

PTEN-HTS – Genotype-phenotype correlations - a single institution's experience

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Introduction:

PTEN hamartoma tumor syndrome (PTEN-HTS or PHTS, OMIM 158350, ORPHA:306498) is the collective term for a group of syndromes, including Cowden syndrome, adult Lhermitte-Duclos disease, Bannayan-Riley-Ruvalcaba syndrome, and Proteus -like syndrome, caused by germline mutations in the *PTEN* gene, located on 10q23.3. Inheritance of PHTS is autosomal dominant. The syndrome is rare, with an incidence of 1 in 200000, however it is very likely to be underestimated. Hamartomas are a common manifestation of the PHTS. The lifetime risk (LTR) of developing breast cancer for women is about 77- 85%, for endometrial cancer 19 - 28%. LTR for thyroid cancer for the carriers is approximately 21-38%, for renal cell cancer 15- 34%, for colorectal cancer 9%-16%, for melanoma up to 6%. Affected individuals usually have macrocephaly and frequently present with rare benign mucocutaneous lesions. Diagnostic criteria for PHTS are regularly updated by the National Comprehensive Cancer Network.

Material and methods:

In our Institution NGS sequencing has been made available for clinical use since 2018 year. Our multigene panel includes *PTEN* gene. During the last 4 years at our Genetic Counselling Unit we identified 6 unrelated patients with symptoms prompting PHTS diagnosis. The probability of finding *PTEN* mutation was calculated for each individual using The Cleveland Clinic Adult Clinical Scoring System.

All the patients were evaluated by the same clinical geneticist before and after the test. Written informed consent for the genetic testing had been obtained by the same medical doctor. After establishing diagnosis all the patients received detailed genetic counsel and were included into surveillance programme, according to the guidelines (ERN-Genturis/ NCCN - combined).

DNA was extracted from the peripheral blood leukocytes using QIASymphony QIAGEN technique. For the first group we used Illumina Platform NextSeq500, for the last 3 patients we used Ion AmpliSeq On-Demand DNA Panel by Thermo Fisher.

The pathogenicity of the variants/ mutations was assessed according to the Recommendations from the ClinGen PTEN Expert Panel and checked in ClinVar database.

Results:

PTEN – HTS (PHTS) diagnosis has been confirmed in 6 patients (4 women, 2 men) carrying 6 different germline pathogenic *PTEN* mutations: one in the 1st exon, one in exon 3/9, two different in exon 5/9, one in exon 6/9, one in intron 7, one also intronic - after exon 8. All the patients had OFC \geq 60 cm. Both men presented with benign only tumours – mainly skin lesions and gastrointestinal polyps and both of them had established diagnosis of autism spectrum disorder. Two of 4 women presented with multiple cancer (breast, endometrial, ovarian in one and breast and rectal cancer in the second one). Unexpected diagnoses in our group of patients were: thyroid cancer at the age of 5 years, schwannoma and neurofibroma.

Conclusions:

This is the first Polish study of the genotype – phenotype correlations among patients with PHTS. We were not able to prove any founder/ recurrent mutations in this group. We found 6 different pathogenic mutations in our unrelated 6 patients. Our study confirms value of the established clinical criteria and online tools for identifying PTEN-HTS/Cowden syndrome in Polish patients. The routine measuring of head circumference in hereditary cancer clinics seems to be a good recommendation.