**Supplemental** **Table 3**. Summary of the numbers of variants per gene nominated

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| --- | --- | --- | --- | --- |
| **Gene** | **HGNC Gene ID** | **# Variants nominated** | **Disorder** | **On ACMG 73 List^** |
| ACADVL | HGNC:92 | 10 | Very long-chain acyl-CoA dehydrogenase deficiency | No |
| ACVRL1 | HGNC:175 | 3 | Hereditary hemorrhagic telangiectasia, type 2 | Yes |
| APC | HGNC:583 | 4 | Familial adenomatous polyposis | Yes |
| ATM | HGNC:795 | 6 | Hereditary breast carcinoma (AD)   Ataxia telangiectasia (AR) | No |
| BARD1 | HGNC:952 | 5 | Hereditary breast carcinoma | No |
| BRAF | HGNC:1097 | 1 | Cardiofaciocutaneous syndrome | No |
| BRCA1 | HGNC:1100 | 26 | Breast-ovarian cancer, familial, susceptibility to, 1 (AD) | Yes |
| BRCA2 | HGNC:1101 | 22 | Breast-ovarian cancer, familial, susceptibility to, 2 (AD) | Yes |
| BRIP1 | HGNC:20473 | 5 | Familial ovarian cancer (AD)   Fanconi anemia complementation group J (AR) | No |
| BTK | HGNC:1133 | 10 | X-linked agammaglobulinemia (XLA) | No |
| CARD11 | HGNC:16393 | 5 | CARD11 defects | No |
| CDH1 | HGNC:1748 | 10 | Hereditary diffuse gastric adenocarcinoma | No |
| CFH | HGNC:4883 | 5 | Atypical hemolytic uremic syndrome (aHUS)/Thrombotic microangiopathy (TMA) | No |
| CFTR | HGNC:1884 | 14 | Cystic fibrosis | No |
| CHEK2 | HGNC:16627 | 5 | Hereditary breast carcinoma | No |
| COL6A1 | HGNC:2211 | 1 | Congenital muscular dystrophy | No |
| CYP1B1 | HGNC:2597 | 3 | Congenital glaucoma | No |
| DCLRE1C | HGNC:17642 | 8 | Severe combined immunodeficiency due to DCLRE1C deficiency | No |
| DES | HGNC:2770 | 17 | Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic cardiomyopathy) | No |
| DICER1 | HGNC:17098 | 7 | Pleuropulmonary blastoma | No |
| DNM2 | HGNC:2974 | 3 | Centronuclear myopathy | No |
| DSC2 | HGNC:3036 | 5 | Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic cardiomyopathy) | Yes |
| DSG2 | HGNC:3049 | 7 | Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic cardiomyopathy) | Yes |
| DSP | HGNC:3052 | 10 | Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic cardiomyopathy) | Yes |
| ENG | HGNC:3349 | 4 | Hereditary hemorrhagic telangiectasia | Yes |
| FBN1 | HGNC:3603 | 10 | Marfan syndrome, familial thoracic aortic aneurysm and aortic dissection | Yes |
| GAA | HGNC:4065 | 8 | Glycogen storage disease type II | Yes |
| GATA2 | HGNC:4171 | 15 | GATA2 deficiency with susceptibility to MDS/AML; GATA2 haploinsufficiency | No |
| GCK | HGNC:4195 | 11 | Monogenic diabetes | No |
| HBA1\* | HGNC:4823 | 4 | Alpha thalassemia, Hemoglobin H disease, Hemoglobin Bart's hydrops fetalis | No |
| HBA2\* | HGNC:4824 | 7 | Alpha thalassemia, Hemoglobin H disease, Hemoglobin Bart's hydrops fetalis | No |
| HBB\* | HGNC:4827 | 10 | Sickle cell anemia, sickle cell disease associated with another hemoglobin anomaly, Beta thalassemia, Sickle cell-beta-thalassemia disease syndrome, Sickle cell-hemoglobin C disease syndrome, Hemoglobin C-beta-thalassemia syndrome, Hemoglobin C disease, Sickle cell-hemoglobin D disease syndrome, Hemoglobin D disease, Sickle cell-hemoglobin E disease syndrome, Hemoglobin E-beta-thalassemia syndrome, Hemoglobin E disease, Hemoglobin Lepore-beta-thalassemia syndrome | No |
| HBD\* | HGNC:4829 | 1 | Hemoglobin Lepore-beta-thalassemia syndrome, sickle cell-beta-thalassemia disease syndrome | No |
| HBQ1 | HGNC:4833 | 1 | Alpha thalassemia, Hemoglobin H disease, Hemoglobin Bart's hydrops fetalis | No |
| HNF1A | HGNC:11621 | 2 | Monogenic diabetes | Yes |
| HNF1B | HGNC:11630 | 1 | Monogenic diabetes | No |
| HNF4A | HGNC:5025 | 3 | Monogenic diabetes | No |
| HRAS | HGNC:5173 | 1 | Costello syndrome | No |
| IKBKG | HGNC:5961 | 6 | NEMO (NFkB essential modulator) deficiency | No |
| IL2RG | HGNC:6010 | 10 | SCID (severe combined immunodeficiency) | No |
| INS | HGNC:6081 | 1 | Monogenic diabetes | No |
| JAK3 | HGNC:6193 | 5 | SCID (severe combined immunodeficiency) | No |
| LDLR | HGNC:6547 | 10 | Familial hypercholesterolemia | Yes |
| LRBA | HGNC:1742 | 5 | LRBA deficiency | No |
| LYST | HGNC:1968 | 5 | Chediak-Higashi syndrome (CHS) | No |
| MAP2K1 | HGNC:6840 | 1 | Cardiofaciocutaneous syndrome | No |
| MLH1 | HGNC:7127 | 19 | Colorectal cancer, hereditary nonpolyposis, type 2   Constitutional mismatch repair deficiency syndrome | Yes |
| MSH2 | HGNC:7325 | 16 | Lynch syndrome | Yes |
| MSH6 | HGNC:7329 | 7 | Lynch syndrome | Yes |
| MUTYH | HGNC:7527 | 2 | MUTYH-related attenuated familial adenomatous polyposis (AR/AD) | Yes |
| MYBPC3 | HGNC:7551 | 16 | Hypertrophic cardiomyopathy | Yes |
| MYH7 | HGNC:7577 | 6 | Hypertrophic cardiomyopathy | Yes |
| MYOC | HGNC:7610 | 4 | Open angle glaucoma | No |
| NCF1 | HGNC:7660 | 6 | Chronic Granulomatous Disease (CGD) | No |
| NEB | HGNC:7720 | 2 | Nemaline myopathy | No |
| NTHL1 | HGNC:8028 | 1 | Familial adenomatous polyposis | No |
| PAH | HGNC:8582 | 17 | Phenylketonuria | No |
| PALB2 | HGNC:26144 | 5 | Hereditary breast carcinoma (AD), Fanconi anemia complementation group N (AR) | Yes |
| PKP2 | HGNC:9024 | 22 | Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic cardiomyopathy) | Yes |
| PLN | HGNC:9080 | 4 | Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic cardiomyopathy) | No |
| POLD1 | HGNC:9175 | 1 | Polymerase proofreading-related adenomatous polyposis | No |
| POLE | HGNC:9177 | 1 | Polymerase proofreading-related adenomatous polyposis | No |
| PTEN | HGNC:9588 | 5 | PTEN hamartoma tumor syndrome | Yes |
| PTPN11 | HGNC:9644 | 4 | Noonan syndrome, Noonan syndrome with multiple lentigines | No |
| RAD51C | HGNC:9820 | 5 | Familial ovarian cancer (AD) | No |
| RAD51D | HGNC:9823 | 5 | Familial ovarian cancer (AD) | No |
| RAF1 | HGNC:9829 | 1 | Noonan syndrome | No |
| RAG1 | HGNC:9831 | 7 | SCID (severe combined immunodeficiency) | No |
| RUNX1 | HGNC:10471 | 10 | Familial platelet disorder with associated myeloid malignancy | No |
| RYR1\*\* | HGNC:10483 | 17 | Susceptibility to malignant hyperthermia (AD)  Central core myopathy (AR/AD) | Yes |
| SELENON | HGNC:15999 | 4 | Rigid spine myopathy | No |
| SHOC2 | HGNC:15454 | 1 | Noonan syndrome-like disorder with loose anagen hair | No |
| SMAD4 | HGNC:6770 | 3 | Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome | Yes |
| SOS1 | HGNC:11187 | 1 | Noonan syndrome | No |
| TMEM43 | HGNC:28472 | 1 | Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic cardiomyopathy) | Yes |
| TNNI3 | HGNC:11947 | 1 | Hypertrophic cardiomyopathy | Yes |
| TNNT2 | HGNC:11949 | 2 | Hypertrophic cardiomyopathy, dilated cardiomyopathy | Yes |
| TP53 | HGNC:11998 | 10 | Li-Fraumeni syndrome | Yes |
| TPM2 | HGNC:12011 | 1 | Nemaline myopathy | No |
| TPM3 | HGNC:12012 | 3 | Nemaline myopathy | No |
| TTN | HGNC:12403 | 7 | Distal titinopathy, tibial muscular dystrophy, hereditary myopathy with early respiratory failure | Yes |
| VHL | HGNC:12687 | 7 | Von Hippel-Lindau disease | Yes |
| WAS | HGNC:12731 | 13 | Wiskott- Aldrich syndrome (WAS) | No |
| WFS1 | HGNC:12762 | 1 | Monogenic diabetes | No |
| \* Some variants in these genes are multi-gene deletions or fusions. | | | | |
| \*\*One variant in RYR1 was submitted by both the Congenital Myopathies and Malignant Hyperthermia Susceptibility VCEPs. | | | | |
| ^ Miller, D.T., Lee, K., Chung, W.K. et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med (2021). https://doi.org/10.1038/s41436-021-01172-3 | | | | |