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Genotype-phenotypic correlation of Peutz-Jeghers syndrome

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ABSTRACT *INTRODUCTION: Peutz-Jeghers syndrome (PEUTZ-JEGHERS SYNDROME; PJS; OMIM#175200) is hereditary tumor syndrome and is characterized by the occurrence of hamartomatous polyps of gastrointestinal tract, melanocytic pigmentation of the skin and mucous membranes, as well as a high predisposition to malignant tumors of various locations. Despite the fact that the clinical features of PJS are currently well understood, the nature of the variability in the phenotypic manifestations of the disease has not been fully described.*

AIMS: to determine the phenotypic and clinical features in patients with PJS depending on the type of mutation in the STK11 gene.

PATIENTS AND METHODS: the clinical and genetic data of 3 patients aged 21, 28 and 39 years with clinical signs of PJS are presented. All patients underwent medical genetic counseling and molecular genetic diagnostics of the STK11 gene using NGS and MLPA methods.

RESULTS: large deletions of ex2-8 and ex1 in the STK11 gene were revealed in two patients, and one patient showed a splice site variant c.921-1G > A. The identified variant ex2-8 has not previously been described in international databases. When evaluating the clinical and genetic features, the most severe picture of the disease was in a patient with an extended deletion of exons 2-8, large number of polyps and surgical procedures in history. However, in this case, melanocytic pigmentation became less with age, in contrast to patients with a splice site mutation and a single exon deletion. No cancers were detected in the patients.

CONCLUSION: the molecular genetic test made it possible to confirm the clinical diagnosis of PJS, based on various phenotypic features, and to work out the personalized plan for follow-up. Evaluation of the genotype-phenotype correlations will be possible with the development of a unified register of mutation carriers.

KEYWORDS: *Peutz-Jeghers syndrome, gastrointestinal polyposis, hamartoma polyps, melanocytic hyperpigmentation, splicing site mutation, deletion, STK11 gene*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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INTRODUCTION

Peutz-Jeghers syndrome(PJS, PEUTZ-JEGHERS SYNDROME; OMIM# 175200) is a rare hereditary autosomal dominant syndrome characterized by the occurrence of tens to hundreds of hamartomic polyps in the small intestine (60%-90%), stomach (15%-30%), and large intestine (50%-64%), melanocytic pigmentation of the skin and mucous membranes (95% of cases), as well as an increased risk of malignant neoplasms (MN). The prevalence of the syndrome in the population ranges from 1:25,000 to 1:200,000 newborns [1]. To date, the criteria for making a clinical diagnosis include [2,3]: — The presence of three or more hamartomic polyps of the gastrointestinal tract (GIT); — Melanocytic pigmentation of the face skin and/or mucous

membranes; — Burdened family history of diseases from the PJSrange.

The diversity of these criteria and the variability of the clinical picture of PJS do not always allow to establish a diagnosis without a molecular genetic study. The peculiarities of this syndrome are caused by disorders in the *STK11* gene, which encodes the protein serine-threonine kinase 11, which participates in the regulation of cellular metabolism, cell polarization and response to DNA lesion. The *STK11* gene is located at 19p13.3, includes 9 coding exons. Germinal mutations in the *STK11* gene lead to loss of gene product function, in particular, activation *pik3A/AKT/* of the target of the mTOR signaling pathway and carcinogenesis [4]. Identification of the pathogenic variant in the *STK11* gene allows to confirm the diagnosis, as well as to establish a carrier among the patient's relatives, to reduce the incidence of emergency surgery and the risk of MN [5]. In general, the risk of MN of various sites is 15 times higher in patients with PJSin comparison with the general population, and by the age of 65 years old it can reach 93% [6,7]. Currently, there is no pathogenetically based treatment for Peitz-Jaegers syndrome. The main approach is dynamic control and prevention of severe complications.

Often, the diagnosis of PJS is established at the stage of surgical complications, such as intussusception of the small intestine, intestinal obstruction, bleeding, and others, which emphasizes the importance of early diagnosis of the disease [8,9]. Recently, the lack of reliable data on phenotype-genotypic correlation does not allow predicting the course of the disease and the risk of MN [10–11]; further study of this issue may lead to an improvement in the prognosis for such patients.

PATIENTS AND METHODS

The paper presents the clinical and genetic data of 3 patients aged 21, 28 and 39 years with clinical signs of PJSin 2021. All patients underwent medical and genetic counseling, as a result of which it was recommended to make DNA test of the *STK11* gene using NGS (next generation sequencing) methods on the Illumina MiSeq sequencer. The MLPA (Multiplex Ligation-dependent Probe Amplification) method was performed using the MRC Holland kit, SALSA MLPA Probemix P101-B4 STK11.

This study was approved by the local ethics committee and informed consent was received from each patient.

RESULTS

Clinical Observation 1

Patient A., aged 21, consulted a geneticist to clarify the hereditary nature of polyposis. It is known from the history that for the first time at the age of 11 months after an episode of prolapse of the rectal mucosa during defecation, a tumor of the rectum was revealed, which was removed; during histology, it was a villous adenoma. From the age of 7, the patient had episodes of bloodin the stool, iron deficiency anemia. At the age of 14, multiple diffuse polyps in the stomach, smalland large intestine were detected, and the diagnosis of PJS was clinically approved.

In this regard, elective endoscopic polypectomies from the stomach, small and large intestine were repeatedly performed. At the age of 21, an enterography revealed an invaginate with polyps of 1.6 and 2.0 cm in the middle third of the jejunum, a polyp up to 3.5 cm in the proximal loops of the ileum.Shadows of small polyps up to 0.3–0.8 cm were also detected throughout the small intestine. However, it should be noted that the lumen of the small intestine was uniform throughout. Due to the threat of small intestine obstruction, the patient underwent elective surgery. Laparotomy was performed, the invaginate was straightened, 3 enterotomies were performed and 7 of the largest polyps with a diameter of up to 3.5 cm were removed. According to the morphology of the removed polyps, hamartomas were revealed. When examining the patient, attention is drawn to the light brown pigmentation of the lips, which was more pronounced in childhood. In the family history, attention is drawn to multiple operations for small intestine obstruction in the father at the age of 16, 20 and 45 years; taking into account clinical data, he was diagnosed with PJS without confirmation by molecular genetic diagnosis.

Table 1. *Clinical characteristics and results of check-up*

Patients/ Examples	А.	Б.	В.
Melanocytic pigmentation	Lipmucosa	The mucous part of the lips, cheeks, skin around the lips, periorbital, back surface of the hands and palms	Periorbital
Age of detection of polyposis	11 months	28 years old	24 years old
Location of polyps	S, SI, C	S, SI, C	S, SI, C
Total number of hamartomic polyps during life	> 70	> 40	> 20
Variant in the *STK11* gene (NM_000455.5)	ex2-8 del [g.(?_001169421)_ (001174101_?)del]	ex1 del [g.(?_001156776)_ (001157954_?)del]	chr19:1222984G > A, c.921-1G > A
Clinical significance of the variant	Pathogenic	Pathogenic	Pathogenic
MN in relatives of I-II degree of kinship	None	CC (II-2), MN in B (I-2), BC (II-3)	None
The number of operations in the history	15	1	3

ABBREVIATIONS: S — stomach, SI — small intestine, C — colon, BC — breast cancer, CRC — colorectal cancer, B — brain; (II-2) — mother of patient B, (I-2) — paternal grandmother of patient B, (II-3) — maternal aunt.

In his half-siblings (his brothers aged 6 and 9 on his father's side), hamartomicgastric polyps were revealed.

Taking into account the results of endoscopy and histology (multiple hamartomic polyps), complicated family history, phenotype data (the patient and half-siblings had pigmentation of the skin and oral mucosa from the age of two years), a presumptive diagnosis was established — PJS. The patient's phenotypic data and family history are presented in Fig. 1.

The patient provided data from a molecular genetic test of the siblings: no causative variants were detected in the coding part of the *STK11* gene. The proband was searched for extended deletions/duplications in the *STK11* gene by MLPA, which allowed to determine the mutation ex2-8 del [g.(?_001169421)_(001174101_?)del] and confirm the diagnosis of Peitz-Jaegers syndrome (Table 1).

Clinical Observation 2

Patient B., aged 28 years old, when complaints of spastic pain in the epigastrium appeared, a check-up was performed (esophagogastroduodenoscopy, colonoscopy, abdominal CT), as a result of which invagination of the vermiform appendix into the lumen of the cecum and multiple invaginates in the small intestine caused by multiple hamartomic polyps of the small intestine, as well as an exophytic villous tumor of the splenic flexureof 8 × 3 × 5 cm and 3 polyps of the sigmoid colon up to 4, 5 and 7 cm in diameter on long legs were revealed (Fig. 2, 3).

The patient underwent elective surgery. The intraoperative revision revealed invaginates of the small intestine at 100 and 110 cm from the Treitz ligament and one invaginate at 100 cm from the ileocecal valve. The procedure includedstraightening of the jejunum invaginates, enterotomy, removal of two polyps up to 3 cm in diameter on long pedicle, segmental resection of the ileum with the hand-sewn ileo-ileoanastomosis "side-to-side", resection of the dome of the cecum with an appendix and resection of the left colon with the hand-sewn transverso-sigmoid anastomosis "side-to-side" due to the impossibility of endoscopic removal of tumors of the descending and sigmoid colon. The morphology revealed a tubulovillous adenoma with low grade epithelial dysplasia. Polyps of the vermiform appendix of the small intestine were hamartomas.

Taking into account the pigmentation characteristic of the PJS in the proband, the family history (Fig. 1) and the results of the check-up, the patient was referred to the consultation of a geneticist. Based on the available facts, it was decided to search for mutations in the *STK11* gene by the NGS method.

As a result, pathogenic and probably pathogenic variants were not identified. In order to search for extended deletions/duplications, the *STK11* gene was further analyzed by the MLPA method. The mutation ex1 del [g.(?_001156776)_(001157954_?)del]was detected. The detailed clinical and anamnestic data and the results of the patient's DNA diagnosis are given in Table 1. Based on the result of the molecular genetic test, the diagnosis of PJS was confirmed.

Clinical Observation 3

Patient V., aged 39 years old, consulted a geneticist to clarify the prognosis of the disease (Fig. 1). It is known from the history that since 2006 she has been observed by a gastroenterologist for iron deficiency anemia, gastric polyposis. The patient repeatedly has undergone endoscopic removal of gastric polyps. In November 2019, the patient was hospitalized by an ambulance team with a clinical picture of small intestine obstruction, for which laparotomy, resection of the small intestine invaginate was urgently performed. With control esophagogastroduodenoscopy in 2020 diffuse gastric polyposis, multiple duodenal polyps were

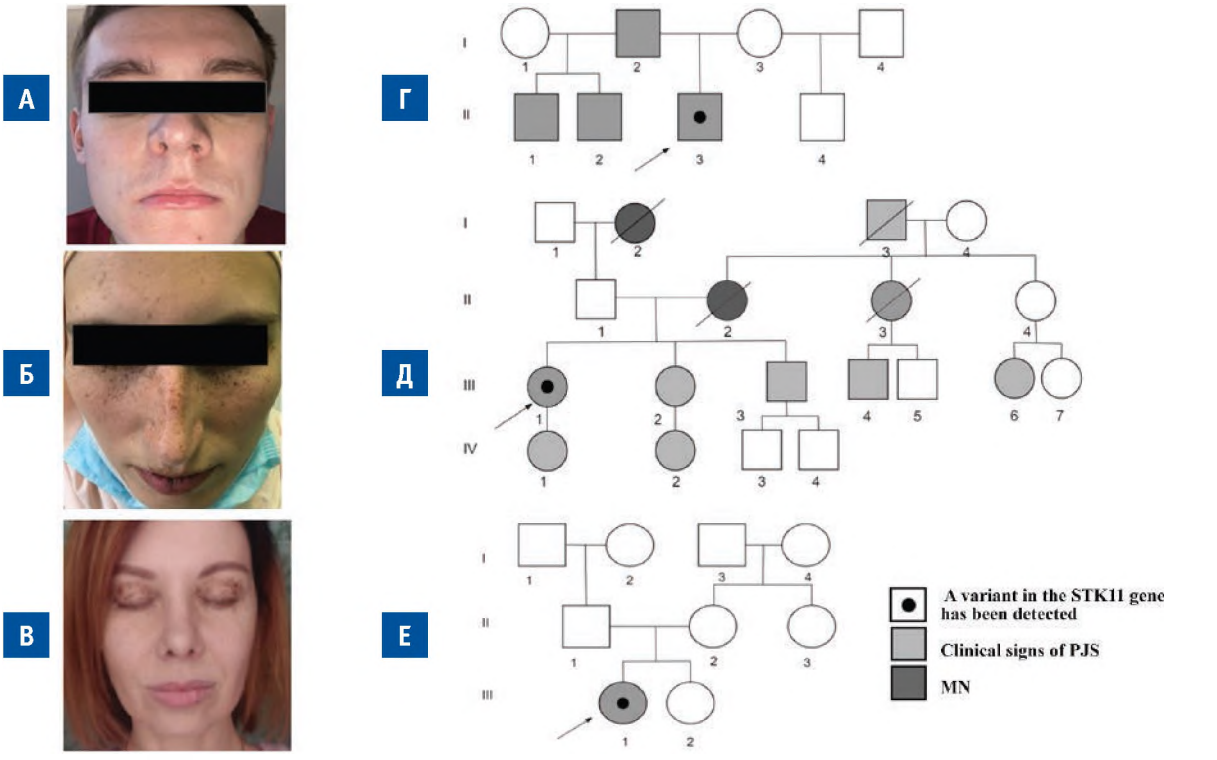

Figure 1. *А — Light brown lip pigmentation of patient A, Г — Pedigree of patient A; Б — Hyperpigmentation of the facial skin of patient B; Д — Pedigree of patient B; В — Hyperpigmentation of the skin around the eyes of patient B, Е — Pedigree of patient B.*

revealed. Histology revealed fragments of a glandular polyp of the stomach, hyperplastic polyps of the duodenum. Colonoscopy showed a sigmoid colon polyp with a diameter of 4–5 mm on a narrowed base, according to the histology — an adenomatous polyp.

The search for pathogenic and likely pathogenic mutations in genes associated with hereditary tumor syndromes and hereditary polyposes, and in particular the study of the coding sequence of the genes *STK11, MutYH, APC* were performed. A mutation c.921-1G>A was detected in the *STK11* gene (Table 1). Based on genetic testing, the patient was diagnosed with PJS, and regular intestinal control was recommended to exclude the growth of new polyps.

DISCUSSION

The study included the clinical data of three patients with a molecular-genetically confirmed PJS with identified mutations in the *STK11* gene.

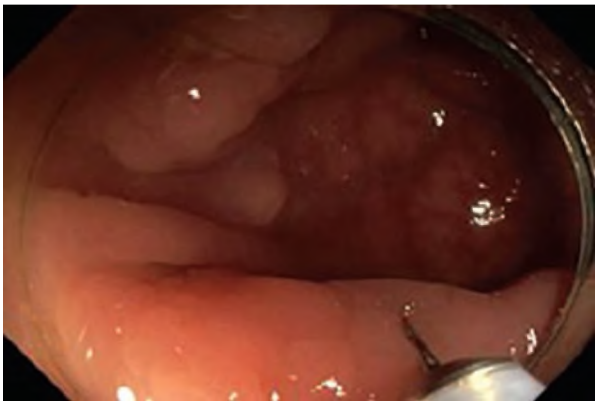

Figure 2. *Endoscopy of colorectal polyposis (patient B)*

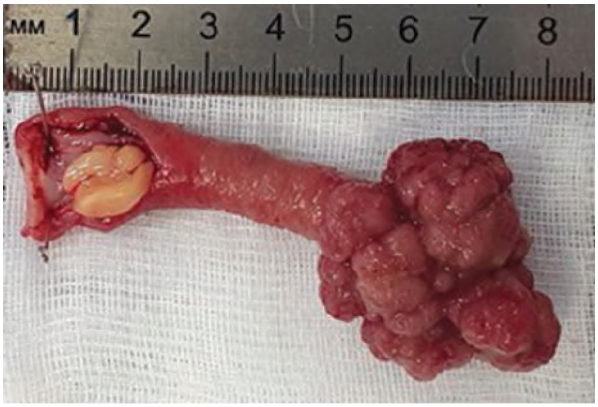

Figure 3. *Removed specimen of appendix intussusceptions with Peutz-Jeghers polyps of patient B*

All variants lead to a violation of the function of the STK11 protein. Variant ex2-8 del, not previously described in international databases, leads to shortening (truncating mutation) and disruption of protein function, which causes clinical significance. The variant of the splicing site c.921-1G>A and the extended deletion of ex1 were previously described in patients with Peutz-Jeghers syndrome, colorectal cancer, pancreatic adenocarcinoma, gastrointestinal polyposis [12–15]. According to the information given in the literature, it is impossible to conduct a comparative analysis of the patient data, since each article highlights various aspects of PJS. For example, Resta N. et.al [12] described a patient with PJS, about whom it is known that she has no family history, there is no MN, and a variant c.921-1G>A was identified in the *STK11* gene. Bannon S.A. et.al [13] conducted a study of genes associated with pancreatic MN; among the identified variants there was an extended deletion of ex1 in the *STK11* gene in a patient with pancreatic adenocarcinoma; Ngeow J. et.al [15] revealed the same genetic variant in a patient with hamartomic polyps, while other clinical manifestations of PJS are not described in both papers.

When assessing the clinical and genetic features, the most severe disease was observed in a patient with an extended deletion of 2–8 exons, who had a large number of polyps and a history of surgeries. However, it is worth noting separately that in the described patient, melanocytic pigmentation has become less pronounced with age, unlike the patients with a point mutation and deletion of the first exon.

The risk of developing MN of various sites and the algorithm of dynamic control of carriers of germinal mutations in the *STK11* gene is presented in Table 2 [16–21]. Despite the fact that according to the literature, the carrier of truncating mutations correlates with a higher risk of cancer in comparison with the carriers of the missense variants in the patients described by us, MN was not observed. This may be due to the young age of the patients, the non-progressive disease, as well as their personalized approach, including check-up and removal of identified polyps, which probably reduced the risk of developing MN.

Table 2. *Cancer risk and National Comprehensive Cancer Network follow-up guidelines for Peutz-Jeghers syndrome*

MN Localization	Cumulative risk of developing MN during life, %	Age of screening initiation, years	Methods of dynamic control	Dynamic control intervals
Mammary gland	32–54	30	-Clinical examination of an oncologist-mammologist -Mammography and MRI of the mammary glands	– 1 time every 6 months – Every year
Stomach	29	8–10*, but no later than 18	EGDS	Every 2–3 years**
Small intestine	13	8–10*, but no later than 18	CT/MRI enterography or videocapsular endoscopy	Every 2–3 years**
Large intestine	39	8–10*, but no later than 18	Colonoscopy	Every 2–3 years**
Pancreas	11–36	30–35	-USAO or MRI/MRCPG	Every year
Cervix (malignant adenoma)	10	18–20	-Gynecological examination -Cytological examination with Papanicolaou staining	Every year
The uterus body	10	18–20	-Gynecological examination -Cytological examination with Papanicolaou staining	Every year
Ovaries (Tumor of the genital cord with annular tubules)	18–21	~8	-Gynecological examination -Cytological examination with Papanicolaou staining	Every year
Testicles (Tumor from Sertoli cells)	9	~10	Urological examination	Every year
Lungs	7–17	No specific recommendations		

*Note: * Possible earlier start of periodic examinations in the presence of clinical signs of lesion; **It is permissible to reduce the time intervals between examinations in the case of a larger number or size of polyps*
ABBREVIATIONS: MRI — magnetic resonance imaging, EGDS — esophagogastroduodenoscopy, CT — computed tomography, US — ultrasound examination, AO — abdominal organs, MRCPG — magnetic resonance cholangio-pancreatography.

According to the literature, point mutations in the *STK11* gene are most often detected. However, about 15%-20% of cases of PJS are associated with extended deletions/insertions [22,23]. Therefore, in the absence of a causative variant in the study by NGS sequencing, it is necessary to use an additional diagnostic method — MLPA. It is thanks to this method that we were able to confirm the diagnosis in two of the patients described in the paper.

To date, numerous studies have been aimed at studying the effect of the location of mutations on the protein structure and the severity of clinical manifestations [10,24] to establish a correlation between the severity of the course of PJS and the molecular variant in the *STK11* gene. Equally, efforts are being made to identify the dependence of the risk of developing MN on the type of mutation in the *STK11* gene [25,26]. Zhao Na et al. report about their functional analysis of the effect on the structure of the final product of variant C.921-2A>C, located at the same splicing site as the mutation in patient B.

This variant is considered as the cause of the disease in two patients aged 5 and 35 years old with a variable phenotype of PJS [27]. Orellana P. et al. as well as Shelygin Yu.A. et al. described mutations of the splicing site and deletion of the *STK11* gene, in which hyperpigmentation and polyposis of the stomach, small and large intestine were present in most patients, and the age of diagnosis ranged from 1 to 37 years [5,28].

CONCLUSION

Given the low prevalence of Peutz-Jeghers syndrome, it is necessary to create a unified register of patients carrying pathogenic variants in the *STK11* gene associated with PJS, which will allow identifying genotype-phenotypic correlations, as well as developing a personalized follow-up and treatment plan.

AUTHORS CONTRIBUTION

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Statistical processing: *Vera V. Polyakova, Tatiana I. Yanova*
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