assignees (both non-commercial and commercial organizations) for each of three diseases: (D) ALS, (E) HD and (F) MG. Countries are indicated by their standard three letter

codes – United States (USA), South Korea (KOR), China (CHN), Japan (JPN), Switzerland (CHE), Germany (DEU), United Kingdom (GBR), France (FRA), Israel (ISR), Denmark (DEN), Spain (ESP), Canada (CAN). Data includes journal and patent publications related to each individual rare disease sourced from the CAS Content Collection for 2003-2023.

The relative growth in the number of documents related to the three rare diseases in the CAS Content Collection in the last two decades (2003-2023) is shown in Figure 12. While MG exhibited the fastest growth in the years 2003-2006, ALS took the lead since 2014, with nearly 8% relative growth in 2023. This increase coincides with and therefore might be attributed to the viral "ice bucket" challenge that started in 2014.

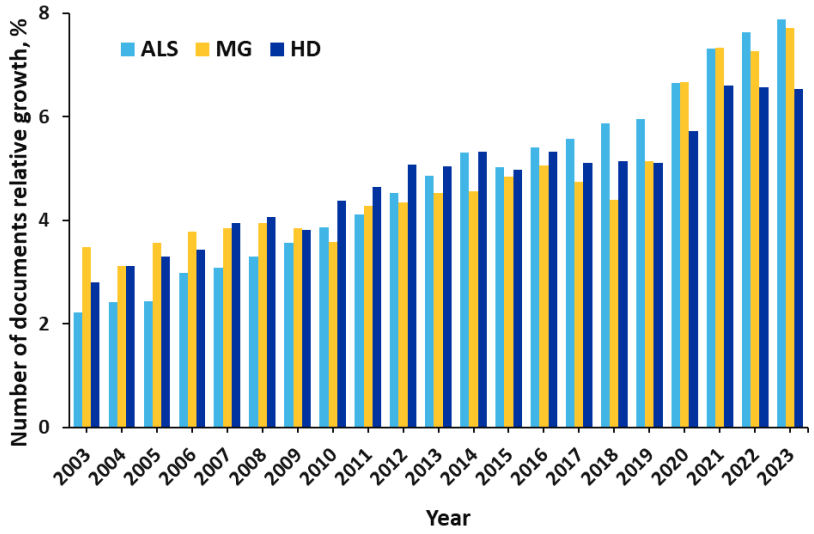


**Figure 12.** Relative growth in the number of documents related to ALS, MG, and HD in 2003-2023.

Using our access to robust CAS indexing data, we further explored co-occurrences of the three rare diseases – ALS, HD, and MG, with a host of concepts such as other non-rare and rare diseases (Figure 13A), therapy types and drugs (Figure 13B), as well as proteins and cells (Figure 13C).

## Disease comorbidities

*Amyotrophic lateral sclerosis (ALS)*

Hypertension and dyslipidemia are the most commonly reported comorbidities.[747] These results are of particular interest considering the debate related to the protective role of hypertension and other cardiovascular disorders for the prognosis and survival of ALS.[748, 749] The occurrence of autoimmune diseases in ALS patients is frequently reported, but little is known about the related clinical phenotype.[750] Association of ALS and cancer (overall cancer, as well as certain specific cancers) has been examined, and the results have been ambiguous and inconsistent regarding the risk of cancer in general, and of specific cancers.[751-754] A study examined co-occurrences of ALS and multiple sclerosis, both associated with upper motor neuron degeneration, checking the possibility for common biological pathways. The study concluded

though that rather than a shared biology, the co-occurrences are random, although a common risk factor cannot be excluded.[755]

*Huntington's disease*

Examination of comorbidities associated with HD showed depression as the most common, affecting nearly 43% of patients, with females more frequently affected than males. [756] Other reported comorbidities of HD include dementia (~ 38% of patients), urinary incontinence (over 32.% of patients), extrapyramidal and movement disorders (over 30% of patients), dysphagia (nearly 30% of patients), and disorders of lipoprotein metabolism (over 28% of patients). [756] Another study found that the prevalence of comorbidities, especially in the musculoskeletal, cardiovascular, and psychiatric diseases, was higher in patients with HD than in a control group of healthy individuals. [757] The observed psychiatric comorbidities comprise obsessive-compulsive disorder, depression, insomnia, bipolar affective disorders, dementia, and neurosis. [757] A recent study reported higher incidence rate of multiple comorbidities, such as obsessive-compulsive disorder, psychosis, communication disorders, depression, anxiety, dementia, and others, in individuals with adult-onset HD than in controls; in patients with juvenile-onset HD, the incidence rates of epilepsy, and acute respiratory symptoms have been found higher. [758] Reports exist of the co-occurrence of HD with ALS. [759] The number of reported cases of co-occurrence are low, which obstruct systematic observational studies or clinical trials. A single case of multiple sclerosis with comorbid HD has been reported. [760]

*Myasthenia gravis*

Patients with MG may be associated with autoimmune as well as non-autoimmune comorbidities. [761, 762] Autoimmune comorbidities such as autoimmune thyroiditis, followed by systemic lupus erythematosus, and rheumatoid arthritis have been reported as the most frequent comorbidities of MS. [763] Co-occurrence of thymoma MG and late-onset MG with cardiomyositis and subclinical cardiac dysfunction have been reported, however, these conditions have not been considered a significant risk. Lymphomas and some other cancers have been documented with a slightly higher frequency, autoimmune MG does not appear to be a separate cancer risk factor. [763] MG has been reported in 0.2% of the diagnosed cases of autoimmune thyroid disease. Pernicious anemia, psoriasis, systemic vasculitis, and other disorders have also been reported. [761-764] The prevalence of autoimmune comorbidity is different for MG subtypes: individuals with early-onset MG are more likely to develop an additional autoimmune disease than those with late-onset MG. [763] Another group of diseases co-occurring frequently with MG are cardiovascular diseases. Arterial hypertension is noted to prevail in patients with MG. [764] With respect to cancers – lymphoma, breast cancer, and lung cancer have been found more common in the group of MG patients. [762, 764] Mental health disorders such as depression and anxiety are frequent among MG patients. Concurrent MG and ALS have also been registered in many cases. [762, 764]

The results of examination of co-occurrences of ALS, HD, and MG terms with other rare and non-rare diseases in the CAS Content Collection are illustrated in Figure 13A. ALS and HD most frequently co-occurs with Alzheimer's, and Parkinson's diseases, and multiple sclerosis, as well as between themselves. MG most frequently co-occurs with multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus (Figure 13A).

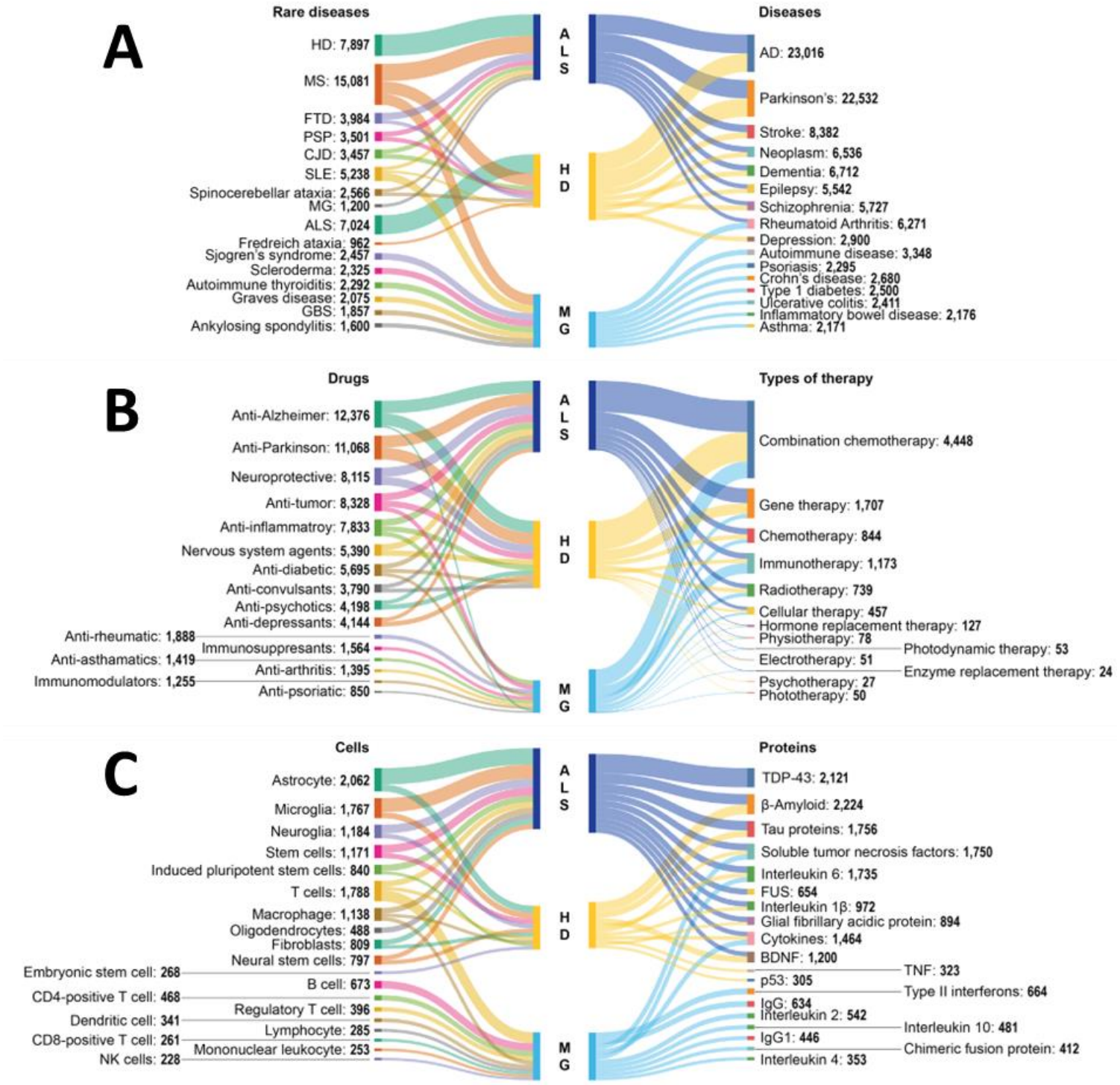


**Figure 13.** Co-occurrences of amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and myasthenia gravis (MG) with various concepts such as (**A**) other rare and non-rare diseases, (**B**) types of therapy and drugs used to treat symptoms and (**C**) cells and proteins. Data includes both patent and journal publications sourced from the CAS Content Collection for the period 2003-2023 in the field of rare diseases. Abbreviations: HD – Huntington's disease, MS – multiple sclerosis, FTD – frontotemporal dementia, PSP – progressive supranuclear palsy, CJD – Creutzfeldt-Jakob disease, SLE – systemic lupus erythematosus,

MG – myasthenia gravis, ALS – amyotrophic lateral sclerosis, GBS – Guillain Barre syndrome and AD - Alzheimer's disease.

## Types of therapy

Combination therapies are the most common type of therapy for the three rare diseases, according to the co-occurrence analysis on data from the CAS Content Collection (Figure 13B). Current research indicates that drugs acting at a single target may be insufficient for the treatment of multifactorial neurodegenerative diseases such as HD and ALS, typified by the coexistence of multiple etiopathologies including oxidative stress, protein misfolding and aggregation, mitochondrial dysfunction, inflammation, and metal accumulation at the sites of neurodegeneration. Clearly, combination drug therapy of neurodegenerative diseases with multifunctional remedies exhibiting diverse biological properties is supposed to have distinct advantage. [765]

ALS and HD frequently co-occur with gene therapy, while for MG, immunotherapy is the second most frequently occurring after combination therapy (Figure 13B). Indeed, with respect to ALS, over 50 genes have been identified as either cause or modifier in ALS and ALS/frontotemporal dementia spectrum disease. Substantial effort has been made to discover pathways underlying the pathogenesis of these gene mutations. Accordingly, targeting etiologic genes to suppress their toxic impacts have been investigated widely, with the major strategies including: removal or inhibition of abnormally transcribed RNA using miRNA or antisense oligonucleotides (ASOs); degradation of abnormal mRNA using RNA interference (RNAi); decrease or inhibition of mutant proteins by using, e.g., antibodies against misfolded proteins; and/or DNA genome editing with methods such as CRISPR or CRISPR/Cas. [766] The favorable results of these studies have resulted in application of some of these strategies in clinical trials for ALS, especially for C9orf72 and SOD1. [766-769] Regarding HD, gene therapies are being explored using genetic material to ramp up expression of genes whose functions are declined or are damaged over the course of the disease, to boost the brain and body's natural resilience against disease progression. [770] As a monogenic disease, HD is a good target for gene therapy approaches, including the use of programmable endonucleases. A protocol for HTT gene knock-out using a modified Cas9 protein (nickase, Cas9n) has been recently tested with promising results. [771]

Regarding MG, immunotherapeutic biologics are emerging as important therapeutic tools. The monoclonal antibody eculizumab has been approved by the US FDA for refractory MG on the basis of a Phase III trial. [772] Another monoclonal antibody, rituximab, is in advanced stage of clinical trials. A selection of newer anti-CD20 antibodies such as ocrelizumab (CAS RN: 637334-45-3), ofatumumab (CAS RN: 679818-59-8), obinutuzumab (CAS RN: 949142-50-1), ublituximab (CAS RN: 1174014-05-1) or inebilizumab (CAS RN: 1299440-37-1) are also being tested. [772] Enhanced availability of new biologics provides targeted immunotherapies and the chance to develop more specific therapies for MG.

## Drugs

A co-occurrence search in the CAS Content Collection showed the highest frequency of co-occurrence of ALS and HD with anti-Alzheimer and anti-Parkinson drugs (Figure 13B).

For example, ropinirole, a drug used to treat Parkinson's disease, has showed potential in delaying the progression of ALS. [773] The multifunctional brain permeable iron chelator M30 was shown to possess neuroprotective activities against various neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, and ALS. [774, 775] Recently, allopurinol (CAS RN: 315-30-0) and carvedilol (CAS RN: 72956-09-3), medications used to manage gout and high blood pressure, respectively, were reported to significantly reduce the risk of developing ALS, Alzheimer's, or Parkinson's disease. [776, 777]

MG frequently co-occurs with immunosuppressant and anti-rheumatic drugs (Figure 13B). Immunosuppressant medications act to lessen the immune system's response in order to avoid the immune attacks on NMJs, thereby limiting muscle fatigue. Common immunosuppressive medications used in treating MG include prednisone (CAS RN: 53-03-2), azathioprine (CAS RN: 446-86-6), cyclophosphamide (CAS RN: 50-18-0), methotrexate (CAS RN: 59-05-2), tacrolimus (CAS RN: 104987-11-3), and mycophenolate mofetil (CAS RN: 128794-94-5). [778-782] Patients with rheumatoid arthritis exhibit high prevalence of MG compared to the general population. [783] The rheumatoid arthritis drug abatacept has been reported to prevent MG in clinical trial. [782] Another drug used in the treatment of rheumatoid arthritis, rituximab (CAS RN: 174722-31-7), has been also shown able to reduce the risk of deterioration in MG. [784]

Since there is no cure for these rare diseases, drug repurposing studies have been intensely searching to identify existing drugs that could be repositioned to be used as viable treatment options. As the pharmaceutical development process is both time-consuming and costly, drug repurposing provides a chance to accelerate it by exploring the beneficial effects of agents approved for other disorders. These drugs have established safety profiles, pharmacokinetic description, formulations, dosages, and manufacturing procedures. Recently, *in silico* pharmacology has been widely applied and various computer applications including machine learning and artificial intelligence approaches have been explored in identifying potential drugs for repurposing to various diseases.

There have been number of studies on the potential of old drugs for the treatment of neurodegenerative diseases, including HD and ALS. [785] Tetrabenazine (CAS RN: 58-46-8) has been developed as antipsychotic drug but has been later repurposed for diseases involving abnormal, involuntary hyperkinetic movements, such as HD. [786] Another antipsychotic, tiapride (CAS RN: 51012-32-9), has been also tested for the treatment of HD. [787] Olanzapine (CAS RN: 132539-06-1) [786, 788], risperidone (CAS RN: 106266-06-2)[789], quetiapine (CAS RN: 111974-69-7)[790] are also antipsychotic drugs widely prescribed for the treatment of the motor and behavioral symptoms of HD. [785] Other examples of drugs under clinical trial to be repurposed for the treatment ALS include the anti-cancer masitinib (CAS RN: 790299-79-5), the anti-inflammatory ibudilast (CAS RN: 50847-11-5), the antiretroviral triumeq (CAS RN: 1319715-09-7), the anticonvulsant retigabine (CAS RN: 150812-12-7), and the antiestrogen tamoxifen (CAS RN: 10540-29-1). [785]

## Proteins

A search for co-occurrence with proteins showed that ALS exhibits the highest co-occurrence with TDP-43 (Figure 13C). TDP-43 (TAR DNA-binding protein 43) is a key pathological hallmark associated with ALS and related motor neuron diseases. [791] Loss of TDP-43 from the nucleus and abnormal accumulation of TDP-43 aggregates in the cytoplasm of affected neurons is a prominent pathological feature observed in the majority (>97%) of cases, particularly in

sporadic ALS. [218, 792-794] TDP-43 pathology correlates with disease severity and progression, suggesting a central role in ALS pathogenesis. [224]

While HD etiology has been traditionally associated with abnormalities in the huntingtin protein, recent research has explored the involvement of β-amyloid and tau (τ) protein, typically associated with Alzheimer's disease, in HD pathology, as reflected by the frequent co-occurrence of these proteins with HD in the CAS Content Collection (Figure 13C). Studies have shown the presence of β-amyloid deposits as well as elevated levels of phosphorylated tau in the brains of HD patients, particularly in regions affected by neurodegeneration. [795-798]

## Cells

Astrocytes and microglial cells are the most frequently co-occurring cell types with ALS and HD in the rare diseases-related documents of the CAS Content Collection, while MG exhibits high co-occurrence with T-cells and B-cells (Figure 13C). While ALS is traditionally considered a motor neuron disease and HD – a neuronal disorder caused by mutant huntingtin protein (mHTT), emerging evidence suggests that non-neuronal cells, particularly astrocytes, microglia, and other types of neuroglia, play crucial roles in ALS and HD pathogenesis. [162, 799-803]

Astrocytes, the most abundant glial cells in the central nervous system, are implicated in ALS and HD through various mechanisms. [799, 804, 805] Reactive astrocytes can secrete toxic molecules, such as pro-inflammatory cytokines and ROS, contributing to neuronal damage and death. Dysfunctional astrocytes also fail to provide adequate support to neurons, impairing their survival and function. Furthermore, mutations in genes like SOD1 and C9orf72, associated with familial ALS cases, have been shown to induce astrocyte dysfunction, exacerbating disease progression. [806-808] Reactive astrocytes in HD exhibit altered morphology and dysregulated function, including impaired glutamate uptake and disrupted calcium signaling. [809-811] Dysfunction of astrocytes contributes to excitotoxicity, oxidative stress, and neuronal dysfunction in HD. Additionally, astrocytes expressing mHTT can release toxic factors, exacerbating neuronal damage and disease progression. [812-814]

Microglia, the resident immune cells of the central nervous system, play dual roles in ALS and HD pathology. [799, 802, 815-817] While initially recruited to sites of neuronal injury to clear cellular debris and promote tissue repair, microglia can become chronically activated and contribute to neuroinflammation and neurotoxicity. Dysregulated microglial responses, characterized by the release of pro-inflammatory cytokines and neurotoxic factors, have been implicated in motor neuron degeneration. Modulating microglial activation and promoting their neuroprotective functions represent potential therapeutic strategies for ALS and HD.

Other neuroglial cells, such as oligodendrocytes and NG2 glia, may also contribute to ALS and HD pathology. [801, 818-820] Oligodendrocyte dysfunction can disrupt myelination and impair neuronal signaling, contributing to cognitive and motor impairments. NG2 glia, also known as oligodendrocyte progenitor cells, respond to injury and participate in remyelination processes. Dysregulation of these neuroglial cell types may exacerbate neuronal dysfunction and degeneration in ALS and HD.

## Overview of substance data

We leveraged our access to the CAS Registry, consisting of data for >250 million substances, and examined substances belonging to diverse classes such as small molecules, protein/peptide sequences, nucleic acid sequences, and others, explored in the documents related to ALS, HD, and MG in the CAS Content Collection (Figure 14). For all three diseases small molecules constituted the largest fraction of explored substances (Figure 14, right column). While for journal publications (Figure 14, left column) the growth in the number of explored substances does not exhibit any particular trend, for patents there is clear upward trend in the number of substances as seen by their relative growths (Figure 14, middle column). All three classes of substances (small molecules, protein/peptide sequences, and nucleic acid sequences) show an increase in patent publications indicative of commercial interest in developing these substances as therapeutics. In particular, the nucleic acid sequence and small molecule sub-class of substances exhibit a marked increase around 2018-2019 for ALS and HD, respectively. Some specific representative substances from the protein/peptide classes are displayed in Figure S3 in the Supporting Information and include immunosuppressive agents such as cyclosporin (CAS RN: 59865-13-3), chemotherapeutic agents such as actinomycin D (CAS RN: 50-76-0) and peptide hormone amylin (CAS RN: 106602-62-4). Other protein/peptide molecules co-occurring frequently with ALS, HD and MG include antibodies such as the CD-52 directed antibody alemtuzumab (CAS RN: 216503-57-0), VEGF-A directed antibody bevacizumab (CAS RN: 216974-75-3), and α4 integrin directed antibody natalizumab (CAS RN: 189261-10-7), among others.

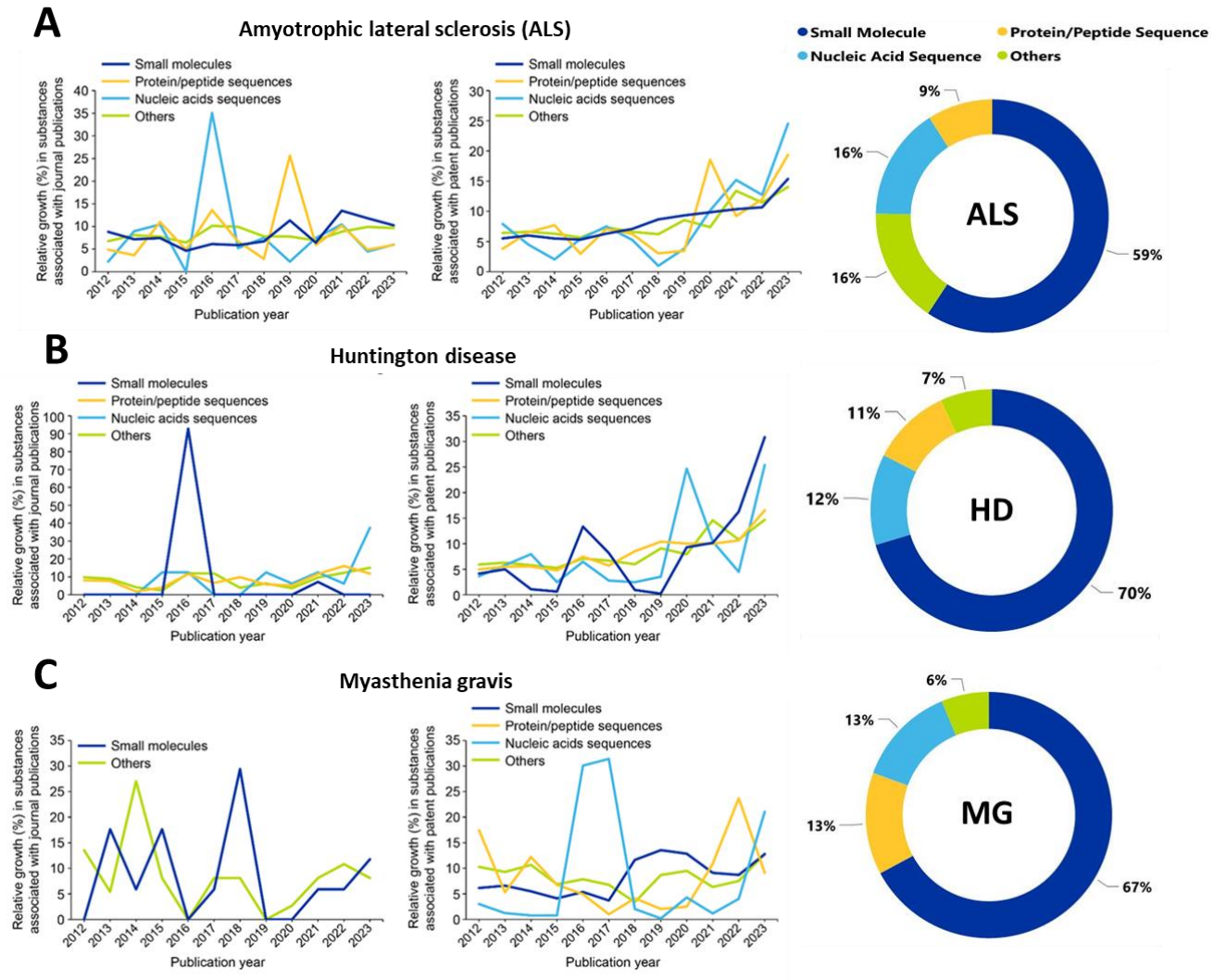


**Figure 14.** Substance data from the CAS Registry associated with (**A**) amyotrophic lateral sclerosis (ALS), (**B**) Huntington's disease (HD) and (**C**) myasthenia gravis (MG). Data includes substances associated with both patent and journal publications sourced from the CAS Registry and the CAS Content Collection for the period 2012-2023.

## 4. Capital investment

Capital investment data from Pitchbook – an online platform for investment data, reveals a more or less consistent level of capital that has been invested in the fields of ALS, HD, and MG over the past 10 years (Figure 15) while the number of deals shows a moderate increase during the same period. Interestingly, there is a mild decline in the amount of money invested in this field over the last 3 years (2021-2023) which could be indicative of a slight decrease in commercial interest but the exact reason for this remains unknown. In terms of the geographical distribution of capital investment in the field of rare diseases, the US led with respect to capital investment from 2013 to 2023, followed by Belgium, the Netherlands, and the UK (Figure 16A). The investment in the US is ~14 times that of the next top contributor-Belgium and ~27 times that of

the Netherlands. Growth in the capital investment made from 2013-2023 for the few leading countries/regions (Figure 16B) shows a moderate overall increase till 2021, post which it shows a minor dip till 2023. Of note, the capital investment by Belgium and the UK has increased in the last 2 years (2021-2023).

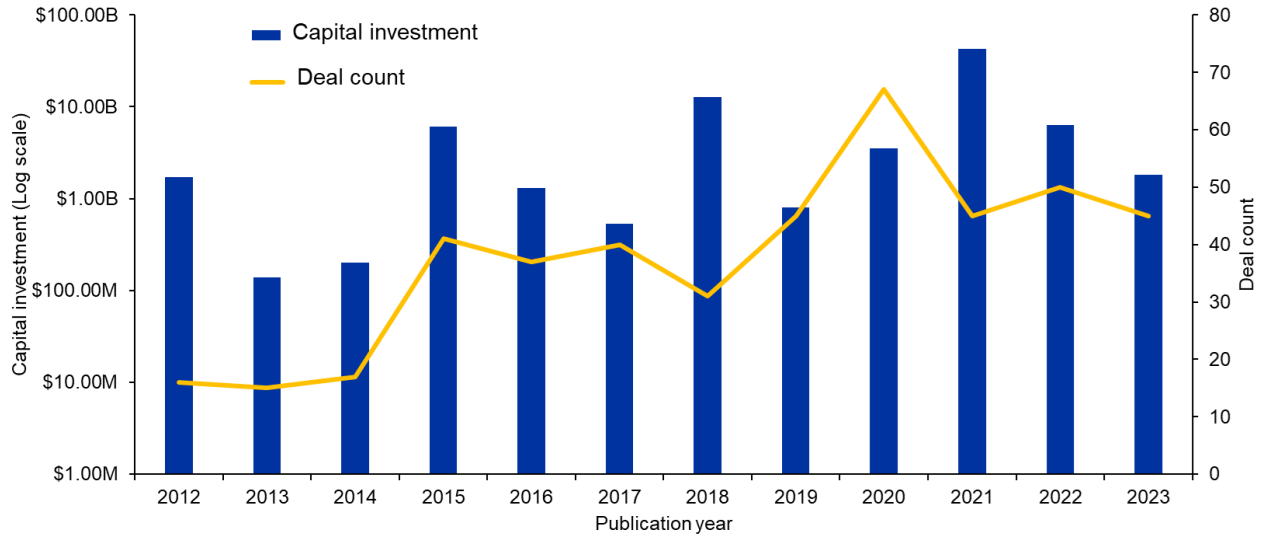


**Figure 15.** Commercial interest in rare diseases (data sourced from PitchBook). Capital invested and deals related to rare diseases (ALS, HD, and MG) for the past decade (2012−2023).

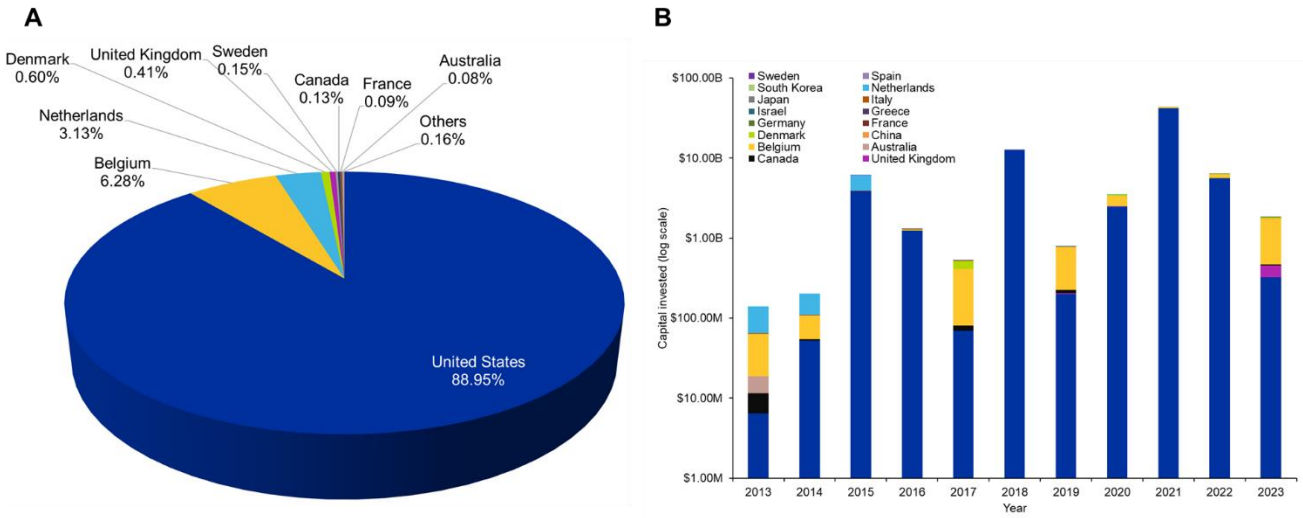


**Figure 16. (A)** Geographical distribution of the number of companies engaged in the field of rare diseases (ALS, HD, and MG). **(B)** Growth in the number of deals in the field of rare diseases by different countries/regions from 2013 to 2022.

A closer look at the data suggests that life sciences-based industries are the top investors followed by oncology-based and health technology industries (Figure 17). Vaccinex has the maximum number of deals in this field. Vaccinex lead drug candidate, pepinemab (CAS RN: 2097151-87-4), blocks semaphorin 4D (SEMA4D), a key driver of neuroinflammation. This drug

has the potential as a disease-modifying treatment for HD, Alzheimer's, and other neurodegenerative diseases and is currently in Phase II clinical trials. [821, 822] Similarly, Cytokinetics is investing in diseases linked to neuromuscular junction such as ALS. [823] Sangamo Therapeutics is working towards the preclinical development of a zinc finger transcriptional repressor targeting the SCN9A gene as a novel therapy for peripheral neuropathic pain which could be effective against ALS. [824] These investment trends indicate the steady interest of companies in the field of rare diseases such as ALS, HD, and MG.

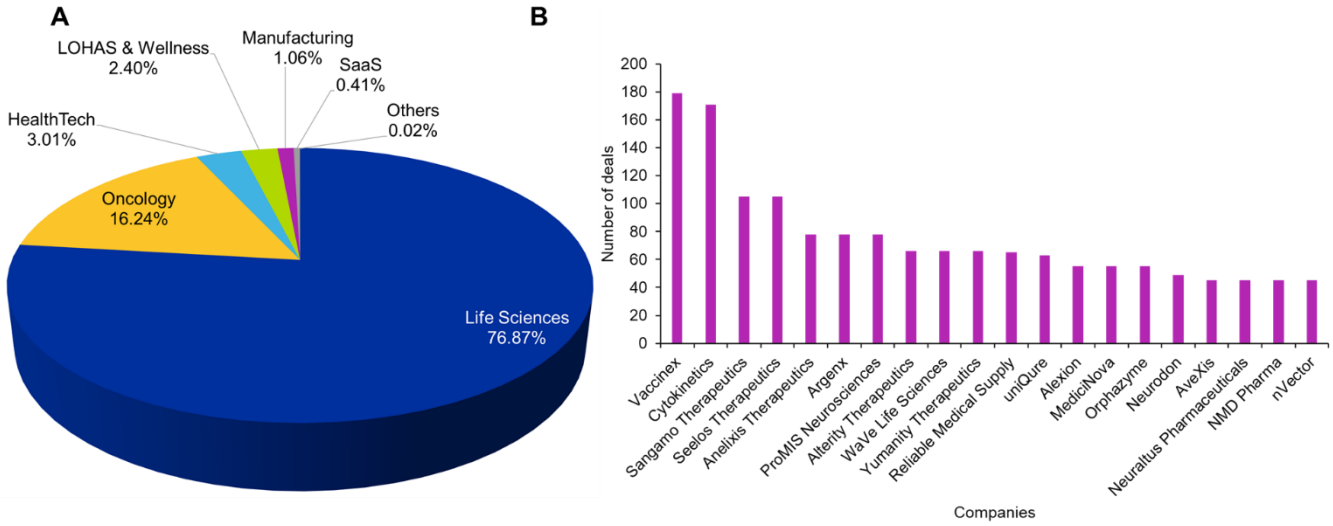


**Figure 17. (A)** Sector-wise distribution of various industry types investing in the field of rare diseases (ALS, HD, and MG) **(B)** Growth in the number of deals in the field of rare diseases by different companies from 2013 to 2022.

## 5. Therapeutic Development Pipelines

## Commercial preclinical development

Nearly 250 substances are being researched and developed preclinically for the treatment of ALS, HD, and MG (Table 4) The vast majority (74%) of these substances are for the treatment of ALS but therapies for the treatment of HD (18%) and MG (8%) are also in the development pipeline (Table 4). A wide range of therapies are being investigated. Small molecule drugs dominate in the total number of drug candidates followed by gene, antibody, RNA, antisense oligonucleotide (ASO), and stem cell therapies, amongst others (Figure 18). Small molecule drugs make up about 50% of the drug candidates for ALS and MG, in contrast to only 10% for HD where gene therapy, RNA intererence agents, and other biologic treatments dominate (Figure 18).

**Table 4**. Rare disease therapeutic drug candidates in commercial preclinical development (Source: https://clinicalintelligence.citeline.com/)

| Therapy type | Drug | Mechanism | Company, location |
|---|---|---|---|
| **Amyotrophic lateral sclerosis** | | | |
| Antibody therapy | VTX-001 | Protein degrader, targeting oxidized phosphatidylcholines | VectoryTx, Netherlands |
| | VTX-002 | Protein degrader; TDP-43 inhibitor | VectoryTx, Netherlands |
| Antisense oligonucleotide therapy | ALS therapy, AcuraStem | PIKFYVE inhibitor | AcuraStem, USA |
| | ALS therapy, AcuraStem | SYF2 pre-mRNA splicing factor antagonist | AcuraStem, USA |
| | ALS therapy, AcuraStem | Unc-13 homolog A agonist | AcuraStem, USA |
| | ALS therapy, Genetic Leap-1 | Targeting FLCN | Genetic Leap, USA |
| | ALS therapy, Maze Therapeutics | UNC13A inhibitor, Protein synthesis inhibitor | Maze Therapeutics, USA |
| | ALS therapy, Regulus | MicroRNA inhibitor | Regulus Therapeutics, USA |
| | AMX-114 | Calpain 2 inhibitor | Amylyx Pharmaceuticals, USA |
| | AS-202 | Phosphatidylinositol 3-phosphate 5-kinase inhibitor; TDP-43 inhibitor | AcuraStem, USA; Takeda, Japan |
| | BMD-001 | MicroRNA inhibitor | Biorchestra, South Korea |
| | QRL-202 | TDP-43 inhibitor | QurAlis, USA |
| | QRL-204 | Undisclosed | QurAlis, USA |
| CAR T-cell therapy | ALS therapy, PolTREG | T cell stimulant | PolTREG, Poland |
| Cognition enhancer, neuroprotectant | ADV-368 | Sigma 1 receptor agonist, sigma 2 receptor antagonist | Advantx Pharmaceuticals, USA |
| | AGS-499 | Telomerase stimulant | Neuromagen Pharma, Israel |
| | Alpha-cyclodextrin derivatives | Arachidonic acid inhibitor, down-regulates the activity of the phosphatidylinositol cycle | ASDERA, USA |

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|---|---|---|
| ALS therapy, Myrobalan Therapeutics | Colony stimulating factor 1 receptor antagonist | Myrobalan Therapeutics, USA |
| ALS therapy, Myrobalan Therapeutics | G protein-coupled receptor 17 antagonist | Myrobalan Therapeutics, USA |
| ALS therapy, Nevrargenics | RAR modulators | Nevrargenics, UK |
| ALS therapy, WaveBreak | TDP-43 inhibitor | WaveBreak, USA |
| ALTA-808 | TDP-43 inhibitor | Alteron Therapeutics, USA |
| ALS therapy, Sharp Therapeutics | Undisclosed | Sharp Therapeutics, USA |
| ALS therapy, Yumanity Therapeutics | Undisclosed | Kineta, USA |
| ALS therapy, Yumanity Therapeutics | Undisclosed | Merck & Co., USA |
| ALS therapy, Yumanity Therapeutics | Undisclosed frontotemporal lobar dementia therapy | Kineta, USA |
| Anhydrous enol-oxaloacetate, Metvital | Undisclosed | MetVital, USA |
| Antroquinonol | Ras inhibitor | Golden Biotechnology, Taiwan |
| AS-201 | Phosphatidylinositol 3-phosphate 5-kinase inhibitor | AcuraStem, USA |
| BLX-0279 | Undisclosed | Biolexis Therapeutics, USA |
| BrAD-R13 | TrkB tyrosine kinase stimulant | Shanghai Braegen Pharmaceutical, China |
| BSC-3301 | Receptor-interacting serine/threonine kinase 1 inhibitor | BiSiChem, South Korea |
| FB101 | Abl receptor tyrosine kinase inhibitor | 1st Biotherapeutics, South Korea |
| FB418 | Abl receptor tyrosine kinase inhibitor | 1st Biotherapeutics, South Korea |
| GP-119 | Undisclosed | GliaPharm, Switzerland |

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|---|---|---|---|
| | INF-11 | Undisclosed | Beijing Joekai Biotechnology, China |
| | IRX-4204 | Retinoid X receptor agonist | Io Therapeutics, USA |
| | Mitometin | Carnitine palmitoyltransferase 1 inhibitor | 2N Pharma, Denmark |
| | NB-001 | Parkin E3 ubiquitin ligase stimulant | NysnoBio, USA |
| | NMRA-CK1d | Casein kinase 1 inhibitor | Neumora Therapeutics, USA |
| | NVG-300 | Undisclosed | NervGen Pharma, Canada |
| | NX-210c | Beta 1 integrin agonist | Axoltis Pharma, France |
| | Resveratrol | Apoptosis stimulant; Reducing agent | Jupiter Neurosciences, USA |
| | Rifampicin | DNA directed RNA polymerase inhibitor | Medilabo RFP, Japan |
| | Progranulin | Undisclosed | Alpha Cognition, Canada |
| | Pur XX-01 | Beta-N-acetylglucosaminidase inhibitor | PurMinds NeuroPharma, Canada |
| | SEL-148,742 | Undisclosed | Sharp Therapeutics, USA |
| | SLS-009 | Ubiquitin ligase E3 stimulant; Protein degrader | Seelos Therapeutics, USA |
| | SMB-001 | Undisclosed | Symbinas Pharmaceuticals, USA |
| | SRT-055 series | Mitogen-activated protein kinase kinase kinase 5 inhibitor | Seal Rock Therapeutics, USA |
| Exosome therapy | AB-126 | Reduces neuroinflammation, promotes neuroprotection, and stimulates neuroregeneration | Aruna Bio, USA |
| Fusion protein therapy | PF-1802 | Undisclosed | Immunoforge, South Korea |
| Fusion protein therapy; Cytokine therapy | COYA-302 | CD80 antagonist; CD86 antagonist; Immune checkpoint modulator; Interleukin 2 receptor agonist; T cell inhibitor; T cell stimulant | Coya Therapeutics, USA; Dr. Reddy's Laboratories, India |
| Gene therapy | ABO-201 | Genome editing, C9orf72 inhibitor | Arbor Biotechnologies, USA |
| | ABO-202 | Genome editing, stathmin 2 agonist | Arbor Biotechnologies, USA; 4D Molecular Therapeutics, USA |
| | ABO-204 | Genome editing, superoxide dismutase-1 inhibitor | Arbor Biotechnologies, USA |

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|---|---|---|
| ALS therapy, AviadoBio | Gene supplementation, PGRN | AviadoBio, UK |
| ALS therapy, Hui-Gene Therapeutics | Genome (DNA) editing | HuidaGene Therapeutics, China |
| ALS therapy, Korro Bio | Genome editing, TDP-43 stimulant | Korro Bio, USA |
| ALS therapy, Maze Therapeutics | Ataxin 2 inhibitor, Protein synthesis inhibitor | Maze Therapeutics, USA |
| ALS therapy, NeuShen Therapeutics | SOD1 silencing | NeuShen Therapeutics, China |
| ALS therapy, NeuShen Therapeutics | Undisclosed | NeuShen Therapeutics, China |
| ALS therapy, Prime Medicine | Genome editing | Prime Medicine, USA |
| ALS therapy, Sangamo Therapeutics | C9orf72 inhibitor, ZFP-TF gene therapy | Alexion, UK; Sangamo Therapeutics, USA |
| ALS therapy, Scribe Therapeutics | CRISPR-Cas9 Genome editing | Biogen, USA; Scribe Therapeutics,USA |
| AMA-007 | Undisclosed | Amarna Therapeutics, Netherlands |
| ANEW-202 | Undisclosed | Anew Medical, USA |
| ANL-303 | Undisclosed | ANLBIO, South Korea |
| CTx-1000 | TDP-43 inhibitor | Celosia Therapeutics, Australia |
| CTx-2000 | TDP-43 inhibitor | Celosia Therapeutics, Australia |
| CTx-TFEBx | Undisclosed | Coave Therapeutics, France |
| ET-101 | Caveolin stimulant | Eikonoklastes Therapeutics, Japan |
| NM-301 | Undisclosed | Helixmith, South Korea; Neuromyon, South Korea |
| NM-302 | Undisclosed | Helixmith, South Korea |
| NXL-003 | Undisclosed | NeuExcell Therapeutics, USA |
| PBAL-05 | Undisclosed | Passage Bio, USA |
| SNUG-01 | Unidentified pharmacological activity | Sineugene, China |
| SOL-257 | TDP-43 inhibitor | SOLA Biosciences, USA |

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| | SOL-258 | Undisclosed | SOLA Biosciences, USA |
| | VY-SOD102 | Superoxide dismutase-1 inhibitor | Voyager Therapeutics, USA |
| Monoclonal antibody | BT-3814 | TDP-43 inhibitor | BioArctic Neuroscience, Sweden |
| | LP-005 | C5 and C3 inhibitor | LongBio Pharma, China |
| | ND-3014 | TDP-43 inhibitor | BioArctic Neuroscience, Sweden |
| | PAS-003 | Undisclosed | Pasithea Therapeutics, USA |
| | PMN-267 | TDP-43 inhibitor | ProMIS Neurosciences, Canada |
| | Anti-TDP-43 antibody, Prothena | TDP-43 inhibitor | Bristol-Myers Squibb, USA; Prothena, Ireland |
| Monoclonal antibody, humanized | ALS therapy, Mabylon | Undisclosed | Mabylon, Switzerland; SciNeuro Pharmaceuticals, USA |
| | ARGX-119 | Muscle-specific receptor kinase stimulant | Argenx, Netherlands |
| | EME-023 | Undisclosed | Epsilon Molecular Engineering, Japan |
| | Foralumab | CD3 antagonist | Tiziana Life Sciences, UK |
| | Hu-GNK-301 | Undisclosed | GeNeuro, Switzerland |
| | NC-B8 | IgG4 inhibitor | ENCEFA, France |
| | NI-308 | Immunostimulant | Neurimmune, Switzerland |
| Monoclonal antibody, murine | ALS therapy, ProMIS Neurosciences | Protein kinase C inhibitor, RACK1-targeting antibodies | ProMIS Neurosciences, Canada |
| | ALS therapy, ProMIS Neurosciences | SOD1-targeting antibodies, Superoxide dismutase-1 inhibitor | ProMIS Neurosciences, Canada |
| Neuroprotectant | AKV-9 | Protein aggregation inhibitor | Akava Therapeutics, USA |
| | ALS therapy, Amylyx Pharmaceuticals | Bax and Bak protein inhibitors | Amylyx Pharmaceuticals, USA |
| | ALS therapy, Dewpoint Therapeutics | TDP-43 inhibitor | Dewpoint Therapeutics, USA |
| | ALS therapy, Genetic Leap-2 | RNA binder targeting FLCN | Genetic Leap, USA |

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| ALS therapy, ImmunoBrain Checkpoint | Immune checkpoint modulator | ImmunoBrain Checkpoint, Israel |
| ALS therapy, Miramoon Pharma | Ryanodine receptor antagonist; Oxygen scavenger | Miramoon Pharma, Spain |
| ALS therapy, Nine Square Therapeutics | Undisclosed | Nine Square Therapeutics, USA |
| ALS therapy, NRG Therapeutics | mPTP inhibitor | NRG Therapeutics, UK |
| ALS therapy, Origami Therapeutics | Undisclosed | Origami Therapeutics, USA |
| ALS therapy, Path Biotech | Undisclosed | Path Biotech, USA |
| ALS therapy, Pikralida | Undisclosed | Pikralida, Poland |
| ALS therapy, PrecisionLife | Undisclosed | PrecisionLife, UK |
| ALS therapy, reMYND | Undisclosed | reMYND, Belgium |
| ALS therapy, Treventis | TDP-43 inhibitor | Treventis, Canada |
| ALS therapy, Zhittya Genesis Medicine | Fibroblast growth factor 1 agonist | Zhittya Genesis Medicine, USA |
| Amisodin | Superoxide dismutase-1 inhibitor | Pioneer of Rare Genopathies, South Korea |
| ALS therapy, Verge Genomics-1 | Undisclosed | Eli Lilly, USA |
| ALS therapy, Verge Genomics-1 | Undisclosed | Verge Genomics, USA |
| ATC-104 | Protein degrader; Sequestosome 1 stimulant; TDP-43 inhibitor | Autotac Bio, South Korea |
| ATH-1105 | Undisclosed | Athira Pharma, USA |
| BEN-34712 | Retinoic acid alpha receptor agonist; Retinoic acid beta receptor agonist | BenevolentAI, UK |
| BIOIO-1001 | Sirtuin 3 stimulant | BIOIO, USA |
| BL-002, Bloom Science | Microbiome modulator, live microorganisms | Bloom Science, USA |
| BREN-02 | Undisclosed | BrainEver, France |
| BT-003 | Undisclosed | BAKX Therapeutics, USA |
| CB03-154 | Potassium channel agonist | Shanghai Zhimeng Biopharma, China |

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|---|---|---|
| Donepezil hydrochloride + nebivolol hydrochloride | Acetylcholinesterase inhibitor; Beta 1 adrenoreceptor antagonist | Dr. Noah Biotech, South Korea |
| EVT-8683 | Protein degrader; Translation initiation factor 2B stimulant | Bristol-Myers Squibb, USA |
| EVT-8683 | Protein degrader; Translation initiation factor 2B stimulant | Evotec, Germany |
| FB-1002 | Unidentified pharmacological activity | 4B Technologies, China |
| FP-802 | Transient receptor potential cation channel M antagonist; NMDA receptor antagonist | FundaMental Pharma, Germany |
| Glycolic acid + D-lactic acid | Undisclosed | Neurevo, Germany |
| HLX-94 | Undisclosed | Shanghai Fosun Pharmaceutical, China |
| HS-03 | Undisclosed | Foshan Rexiu Biotechnology, China |
| ILB | Undisclosed | TikoMed, Sweden |
| iN3011-K23 | Undisclosed | iN Therapeutics, South Korea |
| IPG 008 | Hydrolase inhibitor | Nanjing Immunophage Biotech, China |
| KFRX-03 | Tyrosine kinase inhibitor (TKI) | KeifeRx, USA |
| LAUR-301 | Glial cell derived neurotrophic growth factor agonist | Lauren Sciences, USA |
| M-102 | Undisclosed | Aclipse Therapeutics, USA |
| mecobalamin | Vitamin B12 agonist | Eisai, Japan |
| MP-101 | Undisclosed | Mitochon Pharmaceuticals, USA |
| MT-2 | Undisclosed | MimeTech, Italy |
| Nibrozetone (RRx-001) | NLRP3 inhibitor and Nrf2 upregulator | EpicentRx, USA |
| OC-514 | Undisclosed | Oncocross, South Korea |
| ORY-4001 | Histone deacetylase 6 inhibitor | Oryzon, Spain |
| otaplimastat | Undisclosed | Shin Poong Pharmaceutical, South Korea |
| P-202320 | Undisclosed | EDDC, Singapore |
| Pimicotinib | Colony stimulating factor 1 receptor antagonist; Immuno-oncology therapy | Sperogenix Therapeutics, China |

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|---|---|---|---|
| | Riluzole | Dopamine receptor agonist; Glutamate antagonist; Voltage-gated sodium channel antagonist | Brain Trust Bio, USA |
| | RT-1968 | Undisclosed | Raya Therapeutic, Canada |
| | RT-1972 | Undisclosed | Raya Therapeutic, Canada |
| | RT-1978 | Undisclosed | Raya Therapeutic, Canada |
| | RT-1999 | Undisclosed | Raya Therapeutic, Canada |
| | RT-2010 | Undisclosed | Raya Therapeutic, Canada |
| | RVL-027 | Undisclosed | Unravel Biosciences, USA |
| | SAM-001 | Transient receptor potential cation channel member 1 agonist | Samsara Therapeutics, UK |
| | SAM-19272 | GTPase stimulant | Samsara Therapeutics, UK |
| | SNP-210 | TDP-43 inhibitor | SciNeuro Pharmaceuticals, USA |
| | S-oxprenolol | Beta adrenoreceptor antagonist | Actimed Therapeutics, UK |
| | TDP-43 inhibitors, Aquinnah | TDP-43 inhibitor | Aquinnah Pharmaceuticals, USA; Roche, Switzerland |
| | WD-920 | Undisclosed | Zhejiang Wenda Medical Technology, China |
| | Y-8 | Undisclosed | Neurodawn Pharmaceutical, China |
| RNA interference | ALN-SOD1 | Gene expression inhibitor, Superoxide dismutase-1 inhibitor | Alnylam, USA; Regeneron, USA |
| | ALS therapy, AviadoBio | Gene expression inhibitor, ATXN2 | AviadoBio, UK |
| | ALS therapy, AviadoBio | Gene expression inhibitor, c9orf72 | AviadoBio, UK |
| | ALS therapy, AviadoBio | Gene expression inhibitor, SOD1 | AviadoBio, UK |
| | AMT-161 | C9orf72 inhibitor; Gene expression inhibitor | uniQure, Netherlands |
| Stem cell therapy | ALS therapy, Neuroplast | Undisclosed | Neuroplast, Netherlands |
| | ALS therapy, Takeda | Undisclosed | Takeda, Japan |
| | BMS-xxxx | Not applicable | Bristol-Myers Squibb, USA; Evotec, Germany |
| | Cognistem | Undisclosed | Amniotics, Sweden |
| | CUR-201 | Undisclosed | Curamys, South Korea |

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| | CUR-202 | Undisclosed | Curamys, South Korea |
| | CUR-204 | Undisclosed | Curamys, South Korea |
| | hNPC-02 | Not applicable | Hopstem Biotechnology, China |
| | NCP-01 | Undisclosed | Hemostemix, Canada |
| **Huntington's disease** | | | |
| Antibody therapy | VTX-003 | mHTT protein inhibitor, selectively binds mutant HTT (and not normal HTT) to clear mutant HTT | VectorY Therapeutics, Netherlands |
| Anti inflammatory | IC 100-05 | Inflammasome ASC Inhibitor | ZyVersa Therapeutics, USA |
| Antisense oligonucleotide therapy | Huntington's disease therapy, Ionis | Undisclosed | Ionis, USA; Roche, Switzerland |
| Cognition enhancer | ASK-005 | Arachidonic acid inhibitor | ASDERA, USA |
| Cognition enhancer, neuroprotectant | Huntington's disease therapy, MitoRx | Reverses mitochondrial dysfunction | MitoRx Therapeutics, UK |
| | NP-001 | Oxidizing agent | Neuraltus, USA; Neuvivo, USA |
| Gene therapy | ET-101 | Caveolin stimulant | Eikonoklastes Therapeutics, USA |
| | Huntington's disease therapy, Hudiagene | DNA editing, CRISPR | HuidaGene Therapeutics, China |
| | Huntington's disease therapy, Life edit | Genome editing targeting both the T and C alleles of an exonic SNP in the HTT gene utilizing AAV vector | Life Edit Therapeutics, USA |
| | Huntington's disease therapy, Passage | Deliver functional gene utilizing AAV vector | Passage Bio, USA |
| | Huntington's disease therapy, Prime | Genome editing | Prime Medicine, USA |
| | NXL-002 | Regenerates neurons | NeuExcell Therapeutics, USA; Spark Therapeutics, USA |
| | SOL175 | Reduces abnormally folded protein | SOLA Biosciences, USA |
| | INT41 | mHTT protein inhibitor, selectively binds to mHTT protein | Vybion, USA |
| | SOL176 | Reduces abnormally folded protein | SOLA Biosciences, USA |
| | TAK-686 | Zinc finger nucleases can target regions of DNA to modify them or stop RNA from being made | Sangamo Therapeutics, USA; Takeda, Japan |

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|---|---|---|---|
| | ReS18-H | Restores function and improve survival of medium spiny neurons leading to reactivation of corticostriatal transmission | reMYND, Belgium |
| Monoclonal antibody, humanized | ATLX-1095 | HTT inhibitor | Alchemab Therapeutics, UK |
| Monoclonal antibody | Huntington's disease therapy ProMIS | Targeting protein RACK-1, Protein kinase C inhibitor | ProMIS Neurosciences, USA |
| mRNA therapy | Anima Huntingtin translation inhibitor | Gene expression inhibitor | Anima Biotech, USA;<br>Takeda, Japan |
| Neuroprotectant | AJ-201 | Transcription factor Nrf2 stimulant | Avenue Therapeutics, USA |
| | Huntington's disease therapy, BPGbio | Undisclosed | BPGbio, USA |
| | Huntington's disease therapy LoQus23 | DNA damage repair | LoQus23 Therapeutics, USA |
| | M102 | Activates Nrf2 and HSF1 | Aclipse Therapeutics, USA |
| | TQS-168 | PPARG coactivator 1 alpha agonist | Tranquis Therapeutics, USA |
| Peptide therapy | TT-P34 | Activates pathways that can bypass mHTT to reactivate CREB | Teitur Trophics, Denmark |
| | NT-0100 | Gene expression inhibitor | NeuBase Therapeutics, USA |
| PROTAC | Huntington's disease therapy, Arvinas | HTT inhibitor, E3 ubiquitin ligase stimulant, protein degrader | Arvinas, USA |
| Protein degrader | ORI-113 | HTT protein degrader | Origami Therapeutics, USA |
| Protein conformation correctors | ORI-503 | HTT proteins conformation corrector | Origami Therapeutics, USA |
| Protein degrader | SLS009 | Protein targeted autophagy | Seelos Therapeutics, USA |
| RNA interference | ALN-HTT | Gene expression inhibitor | Alnylam, USA |
| | ALN-HTT02 | Gene expression inhibitor | Alnylam, USA |
| | Huntington's disease therapy Atalanta | Gene expression inhibitor | Atalanta Therapeutics, USA;<br>Biogen, USA |
| | Huntington's disease therapy, novartis | Utilized a small hairpin RNA or short hairpin RNA for gene expression inhibition | Novartis, Switzerland;<br>Voyager Therapeutics, USA |
| | OCCT-HTT siRNA | Gene expression inhibitor, HTT inhibitor | Ophidion, USA |

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|---|---|---|---|
| RNA therapy | SMDG-HD11 | Undisclosed | S. M. Discovery Group, UK |
| Stem cell therapy | Debamestrocel | Glial cell derived neurotrophic growth factor agonist | BrainStorm Cell Therapeutics, USA |
| | HB AdMSC | Undisclosed | Hope Biosciences, USA |
| | Huntington's disease therapy, trailhead | Mesenchymal Stem Cells | Trailhead Biosystems, USA |
| | SC-379 | Glial progenitor cells | Sana Biotechnology, USA |
| Undisclosed | Huntington's disease therapy Aitia | Undisclosed | UCB, Belgium; Aitia, USA |
| **Myasthenia gravis** | | | |
| CAR T-cell therapy | CABA-201 | T cell stimulant | Cabaletta Bio, USA |
| | Equecabtagene autoleucel | Immuno-oncology therapy; T cell stimulant | Nanjing IASO Biotechnology, China |
| | KYV-101 | T cell stimulant | Kyverna Therapeutics, USA |
| Fusion protein therapy | Myasthenia gravis therapy, Rongchang Pharmaceuticals | Lymphocyte stimulant | Rongchang Pharmaceuticals, China |
| | TOL-2 | Undisclosed | Toleranzia, Sweden |
| Monoclonal antibody | EA-5 | Complement inhibitor | Lan-yi Therapeutics, China |
| | LP-005 | C5a inhibitor | LongBio Pharma, China |
| | MV-2C2 | Survivin inhibitor | MimiVax, USA |
| Monoclonal antibody, humanized | CAN-106 | Complement factor C5 inhibitor | CANbridge Life Sciences, China |
| | MIL-62 | CD20 antagonist; Immuno-oncology therapy | Beijing Mabworks Biotech, China |
| | Pozelimab | C5a inhibitor | Regeneron, USA |
| Musculoskeletal therapy | BHV-1310 | Protein degrader | Biohaven, British Virgin Islands |
| | Myasthenia gravis therapy, BioCryst Pharmaceuticals | Complement factor C5 inhibitor | BioCryst Pharmaceuticals, USA |
| | CNP-MYG | B-cell inhibitor; CD8 antagonist | Cour Pharmaceuticals, USA |

| | | | |
|---|---|---|---|
| | CV-MG-02 | Immunostimulant | CuraVac, USA |
| | Myasthenia gravis vaccine, ImCyse | Immunosuppressant | ImCyse, Belgium |
| | Myasthenia gravis therapy, NovelMed Therapeutics | Complement inhibitor | NovelMed Therapeutics, USA |
| | prednisone, Sarcomed AB | Glucocorticoid agonist | Sarcomed AB |
| | ZP-10068 | Complement C3 inhibitor | Alexion, UK;<br>Zealand Pharma, Denmark |

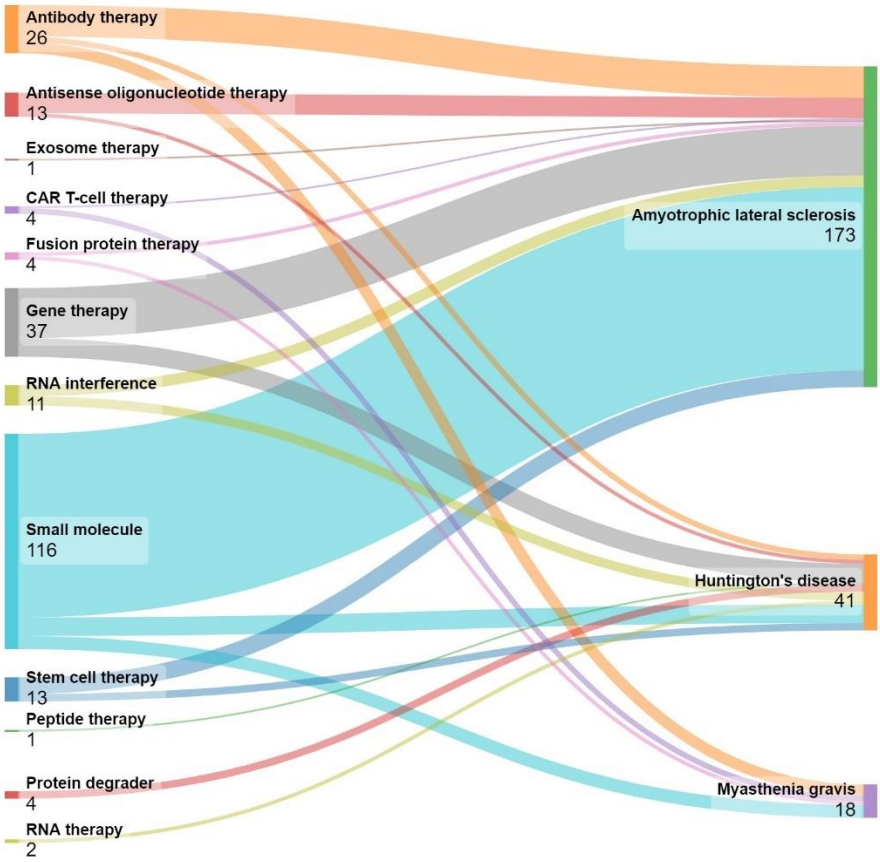


**Figure 18.** Preclinical drug therapy candidates and their respective rare disease indication currently in the development pipeline

## Clinical Trials

Clinical trials researching the treatment of rare diseases ALS, HD, and MG are explored in this section to gain an overall view of the past and current state of clinical development. Over 1000 clinical trials have been registered on the US National Institutes of Health (NIH) clinical trial website over the last 10 years for these rare diseases. In terms of sheer number, ALS has the highest number of registered clinical trials, followed by HD and MG. [825] Figure 19 shows an oscillating curve for clinical trials of these rare disease , between the years 2013 to 2023. ALS clinical trials gradually increase over the years, while HD's stayed more consistent. One note of interest is that the number of clinical trials for MG stay consistent through 2018 and then triple into 2019, maintaining consistency moving forward. One contributing factor to this surge is the US FDA approval of Solaris (eculizumab) in 2017, the first for MG, increasing industry-sponsored clinical research to monitor and develop new therapy options for patients with this rare disease.

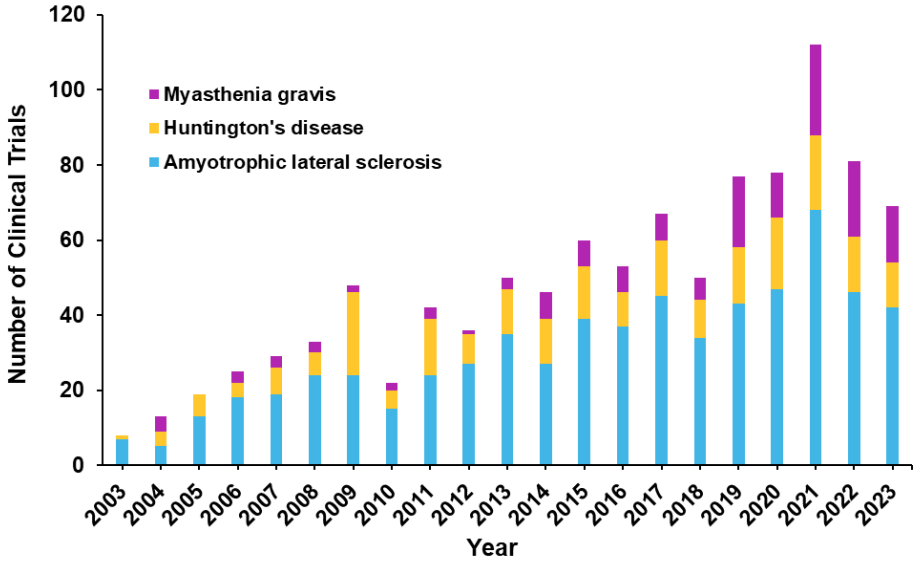


**Figure 19.** Number of clinical trials by rare disease indications for years 2003-2023

Further analysis of these rare disease clinical trials reveals that nearly half of all trials for the different indications are not phased (Figure 20A). The phase that contains the next largest group of trials is Phase II studies for ALS and HD and Phase III studies for MG. Nearly half of all clinical trials for ALS, HD, and MG have been completed (Figure 20B). The status with the next largest group of trials is the recruiting status, which is encouraging as new clinical trials are created and carried out to research the treatment of these rare diseases, offering hope to patients worldwide.

**A**

| Rare disease indication | Early Phase I | Phase I | Phase I/II | Phase II | Phase II/III | Phase III | Phase IV | NA |
|---|---|---|---|---|---|---|---|---|
| Amyotrophic lateral sclerosis | 1% | 10% | 7% | 19% | 4% | 7% | 1% | 51% |
| Huntington's disease | 2% | 14% | 6% | 22% | 0% | 1% | 1% | 53% |
| Myasthenia gravis | 2% | 3% | 2% | 16% | 4% | 26% | 2% | 45% |

**B**

| Rare disease indication | Not yet recruiting | Recruiting | Active | Completed | Withdrawn/Terminated/Suspended |
|---|---|---|---|---|---|
| Amyotrophic Lateral Sclerosis | 5% | 21% | 6% | 55% | 13% |
| Huntington's disease | 4% | 19% | 6% | 61% | 10% |
| Myasthenia gravis | 9% | 38% | 7% | 39% | 7% |

**Figure 20.** Percentage of rare disease clinical trials in various: (A) phases; (B) statuses.

Finally, representative clinical trials examining rare disease therapeutics are highlighted in Table 5 categorized by rare disease indication and therapy type. These are examined in further detail below to showcase a variety of promising therapeutic strategies, interventions, and targeted conditions in clinical development along with their status, phase, and any published results.

Therapy types in clinical development highlighted below for the treatment of ALS include cell and gene therapies along with small molecule drugs. An autologous T-cell therapy, RAPA-501, was developed by RAPA Therapeutics to address the lack of compounds for treatment of

neuroinflammation in ALS and is currently recruiting for a Phase II/III clinical trial (NCT04220190). This trial is an expansion cohort that was added to access RAPA-501 cells efficiency in standard-risk ALS patients. In this ongoing clinical trial, RAPA-501 cells were found to be safe, have multiple anti-inflammatory effects, and showed early signs of preserving pulmonary function. [826] RAPA-501 cells express both the TREG and Th2 transcription factors forkhead box P3 (FOXP3) and GATA-binding protein 3 (GATA3), are enriched for expression of the T-cell homing molecule CD103 and the ATP ectonucleotidase molecules CD39 and CD73. [827] They also suppress effector T-cell inflammatory molecules and CNS microglial cell inflammatory molecules. [827] RAPA-501 cells are also available through an expanded access clinical trial (NCT06169176) to patients living with high-risk ALS and not eligible for other ALS clinical trials. These trials will research therapy feasibility, safety, and efficacy including biomarker measurements for neuroinflammation.

Gene therapy agent, AMT-162, developed by UniQure Biopharma, is not yet actively recruiting but will soon start a clinical trial, NCT06100276, to research the use of AMT-162 in patients with rapidly progressive ALS and SOD1 mutations. AMT-162, a one-time treatment, is comprised of a recombinant AAVrh10 vector that expresses a miRNA targeting the SOD1 gene. This clinical trial will research the safety and efficacy of AMT-162, evaluating if it will silence the expression of mutant SOD1 and improve the course of ALS. [828]

Small molecule drug FB1006, fully discovered and developed using artificial intelligence (AI), is being advanced as a new potential treatment for ALS. 4B Technologies with collaborative efforts completed the development process of FB1006, from target identification and compound screening to patient enrollment, in less than 2 years. [829] Phase IV clinical trial NCT05923905 recently completed enrollment of 64 patients which will evaluate the efficacy of safety of FB1006 in the treatment of ALS patients. The trial is being conducted at the Third Hospital of Peking University and is expected to complete double-blind dosing in August 2024, followed by 1-year of clinical observation in February 2025. [829]

The last two small molecules we highlight for the treatment of ALS are both part of the HEALEY ALS Platform trial (NCT04297683). This trial is a perpetual multi-center, multi-regimen clinical trial evaluating the safety and efficacy of ALS treatments. There is a single master protocol dictating the conduct of the trials with each regimen sharing placebo patients. The first drug ibudilast is being investigated by MediciNova. A Phase I/II clinical trial NCT02714036 revealed ibudilast to be safe and showed no drug related severe adverse reactions. However, the tolerability was limited due to gastrointestinal side effects, fatigue, and insomnia. [830] Data from another completed Phase II study NCT02238626 showed ibudilast, when in combination with approved therapy Rilutek showed a marked increase in number of patients who saw no functional decline in six months comparted to Rilutek alone and it also helped increase patient lifespan. [831] Ibudilast will also be investigated in a Phase II/III clinical trial (NCT04057898) currently recruiting and enrolling up to 230 participants across the USA and Canada to evaluate the efficacy, safety, and tolerability of ibudilast for 12 months followed by a 6-month open-label extension phase. Ibudilast is a glial attenuator that suppresses pro-inflammatory cytokines IL-1β, TNF-α, and IL-6, and may upregulate the anti-inflammatory cytokine IL-10. [832] It has additionally been shown to be a toll-like receptor 4 antagonist that may contribute to its attenuation of neuroinflammation. [832] Ibudilast received both fast track [833] and orphan drug designations [834] in 2016 from the US FDA for treating ALS.

The second small molecule drug pridopidine (CAS RN: 346688-38-8), also a regimen in the HEALEY ALS Platform trial (NCT04297683), was investigated in a completed Phase II/III

clinical trial (NCT04615923). While there was no significant improvements in the primary outcome measures of disease progression and mortality rate, there were positive results reported for secondary outcome measures such as improved respiratory and speech measurements. Improvement in disease progression and neurofilament light levels (biomarker for neuronal injury) for rapidly declining ALS participants who were early in the disease were also seen. Pridopidine is also available through an expanded access clinical trial (NCT06069934) for up to 200 patients with ALS who are ineligible for other clinical trials. Pridopidine is a highly selective sigma-1 agonist. Sigma-1 receptor is highly expressed in the brain and CNS and activation by pridopidine stimulates multiple cellular pathways, including autophagy, which are essential to neuronal function and survival, and may lead to neuroprotective effects. [835] Prilenia Therapeutics was granted orphan drug designation for pridopidine in 2021 from the US FDA for treating ALS. [836]

Highlighted therapies in clinical development for the treatment of HD include antisense oligonucleotides, cell-based, and monoclonal antibody therapies along with computer based cognitive stimulation and small molecule agents. One such antisense oligonucleotide (ASO) therapeutic is Wave Life Sciences' gene silencing therapeutic, WVE-003. Interim results for Phase I/Phase II clinical trial NCT05032196, reveals that a single dose of WVE-003 (30 or 60 mg) led to a mean 35% reduction in mHTT in the cerebrospinal fluid compared to a placebo. [837] More upcoming trial findings are expected by June 2024. Phase I and Phase II/Phase III clinical trials (NCT02728115 and NCT04219241) assessing the safety and efficacy of Cellavita's NestaCell, a stem cell therapy derived from immature human dental pulp, are currently active for the treatment of HD. Another Phase III clinical trial (NCT06097780) researching NestaCell is not yet recruiting but has an estimated start date of June 2024 and will also investigate the efficacy and safety of NestaCell. A previous Phase I clinical trial revealed no serious adverse events and improved HD motor symptoms with the use of NestaCell in the treatment of HD. [838]

Another treatment of HD utilizing a computer based cognitive rehabilitation program is being researched by the Santa Cre Hospital in Spain. Researchers are currently recruiting for their study (NCT05769972) to examine the use of this method in patients with HD with expectations that the program will have a greater beneficial effect on the cognitive status of HD patients compared to control modalities such as music therapy. Monoclonal antibody therapeutic Pepinemab, a semaphorin 4D blocking antibody developed by Vaccinex, was researched in a Phase II clinical trial (NCT02481674) to determine safety, tolerability, pharmacokinetics, and efficacy. While this trial did not meet its primary endpoints, it did have a favorable safety profile, showed a reduction in brain atrophy, and improvement in decline in brain metabolic activity that is typically seen in HD progression. [821]

Lastly for the treatment of HD, Sage Therapeutics' small molecule drug SAGE-718 is currently recruiting for their Phase II/Phase III clinical trials. These trials (NCT05107128, NCT05358821, and NCT05655520) will investigate the safety, tolerability, and efficacy of these drugs for the treatment of HD. SAGE-718, a NMDA receptor positive allosteric modulator has completed initial single and multiple ascending dose clinical studies, where it demonstrated efficacy in disease-relevant populations. [839] In addition, SAGE-718 was granted both FDA Fast track designation [840] in 2022 and FDA Orphan Drug Designation in 2023. [841]

Therapy types in clinical development highlighted for the treatment of MG include antigen, cell, and fusion protein therapies along small molecule drugs. COUR Pharmaceutical is developing CNP-106, an antigen specific therapeutic designed to prevent immune mediated neuromuscular destruction and aims to reprogram the immune system to address the immunological root cause

of myasthenia gravis. [842] The not yet recruiting Phase I/II clinical trial (NCT06106672) will enroll up to 54 adult patients and assess the treatment's safety, tolerability, pharmacological properties, and efficacy. Descartes-08, a mRNA CAR T-cell therapy expressing a chimeric antigen receptor directed to B-cell maturation antigen is currently recruiting for an ongoing Phase II clinical trial (NCT04146051). Results from the Phase IIa portion of the study revealed that Descartes-08 is well tolerated and participants saw meaningful improvement in MG disease scorings. [843] Descartes-08 was granted Orphan Drug Designation by the US FDA for the treatment of MG in 2024. [844]

RemeGene is currently recruiting for its Phase III clinical trial (NCT05737160) investigating fusion protein Telitacicept for the treatment of MG. Telitacicept is constructed with the extracellular domain of the transmembrane activator and calcium modulator and cyclophilin ligand interactor receptor and the fragment crystallizable domain of immunoglobulin G. [845] Telitacicept targets two cell-signaling molecules critical for B-lymphocyte development: B-cell lymphocyte stimulator and a proliferation inducing ligand, which allows it to effectively reduce B-cell mediated autoimmune responses. Results from a previous Phase II study showed that Telitacicpet improved MG symptoms and had a good safety profile. [845] Lastly, we look at a small molecule factor D inhibitor developed by Alexion Pharmaceuticals. ALXN2050 is currently being investigated in an active Phase II clinical trial (NCT05218096) for its ability to improve the disease symptoms and the daily life of people with MG along with its safety. Seventy patients are enrolled with a study completion date of late 2025, results with be forthcoming soon.

**Table 5.** Highlighted rare disease therapeutic clinical trials

| Therapy type | Intervention | CAS RN | Sponsor, location | Status | Phase | NCT Number |
|---|---|---|---|---|---|---|
| **Amyotrophic lateral sclerosis** | | | | | | |
| Cell therapy | RAPA-501 | N/A | Rapa Therapeutics, USA | Recruiting | Phase II/ III | NCT04220190 |
| Gene therapy | AMT-162 | N/A | UniQure Biopharma, Netherlands | Not yet recruiting | Phase I/ II | NCT06100276 |
| Small molecule | FB1006 | N/A | 4B Technologies, China | Recruiting | Phase IV | NCT05923905 |
| Small molecule | Ibudilast (MN-166) | 50847-11-5 | MediciNova, USA | Completed | Phase I/ II | NCT02714036 |
| | | | | | Phase II | NCT02238626 |
| | | | | Recruiting | Phase II/ III | NCT04057898 |
| Small molecule | Pridopidine | 346688-38-8 | Prilenia, USA | Recruiting | Phase II/ III | NCT04297683 |
| | | | | Completed | Phase II/ III | NCT04615923 |
| | | | | Available | Expanded access | NCT05281484 |
| **Huntington's disease** | | | | | | |
| Antisense oligo-nucleotide | WVE-003 | 3029749-53-6 | Wave Life Sciences, USA | Recruiting | Phase I/Phase II | NCT05032196 |
| | | | | Active, not recruiting | Phase II/Phase III | NCT04219241 |
| | | | | Not yet recruiting | Phase III | NCT06097780 |
| Computer based cognitive stimulation | Virtual reality computer simulation | N/A | Santa Creu Hospital, Spain | Active, not recruiting | NA | NCT05769972 |
| Monoclonal antibody | Pepinemab | 2097151-87-4 | Vaccinex, USA | Completed | Phase II | NCT02481674 |
| Small molecule | SAGE-718 | 1629853-48-0 | Sage Therapeutics, USA | Recruiting | Phase II | NCT05107128 |
| | | | | | Phase II | NCT05358821 |
| | | | | | Phase III | NCT05655520 |
| Stem cell therapy | NestaCell | N/A | Azidus, Brazil | Active, not recruiting | Phase I | NCT02728115 |
| | | | | Active, not recruiting | Phase II/Phase III | NCT04219241 |
| | | | | Not yet recruiting | Phase III | NCT06097780 |
| **Myasthenia gravis** | | | | | | |
| Antigen therapy | CNP-106 | N/A | COUR Pharmacetucial, USA | Not yet recruiting | Phase I/II | NCT06106672 |
| Cell therapy | Descartes-08 | 2784598-58-7 | Cartesian Therapeutics, USA | Recruiting | Phase II | NCT04146051 |
| Fusion protein | Telitacicept | 2136630-26-5 | RemeGen, China | Recruiting | Phase III | NCT05737160 |
| Small molecule | Vemircopan (ALXN2050) | 2086178-00-7 | Alexion, UK | Active, not recruiting | Phase II | NCT05218096 |

## FDA approved therapeutic agents

While there is no current cure for ALS, HD, or MG, there are treatments to slow disease progression and treat symptoms. Table 6 examines the US FDA approved treatments for these rare diseases along with their CAS RN, therapy types, mechanism of action, and company information. Small molecule drugs dominate the approved drugs for both ALS and HD, with biologic therapies such as monoclonal antibodies, antibody fragments, and peptide therapy making up the approved treatments for MG.

There are 13 unique drugs currently approved by the US FDA for the treatment of these rare diseases. Three of these compounds have multiple approved formulations, as well. One example, the drug riluzole has three different formulations approved. The first being an oral tablet, there is also an oral film, and a thickened suspension available for patients dealing with muscle tone and swallowing issues. One of the approved drugs for the treatment of ALS, Relyvrio, has been recently discontinued. Amylyx Pharmaceuticals has started the process with the US FDA of discontinuing authorizations for Relyvrio and removing it from the market. [846] While Relyvrio is generally safe and well tolerated, it unfortunately failed to meet primary and secondary endpoints in a Phase III clinical trial (NCT05021536). [846]

**Table 6.** US FDA approved drugs for the treatment of specified rare diseases (Source: The CAS Content Collection)

| Drug | Therapy type | CAS RN | Rare disease indication | Mechanism/ notes | Company, location |
|---|---|---|---|---|---|
| Exservan (riluzole) | Small molecule | 1744-22-5 | Amyotrophic lateral sclerosis | Glutamate signaling blocker/ oral film formulation | Mitsubishi Tanabe Pharma America, USA |
| Nuedexta (dextromethorphan hydrobromide and quinidien sulfate) | Small molecule | 2445595-41-3 | Amyotrophic lateral sclerosis | Sigma-1 receptor agonist, NMDA receptor antagonist | Otsukac America Pharmaceutical, USA |
| Qalsody (tofersen) | Gene therapy | 2088232-70-4 | Amyotrophic lateral sclerosis | Targets SOD1 mRNA to reduce SOD1 protein production | Biogen, USA |
| Radicava (edaravone) | Small molecule | 89-25-8 | Amyotrophic lateral sclerosis | Free radical scavenger | Mitsubishi Tanabe Pharma America, USA |
| Relyvrio (sodium phenylbutyrate and taursodiol) | Small molecule | 2436469-04-2 | Amyotrophic lateral sclerosis | Small molecule chaperone and Bax inhibitor/ withdrawn 2024 | Amylyx, USA |
| Rilutek (riluzole) | Small molecule | 1744-22-5 | Amyotrophic lateral sclerosis | Glutamate signaling blocker/ oral tablet formulation | Sanofi, USA |
| Tiglutik (riluzole) | Small molecule | 1744-22-5 | Amyotrophic lateral sclerosis | Glutamate signaling blocker/ oral thickened suspension | ITF Pharma, USA |
| Austedo (deutetrabenazine) | Small molecule | 1392826-25-3 | Huntington's disease | VMAT2 inhibitor | Teva Pharmaceutical, Israel |
| Austedo XR (deutetrabenazine) | Small molecule | 1392826-25-3 | Huntington's disease | VMAT2 inhibitor/ extended release formulation | Teva Pharmaceutical, Israel |
| Ingrezza (valbenazine) | Small molecule | 1025504-45-3 | Huntington's disease | VMAT2 inhibitor | Neurocrine Biosciences, USA |
| Xenazine (tetrabenazine) | Small molecule | 58-46-8 | Huntington's disease | VMAT2 inhibitor | Lundbeck Pharmaceuticals, Denmark |
| Rystiggo (rozanolixizumab-noli) | Monoclonal antibody | 1584645-37-3 | Myasthenia gravis | Targets FcRn to prevent IgG recycling | UCB, USA |
| Soliris (eculizumab) | Monoclonal antibody | 219685-50-4 | Myasthenia gravis | Complement factor C5 inhibitor | Alexion, UK |

| | | | | | |
|---|---|---|---|---|---|
| Ultomiris (ravulizumab-cwvz) | Monoclonal antibody | 1803171-55-2 | Myasthenia gravis | Complement factor C5 inhibitor | Alexion, UK |
| Vyvgart (efgartigimod alfa-fcab) intravenous injection | Antibody fragment | 1821402-21-4 | Myasthenia gravis | Fc receptor blocker | Argenx, Netherlands |
| Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) subcutaneous injection | Antibody fragment | 1821402-21-4 | Myasthenia gravis | Fc receptor blocker | Argenx, Netherlands |
| Zilbrysq (zilucoplan) | Peptide therapy | 1841136-73-9 | Myasthenia gravis | Complement factor C5 inhibitor | UCB, USA |

## 6. Notable patents on rare diseases

**Table 7** shows notable patents in the field of rare diseases such as ALS, HD and MG published in recent years (2020 to 2023). Patents were selected based on relevance, novelty, applicability, and field of study. Most of these involve therapeutic strategies, disease markers and recent advancements in these disease areas.

For instance, a recently published patent CN117050134 describes the synthesis and characterization of a novel oleanamide derivative for activating KEAP/NRF2/ARE signaling pathway which is a signature of oxidative stress. This treatment activates NRF2 transcription factor that can help in preventing and treating various neurological disorders including ALS. In context of HD, WO2023099648 by AstraZeneca AB, Sweden, describes pyrazolo- and triazolo-azinone compounds that inhibits receptor-interacting protein kinase 1 (RIPK1) and can be used in the treatment of neurological disorders including HD. In another example, patent application WO2023236967A1 by RemeGen Co., Ltd., China, describes the development of the drug, a dosage regimen, an administration interval, and a mode for treating MG using - Telitacicept (TACI-Fc fusion protein). It is shown that this formulation exhibits good clinical efficacy and safety in the treatment of MG patients. These patents higlight the constant research endevours in the feild of rare diseases.

**Table 7.** List of notable patents pertaining to the three rare diseases – ALS, HD, and MG – identified from the CAS Content Collection.

| Patent Number | Year | Patent assignee, location | Description |
|---|---|---|---|
| **Amyotrophic lateral sclerosis** | | | |
| US20200002723 | 2020 | Deutsches Krebsforschungszentrum, Germany | It describes nucleotide sequences called MSBI (Multiple Sclerosis Brain Isolate) as well as probes, primers, and antibodies against polypeptides encoded by MSBI sequences. These could serve as early markers for the future development of cancer and diseases of the CNS (multiple sclerosis, prion-linked diseases, ALS, transmissible spongiform encephalitis, Parkinson's disease, and Alzheimer's disease). |
| WO2020010049 | 2020 | The General Hospital Corporation, AZ Therapies, Inc., USA | It describes a composition comprising micronized cromolyn sodium, α-lactose, and salt of fatty acid (preferably magnesium stearate) used to treat certain neurological diseases including Alzheimer's disease, ALS, and Parkinson's disease. |
| CN117050134 | 2023 | Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China | It describes a novel oleanamide derivative for activating a KEAP/NRF2/ARE signaling pathway which can be used for treating and preventing various neurological disorders including ALS. |

| | | | |
|---|---|---|---|
| EP4255406A1 | 2020 | Massey Ventures Ltd | It relates to (2S)-2-Aminopentanethioic S-acid or a pharmaceutically acceptable salt as a medication for the treatment of ALS. |
| WO2022138707 | 2022 | Eisai R&D Management Co., Ltd., Japan | It describes the development of pharmaceutical composition comprising anti-EphA4 antibodies capable of binding to and promoting the cleavage of EphA4, which is used for treating ALS. |
| **Huntington's disease** | | | |
| WO2023099648 | 2023 | AstraZeneca AB, Sweden | It describes pyrazolo- and triazolo-azinone compounds that inhibit receptor-interacting protein kinase 1 ("RIPK1") and can be used in the treatment of neurological disorders including HD. |
| US20240076310A1 | 2023 | Sage Therapeutics Inc, USA | Neuroactive steroids (or their combinations), that target GABA receptor complex (GRC) can be used for the treatment of neurodegenerative disorders including HD. |
| WO2022235329A1 | 2022 | University of South Carolina, USA | It comprises hydrophilic nanogels based on polyethylene glycol (PEG) copolymers. The nanogels can encapsulate an antibody for delivery to the brain and can include ligands for blood brain barrier (BBB) receptors on the surface. These nanogels can the treatment of neurological disorders including HD. |
| WO2022132894A1 | 2022 | Rush University Medical Center, USA | It describes a pharmaceutical composition comprising glycerol tribenzoate and glycerol phenylbutyrate which can be used for treating HD. |
| WO2020068913A1 | 2020 | Chase Therapeutics Corporation, United States | It describes a combination $5HT_3$ antagonist and/or a NK-l antagonist, in combination with 6-propylamino-4,5,6,7-tetrahydro-l,3-benzothiazole-2-amine and with fluoxetine, zonisamide, or a statin to treat protein misfolding neurodegenerative diseases. |
| **Myasthenia gravis** | | | |
| WO2020106724A1 | 2020 | Alexion Pharmaceuticals, Inc., United States | It describes a formulation that specifically binds complement component 5 (C5) and can be used for treating MG in the pediatric population. |
| WO2020014072A1 | 2020 | GT Biopharma, Inc., United States | It describes the use of an NK1-antagonist (e.g. aprepitant), in combination with neostigmine, to facilitate the treatment of a patient suffering from MG. |
| WO2023236967A1 | 2023 | RemeGen Co., Ltd., China | This describes the development of the drug, a dosage regimen, an administration interval, and a mode for treating MG using TACI-Fc fusion protein. It is shown that this formulation exhibits good clinical efficacy and safety in the treatment of MG patients. |
| WO2020086506A1 | 2020 | Ra Pharmaceuticals, Inc., United States | The present disclosure relates methods of treating MG with zilucoplan (complement inhibitor), including devices and kits available for administering zilucoplan. |
| CN112048565A | 2020 | Shijiazhuang People's Hospital, China | The invention discloses a microbial marker (comprising *Megamonas hypermegale* and/or *Fusobacterium mortiferum*) for the diagnosis of MG which offers the advantages of good specificity and high sensitivity. |

## 7. Outlook and Perspectives

In the vast landscape of medical conditions, rare diseases occupy a unique and often overlooked niche. Defined by their low prevalence, these disorders collectively affect millions worldwide [8, 9], presenting a multitude of challenges to patients, healthcare professionals, and researchers. Moreover, rare diseases offer a window into the diversity of human health and the complexity of biological systems. Each condition represents a unique manifestation of genetic, environmental, or infectious factors, often with distinct clinical presentations and treatment challenges. From rare genetic disorders like cystic fibrosis and Huntington's disease to autoimmune conditions like lupus, myasthenia gravis, and rare cancers, the spectrum of rare diseases encompasses a broad array of pathologies.

Significant roadblocks remain on the path to progress in rare disease research and care. The small size of patient populations presents challenges for conducting robust clinical trials, leading to limited evidence-based treatment options. Furthermore, the fragmented nature of rare disease research and healthcare delivery can impede collaboration and knowledge sharing. Fragmented approaches to research and care may limit opportunities for interdisciplinary collaboration and hinder the translation of scientific discoveries into clinical practice. Commercial incentives for developing treatments for rare diseases have been relatively low accounting for low interest from pharmaceutical industry.

Despite the challenges, there is reason for optimism in the rare disease landscape. Advances in genomics, molecular biology, and precision medicine hold promise for improved diagnosis and targeted therapies. Technologies such as next-generation sequencing have revolutionized our ability to identify genetic mutations underlying rare diseases. Whole exome sequencing (WES) [847-849] and whole genome sequencing (WGS) [850, 851] have become indispensable tools for unraveling the genetic basis of rare diseases, facilitating personalized medicine approaches and targeted therapies. Research into rare diseases has uncovered a plethora of novel disease mechanisms, shedding light on fundamental biological processes and pathways underlying human health and disease. Insights gained from studying rare diseases have broad implications for understanding more prevalent disorders and have led to the identification of druggable targets and therapeutic strategies. The general public is also becoming increasingly aware of the existence of these rare diseases, driving the overall interest up.

Despite the inherent challenges in developing treatments for rare diseases, there have been significant advancements in therapeutic innovations. From small molecule drugs to gene and cell-based therapies, researchers are exploring diverse modalities to address the unmet medical needs of individuals with rare diseases. Collaborative initiatives, regulatory incentives, and patient-centered trial designs are accelerating the translation of scientific discoveries into clinically meaningful interventions. AI is also being utilized from drug target discovery to the clinical pipeline, and beyond, to speed pharmaceutical progress and development. The sharing of data and resources through collaborative platforms and consortia has emerged as a cornerstone of rare disease research. Initiatives such as the Global Alliance for Genomics and Health (GA4GH) [852] and the Undiagnosed Diseases Network (UDN) [853] facilitate data exchange, harmonize standards, and foster interdisciplinary collaborations, thereby maximizing the impact of research efforts and empowering patients and families with rare diseases.

Looking ahead, continued investment in rare disease research, infrastructure, and policy initiatives is critical for overcoming existing challenges and maximizing the potential of scientific advancements to improve the lives of individuals with rare diseases. Multidisciplinary collaborations and inclusive research practices are needed to effectively address the complex and evolving landscape of rare diseases.

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## Notes

The authors declare no competing financial interest.


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## Supporting Information

Supporting Information. Methodology for collating genes associated with rare diseases utilizing the CAS Content Collection

Supporting Information Figure S1. Heat map indicating number of patents filed by commercial organizations with respect to rare cancers. Patent assignees shown here are among the top 6 commercial patent assignees shown in Figure 4B. Data includes patent publications in the field of rare diseases from the CAS Content Collection for 2003-2023

Supporting Information Figure S2. (A) Number of publications (journal and patent) and (B) patent-to-journal ratios for leading rare cancers in our dataset. Data includes both patent and journal publications sourced/extracted from the CAS Content Collection for the period 2018-2023 in the field of rare diseases.

Supporting Information Figure S3. Leading substances from the CAS Registry associated with amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and myasthenia gravis (MG) for the protein/peptide sequences subclass of substances. Data includes substances associated with both patent and journal publications sourced from the CAS Registry and the CAS Content Collection for the period 2012-2023.

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