P R A C E   P O G L Ą D O W E   R E V I E W   P A P E R S

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Hamartomous polyposis syndromes

Zespoły polipowatości hamartomatycznych

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S u m m a r y

Hamartomas are malformations of mucosa, consisting of disorganized normal tissues. The manifestation of hamartomatous polyps is characteristic of juvenile polyposis syndrome, Peutz-Jeghers' syndrome, hereditary mixed polyposis syndrome and PTEN hamartoma tumour syndrome. All the aforementioned syndromes are inherited in an autosomal dominant manner. They form a rather heterogeneous group of disorders both in respect to the number and localization of polyps and the risk of cancer in the alimentary tract and other organs. Individual syndromes frequently manifest similar symptoms, particularly during the early stage of the diseases when in several cases their clinical pictures do not allow to make a differential diagnosis. The correct diagnosis of the disease using molecular methods allows to implement early treatment and therefore more effectively since it is followed by a strict monitoring of organs that manifest a predisposition to neoplastic transformation.

Research on the inherited hamartomatous polyposis has been conducted by the authors of this article at the Institute of Human Genetics, Polish Academy of Sciences in Poznań. In the DNA bank of Polish patients with polyposis material from 81 families with hamartomatous polyposis has been collected.

S t r e s z c z e n i e

Polipy hamartomatyczne są rodzajem malformacji błony śluzowej zbudowanych ze zdrowej, zdezorganizowanej tkanki. Ich rodzinne występowanie jest charakterystyczne dla zespołu polipowatości młodzieńczej, zespołu Peutza-Jeghersa, zespołu polipowatości mieszanej oraz zespołów guzów hamartomatycznych związanych z mutacjami PTEN. Wszystkie wyżej wymienione zespoły są dziedziczone w sposób autosomalnie dominujący i tworzą grupę chorób heterogennych pod względem liczebności i miejsca występowania polipów, a także ryzyka wystąpienia nowotworów układu pokarmowego i innych narządów. Poszczególne polipowatości często objawiają podobne symptomy, szczególnie we wczesnych etapach rozwoju, co w wielu przypadkach nie pozwala na ich rozróżnienie. Ich poprawna diagnoza, z wykorzystaniem metod z zakresu biologii molekularnej, pozwala na zastosowanie efektywnego leczenia na wczesnych etapach choroby oraz monitoring narządów, które zagrożone są rozwojem nowotworu.

Badania nad dziedzicznymi predyspozycjami do występowania polipowatości hamartomatycznych prowadzone są przez autorów pracy w Instytucie Genetyki Człowieka PAN w Poznaniu. W banku DNA polskich pacjentów z polipowatościami zgromadzono materiał 81 rodzin z polipowatościami hamartomatycznymi.

INTRODUCTION

The term of hamartoma corresponds to a non-neoplastic tumour, consisting of disorganized normal tissues and characteristic of the site of manifestation of the tumour. This term was introduced in 1904 by a German pathologist, Eugen Albrecht (1). Familial manifestation of hamartomatous polyps can be observed in a number of syndromes. The following are hamartomatous

diseases: juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), Hereditary Mixed Polyposis Syndrome (HMPS) and the syndrome of hamartomatous tumours linked to the PTEN gene mutations (PTEN hamartoma tumour syndrome – PHTS). Among others, the following were classed as belonging to PHTS: Cowden syndrome (CS), Bannayan--Riley-Ruvalcaba syndrome (BRRS) and Proteus syndrome (PS). All the above mentioned syndromes are inherited in an autosomal dominant manner. Apart from the manifestation in the alimentary tract of the hamartomatous polyps these syndromes are also characterized by an increased risk of neoplastic transformation. The development of neoplasms is not restricted to the alimentary tract, but they can also be manifested in other organs. Progression of neoplastic lesions in this type of polyps has not been fully researched, but it shows a different mechanism of formation than the one observed in adenomas.

Particular syndromes of hamartomatous polyposis are often characterized by the manifestation of similar symptoms, especially at the initial stage of the development of the disease the clinical pictures in many cases do not make it possible to differentiate them (2). Proper diagnosis of the disease by means of molecular differential methods makes it possible to begin faster and more efficient treatment since those organs are monitored which show an increased predisposition to neoplastic transformastion (3).

JUVENILE POLYPOSIS

Juvenile polyposis syndrome (JPS) (MIM # 174900) is a rare disease inherited in an autosomal dominant manner as described by McColl in 1966 (4). **JPS incidence is 1 per 100 000 births** (5). **In most of the noted cases it is a familial disease.** Its diagnosis is based on finding the presence of polyps, which histopathologically are described as juvenile ones. Juvenile polyps are distinguished by hyperplasia of mucous glands, retention cysts accompanied by oedema, emboli in gland openings, rich lamina propria and an absence of smooth muscles, inflammatory infiltrates and a dominance of stroma (6). The diameter of polyps is between 1 millimeter to several centimeters. Polyps are most common in the colon and the anus (80%), although they can also be found in the upper parts of alimentary tract such as the stomach and the small intestine. Single polyps are manifested in 75% of the patients while in the rest of the cases multiple polyps are noted. As far as the number of polyps is concerned their different numbers were found even among members of a single family. Single juvenile polyps are found in about 2% of children and adolescents, however, they have no malignant potential (7). Meanwhile among patients with juvenile polyposis the risk of neoplasms is significantly higher. According to different data from literature the risk of neoplasms in the colon is between several to several dozen percent – from 9 to 50%.

Juvenile polyposis is diagnosed based on the following criteria (tab. 1) (8):
– at least three polyps detected on colonoscopy,
– juvenile polyps in the entire digestive tract,
– any number of juvenile polyps in cases of family history of the disease.
Three be distinguished (9, 10):
– juvenile polyposis of infants,
– juvenile polyposis coli,
– general form of juvenile polyposis.

Table 1. Diagnostic criteria for recognition of hamartomatous polyposis syndrome.

Hamartomatous polyposis syndrome	Diagnostic criteria
Juvenile polyposis syndrome	– Numerous juvenile polyps (3-10 polyps) in colon and rectum – Any number of juvenile polyps in patients with family history of the disease – Juvenile polyps beyond colon (in stomach or small intestine)
Peutz-Jeghers syndrome	– Three or more polyps histologically confirmed – Any number of polyps characteristic of PJS in patients with family history of disease – Characteristic dermomucosal pigment lesions in patients with family history of disease – Any numer of PJS-specific polyps and characteristic dermomucosal pigment lesions
Cowden syndrome	Symptomatic criteria: Dermomucosal lesions – Trichilemmal cyst – Acral papilla – Pappilary lesions – Mucosa lesions The major criteria: Breast cancer Thyroid cancer (especially the follicular thyroid cancer) Macrocephaly Lhermitte-Duclos disease Uterine (endometrial) cancer The minor criteria: Other changes in thyroid (e.g. augmentation of thyroid gland) Mental retardation (IQ ≤ 75) hamartomatous polyps Fibromatic-cystic dysplasia of the nipple Lipomas Fibromas Neoplasms of the genito-urinary organs
Mixed polyposis syndrome	Lack of definite diagnostic criteria for this syndrome Diagnosis is based on the incidence of numerous polyps which differ histopathologically

The division into juvenile polyposis of the colon and the general form of juvenile polyposis has been conventionally assumed on the basis of the site where polyps are located. It is estimated that in more than 20% of JPS patients' inborn defects are found in various organs (tab. 2). In the alimentary tract Meckel's diverticula with umbilical fistula and malrotations of small intestine are found. In the urogenital system cases are registered of undescended testes, unilateral renal agenesia and split uterus. Inborn errors in the chest include a defect in the interatrial septum, arterionevous

haemangiomas, and stenosis of the pulmonary valve, Fallot's tetralogy, aortal stenosis, and persisting arterial duct. And within the central nervous system macrocephaly, a communicating hydrocephalus and rachischisis were found. Moreover, osteomas, mesenteric haemangioma, inherited telangiectasia, hypertelorism, inborn amniotony, supernumerary toes and acute intermittent porphyria have also been observed. Mutations in the *SMAD4* and *BMPR1A* genes (5, 11, 12) are responsible for the manifestations of juvenile polyposis. The *BMPR1A* gene (OMIM *601299; Bone Morphogenetic Protein Receptor, Type IA) is found in chromosome 10 in the q22-23 region (tab. 3). This gene consists of 11 exons and codes 532 amino acids protein of belonging to the TGF-β/BMP family, representing a type I receptor of properties of serine-threonine kinase (13). The transcript of the *BMPR1A* gene consists of 3613 nucleotides (14, 15). It is submitted to expression in the majority of tissues including skeletal muscles and to a lesser degree in the heart and placenta.

Table 2. Risk of incidence of neoplastic disease in the hamartomatous polyposis in particular organs.

Organ	Cumulative risk (%) of the development of neoplasm in particular syndromes of hamartomatous polyposis		
	Juvenile polyposis syndrome	Peutz-Jeghers syndrome	PHTS
Thyroid			3-7
Breasts		54	19-28
Stomach			
Pancreas	Two cases	36	
Small intestine		15	
Colon	9-68 (17th-22nd to 25th year of life)	57 (9th to 40th year of life)	
Kidneys			2
Urinary bladder			3
Uterus		9	6
Cervix		10	3
Ovaries		21	2
Testes		9	S

The *SMAD4* (OMIM*600993 gene, mothers against decapentaplegic, drosophila, homolog of, 4) is located in chromosome 18, in the q21.1 region. It consists of 11 exons. The genomic sequence of this gene consists of 50 thousand base pairs and its respective mRNA consists of 3.197 nucleotides. *SMAD4* is a suppressor gene and it codes for a protein including 552 amino acids and this protein participates in the transmission of signal on the pathway of the transforming growth factor β (TGF β) and its ligands (13). The SMAD4 protein included into "the common" SMAD has two conserved domains of MH1 and MH2 (Mad Homology domain). At the amine terminus of the protein there is the hair-pin domain MH1, which shows DNA binding activity. At the carboxyl terminus of SMAD proteins there is a much

Table 3. Genes preconditioning manifestation of the hamartomatous polyposis syndromes.

Gene	BMPR1A	SMAD4	PTEN	STK11
Name	Bone morphogenetic protein receptor, type Ia	Mothers against decapentaplegic, drosophila, homolog of, 4	Phosphatase and tensin homolog	Serine/threonine protein kinase 11
Protein function	Receptor	Signal protein	Phosphatase	Kinase
MIM	*601299	*600993	*601728	*602216
Chromosome	10q22.3	18q21	10q23.31	19q13.3
Size	168.5 kb	38.5 kb	108 kb	23 kb
Exons	13	11	9	10
Amino acids	532	552	403	433
Transcript	3613 nt	8365 nt	9007 nt	3276 nt
Protein mass	60 kDa	60 kDa	47 kDa	48.6 kDa

conserved MH2 domain. It is responsible for the interaction with proteins involved in the translocation of the complex to cell nucleus as well as interaction with DNA-binding factors (16). Linker Co-SMAD has a leucine rich NES (nuclear export signal) recognized by CMR1. Interaction of SMAD4 with phosphorylated Co-SMAD masks NES, protecting SMAD4 from recognition by CMR1 and from export to the cell nucleus. It is only dephosphorylation of the receptor SMAD and dissociation of the complex that makes export of SMAD4 possible. The import of SMAD proteins to the nucleus takes place without involvement of nuclear transport factors. Such transport, independent of import, has also been described in the case of components taking part in other transformations, e.g. β-catenin along the Wnt pathway. This is possible due to the direct influence of interaction of SMAD with nucleoporins and due to the interaction of hydrophobic corridor in the MH2 domain with the region of repetitions of FG nucleoporins (17).

The phosphorylated receptor SMAD bind with Co-SMAD. The complex created in this way is transferred into the nucleus where is involved in the control of expression of numerous genes as either positive or negative regulator (18, 19). Activation as well as repression requires participation of the same SMAD proteins and the cell-specific interaction with factors which are coactivators and corepressors creates the appropriate response. The complex of SMAD4 with R-SMAD binds to DNA through the MH1 domain, which recognizes the palindrome DNA sequence of GTCTAGAC. Such a SMAD (SBE) binding sequence is often observed in genes which are submitted to expression as a result of the presence of TGF β/BMP ligands. GTCTAGAC SBE is present in every 1.024 base pairs in the genome or at least one such place is in a control region of every moderate size gene (17). In the literature of the subject three mechanisms of control of transcription in either

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a promotor or an enhancer by SMAD and other transcription factors have been described (16). The first mechanism is binding of the active R-SMAD and Co-SMAD complex to a transcription factor and binding of such a complex to a recognized DNA sequence. The second mechanism consists in a separate binding of SMAD and of a cofactor to DNA, but it is only the interaction of these proteins that stabilizes the enhancer properties. The last way of control includes the independent binding of SMAD and the additional factor to a specific DNA site. Their activity is separate, however, they act synergistically.

Mutations in the *SMAD4* gene have been noted in about 20% of patients with familial juvenile polyposis (11, 20). Of a similar incidence have been mutations of the *BMPR1A* gene. On the whole in both genes nearly 200 types of mutations have already been detected, which lead to the development of polyps linked to the juvenile polyposis syndrome. The detected mutations are mostly small alterations, point mutations and small deletions. A rather high proportion of lesions detected in patients with juvenile polyposis are extensive ones. Large deletions were observed in the q22-q23 region of chromosome 10. These alterations affected two neighbouring genes *PTEN* and *BMPR1A*. Mutations in both these genes are engaged in the development of different syndromes of hamartomatous polyposis. The mutations that have been described so far are of a heterogeneous character with the exception of one mutation, i.e. c.1244-1247delAGAC in exon 9 of the *SMAD4* gene. This mutation is found in a hot spot, which is a region containing four binucleotide repetitions of AG, where probably the looping off of a DNA strand fragment probably takes place, which undergoes a deletion.

Some correlations were detected between phenotype and genotype in JPS patients. With mutations in the *SMAD4* gene was linked a higher frequency of manifestation of large polyps in stomach. Germline mutations of this gene are responsible for a more aggressive phenotype of juvenile intestinal polyposis, which is manifested in the form of vascular malformation within the sublayer components when the mutation was located before the codon of 423. It was also observed that polyps with mutation in the *SMAD4* gene are detected in both the upper and the lower parts of the digestive tract while those with mutations in the *BMPR1A* gene are restricted to the colon and anus.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS; OMIM 175200) is a hereditary disease which is inherited in an autosomal dominant manner. The syndrome was first described by L.A. Peutz in 1921. 28 years later, in 1949, H. Jeghers described in detail the clinical presentation of the disease (tab. 1). The first signs of the disease in the form of hamartomatous polyps and pigment skin lesions appear even in childhood. The incidence of this syndrome ranges from 1/29 000 to 1/120 000 births. The polyps appear during the second and the third decade of life in 80-100% of patients (21). They may be located along the whole length of the alimentary tract although the frequency of their manifestation varies and depends on the part of the digestive tract. Most frequently they are detected in the small intestine (96%), next in the colon and the stomach. In the histopathological picture they are present as tree-resembling branches of smooth muscle bundles. The core of the polyps is formed by connective tissue of the sublayer and smooth muscles. The entire alteration is covered in an epithelium that looks normal. In the patients benign polyps were detected outside the digestive tract: in the nose, the bronchi, the gallbladder and the urinary bladder. They are numerous and their sizes range from 1 to 3 cm. The risk of the development of intestinal cancer in the PJS patients is slightly higher than that in the general population. However, it should be noted that hamartomatous polyps, and particularly multiple ones, may result in many complaints from the digestive tract. They may be the cause of ileus (due to intussusception) and bleeding from the lower part of the digestive tract due to an easy polyp autoamputation (22, 23). In articles considering Peutz-Jeghers syndrome patients, the higher risk of cancers incidence in the pancreas, the breasts, the lungs, the ovary and the uterus have been described (tab. 2) (24, 25). Another characteristic sign of the disease is the development of muco-cutaneous melanosis, which appears in infancy as well as in the early childhood. The dark brown, black or blue spots of the size of 1-5 mm are manifested in more than 90% of patients. They may develop around the mouth, the nostrils, and the eyes, the cheeks, on the tongue and on the palate. Also cases were described in which melanosis appeared on the hands, feet, around the umbilicus or in the perianal region. The spots may become pale after pubescence and during adulthood. Diagnosis of Peutz-Jeghers polyposis is based on the recognition of clinical symptoms. The diagnostic criteria adopted for this disease in case of persons with a familial history of the disease are restricted only to the detection of melanin deposits. While in the absence of the familial history it is required to confirm the manifestation of at least two hamartomatous polyps.

Peutz and Jeghers syndrome is preconditioned by mutations in the *STK11* gene (OMIM*602216; Serine/Threonine Protein Kinase 11) located in the short arm of chromosome 19 in the 13.3 region. This gene consists of 10 exons, 9 of which code a protein manifesting a serine-threonine kinase activity (tab. 3). It undergoes comprehensive expression during the embryonal development, however also in the organs of adults, particularly in the pancreas, the liver, and in skeletal muscles. The STK11 protein consists of three main domains, N-terminal, non-catalytic domain with two signals for nuclear localization, the highly conserved kinase domain and the regulatory domain at the carboxyl end. The kinase domain of this 433 amino acid protein is located between the 49th and 309th amino

acid. The STK11 protein contains a few sites which undergo phosphorylation and prenylation and it also contains the nuclear localization signal (NLS). Due to the activity of kinases, serines are phosphorylated at positions of 31 and 325 and threonine at position 363. STK11 is also capable of undergoing phosphorylation on threonines at positions 185, 189, 336 as well as on serine at position 402. Autophosphorylation of STK11 at position Thr189 is of great importance to the kinase activity of this protein. On the other hand, the prenylation motive of Cys^{430}-Lys-Gln-Gln^{433} is positioned at the carboxyl terminus. The loss of STK11 protein function precipitates the development of various defects. This reflects the fact that the STK11 protein participates in many important cellular processes. In *Xenopus*, a homologue of the *STK11* gene, XEEX1, is engaged in the process of early embryonal development. On the other hand, mice which lack the *Stk11* gene die around the eighth day during embryogenesis. In the case of *Stk11+/-* mice, manifestation of polyps is seen, which in histopathology are very similar to those observed in PJS. Molecular analysis showed that for the development of polyps the loss of only one allele of the *STK11* is sufficient. Following the 45th week of life in > 70% male *Stk11+/-* mice and 20% female *Stk11+/-* mice histopathologically variable types of liver cancers are observed. The cancer cells showed a loss of both alleles of the *STK11* gene (26, 27). It was shown that *STK11* controls the TGF β pathway, forming a complex with the SMAD4 protein through LIP1. LIP1 forms a specific bridge between the two proteins (28). STK11 also interacts with the PTEN protein (29). Moreover, *STK11* kinase participates in the p53-dependent apoptosis.

Germline mutations of the *STK11* gene have been detected in 70% patients with an inherited form of the disease. In cases of patients with negative family history detectability of the mutations is around 50% (30). In the *STK11* gene more than 230 mutations have been described so far, including 70 point mutations. A large portion of these mutations include small deletions − 54, and small insertions − 33. Among the PJS patients large deletions including individual exons and even deletions of the entire gene are also frequent (31).

COWDEN SYNDROME

Cowden syndrome (OMIM #158350; Cowden Disease – CD) is a very rare syndrome of hamartomatous polyposis. Its incidence is estimated at 1 per 200 000 births. Its characteristic trait is various hamartomatous lesions in tissues originating from three germ layers: the endoderm, ectoderm and mesoderm. Apart from the gastro-intestinal region (71% of the patients), these lesions are manifested in the skin, mucous membranes and other organs. An international consortium dealing with Cowden syndrome developed diagnostic criteria, which includes dermomucosal lesions, including fibromas of the mucosa of the oral cavity and papillary and hyperkeratotic alterations on the face and extremities (tab. 1) (32). In almost 99% of patients dermomucosal lesions develop before the 30th year of age. Hamartomatous lesions within the alimentary tract are found along its whole length (33). However, they are most frequent in the stomach, the colon and the oesophagus. In the oesophagus they appear as glycogenic keratinization. In this syndrome the hamartomatous lesions include, first of all, polyps, adipomas and gangliomas. In Cowden syndrome polyps are distinguished by the presence of nerve elements, which are not observed in other syndromes of hamartomatomous polyposis. Apart from that, in patients with Cowden syndrome are also observed defects of the central nervous system such as macrocephaly (38%), mental retardation, Lhermitte-Dulclos disease (LDD) and cereberral gangliomas. What is also noted are defects of eyes and arterio-venous developmental lesions (34-36). Defects of bones in the skull, the spinal column and the hands are found in every third patient. In this syndrome there is a higher risk of the development of benign or malignant tumours in the thyroid gland, the lungs, the kidneys, the retina, the breasts, the uterus and the skin. In 30 to 50% of women with Cowden syndrome breast cancer is observed, and in 25% of cases the cancer is bilateral. Breast cancer in these women develops at the very young age, approximately 10 years earlier than in the general population (34). In the case of Cowden syndrome 53% of patients are at a risk of developing thyroid gland cancer 53%. Most frequently goitre is manifested (22%) while adenomas are found in 12%. The follicular thyroid cancer is manifested in around 4% of patients with Cowden syndrome and the papillary cancer in 3% of them. There are also individual cases of the medullary thyroid carcinoma (tab. 2) (37, 38). The *PTEN* gene (OMIM*601728; Phosphatase And Tensin Homolog), responsible for the development of Cowden syndrome, was mapped in 1997 on chromosome 10, in the region q23 (tab. 2).

This is a suppressor gene, coding for protein consisting of 403 amino acids, representing phosphatase. Definition of the PTEN crystalline structure revealed that the N-terminal domain of phosphatase strictly adheres to the C2 domain at the carboxyl terminus. Two domains together form a basic catalytic unit including almost whole peptide sequence of the protein apart from the small tail in the N-terminal portion and a longer 50 amino acid fragment at the carboxyl terminus. The domains of phosphatase and C2 creating the catalytic core of the protein are sufficient for its normal function. The remaining parts seem to be involved in the control of activity or/and interaction of PTEN with other proteins (28). PTEN is able to dephosphorylate both proteins and lipids of cell membrane. It removes the phosphate group from position D3 from the isinositol ring from 3,4,5-phosphatidylinositol triphosphate and 3,4-phophatidynositol diphophate produced during transmission of cellular signals through the activity of phosphoinositol 3' kinase (PI3K) (39). PTEN acts as a specific switch-off for signal transmission along the PI3K pathway, and in this way stops the cell cycle at the

G1 phase. The activity of the *PTEN* gene, which involves antagonization of phosphoinositol 3' kinase action, inhibits the activity of multiple oncoproteins, which exert their effect just through the PI3K kinase. PTEN-PI3K control fundamental cellular processes linked to the mechanism of neoplastic transformation. PTEN participates in the control of the cell cycle through Akt kinase. Among the substrates of Akt kinase which play a significant role in the cell cycle transcriptional factors such as: *FKHR* (Forkhead transcription factor), *AFX*, *FKHRL1* or *GSK3* can be distinguished. PTEN also participates in the control of cell divisions. In *PTEN*-/- fibroblasts the response to stimulation of apoptosis is lowered due to the augmented transcription of proapoptotic genes, i.e. FAS and Bim. The activity of the PTEN protein phosphotase leads to the inhibition of FAK (Focal Adhesion Kinase), which is responsible for cellular adhesion and the capacity of cells to migrate (40). The PTEN protein plays also an important role in the process of angiogenesis and participates in the control of the mTOR pathway. In *D melanogaster* loss of the *dpten* gene function causes an increased size of cells and organs while overexpression of dpten in yeasts causes an inverse phenotypic effect. In the case of mice the loss of the *PTEN* gene in neurons leads to the development of a set of traits similar to those that are present in Lhermitte-Duclos disease, which is one of the clinical presentations of Cowden syndrome (41).

Somatic mutations in the *PTEN* gene lead to the development of a number of various neoplasms. They are detected in 80% of patients with Cowden syndrome. Mutations in the *PTEN* gene are also detected in other syndromes of hamartomatous polyposis, among others in Bannayan-Riley-Ruvalcaba syndrome (42). Detectability of lesions in the *PTEN* gene approaches 60%. In the database of mutations in the *PTEN* gene 208 mutations are described the majority of which involved mutations of altered sense and nonsense mutations (87 mutations) and small deletions and insertions (75 mutations). In patients with Cowden syndrome mutations in the *PTEN* gene are observed in the promotor region while deletions of a portion or of an entire gene are usually seen in patients with Bannayan--Riley-Ruvalcaba syndrome.

HEREDITARY MIXED POLYPOSIS

Hereditary mixed polyposis syndrome (MIM #610069; Hereditary Mixed Polyposis Syndrome – HMPS) appeared in literature in 1971. It was then that a case was described of an 11-old girl with juvenile polyps and adenomas of the colon and the small intestine. However, it was only in 1987 that Sarles suggested the term of mixed polyposis when describing the cases of a father and son with numerous and various types of polyps in the colon. In the father metaplastic polyps and adenomas were found while in the son apart from these polyps also juvenile polyps were diagnosed. Most precisely clinical traits of mixed polyposity syndrome were presented in a family consisting of a few generations and called SM96 (43, 44). Among more than 200 members of the family in 42 individuals the presence of different types of polyps were shown such as tubular adenomas, papillary adenomas, flat adenomas and hyperplastic polyps as well as juvenile polyps. Histologically, the atypical juvenile polyps had traits of hyperplastic polyps and adenomas. Colonoscopic tests that were used usually demonstrated the presence of about ten polyps in the colon and the anus. The average age of the patients diagnosed with HMPS in the SM96 family was 40 years.

On the other hand, Cao et al. presented two families consisting of three generations with the course of the disease very similar to that of the SM96 family (43). In most of these cases polyps were located in the colon. Cao did not observe any extraintestinal alterations. It was also found that patients with HMPS manifested an increased predisposition to the development of cancers in the colon.

The gene responsible for the development of mixed polyposis has not yet been identifed. As a result of analysis of linkages the region strictly bound to the appearance of the signs of the disease was defined. This was termed CRAC1 and it is located on the long arm of chromosome 15. In a proband from one of the families presented by Cao a heterozygous mutation was discovered, a deletion of 11 nucleotides in exon 2 of the *BMPR1A* gene. In the other family members this mutation has not been detected. In 2012 a work was published on duplication within the 3` end of the SCG5 gene and the 5` end of the *GREM1* gene, which duplicates the enhancer region of the *GREM1* gene. This duplication includes 40kbp and results in the increase in the allelo-specific expression of the *GREM1* gene which blocks the activity of the BMP pathway (45). Similar mechanism is a base of the manifestation of colon cancer in juvenile polyposis. Mixed polyposis is the least recognized disease among the hamartomatous polyposis syndromes and it still requires further studies.

CARE OF PATIENTS WITH HAMARTOMATOUS SYNDROMES

Syndromes linked to hamartomatous polyposis are a rather heterogeneous group both in respect to the number and localization of polyps as well as the risk of the development of cancers in the alimentary tract and in other organs. Despite the fact that these diseases are not the most frequent ones still they remain dangerous to patients not only due to the predisposition to manifest themselves as a neoplastic disease but also due to non-neoplastic symptoms such as haemorrhages, intussusception and intestinal occlusions. Every hamartomatous polyposis syndrome manifests its own organ-specific localization of symptom manifestation and that is why each of them requires a different strategy of diagnostic procedures. Due to this the accurate qualification of patients to a specific syndrome is a main step towards an appropriate care of patients with these

predispositions. Recommendations concerning diagnostic studies in hamartomatous polyposis are based only on the opinions of experts. No randomized diagnostic studies have been conducted on the efficacy of medical care programmes so far (46). For the Peutz-Jeghers syndrome diagnostic care is focused on the organs endangered with a neoplastic transformation which vary according to the gender of the patients. Both for males and females examinations of small intestine (small intestine passage) is recommended beginning at the 8th year of age and performed every two or three years. Colonoscopy is recommended every two or three years from the age of 18. From the age of 24 a USG examination of the pancreas is recommended. In women breast examination should be performed from the 18th year of life and self-examination should be done monthly. Since the age 24 annual breast ultrasound and MRI examinations should be performed while from the age of 35 annual mammography should be performed. The ovaries should be examined once a year between birth and the 12th year of life and then from the 21st year of age. In male patients testes should be examined once a year starting from birth till the 12th year of age. In juvenile polyposis the care of patients is focused on monitoring the alimentary tract. However, in several families was observed the co-manifestation of hereditary hemorrhagic telangiectasia in case of mutation in the *SMAD4* gene, therefore the abnormalities of the vessels development are also possible. Attention should be paid to the haemorrhages, anaemia, abdominal pains, diarrhoea or changes in the shape or colour of the faeces in the patients. Appearance of such alterations is an indication of the necessity to conduct additional tests, including colonoscopy. In patients without such symptoms endoscopic examinations: gastroduodenoscopy and colonoscopy should be conducted starting at the age of 15. If in the endoscopic examination polyps are detected they should be removed and in such a situation the tests and the removal of polyps should be repeated annually (46). If polyps are not detected, tests can be performed once every three years. In severe courses of the disease colectomy may be the only way to treat the patient (3). In the mixed polyposis endosopic examination of the colon is recommended once a year and

the diagnosed polyps should be removed by means of polypectomy (47, 48). Cowden syndrome carries the risk of a neoplastic disease in various organs; therefore prophylactic tests should include the thyroid gland, the breasts and endometrium. There are no specific recommendations as to the examination of the alimentary tract, however, some authors recommend periodical radiological examination (3, 46, 49). Examination of breasts should begin at the 30 year. Self-examination of breasts should be performed monthly while USG and MRI should be performed annually, and from the age of 35 mammography should be performed annually. USG of the thyroid gland should be supplemented with an aspiration thin-needle biopsy of the detected tumours (3, 49).

STUDIES OF HAMARTOMATOUS POLYPOSIS IN POLAND

Studies of the hereditary predispositions for the manifestation of the hamartomatous polyposis have been conducted by the authors of this paper at the Institute of Human Genetics, Polish Academy of Sciences in Poznań. In the DNA bank of Polish patients with polyposis material has been collected from 81 families with hamartomatous polyposis. The bank contains 28 families with JPS, 48 with PJS and 5 cases of Cowden syndrome. On the basis of studies of this material a mutation spectrum was described in the *BMPR1A*, *SMAD4*, *PTEN*, *STK11* genes in patients with the diagnosed JPS, PJS and the Cowden syndrome respectively. Mutations in these genes in Polish population are of heterogeneous character and no founder mutations have been found in these genes for our population. The largest percentage of the diagnosed families was observed in the case of PJS in which mutations were diagnosed in 32 families and 25% of them were CNV (copy number variations). In case of JPS mutations were diagnosed in12 cases. Our attention has been focused on the high percentage of CNV in these diseases. The studies we conducted have contributed to the definition of the mutation spectrum in the predisposition genes to the occurrence of hamartomatous polyposis in the Polish population (50-53).

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