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Estimating the Prevalence of Autosomal Recessive Neuromuscular Diseases in the Korean Population

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ABSTRACT

Background: Genetic neuromuscular diseases (NMDs) are a heterogeneous group of conditions that primarily affect the peripheral nerves, muscles, and neuromuscular junctions. This study was performed to identify pathogenic or likely pathogenic variants (PLPVs), calculate carrier frequencies, and predict the genetic prevalence of autosomal recessive-NMDs (AR-NMDs) in a Korean population.
Methods: In total, 267 genes were associated with AR-NMDs. We analyzed genetic variants from 984 Korean whole genomes and identified PLPVs to assess the carrier frequency and genetic prevalence of the variants.
Results: We identified 165 PLPVs, including 75 literature verified and 90 manually verified variants. Most PLPVs in AR-NMD genes were frameshifts (61, 37.0%), followed by nonsense (36, 21.8%), missense (35, 21.2%), and splice variants (28, 17.0%). The carrier frequency of the AR-NMDs was 27.1%. *DYSF* exhibited the highest carrier frequency (1.63%), followed by *GAA* (1.55%), *HEXB* (1.53%), *PREPL* (0.76%), *NEB* (0.66%), *ADSS1* (0.65%), *ALPK3* (0.65%), and *CHRNG* (0.65%). The predicted genetic prevalence of AR-NMDs in the Korean population was 38.0 cases per 100,000 individuals. *DYSF* (6.7 cases per 100,000 individuals) showed the highest genetic prevalence. The variant with the highest allele frequency was c.1250C>T in *HEXB* at 0.00764, followed by c.[752T>C; c.761C>T] in *GAA* at 0.00505, and c.2055+2T>G in *DYSF* at 0.00437.
Conclusion: Our study suggests that 27.1% of the Korean population are healthy carriers of at least one AR-NMD causing PLPV, revealing the genetic prevalence of NMDs in the Korean population.

Keywords: Genetic Prevalence; Carrier Frequency; Human Genome; Genetic Neuromuscular Disease; Pathogenic Variant

INTRODUCTION

Genetic neuromuscular diseases (NMDs) represent a heterogeneous group of genetic conditions that primarily affect the peripheral nerves, muscles, and neuromuscular junctions. These diseases manifest as a broad spectrum of clinical symptoms, including

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Disclosure

The authors have no potential conflicts of interest to disclose.

Data Availability Statement

The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request. The Korea1K dataset is available from the Ulsan National Institute of Science and Technology (UNIST) under specific terms and conditions.

Author Contributions

Conceptualization: Kim SH. Data curation: Kim SH. Formal analysis: Kim SH. Funding acquisition: Park HJ. Investigation: Choi YJ. Methodology: Choi YJ. Project administration: Park HJ. Supervision: Choi YC, Park HJ. Validation: Choi YJ. Writing - original draft: Kim SH. Writing - review & editing: Choi YC, Kim SW, Shin HY, Park HJ.

muscle weakness, muscle atrophy, joint contractures, cardiomyopathy, exercise intolerance, sensory deficits, fatigue, myalgia, tremors, ataxia, and dysarthria. However, the specific symptoms depend on the disease subtype and implicated genes. Approximately 600 causative genes of NMDs have been identified.[1]

Epidemiological studies have investigated the occurrence, timing, and causes of diseases within populations.[2] These investigations provide essential data on the origin and risk factors of various diseases. The utility of epidemiological studies is multifaceted; they identify disease-associated risk factors, guide disease interventions, reveal disease incidence and prevalence over time, which is critical for recognizing public health threats, and inform the creation of health guidelines and policies. However, conducting epidemiological studies of genetic NMDs is challenging because of the infrequency, widespread distribution, and diagnostic intricacies of these diseases.[3] These diagnostic difficulties are compounded by the diverse and intricate processes involved in such studies, including history taking, physical examination, electrodiagnostic testing, pathological evaluation, and genetic analysis. Therefore, many epidemiological studies on NMDs have been conducted using diverse and non-unified diagnostic criteria and research methods.[4-8]

With the advent of next-generation sequencing, public databases including the Genome Aggregation Database (gnomAD) have been established to provide comprehensive information on human exomes and genomes.[9] These databases provide the proportion of individuals in the general population who carry pathogenic or likely pathogenic variants (PLPVs) in specific genes. This information is crucial for predicting the carrier frequency and genomic prevalence of autosomal recessive (AR) Mendelian diseases. Compared with previous studies that only analyzed patients diagnosed in hospitals, this epidemiological approach offers the advantage of analyzing wider populations and obtaining accurate genotypic information. Epidemiological studies have been conducted to evaluate several AR Mendelian diseases, including inherited retinal diseases and Upshaw-Schulman syndrome.[10,11]

We recently analyzed the carrier frequency and genetic prevalence of AR-NMDs worldwide using the gnomAD.[12] The Korea 1 K dataset contains approximately 1,000 Korean genomes with systematically collected clinical and biochemical data from blood and urine samples, thus providing valuable genomic information.[13] This dataset represents the general population, sourced from residents of Ulsan, a major city in South Korea. Given the high mobility characteristic of large urban areas, it is thought to encompass a broader genetic diversity. To evaluate the carrier frequency and predicted genomic prevalence of AR-NMDs, we investigated PLPVs within the genomic data from the Korea 1 K dataset, aiming to better understand the genetic landscape of AR-NMDs specific to Korean population.

METHODS

Selection of AR-NMD genes

We analyzed 584 NMD genes based on a gene list from an NMD database available at https://www.musclegenetable.fr. From this list, 269 AR NMD genes were identified. We excluded *LAMA5* and *LAMB2* because of their associations with multisystem disorders. However, we included *CAPN3* despite its dual inheritance patterns (autosomal dominant and recessive) because of its important role in AR-NMDs. We analyzed the genomic data of 267 AR-NMD genes (**Supplementary Table 1**).

Analysis of pathogenicity of variants from the 984 Korean whole genomes

We analyzed genetic variants from 984 Korean whole genomes from among the 1,094 genomes in the Korea1K dataset.[13] All variants in AR-NMD genes were classified according to pathogenicity as described previously.[12] Information on literature verified variants was compiled from genetic databases such as the Leiden Open Variation Database (https://databases.lovd.nl/shared/genes), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), and Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/). Previously unreported variants were manually analyzed for their pathogenic potential according to the 2015 guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology.[14]

Analysis of allele frequency, carrier frequency, and predicted genetic prevalence

All PLPVs were heterozygous in all 984 whole Korean genomes. We calculated the allele and carrier frequencies for a single variant as follows: allele frequency was defined as the allele count for a single variant divided by the total allele number, and carrier frequency was defined as two-fold of the allele frequency, as previously described.[11] We then determined the carrier frequency and predicted genetic prevalence at the gene level as described previously.[11,12]

$$\text{Carrier Frequency at the Gene Level} = 1 - \prod_{i=1}^{n}(1 - \text{Carrier Frequency for a Single Variant})$$

$$\text{Predicted Genetic Prevalence at the Gene Level} = \sum_{k=1}^{n}(\text{Carrier Frequency for a Single Variant})_{ik} \times (\text{Carrier Frequency of a Single Variant})_{ik}$$

Ethics statement

This study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Korea (approval number: 3-2024-0130). The requirement for written informed consent was waived by the board because all data were obtained from a dataset of 984 Korean whole genomes, and all personal information was anonymously encrypted according to a strict confidentiality protocol.

RESULTS

Identification of PLPVs of AR-NMD genes

Fig. 1 and **Supplementary Table 2** illustrate the analytical process used to evaluate the variants in the AR-NMD genes. We identified 356,794 AR-NMD variants in the 984 Korean genomes. These variants were divided into two main groups: 815 truncating variants and 355,979 non-truncating variants. Among the truncating variants, the majority (633) had an allele frequency of less than 0.005. We identified 126 truncating PLPVs (36 literature verified and 90 manually verified variants). Among the 355,979 non-truncating variants, 3,157 variants had references in scientific literature, whereas 352,822 did not. We identified 39 non-truncating PLPVs, all of which have been verified in the literature. Overall, 165 PLPVs

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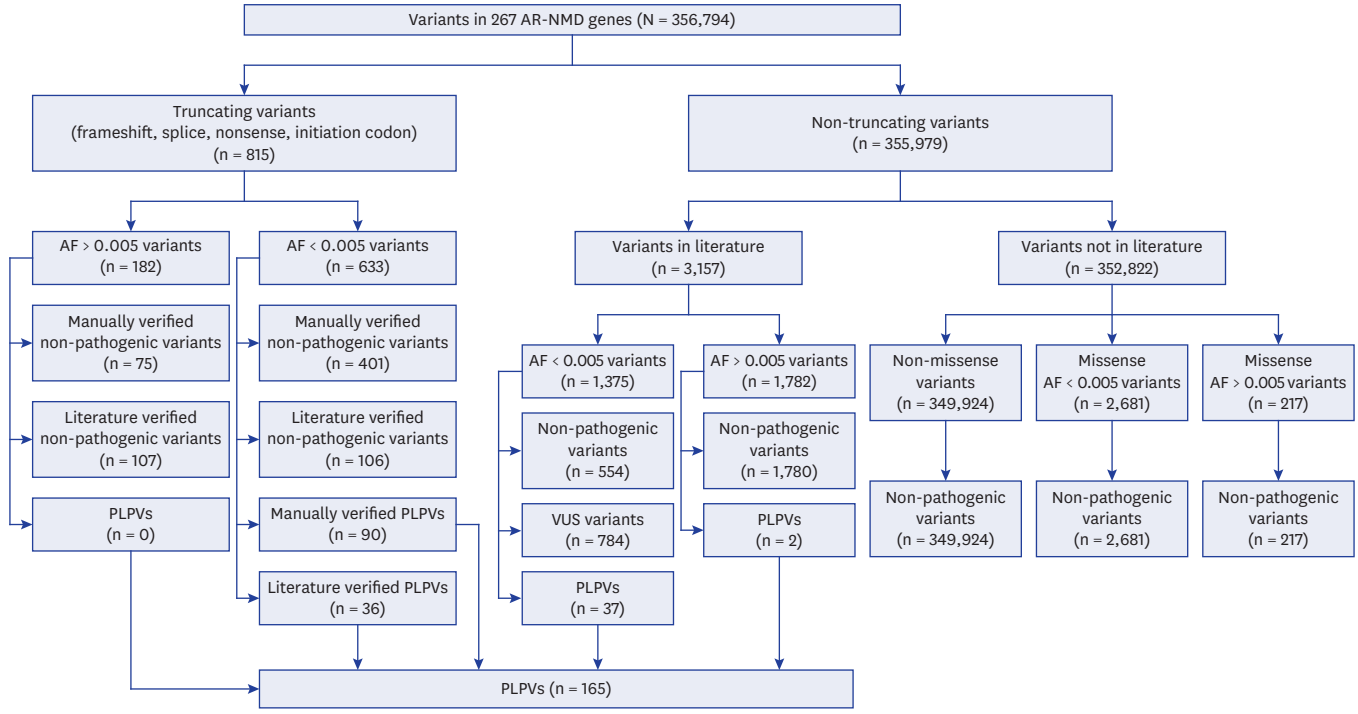

Fig. 1. Analytical scheme for AR-NMDs gene variants. Flowchart of the evaluation of 356,794 AR-NMD variants from 984 Korean whole genomes. We identified 126 truncating and 39 non-truncating PLPVs, totaling 165 PLPVs.
AR-NMD = autosomal recessive neuromuscular disease, AF = allele frequency, PLPV = pathogenic or likely pathogenic variant, VUS = variant of uncertain significance.

were identified, of which 75 (45.5%) were verified PLPVs and 90 (54.5%) were manually verified (**Supplementary Table 3**). All manually verified PLPVs (90) were truncating variants and classified as PLPVs based on two criteria: 1) being a null variant in a gene where loss-of-function is a known disease mechanism and 2) its absence or extremely low frequency in the gnomAD.

Characterization of PLPVs

The distribution of PLPVs is presented in three pie charts (**Fig. 2**). Most PLPVs in AR-NMD genes were frameshifts (61, 37.0%), followed by nonsense (36, 21.8%), missense (35, 21.2%), and splice variants (28, 17.0%) (**Fig. 2A**). Missense variants (35, 46.7%) were predominant among the PLPVs reported in the literature (**Fig. 2B**). However, all manually verified PLPVs were null variants, with frameshift variants (44, 48.9%) being the most common (**Fig. 2C**).

Common AR-NMD genes in the Korean population

Fig. 3 and **Supplementary Table 4** show the carrier frequency and predicted genetic prevalence of each AR-NMD gene in the Korean population. Carriers of AR-NMDs were predicted to comprise 27.10% of the Korean population (**Fig. 3A**). Among them, *DYSF* showed the highest carrier frequency (1.63%), followed by *GAA* (1.55%), *HEXB* (1.53%), *PREPL* (0.76%), *NEB* (0.66%), *ADSS1* (0.65%), *ALPK3* (0.65%), and *CHRNG* (0.65%). The predicted genetic prevalence of AR-NMD was 38.0 cases per 100,000 individuals in the Korean population (**Fig. 3B**). The highest predicted genetic prevalence was *DYSF* (6.7 cases per 100,000 individuals), followed by *GAA*, *HEXB*, *PREPL*, *NEB*, *ADSS1*, *ALPK3*, and *CHRNG* at 6.1, 5.8, 1.5, 1.1, 1.1, 1.1, and 1.1 cases per 100,000 individuals, respectively.

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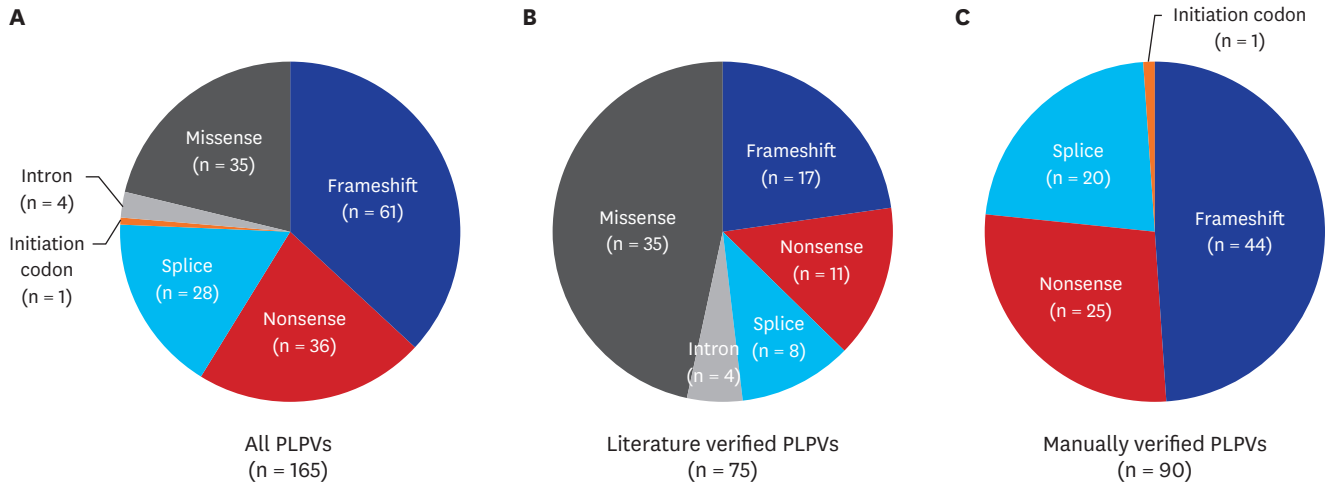

Fig. 2. Characterization of PLPVs. Distribution of 165 PLPVs across 267 autosomal recessive neuromuscular disease-related genes. (**A**) All PLPVs. (**B**) Literature verified PLPVs. (**C**) Manually verified PLPVs. Pie charts show frameshift (37.0%), nonsense (21.8%), missense (21.2%), and splice site (17.0%) variants.
PLPV = pathogenic or likely pathogenic variant.

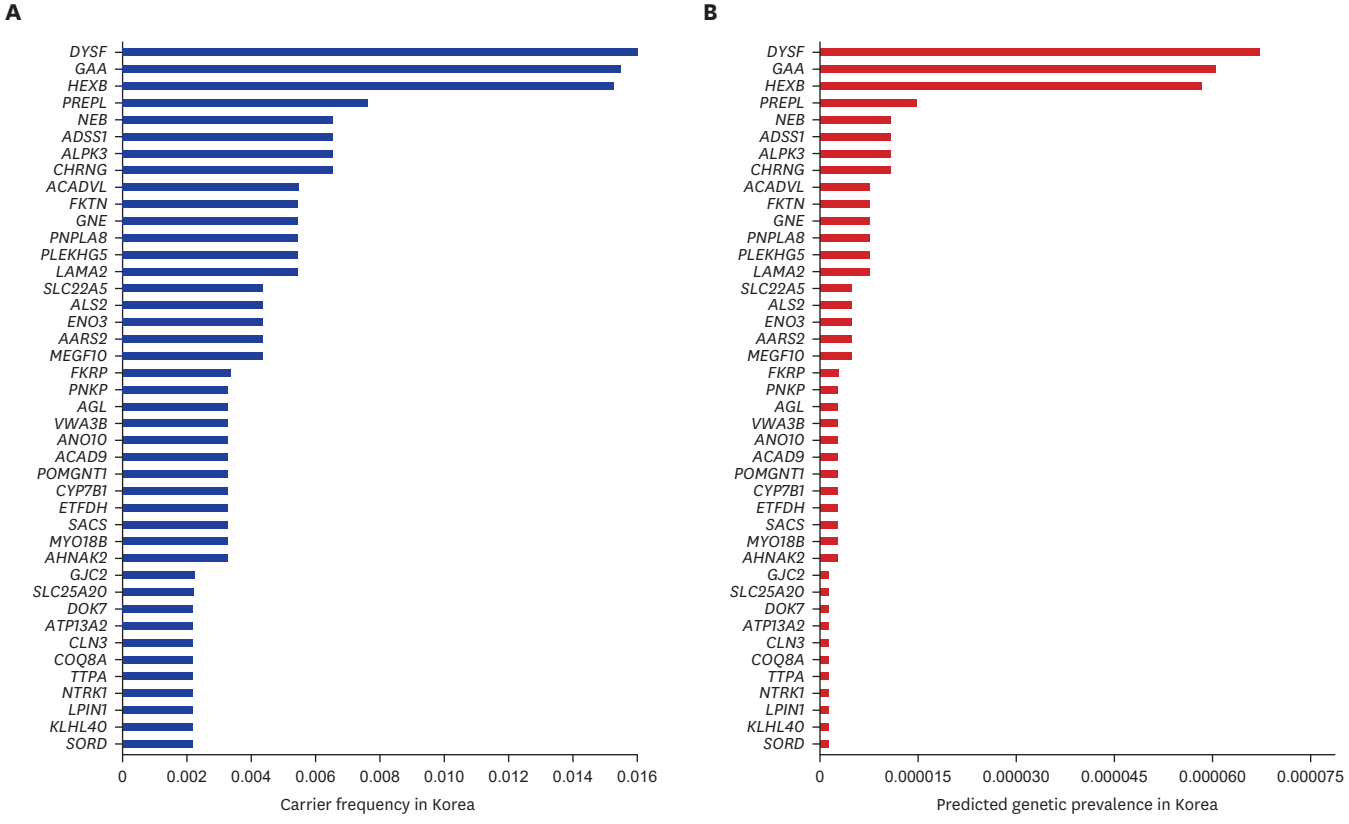

Fig. 3. Carrier frequency and predicted genetic prevalence of AR-NMDs genes in Korea. (**A**) Carrier frequency of AR-NMD related genes, with *DYSF* (1.63%), *GAA* (1.55%), and *HEXB* (1.53%) showing the highest frequencies. (**B**) Genetic prevalence, highlighting *DYSF*, *GAA*, and *HEXB*.
AR-NMD = autosomal recessive neuromuscular disease.

Allele frequencies of PLPVs of AR-NMD genes

Table 1 shows the allele frequencies of each PLPV associated with AR-NMDs in the Korean population. The variants with the highest allele frequency were c.1250C>T in *HEXB* at 0.00764, followed by c.[752T>C; c.761C>T] in *GAA* at 0.00505, c.2055+2T>G in *DYSF* at

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Table 1. Allele frequencies of top 36 pathogenic or likely pathogenic variants linked to autosomal recessive neuromuscular disease genes in Korea population

Genes	Reference transcript	Transcript consequence	Allele frequency
HEXB	ENST00000261416.7	c.1250C>T	0.00764
GAA	ENST00000302262.3	c.[752C>T: c.761C>T]	0.00505
DYSF	ENST00000258104.3	c.2055+2T>G	0.00437
PREPL	ENST00000260648.6	c.2020+1G>T	0.00382
NEB	ENST00000397345.3	c.21522+3A>G	0.00328
ADSS1	ENST00000330877.2	c.919delA	0.00273
SLC22A5	ENST00000245407.3	c.1400C>G	0.00218
GNE	ENST00000396594.3	c.1807G>C	0.00218
FKTN	ENST00000357998.5	c.648-1243G>T	0.00218
PLEKHG5	ENST00000422087.1	c.1988C>T	0.00164
DYSF	ENST00000258104.3	c.1284+2T>C	0.00164
ALS2	ENST00000264276.6	c.3182+2T>G	0.00164
DST	ENST00000244364.6	c.8740-1G>T	0.00164
PNPLA8	ENST00000257694.13	c.432dup	0.00164
ALPK3	ENST00000258888.5	c.4234C>T	0.00164
GJC2	ENST00000366714.2	c.-19-2A>G	0.00112
POMGNT1	ENST00000371992.1	c.1011dupT	0.00109
PLEKHG5	ENST00000422087.1	c.2458G>C	0.00109
NTRK1	ENST00000524377.1	c.851-33T>A	0.00109
AGL	ENST00000361915.3	c.3204_3205dup	0.00109
ADCK3	ENST00000366777.3	c.1027C>T	0.00109
VWA3B	ENST00000477737.1	c.1865A>C	0.00109
LPIN1	ENST00000449576.2	c.2656C>T	0.00109
DYSF	ENST00000258104.3	c.2494C>T	0.00109
CHRNG	ENST00000389494.3	c.240+1del	0.00109
CHRNG	ENST00000389494.3	c.428C>G	0.00109
KLHL40	ENST00000287777.4	c.1582G>A	0.00109
ANO10	ENST00000292246.3	c.132del	0.00109
ACAD9	ENST00000308982.7	c.1552C>T	0.00109
LAMA2	ENST00000421865.2	c.2049_2050del	0.00109
PNPLA8	ENST00000257694.13	c.438_439insAAAAAAAAAA	0.00109
TTPA	ENST00000260116.4	c.303T>G	0.00109
CLN3	ENST00000569430.1	c.838-2A>G	0.00109
ENO3	ENST00000519584.1	c.399_400insG	0.00109
SORD	ENST00000267814.9	c.757del	0.00109
ALPK3	ENST00000258888.5	c.691C>T	0.00109

0.00437, c.2020+1G>T in *PREPL* at 0.00382, c.21522+3A>G in *NEB* at 0.00328, and c.919del in *ADSS1* at 0.00273.

DISCUSSION

We analyzed the carrier frequency and predicted the genetic prevalence of AR-NMDs in the Korean population using 984 whole-genome sequences. We identified 165 PLPVs among 267 AR-NMD-related genes. The pathogenicity of 75 variants was confirmed using databases and the literature, whereas 90 variants were manually verified according to the 2015 ACMG guidelines. Therefore, we revealed the precise pathogenicity of AR-NMDs variants in the Korean population.

Characterization of PLPVs in AR-NMDs revealed that frameshift variants were the most prevalent, accounting for 37.0% of all identified PLPVs. In contrast, literature verified variants encompassed a broad spectrum of variant types; all manually verified variants were null, including frameshift, nonsense, splice, and initial codon variants. This predominance of

null variants may be attributed to the relative ease of classifying them as PLPVs, whereas classifying missense variants is challenging because of their complex nature according to the 2015 ACMG guidelines.[14] This finding is consistent with that of a previous analysis of the gnomAD.[12]

The carrier frequency of AR-NMDs in the Korean population is 27.1%, which is lower than the global average of 32.9%.[12] **Table 2** shows a comparison of the carrier frequencies of the top 20 causative AR-NMDs genes in Korea with those in global and regional populations.[12] Both similarities and differences were observed in carrier frequencies between Korean and global populations. Notably, the carrier frequency of individuals with PLPVs in *DYSF* was highest in Korea (1.63%), surpassing those in the global population (0.46%).[12] Our study is the first to analyze the frequency of AR-NMD carriers in Koreans, and there is insufficient evidence to determine whether carriers with PLPVs in *DYSF* are the most common among AR-NMD carriers. However, we previously reported that dysferlinopathy caused by PLPVs in *DYSF* was the most common AR genetic myopathy in Korea.[15-17] The carrier frequency of individuals with PLPVs in *GAA* in the Korean population (1.55%) was similar to that in the global population (1.31%), including in East Asian (1.58%), non-Finnish European (1.70%), and African/African American (1.26%). Additionally, a separate dataset analysis of the Korean population reported a GAA carrier frequency of 1.7%, consistent with our findings, further validating that our dataset accurately represents the Korean genotype. Furthermore, an independent analysis of another dataset based on the Korean population reported a *GAA* carrier frequency of 1.7%, consistent with our findings, confirming that our dataset accurately reflects the Korean genotype.[18] The similar carrier frequencies of individuals with *GAA* in the Korean and various other populations indicate that Pompe disease is a prevalent condition caused by PLPVs in *GAA* across various ethnicities.[12,19] The carrier frequency of individuals with *ADSS1* in the Korean population (0.65%) was high compared with that of the

Table 2. Top 20 causative genes associated with autosomal recessive neuromuscular diseases between Korea and the previously reported gnomAD

Korea		gnomAD [12]											
		Global		AFR		AMR		EAS		NFE		SAS	
Genes	CF (%)	Genes	CF (%)	Genes	CF (%)	Genes	CF (%)	Genes	CF (%)	Genes	CF (%)	Genes	CF (%)
DYSF	1.63	*GAA*	1.31	*PGAM2*	1.38	*ANO5*	1.43	*GAA*	1.58	*GAA*	1.70	*GNE*	2.71
GAA	1.55	*ANO5*	0.88	*GAA*	1.26	*GAA*	0.85	*SLC22A5*	1.38	*ANO5*	1.07	*GAA*	0.69
HEXB	1.53	*NEB*	0.75	*NEB*	0.81	*LAMA2*	0.80	*NEB*	1.08	*PYGM*	0.78	*NEB*	0.56
PREPL	0.76	*PYGM*	0.59	*LAMA2*	0.81	*CRPPA*	0.72	*CAPN3*	0.81	*ACADVL*	0.71	*MYO9A*	0.56
NEB	0.66	*LAMA2*	0.55	*CAPN3*	0.72	*PYGM*	0.65	*ETFDH*	0.79	*NEB*	0.69	*AHNAK2*	0.55
ADSS1	0.65	*CAPN3*	0.54	*DYSF*	0.70	*MYO18B*	0.61	*DYSF*	0.73	*RAPSN*	0.64	*LAMA2*	0.50
ALPK3	0.65	*GNE*	0.49	*PEX7*	0.62	*NEB*	0.60	*AGRN*	0.66	*CAPN3*	0.61	*VWA3B*	0.44
CHRNG	0.65	*ATM*	0.49	*SPG11*	0.55	*DYSF*	0.57	*WWOX*	0.64	*ATM*	0.61	*ANO5*	0.38
ACADVL	0.55	*ACADVL*	0.47	*PYGM*	0.50	*HEXB*	0.55	*FKRP*	0.62	*LAMA2*	0.55	*SLC22A5*	0.37
GNE	0.55	*DYSF*	0.47	*VWA3B*	0.50	*PHYH*	0.54	*SPG11*	0.58	*FKRP*	0.54	*DYSF*	0.37
FKTN	0.55	*SPG11*	0.46	*APTX*	0.49	*CAPN3*	0.48	KLHL40	0.55	*SPG11*	0.53	*CAPN3*	0.36
PLEKHG5	0.55	*SLC22A5*	0.44	*AGL*	0.45	*AGL*	0.45	*LAMA2*	0.54	*UBA5*	0.51	*SPG11*	0.33
PNPLA8	0.55	*RAPSN*	0.41	*PLEKHG5*	0.42	*ALPK3*	0.40	*VPS41*	0.54	*GMPPB*	0.46	*WDR73*	0.30
LAMA2	0.55	*UBA5*	0.40	*SACS*	0.41	*SLC22A5*	0.40	*MARS2*	0.52	*DOK7*	0.46	*ATM*	0.28
SLC22A5	0.44	*FKRP*	0.37	*TRDN*	0.39	*ATM*	0.39	*ATM*	0.49	*DYSF*	0.43	*MYO18B*	0.27
ALS2	0.44	*GBE1*	0.36	*DOK7*	0.39	*PNKP*	0.36	*ZFYVE26*	0.45	*SLC22A5*	0.40	*CHRNG*	0.26
ENO3	0.44	*GMPPB*	0.36	*CAPN1*	0.37	*AP4B1*	0.35	*VWA3B*	0.43	*GBE1*	0.40	*HSPG2*	0.25
MEGF10	0.44	*GLE1*	0.35	*ATM*	0.37	*APTX*	0.35	*GNE*	0.41	*ADSS1*	0.38	EXOSC8	0.24
AARS2	0.44	*DOK7*	0.34	*MYO18B*	0.37	*ATP13A2*	0.33	*PYGM*	0.39	*AGL*	0.37	*PYGM*	0.23
FKRP	0.34	*MYO18B*	0.32	*MAP3K20*	0.36	*ADSS1*	0.32	*MYO9A*	0.38	*HEXB*	0.36	*RAPSN*	0.23

Colors are presented as unique identifiers for each gene, with the shades transitioning towards red to represent higher CF based on the Korean population. Deeper red tones indicate genes with the highest CF values within this dataset.
CF = carrier frequency, AFR = African/African American, AMR = Latino/admixed American, EAS = East Asian, NFE = non-Finnish European, SAS = South Asian.

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global population (0.28%).[12] *ADSS1* was first identified as causative gene for genetic myopathy in Korea and is the most common nemaline myopathy in Japan, a neighboring country of Korea.[20,21] However, the carrier frequency of individuals with PLPVs in *ANO5* (0.00%) was low compared with that in global populations (0.88%), including Latino/admixed American (1.43%) and non-Finnish European (1.07%) subpopulations. This result aligns with those of previous studies showing that anoctaminopathy caused by PLPVs in *ANO5* has a high prevalence in Northern European populations because of a founder PLPV[22] but is rare in Asian and Middle Eastern populations.[23-27]

We estimated the predicted genetic prevalence of AR-NMDs to be 38.0 cases per 100,000 individuals in Korea. A previous study of the global prevalence of NMDs using the same method reported a prevalence of 24.3 per 100,000 individuals, which is lower than that in Koreans.[12] This discrepancy may be attributed to the small study population (984 cases), potentially leading to over- or underestimation of allele frequencies. Although the carrier frequency of AR-NMDs in Korea (27.1%) is lower than the global average, the higher genetic prevalence could be influenced by the presence of dominant PLPVs in specific genes, particularly in smaller sample sizes. Additionally, high ethnic homogeneity and selective marriages influenced by social stratification may contribute to this higher prevalence.[28-30] Prevalence studies performed using classical methods showed that the prevalence of total NMDs ranges from 28.6 to 82.8 per 100,000 individuals.[31,32] Our results, based on PLPVs in causative genes, differ from those obtained in previous studies that relied on clinically diagnosed patients, making direct comparison challenging. Nevertheless, the predicted genetic prevalence of AR-NMDs in our study was higher than expected. This result can be explained by the following reasons. First, many major genes responsible for NMDs, including dystrophinopathy, myotonic dystrophy, facioscapulohumeral muscular dystrophy, and most cases of Charcot-Marie-Tooth diseases, are not inherited in an AR manner.[7] Second, we could not evaluate deletions or duplications of exons, including the exon 7 deletion found in 95% of patients with spinal muscular atrophy.[33] Third, exome and genome sequencing can only diagnose 30–40% of Mendelian diseases, suggesting that many patients cannot be identified using these methods alone.[34] Thus, AR-NMDs may be more prevalent than currently estimated, and further comprehensive studies are needed to better understand their true frequencies in the population.

Our study revealed high allele frequencies of PLPVs in *HEXB*, *GAA*, and *DYSF* in the Korean population. Our results are similar to the previously reported allele frequency of these PLPVs in the East Asian population, which included Koreans.[12] The allele frequency of c.1250C>T in *HEXB* was also very high at 0.00095 in the East Asian group compared with those in other groups in a previous study based on the gnomAD v2.1.1, but was around 1/8 lower than that in our study (0.00764).[12] In the most recent version of the gnomAD v.4.1.0 (https://gnomad.broadinstitute.org/), the allele frequency of this variant was highest in the East Asian population, at 0.00354, which is similar to our finding. The allele frequency of the second most common PLPV, c.[752C>T:c.761C>T] in *GAA*, was 0.00505 in our study. This result is comparable to the high allele frequency in the East Asian population at 0.00261, in contrast to those in other populations: 0.0000 in African/African American, 0.00000 in Latino/Admixed American, 0.00000 in non-Finnish European, 0.00000 in South Asian subpopulations.[12] The c.919delA in *ADSS1* and c.1400C>G in *SLC22A5* also showed much higher allele frequencies in the Korean population (0.00273 and 0.00218, respectively) and East Asian subpopulation (0.00110 and 0.00226, respectively) than in the global population (0.00008 and 0.00017, respectively).[12] However, there were some differences between our

results and previous results. We identified the c.2055+2T>G variant as the most prevalent PLPV in *DYSF*. However, the c.2494C>T variant is the most common PLPV in *DYSF* among Korean patients with dysferlinopathy.[16] Our findings have important implications for clinical practice. The high carrier frequencies of certain AR-NMD genes, such as *DYSF* and *GAA*, suggest that targeted genetic screening programs in Korea could help with early diagnosis and treatment. This would enable effective genetic counseling for at-risk couples to make informed reproductive decisions. Furthermore, public health policies could focus on AR-NMDs with higher genetic prevalence, improving healthcare planning and resource allocation for these conditions. Identification of common PLPVs specific to the Korean population underscores the importance of regional genetic studies, which are crucial for developing targeted interventions and public health strategies customized for the distinct genetic profiles of specific populations.[35]

Our study had some limitations. First, our data were derived from a small sample of 984 Korean whole genomes collected from a specific region. Thus, our results may not be representative of the entire Korean population.[36] Further studies of larger sample sizes and more diverse regions are needed to enhance the representativeness of the findings. Second, many non-truncating PLPVs that have not been documented in the literature are classified as variants of unknown significance because of a lack of evidence. Comprehensive studies focusing on these variants are required to determine their clinical importance in disease. Third, we did not analyze large deletions or duplications of exons.[13] Finally, comparisons of our allele frequencies with global data should be performed with caution because of differences in data sources and methodologies.

We determined the carrier frequency and genetic prevalence of AR-NMDs in the Korean population, highlighting important variants and their potential implications. These findings emphasize the importance of regional genetic studies, expanded carrier screening, and targeted public health strategies for effective management and prevention of genetic NMDs. In conclusion, our results suggest that 27.1% of the Korean population is a healthy carrier of at least one PLPV gene in AR-NMD. This is the first study to analyze the carrier frequency and genetic prevalence of AR-NMDs in a Korean population.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
List of autosomal recessive neuromuscular disease genes

Supplementary Table 2
Classification of 356,764 variants of 267 autosomal recessive neuromusular diseases in the Korean population

Supplementary Table 3
A list of all 165 literature or manually verified variants in autosomal recessive neuromuscular disease genes

Supplementary Table 4
Carrier frequency and predicted genetic prevalence in the Korean population

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