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Physician-directed genetic screening to evaluate personal risk for medically actionable disorders: a large multi-center cohort study

Eden V. Haverfield[1*], Edward D. Esplin[1], Sienna J. Aguilar[1], Kathryn E. Hatchell[1], Kelly E. Ormond[2], Andrea Hanson-Kahn[2], Paldeep S. Atwal[3,4,5], Sarah Macklin-Mantia[3], Stephanie Hines[3], Caron W.-M. Sak[6], Steven Tucker[6], Steven B. Bleyl[7], Peter J. Hulick[8], Ora K. Gordon[9,10], Lea Velsher[11], Jessica Y. J. Gu[11], Scott M. Weissman[7,12], Teresa Kruisselbrink[13], Christopher Abel[14], Michele Kettles[14], Anne Slavotinek[15], Bryce A. Mendelsohn[16], Robert C. Green[17,18,19,20], Swaroop Aradhya[1] and Robert L. Nussbaum[1,21]

Abstract

Background: The use of proactive genetic screening for disease prevention and early detection is not yet widespread. Professional practice guidelines from the American College of Medical Genetics and Genomics (ACMG) have encouraged reporting pathogenic variants that confer personal risk for actionable monogenic hereditary disorders, but only as secondary findings from exome or genome sequencing. The Centers for Disease Control and Prevention (CDC) recognizes the potential public health impact of three Tier 1 actionable disorders. Here, we report results of a large multi-center cohort study to determine the yield and potential value of screening healthy individuals for variants associated with a broad range of actionable monogenic disorders, outside the context of secondary findings.

Methods: Eligible adults were offered a proactive genetic screening test by health care providers in a variety of clinical settings. The screening panel based on next-generation sequencing contained up to 147 genes associated with monogenic disorders within cancer, cardiovascular, and other important clinical areas. Sequence and intragenic copy number variants classified as pathogenic, likely pathogenic, pathogenic (low penetrance), or increased risk allele were considered clinically significant and reported. Results were analyzed by clinical area and severity/burden of disease using chi-square tests without Yates' correction.

Results: Among 10,478 unrelated adults screened, 1619 (15.5%) had results indicating personal risk for an actionable monogenic disorder. In contrast, only 3.1 to 5.2% had clinically reportable variants in genes suggested by the ACMG version 2 secondary findings list to be examined during exome or genome sequencing, and 2% had reportable variants related to CDC Tier 1 conditions. Among patients, 649 (6.2%) were positive for a genotype associated with a disease of high severity/burden, including hereditary cancer syndromes, cardiovascular disorders, or malignant hyperthermia susceptibility.

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* Correspondence: eden.haverfield@invitae.com
[1]Invitae, 1400 16th Street, San Francisco, CA 94103, USA
Full list of author information is available at the end of the article

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Conclusions: This is one of the first real-world examples of specialists and primary care providers using genetic screening with a multi-gene panel to identify health risks in their patients. Nearly one in six individuals screened for variants associated with actionable monogenic disorders had clinically significant results. These findings provide a foundation for further studies to assess the role of genetic screening as part of regular medical care.

Keywords: Cardiovascular disorders, Clinical genetics, Hereditary cancer syndromes, Monogenic disorders, Population screening, Proactive genetic screening

Background

Screening healthy individuals for genetic risk for monogenic disorders has largely been limited to preconception or prenatal carrier and newborn screening for severe autosomal recessive or X-linked disorders [1]. One exception is the American College of Medical Genetics and Genomics (ACMG) recommendation that clinically significant variants within 59 genes associated with monogenic disorders be analyzed as optional secondary findings during clinically indicated exome or genome sequencing [2, 3]. These 59 genes are primarily associated with adult-onset cancer syndromes and cardiovascular disorders that have established clinical guidelines for further surveillance and preventive therapies. Analyses of large genomic data sets indicate that some asymptomatic individuals carry clinically significant, actionable variants [4, 5].

Emerging evidence supports primary genetic screening for a few hereditary disorders, such as hereditary breast and ovarian cancer syndromes [6, 7]. The Centers for Disease Control and Prevention (CDC) recognizes that hereditary breast and ovarian cancer, familial hypercholesterolemia, and Lynch syndrome have sufficient evidence for intervention that could positively impact public health [8, 9]. Scientists in the UK have made similar recommendations [10, 11], and some countries are characterizing the genomes of large population segments to explore the complexities and precautions to be considered in integrating genomics into health care to provide preventive health information [12]. Finally, some medical institutions are returning genomic information to individuals independent of any existing medical concern, as part of a research study within an integrated health care delivery system [13]. Research studies have shown that most adults offered this type of information consent to receiving it [14, 15].

Recently, the National Academy of Medicine (NAM) published a document on the implementation of genomics-based screening for healthy adults in CDC Tier 1 genes [16]. The statement noted that 1 to 2% of the US population is expected to have a pathogenic variant conferring substantial risk for a serious but preventable disease and, accordingly, acknowledged the opportunity to use screening to identify these otherwise healthy individuals to allow preventive interventions. The statement also called for thoughtfully conducted clinical studies on the implementation of genomic-based screening programs to inform our understanding of their clinical utility.

These developments have created an opportunity to apply genetic screening for actionable disorders to identify personal risk and improve health care. To explore the feasibility and utility of this emerging paradigm, we examined the prevalence of clinically significant variants related to actionable disorders in a large cohort of adults referred from a variety of clinical settings to a commercial laboratory for genetic screening. We anticipated that a notable fraction of individuals who would otherwise not be eligible for genetic testing for hereditary disease would be identified as carrying pathogenic variants that put them at risk for disorders of moderate to high clinical impact.

Methods

Gene selection

We reviewed the genes recommended by the ACMG for secondary analyses during exome or genome sequencing [2] and the ClinGen Working Group's process for selecting genes with clinical actionability [17]. We also examined gene lists used by clinical centers that perform research on reporting personal risk for monogenic disorders [18, 19]. An internal group of geneticists and genetic counselors from Invitae reviewed the clinical actionability of additional genes based on disease severity, penetrance, the availability of published recommendations for medical management, and the strength of gene-disease associations.

The resulting additional genes consisted mainly of those associated with hereditary cancer and cardiovascular conditions beyond those on the ACMG gene list and allowed for a broader spectrum of disease severity. Genes associated with autosomal dominant, autosomal recessive, and X-linked clinical conditions were included. Proactive screening was introduced in 2016 with 124 genes but, after additional curationand strengthening of gene-disease associations, was enlarged to up to 147 genes by the time the study closed in 2020 (Table 1 and Additional file 1: Table S1).

Table 1 List of 147 genes for proactive testing

ACTA2	***BRCA2***	*CHEK2*	*F9*	*JUP*	***MLH1***	*NTHL1*	*PTCH1*	***SDHC***	*TMEM127*
ACTC1	*BRIP1*	***COL3A1***	***FBN1***	*KCNE1*	***MSH2***	***OTC***	***PTEN***	***SDHD***	***TMEM43***
ACTN2	*CACNA1C*	*CRYAB*	*FH*	*KCNE2*	*MSH3*	*PALB2*	*RAD51C*	*SGCD*	*TNNC1*
ACVRL1	***CACNA1S***	*CSRP3*	*FHL1*	***KCNH2***	***MSH6***	***PCSK9***	*RAD51D*	*SLC40A1*	***TNNI3***
APC	*CACNB2*	*DES*	*FLCN*	*KCNJ2*	***MUTYH***	*PDGFRA*	***RB1***	***SMAD3***	***TNNT2***
APOB	*CALM1*	*DICER1*	*FLNC*	***KCNQ1***	***MYBPC3***	***PKP2***	*RBM20*	***SMAD4***	***TPM1***
ATM	*CALM2*	*DMD*	*GDF2*	*KIT*	***MYH11***	*PLN*	***RET***	*SMARCA4*	*VCL*
ATP7B	*CALM3*	***DSC2***	***GLA***	*LAMP2*	***MYH7***	***PMS2***	***RYR1***	*SMARCB1*	***TP53***
AXIN2	*CASQ2*	***DSG2***	*GPDIL*	***LDLR***	***MYL2***	*POLD1*	***RYR2***	***STK11***	***TSC1***
BAG3	*CAV1*	***DSP***	*GREM1*†	*LDLRAP1*	***MYL3***	*POLE*	*SERPINA1*	*TCAP*	***TSC2***
BAP1	*CAV3*	*EMD*	*HAMP*	***LMNA***	*MYLK*	***PRKAG2***	*SERPINC1*	*TFR2*	***VHL***
BARD1	*CDC73*	*ENG*	*HCN4*	*MAX*	*NBN*	*PRKAR1A*	***SCN5A***	*TGFB2*	***WT1***
BMPR1A	*CDH1*	*EPCAM*†	*HFE*	***MEN1***	*NF1*	*PRKG1*	*SDHA*	*TGFB3*	
BMPR2	*CDK4*	*F2*†	*HJV*	*MET*	***NF2***	*PROC*	***SDHAF2***	***TGFBR1***	
BRCA1	*CDKN2A*	*F5*†	*HOXB13*†	*MITF*†	*NKX2-5*	*PROS1*	***SDHB***	***TGFBR2***	

Genes shown in bold are the 59 genes prescribed by the ACMG as medically actionable. Genes shown underlined are genes associated with CDC Tier 1 conditions. Genes shown in bold and underlined represent overlap between the two gene lists

†Genes that have analytic limitations. *F2*: prothrombin G20210A (c.*97G>A) variant only. *F5*: Factor V Leiden variant only. *GREM1*: promoter region deletion/duplication testing only. *MITF*: c.952G>A, p.Glu318Lys variant only. *HOXB13*: c.251G>A, p.Gly84Glu variant only. *EPCAM*: deletion/duplication testing only

Patient accrual

Patients were offered a proactive genetic screening test by their health care providers in a variety of domestic and international clinical settings including primary care, executive health, hereditary cancer, and cardiovascular risk clinics. Personal and familial health histories were reviewed, if provided.

Data were collected on individuals 18 years of age or older. Personal or family history of cancer or cardiovascular disease was not an exclusion criterion. However, those who had undergone previous diagnostic genetic testing and were positive for a familial variant associated with a condition represented on the screening panel were excluded from this analysis. Study size was not predetermined but included all patients referred for testing whose samples were returned between January 2016 and May 2020.

Next-generation sequencing

Each gene was targeted with oligonucleotide baits (Agilent Technologies, Santa Clara, CA; Roche, Pleasanton, CA; IDT, Coralville, IA) to capture exons, the 10 to 20 bases flanking intronic sequences, and noncoding regions of clinical interest. Baits were iteratively balanced to obtain a minimum of 50X and an average of 350X depth-of-sequence read coverage across all targeted areas. Sequencing was performed on HiSeq and NovaSeq instruments (Illumina, San Diego, CA). A suite of bioinformatics methods was used to identify single nucleotide variants, small and large insertions/deletions, exon-level deletions and duplications, and rare structural or mosaic variants [20, 21].

Genomic DNA extracted from patient blood or saliva was processed by next-generation sequencing as described previously [20]. Variants requiring confirmation were confirmed using an orthogonal method, such as PacBio sequencing (Pacific Biosciences, Menlo Park, CA) or exon-focused microarray-based comparative genomic hybridization (Agilent Technologies, Santa Clara, CA) [21]. Clinically reported variants and de-identified clinical information, if provided, were collected for analyses.

Clinical classification of variants

Sequence and intragenic copy number variants were clinically interpreted using a five-tier system for grading evidence for pathogenicity as implemented in Sherloc [22], a point-based scoring system that expands upon the ACMG/Association for Molecular Pathology variant interpretation guidelines [23]. Variants classified as pathogenic (P), likely pathogenic (LP), pathogenic (low penetrance), or increased risk allele were considered clinically significant and reported. Variants of uncertain significance (VUS) were not reported per professional guidelines [3].

P/LP variants are defined as those that demonstrate the typical penetrance seen in individuals with a disease-associated genotype (i.e., one copy for autosomal dominant conditions or two copies for autosomal recessive conditions). P/LP variants often cause a recognizable Mendelian inheritance pattern of disease, although not all individuals with a disease-associated genotype are

affected. Examples include variants in the *BRCA1* and *BRCA2* genes, associated with hereditary breast and ovarian cancer, and variants in the genes associated with Lynch syndrome. Although silent carrier status of a single P/LP variant for a condition that has an autosomal recessive inheritance pattern was reported if present, this type of finding was not considered in the overall yield of clinically significant results.

Pathogenic (low penetrance) variants are found in the same genes where P/LP variants may exist, but their penetrance is measurably lower. Pathogenic (low penetrance) variants may cause a less obvious Mendelian inheritance pattern than P/LP variants, given that fewer individuals with the disease-associated genotype manifest signs of the disorder; nonetheless, a sufficient number of family members will be affected to reveal a Mendelian inheritance pattern. Examples include homozygous *HFE* p.Cys282Tyr or p.His63Asp variants and compound heterozygous p.His63Asp/p.Cys282Tyr variants, associated with hereditary hemochromatosis.

Increased risk alleles are variants that increase risk for a condition that is generally not of sufficient magnitude to reveal a Mendelian inheritance pattern. They are usually identified through association studies comparing the relative risks or odds of disease in individuals with versus without the variants in case-control or cohort studies. Establishing a variant as an increased risk allele based on an association requires the association to meet stringent criteria for statistical significance, effect size, replication, and lack of bias [24]. Increased risk alleles can be more common in a specific population, such as the *APC* p.Ile1307Lys variant, which increases the risk for colon cancer among individuals of Ashkenazi Jewish descent.

Subdivision of genotypes by impact

Genotypes were subdivided into two categories: "moderate impact" and "high impact." The level of impact was based on a joint assessment of whether the variants making up the genotype were P/LP, pathogenic (low penetrance), or an increased risk allele and what the severity or burden of the disease associated with that genotype was judged to be. We assigned being heterozygous for certain alleles (i.e., *APC* p.Ile1307Lys, *HOXB13* p.Gly84Glu, or *CHEK2* p.Ile157Thr or p.Ser428Phe), heterozygous for any P/LP allele in *MUTYH*, heterozygous for any P/LP allele in *NBN* except the *NBN* c.657_661delACAAA variant, heterozygous or homozygous for *F2* G20210A or *F5* Leiden, or biallelic for *HFE* and *SERPINA1* pathogenic variants as a moderate impact genotype. All positive results in the other included genes were considered high impact.

Statistical analysis

Differences in the numbers of patients within specified testing and result categories were compared in 2 × 2 tables using the chi-square test without Yates' correction and confirmed by the Fisher exact test for 2 × 2 tables. Statistical significance was defined as $p < 0.05$.

Results

Demographics

Among 10,478 unrelated adults who underwent proactive screening and genetic analysis, 5367 (51.2%) were between 40 and 59 years old, with an average age of 49.5 years; 6177 (59.0%) were female, and 6274 (59.9%) were self-described as Caucasian (Table 2).

Positive yield

Using the definitions described in the "Methods" section, screening identified clinically significant results in 1619 (15.5%) of the 10,478 patients (Fig. 1). One hundred thirty-eight individuals harbored multiple variants related to risk for more than one clinical condition, representing 1.3% of this cohort and 8.5% of all positive findings. Overall, 4637 clinically significant sequence variants were reported, including 611 unique variants (Additional file 2: Table S2).

Table 2 Cohort demographics

Demographic	Number (%)
Self-reported ancestry	
White/Caucasian	6274 (59.9)
Unknown	1608 (15.3)
Asian	604 (5.8)
Multiple ancestries	813 (7.8)
Ashkenazi Jewish	412 (3.9)
Hispanic	246 (2.3)
Black/African American	133 (1.3)
Others	388 (3.7)
Age in years	
<20	35 (0.3)
20–29	598 (5.7)
30–39	1965 (18.8)
40–49	2752 (26.3)
50–59	2615 (25.0)
60–69	1746 (16.7)
70–79	682 (6.5)
≥80	85 (0.8)
Sex	
Female	6177 (59.0)
Male	4301 (41.0)

Information provided is self-reported ancestry. Age represents the age of an individual at the time of testing

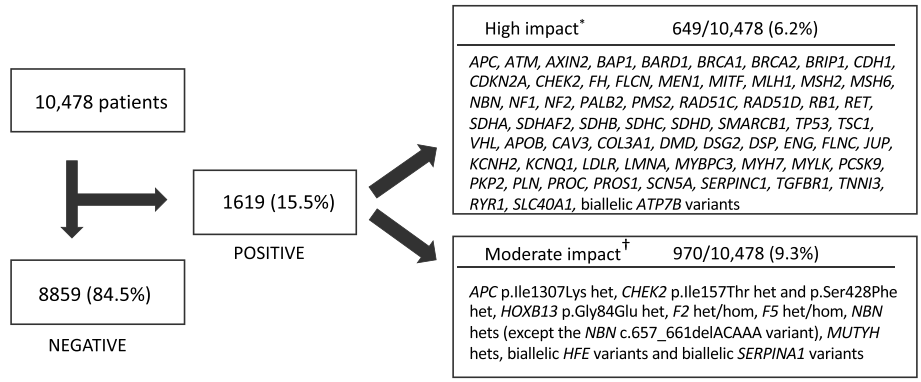

Fig. 1 Positive findings, by impact, in a cohort of 10,478 individuals. The asterisk indicates that a genotype was considered high impact when the variants were P/LP and conveyed a substantial risk for disease with substantial burden that requires serious clinical diagnostic and management interventions to prevent or reduce risk from cancer or cardiovascular disease. The dagger indicates that a genotype was considered moderate impact when it contained pathogenic (low penetrance) variants or increased risk alleles (described in the "Methods" section) associated with diseases for which individuals could derive benefit from enhanced surveillance

Among all patients, 649 (6.2%) were positive for a genotype with high impact, including P/LP variants associated with a hereditary cancer syndrome, a cardiovascular disorder, or malignant hyperthermia susceptibility. Positive findings of moderate impact were reported in 970 individuals (9.3%), including 450 (4.3%) with a common variant associated with F2- or F5-related thrombophilias, 196 (1.9%) with biallelic variants associated with hereditary hemochromatosis (HH) or alpha-1 antitrypsin deficiency (AATD), and the remaining 324 (3.1%) with genotypes that included other heterozygous pathogenic (low penetrance) or increased risk alleles (Table 4).

Results by clinical area

Among the 1619 individuals with positive results, 807 (49.8%) had disease-predisposing variants related to a hereditary cancer syndrome. Clinically significant variants were commonly detected in *MUTYH*, *CHEK2*, *APC*, *ATM*, *BRCA1*, *BRCA2*, *MITF*, *HOXB13*, *PMS2*, *PALB2*, *NBN*, *BRIP1*, *MSH6*, *SDHA*, and *BARD1* (Additional file 2: Table S2). Variants in genes associated with colorectal cancer accounted for the highest percentage of reported alleles (including moderate impact heterozygous *MUTYH* variants and *APC* increased risk alleles), followed by variants in genes associated with breast cancer, breast and ovarian cancer, and melanoma (Table 3). Six hundred eight (37.6%) of the 1619 individuals with positive results had variants in genes associated with cardiovascular disorders, with most reportable variants in *F5*, *F2*, *LDLR*, *MYBPC3*, *MYH7*, *APOB*, *SERPINC1*, and *PKP2* (Additional file 2: Table S2). Of the positive cardiovascular disease findings, 158 were high impact variants related to arrhythmias, aortopathies, or cardiomyopathies (88 variants); genes associated with familial hypercholesterolemia (45 variants); and rare forms of hereditary thrombophilia (25 variants). The remaining individuals had moderate impact genotypes in the *F2* (G20210A) and *F5* (Factor V Leiden variant) genes.

Yield from ACMG and CDC Tier 1 prescribed genes

Restricting results to only the 59 genes recommended by the ACMG for secondary analysis during exome or genome sequencing (version 2) [3] demonstrated a positive yield of 5.2% (Table 4) when including all high impact P/LP variants and all moderate impact increased risk alleles and genotypes regardless of inheritance pattern. Monoallelic changes that result in silent carrier status without disease were not included in any yield calculation. When increased risk alleles and genotypes with moderate impact were excluded, the positive yield decreased to 3.1%. Similarly, when positive results were limited to the CDC Tier 1 genes (*BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PMS2*, *APOB*, *LDLR*, and *PCSK9*), the yield was 2% (Table 4).

Among all 10,478 individuals, 1077 (10.3%) had a clinically significant variant in a gene that was not included in the 59 ACMG genes: 3.7% in a cancer-related gene, 4.7% in a gene associated with a cardiovascular disorder (including the thrombophilias), and 1.9% with biallelic variants associated with HH or AATD.

Implications of provided health information

We received voluntary health histories from 6710 (64.0%) of the 10,478 individuals. Among the 6710 returning health histories, 96 (1.4%) reported an absence of family health information due to adoption, 2801 (41.7%) indicated no relevant personal or family history, 242 (3.6%) disclosed a personal history of cancer, 2409 (35.9%) reported a family history of cancer, and 411 (6.1%) reported both a personal and family history of

Table 3 Positive findings grouped by cancer type

Cancer type	Number (%)	Genes with clinically significant variants detected
Gastrointestinal	271 (33.6)	*APC*, *AXIN2*, *CDH1*[†], *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*
Breast	260 (32.2)	*ATM*, *BARD1*, *CHEK2*, *NBN*, *PALB2*, *TP53*[‡]
Breast and ovarian	114 (14.1)	*BRCA1*, *BRCA2*
Melanoma/skin	43 (5.3)	*CDKN2A*, *MITF*, *TGFBR1* (MSSE)
Ovarian	37 (4.6)	*BRIP1*, *RAD51C*, *RAD51D*
Endocrine	33 (4.1)	*MEN1*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*
Prostate	27 (3.3)	*HOXB13*
CNS	11 (1.4)	*NF1*, *NF2*[§], *TSC1*, *VHL*
Others	6 (0.7)	*BAP1*, *RB1*, *SMARCB1*
Renal	5 (0.6)	*FH*, *FLCN*

CNS central nervous system
Indications of higher risk from screening genes associated with hereditary cancer syndromes were most commonly related to gastrointestinal, breast, ovarian, and skin cancers. The genetic changes recorded here for each gene represent a heterozygous finding associated with an autosomal dominant condition, or a single heterozygous variant in the *MUTYH* gene. Certain genetic changes in the *TGFBR1* gene can cause multiple self-healing squamous epithelioma (MSSE), which was classified as a hereditary cancer risk
[†]*CDH1* is also associated with breast cancer risk
[‡]*TP53* is associated with Li-Fraumeni syndrome, which is associated with multiple cancer types
[§]*NF2* is associated with non-malignant nervous system tumors

cancer. Similarly, 328 (4.9%) had a personal or family history of cardiovascular disorders, and 423 (6.3%) had a personal or family history of both cancer and cardiovascular conditions.

Comparing the positive yield of hereditary cancer syndrome tests among individuals with different cancer histories, 4.3% of individuals (120/2801) without a personal or family history had a P/LP finding in one of the hereditary cancer syndrome genes (excluding the *APC* increased risk allele and *MUTYH* heterozygotes). This was significantly lower than the 9.5% (62/653, $\chi^2 = 28.8$, $p << 10^{-5}$, 1 d.f.) positivity rate in individuals reporting a

Table 4 Stratification of findings by genes or variants

All findings	Number (%)
Individuals with reportable findings	1619 (15.5)
Yield after excluding biallelic *HFE* and *SERPINA1* findings	1423 (13.6)
Yield after excluding *F2* and *F5* findings and genes in the row above	973 (9.3)
Yield after excluding *MUTYH* heterozygotes and genes in rows above	829 (7.9)
Yield after excluding *CHEK2* p.Ile157Thr and p.Ser428Phe heterozygotes, *NBN* heterozygotes (except for the *NBN* c.657_661delACAAA variant), and genes in rows above	746 (7.1)
Yield after excluding increased risk alleles (*APC* p.I1307K, *HOXB13* p.Gly84Glu) and genes or variants in rows above	649 (6.2)
Findings in 59 genes prescribed by the ACMG	
Individuals with reportable findings in the 59 ACMG genes	542 (5.2)
Yield after excluding *MUTYH* heterozygotes and increased risk alleles	326 (3.1)
Findings in CDC Tier 1 genes	
All reportable findings in genes associated with HBOC, FH, and Lynch syndrome	205 (2.0)
HBOC findings only	114 (1.1)
Lynch syndrome findings only	51 (0.5)
FH findings only	40 (0.4)

ACMG American College of Medical Genetics and Genomics, *CDC* Centers for Disease Control and Prevention, *HBOC* hereditary breast and ovarian cancer, *FH* familial hypercholesterolemia
Stratification of results in the 59 genes prescribed by the ACMG is done by incrementally removing specific categories of gene groups (shown in successive rows) that are excluded per ACMG secondary findings guidelines. Similarly, stratification of results from CDC Tier 1 genes is shown based on different disease categories: HBOC syndrome (*BRCA1* and *BRCA2*), Lynch syndrome (*EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*), and FH (*APOB* gain-of-function variants, *LDLR*, and *PCSK9*)

personal history of cancer (with or without a family history) and significantly lower than the 7.1% (171/2409, χ^2 = 19.45, $p << 10^{-5}$, 1 d.f.) positivity rate in individuals with only a *family* history of cancer. There was no significant difference in the positivity rate among individuals with personal history alone (8.7%), family history alone (7.1%), or both personal and family history (10%) (χ^2 = 4.56, p=0.10, 2 d.f.).

Discussion

Recent discussion has centered around the potential of proactive genetic screening to determine personal risk for actionable monogenic disorders and improve public health outcomes [16, 25, 26]. The overall positive yield of 15.5% in our cohort of 10,478 individuals represents an early example of the expected yield of proactive screening implemented in a variety of practice settings. A yield of 1.5 to 6% has been reported in secondary findings for the 59 genes that the ACMG suggests be analyzed during whole exome or genome sequencing [5, 15, 27], and large databases containing genomic information from healthy individuals have demonstrated a comparable yield [4, 28, 29]. We found a similar yield of 3.1% in the 59 genes when we applied the narrower criteria for reporting variants as described by the ACMG [2, 3]. These results are clinically meaningful because variants in these genes confer a high risk of serious disease compared with the risk in the general population. Identifying this risk facilitates the application of precision preventive medical interventions, including appropriate screening protocols to either prevent disease or detect it early to reduce morbidity and mortality [6].

The clinical yield in the 59 ACMG genes increased from 3.1 to 5.2% when the *APC* p.Ile1307Lys increased risk allele and *MUTYH* heterozygotes were included. However, debate continues about whether variants in genes that may confer only low risk for disease should be reported [30, 31]. Although these variants confer lower risk than variants in other tested genes, the cancer risk they confer is still higher than the risk in the general population and can trigger changes in risk management. For example, for individuals of Ashkenazi Jewish ancestry, the *APC* p.I1307K increased risk allele indicates an elevated risk of colorectal cancer that warrants modifications to clinical management [31, 32]. Similarly, all individuals with a single, heterozygous P/LP variant in *MUTYH* have an estimated twofold increased risk of colorectal cancer [30, 33], and current guidelines indicate that carriers who have a first-degree relative with colorectal cancer should consider more frequent colonoscopy screenings [34]. Such cases represent additional opportunities for precision preventive medical interventions that could otherwise be missed without genetic screening.

When using genetic screening to assess personal risk, reduced specificity in classifying variants can lead to false-positive clinical results, particularly for rare disorders [35]. To increase test specificity and positive predictive values [33], only well-established pathogenic variants or those predicted with high confidence to be pathogenic were reported. In contrast, VUS were not reported, per professional guidelines and the NAM's proposal for genomics-based screening [16, 25, 26]. During this study, however, a few variant interpretations were changed, resulting in amended reports. Some variants initially documented as clinically significant were downgraded to VUS, while some VUS (which had not been reported) were reclassified as clinically significant as a result of new evidence. Reclassification of VUS to clinically significant is a particular challenge because the individuals and their providers were not aware of these variants until they received amended reports, giving the false impression that clinically relevant variants had been missed during initial testing. Nonetheless, given that a duty to reinterpret variants and inform patients and their providers of clinically impactful changes has been proposed [36], amended reports were provided. This highlights the importance of disclosing during pre-test counseling that a report could be amended if new information becomes available.

Our findings also show that individuals with personal or family history of cancer or cardiovascular disorders who may not meet guidelines-based criteria for diagnostic genetic testing often seek proactive genetic screening. Such individuals have historically had few options for obtaining physician-directed clinical genetic testing. Recent studies show that a substantial proportion of individuals with cancer who do not meet established clinical criteria for testing have a rate of clinically significant findings comparable to that of individuals who do meet criteria [37, 38]. A similar pattern was observed in a recent study reporting secondary findings in the 59 ACMG-recommended genes [15]. That study demonstrated a significantly greater yield of P/LP variants in hereditary cancer syndrome genes in individuals with a personal or family history of cancer than in individuals with no such history; however, no statistical differences were found in the yield of medically actionable variants among individuals with a personal history of cancer, a family history of cancer, or both. In this study, although 1 in 23 healthy individuals with no personal or family history of cancer received a medically actionable result for a hereditary cancer syndrome gene, screening was even more informative for individuals who had a personal or family history but may not have met genetic testing criteria within existing standards, for whom the positivity rate was about two- to threefold higher [39].

Another potential benefit of genetic screening is the ability to find individuals with undiagnosed Mendelian disease presenting in primary care practices. This has been demonstrated by the application of a phenotype risk score (developed by mapping clinical features of Mendelian diseases into phenotypes derived from electronic health records) in which phenotype-genotype associations were used to identify patients with five Mendelian disorders that had previously been undiagnosed or diagnosed incorrectly in a primary care setting [40]. One may conclude that many individuals with significant risk for, or already manifesting, actionable hereditary disorders are likely escaping diagnosis [41]. In fact, the genes responsible for three of the five disorders that went undiagnosed but were flagged by the phenotype risk score (i.e., Marfan syndrome, hereditary hemochromatosis, and Li-Fraumeni syndrome) were part of the proactive screening panel. Proactive genetic screening could identify more at-risk individuals, especially as technologies make it easier to screen more broadly and variant interpretation capabilities continue to improve.

Complex and interrelated challenges will impact the use and utility of genetic screening for assessing personal risk for actionable disorders. First, inadequate understanding of the penetrance associated with these disorders, differences in risk based on ethnicity or lifestyle, and the spectra of variants in diverse populations may limit the current ability of proactive genetic screening to precisely determine risks [42]. As a result of differences in penetrance, the probability that a clinically significant finding will accurately predict whether someone eventually develops that condition may vary between symptomatic individuals and healthy individuals without a personal or family history. Although disease risk may be lower in the latter group, it is still expected to be higher than in the general population. This was the premise behind the ACMG secondary findings guidelines and the NAM recommendations. In fact, we have seen in this clinical cohort and other studies [15, 40] that a small number of individuals who are considered healthy and undergo recommended clinical follow-up due to a genetic variant identified through proactive genetic screening are found to be affected with a subclinical or atypical Mendelian phenotype. It is therefore important that positive reports clearly encourage further clinical evaluation, including increased surveillance and ongoing monitoring, but that they not be used in isolation to justify irreversible clinical actions. As longitudinal studies worldwide provide better estimates of penetrance for many disorders, the precision of the predictive value of population-level screening will increase. These issues as well as additional challenges associated with implementing DNA-based population screening programs will require further consideration and are beginning to be discussed broadly [43, 44].

Limited genetics expertise in adult primary care poses another challenge to the broader use of proactive genetic screening. The National Society of Genetic Counselors, the ACMG, and other professional societies are developing professional practice guidelines for personal genetic risk assessment [45, 46] and novel service delivery models for pre- and post-test genetic counseling [47, 48]. Because of the persistent shortage of genetics professionals, consideration and research must continue to be devoted to developing these models as well as scalable mechanisms for communicating genomic test results to more individuals and coordinating appropriate medical follow-up.

Conclusions

This large multi-center cohort study is one of the first real-world examples of specialists and primary care providers using genetic screening with a targeted multigene panel to identify health risks in their patients. Nearly one in six individuals screened for variants associated with actionable monogenic disorders had clinically significant results. Many of these results were in genes beyond the 59 recommended for secondary reporting by the ACMG (version 2) or the 10 recognized as Tier 1 genes (associated with three Tier 1 conditions) by the CDC.

Our results are a first step toward gathering the data needed to address the medical, ethical, and economic implications of proactive genetic screening. These data also provide a foundation for further studies to assess the role of genetic screening, as part of regular medical care, in reducing morbidity and mortality from actionable genetic disorders and to determine its clinical utility and cost-effectiveness.

Abbreviations

AATD: Alpha-1 antitrypsin deficiency; ACMG: American College of Medical Genetics and Genomics; CDC: Centers for Disease Control and Prevention; HH: Hereditary hemochromatosis; LP: Likely pathogenic; NAM: National Academy of Medicine; P: Pathogenic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-021-01999-2.

Additional file 1: Table S1. Details of genes included in proactive screening.

Additional file 2: Table S2. Clinically significant variants detected in this patient cohort.

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Authors' contributions
EVH, EDE, SJA, SA, and RLN designed the work, interpreted the data, and drafted the manuscript; KEO, AH-K, PSA, SM-M, SH, CW-MS, ST, SBB, PJH, OKG, LV, JYJG, SMW, TK, CA, MK, AS, BAM, and RCG contributed to the acquisition of the data; and EVH and KEH analyzed the data. BAM and RCG were also instrumental in the conception of the work. The authors read and approved the final manuscript.

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Each proactive screen ordered by a clinician for a patient was associated with a fee-for-service test cost. No additional funding was obtained for this study. No co-author received funding for this study.

Availability of data and materials
Most of the datasets generated or analyzed during the current study are shared in this published article. Other data that support the findings of this study are available from the corresponding author upon reasonable request. In addition, all variants are shared with the public database ClinVar for patients who provide consent. ClinVar can be accessed at https://www.ncbi.nlm.nih.gov/clinvar/.

Declarations

Ethics approval and consent to participate
All patients provided informed consent (either written or verbal) before genetic screening tests were ordered. Relevant clinically reported variants and de-identified clinical information were collected for analyses with institutional review board approval (Western IRB, #20160282). The need for additional consent was waived.

Consent for publication
Not applicable

Competing interests
EVH, EDE, SJA, KEH, SA, and RLN are employees and stockholders of Invitae. SBB is an employee and stockholder of Genome Medical. LV receives a stipend from MedCan for her contributions as a medical advisor. RCG is a co-founder of Genome Medical and receives compensation for advising AIA, Grail, OptumLabs, Verily, and Wamburg. KEO, AH-K, PSA, SM-M, SH, CW-MS, ST, PJH, OKG, JYJG, SMW, TK, CA, MK, AS, and BAM declare no conflicts of interest.

Author details
[1]Invitae, 1400 16th Street, San Francisco, CA 94103, USA. [2]Stanford University School of Medicine, Stanford, CA, USA. [3]Mayo Clinic, Jacksonville, FL, USA. [4]Atwal Clinic, Jacksonville, FL, USA. [5]PWNHealth, New York, NY, USA. [6]Tucker Medical, Singapore, Singapore. [7]Genome Medical, San Francisco, CA, USA. [8]NorthShore University HealthSystem, Chicago, IL, USA. [9]Providence Research Network, St John Cancer Institute, Los Angeles, CA, USA. [10]University of California, Los Angeles, CA, USA. [11]Medcan, Toronto, Ontario, Canada. [12]Chicago Genetic Consultants, Northbrook, IL, USA. [13]Mayo Clinic, Rochester, MN, USA. [14]Cooper Clinic, Dallas, TX, USA. [15]University of California San Francisco, San Francisco, CA, USA. [16]Kaiser Permanente, Oakland, CA, USA. [17]Brigham and Women's Hospital, Boston, MA, USA. [18]The Broad Institute, Boston, MA, USA. [19]Ariadne Labs, Boston, MA, USA. [20]Harvard Medical School, Boston, MA, USA. [21]Volunteer Faculty, University of California San Francisco, San Francisco, CA, USA.

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Publisher's Note

Table S1. Details of genes included in proactive screening.

Gene	Conditions*	MIM	Inheritance Patterns
ACTA2	Thoracic aortic aneurysms and dissections	102620	AD
ACTC1	Atrial septal defect Dilated cardiomyopathy Hypertrophic cardiomyopathy Left ventricular noncompaction cardiomyopathy	102540	AD
ACTN2	Dilated cardiomyopathy Hypertrophic cardiomyopathy	102573	AD
ACVRL1	Hereditary hemorrhagic telangiectasia Pulmonary hypertension	601284	AD
APC	Familial adenomatous polyposis (FAP) and attenuated FAP	611731	AD
APOB	Familial hypercholesterolemia Familial hypobetalipoproteinemia	107730	AD, AR
ATM	*ATM*-related cancers	607585	AD, AR
ATP7B	Wilson disease	606882	AR
AXIN2	Oligodontia-colorectal cancer syndrome	604025	AD
BAG3	Dilated cardiomyopathy Myofibrillar myopathy	603883	AD
BAP1	*BAP1* tumor predisposition syndrome	603089	AD
BARD1	*BARD1*-related cancers	601593	AD
BMPR1A	Juvenile polyposis syndrome	601299	AD
BMPR2	Pulmonary arterial hypertension	600799	AD
BRCA1	Hereditary breast and ovarian cancer syndrome Fanconi anemia	113705	AD, AR
BRCA2	Hereditary breast and ovarian cancer syndrome Fanconi anemia	600185	AD, AR
BRIP1	*BRIP1*-related cancers Fanconi anemia	605882	AD, AR
CACNA1C	Brugada syndrome Short QT syndrome Timothy syndrome	114205	AD
CACNA1S	Hypokalemic periodic paralysis Malignant hyperthermia susceptibility	114208	AD
CACNB2	Brugada syndrome Short QT syndrome	600003	AD
CALM1	Catecholaminergic polymorphic ventricular tachycardia Long QT syndrome	114180	AD
CALM2	Catecholaminergic polymorphic ventricular tachycardia Long QT syndrome	114182	AD
CALM3	Catecholaminergic polymorphic ventricular tachycardia Long QT syndrome	114183	AD
CASQ2	Catecholaminergic polymorphic ventricular tachycardia	114251	AR
CAV1	Pulmonary arterial hypertension	601047	AD
CAV3	*CAV3*-related neuromuscular conditions Hypertrophic cardiomyopathy Long QT syndrome	601253	AD

CDC73	Hyperparathyroidism-jaw tumor syndrome Familial isolated hyperparathyroidism Parathyroid carcinoma	607393	AD
CDH1	Hereditary diffuse gastric cancer syndrome	192090	AD
CDK4	Hereditary cutaneous melanoma	123829	AD
CDKN2A	Hereditary melanoma-pancreatic cancer syndrome	600160	AD
CHEK2	*CHEK2*-related cancers	604373	AD
COL3A1	Ehlers-Danlos syndrome, vascular type	120180	AD
CRYAB	Dilated cardiomyopathy Myofibrillar myopathy	123590	AD, AR
CSRP3	Dilated cardiomyopathy Hypertrophic cardiomyopathy	600824	AD
DES	Dilated cardiomyopathy Myofibrillar myopathy	125660	AD, AR
DICER1	*DICER1*-related pleuropulmonary blastoma familial tumor predisposition syndrome	606241	AD
DMD	Becker muscular dystrophy Dilated cardiomyopathy Duchenne muscular dystrophy	300377	X-linked
DSC2	Arrhythmogenic right ventricular cardiomyopathy	125645	AD, AR
DSG2	Arrhythmogenic right ventricular cardiomyopathy Dilated cardiomyopathy	125671	AD, AR
DSP	Arrhythmogenic right ventricular cardiomyopathy Dilated cardiomyopathy	125647	AD, AR
EMD	Emery-Dreifuss muscular dystrophy	300384	X-linked
ENG	Hereditary hemorrhagic telangiectasia	131195	AD
EPCAM	Lynch syndrome	185535	AD
F2	Hereditary thrombophilia	176930	AD, AR
F5	Hereditary thrombophilia	612309	AD, AR
F9	Hemophilia Hereditary thrombophilia	300746	X-linked
FBN1	*FBN1*-related conditions	134797	AD
FH	Hereditary leiomyomatosis and renal cell cancer Fumarase deficiency	136850	AD, AR
FHL1	Emery-Dreifuss muscular dystrophy Hypertrophic cardiomyopathy Reducing body myopathy	300163	X-Linked
FLCN	Birt-Hogg-Dubé syndrome	607273	AD
FLNC	Dilated cardiomyopathy Distal myopathy Hypertrophic cardiomyopathy Myofibrillar myopathy Restrictive cardiomyopathy	102565	AD
GDF2	Hereditary hemorrhagic telangiectasia	605120	AD
GLA	Fabry disease	300644	X-linked
GPD1L	Brugada syndrome	611778	AD
GREM1	Hereditary mixed polyposis syndrome	603054	AD
HAMP	Hereditary hemochromatosis	606464	AR

HCN4	Brugada syndrome Left ventricular noncompaction cardiomyopathy Sinus node dysfunction or bradycardia	605206	AD
HFE	Hereditary hemochromatosis	613609	AR
HJV	Hereditary hemochromatosis	608374	AR
HOXB13	Prostate cancer	604607	AD
JUP	Arrhythmogenic right ventricular cardiomyopathy Naxos disease	173325	AD, AR
KCNE1	Long QT syndrome Jervell and Lange-Nielsen syndrome	176261	AD, AR
KCNE2	Long QT syndrome	603796	AD
KCNH2	Brugada syndrome Long QT syndrome Short QT syndrome	152427	AD
KCNJ2	Andersen-Tawil syndrome Catecholaminergic polymorphic ventricular tachycardia Short QT syndrome	600681	AD
KCNQ1	Atrial fibrillation Long QT syndrome Short QT syndrome Jervell and Lange-Nielsen syndrome	607542	AD, AR
KIT	Gastrointestinal stromal tumors	164920	AD
LAMP2	Danon disease	309060	X-linked
LDLR	Familial hypercholesterolemia	606945	AD, AR
LDLRAP1	Familial hypercholesterolemia	605747	AR
LMNA	Congenital muscular dystrophy Dilated cardiomyopathy Emery-Dreifuss muscular dystrophy Limb-girdle muscular dystrophy	150330	AD, AR
MAX	Hereditary paraganglioma-pheochromocytoma syndrome	154950	AD
MEN1	Multiple endocrine neoplasia type 1	613733	AD
MET	Hereditary papillary renal cell carcinoma	164860	AD
MITF	Hereditary cutaneous malignant melanoma	156845	AD
MLH1	Lynch syndrome Constitutional mismatch repair deficiency syndrome	120436	AD, AR
MSH2	Lynch syndrome Constitutional mismatch repair deficiency syndrome	609309	AD, AR
MSH3	*MSH3*-associated polyposis	600887	AR
MSH6	Lynch syndrome Constitutional mismatch repair deficiency syndrome	600678	AD, AR
MUTYH	*MUTYH*-associated polyposis	604933	AR
MYBPC3	Dilated cardiomyopathy Hypertrophic cardiomyopathy Left ventricular noncompaction cardiomyopathy	600958	AD
MYH11	Thoracic aortic aneurysms and dissections	160745	AD

MYH7	Dilated cardiomyopathy Hypertrophic cardiomyopathy Laing distal myopathy Left ventricular noncompaction cardiomyopathy Myosin storage myopathy	160760	AD, AR
MYL2	Hypertrophic cardiomyopathy	160781	AD
MYL3	Hypertrophic cardiomyopathy Restrictive cardiomyopathy	160790	AD, AR
MYLK	Thoracic aortic aneurysms and dissections	600922	AD
NBN	*NBN*-related cancers Nijmegen breakage syndrome	602667	AD, AR
NF1	Neurofibromatosis type 1 Neurofibromatosis-Noonan syndrome Watson syndrome	613113	AD
NF2	Neurofibromatosis type 2	607379	AD
NKX2-5	*NKX2-5* related cardiovascular conditions	600584	AD
NTHL1	*NTHL1*-associated polyposis	602656	AR
OTC	Ornithine transcarbamylase deficiency	300461	X-linked
PALB2	*PALB2*-related cancers Fanconi anemia	610355	AD, AR
PCSK9	Familial hypercholesterolemia	607786	AD
PDGFRA	Gastrointestinal stromal tumors	173490	AD
PKP2	Arrhythmogenic right ventricular cardiomyopathy Brugada syndrome Dilated cardiomyopathy	602861	AD
PLN	Arrhythmogenic right ventricular cardiomyopathy Dilated cardiomyopathy Hypertrophic cardiomyopathy	172405	AD
PMS2	Lynch syndrome Constitutional mismatch repair deficiency syndrome	600259	AD, AR
POLD1	*POLD1*-related cancers Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy	174761	AD
POLE	*POLE* -related cancers Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS) syndrome	174762	AD, AR
PRKAG2	Hypertrophic cardiomyopathy Wolff-Parkinson-White syndrome	602743	AD
PRKAR1A	Carney complex	1188830	AD
PRKG1	Thoracic aortic aneurysms and dissections	176894	AD
PROC	Hereditary thrombophilia	612283	AD, AR
PROS1	Hereditary thrombophilia	176880	AD, AR
PTCH1	Basal cell nevus syndrome	601309	AD
PTEN	*PTEN* hamartoma tumor syndrome	601728	AD
RAD51C	*RAD51C*-related cancers	602774	AD
RAD51D	*RAD51D*-related cancers	602954	AD
RB1	Retinoblastoma	614041	AD
RBM20	Dilated cardiomyopathy	613171	AD

RET	Multiple endocrine neoplasia type 2	164761	AD
RYR1	Central core disease Centronuclear myopathy Malignant hyperthermia susceptibility	180901	AD, AR
RYR2	Arrhythmogenic right ventricular cardiomyopathy Catecholaminergic polymorphic ventricular tachycardia Left ventricular noncompaction cardiomyopathy	180902	AD
SCN5A	Atrial fibrillation Brugada syndrome Dilated cardiomyopathy Long QT syndrome	600163	AD
SERPINA1	Alpha-1 antitrypsin deficiency	107400	AR
SERPINC1	Hereditary thrombophilia	107300	AD, AR
SDHA	Hereditary paraganglioma-pheochromocytoma syndrome Gastrointestinal stromal tumors Mitochondrial complex II deficiency	600857	AD, AR
SDHAF2	Hereditary paraganglioma-pheochromocytoma syndrome	613019	AD
SDHB	Hereditary paraganglioma-pheochromocytoma syndrome Gastrointestinal stromal tumors Renal cancer Mitochondrial complex II deficiency	185470	AD, AR
SDHC	Hereditary paraganglioma-pheochromocytoma syndrome Gastrointestinal stromal tumors Renal cancer	602413	AD
SDHD	Hereditary paraganglioma-pheochromocytoma syndrome Gastrointestinal stromal tumors	602690	AD
SGCD	Limb-girdle muscular dystrophy	601411	AR
SLC40A1	Hereditary hemochromatosis	604653	AR
SMAD3	Loeys-Dietz syndrome Thoracic aortic aneurysms and dissections	603109	AD
SMAD4	Hereditary hemorrhagic telangiectasia Juvenile polyposis syndrome	600993	AD
SMARCA4	*SMARCA4*-related cancers	603254	AD
SMARCB1	Rhabdoid tumor predisposition syndrome Schwannomatosis	601607	AD
STK11	Peutz-Jeghers syndrome	602216	AD
TCAP	Dilated cardiomyopathy Limb-girdle muscular dystrophy	604488	AD, AR
TFR2	Hereditary hemochromatosis	604720	AR
TGFB2	Loeys-Dietz syndrome	190220	AD
TGFB3	Arrhythmogenic right ventricular cardiomyopathy Loeys-Dietz syndrome	190230	AD
TGFBR1	Loeys-Dietz syndrome Thoracic aortic aneurysms and dissections Multiple self-healing squamous epithelioma	190181	AD
TGFBR2	Loeys-Dietz syndrome Thoracic aortic aneurysms and dissections	190182	AD
TMEM127	Hereditary paraganglioma-pheochromocytoma syndrome	613403	AD

TMEM43	Arrhythmogenic right ventricular cardiomyopathy	612048	AD
TNNC1	Dilated cardiomyopathy Hypertrophic cardiomyopathy	191040	AD
TNNI3	Dilated cardiomyopathy Hypertrophic cardiomyopathy Restrictive cardiomyopathy	191044	AD
TNNT2	Dilated cardiomyopathy Hypertrophic cardiomyopathy Left ventricular noncompaction cardiomyopathy Restrictive cardiomyopathy	191045	AD
TPM1	Dilated cardiomyopathy Hypertrophic cardiomyopathy Left ventricular noncompaction cardiomyopathy	191010	AD
VCL	Dilated cardiomyopathy	193065	AD
TP53	Li-Fraumeni syndrome	191170	AD
TSC1	Tuberous sclerosis complex	605284	AD
TSC2	Tuberous sclerosis complex	191092	AD
VHL	Von Hippel-Lindau syndrome Familial erythrocytosis, type 2	608537	AD, AR
WT1	*WT1*-related Wilms tumor	607102	AD

AD = autosomal dominant; AR = autosomal recessive.*Genes listed in this table may also have additional reported clinical associations outside of the conditions listed. Additional information about gene-condition associations can be found at http://www.omim.org

Table S2. Clinically significant variants detected in this patient cohort. For further details related to the classification of each variant, see https://www.ncbi.nlm.nih.gov/clinvar/

Gene	Variant (HGVS)	Effect	Variant Type	Interpretation
APC	NM_000038.5:c.4733_4734del	p.Cys1578Tyrfs	indel	Pathogenic
APC	NM_000038.5:c.1415dup	p.Gln473Thrfs	indel	Pathogenic
APC	NM_000038.5:c.3920T>A	p.Ile1307Lys	substitution	Increased Risk Allele
APOB	NM_000384.2:c.6543del	p.Phe2181Leufs	indel	Pathogenic
APOB	NM_000384.2:c.671del	p.Pro224Hisfs	indel	Pathogenic
APOB	NM_000384.2:c.7537C>T	p.Arg2513*	substitution	Pathogenic
APOB	NM_000384.2:c.10580G>A	p.Arg3527Gln	substitution	Pathogenic
APOB	NM_000384.2:c.10579C>T	p.Arg3527Trp	substitution	Pathogenic
APOB	NM_000384.2:c.11764C>T	p.Gln3922*	substitution	Pathogenic
APOB	NM_000384.2:c.11789-1G>C	Splice site	substitution	Likely Pathogenic
ATM	NM_000051.3:c.5675-?_5762+?del	Deletion (Exon 38)	cnv	Pathogenic
ATM	NM_000051.3:c.8851-?_*3591+?del	Deletion (Exons 62-63)	cnv	Pathogenic
ATM	NM_000051.3:c.7517_7520del	p.Arg2506Thrfs	indel	Pathogenic
ATM	NM_000051.3:c.7638_7646del	p.Arg2547_Ser2549del	indel	Pathogenic
ATM	NM_000051.3:c.4683_4689del	p.Asp1563Phefs	indel	Pathogenic
ATM	NM_000051.3:c.7010_7011del	p.Cys2337Serfs	indel	Pathogenic
ATM	NM_000051.3:c.8823_8824del	p.Gln2942Glyfs	indel	Pathogenic
ATM	NM_000051.3:c.1027_1030del	p.Glu343Ilefs	indel	Pathogenic
ATM	NM_000051.3:c.1564_1565del	p.Glu522Ilefs	indel	Pathogenic
ATM	NM_000051.3:c.7886_7890del	p.Ile2629Serfs	indel	Pathogenic
ATM	NM_000051.3:c.6228del	p.Leu2077Phefs	indel	Pathogenic
ATM	NM_000051.3:c.7669_7670del	p.Leu2557Valfs	indel	Pathogenic
ATM	NM_000051.3:c.2284_2285del	p.Leu762Valfs	indel	Pathogenic
ATM	NM_000051.3:c.8432del	p.Lys2811Serfs	indel	Pathogenic
ATM	NM_000051.3:c.5894_5900dup	p.Met1967Ilefs	indel	Pathogenic
ATM	NM_000051.3:c.2838del	p.Met946Ilefs	indel	Pathogenic
ATM	NM_000051.3:c.5631_5635delinsA	p.Phe1877Leufs	indel	Pathogenic
ATM	NM_000051.3:c.1597_1600dup	p.Pro534Glnfs	indel	Pathogenic
ATM	NM_000051.3:c.6997dup	p.Thr2333Asnfs	indel	Pathogenic
ATM	NM_000051.3:c.1355del	p.Thr452Asnfs	indel	Pathogenic
ATM	NM_000051.3:c.7542_7543delTA	p.Tyr2514*	indel	Pathogenic
ATM	NM_000051.3:c.3802del	p.Val1268*	indel	Pathogenic
ATM	NM_000051.3:c.381delA	p.Val128*	indel	Pathogenic
ATM	NM_000051.3:c.4804_4805del	p.Val1602Leufs	indel	Pathogenic
ATM	NM_000051.3:c.1997del	p.Val666Glyfs	indel	Pathogenic
ATM	NM_000051.3:c.5177+5G>A	Intronic	substitution	Likely Pathogenic
ATM	NM_000051.3:c.5763-1050A>G	Intronic	substitution	Pathogenic
ATM	NM_000051.3:c.5825C>T	p.Ala1942Val	substitution	Pathogenic
ATM	NM_000051.3:c.4396C>T	p.Arg1466*	substitution	Pathogenic
ATM	NM_000051.3:c.5623C>T	p.Arg1875*	substitution	Pathogenic
ATM	NM_000051.3:c.67C>T	p.Arg23*	substitution	Pathogenic
ATM	NM_000051.3:c.8977C>T	p.Arg2993*	substitution	Pathogenic
ATM	NM_000051.3:c.103C>T	p.Arg35*	substitution	Pathogenic
ATM	NM_000051.3:c.5515C>T	p.Gln1839*	substitution	Pathogenic
ATM	NM_000051.3:c.2341C>T	p.Gln781*	substitution	Pathogenic
ATM	NM_000051.3:c.5932G>T	p.Glu1978*	substitution	Pathogenic
ATM	NM_000051.3:c.6115G>A	p.Glu2039Lys	substitution	Likely Pathogenic
ATM	NM_000051.3:c.841G>T	p.Glu281*	substitution	Pathogenic
ATM	NM_000051.3:c.967A>G	p.Ile323Val	substitution	Pathogenic
ATM	NM_000051.3:c.8549T>A	p.Leu2850*	substitution	Pathogenic
ATM	NM_000051.3:c.2849T>G	p.Leu950Arg	substitution	Likely Pathogenic
ATM	NM_000051.3:c.5890A>T	p.Lys1964*	substitution	Pathogenic
ATM	NM_000051.3:c.8266A>T	p.Lys2756*	substitution	Pathogenic
ATM	NM_000051.3:c.875C>T	p.Pro292Leu	substitution	Pathogenic
ATM	NM_000051.3:c.5228C>T	p.Thr1743Ile	substitution	Likely Pathogenic
ATM	NM_000051.3:c.8879G>A	p.Trp2960*	substitution	Pathogenic
ATM	NM_000051.3:c.6258T>G	p.Tyr2086*	substitution	Pathogenic

ATM	NM_000051.3:c.7271T>G	p.Val2424Gly	substitution	Pathogenic
ATM	NM_000051.3:c.8419-2A>G	Splice site	substitution	Likely Pathogenic
ATM	NM_000051.3:c.8786+1G>A	Splice site	substitution	Pathogenic
ATM	NM_000051.3:c.5006-1G>A	Splice site	substitution	Likely Pathogenic
ATM	NM_000051.3:c.2921+1G>A	Splice site	substitution	Pathogenic
ATM	NM_000051.3:c.186-2A>G	Splice site	substitution	Likely Pathogenic
ATM	NM_000051.3:c.5497-2A>C	Splice site	substitution	Pathogenic
ATP7B	NM_000053.3:c.-157-?_51+?del	Deletion (Exon 1)	cnv	Pathogenic
ATP7B	NM_000053.3:c.3402del	p.Ala1135Glnfs	indel	Pathogenic
ATP7B	NM_000053.3:c.19_20del	p.Gln7Aspfs	indel	Pathogenic
ATP7B	NM_000053.3:c.1745_1746del	p.Ile582Argfs	indel	Pathogenic
ATP7B	NM_000053.3:c.2304dup	p.Met769Hisfs	indel	Pathogenic
ATP7B	NM_000053.3:c.2781del	p.Phe927Leufs	indel	Pathogenic
ATP7B	NM_000053.3:c.956del	p.Pro319Hisfs	indel	Pathogenic
ATP7B	NM_000053.3:c.2009_2015del	p.Tyr670*	indel	Pathogenic
ATP7B	NM_000053.3:c.3649_3654del	p.Val1217_Leu1218del	indel	Likely Pathogenic
ATP7B	NM_000053.3:c.2532del	p.Val845Serfs	indel	Pathogenic
ATP7B	NM_000053.3:c.51+4A>T	Intronic	substitution	Pathogenic
ATP7B	NM_000053.3:c.2122-3C>T	Intronic	substitution	Likely Pathogenic
ATP7B	NM_000053.3:c.-676A>G	Non-coding	substitution	Likely Pathogenic
ATP7B	NM_000053.3:c.3007G>A	p.Ala1003Thr	substitution	Pathogenic
ATP7B	NM_000053.3:c.3451C>T	p.Arg1151Cys	substitution	Likely Pathogenic
ATP7B	NM_000053.3:c.3955C>T	p.Arg1319*	substitution	Pathogenic
ATP7B	NM_000053.3:c.1847G>A	p.Arg616Gln	substitution	Pathogenic
ATP7B	NM_000053.3:c.2333G>T	p.Arg778Leu	substitution	Pathogenic
ATP7B	NM_000053.3:c.122A>G	p.Asn41Ser	substitution	Pathogenic
ATP7B	NM_000053.3:c.3191A>C	p.Glu1064Ala	substitution	Pathogenic
ATP7B	NM_000053.3:c.3517G>A	p.Glu1173Lys	substitution	Pathogenic
ATP7B	NM_000053.3:c.3796G>A	p.Gly1266Arg	substitution	Pathogenic
ATP7B	NM_000053.3:c.2071G>A	p.Gly691Arg	substitution	Pathogenic
ATP7B	NM_000053.3:c.2128G>A	p.Gly710Ser	substitution	Pathogenic
ATP7B	NM_000053.3:c.2605G>A	p.Gly869Arg	substitution	Likely Pathogenic
ATP7B	NM_000053.3:c.3207C>A	p.His1069Gln	substitution	Pathogenic
ATP7B	NM_000053.3:c.2383C>T	p.Leu795Phe	substitution	Pathogenic
ATP7B	NM_000053.3:c.1934T>G	p.Met645Arg	substitution	Pathogenic
ATP7B	NM_000053.3:c.2305A>G	p.Met769Val	substitution	Pathogenic
ATP7B	NM_000053.3:c.2975C>T	p.Pro992Leu	substitution	Pathogenic
ATP7B	NM_000053.3:c.4088C>T	p.Ser1363Phe	substitution	Pathogenic
ATP7B	NM_000053.3:c.2924C>A	p.Ser975Tyr	substitution	Pathogenic
ATP7B	NM_000053.3:c.4058G>A	p.Trp1353*	substitution	Pathogenic
ATP7B	NM_000053.3:c.3316G>A	p.Val1106Ile	substitution	Pathogenic
ATP7B	NM_000053.3:c.2668G>A	p.Val890Met	substitution	Likely Pathogenic
AXIN2	NM_004655.3:c.1908-2A>G	Splice site	substitution	Likely Pathogenic
BAP1	NM_004656.3:c.1383dup	p.Pro462Serfs	indel	Pathogenic
BAP1	NM_004656.3:c.783+2T>C	Splice site	substitution	Likely Pathogenic
BARD1	NM_000465.3:c.1315-?_1568+?del	Deletion (Exons 5-6)	cnv	Pathogenic
BARD1	NM_000465.3:c.1904-3360_2020del	Partial Deletion (Exons 10-11)	cnv	Likely Pathogenic
BARD1	NM_000465.3:c.1865_1903+274del	Partial Deletion (Exon 9)	cnv	Likely Pathogenic
BARD1	NM_000465.3:c.69_70delins25	p.Ala25Glyfs	indel	Pathogenic
BARD1	NM_000465.3:c.2229dup	p.Asn744*	indel	Likely Pathogenic
BARD1	NM_000465.3:c.176_177del	p.Glu59Alafs	indel	Pathogenic
BARD1	NM_000465.3:c.1935_1954dup	p.Glu652Valfs	indel	Pathogenic
BARD1	NM_000465.3:c.1996C>T	p.Gln666*	substitution	Likely Pathogenic
BARD1	NM_000465.3:c.1212C>G	p.Tyr404*	substitution	Pathogenic
BRCA1	NM_007294.3:c.5333-?_5406+?del	Deletion (Exon 21)	cnv	Pathogenic
BRCA1	NM_007294.3:c.-232-?_5467+?del	Deletion (Exons 1-22)	cnv	Pathogenic
BRCA1	NM_007294.3:c.4186-?_4675+?del	Deletion (Exons 12-14)	cnv	Pathogenic
BRCA1	NM_007294.3:c.4358-?_5277+?del	Deletion (Exons 13-19)	cnv	Pathogenic
BRCA1	NM_007294.3:c.548-?_4185+?del	Deletion (Exons 8-11)	cnv	Pathogenic
BRCA1	NM_007294.3:c.4186-?_4357+?dup	Gain (Exon 12)	cnv	Pathogenic
BRCA1	NM_007294.3:c.2071del	p.Arg691Aspfs	indel	Pathogenic

BRCA1	NM_007294.3:c.2989_2990dup	p.Asn997Lysfs	indel	Pathogenic
BRCA1	NM_007294.3:c.3485del	p.Asp1162Valfs	indel	Pathogenic
BRCA1	NM_007294.3:c.676del	p.Cys226Valfs	indel	Pathogenic
BRCA1	NM_007294.3:c.3331_3334del	p.Gln1111Asnfs	indel	Pathogenic
BRCA1	NM_007294.3:c.5266dupC	p.Gln1756Profs	indel	Pathogenic
BRCA1	NM_007294.3:c.4035del	p.Glu1346Lysfs	indel	Pathogenic
BRCA1	NM_007294.3:c.66dup	p.Glu23Argfs	indel	Pathogenic
BRCA1	NM_007294.3:c.68_69delAG	p.Glu23Valfs	indel	Pathogenic
BRCA1	NM_007294.3:c.3228_3229del	p.Gly1077Alafs	indel	Pathogenic
BRCA1	NM_007294.3:c.2517_2518del	p.His839Glnfs	indel	Pathogenic
BRCA1	NM_007294.3:c.5470_5477del	p.Ile1824Aspfs	indel	Pathogenic
BRCA1	NM_007294.3:c.432_433del	p.Pro145Phefs	indel	Pathogenic
BRCA1	NM_007294.3:c.2926_2941dup	p.Pro981Glnfs	indel	Pathogenic
BRCA1	NM_007294.3:c.2865del	p.Ser956Leufs	indel	Pathogenic
BRCA1	NM_007294.3:c.1961dup	p.Tyr655Valfs	indel	Pathogenic
BRCA1	NM_007294.3:c.697_698del	p.Val233Asnfs	indel	Pathogenic
BRCA1	NM_007294.3:c.2T>C	Initiator codon	substitution	Pathogenic
BRCA1	NM_007294.3:c.5503C>T	p.Arg1835*	substitution	Pathogenic
BRCA1	NM_007294.3:c.191G>A	p.Cys64Tyr	substitution	Pathogenic
BRCA1	NM_007294.3:c.1687C>T	p.Gln563*	substitution	Pathogenic
BRCA1	NM_007294.3:c.4057G>T	p.Glu1353*	substitution	Pathogenic
BRCA1	NM_007294.3:c.427G>T	p.Glu143*	substitution	Pathogenic
BRCA1	NM_007294.3:c.5117G>A	p.Gly1706Glu	substitution	Pathogenic
BRCA1	NM_007294.3:c.4508C>A	p.Ser1503*	substitution	Pathogenic
BRCA1	NM_007294.3:c.5346G>A	p.Trp1782*	substitution	Pathogenic
BRCA1	NM_007294.3:c.5152+1G>T	Splice site	substitution	Pathogenic
BRCA1	NM_007294.3:c.4485-1G>A	Splice site	substitution	Likely Pathogenic
BRCA1	NM_007294.3:c.5277+1G>A	Splice site	substitution	Pathogenic
BRCA2	NM_007294.3:c.425+415_4780dup	Gain (Exons 5-11)	cnv	Pathogenic
BRCA2	NM_000059.3:c.2808_2811del	p.Ala938Profs	indel	Pathogenic
BRCA2	NM_000059.3:c.5238dup	p.Asn1747*	indel	Pathogenic
BRCA2	NM_000059.3:c.5350_5351del	p.Asn1784Hisfs	indel	Pathogenic
BRCA2	NM_000059.3:c.6408_6414del	p.Asn2137Lysfs	indel	Pathogenic
BRCA2	NM_000059.3:c.1265del	p.Asn422Ilefs	indel	Pathogenic
BRCA2	NM_000059.3:c.2836_2837del	p.Asp946Phefs	indel	Pathogenic
BRCA2	NM_000059.3:c.9699_9702del	p.Cys3233Trpfs	indel	Pathogenic
BRCA2	NM_000059.3:c.4284dup	p.Gln1429Serfs	indel	Pathogenic
BRCA2	NM_000059.3:c.6024dup	p.Gln2009Alafs	indel	Pathogenic
BRCA2	NM_000059.3:c.6468_6469del	p.Gln2157Ilefs	indel	Pathogenic
BRCA2	NM_000059.3:c.9891_9894dup	p.Gln3299Ilefs	indel	Pathogenic
BRCA2	NM_000059.3:c.5722_5723del	p.Leu1908Argfs	indel	Pathogenic
BRCA2	NM_000059.3:c.6275_6276del	p.Leu2092Profs	indel	Pathogenic
BRCA2	NM_000059.3:c.6757_6758del	p.Leu2253Phefs	indel	Pathogenic
BRCA2	NM_000059.3:c.3170_3174delAGAAA	p.Lys1057Thrfs	indel	Pathogenic
BRCA2	NM_000059.3:c.469_470delAA	p.Lys157Valfs	indel	Pathogenic
BRCA2	NM_000059.3:c.6486_6489del	p.Lys2162Asnfs	indel	Pathogenic
BRCA2	NM_000059.3:c.3545_3546del	p.Phe1182*	indel	Pathogenic
BRCA2	NM_000059.3:c.2672dup	p.Phe892Leufs	indel	Pathogenic
BRCA2	NM_000059.3:c.6998dup	p.Pro2334Thrfs	indel	Pathogenic
BRCA2	NM_000059.3:c.3744_3747del	p.Ser1248Argfs	indel	Pathogenic
BRCA2	NM_000059.3:c.5828del	p.Ser1943Leufs	indel	Pathogenic
BRCA2	NM_000059.3:c.5946delT	p.Ser1982Argfs	indel	Pathogenic
BRCA2	NM_000059.3:c.3199del	p.Thr1067Leufs	indel	Pathogenic
BRCA2	NM_000059.3:c.4133_4136del	p.Thr1378Argfs	indel	Pathogenic
BRCA2	NM_000059.3:c.9097dup	p.Thr3033Asnfs	indel	Pathogenic
BRCA2	NM_000059.3:c.9253dup	p.Thr3085Asnfs	indel	Pathogenic
BRCA2	NM_000059.3:c.2716dup	p.Thr906Asnfs	indel	Pathogenic
BRCA2	NM_000059.3:c.5130_5133del	p.Tyr1710*	indel	Pathogenic
BRCA2	NM_000059.3:c.6641dup	p.Tyr2215Leufs	indel	Pathogenic
BRCA2	NM_000059.3:c.3847_3848del	p.Val1283Lysfs	indel	Pathogenic
BRCA2	NM_000059.3:c.156_157insAlu	Splicing	indel	Pathogenic

BRCA2	NM_000059.3:c.3G>A	Initiator codon	substitution	Pathogenic
BRCA2	NM_000059.3:c.7007G>A	p.Arg2336His	substitution	Pathogenic
BRCA2	NM_000059.3:c.7007G>C	p.Arg2336Pro	substitution	Pathogenic
BRCA2	NM_000059.3:c.7976G>A	p.Arg2659Lys	substitution	Pathogenic
BRCA2	NM_000059.3:c.5864C>A	p.Ser1955*	substitution	Pathogenic
BRCA2	NM_000059.3:c.1103C>A	p.Ser368*	substitution	Pathogenic
BRCA2	NM_000059.3:c.8909G>A	p.Trp2970*	substitution	Pathogenic
BRCA2	NM_000059.3:c.5286T>G	p.Tyr1762*	substitution	Pathogenic
BRCA2	NM_000059.3:c.8488-1G>A	Splice site	substitution	Likely Pathogenic
BRCA2	NM_000059.3:c.-39-1G>C	Splice site	substitution	Likely Pathogenic
BRIP1	NM_032043.2:c.2010dup	p.Glu671*	indel	Pathogenic
BRIP1	NM_032043.2:c.1442_1443dup	p.Ile482Valfs	indel	Pathogenic
BRIP1	NM_032043.2:c.1510dup	p.Ile504Asnfs	indel	Pathogenic
BRIP1	NM_032043.2:c.2992_2995del	p.Lys998Glufs	indel	Pathogenic
BRIP1	NM_032043.2:c.3401del	p.Pro1134Leufs	indel	Likely Pathogenic
BRIP1	NM_032043.2:c.1853_1854insG	p.Pro619Thrfs	indel	Pathogenic
BRIP1	NM_032043.2:c.2684_2687del	p.Ser895*	indel	Pathogenic
BRIP1	NM_032043.2:c.1045G>C	p.Ala349Pro	substitution	Likely Pathogenic
BRIP1	NM_032043.2:c.1315C>T	p.Arg439*	substitution	Pathogenic
BRIP1	NM_032043.2:c.2392C>T	p.Arg798*	substitution	Pathogenic
BRIP1	NM_032043.2:c.1372G>T	p.Glu458*	substitution	Pathogenic
BRIP1	NM_032043.2:c.161T>G	p.Leu54*	substitution	Pathogenic
BRIP1	NM_032043.2:c.3167C>G	p.Ser1056*	substitution	Likely Pathogenic
BRIP1	NM_032043.2:c.1694C>A	p.Ser565*	substitution	Pathogenic
BRIP1	NM_032043.2:c.1343G>A	p.Trp448*	substitution	Pathogenic
BRIP1	NM_032043.2:c.2400C>G	p.Tyr800*	substitution	Pathogenic
BRIP1	NM_032043.2:c.1340+1G>A	Splice site	substitution	Likely Pathogenic
CACNA1S	NM_000069.2:c.5227-2del	Splice site	indel	Likely Pathogenic
CACNA1S	NM_000069.2:c.19C>T	p.Gln7*	substitution	Pathogenic
CACNA1S	NM_000069.2:c.1948+1G>A	Splice site	substitution	Likely Pathogenic
CACNA1S	NM_000069.2:c.4442-2A>G	Splice site	substitution	Likely Pathogenic
CACNA1S	NM_000069.2:c.2854-2A>C	Splice site	substitution	Likely Pathogenic
CACNA1S	NM_000069.2:c.3525+1G>A	Splice site	substitution	Likely Pathogenic
CASQ2	NM_001232.3:c.475G>T	p.Glu159*	substitution	Pathogenic
CASQ2	NM_001232.3:c.856G>T	p.Glu286*	substitution	Pathogenic
CAV3	NM_033337.2:c.277G>A	p.Ala93Thr	substitution	Pathogenic
CAV3	NM_033337.2:c.294C>A	p.Cys98*	substitution	Likely Pathogenic
CDH1	NM_004360.3:c.1973dup	p.Leu658Phefs	indel	Pathogenic
CDH1	NM_004360.3:c.2287G>T	p.Glu763*	substitution	Pathogenic
CDKN2A (p16INK4a)	NM_000077.4:c.225_243del	p.Ala76Cysfs	indel	Pathogenic
CDKN2A (p16INK4a)	NM_000077.4:c.335_337dup	p.Arg112dup	indel	Likely Pathogenic
CDKN2A (p16INK4a)	NM_000077.4:c.189del	p.Leu64Cysfs	indel	Pathogenic
CDKN2A (p16INK4a)	NM_000077.4:c.176T>G	p.Val59Gly	substitution	Pathogenic
CHEK2	NM_007194.3:c.-6-?_319+?del	Deletion (Exon 2)	cnv	Pathogenic
CHEK2	NM_007194.3:c.909-?_1095+?del	Deletion (Exons 9-10)	cnv	Pathogenic
CHEK2	NM_007194.3:c.847-?_908+?dup	Gain (Exon 8)	cnv	Likely Pathogenic
CHEK2	NM_007194.3:c.320-?_592+?dup	Gain (Exons 3-4)	cnv	Likely Pathogenic
CHEK2	NM_007194.3:c.846+4_846+7del	Intronic	indel	Likely Pathogenic
CHEK2	NM_007194.3:c.655del	p.Glu219Asnfs	indel	Pathogenic
CHEK2	NM_007194.3:c.1368dupA	p.Glu457Argfs	indel	Pathogenic
CHEK2	NM_007194.3:c.1371_1372del	p.Lys458Serfs	indel	Pathogenic
CHEK2	NM_007194.3:c.629_632del	p.Ser210Phefs	indel	Pathogenic
CHEK2	NM_007194.3:c.1263delT	p.Ser422Valfs	indel	Pathogenic
CHEK2	NM_007194.3:c.152_155dup	p.Ser53Valfs	indel	Pathogenic
CHEK2	NM_007194.3:c.1100delC	p.Thr367Metfs	indel	Pathogenic
CHEK2	NM_007194.3:c.277del	p.Trp93Glyfs	indel	Pathogenic
CHEK2	NM_007194.3:c.1188del	p.Val397Phefs	indel	Pathogenic
CHEK2	NM_007194.3:c.349A>G	p.Arg117Gly	substitution	Likely Pathogenic
CHEK2	NM_007194.3:c.433C>T	p.Arg145Trp	substitution	Likely Pathogenic
CHEK2	NM_007194.3:c.1555C>T	p.Arg519*	substitution	Likely Pathogenic
CHEK2	NM_007194.3:c.190G>A	p.Glu64Lys	substitution	Likely Pathogenic

CHEK2	NM_007194.3:c.470T>C	p.Ile157Thr	substitution	Pathogenic (low penetrance)
CHEK2	NM_007194.3:c.707T>C	p.Leu236Pro	substitution	Likely Pathogenic
CHEK2	NM_007194.3:c.1283C>T	p.Ser428Phe	substitution	Pathogenic (low penetrance)
CHEK2	NM_007194.3:c.1232G>A	p.Trp411*	substitution	Pathogenic
CHEK2	NM_007194.3:c.444+1G>A	Splice site	substitution	Pathogenic
CHEK2	NM_007194.3:c.908+2T>C	Splice site	substitution	Likely Pathogenic
CHEK2	NM_007194.3:c.1462-1G>A	Splice site	substitution	Likely Pathogenic
COL3A1	NM_000090.3:c.2248G>C	p.Gly750Arg	substitution	Likely Pathogenic
COL3A1	NM_000090.3:c.852+2T>C	Splice site	substitution	Likely Pathogenic
CRYAB	NM_001885.2:c.343del	p.Ser115Profs	indel	Pathogenic
DES	NM_001927.3:c.-86-?_*749+?del	Deletion (Entire coding sequence)	cnv	Pathogenic
DES	NM_001927.3:c.1A>G	Initiator codon	substitution	Likely Pathogenic
DES	NM_001927.3:c.322G>T	p.Glu108*	substitution	Pathogenic
DES	NM_001927.3:c.1371+1G>A	Splice site	substitution	Likely Pathogenic
DMD	NM_004006.2:c.6913-?_7098+?del	Deletion (Exon 48)	cnv	Pathogenic
DMD	NM_004006.2:c.94-?_960+?del	Deletion (Exons 3-9)	cnv	Likely Pathogenic
DMD	NM_004006.2:c.7310-?_7660+?del	Deletion (Exons 51-52)	cnv	Pathogenic
DMD	NM_004006.2:c.8028-?_8217+?dup	Gain (Exon 55)	cnv	Likely Pathogenic
DMD	NM_004006.2:c.6474del	p.Val2159Serfs	indel	Pathogenic
DSG2	NM_001943.3:c.2620del	p.Thr874Leufs	indel	Pathogenic
DSG2	NM_001943.3:c.1672C>T	p.Gln558*	substitution	Pathogenic
DSP	NM_004415.2:c.5671_*1792delins16	p.Glu1891Argfs	cnv	Pathogenic
DSP	NM_004415.2:c.2870_2874del	p.Ser957*	indel	Pathogenic
DSP	NM_004415.2:c.5212C>T	p.Arg1738*	substitution	Pathogenic
DSP	NM_004415.2:c.250C>T	p.Arg84*	substitution	Pathogenic
DSP	NM_004415.2:c.85G>T	p.Glu29*	substitution	Pathogenic
DSP	NM_004415.2:c.2437-1G>C	Splice site	substitution	Likely Pathogenic
ENG	NM_000118.3:c.511C>T	p.Arg171*	substitution	Pathogenic
EPCAM	NM_002354.2:c.-358-?_76+?del	Deletion (Exon 1)	cnv	Pathogenic
F2	NM_000506.3:c.*97G>A	Non-coding	substitution	Pathogenic (low penetrance)
F5	NM_000130.4:c.1601G>A	p.Arg534Gln	substitution	Pathogenic
FH	NM_000143.3:c.1431_1433dupAAA	p.Lys477dup	indel	Likely Pathogenic
FH	NM_000143.3:c.782G>T	p.Arg261Ile	substitution	Likely Pathogenic
FH	NM_000143.3:c.194A>G	p.Asp65Gly	substitution	Likely Pathogenic
FH	NM_000143.3:c.1189G>A	p.Gly397Arg	substitution	Pathogenic
FH	NM_000143.3:c.521C>G	p.Pro174Arg	substitution	Pathogenic
FH	NM_000143.3:c.1093A>G	p.Ser365Gly	substitution	Pathogenic
FLCN	NM_144997.5:c.-504-?_-228+?del	Deletion (Exon 1)	cnv	Pathogenic
FLCN	NM_144997.5:c.584del	p.Gly195Glufs	indel	Pathogenic
FLCN	NM_144997.5:c.521_527del	p.Thr174Argfs	indel	Pathogenic
FLNC	NM_001458.4:c.4581-?_4927+?del	Deletion (Exons 27-28)	cnv	Pathogenic
FLNC	NM_001458.4:c.2084del	p.Arg695Leufs	indel	Pathogenic
FLNC	NM_001458.4:c.4882_4886delinsGCT	p.Ile1628Alafs	indel	Pathogenic
FLNC	NM_001458.4:c.4926_4927insACGTCACA	p.Val1643Thrfs	indel	Pathogenic
FLNC	NM_001458.4:c.2119C>T	p.Gln707*	substitution	Pathogenic
FLNC	NM_001458.4:c.3791-1G>C	Splice site	substitution	Pathogenic
GLA	NM_000169.2:c.640-801G>A	Intronic	substitution	Pathogenic
GLA	NM_000169.2:c.335G>A	p.Arg112His	substitution	Pathogenic
GLA	NM_000169.2:c.644A>G	p.Asn215Ser	substitution	Pathogenic
HFE	NM_000410.3:c.762del	p.Asp255Thrfs	indel	Pathogenic
HFE	NM_000410.3:c.211C>T	p.Arg71*	substitution	Pathogenic
HFE	NM_000410.3:c.845G>A	p.Cys282Tyr	substitution	Pathogenic (low penetrance)
HFE	NM_000410.3:c.502G>T	p.Glu168*	substitution	Pathogenic
HFE	NM_000410.3:c.187C>G	p.His63Asp	substitution	Pathogenic (low penetrance)
HFE	NM_000410.3:c.341-1G>A	Splice site	substitution	Likely Pathogenic
HJV	NM_213653.3:c.959G>T	p.Gly320Val	substitution	Pathogenic
HJV	NM_213653.3:c.1097T>A	p.Leu366*	substitution	Pathogenic
HOXB13	NM_006361.5:c.251G>A	p.Gly84Glu	substitution	Increased Risk Allele
JUP	NM_002230.2:c.532_542del	p.Ala178Leufs	indel	Pathogenic
JUP	NM_002230.2:c.902A>G	p.Glu301Gly	substitution	Likely Pathogenic
JUP	NM_002230.2:c.545C>A	p.Ser182*	substitution	Pathogenic

KCNE1	NM_000219.5:c.292C>T	p.Arg98Trp	substitution	Likely Pathogenic
KCNE1	NM_000219.5:c.226G>A	p.Asp76Asn	substitution	Pathogenic
KCNE1	NM_000219.5:c.172_177delinsCCCCCT	p.Thr58_Leu59delinsProPro	substitution	Likely Pathogenic
KCNH2	NM_172057.2:c.2692_2692+1insACACGG	Splice site	indel	Likely Pathogenic
KCNQ1	NM_000218.2:c.1893dup	p.Arg632Glnfs	indel	Pathogenic
KCNQ1	NM_000218.2:c.524_534del	p.Leu175Argfs	indel	Pathogenic
KCNQ1	NM_000218.2:c.905C>T	p.Ala302Val	substitution	Likely Pathogenic
KCNQ1	NM_000218.2:c.776G>A	p.Arg259His	substitution	Pathogenic
KCNQ1	NM_000218.2:c.502G>A	p.Gly168Arg	substitution	Pathogenic
KCNQ1	NM_000218.2:c.1085A>G	p.Lys362Arg	substitution	Pathogenic
KCNQ1	NM_000218.2:c.153C>G	p.Tyr51*	substitution	Pathogenic
LDLR	NM_000527.4:c.-187-?_67+?del	Deletion (Exon 1)	cnv	Pathogenic
LDLR	NM_000527.4:c.1846-?_2140+?del	Deletion (Exons 13-14)	cnv	Pathogenic
LDLR	NM_000527.4:c.2390-?_*2514+?del	Deletion (Exons 17-18)	cnv	Pathogenic
LDLR	NM_000527.4:c.1187-?_2140+?del	Deletion (Exons 9-14)	cnv	Pathogenic
LDLR	NM_000527.4:c.2416dup	p.Val806Glyfs	indel	Pathogenic
LDLR	NM_000527.4:c.-152C>T	Non-coding	substitution	Pathogenic
LDLR	NM_000527.4:c.1195G>A	p.Ala399Thr	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.1246C>T	p.Arg416Trp	substitution	Pathogenic
LDLR	NM_000527.4:c.1721G>A	p.Arg574His	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.1898G>A	p.Arg633His	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.241C>T	p.Arg81Cys	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.798T>A	p.Asp266Glu	substitution	Pathogenic
LDLR	NM_000527.4:c.912C>G	p.Asp304Glu	substitution	Pathogenic
LDLR	NM_000527.4:c.81C>G	p.Cys27Trp	substitution	Pathogenic
LDLR	NM_000527.4:c.1135T>C	p.Cys379Arg	substitution	Pathogenic
LDLR	NM_000527.4:c.2029T>C	p.Cys677Arg	substitution	Pathogenic
LDLR	NM_000527.4:c.301G>A	p.Glu101Lys	substitution	Pathogenic
LDLR	NM_000527.4:c.337G>A	p.Glu113Lys	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.1003G>A	p.Gly335Ser	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.1027G>A	p.Gly343Ser	substitution	Pathogenic
LDLR	NM_000527.4:c.1775G>A	p.Gly592Glu	substitution	Pathogenic
LDLR	NM_000527.4:c.1747C>T	p.His583Tyr	substitution	Pathogenic
LDLR	NM_000527.4:c.1745T>C	p.Leu582Pro	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.2054C>T	p.Pro685Leu	substitution	Pathogenic
LDLR	NM_000527.4:c.2096C>T	p.Pro699Leu	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.858C>A	p.Ser286Arg	substitution	Likely Pathogenic
LDLR	NM_000527.4:c.11G>A	p.Trp4*	substitution	Pathogenic
LDLR	NM_000527.4:c.2389G>A	p.Val797Met	substitution	Pathogenic
LDLRAP1	Deletion	Entire coding sequence	cnv	Pathogenic
LDLRAP1	NM_015627.2:c.65G>A	p.Trp22*	substitution	Pathogenic
LMNA	NM_170707.3:c.992G>A	p.Arg331Gln	substitution	Pathogenic
LMNA	NM_170707.3:c.1130G>A	p.Arg377His	substitution	Pathogenic
LMNA	NM_170707.3:c.1580G>A	p.Arg527His	substitution	Pathogenic
MEN1	NM_130799.2:c.914del	p.Gly305Alafs	indel	Pathogenic
MITF	NM_000248.3:c.952G>A	p.Glu318Lys	substitution	Pathogenic
MLH1	NM_000249.3:c.1852_1854del	p.Lys618del	indel	Pathogenic
MLH1	NM_000249.3:c.116+5G>A	Intronic	substitution	Likely Pathogenic
MLH1	NM_000249.3:c.2041G>A	p.Ala681Thr	substitution	Pathogenic
MLH1	NM_000249.3:c.2142G>A	p.Trp714*	substitution	Pathogenic
MLH1	NM_000249.3:c.1517T>C	p.Val506Ala	substitution	Likely Pathogenic
MLH1	NM_000249.3:c.1896+1G>A	Splice site	substitution	Pathogenic
MSH2	NM_000251.2:c.1151dup	p.Asp386Argfs	indel	Pathogenic
MSH2	NM_000251.2:c.2633_2634del	p.Glu878Alafs	indel	Pathogenic
MSH2	NM_000251.2:c.190del	p.Ile64Serfs	indel	Pathogenic
MSH2	NM_000251.2:c.1571G>C	p.Arg524Pro	substitution	Pathogenic
MSH2	NM_000251.2:c.2635-1G>T	Splice site	substitution	Likely Pathogenic
MSH3	NM_002439.4:c.1654-?_1763+?del	Deletion (Exon 12)	cnv	Pathogenic
MSH3	NM_002439.4:c.2668_2671del	p.Arg890*	indel	Pathogenic
MSH3	NM_002439.4:c.1648_1649dup	p.Asn550Lysfs	indel	Pathogenic
MSH3	NM_002439.4:c.1035del	p.Leu347*	indel	Pathogenic

MSH3	NM_002439.4:c.978_984del	p.Phe326Leufs	indel	Pathogenic
MSH3	NM_002439.4:c.1417dup	p.Thr473Asnfs	indel	Pathogenic
MSH3	NM_002439.4:c.2179C>T	p.Arg727*	substitution	Pathogenic
MSH3	NM_002439.4:c.697G>T	p.Glu233*	substitution	Pathogenic
MSH3	NM_002439.4:c.2686G>T	p.Gly896*	substitution	Pathogenic
MSH3	NM_002439.4:c.2663C>G	p.Ser888*	substitution	Pathogenic
MSH3	NM_002439.4:c.2319-1G>A	Splice site	substitution	Pathogenic
MSH3	NM_002439.4:c.2655+1G>A	Splice site	substitution	Likely Pathogenic
MSH6	NM_000179.2:c.3959_3962del	p.Ala1320Glufs	indel	Pathogenic
MSH6	NM_000179.2:c.1519dup	p.Arg507Lysfs	indel	Pathogenic
MSH6	NM_000179.2:c.3964_3980dup	p.Asn1327Lysfs	indel	Pathogenic
MSH6	NM_000179.2:c.706_707del	p.Gln236Argfs	indel	Pathogenic
MSH6	NM_000179.2:c.3744_3773del	p.His1248_Ser1257del	indel	Pathogenic
MSH6	NM_000179.2:c.3984_3987dup	p.Leu1330Valfs	indel	Pathogenic
MSH6	NM_000179.2:c.2677_2678del	p.Leu893Alafs	indel	Pathogenic
MSH6	NM_000179.2:c.3261dup	p.Phe1088Leufs	indel	Pathogenic
MSH6	NM_000179.2:c.2269_2270del	p.Thr757Profs	indel	Pathogenic
MSH6	NM_000179.2:c.3226C>T	p.Arg1076Cys	substitution	Pathogenic
MSH6	NM_000179.2:c.3227G>A	p.Arg1076His	substitution	Likely Pathogenic
MSH6	NM_000179.2:c.2731C>T	p.Arg911*	substitution	Pathogenic
MSH6	NM_000179.2:c.463A>T	p.Lys155*	substitution	Pathogenic
MSH6	NM_000179.2:c.901A>T	p.Lys301*	substitution	Pathogenic
MSH6	NM_000179.2:c.1721C>G	p.Ser574*	substitution	Pathogenic
MSH6	NM_000179.2:c.3556+2T>C	Splice site	substitution	Likely Pathogenic
MUTYH	NM_001128425.1:c.504+19_504+31del	Intronic	indel	Pathogenic
MUTYH	NM_001128425.1:c.1147delC	p.Ala385Profs	indel	Pathogenic
MUTYH	NM_001128425.1:c.1437_1439delGGA	p.Glu480del	indel	Pathogenic
MUTYH	NM_001128425.1:c.933+3A>C	Intronic	substitution	Pathogenic
MUTYH	NM_001128425.1:c.55C>T	p.Arg19*	substitution	Pathogenic
MUTYH	NM_001128425.1:c.722G>A	p.Arg241Gln	substitution	Likely Pathogenic
MUTYH	NM_001128425.1:c.734G>A	p.Arg245His	substitution	Pathogenic
MUTYH	NM_001128425.1:c.739C>T	p.Arg247*	substitution	Pathogenic
MUTYH	NM_001128425.1:c.1012C>T	p.Gln338*	substitution	Pathogenic
MUTYH	NM_001128425.1:c.1187G>A	p.Gly396Asp	substitution	Pathogenic
MUTYH	NM_001128425.1:c.884C>T	p.Pro295Leu	substitution	Likely Pathogenic
MUTYH	NM_001128425.1:c.1214C>T	p.Pro405Leu	substitution	Pathogenic
MUTYH	NM_001128425.1:c.521G>A	p.Trp174*	substitution	Pathogenic
MUTYH	NM_001128425.1:c.536A>G	p.Tyr179Cys	substitution	Pathogenic
MUTYH	NM_001128425.1:c.789-2A>C	Splice site	substitution	Likely Pathogenic
MUTYH	NM_001128425.1:c.1187-2A>G	Splice site	substitution	Pathogenic
MUTYH	NM_001128425.1:c.1477-1G>A	Splice site	substitution	Likely Pathogenic
MYBPC3	NM_000256.3:c.3628-41_3628-17del	Intronic	indel	Pathogenic
MYBPC3	NM_000256.3:c.2864_2865del	p.Pro955Argfs	indel	Pathogenic
MYBPC3	NM_000256.3:c.1504C>T	p.Arg502Trp	substitution	Pathogenic
MYBPC3	NM_000256.3:c.1828G>C	p.Asp610His	substitution	Likely Pathogenic
MYBPC3	NM_000256.3:c.1624G>C	p.Glu542Gln	substitution	Pathogenic
MYBPC3	NM_000256.3:c.1591G>C	p.Gly531Arg	substitution	Likely Pathogenic
MYBPC3	NM_000256.3:c.655G>C	p.Val219Leu	substitution	Pathogenic
MYBPC3	NM_000256.3:c.821+1G>A	Splice site	substitution	Pathogenic
MYBPC3	NM_000256.3:c.927-2A>G	Splice site	substitution	Pathogenic
MYH11	NM_001040113.1:c.-17-?_*8+?del	Deletion (Entire coding sequence)	cnv	Pathogenic
MYH11	NM_001040113.1:c.-107-?_*997+?del	Deletion (Entire coding sequence)	cnv	Pathogenic
MYH11	NM_001040113.1:c.3624_3628dup	p.Gln1210Profs	indel	Pathogenic
MYH7	NM_000257.3:c.3134G>T	p.Arg1045Leu	substitution	Pathogenic
MYH7	NM_000257.3:c.5135G>A	p.Arg1712Gln	substitution	Likely Pathogenic
MYH7	NM_000257.3:c.5134C>T	p.Arg1712Trp	substitution	Pathogenic
MYH7	NM_000257.3:c.5342G>A	p.Arg1781His	substitution	Likely Pathogenic
MYH7	NM_000257.3:c.611G>A	p.Arg204His	substitution	Pathogenic
MYH7	NM_000257.3:c.1207C>T	p.Arg403Trp	substitution	Pathogenic
MYH7	NM_000257.3:c.1988G>A	p.Arg663His	substitution	Pathogenic
MYH7	NM_000257.3:c.2080C>T	p.Arg694Cys	substitution	Likely Pathogenic

MYH7	NM_000257.3:c.2167C>T	p.Arg723Cys	substitution	Pathogenic
MYH7	NM_000257.3:c.2221G>T	p.Gly741Trp	substitution	Pathogenic
MYH7	NM_000257.3:c.1727A>G	p.His576Arg	substitution	Likely Pathogenic
MYH7	NM_000257.3:c.5561C>T	p.Thr1854Met	substitution	Likely Pathogenic
MYH7	NM_000257.3:c.5655G>A	Silent	substitution	Pathogenic
MYLK	NM_053025.3:c.3715del	p.Gln1239Argfs	indel	Pathogenic
NBN	NM_002485.4:c.897-?_2184+?del	Deletion (Exons 8-14)	cnv	Pathogenic
NBN	NM_002485.4:c.35_37+10del	Partial deletion (Exon 1)	cnv	Likely Pathogenic
NBN	NM_002485.4:c.163_171+3del	Partial deletion (Exon 2)	cnv	Likely Pathogenic
NBN	NM_002485.4:c.657_661delACAAA	p.Lys219Asnfs	indel	Pathogenic
NBN	NM_002485.4:c.698_701del	p.Lys233Serfs	indel	Pathogenic
NBN	NM_002485.4:c.156_157del	p.Ser53Cysfs	indel	Pathogenic
NBN	NM_002485.4:c.1737del	p.Val580Phefs	indel	Pathogenic
NBN	NM_002485.4:c.2140C>T	p.Arg714*	substitution	Pathogenic
NBN	NM_002485.4:c.1903A>T	p.Lys635*	substitution	Pathogenic
NBN	NM_002485.4:c.1496C>A	p.Ser499*	substitution	Pathogenic
NBN	NM_002485.4:c.481-2A>T	Splice site	substitution	Likely Pathogenic
NBN	NM_002485.4:c.2234+2T>G	Splice site	substitution	Likely Pathogenic
NF1	NM_000267.3:c.244_247del	p.Gln83*	indel	Pathogenic
NF1	NM_000267.3:c.4537C>T	p.Arg1513*	substitution	Pathogenic
NF1	NM_000267.3:c.7486C>T	p.Arg2496*	substitution	Pathogenic
NF1	NM_000267.3:c.2044C>T	p.Gln682*	substitution	Pathogenic
NF1	NM_000267.3:c.5431G>T	p.Glu1811*	substitution	Pathogenic
NF2	NM_000268.3:c.-443-?_*3798+?del	Deletion (Entire coding sequence)	cnv	Pathogenic
NF2	NM_000268.3:c.1575-?_1737+?dup	Gain (Exon 15)	cnv	Likely Pathogenic
NTHL1	NM_002528.6:c.235dup	p.Ala79Glyfs	indel	Pathogenic
NTHL1	NM_002528.6:c.484del	p.Asp162Thrfs	indel	Pathogenic
NTHL1	NM_002528.6:c.859C>T	p.Gln287*	substitution	Likely Pathogenic
NTHL1	NM_002528.6:c.268C>T	p.Gln90*	substitution	Pathogenic
NTHL1	NM_002528.6:c.806G>A	p.Trp269*	substitution	Likely Pathogenic
NTHL1	NM_002528.6:c.390C>A	p.Tyr130*	substitution	Pathogenic
NTHL1	NM_002528.6:c.139+1G>A	Splice site	substitution	Likely Pathogenic
NTHL1	NM_002528.6:c.550-1G>A	Splice site	substitution	Pathogenic
PALB2	NM_024675.3:c.3114-?_3201+?del	Deletion (Exon 11)	cnv	Pathogenic
PALB2	NM_024675.3:c.509_510del	p.Arg170Ilefs	indel	Pathogenic
PALB2	NM_024675.3:c.3179_3180ins(?)	p.Cys1060fs	indel	Pathogenic
PALB2	NM_024675.3:c.1675_1676delinsTG	p.Gln559*	indel	Pathogenic
PALB2	NM_024675.3:c.172_175del	p.Gln60Argfs	indel	Pathogenic
PALB2	NM_024675.3:c.532del	p.Glu178Asnfs	indel	Pathogenic
PALB2	NM_024675.3:c.1824dup	p.Ile609Tyrfs	indel	Pathogenic
PALB2	NM_024675.3:c.1592del	p.Leu531Cysfs	indel	Pathogenic
PALB2	NM_024675.3:c.3482_3483del	p.Phe1161Cysfs	indel	Pathogenic
PALB2	NM_024675.3:c.3456dup	p.Pro1153Thrfs	indel	Pathogenic
PALB2	NM_024675.3:c.1965del	p.Pro656Glnfs	indel	Pathogenic
PALB2	NM_024675.3:c.758dup	p.Ser254Ilefs	indel	Pathogenic
PALB2	NM_024675.3:c.899del	p.Thr300Lysfs	indel	Pathogenic
PALB2	NM_024675.3:c.1677del	p.Val560*	indel	Pathogenic
PALB2	NM_024675.3:c.2964del	p.Val989*	indel	Pathogenic
PALB2	NM_024675.3:c.2257C>T	p.Arg753*	substitution	Pathogenic
PALB2	NM_024675.3:c.196C>T	p.Gln66*	substitution	Pathogenic
PALB2	NM_024675.3:c.1010T>A	p.Leu337*	substitution	Pathogenic
PALB2	NM_024675.3:c.3113G>A	p.Trp1038*	substitution	Pathogenic
PALB2	NM_024675.3:c.3549C>A	p.Tyr1183*	substitution	Pathogenic
PALB2	NM_024675.3:c.3549C>G	p.Tyr1183*	substitution	Pathogenic
PCSK9	NM_174936.3:c.1394C>T	p.Ser465Leu	substitution	Likely Pathogenic
PKP2	NM_004572.3:c.1171-?_1378+?del	Deletion (Exon 5)	cnv	Pathogenic
PKP2	NM_004572.3:c.2293_2299+1008del	Partial deletion (Exon 11)	cnv	Likely Pathogenic
PKP2	NM_004572.3:c.1237C>T	p.Arg413*	substitution	Pathogenic
PKP2	NM_004572.3:c.1978C>T	p.Gln660*	substitution	Pathogenic
PKP2	NM_004572.3:c.1613G>A	p.Trp538*	substitution	Pathogenic
PKP2	NM_004572.3:c.337-2A>T	Splice site	substitution	Pathogenic

PKP2	NM_004572.3:c.2146-1G>C	Splice site	substitution	Pathogenic
PKP2	NM_004572.3:c.2489+1G>A	Splice site	substitution	Pathogenic
PLN	NM_002667.3:c.26_29dup	p.Ala11Leufs	indel	Pathogenic
PLN	NM_002667.3:c.26G>A	p.Arg9His	substitution	Likely Pathogenic
PLN	NM_002667.3:c.116T>G	p.Leu39*	substitution	Pathogenic
PMS2	NM_000535.5:c.24-?_163+?del	Deletion (Exon 2)	cnv	Pathogenic
PMS2	NM_000535.5:c.904-?_1144+?del	Deletion (Exons 9-10)	cnv	Pathogenic
PMS2	Deletion	Entire coding sequence	cnv	Pathogenic
PMS2	Deletion	Exons 12-15	cnv	Pathogenic
PMS2	NM_000535.5:c.862_863del	p.Gln288Valfs	indel	Pathogenic
PMS2	NM_000535.5:c.1831dup	p.Ile611Asnfs	indel	Pathogenic
PMS2	NM_000535.5:c.736_741delinsTGTGTGTGAAG	p.Pro246Cysfs	indel	Pathogenic
PMS2	NM_000535.5:c.1638_1639del	p.Ser547Argfs	indel	Pathogenic
PMS2	NM_000535.5:c.1009dup	p.Thr337Asnfs	indel	Pathogenic
PMS2	NM_000535.5:c.943C>T	p.Arg315*	substitution	Pathogenic
PMS2	NM_000535.5:c.949C>T	p.Gln317*	substitution	Pathogenic
PMS2	NM_000535.5:c.2249G>A	p.Gly750Asp	substitution	Likely Pathogenic
PMS2	NM_000535.5:c.1939A>T	p.Lys647*	substitution	Pathogenic
PMS2	NM_000535.5:c.137G>A	p.Ser46Asn	substitution	Pathogenic
PMS2	NM_000535.5:c.137G>T	p.Ser46Ile	substitution	Pathogenic
PMS2	NM_000535.5:c.2444C>T	p.Ser815Leu	substitution	Likely Pathogenic
PMS2	NM_000535.5:c.765C>A	p.Tyr255*	substitution	Pathogenic
PROC	NM_000312.3:c.1212dup	p.Pro405Alafs	indel	Pathogenic
PROC	NM_000312.3:c.925G>A	p.Ala309Thr	substitution	Pathogenic
PROC	NM_000312.3:c.631C>T	p.Arg211Trp	substitution	Pathogenic
PROC	NM_000312.3:c.659G>A	p.Arg220Gln	substitution	Likely Pathogenic
PROC	NM_000312.3:c.811C>T	p.Arg271Trp	substitution	Likely Pathogenic
PROC	NM_000312.3:c.169C>T	p.Arg57Trp	substitution	Pathogenic
PROC	NM_000312.3:c.889G>C	p.Asp297His	substitution	Pathogenic
PROC	NM_000312.3:c.41G>A	p.Trp14*	substitution	Pathogenic
PROS1	NM_000313.3:c.1155+5G>A	Intronic	substitution	Pathogenic
PROS1	NM_000313.3:c.1064G>A	p.Arg355His	substitution	Likely Pathogenic
PROS1	NM_000313.3:c.200A>C	p.Glu67Ala	substitution	Likely Pathogenic
PROS1	NM_000313.3:c.586A>G	p.Lys196Glu	substitution	Pathogenic
PROS1	NM_000313.3:c.601+1G>A	Splice site	substitution	Likely Pathogenic
RAD51C	NM_058216.2:c.572-?_*120+?del	Deletion (Exons 4-9)	cnv	Pathogenic
RAD51C	NM_058216.2:c.838-?_*120+?del	Deletion (Exons 6-9)	cnv	Pathogenic
RAD51C	NM_058216.2:c.732del	p.Ile244Metfs	indel	Pathogenic
RAD51C	NM_058216.2:c.181_182del	p.Leu61Alafs	indel	Pathogenic
RAD51C	NM_058216.2:c.50del	p.Phe17Serfs	indel	Pathogenic
RAD51C	NM_058216.2:c.93del	p.Phe32Serfs	indel	Pathogenic
RAD51C	NM_058216.2:c.904+5G>T	Intronic	substitution	Likely Pathogenic
RAD51C	NM_058216.2:c.397C>T	p.Gln133*	substitution	Pathogenic
RAD51C	NM_058216.2:c.905-2A>C	Splice site	substitution	Pathogenic
RAD51D	NM_002878.3:c.-256-?_738+?del	Deletion (Exons 1-8)	cnv	Pathogenic
RAD51D	NM_002878.3:c.896_*505del	Partial deletion (Exons 9-10)	cnv	Likely Pathogenic
RAD51D	NM_002878.3:c.363del	p.Ala122Glnfs	indel	Pathogenic
RAD51D	NM_002878.3:c.270_271dup	p.Lys91Ilefs	indel	Pathogenic
RAD51D	NM_002878.3:c.620C>T	p.Ser207Leu	substitution	Pathogenic
RAD51D	NM_002878.3:c.803G>A	p.Trp268*	substitution	Pathogenic
RAD51D	NM_002878.3:c.83-1G>A	Splice site	substitution	Likely Pathogenic
RAD51D	NM_002878.3:c.577-2A>G	Splice site	substitution	Likely Pathogenic
RB1	NM_000321.2:c.309_312del	p.Phe104Leufs	indel	Pathogenic
RB1	NM_000321.2:c.1981C>T	p.Arg661Trp	substitution	Pathogenic
RET	NM_020975.4:c.1826G>A	p.Cys609Tyr	substitution	Pathogenic
RET	NM_020975.4:c.2304G>C	p.Glu768Asp	substitution	Likely Pathogenic
RET	NM_020975.4:c.1998G>T	p.Lys666Asn	substitution	Pathogenic
RET	NM_020975.4:c.2410G>A	p.Val804Met	substitution	Pathogenic
RYR1	NM_000540.2:c.5077_5078delinsG	p.Leu1693Glyfs	indel	Pathogenic
RYR1	NM_000540.2:c.9554dup	p.Leu3186Alafs	indel	Pathogenic
RYR1	NM_000540.2:c.10960del	p.Leu3654Trpfs	indel	Pathogenic

RYR1	NM_000540.2:c.13335del	p.Phe4446Serfs	indel	Pathogenic
RYR1	NM_000540.2:c.8843del	p.Ser2948Cysfs	indel	Pathogenic
RYR1	NM_000540.2:c.4225C>T	p.Arg1409*	substitution	Pathogenic
RYR1	NM_000540.2:c.6721C>T	p.Arg2241*	substitution	Pathogenic
RYR1	NM_000540.2:c.11314C>T	p.Arg3772Trp	substitution	Pathogenic
RYR1	NM_000540.2:c.11708G>A	p.Arg3903Gln	substitution	Pathogenic
RYR1	NM_000540.2:c.1589G>A	p.Arg530His	substitution	Pathogenic
RYR1	NM_000540.2:c.1597C>T	p.Arg533Cys	substitution	Pathogenic
RYR1	NM_000540.2:c.10204T>G	p.Cys3402Gly	substitution	Pathogenic
RYR1	NM_000540.2:c.7300G>A	p.Gly2434Arg	substitution	Pathogenic
RYR1	NM_000540.2:c.14344G>A	p.Gly4782Arg	substitution	Pathogenic
RYR1	NM_000540.2:c.14645C>T	p.Thr4882Met	substitution	Pathogenic
RYR1	NM_000540.2:c.3381+1G>A	Splice site	substitution	Pathogenic
RYR1	NM_000540.2:c.8311-1G>C	Splice site	substitution	Likely Pathogenic
SCN5A	NM_198056.2:c.845G>A	p.Arg282His	substitution	Pathogenic
SCN5A	NM_198056.2:c.5302A>G	p.Ile1768Val	substitution	Pathogenic
SDHA	NM_004168.3:c.253_256dup	p.Asn86Ilefs	indel	Pathogenic
SDHA	NM_004168.3:c.667del	p.Asp223Ilefs	indel	Pathogenic
SDHA	NM_004168.3:c.688del	p.Glu230Serfs	indel	Pathogenic
SDHA	NM_004168.3:c.378del	p.Val127*	indel	Pathogenic
SDHA	NM_004168.3:c.91C>T	p.Arg31*	substitution	Pathogenic
SDHA	NM_004168.3:c.223C>T	p.Arg75*	substitution	Pathogenic
SDHA	NM_004168.3:c.1064+2T>A	Splice site	substitution	Likely Pathogenic
SDHA	NM_004168.3:c.621+1G>A	Splice site	substitution	Likely Pathogenic
SDHA	NM_004168.3:c.150+1G>A	Splice site	substitution	Likely Pathogenic
SDHAF2	NM_017841.2:c.199del	p.Arg67Glufs	indel	Pathogenic
SDHB	Deletion	Entire coding sequence	cnv	Pathogenic
SDHB	NM_003000.2:c.311delinsGG	p.Asn104Argfs	indel	Pathogenic
SDHB	NM_003000.2:c.640C>T	p.Gln214*	substitution	Pathogenic
SDHB	NM_003000.2:c.380T>G	p.Ile127Ser	substitution	Pathogenic
SDHB	NM_003000.2:c.600G>T	p.Trp200Cys	substitution	Pathogenic
SDHB	NM_003000.2:c.72+1G>T	Splice site	substitution	Pathogenic
SDHC	NM_003001.3:c.397C>T	p.Arg133*	substitution	Pathogenic
SDHC	NM_003001.3:c.148C>T	p.Arg50Cys	substitution	Likely Pathogenic
SDHD	NM_003002.3:c.242C>T	p.Pro81Leu	substitution	Pathogenic
SERPINA1	NM_000295.4:c.1108_1115delinsAAAAACA	p.Glu370Lysfs	indel	Pathogenic
SERPINA1	NM_000295.4:c.227_229delTCT	p.Phe76del	indel	Pathogenic
SERPINA1	NM_000295.4:c.187C>T	p.Arg63Cys	substitution	Likely Pathogenic
SERPINA1	NM_000295.4:c.839A>T	p.Asp280Val	substitution	Pathogenic
SERPINA1	NM_000295.4:c.863A>T	p.Glu288Val	substitution	Pathogenic (low penetrance)
SERPINA1	NM_000295.4:c.1096G>A	p.Glu366Lys	substitution	Pathogenic
SERPINA1	NM_000295.4:c.194T>C	p.Leu65Pro	substitution	Likely Pathogenic
SERPINA1	NM_000295.4:c.1177C>T	p.Pro393Ser	substitution	Pathogenic
SERPINC1	NM_000488.3:c.236G>A	p.Arg79His	substitution	Likely Pathogenic
SERPINC1	NM_000488.3:c.391C>T	p.Leu131Phe	substitution	Pathogenic
SERPINC1	NM_000488.3:c.218C>T	p.Pro73Leu	substitution	Pathogenic
SGCD	NM_000337.5:c.-43-?_192+?del	Deletion (Exons 2-3)	cnv	Pathogenic
SLC40A1	NM_014585.5:c.626C>T	p.Ser209Leu	substitution	Pathogenic
SMARCB1	NM_003073.3:c.629-?_795+?dup	Gain (Exon 6)	cnv	Pathogenic
TCAP	NM_003673.3:c.26_33dup	p.Glu12Argfs	indel	Pathogenic
TFR2	NM_003227.3:c.-41-?_473+?del	Deletion (Exons 1-3)	cnv	Pathogenic
TFR2	NM_003227.3:c.2014C>T	p.Gln672*	substitution	Pathogenic
TGFBR1	NM_004612.2:c.469C>T	p.Arg157*	substitution	Pathogenic
TNNI3	NM_000363.4:c.497C>T	p.Ser166Phe	substitution	Likely Pathogenic
TP53	NM_000546.5:c.810dup	p.Glu271*	indel	Pathogenic
TP53	NM_000546.5:c.524G>A	p.Arg175His	substitution	Pathogenic
TP53	NM_000546.5:c.542G>A	p.Arg181His	substitution	Pathogenic
TP53	NM_000546.5:c.530C>T	p.Pro177Leu	substitution	Likely Pathogenic
TP53	NM_000546.5:c.655C>T	p.Pro219Ser	substitution	Likely Pathogenic
TP53	NM_000546.5:c.380C>T	p.Ser127Phe	substitution	Likely Pathogenic
TP53	NM_000546.5:c.374C>T	p.Thr125Met	substitution	Pathogenic

TSC1	NM_000368.4:c.10C>T	p.Gln4*	substitution	Pathogenic
TSC1	NM_000368.4:c.1439-1G>A	Splice site	substitution	Likely Pathogenic
VHL	NM_000551.3:c.179_192del	p.Arg60Leufs	indel	Pathogenic
VHL	NM_000551.3:c.598C>T	p.Arg200Trp	substitution	Pathogenic
VHL	NM_000551.3:c.467A>G	p.Tyr156Cys	substitution	Likely Pathogenic