Original Article
Diagnostic Genetics

Ann Lab Med 2025;45:77-84
https://doi.org/10.3343/alm.2024.0242
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Carrier Frequency and Incidence of *MUTYH*-Associated Polyposis Based on Database Analysis in East Asians and Koreans

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Background: *MUTYH*-associated polyposis is an autosomal recessive disorder associated with an increased lifetime risk of colorectal cancer and a moderately increased risk of ovarian, bladder, breast, and endometrial cancers. We analyzed the carrier frequency and estimated the incidence of *MUTYH*-associated polyposis in East Asian and Korean populations, for which limited data were previously available.

Methods: We examined 125,748 exomes from the gnomAD database, including 9,197 East Asians, and additional data from 5,305 individuals in the Korean Variant Archive and 1,722 in the Korean Reference Genome Database. All *MUTYH* variants were interpreted according to the American College of Medical Genetics and Genomics and Association for Molecular Pathology guidelines and the Sequence Variant Interpretation guidelines from ClinGen.

Results: The global carrier frequency of *MUTYH*-associated polyposis was 1.29%, with Europeans (non-Finnish) having the highest frequency of 1.86% and Ashkenazi Jews the lowest at 0.06%. East Asians and Koreans had a carrier frequency of 0.35% and 0.37% and an estimated incidence of 1 in 330,409 and 1 in 293,304 in Koreans, respectively, which were substantially lower than the global average of 1 in 24,160 and the European (non-Finnish) incidence of 1 in 11,520.

Conclusions: This was the first study to investigate the frequency of carriers of *MUTYH*-associated polyposis in East Asians, including specific subgroups, utilizing gnomAD and a Korean genome database. Our data provide valuable reference information for future investigations of *MUTYH*-associated polyposis to understand the genetic diversity and specific variants associated with this condition in East Asian populations.

Key Words: *MUTYH*-associated polyposis, Carrier frequency, Incidence, East Asian

Received: May 13, 2024
Revision received: June 23, 2024
Accepted: September 11, 2024
Published online: November 5, 2024

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INTRODUCTION

MUTYH-associated polyposis, an autosomal recessive disease (OMIM #608456), results from mutations in *MUTYH*. Biallelic pathogenic variants of *MUTYH* are associated with an increased lifetime risk of colorectal cancer and a moderately increased risk for malignancies of the ovaries, bladder, breast, and endometrium [1-5]. Adenine DNA glycosylase, encoded by *MUTYH*, participates in the repair of base excisions and endogenous DNA damage, including oxidative stress, in human cells. Defects in this repair mechanism due to loss-of-function mutations in *MUTYH* can lead to an accumulation of mutations, contributing to the development of colorectal adenomas and carcinomas [6, 7].

The risk of colorectal cancer in patients with biallelic *MUTYH*-associated polyposis is significantly high, with a 43% risk by the age of 60 yrs [8]. Win, *et al*. [9] reported that monoallelic *MUTYH* variants are associated with lower risk but still increase the likelihood of developing colorectal cancer, with an odds ratio of 1.15 (95% confidence interval [CI]=0.98–1.36). However, Thompson *et al*. [10] reported no association between monoallelic *MUTYH* variants and increased cancer risk.

The prevalence of carriers of heterozygous germline pathogenic variants in *MUTYH* reportedly is 1%–2% in populations in the United Kingdom, Australia, Canada, and the United States [4, 11, 12]. To date, studies have primarily been conducted in Western populations, and investigations into the frequency of *MUTYH* carriers in East Asians are limited, highlighting the importance of further investigation in this region and population-specific studies.

While *MUTYH*-associated polyposis is characterized by genetic heterogeneity, with most mutations being distinct to individual families, a few relatively common mutations have been identified. The prevalent variants NM_001048174.2:c.452A>G, p.(Tyr151Cys) (also annotated as c.536A>G, p.(Tyr179Cys) or c.494A>G, p.(Tyr165Cys)) and NM_001048174.2:c.1103G>A, p.(Gly368Asp) (also annotated as c.1187G>A, p.(Gly396Asp) or c.1145G>A, p.(Gly382Asp)) are generally recognized as founder mutations of northwestern European origin. These variants account for approximately 80% of *MUTYH* pathogenic variants observed in Europeans but are extremely rare in Asia [13].

Genomic databases comprised of diverse ethnic groups are an important resource for predicting carrier frequencies and performing prospective incidence studies. GnomAD v2 is a global genomic database that contains 125,748 exomes, including 9,197 from East Asian populations [14]. The Korean Variant Archive (KOVA) database offers a reference for genetic variations in the Korean population and comprises 1,896 whole-genome sequencing and 3,409 whole-exome sequencing projects [15]. The Korean Reference Genome Database (KRGDB) contains whole-genome sequencing data from 1,722 Koreans [16].

We applied the 2015 American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP) guidelines to examine *MUTYH* variants using exome and genomic data from these databases [17]. Our primary objective was to determine the worldwide carrier frequency and to estimate the incidence of *MUTYH*-associated polyposis, with a particular focus on East Asian populations, which have been underrepresented in previous studies [4, 11, 12].

MATERIALS AND METHODS

Population database

We acquired data on *MUTYH* from gnomAD (v2.1.1) (https://gnomad.broadinstitute.org/). We analyzed 125,748 exomes from various populations: 9,197 from East Asian, 8,128 from African/African-American, 17,296 from Latino/Admixed American, 5,040 from Ashkenazi Jewish, 10,824 from Finnish, 56,885 from non-Finnish European, 15,308 from South Asian, and 3,070 from other populations. The East Asian population comprised 1,909 Koreans, 76 Japanese, and 7,212 individuals from other East Asian ancestries. We excluded variants marked with "InbreedingCoeff," "AC0," or "RF" QC filters in gnomAD. For Korean-specific data, we utilized KOVA, housing information from 5,305 Koreans (https://www.kobic.re.kr/kova/, accessed on November 6, 2023), and KRGDB, which contains data from 1,722 Koreans (http://coda.nih.go.kr/coda/KRGDB/index.jsp, accessed on September 25, 2021). We included single-nucleotide variants and small insertions/deletions but not copy-number variants.

Classification and statistical analysis of *MUTYH* variants

All *MUTYH* variants were interpreted according to the ACMG/AMP guidelines and Sequence Variant Interpretation guidelines from ClinGen (https://clinicalgenome.org/working-groups/sequence-variant-interpretation/, accessed on November 11, 2023). These guidelines recommend classifying variants into five categories: pathogenic variants (PVs), likely pathogenic variants (LPVs), variants of uncertain significance, likely benign variants, and benign variants. For *in-silico* prediction of variant pathogenicity, we used REVEL [18] and SpliceAI [19]. We compared all *MUTYH* variants identified in the population databases

with previously characterized disease-causing variants sourced from ClinVar and the Human Gene Mutation Database (HGMD). ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/, accessed on November 11, 2023) is an openly accessible repository hosting variant classifications contributed by clinical laboratories. The HGMD professional database (http://www.hgmd.org/, released in March, 2023) is an extensive repository of germline variants categorized into six groups. We focused on disease-causing mutations (DM). All analyses were performed using the reference sequence NM_001048174.2 as the standard for identifying and categorizing *MUTYH* variants.

MUTYH–associated polyposis carrier frequency and incidence estimation

This study was approved by the Institutional Review Board of Hanyang University Guri Hospital, Guri, Korea (2021-06-029) in 2021 and was conducted in strict accordance with the Declaration of Helsinki. The carrier frequencies of *MUTYH*-associated polyposis were determined using a population database. We included variants classified as PVs and LPVs based on our interpretation according to the ACMG/AMP guidelines, DM entries from HGMD, as well as PV and LPV annotations from ClinVar. To estimate the incidence of *MUTYH*-associated polyposis, we used the Hardy–Weinberg equilibrium principle ($1=p^2+2pq+q^2$), where p represents the major allele (non-disease), and q the minor allele (disease). Given the approximation of the major allele p close to 1, carriers and disease states are indicated using 2pq and q^2, respectively. By deriving the q-value from carrier frequency data obtained from population databases, we predicted the estimated disease incidence q^2. Statistical analysis was conducted using R version 4.3.2 (R Core Team, 2023), and 95% CI was computed using the prop.test function in the stats package.

RESULTS

Global analysis of *MUTYH* variants

We analyzed 125,748 exomes from the gnomAD database, including 9,197 East Asian exomes, focusing on variants in *MUTYH* (Table 1). The carrier frequency and incidence for each population are shown in Fig. 1. When calculating the carrier frequency according to the classification based on the ACMG/AMP guidelines, the global prevalence of *MUTYH*-associated polyposis was 1.29%. The carrier frequency varied significantly among the populations. European (non-Finnish) populations had the highest carrier frequency of 1.86%, whereas Ashkenazi Jewish populations had the lowest carrier frequency of 0.06%. East Asians exhibited the second lowest carrier frequency of 0.35%. According to the ACMG/AMP guidelines, the incidence of *MUTYH*-associated polyposis is 1 in 24,160 worldwide, 1 in 11,520 in Europeans (non-Finnish), and 1 in 330,409 in East Asians.

Comparative global incidence based on various databases

According to ClinVar, the global carrier frequency for *MUTYH*-associated polyposis is 1.14%, corresponding to an estimated incidence of 1 in 30,801. According to HGMD data, the overall carrier frequency of *MUTYH*-associated polyposis was higher, at 2.08%, with an estimated incidence of 1 in 9,285. According to the ACMG/AMP guidelines, among East Asian populations in the gnomAD database, the carrier frequency among Koreans was 0.26%, with an estimated incidence of 1 in 583,085 (Table 2). Moreover, the analysis performed in line with these guidelines showed a *MUTYH*-associated polyposis carrier rate of 0.41% in the Korean population database KOVA (N=5,305). Similarly, in the KRGDB database (N=1,722), the carrier frequency was 0.35%. The estimated incidence of *MUTYH*-associated polyposis was 1 in 232,587 based on KOVA data and 1 in 329,476 based on KRGDB data. Integrating gnomAD, KOVA, and KRGDB data from 8,936 subjects, the carrier frequency of *MUTYH*-associated polyposis in the Korean population was 0.37%, with an estimated incidence of 1 in 293,304.

PVs and LPVs in *MUTYH*

The summary in Supplemental Data Table S1 describes *MUTYH* PVs/LPVs in the gnomAD database. Among these variants, c.1103G>A, p.(Gly368Asp) was the most prevalent globally, identified in 756 alleles. This variant was observed in several ethnic groups, especially European (non-Finnish) populations. The next most commonly observed variant was c.452A>G, p.(Tyr151Cys), found in 386 alleles. The c.452A>G variant was predominantly found in European (non-Finnish) ancestries but has not been found in East Asians. A comparison of PVs/LPVs in East Asians and other ethnic groups revealed notable differences. Specifically, the c.383G>A, p.(Typ128Ter) variant was most common in East Asian populations but was not observed in other ethnic groups.

PVs/LPVs found in the Korean database are summarized in Supplemental Data Table S2. In gnomAD, c.383G>A, which was the most common variant found in East Asians, was not found in Koreans. The c.13C>T, p.(Arg5Ter) variant was most commonly found in Koreans, followed by c.773G>A, p.(Gly258Glu) and c.715C>T, p.(Gln239Ter). These were rarely found in other ethnicities.

Table 1. Carrier frequency and estimated incidence of *MUTYH*-associated polyposis

Classification	Total alleles (N)	Carrier frequency (%) (95% CI)	Estimated incidence (1/N) (95% CI)
Total (N=125,748)			
ACMG/AMP (PV/LPV)	1,618	1.29 (1.23–1.35)	1/24,160 (1/26,634–1/21,919)
ClinVar (PV/LPV)	1,433	1.14 (1.08–1.20)	1/30,801 (1/34,167–1/27,770)
HGMD (DM)	2,610	2.08 (2.00–2.16)	1/9,285 (1/10,022–1/8,603)
East Asian (N=9,197)			
ACMG/AMP (PV/LPV)	32	0.35 (0.24–0.50)	1/330,409 (1/682,611–1/161,863)
ClinVar (PV/LPV)	27	0.29 (0.20–0.43)	1/464,114 (1/1,026,309–1/213,110)
HGMD (DM)	779	8.47 (7.91–9.06)	1/558 (1/639–1/487)
African (N=8,128)			
ACMG/AMP (PV/LPV)	38	0.47 (0.34–0.65)	1/183,004 (1/355,085–1/95,224)
ClinVar (PV/LPV)	32	0.39 (0.27–0.56)	1/258,064 (1/533,090–1/126,450)
HGMD (DM)	68	0.84 (0.66–1.07)	1/57,149 (1/93,211–1/35,198)
Latino (N=17,296)			
ACMG/AMP (PV/LPV)	232	1.34 (1.18–1.53)	1/22,232 (1/28,840–1/17,155)
ClinVar (PV/LPV)	211	1.22 (1.06–1.40)	1/26,877 (1/35,324–1/20,473)
HGMD (DM)	237	1.37 (1.20–1.56)	1/21,304 (1/27,558–1/16,485)
Ashkenazi Jewish (N=5,040)			
ACMG/AMP (PV/LPV)	3	0.06 (0.02–0.19)	1/11,289,600 (1/169,230,545–1/1,113,682)
ClinVar (PV/LPV)	3	0.06 (0.02–0.19)	1/11,289,600 (1/169,230,545–1/1,113,682)
HGMD (DM)	7	0.14 (0.06–0.30)	1/2,073,600 (1/10,794,561–1/445,248)
European (Finnish) (N =10,824)			
ACMG/AMP (PV/LPV)	84	0.78 (0.62–0.96)	1/66,417 (1/102,999–1/42,970)
ClinVar (PV/LPV)	81	0.75 (0.60–0.93)	1/71,428 (1/111,698–1/45,834)
HGMD (DM)	91	0.84 (0.68–1.04)	1/56,592 (1/86,212–1/37,261)
European (non-Finnish) (N=56,885)			
ACMG/AMP (PV/LPV)	1,060	1.86 (1.75–1.98)	1/11,520 (1/12,992–1/10,216)
ClinVar (PV/LPV)	942	1.66 (1.55–1.77)	1/14,587 (1/16,575–1/12,839)
HGMD (DM)	1,189	2.09 (1.97–2.21)	1/9,156 (1/10,255–1/8,176)
South Asian (N=15,308)			
ACMG/AMP (PV/LPV)	117	0.76 (0.64–0.92)	1/68,474 (1/99,141–1/47,392)
ClinVar (PV/LPV)	90	0.59 (0.48–0.73)	1/115,721 (1/176,788–1/75,964)
HGMD (DM)	175	1.14 (0.98–1.33)	1/30,607 (1/41,346–1/22,689)
Other (N=3,070)			
ACMG/AMP (PV/LPV)	52	1.69 (1.28–2.23)	1/13,942 (1/24,418–1/8,024)
ClinVar (PV/LPV)	47	1.53 (1.14–2.05)	1/17,066 (1/30,819–1/9,534)
HGMD (DM)	64	2.08 (1.62–2.67)	1/9,204 (1/15,211–1/5,605)

Abbreviations: ACMG/AMP, 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines; 95% CI, 95% confidence interval; DM, disease-causing variant; gnomAD, Genome Aggregation Database; LPV, likely pathogenic variant; PV, pathogenic variant; HGMD, Human Gene Mutation Database.

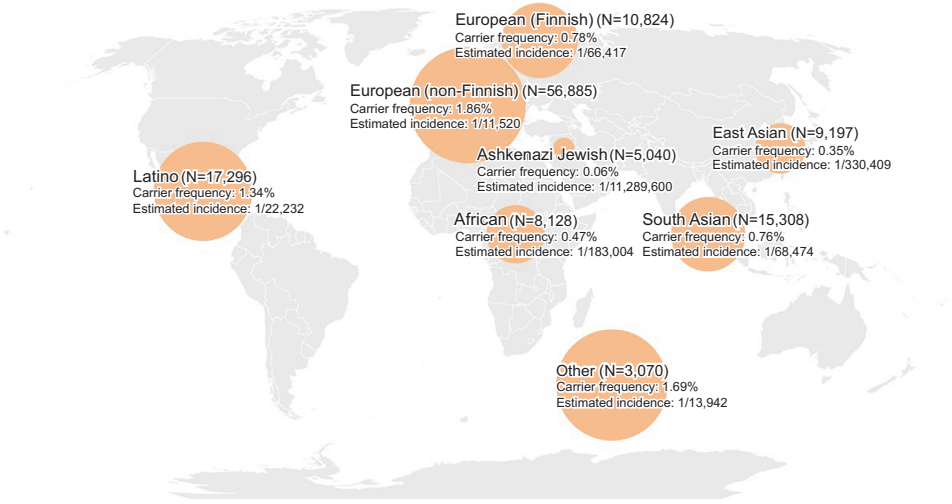

Fig. 1. Carrier frequency and estimated incidence of *MUTYH*-associated polyposis in gnomAD (v2.1.1) according to population. Circle size corresponds to the carrier frequency of *MUTYH*-associated polyposis.

DISCUSSION

This was the first study to investigate the carrier frequency and incidence of *MUTYH*-associated polyposis in an East Asian population. We used data from gnomAD and two Korean databases to analyze the carrier frequency and to estimate the incidence of *MUTYH*-associated polyposis. Our results revealed that East Asians have the second lowest carriage frequency globally for *MUTYH*-associated polyposis (0.35%). Combining data from the KOVA and KRGDB databases and analyzing data from 8,936 Koreans, we found a similar carrier frequency of 0.37%, closely mirroring the overall frequency in East Asia.

Carrier frequency studies of *MUTYH*-associated polyposis are rare, but previous studies have reported a frequency of 1%–2% [4, 5]. Concordantly, based on a genomic database, we found a carrier frequency of 1.29%. However, our analysis, focusing on different ethnic groups, revealed notable variations in carrier frequencies across ethnic groups. Specifically, the European (non-Finnish) population had the highest carrier frequency of 1.86%, whereas the Ashkenazi Jewish population had the lowest carrier frequency of 0.06%. East Asians had the second lowest carrier frequency of 0.30%.

When comparing variants identified in population databases, we observed differences in carrier frequencies based on interpretations according to the ACMG/AMP guidelines, ClinVar, and HGMD, especially for East Asians. The carrier frequency was 0.35% according to the ACMG/AMP guidelines and 0.29% according to ClinVar, but was substantially higher, at 8.47%, according to HGMD. This discrepancy can be attributed to the inclusion of certain variants classified as DM in HGMD, which are considered benign polymorphisms in East Asians. For instance, the c.11C>T, p.(Pro4Leu) and c.32G>A, p.(Gly11Asp) variants, which are benign in East Asians, are classified as DM in HGMD, leading to an inflated carrier frequency in this population.

According to data retrieved from the Korea Statistical Information Service (http://kosis.kr/, accessed on January 9, 2024), the total population of Korea as of 2022 is 51.7 million, and the number of births per year is 249,186. Our assessment of carrier frequency suggests that there are approximately 191,000 carriers in the overall population, with approximately 922 carriers born each year. Using Hardy–Weinberg equilibrium, the annual incidence of *MUTYH*-associated polyposis in Korea was calculated to be 0.9 cases.

The ACMG has published guidelines on secondary findings in subjects with two PVs/LPVs in *MUTYH* [20]. Additionally, the BabySeq project, a randomized controlled trial for newborn genetic screening, classified *MUTYH* as a category A gene, highlighting its importance for screening for highly penetrant childhood-onset disorders [21]. Therefore, carefully evaluating the presence of *MUTYH* variants during genetic testing, especially for individuals of European (non-Finnish) descent, who had the highest carrier frequency in this study, is crucial. Without timely surveillance, patients with *MUTYH*-associated polyposis have a lifetime risk of colorectal cancer of up to 90% [22, 23]. Once two PVs/LPVs are detected, establishing a corresponding surveillance plan is imperative to effectively monitor and manage their potential health effects.

Among the PVs/LPVs in *MUTYH* in the gnomAD database, the two most prevalent variants worldwide were c.1103G>A, p.(Gly368Asp) and c.452A>G, p.(Tyr151Cys). This finding is consistent with

Table 2. Carrier frequency and estimated incidence of *MUTYH* in East Asians and Koreans

Classification	Total alleles (N)	Carrier frequency (%)	Estimated incidence (1/N)
gnomAD East Asian exomes (N = 9,197)			
ACMG/AMP (PV/LPV)	32	0.35 (0.24–0.50)	1/330,409 (1/161,863–1/682,611)
ClinVar (PV/LPV)	27	0.29 (0.20–0.43)	1/464,114 (1/213,110–1/1,026,309)
HGMD (DM)	779	8.47 (7.91–9.06)	1/558 (1/487–1/639)
gnomAD Korean exomes (N = 1,909)			
ACMG/AMP (PV/LPV)	5	0.26 (0.10–0.65)	1/583,085 (1/95,243–1/4,298,410)
ClinVar (PV/LPV)	4	0.21 (0.07–0.57)	1/911,070 (1/121,041–1/8,872,642)
HGMD (DM)	137	7.18 (6.08–8.45)	1/777 (1/560–1/1,083)
gnomAD Japanese exomes (N = 76)			
ACMG/AMP (PV/LPV)	0	0 (0–6.00)	NA (1/1,113–NA)
ClinVar (PV/LPV)	0	0 (0–6.0)	NA (1/1,113–NA)
HGMD (DM)	4	5.26 (1.70–13.64)	1/1,444 (1/215–1/13,850)
gnomAD Other East Asian exomes (N = 7,212)			
ACMG/AMP (PV/LPV)	27	0.37 (0.25–0.55)	1/285,393 (1/131,103–1/630,970)
ClinVar (PV/LPV)	23	0.32 (0.21–0.49)	1/393,293 (1/169,061–1/932,900)
HGMD (DM)	638	8.85 (8.21–9.53)	1/511 (1/440–1/594)
All Korean (N = 8,936)			
ACMG/AMP (PV/LPV)	33	0.37 (0.26–0.52)	1/293,304 (1/145,303–1/598,920)
ClinVar (PV/LPV)	28	0.31 (0.21–0.46)	1/407,409 (1/189,781–1/887,395)
HGMD (DM)	474	5.30 (4.85–5.79)	1/1,422 (1/1,191–1/1,698)
gnomAD Korean exomes (N = 1,909)			
ACMG/AMP (PV/LPV)	5	0.26 (0.10–0.65)	1/583,085 (1/95,243–1/4,298,410)
ClinVar (PV/LPV)	4	0.21 (0.07–0.57)	1/911,070 (1/121,041–1/8,872,642)
HGMD (DM)	137	7.18 (6.08–8.45)	1/777 (1/560–1/1,083)
KOVA (N = 5,305)			
ACMG/AMP (PV/LPV)	22	0.41 (0.27–0.64)	1/232,587 (1/98,129–1/563,047)
ClinVar (PV/LPV)	18	0.34 (0.21–0.55)	1/347,445 (1/133,564–1/929,528)
HGMD (DM)	329	6.20 (5.57–6.89)	1/1,040 (1/842–1/1,287)
KRGDB (N = 1,722)			
ACMG/AMP (PV/LPV)	6	0.35 (0.14–0.80)	1/329,476 (1/62,877–1/1,991,652)
ClinVar (PV/LPV)	6	0.35 (0.14–0.80)	1/329,476 (1/62,877–1/1,991,652)
HGMD (DM)	8	0.46 (0.22–0.95)	1/185,330 (1/44,105–1/855,943)

Abbreviations: ACMG/AMP, 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guideline; 95% CI, 95% confidence interval; DM, disease-causing variant; gnomAD, Genome Aggregation Database; LPV, likely pathogenic variant; NA, not applicable; PV, pathogenic variant.

previous studies that consistently reported this variant as the most frequently observed in patients with *MUTYH*-associated polyposis [13]. Additionally, the c.452A > G variant is prevalent in European populations but has not been observed in East Asian or Ashkenazi Jewish populations. The c.383G > A, p.(Tyr128Ter) variant is most prevalent in East Asian populations but is noticeably absent in other ethnic groups. As a result of a comparative analysis of variants in Korean databases, c.1103G > A and c.452A > G, the two most frequently identified variants worldwide, were not observed in Koreans. Additionally, the c.383G > A mutation, which is most common in East Asians, has not been found in Koreans and has only been identified in other East

Asians. This highlights that differences exist among ethnicities and within East Asian populations.

PVs/LPVs found in Korean patients with *MUTYH*-associated polyposis patients were compared with variants identified in a Korean database. Among the total of 570 reported Korean patients with multiple polyposis, only two patients with biallelic variants were identified [24-27]. These patients had the following variants: NM_001048174.2:c.773G>A;c.1001C>T and NM_001048174.2:c.715C>T;c.1277A>C. Upon comparing the variants reported in patients in the Korean database, we found that the variants c.715C>T and c.773G>A identified in the Korean database were also present in Korean patients with multiple colonic polyps. c.715C>T is found only in East Asians, including Koreans, and c.773G>A is found only in Koreans, excluding other South Asians. Our findings suggest that predicting carriers from a population database helps predict the genetic spectrum of actual patients.

There are some limitations to this study. First, the analysis did not include large deletions or insertions in *MUTYH*, potentially resulting in an underestimate of the *MUTYH*-associated polyposis carrier frequency. The presence of *MUTYH* deletions has been reported in various patients [28, 29]. However, such variants could not be detected in the present study. Second, the predicted incidence may contain inaccuracies because it was based solely on genes registered in the genome database. Additionally, incorporating clinical information from patients was challenging; therefore, actual PVs/LPVs may have been interpreted as variants of uncertain significance. Additionally, because the penetrance of *MUTYH* is not 100%, the actual number of patients may be lower than expected. Finally, our analysis of the *MUTYH* variant spectrum among ethnicities revealed noticeable genetic differences; however, whether these correspond to known racial or ethnic genetic differences or have another significance remains unclear. While our study provides a preliminary overview, future studies with more comprehensive genetic data and analyses will be necessary to elucidate these relationships.

Despite the mentioned limitations, our findings positively validated the carrier frequency and estimated the incidence of *MUTYH*-associated polyposis across ethnic groups. Additionally, this is the most extensive *MUTYH* study conducted on East Asians, especially Koreans. Hence, our findings offer a more precise prediction of the carrier frequency and incidence among both East Asians and Koreans. Considering the recent progress in surveillance and treatments for *MUTYH*-associated polyposis, identifying the carrier frequency and incidence is crucial for effective management and intervention.

In summary, this study was the first to investigate the carrier frequency of *MUTYH*-associated polyposis in East Asians. We used gnomAD and the Korean genome database to confirm that, among various ethnic groups, East Asians have the second lowest frequency of *MUTYH*-associated polyposis carriers. The *MUTYH* variant spectrum of East Asians showed significant differences from those of other ethnic groups. Even within the same East Asian population, different variant distributions have been observed. These findings provide valuable reference data for future investigations of *MUTYH*-associated polyposis, contributing to a better understanding of the genetic diversity and specific variants associated with the condition in Eastern Asia.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3343/alm.2024.0242

ACKNOWLEDGEMENTS

The authors are grateful to those responsible for creating and maintaining the gnomAD, ClinVar, and HGMD databases.

AUTHOR CONTRIBUTIONS

Park JE participated in the analysis and interpretation of the data and the drafting of the manuscript; Lee T participated in the acquisition and analysis of data. Cho EH, Jang MA, Won D, and Park B participated in the analysis and interpretation of the data; Ki CS and Kong SY participated in the study concept and design, drafting of the manuscript, and providing important intellectual content. All authors have read and approved the manuscript.

CONFLICTS OF INTEREST

None declared.

RESEARCH FUNDING

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (NRF-2021R1I1A1A01049183), and by a grant of the Korean Cancer Survivors Healthcare R&D Project through the National Cancer Center

funded by the Ministry of Health & Welfare, Korea (RS-2023-CC139201).

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