## **Supplementary Table 1.** **Variants in genes related to immune signaling, autophagy or apoptosis excluded based on uncertain relevance to VZV/HSV infection**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| P ID | Gene Symbol | Biological Category | Transcript ID | Transcript Variant; Protein Variant | Translation Impact | CADD; MSC Scores | SIFT Function Prediction | GnomAD  Frequency  (%) |
| P1 | *NRP1* | Innate Immunity & Virus Interaction | NM\_003873.7 | c.1699G>A;  p.Glu567Lys | Missense | 31.0; 3.313 | Damaging | 0.000003977 |
| *MSN* | Adaptive immunity | NM\_002444.3 | c.1123C>G;  p.Leu375Val | Missense | 23.9; 16.612 | Damaging | Not described |
| *GLA* | Innate Immunity | NM\_000169.3 | c.427G>A  p.Ala143Thr | Missense | 24.9; 0.085 | Damaging | 0.0005062 |
| *DDRGK1* | Innate Immunity & Autophagy | NM\_023935.3 | c.605G>A;  p.Gly202Asp | Missense | 26.5; 8.323 | Damaging | 0.00005662 |
| *ADGRE2* | Innate Immunity | NM\_013447.4 | c.2231C>T;  p.Thr744Met | Missense | 23.5;  N/S | Damaging | 0.00006014 |
| *MGST1* | Innate Immunity | NM\_020300.5 | c.217C>T;  p.Arg73Cys | Missense | 28.3; 6.517 | Damaging | 0.0001753 |
| *PTGS1* | Innate Immunity | NM\_000962.4 | c.826C>T;  p.Arg276Ter | Stop Gain | 34.0; 3.313 | N/S | 0.00001062 |
| *VIM* | Virus Interaction | NM\_003380.5 | c.690G>C;  p.Glu230Asp | Missense | 25.0; 6.123 | Damaging | Not described |
| *SPNS2* | Innate Immunity | NM\_001124758.3 | c.1607+6T>G | Splice-Site | 22.7; 7.488 | N/S | Not described |
| *SPNS2* | Innate Immunity | NM\_001124758.3 | c.1607+5\_1607+6insGG | Splice-Site | 25.4; 7.488 | N/S | Not described |
| *CPNE3* | Autophagy | NM\_003909.5 | c.958\_960delAAT;  p.Asn320del | In-Frame Deletion | 21.5; 5.764 | N/S | 0.0005339 |
| CCDC177 | Virus Interaction | NM\_001271507.2 | c.133T>G;  p.Ser45Ala | Missense | 17.6; 3.313 | N/S | Not described |
| P2 | *CFH* | Innate Immunity | NM\_000186.4 | c.350G>C;  p.Gly117Ala | Missense | 33.0; 0.001 | Damaging | Not described |
| *SPHK2* | Innate Immunity | NM\_020126.5 | c.457T>G;  p.Trp153Gly | Missense | 26.2; 3.313 | Damaging | Not described |
| *ZFHX3* | Innate Immunity | NM\_006885.4 | c.3257G>A;  p.Cys1086Tyr | Missense | 26.2; 3.313 | Damaging | Not described |
| *SNX30* | Autophagy | NM\_001012994.2 | c.425A>C;  p.Lys142Thr | Missense | 27.6; 3.313 | Damaging | 0.00005339 |
| *FBXO30* | Innate & Adaptive Immunity | NM\_032145.5 | c.337G>T;  p.Asp113Tyr | Missense | 27.1; 3.313 | Damaging | 0.00001592 |
| *TRPM1* | Autophagy | NM\_002420.6 | c.1349G>A;  p.Arg450Gln | Missense | 22.6; 0.091 | Damaging | 0.00005745 |
| *APPL2* | Innate Immunity | NM\_018171.5 | c.992T>C;  p.Met331Thr | Missense | 23.9; 3.313 | Tolerated | 0.0007990 |
| *NOD1* | Innate Immunity | NM\_006092.4 | c.434T>C;  p.Leu145Pro | Missense | 21.0; 3.313 | Tolerated | 0.0001888 |
| P3 | *SPHK2* | Innate Immunity | NM\_020126.5 | c.457T>G;  p.Trp153Gly | Missense | 26,2; 3,313 | Damaging | Not described |
| *HAND2* | Innate Immunity & Autophagy | NM\_021973.3 | c.275T>G;  p.Leu92Arg | Missense | 22.3;  3.313 | Damaging | 0.00004871 |
| *CREBBP* | Innate Immunity | NM\_004380.3 | c.2318C>A;  p.Pro773Gln | Missense | 17.1;  0.280 | Tolerated | Not described |
| *BRWD1* | Adaptive Immunity | NM\_033656.4 | c.3900+3A>T | Splice-Site | 24,3;  3,313 | N/S | 0.00003487 |
| *TNKS2* | Innate Immunity | NM\_025235.4 | c.570delA;  p.Glu191Lysfs\*3 | Frameshift | 32.0;  11.999 | N/S | Not described |
| *GBP2* | Virus Interaction | NM\_004120.5 | c.451C>T;  p.Arg151Ter | Stop Gain | 33.0;  3.313 | Damaging | 0.00002399 |
| HOXD11 | Autophagy | NM\_021192.3 | c.612\_613insCCCG; p.Glu205Profs\*85 | Frameshift | 36.0;  7.290 | N/S | Not described |
| HOXD11 | Autophagy | NM\_021192.3 | c.608delA; p.Gln203Argfs\*89 | Frameshift | 20.7;  7.290 | N/S | Not described |
| P4 | *CYB5R3* | Virus Interaction | NM\_000398.7 | c.757G>A;  p.Val253Met | Missense | 26.3;  3.415 | Damaging | 0.0001031 |
| *MADD* | Innate Immunity | NM\_003682.4 | c.4633G>A;  p.Glu1545Lys | Missense | 32.0;  24.4 | Damaging | Not described |
| *ZFHX4* | Virus Interaction | NM\_024721.5 | c.969G>C;  p.Gln323His | Missense | 25.9;  3.313 | Damaging | 0.000004016 |
| *FGL1* | Adaptive Immunity | NM\_004467.4 | c.842A>T;  p.Asn281Ile | Missense | 26.2;  3.313 | Damaging | Not described |
| *BAG1* | Apoptosis | NM\_004323.6 | c.929G>A;  p.Gly310Asp | Missense | 19.1;  3.313 | Tolerated | Not described |
| *RACGAP1* | Virus Interaction | NM\_001319999.2 | c.205G>A;  p.Asp69Asn | Missense | 25.4;  3.313 | Damaging | 0.0005727 |
| *PIK3R6* | Innate Immunity | NM\_001010855.4 | c.1177C>A;  p.Leu393Met | Missense | 24.5;  3.313 | N/S | 0.000004229 |
| *PTPN13* | Innate Immunity & Apoptosis | NM\_080685.3 | c.6272-1G>A | Splice-Site | 33.0;  3.313 | N/S | Not described |
| *DERA* | Innate Immunity | NM\_015954.4 | c.637+3\_637+6delAAGT | Splice-Site | 35.0;  3.313 | N/S | Not described |
| *HTATSF1* | Virus Interaction | NM\_014500.5 | c.794T>C;  p.Val265Ala | Missense | 26.5;  3.313 | Damaging | 0.000005593 |
| *ANAPC10* | Innate Immunity | NM\_001256706.2 | c.527T>C;  Ile176Thr | Missense | 21.7;  21.226 | Tolerated | Not described |
| P5 | *PIK3R2* | Autophagy | NM\_005027.4 | c.1958G>T;  p.Gly653Val | Missense | 27.6;  23.5 | Damaging | Not described |
| *OCIAD2* | Innate Immunity | NM\_001014446.3 | c.304T>C;  p.Tyr102His | Missense | 24.3;  3.313 | Damaging | 0.0002354 |
| *STAB1* | Innate Immunity | NM\_015136.3 | c.3094C>T;  p.Arg1032Cys | Missense | 24.2;  3.313 | Damaging | 0.0005381 |
| *TIAM1* | Adaptive Immunity | NM\_001353694.2 | c.2108C>G;  p.Ser703Cys | Missense | 28.6;  3.3131 | Damaging | 0.0006688 |
| *SERPING1* | Innate Immunity | NM\_000062.3 | c.1198C>T;  p.Arg400Cys | Missense | 23.0;  0.003 | Damaging | 0.00004772 |
| *FLCN* | Autophagy | NM\_144997.7 | c.268G>T;  p.Ala90Ser | Missense | 21.1;  5.546 | Tolerated | 0.0003660 |
| *ITGB6* | Virus Interaction | NM\_000888.5 | c.1175C>T;  p.Ala392Val | Missense | 24.1;  23.400 | Damaging | 0.00003184 |
| *ILRUN* | Innate Immunity | NM\_024294.4 | c.745\_765del;  p.Thr249\_Asp255del | Inframe-Deletion | 21.8;  N/S | N/S | Not described |
| *LYST* | Innate & Adaptive Immunity | NM\_000081.4 | c.10143+6T>G | Splice-Site | 21.8;  0.456 | N/S | 0.00004378 |
| *ACKR1* | Innate Immunity | NM\_002036.4 | c.940\_943dupACCC;  p.Leu315Hisfs\*10 | Frameshift | 1.94;  N/S | N/S | Not described |
| *CPN1* | Innate Immunity | NM\_001308.3 | c.272T>G;  p.Leu91Trp | Missense | 25.0;  3.069 | Damaging | Not described |
| EPHA5 | Adaptive Immunity | NM\_001281766.3 | c.368C>T;  p.Ala123Val | Missense | 24.7;  3.313 | Damaging | 0.000007958 |
| P6 | *APPL2* | Innate Immunity | NM\_018171.5 | c.1408C>T;  p.Arg470Cys | Missense | 33.0;  3.313 | Damaging | 0.0001870 |
| *WDFY1* | Innate Immunity | NM\_020830.5 | c.1136G>A;  p.Gly379Glu | Missense | 26.3;  6.122 | Damaging | 0.0001752 |
| *ZFHX3* | Innate Immunity | NM\_006885.4 | c.1565A>G;  p.Asp522Gly | Missense | 24.3;  3.313 | Damaging | 0.00005567 |
| *PRKD1* | Innate Immunity | NM\_002742.3 | c.1271T>C;  p. Met424Thr | Missense | 23.9;  5.778 | Damaging | Not described |
| *ITLN1* | Innate Immunity | NM\_017625.3 | c.454G>A;  p.Val152Met | Missense | 25.7;  3.313 | Damaging | 0.00005629 |
| *CPNE3* | Autophagy | NM\_003909.5 | c.130G>A;  p.Glu44Lys | Missense | 33.0;  5.764 | Damaging | 0.000004053 |
| P7 | *PMM2* | Innate Immunity | NM\_000303.3 | c.669C>A;  p.Asp223Glu | Missense | 23.9;  2.652 | Damaging | Not described |
| *RBBP8* | Adaptive Immunity | NM\_002894.3 | c.248G>A;  p.Arg83Gln | Missense | 35.0;  3.143 | Damaging | 0.000007963 |
| *FNIP1* | Autophagy & Adaptive Immunity | NM\_133372.3 | c.674T>G;  p.Leu225Arg | Missense | 27.6;  3.313 | Damaging | 0.000007965 |
| *PARP3* | Adaptive Immunity | NM\_001003931.4 | c.1223G>A;  p.Arg408His | Missense | 25.6;  3,.313 | Damaging | 0.0002212 |
| *BDKRB1* | Virus Interaction | NM\_000710.4 | c.122C>T;  p.Pro41Leu | Missense | 24.0;  3.313 | Damaging | 0.0006244 |
| *PIDD1* | Apoptosis | NM\_145886.4 | c.2363C>T;  p.Thr788Met | Missense | 25.4;  N/S | Damaging | 0.0001294 |
| *SCNN1A* | Virus Interaction | NM\_001038.6 | c.1793G>A;  p.Gly598Glu | Missense | 22.8;  1.766 | Tolerated | 0.000007980 |
| *ZFP36L2* | Innate Immunity | NM\_006887.5 | c.1205delG;  p.Gly402Alafs\*59 | Frameshift | 23.4;  3.313 | N/S | Not described |
| *GCA* | Innate Immunity & Autophagy | NM\_012198.5 | c.27+5G>A | Splice-Site | 26.4;  3.313 | N/S | 0.000004020 |
| P8 | *FGF13* | Innate Immunity | NM\_001139500.2 | c.103T>A;  p.Ser35Thr | Missense | 25.1;  N/S | Damaging | 0.000005646 |
| *HSF4* | Innate Immunity | NM\_001538.4 | c.523C>G;  p.Arg175Gly | Missense | 2.,5;  7.173 | Damaging | 0.00002524 |
| *USP31* | Innate Immunity | NM\_020718.4 | c.1744A>G;  p.Ser582Gly | Missense | 26.6;  3.313 | Damaging | Not described |
| *HERC2* | Innate & Adaptive Immunity & Autophagy | NM\_004667.6 | c.845C>G;  p.Pro282Arg | Missense | 26.5;  3.313 | Damaging | Not described |
| *CTBP2* | Innate Immunity | NM\_022802.3 | c.322C>T;  p.Arg108Trp | Missense | 24.7;  3.313 | Damaging | 0.00009547 |
| *PIK3C2G* | Autophagy | NM\_001288772.2 | c.3536A>G;  p.Tyr1179Cys | Missense | 25.8;  3.313 | Damaging | 0.000004290 |
| *GBF1* | Autophagy | NM\_001377137.1 | c.3407T>C;  p.Met1136Thr | Missense | 26.8;  3.313 | Damaging | 0.000007964 |
| *DLG5* | Innate Immunity | NM\_004747.4 | c.5635G>C;  p.Glu1879Gln | Missense | 28.1;  3.313 | Damaging | Not described |
| *CHMP7* | Autophagy | NM\_152272.5 | c.881G>A;  p.Arg294His | Missense | 27.9;  3.313 | Tolerated | 0.00001989 |
| *ZC3HAV1* | Virus Interaction | NM\_020119.4 | c.1994-2A>T | Splice-Site | 33.0;  3.313 | N/S | Not described |
| *AKAP8* | Innate Immunity | NM\_005858.4 | c.169\_189del;  p.Ser57\_Ala63del | In-Frame Deletion | 16.8;  3.313 | N/S | Not described |
| *SCRIB* | Innate & Adaptive Immunity | NM\_182706.5 | c.2497\_2499delGAT;  p.Asp833del | In-Frame Deletion | 21.6;  14.420 | N/S | Not described |
| *SLAMF8* | Adaptive Immunity | NM\_020125.3 | c.211\_212delCT;  p.Leu71Valfs\*92 | Frameshift | 24.3;  3.313 | N/S | Not described |
| *FLNC* | Autophagy | NM\_001458.5 | c.2416G>A;  p.Ala806Thr | Missense | 23.2;  0.001 | Tolerated | Not described |
| P9 | *CFHR5* | Innate Immunity | NM\_030787.4 | c.1291T>G;  p.Cys431Gly | Missense | 22.7;  8.495 | Damaging | Not described |
| *BRCA2* | Adaptive Immunity & Autophagy | NM\_000059.4 | c.9501+3A>T | Splice-Site | N/S;  0.001 | N/S | Not described |
| *SPG7* | Innate Immunity | NM\_003119.2 | c.2191G>A;  p.Ala731Thr | Missense | 24.0;  0.001 | N/S | 0.0000319 |
| *STAM2* | Innate Immunity | NM\_005843.6 | c.959T>C;  p.Leu320Ser | Missense | 24.9;  5.448 | Tolerated | Damaging |
| *IL22RA2* | Innate Immunity | NM\_052962.2 | c.596A>G;  p.Tyr199Cys | Missense | 24.9;  5.448 | Damaging | 0.0000201 |
| *CFTR* | Innate Immunity | NM\_000492.4 | c.2770G>A;  p.Asp924Asn | Missense | 31.0;  0.001 | Damaging | 0.0000676 |
| *ZP4* | Innate Immunity | NM\_021186.5 | c.530delA;  p.Asn177Ilefs\*9 | Frameshift | N/S;  3.313 | N/S | Not described |
| *TOP1* | Virus Interaction | NM\_003286.4 | c.1951-17A>- | Splice-Site | N/S;  3.313 | N/S | 0.00000398 |
| *ZNF335* | Adaptive Immunity | NM\_022095.4 | c.3298\_3300delCTC;  p.Glu1100del | In-Frame Deletion | N/S;  3.313 | N/S | Not described |
| *MAP3K15* | Innate Immunity | NM\_001001671.4 | c.3353\_3355delTGT;  p.Asn1118del | In-Frame Deletion | N/S;  0.305 | N/S | Not described |
| P10 | *TNKS2* | Innate & Adaptive Immunity | NM\_025235.4 | c.354T>A;  p.Asn118Lys | Missense | 24,6;  11.999 | Damaging | 0.0000716 |
| *CUEDC2* | Innate Immunity | NM\_024040.3 | c.703A>G;  p.Met235Val | Missense | 16.74;  3.313 | Tolerated | 0.00002 |
| *EIF2AK4* | Virus Interaction | NM\_001013703.4 | c.1661-18C>G | Splice-Site | N/S;  0.005 | N/S | 0.00000417 |
| *CLEC10A* | Innate & Adaptive Immunity | NM\_182906.4 | c.82C>T;  p.GLN28X | Stop Gain | 36.0;  3.313 | N/S | 0.0002 |
| *MYO9B* | Adaptive Immunity | NM\_004145.4 | c.2811+19C>T | Splice-Site | N/S;  3.313 | N/S | 0.0000296 |
| *TEC* | Innate & Adaptive Immunity | NM\_003215.3 | c.1603G>C;  p.Glu535Gln | Missense | 29.3;  3.313 | Damaging | Not described |
| *DCST1* | Innate Immunity | NM\_152494.4 | c.1074\_1088del;  p.Val359\_Val363del | In-Frame Deletion | N/S;  3.313 | N/S | 0.0006 |
| *HPGD* | Innate Immunity | NM\_001256307.2 | c.120delAla;  p.Ala41Glnfs\*31 | Frameshift | N/S;  16.370 | N/S | 0.0000517 |
| P11 | *PTPRS* | Innate Immunity | NM\_002850.4 | c.2845C>T;  p.Arg949Cys | Missense | 27.2;  3.313 | N/S | 0.0002 |
| *MSH6* | Adaptive Immunity | NM\_000179.3 | c.3940C>G;  p.Gln1314Gu | Missense | 21.9;  0.026 | Tolerated | 0.000004 |
| *GGT5* | Adaptive Immunity | NM\_001099781.2 | c.184C>T;  p.Gln62X | Stop Gain | 37.0;  3.313 | N/S | 0.0000493 |
| *FZD1* | Innate & Adaptive Immunity | NM\_003505.2 | c.173T>C;  p.Leu58Pro | Missense | 19.3;  3.313 | Tolerated | 0.0000304 |
| *HAX1* | Innate Immunity | NM\_006118.4 | c.116\_117insAGAAGG;  p.Gly41\_Gly42insGluGly | In-Frame Insertion | N/S;  0.003 | N/S | 0.0004 |
| *STAP1* | Adaptive Immunity | NM\_012108.4 | c.827-1G>- | Splice-Site | N/S;  23.000 | N/S | 0.0000207 |
| *FBXW7* | Innate Immunity | NM\_033632.3 | c.349\_351del;  p.Glu117del | In-Frame Deletion | N/S;  3.313 | N/S | 0.0002 |
| P12 | *IPO13* | Innate & Adaptive Immunity | NM\_014652.4 | c.821+20C>T | Splice-Site | N/S;  3.313 | N/S | 0.0002 |
| *RNF187* | Innate Immunity | NM\_001010858.3 | c.391-17C>A | Splice-Site | N/S;  9.592 | N/S | Not described |
| *MYOF* | Innate & Adaptive Immunity | NM\_013451.4 | c.3214C>T;  p.Arg1072Cys | Missense | 32.0;  3.313 | Damaging | 0.0003 |
| *MPEG1* | Innate Immunity | NM\_001039396.2 | c.404G>T;  p.Arg135Met | Missense | 22.7;  3.313 | Damaging | 0.0000682 |
| *KLRG1* | Adaptive Immunity | NM\_001329099.2 | c.164T>C  p.Leu55Pro | Missense | 22.8;  3.838 | Damaging | 0.0004 |
| *LRP6* | Innate & Adaptive Immunity | NM\_002336.3 | c.3773C>T;  p.Thr1258Met | Missense | 28.1;  15.970 | Damaging | 0.0000279 |
| *ITPR2* | Autophagy | NM\_002223.4 | c.2639G>A;  p.Ser880Asn | Missense | 20.6;  5.744 | Tolerated | 0.00000935 |
| *MMP14* | Virus Interaction | NM\_004995.4 | c.1403T>C;  p.Met468Thr | Missense | 23.3;  5.744 | Tolerated | Not described |
| *SOS2* | Innate & Adaptive Immunity | NM\_006939.4 | c.374A>T;  p.His125Leu | Missense | 22.5;  3.313 | Damaging | 0.0000249 |
| *BANP* | Adaptive Immunity | NM\_017869.4 | c.673C>G;  p.Leu225Val | Missense | 25.3;  3.313 | Damaging | Not described |
| *COLEC11* | Innate Immunity | NM\_024027.5 | c.434G>T;  p.Gly145Val | Missense | 23.8;  0.062 | Damaging | 0.0000519 |
| *TBC1D5* | Autophagy | NM\_001134381.1 | c.1819-20T>C | Splice-Site | N/S;  3.313 | N/S | 0.0000364 |
| *EPHA5* | Adaptive Immunity | NM\_004439.8 | c.1924+20T>A | Splice-Site | N/S;  3.313 | N/S | 0.0003 |
| *MYOCD* | Innate Immunity | NM\_001146312.3 | c.2771\_2772insTGGG;  p.Leu926Trpfs\*8 | Frameshift | N/S;  3.313 | N/S | Not described |
| *PDLIM7* | Innate Immunity | NM\_005451.5 | c.1319\_1321delAGA;  p.Phe440del | In-Frame Deletion | N/S;  5.392 | N/S | 0.0000201 |
| P13 | *MACF1* | Innate Immunity | NM\_012090.5 | c.14591A>G;  p.Lys4864Arg | Missense | 29.3;  3.313 | Tolerated | 0.00000398 |
| *DMAP1* | Innate Immunity | NM\_019100.5 | c.848G>A;  p.Arg283His | Missense | 31.0;  3.313 | Tolerated | 0.0003 |
| *DRAM2* | Autophagy | NM\_178454.6 | c.737T>C;  p.Leu246Pro | Missense | 28.6;  3.313 | Damaging | 0.0003 |
| *PTPN22* | Innate & Adaptive Immunity | NM\_015967.8 | c.684-20A>G | Splice-Site | N/S;  3.313 | N/S | Not described |
| *CD244* | Innate & Adaptive Immunity | NM\_016382.4 | c.61+18G>C | Splice-Site | N/S;  3.313 | N/S | 0.0001 |
| *CAPN2* | Innate Immunity | NM\_001748.5 | c.281G>A;  p.Arg94His | Missense | 32.0;  3.313 | Damaging | 0.0000279 |
| *DNA2* | Innate Immunity | NM\_001080449.3 | c.239G>T;  p.Cys80Phe | Missense | 28.6;  0.204 | Damaging | Not described |
| *RAC2* | Adaptive Immunity | NM\_002872.5 | c.40G>A;  p.Val14Met | Missense | 32.0;  25.874 | Damaging | Not described |
| *PLA2G6* | Innate Immunity | NM\_003560.4 | c.1424G>A;  p.Arg475Gln | Missense | 23.5;  1.955 | Tolerated | 0.0002 |
| *PLD1* | Innate & Adaptive Immunity | NM\_002662.5 | c.665+1G>A | Splice-Site | 34.0;  3.313 | N/S | 0.0000478 |
| *HTR4* | Innate & Adaptive Immunity | NM\_001040169.2 | c.691C>T;  p.Arg231Trp | Missense | 24.1;  3.313 | Damaging | 0.0001 |
| *EEF1D* | Virus Interaction | NM\_032378.7 | c.1488+17C>T | Splice-Site | N/S;  3.313 | N/S | 0.0000802 |
| *RASAL3* | Adaptive Immunity | NM\_022904.3 | c.2455\_2456del;  p.Ser819Cysfs\*84 | Frameshift | N/S;  3.313 | N/S | 0.0000132 |
| *TWIST1* | Innate Immunity | NM\_000474.4 | UTR3 | Splice-Site | N/S;  6.18 | N/S | Not described |
| ZFHX4 | Virus Interaction | NM\_024721.5 | c.8847T>G;  p.Ser2949Arg | Missense | 16.0;  3.313 | Damaging | 0.00000803 |
| P14 | *UBR4* | Innate Immunity | NM\_020765.3 | c.1709A>G;  p.Tyr570Cys | Missense | 27.5;  3.313 | Damaging | Not described |
| *DDX51* | Innate & Adaptive Immunity | NM\_175066.4 | c.995+19C>T | Splice-Site | N/S;  3.313 | N/S | 0.0000363 |
| *TRPC3* | Adaptive Immunity | NM\_001130698.2 | c.2547+3A>G | Splice-Site | N/S;  3.313 | N/S | 0.000056 |
| P15 | *SLC7A1* | Adaptive Immunity & Virus Interaction | NM\_003045.5 | c.1084A>G;  p.Ile362Val | Missense | 23.5;  5.744 | Tolerated | 0.00000398 |
| *HK3* | Innate & Adaptive Immunity | NM\_002115.3 | c.1903G>A;  p.Glu635Lys | Missense | 26.2;  3.313 | Tolerated | 0.0001 |
| *MTMR9* | Autophagy & Apoptosis | NM\_015458.4 | c.1108C>A;  p.Leu370Met | Missense | 25.3;  3.313 | Damaging | 0.0002 |
| *WRN* | Innate Immunity | NM\_000553.6 | c.130C>G;  p.Leu44Val | Missense | 20.7;  0.001 | Damaging | 0.0004 |
| *NSF* | Autophagy | NM\_006178.4 | c.2111\_2113delGGA;  p.Trp704\_Ile705delinsLeu | In-Frame Deletion | N/S;  17.812 | N/S | Not described |
| *NSF* | Autophagy | NM\_006178.4 | c.2115\_2126deAGGAATCAAGAAl;  p.Ile705\_Lys709delinsMet | In-Frame Deletion | N/S;  17.812 | N/S | Not described |
| *BPIFA1* | Innate Immunity | NM\_016583.4 | c.586delG;  p.Gly196Alafs\*16 | Frameshift | N/S;  3.313 | N/S | 0.00000398 |
| P16 | *TIGAR* | Innate Immunity | NM\_020375.3 | c.124G>A;  p.Ala42Thr | Missense | 21.5;  N/S | Damaging | Not described |
| *RGMA* | Innate Immunity | NM\_001166283.2 | c.578C>T;  p.Ala193Val | Missense | 21.3;  3.313 | Tolerated | 0.0000213 |
| *TNFSF12* | Innate Immunity & Apoptosis | NM\_003809.3 | c.353G>A;  p.Gly118Glu | Missense | 27.2;  8.923 | Damaging | 0.0002 |
| *TNFSF12-TNFSF13* | Innate Immunity | NM\_172089.4 | c.353G>A;  p.Gly118Glu | Missense | N/S;  N/S | N/S | 0.0002 |
| *DNAJC27* | Innate Immunity | NM\_016544.3 | c.171-20T>G | Splice-Site | 20.2;  5.778 | Damaging | 0.0001 |
| *AGA* | Virus Interaction | NM\_000027.4 | c.481C>T;  p.Arg161Trp | Missense | N/S;  3.940 | N/S | 0.00000901 |
| *PTGES2* | Innate Immunity | NM\_025072.7 | c.1006-20C>T | Splice-Site | N/S;  3.313 | N/S | 0.00000948 |
| P17 | *TP73* | Apoptosis | NM\_005427.4 | c.1074+19A>G | Splice-Site | N/S;  3.313 | N/S | Not described |
| *NASP* | Innate Immunity | NM\_002482.4 | c.1593-18C>A | Splice-Site Variant | N/S;  3.313 | N/S | 0.0000756 |
| *SLC18A2* | Adaptive Immunity | NM\_003054.6 | c.127A>G;  p.Ile43Val | Missense | 24.4;  3.313 | Damaging | 0.00000402 |
| *NR1H3* | Innate Immunity | NM\_005693.4 | c.931G>A;  p.Glu311Lys | Missense | 26.1;  3.313 | Tolerated | 0.00000398 |
| *APAF1* | Adaptive Immunity & Apoptosis | NM\_013229.3 | c.139-17T>C | Splice-Site | N/S;  17.650 | N/S | Not described |
| *POLE* | Adaptive Immunity | NM\_006231.4 | c.2773T>C;  p.Ser925Pro | Missense | 24.0;  12.420 | Damaging | 0.0000557 |
| *CCDC177* | Virus Interaction | NM\_001271507.2 | c.1495C>T;  p.Arg499Trp | Missense | 24.9;  3.313 | N/S | Not described |
| *TRAF7* | Innate Immunity | NM\_032271.3 | c.421C>G;  p.Pro141Ala | Missense | 23.2;  5.751 | Damaging | Not described |
| *PIK3R5* | Autophagy | NM\_001142633.3 | c.2577G>C;  p.Gln859His | Missense | 21.4;  3.313 | Damaging | Not described |
| *MED16* | Innate Immunity | NM\_005481.3 | c.2101C>T;  p.Arg701Cys | Missense | 25.0;  3.313 | Damaging | 0.0003 |
| *GRAMD1A* | Autophagy | NM\_020895.5 | c.1512G>T;  p.Trp504Cys | Missense | 32.0;  3.313 | Damaging | Not described |
| *RIF1* | Adaptive Immunity | NM\_018151.5 | c.7095+18A>G | Splice-Site | N/S;  34.000 | N/S | 0.00000437 |
| *HOXD11* | Autophagy | NM\_021192.3 | c.1A>T;  p.Met1? | Start Loss | 25.4;  7.290 | Damaging | 0.0000943 |
| *ARHGEF3* | Autophagy | NM\_001128615.2 | c.301-17T>C | Splice-Site Variant | N/S;  3.313 | N/S | 0.00000809 |
| *ATP6V1A* | Virus Interaction | NM\_001690.4 | c.1688A>G;  p.Asn563Ser |  | 19.8;  4.946 | Tolerated | 0.0000438 |
| *RPA3* | Autophagy | NM\_002947.5 | c.99+16A>G | Splice-Site | N/S;  5.374 | N/S | 0.0002 |
| *GLI3* | Adaptive Immunity & Autophagy | NM\_000168.6 | c.1813-20G>A | Splice-Site | N/S;  5.176 | N/S | 0.0000208 |
| *FLNC* | Autophagy | NM\_001458.5 | c.5311C>G;  p.Pro1771Ala | Missense | 22.7;  0.001 | Tolerated | 0.0002 |
| *MUC1* | Innate & Adaptive Immunity | NM\_002456.6 | c.516\_534del GCCCCAGCCTGG CACCCCA;  p.Gly173Serfs\*46 | Frameshift | N/S;  3.313 | N/S | 0.00000401 |
| *LTK* | Innate Immunity | NM\_002344.6 | c.401delA;  p.Asn134Thrfs\*107 | Frameshift | N/S;  3.313 | N/S | 0.0003 |
| *TRNT1* | Autophagy | NM\_182916.3 | c.126\_128del;  p.Glu43del | In-Frame Deletion | N/S;  1.812 | N/S | 0.0000318 |
| *ERAP2* | Adaptive Immunity | NM\_022350.5 | c.151delG;  p.Ala52Leufs\*4 | Frameshift | N/S;  3.313 | N/S | Not described |

Variants identified in patients with ARN. Abbreviations: P, patient; ID, identification; ARN, acute retinal necrosis, N/S, not specified; CADD, combined annotation dependent depletion; MSC, mutation significance cutoff; SIFT, Sorting Intolerant from Tolerant; gnomAD, genome aggregation database.

## **Supplementary Table 2.** **Variants identified in the patient cohort without substantial known role in immunity, autophagy or apoptosis.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| P ID | Gene Symbol | Transcript ID | Transcript Variant; Protein Variant | Translation Impact | CADD; MSC Scores | SIFT Function Prediction | GnomAD Frequency (%) |
| P1 | *RCBTB2* | NM\_001268.4 | c.142G>C;  p.Ala48Pro | Missense | 27.9; 3.313 | Damaging | 0.00008136 |
| *E2F6* | NM\_198256.4 | c.565C>T;  p.His189Tyr | Missense | 22.8; 3.313 | Damaging | 0.00004415 |
| *SEMA4G* | NM\_017893.4 | c.2068G>A;  p.Gly690Ser | Missense | 24.1; 3.313 | Damaging | 0.0006673 |
| *HEXB* | NM\_000521.4 | c.1199A>G;  p.Lys400Arg | Missense | 23.0; 0.004 | Tolerated | 0.00003184 |
| *RBM26* | NM\_001366735.2 | c.2912\_2914delAAG; p.Glu971del | In-Frame Deletion | 21.9; 5.771 | N/S | 0.000007985 |
| P2 | *DYSF* | NM\_003494.4 | c.244G>A;  p.Gly82Arg | Missense | 27.9; 0.009 | Damaging | 0.00001989 |
| *TLX1* | NM\_005521.4 | c.431T>G;  p.Val144Gly | Missense | 19.9; 3.313 | Tolerated | Not described |
| *LNPK* | NM\_030650.3 | c.224C>T;  p.Ala75Val | Missense | 16.6; N/S | Tolerated | 0.0001503 |
| *SRRM5* | NM\_001145641.2 | c.352delC; p.His118Thrfs\*28 | Frameshift | 20.3; 3.313 | N/S | Not described |
| *GALC* | NM\_000153.4 | c.74\_75insGGGGGGGC; p.Arg26Glyfs\*49 | Frameshift | 23.3; 8.428 | N/S | Not described |
| *CNOT6* | NM\_001370472.1 | c.718-5T>C | Splice-Site | 16.7; 3.313 | N/S | 0.00004218 |
| *AOX1* | NM\_001159.4 | c.2655+3\_2655+6delAAGT | Splice-Site | 32.0; 3.313 | N/S | Not described |
| *RECQL5* | NM\_004259.7 | c.1504C>T;  p.Arg502Trp | Missense | 28.7; 3.313 | Damaging | Not described |
| P3 | *NUP205* | NM\_015135.3 | c.2182C>T;  p.Arg728Trp | Missense | 28.6; 5.785 | Damaging | Not described |
| *ABCB4* | NM\_000443.4 | c.3296A>G;  p.Glu1099Gly | Missense | 27.3;  0.009 | Damaging | 0.0004061 |
| *SYNJ2* | NM\_003898.4 | c.3556G>A;  p.Ala1186Thr | Missense | 25.6;  3.313 | Damaging | 0.0004024 |
| *PAICS* | NM\_001079524.2 | c.158A>G;  p.Lys53Arg | Missense | 24.1;  3.313 | Damaging | 0.0007931 |
| *MRPS17* | NM\_015969.3 | c.121A>C;  p.Lys41Gln | Missense | 24.3;  3.313 | Tolerated | Not described |
| *CAD* | NM\_004341.5 | c.5444G>T;  p.Gly1815Val | Missense | 21.3;  6.004 | Tolerated | 0.00002564 |
| *MYO1C* | NM\_033375.5 | c.1611+2T>G | Splice-Site | 33.0;  5.516 | N/S | Not described |
| P4 | *MYO1F* | NM\_012335.4 | c.1867T>C;  p.Tyr623His | Missense | 28.0;  3.313 | Damaging | 0.00001205 |
| *KLKB1* | NM\_000892.5 | c.1561G>A;  p.Gly521Arg | Missense | 25.2;  25.800 | Damaging | 0.0001353 |
| *CRYAA* | NM\_000394.4 | c.275A>G;  p.Asp92Gly | Missense | 24.1;  14.420 | Damaging | 0.000003986 |
| *BLMH* | NM\_000386.4 | c.653G>A;  p.Arg218Gln | Missense | 32.0;  7.253 | Damaging | 0.00001993 |
| *MYH2* | NM\_017534.6 | c.5122G>A;  p.Ala1708Thr | Missense | 24.3;  0.003 | Damaging | 0.00009947 |
| P5 | *CNKSR2* | NM\_014927.5 | c.857C>T;  p.Pro286Leu | Missense | 26.0;  5.764 | Damaging | 0.000005484 |
| P6 | *AGL* | NM\_000642.3 | c.1028G>A;  p.Arg343Gln | Missense | 25.2;  0.021 | Damaging | 0.0004218 |
| *BMP1* | NM\_006129.5 | c.2498C>T;  p.Thr833Ile | Missense | 26.3;  19.040 | Damaging | 0.000004006 |
| *GPR146* | NM\_001303473.2 | c.392G>A;  p.Arg131His | Missense | 23.9;  3.313 | Damaging | 0.000004046 |
| *GPR17* | NM\_001161417.2 | c.914G>A;  p.Arg305His | Missense | 29.8;  3.313 | Damaging | 0.0006294 |
| *VTI1B* | NM\_006370.3 | c.146A>G;  p.Asp49Gly | Missense | 23.9;  3.313 | Damaging | Not described |
| *COL28A1* | NM\_001037763.3 | c.2589G>C;  p.Leu863Phe | Missense | 23.9;  3.313 | Tolerated | Not described |
| P7 | *CENPJ* | NM\_018451.5 | c.3589G>A;  p.Val1197Met | Missense | 22.9;  10.020 | Damaging | 0.00009943 |
| *CHD7* | NM\_017780.4 | c.3347A>G;  p.Lys1116Arg | Missense | 28.5;  0.019 | Damaging | 0.000004018 |
| *CLPTM1L* | NM\_030782.5 | c.1246G>C;  p.Ala416Pro | Missense | 23.8;  3.313 | Damaging | 0.000003979 |
| *PRSS27* | NM\_031948.5 | c.293C>T;  p.Pro98Leu | Missense | 23.7;  3.313 | Tolerated | 0.0005244 |
| *MGA* | NM\_001164273.2 | c.8126G>T;  p.Gly2709Val | Missense | 22.5;  3.313 | Tolerated | 0.00005225 |
| *DDR1* | NM\_001297654.2 | c.2695delT;  p.Ser899Profs | Missense | 29.4;  5.708 | N/S | Not described |
| P8 | *PTPN3* | NM\_002829.4 | c.650A>G;  p.Tyr217Cys | Missense | 27.3;  3.313 | Damaging | 0.00001194 |
| *EVI2A* | NM\_014210.4 | c.39T>A;  p.His13Gln | Missense | 21.4;  3.313 | Damaging | Not described |
| *GPNMB* | NM\_001005340.2 | c.1574A>C;  p.Tyr525Ser | Missense | 25.4;  3.313 | Damaging | 0.00004406 |
| *EP400* | NM\_015409.5 | c.7703C>T;  p.Thr2568Met | Missense | 22.5;  3.313 | Damaging | 0.00005341 |
| *PRDM4* | NM\_012406.4 | c.484A>G;  p.Ile162Val | Missense | 22.7;  3.313 | Damaging | 0.000003976 |
| *CEP290* | NM\_025114.4 | c.2090C>G;  p.Ala697Gly | Missense | 25.2;  2.165 | Damaging | 0.0003743 |
| *RSF1* | NM\_016578.4 | c.1819C>G;  p.Pro607Ala | Missense | 20.5;  3.313 | Damaging | 0.00008000 |
| *PPM1J* | NM\_005167.7 | c.1409G>A;  p.Arg470Gln | Missense | 32.0;  3.313 | Tolerated | 0.00006654 |
| *MNT* | NM\_020310.3 | c.73+1G>C | Splice-Site | 35.0;  3.313 | N/S | Not described |
| *NELFB* | NM\_015456.5 | c.28C>T;  p.Arg10Trp | Missense | 17.4;  3.313 | N/S | Not described |
| *SMC2* | NM\_006444.3 | c.2118\_2120delAAA;  p.Lys706del | In-Frame Deletion | 21.1;  5.324 | N/S | Not described |
| *ODF1* | NM\_024410.4 | c.673\_683delAACCCGTGCAG;  p.Asn225Profs\*3 | Frameshift | 35.0  3.313 | N/S | Not described |
| *ARID4B* | NM\_016374.6 | c.666-3\_666-2delTA | Splice-Site | 23.4;  3.313 | N/S | Not described |
| P9 | *CDC42BPA* | NM\_014826.4 | c.4034G>A;  p.Arg1345Gln | Missense | 29.1;  3.313 | Damaging | 0.0000122 |
| P10 | *ZSCAN29* | NM\_152455.4 | c.929G>A;  p.Arg310Gln | Missense | 28.0;  3.313 | Damaging | 0.0000597 |
| *RPL27* | NM\_000988.5 | 5´ UTR | Splice-Site | N/S;  N/S | N/S | Not described |
| *ZNF512* | NM\_032434.3 | c.373+20A>G | Splice-Site | N/S;  5.798 | N/S | 0.000024 |
| *KMT5B* | NM\_017635.5 | c.2490\_2492delGAG;  p.Ser832del | In-Frame Deletion | N/S;  N/S | N/S | 0.0000559 |
| P11 | *VPS72* | NM\_001271087.2 | c.266A>G;  p.Tyr89Cys | Missense | 29.6;  3.313 | Damaging | 0.0002 |
| *CDC42BPA* | NM\_014826.5 | c.4712C>T;  p.Pro1571Leu | Missense | 24.5;  3.313 | Tolerated | 0.00000398 |
| *CDC42BPG* | NM\_017525.3 | c.4229T>G;  p.Phe1410Cys | Missense | 26.0;  3.313 | Damaging | 0.0000159 |
| *TCN2* | NM\_000355.4 | c.449C>T;  p.Pro150Leu | Missense | 23.2;  0.001 | Damaging | N/S |
| P12 | *MYH2* | NM\_017534.6 | c.193G>C;  p.Glu65Gln | Missense | 22.5;  0.003 | Tolerated | 0.0000358 |
| P13 | *CYFIP1* | NM\_014608.6 | c.2159+10T>C | Splice-Site | N/S;  5.764 | N/S | 0.0000517 |
| *CAD* | NM\_004341.5 | c.5147C>T;  p.Thr1716Met | Missense | 26.1;  6.004 | Damaging | 0.000056 |
| *CAD* | NM\_004341.5 | c.5561G>A;  p.Arg1854Gln | Missense | 24.2;  6.004 | Tolerated | 0.0000437 |
| *ESRRB* | NM\_004452.4 | c.602delT;  p.Ser202Lfs\*8 | Frameshift | N/S;  11.410 | N/S | Not described |
| P14 | *TUBAL3* | NM\_024803.2 | c.245T>C;  p.Ile82Thr | Missense | 18.8;  3.313 | Damaging | 0.0000677 |
| *MYO9A* | NM\_024803.3 | c.511A>G;  p.Lys171Glu | Missense | 21.3;  3.313 | Tolerated | Not described |
| *ERCC4* | NM\_005236.3 | c.2395C>T;  p.Arg799Trp | Missense | 31.0;  0.001 | Damaging | 0.0005 |
| *TRPV6* | NM\_018646.6 | spl | Splice-Site | N/S;  3.313 | N/S | Not described |
| P15 | *SREK1* | NM\_001077199.3 | c.847C>T;  p.Arg283X | Stop Gain | 37.0;  5.256 | N/S | Not described |
| P16 | *DENND4C* | NM\_017925.7 | c.4634+7C>A | Splice-Site | N/S;  3.313 | N/S | 0.0000419 |
| P17 | *MYO5B* | NM\_001080467.3 | c.4240G>A;  p.Glu1414Lys | Missense | 32.0;  0.017 | Damaging | 0.0004 |
| *MYH9* | NM\_002473.6 | c.5026A>G;  p.Lys1676Glu | Missense | 25.4;  5.427 | Damaging | 0.0003 |
| *ANKRD28* | NM\_015199.4 | c.574G>A;  p.Ala192Thr | Missense | 28.1;  5.751 | Damaging | 0.0003 |
| *RAD50* | NM\_005732.4 | c.353delT;  p.Thr119Leufs\*11 | Frameshift | N/S;  0.001 | N/S | 0.000012 |

Variants identified in patients with ARN. Abbreviations: P, patient; ID, identification; ARN, acute retinal necrosis, N/S, not specified; CADD, combined annotation dependent depletion; MSC, mutation significance cutoff; SIFT, Sorting Intolerant from Tolerant; gnomAD, genome aggregation database.