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

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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, with 80% of these diseases being identified as having 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, and specifically on the biology and genetics of the three spotlighted diseases, to outline challenges and evaluate growth opportunities, 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 CAS Content Collection is the largest human-curated collection of published scientific information, supporting comprehensive quantitative analysis of global research across parameters including time, geography, scientific discipline, application, disease, chemical composition, etc. Covering

scientific literature published around the world in more than 50 languages, the CAS Content Collection encompasses data and discoveries published in more than 50,000 scientific journals and by over 100 patent offices. A major advantage provided by the CAS Content Collection is that, along with the standard reference information, it also provides human curated data on major substances and concepts explored in the scientific publications. The CAS REGISTRY® [19], the authoritative source for information on more than 250 million unique organic and inorganic substances and 70 million protein and nucleic acid sequences, is part of the CAS Content Collection. The CAS Content Collection is broadly accessible through CAS solutions including CAS SciFinder® [20] and CAS STNext® [21].

Here 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).

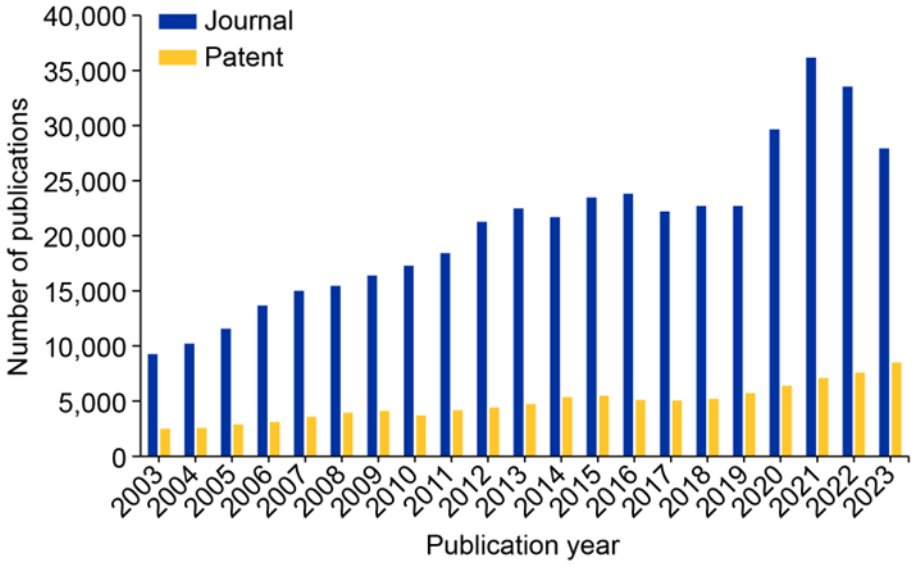


Figure 1. Publications in the field of rare diseases from the CAS Content Collection for the period 2003 to 2023.

Figure 2A presents the leading research organizations ranked by the volume of journal articles and by the average number of citations per publication, a viable indicator of the scientific impact for published work. More details on the data analysis regarding research organizations and journals is included in the Supporting Information. Examples of recent journal articles published by researchers at Harvard Medical School include articles related to HD,[22, 23] MG,[24] ALS,[22, 23] as well rare tumors and cancers such as thymomas,[25] multiple myeloma,[24] and thyroid cancer.[26-28] Similarly, examples of research output from other leading US-based organizations revolve around rare diseases such as multiple sclerosis,[29, 30] ALS,[31-33] systemic lupus erythematosus (SLE),[34, 35] sickle cell anemia,[36, 37] among others and rare cancers such as hematological malignancies including multiple myeloma,[25] acute myeloid leukemia (AML),[38, 39] and non-Hodgkin's lymphoma.[40, 41] 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,[42-45] HD,[46-49] SLE,[50-53] and ALS,[54, 55] among others.

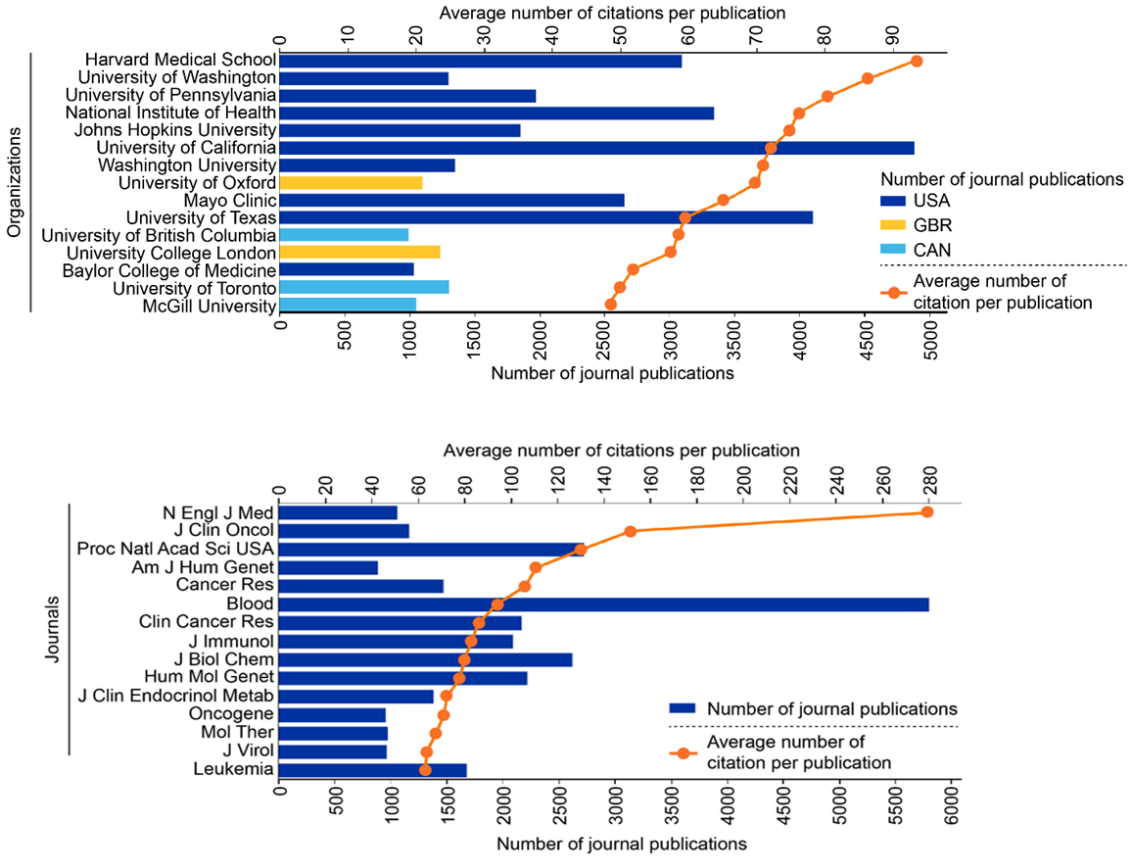


Figure 2. (A) Leading research organizations and (B) Leading scientific journals in the field of rare diseases based on data from the CAS Content Collection for the period 2003 to 2023. Ranking was based on total number of journal publications and average number of citations per publication, an indicator of publication impact. (Rankings based solely on total number of (A) journal publications and (B) citations are provided in the Supporting Information, Figure S1).

Using a similar methodology as described in the Supporting Information for research organizations, we identified leading scientific journals in the area of rare diseases (Figure 2B). More extensive data analysis on the scientific journals is included in the Supporting Information. A few highly cited journal articles published in the New England Journal of Medicine revolve around rare cancers such as melanoma,[56, 57] multiple myeloma,[58] and AML[56, 57] as well as other rare diseases such as SLE,[58] multiple sclerosis,[59, 60] and cystic fibrosis.[61] The 2019 article titled “Targeting huntingtin expression in patients with Huntington's disease”[62] 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.[63] Similar well-cited publications for MG include a review article published in the New England Journal of Medicine.[64]

Geographical distribution of patent assignees in the field of rare diseases indicates a high degree of overlap in leading countries/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 3). 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 3A). 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,[34] HD,[34] multiple sclerosis,[65-67] and the more obscure ones such as disabling pansclerotic morphea[68] and Von Hippel-Lindau disease.[69] 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,[70] WO2022104148[71]), using a SARS-Cov-2 pseudoviral delivery system for therapeutic transgene as potential treatment for HD (WO2022165538A1[72]), and development of GABA positive allosteric modulators (WO2018236955[73]) and peptide-based inhibitors for treatment of MG, (WO2018049053[74]).

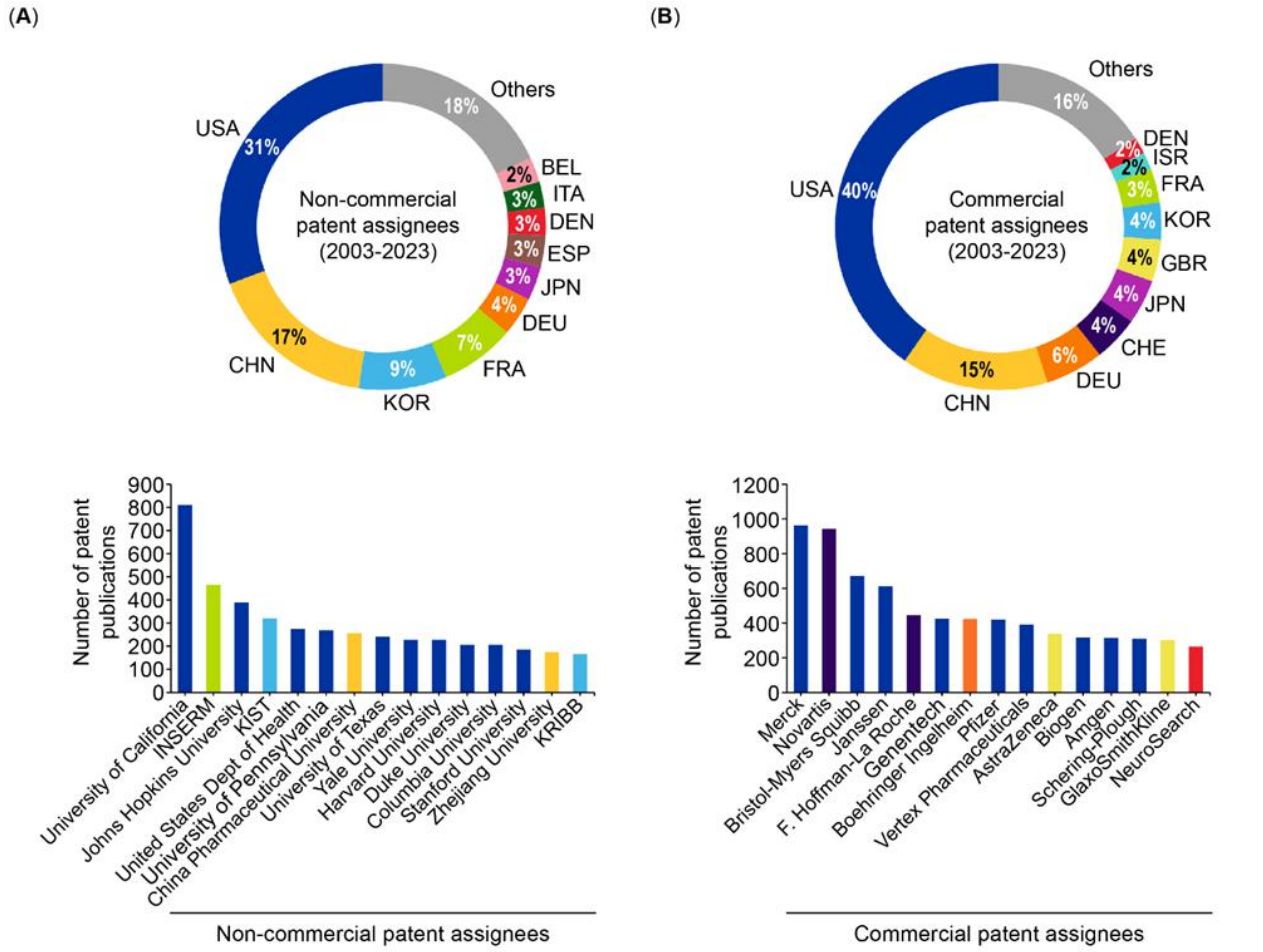


Figure 3. Leading organizations in the field of rare diseases based on patent publication data from the CAS Content Collection for the period 2003 to 2023. (**A)** Donut and (**B**) bar charts showing geographical distribution and leading organizations, respectively. Entities were separated into non-commercial 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), Israel (ISR), Italy (ITA), Belgium (BEL), Switzerland (CHE), and United Kingdom (GBR).

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 heat maps in Figure 4A,B – ALS, HD, and MG all feature in the list. Other well-studied rare diseases include autoimmune diseases such as multiple sclerosis,[75] SLE,[76] scleroderma,[77] Sjögren's syndrome,[78] and inherited disorders such as cystic fibrosis[79] and sickle cell anemia.[80] Among the top 10 well-studied rare cancers, ~30% are hematological malignancies (blood cancers) such as multiple myeloma,[81] non-Hodgkin's lymphoma,[82] and AML.[83] The list is also populated with rare cancers such as pheochromocytoma, type of neuroendocrine tumor[84]; cholangiocarcinoma, cancer of the bile duct,[85] and melanoma, a type of skin cancer.[86] Other examples of leading rare cancers include hepatocellular carcinoma,[87] a type of liver cancer, mesothelioma[88] which is cancer occurring in the tissue surrounding internal organs (mesothelium), and an aggressive form of brain cancer called glioblastoma.[89]

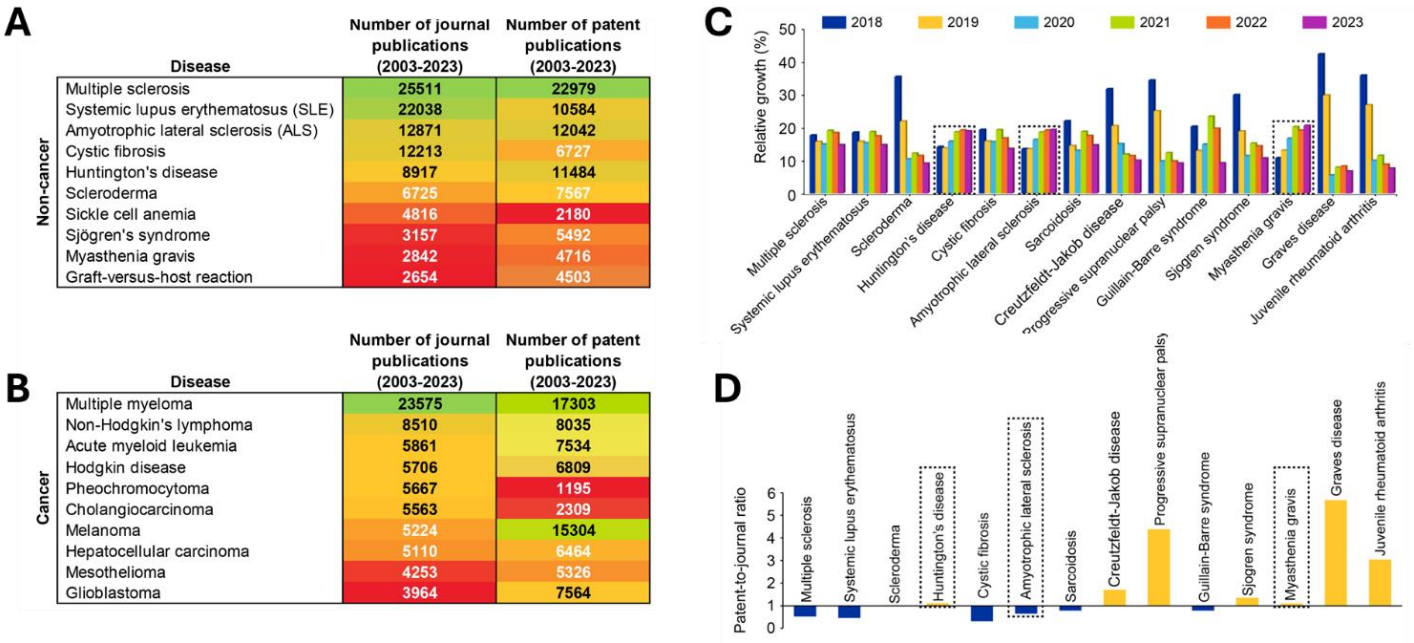


Figure 4. Left panel: Heat maps depicting number of journal and patent publications for leading rare diseases (A) and rare cancers (B) in our dataset of rare diseases. Right panel: (C) Number of publications (journal and patent) and (D) patent-to-journal ratios for selected leading rare diseases in our dataset. Highlighted in dashed black boxes are the three rare diseases that we analyzed in detail. Data includes 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 4C). HD, ALS, and MG show a clear, steady, and consistent increase in publications over the 5-year period. This increase is perhaps most evident for MG with publications nearly doubling between 2018 and 2022. A few rare diseases such as scleroderma,[77] an autoimmune disease resulting in hardening of skin, Creutzfeld-Jakob disease,[90] an aggressive neurodegenerative disorder resulting in death and progressive supranuclear palsy,[91] neurodegenerative disorder affecting muscles and movement, show waning publications over the years. Sjögren's syndrome,[78] Graves' disease,[92] and juvenile rheumatoid arthritis[93] also show a downward trend in publications indicative of decrease in interest from the scientific community. Multiple sclerosis, SLE, sarcoidosis,[94] and Guillain-Barre syndrome,[95] 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 4D). 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 4D).

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 S4A). Of special note are Kaposi's sarcoma,[96] cancer affecting the lining of blood vessels and lymph nodes, glioblastoma,[89] cancer of the brain and/or spinal cord, and thyroid cancer[97] showing the greatest increase with publications more than doubling between 2019 and 2022 (Supporting Information, Figure S4A). 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 S4B). The exceptions to this are multiple myeloma, esophagus cancer[98] and hepatocellular carcinoma,[87] a type of liver cancer, with low patent-to-journal ratios (Supporting Information, Figure S4B).

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.[99-104] Global estimates of ALS range from 1.9 per 100,000 to 6 per 100,000.[105-107] ALS shot to public attention because of the viral "ice bucket challenge" in 2014.[108] Though the exact impact of the viral challenge remains unknown[109-111] 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.[112]

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.[113, 114] 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.[102] 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.[113, 115-117]

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.[118-120]

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.[121, 122]

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.[123] 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[124, 125] including the benzothiazole Riluzole (Rilutek, Exservan, Tiglutik)[126, 127] in 1995, the antioxidant Edaravone (Radicava)[128] in 2017, and Sodium phenylbutyrate-Taurursodiol (Relyvrio)[129, 130], 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.[131] The Phase 3b trial of Radicava has been also discontinued in 2023, as well as its extension study.[132, 133] 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.[134-136]

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.[117, 118, 137-140]

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.[141, 142] 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.[143-145] 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.[146, 147] 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.[148-151]

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.[152-154] 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.[155-158] 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.[159, 160] 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.[161-163] 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. [164, 165] 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.[119, 120, 166-169]

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. [170] 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. [171-173]

- 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.[118, 174-177]

- 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.[178-180]

- 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.[181-183]

- 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. [184-187]

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.[188, 189]

Genes associated with ALS based on data from the CAS Content Collection are explored in Figure 5A to facilitate the identification of potential therapeutic targets and biological mechanisms underlying disease processes. A comprehensive table, including extensive details on genes, related proteins, expression profiles, function, and other related information, as well as multiple examples, is included in the Supporting Information, Table S1.

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.[119, 190, 191] 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.

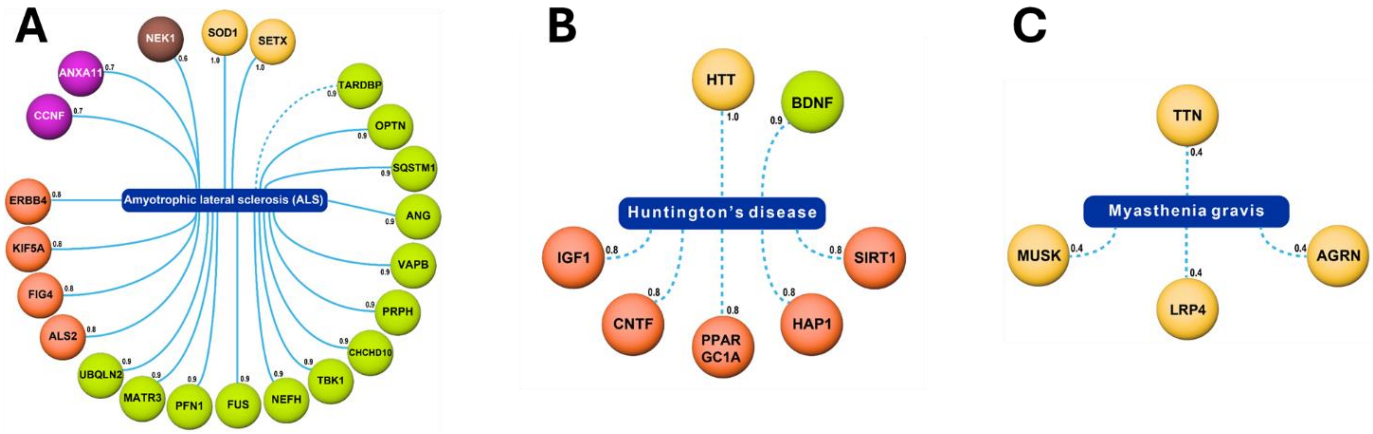


Figure 5. (A) Genes associated with amyotrophic lateral sclerosis (ALS) based on data from the CAS Content Collection. Only genes with an association score of greater than 0.6 and with at least 10 records are shown here. Color corresponds to association score – yellow (1.0), green (0.9), orange (0.8), purple (0.7) and brown (0.6); (B) 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); (C) Genes associated with myasthenia gravis based on data from the CAS Content Collection. Only genes with an association score 160 of 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.

The field of ALS research is experiencing a surge in novel developments [192-199]

Gene therapy targets specific genetic forms of ALS by introducing healthy copies of genes or using tools to silence mutated genes. Although gene therapy is still in early stages for ALS, it holds promise for personalized medicine in the future.

Similar to gene therapy, **antisense oligonucleotides (ASOs)** target mutant RNA transcripts associated with ALS. These short DNA or RNA molecules bind to specific RNA sequences, preventing them from being translated into harmful proteins. Several ASOs are undergoing clinical trials for the treatment of ALS, with some showing early signs of effectiveness in slowing disease progression.

RNA editing is an emerging technique, which involves using tools like CRISPR-Cas9 to directly edit mutated genes that cause ALS. While still in pre-clinical stages, RNA editing has the potential to be a game-changer for ALS if safety and efficacy can be established.

Since the abnormal clumping of proteins in motor neurons is a hallmark of ALS, it is in the focus in ALS treatment. Researchers are exploring various strategies to prevent protein misfolding or clear these aggregates, potentially slowing neurodegeneration. This includes drugs targeting specific proteins and potential gene therapies aimed at reducing mutant protein production.

Neuroprotective therapies aim to protect motor neurons from damage caused by the disease process. Some approaches focus on reducing oxidative stress, inflammation, or other factors contributing to neurodegeneration. Several neuroprotective agents are undergoing clinical trials, but finding effective medications with manageable side effects remains a challenge.

Cerebral dopamine neurotrophic factor (CDNF) is an ER-resident protein expressed in the central nervous system. A single dose of a novel CDNF variant can improve motor coordination and increase survival in ALS animal models. It can also delay symptom onset and protect motor neurons in the spinal cord. [192, 193]

A novel treatment strategy uses a small molecule linker, S-XL6, to prevent the separation of the SOD1 protein. The experiments confirmed that this treatment method works in mice for a specific mutation of the SOD1 protein associated with familial ALS. [194, 195]

Neurofilament light chain (NfL) is being investigated as a potential biomarker for ALS. A new drug is under review by the U.S. Food and Drug Administration that is based on its effects on this molecule. The level of NfL in blood and cerebrospinal fluid has been shown to correlate with the speed and severity of ALS progression. [196-199]

The main focus of the ALS research lies on: (i) addressing the underlying genetic causes through gene therapy and RNA editing; (ii) targeting protein misfolding and aggregation to protect motor neurons; (iii) developing neuroprotective therapies to slow disease progression.

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).[200-206] The estimates are that the global prevalence of HD is ~2.7 per 100,000 persons.[207]

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. [208-211]

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.[212, 213] 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.[208, 214, 215]

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.[216-218] 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. [219, 220] 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.[221, 222] 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.[200, 216, 223]

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)[224] and deutetrabenazine (Austedo)[225, 226] 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.[210, 227, 228] 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.[216, 229] 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.[230-232] 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. [211, 233-235]

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.[208, 216, 236] 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.[237-239]

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.[240-242] 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.[243-246]

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. [247-249] 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. [250-252]

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.[253-255] 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.[256, 257] 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.[258-260]

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).[209, 213] 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.[233, 235, 261, 262]

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. [209, 216] 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. [263, 264] 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. [265-267]

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.[268-271]

While the role of HTT in HD is well-established [272-275], we wished to collate a comprehensive list of other genes that might play a role in the development of HD. Results from our anlysis are visualized in Figure 5B. 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. A comprehensive table, including extensive details regarding genes, related proteins, expression profiles, function, and other diseases, as well as multiple examples, is included in the Supporting Information, Table S2)

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.[276-278] Understanding the genetic basis of HD is essential for accurate diagnosis, genetic counseling, and the development of targeted treatments for this devastating neurodegenerative disorder.

Huntington's disease research is exciting and constantly evolving [279-283]

Gene therapy and gene editing represent a promising avenue that aims to modify the faulty gene that causes HD. Gene therapy involves introducing healthy copies of the huntingtin gene or tools to silence the mutant gene. Gene editing techniques like CRISPR-Cas9 are being explored to directly edit the mutated gene. These approaches are still in early stages of clinical trials, but they hold immense potential for future treatment. [281]

RNA silencing focuses on using small molecules called interfering RNA (RNAi) to silence the mutant huntingtin gene. RNAi essentially targets the mutant messenger RNA (mRNA) and prevents it from being translated into the harmful protein. Similar to gene therapy, RNA silencing is undergoing clinical trials to assess its safety and effectiveness. [282]

Antisense oligonucleotides (ASOs) are another strategy to target mutant huntingtin mRNA. These are short, single-stranded pieces of DNA designed to bind to the mutant mRNA and prevent its translation into protein. ASOs have shown promise in early studies, and researchers are exploring their potential for HD treatment. [281-283]

Researchers are investigating various cellular processes involved in HD progression. This includes studying the role of protein aggregation, oxidative stress, and inflammation. By targeting the **specific molecular** pathways with medications, they hope to slow down neurodegeneration. Several drugs targeting these pathways are undergoing clinical trials.

A novel mouse model expressing the full-length human HTT gene with expanded CAG repeats has been developed. This model accurately replicates the progressive and age-dependent phenotypes of HD, making it a valuable tool for studying disease mechanisms and testing new therapies. [281]

New HD Integrated Staging System groups individuals with HD based on their biological, clinical, and functional characteristics. It is the first staging system developed for a genetic neurological condition and aims to improve the precision of clinical trials and patient care. [281]

The main focus of novel developments in Huntington's disease is on: (i) intervening at the genetic level to silence or modify the mutant gene; (ii) developing medications that can slow or halt disease progression by targeting specific cellular pathways.

Myasthenia gravis

Overview

Myasthenia gravis (MG) is a rare chronic neuromuscular disorder characterized by weakness and rapid fatigue of voluntary muscles.[284-286] With the earliest accounts dating back to the late 1600s,[287] MG is described as an autoimmune disorder affecting neuromuscular junctions.[288] Thought to arise as a result of the body generating antibodies against the acetylcholine receptor (AChR) or muscle specific kinase,[288, 289] resulting in the immune system mistakenly attacking receptors on muscle cells, particularly at the neuromuscular junction where nerve impulses stimulate muscle contractions,[290-292] MG leads to muscle weakness and a host of other symptoms.[293, 294] During the Covid-19 pandemic, reports have emerged of onset of MG after SARS-Cov-2 infection. [295, 296] 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. [297, 298]

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. [299-303]

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. [304-306] 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. [307] 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. [308-314]

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. [298, 315] 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. [288, 316, 317]

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. [289, 318-320]

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. [321-323]

The thymus gland plays a role in the development of MG in some individuals. [324] 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. [324-326]

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. [327-333]

MG can sometimes run in families, indicating a potential genetic component. [334] 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. [334, 335]

Certain HLA alleles, particularly those within the major histocompatibility complex (MHC) region, have been consistently linked to an increased risk of MG. [336] For example, the HLA-DR3 allele has been associated with MG, especially in individuals with early-onset disease and thymic abnormalities. [332] 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. [327, 337, 338]

Using data from the CAS Content Collection, we have put together genes known to have an association with MG (Figure 5C). These genes include AGRN, LRP4, MUSK, and TTN. A comprehensive table, including extensive details regarding genes, related proteins, expression profiles, function, and other diseases, as well as multiple examples, is included in the Supporting Information, Table S3)

It is important to note that the development of MG likely involves complex interactions between genetic susceptibility factors and environmental triggers. [332] 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. [318, 339, 340]

Myasthenia gravis research is actively exploring new treatment options beyond traditional medications [341-344]

- **Immunotherapies** target specific aspects of the immune system involved in MG pathogenesis.
    - **Complement inhibitors:** The complement system is part of the immune response. These drugs block specific proteins in this cascade, preventing damage to the neuromuscular junction. Examples include eculizumab and ravulizumab, which work by inhibiting the complement system that plays a role in the autoimmune attack on the neuromuscular junction.
    - **FcRn blockers:** FcRn receptors are involved in antibody recycling. Blocking these receptors leads to a decrease in circulating antibodies, including those targeting the neuromuscular junction. Efgartigimod and rozanolixizumab are new therapies that block the neonatal Fc receptor, reducing the levels of pathogenic antibodies in the blood.
    - **B-cell depleting therapies:** B cells are immune cells that produce antibodies. These therapies target and deplete B cells, reducing antibody production associated with MG. One such therapy, Rituximab, is a medication used for some MG patients, and other B-cell targeting drugs are being investigated.
- **Targeted therapies** aim to address specific mechanisms involved in neuromuscular dysfunction:
    - **Proteasome inhibitors:** Proteasomes are cellular structures that break down proteins. MG-causing antibodies can impair this process. Drugs like carfilzomib are being explored to see if they can improve neuromuscular function.
- **Several other approaches** are under investigation:
    - **Autologous stem cell and CAR-T cell therapy:** This involves collecting a patient's stem cells, treating them, and reintroducing them, potentially resetting the immune system.
    - **Thymus-specific therapies:** As the thymus gland may play a role in MG for some patients, researchers are exploring ways to target it more precisely than with thymectomy surgery.

Genes associated with the three spotlighted rare diseases with the association type as causal or contributing, as presented in Figure 5, are summarized in Table 1. Comprehensive Tables, including extensive details regarding genes, related proteins, expression profiles, function, and other diseases, as well as multiple examples for the three diseases, are included in the Supporting Information, Tables S1-S3)

Table 1. Genes associated with ALS, HD, and MG, as presented in Figure 5. Comprehensive tables for each of the three diseases, including extensive details on the genes and related information, as well as multiple examples, are included in the Supporting Information, Tables S1-S3)

Disease	Gene
Amyotrophic lateral sclerosis (ALS)	SOD1, SETX, TARDBP, OPTN, SQSTM1, ANG, VAPB, PRPH, CHCHD10, TBK1, NEFH, FUS, PFN1, MATR3, UBQLN2, ALS2, FIG4, KIF5A, ERBB4, CCNF, ANXA11, NEK1
Huntington's disease (HD)	BDNF, SIRT1, HAP1, PPARGC1A, CNTF, IGF1
Myasthenia gravis (MG)	AGRN, LRP4, MUSK, TTN

Landscape analysis of data on ALS, HD, and MG in the 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 6A).
- 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 6B).
- 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 6C).
- 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 6D-F).

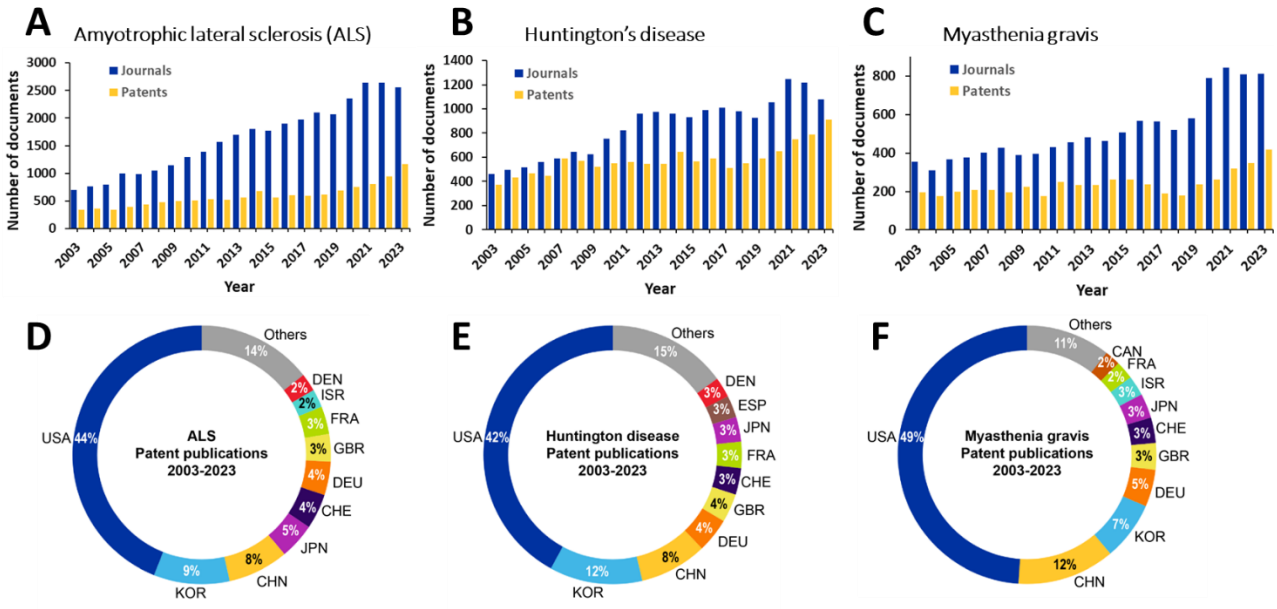


Figure 6. Publications for specific rare diseases: (A) amyotrophic lateral sclerosis (ALS), (B) Huntington's disease (HD) and (C) myasthenia gravis (MG). Donut graphs showing geographical distribution of patent assignees (both non-commercial and commercial organizations) for each of three diseases: (D) 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 the Supporting Information, Figure S7. 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.

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 rare and non-rare diseases (Figure 7A), therapy types and drugs (Figure 7B), as well as proteins and cells (Figure 7C).

Disease comorbidities

Amyotrophic lateral sclerosis (ALS)

Hypertension and dyslipidemia are the most commonly reported comorbidities.[345] 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.[346, 347] The occurrence of autoimmune diseases in ALS patients is frequently reported, but little is known about the related clinical phenotype.[348] 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.[349-352] 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.[353]

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. [354] 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). [354] 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. [355] The observed psychiatric comorbidities comprise obsessive-compulsive disorder, depression, insomnia, bipolar affective disorders, dementia, and neurosis. [355] 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. [356] Reports exist of the co-occurrence of HD with ALS. [357] 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. [358]

Myasthenia gravis

Patients with MG may be associated with autoimmune as well as non-autoimmune comorbidities. [359, 360] Autoimmune comorbidities such as autoimmune thyroiditis, followed by systemic lupus erythematosus, and rheumatoid arthritis have been reported as the most frequent comorbidities of MS. [361] 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. [361] 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. [359-362] 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. [361] Another group of diseases co-occurring frequently with MG are cardiovascular

diseases. Arterial hypertension is noted to prevail in patients with MG. [362] With respect to cancers – lymphoma, breast cancer, and lung cancer have been found more common in the group of MG patients. [360, 362] Mental health disorders such as depression and anxiety are frequent among MG patients. Concurrent MG and ALS have also been registered in many cases. [360, 362]

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 7A. 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 7A).

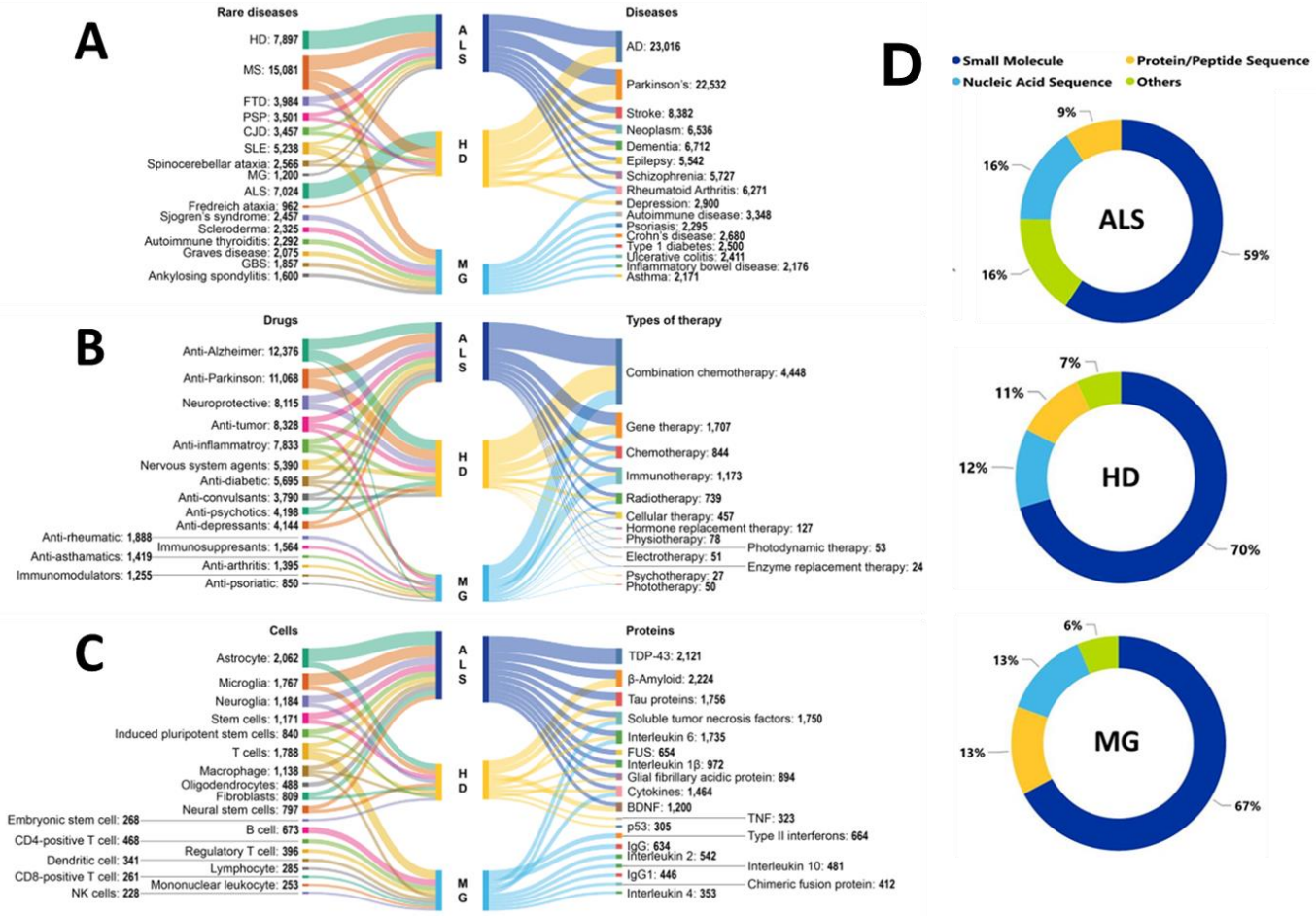


Figure 7. Co-occurrences of amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and myasthenia gravis (MG) with various concepts such as (A) other rare and non-rare diseases, (B) types of therapy and drugs used to treat symptoms and (C) cells and proteins. (D) Substance data from the CAS REGISTRY associated with ALS, HD, and MG. Data includes both patent and journal publications sourced from the CAS Content Collection for 2003-2023 in the field of rare diseases. Annual growth for individual classes of substances is provided in Supporting Information Figure S6.

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 7B). 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. [363]

ALS and HD frequently co-occur with gene therapy, while for MG, immunotherapy is the second most frequently occurring after combination therapy (Figure 7B). 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. [364] 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. [364-367] 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. [368] 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. [369]

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. [370] 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. [370] 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 7B).

For example, ropinirole, a drug used to treat Parkinson's disease, has showed potential in delaying the progression of ALS. [371] 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. [372, 373] 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. [374, 375]

MG frequently co-occurs with immunosuppressant and anti-rheumatic drugs (Figure 7B). 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). [376-380] Patients with rheumatoid arthritis exhibit high prevalence of MG compared to the general population. [381] The rheumatoid arthritis drug abatacept has been reported to prevent MG in clinical trial. [380] 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. [382]

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. [383] 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. [384] Another antipsychotic, tiapride (CAS RN: 51012-32-9), has been also tested for the treatment of HD. [385] Olanzapine (CAS RN: 132539-06-1) [384, 386], risperidone (CAS RN: 106266-06-2)[387], quetiapine (CAS RN: 111974-69-7)[388] are also antipsychotic drugs widely prescribed for the treatment of the motor and behavioral symptoms of HD. [383] 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). [383]

Proteins

A search for co-occurrence with proteins showed that ALS exhibits the highest co-occurrence with TDP-43 (Figure 7C). TDP-43 (TAR DNA-binding protein 43) is a key pathological hallmark associated with ALS and related motor neuron diseases. [389] 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. [390-393] TDP-43 pathology correlates with disease severity and progression, suggesting a central role in ALS pathogenesis. [394]

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 7C). 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. [395-398]

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 7C). 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. [157, 399-403]

Astrocytes, the most abundant glial cells in the central nervous system, are implicated in ALS and HD through various mechanisms. [399, 404, 405] 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. [406-408] Reactive astrocytes in HD exhibit altered morphology and dysregulated function, including impaired glutamate uptake and disrupted calcium signaling. [409-411] 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. [412-414]

Microglia, the resident immune cells of the central nervous system, play dual roles in ALS and HD pathology. [399, 402, 415-417] 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. [401, 418-420] 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 7D). For all three diseases small molecules constituted the largest fraction of explored substances (Figure 7D). Analysis of

the annual growth of the individual substance classes is illustrated in the Supporting Information Figure S6) While for journal publications 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. 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 S6 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.

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 8) 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 8B). 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 shows a moderate overall increase till 2021, post which it shows a minor dip till 2023 (Figure S8). Of note, the capital investment by Belgium and the UK has increased in the last 2 years (2021-2023).

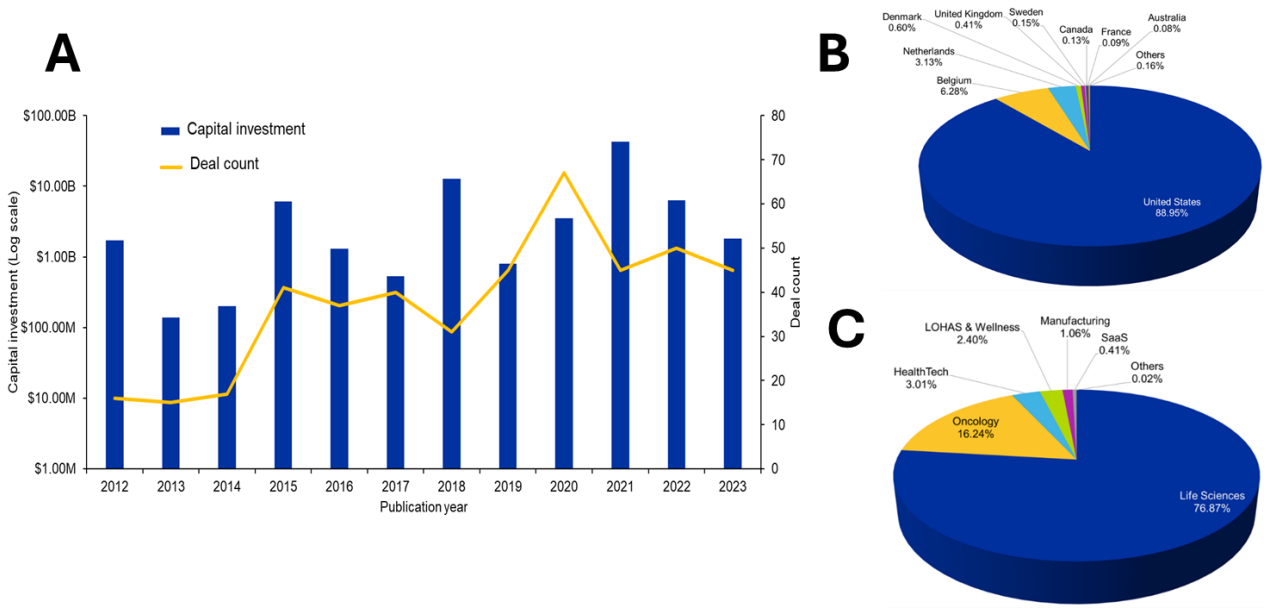


Figure 8. (A) Commercial interest in rare diseases (data sourced from PitchBook). Capital invested and deals related to rare diseases (ALS, HD, and MG) for the past decade (2012−2023); (B) Geographical distribution of the number of companies engaged in the field of rare diseases (ALS, HD, and MG); (C) Sector-wise distribution of various industry types investing in the field of rare diseases (ALS, HD, and MG)

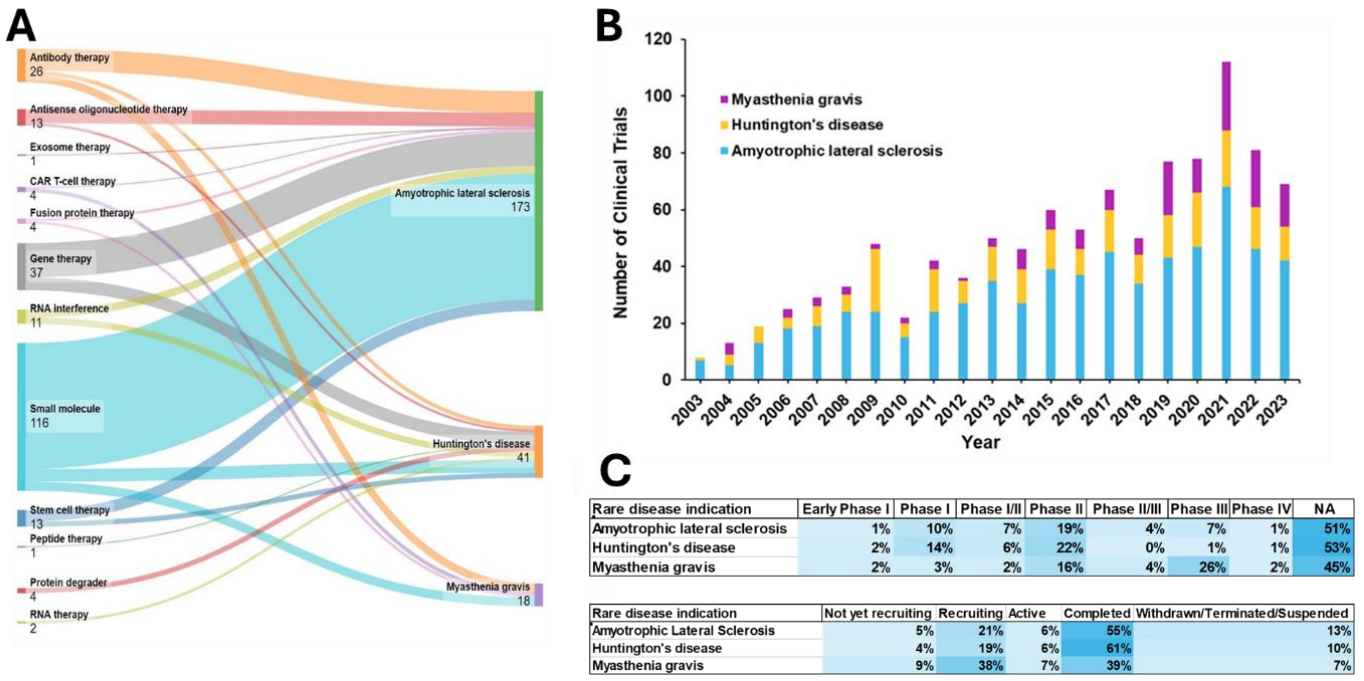
A closer look at the data suggests that life sciences-based industries are the top investors followed by oncology-based and health technology industries (Figure 8C). Vaccinex has the maximum number of deals in this field. Vaccinex lead drug candidate, pepinemab (CAS RN: 2097151-87-4), blocks semaphorin 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. [421, 422] Similarly, Cytokinetics is investing in diseases linked to neuromuscular junction such as ALS. [423] 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. [424] These investment trends indicate the steady interest of companies in the field of rare diseases such as ALS, HD, and MG.

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 S4 in the Supporting Information lists these compounds, along with their suggestive mechanism of action, therapy type, and the company developing them). 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 S4 in the Supporting

Information). 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 9A). 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 interference agents, and other biologic treatments dominate (Figure 9A).



C

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%

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 9. (A) Preclinical drug therapy candidates and their respective rare disease indication currently in the development pipeline; (B) Number of clinical trials by rare disease indications for years 2003-2023; (C) Percentage of rare disease clinical trials in various: phases (upper panel) and statuses (lower panel).

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. [425] Figure 9B 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 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.

Further analysis of these rare disease clinical trials reveals that nearly half of all trials for the different indications are not phased (Figure 9C). 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 9C). 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.

Finally, representative clinical trials examining rare disease therapeutics are highlighted in Table 2 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. [426] 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. [427] They also suppress effector T-cell inflammatory molecules and CNS microglial cell inflammatory molecules. [427] RAPA-501 cells are also available through an expanded access clinical trial (NCT06169176) to patients living with high-risk ALS and are 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. [428]

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. [429] 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. [429]

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. [430] 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. [431] 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. [432] It has additionally been shown to be a toll-like receptor 4 antagonist that may contribute to its attenuation of neuroinflammation. [432] Ibudilast received both fast track [433] and orphan drug designations [434] 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 were 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. [435] Prilenia Therapeutics was granted orphan drug designation for pridopidine in 2021 from the US FDA for treating ALS. [436]

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. [437] 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. [438]

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. [421]

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. [439] In addition, SAGE-718 was granted both FDA Fast track designation [440] in 2022 and FDA Orphan Drug Designation in 2023. [441]

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. [442] 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. [443] Descartes-08 was granted Orphan Drug Designation by the US FDA for the treatment of MG in 2024. [444]

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. [445] 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. [445] 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 2. 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 3 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. [446] While Relyvrio is generally safe and well tolerated, it unfortunately failed to meet primary and secondary endpoints in a Phase III clinical trial (NCT05021536). [446]

Table 3. 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 taurursodiol)	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 ALS, Huntington's disease, and myasthenia gravis

Table 4 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 4. 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, New Zealand	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, USA	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., USA	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., USA	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) [447-449] and whole genome sequencing (WGS) [450, 451] 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) [452] and the Undiagnosed Diseases Network (UDN) [453] facilitate data exchange, harmonize standards, and foster interdisciplinary collaborations, thereby maximizing the impact of research efforts and empowering patients and families with rare diseases.

Table 5 summarizes specifically the outlook and perspectives on amyotrophic lateral sclerosis, Huntington’s disease, and myasthenia gravis.

Table 5. Summary of the outlook and perspectives on ALS, HD, and MG

	Amyotrophic lateral sclerosis (ALS)	**Huntington's disease (HD)**	**Myasthenia gravis (MG)**
Prognosis	ALS typically progresses rapidly, with most patients surviving 3 to 5 years after diagnosis. However, some individuals may live much longer, with variations in the rate of disease progression.	Huntington's disease typically manifests in mid-adulthood, with symptoms gradually worsening over 10 to 25 years. The progression and severity of the disease can vary widely among individuals. Juvenile Huntington's disease, which occurs before the age of 20, tends to progress more rapidly.	The course of MG varies widely among individuals. With proper treatment, many people can manage their symptoms and lead relatively normal lives. The disease can fluctuate, with periods of worsening (exacerbations) and improvement (remissions).
Treatment options	• Currently, there is no cure for ALS. Treatments aim to slow disease progression, manage symptoms, and improve quality of life. • Riluzole and edaravone are FDA-approved drugs that modestly slow disease progression. • Supportive therapies, including physical therapy, occupational therapy, speech therapy, and nutritional support, are crucial for maintaining function and comfort.	• There is no cure for HD, and treatments focus on managing symptoms and improving quality of life. • Medications such as tetrabenazine and deutetrabenazine are used to treat chorea (involuntary movements). The use of valbenazine, a medication that has shown effectiveness in reducing chorea is awaiting FDA approval. • Antipsychotic drugs, antidepressants, and mood-stabilizing medications help manage psychiatric symptoms and mood disorders. • Physical therapy, occupational therapy, and speech therapy can support motor and functional abilities.	• Anticholinesterase agents (e.g., pyridostigmine) improve communication between nerves and muscles. • Immunosuppressive drugs (e.g., prednisone, azathioprine, mycophenolate mofetil) reduce the abnormal immune response. • Surgical removal of the thymus gland (thymectomy) can improve symptoms in some patients, particularly those with thymomas or generalized MG. • Plasmapheresis and Intravenous Immunoglobulin (IVIg) are used to manage severe exacerbations by removing antibodies from the blood or providing normal antibodies to modulate the immune response. • New therapies, such as monoclonal antibodies (e.g., eculizumab and ravulizumab), target specific components of the immune system.

Ongoing research	• **Genetic research:** Advances in genetic research have identified several genes associated with familial ALS, such as SOD1, C9orf72, and TARDBP. Understanding these genetic factors is crucial for developing targeted therapies. • **Stem cell therapy:** Research is exploring the potential of stem cell therapy to replace damaged neurons or protect existing neurons from degeneration. Clinical trials are ongoing to evaluate the safety and efficacy of these approaches. • **Gene therapy:** Gene therapy aims to correct or mitigate the effects of defective genes associated with ALS. Techniques like CRISPR-Cas9 are being investigated for their potential to edit genetic mutations. • **Neuroprotective agents:** Scientists are investigating various compounds and drugs that could protect motor neurons from degeneration. These include anti-inflammatory agents, antioxidants, and mitochondrial protectants. • **Biomarkers:** Identifying biomarkers for early diagnosis and monitoring disease progression is a significant area of research. Reliable biomarkers could improve clinical trials and lead to more effective treatments.	• **Genetic research:** HD is caused by a mutation in the HTT gene, leading to the production of an abnormal huntingtin protein. Research aims to understand how this protein causes neurodegeneration. Studies on gene silencing techniques, such as antisense oligonucleotides (ASOs) and RNA interference (RNAi), are exploring ways to reduce or inhibit the production of the mutant huntingtin protein. • **Stem cell therapy:** Researchers are investigating the potential of stem cell therapy to replace damaged neurons or support the survival of existing neurons. Clinical trials are assessing the safety and efficacy of these approaches. • **Neuroprotective agents:** Various compounds and drugs are being studied for their potential to protect neurons from degeneration. These include antioxidants, anti-inflammatory agents, and compounds targeting cellular energy production. • **Biomarkers:** Identifying biomarkers for early diagnosis and monitoring disease progression is a key area of research. Reliable biomarkers could enhance clinical trials and lead to earlier intervention.	• **Targeted therapies:** Researchers are exploring monoclonal antibodies that target specific components of the immune system. For example, eculizumab, a complement inhibitor, has shown promise in treating MG by blocking the part of the immune system that attacks the neuromuscular junction. • **Biomarkers:** Identifying biomarkers for MG can help diagnose the disease earlier and monitor the effectiveness of treatments. Ongoing research aims to find reliable biomarkers that can predict disease progression and response to therapy. • **Novel immunosuppressive agents:** New immunosuppressive drugs with fewer side effects and improved efficacy are being developed. These drugs aim to provide better control of the immune system while minimizing adverse effects. • **Gene therapy:** Research into gene therapy for MG is in the early stages, focusing on correcting the underlying genetic causes or modulating the immune response at the genetic level.

Future perspectives	• **Precision medicine:** Advances in genetic and molecular profiling may enable personalized treatment approaches tailored to the specific genetic and molecular characteristics of an individual's ALS. • **Combination therapies:** Future treatments may involve combinations of drugs and therapies targeting different aspects of the disease, such as neuroprotection, inflammation reduction, and muscle function enhancement. • **Improved diagnostic tools:** Development of advanced diagnostic tools for early detection and accurate monitoring of ALS progression could lead to earlier intervention and better outcomes.	• **Gene therapy:** Advances in gene therapy hold promise for treating HD by targeting the underlying genetic mutation. Techniques like CRISPR-Cas9 are being explored for their potential to edit or correct the HTT gene mutation. • **Precision medicine:** Personalized treatment approaches based on an individual's genetic and molecular profile could lead to more effective therapies tailored to the specific characteristics of their HD. • **Combination therapies:** Future treatments may involve combining different therapeutic strategies, such as gene silencing, neuroprotective agents, and symptomatic treatments, to address multiple aspects of the disease. • **Improved diagnostic tools:** Development of advanced diagnostic tools for early detection and accurate monitoring of HD progression could lead to earlier and more effective interventions.	• **Personalized medicine:** Advances in genetic and molecular profiling may enable personalized treatment approaches tailored to the specific characteristics of an individual's MG. This could lead to more effective and targeted therapies with fewer side effects. • **Combination therapies:** Future treatments may involve combining different therapeutic strategies, such as immunosuppressive drugs, targeted therapies, and lifestyle interventions, to provide comprehensive management of MG. • **Improved diagnostic tools:** Development of advanced diagnostic tools for early detection and accurate monitoring of MG progression could lead to earlier intervention and better outcomes.

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

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Supporting Information

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

Figure S1. Leading research journals in the field of rare diseases based solely on total number of (A) journal publications and (B) citations.

Figure S2. 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 4. Data includes patent publications in the field of rare diseases from the CAS Content Collection for 2003-2023.

Figure S3. 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.

Figure S4. (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.

Figure S5. 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.

Figure S6. Annual growth of the individual substance classes associated with (A) amyotrophic lateral sclerosis (ALS), (B) Huntington's disease and (C) myasthenia gravis. 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.

Figure S7. Relative growth in the number of documents related to ALS, MG, and HD in 2003-2023.

Figure S8. (A) Growth in the number of deals in the field of rare diseases by different countries/regions from 2013 to 2022;) (B) Growth in the number of deals in the field of rare diseases by different companies from 2013 to 2022.

Table S1. List of genes associated with amyotrophic lateral sclerosis (ALS), as shown in Figure 5A, with the association type as causal or contributing. A comprehensive table, including extensive details on the genes and related information, as well as multiple examples.

Table S2. List of genes associated with Huntington's disease (HD), as shown in Figure 5B, with the association type as causal or contributing. A comprehensive table, including extensive details on the genes and related information, as well as multiple examples.

Table S3. List of genes associated with myasthenia gravis (MG), as shown in Figure 5C, with the association type as causal or contributing. A comprehensive table, including extensive details on the genes and related information, as well as multiple examples.

Table S4. Rare disease therapeutic drug candidates in commercial preclinical development. A comprehensive table, including over 230 substances being researched and developed preclinically for the treatment of ALS, HD, and MG, along with their suggestive mechanism of action.

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