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Genotype-phenotype correlation in children with adenomatous polyposis syndrome

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ABSTRACT *AIM: to identify the genotype-phenotype correlation in children with familial adenomatous polyposis (FAP) and to assess the risk of surgery.*
PATIENTS AND METODS: a retrospective study included children with FAP from January 2000 to December 2023. For analysis they were divided in two groups ("severe" and "non-severe" genotype) according to the results of the genetics.
RESULTS: forty-two patients from 36 families with FAP were included in the study. Statistical analysis revealed that the mean age at the time of surgery was significantly different and was 13 ± 4 years in the "severe" genotype group vs. 16 ± 1 in the "non-severe" group (p = 0.04). The age of first colonoscopy (OR: 0.74, 95% CI: 0.53–0.94, p = 0.03) and the carpeting of polyps (OR: 8.06, 95% CI: 1.71–81.1, p = 0.04) were significantly associated with severe genotype.
CONCLUSION: the "severe" genotype is characterized by earlier onset of the disease and age of colonoscopy, of polyps carpeting.

KEYWORDS: *adenomatous polyposis syndrome, APC, children*

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

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INTRODUCTION

Familiar adenomatous polyposis syndrome (FAP) is a hereditary disease characterized by adenomas in the large intestine and other organs such as the stomach, duodenum, thyroid gland, etc. [1]. Colorectal cancer in FAP develops inevitably in 100% of patients in the absence of timely surgery. The prevalence of the disease is estimated at 2.29–3.2 cases per 100,000 people, as a rule, with the same lesion of both genders. It is worth noting that in one third of patients, pathogenic variants arise *de novo*, that is, the found variant occurs for the first time in the patient and is absent in both parents [2]. The diagnosis of FAP is established when adenomas are detected in the large intestine, as well as during a molecular genetic study for the presence of a pathogenic variant of the *APC* gene. However, genetic testing of patients with FAP is necessary not only for the final verification of the diagnosis, but also to determine the severity of the disease, the risk of extra-intestinal manifestations, and to predict the time for surgery [2]. The aim of the study was to identify the genetic and phenotypic correlation in children with FAP and to determine the relationship of the genotype with the risk of surgery before the age of 18.

PATIENTS AND METHODS

An observational study included children with FAP in the surgical unit from January 2000 to December 2023.

The inclusion criteria in the study were:

1. The age of patients under 18 years;
2. A confirmed pathogenic variant in the *APC* gene.

The study did not include patients with FAP without performed genetic testing.

Data Collection Methodology

To describe the number of adenomas, the indicator 'more/less than 100' was used, based on current Russian Guidelines for FAP [3]. When detecting the endoscopic picture of 'multiple polyposis', the inability to count the number of adenomas, as well as in cases where most of the mucous layer of the large intestine is covered with adenomas with rare 'islands' of the normal mucous layer, the indicator 'carpeting' of the intestine with polyps was used [4].

To analyze the genetic and phenotypic correlation, we divided the data of the molecular genetic study taking into account the site of the pathogenic variant, that is, by codons. Based on the Guidelines for the treatment of FAP in children (European Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists (ESPGHAN)) [5], as well as updated European Guidelines for the FAP, *MutYH*-associated polyposis, gastric adenocarcinoma, proximal polyposis of stomach (GAPPS) and other rare syndromes of adenomatous polyposis (European Group on the Study of Hereditary Tumors (EHTG) and the European Society of Coloproctologists (ESCP)) [6,7,8] 3 forms of the disease were identified (Table 1):

- severe disease — when the pathogenic variant is localized in the region from 1250 to 1464 codons;
- classical disease — when the pathogenic variant is localized in the area from 168 to 1580 codons (with the exception of the area from 1250 to 1464 codons);
- attenuated disease — when the pathogenic variant is localized in areas before 168 and after 1580 codons.

The descriptive characteristics of the patients are shown in Table 2.

Since the purpose of this study was to identify differences between the manifestations of the disease in children with severe forms compared with classical and attenuated forms, for subsequent analysis, we combined patients with classical and weakened forms into one group, thus forming 2 groups of patients: 'severe' (n = 23) and 'non-severe' (n = 19) genotypes [5,7].

Statistical Data Processing

Descriptive characteristics of variables are presented in the form of absolute values (indicating %) for categorical data. For quantitative data, the first step was to assess the normality of the distribution using the D'Agostine-Pearson method. With a normal distribution, the variables are presented as an arithmetic mean with an indication of the standard deviation (± SD). With a distribution other than normal, the medians are indicated with an indication of the interquartile range (Q1;Q3).

A comparative analysis of numerical variables was performed using the Mann-Whitney U-test for median values and the Student t-test for averages. Categorical data were compared using the two-way Fisher exact test or χ^2 Pearson test. The differences between the groups were considered as statistically significant at $p < 0.05$. A univariant analysis of the selected predictors was performed by constructing four-field tables. The multiple logistic regression included indicators associated (at $p \leqslant 0.2$) with the target outcome based on the results of the univariate analysis. As a result, the values of the odds ratio with 95% coincidence intervals, p-value and the coefficient of variance inflation (VIF) were obtained.

To test the diagnostic value of the multivariate regression model, the area under the curve (AUC), the likelihood ratio and the Hosmer-Lemeshov test and McFadden R^2 were calculated. In order to determine the cumulative risk of surgery in childhood, the comparative Mantel-Cox

Table 1. *Pathogenic variants of the APC gene and their distribution by form*

Variant	Number of patients (%), (*n* = 42)
Codons 1250-1464 (severe form of FAP, *n* = 23 (55))	
c.3815C>G (p.Ser1272*)	1 (2.3)
c.3888delAinsCCT (p.Asp1297Leufs*9)	1 (2.3)
c.3927_3931delAAAGA (p.Glu1309Aspfs*4)	10 (from 8 families) (24)
c.3982C>T (p.Gln1328*)	1 (2.3)
c.4064_4128del (p.Ser1355Cysfs*9)	1 (2.3)
c.4067C>G (p.Ser1356*)	1 (2.3)
c.4127-4128delAT (p.Tyr1376Cysfs*9)	1 (2.3)
c.4201del (p.Ile1401Leufs*14)	6 (from 2 families) (14)
c.4216C>T (p.Gln1406*)	1 (2.3)
Codons 168–1249 and 1465-1580 (classical FAP form, *n* = 17 (40)	
c.530_531del (p.Asn177Ilefs*15)	1 (2.3)
c.1297C>T (p.Gln433*)	1 (2.3)
c.1312+1G>C	1 (2.3)
c.1408+1delG	1 (2.3)
c.1409-2A>G	1 (2.3)
c.1485delT (p.Thr496Hisfs*2)	1 (2.3)
c.1660C>T (p.Arg554*)	1 (2.3)
c.1690C>T (p.Arg564*)	1 (2.3)
c.1744-2A>G	1 (2.3)
c.1778G>A (p.Trp593*)	1 (2.3)
c.1816dupA (p.Ile606Asnfs*28)	1 (2.3)
c.2708_2714delACAGAAG (p.Asp903Valfs*11)	1 (2,3)
c.2960_2963dup (p.Glu988 Aspfs*2)	1 (2.3)
c.3036del (p.His1013Ilefs*9)	1 (2.3)
c.3249del (p.Asp1083Glufs*43)	1 (2.3)
c.3340 C>T (p.Arg1114*)	1 (2.3)
c.3682C>T (p.Gln1228Ter)	1 (2.3)
Codons before 168 and after 1580 (attenuated form of FAP, n = 2 (5)	
c.455_459delAAAAG (p.Glu152Glyfs*14)	1 (2.3)
delpr B (g.112071090_112071450)	1 (2.3)

analysis was performed with the calculation of the relative risk index (RR). The data analysis was carried out using the GraphPadPrism statistical software package, version 9.3.1 (GraphPad Software, USA).

RESULTS

In the period from 2000 to 2023, 42 patients from 36 families with a diagnosis of FAP were included in the study.

According to the site of pathogenic variants, the groups were distributed almost equally, with a slight predominance of the 'severe' genotype group (with 1250–1464 codons) — 23 (55%) patients. Among them, the most common site were codons 1309-10 (43%) patients from 8 families and 1401-6 (26%) patients from 2 families. The classical and attenuated forms were 40% and 5%, respectively.

A comparative analysis of groups with 'severe' and 'non-severe' genotypes was carried out. It was revealed that in the group of the 'severe' genotype, an earlier age of the beginning of the checkup was noted (12 ± 4 vs. 15 ± 2, $p = 0.01$). In patients from the 'severe' genotype group, more than 100 adenomas ($p = 0.01$) and 'carpeting' adenomas ($p = 0.03$) were more often found. Surgery before the age of 18 was performed in 74% of cases for patients from the 'severe' genotype group and in 42% of cases for children from the 'non-severe' genotype group, although we failed to achieve statistical significance in this parameter ($p = 0.06$) (Table 3).

Table 2. *Characteristics of patients*

Feature	*n* = 42 (%)
Gender: Female Male	 24 (57) 18 (43)
Patients with a family history: Examined without complaints Age of patients examined without complaints, years Examined after the appearance of complaints The age of the patients examined after the appearance of complaints, years	34 (81) 11 (26) 14 (11;14) 23 (55) 15 (12;16)
Patients with no family history	8 (19)
'Severe' genotype: Examined without complaints, due to family history Examined after the appearance of complaints	23 (55) 6 (26) 17 (74)
'Non-severe' genotype: Examined without complaints, due to family history Examined after the appearance of complaints	19 (45) 5 (26) 14 (74)
Age at the time of manifestation of the disease, years (median)	14 (10;15)
Age at the time of the first colonofibroscopy, years (median)	14.5 (12;16)
The number of polyps is more than 100	30 (71)
'Carpeting' of the large intestine mucosa with polyps	23 (55)
Sizes of polyps, mm (median)	5 (4;8)
A history of endoscopic polypectomy	8 (19)
Malignant tumor of the thyroid gland	3 (7)
Gardner's syndrome	3 (7)
Adenocarcinoma before the age of 18	1 (2)
Operated before the age of 18	25 (59)
Age at the time of surgery, years (median)	16 (12;17)

Table 3. *Patients with 'severe' and 'non-severe' genotypes*

Indicators			*p*
	'Severe' genotype *n* = 23 (55%)	'Non-severe' genotype *n* = 19 (45%)	
Gender (female)	13 (57%)	11 (58%)	0.82
Age of FAP debut, years (median)	13 (7;15)	14.5 (12;16)	0.08
Age of the first colonoscopy, years (medium ± SD)	12 ± 4	15 ± 2	0.01
Familial APS history	19 (83%)	15 (79%)	0.92
Intestinal bleeding	12 (52%)	6 (32%)	0.22
The maximum size of polyps, mm (median)	4.5 (4;8)	5.5 (5;9)	0.17
The number of colonoscopies (median)	2 (2;2)	2 (2;2)	0.35
The number of polyps is over 100	20 (87%)	10 (53%)	0.01
'Carpeting' of the large intestine mucosa with polyps	16 (70%)	7 (37%)	0.03
High degree of dysplasia detected before surgery	1 (4%)	1 (5%)	0.62
High degree of dysplasia detected after surgery	2 (9%)	1 (5%)	0.86
Polyposis of the upper GI	8 (35%)	8 (42%)	0.33
A history of polypectomy	3 (13%)	5 (26%)	0.43
Age at the time of surgery, years (medium ± SD)	13 ± 4	16 ± 1	0.04
Operated before the age of 18	17 (74%)	8 (42%)	0.06

The logistic regression revealed that the factor 'carpeting' with adenomas (OR = 8.06, 95% CI:1.71–81.1, p = 0.04) was significantly associated with the 'severe' genotype of the disease (Table 4).

The diagnostic value of the regression model has been determined. The area under the curve was 0.85 ± 0.06 (95% CI: 0.72–0.96), p = 0.0002. The predictive value of a positive result is 78%, the predictive value of a negative result is 72%,

Table 4. *Univariate analysis and multiple logistic regression*

Indicators	Univariate Analysis OR (95% CI)	p	ОШ (95% ДИ) Multiple logistic regression OR (95% CI)	p	VIF
Female gender	0.95 (0.3–3.07)	0.82	–	–	–
Age of the first colonoscopy	0.74 (0.53–0.94)	0.03	0.71 (0.42–1.02)	0.1	1.3
Familial history of FAP	1.26 (0.32–4.9)	0.92	–	–	–
Intestine bleeding	2.81 (0.81–10.6)	0.11	2.67 (0.48–17.34)	0.3	1.2
Maximal size of polyps	0.88 (0.74–1)	0.1	0.89 (0.69 — 1.07)	0.3	1.2
'Carpeting' of the mucous layer with polyps	3.9 (1.2–15)	0.03	8.06 (1.71–81.1)	0.04	1.5
High degree of dysplasia detected before surgery	0.69 (0.03–14)	0.62	–	–	–
Polyposis of the upper GI	0.5 (0.14–1.9)	0.33	–	–	–
A history of polypectomy	0.42 (0.1–2.1)	0.43	–	–	–
Operated before the age of 18	3.9 (1.1–15.2)	0.04	1.29 (0.17–8.39)	0.8	1.6

the likelihood ratio is 16 (p = 0.007), the Hosmer-Lemeshov test is 4 (p = 0.8), R^2McFadden = 0.29 (Fig. 1).

Also, within the framework of the study, the risk assessment of surgery was calculated depending on the identified pathogenic variant. As a result, the cumulative risk of surgery before the age of 18 in the 'severe' genotype group was 74%, versus 42% in the 'non-severe' genotype group (RR = 2.6, 95% CI: 1.2–5.7, p = 0.01) (Fig. 2).

DISCUSSION

In international literature, a severe or fulminant form of FAP is distinguished, in which the disease manifests itself in early childhood and is manifested by a large number of large intestine adenomas or the so-called 'carpeting' adenomas of the mucous layer of the large intestine, as well as earlier manifestation and development of CRC. However, both in our country and around the world, the need to isolate the severe form of FAP remains the subject of discussion, as well as the choice of timing and optimal age for preventive colectomy in patients with FAP, including children.

It is worth noting that the genetic-phenotypic correlation is actively studied not only in the context of the relationship of the pathogenic variant with the severity of the disease [10]. In the literature, much attention is paid to the study of

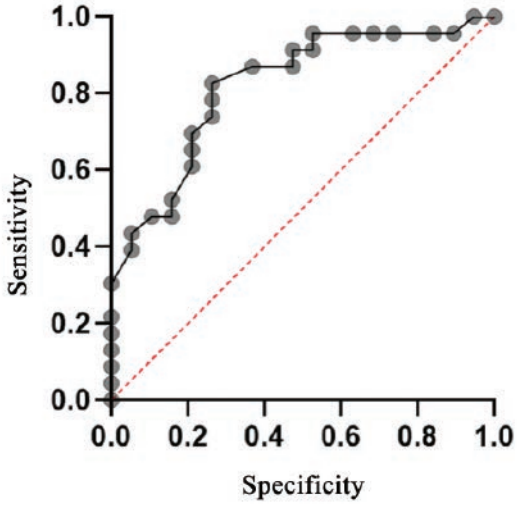

Figure 1. *ROC curve to determine the diagnostic value of a regression model*

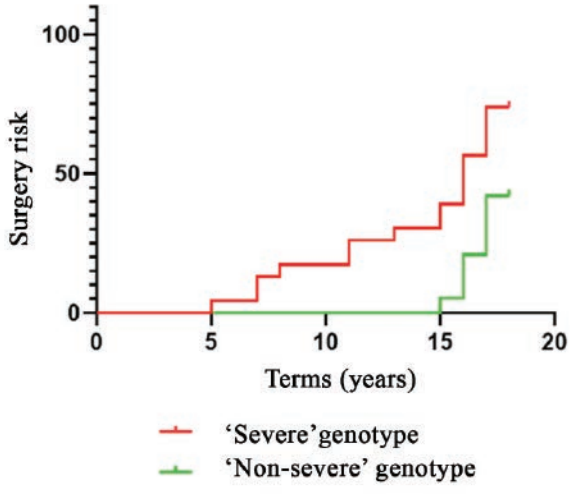

Figure 2. *The Kaplan–Meier curve demonstrates the cumulative risk of surgery in children with FAP*

the relationship of the genotype with the risk of desmoid tumors, small intestine adenomas, as well as diseases such as congenital hypertrophy of the retinal pigment epithelium, thyroid cancer and others [1,11–13]. In addition, a number of studies have traced the relationship of the FAP genotype with the rate of progression of polyposis, that is, an increase in the number of large intestine adenomas, where it was found that the highest rate of overgrowth was associated with the pathogenic variant in codon 1309 [14,15]. Russian scientists, in turn, have demonstrated the absence of genetic and phenotypic correlation in patients with FAP. So, according to the results of the study by Tsukanov A.S. et al., when comparing the average age of diagnosis of CRC in patients with localization of the pathogenic variant in codons 1309 and 200-300, the authors did not reveal a significant difference (33 years versus 34 years) [16]. Probably, based on the results obtained, the severe form of FAP is excluded from the classification of the updated edition of the clinical guidelines of the Association of Coloproctologists of Russia [3]. The current updated clinical guidelines for the treatment of patients with FAP, created by the European Group for the Study of hereditary tumors (EHTG), together with the European Society of Coloproctologists (ESCP), highlight the following criteria as absolute indications for surgery: identified or suspected CRC, the presence of severe symptoms of the disease, more than 1000 large intestine adenomas, the results of histology (detection of villous adenoma or high degree dysplasia). It is also recommended to perform planned surgery when polyps over 10 mm in diameter are detected, a significant increase in the number of polyps during follow-up and the detection of 100 to 1000 polyps (93% expert agreement). It was separately noted that patients with pathogenic variants in codons 1250–1464 should be offered colectomy earlier, due to the manifestation of CRC at an early date [7]. It was the uncertainty in the relationship between genotype and phenotype in FAP that prompted this study to analyze the relationship between the features of the course of the disease and the genotype in children. At the same time, according to the results obtained, it was revealed that the 'severe' genotype in children is associated with earlier colonoscopy (OR: 0.74, 95% CI: 0.53–0.94, p = 0.03), as well as with 'carpeting' adenomas of the large intestine mucosa (OR: 8.06, 95% CI:1.71–81.1, p = 0.04). The allocation of 'carpeting' adenomas of the mucous layer of the large intestine seems to us more indicative and applicable in practice than the parameter 'over 1000 large intestine adenomas' applicable in international guidelines, since counting polyps with a large number of them is not always feasible in conditions of large or 'total' large intestine lesion. Additional analysis also revealed that the 'severe' genotype is significantly associated with an increased likelihood of surgery before the age of 18 (OR: 3.9, 95% CI:1.1–15.2, p = 0.04). However, this factor did not confirm its significance during multiple logistic regression (OR: 1.29, 95% CI: 0.17–8.39, p = 0.8). However, speaking about the need for surgery, it should be noted that not every child with FAP should be operated on in childhood. Some children with FAP require monitoring, endoscopic polypectomies and monitoring of other target organs, which are characterized by the development of tumors. However, there are clinical situations where surgery cannot be avoided. Thus, in a previously published study by Khabibullina L.R. et al., it was demonstrated that the number of polyps, together with the presence of clinical manifestations in the form of recurrent, severe intestinal bleeding, were significantly associated with the need to perform surgery for FAP in childhood [17]. In addition, according to the published data, the proportion of operated patients from the general sample did not exceed 52%, while the median age at the time of surgery was 16 (14;17) years old. International authors also demonstrate comparable data. Thus, in a study from the reputable St. Mark's Hospital (Great Britain), it was demonstrated that among the patients with FAP in childhood, 54% underwent surgery at the age of 17 (11–22) years. Some patients with a pathogenic variant in the central region of the *APC*

gene (1309) underwent surgery at the age of 12 [18]. In a large study from the United States of America, which described the results of treatment of 428 patients with FAP, the age at the time of surgery was 14 (2–21) years old [19]. A study from the Cleveland Clinic comparing the outcomes of surgery in adults and children (with FAP and UC) demonstrates the mean age at the time of ileal pouch in a group of children of 13.4 ± 3.6 years old, which is the youngest age at the time of surgery than previously described in the literature [20].

It is also generally accepted that surgery in patients with FAP is necessary only in large specialized centers with extensive experience in performing various surgeries for FAP to minimize the risk of postoperative complications and ensure satisfactory functional results and acceptable quality of life. It should be noted that the results obtained in the study reflect the actual clinical practice of treating children with FAP in our country. The 'carpeting' of the mucous layer of the large intestine, associated with a specific genotype of the disease, causes a more severe course of the disease in children, in which patients seek colonoscopy due to complaints of intestinal bleeding or abdominal pain at an earlier age and are more likely to undergo surgery under the age of 18. In addition, cases of CRC before the age of 18, which, despite their small percentage, are found in the practice, force us to continue searching for indications for surgery in children with FAP, setting clear criteria for performing surgery. The results of this study demonstrate that pathogenic variants in the *APC* gene may cause a similar clinical form of FAP in childhood.

However, it is necessary to continue the data collection with the inclusion of a larger number of patients.

Taking into account these data, as well as the results of this study, we can assume that there is a relationship between the genotype and phenotype of the disease in children with FAP. At the same time, the obtained results do not contradict the data of international studies [5,9,21]. The presented observational study, of course, has a number of limitations and possible systematic errors, such as possible bias of researchers, selection and analysis of material (for example, counting polyps), which together could affect the result. In addition, the rarity of the pathology complicates the recruitment of a large number of patients, and therefore the study also has a limitation on the number of patients included. Nevertheless, the study showed a difference in the significance of pathogenic variants depending on the localization in the gene and their effect on treatment tactics in children.

The creation of a registry of patients with FAP remains an urgent issue [22]. In our opinion, the creation of a common national registry of patients with FAP will help to monitor families and identify a group of children who may need a colectomy in time, as well as transfer the patient to a specialized institution for treatment after the age of 18 in a timely manner.

CONCLUSION

According to the data obtained, the 'severe' FAP genotype is characterized by an early onset of the disease and the age at which the checkup began.

AUTHORS CONTRIBUTION

Concept and design of the study: *Linara R. Khabibullina, Olga V. Shcherbakova*

Collection and processing of the material: *Linara R. Khabibullina*

Statistical processing: *Linara R. Khabibullina*

Writing of the text: *Linara R. Khabibullina, Vitaly P. Shubin*

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