**Table 1. *APOA5* variants reported in literature and/or clinical testing.**

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| --- | --- | --- | --- | --- | --- |
| **Variant Type** | **Nucleotide Change** | **Amino Acid Changea,b** | **ACMG classificationc** | **Molecular defect (if applicable) and related notes** | **Previously reported in literature?** |
| Regulatory | c.-1464T>C | N/A | VUS | Creates a putative vitamin D receptor binding site which increases *APOA5* promoter activity. Also associated with decreased HDL-C in vitamin D deficient patients. | Yes [1] |
| Regulatory | c.-1131T>C | N/A | Benign | In 100% linkage disequilibrium with c.-3A>G and c.\*158T>C. Together, these 3 variants have been shown to reduce *APOA5* expression, though the exact role of c.-1131T>C in this is unclear, unlike the other two variants. Component of *APOA5*\*2 Haplotype. | Yes [2-7] |
| Splicing | c.-33+1G>A | N/A | Likely Pathogenic | Splicing donor site null variant that results in skipping of exon 1 during transcription, which contains a portion of the signal peptide of APOA5. | Yes [8] |
| Regulatory | c.-3A>G | N/A | Benign | In 100% linkage disequilibrium with c.-1131T>C and c.\*158T>C. Together, these 3 variants have been shown to reduce APOA5 expression. Specifically, this variant has two purported functional impacts. Firstly, the transcription factor GATA4 only binds the wild-type allele of this variant. Secondly, this variant impacts the Kozak sequence of *APOA5*, which is thought to impact translation initiation. Component of *APOA5*\*2 Haplotype. | Yes [7,9,10] |
| Gross Deletion | c.16\_39del | p.Ala6\_Ala13del | Likely pathogenic | Partial deletion of signal sequence leads to hepatic missorting of protein to lipid droplets which subsequently results in impaired secretion of protein. | Yes [11] |
| Splicing | c.49+1G>A | N/A | Likely Pathogenic | Abolishes donor splice site of intron 2 leading to altered mRNA that encodes a truncated protein. | Yes [12] |
| Splicing | c.49+5G>C | N/A | Likely Pathogenic | Predicted to abolish donor splice site of intron 2 leading to altered mRNA that encodes a truncated protein. | Yes [13] |
| Splicing | c.50-1G>A | N/A | Likely Pathogenic | Predicted to abolish functionality of acceptor splice site of intron 2 leading to altered mRNA that encodes a truncated protein. | Yes [14] |
| Missense | c.56C>G | p.Ser19Trp | VUS | Variant produces a less efficient signal peptide that is predicted to reduce APOA5 secretion by up to 49%. Variant is considered VUS due to preserved protein function, inconsistent segregation with disease, high population frequency, etc. Best regarded as a risk factor and not a disease-causing variant in isolation. Only component of *APOA5*\*3 haplotype. | Yes [5,15-19] |
| Small Deletion | c.58delG | p.Ala20Profs\*37 | Likely Pathogenic | Deletion alters reading frame, resulting in altered mRNA that encodes a truncated protein. Truncation at amino acid 37 eliminates ~90% of the protein, abolishing all functional domains of APOA5. | No (found in our own clinical testing) |
| Small duplication | c.73\_76dup | p.Gly26Glufs\*37 | Likely Pathogenic | Duplication alters reading frame resulting in mRNA encoding truncated protein. ~90% of the protein is lost, abolishing all functional domains. | No (reported in LOVD3 only) |
| Missense | c.77G>T | p.Gly26Val | VUS | Unknown | Yes [20] |
| Small Deletion | c.77delG | p.Gly26Alafs\*31 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~90% of protein is lost, abolishing all functional domains of APOA5. | Yes [8] |
| Missense | c.104G>A | p.Ser35Asn | VUS | Unknown | Yes [20] |
| Small Deletion | c.109delG | p.Asp37Thrfs\*20 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. >90% of protein is lost, abolishing all functional domains of APOA5. | No (found in our own clinical testing) |
| Small Deletion | c.117\_120del | p.Arg40Trpfs\*16 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. >90% of protein is lost, abolishing all functional domains of APOA5. | No (reported in ClinVar only) |
| Missense | c.119G>T | p.Arg40Met | Likely Benign | Unknown. Considered benign due to gnomAD maximal non-founder subpopulation allele frequency of 0.269% which is greater than threshold for disease (0.1%). | Yes [21] |
| Small Deletion | c.138del | p.Gln46Hisfs\*11 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. >90% of protein is lost, abolishing all functional domains of APOA5. | No (reported in LOVD3 only) |
| Missense | c.154G>A | p.Glu52Lys | VUS | Unknown | Yes [22] |
| Nonsense | c.154G>T | p.Glu52Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~85% of the protein is eliminated resulting in loss of all functional domains. | No (reported in ClinVar only) |
| Splicing | c.161+3G>C | N/A | Likely Pathogenic | Abolishes donor splice site of intron 3 leading to altered mRNA that skips exon 3 entirely and results in a truncated peptide that is a predicted 18 amino acids long. | Yes [23] |
| Splicing | c.161+5G>C | N/A | Likely Pathogenic | Predicted to severely decrease the binding capacity of the donor splice site of intron 3 suggesting splicing defect. Patient homozygous for this variant and seemingly no other rare pathogenic *APOA5* variants was APOA5 deficient. | Yes [8,24,25] |
| Splicing | c.162-43G>A | N/A | VUS | Unknown | Yes [26] |
| Missense | c.197A>G | p.Asn66Ser | VUS | Unknown | Yes [27] |
| Small Deletion | c.211delC | p.Leu71Trpfs\*4 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~80% of protein is lost, abolishing all functional domains of APOA5. | Yes [8] |
| Missense | c.278G>A | p.Arg93Gln | VUS | Unknown | Yes [21] |
| Missense | c.280C>T | p.Arg94Trp | VUS | Unknown | Yes [21] |
| Nonsense | c.283C>T | p.Gln95Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~75% of the protein is eliminated resulting in loss of all functional domains. | Yes [21] |
| Nonsense | c.289C>T | p.Gln97Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~75% of the protein is eliminated resulting in loss of all functional domains. | Yes [8,21,28-35] |
| Nonsense | c.292G>T | p.Glu98Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~75% of the protein is eliminated resulting in loss of all functional domains. | Yes [8,35,36] |
| Missense | c.295G>A | p.Glu99Lys | VUS | Unknown | Yes [20] |
| Small Deletion | c.295\_297delGAG | p.Glu99del | VUS | Predicted to disrupt amphipathic N-terminal domain α-helix configuration due to elimination of negatively-charged amino acid on the hydrophilic site of the helix. | Yes [8,37] |
| Small Deletion | c.305\_307del | p.Glu102del | VUS | Unknown. Does not appear to be an α-helix forming residue[37,38,39] so effect is difficult to predict. | No (reported in LOVD3 only) |
| Missense | c.313G>T | p.Ala105Ser | VUS | Unknown | Yes [21] |
| Small Insertion | c.326\_327insC | p.Tyr110Leufs\*158 | Likely Pathogenic | Insertion alters reading frame resulting in mRNA encoding truncated protein. >50% of protein is lost. N-terminal hydrophilic domain is in-tact. All other functional domains are interrupted or eliminated. | Yes [14,40] |
| Missense | c.331A>G | p.Met111Val | VUS | Unknown | Yes [8] |
| Missense | c.346G>C | p.Glu116Gln | VUS | Unknown but has been studied amongst numerous other variants as part of several investigations into the role *de novo* variants in Autism Spectrum Disorder. | Yes [41-43] |
| Nonsense | c.346G>T | p.Glu116Term | Likely pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~70% of the protein is eliminated resulting in loss of or serious interruption of all functional domains. | Yes [21] |
| Missense | c.352G>A | p.Val118Met | VUS | Unknown | Yes [8] |
| Missense | c.377G>A | p.Arg126Gln | VUS | Unknown | No (reported in LOVD3 only) |
| Missense | c.398C>G | p.Thr133Arg | VUS | Found in heterozygosity in patient with normal post-heparin LPL mass but no post-heparin LPL activity. | Yes [44] |
| Nonsense | c.415C>T | p.Gln139Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. >60% of the protein is eliminated resulting in loss of and serious interruption of all functional domains. | Yes [40,45] |
| Small Deletion | c.427delC | p.Arg143Alafs\*57 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~45% of protein is lost, leading to loss of GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding Domain. | Yes [8,21,22,46-50] |
| Missense | c.434A>G | p.Gln145Arg | VUS | Unknown | Yes [21,22] |
| Missense | c.436G>A | p.Glu146Lys | VUS | Unknown | Yes [8] |
| Nonsense | c.442C>T | p.Gln148Term | Likely pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~60% of the protein is eliminated resulting in loss of and serious interruption of all functional domains. | Yes [51] |
| Small Deletion | c.447\_450delGCAG | p.Glu149Aspfs\*50 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~45% of protein is lost, leading to loss of GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. | Yes [8] |
| Small Insertion-Deletion | c.447delGinsCTC | p.Glu149Aspfs\*52 | Likely Pathogenic | Insertion-deletion alters reading frame resulting in mRNA encoding truncated protein. ~45% of protein is lost, leading to loss of GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. | Yes [52] |
| Missense | c.457G>A | p.Val153Met | Benign | Unknown. Benign because of very high gnomAD maximal non-founder and founder subpopulation allele frequencies of 11.917% and 4.936%, respectively. It has also been observed in the homozygous state in population databases more than expected for disease. | Yes [20,46,53,54] |
| Nonsense | c.466G>T | p.Glu156Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~60% of the protein is eliminated resulting in loss of and serious interruption of all functional domains. | No (reported in ClinVar only) |
| Missense | c.473C>T | p.Thr158Ile | VUS | Unknown | Yes [8] |
| Missense | c.482A>G | p.Gln161Arg | VUS | Unknown | No (reported in LOVD3 only) |
| Missense | c.482A>T | p.Gln161Leu | VUS | Unknown | No (reported in LOVD3 only) |
| Missense | c.494G>A | p.Gly165Asp | VUS | Unknown | Yes [22] |
| Missense | c.494G>C | p.Gly165Ala | VUS | Unknown | Yes [46] |
| Small duplication | c.494dup | p.Val166Argfs\*102 | Likely Pathogenic | Duplication alters reading frame resulting in mRNA encoding truncated protein. Loss of 201 amino acids, leading to loss of the lipid droplet binding domain, GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. Additionally, ClinVar comments indicate that this variant has been observed in a patient with chylomicronemia. | No (reported in ClinVar only) |
| Missense | c.518T>C | p.Leu173Pro | VUS | Unknown | Yes [34] |
| Small Duplication | c.550dup | p.Thr184Asnfs\*84 | Likely Pathogenic | Duplication alters reading frame resulting in mRNA encoding truncated protein. Loss of ~50% of protein leading to elimination of the lipid droplet binding domain, GPIHBP1 interacting binding domain, and C-terminal lipid binding domain. | No (reported in LOVD3 only) |
| Missense | c.551C>G | p.Thr184Ser | VUS | Unknown | Yes [8,55,56] |
| Missense | c.553G>T | p.Gly185Cys | VUS | Unknown. Likely a risk factor much like S19W or -1131T>C are in some populations. Interestingly, this variant is negatively associated with obesity risk in the Chinese population while still raising TG. | Yes [21,57-59] |
| Missense | c.563A>G | p.Lys188Arg | VUS | Unknown | Yes [36] |
| Missense | c.578C>T | p.Pro193Leu | VUS | Unknown | Yes [8] |
| Small Deletion | c.579\_592del14 | p.Tyr194Glyfs\*69 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~28% of protein is lost, leading to loss of GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. | Yes [60] |
| Missense | c.589A>G | p.Ser197Gly | VUS | Unknown | Yes [21] |
| Small Deletion | c.593\_606del14 | p.Leu198Argfs\*65 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~28% of protein is lost, leading to loss of GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. | Yes [49] |
| Missense | c.610C>T | p.Arg204Cys | VUS | Unknown | Yes [8] |
| Small Deletion | c.614\_624del11 | p.His205Profs\*59 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~28% of protein is lost, leading to loss of GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. | Yes [61] |
| Missense | c.640G>C | p.Ala214Pro | VUS | Unknown | Yes [8] |
| Missense | c.644C>T | p.Pro215Leu | Likely Benign | Unknown. Considered benign because allele frequency in gnomAD maximal non founder subpopulations is higher than expected for disease at 0.216%. It has also been observed in the homozygous state in population databases. | Yes [21,40] |
| Small Duplication | c.653\_654dup | p.Ala219Profs\*79 | Likely Pathogenic | Duplication alters reading frame resulting in mRNA encoding truncated protein. ~18% of protein is lost, leading to loss of C-terminal portion of the GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. | No (reported in LOVD3 only) |
| Small Deletion | c.654delC | p.Ala219Profs\*78 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~18% of protein is lost, leading to loss of C-terminal portion of the GPIHBP1 and Heparin binding domain and C-terminal Lipid Binding domain. | Yes [61] |
| Missense | c.655G>C | p.Ala219Pro | VUS | Unknown | Yes [62] |
| Missense | c.659G>T | p.Ser220Ile | VUS | Unknown | Yes [20] |
| Missense | c.665C>T | p.Ala222Val | VUS | Unknown | Yes [21] |
| Missense | c.667C>T | p.Arg223Cys | VUS | Unknown | Yes [20] |
| Nonsense | c.685C>T | p.Gln229Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~37% of the protein is eliminated which eliminates a portion of the GPIHBP1/Heparin binding domain and also eliminates the C-terminal lipid binding domain. | No (reported in LOVD3 only) |
| Missense | c.694C>T | p.Ser232Pro | VUS | Unknown | Yes [63] |
| Small Deletion | c.694\_705del12 | p.Ser232\_Leu235del | Likely pathogenic | Impaired binding to immobilized heparin due to slower association, somewhat defective sortilin interaction and complete SorLA/LR11 binding deficiency. | Yes [31] |
| Missense | c.697C>T | p.Arg233Trp | VUS | Unknown | Yes [21] |
| Small Deletion | c.724delC | p.Leu242Cysfs\*55 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. ~18% of protein is lost, leading to loss of C-terminal portion of the GPIHBP1/Heparin binding domain and C-terminal Lipid Binding domain. | Yes [22] |
| Missense | c.725T>C | p.Leu242Pro | VUS | Unknown. Was found in hyperchylomicronemia proband but its involvement is unclear. | Yes [29] |
| Missense | c.733C>T | p.Arg245Cys | VUS | Unknown | Yes [21] |
| Missense | c.756G>C | p.Gln252His | VUS | Unknown | Yes [22] |
| Missense | c.758T>C | p.Leu253Pro | Likely pathogenic | Decreased liposome binding, almost completely deficient in sortilin and SorLA/LR11 binding, and finally variant potently inhibits LPL activity. | Yes [8,14,31,37] |
| Missense | c.763G>A | p.Glu255Lys | VUS | Unknown | Yes [21,22] |
| Missense | c.764A>G | p.Glu255Gly | Benign | Unknown. There is some evidence that it has some reduced ability to enhance LPL but allele frequency is too high for what is expected of disorder according to gnomAD (0693%) and has been observed in homozygous state in population databases more than is expected for disease. | Yes [64] |
| Nonsense | c.775A>T | p.Arg259Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~30% of the protein is eliminated which eliminates a portion of the GPIHBP1/Heparin binding domain and eliminates the C-terminal lipid binding domain. | No (reported in ClinVar only) |
| Small Deletion | c.795del | p.Thr266Leufs\*31 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein leading to loss of C-terminal portion of the GPIHBP1/Heparin binding domain and C-terminal Lipid Binding domain. | No (reported in ClinVar only) |
| Missense | c.811G>T | p.Gly271Cys | VUS | Forms dimers and multimers due to formation of disulfide bonds at this position being available. This variant does not bind LDL-family receptors, LR8 or LRP1. Does not seem to impact LPL activity directly. | Yes [64] |
| Missense | c.815C>A | p.Pro272Gln | VUS | Unknown | Yes [21] |
| Nonsense | c.823C>T | p.Gln275Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~25% of the protein is eliminated which eliminates a portion of the GPIHBP1/Heparin binding domain and eliminates the C-terminal lipid binding domain. | Yes [8,32,65-69] |
| Missense | c.830T>C | p.Leu277Pro | VUS | Unknown | Yes [8,21,36] |
| Missense | c.844C>A | p.Arg282Ser | VUS | Associated with a reduction in TG levels and serum APOAV levels. | Yes [8,70] |
| Missense | c.844C>T | p.Arg282Cys | VUS | Unknown | Yes [21] |
| Nonsense | c.847C>T | p.Gln283Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~20% of the protein is eliminated which eliminates a portion of the GPIHBP1/Heparin binding domain and eliminates the C-terminal lipid binding domain. | No (reported in ClinVar only) |
| Missense | c.875C>T | p.Thr292Ile | VUS | Unknown | Yes [8,21] |
| Nonsense | c.883C>T | p.Gln295Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. ~20% of the protein is eliminated which eliminates a portion of the GPIHBP1/Heparin binding domain and eliminates the C-terminal lipid binding domain. | Yes [8,21,22,46] |
| Missense | c.887T>G | p.Ile296Arg | VUS | Unknown | Yes [8,61] |
| Small Deletion | c.888delA | p.Ile296Metfs\*42 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. Disrupts the C-terminal lipid binding domain. | Yes [8] |
| Missense | c.902G>C | p.Arg301Pro | VUS | Unknown | Yes [22] |
| Nonsense | c.913C>T | p.Gln305Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. C-terminal lipid binding domain is disrupted. | Yes [27] |
| Small Deletion | c.926\_928delAGG | p.Glu309del | VUS | Unknown | Yes [22] |
| Nonsense | c.937C>T | p.Gln313Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. C-terminal lipid binding domain is disrupted. | Yes [21,71] |
| Missense | c.941T>G | p.Leu314Arg | VUS | Unknown | Yes [22] |
| Missense | c.944C>T | p.Ala315Val | VUS | Unknown but evidence currently suggests that in isolation this variant is not pathogenic but since it has increased frequency in HTG patient population, it may interact with other variants to cause HTG. | Yes [8,21,36,72] |
| Missense | c.956C>T | p.Pro319Leu | VUS | Unknown | Yes [21] |
| Missense | c.962A>T | p.His321Leu | Benign | Unknown but is considered benign since it has been reported in the homozygous state in population databases more than is expected for disease-causing variant (gnomAD homozygous count is 4 individuals) | Yes [21,64] |
| Missense | c.972C>G | p.Phe324Leu | VUS | Unknown | Yes [36] |
| Small Deletion | c.980\_981delAG | p.Glu327Valfs\*19 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. Disrupts the C-terminal lipid binding domain. | Yes [22] |
| Small Deletion | c.990\_993delAACA | p.Asp332Valfs\*5 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. Disrupts the C-terminal lipid binding domain. | Yes [8,18,20,31,32,50] |
| Small Deletion | c.995\_998delACAG | p.Asp332Valfs\*5 | Likely Pathogenic | Deletion alters reading frame resulting in mRNA encoding truncated protein. Disrupts the C-terminal lipid binding domain. | Yes [27] |
| Gross Insertion | c.999insGGCAAGGTTGTGAGCAAGCTGCAGGCCC | p.Ser333Argfs\*5 | Likely pathogenic | Large insertion alters reading frame resulting in mRNA encoding truncated protein. Disrupts the C-terminal lipid binding domain. | Yes [22] |
| Missense | c.1001G>T | p.Gly334Val | Likely Benign | Unknown. Benign as this variant has been observed in homozygous state in gnomAD population database. | Yes [21] |
| Missense | c.1027C>T | p.Arg343Cys | VUS | Unknown. Interestingly, even in the homozygous state, this variant does not seem to impact LPL activity. | Yes [21,40,46] |
| Missense | c.1036G>C | p.Asp346His | VUS | Unknown | Yes [8] |
| Nonsense | c.1044G>A | p.Trp348Term | Likely Pathogenic | Nonsense SNP produces mRNA that encodes truncated protein due to premature stop codon. C-terminal lipid binding domain is disrupted. | No (reported in ClinVar only) |
| Missense | c.1088T>A | p.Leu363Gln | VUS | Unknown | Yes[21] |
| Regulatory | c.\*158T>C | N/A | Likely Benign | Creates a functional miRNA (miR-485-5p) binding site in the 3’ UTR of the APOA5 gene, which enables miRNA-mediated degradation of the mRNA, thereby reducing allele expression. Does not seem to be pathogenic in isolation. Component of *APOA5*\*2 haplotype. | Yes [26,73,74,75] |

a For frameshift variants resulting in premature stop codon, the notation “fs\*(number)” indicates that the frameshift variant results in stop codon at the position (number) residues downstream of the variant site.

b N/A = Not Applicable

c VUS = Variant of Uncertain Significance

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