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Analysis of Germline Variants with Low Allele Frequencies in Turkish Healthy Cohort

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Abstract

BACKGROUND/AIMS: Within a specific population, rare variants with minor allele frequencies (MAFs) below 0.01% may underlie a particular genetic disorder when Mendelian diseases are investigated. Although MAFs can be determined by universal databases, the importance of a variant with a low MAF may vary across populations. Hence, documentation of rare variants in healthy individuals could be remarkably valuable. However, such approaches have not yet been applied in the Turkish population. Thus, we aimed to identify rare germline variants in a healthy Turkish population.

MATERIALS AND METHODS: We re-analyzed whole-exome sequencing data from 80 healthy Turkish individuals and filtered variants using a MAF threshold of <0.01%. We further assessed the pathogenicity of the filtered variants according to the American College of Medical Genetics criteria.

RESULTS: There were numerous rare variants, some of which were common to all participants. Importantly, those variants were classified as of unknown significance or as likely pathogenic; however, this classification should be revised because the variants were observed in healthy individuals.

CONCLUSION: We propose that these variants could be benign, as they were detected in healthy Turkish participants. Finally, the rare variants in the Turkish population should still be reported to guide clinicians during routine molecular diagnosis.

Keywords: Exome sequencing, Turkish population, rare variants, minor allele frequencies

INTRODUCTION

Molecular causes of genetic disorders have been identified using genetic variants. Although many variants have been reported for specific genetic disorders, additional variants remain to be discovered.[1] Thus, studies in human genetics focus on exploring variants associated with, or resulting in, a particular phenotype.[2] Here, using the single-gene single-phenotype approach, Mendelian diseases are generally diagnosed by detecting rare variants in a population.[3]

Rare variants are defined as deoxyribonucleic acid (DNA) alterations with minor allele frequencies (MAFs) of less than 0.01% in a specific population.[4] According to the American College of Medical Genetics (ACMG) criteria[5], a variant with low allelic frequency is classified with moderate piece of evidence for pathogenicity (PM2). Thus, low MAFs could be informative for evaluating the unreported variant. However, the MAF cutoff may vary between populations.[6] Moreover, unreported or not molecularly proven variants, even those with low MAFs, are classified as variants of unknown significance (VUS), which limits molecular diagnosis.[7]

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To determine the pathogenicity of a variant, population databases are required. Although global databases such as gnomAD[8], ExAc[9], and 1000 Genomes Project[10] are available, some countries have established population-specific databases to reduce biases arising from population-based differences.[11-13] Similarly, Türkiye has reported a whole-exome and whole-genome database[14] and launched a portal for variant search (https://tgd.tuseb.gov.tr/) based on data from healthy participants. Nonetheless, the portal allows only single-variant searches, restricting cumulative evaluation of variants with low MAFs. Moreover, some variants of interest were not listed in the database. Hence, a more comprehensive report on variants with low frequencies in healthy cohorts is still needed.

In the present study, we re-analyzed whole exome sequencing (WES) data from 80 healthy Turkish individuals with respect to rare variants. After filtering the variants according to MAF values (<0.01%) from universal databases, we used the Franklin by Genoox tool (https://franklin.genoox.com/)to clarify variant pathogenicity according to ACMG criteria and listed the non-benign variants. Our results indicated that numerous variants had low MAFs, including variants in critical genes that were classified as VUS or likely pathogenic (LP). However, the proportion of those variants in the healthy cohort led to the conclusion that those variants, especially those linked to early-onset genetic disorders, should be re-categorized as benign in the Turkish population. The present study is the first to underscore the importance of rare variants in healthy individuals in the Turkish population, and such studies are still required.

MATERIALS AND METHODS

Ethics and Participants

In the present study, the WES data previously obtained from 80 healthy individuals in the sport genetics studies[15,16] were re-analyzed. In previous studies, only polymorphisms of the participants were evaluated using an exome-wide association study. Sixty participants were elite Turkish athletes, and twenty were healthy, unrelated Turkish individuals. In the present study, all participants (27 females, 33.75%; 53 males, 66.25%; age >18 years) were regarded as healthy individuals and were not grouped, as none had any known (declared) genetic disorders. The study was approved by the Gazi University Non-Interventional Clinical Research Ethics Committee (approval number: 09, date: 05.04.2021). Under this ethical approval, all variants were already approved for analysis. Both written and verbal consents were obtained from the participants before the study. Moreover, the data were publicly available at https://doi.org/10.6084/m9.figshare.24496216.v1.

Variant Prioritization

In the study, data generated by WES, which was performed using the Twist Human Comprehensive Exome Panel (Twist Biosciences, USA) and the Illumina NextSeq500 (Illumina Inc., USA) on genomic DNAs from peripheral blood samples of the participants, were further examined. For the analysis of rare variants, the variants in variant call format for each participant were annotated using the ANNOVAR tool[17] with the hg19 human reference genome. Next, variants located in exons or exon-intron boundaries were prioritized using VarAFT software[18], where variants with read depth >10 were filtered by MAF <0.01%, considering only morbid genes.[19] To limit the number of variants and to avoid manipulating any possible *de novo* variants, only homozygous variants were evaluated, while hemizygous or homozygous variants on chromosome X were documented regardless of participant sex. Finally, the pathogenicity of the variants was determined using the Franklin by Genoox tool (https://franklin.genoox.com/) according to the ACMG criteria.[5] Moreover, we queried the Turkish Genome Project (TGP) database (TGP; https://tgd.tuseb.gov.tr/) for each variant, using a single-variant search when the variant was listed, and excluded variants reported in the database.

Statistical Analysis

No statistical analysis was performed in the study.

RESULTS

Each participant had nearly 700,000 variants before filtering. Applying a MAF <0.001 filter to homozygous variants in morbid genes yielded approximately 15 variants per patient. Variant assessment using Franklin by Genoox according to the ACMG criteria showed approximately three variants per patient classified as VUS or LP; on average, one such variant per patient was not documented in the TGP database. Those variants listed in Table 1 were detected in at least one participant. Variants that met ACMG criteria BS2 (observed in a homozygous state in population databases more than expected for disease), BS3 (well-established functional studies show no damaging effect on protein function or splicing), BP3 (in-frame deletions/insertions in a repetitive region with no known function), or BP6 (reported as benign but lacking evidence for independent laboratory evaluation), as well as variants classified as VUS by the Franklin tool were not reported in the results.

DISCUSSION

In the present study, we re-analyzed the WES data from 80 healthy Turkish individuals and documented homozygous rare variants that were recurrently observed in the participants and not reported in the TGP database. Regarding the early-onset status of diseases linked to genes harboring detected variants, we documented 62 variants in 60 genes associated with diverse genetic disorders.

Rare variants are regarded as absent from control (healthy) individuals, and their frequencies are extremely low in population-based genome databases.[20] Thus, they are annotated with moderate evidence of pathogenicity (PM2) according to the ACMG criteria (5). Even though marking a variant with the PM2 criterion is suggestive of pathogenicity, studies have pointed out benign or likely benign variants in the presence of the PM2 criterion.[21] Hence, reporting rare variants in healthy individuals may be useful to determine whether variants meeting the PM2 criterion are benign or likely benign. In the present cohort, 60 variants were annotated with the PM2 criterion, indicating that their frequencies were markedly low in public genome databases.

The frequency of a variant of interest can be determined using various genomic databases. Nonetheless, those databases are population-specific, and the exact frequencies vary across populations.[22] Recently, Türkiye initiated a genome project called TGP, containing genomic information from 557 so-called healthy individuals. The platform allows users to search for individual variants of interest and provides a valuable opportunity to determine variant frequencies in a manner specific to the Turkish population. However, we noted that the platform does not document variants on the sex chromosomes, particularly indel variants. Therefore, listing rare variants in healthy Turkish individuals is fundamental to the assessment of variant pathogenicity in medical genetics in Türkiye.

Table 1. List of the rare variants with VUS or LP classification and not reported in the TGP database in 80 healthy participants

Gene	Variant	Depth/allele frequency	Pathogenicity	ACMG Criteria	Disease, inheritance pattern (OMIM#)
ADAMTS17	NM_139057.4: c.353G>A: p.Arg118His	11/0.91	VUS	PM2, BP4	-Weill-Marchesani 4 syndrome, AR (613195)
ADGRG6	NM_198569.3: c.2906G>A: p. Arg969Gln	38/1.0	VUS	PM2	Lethal congenital contracture syndrome 9, AR (616503)
ASPM	NM_018136.5: c.8357C>T: p.Ala2786Val	53/1.0	VUS	PM2, BP4	-Microcephaly 5, primary, AR (608716)
ASPN	NM_017680.5: c.153_154insTGATGA: p.Asp52*	27/1.0	VUS	PM2	-{Lumbar disc degeneration}, ? (603932) -{Osteoarthritis susceptibility 3}, AD, (607850)
ATXN1	NM_001128164.2: c.678_679insGCA: p.His226_Leu227insAla	75/0.91	VUS	PM2, PM4	-Spinocerebellar ataxia 1, AD (164400)
ATXN3	NM_004993.6: c.916_917insCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG: p.Gln305_Gly306insAlaAlaAlaAlaAlaAlaAlaAlaAlaAlaAlaAla	85/0.98	VUS	PM2, PM4	-Machado-Joseph disease, AD (109150) -{Parkinson disease, late-onset, susceptibility to}, AD (168600)
	NM_004993.6: c.917_918insC: p.Asp307Glyfs*11	79/0.96	VUS	PM2	
BPTF	NM_182641.4: c.8027_8028insCCTCCAGCCCCTCCAGCC: p.Ala2676_Pro2677insLeuGlnProLeuGlnPro	60/1.0	VUS	PM2, PM4	-{Kaposi sarcoma, susceptibility to}, AD (148000) -Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies, AD (617755)
CNTNAP1	NM_003632.3: c.2992+10G>C	18/1.0	VUS	PM2, BP4	-Hypomyelinating neuropathy, congenital, 3, AR (618186) -Lethal congenital contracture syndrome 7, AR (616286)
DIP2B	NM_173602.3: c.1122G>T: p.Leu374Phe	28/1.0	VUS	PM2, PP2	-Intellectual developmental disorder, autosomal dominant, FRA12A type, AD (136630)
DKC1	NM_001363.5: c.1490_1491insAAG: p.Thr497_Lys498insSer	30/0.97	VUS	PM2, PM4	-?Cataracts, hearing impairment, nephrotic syndrome, and enterocolitis 1, XLD (301108) -Dyskeratosis congenita, X-linked, XLR (305000)
DLG5	NM_004747.4: c.4938C>G: p.Ile1646Met	81/1.0	VUS	PM2, BP4	-Yuksel-Vogel-Bauser syndrome, AR (620703)
DMD	NM_004006.3: c.5788C>T: p.Arg1930Cys	32/1.0	VUS	PM2	-Becker muscular dystrophy, XLR (300376) -Cardiomyopathy, dilated, 3B, XL (302045) -Duchenne muscular dystrophy, XLR (310200)
DMXL2	NM_001378457.1: c.88-2_88-1insTTTTTTTTTTTTT	24/1.0	VUS	PVS1, PM2	-?Deafness, autosomal dominant 71, AD (617605) -?Polyendocrine-polyneuropathy syndrome, AR (616113) -Developmental and epileptic encephalopathy 81, AR (618663)
DUOX2	NM_001363711.2: c.3175C>T: p.Arg1059Cys	60/1.0	VUS	PM2, PP3	-Thyroid dyshormonogenesis 6, AR (607200)
FAM20C	NM_020223.4: c.951_952insACAGGTGAGCCCTTCCTTCCTCCCTCCATCCGCG: p.Asp318Thrfs*118	44/0.98	VUS	PVS1, PM2, PM4	-Raine syndrome, AR (259775)
FBXL3	NM_012158.4: c.483C>G: p.Ile161Met	39/1.0	VUS	PM2	-Intellectual developmental disorder with short stature, facial anomalies, and speech defects, AR (606220)
FCSK	NM_145059.3: c.1873C>T: p.Arg625Trp	94/1.0	VUS	PM2	-Congenital disorder of glycosylation with defective fucosylation 2, AR (618324)
FLVCR1	NM_014053.4: c.1463A>G: p.Tyr488Cys	41/1.0	VUS	PM2	-Neurodevelopmental disorder with microcephaly, absent speech, and hypotonia, AR (621060) -Retinopathy-sensory neuropathy syndrome, AR (609033)
FRMPD4	NM_001368397.1: c.3862C>T: p.Arg1288Trp	55/1.0	VUS	PM2	-Intellectual developmental disorder, X-linked 104, XL (300983)

Table 1. Continued

Gene	Variant	Depth/allele frequency	Pathogenicity	ACMG Criteria	Disease, inheritance pattern (OMIM#)
GCM2	NM_004752.4: c.283G>C: p.Asp95His	53/1.0	VUS	PM2	-Hyperparathyroidism 4, AD (617343) -Hypoparathyroidism, familial isolated 2, AD/AR (618883)
GFI1	NM_005263.5: c.925-3_925-2insTCTCTC	12/0.92	VUS	PM2	-?Neutropenia, nonimmune chronic idiopathic, of adults, AD (607847) -Neutropenia, severe congenital 2, AD (613107)
HTT	NM_002111.8:c.51_52insAGCAGCAGCAGCAGC:p.Phe17_Gln18insSerSerSerSerSer	74/1.0	VUS	PM2, PM4	-Huntington disease, AD (143100) -Lopes-Maciel-Rodan syndrome, AR (617435)
INPP5E	NM_019892.6:c.1159+8_1159+9insTGGCTGGAGGGGTGGGCG	28/1.0	VUS	PM2	-Impaired intellectual development, truncal obesity, retinal dystrophy, and micropenis syndrome, AR (610156) -Joubert syndrome 1, AR (213300)
INTU	NM_015693.4: c.1091+6A>C	32/1.0	VUS	PM2, BP4	-?Orofaciodigital syndrome XVII, AR (617926) -?Short-rib thoracic dysplasia 20 with polydactyly, AR (617925)
JPH3	NM_001271604.4: c.430_431insTGCTGC: p.Leu143_Pro144insLeuLeu	104/0.98	VUS	PM2, PM4	-Huntington disease-like 2, AD (606438)
KCNN3	NM_002249.6: c.243_244insGCAGCAGCAGCAGCA: p.Pro81_Pro82insAlaAlaAlaAlaAla	93/1.0	VUS	PM2, PM4	-Zimmermann-Laband syndrome 3, AD (618658)
KDM5C	NM_004187.5:c.2517-6_2517-5insACT	22/1.0	VUS	PM2	-Intellectual developmental disorder, X-linked syndromic, Claes-Jensen type, XLR (300534)
KDM6B	NM_001348716.2:c.751_752insACCACC: p.Pro250_Leu251insTyrHis	59/0.95	VUS	PM2, BP3	-Stolerman neurodevelopmental syndrome, AD (618505)
KIF4A	NM_012310.5: c.1924A>G: p.Met642Val	22/1.0	VUS	PM2, PM4	-Intellectual developmental disorder, X-linked 100, XLR (300923) -Taurodontism, microdontia, and dens invaginatus, XLR (313490)
KLHL15	NM_030624.3: c.1805G>A: p.Arg602His	22/1.0	VUS	PM2, PP2	-Intellectual developmental disorder, X-linked 103, XLR (300982)
KRT10	NM_000421.5: c.1684_1685insAGCTCCGGCGGCGGATACGGCGGCGGCAGC: p.Ser562*	34/1.0	LP	PVS1, PM2	-?Ichthyosis histrix, Lambert type, AD (146600) -Epidermolytic hyperkeratosis 2A, AD (620150) -Epidermolytic hyperkeratosis 2B, AR (620707) -Ichthyosis with confetti, AD (609165) -Ichthyosis, annular epidermolytic 1, AD (607602)
LFNG	NM_001166355.2:c.137_138insGATG: p.Asp47Metfs*11	83/1.0	VUS	PM2	-Spondylocostal dysostosis 3, AR (609813)
LRSAM1	NM_001005373.4: c.593C>T: p.Ala198Val	67/1.0	VUS	PM2, BP4	-Charcot-Marie-Tooth disease, axonal, type 2P, AD/AR (614436)
MLC1	NM_015166.4: c.1053_1054insCGGGGAGGTGAGTGGCCTGTGGGGTGGGGGTGC: p.Ala351_Gly352insArgGlyGlyGluTrpProValGlyTrpGlyCys	41/1.0	VUS	PM2, PM4	-Megalencephalic leukoencephalopathy with subcortical cysts 1, AR (604004)
NEFH	NM_021076.4:c.1939_1940insGTCCCCT GAGAAGGCCAA:p.Ala646_Lys647insSer ProLeuArgArgPro	95/0.97	VUS	PM2, BP4	-{?Amyotrophic lateral sclerosis, susceptibility to}, AD, AR (105400) -Charcot-Marie-Tooth disease, axonal, type 2CC, AD (616924)
OGT	NM_181672.3: c.922A>G: p.Ser308Gly	33/0.97	VUS	PM2, PP2	-Intellectual developmental disorder, X-linked 106, XLR (300997)
OTC	NM_000531.6: c.76C>T: p.Arg26Trp	29/1.0	VUS	PM2, PM5, PP2	-Ornithine transcarbamylase deficiency, XL (311250)

Table 1. Continued

Gene	Variant	Depth/allele frequency	Pathogenicity	ACMG Criteria	Disease, inheritance pattern (OMIM#)
OTOG	NM_001292063.2: c.89G>A: p.Arg30His	57/1.0	VUS	PM2, BP4	-Deafness, autosomal recessive 18B, AR (614945)
PAPPA2	NM_020318.3: c.2162A>G: p.Tyr721Cys	32/1.0	VUS	PM2	-Short stature, Dauber-Argente type, AR (619489)
PAPSS2	NM_001015880.2: c.381+1_381+2insAAAAA	12/1.0	VUS	PVS1	Brachyolmia 4 with mild epiphyseal and metaphyseal changes, AR (612847)
PCNT	NM_006031.6: c.427_428insTGGGATGTTCACAGTCAGTGACCACCCACCAGAACA: p.Arg143delinsLeuGlyCysSerGlnSerValThrThrHisGlnAsnSerSer	24/1.0	VUS	PM2, PM4	-Microcephalic osteodysplastic primordial dwarfism, type II, AR (210720)
POGZ	NM_015100.4: c.3606C>G: p.Asp1202Glu	64/1.0	VUS	PM2, PP2	-White-Sutton syndrome, AD (616364)
POLR3A	NM_007055.4: c.3503A>C: p.His1168Pro	60/1.0	VUS	PM2, PP2	-Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism, AR (607694) -Wiedemann-Rautenstrauch syndrome, AR (264090)
POU3F4	NM_000307.5: c.517G>C: p.Gly173Arg	34/1.0	VUS	PM2	-Deafness, X-linked 2, XLR (304400)
PPFIBP1	NM_003622.4:c.2764A>G:p.Met922Val	72/1.0	VUS	PM2	-Neurodevelopmental disorder with seizures, microcephaly, and brain abnormalities, AR (620024)
RBM10	NM_005676.5: c.1166T>C: p.Met389Thr	34/0.97	VUS	PM2, PP2, BP4	-TARP syndrome, XLR (311900)
SEC63	NM_007214.5: c.1936-6_1936-5dup	18/.94	VUS	-	-Polycystic liver disease 2, AD (617004)
SH3BP2	NM_001122681.2: c.1507G>A: p.Glu503Lys	52/1.0	VUS	PM2	-Cherubism, AD (118400)
SLC12A2	NM_001046.3: c.284_285insGCGGCGGCGGCG: p.Ala95_Ala96insArgArgArgArg	14/0.93	VUS	PM2, PM4	-Deafness, autosomal dominant 78, AD (619081) -Delpire-McNeill syndrome, AD (619083) -Kilquist syndrome, AR (619080)
SLC4A10	NM_001178016.2: c.81+2T>C	49/1.0	VUS	PM2	-Neurodevelopmental disorder with hypotonia and characteristic brain abnormalities, AR (620746)
SLC44A4	NM_025257.3: c.845T>C: p.Val282Ala	73/1.0	VUS	PM2, BP4	-?Deafness, autosomal dominant 72, AD (617606)
SLC9A6	NM_001379110.1: c.1581+8T>A	32/1.0	VUS	PM2	-Intellectual developmental disorder, X-linked syndromic, Christianson type, XL (300243)
SMC1A	NM_006306.4: c.1911+3G>A	54/1.0	VUS	PM2, BP4	-Cornelia de Lange syndrome 2, XLD (300590) -Developmental and epileptic encephalopathy 85, with or without midline brain defects, XLD (301044)
SMS	NM_004595.5: c.536G>A: p.Arg179Gln	66/1.0	VUS	PM2, PP2	-Intellectual developmental disorder, X-linked syndromic, Snyder-Robinson type, XLR (309583)
SPNS2	NM_001124758.3: c.1607+5dup	43/1.0	VUS	PM2, PP3	-?Deafness, autosomal recessive 115, AR (618457)
SV2A	NM_014849.5: c.730G>T: p.Val244Phe	57/1.0	VUS	PM2	-Developmental and epileptic encephalopathy 113, AR (620772)
TTC8	NM_144596.4: c.909G>C: p.Glu303Asp	51/1.0	VUS	PM2, PP3	-?Retinitis pigmentosa 51, AR (613464) -Bardet-Biedl syndrome 8, AR (615985)

Table 1. Continued

Gene	Variant	Depth/allele frequency	Pathogenicity	ACMG Criteria	Disease, inheritance pattern (OMIM#)
USP9X	NM_001039591.3: c.3496C>T: p.His1166Tyr	21/1.0	VUS	PM2, PP2	-Intellectual developmental disorder, X-linked 99, XLR (300919) -Intellectual developmental disorder, X-linked 99, syndromic, female-restricted, XLD (300968)
WNK3	NM_020922.5: c.4870+8T>A	25/1.0	VUS	PM2	-Prieto syndrome, XLR (309610)
	NM_020922.5: c.3652-8_3652-7insTTGTT	13/1.0	VUS	PM2	
ZNF711	NM_001330574.2: c.547A>G: p.Thr183Ala	36/1.0	VUS	PM2, BP4	-Intellectual developmental disorder, X-linked 97, XL (300803)

VUS: Variants of unknown significance, LP: Likely pathogenic, AD: Autosomal dominant, AR: Autosomal recessive, XLR: X-linked recessive, XLD: X-linked dominant, ACMG: American College of Medical Genetics, OMIM: Online Mendelian Inheritance in Man, PVS1: Pathogenic very strong 1.

Among the rare variants detected in the healthy cohort, two variants (*FAM20C*: NM_020223.4:c.951_952insACAGGTGAGCCCTTCCTTCCTCCCTCCATCCGCG:p.Asp318Thrfs*118 and *KRT10*:NM_000421.5:c.1684_1685insAGCTCCGGCGGCGGATACGGCGGCGGCAGC:p.Ser562*) were classified as LP based on PM2 and the very strong pathogenic very strong 1 (PVS1) criteria for pathogenicity. The PVS1 criterion applies to variant types that result in loss of protein function, including frameshifts, altered splicing, and exonic deletions.[23] Those variants were detected in at least three healthy participants in the Turkish population. *FAM20C* (Golgi-associated secretory pathway kinase) encodes a protein that functions as a Golgi casein kinase, regulates phosphorylation of secreted proteins, and is linked to Raine Syndrome (Online Mendelian Inheritance in Man #259775), which is characterized by neonatal osteosclerotic bone dysplasia.[24] However, the LP variant in the *FAM20C* gene was detected in five independent healthy individuals in the Turkish population, and therefore is unlikely to be the cause of lethal Raine Syndrome. Interestingly, the frameshift variant localizes to the kinase domain of the protein.[25] Thus, further molecular studies are required to determine how protein function is conserved in the presence of this variant. The other variant in *KRT10* was observed in three participants. The *KRT10* gene encodes a type I keratin that is mainly expressed in epidermal cells. The mutations in this gene have been associated with rare skin anomalies. Importantly, the C-terminus of the protein was identified as a mutation hotspot.[26,27] According to the ENSEMBL database[28], *KRT10* gene (NM_000421.5) encodes a 584 amino acid-length protein. Hence, the variant detected in the healthy participants was localized to the end of the protein, which may not affect the protein's structure and function.[29]

During classification, unreported or unproven variants are classified as VUS.[30] In the present study, 60 variants were classified as VUS. The classification would change when the variant is detected in healthy individuals.[31] Therefore, we propose that the classification of those variants be re-evaluated in medical genetics in Türkiye.

In the present study, we report biallelic variants identified in healthy individuals. Among the 60 genes affected in the homozygous state, 14 have been linked exclusively to dominant genetic disorders. In specific cases, the homozygous variants in dominant diseases have been reported to be neutral[32], further proving the non-pathogenic nature of the listed variants.

Study Limitations

Although the study submitted variant lists for a limited number of healthy individuals, similar studies with larger group of participants or a wider sequencing approach as whole genome sequencing should be conducted to define more variants that would be reclassified in Turkish population.

CONCLUSION

The present study documented rare germline and homozygous variants in genes linked to early-onset genetic disorders in healthy Turkish individuals. Although the variants were classified as VUS or LP, their detection in the healthy cohort may indicate that those variants are benign. Moreover, the listed variants were not reported in the TGP database. Thus, reporting rare variants in a population-specific manner, as in the present study, is still valuable for guiding medical geneticists when prioritizing variants. Nevertheless, possible multigenic or multifactorial inheritance patterns should be considered when referring to those variants.

MAIN POINTS

- Rare variants are common in Turkish healthy cohort.
- The reported rare variants of unknown significance may be reclassified as benign in the Turkish population.
- Further population-based studies could facilitate variant prioritization.

ETHICS

Ethics Committee Approval: The study was approved by the Gazi University Non-Interventional Clinical Research Ethics Committee (approval number: 09, date: 05.04.2021).

Informed Consent: Informed consent was obtained from all subjects involved in the study.

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Footnotes

Authorship Contributions

Concept: S.G.E., C.B., H.H.K., Design: S.G.E., G.A., C.B., H.H.K., Data Collection and/or Processing: C.B., H.H.K., Analysis and/or Interpretation: S.G.E., F.Y.T., G.A., H.H.K., Writing: S.G.E., F.Y.T., G.A., C.B., H.H.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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