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Genotype-Phenotype Correlations of the Course of Cystic Fibrosis in Russian Children. The First Description of Eleven New Mutations

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Article received: Dec 21, 2017; **submitted to publication:** Feb 26, 2018

Background. *Cystic fibrosis is a hereditary disease that occurs as a result of mutations in the regulator gene of chloride ion transmembrane transport (CFTR). Finding mutations in the CFTR gene is necessary for identification of the clinical features of cystic fibrosis.* ***Objective.*** *Our aim was to identify genotype-phenotype correlations between mutations of the first class of pathogenicity and clinical manifestations of cystic fibrosis based on studying the prevalence and structure of CFTR gene mutations.* ***Methods.*** *The study included children under 18 years with cystic fibrosis admitted to hospital between 2013 and 2017. Biallelic mutations in the CFTR gene were the non-inclusion criterion. The CFTR gene variants were analyzed by next-generation sequencing method.* ***Results****. In 125 patients with cystic fibrosis, 59 different variants of the CFTR gene were detected, 11 of them not previously described. The most common was the deletion c.1521_1523del found in 98 (39.2%) of the 250 analyzed CFTR gene alleles and the deletion c.1545_1546del found in 22/250 (8.8%) alleles. It has been shown that the mutation c.1545_1546del, p.Y515* was more often found in children of the Chechen nation – odds ratio (OR) 139 (95% confidence interval 15–1,257). It has been established that meconium ileus, pancreatic deficiency and cirrhosis are more common in patients with mutations of the first category of pathogenicity: OR 3.9 (95% CI 1.0–15.0), 4.4 (95% CI 1.8–11.1), and 351 (95% CI 17.5–7,046), respectively. The association of CFTR gene mutations with the development of bronchiectases and polypous pancinusitis has not been found.* ***Conclusion****. Correlations between the genotype and clinical manifestations of cystic fibrosis in Russian children with CFTR gene mutations of the first class of pathogenicity have been established.*
Key words: *children, cystic fibrosis, CFTR gene, new mutations, next-generation sequencing, phenotype, genotype, correlations.*
(For citation: Gorinova Yulia V., Savostyanov Kirill V., Pushkov Alexandr A., Nikitin Alexey G., Pen'kov Evgeniy L., Krasovskiy Stanislav A., Simonova Olga. I., Namazova-Baranova Leyla S. Genotype-Phenotype Correlations of the Course of Cystic Fibrosis in Russian Children. The First Description of Eleven New Mutations. Voprosy sovremennoi pediatrii — Current Pediatrics. 2018; 17 (1): 61-69. doi: 10.15690/vsp.v17i1.1856)

FINANCING SOURCE
Not specified.

CONFLICT OF INTERESTS
Stanislav A. Krasovskiy — lecturing for Chiesi.
Olga. I. Simonova – lecturing for Genfa LLC.
Leyla S. Namazova-Baranova – receiving research grants from pharmaceutical companies Pierre Fabre, Genzyme Europe B. V., AstraZeneca Pharmaceuticals LP, Gilead / PRA Pharmaceutical Research Associates CAS, Teva Branded Pharmaceutical products R& D, Inc. / PPD Development (Smolensk) LLC, Stallergen SA / Quintiles GesmbH (Austria).
The other contributors confirmed the absence of a reportable conflict of interests.

Table 1. Comparative analysis of the incidence of mutations in children with cystic fibrosis according to the present study and the Russian register of patients with cystic fibrosis (data from 2015)

No.	Mutation	Mutation type	Frequency of alleles, abs. (%)	
			***n* =125[#]**	**According to [3]**
1	*c.1521_1523del, p.F508del*	Deletion	96 (38.4)	51.7
2	*c.1545_1546del, p.Y515**	Deletion	22 (8.8)	1.3
3	*c.274G>A, p.E92K*	Missense	17 (6.8)	2.4
4	*c.54-5940_273+10250del21kb*	Deletion	12 (4.8)	5.7
5	*c.3846G>A, W1282**	Nonsense	7 (2.8)	1.8
6	*c.1766+1G>C*	Intronic	5 (2.0)	0.1
7	*c.2052dup, p.Q685Tfs*4*	Insertion	5 (2.0)	1.8
8	*c.3909C>G, p.N1303K*	Missense	5 (2.0)	1.4
9	*c.1243_1247del, p.N415**	Deletion	4 (1.6)	0.2
10	*c.4004T>C, p.L1335P*	Missense	4 (1.6)	0.1
11	*c.580-1G>T*	Intronic	4 (1.6)	0.2
12	*c.1000C>T, p.R334W*	Missense	4 (1.6)	0.8
13	*c.2012del, p.L671**	Deletion	4 (1.6)	1.9
14	*c.3196C>T, p.R1066C*	Missense	4 (1.6)	0.3
15	*c.3844T>C, p.W1282R*	Missense	3 (1.2)	0.3
16	*c.1397C>G, p.S466**	Nonsense	2 (0.8)	0.3
17	*c.3209G>A, p.R1070Q*	Missense	2 (0.8)	NA
18	*c.1624G>T, p.G542**	Nonsense	2 (0.8)	1.2
19	*c.287C>A, p.A96E*	Missense	2 (0.8)	0.04
20	*c.3718-2477C>T*	Intronic	2 (0.8)	2.1
21	*c.550del, p.L184Ffs*5*	Deletion	2 (0.8)	NA
22	*c.1735G>T, p.D579Y*	Missense	2 (0.8)	0.1
23	*c.3816_3817del,p.S1273Lfs*28*	Deletion	2 (0.8)	0.3
24	*c.442del, p.I148Lfs*5*	Deletion	2 (0.8)	NA
25	*c.349C>T, p.R117C*	Missense	2 (0.8)	0.02
26	*c.174_177del, p.D58Efs*32*	Deletion	2 (0.8)	NA
27	*c.3107C>A, p.T1036N*	Missense	1 (0.4)	NA
28	*c.412_413insACT, p.L137_L138insH*	Insertion	1 (0.4)	1.1
29	*c.3475T>C, p.S1159P*	Missense	1 (0.4)	0.1
30	*c.2589_2599del, p.I864Sfs*28*	Deletion	1 (0.4)	NA

31	*c.43del, p.L15Ffs*10*	Deletion	1 (0.4)	0.04
32	*c.254G>A, p.G85E*	Missense	1 (0.4)	0.1
33	*c.358G>A, p.A102T*	Missense	1 (0.4)	NA
34	***c.4298A>G, p.E1433G***	Missense	1 (0.4)	0.02
35	***c.1219del, p.E407Nfs*35***	Deletion	1 (0.4)	0.02
36	***c.353del, p.S118Lfs*6***	Deletion	1 (04)	NA
37	*c.1657C>T, p.R553**	Nonsense	1 (0.4)	0.2
38	*c.2834C>T, p.S945L*	Missense	1 (0.4)	0.1
39	***c.1488G>A, p.W496****	Nonsense	1 (0.4)	0.02
40	***c.831G>A, p.W277****	Nonsense	1 (0.4)	NA
41	*c.1584+1G>A*	Intronic	1 (0.4)	0.1
42	***c.237G>A, p.W79****	Nonsense	1 (0.4)	0.02
43	*c.2125C>T, p.R709**	Nonsense	1 (0.4)	0.02
44	*c.1735G>T, p.D579Y*	Missense	1 (0.4)	0.04
45	*c.3140-26A>G*	Intronic	1 (0.4)	0.02
46	*c.1399C>T, p.L467F*	Missense	1 (0.4)	NA
47	***c.1853_1863del, p.I618Rfs*2***	Deletion	1 (0.4)	NA
48	*c.3691del, p.S1231Pfs*4*	Deletion	1 (0.4)	0.5
49	*c.2491G>T, p.E831**	Nonsense	1 (0.4)	NA
50	***c.252T>A, p.Y84****	Nonsense	1 (0.4)	0.1
51	*c.1130dup, p.Q378Afs*4*	Insertion	1 (0.4)	NA
52	*c.3929G>A, p.W1310**	Nonsense	1 (0.4)	0.13
53	*c.3454G>C, p.D1152H*	Missense	1 (0.4)	0.1
54	***c.580G>A, p.G194R***	Missense	1 (0.4)	NA
55	***c.3927_3938del, p.W1310_Q1313del***	Deletion	1 (0.4)	NA
56	*c.3528del, p.K1177Sfs*15*	Deletion	1 (0.4)	0.1
57	***c.1708_1712del, p.L570Rfs*17***	Deletion	1 (0.4)	NA
58	***c.2619+1G>A***	Intronic	1 (0.4)	NA
59	*c.328G>C, p.D110H*	Missense	1 (0.4)	0.02

Note. # — the frequency is calculated for 250 sequenced alleles. The boldface characters the CFTR gene variants previously not described in the HGMD. Four variants of them are presented in the Russian register of patients with cystic fibrosis for 2015 under the numbers 34, 35, 39, and 42 (based on the results of this study). NA — not available.

Table 2. Genotype-phenotype correlations in children with cystic fibrosis

Phenotypic trait	**Mutation type**	**Absence/presence of the trait, abs. (%)**		**OR (95% CI)**	***p***
		No	**Yes**		
Meconium ileus	Class 1 mutations	48 (41.0)	10 (8.5)	3.9 (1.0-15.0)	0.043
	Other mutations	56 (47.9)	3 (2.6)		
Pancreatic deficiency	Class 1 mutations	9 (7.3)	68 (54.3)	4.4 (1.8-11.1)	0.001
	Other mutations	17 (13.8)	29 (23.5)		
Pancreatic deficiency	Missense mutations	5 (4.1)	8 (6.5)	0.47 (0.14-0.55)	0.302
	Other mutations	21 (17.1)	89 (72.4)		
Cirrhosis	Class 1 mutations	44 (35.8)	13 (10.6)	19.2 (2.4-152.1)	0.001
	Other mutations	65 (52.8)	1 (0.8)		
Bronchiectases	Class 1 mutations	34 (27.6)	40 (32.5)	1.2 (0.6-2.4)	0.661

	Other mutations	25 (20.3)	24 (19.5)		
Polyps	Class 1 mutations	49 (39.8)	25 (20.3)	0.9 (0.4-1.9)	0.771
	Other mutations	34 (27.6)	15 (12.2)		

Note. The statistical analysis for meconium ileus indicator included 117 patients; the analysis for pancreatic deficiency, cirrhosis, bronchiectases and polyps — 123 patients. For the rest of the patients, there was no evidence of a phenotypic trait.

Fig. The incidence of different mutation types in 125 children with cystic fibrosis