# The CFTR gene variants in paediatric nasal polyposis: a study in the Italian population*

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**Dear Editor:**

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a relatively uncommon condition in the paediatric population, with a prevalence estimated at 0.1–0.8%, compared to approximately 4% in adults [1, 2]. The early onset of CRSwNP emphasises the significant role of genetic factors in its pathophysiology [3]. Approximately 20% of paediatric patients with CRSwNP are associated with systemic genetic disorders, with cystic fibrosis (CF) being the most prevalent [2]. CF is characterised by a dysfunction of the CF transmembrane conductance regulator (CFTR) protein. Over 2,000 distinct CFTR variants have been identified, resulting in varying organ involvement and disease severity. In 2000, the World Health Organization introduced the term "CFTR-related disorders" (CFTR-RDs) to include clinical entities associated with CFTR dysfunction that do not meet the diagnostic criteria for CF [4]. CFTR-RDs include congenital bilateral absence of the vas deferens (CBAVD), recurrent pancreatitis (RP), and disseminated bronchiectasis (DB). However, recent studies emphasised a significant prevalence of heterozygous CFTR pathogenic variants in paediatric and adult CRSwNP populations without CF [4–8]. We assessed the prevalence of CFTR variants in a paediatric population with CRSwNP.

Detailed methods and results are provided in the Supplementary Material. We included 34 patients aged 5–18 years diagnosed with CRSwNP based on nasal endoscopy and computed tomography findings, excluding those with other known causes of CRSwNP (Table 1). We evaluated patients for CFTR variants, the sweat chloride test (SCT), comorbidities (CFTR-RD and lower airway diseases, including asthma and recurrent bronchitis), and predisposing factors for CRSwNP, including familial risk, cigarette smoke exposure, adenoidal pathology, allergic rhinitis (AR), non-allergic rhinitis (NAR), and gastroesophageal reflux disease (GERD).

In 17 patients (50%), 11 distinct CFTR variants were identified, with c.1210-12T being the most prevalent (n = 7) [5]. SCT yielded borderline results in 3 CFTR carriers and negative results in all others. None of the CFTR carriers or their families exhibited CBAVD, RP, and DB. The incidence of asthma in CFTR- carriers was 29.41%, while in CFTR-negative patients it was 11.76%.
Our findings support the hypothesis that paediatric CRSwNP patients exhibit a higher prevalence of CFTR variants compared to the general Italian population (3–4%) [6]. Several identified variants are documented in international databases as associated with CFTR-RDs, including some previously reported in CRSwNP (Supplementary Material) [6–8].
We evaluated potential predisposing factors associated with CRSwNP. A family history of CRSwNP was reported in six CFTR carriers, including three sibling pairs; no parents or other relatives were affected. Nasal endoscopy revealed significantly higher grades of adenoid hypertrophy (grades III and IV) in CFTR-carriers compared to CFTR-negative patients (47.06% vs. 11.76%).
This study has several limitations. First, we did not perform nasal potential difference testing due to its limited availability in specialised centres, rendering it impractical for routine clinical use. Second, the limited number of our sample may have caused a selection bias, therefore the evaluation of the real incidence of CFTRs variants in Italian paediatric CRSwNP requires a larger sample.

In conclusion, screening for CFTR variants is warranted in paediatric patients with CRSwNP. Current diagnostic criteria accept CFTR genotyping as a surrogate marker for CFTR dysfunction [4, 8]. Furthermore, single allelic CFTR variants and other cofactors may predispose individuals to CRSwNP [6–8]. Notably, evaluation of siblings of affected children is recommended, regardless of parental carrier status. Asthma, the most common comorbidity,

Table 1. Clinical characteristics of 34 patients with CRSwNP.

| Patient's No., age (y), sex | Familiar history of CRSwNP | Cigarette smoke | Predisposing factors/ Comorbidities | AH grade | SCT | CFTR variant(s) |
|---|---|---|---|---|---|---|
| No.1, 13 y, M | No | No | AR, recurrent bronchitis | I | borderline | c.1210-12T[5] |
| No.2, 9 y, F | No | No | NARMA, recurrent bronchitis | III | negative | c.1210-12T[5] |
| No.3, 9 y, M | No | No | AR | III | negative | undetected |
| No.4, 18 y, M | No | No | NARES | I | negative | undetected |
| No.5, 14 y, M | No | Yes | AR | I | negative | undetected |
| No.6, 12 y, F | Yes§ | No | AR, asthma, GERD | III | negative | c.3322G>C |
| No.7, 9 y, M | Yes§ | No | AR, asthma | III | negative | c.3322G>C; c.3705T>G |
| No.8, 11 y, F | No | No | NARES, recurrent bronchitis | II | negative | undetected |
| No.9, 18 y, F | No | Yes | AR, asthma | I | negative | c.91C>T |
| No.10, 10 y, M | Yes§ | No | AR, asthma | III | borderline | c.1210-12T[5]; c.1736A>G |
| No.11, 5 y, F | Yes§ | No | AR, asthma | IV | negative | c.2991G>C |
| No.12, 16 y, M | No | No | AR | I | negative | undetected |
| No. 13, 15 y, M | No | No | NARESMA, recurrent bronchitis | I | negative | undetected |
| No. 14, 16 y, M | No | No | NARESMA | I | negative | undetected |
| No. 15, 12 y, F | No | Yes | AR | II | negative | undetected |
| No. 16, 14 y, M | No | No | NARESMA | I | negative | c.91C>T |
| No. 17, 13 y, M | No | No | AR | I | negative | undetected |
| No. 18, 18 y, M | No | No | NARESMA | I | negative | c.2900T>C |
| No. 19, 17 y, M | No | Yes | AR | I | negative | undetected |
| No. 20, 14 y, F | No | No | NARESMA | II | negative | c.1210-12T[5] |
| No. 21, 18 y, F | No | No | NARES | I | negative | undetected |
| No. 22, 17 y, M | No | No | NARESMA | I | negative | undetected |
| No. 23, 12 y, F | No | No | NARES | III | negative | c.1210.11T>G |
| No. 24, 8 y, F | No | No | NARES, asthma | III | negative | undetected |
| No. 25, 15 y, M | No | No | NARMA | I | negative | undetected |
| No. 26, 18 y, M | No | No | AR | I | negative | c.1210-12T[5] |
| No. 27, 18 y, M | No | No | AR, astmha | I | negative | undetected |
| No. 28, 18 y, M | No | No | NARESMA | I | negative | undetected |
| No. 29, 6 y, F | Yes§ | No | AR | III | negative | c.1210-12T[5] |
| No. 30, 12 y, F | Yes§ | No | AR | II | negative | c.1210-12T[5] |
| No. 31, 11 y, F | No | No | NARES, recurrent bronchitis | II | negative | undetected |
| No. 32, 15 y, M | No | No | NARES | I | negative | c.3485G>T |
| No. 33, 13 y, M | No | No | NARESMA, recurrent bronchitis | III | borderline | c.3154T>G |
| No. 34, 12 y, F | No | No | NARES | I | negative | c.3909C>G |

List of abbreviations: No: Patient's Identification number; age in years (y); sex male (M), or female (F); CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; AH: adenoidal hypertrophy; SCT: Sweat Chloride Test; CFTR: Cystic Fibrosis Transmembrane Regulator; AR: allergic rhinitis; NARMA: non allergic rhinitis with mast cells; NARES: non allergic rhinitis with eosinophils; GERD: gastroesophageal reflux disease; NARESMA: non allergic rhinitis with eosinophils and mast cells; NARNE: non allergic rhinitis with neutrophils. Legend of symbols: § Patients No. 6 and 7, 10 and 11, and 29 and 30 are brother/sister pairs.

should be promptly evaluated and managed to prevent complications. Finally, high-grade adenoid hypertrophy may contribute to the phenotypic expression of CRSwNP. A comprehensive approach to managing paediatric CRSwNP is essential, particularly considering the anticipated emergence of novel therapeutic options, such as CFTR modulator drugs [9].

## Authorship contribution

Acquisition, analysis, or interpretation of data: SS, ES, GM, FC, CS, MCA. Drafts and revisions during the writing process: FM, LS, GC, RC, AGF. Final approval of the article: All the authors.

## Conflict of interest

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**This manuscript contains online supplementary material**

## SUPPLEMENTARY MATERIAL

### Materials and methods

This retrospective study analysed patients admitted to the multidisciplinary Chronic Rhinosinusitis Allergo-Rhinologic Team [1] at our hospital between September 2021 and December 2023. We included children and adolescents aged 2–18 years, diagnosed with CRSwNP based on findings from nasal endoscopy and computed tomography (CT). We investigated CFTR variants, comorbidities, and predisposing factors in the enrolled patients. Individuals with known pathologies causing CRSwNP, such as CF, primary ciliary dyskinesia (PCD), and primary immunologic disorders (PID), were excluded. We collected genetic and clinical data, and descriptive statistics were analysed using IBM® SPSS statistical software. The study design adhered to internationally recognised clinical study guidelines and was approved by the local Ethics Committee. Written assent from the young patients and informed consent from their legal guardians were obtained.
Genetic testing was performed using next-generation sequencing with the Devyser CFTR Kit (Devyser®) on the MiSeq platform (Illumina®). The test sequenced the promoter, coding regions, exon-intron junctions, and intronic regions containing pathogenic variants, including c.1585-9412A>G (c.1584+18672A>G), c.1680-886A>G (1811+1.6kbA->G), and c.3718-2477C>T (3849+10kbC->T). Additionally, it analysed genomic rearrangements, such as exonic microdeletions or microduplications of the CFTR gene (NM_000492.3). The detection rate was 97%, with an analytical sensitivity and specificity of 99%. Confirmatory testing was performed through Sanger sequencing using the BigDye® Terminator v 3.1 kit and capillary electrophoresis with an automatic Genetic Analyser (Applied Biosystems). Variant nomenclature followed the Human Genome Variation Society guidelines. Identified CFTR variants were cross-referenced with major databases, including the American College of Medical Genetics and Genomics, ClinVar, CFTR2, and CFTR- France.
All patients underwent the SCT, which was conducted and interpreted using standardised techniques. A chloride level ≤ 29 mmol/L was considered a normal (negative) SCT result. Levels ≥ 60 mmol/L were deemed "pathologic," while values of 30–59 mmol/L were classified as "borderline" [2].
We assessed patients with CFTR variants and their family members for any CFTR-RDs. All patients were evaluated for lower airway diseases through clinical chest examination, spirometry (Cosmed Micro Quark®, Italy), and in selected cases, radiologic imaging (X-ray or CT). We recorded any family history of CRSwNP as well as exposure to active or passive cigarette smoke. Adenoidal hypertrophy (AH) was assessed through nasal endoscopy and classified into grades I–IV [3]. We also evaluated patients for allergic rhinitis (AR) and non-allergic rhinitis (NAR). Sensitisation to inhalants was determined using either a skin prick test or a specific IgE measurement. NAR was diagnosed when nasal cytology revealed inflammatory cells in the nasal mucosa. Standardised procedures were used for sample collection, optical microscopy, and preparation of final rhinocytograms [4]. NAR was further classified into four types according to the ARIA guidelines: NAR with neutrophils (NARNE), eosinophils (NARES), mast cells (NARMA), and a combination of eosinophils and mast cells (NARESMA) [5]. Standard diagnostic criteria were followed for the evaluation of GERD [6].

### Results

In total, 34 patients (20 males and 14 females), with a mean age of 13.41 ± 3.60 years (range: 5–18 years), were included in the study. CFTR variants were detected in 17 patients (50%). No statistically significant difference in age and sex distribution was observed between CFTR-positive and CFTR-negative patients (respectively $\chi^2 = 1.4706$, P = 0.2252, and $\chi^2 = 1.9429$, P = 0.1633). In total, 11 different CFTR variants were identified. Of these, 14 patients carried a single heterozygous variant, 2 carried 2 different heterozygous variants (Nos. 7 and 10), and 1 (No.23) was homozygous for the c.1210-11T>G variant.
The intronic c.1210-12T[5] variant was present in 7 patients (Nos. 1, 2, 10, 20, 26, 29, and 30), being the most common in our series. Among these 7 patients, ages ranged from 6 to 18 years, with an approximately equal male-to-female ratio (3 males and 4 females). This variant is classified as a class V variant, resulting in reduced functional CFTR protein levels due to variable decreases in its function. Its penetrance could be modulated by other CFTR variants and environmental factors. A recent study on Chinese children with CRS also reported a high prevalence of the c.1210-12T[5] variant [7].The c.1210-12T[5], as well as the c.1210-11T>G variant, are classified as pathogenic with variable clinical consequences in CFTR-RDs (Tables S1 and S2). The c.1210-11T>G variant is another intronic variant similar to c.1210-12T[5], but involving a single nucleotide change rather than a deletion. This variant has been associated with reduced CFTR function and variable penetrance, linked to conditions, such as monosymptomatic CF, CFTR-RDs, and NPs (Tables S1 and S2).
The c.3322G>C variant was detected in 2 patients, a 12-year-old female (No. 6) and a 9-year-old male (No. 7), who also carried the c.3705T>G variant. Both the c.3322G>C and c.3705T>G variants are classified as variants of uncertain significance (VUS) due to limited database information. Recently c.3705T>G and c.91C>T have been classified as exonic missense variants of class IV, associated with defective ion conductance in the CFTR channel (Tables S1 and S2). Han et al. [7] reported high expression of c.91C>T in children with CRS, suggesting an increased risk of

the disease. The c.91C>T variant was identified in 2 patients, an 18-year-old female (No. 9) and a 14-year-old male (No. 16). This variant is classified as VUS class 4 (VUS4), having been associated with CFTR-RDs and some CF cases. Ten additional variants were identified across all groups (Table S1). Further details along with database links for all CFTR variants are provided in Table S2.
Borderline SCT results were observed in 3 patients. A 10-year-old male (No. 10) with 2 HEZ CFTR variants (c.1210-12T[5] and c.1736A>G) showed borderline results, as did a 13-year-old male (No. 1) with the c.1210-12T[5] variant, and a 13-year-old male (No. 33) who carried the c.3154T>G variant.
None of the patients or their families had a diagnosis of CBAVD, RP, or DB. Although not statistically significant, patients with CFTR variants exhibited a higher incidence of lower airway disease compared to CFTR-negative patients (47.06% vs. 29.41%, $\chi^2 = 1.1209$, P = 0. 2896). Among CFTR-positive patients, asthma was diagnosed in 5 patients, whereas recurrent bronchitis was identified in 3 others. In contrast, asthma was diagnosed in only 2 CFTR-negative patients (29.41% vs 11.76%, $\chi^2 = 1.619$, P = 0.2032), while chronic bronchitis was also present in 3 CFTR-negative patients.
A family history of CRSwNP was reported in 6 patients, involving 3 sibling pairs (Nos. 6 and 7, Nos. 10 and 11, and Nos. 29 and 30). None of their parents or other relatives had CRSwNP. Four patients were passively exposed to cigarette smoke, including an 18-year-old female (No. 9) with asthma and the c.91C>T variant, and 3 CFTR-negative patients (Nos. 5, 15, and 19). Nasal endoscopy revealed significant adenoid hypertrophy (grades III and IV) in 8 CFTR-positive and 2 CFTR-negative patients (47.06% vs. 11.76%, $\chi^2 = 5.1$, P = 0.0239). AR was diagnosed in 9 CFTR-positive and 7 CFTR-negative patients, with no statistically significant difference observed (52.94% vs 41.18%). NAR was identified in all non-allergic patients in both groups (47.06% vs. 58.82%), with no significant difference. NARES (8 patients, 3 CFTR-positive and 5 CFTR-negative) and NARESMA (8 patients, 4 CFTR-positive and 4 CFTR-negative) were the most common types of NAR. NARMA was detected in 1 patient from each group, whereas NARNE was not identified. GERD was diagnosed in two 12-year-old girls with CRSwNP, AR, and CFTR variants. One of these patients, who carried the c.3322G>C variant, also had asthma, while the other patient had the c.1210-12T[5] variant.

## Conclusions

Defining the role of CFTR variants in pediatric CRSwNP is crucial for future perspectives. To better define the pathogenetic role of these genetic background, proteomic and transcriptomic studies will be desirable. Furthermore, studies on a larger sample should be carried out considering the different incidence of CFTR variants in different ethnies and countries, and the significant impact of the environment on genetic expression.
In recent years, CFTR modulators have emerged as the standard of care for CF-affected patients. These mutation-specific therapies restore CFTR protein function, leading to significant improvements in clinical outcomes, including for CRSwNP patients. Although currently indicated for patients with at least one F508del CFTR mutation, the potential benefits of these modulators extend to individuals with other CFTR variants that impair protein function [8].

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Table S1. CFTR variants in 17 patients with CRSwNP: classification and clinical correlations in different databases.

| Patient's No, age (y), sex | HGVS nomenclature | Allele frequency § | ACMG 2015 classification | ClinVar database * | CFTR2 database | CFTR-France database | Clinical conditions associated in literature |
|---|---|---|---|---|---|---|---|
| No. 1, 13y, M | c.1210-12T[5] (HEZ) | GMAF: 0.02316 (TTTTT) | Pathogenic/Likely Pathogenic | Pathogenic (13); Likely pathogenic (1); Uncertain significance (2); Likely benign (1) | VVCC | VVCC | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD; OZ; HP. |
| No. 2, 9y, F | c.1210-12T[5] (HEZ) | GMAF: 0.02316 (TTTTT) | Pathogenic/Likely Pathogenic | Pathogenic (13); Likely pathogenic (1); Uncertain significance (2); Likely benign (1) | VVCC | VVCC | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD; OZ; HP. |
| No. 6, 12y, F | c.3322G>C (p.Val1108Leu; legacy: V1108L) (HEZ) | GMAF: - gnomAD, TOPMed: 0.0002 | VUS | Uncertain significance (7) | Not found | VUS2 | CF; CFTR-RD |
| No. 7, 9y, M | c.3322G>C (p.Val1108Leu; legacy: V1108L) (HEZ) | GMAF: - gnomAD, TOPMed: 0.0002 | VUS | Uncertain significance (7) | Not found | VUS2 | CF; CFTR-RD |
| | c.3705T>G (p.Ser1235Arg; legacy: S1235R) (HEZ) | GMAF: - gnomAD: 0.00573 TOPMed: 0.00526 NHLBI ESP: 0.00577 | VUS | Uncertain significance (3); Benign (6); Likely benign (5) | Non-CF causing | | CF; CFTR-RD; OZ; HP; CBAVD |
| No. 9, 18y, F | c.91C>T (p.Arg31Cys; legacy: R31C) (HEZ) | GMAF: 0.00140 (T); gnomAD: 0.00134; TOPMed: 0.00147; NHLBI ESP: 0.00077 | VUS | Uncertain significance (9); Benign (3); Likely benign(4) | Non-CF causing | | CF; bronchiectasis (with or without elevated SCT); CFTR-RD; HP; CBAVD |
| No. 10, 10y, M | c.1210-12T[5] (HEZ) | GMAF: 0.02316 (TTTTT) | Pathogenic/Likely Pathogenic | Pathogenic (13); Likely pathogenic (1); Uncertain significance (2); Likely benign (1) | VVCC | VVCC | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD; OZ; HP. |
| | c.1736A>G (p.Asp579Gly; legacy: D579G) (HEZ) | GMAF: - gnomAD: 0.00000 | Pathogenic | Drug Response (1); Pathogenic (12) | VVCC | VVCC | CF; CBAVD; CFTR-RD; ivacaftor response – efficacy; bronchiectasis (with or without elevated SCT). |
| No. 11, 5y, F | c.2991G>C (p.Leu997Phe; legacy: L997F) (HEZ) | GMAF: 0.00180 (C) gnomAD: 0.00208 TOPMed: 0.00262 | VUS | Pathogenic (4); Likely pathogenic(1); Uncertain significance(11); Benign(2); Likely benign(1) | Non-CF causing | CFTR-RD-causing | Susceptibility to idiopathic pancreatitis, and neonatal hypertrypsinemia; CF; pancreatitis; CFTR-RD; ID ; OA. |
| No. 16, 14y, M | c.91C>T (p.Arg31Cys; legacy: R31C) (HEZ) | GMAF: 0.00140 (T); gnomAD: 0.00134; TOPMed: 0.00147; NHLBI ESP: 0.00077 | VUS | Uncertain significance (9); Benign (3); Likely benign(4) | Non-CF causing | VUS4 | CF; bronchiectasis (with or without elevated SCT); CFTR-RD; HP; CBAVD |
| No. 18, 18y, M | c.2900T>C (p.Leu967Ser; legacy: L967S) (HEZ) | GMAF: 0.00040 (C) NHLBI ESP: 0.00038 TOPMed: 0.00104 gnomAD: 0.00106 | Likely Pathogenic | Pathogenic (1); Likely pathogenic(3); Uncertain significance(15) | VVCC | VUS2 | CF; ID; bronchiectasis (with or without elevated SCT); CFTR-RD; HP. |
| No. 20, 14y, F | c.1210-12T[5] (HEZ) | GMAF: 0.02316 (TTTTT) | Pathogenic/Likely Pathogenic | Pathogenic (13); Likely pathogenic (1); Uncertain significance (2); Likely benign (1) | VVCC | VVCC | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD; OZ; HP. |

| Patient's No, age (y), sex | HGVS nomenclature | Allele frequency § | ACMG 2015 classification | ClinVar database * | CFTR2 database | CFTR-France database | Clinical conditions associated in literature |
|---|---|---|---|---|---|---|---|
| No. 23, 12y, F | c.1210.11T>G (HOZ) | GMAF: - gnomAD: 0.00886 NHLBI ESP: 0.00331 | Pathogenic | Pathogenic(12); Likely pathogenic(2); Uncertain significance(2) | VVCC | Not found | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD |
| No. 26, 18y, M | c.1210-12T[5] (HEZ) | GMAF: 0.02316 (TTTTT) | Pathogenic/Likely Pathogenic | Pathogenic (13); Likely pathogenic (1); Uncertain significance (2); Likely benign (1) | VVCC | Varying clinical consequence | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD; OZ; HP. |
| No. 29, 6y, F | c.1210-12T[5] (HEZ) | GMAF: 0.02316 (TTTTT) | Pathogenic/Likely Pathogenic | Pathogenic (13); Likely pathogenic (1); Uncertain significance (2); Likely benign (1) | VVCC | Varying clinical consequence | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD; OZ; HP. |
| No. 30, 12y, F | c.1210-12T[5] (HEZ) | GMAF: 0.02316 (TTTTT) | Pathogenic/Likely Pathogenic | Pathogenic (13); Likely pathogenic (1); Uncertain significance (2); Likely benign (1) | VVCC | Varying clinical consequence | CBAVD; bronchiectasis (with or without elevated SCT); CF; CFTR-RD; OZ; HP. |
| No. 32, 15y, M | c.3485G>T (p.Arg1162Leu; legacy: R1162L) | GMAF: 0.00080 (T) NHLBI ESP: 0.00062 TOPMed: 0.00063 | VUS | Pathogenic (2); Likely pathogenic (2); Uncertain significance (5); Benign (2); Likely benign (3) | Non-CF causing | CFTR-RD-causing | CF; CFTR-RD; OZ. |
| No. 33, 13y, M | c.3154T>G (p.Phe1052Val; legacy: F1052V) | GMAF: - gnomAD: 0.00039 TOPMed: 0.00079 NHLBI ESP: 0.00100 | VUS | Uncertain significance (12); Drug Response (1); Pathogenic (4) | VVCC | CFTR-RD-causing | CF; ivacaftor response – efficacy; HP; CBAVD; CFTR-RD; bronchiectasis (with or without elevated SCT). |
| No. 34, 12y, F | c.3909C>G (p.Asn1303Lys; legacy: N1303K) | GMAF: 0.00020 (G) gnomAD: 0.00016 TOPMed: 0.00020 | Pathogenic | Pathogenic (40) | CF-causing# | CF-causing | CF; CBAVD; Y-linked spermatogenic failure; CFTR-RD; HP; bronchiectasis (with or without elevated SCT). |

List of abbreviations: No: Patient's Identification number; age in years (y); sex male (M), or female (F); ACMG: American College of Medical Genetics; HGVS: Human Genome Variation Society; CFTR: Cystic Fibrosis Transmembrane Regulator; CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; HEZ: Heterozygous; GMAF: Global Minor Allele Frequency; VVCC: Variant of Varying Clinical Consequence; CBAVD: Congenital Bilateral Aplasia of Vas Deferens; SCT: Sweat Chloride Test; CF: Cystic Fibrosis; CFTR-RD: CFTR-Related Disorders; gnomAD: Genome Aggregation Database; TOPMed: TransOmix for Precision Medicine; HOZ: Homozygous; HP: Hereditary pancreatitis; VUS: Variant of Uncertain Significance; ID: infertility disorder; OA: Obstructive Azoospermia; NHLBI: National Heart, Lung, and Blood Institute; ESP: Exome Variant Server. Legend of symbols: § From ClinVar database; reference sequence: NM_000492.3. * In case of conflicting classification of pathogenicity, the number of the studies reporting the evidence is in brackets. # When combined with another CF-causing variant.

Table S2. Links to the databases of CFTR mutations are provided for each variant.

| CFTR variant | ClinVar database | CFTR2 database | CFTR France database |
|---|---|---|---|
| c.1210-12T[5] | https://www.ncbi.nlm.nih.gov/clinvar/variation/242535/ | https://cftr2.org/mutation/general/5T/; https://cftr2.org/mutation/general/5T%253BTG12 | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.1210-12T%5B5%5D |
| C.3322G>C | https://www.ncbi.nlm.nih.gov/clinvar/variation/53719/ | not found | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.3322G%3EC |
| c.3705T>G | https://www.ncbi.nlm.nih.gov/clinvar/variation/35872/?oq=c.3705T%3EG[varname]+CFTR&m=NM_000492.4(CFTR):c.3705T%3EG%20(p.Ser1235Arg) | https://cftr2.org/mutation/general/S1235R/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.3705T%3EG |
| c.91C>T | https://www.ncbi.nlm.nih.gov/clinvar/variation/35893/?oq=c.91C%3ET[varname]+CFTR&m=NM_000492.4(CFTR):c.91C%3ET%20(p.Arg31Cys) | https://cftr2.org/mutation/general/R31C/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.91C%3ET |
| c.1736A>G | https://www.ncbi.nlm.nih.gov/clinvar/variation/53365/?oq=c.1736A%3EG[varname]+CFTR&m=NM_000492.4(CFTR):c.1736A%3EG%20(p.Asp579Gly) | https://cftr2.org/mutation/general/D579G/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.1736A%3EG |
| c.2991G>T | https://www.ncbi.nlm.nih.gov/clinvar/variation/7229/?oq=c.2991G%3EC[varname]+CFTR&m=NM_000492.4(CFTR):c.2991G%3EC%20(p.Leu997Phe) | https://cftr2.org/mutation/general/L997F/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.2991G%3EC |
| c.2900T>C | https://www.ncbi.nlm.nih.gov/clinvar/variation/219537/?oq=c.2900T%3EC[varname]+CFTR&m=NM_000492.4(CFTR):c.2900T%3EC%20(p.Leu967Ser) | https://cftr2.org/mutation/general/L967S/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.2900T%3EC |
| c.1210-11T>G | https://www.ncbi.nlm.nih.gov/clinvar/variation/178713/ | https://cftr2.org/mutation/general/5T%253BTG12/ | not found |
| c.3485G>T | https://www.ncbi.nlm.nih.gov/clinvar/variation/256253/?oq=c.3485G%3ET[varname]+CFTR&m=NM_000492.4(CFTR):c.3485G%3ET%20(p.Arg1162Leu) | https://cftr2.org/mutation/general/R1162L/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.3485G%3E |
| c.3154T>G | https://www.ncbi.nlm.nih.gov/clinvar/variation/35865/?oq=c.3154T%3EG[varname]+CFTR&m=NM_000492.4(CFTR):c.3154T%3EG%20(p.Phe1052Val) | https://cftr2.org/mutation/general/F1052V/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.3154T%3EG |
| c.3909C>G | https://www.ncbi.nlm.nih.gov/clinvar/variation/7136/?oq=c.3909C%3EG[varname]+CFTR&m=NM_000492.4(CFTR):c.3909C%3EG%20(p.Asn1303Lys) | https://cftr2.org/mutation/general/N1303K/ | https://cftr.iurc.montp.inserm.fr/cgi-bin/affiche.cgi?variant=c.3909C%3EG |