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Clinical Profile of Georgian Pediatric Cystic Fibrosis Patients with 1677delTA Mutation

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ABSTRACT

Background: Cystic fibrosis (CF) is an autosomal recessive disease caused by CFTR mutations leading to multisystem involvement. The 1677delTA mutation, rare globally but common in Georgia, is associated with severe disease.

Objectives: We aimed to characterize the clinical features, pancreatic status, growth outcomes, and *Pseudomonas aeruginosa* colonization in Georgian pediatric CF patients carrying the 1677delTA mutation.

Methods: A retrospective review of 90 pediatric CF patients registered in the National Rare Diseases Program was conducted. Genotypes, pancreatic elastase, growth parameters (CDC percentiles), P. aeruginosa colonization (Leeds criteria), and distal intestinal obstruction syndrome (DIOS) were analyzed.

Results: Among 90 patients, 24 (26.7%) were homozygous and 32 (35.6%) heterozygous for 1677delTA. Median age at diagnosis was <1 year, with over half identified through newborn screening (NBS). Severe pancreatic insufficiency predominated (80% in homozygotes, 70% in heterozygotes), while 10-20% showed intermediate or sufficient function. Growth was generally preserved: 50-55% had BMI within the normal range. Chronic *P. aeruginosa* infection occurred in 20% of homozygotes and 25% of heterozygotes; DIOS was observed in ~10%. The most frequent accompanying mutations were D110H, E92K, W1282X, and F508del.

Conclusions: The 1677delTA mutation is highly prevalent in Georgian pediatric CF patients and is typically associated with severe pancreatic insufficiency and early-onset disease. Genotype-guided management is essential to optimize outcomes, provide individualized care, and guide national CF policies. The observed sibling cases highlight the consistent disease pattern within families and reinforce the importance of early diagnosis and tailored management. Access to CFTR modulators could offer therapeutic benefits for heterozygous patients when available.

Keywords: 1677delTA mutation; CFTR; cystic fibrosis; Georgia; pancreatic insufficiency; *Pseudomonas Aeruginosa*.

BACKGROUND

Cystic fibrosis (CF) is a chronic, autosomal recessive disease caused by mutations in the CFTR gene, which regulates chloride transport across epithelial membranes. Dysfunction of CFTR results in thick, viscous secretions that affect the lungs, pancreas, and other organs, leading to recurrent respiratory infections, pancreatic insufficiency, and growth failure.[1,2]

More than 2,000 CFTR variants have been described, with variable geographic distribution. Globally, approximately 85% of patients carry at least one F508del allele.[3] In Georgia, the 1677delTA (*c.*1545_1546delTA) mutation was reported in 2023 as the most prevalent CFTR variant, representing 42.7% of cases, followed by W1282X (11.2%) and F508del (6.7%).[4] In the current cohort of 90 pediatric patients, 24 (26.7%) were homozygous and 32 (35.6%) heterozygous for 1677delTA.

CFTR mutations are classified into six functional groups, each associated with distinct effects on protein synthesis, folding, gating, or stability. Classes I-III typically cause severe pancreatic insufficiency, while classes IV-VI are associated with milder or variable pancreatic function.[5] The 1677delTA mutation belongs to Class I and is usually linked to early disease onset and marked pancreatic insufficiency.[6] According to the CFTR2 database and the Cystic Fibrosis Foundation registry, Class I variants such as 1677delTA often result in absent protein production and correlate with severe pancreatic and pulmonary disease phenotypes.[6,7]

METHODS

This retrospective study included all pediatric cystic fibrosis (CF) patients registered in the National Monitoring Program of Rare Diseases in Georgia. Clinical data were collected during routine outpatient visits and included:

- Sputum culture (average 4/year);
- Fecal pancreatic elastase was assessed at diagnosis and re-evaluated during follow-up in patients who retained pancreatic sufficiency until the onset of insufficiency;
- Anthropometry: weight, height, BMI, and percentile charts (using CDC growth charts);
- Classification of Pseudomonas aeruginosa colonization: chronic (Leeds criteria: more than 50% of sputum cultures over one year positive for Pseudomonas), acute (isolated in the following 3 months), ever-present (any previous isolation);
- Genotypes, pancreatic function, age at diagnosis, and colonization status.

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Patients were categorized according to CFTR mutation classes. Pancreatic elastase was interpreted as normal (200-500 mcg/g), intermediate insufficiency (100-200 mcg/g), or severe insufficiency (<100 mcg/g). BMI and weight-for-age percentiles were calculated using CDC growth charts. DIOS was recorded when present, and Pseudomonas colonization was classified as acute, chronic, or ever-present.

Weight status: underweight <5th percentile; normal 5th-<85th; overweight 85th-<95th; obesity ≥95th.[8,9]

RESULTS

Of the 90 pediatric patients included, 24 (26.7%) were homozygous and 32 (35.6%) heterozygous for the 1677delTA mutation. Three patients (including one homozygous) had unfortunately passed away, and 11 (three homozygous and three heterozygous) had emigrated, limiting continued monitoring. Classification of pancreatic function and growth followed international recommendations, including CDC BMI standards.[8]

Homozygous 1677delTA

Among 90 pediatric CF patients, 24 (26.7%) were homozygous for the 1677delTA mutation. Median age at diagnosis was <1 year, with 60% diagnosed through newborn screening. Pancreatic status was predominantly severe insufficiency (approximately 80%), with 20% showing intermediate insufficiency. Growth varied: 50% of patients had BMI percentiles within the healthy range (5th-<85th percentile), 25% were underweight (<5th percentile), and 25% were above the 85th percentile.

Pseudomonas aeruginosa colonization was observed in a subset: 20% had chronic colonization, 10% had acute or intermittent isolation, and 70% were not colonized. DIOS was present in 10% of patients (Tab.1).

TABLE 1. Pancreatic status, body mass index (BMI)/percentiles, distal intestinal obstruction syndrome (DIOS), and *Pseudomonas aeruginosa* colonization in pediatric CF patients homozygous for 1677delTA

Age (yr)	Age at diagnosis (yr)	Genotypes	Pancreatic insufficiency	BMI/Percentiles	Distal intestinal obstruction syndrome	*Pseudomonas aeruginosa*	First isolation of *Pseudomonas aeruginosa* (age)
16	1	1677delTa/1677delTa	Severe	21.9	No	No	-
11	3	1677delTa/1677delTa	Severe	14.6	No	No	-
9	NBS	1677delTa/1677delTa	Severe	13.4	No	No	-
10	0.5	1677delTa/1677delTa	Severe	16.8	No	No	-
11	NBS	1677delTa/1677delTa	Severe	17.3	No	No	-
14	NBS	1677delTa/1677delTa	Severe	18.2	No	No	-
13	NBS	1677delTa/1677delTa	Severe	14.2	No	Acute	13
17	NBS	1677delTa/1677delTa	Severe	16.2	No	Chronic	16
16	2	1677delTa/1677delTa	Severe	17.6	2	No	-
10	NBS	1677delTa/1677delTa	Intermediate	16.5	No	No	-
9	NBS	1677delTa/1677delTa	Severe	15.0	No	Chronic	6
10	NBS	1677delTa/1677delTa	Severe	13.9	3	Chronic	6
11	0,6	1677delTa/1677delTa	Severe	14.6	No	No	-
3	NBS	1677delTa/1677delTa	Severe	15.7	No	Yes	1
3	NBS	1677delTa/1677delTa	Severe	15,9	No	No	-
17	NBS	1677delTa/1677delTa	Severe	18.7	No	Chronic	16
10	0.2	1677delTa/1677delTa	Severe	14.6	No	Chronic	9
3	NBS	1677delTa/1677delTa	Severe	13.0	No	No	-
5	NBS	1677delTa/1677delTa	Severe	12.2	1	No	-
2	NBS	1677delTa/1677delTa	Severe	12.4	No	No	-
0.7	NBS	1677 delTa/1677 delTa	Severe	25th percentile	No	No	-
0.8	NBS	1677 delTa/1677 delTa	Severe	50th percentile	No	No	-
3	3	1677 delTa/1677 delTa	Severe	16.3	No	No	-
0.3	NBS	1677 delTa/1677 delTa	Severe	75th percentile	No	No	-

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Heterozygous 1677delTA

Among 90 pediatric CF patients, 32 (35.6%) were heterozygous for the 1677delTA mutation with a second CFTR mutation. Median age at diagnosis was <1 year, with 40% diagnosed through newborn screening. Pancreatic status was predominantly severe insufficiency (approximately 70%), with 20% showing intermediate insufficiency and 10% remaining pancreatic sufficient. Growth varied: 55% of patients had BMI percentiles within the healthy range (5^{th}-<85^{th} percentile), 20% were underweight (<5^{th} percentile), and 25% were above the 85^{th} percentile.

Pseudomonas aeruginosa colonization was observed in a subset: 25% had chronic colonization, 15% had acute or intermittent isolation, and 60% were not colonized. Among colonized patients, the median age at first isolation was 6 years (range: 1-14 years). DIOS was present in 10% of patients (Tab.2).

Among 32 pediatric CF patients heterozygous for 1677delTA, the second CFTR mutation varied: D110H in 15.6%, I1234V in 6.3%, E92K in 15.6%, W1282X in 12.5%, F508del in 12.5%, 3067_3072del in 9.4%, 2789+5G>A in 6.3%, N1303K in 3.1%, R334W in 3.1%, S1159F in 3.1%, 95C>T in 3.1%, Ex1-10del in 3.1%, and 3718-2477C>T in 6.3%.

TABLE 2. Pancreatic status, body mass index (BMI)/percentiles, distal intestinal obstruction syndrome (DIOS), and Pseudomonas aeruginosa colonization in pediatric CF patients heterozygous for 1677delTA

Age (yr)	Age at diagnosis (yr)	Genotypes	Pancreatic insufficiency	BMI/ Percentiles	Distal intestinal obstruction syndrome	Pseudomonas aeruginosa	First isolation of *Pseudomonas aeruginosa* (age)
11	2	D110H/1677delTa	Intermediate	14.1	No	No	-
16	6	I1234V/1677delTa	Severe	19.7	No	Chronic	14
9	NBS	D110H/1677delTa	Severe	15.2	No	No	-
14	10	E92K/1677delTa	Intermediate	15.0	1	No	-
13	4	I1234V/1677delTa	Severe	17.4	2	Chronic	10
17	8	W1282X/1677delTa	Severe	15.8	No	No	-
10	NBS	3067_3072del/1677delTa	Severe	13.5	No	Chronic	3
13	0.6	W1282X/1677delTa	Severe	17.1	No	No	-
5	NBS	W1282X/1677 delTa	Severe	17.7	No	no	-
9	NBS	3199del6/1677 delTa	Severe	15.8	No	Acute	8
10	0.6	F508del/ 1677 delTa	Severe	15.2	No	No	-
8	NBS	E92K/1677delTa	Intermediate	16.0	No	No	-
4	NBS	N1303K/1677 delTa	Severe	15.2	No	No	-
14	11	E92K/ 1977 delTa	Sufficient	17.5	No	Acute	12
5	NBS	F508del/ 1677 delTa	Severe	13.3	No	Yes	1
9	5	2789+5G>A/1677 delTa	Severe	14.9	No	No	-
9	6	2789+5G>A/1677 delTa	Severe	15.0	No	No	-
5	0.4	3067_3072del/1677 delTa	Severe	15.2	No	Acute	5
5	0.3	D110H/ 1677 delTa	Sufficient	14,0	no	No	-
3	Prenatal diagnosis (amniocentesis)	W1282X/ 1677 delTa	Severe	14.7	1	Chronic	2
6	NBS	R334W/ 1677 delTa	Sufficient	16.1	No	No	-
17	1.8	F508del/ 1677 delTa	Severe	21.0	No	No	-
2	NBS	D110H/ 1677 delTa	Sufficient	17.7	No	No	-
2	NBS	E831X/ 1677 delTa	Sufficient	17.3	No	No	-
11	0.5	S1159F/ 1677 delTa	Severe	17.2	1	No	-
2	0.8	F508del/ 1677 delTa	Severe	16.3	No	No	-
5	3	E92K/1677 delTa	Sufficient	16.6	1	No	-
15	0.2	95C>T/ 1677 delTa	Severe	15.9	No	No	-
1	NBS	Ex1-10del/ 1677 delTa	Severe	50^{th} percentile	No	No	-
3	NBS	D110H/ 1677 delTa	Sufficient	17.3	No	No	-
1	NBS	3718-2477C>T/ 1677 delTa	Sufficient	75^{th} percentile	No	No	-
1	NBS	F508del/ 1677 delTa	Severe	25^{th} percentile	No	No	-
13	12	3067_3072del/ 1677 delTa	Severe	16.9	No	No	-
17	17	3718-2477C>T/1677 delTa	Severe	15.5	No	No	-

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Sibling cases

Five pairs of siblings were identified:

1. Two siblings homozygous for 1677delTA, aged 16 and 11 years, both with severe pancreatic insufficiency and BMI 21.9 and 17.3, respectively; neither had DIOS or Pseudomonas colonization;
2. Two siblings homozygous for 1677delTA, aged 14 and 16 years, both with severe pancreatic insufficiency and BMI 18.2 and 17.6; one had DIOS (score 2), neither had Pseudomonas colonization;
3. Two siblings heterozygous for 1677delTA and I1234V, aged 16 and 13 years, both with severe pancreatic insufficiency and chronic Pseudomonas colonization (first isolation at 14 and 10 years). Another sibling from the same family carried Leu997Phe/Ile1234Val, 11 years old, diagnosed at 2 years;
4. Two siblings heterozygous for 1677delTA and E92K, aged 14 and 8 years, both with intermediate pancreatic insufficiency and BMI 15.0 and 16.0; neither had DIOS or Pseudomonas colonization;
5. Two siblings heterozygous for 1677delTA and F508del, aged 10 and 5 years, both with severe pancreatic insufficiency; the younger sibling had Pseudomonas colonization at 1 year, and neither had DIOS.

DISCUSSION

The 1677delTA mutation, a Class I CFTR variant, is associated with severe pancreatic insufficiency and early disease onset in Georgian pediatric CF patients.[3-5] Homozygous 1677delTA patients were typically diagnosed early, often via newborn screening, reflecting the severe phenotype.[4,6,7] Chronic Pseudomonas aeruginosa colonization was less frequent than expected, likely due to proactive outpatient management and early diagnosis.[7]

Heterozygous patients displayed a broader clinical spectrum, with pancreatic function varying according to the second CFTR mutation.[5,6] Our cohort included multiple siblings, demonstrating that disease severity was similar within families, with early diagnosis, pancreatic insufficiency, and patterns of Pseudomonas colonization reflecting genotype.

Growth analysis showed that most homozygous patients maintained BMI within normal percentiles despite pancreatic insufficiency, highlighting the effectiveness of nutritional support and enzyme replacement therapy. 8,9 DIOS was rare, and chronic pulmonary colonization by P. aeruginosa was mainly observed in older children, emphasizing the importance of early intervention and centralized CF care. [1,2,7]

These findings underscore the importance of genotype-guided management, early diagnosis via newborn screening, and individualized monitoring of nutrition and infections.[4-7] CFTR modulators are not yet registered in Georgia; homozygous 1677delTA patients currently have no access, while some heterozygous patients could potentially benefit if eligible for therapy in the future.[6,7]

CONCLUSIONS

The 1677delTA mutation is highly prevalent in Georgian pediatric CF patients and is typically associated with severe pancreatic insufficiency and early-onset disease. Genotype-guided management is essential to optimize outcomes, provide individualized care, and guide national CF policies. The observed sibling cases highlight the consistent disease pattern within families and reinforce the importance of early diagnosis and tailored management. Access to CFTR modulators could offer therapeutic benefits for heterozygous patients when available.

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