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Meta-Analysis of Prevalence of CFTR Mutations in Middle East Populations

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ABSTRACT

Cystic fibrosis (CF) is a progressive, genetic disease that causes persistent lung infections and limits the ability to breathe over time. In this study, we performed a systematic review and meta-analysis of middle east CFTR gene mutations in CF patients to find out the most common mutations in this area. Tree mutations are common in all middle-east populations: Del 508, W1282X and N1303K which can have detection rate as high as 60.9 %.

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Introduction

Cystic fibrosis (CF) is a chronic and life-limiting autosomal recessive disorder which is characterized by irregular viscous excretions in the lungs, bronchial airways, and pancreatic ducts, as well as, organs consisting of epithelia such as the liver, biliary duct, male reproductive system and intestinal tract [1-2].

These infective exudations caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* lead to eventual obstructions, inflammation, and irreversible destruction of lung parenchyma [3]. Lung obstruction and degradation accounts for approximately 80% of mortality in patients with CF [4]. Approximately 70,000 individuals worldwide are affected by CF with a affects 70,000 individuals worldwide, with a higher prevalence in pediatric individuals deriving from Western Europe [3, 5-6]. African, South Asian and South East Asian groups are less frequently affected by CF [7-8].

It has been reported that gene flow between European and non-European populations has complexified CF inheritance due to differences in CF producing mutations between these populations [3, 9]. Current median survival rates for individuals with Cystic Fibrosis is 36.8 years [10]. Due to medical improvements and better understanding of CF, more individuals with the disease are entering middle age. For example, in the United Kingdom adult patients with CF exceed children with CF. Additionally, survival rates for patients with CF improve by five years for each successive decade [3, 11]. Cystic fibrosis (CF) was described by Fanconi in 1936. However, in 1938 Dorothy Anderson made a more detailed description of CF symptomatology [12].

In 1953, Paul di Sant'Agnese developed a sweat test (where excess levels of sodium chloride were measured in pediatric patients) for diagnosing CF, which has remained a gold standard for CF identification [1] . In 1989 the CFTR (cystic fibrosis transmembrane conductance regulator) gene was found to be responsible for CF via cloning techniques, having been identified on chromosome 7 (7q31) [13-14]. The CFTR gene comprises 27 exons covering approximately 190 kb of chromosome 7, encoding 1,480 amino acids [15-16].

Approximately, 2,000 CFTR variants have been identified. Of these 36% are anticipated to modify RNA processing, 40% which may lead to single amino acid replacement and 14% which are neutral variants [1]. These variants are classified according to a class system (five or six classes) which provides a functional framework for understanding the degree of molecular defect [1, 17]. The ΔF508 mutation is the most frequent CF variant. The CFTR gene is highly expressed in the epithelium of fetal organs such as the pancreatic duct, lung parenchyma, small intestinal crypts, while there are lower levels of CFTR gene expression in the fetal epididymis [15].

The mechanism of CFTR gene variants considerably decrease Cl permeability in exocrine cell epithileum. Identifying CFTR mutations has contributed to diagnosing cystic fibrosis in the first instance, as well as identifying CFTR carriers [1, 18]. It is now evident that that the degree of CFTR expression correlates with clinical symptoms in CF [19]. This meta-analysis examines the rate of prevalence of CFTR mutations in middle-eastern populations. An aim of this study is to propose cost effective methods in detecting CFTR mutations especially in the Kurdistan region of Iraq where diagnosis and treatment of individuals with CF is expensive and may procure catastrophic medical costs.

Materials and Methods

This research attempts to survey variety of mutation in CFTR genetic disorder among Middle East different countries and populations, include, Arab countries such as Saudi Arabia, Jordan, Bahrain, Qatar and also other countries like Iran, Israeli, Lebanese, Palestine. Specifically, highlights the most important mutations with high percentage in CFTR patients, in addition, also tries to emphasize the rapid and less costly detection method. Final analyses were based on 72,431 CF chromosomes, using data compiled from over 100 original papers, and over 80 regions from around the world, including all nations where CF has been studied using analytical molecular genetics. Initial results confirmed wide mutational heterogeneity throughout the world; however, characterization of the most common mutations across most populations was possible. We also examined CF incidence, DF508 frequency, and regional mutational heterogeneity in a subset of populations. Final analyses were based on 1181 CFTR patients from different countries, using data

compiled from over 50 original papers published in last ten years, and 11 countries from Middle East, where CF has been studied using analytical molecular genetics.

Results

Table 1

Spectrum of Most Common Mutations or Genotype Reported in the Cystic Fibrosis Patients [41]

Class	Effect	Mutations		
1	Defective CFTR protein and does not reach the cell surface	G542X	W1282X 1717-8G->A 1898+3A->G	R1162X CFTRdel9
2	Total loss of protein because of incorrect processing of CFTR	F508del	N1303K	R1066C
3	Deregulates the ion channel	No mutation reported in middle east		
4	Reduced ion fluxes and altered selectivity	R334W	R117H	
5	Functional proteins with normal chloride channel activity but reduced rate of synthesis	2789+5G->A	3849 + 10kbC->T	
6	Reduced expression of mutated CFTR protein because of rapid removal from the apical membrane	No mutation reported in middle east		

Table 2
Important Mutational Finding in Cystic Fibrosis in the Middle East

Country	Year	Authors	Major CFTR Mutation
Iran	2007 2017 2013	[20] [21] [22]	ΔF508 2183AA→G N1303K G542X 3120+1G→A 2789+5G→A
Lebanese	2010	[23]	ΔF508 N1303K w1282x 4016insG S4X
Jewish	2005	[24]	w1282x ΔF508 G542X N1303K
Arab communities	1997	[25]	ΔF508 w1282x 4010del4 N1303K
UAE	2015	[26]	ΔF508 S549R
Saudi Arabia	2015	[26]	ΔF508 N1303K S549R 1548delG 3120+1G→A I1234V
Palestine	2015	[27]	3120+LKdel8.6kg
Jordan	2015	[26]	ΔF508
Bahrain	2015	[26]	2043delG
Qatar	2015	[26]	I1234V
Israeli	1999	[28]	ΔF508 N1303K 3120+LKdel8.6kg w1282x 2183AA→G

The most common CFTR mutation diagnosed in United States and Europe is F508del, which consist of 50%-80% of the CF population [29], While the result for Middle East were different, so that indicates F508del, N1303K and W1282X are most common mutations.

Discussion

The incidence of CF in the Middle East varies according to the ethnic background and the degree of consanguinity. Consanguinity is claimed to be approximately 65% in the Arab world. Estimates range from 1 in 2,560 to 1 in 15,876. A few mutations in the Middle East are shared in other regions in the world, i.e. F508del, N1303K and W1282X. Although F508del is more frequent in Europe than in the Middle East, it is relatively common in Israel and Lebanon. Alternatively, 3120+1G>A is more frequent in individuals of African descent and may have spread from African to Arabic

populations. There are mutations that appear to be more spread in the near and Middle East but are rarely observed elsewhere. In some cases, these more frequent mutations may be specific for a subset of the people in the Middle East defined by a common ethnic or religious background, e.g. Christian Arabs in case of 4010delTAAT, the S549R(T>G) mutation in Jewish population, the 2183 AA>A mutation in Iran, and the 3849 IVS19 mutation in Jewish population. Thus, CF further illustrates that, in addition to its indigenous founder mutations, the geographic location and ethnic admixture has made the Middle East a "melting pot" of different genetic influences from non-middle eastern countries and over time.

According to this study sequencing of 4 to 6 exons of 27 exons in CFTR gene can detect mutations in 74% of CF patients (53.79%-96.65%). It is also evident that Jewish population detection rates are higher than other populations. This may be due to more consanguinity marriage in the Jewish population and also immigration of European Jewish to this area.

Tree mutations are common in all middle-east populations: Del 508, W1282X and N1303K which can have detection rate as high as 60.9 %. For example, in Iranian populations there is small differentiation due to mixed ethnicity which increases detection rate to 70.74%.

Furthermore, Iranian populations indicate that the different types of mutations in CFTR gene are dependent on 1(different ethnicities 2) less consanguinity marriage compared to other Middle-Eastern countries. Most compound heterozygosity mutations are detected 3) less severity of clinical symptoms.

Conflict of interest

None

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