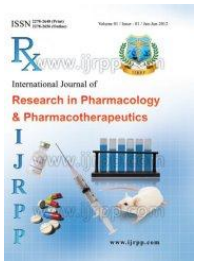
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648
ISSN Online: 2278-2656

IJRPP |Vol.4 | Issue 2 | April-June-2015
Journal Home page: www.ijrpp.com

Review article | Open Access

A review on AKT1 and PTEN gene of proteus syndrome

Ved Kumar Mishra[1], Ayushi Arya[2], Naveen Dwivedi[3], Shubha Dwivedi[4], Ashwani Kumar Singh[5], Vineeta Singh[6], Prashant Kumar Mishra[7]

[1,2,3,4&5]*Department of Biotechnology, S.D. College of Engineering & Technology, Jansath Road, Muzaffarnagar, U.P.-India,*

[6]*Department of Biotechnology, NIET Greater Noida, U.P.-India.*

[7]*Zoology Department, Allahabad University, Allahabad, U.P.-India.*

***Corresponding author: Ved Kumar Mishra**

E-mail id: ved.m45@gmail.com

ABSTRACT

Proteus syndrome is a very complex and rare to find in the world. It consists of asymmetric and disproportionate overgrowth in bones and skins. There are very few cases that have been come in light all over the world. The responsible genes for the proteus syndrome were AKT1 gene and PTEN. AKT1 is causing of proliferation, growth in cell cycle and PTEN is tumour suppressor gene in which the change causes the growth in cells. Proteus syndrome is a mutation occurs in chromosomes and it is a disorder not a disease. The major breaks of pathway are commonly found and eventually lead to the clinical approaches as their effect.

Keywords: AKT1, PTEN, mTOR, PI3K, PIP.

INTRODUCTION

Proteus syndrome was firstly found in a man who belonged to England and was known by the name 'Joseph Carey Merrick'. He was also known as the 'Elephant Man'. Joseph Merrick had disproportionate overgrowth on his face and limbs. His left arm was normal but right limb was affected with overgrowth (1). Basically, his body was seen very strange. He could not able to do his work properly and even he could not able to speak properly. His one eye was also half covered with overgrowth tissues. He was suffering many difficulties due to this syndrome. Proteus syndrome is basically a disorder. It is not a disease. It is very rare to be found. It is found less than 1 man over 1 million. Proteus syndrome is named after a Greek Sea-God 'Proteus' who could take any form (2). Cohen and Hayden were first who described the disorder in 1979 (3) but 'Proteus syndrome' term was coined by Wiedemann *et al.* in 1983. Proteus Syndrome also known as 'Wiedemann Syndrome' (4). Proteus syndrome starts in human when mutation occurs in chromosome 10 and 16. It is characterized by asymmetrical and disproportionate overgrowth of skin and bones. Many of the cases have been reported of this disorder but these are few hundred in number.

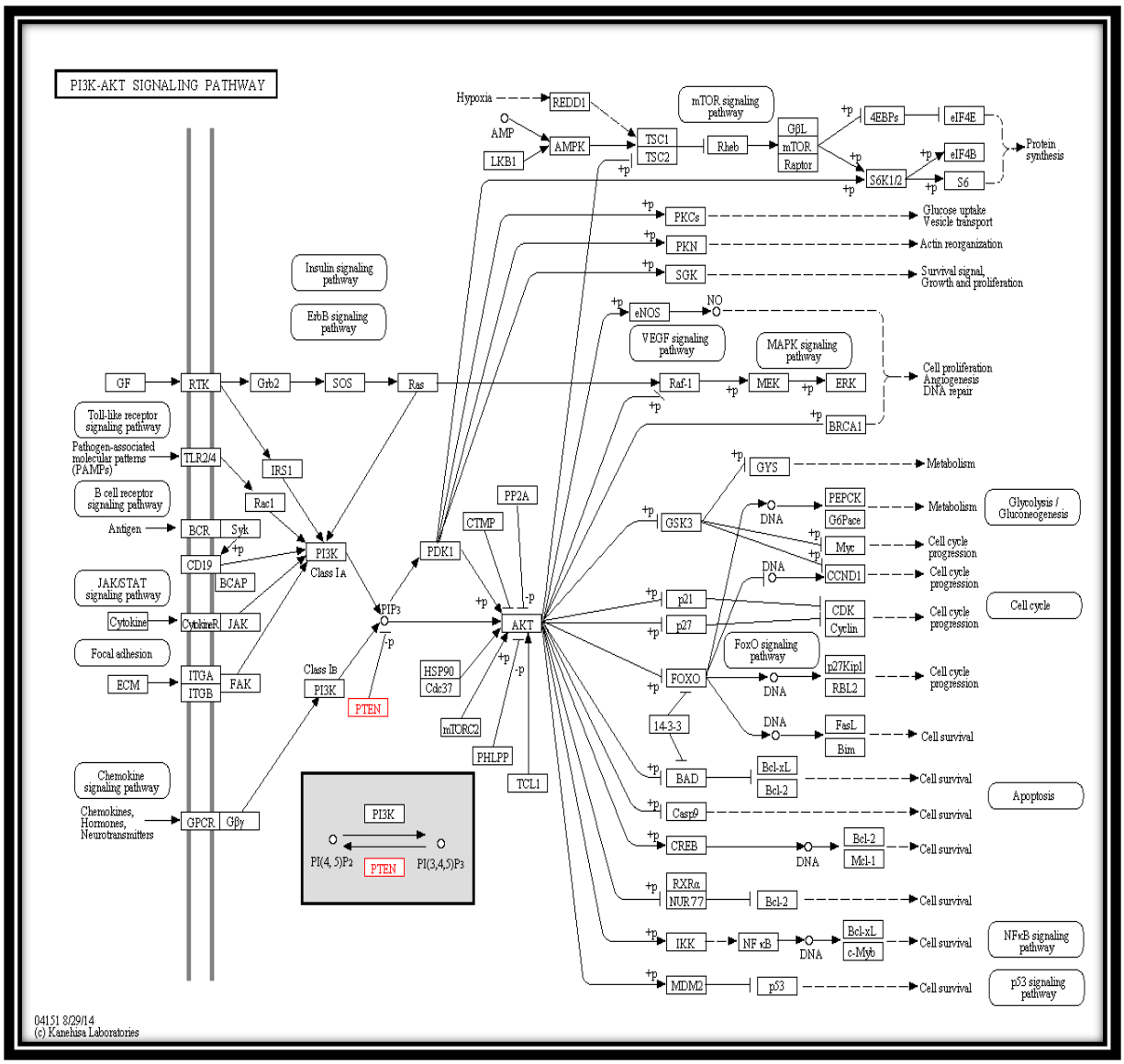


Fig 1: PI3K-AKT Signaling Pathway

PI3K-AKT Signaling Pathway and mTOR pathway are those pathways which are intracellular pathways. These are very important in cell cycle. The PI 3′-OH kinase(PI3K) family comprises 3 classes of proteins that phosphorylate PI, PI-4-phosphate (PI-4-P), or PI-4,5-bisphosphate(PI-4,5-P2 or PIP2) on position 3′ (5). PI3Ks generate PI-3,4,5-trisphosphate (PIP_3) from PIP_2 and PIP_3 acts as a second messenger by binding to and activating pleckstrin homology (PH) domain-containing proteins. The activation of Akt by PIP_3 production triggers signaling through a multitude of Akt phosphorylation targets that control cell survival, growth, proliferation, and other cellular processes (6). The net effect of Akt activation is activation of mTORC1, which is responsible for the up-regulation of protein synthesis in cells (7).

PTEN plays a role in the regulation of PI3 kinase signaling, which is involved in the control of apoptosis and cell cycle progression (8). PTEN plays role in the pathways as a tumour suppressor when it is inactivated due to some reasons its can cause the tumor. PTEN is frequently inactivated by mutation with loss of heterozygosity (LOH). Initial studies have shown that the expression of PTEN induces a marked decrease of proliferation because of cell cycle arrest in G1 phase (9,10). The discovery of *PTEN* as

a tumor suppressor gene and the breakthrough finding that it functions as a PIP_3 Phosphatase have put the PI3K-Akt pathway on the map of important cancer pathways (11-13). In this pathway PTEN works as a natural inhibitor.

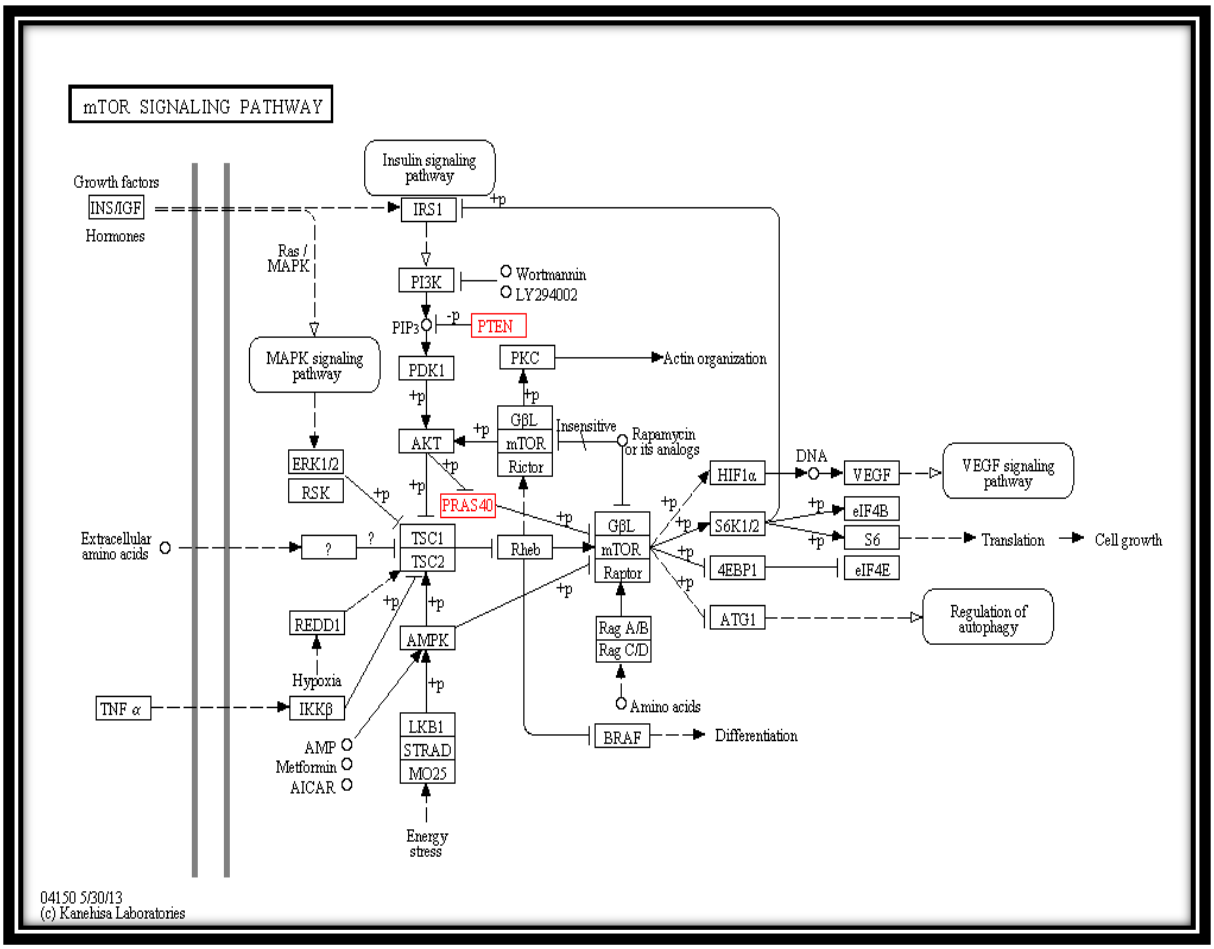
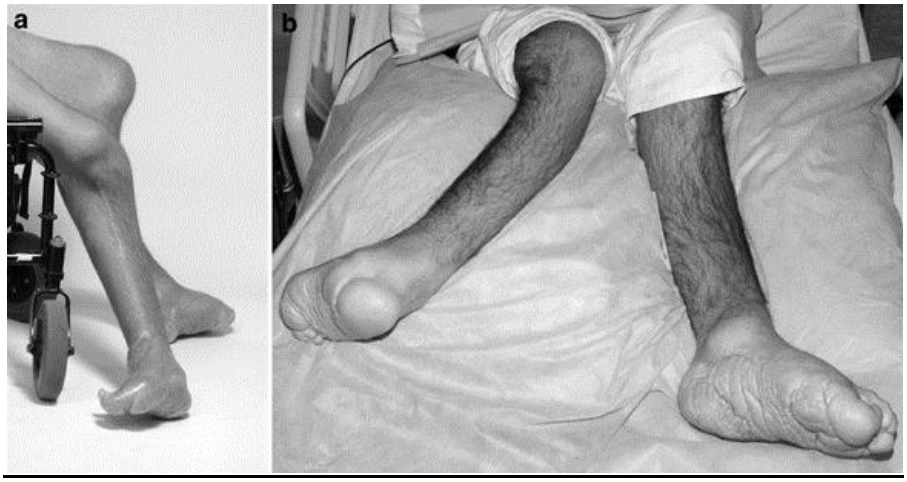


Fig. 2: mTOR Pathway

These figures show the metabolic pathway of AKT1 gene and PTEN which are responsible for the Proteus syndrome.

Signs and Symptoms

- It includes overgrowth occurring in skeleton part and tissues.
- It may rapidly progressive in childhood but slow or stabilize during adolescence.
- It consists rapidly growth occurring in one cell during the early stages from birth.
- The signs of overgrowth are apparent in 6 to 18 months.
- The overgrowth occurring in limbs, facial bones, skull and adipose tissues are affective.
- The overgrowth skin is rough as it seen.
- The skin is very thick and groovy lesions which is got overgrowth.
- The patient also faces the abnormalities such as vision loss etc.
- The affected part of the body, whether it is head or limb or any part of the body, gets overgrowth rapidly and the patient suffers.
- It may include immobility of joints.
- Deficiency of soft skin.
- Premature death is not common and it is caused by embolism and respiratory failure (14).



(a) And (b) Showing legs affected by proteus syndrome

(c) Joseph M errick 'The Elephant Man'

How does it infect our cells and bones

Proteus syndrome is very uncommon disorder which is rarely found worldwide. Proteus syndrome, mainly has been reported, is caused by two genes. AKT1 and PTEN are mainly responsible for the proteus syndrome. These are responsible for the overgrowth in the bones and tissues. AKT1 gene is the first gene found responsible for proteus syndrome. Proteus syndrome occurs when abnormality occurs in AKT1 gene which includes mutation in AKT1 gene. AKT1 gene is also known as serine-threonine-protein kinase which is responsible for the growth.

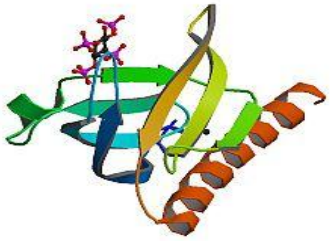


Fig. Structure of AKT1 gene from PDB

AKT1 gene regulates cells growth, cell division and cell death. So, it regulates the overgrowth of the cell. A single-nucleotide polymorphism in this gene causes Proteus syndrome (15,16). PTEN gene is the other gene found responsible for the proteus syndrome.

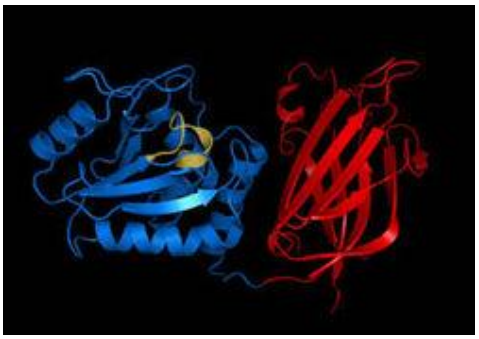


Fig. Structure of PTEN gene from PDB

Phosphatase and tensin homolog or PTEN acts as a tumor suppressor. The protein encoded by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase (17). PTEN acts as a signaling cell to stop dividing the cells. It can cause cancer in the body. PTEN regulates Proteus syndrome when mutation occurs in the chromosome 10 and 16 (18-19). Proteus syndrome is not inherited. It is not necessary if one of the parents have the disorder the progeny will also suffer with this.

Diagnosis and Treatments

Rapamycin is the only drug is obtained in the world till now (20). Surgery is available.

CONCLUSION

In this review, the main objective is to obtain a drug which can suppress the activity of AKT1 gene and PTEN gene which is responsible for the proteus syndrome. The drug which will be obtained can be highly effective which can oppose and suppress the activity of the responsible genes.The mutation which occurs on chromosome 10 and 16 can be identified before and the patient can be diagnosed. Thus, this can lead to clinical trials.

ACKNOWLEDGEMENT

The first two authors contributed equally to the study. Part of this work was undertaken in The S.D. College of Engineering and Technology, Jansath road, Muzaffarnagar, U.P.-India. We would like to specially thank to Naveen Dwivedi Associate Professor & Head and Shubha Dwivedi Assistant Professor of Biotechnology Department, S. D. College of Engineering, and Technology, Jansath road, Muzaffarnagar, U.P.-India for support of this study.

REFERENCES

[1] Cohen M. M. Jr. and J. A. R. Tibbles *The Proteus syndrome: the Elephant Man diagnosed* 1986.
[2] Wiedemann HR, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E: The proteus syndrome. Partial gigantism of the hands and/or feet, nevi, hemihypertrophy, subcutaneous tumors, macrocephaly or other skull anomalies and possible accelerated growth and visceral affections. Eur J Pediatr 1983; 140: 5–12.
[3] Wiedemann H-R, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E. The Proteus syndrome: partial gigantism of the hands and/or feet, nevi, hemihypertrophy, subcutaneous tumors, macrocephaly or other skill anomalies and possible accelerated growth and visceral affections**.** *Eur J Pediatr* 1983;140:5–12
[4] Cohen MM Jr, Hayden PW. A newly recognized hamartomatous syndrome**.** In: O'Donnell JJ, Hall BD, eds. Penetrance and variability in malformation syndromes. The National Foundation— March of Dimes. *Birth Defects: Original Article Series* 1979;15:291–296
[5] Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet.2006;7:606-19.
[6] Luo J, Manning BD, Cantley LC. Targeting the PI3K-Akt pathway in human cancer: rationale and promise. Cancer Cell. 2003;4:257-62.
[7] Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. Cancer Cell. 2007;12:9-22.
[8] Di Cristofano A, Pandolfi PP. The multiple roles of PTEN in tumor suppression. *Cell* 2000;**100**:387-90.

[9] CohenMMJr. Causes of premature death in Proteus syndrome. Am J Med Genet 2001; 101:1–3.
[10] Furnari FB, Huang HJ, Cavenee WK. The phosphoinositol phosphatase activity of PTEN mediates a serum- sensitive G1 growth arrest in glioma cells. Cancer Res. 1998;58:5002-8.
[11] Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem. 1998;273:13375-8.
[12] Li J, Yen C, Liaw D, *et al*. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science.1997;275:1943-7.
[13] Steck PA, Pershouse MA, Jasser SA, *et al*. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet. 1997;15:356-62.
[14] Li DM, Sun H. PTEN/MMAC1/TEP1 suppresses the tumorigenicity and induces G1 cell cycle arrest in human glioblastoma cells. Proc Natl Acad Sci U S A. 1998;95:15406-11.
[15] Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, Turner J, Cannons JL, Bick D, Blakemore L, Blumhorst C, Brockmann K, Calder P, Cherman N, Deardorff MA, Everman DB, Golas G, Greenstein RM, Kato BM, Keppler-Noreuil KM, Kuznetsov SA, Miyamoto RT, Newman K, Ng D, O'Brien K, Rothenberg S, Schwartzentruber DJ, Singhal V, Tirabosco R, Upton J, Wientroub S, Zackai EH, Hoag K, Whitewood-Neal T, Robey PG, Schwartzberg PL, Darling TN, Tosi LL, Mullikin JC, Biesecker LG (2011). "A mosaic activating mutation in AKT1 associated with the Proteus syndrome". *N. Engl. J. Med.***365** (7): 611–9. doi:10.1056/NEJMoa1104017. PMC 3170413. PMID 21793738.
[16] Cohen MM (2014). "Proteus syndrome review: molecular, clinical, and pathologic features". *Clin. Genet.* **85** (2): 111–9. doi:10.1111/cge.12266. PMID 23992099.
[17] Steck P, Pershouse M, Jasser S, Yung W, Lin H, Ligon A et al. (Apr 1997). "Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers". *Nature Genetics* **15** (4): 356–62. doi:10.1038/ng0497-356. PMID 9090379.
[18] Smith JM, Kirk EP, Theodosopoulos G, Marshall GM, Walker J, Rogers M, Field M, Brereton JJ, Marsh DJ (2002). "Germline mutation of the tumour suppressor PTEN in Proteus syndrome". *J. Med. Genet.* **39** (12): 937–
[19] Cardoso MT, de Carvalho TB, Casulari LA, Ferrari I (2003). "Proteus syndrome and somatic mosaicism of the chromosome 16". *Panminerva medica* **45** (4): 267–71.PMID 15206168.
[20] Marsh DJ, Trahair TN, Martin JL, Chee WY, Walker J, Kirk EP, Baxter RC, Marshall GM (April 22, 2008). "Rapamycin treatment for a child with germline PTEN mutation". *Nature Clinical Practice Oncology* **5** (6): 357–361. doi:10.1038/ncponc1112. PMID 18431376.