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Recurrent *APC* gene mutations in Polish FAP families

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Abstract

The molecular diagnostics of genetically conditioned disorders is based on the identification of the mutations in the predisposing genes. Hereditary cancer disorders of the gastrointestinal tracts are caused by mutations of the tumour suppressor genes or the DNA repair genes. Occurrence of recurrent mutation allows improvement of molecular diagnostics. The mutation spectrum in the genes causing hereditary forms of colorectal cancers in the Polish population was previously described. In the present work an estimation of the frequency of the recurrent mutations of the *APC* gene was performed. Eight types of mutations occurred in 19.4% of our FAP families and these constitute 43% of all Polish diagnosed families.

Introduction

Molecular diagnostics of cancer predisposition is very important for the medical treatment of the patient and persons belonging to the high risk group. Molecular studies enable the detection of mutation carriers and release from unreasonable stress of persons from the group with increased risk of cancer occurrence. The mutation spectrums in the genes predisposing to colorectal cancer in the Polish population have been described [1-4]. In the present work we focused on recurrent mutations of the *APC* gene causing FAP [5].

Familial adenomatous polyposis (FAP) is characterized by the appearance of numerous polyps in the large intestine. Untreated polyps lead to the development of colorectal cancer before age of 50 years. FAP is a genetically determined disorder, inherited in an autosomal dominant manner. The correlation between mutations of the *APC* gene and the occurrence of familial adenomatous polyposis was described in 1991 [1, 2] and since then, mutations of the *APC* gene have been investigated in research centres leading to identification of various mutation types. *APC* gene mutations arise de novo in 1 per 10,000 newborns. The *APC* gene is localized on chromosome 5q21 and consists of 21 exons. Mutations of the *APC* gene, in most cases, are small deletions or insertions with the most frequent mutations, in the greater part of the described populations, being the AAAGA deletion at codon 1309 and the ACAAA deletion at codon 1061.

Patients

Clinical diagnoses of FAP patients were conducted in collaborating genetic centres or gastroenterology clinics in the place of residence of patients. So far, samples of DNA belonging to 280 Polish FAP families have been collected in the DNA bank of Polish FAP families established in 1997 at the Institute of Human Genetics, Polish Academy of Science in Poznan.

Molecular methods

DNA was extracted from peripheral blood cells by the classical phenol purification method and entire coding sequence of *APC* gene was screened for mutations by PCR-HD and SSCP methods in 280 probands. DNA fragments showing heteroduplex or additional pattern in SSCP analysis were sequenced by direct PCR product sequencing and analyzed using a MegaBace 500 sequencer according to the manufacturer's specifications.

Results and discussion

We identified 72 mutations in 124 of our 280 FAP families and observed eight types of recurrent mutations. The mutations and age of onset are presented in Table 1. Two of them were localized in exon 11 and the remaining six in the 3' part of exon 15. The most frequent mutation, 3927-3931delAAAGA, occurred in twenty-eight families (10%); the second one was 3183-3187delACAAA, occurring in eight families (2.8%); and the third most frequent mutation was 3202-3205delTCAA, detected in 5 families (1.7%). In our FAP patients Y500X occurred in four families (1.4%) while Q978X was detected in three families. Each of the remaining four types of mutation occurred in two families and the frequencies of these mutations were below one percent.

In the Human Mutations Database at the Institute of Medical Genetics in Cardiff (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=APC), considered the most representative population in the world, seven hundred mutations are listed for the *APC*

Table 1. Fifty-four recurrent mutations identified in *APC* gene and age of onset in a group of 124 diagnosed Polish FAP families

No.	Family	Clinical manifestation	Mutation	Exon	Age of onset
1.	9001	FAP	1490-1491insT	11	35
2.	9129	FAP	1490-1491insT	11	10
3.	9117	FAP	1500T>A	11	ND
4.	9141	FAP	1500T>A	11	ND
5.	9158	FAP	1500T>A	11	ND
6.	9182	FAP	1500T>A	11	ND
7.	9031	FAP	2626subC>T	15	ND
8.	9043	FAP	2626subC>T	15	30
9.	9099	FAP	2932C>T	15	ND
10.	9139	FAP	2932C>T	15	ND
11.	9152	FAP	2932C>T	15	ND
12.	9028	FAP	3183-3187delACAAA	15	28
13.	9067	FAP	3183-3187delACAAA	15	19
14.	9093	FAP	3183-3187delACAAA	15	17
15.	9108	FAP	3183-3187delACAAA	15	ND
16.	9111	FAP	3183-3187delACAAA	15	ND
17.	9192	FAP	3183-3187delACAAA	15	ND
18.	9262	FAP	3183-3187delACAAA	15	24
19.	9311	FAP	3183-3187delACAAA	15	ND
20.	9088	FAP	3202-3205delTCAA	15	30
21.	9106	FAP	3202-3205delTCAA	15	26
22.	9213	FAP	3202-3205delTCAA	15	28
23.	9226	FAP	3202-3205delTCAA	15	ND
24.	9342	FAP	3202-3205delTCAA	15	12
25.	9016	FAP	3927-3931delAAAGA	15	20
26.	9032	FAP	3927-3931delAAAGA	15	ND
27.	9036	FAP	3927-3931delAAAGA	15	13
28.	9059	FAP	3927-3931delAAAGA	15	18

Table 1. Fifty-four recurrent mutations identified in APC gene and age of onset in a group of 124 diagnosed Polish FAP families

No.	Family	Clinical manifestation	Mutation	Exon	Age of onset
29.	9065	FAP	3927-3931delAAAGA	15	36
30.	9069	FAP	3927-3931delAAAGA	15	ND
31.	9071	FAP	3927-3931delAAAGA	15	36
32.	9075	FAP	3927-3931delAAAGA	15	ND
33.	9084	FAP	3927-3931delAAAGA	15	ND
34.	9103	FAP	3927-3931delAAAGA	15	26
35.	9104	FAP	3927-3931delAAAGA	15	ND
36.	9105	FAP	3927-3931delAAAGA	15	20
37.	9118	FAP	3927-3931delAAAGA	15	ND
38.	9142	FAP	3927-3931delAAAGA	15	ND
39.	9147	FAP	3927-3931delAAAGA	15	29
40.	9149	FAP	3927-3931delAAAGA	15	16
41.	9162	FAP	3927-3931delAAAGA	15	ND
42.	9187	FAP	3927-3931delAAAGA	15	ND
43.	9193	FAP	3927-3931delAAAGA	15	ND
44.	9229	FAP	3927-3931delAAAGA	15	22
45.	9235	FAP	3927-3931delAAAGA	15	ND
46.	9237	FAP	3927-3931delAAAGA	15	21
47.	9244	FAP	3927-3931delAAAGA	15	16
48.	9292	FAP	3927-3931delAAAGA	15	19
49.	9300	FAP	3927-3931delAAAGA	15	17
50.	9312	FAP	3927-3931delAAAGA	15	ND
51.	9321	FAP	3927-3931delAAAGA	15	31
52.	9324	FAP	3927-3931delAAAGA	15	ND
53.	9070	Gardner syndrome	4129-4130delGT	15	ND
54.	9119	FAP	4129-4130delGT	15	ND

ND – no data available

gene. The most important mutation of the *APC* gene is 3927-3931delAAAGA. The frequency of these mutations varies depending on populations. The mutation reports describe the frequency of this mutation from 0% in northwest Spain, 2.4% in the Australian population, 5% in Dutch, 7% in Israeli to 16% in the group of Italian FAP patients [6-9]. The second most frequent mutation, 3183-3187delACAAA, is reported with frequency ranging from 0% in northwest Spain, 1.5% in Israeli populations to 8.4% in Australia [6-9]. A study of over 100 Dutch families revealed equal frequency of those two most frequent mutations (3927-3931delAAAGA and 3183-3187delACAAA) [10]. The largest studies of *APC* gene mutations were performed on a German population [11, 12]. The latest published report in 2005 involved the analysis of over 1000 patients. In comparison to this study, the representative study of mutation frequency in the neighbouring population indicated two times higher frequency of 3927-3931delAAAGA, whereas a difference in frequency of 3183-3187del-ACAAA was not observed (Germany 3.8%, Poland 2.7%). The frequency of 3202-3205delTCAA was equal (1.7%) in both populations. In worldwide comparison differences in the frequency of mutations were observed. The Polish population of FAP patients belongs to the group where 3927-3931delAAAGA occurred with higher frequency, whereas the frequency of mutation 3183-3187del-ACAAA occurred with medium frequency in comparison with other populations. The two recurrent mutations localized on exon 11 were observed only in the Polish population. In our two unrelated families with 1490-1491insT brain tumours were observed. Additionally in one family desmoid tumours occurred [10, 13]. Another mutation (Q978X) did not occur with higher

frequency as described for other populations [14]. In our FAP patient group Q283X, which occurs with frequency of 4.5% in UK FAP patients, was not observed [13]. Recurrent mutations occurred in 54 Polish FAP families. Screening for these mutations permitted us to diagnose 19% of all families in our population but eight types of mutations constitute 43.5% of all our diagnosed families. The mutation study in our population should involve these eight mutations to improve molecular diagnostics of the *APC* gene.

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