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The Genetic Multi-Variates-PTEN Hamartoma Tumour Syndrome

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Preface

Phosphatase and tens in homologue as detected upon chromosome ten is enunciated as 10q23(PTEN). The PTEN gene usually encodes cytosolic lipid phosphatase composed of 403 amino acids which negatively regulates AKT (serine/threonine-specific protein kinase) activity by delineating dephosphorylating phosphatidylinositol 3,4,5, -trisphosphate (PIP3) molecule. A secretory form of PTEN is exemplified as PTEN-long or PTEN-L with the incorporation of an excess of 173 amino acid which adheres to the N- terminal of PTEN. Molecules of PTEN-L which are secreted from a singular cell can display phosphatase activity in adjacent cellular zones. PTEN-α is an isoform of PTEN which also demonstrates an extension of 173 amino acids at the N-terminal and is situated within the mitochondria. It constitutes tumour suppressor gene which is generally misrepresented and dysfunctional in human malignancies and contributes critically in regulating the cell cycle and cellular apoptosis. PTEN gene is extensively modified by post- translational alterations such as oxidation, nitrosylation, ubiquitination, SUMOylating or acetylation. PTEN is additionally cogitated as a mutated gene in multiple advanced cancers1 (MMAC1) [1,2]. PTEN chromosomal mutations are discerned in an estimated 30% of 35% of subjects with Cowden syndrome and around 55% of Bannayan-Riley-Ruvalcaba syndrome. Approximately one fifth to half (11% to 48%) of the individuals demonstrate de novo chromosomal mutations. Nearly one third (37%) subjects depicting PTEN genetic mutations lack the diagnostic criterion of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome. PTEN gene demonstrates a variable expression and age-related penetrance with Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. Genomic mutations of PTEN concur inactive proteins with the emergence of a severe phenotype, in contrast to predominant mutations which enunciate proteins with partially retained function. Autism associated chromosomal mutations display proteins with the ability to suppress AKT signalling mechanism [1,2].

Disease Characteristics

Minimal elucidation of PTEN can predict tumour relapse in subjects of carcinoma breast on treatment with tamoxifen. Prominent genetic rearrangements of PTEN locus can appear in individuals of carcinoma prostate which can be appropriately discerned by break- apart fluorescent in situ hybridization (FISH) assay. Absence of cytoplasmic PTEN expression can segregate intra-ductal carcinoma prostate from high grade of prostatic intra-epithelial neoplasia (PIN). Thus, PTEN immune staining is delineated in various malignancies. Contrastingly, immune non reactivity indicates a frequent absence of PTEN expression in carcinoma.

PTEN hamartoma tumour syndrome is inherited as an autosomal dominant condition. Percentage of "simplex" instances comprising of individuals devoid of a family history of hamartoma tumour syndrome and familial subjects exceeding ≥2 implicated individuals cannot be efficaciously determined. Majority of persons demonstrate a simplex Cowden syndrome wherein around 10 % to 50% subjects with Cowden syndrome display a singular, affected parent [2,3]. Children born to affected parents exhibit an approximately 50% possibility of inheriting PTEN variant disease and incurring a PTEN hamartoma tumour syndrome. Prenatal evaluation of pregnant females suspected of enhanced possibility of hamartoma tumour syndrome can be obtained [3,4].

Diagnostic Criterion

National Comprehensive Cancer Network designates specific criterion applicable to delineation of variants of PTEN hamartoma tumour syndrome.

Pathognomonic Criterion

Adult Lhermitte-Duclos disease is defined as occurrence of cerebellar dysplastic gangliocytoma. Muco-cutaneous lesions cogitate as the appearance of facial trichilemmomas, acral keratoses, papillomatosis and mucosal lesions [2,4].

Major Criterion Emergence of carcinoma breast, non-medullary carcinoma of thyroid especially follicular carcinoma thyroid, macrocephaly which is denominated by an elevated

occipital- frontal head circumference exceeding ≥ 97th percentile and carcinoma endometrium.

Minor Criterion Adjunctive lesions denominate minor diagnostic criterion such as thyroid lesions cogitated as a follicular adenoma or multi nodular goitre. Intellectual disability with an intelligence quotient ≤75 is enunciated. Cogent lesions such as hamartomatous intestinal polyp, fibrocystic disease of breast, lipoma, fibroma, genitourinary tumours especially renal cell carcinoma, genitourinary malformation or uterine fibroid can be exemplified [3,4].

Disease Variants

PTEN hamartoma tumour syndrome is a condition described by the occurrence of Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, PTEN related Proteus syndrome and Proteus-like syndrome. Inherited PTEN mutations appear in conjunction with Lhermitte- Duclos syndrome or cerebellum dysplastic hamartoma, juvenile polyposis of infancy, segmental overgrowth and autism with macrocephaly. Apart from Cowden syndrome, various malignancies such as carcinoma of bladder, breast, stomach, thyroid, prostate, endometrium, oesophagus, head and neck, squamous cell carcinoma, renal cell carcinoma, pulmonary carcinoma, glioblastoma multiforme and malignant melanoma can ensue. Inherited PTEN mutations are accompanied by refractoriness to anti androgen therapy [5,6].

Cowden Syndrome

Cowden syndrome is designated as a multiple hamartoma syndrome demonstrating an enhanced emergence of benign and malignant tumours particularly within breast, endometrium and thyroid tissue. Cowden syndrome demonstrates a benign overgrowth of various soft tissues such as colon, thyroid and cutaneous surfaces. Macrocephaly and cutaneous lesions such as trichilemmoma or papillomatous papules are cogitated and clinical features appear within the second decade. Absence of nuclear PTEN manifestation is cogitated in adenomatous thyroid nodule and is indicative of Cowden syndrome. Carcinoma breast depicts a probable emergence in an estimated 85% instances and is commonly discerned at 38 years to 46 years. Carcinoma thyroid with predominantly specific variants of follicular or infrequently papillary carcinoma can be detected in around 35% instances. Emergence of medullary carcinoma thyroid is absent. Carcinoma endometrium appears in around 28% subjects [1,2]. Cowden syndrome can be diagnosed with the appearance of singular criterion such as pathognomonic, muco-cutaneous lesions appearing in combination with particular attributes as described with

a) Facial papules exceeding ≥ six and a minimal of three trichilemmomas

b) Cutaneous facial papules and oral mucosal papillomatosis

c) Oral mucosal papillomatosis and acral keratosis or the emergence of

d) Palmoplantar keratosis beyond ≥ six lesions.

Cowden syndrome can also be distinguished with the amalgamation of two or more major diagnostic criterion, one major diagnostic criterion in conjunction with three or more minor criterion or the concordance of four or more minor diagnostic criterion [2,3]. Cowden syndrome appearing in a family requires the discernment of an individual or a relative with Cowden syndrome which can be achieved with assessment of a pathognomonic criterion, a singular major criterion with or without the accompaniment of minor criterion or the concurrence of two minor criterion or a concordant history of Bannayan-Riley-Ruvalcaba syndrome. Children with Cowden syndrome can depict autism, developmental delay, cutaneous manifestations such as lipoma, trichilemmoma, oral papilloma or penile freckling, arteriovenous malformations, haemangioma and gastrointestinal polyps [5,6].

Bannayan-Riley-Ruvalcaba Syndrome

Bannayan-Riley-Ruvalcaba Syndrome is denominated as a congenital disorder with characteristic macrocephaly, intestinal hamartomatous polyposis, lipoma and pigmented macules emerging within glans penis. An estimated three fifths (60%) of instances depict a PTEN genetic mutation [1,2].

Proteus Syndrome

A mosaic pattern of disease emergence is detected with segmental distribution and organ or tissue incrimination of various disease processes. The disorder is frequently misinterpreted. Proteus syndrome is a complex, divergent disorder comprised of congenital malformations, hamartomatous expansion of multivariate soft tissues accompanied by connective tissue or epidermal nevus and bony hyperostosis [1,3].

Proteus Like Syndrome

Proteus Like Syndrome is essentially an undetermined entity. However, prominent clinical features of Proteus syndrome are enunciated with an incomplete expression of diagnostic criterion of Proteus syndrome [1,2].

Clinical Elucidation

PTEN hamartoma tumour syndrome (PHTS) denominates a diverse spectrum arising as a consequence of mutations within PTEN gene.

Cowden Syndrome

Cowden syndrome is enunciated in a majority (>90%) of individuals and clinical manifestations can arise within the second decade. An estimated 99% subjects develop muco-cutaneous stigmata such as trichilemmoma, papillomatous papule or acral and plantar keratoses within the third decade. Macrocephaly and dolicocephaly are additionally enunciated.

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Intestinal hamartomata and mixed gastro-intestinal polyps are exemplified which enhance the emergence of colorectal carcinoma. Glycogenic acanthosis occurring in concurrence with Cowden syndrome is contingent to a concurrent PTEN genomic variant.

Probable Malignant Emergence

Probable Malignant Emergence Benign breast disease appears in an estimated two third (67%) individuals. PTEN genetic variations demonstrate the occurrence of carcinoma female breast in roughly 85% subjects. The variant gene depicts penetrance in around half (50%) the instances at approximately 50 years of age Benign multinodular goitre of the thyroid gland, adenomatous thyroid nodule and follicular adenoma can emerge in three fourths (75%) of individuals with a possible occurrence in approximately one third(35%) persons and a median age of onset at 37 years. Medullary carcinoma thyroid is a non-occurring condition [1,3].

Endometrial tissue is frequently implicated in PTEN hamartoma tumour syndrome and benign fibroid uterus is a common occurrence. Endometrial carcinoma appears in nearly one third (28%) females and usually arises within the third or fourth decade. Gastrointestinal neoplasia occurs in a majority (>90%) of instances displaying a PTEN variant gene. Gastrointestinal polyps such as ganglio neuromatous polyp, hamartomatous polyp, juvenile polyp or adenomatous polyp can ensue. Colorectal carcinoma appears in around 9% individuals and commences within the third decade. Renal cell carcinoma appears in an estimated one third (35%) individuals and arises within the fourth decade. Papillary variant of renal cell carcinoma is commonly encountered [2,4]. Apart from aforesaid malignancies, malignant melanoma arises with an estimated possibility of >5%. Brain tumours or organ-specific vascular malformations are occasionally enunciated. Cerebellar dysplastic gangliocytoma or Lhermitte- Duclos disease can be cogitated in association with Cowden syndrome.

Bannayan Riley Ruvalcaba Syndrome

Bannayan-Riley-Ruvalcaba Syndrome as an exceptional paediatric syndrome commonly demonstrates clinical features such as macrocephaly, hamartomatous intestinal polyps, lipoma and pigmented macules on the penis. Associated clinical symptoms configure developmental delay, vascular anomalies, elevated birth weight, intellectual disability and scoliosis exemplified in an estimated half (50%) of the individuals, proximal muscle myopathy in around 60% subjects, hyper-extension of the joints and pectum excavatum. Probability of emerging of malignancies is identical as elucidated with Cowden syndrome [2,3]. Gastrointestinal hamartomatous polyp occurring in aforesaid syndrome appears to be at approximately half (45%) the individuals and delineates rectal bleeding, serum exudation and occasional emergence of intussusception. Possibility of colorectal carcinoma is not enhanced.

Proteus Syndrome

Proteus Syndrome is denominated by a continuous, segmental overgrowth of diverse soft tissues arising from germ cell layers. Localized tissue overgrowth implicates the skeleton, cutaneous surfaces, adipose tissue and central nervous system. The syndrome lacks manifestation at birth, appears within toddlers, evolves rapidly during childhood and delineates a severe tissue overgrowth with consequent physical disfigurement. Several benign and malignant tumours, deep vein thrombosis and pulmonary embolism are associated with the syndrome [3,4].

Proteus Like Syndrome

Proteus Like Syndrome appears in individuals displaying specific features of Proteus syndrome although the diagnostic criterion remains unfulfilled.

Concomitant Allelic Variants

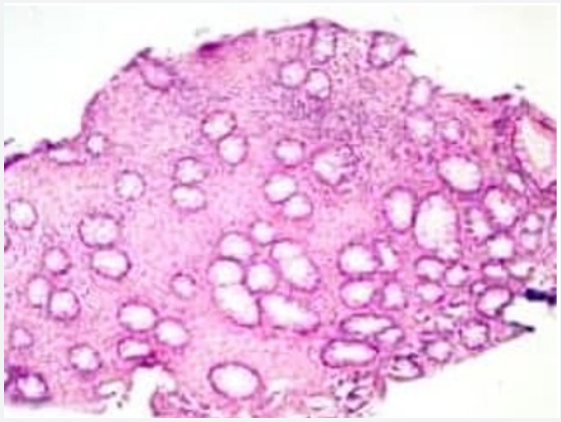

Figure 1: PTEN hamartoma tumour syndrome with accompanying Cowden syndrome comprised of hamartomatous gastrointestinal polyps (Pathology outlines).

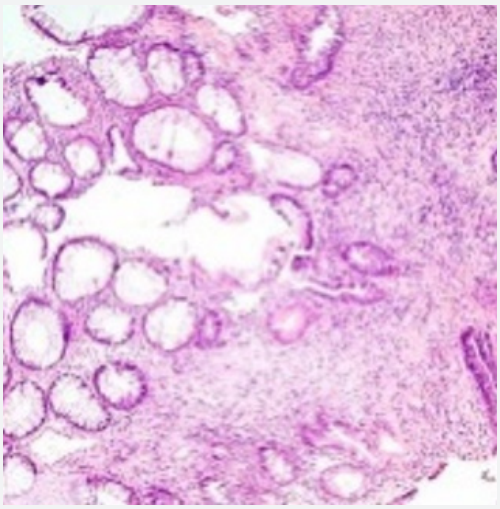

Figure 2: PTEN hamartoma tumour syndrome with the constituent Cowden syndrome with incorporated gastrointestinal polyps (Pathology outlines).

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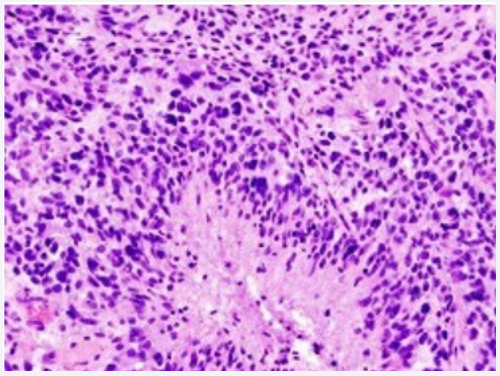

Figure 3: PTEN hamartoma tumour syndrome with accompanying glioblastoma multiforme which is predominantly deficient in macrophages (Medical express).

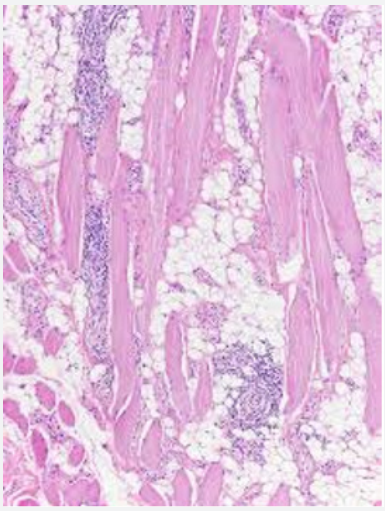

Figure 4: PTEN hamartoma tumour syndrome composed of a soft tissue hamartoma with constituent skeletal muscle and fibro-connective tissue (Esp. congress.org).

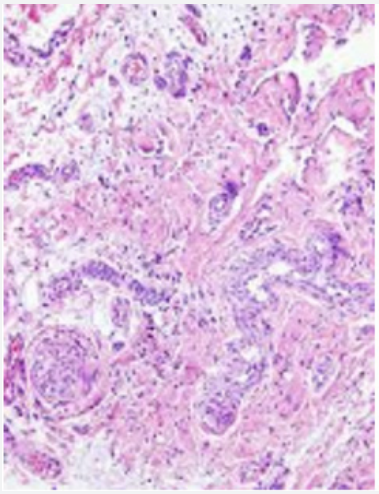

Figure 5: PTEN hamartoma tumour syndrome with a disorganized soft tissue hamartoma with composed of skeletal muscle, epithelial lining and fibrous tissue (Esp. congress.org).

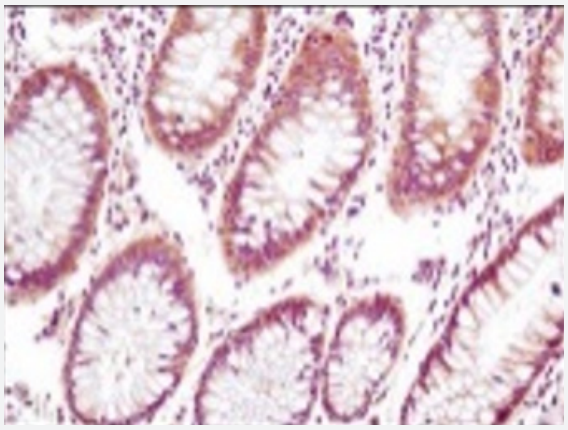

Figure 6: PTEN hamartoma tumour syndrome with immune reactive rabbit monoclonal antibody (Cell signalling technology).

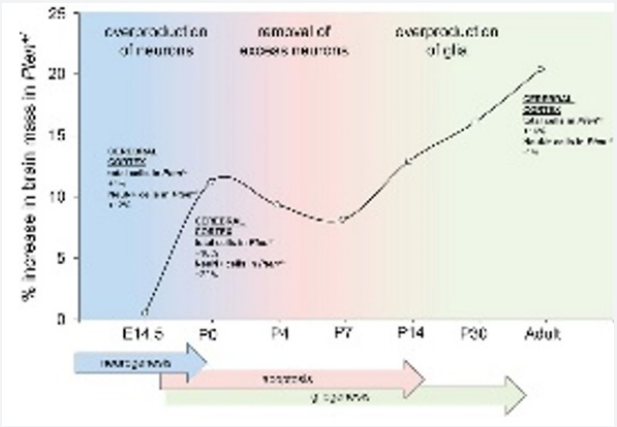

Figure 7: PTEN hamartoma tumor syndrome depicting genetic mutations subsequent to expansion of brain tissue (Journal of Neurosciences.)

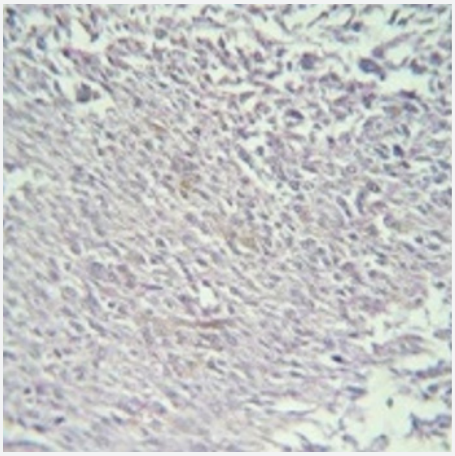

Figure 8: PTEN hamartoma tumour syndrome associated with foci of malignant fibrous histiocytoma with classical storiform-pleomorphic pattern (Semantic scholar).

a) Lhermitte-Duclos disease is an adult onset condition displaying dysplastic gangliocytoma of the cerebellum which is a specific tumour enunciating a hamartomatous tissue overgrowth commonly delineated in Cowden syndrome. The

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condition is a PTEN genomic variant with the absence of clinical symptoms of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome.

b) Autism or pervasive developmental disorder and macrocephaly are accompanied by PTEN genomic variants in around one fifth (20%) subjects in association with clinical enunciation of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome.

c) Juvenile polyposis of infancy delineates a germline chromosomal deletion of BMPR1A and PTEN gene. The condition is commonly discerned before six years of age [2,3] (Figure 1- 8).

Molecular Elucidation

PTEN hamartoma tumour syndrome can be established in a proband with the elucidation of heterozygous, germline mutation of PTEN variant.

a) Analysis of a single gene with assessment of the genomic sequence of PTEN promoter region is performed with a sequential, targeted assay of genetic deletion or duplication in the absence of a PTEN variant.

b) Analysis of multiple genes incorporates the detection of a PTEN mutant gene along with discernment of associated genetic aberrations. Panel procedures are comprised of genomic sequence analysis, assessment of genetic deletion or duplication and the employment of non-sequencing chromosomal investigations.

c) Analysis of the comprehensive genomic expression with the adaptation of whole exome sequencing or comprehensive genomic sequencing can be contemplated as an option in instances with inadequate outcomes of single and/or multigene genetic testing in subjects with clinical features of PTEN hamartoma tumour syndrome and a PTEN chromosomal array. Aforesaid investigations can indicate a previously unconsidered diagnosis [7,8].

Indications of Surveillance

Emergent tumours associated with PTEN hamartoma tumour syndrome require delineation within a therapeutically suitable phase. Children below 18 years of age and adults with hamartoma tumour syndrome require an annual ultra-sonographic assessment of thyroid commencing at diagnosis along with evaluation of comprehensive cutaneous surfaces and an extensive physical examination. Female subjects require a monthly self-examination of breast commencing at 30 years of age with an annual breast screening with manoeuvres such as a mammogram or magnetic resonance imaging (MRI). A transvaginal ultrasound or endometrial biopsy can also be adopted to enunciate alterations relevant to the syndrome. Implicated subjects regardless of gender predisposition necessitate a colonoscopy initiated at 35 years and a procedural frequency contingent to percentage of polyposis [7,8]. Computerized tomography or magnetic resonance imaging of renal tissue at a two-year interval with a preliminary investigation at 40 years of age is mandated to discern cogent manifestations. Individuals with family history of a specific cancer require investigation at an earlier age. Screening for specific malignancies can be initiated five to ten years preceding the age of the youngest diagnosed subject. Additionally, with discernment of a PTEN disease variant, molecular genetic testing of asymptomatic, at risk subjects is required to identify individuals within a family with specific PTEN variants besides commencement of continuous surveillance [8,9].

Differential Diagnosis

PTEN hamartoma tumour syndrome requires as demarcation from juvenile polyposis syndrome which is an autosomal dominant condition exemplifying modification within BMPR1A and SMAD4 genes. Benign hamartomatous gastrointestinal polyps are enunciated usually up to second decade. Individuals can demonstrate varying quantification of polyps ranging from five to hundreds. Untreated gastrointestinal polyps can exemplify bleeding and anaemia. Juvenile polyps can undergo malignant transformation. Peutz Jeghers syndrome as an autosomal dominant disorder requires distinction from hamartoma tumour syndrome. Gastrointestinal polyposis, predilection to malignancies and muco-cutaneous pigmentation ensues along with chromosomal alterations of STK11 gene. Hamartomatous gastrointestinal polyps and pigmentation of perioral region exceeding the vermilion border is cogitated. Hyper-pigmented macules can arise upon the fingers [8,9]. Birt Hogg Dube syndrome is an autosomal dominant condition necessitating segregation from hamartoma tumour syndrome. Chromosomal modifications are enunciated within the FLCN gene. Subjects delineate cutaneous tags and benign neoplasm such as fibroma and trichoepithelioma. Apart from cutaneous manifestations, pulmonary cysts, preceding pneumothorax and diverse categories of renal tumours can be discerned. Pulmonary cysts are asymptomatic, bilateral and multifocal. Type 1 neurofibromatosis requires a distinction from hamartoma tumour syndrome. The autosomal dominant disorder depicts a chromosomal mutation in neurofibromatosis type 1 gene and is accompanied by cutaneous representation such as café au lait macules and fibromatous tumours. Neurofibromatosis type 1 can be misrepresented as a Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome on account of ganglioneuromas accumulating within the gastrointestinal tract. Nevoid basal cell carcinoma syndrome or Gorlin syndrome is an autosomal dominant condition requiring a segregation from hamartoma tumour syndrome. Genetic alterations are observed within the PTCH1 and SUFU chromosomal regions. Hamartomatous gastrointestinal polyps, multiple keratocysts of the jaw, basal cell carcinoma, adjunctive benign and malignant tumours, cutaneous fibromas, medulloblastoma and segmental expansion of soft

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tissue contingent to representative germ cell layer is exemplified [9,10]. Proteus syndrome with cogent manifestations of AKT1 pathway is a synagogue of PTEN genomic modifications while enunciating macrocephaly and soft tissue overgrowth. Pulmonary complications, a marked predilection to deep vein thrombosis, pulmonary embolism and diverse benign and malignant tumours are delineated [8,10].

Therapeutic Options

PTEN hamartoma tumour syndrome requires specific evaluations such as a comprehensive medical, family history and organ-specific physical examination, neurodevelopmental assessment, sonographic screening of thyroid, breast, transvaginal ultrasound, renal imaging, endometrial tissue specimen, colonoscopy and cogent genetic counselling Table 1.

Therapy for benign and malignant manifestations of PTEN hamartoma tumour syndrome recapitulate treatment preferences of sporadic, associated disorders [9,10]. Asymptomatic instances can be adequately managed with simple observation. Cutaneous lesions require pertinent surgical excision in instances indicating a malignant transformation or with the appearance of specific symptoms such as pain, physical or localized deformity or enhanced tissue scarring. Symptomatic individuals can be administered topical agents such as 5- fluorouracil along with curettage of cutaneous lesions, cryosurgery or laser ablation. Aforesaid manoeuvers can temporarily alleviate muco-cutaneous manifestations of Cowden syndrome. Surgical eradication of lesions can be complicated with formation of keloid and a brisk reoccurrence of lesions. m TOR inhibitors can be employed to treat germline, variant mutations of PTEN although appropriate clinical trials are necessitated [9,10].

Table 1: Revised PTEN hamartoma syndrome (PHTS) diagnostic criterion [1].

Individual
Three or more major criterion inclusive of macro-cephaly, Lhermitte-Duclos disease, gastrointestinal hamartoma OR
Two major and three minor criterions
Family with ONE implicated individual
Any two major criterion with or without minor criterion OR
One major and two minor criterion OR
Three minor criterions
Major Criterion
Carcinoma breast
Carcinoma endometrium (epithelial)
Carcinoma thyroid (follicular)
Gastrointestinal hamartomas (including ganglioneuromas, excluding hyperplastic polyps) ≥3.
Lhermitte-Duclos disease (LDD) in adults
Macrocephaly (≥97)
Macular pigmentation of the glans penis
Multiple muco-cutaneous lesions
Multiple trichilemmomas ≥3, at least one biopsy-proven lesion
Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
Muco-cutaneous neuromas (≥3)
Oral papillomas (tongue / gingiva), multiple (≥3) OR biopsy-proven or dermatologist- diagnosed lesions
Minor Criterion
Autism spectrum disorder
Carcinoma colon
Oesophageal glycogenic acanthosis (≥3)
Lipomas (≥ 3)
Mental retardation (intelligence quotient ≤75)
Renal cell carcinoma
Testicular lipomatosis
Carcinoma thyroid (papillary or follicular variant of papillary)
Thyroid structural lesions (adenoma, multi-nodular goitre)
Vascular anomalies (multiple intracranial developmental venous anomalies)

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