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Review

# PTENopathy: A review on pathology, mechanisms, and treatment strategies

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***ABSTRACT***

PTENopathy refers to a class of uncommon genetic disorders brought on by changes or mutations in the phosphatase and tensin homologue (PTEN) gene. A wide range of clinical characteristics, such as an elevated risk of tumor growth, neurodevelopmental problems, macrocephaly, and other specific phenotypes, are present in these disorders. As a tumor suppressor gene, PTEN is essential for controlling cellular functions such as cell proliferation, survival, and metabolism. This is accomplished by modifying the phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin signaling pathway. Pathogenesis of PTENopathy is aided by dysregulation of this system brought on by PTEN gene mutations. The clinical range of PTENopathy encompasses overlapping disorders with various symptoms as well as distinct syndromes with different presentations, such as Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus and Proteus-like syndrome. A thorough clinical evaluation, family history analysis, and genetic testing to uncover PTEN gene mutations or changes are all necessary for the diagnosis of PTENopathy. PTENopathy treatment plans focus on addressing the disease's distinctive symptoms and effects. This may entail ongoing monitoring for the emergence of cancers, their early discovery and treatment, as well as the surgical removal of tumors. The quality of life for people with PTENopathy can be greatly enhanced by symptom-specific interventions, such as therapies for neurodevelopmental disorders and psychological assistance. Accurate information, support for family planning choices, and facilitation of thorough treatment are all dependent on genetic counseling. Despite being an uncommon ailment, PTENopathy has become easier to identify and comprehend thanks to improvements in genetic testing and raised awareness. In this review, the definition of PTENopathy, the structure and function of the PTEN gene, conditions causing PTENopathy, signs and symptoms, associated cancer types and other diseases and disorders, treatment methods, and the worldwide prevalence of the disease will explained.

***Keywords:*** Disease, gene, genetic disorders, PTEN, PTENopathy, treatment.

PTENopathy refers to a group of disorders caused by mutations in the phosphatase and tensin homologue (PTEN) gene. PTEN is a tumor suppressor gene that plays a crucial role in regulating cell growth, proliferation, and survival.[1] Mutations in the PTEN gene can lead to a variety of clinical manifestations, including macrocephaly (enlarged head size), developmental delay, intellectual disability, autism spectrum disorder (ASD), and an increased risk of certain types of cancer.[1-3]

PTEN mutations have been found in several rare autosomal-dominant disorders, including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), and Lhermitte-Duclos disease (LDD).[3] These disorders are characterized by the development of hamartomas, which are noncancerous growths that can occur in various organs and tissues.[2] In addition to these syndromes, PTEN mutations have also been associated with Proteus and Proteus-like syndromes.[4]

The clinical features of PTENopathy can vary widely, even among individuals with the same mutation. This is known as variable expressivity, and it is thought to be influenced by genetic and environmental factors.[3] For example, individuals with PTEN mutations may exhibit different combinations of symptoms, such as macrocephaly, intellectual disability, and ASD.[5] The severity of symptoms can also vary, ranging from mild to severe.[6]

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The underlying mechanisms by which PTEN mutations lead to the development of PTENopathy are not fully understood. However, it is known that PTEN is involved in the regulation of the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, which plays a critical role in cell growth, survival, and proliferation.[7] PTEN acts as a negative regulator of this pathway by dephosphorylating phosphatidylinositol-3,4,5-trisphosphate (PIP3), thereby inhibiting Akt activation.[8] Mutations in PTEN can disrupt this regulatory function, leading to dysregulation of the PI3K/Akt pathway and abnormal cell growth and development.[7]

Understanding the molecular and cellular mechanisms underlying PTENopathy is important for the development of targeted therapies. Recent studies have used human brain organoids and induced pluripotent stem cell-derived neural progenitor cells to model PTEN overexpression and investigate its effects on neurodevelopment. These models have provided insights into the role of PTEN in regulating cortical neurogenesis and have the potential to uncover new therapeutic targets for PTENopathy.[6,9]

PTENopathy refers to a group of disorders caused by mutations in the PTEN gene. These mutations can lead to a wide range of clinical manifestations, including macrocephaly, developmental delay, intellectual disability, and an increased risk of certain types of cancer. The underlying mechanisms of PTENopathy involve dysregulation of the PI3K/Akt signaling pathway. Further research is needed to fully understand the pathogenesis of PTENopathy and develop targeted therapies for affected individuals.[10]

## PTEN GENE

The PTEN gene is a multifunctional tumor suppressor gene that plays a crucial role in regulating cell growth, proliferation, and survival.[11] It is involved in various oncogenic pathways and its expression is tightly regulated by microribonucleic acids (miRs).[11] PTEN mutations have been implicated in the development and progression of several types of cancer, including glioblastoma, breast cancer, lung cancer, endometrial carcinoma, hepatocellular carcinoma (HCC), and colorectal cancer.[12-15]

In glioblastoma, amplifications at the miR-26a locus have been associated with downregulation of PTEN expression.[11] In breast cancer, PTEN mutations have been detected in a significant proportion of patients, and they are associated with the regulation of cell cycle, apoptosis, and metastasis.[12] In lung cancer, PTEN gene therapy has shown promise as a potential treatment strategy, particularly for non-small cell lung cancer.[16] In endometrial carcinoma, PTEN deficiency is considered an early event in the development of the disease, and PTEN mutations are frequently observed.[13] In HCC, PTEN acts as a negative regulator of the PI3K pathway, and mutations in the PTEN gene are associated with a wide variety of human tumors.[14] In colorectal cancer, high expression of PTEN has been linked to a good prognosis in patients.[15]

PTEN has been implicated in the regulation of renal tubular reabsorption function and normal kidney development. Loss of PTEN in renal tubular cells has been shown to lead to water retention by upregulating Aquaporin-2 expression. Overall, the PTEN gene plays a critical role in various cellular processes and its dysregulation has been implicated in the development and progression of multiple types of cancer. Understanding the molecular mechanisms underlying PTEN function and its involvement in different diseases can provide insights into potential therapeutic strategies and prognostic markers.[17]

## THE EFFECT OF THE PTEN GENE IN PTENOPATHY

PTEN gene mutations are the root cause of a set of disorders known as PTENopathy. A tumor suppressor gene called PTEN controls cell proliferation, death, and metastasis.[12] Melanoma, breast cancer, glioma, endometrial carcinoma, and cervical cancer are only a few of the cancers that have been linked to mutations and deletions in the PTEN gene.[18]

PTENopathy is associated with a wide range of clinical manifestations. Patients with PTEN mutations may exhibit macrocephaly, developmental delay, intellectual disability, and an increased risk of certain types of cancer.[19] Additionally, PTEN mutations have been linked to neurological and psychiatric disorders such as autism, seizures, mental retardation,

and schizophrenia.[7] The impact of PTEN overexpression on human health is still being studied, but loss of PTEN function has been associated with brain cancers, macrocephaly, autism, and epilepsy.[6]

Understanding the molecular mechanisms underlying PTENopathy is crucial for the development of targeted therapies. Gene editing techniques, such as adeno-associated virus-mediated gene editing, have shown promise in correcting PTEN mutations in glioblastoma cell lines.[20] Furthermore, PTEN promoter methylation and reduced PTEN expression have been observed in various cancers, suggesting that PTEN plays a role in tumorigenesis.[21]

In addition to PTENopathy, alterations in genes downstream of PTEN, such as those encoding PI3K/Akt and mammalian target of rapamycin (mTOR), have been associated with a collection of disorders known as PTENopathies. These conditions are characterized by alterations in the PI3K/Akt/mTOR pathway and can present with overlapping features with PTENopathy. PTENopathy is a group of disorders caused by mutations in the PTEN gene. These mutations can lead to a wide range of clinical manifestations, including macrocephaly, developmental delay, intellectual disability, and an increased risk of certain types of cancer. Dysregulation of the PI3K/Akt signaling pathway is a key mechanism underlying PTENopathy. Further research is needed to fully understand the pathogenesis of PTENopathy and develop targeted therapies for affected individuals.[22]

## CELLULAR AND MOLECULAR MECHANISM OF PTENOPATHY

A tumor suppressor gene called PTEN is implicated in a number of cellular and molecular pathways in a variety of disorders. PTEN is regulated by miRs, which is one of its cellular and molecular processes. Transforming growth factor-beta 1 (TGF-β1) stimulates Akt kinase in diabetic kidneys by targeting PTEN through a miR-dependent amplification circuit. miR-216a and miR-217, which downregulate PTEN, are expressed in response to TGF-β, which encourages fibrosis, hypertrophy, and cell survival in glomerular mesangial cells by activating Akt kinase.[23]

miR-216a and miR-217, which are activated by transforming growth TGF-β, target PTEN in the context of diabetic kidneys. These miRs suppress PTEN, which activates Akt kinase and encourages fibrosis, hypertrophy, and cell survival in glomerular mesangial cells. This pathway of Akt activation via PTEN downregulation by miRs controlled by upstream miR-192 and TGF-β may have ramifications for various diseases in addition to renal ailments.[23]

In glioma cells, PTEN has been found to increase autophagy and inhibit the ubiquitin-proteasome pathway independently of its lipid phosphatase activity. This suggests a new mTOR-independent signaling pathway by which PTEN regulates protein degradation mechanisms in glioma cells.[24]

Germline PTEN mutations are associated with PTEN hamartoma tumor syndrome (PHTS), an inherited cancer predisposition syndrome, and are also found in individuals with ASD. Studies using forebrain organoid cultures generated from gene-edited human induced pluripotent stem cells with PTEN mutations have shown that these mutations disrupt early neuroectoderm formation and neuronal differentiation, leading to abnormal neurodevelopmental processes.[25] PTEN also plays a role in neurodevelopment and behavior. Germline nuclear-predominant Pten murine models have exhibited impaired social and perseverative behavior, microglial activation, and increased oxytocinergic activity. These models provide insights into how disruptions to PTEN function can affect neurodevelopment, neurobiology, and social behavior, which are relevant to understanding the pathogenesis of ASD.[26]

In leukemia, the activation of the PI3K/Akt signaling pathway is commonly observed along with a decrease in PTEN expression. This pathway is involved in tumor angiogenesis, and targeting PI3K and Akt with small interfering RNAs has been shown to decrease tumor growth and angiogenesis.[27] In gliomas, PTEN alterations are frequently observed along with other tumor suppressor gene alterations, such as TP53 and CDKN2A. These alterations in PTEN and other genes are associated with the development and progression of gliomas.[28]

PTEN is also involved in the regulation of the PI3K/Akt signaling pathway, which is

essential for maintaining cellular homeostasis and is dysregulated in various diseases, including cancer. Loss or inactivation of PTEN leads to overactivation of the PI3K/Akt signaling pathway, driving tumorigenesis. The cellular and molecular mechanisms of PTEN involve its regulation by miRs, its impact on proteasome activity, its role in neurodevelopment and behavior, its association with other tumor suppressor gene alterations, and its involvement in the regulation of the PI3K/Akt signaling pathway. Understanding these mechanisms is crucial for elucidating the pathogenesis of various diseases and identifying potential therapeutic targets.[29]

## PTEN SIGNALING PATHWAY

The PTEN signaling pathway plays a crucial role in various cellular processes, including cell cycle regulation, deoxyribonucleic acid (DNA) damage response, chromosomal stability, and cell survival.[30-32] PTEN acts as a negative regulator of the PI3K pathway. The PI3K pathway is responsible for catalyzing the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to PIP3, which activates downstream signaling molecules such as Akt.[33]

PTEN can regulate the PI3K pathway both in the cytoplasm and nucleus. In the cytoplasm, PTEN dephosphorylates PIP3, thereby inhibiting the activation of Akt and downstream signaling. In the nucleus, PTEN may also regulate PI3K signaling and play a role in chromosomal stability, DNA damage response, and cell cycle regulation. The presence of key components of the PI3K pathway, including PIP2, PIP3, PI3Ks, 3-phosphoinositide-dependent protein kinase-1, Akt, and PTEN, in both the cytoplasm and nucleus supports the notion that PTEN can modulate PI3K signaling in these compartments.[30]

PTEN interacts with other proteins, such as p53 and CHK1, to maintain genomic stability and regulate cell cycle progression. The lack of mutual exclusivity of PI3K pathway events suggests that each component, including PTEN, may have nonlinear functions and contribute to the overall regulation of the pathway.[31]

In various disease contexts, PTEN dysregulation has been implicated in the pathogenesis and progression of cancer, glomerular disease, and other conditions.[34-36] Loss of PTEN expression or function can lead to increased cell survival, decreased apoptosis, and activation of the PI3K/Akt pathway, which promotes tumor growth and progression. Conversely, overexpression or activation of PTEN can inhibit cell survival, promote apoptosis, and negatively regulate the PI3K/Akt pathway. The PTEN signaling pathway plays a critical role in regulating the PI3K pathway and various cellular processes. PTEN acts as a negative regulator of the PI3K pathway by dephosphorylating PIP3 and inhibiting downstream signaling. It also interacts with other proteins to maintain genomic stability and regulate cell cycle progression. Dysregulation of PTEN can contribute to the development and progression of various diseases, including cancer and glomerular disease. Understanding the mechanisms and functions of the PTEN signaling pathway is important for developing targeted therapies and interventions for these conditions.[37]

## PI3K SIGNALING PATHWAY

The PI3K signaling pathway is a crucial intracellular pathway involved in various cellular processes, including growth, proliferation, survival, metabolism, and immune response regulation. Activation of the PI3K pathway leads to the production of PIP3, which in turn activates downstream signaling molecules such as Akt.[38]

The PI3K pathway has been implicated in the development and progression of cancer, as well as other diseases and syndromes. Dysregulation of this pathway can result in increased cell proliferation, survival, and migration, which are features of cancer. The PI3K/Akt pathway is frequently deregulated in cancer and represents an important target for anticancer therapies.[39]

In addition to its role in cancer, the PI3K pathway has been shown to play a role in various other biological processes. For example, it has been implicated in the regulation of inflammatory hyperalgesia in the peripheral nervous system. Activation of the PI3K/Akt pathway has also been observed in the propagation of influenza A virus and other viral infections.[40]

The PI3K pathway interacts with and cross-talks with other signaling pathways, leading to a complex network of signals that can

have significant consequences when perturbed. For instance, the NOTCH-MYC pathway has been shown to be activated in response to dual PI3K/mTOR inhibition, conferring resistance to PI3K inhibitors. The PI3K/Akt pathway also interacts with the PTEN pathway, which acts as a negative regulator of PI3K signaling. Understanding the mechanisms and regulation of the PI3K signaling pathway is crucial for developing targeted therapies and interventions for various diseases. The identification of key components and regulators within the pathway has provided potential therapeutic targets for the treatment of cancer and other conditions. Further research is needed to elucidate the precise roles and interactions of the PI3K pathway in different cellular contexts and disease states.[41]

## AKT SIGNALING PATHWAY

The Akt signaling pathway, also known as the PI3K/Akt pathway, is a critical intracellular pathway involved in various cellular processes, including metabolism, cell survival, proliferation, and differentiation. Activation of the Akt pathway occurs downstream of PI3K and is initiated by growth factors and other extracellular signals.[42]

The Akt pathway plays a central role in regulating metabolism in both normal physiology and disease conditions, such as obesity and type 2 diabetes (T2D). It is involved in the regulation of glucose homeostasis, lipid metabolism, protein synthesis, and cell proliferation and survival. Dysregulation of the Akt pathway has been implicated in the pathogenesis of obesity and T2D, highlighting its importance in metabolic disorders.[42]

In addition to its role in metabolism, the Akt pathway has been implicated in various diseases, including cancer, neurological diseases, and infertility. In cancer, the Akt pathway is frequently dysregulated and contributes to tumor growth, survival, and resistance to therapy. In neurological diseases, Akt signaling is involved in processes such as cell regeneration, apoptosis, and cognitive memory. In male infertility, the Akt pathway regulates the expression of proteins involved in the blood-testis barrier and Sertoli cell function.[43]

The Akt pathway interacts with multiple downstream effectors and signaling molecules to mediate its diverse functions. It phosphorylates and regulates various substrates involved in cell survival, apoptosis, and metabolism. The Akt pathway also cross-talks with other signaling pathways, such as the mTOR pathway, to coordinate cellular responses.[44]

Understanding the mechanisms and regulation of the Akt signaling pathway is crucial for developing targeted therapies and interventions for various diseases. The identification of key components and regulators within the pathway has provided potential therapeutic targets for the treatment of metabolic disorders, cancer, and other conditions. Further research is needed to elucidate the precise roles and interactions of the Akt pathway in different cellular contexts and disease states.[45]

## mTOR SIGNALING PATHWAY

Dysregulation of the mTOR pathway has been implicated in various disorders, including autism, epilepsy, neurodegenerative diseases, and cancer.[45-49] The mTOR pathway plays a significant role in brain function and is involved in synaptic plasticity, neuronal transmission, and neuronal size regulation. In the context of cancer, the mTOR pathway is frequently dysregulated and contributes to tumor growth and progression.[49]

The mTOR pathway interacts with various upstream and downstream molecules to mediate its functions. For example, G protein β-subunit-like protein has been identified as a positive regulator of the mTOR pathway, required for the nutrient-sensitive interaction between Raptor and mTOR.[50] The mTOR pathway also regulates nutrient transporters in the human placenta and is involved in altered transport functions observed in pregnancies complicated by pathological fetal growth.[51] Additionally, the mTOR pathway is interconnected with other signaling pathways, such as the PI3K/Akt pathway, tuberous sclerosis complex 1/tuberous sclerosis complex 2/Rheb pathway, and the AMP-activated protein kinase pathway.[49]

Pharmacological manipulation of the mTOR pathway holds therapeutic promise and has entered clinical trials for various disorders.[45]

Natural compounds from botanical drugs have been found to modulate the activity of the mTOR pathway and show potential in the treatment of atherosclerosis and cancer. Understanding the mechanisms and regulation of the mTOR signaling pathway is crucial for developing targeted therapies and interventions for these diseases. The mTOR signaling pathway is a critical cellular signaling hub involved in the regulation of growth, protein synthesis, gene expression, and metabolic balance. Dysregulation of the mTOR pathway is implicated in various disorders, including neurological diseases and cancer. The pathway interacts with upstream and downstream molecules and is interconnected with other signaling pathways. Pharmacological manipulation of the mTOR pathway holds therapeutic promise and is being explored in clinical trials.[49]

## SYMPTOMS AND DIAGNOSIS OF PTENOPATHY

PTENopathy, also known as PHTS, is a genetic disorder caused by mutations in the PTEN gene. The symptoms and diagnosis of PTENopathy can vary depending on the individual and the specific mutations involved. One of the key clinical features of PTENopathy is macrocephaly, which refers to an abnormally large head size. Macrocephaly is often the most evident symptom in early childhood and is an important criterion for initiating genetic testing for PTEN gene mutations.[52] Other neurodevelopmental and neurological symptoms associated with PTENopathy include developmental delay, mental retardation, learning disability, epilepsy, and behavioral difficulties.[53-55]

Individuals with PTEN mutations may also exhibit symptoms of ASD. Studies have shown that at least 23% of individuals with PTEN mutations meet the diagnostic criteria for ASD.[55] However, it has been observed that individuals with PTEN-associated ASD have lower clinical ratings of autism severity and more sensory abnormalities compared to those with macrocephalic ASD who do not have PTEN mutations.[56]

Diagnosing PTENopathy typically involves genetic testing to identify mutations in the PTEN gene. Early diagnosis is crucial for appropriate management and surveillance, particularly for high-risk cancer surveillance and addressing neurodevelopmental symptoms. A study proposed a mutation prediction model based on gender, presenting symptoms, and patient age to aid in the selection of patients for PTEN genetic testing. In summary, the symptoms of PTENopathy can include macrocephaly, developmental delay, mental retardation, learning disability, epilepsy, behavioral difficulties, and features of ASD. Diagnosis is typically made through genetic testing to identify mutations in the PTEN gene. Early recognition and diagnosis are important for appropriate management and surveillance of individuals with PTENopathy.[57]

## PTENOPATHY AND CANCER

### Glioblastoma

Glioblastoma is the most frequent and malignant brain tumor, characterized by rapid progression and poor prognosis.[58] The genetic pathways involved in the development of glioblastoma have been extensively studied. Loss of PTEN expression is one of the genetic alterations observed in glioblastoma. PTEN is a tumor suppressor gene that regulates cell growth, survival, and migration by inhibiting the PI3K/Akt signaling pathway.[59] In glioblastoma, loss of PTEN expression can occur through various mechanisms, including promoter methylation. However, the significance of PTEN methylation in the evolution of glioblastomas is still not fully understood. Studies have shown that PTEN mutations are not associated with the prognosis of glioblastoma patients. This suggests that other genetic alterations and signaling pathways may play a more significant role in determining the clinical outcome of glioblastoma.[59]

Glioblastoma is a highly invasive cancer, and its invasive behavior is a major challenge in treatment.[60] The small GTPase RhoG has been implicated in glioblastoma cell invasion. Depletion of RhoG inhibits the invasion of glioblastoma cells through brain tissue.[61] Additionally, semapimod, a drug that targets microglia, has been shown to inhibit glioblastoma tumor cell invasion. These findings highlight the importance of understanding the molecular mechanisms underlying glioblastoma invasion and identifying potential therapeutic targets.[62]

Alterations in ion channels, such as the intermediate-conductance calcium-activated potassium channel KCa3.1, have also been observed in glioblastoma. KCa3.1 channels are highly expressed in glioblastoma cells and play a role in controlling cell migration. Targeting KCa3.1 channels may have therapeutic potential in the treatment of glioblastoma. Glioblastoma is a highly aggressive brain tumor with a poor prognosis. Loss of PTEN expression is one of the genetic alterations observed in glioblastoma, although its prognostic significance remains unclear. Glioblastoma is characterized by invasive behavior, which is influenced by factors such as RhoG and microglia. Alterations in ion channels, including KCa3.1, are also implicated in glioblastoma pathogenesis.[63]

## COLORECTAL CARCINOMA

Colorectal carcinoma, also known as colorectal cancer, is a type of cancer that originates in the colon or rectum. PTEN is a tumor suppressor gene that plays a crucial role in the development and progression of colorectal carcinoma. Studies have shown that PTEN mutations or alterations are common in colorectal carcinoma. PTEN loss or inactivation can occur through various mechanisms, including gene mutations, deletions, promoter hypermethylation, oxidative inactivation, or suppression by miRs.[64,65] The loss of PTEN function contributes to the development and progression of colorectal carcinoma by dysregulating key signaling pathways involved in cell growth, survival, and migration.[66]

One of the important signaling pathways regulated by PTEN in colorectal carcinoma is the PI3K/Akt pathway. PTEN acts as a negative regulator of this pathway by dephosphorylating PIP3 to PIP2, thereby inhibiting the activation of Akt. Loss of PTEN function leads to increased Akt activation, which promotes cell proliferation, survival, and invasion in colorectal carcinoma. The dysregulation of PTEN in colorectal carcinoma has clinical implications. Studies have shown that PTEN expression levels can serve as prognostic markers in colorectal carcinoma. Decreased PTEN expression has been associated with lymph node metastasis and poor prognosis in colorectal carcinoma patients. Additionally, PTEN expression levels may have predictive value for the response to certain treatments. For example, decreased PTEN expression has been associated with the failure of tamoxifen treatment in colorectal carcinoma.[66]

Understanding the role of PTEN in colorectal carcinoma is important for the development of targeted therapies. PTEN restoration or activation strategies have been explored as potential therapeutic approaches for colorectal carcinoma. For instance, miR-32, which downregulates PTEN expression, has been targeted to inhibit cell proliferation, migration, and invasion in HCC.[67] Similarly, the downregulation of miR-221/222, which targets PTEN, has been shown to promote apoptosis in oral squamous cell carcinoma cells. PTEN plays a critical role in the development and progression of colorectal carcinoma. Loss of PTEN function through various mechanisms contributes to dysregulated signaling pathways, such as the PI3K/Akt pathway, promoting cell proliferation, survival, and invasion. PTEN expression levels have prognostic and predictive value in colorectal carcinoma. Targeting PTEN and its associated pathways may hold promise for the development of novel therapeutic strategies for colorectal carcinoma.[68]

## BREAST CANCER

Breast cancer is a complex disease with various subtypes and molecular alterations. PTEN is a tumor suppressor gene that plays a significant role in breast cancer development and progression. Several studies have investigated the association between PTEN alterations and breast cancer. Loss of PTEN expression has been observed in different subtypes of breast cancer, including ER-negative, PR-negative, and triple-negative breast cancers.[69] PTEN loss has also been associated with aggressive behavior, poor prognosis, and increased risk of distant metastasis in breast cancer.[69-71] Furthermore, PTEN loss has been linked to negative hormone receptor status and basal-like phenotypes in breast cancer.[69,72]

PTEN alterations in breast cancer are often mutually exclusive with mutations in the PIK3CA gene, which is a key component of the PI3K/Akt signaling pathway. The PI3K/Akt pathway is frequently dysregulated in breast cancer and is involved in cell growth, survival,

and migration.[73] Loss of PTEN function leads to increased activation of the PI3K/Akt pathway, promoting tumor progression.[74]

The combination of PTEN status with other molecular markers, such as human epidermal growth factor receptor 2 (HER2) and hormone receptor status, can provide valuable information for risk assessment and treatment strategies in breast cancer.[75] For example, PTEN loss in HER2-positive breast cancers with concurrent PTEN loss has been associated with resistance to HER2-targeted therapy. Understanding the interplay between PTEN and other molecular markers can help guide personalized treatment decisions.[74]

In preclinical studies, PTEN deficiency in breast cancer has been shown to accelerate tumor growth and metastasis. Inhibition or suppression of PTEN expression in breast cancer cells has been associated with increased cell proliferation, migration, invasion, and distant metastasis. These findings highlight the importance of PTEN in regulating malignant behavior in breast cancer. PTEN alterations play a significant role in breast cancer, particularly in aggressive subtypes and negative hormone receptor status. Loss of PTEN function contributes to the dysregulation of the PI3K/Akt pathway and is associated with poor prognosis and resistance to targeted therapies. Understanding the impact of PTEN alterations in breast cancer can aid in risk assessment, treatment decision-making, and the development of novel therapeutic strategies.[70]

## LUNG CANCER

PTEN is a tumor suppressor gene that plays a significant role in lung cancer. Loss of PTEN expression or function has been observed in lung cancer and is associated with disease progression and poor prognosis.[76-78] PTEN loss in lung cancer is often accompanied by dysregulation of the PI3K/Akt signaling pathway, which is involved in cell growth, survival, and migration.[79,80]

Studies using mouse models have demonstrated the importance of PTEN in lung morphogenesis and the development of lung adenocarcinomas. Mice with bronchioalveolar epithelium-specific PTEN deletion developed spontaneous lung adenocarcinomas, highlighting the role of PTEN in lung cancer initiation. Additionally, PTEN deficiency in lung cancer cells has been shown to promote tumor growth and metastasis.[81]

The loss of PTEN expression in lung cancer has clinical implications. It has been associated with characteristics such as male gender, smoking history, poorly differentiated tumors, increased lymph node involvement, distant metastasis, and advanced stage, which are indicators of poor prognosis. PTEN loss in combination with activated Akt has been associated with lower survival rates in lung cancer patients.[77]

Targeting the PTEN/PI3K/Akt pathway has emerged as a potential therapeutic strategy for lung cancer. Inhibition of this pathway has been shown to suppress lung cancer cell proliferation, migration, and invasion.[82,83] PTEN restoration or activation strategies have been explored as potential therapeutic approaches. PTEN plays a crucial role in lung cancer development and progression. Loss of PTEN expression or function is associated with poor prognosis and aggressive tumor characteristics in lung cancer. Dysregulation of the PTEN/PI3K/Akt pathway contributes to lung cancer pathogenesis. Understanding the role of PTEN in lung cancer can provide insights into potential therapeutic targets and strategies for intervention.[78]

## ENDOMETRIAL CARCINOMA

Endometrial carcinoma, also known as endometrial cancer, is a type of cancer that arises from the lining of the uterus. PTEN is a tumor suppressor gene that plays a crucial role in the development and progression of endometrial carcinoma. Several studies have investigated the relationship between PTEN alterations and endometrial carcinoma. Loss of PTEN expression or function has been observed in endometrial carcinoma and is associated with disease progression and poor prognosis.[84,85] PTEN loss in endometrial carcinoma is often accompanied by dysregulation of the PI3K/Akt signaling pathway, which is involved in cell growth, survival, and migration. Loss of PTEN function leads to increased activation of the PI3K/Akt pathway, promoting tumor progression in endometrial carcinoma.[85]

The coexistence of PTEN mutations with other genetic alterations, such as mutations in the PIK3CA gene, has been observed in endometrial carcinoma. These coexistent mutations may contribute to the dysregulation of the PI3K/Akt pathway and the development of endometrial carcinoma.[84]

The loss of PTEN expression in endometrial carcinoma has clinical implications. It has been associated with aggressive tumor characteristics, including high-grade tumors, advanced stage, and lymphovascular invasion. PTEN loss has been linked to endometrioid histology and is inversely associated with the presence of lymphovascular space invasion. Understanding the role of PTEN in endometrial carcinoma is important for the development of targeted therapies. PTEN restoration or activation strategies have been explored as potential therapeutic approaches for endometrial carcinoma. Targeting the PTEN/PI3K/Akt pathway may provide opportunities for personalized treatment and improved outcomes in endometrial carcinoma. PTEN alterations play a significant role in endometrial carcinoma. Loss of PTEN expression or function is associated with poor prognosis and aggressive tumor characteristics. Dysregulation of the PTEN/PI3K/Akt pathway contributes to endometrial carcinoma pathogenesis.[85]

## HEPATOCELLULAR CARCINOMA

PTEN expression is often changed in HCC, according to numerous studies. PTEN expression has been found to be downregulated or lost in a small number of HCC patients. The deregulation of the PTEN pathway caused by this loss of PTEN function can accelerate the development of tumors.[86] In some cases, HCC may be associated with specific mutations in the PTEN gene. These mutations can result in the inactivation or loss of function of the PTEN protein, leading to the dysregulation of downstream signaling pathways involved in cell growth and survival.[87] PTEN is a negative regulator of the PI3K/Akt/mTOR pathway, which is involved in cell growth, survival, and metabolism. Loss of PTEN function leads to increased activation of this pathway, promoting cell proliferation and survival in HCCs.[88] PTEN is considered a tumor suppressor gene, and its functional loss or inactivation has been associated with various cancers, including HCC. Dysregulation of the PTEN pathway contributes to uncontrolled cell growth, reduced apoptosis, and increased tumor progression. While the relationship between HCC and the PTEN pathway is established, it is important to note that the specific mechanisms and molecular alterations may vary among individual cases. Ongoing research continues to explore the molecular mechanisms and potential therapeutic implications of targeting the PTEN pathway in HCC.[89,90]

## ASSOCIATION OF PTENOPATHY WITH OTHER DISEASES AND DISORDERS

### Cowden Syndrome

PTENopathy is the name given to a collection of diseases brought on by changes or mutations in the PTEN gene. Cowden syndrome is one of the most well-known and clinically important PTENopathy-related disorders. Multiple hamartomas, which are benign growths that can appear in a variety of body tissues and organs, are a distinctive feature of the rare genetic condition known as Cowden syndrome. The skin, mucous membranes, gastrointestinal tract, thyroid, breast, and other organs may be impacted by these growths. Because Cowden syndrome is inherited in an autosomal dominant manner, there is a 50% probability that an affected person may pass the disorder on to their offspring. The PTEN protein is made according to instructions from the PTEN gene, which is found on chromosome 10q23. The PTEN protein controls cell survival, division, and growth in order to operate as a tumor suppressor. Its primary role is that of a phosphatase, which involves removing phosphate groups from particular proteins implicated in cell signaling pathways, such as the PI3K/Akt/mTOR pathway. A PTEN gene mutation or modification that results in the synthesis of an aberrant PTEN protein or decreased quantities of functional PTEN protein is inherited by people with Cowden syndrome. The normal control of cell growth and division is disrupted when PTEN function is lost or impaired, which raises the possibility of cancer development and tumor growth. Breast, thyroid, endometrial, colorectal, and kidney cancers are among the many cancers for which Cowden syndrome is linked to an elevated risk.

The specific cancer risks can differ depending on the affected person. Important aspects of clinical care for people with Cowden syndrome include routine surveillance and management of associated cancer risks.[91-94]

### Bannayan-Riley-Ruvalcaba Syndrome

Developmental delays, numerous hamartomatous polyps in the gastrointestinal tract, lipomas (benign fatty tumors), and macrocephaly are only a few of the symptoms of the rare genetic illness known as BRRS. Bannayan-Riley-Ruvalcaba syndrome is regarded as a member of the spectrum of PTENopathies, or diseases brought on by mutations or changes in the PTEN gene. A PTEN gene mutation or change that results in the synthesis of an aberrant PTEN protein or decreased quantities of functional PTEN protein is inherited by people with BRRS. The normal control of cell growth and division is disrupted by the loss or reduction of PTEN function, which aids in the emergence of the BRRS-specific traits. Breast, thyroid, and colorectal cancers are among the cancers that may be more likely to affect people with BRRS. However, BRRS generally carries a lesser risk of developing cancer than other PTEN-related diseases such as Cowden syndrome. For the purpose of managing the accompanying clinical characteristics, such as gastrointestinal polyps, lipomas, and developmental delays, it is crucial that people with BRRS get routine medical surveillance. In order to determine the danger to themselves and their family, it is also advised that those suspected of having BRRS seek out genetic counseling and testing.[95-97]

### Proteus and Proteus-Like Syndrome

Skin, bones, and other tissues, as well as other organs, grow excessively in Proteus syndrome, a rare genetic condition. A somatic mutation in the AKT1 gene, a component of the PI3K/Akt/mTOR signaling cascade, is the cause of it. Proteus-like syndrome, a disorder that shares certain clinical characteristics with Proteus syndrome but is separate from PTENopathy, is associated with PTEN mutations. Proteus-like syndrome describes situations when people have clinical traits like Proteus syndrome but lack the particular AKT1 mutation. Instead, it has been discovered that some people with Proteus-like disease have hereditary PTEN gene abnormalities. PTEN mutations cause the PI3K/Akt/mTOR pathway to be disrupted in some situations, which results in aberrant tissue development and other clinical symptoms resembling Proteus syndrome. Proteus-like syndrome is a descriptive phrase, not a particular clinical entity, it is crucial to remember. It is used to characterize people who don't have the AKT1 mutation but exhibit clinical traits similar to those of Proteus syndrome. The phrase is frequently used when a PTEN mutation is shown to be the root cause.[98-100]

## LHERMITTE-DUCLOS DISEASE

An uncommon tumor-like illness known as LDD, sometimes called dysplastic gangliocytoma of the cerebellum, is characterized by an aberrant proliferation of cells in the cerebellum. LDD is included in the spectrum of PTENopathy, a collection of diseases brought on by mutations or changes in the PTEN gene. By blocking the PI3K/Akt/mTOR pathway, the tumor suppressor gene PTEN controls cell growth, division, and survival. The normal regulation of this pathway is disrupted by mutations or changes in the PTEN gene, which causes uncontrolled cell growth and tumor development in a variety of tissues and organs. PTEN mutation carriers are more likely to experience LDD in the setting of their cerebellar condition. An internal cerebellar mass that is slow-growing is the hallmark of LDD, which is commonly diagnosed in adults. Under a microscope, the aberrant cells in LDD exhibit a recognizable look, with deformed architecture and larger cells. Although PTEN mutations are linked to LDD, not everyone who carries a PTEN mutation will experience LDD and not all cases of LDD are brought on by PTEN mutations. There may be additional genetic and environmental variables that affect LDD development.[101-103]

## AUTISM SPECTRUM DISORDER

A fraction of people with ASD have been shown to have PTEN mutations and changes. PTEN, a tumor suppressor gene, is essential for controlling a number of biological functions, such as cell development, proliferation, and neural signaling. A tiny proportion of people with ASD have germline PTEN mutations or changes, which causes a syndrome known as PHTS. PTEN hamartoma tumor syndrome covers a range of illnesses, such as Cowden syndrome,

BRRS, and Proteus-like syndrome, which are marked by neurodevelopmental characteristics as well as an elevated risk of tumor formation. The neurodevelopmental symptoms of ASD and PTEN mutations may include traits typically associated with the disorder, such as difficulties with social interaction and communication, repressed and repetitive behaviors, and sensory sensitivity. Additional clinical signs of PTENopathy, such as macrocephaly (enlarged head), intellectual disability, developmental delays, and epilepsy, may also be present in these people. Investigations are still ongoing to determine the underlying processes by which PTEN mutations contribute to the emergence of ASD. Various aspects of neuronal development and function, including synapse formation, neuronal migration, and synaptic plasticity processes that are essential for healthy brain development can be affected by disruption of the PTEN signaling pathway. It is crucial to remember that PTEN mutations only account for a small percentage of ASD cases and are a relatively uncommon cause of the disorder. For those with ASD who also show additional clinical signs of PTENopathy, such as macrocephaly or other physical indications, genetic testing and counseling may be advised.[104-108]

## SHANK3 MUTATION

Two separate genetic disorders, PTENopathy and SH3 and multiple ankyrin repeat domains protein 3 (SHANK3) mutations, can both influence neurodevelopmental problems like ASD and intellectual disability. Despite being distinct disorders, there may be considerable overlap in the clinical manifestations and biochemical underpinnings of some conditions. The SHANK3 gene on chromosome 22q13.3 produces a protein that is essential for synaptic activity and neural transmission. Phelan-McDermid syndrome (PMS), an uncommon genetic condition characterized by intellectual disability, delayed or absent speech, ASD symptoms, and other neurodevelopmental problems, has been closely linked to mutations or changes in the SHANK3 gene. PTENopathy, on the other hand, is a group of ailments brought on by changes or mutations in the PTEN gene. PTEN is a tumor suppressor gene that controls cell growth, division, and neural signaling, as was previously described. PTEN mutations can result in a variety of clinical symptoms, such as macrocephaly, intellectual impairment, developmental delays, and an elevated chance of developing specific malignancies. A complicated presentation of overlapping symptoms from PMS and PTENopathy has been described in patients who have both SHANK3 mutations and PTEN mutations. Both of these genetic changes may raise the likelihood of ASD and cause more severe neurodevelopmental problems. Investigations are still ongoing to determine the underlying molecular pathways by which SHANK3 and PTEN mutations lead to neurodevelopmental problems. Both genes are involved in signaling pathways and synaptic function, which are essential for healthy brain growth and operation. These pathways can be disrupted, which can have an impact on synaptic plasticity, neuronal connection, and general brain circuitry, resulting in the neurodevelopmental abnormalities that have been reported.[109-115]

## TREATMENT METHODS OF PTENopathy

The specific symptoms and manifestations linked to PTEN gene mutations or changes are the focus of PTENopathy treatment. Depending on the individual's particular needs, the management strategy frequently comprises a multidisciplinary team of medical experts, including geneticists, neurologists, oncologists, psychiatrists, and other specialists. Depending on the distinct symptoms and problems that each patient experiences, different treatment plans for PTENopathy may be employed. In people with PTEN gene mutations, regular observation and screening for potential tumor growth are necessary. Physical examinations on a regular basis, imaging tests (such as magnetic resonance imaging or ultrasound), and targeted screenings for cancers with a higher risk in PTENopathy, such as breast, thyroid, and endometrial cancers, may all be part of this. Results can be improved by early detection and intervention. For the treatment of different benign tumors linked to PTENopathy, such as thyroid nodules or skin lesions, surgical care may be required. To relieve symptoms, lower the chance of complications, and stop malignant transformation, tumors may be surgically removed. To treat particular PTENopathy-related symptoms or illnesses, doctors may give medications. To manage seizures, for instance, antiepileptic medications may be provided, and hormone

replacement treatment may be utilized in cases of endocrine disorders. The functional restrictions brought on by PTENopathy can be addressed with the aid of physical and occupational therapy. These treatments concentrate on enhancing mobility, strength, coordination, and everyday living abilities. Psychological assistance and behavioral therapies may be helpful for those with PTENopathy, particularly those who also have neurodevelopmental disorders like ASD. These may include counseling, methods for altering behavior, instruction in social skills, and individualized educational support. In the therapy of PTENopathy, genetic counseling is extremely important. Genetic counselors explain family planning alternatives, provide information on the genetic disorder, and offer advice on any dangers or implications for family members. They can also make genetic testing and result interpretation easier. It is significant to remember that treatment strategies should be tailored to the unique requirements and symptoms of each person with PTENopathy. To monitor the patient's condition, administer the proper therapies, and modify the treatment plan as necessary, regular follow-up with medical professionals is crucial.[116-118]

## THE PREVALENCE OF PTENopathy

Limited data on the global prevalence of PTENopathy, which refers to a collection of diseases brought on by mutations or changes in the PTEN gene, are available as of September 2021. PTENopathies are regarded as rare diseases, and the prevalence of each illness within the PTENopathy spectrum varies. PTENopathy has been linked to a number of specific diseases, including Cowden syndrome, BRRS, and Proteus-like syndrome. Although there are specific global prevalence data for PTENopathies as a whole, they are not always available. Each of these disorders has its own prevalence rates. However, it is important to keep in mind that certain PTENopathy disorders, such as Cowden syndrome, are thought to affect 1 in 200,000 to 250,000 people in the general population. Other PTEN-related disorders may have varying prevalence rates. For the most current and thorough information on the frequency of particular PTEN-related disorders in various groups and countries, it is crucial to speak with healthcare practitioners or reference specialized medical literature.[119-125]

In conclusion, the management of PTENopathy's symptoms and side effects is the main goal of treatment. This may entail ongoing tumor monitoring, tumor removal surgery, symptom-specific treatment, emotional support, and genetic counseling. Individualized treatment plans are developed based on each patient's unique needs. For further information on PTENopathy diagnosis, management, and therapy options, it is crucial to speak with healthcare professionals who have experience with PTENopathy and to reference medical literature and clinical recommendations. To better diagnosis, therapy, and outcomes for those who suffer from PTENopathy, further study and progress in knowledge are required.

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