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An Overview of the Homozygous Cystic Fibrosis Transmembrane Conductance Regulator Mutation c.3700 A>G (p.Ile1234Val) in Qatar

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Abstract

Purpose of Review Cystic fibrosis (CF) is a monogenic recessive disease with multisystem involvement. The cause is a mutation in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The aim is to review the literature involving the CFTR I1234V mutation and to provide recommendations for future research activities.

Recent Findings The prevalence rates of CFTR mutations vary across the globe. The CFTR I1234V mutation is the most common mutation in Qatar, and one of the most common in the Arabian Gulf region.

Summary Areas for future research include testing of the CFTR transcript and activity levels in different samples including nasal cells and organoids. Another area is applying Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology as a tool for gene editing.

Keywords Cystic fibrosis · CFTR · CFTR mutation · CFTR I1234V

Introduction

Cystic fibrosis (CF) is a hereditary disease with multisystem involvement [1]. The cause is a mutation in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein [1]. The number of CFTR gene mutations exceeds 2000 so far [2]. CF involves the presence of two disease-causing mutations on two separate chromosomes [3]. The CFTR gene was initially discovered in 1989, and is located on chromosome 7q31.2 and is comprised of 27 exons [4–6].

A comprehensive assessment of the CFTR mutations across the globe showed variations in prevalence rates for the various CFTR mutations [7]. Globally, the F508del is reported to be the most common mutation [8]. F508del was the commonest mutation among European patients in a study that described the spectrum of mutations among more than 25,000 patients [9]. The F508del mutation is also the most common in Latin America [10].

A range of mutations exist across Arab countries [11]. The spectrum of these mutations was recently described in a systematic review [12•]. The Middle East hosts several mutations, some of which are shared with other global regions, such as F508del, N1303K, W1282X, and 3120+1G>A, while others are less common globally, such as I1234V which is reported to be common among certain Arab tribes [10], 1548delG in Saudi Arabia [13], 2043delG in Bahrain [14], or S549R(T>G) in Oman [15].

CFTR I1234V Mutation

Scientists have identified the CFTR I1234V mutation (p.Ile1234Val, c.3700A>G) [16] among patients from Qatar [17], Saudi Arabia [18, 19], France [20], and Israel [21]. In Qatar, 65% of the pediatric CF patients are homozygous for the CFTR I1234V mutation [22]. The I1234V mutation is a missense mutation in exon 19, at nucleotide position 3700, where adenine is replaced by guanine, resulting in the

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substitution of isoleucine by valine at codon 1234 in the mature CFTR protein [17].

The first report of a heterozygous I1234V mutation was in 1992, in a patient that was initially diagnosed at the age of 2 years. The patient carried the ΔF508 allele on the maternally inherited chromosome and presented with the following clinical features: severe pulmonary status, growth retardation, and presence of *Pseudomonas aeruginosa* [20]. The mutation was also described in 1997 as a homozygous I1234V mutation which was found in two sisters from Saudi Arabia, presenting with symptoms of recurrent diarrhea as well as failure to thrive [18]. More than a decade later, a study found a truncated exon 19 (r.3700_3717del; p.Ile1234_Arg1239del) which was similar to p.Phe508del, causing a primary defect in folding and processing [23].

Saudi patients with the I1234V mutation were described in another study to have nasal polyps, pansinusitis, and lung disease [13]. Subsequent studies reported on two Yemenite Jewish patients with the I1234V mutation, one had ΔF508 as the second mutation, while the second patient had W1282X as the second mutation [21]. Another study reported a 1:130 carrier frequency for the I1234V among Yemenite Jews [24].

The Clinical and Functional TRanslation of CFTR Database

The Clinical and Functional TRanslation of CFTR (CFTR2) database contains information on CF patients worldwide; this includes 28 patients with the I1234V variant [16]. The CFTR2 website indicates that those with the I1234V variant and a CF causing variant have a slightly lower average sweat chloride (94 vs. 96 mEq/L), but higher average age (22 vs. 20 years) when compared to the average for all patients with two CF causing variants [16]. As for lung function among patients with the I1234V variant, the website reports a forced expiratory volume test (FEV1%) predicted values of (68–118%, 32–103%,) for ages 10–20 and more than 20 years, respectively, while the FEV1% values for those with two CF causing variants are (42–118%) and (25–104%) for the same age groups [16]. Additionally, 40% of those with the variant I1234V were pancreatic insufficient, compared to 85% of all other patients in the database [16]. The rate of infection with *Pseudomonas aeruginosa* was 35% for those with the I1234V variant compared to 55% among all other patients in the database [16].

CFTR I1234V Mutation Milestones in Qatar

In 2000, a study conducted on 45 CF patients showed that Qatari's have mild to moderate CF when compared to non-Qatari's. The majority of patients suffered respiratory symptoms including cough (91%), crackles (64%), and recurrent chest infections (58%). Other characteristics of the sample included failure to thrive (51%), chronic diarrhea (20%), metabolic alkalosis (38%), and vomiting (20%). Radiographic findings included diffuse pulmonary infiltrates (36%), hyperinflation with peribronchial thickening (31%), normal chest X-ray (18%), atelectasis (9%), and bronchiectasis (7%) [25].

Later on, the homozygous I1234V mutation in exon 19 was discovered in 29 patients from 17 families from the same Arab tribe [17]. The rate of consanguinity among participants of the study was reported to be 96.6%, as parents were reported to be first degree cousins in 16 families. The majority of the sample presented with respiratory symptoms including cough (89.7%) and recurrent chest infections (55.2%). Other characteristics included metabolic alkalosis (44.8%), recurrent wheezy chest in early life (37.9%), and failure to thrive (34.5%) [17].

In 2003, a case report of late diagnosed CF in a multiparous Qatari lady at the age of 35 years, in whom the presenting symptom was chronic lung disease with bronchiectasis, suggested that the I1234V mutation has a variable expression of clinical severity and long survival [26]. Moreover, patients with the CFTR I1234V mutation are characterized by pancreatic sufficiency, as one study showed no statistical difference between fecal elastase-1 (FE1) levels of 40 CF patients from a large Arab kindred family compared to 25 controls [27]. Other research involved measuring sweat chloride levels, as one study reported a significantly higher mean among 41 CF patients homozygous for the I1234V mutation compared to 18 controls (99.2 ± 8.3 mmol/L vs. 15.4 ± 6.7 mmol/L) [28].

Several studies examined the microbiology of patients with the I1234V mutation, one of which reported that the most predominant pathogens among 36 CF patients were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Haemophilus influenzae* [29]. *Alcaligenes xylosoxidans*, *Stenotrophomonas maltophilia*, and *Mycobacterium abscessus* were among the unusual pathogens found in another study [30]. A third article studied the antimicrobial resistance patterns of multidrug-resistant *Pseudomonas aeruginosa* in 30 patients (83.3% were homozygous for the I1234V mutation), and found the following resistance rates: colistin (0%), piperacillin-tazobactam (50%), meropenem (53%), tobramycin (75%), ciprofloxacin (91.7%), gentamycin, amikacin, cefepime (100%) [31].

A fourth study showed a high prevalence rate of *Candida dubliniensis* in secretions of the lower respiratory tract of CF patients [32]. A fifth study showed that patients with persistent *Candida dubliniensis* had a higher BMI and lower FEV1 when compared to patients with intermittent *Candida dubliniensis* [33]. A sixth study conducted on 26 patients with the I1234V mutations showed a *Pseudomonas aeruginosa* infection rate of 61.5% and an FEV1 mean of 82.9 ± 14.7% [34].

Other research conducted on patients with the I1234V mutation involved assessing serum zinc levels. A study conducted on 45 CF patients homozygous for the CFTR I1234V

mutation reported a mean zinc level of 0.78 ± 0.15 mcg/mL. The study also reported that patients diagnosed with hypozincemia (n = 7) had more respiratory exacerbations and more frequent colonization by *Pseudomonas aeruginosa* [35]. Another study with 40 CF patients with the I1234V mutation found them to be characterized by normal linear growth, as well as normal body mass index (BMI). However, the study found them to have a high prevalence rate of vitamin D deficiency [36].

Furthermore, a study that was conducted to assess fractional exhaled nitric oxide (FENO) levels among patients homozygous for the CFTR I1234V mutation and controls found the former to have significantly lower levels when compared to the latter, with females having significantly higher levels when compared to males [37]. Another study found a positive correlation between adiponectin levels in sputum and plasma, and negative correlation between BMI and adiponectin levels in sputum and plasma [38].

Conclusions

Areas for future research include testing of the CFTR transcript and activity levels in different samples including nasal cells and organoids [39•] among patients with the CFTR I1234V mutation, as studies have shown that organoids may be used for the development of personalized treatment for patients with CF [40•, 41•]. Applying Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology as a tool for gene editing along with its promising results as shown elsewhere on other mutations [2] is yet to take place for the CFTR I1234V mutation. In conclusion, a better future for CF patients worldwide and locally in Qatar is contingent upon intensifying research efforts and expanding on current collaborations.

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Compliance with Ethical Standards

Conflict of Interest Samer Hammoudeh, Wessam Gadelhak, Atqah AbdulWahab, Mona Al-Langawi, and Ibrahim A. Janahi each declare no conflict of interest.

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Abbreviations BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator,; CFTR2, Clinical and Functional TRanslation of CFTR; CRISPR, clustered regularly interspaced short palindromic repeats; FE1, fecal elastase-1; FEV1, forced expiratory volume test; FENO, fractional exhaled nitric oxide.

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