Review

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Review

Two Sides of the Same Coin: Genes Involved in Neurodegeneration and Cancer

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Abstract: The relationship between cancer and neurodegeneration has spurred extensive scientific discourse, challenging their historical classification as distinct disorders. While cancer signifies uncontrolled cellular proliferation and neurodegeneration marks progressive neuronal loss, recent insights highlight intriguing interconnections between these seemingly disparate conditions. Cancer entails perpetual signaling for growth, evasion of growth inhibitors, resistance to cell death, acquisition of replicative immortality, stimulation of blood vessel growth (angiogenesis), and initiation of invasion and metastasis. Conversely, investigations emphasize disrupted cellular energy regulation and evasion of immune surveillance as key traits arising from genome instability, mutations, and inflammation driving tumorigenesis. Neurodegeneration involves neuronal malfunction and depletion, synaptic impairment, and protein abnormalities aggregations contributing to muscle atrophy and cognitive deficits. Varied clinical studies underscore contrasting correlations between cancer and neurodegeneration, hinting at mirrored molecular pathways that foster cell resilience or vulnerability. Research explores cellular signaling in tumorigenesis, shared with neurodegenerative disorders. Aberrant expression or mutations in crucial genes implicated in neurodegeneration also surface in cancer contexts. Debates persist on the nature of the relationship between cancer and neurodegeneration, contemplating inverse associations or shared pathways. Understanding their complex interplay, encompassing genetics, cellular mechanisms, and environmental influences, remains pivotal in unraveling their connections. This review explores the intriguing perspective that neurodegeneration and cancer might share fundamental genetic links, delving into potential implications for their onset and progression.

Keywords: Neurodegeneration; inflammation; cancer; Parkinson's Disease; neuron; cell biology; interleukins; disease progression; genetic and somatic mutations; double hit hypothesis

1. Introduction

The intricate relationship between cancer and neurodegeneration has sparked extensive debates within the scientific community. While traditionally viewed as separate entities, cancer is characterized by uncontrolled cell growth and neurodegeneration marked by the progressive loss of neurons; recent research has unveiled intriguing connections between these seemingly disparate conditions [1,2]. Cancer is linked to broad features encompassing continual signals for cell proliferation, circumvention of growth inhibitors, resilience against cell demise, attainment of perpetual replication, stimulation of blood vessel growth (angiogenesis), and instigation of invasion and spread to distant sites (metastasis) [3]. Intriguingly, ongoing investigations have pinpointed attributes like disrupted cellular energy regulation and avoidance of immune system attacks as significant and unique traits [4]. These characteristics stem from genome instability, mutations, and inflammation facilitating tumor development [4].

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Neurodegeneration involves the malfunction and depletion of neurons, impaired synaptic adaptability, protein irregularities like amyloid-β (Aβ) and misfolded tau in Alzheimer's disease (AD), α-synuclein (αS) in Parkinson's disease (PD), and their aggregations, alongside gradual muscle decline or wasting, contributing to memory deficiencies, cognitive lapses, and movement impairments [5,6]. Many clinical and epidemiological studies have underscored contrasting correlations between cancer and neurodegenerative conditions [1,2,7–10]. Current studies propose that the replication of genetic material, minus the subsequent cell division, leads to intrinsic molecular defects that manifest as changes triggering apoptosis [5]. The outcomes of irregular cell cycle activation followed by apoptosis are showcased through heightened levels of molecular stress response and markers associated with apoptosis [11]. These ailments exhibit mirrored molecular pathways, where one fosters resilience against cell demise. At the same time, the other accentuates vulnerability to cellular breakdown potentially serving as diagnostic and prognostic indicators at a physiological level. Research into tumorigenesis extensively investigates various cellular signaling routes regulating cell survival and death, encompassing DNA damage, irregularities in cell cycle regulation, inflammation, immune responses, and oxidative stress [12–15]. Notably, these pathways are now evident in connection with neurodegenerative disorders. Additionally, irregular expression or mutations in critical genes like αS, phosphatase and tensin homolog (PTEN), PTEN-induced kinase 1 (PINK1 or PARK6), DJ-1 (PARK7), leucine-rich repeat kinase 2 (LRRK2 or PARK8), microtubule-associated protein tau (MAPT), amyloid precursor protein (APP), presenilin 1/2 (PSEN1/2), and cyclin-dependent kinase 5 (CDK5) crucial in neurodegeneration have also been identified in cancer contexts [2,8]. However, the exact nature of the relationship between cancer and neurodegeneration remains a subject of ongoing debate and investigation. Some studies propose contrasting perspectives, suggesting a potential inverse relationship, where a lower incidence of certain cancers might coincide with a higher prevalence of neurodegenerative disorders in specific populations [1,16–18]. Others explore the possibility of shared molecular pathways or the impact of environmental factors influencing these conditions. Understanding the complex interplay between genetics, cellular mechanisms, and environmental influences in cancer and neurodegeneration is crucial for unraveling their connections [12,13,19]. Research in this field continues to evolve, aiming to elucidate the intricate network of factors contributing to these conditions, ultimately paving the way for potential therapeutic interventions or preventive strategies targeting shared pathways or genetic predispositions. This review proposes a view that neurodegeneration and cancer may be two sides of the same coin. It also delves into the possible link genes between the two mechanisms and discusses the potential implications of their dysregulation in the onset and progression of neuropathological events.

1.1. Converging Pathways: Unveiling Shared Risk Factors in Cancer and Neurodegeneration

Neurodegenerative diseases and cancer are multifactorial disorders where numerous genes contribute to conditions like AD, PD, and Huntington's disease (HD) [20–24]. Alongside genetic factors, a spectrum of elements, including mutations, single nucleotide polymorphisms, epigenetic variations (non-coding RNA, histone modifications, DNA methylation), oxidative stress, protein degradation, mitochondrial function, cellular trafficking, abnormal proteins, and oligomeric protein propagation, shape the pathophysiological mechanisms involved in the risk of specific cancer types within PD, HD, and AD [25–32].

Disruptions in genetic mutations and transcriptional, protein, and mitochondrial regulations hold substantial sway in these conditions [28,32,33]. For instance, the tumor suppressor gene p53 exhibits contrasting activity in tumors and PD, AD, and HD [7], suggesting a plausible link between cancer and neurodegeneration [2]. This connection stems from shared genes and biological pathways, marked by misregulated cell cycle activation leading to opposing outcomes [1,12].

Proposed mechanisms vary, involving molecular shifts in genes like PARKIN, PINK1, and P53 or the translation of short-interfering RNA (siRNA) in non-coding areas that could be toxic to tumor cells. Additionally, replacement therapies like levodopa (L-DOPA) in PD demonstrate effects on reducing tumor angiogenesis [34–38]. While the direct association between neurodegeneration and

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cancer remains unconfirmed, specific genes manage critical roles in both realms, spanning cell cycle control, DNA repair, and kinase signaling [39]. Conversely, specific reported tumors escalate their incidence between these diseases, such as breast and skin cancers [40].

Shared risk factors between cancer and neurodegeneration uncover common biological mechanisms predisposing individuals to both conditions [12,41]. Chronic inflammation, known to influence various cancers, also appears to play a role in AD and PD [42–44]. Oxidative stress, arising from an imbalance between free radicals and antioxidants, impacts cell survival in cancer development and neurodegenerative processes [9,14,30]. Disruptions in cellular mechanisms, such as impaired DNA repair or protein misfolding, constitute commonalities between cancer and neurodegeneration [15,45]. Additionally, lifestyle factors like diet, exercise, and exposure to environmental toxins influence the risk of both conditions, highlighting the multifaceted nature of shared risk factors [46]. Understanding these commonalities offers prospects for targeted strategies and potentially intersecting therapies for these seemingly distinct diseases [1].

1.2. Parallel Pathogenesis, Divergent Destinies: Double Hit

Despite their divergent outcomes, the intriguing parallel pathogenesis between cancer and neurodegeneration delves into intricate molecular pathways that influence cellular behavior [1,2]. Shared factors like chronic inflammation, oxidative stress, and genetic mutations contribute to both cancer development and neurodegenerative processes [47–49]. Inflammation, for instance, triggers immune responses that can either promote tumor growth or contribute to neuronal damage and degeneration in the brain [10,50]. Similarly, oxidative stress, stemming from an imbalance between reactive oxygen species and antioxidants, impacts cellular health in both cancerous and neurodegenerative conditions, albeit through different mechanisms [49].

Moreover, disruptions in critical cellular processes such as DNA repair and protein quality control mechanisms are common threads in cancer and neurodegeneration. Dysfunctional DNA repair pathways can lead to genetic mutations promoting cancer or neuronal dysfunction in neurodegenerative disorders [51–53]. Meanwhile, protein misfolding and aggregation, seen in diseases like AD or PD, mirror aberrant protein signaling in specific cancers [54–56].

The divergence in clinical outcomes emerges from the unique tissue contexts affected by these shared pathogenic processes. Cancer manifests as uncontrolled cell growth that forms tumors, impacting various organs and tissues [57]. On the contrary, neurodegeneration manifests as the progressive loss of specific neuronal populations, resulting in cognitive decline or motor impairments particular to the affected brain regions [7].

Understanding the intricate interplay between shared pathogenic mechanisms and the divergent fates of cancer and neurodegeneration offers a challenging yet promising opportunity for tailored therapeutic strategies. By dissecting these dual facets of pathogenesis, researchers aim to develop treatments that account for the distinct trajectories of these conditions, ultimately aiming for more effective interventions that address the complexities of both diseases.

2. Exploring Genetic Intersections: Parkinson's Associated Genes and Potential Links to Cancer Pathways

PD is a neurodegenerative condition marked by resting tremors, bradykinesia, and rigidity [58]. In PD, non-motor symptoms such as sleep disturbances, cognitive changes, and autonomic dysfunction often significantly impact patients' quality of life alongside the more recognized motor symptoms [59].

The impact of PD extends beyond patients to their caregivers and society, contributing significantly to disability-adjusted life years and ranking among the leading causes of years lived with disability [58]. Interestingly, research has unearthed a potential correlation between PD diagnosis and the development of cancer. Some studies have unveiled a positive association linking PD with subsequent occurrences of melanoma [60,61], although specific investigations have reported a lack of correlation [62,63]. Additionally, there are observations of melanoma onset after the use of levodopa, the primary pharmacological therapy for PD [64].

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The connection between PD and cancer, particularly involving the LRRK2 gene, is an area of growing interest in medical research [65]. LRRK2 regulates various cellular processes, including cell signaling, vesicle trafficking, and autophagy [65].

The LRRK2 gene is associated with familial and sporadic PD forms [65]. Mutations in this gene have been identified as significant genetic contributors to PD development, affecting cellular processes such as protein degradation and mitochondrial function in neurons [66–68].

Interestingly, studies have revealed that specific mutations in the LRRK2 gene elevate the risk of PD and confer increased susceptibility to certain cancers [69–72]. Notably, these mutations have been linked to an elevated risk of lung cancer and various digestive tract cancers, such as colorectal cancer [73]. The exact mechanisms underlying how LRRK2 mutations contribute to cancer development are not fully understood but may involve alterations in cell proliferation, survival pathways, or immune responses [66–68]. For instance, the impact of LRRK2 mutations on cellular processes like autophagy, inflammation, or DNA repair mechanisms might contribute to the pathogenesis of PD and cancer [66,73]. The PINK1 (PTEN-induced putative kinase 1) gene is another significant genetic factor associated with PD [74,75].

Mutations in the PINK1 gene have been identified in cases of early-onset PD. PINK1 is critical in maintaining mitochondrial function, regulating mitochondrial quality control, and initiating the clearance of damaged mitochondria through mitophagy[74–76]. The PINK1 protein plays a crucial role in mitochondrial quality control and the regulation of cell death pathways [77–81]. Mutations in the PINK1 gene are associated with some instances of PD, leading to mitochondrial dysfunction and impaired removal of damaged mitochondria, contributing to neuronal degeneration [74,75]. A study involving mice lacking the PINK1 gene unveiled intriguing insights into the dual role of caspase-3 (CASP3), a pivotal protein governing programmed cell death. The absence of PINK1 led to adjustments in CASP3 activity. While excessive activation of CASP3 triggers cell demise, moderate activation seems to regulate vital physiological processes, including the modulation of corticostriatal synaptic plasticity [82]. Furthermore, in these PINK1-deficient mice, the suppression of PTEN protein intensified apoptosis rates and raised the levels of Bax and cleaved CASP3. These alterations were associated with heightened cancer-related characteristics like increased cell proliferation, colony formation, and invasiveness [83].

Interestingly, while the PINK1 gene is primarily linked to PD, some research suggests potential cancer implications [84,85]. Studies exploring the broader roles of PINK1 have indicated its involvement in cellular processes beyond PD, including aspects related to cancer biology [86]. Initially linked to cancer biology through its modulation by the tumor suppressor PTEN in a cancer cell model, PINK1 gained prominence as it exhibited robust expression in highly metastatic melanoma and colon carcinoma mouse cancer cell lines [87,88]. Subsequent studies further elucidated PINK1's multifaceted involvement in various aspects of cancer biology and metabolism, echoing pathways relevant to neurodegeneration and oncogenic transformation [89]. Intriguingly, epidemiological investigations uncovered a decreased risk of specific cancers in individuals with PD, aligning with this concept [89]. Notably, PINK1 emerged as a critical factor in tumor cell survival and resistance to chemotherapy in independent RNA interference screens, presenting itself as a promising target for cancer therapy [90,91]. Moreover, analysis of human ovarian carcinoma unveiled a negative correlation between elevated PINK1 mRNA expression and favorable patient outcomes [87,90,91]. These findings consolidate multiple studies highlighting PINK1's pivotal role in sustaining cell proliferation and thwarting cell death mechanisms. Its impact spans fundamental processes such as controlling the cell cycle, regulating apoptosis, managing protein degradation systems, maintaining mitochondrial homeostasis, and modulating cell metabolism [84].

Another gene that has drawn attention due to its potential association with PD and certain cancers is the SNCA gene, which encodes αS. This protein aggregates in the brains of individuals with PD [92].

Mutations or duplications in the SNCA gene have been linked to familial forms of PD. In addition to its role in PD, αS has been implicated in the pathology of various cancers [93,94]. It's been

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observed that elevated levels of αS could influence tumor growth and metastasis in particular cancer types, including breast cancer and colorectal cancer [95].

However, the relationship between SNCA mutations and cancer risk remains a subject of ongoing research and debate. Several other genes have been implicated in PD and have shown potential associations or interactions with certain aspects of cancer (**Table 1**). Parkin, a protein encoded by the PARK2 gene, is vital in removing damaged or unnecessary proteins within cells, a ubiquitination mechanism [96–98]. Mutations in the PARK2 gene are linked to familial forms of PD, impairing Parkin's function and accumulating toxic proteins contributing to neuronal degeneration [99].

While primarily linked to PD, studies have suggested a potential role for Parkin in specific cancers. Some research has explored its involvement in cellular processes related to tumor suppression and apoptosis, indicating a possible connection to cancer biology [96,100,101]. Parkin-7 (PARK7), also known as DJ-1, protects cells from oxidative stress, maintains mitochondrial function, and regulates cellular pathways associated with cell survival [102,103]. Mutations in the PARK7 gene are implicated in familial forms of PD, compromising cellular defenses against oxidative damage, and contributing to neuronal degeneration. However, the relationship between PARK7 and cancer remains unclear and warrants further investigation [104]. Some studies propose a potential role of PARK7 in certain cancer types, indicating its involvement in modulating cell proliferation, apoptosis, and tumor progression [104]. While these genes primarily feature in the context of Parkinson's disease, their broader implications or potential involvement in aspects of cancer biology are areas of ongoing investigation.

Table 1. Outlines the functions and prospective roles of key genes associated with PD and their possible implications in cancer development.

GENE	FUNCTION	ROLE IN NEURODEGENERATION	ROLE IN CANCER
LRRK2	LRRK2 regulates various cellular processes, including cell signaling, vesicle trafficking, and autophagy	The LRRK2 gene is associated with familial and sporadic PD forms. Mutations in this gene have been identified as significant genetic contributor to PD and development, affecting cellular processes such as protein degradation and mitochondrial function in neurons.	Involve alterations in cell proliferation, survival pathways, or immune responses for instance, the impact of LRRK2 mutations on cellular processes like autophagy, inflammation, or DNA repair mechanisms might contribute to the pathogenesis of PD and cancer
PINK1	Critical role in maintaining mitochondrial function, regulating mitochondrial quality control, and initiating the clearance of damaged mitochondria through a process called mitophagy. Plays a crucial role in mitochondrial quality control and the regulation of cell death pathways.	Mutations in the PINK1 gene are associated with certain cases of PD, leading to mitochondrial dysfunction and impaired removal of damaged mitochondria, contributing to neuronal degeneration	Studies exploring the broader roles of PINK1 have indicated its involvement in cellular processes beyond PD, including aspects related to cancer biology Initially linked to cancer biology through its modulation by the tumor suppressor PTEN

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			in a cancer cell model, PINK1 gained prominence as it exhibited robust expression in highly metastatic melanoma and colon carcinoma mouse cancer cell lines
SNCA	Encodes αS	Mutations or duplications in the SNCA gene have been linked to familial forms of PD	It's been observed that elevated levels of αS could influence tumor growth and metastasis in particular cancer types, including breast cancer and colorectal cancer..
PARK2	Parkin, a protein encoded by the PARK2 gene, is vital in removing damaged or unnecessary proteins within cells, a mechanism called ubiquitination	Mutations in the PARK2 gene are linked to familial forms of PD, impairing Parkin's function and accumulating toxic proteins contributing to neuronal degeneration	Some research has explored its involvement in cellular processes related to tumor suppression and apoptosis, indicating a possible connection to cancer biology
PARK 7	Parkin-7 (PARK7), also known as DJ-1, protects cells from oxidative stress, maintains mitochondrial function, and regulates cellular pathways associated with cell survival	Mutations in the PARK7 gene are implicated in familial forms of PD, compromising cellular defenses against oxidative damage and contributing to neuronal degeneration.	Involvement in modulating cell proliferation, apoptosis, and tumor progression. While these genes primarily feature in the context of Parkinson's disease, their broader implications or potential involvement in aspects of cancer biology are areas of ongoing investigation.

3. Exploring Genetic Intersections: Alzheimer's Associated Genes and Potential Links to Cancer Pathways

AD stands as a progressive neurodegenerative disorder marked by cognitive decline, memory impairment, and behavioral changes [105]. The correlation between AD and cancer presents a complex interplay, with emerging research shedding light on potential genetic intersections [106,107]. One of the genes that have garnered attention in both AD and certain cancers is the Apolipoprotein E (APOE) gene. [108]. The APOE gene encodes a protein involved in lipid metabolism and transportation, playing a crucial role in regulating cholesterol levels in the body [109]. In AD, specific variants of the APOE gene, notably the APOE ε4 allele, are known to significantly elevate the risk and influence the age of onset of the disease[108]. Intriguingly, studies exploring the role of APOE in cancer have shown diverse outcomes [108]. While some research suggests that the APOE ε4 allele might confer a decreased risk of certain cancers, particularly in breast and prostate cancers, other studies propose associations between APOE ε4 and an increased risk or poorer prognosis in certain

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malignancies, including ovarian and liver cancers [110–113]. The precise mechanisms underlying the dual roles of APOE in AD and cancer remain unclear.

Beyond APOE, several other genes and molecular pathways have been implicated in AD and certain cancers, contributing to the intriguing correlation between these seemingly disparate conditions **(Table 2)**. TP53 (tumor protein p53), a critical tumor suppressor gene, is commonly mutated in various cancers [110]. Interestingly, studies suggest that alterations in the TP53 gene might also influence neurodegenerative processes, including AD [114,115]
[114,115]. Mutations or dysregulation of TP53 have been observed in the brains of individuals with AD, indicating a potential link between TP53 and the neuropathology of AD [114,116]. Mutations in the Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) genes are strongly linked to early-onset familial AD, promoting the accumulation of amyloid-β peptides, a hallmark of AD pathology [117,118]. PSENs play pivotal roles in various cellular functions, including processing certain proteins like amyloid precursor (APP) [119–121]. However, the direct involvement of PSEN in cancer is less understood. Studies suggest potential roles of PSENs in regulating cell proliferation, apoptosis, and cellular signaling pathways relevant to tumorigenesis [122,123]. Still, their exact contributions to cancer development remain a subject of ongoing research and debate.

Interestingly, abnormal APP and amyloid-β accumulation processing have also been implicated in certain cancers, suggesting a potential intersection in both molecular mechanisms [124].

Beta-secretase 1 (BACE1) is a critical enzyme that produces Aβ peptides, which aggregate to form plaques, a hallmark of AD pathology [125]. BACE1 cleaves APP to generate these Aβ fragments, contributing to the neurotoxicity seen in AD [126,127]. However, the link between BACE1 and cancer remains a subject of investigation. Some studies suggest potential implications of BACE1 in cancer biology, highlighting its involvement in regulating cell proliferation, migration, and tumor growth [128,129].

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Table 2. Outlines the functions and prospective roles of key genes associated with AD and their possible implications in cancer development.

GENE	FUNCTION	ROLE IN NEURODEGENERATION	ROLE IN CANCER
APOE	Encodes a protein involved in lipid metabolism and transportation, playing a crucial role in regulating cholesterol levels in the body.	Specific variants of the APOE gene, notably the APOE ε4 allele, are known to significantly elevate the risk and influence the age of onset of the disease.	Alterations in the HTT gene could impact cell survival, DNA repair mechanisms, or cellular processes relevant to tumorigenesis.
TP53	A critical tumor suppressor gene, is commonly mutated in various cancers.	Mutations of TP53 have been observed in the brains of individuals with AD,	Tumor suppressor genes
PSEN	Play pivotal roles in various cellular functions, including processing certain proteins like APP.	Mutations in the PSEN1 and PSEN2 genes are strongly linked to early-onset familial AD, promoting the accumulation of amyloid-β peptides,	Studies suggest potential roles of PSENs in regulating cell proliferation, apoptosis, and cellular signaling pathways relevant to tumorigenesis
BACE1	Critical enzyme that produces Aβ peptides	BACE1 cleaves APP to generate these Aβ fragments, contributing to the neurotoxicity seen in AD	Potential implications of BACE1 in cancer biology, highlighting its involvement in regulating cell proliferation, migration, and tumor growth

4. Exploring Genetic Intersections: amyotrophic lateral sclerosis (ALS)'s-Associated Genes and Potential Links to Cancer Pathways

The correlation between amyotrophic lateral sclerosis (ALS) and cancer remains an area of interest, with potential genetic intersections providing insight into this complex relationship [130,131]. One gene has sparked attention in both ALS and cancer is the C9orf72 gene.

The C9orf72 gene plays a crucial role in cellular functions, including vesicle trafficking, autophagy, and RNA metabolism [132,133]. Expansions of the hexanucleotide repeat in the C9orf72 gene are ALS's most common genetic cause [134–136]. These expansions lead to toxic RNA and protein aggregates contributing to neuronal degeneration in ALS [134,135,137]. Intriguingly, alterations in C9orf72 have also been implicated in specific cancers [137–139]. Studies have identified associations between C9orf72 mutations and an increased risk of developing various malignancies, including brain tumors and certain types of lymphoma [140,141]. The precise mechanisms by which C9orf72 mutations contribute to both ALS and cancer are not fully understood. Alongside the C9orf72 gene, several other genes and molecular pathways have been proposed to have potential links between ALS and cancer **(Table 3)**. Fused in Sarcoma (FUS) gene is involved in various cellular functions, including RNA processing, transport, and DNA repair [142–144]. Mutations in the FUS gene are linked to familial and sporadic cases of ALS, where aberrant FUS proteins form toxic

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aggregates contributing to neuronal damage [145–147]. Aberrant FUS aggregation and pathology have also been associated with certain cancers, albeit in a relatively limited context compared to its involvement in ALS [139,148–150]. Superoxide dismutase 1 (SOD1) is an enzyme that is crucial in neutralizing harmful free radicals in cells by converting superoxide radicals into less toxic molecules [151,152]. Mutations in the SOD1 gene are associated with familial cases of ALS, where altered SOD1 proteins contribute to motor neuron degeneration [153,154]. While primarily studied in the context of ALS, some research has hinted at a potential role of SOD1 in modulating oxidative stress, inflammation, and cell survival pathways that might have implications in specific cancers [155,156].

Table 3. Outlines the functions and prospective roles of key genes associated with ALS and their possible implications in cancer development.

GENE	FUNCTION	ROLE IN NEURODEGENERATION	ROLE IN CANCER
C9orf72	Crucial role in cellular functions, including vesicle trafficking, autophagy, and RNA metabolism	Expansions of the hexanucleotide repeat in the C9orf72 gene are ALS's most common genetic cause. These expansions lead to toxic RNA and protein aggregates contributing to neuronal degeneration in ALS	Studies have identified associations between C9orf72 mutations and an increased risk of developing various malignancies, including brain tumors and certain types of lymphoma
FUS	Is involved in various cellular functions, including RNA processing, transport, and DNA repair.	Mutations in the FUS gene are linked to familial and sporadic cases of ALS, where aberrant FUS proteins form toxic aggregates contributing to neuronal damage	Aberrant FUS aggregation and pathology have also been associated with certain cancers, albeit in a relatively limited context compared to its involvement in ALS
SOD1	Enzyme that is crucial in neutralizing harmful free radicals in cells by converting superoxide radicals into less toxic molecules	Mutations in the SOD1 gene are associated with familial cases of ALS, where altered SOD1 proteins contribute to motor neuron degeneration	Potential role of SOD1 in modulating oxidative stress, inflammation, and cell survival pathways that might have implications in specific cancers

5. Exploring Genetic Intersections: Huntington's Disease's Associated Genes and Potential Links to Cancer Pathways

HD is a hereditary neurodegenerative disease caused by a polyglutamine (polyQ) expansion in the huntingtin (HTT) gene that profoundly impacts both movement control and cognitive function [157–159]. HD leads to the brain's gradual breakdown of nerve cells, particularly affecting the basal ganglia and cortex [160]. Studies investigating the relationship between HD and cancer have indicated intriguing links beyond the HTT gene mutations characteristic of HD [18,161–163]. Research has suggested a potential association between the HTT gene and specific cancer-related pathways [164,165]. The HTT gene produces the huntingtin protein, and while its primary role is linked to neuronal damage in HD, it might also have implications in cancer [166]. Some studies propose that alterations in the HTT gene could impact cell survival, DNA repair mechanisms, or

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cellular processes relevant to tumorigenesis [167,168]. Additionally, alterations in other genes associated with HD, such as genes involved in DNA repair pathways or cell cycle regulation, might contribute to the observed correlation between HD and certain cancers [162,165–167]. However, the precise mechanisms and the extent of this genetic overlap between HD and cancer remain areas of active investigation in scientific research. While the primary gene associated with HD is HTT, additional genetic factors have been suggested to potentially influence the correlation between HD and cancer [166] **(Table 4)**. For instance, genes involved in DNA repair mechanisms, such as breast cancer type 1 (BRCA1) and type 2 (BRCA2), have been implicated in cancer susceptibility and neurodegenerative disorders like HD [169,170]. The BRCA1 protein exhibits various roles across diverse cellular functions, including DNA repair, transcriptional activation, cell cycle control, and chromatin modification. Similarly, BRCA2 contributes to transcriptional and cell cycle regulation, DNA repair, mitophagy, and fortifying the stability of replication forks within cells [169,170]. BRCA1 and BRCA2 are extensively studied due to their pivotal roles in maintaining DNA integrity, particularly in repairing damaged DNA [170,171]. While their involvement in HD remains less understood, both genes are strongly associated with cancer susceptibility [170,171]. Mutations in BRCA1 and BRCA2 significantly elevate the risk of developing breast, ovarian, and other cancers. In the context of HD, while direct links between BRCA1/2 mutations and the disease are not well-established, exploring their functions in DNA repair mechanisms may shed light on potential intersections with HD pathology [170,171]. Their crucial role in DNA repair pathways suggests a possibility of shared pathways or processes implicated in both cancer and neurodegeneration, necessitating further investigation to unravel their precise roles in Huntington's disease and cancer development [170,171].

Additionally, gene alterations related to cell cycle regulation, such as TDP-43, have been observed in both HD pathogenesis and various cancer types [172,173]. In HD, abnormal aggregates of TDP-43 have been detected in the brain tissues of individuals with the disease [174]. However, the exact role of TDP-43 in the development or progression of HD is still being researched, and its specific contributions to the pathology of HD remain to be fully elucidated [174]. In cancer, alterations in TDP-43 expression or function have been observed in various cancer types, affecting cellular processes like RNA metabolism, splicing, and stability [174]. Dysregulation of TDP-43 has been linked to tumor growth, invasion, and metastasis in some cancers [175]. While its exact role in tumorigenesis is not fully understood, aberrant TDP-43 expression may contribute to the molecular mechanisms underlying certain cancers [175,176]. Other genes involved in oxidative stress response, apoptosis, or DNA damage repair pathways, such as ATM, may also play roles in HD and cancer development [172,177,178]. The intricate interplay of these genetic factors underscores the complex relationship between HD and specific cancer pathways, warranting further investigation into their shared molecular mechanisms and potential implications for disease development and progression [179].

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Table 4. Outlines the functions and prospective roles of key genes associated with HD and their possible implications in cancer development.

GENE	FUNCTION	ROLE IN NEURODEGENERATION	ROLE IN CANCER
HTT	Signaling, transporting materials,binding proteins and other structures, and protecting against apoptosis.	Primary role is linked to neuronal damage in HD.	Alterations in the HTT gene could impact cell survival, DNA repair mechanisms, or cellular processes relevant to tumorigenesis
BRCA1 BRCA2	The BRCA1 protein has multiple functions in different cellular processes, including DNA repair, transcriptional activation, cell cycle regulation and chromatin remodeling. BRCA2 plays a role in transcriptional and cell cycle regulation, DNA repair, mitophagy and replication fork stabilization.	Direct links between BRCA1/2 mutations and the disease are not well-established; exploring their functions in DNA repair mechanisms may shed light on potential intersections with HD pathology.	Mutations in BRCA1 and BRCA2 significantly elevate the risk of developing breast, ovarian, and other cancers.
TDP-43	Cell cycle regulation	Abnormal aggregates of TDP-43 have been detected in the brain tissues of individuals with the disease. However, the exact role of TDP-43 in the development or progression of HD is still being researched	Alterations in TDP-53 expression or function have been observed in various cancer types, affecting cellular processes like RNA metabolism, splicing, and stability. Dysregulation of TDP-53 has been linked to tumor growth, invasion, and metastasis in some cancers.

6. Conclusion and Future Prospective

The convergence of genes implicated in cancer and neurodegeneration represents a captivating area of exploration, offering glimpses into shared molecular pathways that influence these seemingly disparate conditions [2,7,13]. Genes showcase the intricate genetic intersections between cancer and neurodegeneration. Understanding these shared genetic factors presents an avenue for uncovering underlying mechanisms that drive both disease processes. However, these genes' dual roles in different cellular contexts underscore the complexity of their contributions to cancer and neurodegeneration. Future research endeavors are poised to delve deeper into these genetic intersections, deciphering how gene alterations influence diverse cellular processes leading to cancerous growth or neurodegenerative pathology. Further exploration of shared genetic signatures, coupled with advancements in technology and analytical approaches, holds promise for identifying novel therapeutic targets with broader applicability across both conditions. Leveraging this knowledge could pave the way for precision medicine strategies tailored to individual genetic

profiles, aiming for targeted interventions that address the intricacies of cancer and neurodegeneration, potentially transforming treatment paradigms and improving patient outcomes.

Abbreviations

- Aβ: amyloid-β
- AD: Alzheimer's disease
- αS: α-synuclein
- PD: Parkinson's disease
- PTEN: phosphatase and tensin homolog
- PINK1 or PARK6: PTEN-induced kinase 1
- LRRK2 or PARK8: leucine-rich repeat kinase 2
- MAPT: microtubule-associated protein tau
- APP: amyloid precursor protein
- PSEN1/2: presenilin 1/2
- CDK5: cyclin-dependent kinase 5
- HD: Huntington's disease
- siRNA: short-interfering RNA
- L-DOPA: levodopa
- PolyQ: polyglutamine
- Huntingtin (HTT)
- BRCA1: breast cancer type 1
- BRCA2: breast cancer type 2
- APOE: Apolipoprotein E
- TP53: tumor protein p53
- Presenilin 1: PSEN
- Presenilin 2: PSEN2
- Amyloid precursor protein: APP
- Beta-secretase 1: BACE1
- PTEN-induced putative kinase 1: PINK1
- Caspase-3: CASP3
- Amyotrophic lateral sclerosis: ALS
- Fused in Sarcoma: FUS
- Superoxide dismutase 1: SOD1

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