JoS JOURNAL OF STROKE

Journal of Stroke 2025;27(1):136-139
https://doi.org/10.5853/jos.2024.03188

Letter to the Editor

Prevalence of Genetic Variants Causing Mendelian Stroke Among 15,548 Koreans Without Neurological Disorders

Jin Ok Yang,[1] Seul Hee Lee,[1,2] Hong Jun Kim,[3] Chul-Hoo Kang,[3] Joong-Goo Kim,[3] Jay Chol Choi[3,4]

[1]Korea BioInformation Center (KOBIC), Korea Research Institute of Bioscience & Biotechnology (KRIBB), Daejeon, Korea
[2]Department of Bioinformatics, theMOAGEN, Daejeon, Korea
[3]Department of Neurology, Jeju National University & Jeju National University Hospital, Jeju, Korea
[4]Institute for Medical Science, Jeju National University, Jeju, Korea

Dear Sir:

Mendelian stroke is a significant cause of stroke in young individuals.[1,2] However, its exact prevalence remains unclear, as most studies have focused on selective stroke populations targeting specific disorders. A recent study indicated that genetic variants associated with rare Mendelian disorders may also elevate the risk of sporadic strokes.[3] Consequently, identifying these genetic variants in the general population is crucial for understanding the broader risk of stroke.

Interestingly, the prevalence of pathogenic variants causing Mendelian stroke varies significantly across different populations, with the highest prevalence observed among East Asians in a study that analyzed the Genome Aggregation Database (gnomAD) from 101,635 individuals across seven ethnic groups.[4] In particular, pathogenic *NOTCH3* variants, which cause cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) were the most frequently identified genetic variants among East Asians in the report. Recent studies from Taiwan and Jeju Island, South Korea also reported a similarly high prevalence (0.9%) of these variants among the residents.[5,6] Despite this, East Asians only represent 7.1% of the gnomAD, with merely 1,909 Koreans included.[7] This raises questions about whether Koreans have a higher frequency of these pathogenic variants linked to Mendelian stroke. In this study, we screened for genetic variants responsible for Mendelian stroke in a cohort of 15,548 Koreans without neurological disorders, including stroke.

We extracted genetic information from the whole-genome sequencing data of 15,548 individuals obtained through the Pilot Project for National Bio Big Data of Korea at the Clinical & Omics Data Archive (https://coda.nih.go.kr/stats/selectRegList.do). The mean age was 46 years and 47.6% of males. We examined 18 genes identified in an earlier report (*ABCC6*, *APP*, *CCM2*, *CECR1*, *COL3A1*, *COL4A1*, *COL4A2*, *COLGALT1*, *CST3*, *CTSA*, *GLA*, *HTRA1*, *ITM2B*, *KRIT1*, *NOTCH3*, *PDCD10*, *RNF213*, and *TREX1*).[4] Additionally, we analyzed six more genes linked to Mendelian stroke (*ACVRL1*, *CBS*, *ENG*, *FBN1*, *HBB*, and *NF1*) (Table 1). We extracted the rare nonsynonymous variants located within exons with a minor allele frequency (MAF) of less than 0.001, based on the gnomAD v2.1.1 (https://gnomad.broadinstitute.org/) non-neuro dataset. In line with the previous report, two well-established pathogenic founder *NOTCH3* variants (R544C and R1231C) and one well-established *RNF213* pathogenic founder variant (R4810K) were included in the analysis regardless of MAF. Variants were classified into three groups as suggested by Grami et al.[4]: pathogenic clinical variants, variants with a Combined Annotation Dependent Depletion (CADD) score >20, and all nonsynonymous variants. For pathogenic clinical variants, we further classified them as pathogenic or likely pathogenic variants according to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/). To compare variant frequencies between Koreans and gnomAD participants, Fisher's exact test was used with Bonferroni correction for multiple testing. Detailed genomic analysis methods are provided in Supplementary Methods. This study was approved by the Institutional Review Board of Jeju National Uni-

versity Hospital (JEJUNUH 2022-06-006-008).

Pathogenic clinical variants were found in 17 of the 24 genes studied among Koreans, with a prevalence of 2.8% in 15,548 individuals without neurological disorders. Pathogenic clinical variants were most frequently found in the *RNF213* gene (21.8 per 1,000 individuals), followed by *NOTCH3* (1.8), *FBN1* (1.2), and *TREX1* (0.5) (Table 2). Of 39 pathogenic clinical variants found in Koreans, 18 variants were found in only Koreans, but not in gnomAD (Supplementary Table 1). Compared with gnomAD, pathogenic clinical variants of *RNF213* were significantly more common, while variants in *ABCC6*, *CBS*, *CECR1*, *HBB*, and *NOTCH3* were less common among Koreans. The R4810K variant in *RNF213* alone was present in 339 individuals, corresponding to 21.8 per 1,000 individuals. Among the *NOTCH3* pathogenic variants, we identified four pathogenic or likely pathogenic variants (R75P, R544C, R587C, and R1076C), three of which were cysteine-altering variants. Overall, the prevalence of pathogenic variants and likely pathogenic variants in Koreans was 5.4 per 1,000 individuals and 22.5 per 1,000 individuals, respectively (Supplementary Table 2). For CADD-predicted variants, the most frequently involved gene was also *RNF213*, followed by *NOTCH3*, *FBN1*, *COL4A2*, and *NF1*. Among nonsynonymous variants, *RNF213* remained the most frequent gene, showing similar patterns to pathogenic or CADD-predicted variants. Limiting the analysis to the 18 genes suggested in the earlier report kept the pathogenic carrier frequency at 2.5%, as six additional genes contributed little.

Previous studies have reported a high prevalence of pathogenic *NOTCH3* variants among East Asians, particularly the R544C variant.[8] This variant was found in 0.9% of the Taiwanese general population and among the residents of Jeju Island, South Korea.[5,6] However, in our analysis, the overall frequency of pathogenic *NOTCH3* variants was only 0.18%, consistent with our previous report indicating a frequency range of 0.12%–0.44%.[5] Therefore, the prevalent R544C variant does not appear to be a general feature among Koreans, and the effect of genetic drift associated with the founder effect should be considered for Jeju Island and Taiwan.

Table 1. List of the genes associated with Mendelian stroke in this study

Gene	Chromosome	Location	Genetic disorder	Mode of inheritance
ABCC6	Chr16	16p13.11	Pseudoxanthoma elasticum	AR
ACVRL1	Chr12	12q13.13	Hereditary hemorrhagic telangiectasia	AD
APP	Chr21	21q21.3	Hereditary cerebral amyloid angiopathy	AD
CBS	Chr21	21q22.3	Homocystinuria	AR
CCM2	Chr7	7p13	Familial cerebral cavernous malformations	AD
CECR1	Chr22	22q11.1	Deficiency of adenosine deaminase 2 (ADA2)	AR
COL3A1	Chr2	2q32.2	Vascular Ehlers-Danlos syndrome (type IV)	AD
COL4A1	Chr13	13q34	*COL4A1*-related small vessel diseases	AD
COL4A2	Chr13	13q34	*COL4A2*-related small vessel diseases	AD
COLGALT1	Chr19	19p13.11	*COL4A1* and *COL4A2*-related small vessel diseases	AR
CST3	Chr20	20p11.21	Hereditary cerebral amyloid angiopathy	AD
CTSA	Chr20	20q13.12	CARASAL (Cathepsin A-related arteriopathy-strokes-leukoencephalopathy)	AD
ENG	Chr9	9q34.11	Hereditary hemorrhagic telangiectasia	AD
FBN1	Chr15	15q21.1	Marfan syndrome	AD
GLA	ChrX	Xq22.1	Fabry disease	X-Linked
HBB	Chr11	11p15.4	Sickle cell disease	AR
HTRA1	Chr10	10q26.13	CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy)	AR
ITM2B	Chr13	13q14.2	Hereditary cerebral amyloid angiopathy	AD
KRIT1	Chr7	7q21.2	Familial cerebral cavernous malformations	AD
NF1	Chr17	17q11.2	Neurofibromatosis type 1	AD
NOTCH3	Chr19	19p13.12	CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	AD
PDCD10	Chr3	3q26.1	Familial cerebral cavernous malformations	AD
RNF213	Chr17	17q25.3	Moyamoya disease	Unknown
TREX1	Chr3	3p21.31	Retinal vasculopathy with cerebral leukodystrophy	AD

AR, autosomal recessive; AD, autosomal dominant.

Despite the lower-than-expected frequency of *NOTCH3* pathogenic variants, the overall frequency of pathogenic clinical variants associated with Mendelian stroke in Koreans was similar to the frequency reported in East Asians by Grami et al.[4] This was primarily due to the significantly higher frequency of the *RNF213* variant among Koreans in this study compared to the report by Grami et al.[4] The *RNF213* variant is well-known as a susceptibility gene for moyamoya disease, and our findings align with the previously reported prevalence (2.25%–2.65%) of this variant among 1,516 healthy Koreans.[9]

Pathogenic variants in the *ABCC6* gene are known to cause pseudoxanthoma elasticum, a connective tissue disorder characterized by claudication, gastrointestinal hemorrhage, ischemic stroke, or intracranial aneurysms.[10] *ABCC6* variants were reported in 5.1% of early-onset Korean ischemic stroke patients in a recent report and they were the third most common Mendelian stroke variants reported in East Asian general populations.[2,4] However, the frequency was only 0.3 per 1,000 individuals in our analysis, partly due to the reclassification of the most common c.*38G>A variant as benign in this study.

In summary, the prevalence of pathogenic clinical variants associated with Mendelian stroke was 2.8% among 15,548 Korean individuals without neurological disorders. The overall prevalence rate of genetic variants associated with stroke seems to be high among the Korean general population, underscoring the importance for clinicians to be well-informed about genetic disorders that contribute to increased stroke risk.

Table 2. Pathogenic clinical, CADD-predicted deleterious, and nonsynonymous variant carrier frequency (per 1,000) among 15,548 Koreans without neurological disorders

Gene	Pathogenic clinical		CADD-predicted deleterious		Nonsynonymous	
	gnomAD	Korea	gnomAD	Korea	gnomAD	Korea
ABCC6	3.69	0.26*	17.83	3.09	33.62	5.08
ACVRL1	0.18	0.32	4.85	1.74	7.33	4.50
APP	0.08	0	7.19	2.32	13.18	4.82
CBS	2.43	0.45*	5.47	9.58	10.67	13.57
CCM2	0.01	0	10.36	5.47	10.04	9.20
CECR1	1.90	0.39*	5.29	4.63	12.41	5.60
COL3A1	0.09	0.13	9.15	10.36	13.91	15.82
COL4A1	0.05	0	16.63	11.77	23.20	19.87
COL4A2	0.02	0.06	17.37	16.47	27.58	27.72
COLGALT1	0.01	0.19	9.35	6.37	13.05	11.96
CST3	0	0	0.94	0.96	3.37	5.60
CTSA	0.15	0	4.55	10.23	9.30	14.66
ENG	0.04	0.06	4.38	1.67	10.69	5.47
FBN1	0.21	1.16	25.22	29.07	29.16	36.53
GLA	0.07	0.13	2.00	0.39	3.59	3.15
HBB	1.27	0.06*	2.47	1.09	5.41	4.50
HTRA1	0.29	0.13	4.36	6.75	5.45	8.36
ITM2B	0	0	2.31	8.94	3.32	12.80
KRIT1	0.06	0.13	6.86	3.73	7.75	4.18
NF1	0.21	0.39	17.14	15.50	21.53	26.63
NOTCH3	2.82	1.80*	30.48	50.62	43.01	66.95
PDCD10	0	0	1.00	0.39	1.91	0.90
RNF213	0.55	21.80*	31.83	54.86	88.80	111.98
TREX1	0	0.45	0.50	0.13	0.98	1.03
Total	14.12	27.91	237.51	256.11	399.28	420.89

CADD, Combined Annotation Dependent Depletion; gnomAD, Genome Aggregation Database.
*Variant frequencies that differed significantly from those in gnomAD.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.03188.

Funding statement

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF-2020M3E5D7085175) funded by the Ministry of Health and Welfare, Ministry of Science and ICT, Ministry of Trade Industry and Energy, Korea Disease Control and Prevention Agency (The National Project of Bio Big Data).

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: JCC. Study design: JCC, JOY. Methodology: SHL, JOY, JCC. Data collection: all authors. Investigation: all authors. Statistical analysis: SHL, JOY, JCC. Writing—original draft: SHL, JOY, JCC. Writing—review & editing: SHL, JOY, JCC. Approval of final manuscript: all authors.

Acknowledgments

We would like to express our sincere gratitude to Professor Guillaume Paré and Dr. Michael Chong at McMaster University for their invaluable assistance with the design and analysis of this study.

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Correspondence: Jay Chol Choi, MD, PhD
Department of Neurology, Jeju National University College of Medicine, 15 Aran 13-gil, Jeju 63241, Korea
Tel: +82-064-754-8160
E-mail: jaychoi@jejunu.ac.kr
https://orcid.org/0000-0002-3550-2196

Received: August 7, 2024
Revised: October 2, 2024
Accepted: October 17, 2024

Supplementary Methods

Dataset

We extracted information on genetic variants related to stroke from the data of 15,548 individuals obtained through the Pilot Project for National Bio Big Data of Korea at the Clinical & Omics Data Archive (https://coda.nih.go.kr/stats/selectRegList.do). This study includes whole-genome sequencing dataset from the following cohorts (dataset accession numbers): (1) 5,000 individuals from the Korea Epidemiology Study cohort (CODA_D22001, CODA_D23010); (2) 2,504 individuals from the Ulsan 10,000 Genome Project (CODA_D22006, CODA_D23009); (3) 7,722 individuals from families of rare disease patients' families (CODA_D22004, CODA_D23012); and (4) 322 individuals from colorectal patients' families (CODA_D22002, CODA_D23013). There were 7,401 men and 8,147 women, with a mean age of 46 years.

The analysis focused on 24 genes related to stroke: *ABCC6*, *ACVRL1*, *APP*, *CBS*, *CCM2*, *CECR1*, *COL3A1*, *COL4A1*, *COL4A2*, *COLGALT1*, *CST3*, *CTSA*, *ENG*, *FBN1*, *GLA*, *HBB*, *HTRA1*, *ITM2B*, *KRIT1*, *NF1*, *NOTCH3*, *PDCD10*, *RNF213*, and *TREX1*.

Variant annotation

The extracted variants were annotated using the ANNOVAR software (https://annovar.openbioinformatics.org/) with the following databases:

Item	Database	Version/date	Purpose
ANNOVAR	refGene	21.10.19	To identify variant type and information
	gnomAD (exome)	v2.1.1	For allele frequency (AF) filtering
	ClinVar	22.03.20	For pathogenic variant filtering
	dbNSFP	v4.2a	For CADD score filtering
	avsnp150	17.09.29	To confirm variant rsID (dbSNP)

Variant filtering

We filtered the identified variants to retain only those with a minor allele frequency (MAF) of less than 0.001, based on the gnomAD v2.1.1 (https://gnomad.broadinstitute.org/; exome, non-neuro) dataset. However, we included the *NOTCH3* variants (R544C, R1231C) and the *RNF213* variant (R4810K) in our list if they were known to be pathogenic, even if their MAF was above 0.001. For the *TREX1* gene, we included only the variants in the C-terminus, as only these variants were linked to strokes.

Analysis categories

From the filtered list, we performed analyses on the following three categories: (1) pathogenic clinical variant: variants classified as pathogenic or likely pathogenic in the ClinVar_20220320 database ([CLNSIG] entry); (2) CADD to predict variant effect: variants with a PHRED-scaled C-score ([CADD_phred]) over 20 in the dbNSFP v4.2 database (http://database.liulab.science/dbNSFP), indicating a higher likelihood of impacting protein function; (3) all nonsynonymous variants: variants classified as nonsynonymous, stopgain, nonframeshift insertion/deletion, or frameshift insertion/deletion in the refGene database ([ExonicFunc.refGene]), as these changes are likely to affect protein production.

Calculation of population frequency

For each variant that met the criteria, we calculated the number of individuals carrying the variant and determined the population frequency. The population frequency was calculated as follows: population frequency = number of individuals with the variant/total number of individuals (15,548).

Supplementary Table 1. List of pathogenic clinical variants associated with Mendelian stroke in Korean

Chromosome	Gene	Position	rsID	Reference	Alternative	Protein consequences	Annotation	Clinical significance	CADD score	Allele frequency (gnomAD)	Allele frequency (Korean)
chr16	*ABCC6*	16163087	rs28939701	G	A	p.R1024W	Nonsynonymous SNV	Pathogenic	24.6	0.00007	0.00006
chr16	*ABCC6*	16163159	rs63749794	G	A	p.R1000C	Nonsynonymous SNV	Pathogenic	32.0	0.00040	0.00006
chr16	*ABCC6*	16178950	rs72653787	C	T	p.G641R	Nonsynonymous SNV	Pathogenic	25.6	0.00005	0.00006
chr16	*ABCC6*	16190273	rs779408186	G	C	p.A395G	Nonsynonymous SNV	Likely pathogenic	29.1	0.00004	0.00006
chr12	*ACVRL1*	51913237	rs863223414	G	A	p.R67Q	Nonsynonymous SNV	Pathogenic/likely pathogenic	20.4	.	0.00006
chr12	*ACVRL1*	51915388	rs1085307412	C	G	p.H312Q	Nonsynonymous SNV	Pathogenic	23.8	.	0.00026
chr22	*CECR1*	17181904	rs376785840	T	C	p.Y453C	Nonsynonymous SNV	Pathogenic	23.7	0.00010	0.00013
chr22	*CECR1*	17209538	rs200930463	C	A	p.G47V	Nonsynonymous SNV	Pathogenic/likely pathogenic	22.5	0.00020	0.00013
chr22	*CECR1*	17189980	rs368615054	G	A	p.R71X	Stopgain	Pathogenic	36.0	0.00002	0.00006
chr22	*CECR1*	17189998	rs774963498	G	A	p.R65X	Stopgain	Likely pathogenic	34.0	0.00007	0.00006
chr21	*CBS;CBSL*	43060451	rs769080151	G	A	p.R274W	Nonsynonymous SNV	Likely pathogenic	23.7	0.00006	0.00006
chr21	*CBS;CBSL*	43060475	rs372010465	C	T	p.V266M	Nonsynonymous SNV	Pathogenic/likely pathogenic	24.4	0.00006	0.00006
chr21	*CBS;CBSL*	43060528	rs121964972	G	A	p.T248M	Nonsynonymous SNV	Pathogenic/likely pathogenic	19.0	0.00040	0.00006
chr21	*CBS;CBSL*	43066353	rs121964964	G	A	p.A9V	Nonsynonymous SNV	Pathogenic/likely pathogenic	24.3	0.00040	0.00026
chr2	*COL3A1*	188988627	rs587779592	G	T	p.G207V	Nonsynonymous SNV	Pathogenic	29.0	.	0.00006
chr2	*COL3A1*	188994297	rs587779692	G	A	p.G420S	Nonsynonymous SNV	Pathogenic/likely pathogenic	31.0	.	0.00006
chr13	*COL4A2*	110493246	rs1271683445	G	A	p.G1200S	Nonsynonymous SNV	Likely pathogenic	29.6	0.00001	0.00006
chr19	*COLGALT1*	17560428	rs1478523191	T	G	p.L151R	Nonsynonymous SNV	Pathogenic	31.0	.	0.00019
chr9	*ENG*	127854348	rs1588604597	C	T	p.R3H	Nonsynonymous SNV	Pathogenic	7.5	.	0.00006
chr15	*FBN1*	48470646	rs794728223	C	T	p.G1483R	Nonsynonymous SNV	Likely pathogenic	26.2	.	0.00013
chr15	*FBN1*	48488448	rs137854472	T	C	p.K1043R	Nonsynonymous SNV	Pathogenic	22.2	0.00010	0.00084
chr15	*FBN1*	48489956	rs755477434	A	G	p.C993R	Nonsynonymous SNV	Likely pathogenic	29.5	.	0.00006
chr15	*FBN1*	48470664	rs869025407	C	A	p.E1477X	Stopgain	Pathogenic	42.0	.	0.00006
chr15	*FBN1*	48488480	rs1597564359	G	T	p.C1032X	Stopgain	Pathogenic	37.0	.	0.00006
chrX	*GLA*	101403941	rs781838005	C	G	p.G80A	Nonsynonymous SNV	Likely pathogenic	24.9	.	0.00013
chr11	*HBB*	5226961	rs35890959	C	T	p.V21M	Nonsynonymous SNV	Pathogenic	17.4	.	0.00006
chr10	*HTRA1*	122506817	rs113993970	C	T	p.R302X	Stopgain	Likely pathogenic	40.0	0.00003	0.00006
chr10	*HTRA1*	122508758	rs113993971	C	T	p.R370X	Stopgain	Likely pathogenic	43.0	0.00007	0.00006

https://doi.org/10.5853/jos.2024.03188

Supplementary Table 1. Continued

Chromosome	Gene	Position	rsID	Reference	Alternative	Protein consequences	Annotation	Clinical significance	CADD score	Allele frequency (gnomAD)	Allele frequency (Korean)
chr7	*KRIT1*	92222966	rs886039402	G	A	p.R375X	Stopgain	Pathogenic	37.0	.	0.00006
chr7	*KRIT1*	92234558	rs764960797	G	A	p.R294X	Stopgain	Pathogenic	38.0	0.00003	0.00006
chr17	*NF1*	31201044	rs137854563	T	C	p.L357P	Nonsynonymous SNV	Pathogenic	27.9	.	0.00006
chr17	*NF1*	31214524	rs137854557	A	G	p.Y489C	Nonsynonymous SNV	Pathogenic	24.1	0.00006	0.00006
chr17	*NF1*	31327839	rs786202112	G	A	p.R1849Q	Nonsynonymous SNV	Pathogenic	34.0	.	0.00019
chr17	*NF1*	31357319	rs1060500333	T	G	p.Y2619X	Stopgain	Pathogenic/likely pathogenic	40.0	.	0.00006
chr19	*NOTCH3*	15180173	rs1438626607	G	A	p.R1076C	Nonsynonymous SNV	Pathogenic/likely pathogenic	26.5	.	0.00006
chr19	*NOTCH3*	15187186	rs754554486	G	A	p.R587C	Nonsynonymous SNV	Likely pathogenic	26.2	0.00020	0.00013
chr19	*NOTCH3*	15187315	rs201118034	G	A	p.R544C	Nonsynonymous SNV	Pathogenic/likely pathogenic	23.1	0.00370	0.00109
chr19	*NOTCH3*	15192493	rs145069047	C	G	p.R75P	Nonsynonymous SNV	Pathogenic	20.9	.	0.00051
chr3	*TREX1*	48467514	rs79318303	CTGCTGGCCCCACTGGGT	-	p.P280_A285del	Nonframeshift deletion	Pathogenic/likely pathogenic	.	0.00030	0.00045
chr17	*RNF213*	80385145	rs112735431	G	A	p.R4810K	Nonsynonymous SNV	Conflicting interpretations of pathogenicity	7.4	0.00390	0.02180

CADD, Combined Annotation Dependent Depletion; gnomAD, Genome Aggregation Database; SNV, single nucleotide variant.

Supplementary Table 2. Pathogenic and likely pathogenic variant carrier frequency (per 1,000) among 15,548 Koreans without neurological disorders

Gene	Pathogenic		Likely pathogenic	
	gnomAD	Korea	gnomAD	Korea
ABCC6	2.59	0.19	1.08	0.06
ACVRL1	0.09	0.32	0.09	0.00
APP	0.00	0.00	0.08	0.00
CBS	2.35	0.39	0.07	0.06
CCM2	0.01	0.00	0.00	0.00
CECR1	1.84	0.32	0.06	0.06
COL3A1	0.03	0.13	0.07	0.00
COL4A1	0.00	0.00	0.05	0.00
COL4A2	0.00	0.00	0.02	0.06
COLGALT1	0.01	0.19	0.00	0.00
CST3	0.00	0.00	0.00	0.00
CTSA	0.14	0.00	0.01	0.00
ENG	0.03	0.06	0.01	0.00
FBN1	0.17	0.97	0.04	0.19
GLA	0.07	0.00	0.00	0.13
HBB	1.26	0.06	0.01	0.00
HTRA1	0.21	0.00	0.08	0.13
ITM2B	0.00	0.00	0.00	0.00
KRIT1	0.05	0.13	0.01	0.00
NF1	0.19	0.39	0.02	0.00
NOTCH3	0.87	1.80	1.95	0.00
PDCD10	0.00	0.00	0.00	0.00
RNF213	0.00	0.00	0.55	21.80
TREX1	0.00	0.45	0.00	0.00
Total	9.91	5.41	4.20	22.49

gnomAD, Genome Aggregation Database.

https://doi.org/10.5853/jos.2024.03188