Supplementary Table 1: Actionable (likely) pathogenic variants identified in 1,640 healthy individuals in the 59 ACMG genes

Phenotype	MIM disorder	Typical age of onset	Gene	Inheritance	RefSeq ID	Pathogenic variants identified [a.]			ACMG-AMP classification [e.]	
						cDNA position	Protein change	Nr of alleles identified	Conclusion	Categories
Hereditary breast and ovarian cancer	604370	Adult	*BRCA1*	AD	NM_007300.3	c.5566C>T	p.Arg1856*	3	Pathogenic	PVS1 PS4 PP1
						c.5329dup	p.Gln1777fs	1	Pathogenic	PVS1 PS4 PP1
						c.2685_2686del [b.]	p.Pro897fs	1	Pathogenic	PVS1 PS4 PP1
	612555		*BRCA2*	AD	NM_000059.3	c.5576_5579del	p.Ile1859fs	1	Pathogenic	PVS1 PS4 PP1
						c.7878G>C	p.Trp2626Cys	1	Pathogenic	PS3 PS4 PM1 PM5 PP1 PP3
						c.9672dup [b.]	p.Tyr3225fs	1	Pathogenic	PVS1 PS4 PP1
Li-Fraumeni syndrome	151623	Child/Adult	*TP53*	AD	NM_001126112.2					
Peutz-Jeghers syndrome	175200	Child/Adult	*STK11*	AD	NM_000455.4					
Lynch syndrome	120435	Adult	*MLH1*	AD	NM_001258271.1					
			MSH2	AD	NM_000251.2					
			MSH6	AD	NM_001281493.1	c.1444C>T	p.Arg482*	2	Likely pathogenic	PVS1 PM2
			PMS2	AD	NM_000535.6					
Familial adenomatous polyposis coli	175100	Child/ Adult	*APC*	AD	NM_001127511.2					
MYH-associated polyposis	608456	Adult	*MUTYH*	AR	NM_001128425.1	c.1227_1228dup	p.Glu410fs	1	Likely pathogenic	PVS1 PM2
Adenomas, multiple colorectal, *FAP* type 2	132600					c.1214C>T [b.]	p.Pro405Leu	2	Likely pathogenic	PS3 PM1 PM2 PP1
Colorectal adenomatous polyposis with pilomatricomas						c.1187G>A [c.]	p.Gly396Asp	13	Pathogenic	PS3 PS4 PM1 PP1 PP3
						c.1147del	p.Ala385fs	3	Pathogenic	PVS1 PS3 PS4 PP1
						c.1105G>T [b.]	p.Glu369* [d.]	1	Likely pathogenic	PVS1 PM2
						c.884C>T	p.Pro295Leu	1	Likely pathogenic	PS3 PM1 PM2 PP3
						c.545G>A	p.Arg182His	1	Likely pathogenic	PS3 PM2 PM5
						c.536A>G [c.]	p.Tyr179Cys	8	Pathogenic	PS3 PS4 PP1
						c.325C>T	p.Arg109Trp	1	Likely pathogenic	PS3 PM2 PP3
Juvenile polyposis	174900	Child/Adult	*BMPR1A*	AD	NM_004329.2					
			SMAD4	AD	NM_005359.5					
Von Hippel-Lindau syndrome	193300	Child/Adult	*VHL*	AD	NM_198156.2					
Multiple endocrine neoplasia, type 1	131100	Child/Adult	*MEN1*	AD	NM_130801.2					
Multiple endocrine neoplasia, type 2	171400	Child/Adult	*RET*	AD	NM_020975.4					
	162300									
Familial medullary thyroid cancer	1552401	Child/Adult	*RET*	AD	NM_020975.4					
PTEN hamartoma tumor syndrome	153480	Child/Adult	*PTEN*	AD	NM_000314.6					
Retinoblastoma	180200	Child	*RB1*	AD	NM_000321.2					
Hereditary paraganglioma-pheochromocytoma syndrome	168000	Child/Adult	*SDHD*	AD	NM_003002.3					
	601650		*SDHAF2*	AD	NM_017841.2					
	605373		*SDHC*	AD	NM_003001.3					
	115310		*SDHB*	AD	NM_003000.2					
Tuberous sclerosis complex	191100	Child	*TSC1*	AD	NM_000368.4					
	613254		*TSC2*	AD	NM_000548.4	c.2903dup	p.Ser969fs [d.]	1	Likely pathogenic	PVS1 PM2
WT1-related Wilms tumor	194070	Child	*WT1*	AD	NM_001198551.1					
Neurofibromatosis, type 2	101000	Child/Adult	*NF2*	AD	NM_000268.3					
Ehlers-Danlos syndrome, type 4	130050	Child/Adult	*COL3A1*	AD	NM_000090.3	c.1815+2T>C	r.spl? [d.]	1	Likely pathogenic	PVS1 PM2
Marfan's syndrome	154700	Child/Adult	*FBN1*	AD	NM_000138.4					
Loeys-Dietz syndromes	609192		*TGFBR1*	AD	NM_001130916.2					
and familial thoracic aortic aneurysms and dissections	608967		*TGFBR2*	AD	NM_003242.5					
	610168		*SMAD3*	AD	NM_001145103.1					
	610380		*ACTA2*	AD	NM_001613.2					
	613795		*MYH11*	AD	NM_001040114.1					
	611788									
Hypertrophic cardiomyopathy,	115197	Child/Adult	*MYBPC3*	AD	NM_000256.3	c.1831G>A	p.Glu611Lys	3	Likely pathogenic	PM1 PM2 PP2 PP3 PP5
dilated cardiomyopathy						c.1468G>A	p.Gly490Arg	3	Likely pathogenic	PM1 PM2 PP2 PP3 PP5
						c.442G>A	p.Gly148Arg	1	Likely pathogenic	PM1 PM2 PP2 PP5
	192600		*MYH7*	AD	NM_000257.3	c.2644C>T	p.Gln882* [d.]	1	Likely pathogenic	PVS1 PM2
						c.2389G>A	p.Ala797Thr	1	Pathogenic	PS3 PS4 PM5 PP1 PP2

Supplementary Table 1 continued

Phenotype	MIM disorder	Typical age of onset	Gene	Inheritance	RefSeq ID	Pathogenic variants identified [a.]			ACMG-AMP classification [e.]					
						cDNA position	Protein change	Nr of alleles identified	Conclusion	Categories				
Hypertrophic cardiomyopathy,	601494	Child/Adult	*TNNT2*	AD	NM_001276346.1									
dilated cardiomyopathy	613690		*TNNI3*	AD	NM_000363.4	c.354del	p.Thr119fs [d.]	1	Likely pathogenic	PVS1	PM2			
	115196		*TPM1*	AD	NM_001018008.1									
	608751		*MYL3*	AD	NM_000258.2									
	612098		*ACTC1*	AD	NM_005159.4									
	600858		*PRKAG2*	AD	NM_016203.3									
	301500		*GLA*	XLD	NM_000169.2	c.427G>A	p.Ala143Thr	2	Likely Pathogenic	PS3	PM2	PM5	PP5	
	608758		*MYL2*	AD	NM_000432.3	c.403-1G>C	r.spl?	1	Pathogenic	PVS1	PS3	PM2		
	115200		*LMNA*	AD	NM_170707.3									
Catecholaminergic polymorphic ventricular tachycardia	604772	Child/Adult	*RYR2*	AD	NM_001035.2									
Arrhythmogenic right ventricular cardiomyopathy	609040	Child/Adult	*PKP2*	AD	NM_004572.3									
	607450		*DSP*	AD	NM_001008844.2	c.85G>T	p.Glu29* [d.]	1	Likely pathogenic	PVS1	PM2			
						c.4518del	p.Arg1506fs [d.]	1	Likely pathogenic	PVS1	PM2			
						c.6336del	p.Asn2114fs [d.]	1	Likely pathogenic	PVS1	PM2			
	610476		*DSC2*	AD	NM_024422.4									
	604400		*TMEM43*	AD	NM_024334.2									
	610193		*DSG2*	AD	NM_001943.4									
Romano-Ward long QT syndromes 1, 2 and 3	192500	Child/Adult	*KCNQ1*	AD	NM_000218.2	c.961C>T	p.Gln321* [d.]	1	Likely pathogenic	PVS1	PM2			
Brudaga syndrome						c.1066C>T	p.Gln356*	1	Likely pathogenic	PVS1	PM2			
						c.1124_1127del	p.Ile375fs	1	Likely pathogenic	PVS1	PM2			
	613688		*KCNH2*	AD	NM_000238.3	c.2254C>T	p.Arg752Trp	1	Likely pathogenic	PS3	PM1	PM2	PP2	
	601144		*SCN5A*	AD	NM_198056.2	c.4999G>A	p.Val1667Ile	1	Likely pathogenic	PM1	PM2	PP1	PP2	PP3
	603830					c.4978A>G	p.Ile1660Val	1	Pathogenic	PS3	PM1	PM2	PP1	PP2
						c.3956G>T	p.Gly1319Val	1	Pathogenic	PS3	PM1	PM2	PP1	PP2
						c.3911C>T	p.Thr1304Met	1	Pathogenic	PS3	PM1	PM2	PP1	PP2
						c.80G>A	p.Arg27His	1	Pathogenic	PS3	PM1	PM2	PP1	PP2
Familial hypercholesterolemia	143890	Child/ Adult	*LDLR*	AD	NM_000527.4									
			APOB	AD	NM_000384.2	c.10580G>A [c.]	p.Arg3527Gln	3	Pathogenic	PS3	PS4	PM5	PP1	PP2
						c.10579C>T	p.Arg3527Trp	1	Likely pathogenic	PS3	PM2	PM5	PP2	
	603776		*PCSK9*	AD	NM_174936.3									
Wilson disease	277900	Child	*ATP7B*	AR	NM_000053.2	c.3955C>T	p.Arg1319*	1	Likely pathogenic	PVS1	PM2			
						c.3008C>T	p.Ala1003Val	1	Likely pathogenic	PM1	PM2	PM3		
						c.2304dup	p.Met769fs	1	Likely pathogenic	PVS1	PM2			
						c.1708-1G>C	r.spl?	1	Likely pathogenic	PVS1	PM2			
						c.19_20del	p.Gln7fs	1	Likely pathogenic	PVS1	PM2			
Malignant hyperthermia susceptibility	145600	Child/ Adult	*CACNA1S*	AD	NM_000069.2									
			RYR1	AD	NM_000540.2	c.1589G>A	p.Arg530His	2	Likely pathogenic	PS3	PM1	PM2	PP2	
						c.14545G>A	p.Val4849Ile	1	Likely pathogenic	PS3	PM1	PM2	PP1	PP2
Ornithine carbamoyltransferase deficiency	311250		*OTC*	XLR	NM_000531.5									

[a.] Mutation nomenclature is provided according to HGVS recommendations (Den Dunnen et al. *Hum Mutat.* 2016, 37: 564-569).

[b.] Dutch founder mutation.

[c.] European founder mutation.

[d.] Variant was not previously described in literature. It is however a loss-of-function variant in a gene exerting its pathogenic effect by haploinsufficiency.

[e.] Variant pathogenicity is evaluated according to ACMG-AMP guidelines (Richards et al. *Genet Med.* 2015, 17:405-424).