Allergy Asthma Immunol Res. 2022 Sep;14(5):444-446
https://doi.org/10.4168/aair.2022.14.5.444
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Editorial

Pathogenic Variants Spectrum and Allele Frequency of the *CFTR* Gene in Asians

Jong-Won Kim *

Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Received: Aug 17, 2022
Accepted: Aug 30, 2022
Published online: Sep 14, 2022

Correspondence to
Jong-Won Kim, MD, PhD
Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Tel: +82-2-3410-2705
Fax: +82-2-3410-2719
Email: kimjw@skku.edu

ORCID iDs
Jong-Won Kim
https://orcid.org/0000-0002-0708-9242

Disclosure
There are no financial or other issues that might lead to a conflict of interest.

Cystic fibrosis (CF; OMIM #219700) is an autosomal recessive disease caused by the abnormal transport of ions and fluid across epithelial cell membranes. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) are responsible for the disease.[1] CFTR gene consists of 27 exons (OMIM *602421) and forms 1,480 amino acids.[1] Clinical manifestations of CF are pulmonary diseases, pancreatic insufficiency, malabsorption, meconium ileus, failure to thrive, infertility, and elevated chloride concentrations in sweat.[2] According to the American Cystic Fibrosis Foundation patient registry, there are more than 30,000 CF patients in the United States and more than 70,000 worldwide.[3] It is most commonly found in populations with northern European ancestry where the incidence rate is as high as 1 in 2,000 to 3,000 live births. Their predominant mutation is Phe508del (F508Del). In the United States, CF occurs in approximately 1:15,000 blacks, 1:35,000 individuals of Asian descent, and 1:10,800 Native Americans.[4] Nonwhite patients with CF show a wider range of mutations with the F508Del mutation being much less prevalent. Recent advancements in understanding the CFTR gene function and mutational effect on the host developed CFTR gene modulator therapy.[5,6] Modulating drug of Ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor has been approved and applied to patients with specific type mutations.[7] Therefore, mutation identification is essential not just for the diagnosis but for the selection of drugs and specific care.

CFTR gene mutations are classified into 6 categories according to the type of CFTR defect.[1] Class I mutations do not produce functional CFTR protein and include nonsense, frameshift, and canonical splicing variants such as Gly542X, Trp1282X, Arg553X, and 621+1G>T. In class 2, CFTR shows a trafficking defect, and CFTR genes are missense and amino acid deletion such as F508del, Asn1303Lys Ile507del, Arg560Thr, *etc*. Class 3 mutations are missense and amino acid changes such as Gly551Asp, Gly178Arg, Gly551Ser, Ser549Asn, *etc.*, and lead to defective channel regulation. In class 4 mutations, CFTR proteins do not function through the decreased channel conductance and include missense and amino acid changes such as Arg117His, Arg347Pro, Arg117Cys, Arg334Trp, *etc*. In class 5, CFTR protein synthesis is reduced, and mutations are splicing defects and missense changes like 3849+10kbC>T, 2789_5G>A, 3120+1G>A, 5T, *etc*. Class 6 mutations are missense and amino acid changes such as 4326delTC, Gln1412X, 4279insA, *etc.*, and result in decreased CFTR stability. The classification of the identified mutations is very important in every ethnic group because of the selection and combinations of CFTR modulator drugs.

So far, Asian patients with CF have been reported relatively few, except Chinese patients.[8-15] Asian patients do not have a worse clinical phenotype.[16] Asian patients show lower sweat chloride and higher pancreatic sufficiency than non-Asian patients. The reported mutations from Asian patients are quite different from those from Europeans. Among 140 mutations from Caucasians, only 21 mutations share with Chinese, who do not share another 32 mutations. Among the mutations found in Chinese patients with CF, 60.4% {32/(21 + 32)} are Chinese-specific.[15] The other Asian ethnic groups have not been well studied on the scale of population aspect.

Based on the literature, Asian ethnic groups can be divided into 2 groups: East Asians (EAS) including Chinese, Korean, and Japanese, and non-East Asians (ANE) including Southeast Asians and Middle East Asians.[8-15] Reported (likely) pathogenic variants (LPV/PV) from literature are listed and compared between EAS and ANE. A reported number of LPV/PV types are 160 for EAS and 106 for ANE. Overlapped variants are 18 and account for relatively a small portion of each group (for EAS, 18/160 = 11%, ANE, 18/106 = 17%) (**Figure A**). The next question is how much LPV/PV appears in each ethnic group and overlaps. Recently, population genome sequencing databases have been established, and the gnomAD is the largest.[17] In the gnomAD data, 34,029 genomes are represented for non-Finnish Europeans (NFE), 2,604 for EAS, and 2,577 for ANE (Southeast Asians, 2,419 genomes and Middle East Asians 158 genomes). When the variants from the CFTR2 database (www.cftr2.org) were applied to the gnomAD database, 401 CF-causing variants and 49 variants of varying clinical consequences are included as PV/LPVs. Only 10 variants appeared in EAS and 18 in ANE (**Figure B**). A relatively small number of the Asian population genome is included in the gnomAD compared to the European population, and this number does not reflect the accurate feature of the mutation spectrum among different ethnic groups. Based on gnomAD allele count, the LPV/PV allele frequencies can be counted in each ethnic group. For the NFE group, allele frequency is 0.00725 as a whole. In contrast, it is 0.00327 for EAS and 0.01304 for ANE. Surprisingly, the ANE group shows higher allele frequency than Europeans. Considering the relatively small number of population (2,577 genomes), a larger population genome and clinical detection of patients with CF or population screening of patients

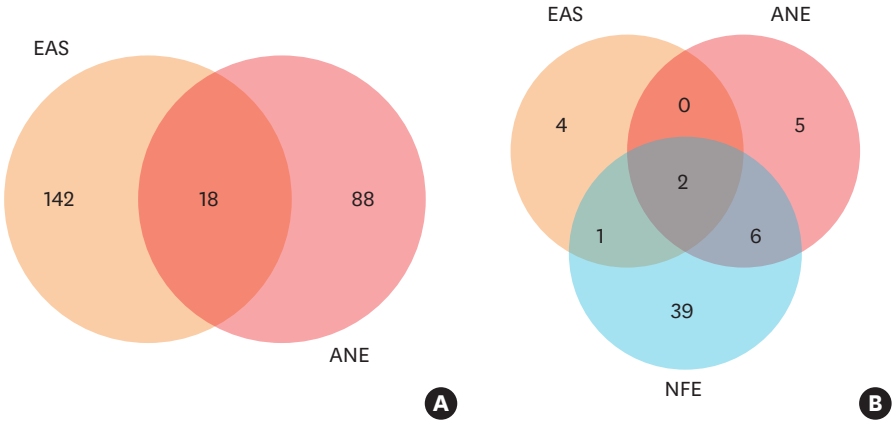

Figure. Comparison of CFTR LPV/PV. (A) LPV/PVs from the literature. Within the Asian area, EAS and ANE (Southeast Asians and Middle East Asians) share a minor portion of variants. (B) In the gnomAD database, the number of LPV/PVs in each ethnic group is counted according to the CFTR2 database. CF-causing and Varying clinical consequence variants are counted as LPV/PV.
CFTR, cystic fibrosis transmembrane conductance regulator; LPV/PV, (likely) pathogenic variants; EAS, East Asian (2,604 genomes); ANE, non-East Asian (2,577 genomes) are counted as Southeast Asians (2,419 genomes) and Middle East Asians (158 genomes); NFE, non-Finnish European (34,029 genomes).

https://doi.org/10.4168/aair.2022.14.5.444

with CF need to justify this finding. Also, the EAS and ANE groups show a broad mutation spectrum and heterogeneity. It implicates the detection, identification, and functional classification of PV/LPVs from patients with CF in the Asian ethnic group is critical.

REFERENCES

1. Elborn JS. Cystic fibrosis. Lancet 2016;388:2519-31.
PUBMED | CROSSREF
2. Chen Q, Shen Y, Zheng J. A review of cystic fibrosis: basic and clinical aspects. Animal Model Exp Med 2021;4:220-32.
PUBMED | CROSSREF
3. Cystic Fibrosis Foundation. CF Foundation estimates increase in CF population [Internet]. Bethesda (MD): Cystic Fibrosis Foundation; c2022 [cited 2022 Jul 28]. Available from: https://www.cff.org/news/2022-07/cf-foundation-estimates-increase-cf-population.
4. Palomaki GE, FitzSimmons SC, Haddow JE. Clinical sensitivity of prenatal screening for cystic fibrosis via CFTR carrier testing in a United States Panethnic population. Genet Med 2004;6:405-14.
PUBMED | CROSSREF
5. Sanders DB, Chmiel JF. Drug development for cystic fibrosis. Pediatr Pulmonol 2021;56 Suppl 1:S10-22.
PUBMED | CROSSREF
6. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2020;8:65-124.
PUBMED | CROSSREF
7. Cystic Fibrosis Foundation. CFTR modulator therapies [Internet]. Bethesda (MD): Cystic Fibrosis Foundation; c2022 [cited 2022 Jul 28]. Available from: https://www.cff.org/managing-cf/cftr-modulator-therapies.
8. Singh M, Rebordosa C, Bernholz J, Sharma N. Epidemiology and genetics of cystic fibrosis in Asia: in preparation for the next-generation treatments. Respirology 2015;20:1172-81.
PUBMED | CROSSREF
9. Semple A, Clark T, Allen NM, Krishnananthan T, Nwokoro C, Girodon E, et al. Identification of a novel cystic fibrosis mutation in three patients of South Asian descent. Clin Respir J 2020;14:586-8.
PUBMED | CROSSREF
10. Feng J, Zhang Y, Yang X, Zhang Y. Heterogeneous spectrum of CFTR gene mutations in Chinese patients with CAVD and the dilemma of genetic blocking strategy. Reproduction 2022;164:R47-56.
PUBMED | CROSSREF
11. Jung H, Ki CS, Koh WJ, Ahn KM, Lee SI, Kim JH, et al. Heterogeneous spectrum of CFTR gene mutations in Korean patients with cystic fibrosis. Korean J Lab Med 2011;31:219-24.
PUBMED | CROSSREF
12. Sohn YB, Ko JM, Jang JY, Seong MW, Park SS, Suh DI, et al. Deletion of exons 16-17b of CFTR is frequently identified in Korean patients with cystic fibrosis. Eur J Med Genet 2019;62:103681.
PUBMED | CROSSREF
13. Zheng B, Cao L. Differences in gene mutations between Chinese and Caucasian cystic fibrosis patients. Pediatr Pulmonol 2017;52:E11-4.
PUBMED | CROSSREF
14. Schrijver I, Pique L, Graham S, Pearl M, Cherry A, Kharrazi M. The spectrum of CFTR variants in nonwhite cystic fibrosis patients: implications for molecular diagnostic testing. J Mol Diagn 2016;18:39-50.
PUBMED | CROSSREF
15. Ni Q, Chen X, Zhang P, Yang L, Lu Y, Xiao F, et al. Systematic estimation of cystic fibrosis prevalence in Chinese and genetic spectrum comparison to Caucasians. Orphanet J Rare Dis 2022;17:129.
PUBMED | CROSSREF
16. Bosch B, Bilton D, Sosnay P, Raraigh KS, Mak DY, Ishiguro H, et al. Ethnicity impacts the cystic fibrosis diagnosis: a note of caution. J Cyst Fibros 2017;16:488-91.
PUBMED | CROSSREF
17. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature 2020;581:434-43.
PUBMED | CROSSREF