

Review Article**PTEN Gene: Genomic Structure, Biological Functions, Role in Human Disease, and Therapeutic Implications*****Arif Akbar Bhat¹, Nissar Ahmad Naikoo², Suhail Shafi Lone², Sabhiya Majid², Ruqaya Aziz¹**¹Department of Biochemistry, Kashmir Medical College & Hospital, I.E Sempora Medicity, Srinagar. 191101.²Department of Biochemistry, Government Medical College Srinagar, Karan Nagar. 190010***Corresponding Author:** Dr Arif Akbar Bhat

Received: 13.07.2026, Revised: 15.08.2026, Accepted: 08.09.2026

Abstract**Background**

This comprehensive review illuminates the complicated landscape of the PTEN (Phosphatase and Tensin Homolog) gene, unravelling its genomic structure, functional significance, and far-reaching implications in health and disease. From the coding sequences shaping its protein structure to its pivotal role as a negative regulator in the PI3K/AKT/mTOR pathway, PTEN's impact spans diverse realms, including cancer, neurodevelopmental disorders, and metabolic conditions. Exploring the genetic mutations and their ripple effects across various diseases, the review reveals the dysregulated signalling pathways that propel disease pathogenesis. It then navigates through PTEN's indispensable contributions to embryonic development, tissue homeostasis, and aging, emphasizing its role in cellular growth, differentiation, and the maintenance of tissue integrity. Zooming into the neurological domain, the review accentuates PTEN's involvement in neurodevelopmental disorders like autism and epilepsy. The potential therapeutic interventions come to the fore, with gene therapy, small molecule inhibitors, and combination therapies emerging as promising avenues to modulate PTEN activity. Looking ahead, the review charts the course for future PTEN research, highlighting emerging areas such as PTEN regulation, non-canonical functions, and interactions with microRNAs. Technological advancements in single-cell analysis, imaging, and genome editing promise to illuminate previously unseen facets of PTEN biology. The clinical implications and therapeutic potential of PTEN steal the spotlight, with precision medicine, targeted therapies, and novel applications beyond oncology offering glimpses into a transformative future. The review concludes by championing ongoing research efforts, calling for the unravelling of the intricate mechanisms governing PTEN, and paving the way for personalized diagnostics and groundbreaking therapies across a spectrum of diseases.

Conclusion: The PTEN gene has multiple functions and plays an important role in controlling the PI3K/AKT/mTOR signalling pathway and cellular homeostasis. It plays a role in tumour suppression as well as in metabolism, insulin signaling, development, aging and neurological and vascular disorders. Genetic and/or functional deregulations of PTEN can be linked to a wide variety of human diseases, such as cancer and metabolic disorders like type 2 diabetes mellitus. The understanding of PTEN regulation and the tissue specific role of this gene can lead to better disease diagnosis and targeted therapeutic approaches.

Keywords: Tumor suppressor gene; insulin signalling; type 2 diabetes mellitus; genetic mutations; metabolic disorders; cancer; therapeutic implications.

INTRODUCTION

The PTEN (Phosphatase and Tensin Homolog) gene is a critical regulator of various cellular processes, including cell growth, proliferation, survival, and metabolism. It is located on chromosome 10q23 and

encodes a dual-specificity phosphatase enzyme, commonly referred to as PTEN(1). This enzyme plays a pivotal role in maintaining cellular homeostasis by dephosphorylating phosphatidylinositol 3,4,5-trisphosphate (PIP3) and

negatively regulating the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signalling pathway(2). The PTEN gene consists of nine exons and eight introns, with a large coding sequence that spans approximately 44 kilobases(3). Alternative splicing of the PTEN mRNA can result in different protein isoforms with distinct functional properties. The PTEN protein contains a phosphatase domain, a C2 domain involved in protein-protein interactions, and a C-terminal tail responsible for membrane association and subcellular localization(4). The study of the PTEN gene has significant implications for both health and disease. PTEN is widely recognized as a potent tumor suppressor gene. Loss or inactivation of PTEN leads to increased activation of the PI3K/AKT/mTOR pathway, resulting in uncontrolled cell proliferation, survival, and tumor growth(5). PTEN mutations have been identified in various human cancers, including breast, prostate, colorectal, endometrial, and glioblastoma. Understanding the role of PTEN in tumor suppression is crucial for developing targeted therapies and improving cancer treatment outcomes(6). In addition to its role in cancer, PTEN mutations are associated with a group of rare genetic disorders collectively known as PTEN hamartoma tumor syndrome (PHTS). PHTS encompasses conditions such as Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome, characterized by the development of multiple hamartomas and an increased risk of developing various cancers(7). PTEN has emerged as a key player in neurodevelopmental disorders, including autism spectrum disorder (ASD) and macrocephaly/autism syndrome(8). Mutations in the PTEN gene have been found in a subset of individuals with ASD and intellectual disabilities(9). Research on PTEN's role in neuronal development, synaptic function, and plasticity can shed light on the underlying mechanisms of these disorders and potentially lead to targeted therapeutic interventions(10). PTEN has been implicated in the aging process and age-related diseases. Studies have shown that PTEN expression and activity decline with age, and dysregulation of PTEN contributes to age-related pathologies such as neurodegenerative disorders, cardiovascular diseases, and metabolic disorders. Investigating the interplay between PTEN and aging-related processes can provide insights into the underlying mechanisms of age-related diseases and potentially uncover novel therapeutic avenues(11). PTEN has emerged as an attractive therapeutic target for various diseases. Modulating PTEN activity holds promise for cancer treatment, as restoration of PTEN function can potentially inhibit tumor growth and sensitize

cancer cells to conventional therapies. Furthermore, developing small molecules or gene therapies that target PTEN may have therapeutic implications in PTEN-related disorders, neurodevelopmental disorders, and age-related diseases(12).

The PTEN gene is a crucial player in maintaining cellular homeostasis and is involved in a wide range of physiological and pathological processes. Understanding the role of PTEN in health and disease is essential for developing targeted therapies, improving diagnostic approaches, and unravelling the complex mechanisms underlying various disorders. Continued research on PTEN promises to contribute significantly to the field of molecular biology, genetics, and clinical medicine, ultimately benefiting human health.

PTEN Gene Structure and Function

PTEN (Phosphatase and Tensin Homolog) is a critical gene involved in regulating cellular processes and maintaining cellular homeostasis. In this section, we will explore the genetic structure of PTEN, the molecular mechanisms and signalling pathways associated with PTEN, and the role of the PTEN protein in various cellular processes.

Genetic structure of PTEN:

The PTEN gene is located on chromosome 10q23 and spans approximately 44 kilobases of DNA. It consists of nine exons and eight introns, with a large coding sequence. Alternative splicing of the PTEN mRNA leads to the generation of different protein isoforms with distinct functional properties(13). The PTEN protein is encoded by the longest transcript and consists of 403 amino acids. The PTEN gene contains several functional domains that contribute to its activity. These domains include the phosphatase domain, the C2 domain, and the C-terminal tail. The phosphatase domain is responsible for PTEN's enzymatic activity, as it possesses dual-specificity phosphatase activity, targeting both protein and lipid substrates. The C2 domain is involved in protein-protein interactions and is important for proper localization and regulation of PTEN. The C-terminal tail, on the other hand, mediates membrane association and subcellular localization of PTEN(14).

Molecular mechanisms and signalling pathways associated with PTEN:

PTEN primarily functions as a lipid phosphatase, dephosphorylating phosphatidylinositol 3,4,5-trisphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2)(15). This enzymatic activity antagonizes the PI3K/AKT/mTOR signalling pathway,

a key pathway involved in cell growth, proliferation, and survival. The PI3K/AKT/mTOR pathway is initiated by the activation of phosphatidylinositol 3-kinase (PI3K) upon receptor tyrosine kinase activation. PI3K phosphorylates PIP2 to generate PIP3, which serves as a crucial second messenger, recruiting proteins such as AKT to the plasma membrane(16). AKT is then phosphorylated and activated, leading to the phosphorylation and inactivation of various downstream targets involved in cell cycle progression, protein synthesis, metabolism, and apoptosis(17). The role of PTEN in this pathway is to dephosphorylate PIP3, thereby antagonizing PI3K activity and inhibiting AKT activation(18). Loss or inactivation of PTEN results in increased levels of PIP3, leading to constitutive activation of the PI3K/AKT/mTOR pathway(19). This dysregulation is frequently observed in cancer and contributes to uncontrolled cell growth, survival, and metastasis(20). In addition to the PI3K/AKT/mTOR pathway, PTEN is also involved in regulating other signalling pathways. PTEN has been shown to modulate the MAPK/ERK pathway, which plays a crucial role in cell proliferation, differentiation, and survival. PTEN can inhibit MAPK/ERK signalling by interacting with and negatively regulating components of this pathway(21).

Furthermore, PTEN is implicated in the regulation of the Wnt signalling pathway, which is involved in embryonic development, stem cell maintenance, and tissue homeostasis. PTEN can interact with and modulate the activity of proteins within the Wnt pathway, affecting downstream transcriptional events(22).

PTEN protein and its role in cellular processes:

The PTEN protein is a multifunctional regulator that plays a crucial role in various cellular processes. PTEN

acts as a tumor suppressor by inhibiting cell growth and proliferation. It accomplishes this by antagonizing the PI3K/AKT/mTOR pathway, which promotes cell cycle progression and protein synthesis. Loss or inactivation of PTEN leads to hyperactivation of this pathway, resulting in uncontrolled cell growth and tumor development(23). PTEN plays a role in regulating cell survival and apoptosis. By inhibiting the PI3K/AKT/mTOR pathway, PTEN reduces the anti-apoptotic signals mediated by AKT and promotes pro-apoptotic signalling. This balance between pro-survival and pro-apoptotic signals is crucial for maintaining cellular homeostasis and preventing the survival of damaged or abnormal cells(24). PTEN is

involved in the regulation of cellular metabolism, particularly glucose metabolism. The PI3K/AKT/mTOR pathway stimulates glucose uptake and utilization by promoting the translocation of glucose transporters to the cell membrane and activating key enzymes involved in glycolysis(25). PTEN's inhibitory effect on this pathway helps maintain proper glucose homeostasis and prevents excessive glucose uptake and metabolism(26). PTEN also contributes to the maintenance of genome stability. Loss of PTEN function has been associated with increased genomic instability, including chromosomal aberrations, DNA damage, and impaired DNA repair mechanisms(27). PTEN's role in genome stability is likely mediated through its influence on multiple cellular processes, including cell cycle progression, DNA damage response, and regulation of DNA repair mechanisms(28). PTEN is involved in the regulation of stem cell maintenance and differentiation. It has been shown to play a role in the self-renewal and differentiation of various stem cell populations, including embryonic stem cells and adult tissue-specific stem cells. PTEN's role in stem cell regulation is intricately linked to its influence on signalling pathways such as PI3K/AKT/mTOR and Wnt(29).

The PTEN gene and its protein product play crucial roles in cellular processes by regulating signalling pathways involved in cell growth, proliferation, survival, and metabolism. Understanding the genetic structure, molecular mechanisms, and functions of PTEN provides insights into its role as a tumor suppressor gene and its involvement in various cellular processes, making it an important focus of research in health and disease.

PTEN Gene Mutations and Human Diseases

PTEN (Phosphatase and Tensin Homolog) gene mutations are associated with a wide range of human diseases and conditions. In this section, we will provide an overview of PTEN-related disorders and syndromes, discuss the link between PTEN mutations and cancer development, and explore other diseases and conditions associated with PTEN gene mutations. PTEN-related disorders encompass a group of genetic conditions caused by mutations in the PTEN gene.

PTEN Hamartoma Tumor Syndrome (PHTS) is a spectrum of disorders characterized by the development of multiple benign and malignant tumors. The two main subtypes of PHTS are Cowden

syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS)(30). CS is characterized by the development of hamartomas (benign growths) in various tissues, including the skin, breast, thyroid, and gastrointestinal tract. BRRS is characterized by multiple hamartomatous polyps in the intestines, lipomas (benign fatty tumors), macrocephaly (enlarged head size), and developmental delays(31).

Proteus syndrome is a rare disorder characterized by the overgrowth of multiple tissues and the development of various tumors(32). It is associated with mosaic PTEN mutations, meaning that the

mutation occurs only in a subset of cells in the body. Proteus syndrome manifests with asymmetric overgrowth of limbs, connective tissue and skeletal abnormalities, and increased risk of developing tumors(33).

PTEN-Related Overgrowth Syndrome (PROS) is a group of disorders characterized by somatic mosaic PTEN mutations leading to overgrowth of specific tissues or organs. Different subtypes of PROS include fibroadipose overgrowth, macrocephaly with or without hydrocephalus, and segmental overgrowth(34).

Table 1: PTEN-Related Disorders

Disorders	Characteristics
PTEN Hamartoma Tumor Syndrome (PHTS)	- Cowden syndrome (CS): Hamartomas in skin, breast, thyroid, gastrointestinal tract.
	- Bannayan-Riley-Ruvalcaba syndrome (BRRS): Intestinal polyps, lipomas, macrocephaly, developmental delays.
Proteus Syndrome	- Overgrowth of multiple tissues, asymmetric limb overgrowth, increased tumor risk (mosaic PTEN mutations).
PTEN-Related Overgrowth Syndrome (PROS)	- Various subtypes with somatic mosaic PTEN mutations causing tissue/organ overgrowth.

Link between PTEN mutations and cancer development:

PTEN mutations are strongly associated with an increased risk of cancer development. The PTEN gene acts as a tumor suppressor, regulating cell growth, survival, and proliferation. Loss of PTEN function through mutations leads to dysregulation of signalling pathways, particularly the PI3K/AKT/mTOR pathway, resulting in uncontrolled cell growth and increased cancer susceptibility(35). PTEN mutations are implicated in both hereditary and sporadic forms of breast cancer. Women with PTEN mutations have a significantly increased risk of developing breast cancer, often at a younger age. Loss of PTEN function in breast cancer leads to increased activation of the PI3K/AKT/mTOR pathway, promoting cell proliferation and tumor growth(36). PTEN mutations are commonly found in

endometrial cancer, with loss of PTEN function observed in a substantial proportion of cases. PTEN loss contributes to the development of endometrial hyperplasia, a precursor to endometrial cancer, and promotes tumor growth and invasion(37). PTEN loss or mutations are detected in a subset of prostate cancers. PTEN inactivation in prostate cancer is associated with increased tumor aggressiveness, metastasis, and resistance to therapy(38). The PI3K/AKT/mTOR pathway is frequently activated in PTEN-deficient prostate cancer, promoting tumor growth and survival(39). PTEN mutations are less common in colorectal cancer compared to other cancers. However, PTEN inactivation contributes to colorectal cancer progression and metastasis(40).

Table 2: Cancers Associated with PTEN Mutations

Cancer Type	Association with PTEN Mutations
Breast Cancer	Increased risk, activation of PI3K/AKT/mTOR pathway, early onset in PTEN mutations.
Endometrial Cancer	Common PTEN mutations, PTEN loss contributes to endometrial hyperplasia and tumor growth.
Prostate Cancer	PTEN loss in a subset of prostate cancers, associated with aggressiveness and metastasis.
Colorectal Cancer	Less common, but PTEN inactivation contributes to progression and metastasis.

Other diseases and conditions associated with PTEN gene mutations:

In addition to cancer, PTEN gene mutations have been linked to several other diseases and conditions.

Diabetes: There is emerging evidence suggesting a link between PTEN mutations and diabetes development. PTEN has been implicated in the regulation of insulin signalling and glucose metabolism. Studies have shown that PTEN deficiency in pancreatic beta cells or in peripheral tissues can lead to impaired insulin signalling, insulin resistance, and glucose intolerance, contributing to the development of type 2 diabetes(41).

Neurodevelopmental Disorders: PTEN mutations have been associated with various neurodevelopmental disorders, including autism spectrum disorder (ASD) and intellectual disability. PTEN is involved in neuronal development, synaptic plasticity, and neuronal connectivity. Loss of PTEN function can disrupt these processes, leading to neurodevelopmental abnormalities and cognitive impairments (42)

Neurological Disorders: PTEN mutations have been implicated in the development of neurological disorders such as epilepsy and macrocephaly. PTEN loss in neurons can lead to dysregulation of neuronal excitability and synaptic function, contributing to the onset of epilepsy. Macrocephaly, characterized by an enlarged head size, can occur as a result of PTEN mutations affecting brain growth and development (10).

Vascular Malformations: PTEN mutations have been associated with vascular malformations, such as vascular overgrowth syndromes and venous malformations. PTEN loss can disrupt vascular

development and angiogenesis, leading to abnormal blood vessel formation and structural abnormalities in the vasculature (43)

Skin Disorders: PTEN mutations have been linked to various skin disorders, including Cowden syndrome and Proteus syndrome, which are characterized by the development of skin lesions, such as hamartomas and lipomas. PTEN is involved in regulating skin cell growth, differentiation, and proliferation, and loss of PTEN function can contribute to abnormal skin development (7).

Understanding the association between PTEN mutations and these diseases and conditions is crucial for diagnosis, prognosis, and the development of targeted therapies. Ongoing research is focused on elucidating the underlying mechanisms by which PTEN mutations contribute to the pathogenesis of these disorders, with the aim of developing novel therapeutic strategies to mitigate their impact.

PTEN Gene in Development and Aging

PTEN (Phosphatase and Tensin Homolog) plays a significant role in both embryonic development and aging-related processes. In this section, we will explore PTEN's involvement in embryonic development, its role in tissue homeostasis, and the changes in PTEN expression and function associated with aging.

PTEN's role in embryonic development and tissue homeostasis:

During embryonic development, PTEN is critical for the proper formation and differentiation of various tissues and organs. It regulates cellular processes that are essential for embryogenesis, including cell

proliferation, migration, differentiation, and morphogenesis (44). Cell Proliferation and Differentiation: PTEN regulates the balance between cell proliferation and differentiation, ensuring the proper formation of tissues and organs. It modulates signalling pathways such as the PI3K/AKT/mTOR pathway, which are crucial for regulating cell growth and differentiation. PTEN's negative regulation of this pathway prevents excessive cell proliferation and promotes cellular differentiation during embryonic development(19).

Cell Migration and Morphogenesis: PTEN also plays a role in cell migration and tissue morphogenesis. It regulates the dynamic processes involved in tissue formation, such as cell migration, cell adhesion, and cytoskeletal remodelling. By modulating signalling pathways involved in these processes, PTEN contributes to the proper arrangement and organization of cells and tissues during embryogenesis (45).

Tissue Homeostasis: PTEN's function extends beyond embryonic development to the maintenance of tissue homeostasis in adult organisms. In various tissues, including the brain, liver, and intestine, PTEN regulates stem cell activity, tissue regeneration, and repair processes. It ensures the balance between stem cell self-renewal and differentiation, helping to maintain tissue integrity and function (46).

Modulation of PTEN Activity:

PTEN Expression and Stabilization: One approach to enhance PTEN activity is to increase its expression or stabilize the PTEN protein. PTEN expression can be upregulated by various mechanisms, including transcriptional activation, epigenetic modifications, and post-transcriptional regulation. Identification of specific transcription factors and signalling pathways that regulate PTEN expression has provided insights into potential therapeutic targets for modulating PTEN levels(47). Moreover, PTEN stability can be enhanced by inhibiting its degradation pathways. PTEN is regulated by ubiquitin-mediated proteasomal degradation, and strategies targeting the proteins involved in PTEN degradation, such as E3 ubiquitin ligases, can stabilize PTEN and increase its activity (48).

PTEN Phosphatase Activity: PTEN's phosphatase activity can be modulated to restore its tumor suppressor function. Small molecules that directly

target the phosphatase domain of PTEN have been investigated as potential therapeutic agents. These molecules aim to enhance PTEN's enzymatic activity and restore its ability to dephosphorylate phosphoinositides, including phosphatidylinositol 3,4,5-trisphosphate (PIP3), thereby inhibiting downstream signalling pathways such as the PI3K/AKT/mTOR pathway(35).

PTEN Protein-Protein Interactions: PTEN interacts with various proteins to regulate its localization, stability, and activity. Disrupting or modulating these protein-protein interactions represents another strategy for therapeutic targeting of PTEN. For instance, compounds that interfere with PTEN's interaction with its negative regulators, such as phosphatase and actin regulator (PAR) proteins, can enhance PTEN activity (49).

PTEN as a Target for Drug Development:

Small Molecule Inhibitors: Small molecule inhibitors targeting PTEN-related signalling pathways have been explored for therapeutic intervention. These inhibitors aim to target downstream effectors or components of the pathways regulated by PTEN. For example, inhibitors targeting components of the PI3K/AKT/mTOR pathway have shown promise in preclinical and clinical studies. These molecules function by blocking the activation of AKT or mTOR, thereby inhibiting cell proliferation, promoting apoptosis, and sensitizing tumors to other therapies(50).

Combination Therapies: Combination therapies involving PTEN-targeted agents and other anticancer drugs are being investigated to enhance treatment efficacy. Combining PTEN modulators with conventional chemotherapeutic agents, immune checkpoint inhibitors, or targeted therapies can potentially improve treatment outcomes by overcoming resistance mechanisms and enhancing tumor cell sensitization (51)

Gene Therapy: Gene therapy approaches to restore PTEN expression or function hold promise for the treatment of PTEN-deficient diseases. These strategies involve delivering functional PTEN genes or gene editing techniques to correct mutations in the PTEN gene. Viral vectors, such as adeno-associated viruses (AAVs) or lentiviruses, can be used to deliver PTEN genes into target cells, aiming to restore PTEN expression and function (52).

Table 3: Approaches for Targeting PTEN in Drug Development

Therapeutic Approach	Mechanism
Small Molecule Inhibitors	Inhibiting specific components of PTEN-related signalling pathways.
Combination Therapies	Enhancing treatment efficacy through combined PTEN-targeted agents.
Gene Therapy	Restoring PTEN expression or function through gene delivery techniques.

Conclusion

The PTEN gene has multiple functions and plays an important role in controlling the PI3K/AKT/mTOR signalling pathway and cellular homeostasis. It plays a role in tumour suppression as well as in metabolism, insulin signalling, development, aging and neurological and vascular disorders. Genetic and/or functional deregulations of PTEN can be linked to a wide variety of human diseases, such as cancer and metabolic disorders like type 2 diabetes mellitus. The understanding of PTEN regulation and the tissue specific role of this gene can lead to better disease diagnosis and targeted therapeutic approaches.

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