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Review

A comprehensive review of cystic fibrosis in Africa and Asia

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ABSTRACT

Cystic fibrosis (CF) was earlier thought to be a disease prevalent in the West among Caucasians. However, quite a number of recent studies have uncovered CF cases outside of this region, and reported hundreds of unique and novel variant forms of *CFTR*. Here, we discuss the evidence of CF in parts of the world earlier considered to be rare; Africa, and Asia. This review also highlighted the *CFTR* mutation variations and new mutations discovered in these regions. This discovery implies that the CF data from these regions were earlier underestimated. The inadequate awareness of the disease in these regions might have contributed towards the poor diagnostic facilities, under-diagnosis or/and under-reporting, and the lack of CF associated health policies. Overall, these regions have a high rate of infant, childhood and early adulthood mortality due to CF. Therefore, there is a need for a thorough investigation of CF prevalence and to identify unique and novel variant mutations within these regions in order to formulate intervention plans, create awareness, develop mutation specific screening kits and therapies to keep CF mortality at bay.
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1. Introduction

Cystic Fibrosis (CF) was initially predominantly recorded within Caucasians of Northern and Western European ancestry (Fernald et al., 1990). Startlingly, recent studies revealed the possibility of more CF cases in regions earlier presumed to be rare. This includes Africa (De Boeck, 2020) and Asia (Banjar et al., 2021). According to CF registries in many of the European countries, it is evident that immigrants from both Africa and Asia have been diagnosed with CF especially in the UK, US, and France (Mekki et al., 2021). More studies have also reported CF cases in Africa and Asia, with some rare and novel mutational variants specific to some ethnic groups (Mathew et al., 2021).

Furthermore, recent studies from the non-Caucasian regions, especially the West Asia and some countries in North Africa that form the Middle East geopolitical zone (the Arab ethnicity), have reported incidence similar to the West (Banjar et al., 2021). This implies that CF might be underestimated in many parts of the world probably due to early Caucasian perception, poor diagnostic tools, lack of medical awareness, under-diagnosed or/and under-reporting (Stewart and Pepper, 2016), or probably due to the lack of CF associated health policies. These regions are presently facing similar challenges earlier recorded by the West from fifty years ago when more than 90% of infants with CF died from persistent diarrhoea and chronic malnutrition due to pancreatic failure before their second birthday (Mehta, G., Macek, M., Jr, Mehta, A., & European Registry Working Group, 2010).

Cystic Fibrosis is grouped into seven classes, denoted as class I–VII, depending on the cellular phenotype and prognostic consequences. These classes are based on either the molecular protein translation, cellular processing, or gating of the CFTR (Wei et al., 2020). Many CFTR variants go unclassified as more unique and novel variants are continuously identified around the globe (Maiuri et al., 2017). Understanding and designing therapies for specific defects have benefited thus far from this classification (Cooney et al., 2018). Class I–III and VII variants typically cause the severe type form of CF, whereas classes IV–VI mutations cause the milder form of CF (Marson et al., 2016).

This review discusses the general outlook of the CF incidences and novel *CFTR* mutations identified from parts of the world earlier considered to be rare; this includes Africa and Asia. We therefore emphasize the need for a thorough investigation of CF prevalence, and identification of unique and novel mutations within these regions. Optimistically, this should assist in the development of intervention plans, and mutation-specific diagnostic kits and drug/therapy.

2. Cystic Fibrosis in Africa

Evidence of CF in Africa dated back to the late 1970s in both the white and black population (Super, 1975), with the European c.1521_1523delCTT(p.Phe508del) variant diagnosed as the most common (more than 80%) among the white population than the coloured CF cohort (Herbert and Retief, 1992). Several other CF variants were identified among native African in diaspora, African-Americans, and African-Europeans (Stewart and Pepper, 2016). According to the newborn screening (NBS) cohort in France, the incidence of CF among people of African descent increased from 1% in 2000 to 10% in 2019, with the most notable variant identified was the c.2988 + 1G>A (3120 + 1G>A), which was most prevalent in patients of Congolese origin (Mayer Lacrosniere et al., 2021). The variant c.3197G>A (p.Arg1066His), c.3607A>G (p.Ile1203Val), c.273 + 4A>G (p.Gly91 =), c.579 + 1G >T (711 + 1G>A), c.C233dup, c.1657C >T (p.Arg553X), and c.54-5940_273 + 10250del21kb (p.Ser18ArgfsX16; CFTRdel19-21) were other variants found in this cohort in patients with Congo, Sierra Leone, Cameroon, Senegal, Côte d'Ivoire and Mali ancestry respectively. Another study from France of a CF cohort of patients with diverse ethnic backgrounds and racial origins has identified novel variants, such as c.2991G>C (p.Leu997Phe) North Africa and c.4230C>A (p.Cys1410) from Sub-Saharan Africa. The c.2290C >T (p.Arg764) variant was also discovered in patients with Sub-Saharan African ancestry. This novel variant was recently discovered in an African-American patient (Mayer Lacrosniere et al., 2021). Although the majority of countries in Sub-Saharan Africa have not reported any incidents of CF to date, this suggests the potential existence of disease in that region.

Presently, the Northern (Morocco, Algeria, Tunisia, Libya, Egypt & Sudan) and Southern (Namibia, Zimbabwe, & South Africa) sections of Africa account for the majority of the continent's CF statistics (Stewart and Pepper, 2016). Preliminary statistics are currently available from three countries in Western Africa (Senegal, Ghana, and Cameroon) and one country in Eastern Africa (Rwanda) (Stewart and Pepper, 2016; Owusu et al., 2021). Historically, South Africa was the first country to report cases of CF in Africa, with white populations experiencing a higher incidence of the disease (70%) than coloured populations (0.7% Indians and 9.7% Blacks), and mixed-race populations (19%) (Zampoli et al., 2021). The c.1521_1523delCTT accounts for 63.1% all variants identified in South Africa, found at 58.1% homozygous and 32% compound heterozygous states. It was the most prevalent variant in the white population (76%) (Zampoli et al., 2021). The c.2988 + 1G>A (9.5%) variant was the second most common in the black population, presenting mostly (56.1–67.6%) in homozygous state (Zampoli et al., 2021; Van Rensburg et al., 2018). Furthermore, c.3140-26A>G (3272-26A>G) was found to be the second most common (3.98%) variant in the white South African population. Other variants discovered included c.1585-1G>A, c.2374C >T (p.Arg792X), c.3731G>A (p.Gly1244Glu), c.2051delA (p.Lys684SerfsX38), and c.3064_3117delGTGATAGTGGCTTTTATTATGTTGAGAGCATATTTCCTCCAAACCTCACAGCAA (p.Val1022_Gln1039del) (Owusu et al., 2021; Zampoli et al., 2021). A novel large CFTR2,3(21 kb); c.54–1161-c.1603del2875 (5.56%) was discovered in the black South African population (Van Rensburg et al., 2018). Several other variants were identified within this population, however at low frequency. They are listed in Table 2.

Although the coverage CF frequency in the Northern part of Africa was not comprehensive, smaller scale studies were able to identify predominantly European variants including c.1521_1523delCTT, c.1624G >T and c.3909C>G alongside several unique/novel variants within this population (Loumi et al., 2008). In the late 1990s, a novel variant; c.422C>A (p.Ala141Asp) was identified in an Algerian patient in France (Gouyat et al., 1997). Using diagnostic sequencing, more novel and distinctive variations were identified in the Algerian population. These variants were notably diagnosed at significant high frequency in this population. They are c.2562T>C (p.Thr854Thr), c.1408A>G (p.Met470Val), c.4521G>A, and c.869 + 11C >T at 27.7%, 15.2%, 12.5% and 9.7% respectively. Other unique variants diagnosed in Algeria include c.2991G>C (p.Leu997Phe), c.743 + 40A>G (875 + 40A>G), c.1210–12T (Mathew et al., 2021), c.1584G>A, and c.3870A>G (p.Pro1290 =). Several additional common variants were also identified, most frequent include the c.1521_1523delCTT(16.7%), c.3909C>G (8.3%), c.579 + 1G >T(8.3%), and 2183AA>G at 4.2% frequency (Loumi et al., 2008).

Unlike Algeria, variants c.1521_1523delCTT (47.06–56%) and c.3310G >T (p.lu1104X) (16.18%) were the most frequent in Tunisia, alongside the common variants c.1624G >T, c.3846G>A, c.3909C>G, c.579 + 1G >T, and c.254G>A (Messaoud et al., 2005; Boussetta et al., 2018). Other variant such as c.2766del8, c.3497T>G (p.Phe1166Cys) and c.3128T>G (p.Leu1043Arg) were

exclusively found in a study of patients in Tunisia (Messaoud et al., 2005), while c.1993A >T (p.Thr665Ser) was initially exclusively identified amongst Tunisians but more recently identified in Egyptian patients (Messaoud et al., 2005; El-Seedy et al., 2017). Two more rare Tunisian specific variants identified were c.57G>A (p.Trp19X), reported in only two cases since 2013, and more recently the c.680T>G (p.Leu227Arg) (Sediki et al., 2016). Additionally, c.3607A>G, c.1679 + 5A>G (1811 + 5A>G), c.4136 + 2T>G (4268 + 2T>G) and c.3729delAinsTCT variants, were also identified among the Tunisians and the Middle Easterns. Morocco and Libya have reported only very few cases of CF from a 32 *CFTR* gene assay screening of random samples, identifying only variants c.1521_1523delCTT and c.1210–12T (Mathew et al., 2021) splicing variants (Ratbi et al., 2008). Earlier studies of Moroccan migrants in Europe were presented with c.1624G >T, c.1652G>A, c.3909C>G, and c.3846G>A variants (Estivill et al., 1997). Some of these variants were also identified in the Libyan population, with the most common were c.3310G >T (40% frequency), c.1521_1523delCTT (30%), c.1670delC (10%) and c.3909C>G (5%) (Fredj et al., 2011).

Although located in Africa, CF incidence in Egypt was mostly reported alongside the countries in West Asia constituting the Middle East geopolitician zone and also be due to ethnicity linkage. Unlike most countries in Africa, Egypt has established a CF centre at Cairo University and a registry since 2006. Since then, 27 mutations have been identified within the Egyptian population as of 2017 (Fathy et al., 2016). The most frequently identified variants were c.1521_1523delCTT (58%), 2183AA>G (10%), c.3870A>G and c.3484C >T (p.Arg1162X) at 6% each. Variants c.1364C>A, c.443T>C (p.Ile148Thr) and c.1408G>A were identified at 4% each (Sahami et al., 2014). Additionally, the c.1210–12T (Mathew et al., 2021) (28.6%) and c.3752G>A(p.Ser1251Asn) (3.6%) variants were also commonly identified in the Egyptians. Two novel mutations identified in the Egyptians were c.1766 + 3A>G (1898 + 3A>C) and c.1993A >T (Stewart and Pepper, 2016). In contrast, Sudan reported only 35 cases mainly recorded from the Northern part of Sudan (Hamouda et al., 2020), uniquely identifying c.1736A>G (p.Asp579Gly) and c.3304A >T (p.Arg1102X) mutations as the most common within the population (Stewart and Pepper, 2016).

Unfortunately, there are relatively non-existing CF reports from countries within the Central, Western and Eastern parts of Africa. However, there are few studies conducted in South Africa and Europe which reported cases of patients from these African regional origins. Variants identified in patients with Central African ancestry include c.2988 + 1G>A, c.3327C>A (p.Tyr1109Ter), c.273 + 1G>A, c.1521_1523delCTT and c.273 + 4A>G (p.Gly91 =) identified in Cameroonians (Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021), while variants c.3197G>A, c.399insT, c.2988 + 1G>A, c.287C>A (p.Ala96Glu), and c.933C>A (p.Phe311-Leu) were identified in the Congolese (Mayer Lacrosniere et al., 2021). Studies in South Africa have recorded CF in patients of Malawi, Zimbabwe, Mozambique (Owusu et al., 2021) and Botswana origins (Super, 1975). Novel variant (c.541161-c.164 + 1603 del2875) was identified in a Zimbabwean patient, alongside the common c.2988 + 1G>A (Stewart and Pepper, 2016). A number of variants were earlier identified in Rwandan patients, some of which are known variants as listed in Table 2. Additionally, novel variants were also identified; these include c.610G>A (p.Ala204Thr), *V348M, T577T*, c.3468 + 5G>A (3272–32T>C), c.*2G>A (4575 + 2G>A), and c.1176 + 30G>C (Ser212Ser) (Mutesa et al., 2009).

Countries in Sub-Saharan Africa lack the availability of sweat testing, which might be a major barrier in diagnosing CF in the region (Owusu et al., 2021). Nonetheless, there were evidences of CF in this region following diagnosis in patients of Sub-Saharan Africa descends in other countries. For instance, a study conducted in South Africa reported CF in a patient of West African descendants of Ghana (Owusu et al., 2020). This finding led to CF screening in Ghana, which resulted in the discovery of positive CF cases with the identification of variants c.1364C>A (p.Ala455Glu), Exon 12d deletion, c.1397C>A or c.1397C>G (p.Ser466X) and c.1373G >T (p.Gly458Val) (Owusu et al., 2021). More CF variants were identified in patients of West African descent, including IVS2 + 28A>G, c.(2988 + 1_2989-1)_(3468 + 1_3469-1)del (Ex17a-Ex18del), c.4136 + 1G>A, 711 + 1G>A, and c.4230C>A in Senegalese. While c.3700A>G and c.1521_1523delCTT variants were also identified in patients of Sierra Leone descend in France (Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021). Furthermore, c.1657C >T, CFTRdel19-21, c.3745delC (3745delC) and c.4242 + 1G>A were identified in the West African descendants of Mali, while c. C233dup variant in patients of Côte d'Ivoire descend (Mayer Lacrosniere et al., 2021).

Variant c.2988 + 1G>A has earlier been linked to the black Africans, with a detection frequency of 40% and 12% in patients of African and European descents, respectively (Stewart and Pepper, 2016). This is supported by data from the West, with the highest frequency (12.3%) detection among African-Americans and in native African patients (Macek et al., 1997). Conversely, the common European variants: c.3846G>A, c.1624G >T and c.3909C>G, were found to be genetically linked to the Arabs of North Africa and to the Caucasians of South Africa through the Mediterranean ancestry (Van Rensburg et al., 2018). Similar to the Caucasian CF, c.1521_1523delCTT is a recurring variant amongst Africans. Other variants common in Africa include c.254G>A(p.Gly85Glu), c.1679 + 1G>C (1811 + 1G>C), c.1210-1G>C(1342-1G>C) (Stewart and Pepper, 2016), c.1652G>A and c.350G>A(p.Arg117His) (Maiuri et al., 2017). Although only a handful of countries in Africa have reported CF cases, the majority of these countries have reported a diagnosis of novel mutations with 100% frequency such as c.1609delA in Algeria, EX17a-EX18del in Senegal, and c.3327C>A in Cameroon (Stewart and Pepper, 2016).

There are no published CF data from many countries in the Western and Central Africa. For instance, a PubMed search review on Nigeria conducted by Akanbi and colleagues (2009) using "*Nigeria and Lung*" resulted in no indexed report of CF cases from the country. Another study by Oguonu et al. (2014) reported no record of CF from a 5-year (2007–2012) hospital data analysis on the prevalence of paediatric respiratory conditions (Oguonu et al., 2014). However, based on anecdotal reports, there have been a few undocumented cases of suspected CF child mortality from the country. Although there is no published current report of CF in Kenya, two cases of CF in patients of Kenyan descent were reported in 1959 (Paodoa et al., 1999).

3. Cystic Fibrosis in Asia

Cystic fibrosis in Asia is reported to be rare as confirmed by data from the West, where fewer people with Asian ancestry have CF (<1% incidence in the UK). Those with CF show relatively milder clinical manifestations as compared to the other populations (Bosch et al., 2017). The incidences of CF among Asian immigrants in Canada, the United Kingdom and United State were 1 in 9200, 1 in 10, 000, and 1 in 40, 000, respectively (Singh et al., 2015). A number of *CFTR* mutational variants have been identified among the Asian population, with the common variant c.1521_1523delCTT recorded at low frequency (Singh et al., 2015).

3.1. Cystic Fibrosis in Western Asia (The Middle East)

A study by Hammoudeh *et al.* collectively summarised the incidence rate of CF from the past few decades in some Arab countries both in West Asia and North Africa, which are categorized as the

under the Middle East geopolitical zone due to their ethnic similarities (Hamouda et al., 2020). The study found that the CF incidence in the West Asia ranges from 1 in 2500 to 1 in 16,000 live births. This includes Bahrain at 1:5800–7700, Jordan 1:2560, Kuwait 1:3500, Oman 1:2410, Saudi Arabia 1:4243, United Arab Emirate (UAE) 1:15876, Egypt 1:2664, and Morocco 1:1680 live births (Hamouda et al., 2020). Even though the F508del variant was not the most common, it was a common variant among the Arab countries both in West Asia and North Africa that include Saudi Arabia, United Arab Emirates (UAE), Oman, Lebanon, Jordan, Syria, Qatar, Algeria, Egypt, and Tunisia (Banjar and Angyalosi, 2015; AbdulWahab et al., 2021).

A study from the Kingdom of Saudi Arabia identified CF cases with a few novel variants that include; c.1418del (p.Gly473fs) which identified (17–20%) as the most common variant in the country (Banjar et al., 2021; Banjar and Angyalosi, 2015). Other novel variants identified include c.416A >T (p.His139Leu) which is unique to Saudi Arabia, c.579 + 1G >T, and c.1507del9 (Banjar and Angyalosi, 2015). These variants have different geographical distributions; c.1418del being most common in the Northern part, c.3700A>G in the Central, Southern and Western parts, while c.2988 + 1G>A in the Eastern part of Saudi Arabia (Banjar and Angyalosi, 2015). The latter variant (c.2988 + 1G>A) had an ancestry origin linked to Africa (Alibakhshi et al., 2008). Variants such as c.254G>A, c.I507del9, and c.3909C>G (Lopes-Pacheco, 2020) were common in the West and the Mediterranean. Some of the other common variants identified within population of Saudi Arabia were c.3700A>G, c.2988 + 1G>A, c.579 + 1G >T, c.416A >T (p.His139Leu), c.1911delG (p.Gln637HisfsX26), c.1645A>C (p.Ser549Arg), and c.1652G>A at 12%, 11%, 9%, 6%, 5% and 1.5% respectively (Banjar et al., 2021).

Variant c.3700A>G was identified as the most common (65–66.7%) within population in Qatar (Hamouda et al., 2020; AbdulWahab et al., 2021). This variant was first described in South France (AbdulWahab et al., 2021). The c.1521_1523delCTT variant (15.5%) was also identified within the population of Qatar. The other variants identified in Qatar are also listed in Tables 1 and 2. The United Arab Emirates (UAE), unlike the neighbouring Saudi Arabia and Qatar, lacked a comprehensive study on CF. Only one article reported of a rare variant c.1647T>G (p.Ser549Arg), which was diagnosed heterogeneously in all CF patients while heterogenous c.1521_1523delCTT mutation was diagnosed in 80% of all cases (Frossard et al., 1998).

One CF case was reported in Kuwait in 1973, eight in 1977 and a few more in the 1980 s at an incidence of 1 in 3500 live births (Kollberg, 1986). However there are no recent available records of incidence and type of variants from Kuwait. Similarly, Bahrain lacks recent records on CF, with the most current incidence at 1 in 5800 live births as at 2002 (Eskandarani, 2002). Unlike Kuwait, some variants have been identified in Bahrain, with 2043delG (30.8%) variant as the most common, followed by p.His139>Leu (548A >T) and c.4041C>G (4041C>G), each at 19.3%. Others variants identified include c.1521_1523delCTT (7.7%), c.1161delC, c.1624G >T (p.Gly542Ter), c.2988 + 1G>A, and c.3529A >T (p.K1177X) variants, at 3.8% each (Eskandarani, 2002). In Oman, c.1647T>A (p.Ser549Arg) (75%) and c.1521_1523delCTT (14%) variants were the most common identified variants, similar to that recorded in the UAE. (Frossard et al., 1998) Variants c.1733-1734delTA and c.1175T>G (p.Val392Gly) identified at the rate of 7% and 4%, respectively, are both rare and novel (Fass et al., 2014). Tow addition novel variants; c. 4242 + 1G>C (Fass et al., 2014; Al Balushi et al., 2021) and c.575A >T (Al Sa'idi, L., Al Busaidi, N., Al Bimani, M., 2021); were also identified within the Omanis. Recently, c.2988 + 1G>A, L578delTA, c.1069G>A (p.Ala357Thr), and c.3718-2477C >T variants were identified for the first time within Omanis (Al Balushi et al., 2021).

Jordan recorded a low frequency of c.1521_1523delCTT (7.4%) as compared to the other countries in the Middle East. Six novel variants; c.164 + 9A >T, c.1163C >T, c.2279C >T, c.360delA (p.K120fs), c.3876delA (p.Val1293TyrfsX35) and c.3731G>A (p.Gly1244Glu) have been identified within the population. More variants such as c.1545_1546delTA (p.Tyr515X), c.3718-2477C >T (3849 + 5A>G) and c.54-5940_273 + 10250del21kb p.Ser18-ArgfsX16; CFTRdele2,3(21 kb) were also identified (Rawashdeh and Manal, 2000). Similarly, low frequency of c.1521_1523delCTT (2.78%) was detected among patients in the Children Welfare Hospital Baghdad in Iraq as compared to other Middle Eastern countries. Iraq detected 34 variants with the majority (~70%) of these variants were associated with the polymorphic variants of IVS8, namely 5T, 7T, and 9T (Abdul-Qadir et al., 2021). Other common variants detected, although in lower frequency, were c.2988 + 1G>A and c.3846G>A at 4.17% each, c.3484C >T (2.78%), c.3140-26A>G (1.38%), c.1040G>C(1.38%), and c.2051_2052delAAinsG (1.38%) variants. A novel variant: c.1519_1521delATC (p.Ile507del) was also reported from this study at the rate of 1.3% (Abdul-Qadir et al., 2021). Contrary, another study from Al-Imamian Al-Kadhimiyain Teaching Hospital Iraq reported c.1408A>G (p.Met470Val) variant as the most common at 36.66%, followed by c.1521_1523delCTT at 16.6% (Zaidan et al., 2020). This supports an earlier finding by Sahami and team, where c.1408A>G was identified at 74.1% frequency, followed by c.1521_1523delCTT (14.81%), c.1397C>A (p.Ser466X) and c.3107C >T (p.Thr1036Ile) at 1.85% each (Katznelson and Ben-Yishay, 1978).

Between 1946 and 1976, Israel had an incidence approximating to the Caucasians of European ancestry with a total of 140 CF cases (Stafler et al., 2016). Unlike most of the countries in West Asia, Israel early on established the population carrier screening (PCS) for CF early on in 1999, which recorded a rapid decline in incidence, from 14.5 per 100,000 live births in 1990 to 6 per 100,000 live births in 2011 (Orgad et al., 2001). CF incidence and variant spectrum varies across the three ethnicities of the Israeli population (75% Jews, 20% Arabs and 5% others). Out of the 95 CF births recorded between 2004 and 2011, 64% were Jews and 36% were Arabs (Orgad et al., 2001). The Israel Jews are made up of subethnic groups; Ashkenazi, Balkan, Tunisian, Libyan, Turkish, Georgian, Moroccan, Iranian, and Sephardi Jews (Quint et al., 2005). These Jewish communities have lived isolated from each other, hence the respective CF genetic load difference, with the highest CF detection amongst the Ashkenazi (69%), followed by Moroccan Jews (12.1%), and Balkan Jews (7.5%). The CF amongst the Iranian and Yemenis Jews (each at 0.7%) in Israel was very rare, presented with rare and unique variants c.2856G>C and c.3911T>G respectively (Mei-Zahav et al., 2018). The only variant identified in the Georgian Jews community was the unique variant c.1075C>A(p.Gln359Lys) (Essawi et al., 2015). In general, most frequent variants identified in Israel Jewish communities include W1282X (31.1%), F508del (35.6%), c.1624G >T (8.5%), c.3718-2477C >T (4.6%), c.3909C>G (3.6%), c.1075C>A and c.273 + 1G>A each at 2.8% (Mei-Zahav et al., 2018). Several others variants identified in the earlier mentioned West Asian countries were present in the cohort notably were c.254G>A, c.1647T>A, c.3700A>G, and, 3121-1G> (Orgad et al., 2001; Quint et al., 2005; Mei-Zahav et al., 2018). Variants c.3266G>A and c.3276C>G were unique to this population while c.1585-1G>A was previously identified in South Africa. On the other hand, variants c.2988 + 1Kbdel8.6 Kb, 2183AA>G and c.3883_3886delATTT were identified also in the Arab populations (Orgad et al., 2001).

More than 17 different CF variants were reported in Palestine (El-Shanti, 2020), at an earlier prevalence of 4 in 100,000 (Siryani et al., 2015) and a current incidence of 2.53 in 10,000 live births (El-Shanti, 2020). About 62.5% of the identified cases have at least

a single allele of c.1521_1523delCTT; hence making it the most frequent (37.5%) variant in Palestine. Just like many countries in West Asia, the common variants apart form c.1521_1523delCTT are c.2988 + 1G>A (12.5%), c.3909C>G (4.69%), c.254G>A (4.69%), as well as c.2988 + 1Kbdel8.6 Kb (4.69%). While c.3846G>A was mostly identified in heterogeneous compound, either with c.1521_1523delCTT (3.13%) or other unidentified (4.69%) variant (Siryani et al., 2015). In another study of a Palestinian cohort, c.1393-1G>A appeared to be the most common variant (Jarjour et al., 2018). Recently, a rare variant; c.3623del (p.Gly1208AlafsX3) was identified in a Palestinian-Lebanese child (Al-Baba and Zetoune, 2021).

As for Syria, 13 variants were identified while 22% of the variants remain undetectable (Des Georges et al., 1997). Just like Palestine, the most common variants identified in the Syrian were c.1521_1523delCTT (18–36%), c.3846G>A (12–17%), and c.3909C>G (6–8%). Other common variants were c.1040G>C (p.Arg347Pro) at 6%, c.399T>C/c.443T>C, CFTR del2-3(21 kb) and c.1766 + 1G >T at 5% each (Des Georges et al., 1997). Recently, four more variants, c.2657 + 5G>A, c.2052delA, c.3718-2477C >T, and c.262_263delTT (p.Leu88IlefsX22), were detected in the Syrian cohort (Farra et al., 2010). Similarly, in Lebanon two putative novel variants, c.2016_2018del (p.Glu672del) and IVS21-28G>A, were diagnosed in the Lebanon cohort (Dogru et al., 2020). However, the most common CF variants were c.1521_1523delCTT, c.3846G>A, c.3909C>G, and c.11C >T at 37.5%, 15.6%, 9.4% and 7% respectively. (Dogru et al., 2020; Yiallouros et al., 2021).

Although Turkey is a European country, part of turkey is in the West Asia. Like Egypt, it is also classified as the Middle East geopolitical zone. The first reported case of CF in Turkey dated back to 1973, and the lack of CF data from that time prompted for the establishment of the Turkish National CF registry in 2017, which swiftly attained 30% (23 CF centres) coverage just between 2017 and 2020, recording an incidence of 2.9 per 10,000 live births. Just like in Europe, c.1521_1523delCTT (28%), c.3909C>G (4.9%), and c.1624G >T (4.5%) were the most common variants observed in Turkey, with 25.2% of the variants remaining unidentified. Other common variants in the Turkish population were c.1545_1546delTA (p.Tyr515X), c.254G>A, 2183AA>G and c.2657 + 5G>A (Izumikawa et al., 2009). Similarly, neighbouring Cyprus also recently established a national CF registry, and identified c.1521_1523delCTT (45.2%) variant as the most common. The novel variant p.Leu346Pro was an indigenous variant in 2007, and is currently diagnosed as the second most common (6.7%) variant in Cyprus (Yamashiro et al., 1997). Two new rare and novel variants, c.2629T>G (p.Ser877Ala) and c.531dupT (p.Gly178TripfsX5), were also recently identified and presumed unique to Cypriot descents. Other rare variants identified in this population were CFTRdup2 (3.8%) and a compound heterogeneous c.4200_4201delTG (p.Cys1400Terfs)/c.489 + 3A>G variant (Yamashiro et al., 1997). Several other variants have also been identified within the population, as seen in Table 1, with linkages to the Arabian ancestry in the West Asia and North Africa, as well as the Jewish Greek and European Caucasian ancestries (Yamashiro et al., 1997).

Many variants identified in West Asia have been identified in both Africa and the other Asian regions. This include c.(2988 + 1_2989-1)_(3468 + 1_3469-1)del, c.1000C >T, c.1210–12T (Mathew et al., 2021), and c.1364C>A. other Caucasian known variants are also common to both Africa and Asia; these include c.1521_1523delCTT, c.1624G >T, c.1652G>A, are among others, this is summarized in Table 1.

3.2. Cystic Fibrosis in East, South and South-East Asia

Over the years, an increase in CF cases have been reported from both East, South and South-East Asia. For instance, Japan had about 150 cases between the year 1951–2009 (Norzila et al., 2005), with an incidence of 1 in 350,000 (Yang et al., 2017). Malaysia reported of 16 cases between 1987 and 2003 based on a positive sweat test (Iwasa et al., 2001), and 10 cases were reported from Korea (Jung et al., 2011). Just as presumed in Africa, with several early deaths resulting from CF in East and South Asia were recorded before the age of 13 from jaundice, malnutrition, pneumonia, and neonatal meconium ileus (Tomoda et al., 2018). Many countries in these regions have little or no detection of the c.1521_1523delCTT variant, with the majority of the CF cases diagnosed at a later age, even though their medical records indicated CF phenotypic expression persisted since their early childhood (Kunitomo et al., 1991; Zilfalil et al., 2006). For instance, a case of a Japanese with medical history of CF symptoms who was tested negative by a CF genetic panel at early childhood (7 months), was later found to have CF at the age of 23 (Zilfalil et al., 2006). Nevertheless, more studies in Asia since the early 2000s have identified known and novel variants through direct genomic DNA sequencing. Although rare, the c.1521_1523delCTTl and c.1657C >T variants have been identified within these population alongside unique variants (Zheng and Cao, 2017; Tian et al., 2016; Kularatnam et al., 2015). For instance, the c.1521_1523delCTTl variant was identified in compound heterogeneous state mostly in children of European and Asian parentage (Eurasians), alongside other Asia variant variants. In China, the c.1521_1523delCTTl was diagnosed heterogeneously alongside the Chinese common variant c.2909G>A (p.Gly970Asp) (Prasad et al., 2010), or with c.2738A>G in Sri Lankan (Mei-Zahav et al., 2005).

3.3. Cystic Fibrosis in South Asia

Although c.1521_1523delCTT is a common variant across South Asia (Iran, India, Pakistan, and Sri Lanka), it has a lesser incidence (19%–44%) compared to that in the Western nations (Kabir et al., 2020). As of the late 1990 s, Canada, the United Kingdom, and the United States all reported similar CF incidence rates in the Indian ethnic group. South Asian immigrants were less likely to have c.1521_1523delCTT than the general population according to these countries national data registries (44–46% versus 65.1% and above). About 56% of the South Asian CF patients in these countries had either c.1647T>A (6%) or had other unidentified variants (Siddique et al., 2018). Furthermore, an extensive analysis to uncover unique variants apart from the c.1647T>A variant, identified variants including c.653T>A (p.Leu218X) (7.7%), c.1393-1G>A, c.3718-2477C >T, and c.1175T>G (p.Val392Gly) each at 3.8%, which were found in the South Asian population of Canada. Additionally, with the exception of c.1521_1523delCTT, none of the common Caucasian variants identified in the Canadian general populations were found in the South Asians (Siddique et al., 2018). Meanwhile, 26.7% of the CF alleles of the Canadian South Asian cohort remained unidentified, which was significantly high compared to the 8.2% unidentified in the general CF population of Canada (Siddique et al., 2018).

A number of CF cases were recorded from three tertiary care hospitals in Bangladesh from 2000 to 2017. However, the type of CF variants identified were not reported. Confirmatory sweat test was conducted using fast, cheap and effective sweat testing technique, which was locally developed. Out of the 224 enrolled CF suspected patients, 95 were confirmed to have CF from sweat chloride test, exhibiting different range of CF symptoms (Sharma Pandey et al., 2019). The first recorded case of CF in Nepal was of a 2 month male infant presented with severe anaemia and hypoproteinaemia, but was negative for the common Caucasian variants c.1521_1523delCTT, c.1624G >T, c.1652G>A and c.1657C >T (Ashavaid et al., 2012). The second case was identified in a day-old infant enrolled in a pilot study for newborn screening in Nepal,

Table 1
List of Common CF Variants Across the Different Regions of Africa and Asia.

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.-8G>C	8G>C
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.-8G>C	8G>C
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.-8G>C	8G>C
Ngukam et al., 2004	Indonesia	c.-8G>C	8G>C/G
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.-8G>C	8G>C/G
Wakabayashi-Nakao et al., 2019	Iran	c.1000C >T (p.Arg334Trp)	R334W
Izumikawa et al., 2009	Turkey	c.1000C >T, p.Arg334Trp)	R334W
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1000C >T(p.Arg334Trp)	R334W
Rawashdeh and Manal, 2000	Jordan	c.1000C >T(p.Arg334Trp)	R334W
Des Georges et al., 1997; Farra et al., 2010	Syria	c.1000C >T(p.Arg334Trp)	R334W
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	japan	c.1040G>A (p.Arg347His)	R347H
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1040G>A (p.Arg347His)	R347H
Dogru et al., 2020	Cyprus	c.1040G>C(p.Arg347Pro)	R347P
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1040G>C(p.Arg347Pro)	R347P
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.1040G>C(p.Arg347Pro)	R347P
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.1040G>C(p.Arg347Pro)	R347P
Des Georges et al., 1997; Farra et al., 2010	Syria	c.1040G>C(p.Arg347Pro)	R347P
Izumikawa et al., 2009	Turkey	c.1040G>C(p.Arg347Pro)	R347P
Loumi et al., 2008	Algeria	c.1210–12T (Mathew et al., 2021)	5T
Dogru et al., 2020	Cyprus	c.1210–12T (Mathew et al., 2021)	5T
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1210–12T (Mathew et al., 2021)	5T
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1210–12T (Mathew et al., 2021)	5T
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.1210–12T (Mathew et al., 2021)	5T
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.1210–12T (Mathew et al., 2021)	5T
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.1210–12T (Mathew et al., 2021)	5T
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1210–12T (Mathew et al., 2021)	IVS-8-T5
Owusu et al., 2021	Ghana	c.1364C>A (p.Ala455Glu)	A455E
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.1364C>A (p.Ala455Glu)	A455E
Rawashdeh and Manal, 2000	Jordan	c.1364C>A (p.Ala455Glu)	A455E
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.1364C>A (p.Ala455Glu)	A455E
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c.1364C>A (p.Ala455Glu)	A455E
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.1393-1G>A	1525-1G->A
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1393-1G>A	1525-1G>A
Wei et al., 2020; Indika et al., 2019	Pakistan	c.1393-1G>A	1525-1G>A
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.1393-1G>A	1525-1G>A
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.1393-1G>A	1525-1G>A
Owusu et al., 2021	Ghana	c.1397C>A or c.1397C>G(p.Ser466X)	S466X
Wakabayashi-Nakao et al., 2019	Iran	c.1397C>A or c.1397C>G(p.Ser466X)	S466X
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.1397C>A or c.1397C>G(p.Ser466X)	S466X
Loumi et al., 2008	Algeria	c.1408A>G(p.Met470Val)	M470
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1408A>G(p.Met470Val)	M470
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.1408A>G(p.Met470Val)	M470
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.1408A>G(p.Met470Val)	M470
Izumikawa et al., 2009	Turkey	c.1408A>G(p.Met470Val)	M470
Nam et al., 2005	Vietnam	c.1408G>A	M470
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1408G>A (p.Val470Met)	V470M
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.1408G>A (p.Val470Met)	V470M; MET470VAL
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.1519_1521delATC(p.Ile507del)	I507del
Ashavaid et al., 2012	Nepal	c.1521_1523delCTT (p.Phe508del)	F508del
Loumi et al., 2008	Algeria	c.1521_1523delCTT(p.Phe508del)	F508del
Eskandarani, 2002	Bahrain	c.1521_1523delCTT(p.Phe508del)	F508del
Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021	Cameroon	c.1521_1523delCTT(p.Phe508del)	F508del
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1521_1523delCTT(p.Phe508del)	F508del
Dogru et al., 2020	Cyprus	c.1521_1523delCTT(p.Phe508del)	F508del
Mayer Lacrosniere et al., 2021	Democratic Republic of the Congo	c.1521_1523delCTT(p.Phe508del)	F508del
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1521_1523delCTT(p.Phe508del)	F508del
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1521_1523delCTT(p.Phe508del)	F508del
Wakabayashi-Nakao et al., 2019	Iran	c.1521_1523delCTT(p.Phe508del)	F508del
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.1521_1523delCTT(p.Phe508del)	F508del
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.1521_1523delCTT(p.Phe508del)	F508del
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1521_1523delCTT(p.Phe508del)	F508del
Rawashdeh and Manal, 2000	Jordan	c.1521_1523delCTT(p.Phe508del)	F508del
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.1521_1523delCTT(p.Phe508del)	F508del
Ratbi et al., 2008; Fredj et al., 2011	Libya	c.1521_1523delCTT(p.Phe508del)	F508del
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.1521_1523delCTT(p.Phe508del)	F508del
Stewart and Pepper, 2016	Namibia	c.1521_1523delCTT(p.Phe508del)	F508del
Frossard et al., 1998	Oman	c.1521_1523delCTT(p.Phe508del)	F508del
Wei et al., 2020; Indika et al., 2019	Pakistan	c.1521_1523delCTT(p.Phe508del)	F508del
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.1521_1523delCTT(p.Phe508del)	F508del
AbdulWahab et al., 2021	Qatar	c.1521_1523delCTT(p.Phe508del)	F508del
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021;	Saudi Arabia	c.1521_1523delCTT(p.Phe508del)	F508del

Table 1 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Alibakhshi et al., 2008; Lopes-Pacheco, 2020			
Mayer Lacrosniere et al., 2021	Sierra Leone	c.1521_1523delCTT(p.Phe508del)	F508del
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.1521_1523delCTT(p.Phe508del)	F508del
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.1521_1523delCTT(p.Phe508del)	F508del
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.1521_1523delCTT(p.Phe508del)	F508del
Des Georges et al., 1997; Farra et al., 2010	Syria	c.1521_1523delCTT(p.Phe508del)	F508del
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c.1521_1523delCTT(p.Phe508del)	F508del
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.1521_1523delCTT(p.Phe508del)	F508del
Izumikawa et al., 2009	Turkey	c.1521_1523delCTT(p.Phe508del)	F508del
Frossard et al., 1998	United Arab Emirates	c.1521_1523delCTT(p.Phe508del)	F508del
Loumi et al., 2008	Algeria	c.1624G >T(p.Gly542X)	G542X
Dogru et al., 2020	Cyprus	c.1624G >T(p.Gly542X)	G542X
Wakabayashi-Nakao et al., 2019	Iran	c.1624G >T(p.Gly542X)	G542X
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.1624G >T(p.Gly542X)	G542X
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.1624G >T(p.Gly542X)	G542X
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.1624G >T(p.Gly542X)	G542X
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.1624G >T(p.Gly542X)	G542X
Des Georges et al., 1997; Farra et al., 2010	Syria	c.1624G >T(p.Gly542X)	G542X
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.1624G >T(p.Gly542X)	G542X
Izumikawa et al., 2009	Turkey	c.1624G >T(p.Gly542X)	G542X
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.1624G >T(p.Gly542X)	G542X
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1647T>A (p.Ser549Arg)	S549N
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.1647T>A (p.Ser549Arg)	S549N
Wei et al., 2020; Indika et al., 2019	Pakistan	c.1647T>A (p.Ser549Arg)	S549N
Dogru et al., 2020	Cyprus	c.1647T>A (p.Ser549Arg)	S549N/R
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Africa	c.1647T>A (p.Ser549Arg)	S549N/R
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.1647T>A (p.Ser549Arg)	S549R
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.1647T>A (p.Ser549Arg)	S549R
Frossard et al., 1998	Oman	c.1647T>A/(p.Ser549Arg)	S549R
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.1647T>A/(p.Ser549Arg)	S549R
Frossard et al., 1998	United Arab Emirates	c.1647T>A/(p.Ser549Arg)	S549R
Ashavaid et al., 2012	Nepal	c.1652G>A(p.Gly551Asp)	G551D
Dogru et al., 2020	Cyprus	c.1652G>A(p.Gly551Asp)	G551D
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1652G>A(p.Gly551Asp)	G551D
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1652G>A(p.Gly551Asp)	G551D
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.1652G>A(p.Gly551Asp)	G551D
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.1652G>A(p.Gly551Asp)	G551D
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.1652G>A(p.Gly551Asp)	G551D
Des Georges et al., 1997; Farra et al., 2010	Syria	c.1652G>A(p.Gly551Asp)	G551D
Ashavaid et al., 2012	Nepal	c.1657C >T(p.Arg553X)	R553X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1657C >T(p.Arg553X)	R553X
Suwanjutha et al., 1998	Hong Kong	c.1657C >T(p.Arg553X)	R553X
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1657C >T(p.Arg553X)	R553X
Mayer Lacrosniere et al., 2021	Mali	c.1657C >T(p.Arg553X)	R553X
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.1657C >T(p.Arg553X)	R553X
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.1657C >T(p.Arg553X)	R553X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1666A>G (p.Ile556Val)	I556V; ILE556VAL
Ngukam et al., 2004	Indonesia	c.1666A>G (p.Ile556Val)	I556V; ILE556VAL
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1666A>G (p.Ile556Val)	I556V; ILE556VAL
Nam et al., 2005	Singapore	c.1666A>G (p.Ile556Val)	I556V; ILE556VAL
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.1666A>G (p.Ile556Val)	I556V; ILE556VAL
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.1766 + 152T>A	1898 + 152T>A
Wei et al., 2020; Indika et al., 2019	Pakistan	c.1766 + 1G >T	1898 + 1G >T
Des Georges et al., 1997; Farra et al., 2010	Syria	c.1766 + 1G >T	1898 + 1G >T
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c.1766 + 1G >T	1898 + 1G >T
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1766 + 3A>G	1898 + 3A>C
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1766 + 3A>G	1898 + 3A>G
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1766 + 5G>A	1898 + 5G>A
Suwanjutha et al., 1998	Hong Kong	c.1766 + 5G >T	1898 + 5G >T
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.1766 + 5G >T	1898 + 5G >T
Eskandarani, 2002	Bahrain	c.1911del (p.Gln637fs)	Q637fs
AbdulWahab et al., 2021	Qatar	c.1911del (p.Gln637fs)	Q637fs
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.1911del (p.Gln637fs)	Q637Fs
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1911del (p.Gln637fs)	Q685fs
Eskandarani, 2002	Bahrain	c.1911delG (p.Gln637HisfsX26)	Q685fs
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021;	Saudi Arabia	c.1911delG (p.Gln637HisfsX26)	Q685fs

(*continued on next page*)

Table 1 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Alibakhshi et al., 2008; Lopes-Pacheco, 2020			
Loumi et al., 2008	Algeria	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Dogru et al., 2020	Cyprus	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Wakabayashi-Nakao et al., 2019	Iran	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Rawashdeh and Manal, 2000	Jordan	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Des Georges et al., 1997; Farra et al., 2010	Syria	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Des Georges et al., 1997; Farra et al., 2010	Syria	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Izumikawa et al., 2009	Turkey	c.2051_2052delAAinsG(p.Lys684SerfsX38)	2183AA>G
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.2051delA(p.Lys684SerfsX38)	2183delAA
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.2052del (p.Lys684fs)	2184delA
Rawashdeh and Manal, 2000	Jordan	c.2052delA(p.Lys684AsnfsX38)	2184delA
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.2052dup (p.Gln685fs)	2184insA
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.2052dup (p.Gln685fs)	2184insA
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.2052dup (p.Gln685fs)	218delA
Wei et al., 2020; Indika et al., 2019	Pakistan	c.2052dup (p.Gln685fs)	218delA
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.220C >T(p.Arg74Trp)	R74W
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.220C >T(p.Arg74Trp)	R74W
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.223C>G (Arg75Gly)	R75G
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.223C >T (Arg75Term)	R75X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.223C >T (p.Arg75X)	R75X
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.223C >T(p.Arg75X)	R75X
Rawashdeh and Manal, 2000	Jordan	c.224G>A (Arg75Gln)	R75Q
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.224G>A (p.Arg75Gln)	R75Q
Rawashdeh and Manal, 2000	Jordan	c.254G>A(p.Gly85Glu)	G85E
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.254G>A(p.Gly85Glu)	G85E
AbdulWahab et al., 2021	Qatar	c.254G>A(p.Gly85Glu)	G85E
Des Georges et al., 1997; Farra et al., 2010	Syria	c.254G>A(p.Gly85Glu)	G85E
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.254G>A(p.Gly85Glu)	G85E
Izumikawa et al., 2009	Turkey	c.254G>A(p.Gly85Glu)	G85E
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.254G>A(p.Gly85Glu)	G85E
Dogru et al., 2020	Cyprus	c.2657 + 5G>A	2789 + 5G>A
Wakabayashi-Nakao et al., 2019	Iran	c.2657 + 5G>A	2789 + 5G>A
Rawashdeh and Manal, 2000	Jordan	c.2657 + 5G>A	2789 + 5G>A
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.2657 + 5G>A	2789 + 5G>A
Des Georges et al., 1997; Farra et al., 2010	Syria	c.2657 + 5G>A	2789 + 5G>A
Izumikawa et al., 2009	Turkey	c.2657 + 5G>A	2789 + 5G>A
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.2657 + 5G>A	2789 + 5G>A
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c.273 + 1G>A	405 + 1G>A
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.273 + 1G>A	405 + 1G>A
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.273 + 1G>A	405 + 1G>A
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.273 + 1G>A	405 + 1G>C
Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021	Cameroon	c.273 + 4G>A	405 + 4A>G
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.273 + 4G>A	405 + 4A>G
Eskandarani, 2002	Bahrain	c.2988 + 1G>A	3120 + 1G>A
Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021	Cameroon	c.2988 + 1G>A	3120 + 1G>A
Mayer Lacrosniere et al., 2021	Democratic Republic of the Congo	c.2988 + 1G>A	3120 + 1G>A
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.2988 + 1G>A	3120 + 1G>A
Wakabayashi-Nakao et al., 2019	Iran	c.2988 + 1G>A	3120 + 1G>A
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.2988 + 1G>A	3120 + 1G>A
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.2988 + 1G>A	3120 + 1G>A
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.2988 + 1G>A	3120 + 1G>A
AbdulWahab et al., 2021	Qatar	c.2988 + 1G>A	3120 + 1G>A
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.2988 + 1G>A	3120 + 1G>A
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.2988 + 1G>A	3120 + 1G>A
Stewart and Pepper, 2016	Zimbabwe	c.2988 + 1G>A	3120 + 1G>A
Suwanjutha et al., 1998	Hong Kong	c.3140-26A>G	3272-26A>G
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.3140-26A>G	3272-26A>G
Rawashdeh and Manal, 2000	Jordan	c.3140-26A>G	3272-26A>G
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.3140-26A>G	3272-26A>G

Table 1 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.3140-26A>G	3272-26A>G
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.3140–32T>C	3272–32T>C
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3196C >T(p.Arg1066Cys)	R1066C
Dogru et al., 2020	Cyprus	c.3196C >T(p.Arg1066Cys)	R1066C
Rawashdeh and Manal, 2000	Jordan	c.3196C >T(p.Arg1066Cys)	R1066C
AbdulWahab et al., 2021	Qatar	c.3196C >T(p.Arg1066Cys)	R1066C
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3196C >T(p.Arg1066Cys)	R1066C
Dogru et al., 2020	Cyprus	c.350G>A(p.Arg117His)	R117H
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.350G>A(p.Arg117His)	R117H
Rawashdeh and Manal, 2000	Jordan	c.350G>A(p.Arg117His)	R117H
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.350G>A(p.Arg117His)	R117H
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.350G>A(p.Arg117His)	R117H
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.350G>A(p.Arg117His)	R117H
Des Georges et al., 1997; Farra et al., 2010	Syria	c.350G>A(p.Arg117His)	R117H
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.350G>A(p.Arg117His)	R117H-T7
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3700A>G (p.Ile1234Val)	I1234V
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3700A>G (p.Ile1234Val)	I1234V
AbdulWahab et al., 2021	Qatar	c.3700A>G (p.Ile1234Val)	I1234V
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.3700A>G (p.Ile1234Val)	I1234V
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3700A>G (p.Ile1234Val)	I1234V
Dogru et al., 2020	Cyprus	c.3718-2477C >T (c.3717 + 12191C >T)	3849 + 10kbC >T
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3718-2477C >T (c.3717 + 12191C >T)	3849 + 10kbC >T
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.3718-2477C >T (c.3717 + 12191C >T)	3849 + 10kbC >T
Rawashdeh and Manal, 2000	Jordan	c.3718-2477C >T (c.3717 + 12191C >T)	3849 + 10kbC >T
Al Balushi et al., 2021	Oman	c.3718-2477C >T (c.3717 + 12191C >T)	3849 + 10KbC >T
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3718-2477C >T (c.3717 + 12191C >T)	3849 + 10kbC >T
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3731G>A(p.Gly1244Glu)	G1244E
Rawashdeh and Manal, 2000	Jordan	c.3731G>A(p.Gly1244Glu)	G1244E
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.3731G>A(p.Gly1244Glu)	G1244E
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.3731G>A(p.Gly1244Glu)	G1249E
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.3808G>A(p.Asp1270Asn)	D1270N
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.3808G>A(p.Asp1270Asn)	D1270N
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.3808G>A(p.Asp1270Asn)	D1270N
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3808G>A(p.Asp1270Asn)	D1270N
Loumi et al., 2008	Algeria	c.3846G>A(p.Trp1282X)	W1282X
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3846G>A(p.Trp1282X)	W1282X
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3846G>A(p.Trp1282X)	W1282X
Rawashdeh and Manal, 2000	Jordan	c.3846G>A(p.Trp1282X)	W1282X
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.3846G>A(p.Trp1282X)	W1282X
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Africa	c.3846G>A(p.Trp1282X)	W1282X
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3846G>A(p.Trp1282X)	W1282X
Dogru et al., 2020	Cyprus	c.3846G>A(p.Trp1282X)	W128X
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.3846G>A(p.Trp1282X)	W128X
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.3846G>A(p.Trp1282X)	W128X
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.3846G>A(p.Trp1282X)	W128X
Des Georges et al., 1997; Farra et al., 2010	Syria	c.3846G>A(p.Trp1282X)	W128X
Izumikawa et al., 2009	Turkey	c.3846G>A(p.Trp1282X)	W128X
Loumi et al., 2008	Algeria	c.3909C>G(p.Asn1303Lys)	N1303K
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3909C>G(p.Asn1303Lys)	N1303K
Dogru et al., 2020	Cyprus	c.3909C>G(p.Asn1303Lys)	N1303K
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3909C>G(p.Asn1303Lys)	N1303K
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3909C>G(p.Asn1303Lys)	N1303K
Wakabayashi-Nakao et al., 2019	Iran	c.3909C>G(p.Asn1303Lys)	N1303K
Rawashdeh and Manal, 2000	Jordan	c.3909C>G(p.Asn1303Lys)	N1303K
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.3909C>G(p.Asn1303Lys)	N1303K
Ratbi et al., 2008; Fredj et al., 2011	Libya	c.3909C>G(p.Asn1303Lys)	N1303K
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.3909C>G(p.Asn1303Lys)	N1303K
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.3909C>G(p.Asn1303Lys)	N1303K
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.3909C>G(p.Asn1303Lys)	N1303K
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.3909C>G(p.Asn1303Lys)	N1303K
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.3909C>G(p.Asn1303Lys)	N1303K
Des Georges et al., 1997; Farra et al., 2010	Syria	c.3909C>G(p.Asn1303Lys)	N1303K
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3909C>G(p.Asn1303Lys)	N1303K
Izumikawa et al., 2009	Turkey	c.3909C>G(p.Asn1303Lys)	N1303K
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3909C>G(p.Asn1303Lys)	N1303K
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.4045G>A (p.Gly1349Ser)	Q1352H
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.4056G>C (p.Gln1352His)	Q1352H
Ngukam et al., 2004	Indonesia	c.4056G>C (p.Gln1352His)	Q1352H
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.4056G>C (p.Gln1352His)	Q1352H
Nam et al., 2005	Singapore	c.4056G>C (p.Gln1352His)	Q1352H
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.4056G>C (p.Gln1352His)	Q1352H
Dogru et al., 2020	Cyprus	c.489 + 1G >T	621 + 1G >T

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Table 1 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.489 + 1G >T	621 + 1G >T
Wei et al., 2020; Indika et al., 2019	Pakistan	c.489 + 1G >T	621 + 2T>C
Loumi et al., 2008	Algeria	c.489 + 1G >T	621 + 3A>G
Dogru et al., 2020	Cyprus	c.489 + 1G >T	621 + 3A>G
Loumi et al., 2008	Algeria	c.54-5940_273 + 10250del21kb p. Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Dogru et al., 2020	Cyprus	c.54-5940_273 + 10250del21kb(p. Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.54-5940_273 + 10250del21kb(p. Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Mayer Lacrosniere et al., 2021	Mali	c.54-5940_273 + 10250del21kb(p. Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.579 + 1G >T	711 + 1G>A
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.579 + 1G >T	711 + 1G>A
Loumi et al., 2008	Algeria	c.579 + 1G >T	711 + 1G >T
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.579 + 1G >T	711 + 1G >T
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.579 + 1G >T	711 + 1G >T
Mayer Lacrosniere et al., 2021	Senegal	c.579 + 1G >T	711 + 1G >T
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.579 + 1G >T	711 + 1G >T
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.579 + 1G >T	711 + 1G >T

who unfortunately did not survive beyond the third month. Based on the pilot study, the prevalence rate of CF in Nepal was 1 per 4360 live births (Aziz et al., 2017).

In India, the increase in the CF incidences was associated with studies tracking the underlying genetic linkages to the high rate of infertility in males. This was due to congenital bilateral absence of vas deferens in more than 95% of males with CF (Kabir et al., 2020; Harendra de Silva et al., 1994). The T5 splicing and c.1521_1523delCTT variants were identified as the most common underlying genetic alteration at the rates of 52% and 23% respectively (Kabir et al., 2020; Harendra de Silva et al., 1994). Like many countries in Asia, several other common and unique variants were identified in India, these are listed in Table 2.

In a study conducted in Pakistan, CF patients were genetically screened the common variants. However, only c.1647T>A and c.1521_1523delCTT were identified. The recent incidence of found at 17.3%. However, a recent study reported c.1521_1523delCTT at an incidence of 27.9% (Indika et al., 2019). This was similar to the study by Shastri and team, who also identified c.1521_1523delCTT at the rate of 26.5% (homozygous in 20 patients and heterozygous in 13 patients of the 100 patients in the studies). The majority of the CF alleles (67%) in their study remained unidentified. Other rare variants identified in their study include c.1161delC (1.5%), c.1647T>A, c.1002-7_1002-5delTTT, c.3718-2477C >T at 1%. Novel variants identified from this cohort include c.1002-7_1002-5delTTT, c.445G >T (p.Gly149Ter) and c.547C>A (p.Leu183Ile). More novel variants identified in Indian and Pakistani population include c.3986-3987delC, p.1792InsA, c.206T>A (p.Leu69His), c.473G>A (Ser158Asn), c.1478A >T (Gln493Leu), c.1507A>C (p. Ile503Leu), c.3985G>C (Glu1329Gln) and c.744-6del4 that represented 15% of the CF alleles (Kabir et al., 2020; Aziz et al., 2017). Variants c.1521_1523delCTT, and c.1647T>A were the most common variants in the Indian/Pakistan cohort at 17% and 5.7% respectively. Apart from c.1521_1523delCTT, a few other Western variants were also identified, although rare, except for c.350G>A which was found at 3.4%. (Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019).

The first available recorded case of CF in Sri Lanka was of a 5 year girl presented with bronchopneumonia and recurrent chest infection since six weeks of age. She was tested positive using the sweat test (Masekela et al., 2013). Rare cases of CF were also reported in Sri Lanka, with unique types of mutation, potentially linked to genetic flow from India and Europe (Alibakhshi et al., 2021). Just like in South Africa's (Kawase et al., 2022), CF cases in Sri Lanka were initially presented as kwashiorkor, but later confirmed as CF with c.1393-1G>A in one allele while the second mutation could not be identified (Siddique et al., 2018). Similar to India and Pakistan, c.1521_1523delCTT (69.74%) mutation is the most common variant in Sri Lankans, mostly diagnosed in a heterogenous state. Variants c.53 + 1G >T, c.2052dup, c.(273 + 1_274-1)_(1679 + 1_1680-1)del (CFTRdele4-11) and c.1393-1G>A identified in this population were previously reported in European CF patients (Alibakhshi et al., 2021). Also detected were rare variant c.1161delC previously identified in India and Pakistan, while variants c.1367T>C (Val456Ala) and c.2738A>G are unique to Sri Lanka. (Mei-Zahav et al., 2005; Alibakhshi et al., 2021).

Earlier investigations Alibakhshi et al (Alibakhshi et al., 2008) were unable to identify more than 40% of the variants in the Iranian population; however, a subsequent study by Alibakhshi et al. in (2021) identified more than 100 variants in Iran. These included eight novel variants c.406-8TNC, p.A566D, c.2576delA, c.2752-1_275delGGTGGCinsTTG, p.T10361, p.W1145R, c.3850-24GNA, and c.1342-?_1524+?del, all identified at a low frequency (Wakabayashi-Nakao et al., 2019). Like many countries, c.1521_1523delCTT (18%-21.22%) was diagnosed as the most common variant in the population (Wakabayashi-Nakao et al., 2019). Other common variants in the population include c.2051_2052delAAinsG (6.5%), c.1397C>G (5.8%), c.3909C>G (4.3%), 2789 + 5G>A (4.3%), c.1624G >T (3.6%), c.2988 + 1G>A (3.6%), c.1000C >T (2.9%) and c.2998delA (p.Ile1000LeufsX2) (2.9%). (Wakabayashi-Nakao et al., 2019).

3.4. Cystic Fibrosis in East Asia

Large deletions and duplications of *CFTR* gene were frequently detected in Japanese CF patients by direct sequencing. This included the most common variant; c.2908 + 1085_3367 + 260del7201 (exon 16–17 deletion/CFTRdele16-17b), which also a unique

variant to CF patients of Asian descent (Iso et al., 2019). This was the most diagnosed variant (70%) in Japanese CF patients (Sohn et al., 2019). Other unique and frequent variants in the population were −966T>G, c.1408A>G, c.2562T>G (p.Thr854 =), c.3468G >T (p.Leu1156Phe), c.4056G>C (p.Gln1352His), c.4357C >T (Koh et al., 2006). More unique variants identified in Japan include c.1040G>A (p.Arg347His), *D979A*, c.3254A>G (p.His1085Arg), c.455T>G (p.Met152Arg), and c.1549T>A (p.Tyr517His) (Norzila et al., 2005). Other variants identified in this populations are listed in Table 2. Recently, another novel variant was identified in Japanese CF patients, which was characterized by the deletion of the entire promoter region (ASZ1 3′ flanking region) of *CFTR* gene (Guo et al., 2018). These variants alongside c.650A>G (p.Glu217Gly), c.1666A>G, and c.3468G >T (p.Leu1156Phe) were also unique to Asia and frequently identified in compound heterogenous states with either c.1408A>G and (TG) polymorphism 5T, 7T, 11/12T variants (Koh et al., 2006).

Similarly, South Korea also reported a 50% allele prevalence of c.2908 + 1085_3367+ (p.(Gly970_Thr1122del), which is also known as CFTRdele16-17b (Liu et al., 2020). Earlier CF studies in South Korea identified c.293A>G and c.658C >T(p.Gln220X) variants which had been previously identified in France and England, respectively (Ahn et al., 2005), and recently in China (Cui et al., 2020; Liu et al., 2015). The c.293A>G (18.8%) variant was found be high recurring variant (Kunitomo et al., 1991). Variants IVS8-T5-M470V and c.1408A>G polymorphism, synonymous to East Asia, is highly associated with congenital bilateral absence of the vas deferens (Lin et al., 2019).

In China, the most common variant was the c.2909G>A, diagnosed at 31.6–37.5% allele frequency (Cui et al., 2020; Liu et al., 2015). Over the years, quite a number of rare novel variants have been identified among patients of Chinese origin. An earlier study reported of a novel and unique c.1766 + 5G >T (1898 + 5G >T) variant, identified in patients of Chinese origin. Other novel mutations identified in the Chinese population are exon 7–11 deletion (ΔE7-E11), c.3635delTa (V1212Afs15), c.1997T4Ga, c.2907A4C, and △E7-E11(c.744-?_1584 +?del) (Prasad et al., 2010). More novel variants discovered include c.579 + 1_579 + 2insACAT, c.753_754delAG, c.699C>A, c.1240X (Q414X), c.1117-1G>C, c.3140-454_c.3367 + 249del931ins13, c.607A >T, c.325T>G (Y109D), exon 2–3 deletion ΔE2-3 (c.54-?_273+?del, △E2–3), and c.1716C>A (Cui et al., 2020; Liu et al., 2015). Other common variants identified in China include c.1766 + 5G >T (13%), c.3911T>G (8.7%), c.263T>A (4.1%), c.293A>G (4.1%), c.1666A>G, and c.595C >T, each at 3.3% frequency. Several other common variants have been identified in this population (Cui et al., 2020; Liu et al., 2015). Interestingly, the c.1521_1523delCTT is extremely rare and when present, was commonly found in a heterozygous state alongside another type of variant (Prasad et al., 2010).

The most common variant in South China-Hong Kong was c.3068T>G, followed by c.1766 + 5G >T, while the China's most frequent variant; c.2909G>A was not diagnosed in the study (Suwanjutha et al., 1998). Just a handful of CF cases have been reported in Taiwan. Nevertheless, three novel CFTR mutations; E7X, 989-992insA and S308X were detected among Taiwanese CF patients (Teeratakulpisarn et al., 2006). Variant c.920G>A (S308X) was diagnosed in a heterogenous state alongside c.1408G>A (Wang et al., 2019). Furthermore, c.1766 + 5G >T and c.3068T>G variants were discovered at the highest frequency. A literature review of Taiwanese CF patients by Wang et al., (Wang et al., 2019), recorded the c.1766 + 5G >T (50%) variant as the most common in the cohort and was predominantly presented in a heterogenous state along with 2215insG + G2816A (33.33%). Only one case of the European variant c.1657C >T (16.67%) was reported, and was presented in a homozygous state (Lumpaopong et al., 2009). Another study of Taiwanese CF patients reported one and two homogenous cases of c.3718-2477C >T and c.1657C >T, respectively, while the both c.1766 + 5G >T and c.3068T>G were presented in heterogeneous states with each other (Teeratakulpisarn et al., 2006).

3.5. Cystic Fibrosis in South-East Asia

Just like Taiwan, the most common identified CF variant in Thailand was the c.1766 + 3A>G, occurring in 9 out of the 14 alleles reported (Van de Vosse et al., 2010). Variants c.1364C>A (p.Ala455-Glu), c.4200_4201delTG (p.Cys1400X), c.3074C>A, and c.273 + 1G>A, were also recorded in Thailand, alongside two novel variants; c.738G>A (p.Lys246=; W202X) and c.869 + 3A >T (1001 + 3A >T). Only two cases of c.1521_1523delCTT were recorded within this population; one case had homozygous c.1521_1523delCTT (Ngiam et al., 2006), while the other was heterozygous c.1521_1523delCTT presented alongside the rare variant p.Phe311Leu (Padilla et al., 2022). Indonesia also reported of one novel variant: c.1303C>G (p.Leu435Val), and some known variant including c.861C>G, c.1666A>G, c.2052dup and eight types of polymorphism (Ngukam et al., 2004). The c.1666A>G and c.2052dup variants were also reported in the Chinese population of Singapore; however, at a higher frequency, alongside I125T and I2TG5T variants (Nam et al., 2005). Malaysia also reported of 16 cases between 1987 and 2003 based on a positive sweat test (Iwasa et al., 2001) however no variants were specifically reported. Recently, the Philippines has successfully implemented expanded newborn screening and is projecting about 100 CF cases per year based on the CF prevalence rate (5 cases per year) in Filipinos in California, USA (Luu and Chilvers, 2011). However, there is currently no available literature record of CF in the Philippines.

3.6. Cystic Fibrosis in Central Asia and other Asian countries

To date, Central Asia, Bangladesh, Brunei, Bhutan, Cambodia, Laos, Maldives, Myanmar, and Vietnam have no literature evidence of CF cases. However, a novel *CFTR* mutation c.3373G>C (Ex17b) was identified in a Laotian patient in France, presented with congenital bilateral absence of the vas deferens (Scotet et al., 2020). Similarly, Japanese researchers reported the first recorded CF cases (37 CF cases) in Vietnamese in Hanoi. All patients were presented with different types of c.1408G>A polymorphism mutations in the *CFTR* gene. The F c.1521_1523delCTT was not detected in any of the patients (Nam et al., 2005). Four other CF cases in Vietnamese have also been recorded in Canada, one of the cases was diagnosed at an advanced stage. The early age CF diagnosis of this patient was overlooked due the ethnicity misconception of CF occurrence in Asians, despite having chronic respiratory symptoms (Luu and Chilvers, 2011).

4. Prospect

The present surge in the CF cases in Africa and Asia is believed to be due to the evidence that CF occurs in patients of diverse ethnicity, based on reports from multi-ethnic countries like the USA, France, South America, Canada and the UK. This confirms that CF is rather a pan-ethnic disease condition than a Caucasian allied disease as earlier presumed (Banjar et al., 2021; Mayer Lacrosniere et al., 2021). This might have created awareness among physicians to further investigate CF in suspected patients with unconfirmed disease conditions with CF symptoms. Nevertheless, awareness is still inadequate in many countries where sweat screening and genetic testing tools are unavailable, especially in the identification of atypical manifestation and different variant spectrum (Cui et al., 2020). Furthermore, the existing mutational diagnostic (panel) kits

Table 2
List of CF Variants Less Common Across the Different Regions of Africa and Asia.

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Eskandarani, 2002	Bahrain	c.1161delC	1161delC
Wei et al., 2020; Indika et al., 2019	Pakistan	c.1161delC	1161delC
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.1161delC	1161delC
Rawashdeh and Manal, 2000	Jordan	c.3670delA	3670delA
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3911T>G (p.Ile1304Arg)	I1203R
Mayer Lacrosniere et al., 2021	Democratic Republic of the Congo	(c.399T>C (p.Thr133 =)	399insT
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	△E18-E20(c.2909-?_3367 +?del) (p.Gly980_Thr1112delinsGly)	CFTR-dele18-20
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	△E7-E11(c.744-?_1584 +?del)(p.Arg248_Glu528delinsArgfsX)	CFTR-dele7-11
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	1029del (p.Phe342_Cys343insTer)	1161delC (C343)
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	3G>A (p.Met1Ile)	M1I
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	920G>A	S308X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c. 388G>A (Gly463Asp)	G463D
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c. 3986-3987delC	3986-3987delC
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c. 738G>A (p.Lys246 =) p. W202X	W202X
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.-226G >T	(-94G >T)
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.-966T>G	(-966T>G)
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.-966T>G	(-966T>G/T)
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.(1766 + 1_1767-1)_(2619 + 1_2620-1)del	CFTR-dele14a
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.(273 + 1_274-1)_(1679 + 1_1680-1)del	CFTRdele4-11
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.(2988 + 1_2989-1)_(3367 + 1_3368-1)del	CFTR-dele17a-17b
Rawashdeh and Manal, 2000	Jordan	c.(2988 + 1_2989-1)_(3468 + 1_3469-1)del	CFTR-dele17a-18
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.(2988 + 1_2989-1)_(3468 + 1_3469-1)del	CFTR-dele17a-18
Mayer Lacrosniere et al., 2021	Senegal	c.(2988 + 1_2989-1)_(3468 + 1_3469-1)del	CFTRdele17a-18
Rawashdeh and Manal, 2000	Jordan	c.(53 + 1_54-1)_(164 + 1_165-1)del	CFTR-dele2
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.(53 + 1_54-1)_(164 + 1_165-1)del	CFTR-dele2
Stewart and Pepper, 2016	Zimbabwe	c.(53 + 1_54-1)_(164 + 1_165-1)del	CFTR-dele2
Rawashdeh and Manal, 2000	Jordan	c.(53 + 1_54-1)_(164 + 1_165-1)del(ins186)	CFTR del2(ins186)
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.[1075C>A;1079C>A](p.[Gln359Lys;Thr360Lys])	Q359K/T360K
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.*2G>A	4575 + 2G>A
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1002-7_1002-5delTTT	1002-7_1002-5delTTT
Dogru et al., 2020	Cyprus	c.1037T>C (p.Leu346Pro)	L346P
Dogru et al., 2020	Cyprus	c.1042A>G	M348K
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1055G>A (p.Arg352Gln)	R352Q
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1055G>A (p.Arg352Gln)	R352Q
Al Balushi et al., 2021	Oman	c.1069G>A(p.Ala357Thr)	A357T
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1075C >T(p.GIn359X)	G359X
Dogru et al., 2020	Cyprus	c.1135G >T(p.Glu379X)	E379X
Rawashdeh and Manal, 2000	Jordan	c.1163C >T (Thr388Met)	T388M
Fass et al., 2014	Oman	c.1175T>G (p.Val392Gly)	-
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.1176 + 30G>C (Ser212Ser)	1176 + 30G>C
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.11C >T (Ser4Term)	S4X
Siryani et al., 2015; Jarjour et al.,	Palestine	c.1209 + 1G>A	1341 + 1G>A

Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
2018			
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1210-11TTT>G	1342-11TTT>G
Nam et al., 2005	Singapore	c.1210-33_1210-6GT (Super, 1975)T (Mekki et al., 2021)	12TG5T
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1210–12T (Mehta, G., Macek, M., Jr, Mehta, A., & European Registry Working Group, 2010)	7T
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.1210–12T (Mehta, G., Macek, M., Jr, Mehta, A., & European Registry Working Group, 2010)	7T
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1210–12T (Maiuri et al., 2017)	9T
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1240C >T	Q414X
Ngukam et al., 2004	Indonesia	c.1303C>G (p.Leu435Val)	L435V
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1322T>C(p.Leu441Pro)	L441P
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.1322T>C(p.Leu441Pro)	L441P
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.1325G >T (p.Gly442Val)	G442V
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1367T>C (p.Val456Ala)	V456A
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.1367T>C(Val456Ala)	V456A
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1373G >T	G458E
Owusu et al., 2021	Ghana	c.1373G >T (p.Gly458ValP	G458V
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1405A>G (p.Met469Val)	M469V
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.1407G >T	M4691
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1408_1417delATGATTATGG/c.1549T>C (p.Met470GlufsX54/p.Tyr517His)	1540del10
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1418del (p.Gly473fs)	1548delG
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1418del (p.Gly473fs)	1548delG
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.1418del (p.Gly473fs)	1548delG
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.1473 + 28C >T	1473 + 28C >T
Loumi et al., 2008	Algeria	c.1477_1478delCA(p.Gln493ValfsX10)	1609delCA
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.1477C >T(p.Gln493X)	Q493X
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1478A >T(Gln493Leu)	Q493L
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1507A>C (p.Ile503Leu)	I503L
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.1519_1521delATC(p.Ile507del)	I507del
Rawashdeh and Manal, 2000	Jordan	c.1545_1546delTA (p.Tyr515X/p.515 fs)	1677delAT
Dogru et al., 2020	Cyprus	c.1545_1546delTA (p.Tyr515X/p.515 fs)	1677delTA
Izumikawa et al., 2009	Turkey	c.1545_1546delTA (p.Tyr515X/p.515 fs)	1677delTA
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	japan	c.1549T>(p.Tyr517His)	1540del10
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1550A>G (p.Tyr517Cys)	Y517C
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1558G >T (p.Val520Phe)	V520F; VAL520PHE
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1572C>A (p.Cys524X)	C524X
Loumi et al., 2008	Algeria	c.1584G>A	E528E
Rawashdeh and Manal, 2000	Jordan	c.1584G>A (p.Glu528 =)	1716G/A(1584G>A)
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.1585-1G>A	1717-1G>A
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.1585-1G>A	17171G>A
Ashavaid et al., 2012	Nepal	c.1624G >T	
Eskandarani, 2002	Bahrain	c.1624G >T (p.Gly542Ter)	1756G >T (G542*; GLY542TER)

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Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1628A>C(Glu543Ala)	E543A
Wei et al., 2020; Indika et al., 2019	Pakistan	c.164 + 12T>C	296 + 12T>C
Rawashdeh and Manal, 2000	Jordan	c.164 + 9A >T	296 + 9A >T
Ratbi et al., 2008; Fredj et al., 2011	Libya	c.1670delC (p.Ser557PhefsX2)	1802delC
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1679 + 1A>G	1811 + 1G>C
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1679 + 1G>C	1811 + 1G->C (1679 + 2T>C)
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.1679 + 5A>G	1811 + 5A>G
Wei et al., 2020; Indika et al., 2019	Pakistan	c.1679G>C	R560S
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1679G>C (p.Arg560Thr)	R560H
Loumi et al., 2008	Algeria	c.1680-1G>A	1812 – 1G>A
Loumi et al., 2008	Algeria	c.1684G>A(p.Val562Ile)	V562I
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1705T>G (p.Tyr569Asp)	Y569D
Wei et al., 2020; Indika et al., 2019	Pakistan	c.1705T>G (p.Tyr569Asp)	Y569D
AbdulWahab et al., 2021	Qatar	c.1705T>G (p.Tyr569Asp)	Y569D
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.1712T>C(p.Leu571Ser)	L571S
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.1716C>A(p.D572E)	D572E
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.1731C>A (p.Tyr577X)	Y577/1863C>A
Fass et al., 2014	Oman	c.1733-1734delTA(p.Leu578Argfs*)	1733-1734delTA (L578delTA)
Stewart and Pepper, 2016	Sudan	c.1736A>G (p.Asp579Gly	-
Stewart and Pepper, 2016	Sudan	c.1736A>G(p.Asp579Gly)	D579G
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.175A >T (Arg59Term)	R59X
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.1993A >T (p.Thr665Ser)	T665S
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.1993A >T (p.Thr665Ser)	T665S (T623S,)
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.19G >T (p.Glu7X)	E7X
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.19G >T (p.Glu7X)	E7X
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.2016_2018del (p.Glu672del)	E672del
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.202A >T(p.Lys68X)	K684fs/K684X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2036G>A	W679X
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.206T>A (p.Leu69His)	L69H
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.2077T>C (p.Phe693Leu)	F693L
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.2089_2090insA (p.Arg697LysfsX33)	2221insA
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.2089_2090insA (p.Arg697LysfsX33)	2221insA
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.2089C >T (Arg697Term)	R697K
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.2125C >T (p.Arg709X)	R709X
Wei et al., 2020; Indika et al., 2019	Pakistan	c.2125C >T (p.Arg709X)	R709X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2125C >T (p.Arg709X)	R709X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.214G>A	A72T
Loumi et al., 2008	Algeria	c.2260G>A(p.Val754Met)	V754M
Rawashdeh and Manal, 2000	Jordan	c.2279C >T (Thr760Met)	T760M
AbdulWahab et al., 2021	Qatar	c.2290C >T(p.Arg764X)	R764
Prasad et al., 2010; Cui et al.,	China	c.2290C >T(p.Arg764X)	R764X

Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
2020; Liu et al., 2015			
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.2290C >T(p.Arg764X)	R764X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2353C >T(p.Arg785X)	R785X
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.2353C >T(p.Arg785X)	R785X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2374C >T(p.Arg792X)	R792X
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.253G>A (p.Gly85Arg)	G85R
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2547C>A(p.Tyr849X)	Y849X
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.2555A >T(Tyr852Phe)	Y852F
Loumi et al., 2008	Algeria	c.2562T>C or c.2562T>G or c.2562T>A(p.Thr854Thr)	T854T
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.2562T>C or c.2562T>G or c.2562T>A(p.Thr854Thr)	T854T
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.2562T>C or c.2562T>G or c.2562T>A(p.Thr854Thr)	T854T
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	japan	c.2562T>G (p.Thr854 =)	2562T>G
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.259T>A(Phe87Ile)	F87I
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.262_263delTT(p.Leu88IlefsX22)	394delTT
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.2620-15C>G	2620-15C>G (2752-26A->G)
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.2620-15C>G	2752-15C>G (2620-15C>G)
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.263T>A or c.263T>G (p.Leu88X)	L88X
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.263T>A or c.263T>G (p.Leu88X)	L88X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2658-1G>C	2790-1G>C
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2658-1G>C	2790-1G>C
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.2684G>A (p.Ser895Asn)	S895N
AbdulWahab et al., 2021	Qatar	c.269T>C (Leu90Ser)	L940
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.271G>A(p.Gly91Arg)	G91R
Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021	Cameroon	c.273 + 4A>G (p.Gly91 =)	273 + 4A>G
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.2738A>G	Y913C_1282C>G
Izumikawa et al., 2009	Turkey	c.274G>A(p.Glu92Lys)	E92K
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.2766C >T (p.Val922_Thr923 =)	2766del8
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.2770G>A (p.Asp924Asn)	D924N
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.2848delA	2848delA
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.2856G>C	M9521
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.2856G>C (p.Met952Ile)	M952I
Mayer Lacrosniere et al., 2021	Democratic Republic of the Congo	c.287C>A (p.Ala96Glu)	A96E
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2907A>C	A969A/E17
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.2908 + 1085_3367+ (p.(Gly970_Thr1122del)-CFTR)	CFTR-dele16-17b
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2909G>A(p.Gly970Asp)	G970D
Wei et al., 2020; Indika et al., 2019	Pakistan	c.292C >T (Gln98Term)	Q98X
Loumi et al., 2008	Algeria	c.2930C >T(p.Ser977Phe)	S977F

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Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.293A>G	Q98R
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.293A>G	Q98R
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.293A>G (Gln1291Term)	Q98R
Rawashdeh and Manal, 2000	Jordan	c.297–10T>G (p.Pro99 =)	297–10T>G
Al Balushi et al., 2021	Oman	c.2988 + 1G>A	3120 + 1G>A
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.2988 + 1G>A	IVS8
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.2988 + 1Kbdel8.6 Kb	3120 + 1Kbdel8.6 Kb
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2988 + 2T>C	3120 + 2T>C
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.2989-1G>A	3121-1G>A
Loumi et al., 2008	Algeria	c.2991G>C(p.Leu997Phe)	L997F
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.2991G>C(p.Leu997Phe)	L997F
Izumikawa et al., 2009	Turkey	c.2991G>C(p.Leu997Phe)	L99TF
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.2997_3000del (p.Leu999_Ile1000insTer)	3129del4 (I1000)
AbdulWahab et al., 2021	Qatar	c.2997_3000del (p.Leu999_Ile1000insTer)	c.2997_3000delAATTA
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.2997_3000del (p.Leu999_Ile1000insTer)	I1000x
Wakabayashi-Nakao et al., 2019	Iran	c.2998delA (p.Ile1000LeufsX2)	3130delA
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.2T>C (p.Met1Thr)	M1T
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.3041-71A>G	3041-71A>G
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.3064_3117delGTGATAGTGGCTTTTATTATGTTGAGAGCATATTTCCTCCAAACCTCACAGCAA (p.Val1022_Gln1039del)	3196del54
Des Georges et al., 1997; Farra et al., 2010	Syria	c.3067_3072delATAGTG (p.Ile1023_Val1024del)	3199del6
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3067_3072delATAGTG(p.Ile1023_Val1024del)	3199del6
Suwanjutha et al., 1998	Hong Kong	c.3068T>G (p.Ile1023Arg)	I1023R
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.3068T>G (p.Ile1023Arg)	I1023R
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c.3074C>A (p.Ala1025Asp)	A1025D
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3080T>C (p.Ile1027Thr)	3123G>C (I1027T)
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.3107C >T (p.Thr1036Ile)	T1036I
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3128T>G (Leu1043Arg)	L1043R
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3154T>G(p.Phe1052Val)	F1052V
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.319-326delGCTTCCTA(p.A107X)	A107X
Mayer Lacrosniere et al., 2021	Democratic Republic of the Congo	c.3197G>A(p.Arg1066His)	R1066H
Ratbi et al., 2008; Estivill et al., 1997	Morocco	c.3208C >T(p.Arg1070Trp)	R107W
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	japan	c.3254A>G (p.His1085Arg)	H1085R
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.3254A>G (p.His1085Arg)	H1085R; HIS1085ARG
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.3257C >T (Thr1086Ile)	T1086I
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3266G>A (p.Trp1089X)	W1089X
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3276C>A or c.3276C>G(p.Tyr1092X)	Y1092X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.327T>A(p.Tyr109X)	Y109D/C
Dogru et al., 2020	Cyprus	c.328G>C (p.Asp110His)	D110H
Izumikawa et al., 2009	Turkey	c.328G>C (p.Asp110His)	D110H

Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Rawashdeh and Manal, 2000	Jordan	c.3299A>C(Gln1100Pro)	Q1100P
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.3299A>C(Gln1100Pro)	Q1100P
Stewart and Pepper, 2016	Sudan	c.3304A >T (p.Arg1102X)	R1102X
Stewart and Pepper, 2016	Sudan	c.3304A >T(p.Arg1102X)	R1102X
Loumi et al., 2008	Algeria	c.3310G >T(p.Glu1104X)	E1104X
Ratbi et al., 2008; Fredj et al., 2011	Libya	c.3310G >T(p.Glu1104X)	E1104X
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3310G >T(p.Glu1104X)	E1104X
Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021	Cameroon	c.3327C>A (p.Tyr1109Ter)	Y1109X
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3327C>A (p.Tyr1109Ter)	Y1109X
Scotet et al., 2020	Laos	c.3373G>C	
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3406G>A (Vp.Ala1136Thr)	A1136T
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3407T>C (p.Ile1136Thr)	I1136T
Rawashdeh and Manal, 2000	Jordan	c.3454G>C (p.Asp1152His)	D1152H
Izumikawa et al., 2009	Turkey	c.3454G>C (p.Asp1152His)	D1152H
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.3454G>C (p.Asp1152His)	D1152H
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3468 + 5G>A	3600 + 6T>C
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.3468G >T (p.Leu1156Phe)	L1156F
Dogru et al., 2020	Cyprus	c.3469-65C>A	3601-65C>A
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3472C >T(p.Arg1158X)	R1158X
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3472C >T(p.Arg1158X)	R1158X
Des Georges et al., 1997; Farra et al., 2010	Syria	c.3484C >T	R1162W
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3484C >T (p.Arg1162Ter)	R1162
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3484C >T(p.Arg1162X)	R1162X
Abdul-Qadir et al., 2021; Katznelson and Ben-Yishay, 1978	Iraq	c.3484C >T(p.Arg1162X)	R1162X
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.3484C >T(p.Arg1162X)	R1162X
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3484C >T(p.Arg1162X)	R1162X
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3490_3491insT (p.Lys1165X)	3622insT
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3497T>G (p.Phe1166Cys)	F1166C
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.349C>G (p.Arg117Gly)	(-117G>C) (R117G)
Owusu et al., 2021; Zampoli et al., 2021; Van Rensburg et al., 2018	South Africa	c.3528delC(p.Lys1177SerfsX15)	3659delC
Eskandarani, 2002	Bahrain	c.3529A >T (p.K1177X)	3661A >T (K1177X)
Rawashdeh and Manal, 2000	Jordan	c.358G>A(p.Ala120Thr)	A120T
Mayer Lacrosniere et al., 2021	Sierra Leone	c.3607A>G (p.Ile1203Val)	I1203V
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3607A>G (p.Ile1203Val)	I1203V
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3634G>A	V1212Afs*15/16
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.366T>A(p.Tyr122X)	Y122X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.3691delT(p.S1231PfsX4)	S1231PfsX4
Rawashdeh and Manal, 2000	Jordan	c.3718-2477C >T	3849 + 5A>G
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.3718-2477C >T (c.3717 + 12191C >T)	3849 + 10 kb

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Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3718-24G>A(3850-24G->A)	3718-24G>A
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3729delAinsTCT	3729delAinsTCT
Mayer Lacrosniere et al., 2021	Mali	c.3745delC	3745delC
Nam et al., 2005	Singapore	c.374T>C (p.Ile125Thr)	I125T
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.374T>C (p.Ile125Thr)	I125T
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3752G>A(p.Ser1251Asn)	S1251N
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.3793G>A (p.Gly1265Arg)	G1265R
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.3793G>A(p.Gly1265Arg)	3793G>A
Wei et al., 2020; Indika et al., 2019	Pakistan	c.3868C >T(Pro1290Ser)	P1290s
Loumi et al., 2008	Algeria	c.3870A>G (p.Pro1290 =)	P1290P
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.3870A>G (p.Pro1290 =)	P1290P
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.3871C >T	Q1291X
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3872A>G(p.Gln1291Arg)	Q1291R
Rawashdeh and Manal, 2000	Jordan	c.3876delA (p.Val1293TyrfsX35)	4006delA
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.3877G>A (Val1293Ile)	V1293I
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.387A>G (p.Ala129 =)	3877G>A
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.3883_3886delATTT(p.Ile1295PhefsX32)	4010del4
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.3889dupG(p.Ser1297PhefsX5)	4016insG
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.3889dupT(p.Ser1297PhefsX5)	4016insT
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.3889dupT(p.Ser1297PhefsX5)	406insA/T
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.38C >T (Ser13Phe)	S13F
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.3985G>C(Glu1329Gln)	E1329Q
Eskandarani, 2002	Bahrain	c.4041C>G	N1303K
Dogru et al., 2020; Yiallouros et al., 2021	Lebanon	c.4096-28G>G	4096-28G>G
Mayer Lacrosniere et al., 2021	Senegal	c.4136 + 1G>A	4136 + 1G>A
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.4136 + 2T>G	4268 + 2T>G
Loumi et al., 2008	Algeria	c.4139delC(p.Thr1380AsnfsX4)	4271delC
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.413T>A	V348M
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.414_415insCTA (p.Leu138_His139insLeu)	414_415insCTA
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.4141T>C (p.Tyr1381His)	Y1381H
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	c.416A >T (p.His139Leu)	H139L
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c.4200_4201delTG (p.Cys1400X)	4330delTG
Loumi et al., 2008	Algeria	c.4200_4201delTG(p.Cys1400X)	4332delTG
Loumi et al., 2008	Algeria	c.422C>A (p.Ala141Asp)	A141D
Mayer Lacrosniere et al., 2021	Senegal	c.4230C >T (p.His1410 =)	4230C>A
Mayer Lacrosniere et al., 2021	Mali	c.4242 + 1G>A	4374 + 1G>A
Dogru et al., 2020	Cyprus	c.4251delA(p.Glu1418ArgfsX14)	4382delA
Siryani et al., 2015; Jarjour et al., 2018	Palestine	c.4251delA(p.Glu1418ArgfsX14)	4382delA
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.4357C >T	R1453W
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.4357C >T	R1453W
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.4389G>A (p.Gln1463 =)	Q1463Q

Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Dogru et al., 2020	Cyprus	c.4426C >T (p.Gln1476X)	Q1476X
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.443T>C(p.Ile148Thr)	I148T
Rawashdeh and Manal, 2000	Jordan	c.443T>C(p.Ile148Thr)	I148T
Des Georges et al., 1997; Farra et al., 2010	Syria	c.443T>C(p.Ile148Thr)	I148T
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.445G >T (p.Gly149Ter)	G149X
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.454A>G (Met152Val)	M152V
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	japan	c.455T>G (p.Met152Arg)	M152R
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.455T>G(Met152Arg)	M152R
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.470T>G(Phe157Cys)	F157C
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.473G>A(Ser158Asn)	S158N
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	c.494T>C (p.Leu165Ser)	L165S
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.496A>G (p.Lys166Glu)	K166E
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.505A>G (Ser169Gly)	S169G
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.53 + 1G>C	185 + 1G>C
Mei-Zahav et al., 2005; Alibakhshi et al., 2021	Sri Lanka	c.53 + 1G >T	185 + 1G >T
Dogru et al., 2020	Cyprus	c.531dup (p.Gly178fs)	G178fs
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.532G>A (p.Gly178Arg)	G178R
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.54-?_273+?del, △E2–3(p.S18Rfs*16)	CFTR-Exon dele2-3
Loumi et al., 2008	Algeria	c.54-5940_273 + 10250del21kb p.Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Dogru et al., 2020	Cyprus	c.54-5940_273 + 10250del21kb(p.Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.54-5940_273 + 10250del21kb(p.Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Mayer Lacrosniere et al., 2021	Mali	c.54-5940_273 + 10250del21kb(p.Ser18ArgfsX16)	CFTRdel2,3(21-kb)
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.547C>A (p.Leu183Ile)	L183I
Wei et al., 2020; Indika et al., 2019	Pakistan	c.547C>A (p.Leu183Ile)	L183I
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.559A>G (p.Asn187Asp)	N187D
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.567C>A	N189K
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.57G>A (p.Trp19X)	W19X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.595C >T(p.His199Tyr)	H199Y
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.595C >T(p.His199Tyr)	H199Y
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.601G>A (p.Val201Met)	V201M
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.601G>A(p.Val201Met)	V201M
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.610G>A (p.Ala204Thr)	A204T
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.647G>A (Trp216Term)	W216X (780G → A)
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.650A>G (p.Glu217Gly)	E217G (GLU217GLY)
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.650A>G (p.Glu217Gly)	E217G (GLU217GLY)
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.650A>G (p.Glu217Gly)	E217G (GLU217GLY)
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.653T>A (p.Leu218X)	L218X
Wei et al., 2020; Indika et al., 2019	Pakistan	c.653T>A (p.Leu218X)	L218X
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	c.658C >T(p.Gln220X)	Q220X

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Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Messaoud et al., 2005; Boussetta et al., 2018; El-Seedy et al., 2017	Tunisia	c.680T>G(p.Leu227Arg)	L22TR/L227R
Loumi et al., 2008	Algeria	c.743 + 40A>G	875 + 40A>G
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.744-6del4	876-6del4
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.753_754delAG	2215insA/G
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.800A >T (p.Glu267Val)	E267V
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.861C>G	N287K
Ngukam et al., 2004	Indonesia	c.861C>G (p.Asn287Lys)	N287K
Suwanjutha et al., 1998	Hong Kong	c.868C >T (p.Gln290X)	Q290
Loumi et al., 2008	Algeria	c.869 + 11C >T	1001 + 11C >T
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	c.869 + 11C >T	1001 + 11C >T
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	c.869 + 3A >T	1001 + 3A >T
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.870-1G>C	870-1G>C
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	c.902A>G (Tyr301Cys)	Y301C
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	c.91C >T	R31C
Mayer Lacrosniere et al., 2021	Democratic Republic of the Congo	c.933C>G or c.933C>A(p.Phe311Leu)	F311del
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.95T>C (p.Leu32Pro)	L32P
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.960_961insA	960_961insA
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	c.960_961insA(p.Ser321IlefsX42)	S321Ifs*42
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	c.989-992insA	989-992insA
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	c.993C>G (p.Ile331Met	I331
Mayer Lacrosniere et al., 2021	Ivory Coast	C.C233dup	C233dup
Dogru et al., 2020	Cyprus	CF 40-kb del 4–10	CF 40-kb del 4–10
AbdulWahab et al., 2021	Qatar	CF 40-kb del 4–10	CF 40-kb del 4–10
Van de Vosse et al., 2010; Ngukam et al., 2004	Thailand	F311L; PHE311LEU	F311L
Eskandarani, 2002	Bahrain	His139 → Leu	548A >T
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	–	A544E
Owusu et al., 2021	Ghana	–	CFTR-dele12
Stewart and Pepper, 2016; Fathy et al., 2016; Sahami et al., 2014	Egypt	–	R31H
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	–	VS731
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	p.E527E	E527E
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	–	(-219insG)
Ratbi et al., 2008; Estivill et al., 1997	Morocco	–	11TG
Ratbi et al., 2008; Estivill et al., 1997	Morocco	–	12TG
Banjar et al., 2021; Banjar and Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Saudi Arabia	–	1507del9
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	–	1792insA
Orgad et al., 2001; Mei-Zahav et al., 2018	Israel	–	2751 + 1insT
Stewart and Pepper, 2016; Mayer Lacrosniere et al., 2021	Cameroon	–	326T>A
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	–	4569H
Banjar et al., 2021; Banjar and	Saudi	–	CFTR-dele19-21

Table 2 (*continued*)

Ref.	Country	Nucleotide/"Variant cDNA name (Variant protein name)	Legacy Name
Angyalosi, 2015; AbdulWahab et al., 2021; Alibakhshi et al., 2008; Lopes-Pacheco, 2020	Arabia		
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	CFTR-dele20
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	china	–	CFTR2,3(21 kb)
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	–	G151T
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	I1295Ffs32
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	–	IVS-12T
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	–	IVS-17a
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	–	IVS-5T
Mayer Lacrosniere et al., 2021	Senegal	–	IVS22 + 1G>A
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	IVS4
Rawashdeh and Manal, 2000	Jordan	–	IVS8-5T
Wang et al., 2019; Teeratakulpisarn et al., 2006; Lumpaopong et al., 2009	Taiwan	–	IVS8-5T
Ngukam et al., 2004	Indonesia	–	IVS8TG
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	L136Hfs*18
Al Balushi et al., 2021	Oman	–	L578delTA
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	L666X
Kunitomo et al., 1991; Ahn et al., 2005; Lin et al., 2019	South Korea	–	L78N
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	Q779X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	R251Sfs * 6
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	R289X
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	–	R80N11Fs*11
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	–	S212S
Dogru et al., 2020	Cyprus	–	S877A
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	T1219X
Prasad et al., 2010; Cui et al., 2020; Liu et al., 2015	China	–	T216X
Stewart and Pepper, 2016; Owusu et al., 2021; Mutesa et al., 2009	Rwanda	–	T577T
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	–	T66P
Norzila et al., 2005; Iso et al., 2019; Guo et al., 2018	Japan	–	V1381I
Wei et al., 2020; Indika et al., 2019	Pakistan	–	V456A
Kabir et al., 2020; Aziz et al., 2017; Indika et al., 2019	India	–	Y808YFs*10

are not suitable for the non-Caucasian populations, resulting in a false-negative test and difficulty in the detection of variants specific to these regions/countries (Mekki et al., 2021; Mayer Lacrosniere et al., 2021). This and the Caucasian allied misconception, might be some of the reasons behind the underdiagnosed or misdiagnosed CF cases in these concerned regions, leading to CF being diagnosed as another common phenocopy illness. The possibility of a false-negative result from panel kits and "the gold standard" sweat test in mild cases, would likely result in mortality due to gradually unchecked damaged organs (Stewart and Pepper, 2016). Therefore, there is a need for a thorough investigation of CF prevalence to identify unique and novel genetic variants of CF, so a specific diagnostic kit could be developed for use within these regions.

A high number of early childhood death in these regions are suspected to be undocumented CF-related, most of which were associated with malnutrition and infectious disease complications (Zampoli et al., 2021; Sharma Pandey et al., 2019). However, this is

unlikely in many countries in the West due to the establishment and implementation of CF national newborn screening (NBS) program, some dated back to 4 decades ago (Scotet et al., 2020). The CF NBS standard practice guidelines developed by the West can be adopted by countries in these regions. A crucial step towards finalizing plans towards the implementation of the NBS programs across the globe would aid in the development of cheaper specific drugs through countries' crowdfunding, research investment and collaboration as seen during the COVID-19 pandemic.

5. Conclusion

Initially thought to be a Caucasian disease, CF was earlier presumed non-existence or rarity of CF in the other parts of the world, particularly in Africa and Asia. This was predominantly due to the lack of CF data in the non-Caucasian population. However, with the recent surge in data and number of *CFTR* mutational variants reported from all parts of the world indicates an immediate need for an intervention to tackle the current challenges in the identification and management of CF in these regions. Therefore, we would like to recommend an intensive investigation and documentation of all genetic mutations and the implementation of CFTR (Clinical and Functional Translation of CFTR) database to analyse the heterogenous origin and distribution of *CFTR* mutations in these regions/countries. This will assist in the development of specific regional genetic screening and diagnostic tools for subsequent development of appropriate therapies and genetic counselling for families.

Authors Contributions

SA: Manuscript writing, funding, final approval of manuscript; KAB: Conception and design, manuscript writing, visualization; UA: visualization; CDM & NN manuscript reviewing and editing, and final approval of the manuscript. All authors have read and agreed to the final version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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