Desmoid-type fibromatosis (DF) is a rare mesenchymal tumor occurring in only 2 to 4 people per 1,000,000 population a year. Desmoid tumors are either seen sporadically or in individuals with familial adenomatous polyposis (FAP). The etiology of sporadic DF is uncertain. The aim of this study was to estimate the potential significance of germline mutations in the APC gene in patients with sporadic DF. APC exons were amplified, studied using conformation sensitive gel electrophoresis and then Sanger-sequenced. The obtained data were processed in Statistica 10. Mutations were detected in 6 (12%) of 51 participants with sporadic DF. Those 6 patients shared a typical DF phenotype characterized by early age of onset (5.8 years on average, in contrast to the patients without APC mutations, who developed DF at 19 years of age; \( p = 0.02 \)), severe clinical course, multifocal localization on the trunk, and poor prognosis. All of the detected APC mutations were localized to the 3’-end of the gene. For the purpose of comparison, we analyzed a sample of 12 patients with FAP-associated DF. Of those patients, 6 carried mutations in the APC gene. In the analyzed sample, the patients with FAP and the mutant APC gene developed DF at older age (35 years) than the patients with sporadic DF (\( p = 0.004 \)) and their tumors were not multifocal. This means that sporadic and FAP-associated desmoids have different phenotypes in patients with APC mutations. Patients with sporadic tumors have mutations at the 3’-end of the APC gene more often than individuals with FAP-associated DF. To our knowledge, this is the first study to characterize the subtype of sporadic desmoid fibromatosis phenotypically determined by germline mutations in the APC gene.

Keywords: sporadic desmoid-type fibromatosis, APC gene, multifocal desmoids, familial adenomatous polyposis

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DF can occur almost anywhere in the body. Based on the lesion site, DF is categorized into extra-abdominal (the abdominal or chest walls, extremities, neck, or pelvis) and intra-abdominal (the mesentery and the retroperitoneum). Technically, desmoid tumors are benign because they do not metastasize. However, they tend to aggressively proliferate and persistently recur after surgical treatment, bearing similarity to cancer [1].

Desmoid tumors can grow enormously large in size and become a life-threatening condition. DF occurs in 2 to 4 per 1 million people a year [2]. Treatment of desmoid tumors is complicated by their propensity for infiltrative growth and locally aggressive behavior. Usually, surgical resection is the preferred option. However, the postoperative recurrence rate remains high, varying from 45 to 90% [3].

Desmoid tumors either occur sporadically or are associated with familial adenomatous polyposis (FAP), an inherited condition of the colon that eventually transforms into colon cancer. The majority of FAP cases are caused by a mutation in the adenomatous polyposis coli (APC) gene. Ten to fifteen percent of patients with FAP also have DF. The risk of developing DF is 2.56 cases per 1,000 FAP patients a year, which is 852 times higher than in the general population [2]. Unlike sporadic DF, 80% of FAP-associated desmoid tumors are intra-abdominal. DF predominantly affects women and can manifest itself at any age although the typical age of onset is between 30 and 40 years. Most FAP-associated desmoids develop within 5 years after surgery [4].

The etiology of sporadic DF is uncertain. Some patients with sporadic DF are reported to carry somatic mutations in the APC gene; however, such type of mutations is more commonly found in the CTNNB1 gene that codes for β-catenin [5–6], a protein involved in the Wnt signaling pathway. Mutations in CTNNB1 result in the accumulation of β-catenin in fibroblast nuclei, which, in turn, disrupts cell differentiation and communication between the cells [7].

Genetic causes of DF and their association with clinical manifestations of the disease remain understudied. Because DF frequently occurs in FAP-stricken patients, it would be natural to hypothesize that predisposition to sporadic DF is determined by mutations in the APC gene. However, the literature on germline mutations in the APC gene in patients with sporadic DF is scarce [8, 9].

In this work we attempted to estimate the potential significance of germline mutations in the APC gene in a sample of patients with sporadic DF and without a family history of adenomatous polyposis. For the purpose of comparison, we also analyzed molecular characteristics of the APC gene in patients with DF and FAP.

**METHODS**

The study was conducted at the Laboratory of Molecular Genetics (Bochkov Research Center for Medical Genetics) in 2012–2017. Two patient samples were analyzed. The first sample consisted of 51 patients (21 males and 30 females) with DF. The patients’ age ranged from 1 month to 60 years (see Fig.); the median age was 16.8 years. Blood samples were provided by Hertsen Moscow Research Oncology Center where the patients had presented at. The following inclusion criteria were applied: a confirmed diagnosis of DF; no gastrointestinal complaints that could be indicative of diffuse polyposis of the colon; no family history of adenomatous polyposis; no family history of DF. All desmoid tumors in the first patient sample were considered sporadic.

The affected sites included the back, chest and abdominal walls, extremities, and the intra-abdominal region. Multifocal DF was observed in 11 patients (see Results). In some patients the lesions were recurrent.

The second sample comprised 12 individuals (2 males and 10 females) shortlisted from a group of 65 patients with FAP who had presented at Ryzhikh State Research Center for Coloproctology; blood samples were provided by the Research Center. The age of onset varied from 24 to 57 years and was 32.5 years on average. The following inclusion criteria were applied: a confirmed diagnosis of colonic polyposis and DF. Eight patients had a family history of adenomatous polyposis. Family histories were not available for 4 patients. In the second patient sample, desmoid tumors appeared after surgery and were localized to the anterior abdominal wall or intra-abdominally. The majority of them were solitary.

DNA was isolated from peripheral blood leukocytes using a standard phenol-chloroform extraction technique [10]. The spectrum of mutations in the APC gene was analyzed as described in literature [11]. The coding exons of the APC gene were amplified using exon-specific primers. The PCR products were studied by conformation-sensitive polyacrylamide gel electrophoresis (silver staining). The gene was Sanger-sequenced in order to identify conformational changes to its primary structure. For sequencing, we used a Big DyeTM Terminator v. 3.1 Cycle Sequencing kit and an ABI Prism 3130x1 genetic analyzer (Applied Biosystems; USA). The obtained chromatograms were analyzed in ChromasPro, NCBI BLAST and Ensembl genome browser 91. The NM_000038.6 sequence of the APC gene was used as a reference. Statistical processing was aided by Statistica 10.0 (StatSoft; USA).

**Fig.** Age distribution of patients with sporadic DF
RESULTS

The APC gene was analyzed in 51 patients with sporadic DF. Six (12%) patients were found to carry germline mutations in this gene. Table 1 lists the mutations we detected, the age of the patients at the time of diagnosis, the number of lesions (single or multiple), and their location in the body.

Of 6 detected mutations, 2 were not described previously, including c.4386-4390 delGAGAG (1462delGAGAG) and c.4575insT (1525insT). Both mutations result in a frame shift and a premature stop codon and are, therefore, deleterious.

The c.4575insT mutation was found in a female patient (patient 1, see Table 1) with severe DF that manifested at 9 years and was multifocal. The endoscopic examination conducted at the age of 19 years revealed no signs of colonic polyposis.

The mutation c.4386-4390 delGAGAG was observed in patient 2 (Table 1). The onset of the disease occurred at the age of 1 month. Since early childhood, the patient had had multiple growing lesions in the chest wall. By the age of 18 years, the patient had gone through 5 surgical interventions, a few chemotherapy courses, hormone treatment, and radiation therapy, to no avail. This case of DF can be classified as extremely severe and resistant to treatment. The mutation found in patient 2 (c.4386-4390 delGAGAG (1462delGAGAG)) was not previously reported in other populations [12–14]. Also, it was not detected in the blood samples of the patient’s parents, so it can be considered a de novo mutation. The sensitivity of the applied method allows detecting 1 to 5% of mutant alleles, which means that APC mosaicism in the parents is highly unlikely [15].

Three unrelated patients had an identical mutation c.4393-4394 delAG (1465delAG), whose clinical manifestations were, nevertheless, different. One of its carriers, a 28-year-old woman, had multiple lesions in the chest and abdominal walls and the intra-abdominal region. The age of onset was 17 years. At the time of our study, her colonoscopy was negative for colon polyps. Among the two other patients with the same mutations were a boy with multiple desmoids present at birth (the lesions were localized to the chest and the low back) and a girl with a solitary desmoid tumor on the low back developed at the age of 2 years. Interestingly, the age of onset, the number and location of the tumors were different in those 3 patients. Perhaps, DF sites varied between the patients because 2 of them were quite young. So, we cannot rule out the possibility of multifocal growth later in the children’s life. It is also possible that the progression of the disease may be affected by environmental factors and differences in the patients’ genotypes.

The c.4348C/T; p.R1450X mutation was detected in 1 patient with multifocal DF. The age at onset was 15 years. The patient had undergone multiple surgeries, a few chemotherapy courses and hormone treatment. By the time of our study, the growth of the tumor had been halted.

All patients with APC mutations reported an early onset of the disease. Most of them (5 of 6) had multiple desmoids resistant to therapy. In spite of the received treatment, the prognosis was still poor for 3 (50%) of patients. DF was severe in 3 of 6 patients with mutant APC, which was more frequent than in the patients who did not carry a germline mutation in this gene (2 of 45). This difference was statistically significant (p = 0.01).

The age of onset varied from 1 month to 17 years in the patients with mutant APC (Table 1), the median age being 5.8 years. In the patients who did not have mutations in the APC gene, the age of onset varied from 1 month to 60 years (Fig. 1), and the median age was 19 years. The difference in the median values was statistically significant (p = 0.022; U-test).

All APC mutations described above were detected in 6 (23%) of 26 patients with desmoid tumors on the trunk. Patients with differently localized DF had no mutations in the APC gene (Table 2). Generally, mutations in the APC gene occurred more often in the patients with DF localized to the trunk than in the patients with different lesion sites (p = 0.023). This phenomenon is not predicated on the accumulation of multiple desmoid tumors on the trunk (which would indicate random accumulation of the lesions in the carriers of APC mutations) because the frequency of their occurrence on the trunk was not significantly higher in comparison with other lesion sites (Table 2; p = 0.17).

Of 51 patients, 11 had multifocal DF. Five (45%) of those individuals had germline mutations in the APC gene (Table 1). In the group of patients with solitary DF (40 individuals) only one carried an APC mutation (1/40, or 2.5%). The difference in the incidence of APC mutations was statistically significant (p = 0.001). The odds ratio value also suggested an association between APC mutations and multifocal DF (OR = 1.90, 95% CI: 3.22–326.31). Thus, mutations in the APC gene were mainly seen in the patients with multiple desmoid tumors.

Summing up, the mutations in the APC gene were linked to the tumor location on the trunk and its multifocal growth (Table 2).

Such significant number of mutations (12%) in the patients with sporadic DF who do not have clinical signs and/or family history of adenomatous polyposis suggest that patients with FAP and patients with sporadic DF can carry different mutations in the APC gene. All mutations detected in the patients with sporadic DF were localized 3’ of codon 1444.

Bearing that in mind, we decided to study a sample of patients with FAP and co-occurring DF. Of 65 patients with FAP, 12 had DF. Germline mutations in the APC gene were observed in 6 out of 12 patients with both FAP and DF (Table 3). Clinical presentations of fibromatosis did not differ between FAP patients regardless of the presence of APC mutations. The age of DF onset in the FAP carriers of APC mutations varied from 28 to 57 years (Table 3). The median age in this group of patients was 35.5 years; it did not differ significantly
from the median value (29 years; the range of 24–36 years) for the patients who did not have APC mutations.

None of the patients with FAP and co-occurring DF had an APC mutation 3' of codon 1444 (Table 3). In patients with sporadic DF, all detected mutations were located 3' of codon 1444 (Table 1). The difference in the sites of APC mutations in sporadic and FAP-associated DF was statistically significant ($p = 0.0022, OR = 144; 95\% CI: 2.43–8517.50$), i.e. in the patients with sporadic DF, mutations tended to occur at the 3'-region of the gene more often than in the individuals with FAP-associated desmoid tumors.

The patients with sporadic DF and APC mutations tended to develop the condition much earlier in life than carriers of the same mutations with FAP-associated DF (the median age was 5.8 and 35.5 years, respectively; $p = 0.004; U$-test). No statistically significant differences were observed between the patients who did not have APC mutations but had sporadic or FAP-associated DF in terms of DF onset ($p = 0.09$).

Multifocal DF was more common in the patients with APC mutations and sporadic DF (5/6) than in the individuals with APC mutations and FAP (0/6): $OR = 60; 95\% CI: 1.64–2187.79; p = 0.015$.

**DISCUSSION**

In this study, we investigated germline mutations in the APC gene using a sample of 51 patients with sporadic desmoid fibromatosis. All patients had no clinical manifestations or family history of FAP. Six patients (12%) were found to have pathogenic mutations, two of which had not been reported previously, including 1525insT and 1462delGAGAG. In previous works, APC mutations were studied in patients with sporadic and FAP-associated DF, but detected them only in individuals with FAP but not sporadic DF. This can be explained by specific research objectives or the characteristics of the studied samples. For instance, only 1 case of multifocal DF was included in the sample studied in [16].

It is quite rare that desmoid-type fibromatosis manifests itself in infancy. The available literature presents only several clinical cases of early DF [17, 18]. In our sample of patients with sporadic DF and APC mutations there were 3 cases of early DF onset: two patients were diagnosed at 1 and 2 months, respectively, and one patient, at the age of 2 years.

In our study, all APC mutations in the patients with sporadic DF were 3’ of codon 1444 and associated with the severe clinical course, multifocal growth and early onset. In this group of patients, the median age at onset was 5.8 years, as compared to 19 years for the patients who did not carry APC mutations. In the carriers of APC mutations, all desmoid tumors were localized to the trunk, although such lesion site was not more frequent than other locations (Table 2; $p = 0.17$). This is one of the findings that were unknown previously. There are reports of families with hereditary desmoid tumors. For example, the literature describes a case of a family in which 3 generations have been affected by desmoid-type fibromatosis. Their condition is linked to a frameshift mutation in codon 1924 of the APC gene. In this family, DF were both extra-abdominal and intra-abdominal and the age of onset varies from birth to 10–20 years. Of 9 members of the family, 3 had polyposis or cancer of the colon. Other known cases of inherited DF are also linked to the mutations at the 3’-end of the APC and characterized by multiple lesions and severe course of the disease [19, 20].

It was interesting to compare the features of the detected mutations and DF phenotypes between patients with FAP-associated and those with sporadic desmoid tumors. Research into the association between the patient’s genotype and clinical presentations of FAP has yielded controversial results. A study of the association between the site of an APC mutation and the risk of DF in patients with FAP found no such association [21]. Another study of a group of 14 patients with FAP and co-occurring DF revealed that only two patients had the mutation 3’ of codon 1444 [22], which might be explained by population characteristics of the sample. In our study, we used

**Table 2. Associations between the mutations in the APC gene and different lesion sites/number of desmoid tumors**

| Lesion site                  | Patients with desmoid-type fibromatosis | Patients with multifocal desmoid-type fibromatosis |
|------------------------------|----------------------------------------|---------------------------------------------------|
|                              | Number of patients | Number of patients with mutant APC | Number of patients | Number of patients with mutant APC |
| Chest and/or abdominal wall  | 26                       | 6                             | 8                 | 5                             |
| Intra-abdominal              | 3                        | –                             | –                 | –                             |
| Extremities                  | 14                       | –                             | 3                 | –                             |
| Other sites                  | 8                        | –                             | –                 | –                             |
| Total                        | 51                       | –                             | –                 | –                             |

**Table 3. Description of APC mutations and clinical data of patients with FAP and co-occurring DF**

| №   | Name of mutations | DF description                                      | Age, years |
|-----|-------------------|-----------------------------------------------------|------------|
| 1   | c.3464-3468delAAGAA (1155del5) | Postoperative DF of the root of the mesentery       | 57         |
| 2   | c.3927-3921delAAGAA (1309del5)  | DF of the postoperative scar tissue                 | 28         |
| 3   | c.3830insA (1310insA)       | Postoperative DF of the root of the mesentery       | 34         |
| 4   | c.3183-3187delAGAAA (1061del5) | Postoperative DF of the root of the mesentery       | 38         |
| 5   | c.2274-2278delAGCCCC p.K758Nhs (758-760delAGCCCC) | Postoperative DF of the abdominal wall               | 30         |
| 6   | 3496delT (1166delT)         | DF of the abdominal wall                              | 33         |
| 7   | –                             | Postoperative DF of the abdominal wall               | 33         |
| 8   | –                             | Postoperative DF of the root of the mesentery       | 29         |
| 9   | –                             | Postoperative DF of the root of the mesentery       | 29         |
| 10  | –                             | Postoperative DF of the abdominal wall               | 29         |
| 11  | –                             | DF of the abdominal wall                              | 24         |
| 12  | –                             | Postoperative DF of the abdominal wall               | 36         |
a sample of Russian patients with FAP. Of 65 candidates with FAP, 12 had DF (18%). This figure is close to that obtained by other researchers: some report a value between 3.5 and 32% [23], while others, 10–15% [24]. Half of our patients with FAP and co-occurring DF had mutations in the APC gene. All 6 detected mutations were located at the 5’ of codon 1444. The difference in the incidence of mutations in the region distal to codon 1444 between sporadic and FAP-associated DF was statistically significant (p = 0.002). We compared the values obtained for the patients with FAP-associated DF with the occurrence of similarly located mutations in the pooled international sample of FAP patients [25]. The difference was insignificant (p = 0.34). At the same time, our values for sporadic DF differed from those for FAP-associated DF reported by other researchers (p = 0.0002) [25]. This leads us to conclude that sporadic desmoid tumors occurring in patients with no signs or family history of FAP are more often caused by mutations 3’ of codon 1444 in comparison with FAP-associated DF.

In our sample, all patients with FAP developed desmoid tumors only after surgery; the tumors occurred either intraperitoneally or in the abdominal wall. Other researchers report the same pattern [26, 27].

In our patients with the mutant APC gene, sporadic DF was mainly multifocal and localized to the chest or abdominal walls. Intrabdominal lesions are typical for patients with FAP and less common in sporadic cases of the disease [25]. Most likely, the abdominal location of the tumor in patients with FAP is the result of tissue injury during surgery [28]. No direct association with tissue injury was observed in our study for the patients with sporadic DF and APC mutations.

In our sample, the median age of onset did not differ between the FAP patients with and without mutations, but was significant in the patients with sporadic DF and germline mutations in the APC gene. For those who did not carry APC mutations, the age at diagnosis did not differ significantly between the patients with sporadic and FAP-associated DF (p = 0.09).

These findings suggest that there is a significant difference in the clinical manifestations of sporadic and FAP-associated desmoid tumors in the carriers of APC mutations; these differences are (at least to some extent) associated with the position of the mutation in the gene.

Summing up, we have studied a sample of individuals with sporadic DF and identified a subgroup of patients with a specific DF phenotype determined by germline mutations in the APC gene. In such patients, DF is severe, multifocal, manifests itself at early age, resists treatment and has a poor prognosis. The causative mutations are localized to the 3’-end of the APC gene.

Our findings can help the physician in deciding on the suitable treatment strategy and elaborating approaches to polyposis prevention. They can also be useful in studying mechanisms underlying multifocal DF.

CONCLUSIONS

We have studied a group of patients with DF and no history of FAP and identified a subgroup of individuals with a specific DF phenotype and germline mutations in the APC gene. Unlike patients who do not have APC mutations, carriers of the mutant gene variant develop multifocal DF on the trunk that manifests itself in infancy. In terms of DF phenotype, patients with sporadic DF and APC mutations differ from patients with FAP-associated DF who also have germline mutations in the APC gene. In patients with sporadic DF, mutations tend to localize to the 3’-region of the gene. This information should be considered when deciding on the treatment strategy against DF and elaborating approaches to polyposis prevention. Our findings provide a basis for the study of molecular mechanisms that trigger primary DF but not FAP.

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