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Cystic fibrosis or not? Familial occurrence of a rare mutation in the *CFTR* gene

Abstract

Cystic fibrosis is a monogenic disease caused by a mutation in the *CFTR* gene. The classic presentation of the disease includes chronic bronchopulmonary symptoms. However, abnormalities in this gene may also be manifested by other phenotypes, so-called CFTR-related disorders. This is a group of entities including disseminated bronchiectasis, congenital bilateral absence of vas deferens, and chronic pancreatitis. In this article, we present a family with a rare F1052V mutation and a polymorphic variant of IVS-5T+11TG. No classical form of the disease was observed in any of the persons affected by the above changes. Results of special investigations are also not typical, which hinders unequivocal diagnosis.

Key words: cystic fibrosis, genes, mutation

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Introduction

Cystic fibrosis (CF) is the most common monogenic disease with autosomal recessive inheritance in the Caucasian population. Cystic fibrosis occurs with a frequency of about 1:4000–5000, asymptomatic carriers represent 2–5% of the white people's population. It is caused by a mutation in the *CFTR* gene encoding a cAMP-dependent chloride channel. Over 2000 mutations in this gene have been described so far [1, 2]. The CFTR protein is a regulator of ion and water transport in epithelia. Disruption of this function leads to increased viscosity and density of mucus, and consequently, to impairment of organ function. The most frequent clinical form of cystic fibrosis is a chronic bronchopulmonary disease. Exocrine pancreas failure and male infertility also commonly occur [3]. The *CFTR* gene is also associated with other phenotypes that do not meet the cystic fibrosis diagnostic criteria. These are so-called CFTR-related disorders, which include, among others, disseminated bronchiectasis, congenital bilateral absence of vas deferens (CBAVD), or chronic pancreatitis [1, 4]. In this paper, we present the case of a family with a rare mutation in the *CFTR* gene. The aim of the study is to draw attention to diagnostic difficulties that a clinician may meet in such a situation.

Case report

We report a case of a 10-year-old boy who had an abnormal level of immunoreactive trypsinogen on screening, presenting early childhood symptoms that suggested cystic fibrosis, primarily frequent respiratory infections. However, the chloride level in sweat was normal. Extended genetic diagnostics revealed mutations in the *CFTR* gene in the proband's family. The following genotypes were found: F1052V/IVS8-5T+11TG in the proband, IVS8-5T+11TG/- in the proband's mother and stepbrother, and F1052V/F1052V at the proband's father. The family tree is presented in Figure 1.

Due to the respiratory tract infections, periodically found atopic skin changes, increased IgE

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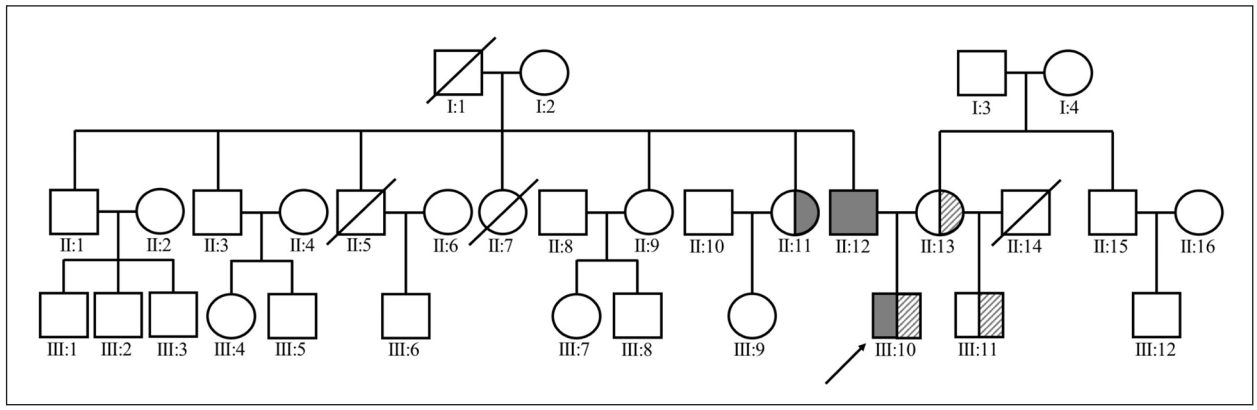

Figure 1. The family tree. The presence of the F1052V mutation is marked in gray and the presence of the variant IVS8-5T+11TG in the hatched box

level and eosinophils in the peripheral blood, the boy was suspected of bronchial asthma. A feature that has also drawn attention in the physical examination was obesity. In addition, the patient remains under the care of a cardiological outpatient clinic due to the tricuspid valve incompetence, pulmonary valve incompetence, and suspicion of hypertension.

A 34-year-old father of the proband has presented symptoms suggesting bronchial asthma, he has suffered from recurrent sinusitis, he has undergone nasal polyp resection, but he has never been diagnosed with cystic fibrosis. There was a case of infant death due to lung disease in the patient's father's family (II:7 in Figure 1). The father's sister has been detected as a carrier of the F1052V mutation (II:11 in Figure 1).

No clinical symptoms suggesting chronic respiratory disease were observed in the mother or stepbrother of the proband. Genetic testing of the mother's parents did not reveal a mutation in the *CFTR* gene, therefore, the IVS8-5T+11TG variant has *de novo* nature.

Discussion

The p.F1052V change is a rare mutation found in cystic fibrosis. It was first described by Mercier *et al*. in 1993 [5]. The substitution of phenylalanine to valine in the second transmembrane span of the CFTR protein is likely to affect the hydrophobic structure of this domain. Cases of patients with heterozygous mutation F1052V who had normal chloride levels in sweat were described in the medical literature [6, 7]. Our observation corresponds with the above reports, despite the presence of the discussed mutation in one allele, the proband has normal results of a sweat chloride test.

The proband's father has a homozygous p.F1052V mutation. This substitution may have varying clinical consequences [8]. According to the Consensus Guidelines from the Cystic Fibrosis Foundation, the presence of undefined *CFTR* genotype or a known mutation of varying clinical consequences indicates the need for CFTR physiologic testing, such as nasal potential difference (NPD). However, the basis of the diagnostic process is the clinical presentation of CF (signs and symptoms) [9]. The proband's father presented symptoms from the respiratory tract, but they did not include the classic CF picture. Further diagnostics would be recommended — the chloride level in sweat, NPD and functional tests of the respiratory system. However, the boy's father denies the possibility of the disease and does not want to undergo examinations.

The presence of a rare F1052V homozygous mutation is striking. This may be due to the random occurrence of the same *de novo* mutation in parents. Another situation is uniparental disomy (UDP), which occurs very rarely, but is possible. In the next stage, the consanguinity of the parents should be considered. No information was obtained about the common ancestor of the parents of the proband's father, but it is known that they came from two neighboring localities. Therefore, the hypothesis of consanguinity seems most likely in this case. Only 1 patient with homozygous F1052V mutation has been registered in the *cftr2.org* database so far [8].

The presence of the IVS8-5T variant in intron 8 in combination with the increased number of TG repeats leads to the elimination of exon 9 and the decrease in the production of mRNA for the CFTR protein [10, 11]. This is not associated with the classic presentation of cystic fibrosis, but it can lead to CFTR-related disorder. The IVS8-

-5T+11TG variant occurring in the proband's family has been reported in patients with congenital bilateral absence of vas deferens [12]. Due to the heterozygosity of this variant in the proband and his stepbrother, it seems right to observe boys for infertility. According to the European diagnostic recommendations for CFTR-related disorders in a patient with male infertility with CBAVD, the presence of one CF-specific mutation and the IVS8-5T variant is sufficient to diagnose CFTR-related disorder [13]. If the proband develops infertility in the future, it will probably be possible to make a final diagnosis.

In the presented case, the familial occurrence of a rare mutation and a polymorphic variant in the *CFTR* gene, an equivocal clinical picture, as well as normal chloride levels in sweat make the diagnosing difficult. In contrast, the proband himself, despite the presence of respiratory symptoms, has only one mutated *CFTR* gene allele. In the second one, there is a polymorphic variant that is associated with CFTR-related disorders. The patient remains under the care of a pulmonological outpatient clinic to control for clinical signs of cystic fibrosis. Due to the above features, the final diagnosis can probably be made after the exclusion or confirmation of male infertility associated with congenital bilateral absence of vas deferens. We believe that it is important to control regularly patients with known *CFTR* genotype, even if they do not present classic clinical symptoms because CF can vary over time. Also, we would like to point out the need to consider the possibility of CF in a not screened adult patient.

Conflict of interest

None declared.

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