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Molecular genetic testing of russian patients with suspected juvenile polyposis syndrome

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ABSTRACT *AIM: to present the results of molecular genetic testing in patients with suspected juvenile polyposis syndrome (JPS).*

PATIENTS AND METHODS: molecular genetic testing was performed on 30 patients from 28 families (one family had three affected relatives) who were followed from 2012 to 2024. DNA was isolated from patients' peripheral blood leukocytes. The initial step involved Sanger sequencing of the SMAD4 (NM_005359.6) and BMPR1A (NM_004329.3) genes, followed by screening for large rearrangements using MLPA (Multiplex Ligation-dependent Probe Amplification). Finally, patient DNA was analyzed by whole-exome sequencing (WES), with confirmation of identified variants by Sanger sequencing.

RESULTS: pathogenic and likely pathogenic variants in the BMPR1A and SMAD4 genes were identified in 18 out of 28 families (64.3%). In the BMPR1A gene, 11 out of 18 (61.1%) germline variants were found, including three large deletions. In the SMAD4 gene, 7 out of 18 (38.9%) germline variants were detected, including one large deletion and one large duplication. Thus, 5 out of 18 (27.8%) germline variants in these genes were large rearrangements. In five families, previously unreported germline variants were identified (three in BMPR1A and two in SMAD4), all classified as likely pathogenic.

CONCLUSION: pathogenic and likely pathogenic variants in the BMPR1A and SMAD4 genes were identified in 18 out of 28 families (64.3%). In the BMPR1A gene, 11 out of 18 (61.1%) germline variants were found, including three large deletions. In the SMAD4 gene, 7 out of 18 (38.9%) germline variants were detected, including one large deletion and one large duplication. In five families, previously unreported germline variants were identified (three in BMPR1A and two in SMAD4), all classified as likely pathogenic. All patients with suspected juvenile polyposis syndrome should be tested for SMAD4 and BMPR1A mutations using Sanger sequencing and MLPA. If the result is negative, high-throughput sequencing should be employed. For patients with 20 or more adenomatous colorectal neoplasms but no pathogenic/likely pathogenic variants in the APC and MUTYH genes, it is advisable to proceed directly to whole-exome sequencing.

KEYWORDS: *juvenile polyposis syndrome, SMAD4, BMPR1A, DNA diagnostics, MLPA*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

Juvenile polyposis syndrome (JPS) is a rare disease with an autosomal dominant type of inheritance, which is characterized by multiple juvenile polyps in the gastrointestinal tract [1]. The diagnosis is based presence of one of the clinical criteria (5 or more juvenile polyps in the large intestine, multiple juvenile polyps throughout the gastrointestinal tract, any number of juvenile polyps with a family history) or with molecular genetic confirmation of the disease [1]. In patients with juvenile polyposis, the number of polyps can vary from 5 to 200, while in addition to juvenile polyps, adenomatous neoplasms can also occur in the large intestine, which significantly complicates the diagnosis [2]. The literature describes clinical cases when only adenomatous neoplasms of the large intestine were detected in patients with a genetically confirmed diagnosis of juvenile

polyposis [3]. Recently, DNA diagnostics makes it possible to find the genetic cause of the disease in 40–60% of patients with JPS, who are found to have pathogenic (probably pathogenic) variants of the *SMAD4* genes (NM_005359.6; OMIM #600993) or *BMPR1A* (NM_004329.3; OMIM #601299), located on chromosomes 18q21 and 10q22, respectively [4]. In about 20–30% of cases, the JPS is caused by pathogenic/probably pathogenic variants of the *BMPR1A* gene, and in 20–30% — by pathogenic/probably pathogenic variants of the *SMAD4* gene [4]. Both genes are suppressors of tumor growth, are involved in the signalling pathways of bone morphogenetic proteins (*BMP*) and transforming growth factor beta (*TGF-β*), and influence cellular processes such as growth, differentiation, and apoptosis [5]. Most pathogenic variants are point mutations or small deletions/insertions in coding regions; however, about 15% of the variants are extensive rearrangements [5,6]. Approximately 20–50% of patients with juvenile polyposis syndrome have no family history and are caused by *de novo* mutations [5–7]. Now, various molecular genetic testing strategies are available for patients with suspected JPS, including simultaneous testing of the *BMPR1A* and *SMAD4* genes, sequential testing of each gene, the use of a multigenic panel, as well as the use of full-exome or full-genome sequencing [8]. For patients with clinical signs of juvenile polyposis syndrome, molecular genetic testing of the *BMPR1A* and *SMAD4* genes should be performed, including analysis of promoter regions and large deletions/duplications [8].

AIM

To assess molecular genetic testing of patients with suspected juvenile polyposis syndrome.

PATIENTS AND METHODS

The molecular genetic testing was performed in 30 patients from 28 families (there were 3 affected relatives in one family simultaneously), who were followed from 2012 to 2024. After colonoscopy, it was found that out of 30 patients, 14 patients with juvenile polyps in the large intestine, 11 patients with mixed (juvenile and adenomatous) polyps, and 5 patients with only adenomatous neoplasms were identified, in whom previously performed DNA diagnostics showed the absence of pathogenic variants in the *APC/MUTYH* genes. The scheme of check-up is shown in Fig. 1.

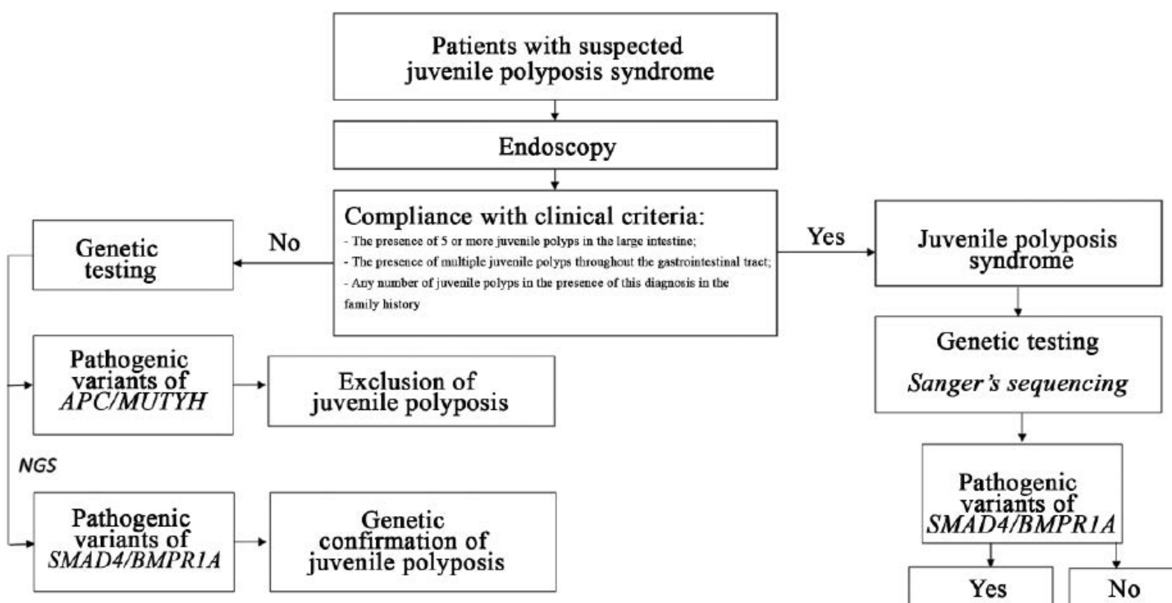

Figure 1. *Diagnostic search scheme for patients with suspected juvenile polyposis syndrome*

Table 1. *Results of a molecular genetic study of the families (n = 28) included in the study*

Hereditary variants	Genes	Rate
Pathogenic/probably pathogenic	*SMAD4 BMPR1A*	18/28 (64.3%)
Variants of unclear value	*BMPR1A*	2/28 (7.1%)
Absent	–	8/28 (28.6%)

Table 2. *Hereditary variants of the BMPR1A gene (NM_004329.3) (n = 11)*

The point variant	Extensive rearrangements	New variant	Pathogenicity (criteria)
c.675 + 4del	–	Yes	**LP*** PM2 (M) PP3 (supp) PP1 (Strong)
c.1081C > T p.(Arg361Ter)	–	–	–
–	del 9–13 ex [NC_000010.9g.(88662150_88667040)_(88673810_?)del]	–	–
–	del 8 ex [NC_000010.9 g.(88649700_88662150)_(88662150_88667040)del]	–	–
c.127_128del p.(Lys43ValfsTer27)	–	Yes	**LP** PVS1 (VS) PM2 (M)
c.333 + 5G > C	–	–	–
c.128_137del p.(Lys43MetfsTer3)	–	–	–
c.1473 + 1G > T	–	–	–
c.1537_1559del p.(Thr513AlafsTer6)	–	Yes	**LP** PVS1 (VS) PM2 (M)
–	del 1–5 ex [NC_000010.9 g.(?_88506400)_(88641940_88649630)del]	–	–
c.355C > T p.(Arg119Cys)	–	–	–

Note: LP — Likely pathogenic

The DNA was isolated from the peripheral blood of patients using an automatic MagNa Pure Compact station using the MagNa Pure Compact Nucleic Acid Isolation Kit (Roche). The DNA concentration was measured using a Denovix instrument using a Qubit HS assay (Thermo Fisher) kit. The *SMAD4* and *BMPR1A* genes (exons with adjacent introns) were sequenced using the Sanger method using an ABI PRISM 3500 device (8 capillaries; Applied Biosystems) using original seed primers. Large rearrangements were detected by the MLPA method (MRC Holland SALSA MLPA Probemix P158-D1 JPS). Full-exome sequencing was performed on a NextSeq 550 sequencer (Illumina), according to the manufacturer's protocol.

The pathogenic and probably pathogenic significance of the detected variants was studied using CanVIG-UK Gene Specific Recommendations, as well as the resources of Franklin, GnomAD, Broad Institute Genomics and the SpliceAI Lookup Broad Institute.

RESULTS

Pathogenic/probably pathogenic variants of the *BMPR1A* and *SMAD4* genes were found in 18 out of 28 families (64.3%): 7/18 (38.9%) families had a pathogenic/probably pathogenic variant of the *SMAD4* gene, 11/18 (61.1%) families had a pathogenic/probably pathogenic variant of the *BMPR1A* gene.

In 2/28 (7.1%) patients, missense variants were found, which were classified as variants of the unclear value of the *BMPR1A* gene: c.385T > G p.(Leu129Val) and c.94G > C p.(Gly32Arg). No hereditary variants of the *BMPR1A* and *SMAD4*

Table 3. *Hereditary variants of the SMAD4 gene (NM_005359.6) (n = 7)*

The point variant	Extensive rearrangements	New variant	Pathogenicity (criteria)
c.346C > T p.(Gln116Ter)	–	Yes	**LP** PVS1 (VS) PM2 (M)
–	dup 2-12 [NC_000018.8 g.(46811230_46827460)_(46858720_?)dup]	–	–
c.1081C > A p.(Arg361Ser)	–	–	–
c.425-6A > G	–	–	–
c.705dup* p.(Gly236ArgfsTer28)	–	Yes	**LP** PVS1 (VS) PM2 (M)
c.403C > T p.(Arg135Ter)	–	–	–
–	del 1 ex [NC_000018.8 g.(?_46810320)_(46811230_46827460)del]	–	–

*Note: LP — Likely pathogenic; * The variant was found in 3 affected relatives from the same family.*

genes were found in 8 probands out of 28 families (28.6%) (Table 1).

11 pathogenic/probably pathogenic variants were identified in the *BMPR1A* gene, of which 3 were large deletions (Table 2).

There are 7 variants in the *SMAD4* gene, including 1 large deletion and 1 large duplication (Table 3). As an example, let us present a patient and his pedigree with the presence of the c.425-6A > G variant in the *SMAD4* gene, which are shown in Figures 2 and 3, respectively.

It is extremely important to note that among patients with only adenomatous polyps, 2 variants were found in the *BMPR1A* gene (c.1081C > T; del 9–13 ex) and 3 variants in the *SMAD4* gene (dup 2-12; c.705dup; c.705dup).

DISCUSSION

If the clinical criteria for juvenile polyposis in a patient are met, the first step is to identify pathogenic/likely pathogenic variants in the *BMPR1A* and *SMAD4*genes. In patients with mixed polyposis or in patients with 20 or more adenomatous neoplasms in the large intestine, pathogenic/probably pathogenic variants in the *APC* and *MUTYH* genes are primarily identified, and in their absence, the method of full-exome sequencing is used [18–20]. This algorithm makes it possible to diagnose the presence of juvenile polyposis syndrome not only in patients with mixed polyps (adenomatous and juvenile) in the large intestine, but also in patients with only adenomatous neoplasms. In the study, the incidence of pathogenic/probably pathogenic hereditary variants was 64.3%, which is higher than the similar incidence in the USA, Germany, Israel, Singapore, but lower than in Denmark (Table 4). At the same time, the incidence of large rearrangements identified by us is significantly higher (27.8%) than in the other countries, which indicates the need to include the MLPA method in routine DNA diagnostics for patients with suspected juvenile polyposis, in the event that Sanger's sequencing does not reveal

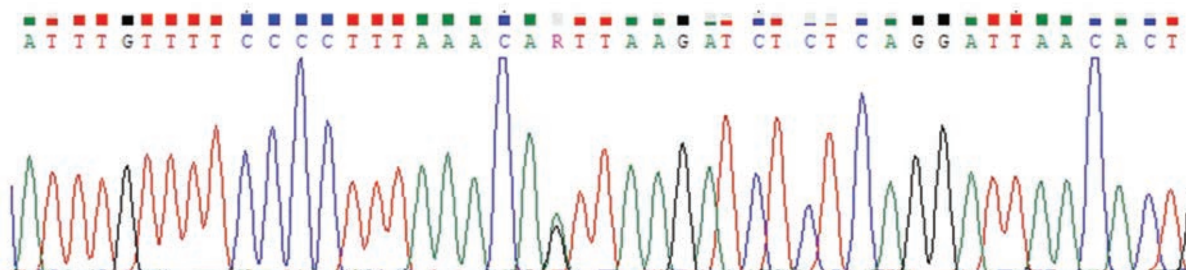

Figure 2. *Sequenogram of the pathogenic variant c.425-6A > G (indicated by arrow) in the sequence of the SMAD4 gene (NM_005359.6)*

Table 4. *Pathogenic variants of SMAD and BMPR1A genes in patients with juvenile polyposis [10,13-15]*

Author	Year	Country	Families (n)	Rate of pathogenic variants (%) / genes	Number of pathogenic variants / genes	
					Point-based	Large deletions
S. Aretz [11]	2007	Germany	80	39/65 (60%) 23/39 (59%) *SMAD4* 16/39 (41%) *BMPR1A*	17 *SMAD4* 13 *BMPR1A*	6 *SMAD4* 3 *BMPR1A*
W.A. Van Hattem [12]	2008	USA	27	13/27 (48%) 7/13 (53.8%) *SMAD4* 6/13 (46.2%) *BMPR1A/PTEN*	4 *BMPR1A* 7 *SMAD4*	2 *BMPR1A/PTEN*
S. Cohen [13]	2024	Israel	124	55/124 (44%) 29/55 (52.7%) *SMAD4* 26/55 (47.3%) *BMPR1A*	–	–
J. Howe [14]	2004	USA	77	30/77 (39%) 14/30 (46.7%) *MADH* 16/30 (53.3%) *BMPR1A*	–	–
D. Calva-Cerqueira [15]	2008	Singapore	102	42/102 (41%) 20/42 (47.5%) *SMAD4* 22/42 (52.5%) *BMPR1A*	10 *SMAD4* 15 *BMPR1A*	10 *SMAD4* 7 *BMPR1A*
S.P. MacFarland [16]	2021	USA	118	54/118 (46%) 27/54 (50%) *SMAD4* и 24/54 (44.4%) *BMPR1A* 3/54 (5.6%) *BMPR1A/PTEN*	24 *BMPR1A* 27 *SMAD4*	3 *BMPR1A/PTEN*
A. M. Jelsig [17]	2023	Denmark	32	27/32 (87%) 19/27 (70.4%) *SMAD4* 7/27 (25.9%) *BMPR1A/PTEN* 1/27 (3.7%) *PTEN*	19 *SMAD4* 6 *BMPR1A* 1 *PTEN*	1 *BMPR1A/PTEN*

their specific hereditary variants. In addition, germinal variants previously undescribed in the world (3 in the *BMPR1A* gene and 2 in the *SMAD4* gene) were found in 5 families, and probably pathogenic value was established for all of them. It is worth noting that all new variants are located in different parts of the studied genes, and not in the "hot spots." Therefore, it is necessary to sequence the

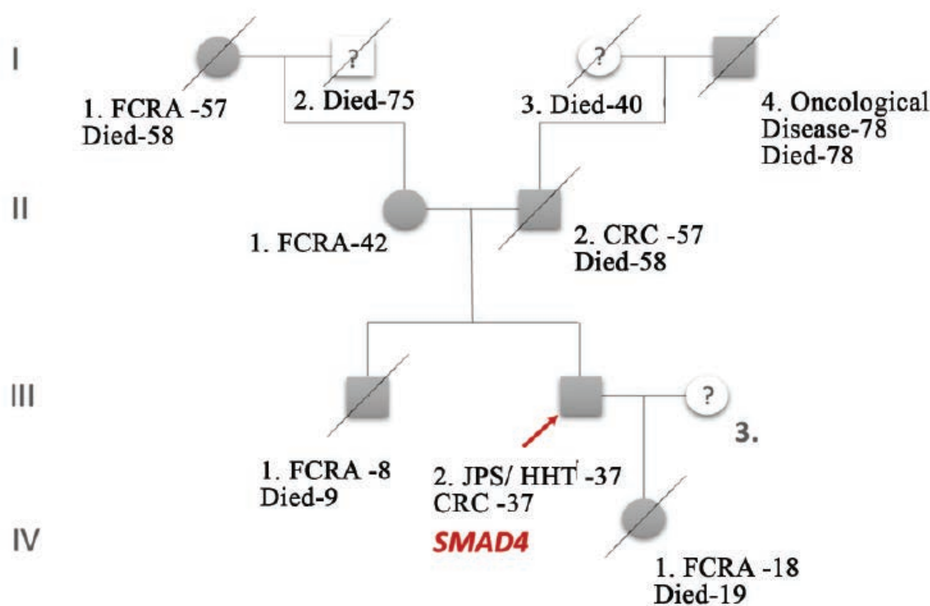

Figure 3. *Pedigree of a patient with JPS and pathogenic variant c.425-6A > Gin the SMAD4 gene*
Note: FCRA — familial colorectal adenomatosis; CRC — Colorectal cancer; JPS — juvenile polyposis syndrome; HHT — hereditary hemorrhagic telangiectasia

entire coding sequence of the gene with adjacent intronic regions.

In patients who have not identified a pathogenic/probably pathogenic variant in the *SMAD4* and *BMPR1A* genes, it is recommended to test the *PTEN* gene [7]. However, during full-exome sequencing in patients, no pathogenic/probably pathogenic variants of the *PTEN* gene were detected. According to HGMD Professional, one of the most comprehensive databases on mutations in the human genome in the world, more than 160 pathogenic/probably pathogenic variants in the *SMAD4* gene and more than 180 in the *BMPR1A* gene have been described so far. Since the incidence of detectable pathogenic variants in various genes in patients with JPS does not exceed 87%, the presence of other genes with pathogenic/probably pathogenic variants responsible for JPS cannot be excluded.

CONCLUSION

The high incidence of pathogenic/probably pathogenic variants, including the presence of previously undescribed variants, indicates the need for an integrated approach to molecular genetic diagnosis for patients with suspected JPS. It is advisable for all patients to start the study with the *SMAD4* and *BMPR1A* genes using Sanger's and MLPA sequencing methods, and if the result is negative, using the high–throughput sequencing method; patients with 20 or more adenomatous neoplasms of the large intestine, but with the absence of pathogenic/probably pathogenic variants in the *APC* and *MUTYH* genes, need to undergo full-exome sequencing.

AUTHORS CONTRIBUTION

Concept and design of the study: *Alexey S. Tsukanov, Alexey A. Barinov, Tatyana A. Vlasko*

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