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Letter to Editor

The Importance of Genetic Study in Cystic Fibrosis

Letter to Editor

Cystic fibrosis (CF) is the most common and fatal autosomal recessive genetic disease in euro-descendents. It affects about 85,000 people worldwide [1]. It is characterized by multiple and systemic clinical manifestations that primarily affect exocrine sweat glands, lungs and pancreas while presenting great variability in its severity [2]. It is caused by mutations in the *cystic fibrosis transmembrane conductance regulator gene* (*CFTR* gene), which encodes the cystic fibrosis transmembrane regulatory protein (CFTR), located on chromosome 7 (locus 7q31), leading to the absence or loss of CFTR function which, under normal conditions, acts as a chloride channel [3].

At present, more than 2,000 *CFTR* gene variants have been identified, of which about 300 have been characterized as definitely pathogenic [4]. Among these, the deletion of 3 base pairs that code for phenylalanine at position 508 (F508del) is the most frequent and can be found in about 80% of patients worldwide, being more common in euro-descendents [1]. Mutations in the *CFTR* gene are categorized into six functional classes according to the change in CFTR protein. In classes I, II and III, there is no protein production, causing a more severe disease pattern, whereas in classes IV, V and VI, the protein produced is defective but remains with some function [2]. However, this classification has been reconsidered and a seventh functional class has been proposed, which would contemplate larger gene depletions [4].

In the last years great progress has been made towards understanding the pathogenesis of CF, leading to the emergence of several therapeutic advances, which include the use of mucolytics, inhaled antimicrobials and systemic anti-inflammatory drugs that play an important role in increasing patients' life quality and expectancy. Likewise, advances have been made in the search for drugs that may act directly on the molecular defect that causes the disease. There are two types of CFTR modulator treatments (potentiators and correctors) approved for human use by the United States Food and Drug Administration (FDA) and they target the defective transport of ions in their various stages of impairment[4]. Potentiators enhance the function of CFTR protein, which is expressed on the plasma membrane (class III to VI mutations), while the correctors improve abnormal CFTR protein that is not expressed in the cell membrane (class I and II mutations).

Ivacaftor is a potentiator, initially studied in patients with the G551D (class III) mutation. The use of this drug in patients with CF demonstrated a reduction in sweat chloride levels while improving FEV_1 and weight gain; In addition, there was a reduction in the number of exacerbations and increase in quality of life [5]. Subsequently, drug indication was broadened to other mutations and more recently its use has been approved for other class III and IV mutations. At this moment ongoing studies are investigating the possible use of Ivacaftor in class II, IV and V mutations [4].

Lumacaftor was the first CFTR-corrector tested in individuals homozygous for the F508del (class II) mutation. The clinical response in these patients was not significant, evidencing that the Lumacaftor was not effective as a single agent. Therefore, the Ivacaftor/Lumacaftor association (potentiator / corrector) was tested in patients with this mutation and demonstrated a reduction in the number of exacerbations, a slight improvement in FEV_1 and quality of life for homozygous patients, but without significant effects on heterozygotes [6]. Since 2015, the use of this combination has been approved by the FDA for F508del4 homozygous patients.

The onset of CF signs and symptoms may vary, from the first weeks of life to adulthood. Manifestations in pulmonary and gastrointestinal systems, growth retardation and developmental delays, associated with positive sweat chloride tests (above 60 mEq/L), are considered to be classic presentations of the disease [7]. Nonetheless, clinical manifestations may be mild and present only in one organ or system and sweat test might be normal or intermediate (30 to 59 mEq/L), characterizing atypical CF [7,8].

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Moreover, it can occur a monosymptomatic clinical entity (congenital bilateral absence of the vas deferens/pancreatitis/bronchiectasis) associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF (CFTR-related disorder) [9]. The study of mutations in *CFTR* is of great importance for the diagnosis of these forms of the disease.

The great variability in CF expression among individuals with the same genotype suggests that in addition to the variation in severity produced by the effects of different mutations and intragenic polymorphisms in the *CFTR* gene, other genetic elements such as polymorphisms in non-*CFTR* genes responsible for the innate response could be modulating the expression of this disease [10]. Recently, studies with modifier candidate genes have been developed trying to associate the relationship between genotype/phenotype variability. Some genes have already been associated with specific clinical manifestations: obstructive pulmonary disease (TGFβ1, MBL2, EHF, APIP, SLC9A3, SLC6A14, MC3R, CASS4, AURKA); intestinal obstruction (MSRA, SLC6A14, SLC9A3); CF-related diabetes (TCF7L2, CDKAL1, CDKN2A / B, IGF2BP2, SLC26A9); infection by *Pseudomonas aeruginosa* (MBL2, DCTN4, SLC6A14); (Chr1p36.1 and Chr5q14) [10]. Also, the environment can be considered a disease modifier [10]. These findings emphasize even more the importance of a personalized medicine for the diagnosis and treatment of CF.

As a result of increased life expectancy many women have reached reproductive age. Men with CF have infertility due to obstructive azoospermia but can also have children with the aid of assisted human reproduction techniques [7]. The risk of a person with CF having affected children depends on their partner, thus in addition to the other benefits of the study of mutations in the *CFTR* gene already described Genetic Counseling (GC) is also of great importance. GC, besides contributing to the understanding of CF and its medical, psychological and family implications, includes the provision of information about the disease (such as estimating the risk of recurrence for future pregnancies in both the couple and other family members), support in accepting the diagnosis and also presents alternatives for prevention (such as pre-implantation diagnosis) [7].

The relevance of the genetic study in CF can be summarized as: a) in patients with established CF diagnosis, for indication of mutation-specific therapy and prognostic determination (genotype-phenotype correlation), including the study of non-*CFTR* modifying genes; b) investigation of atypical CF forms/CFTR-related disorder; c) GC when one of the spouses has CF or is an asymptomatic *CFTR* mutation carrier and for asymptomatic individuals who are first, second or third degree relatives of affected individuals; d) pre-natal/pre-implantation diagnosis of CF: in future gestation or current gestation, for couples who already have CF children and for heterozygous couples if the test cannot be performed on a child with CF, in embryos of heterozygous couples or when the fetus presents hyperechogenic intestine, dilatation of intestinal loops, growth retardation or overgrowth suggestive of uniparental disomy [7].

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