

Supplemental Tables

Supp. Table S1 | ACMG Recommended Genes for Reporting of Incidental Findings in Exome and Genome Sequencing.

Disease Phenotype	Gene	Variants to report
Hereditary breast and ovarian cancer	<i>BRCA1</i>	KP and LP LOF
	<i>BRCA2</i>	
Li-Fraumeni syndrome	<i>TP53</i>	KP and LP LOF
Peutz-Jeghers syndrome	<i>STK11</i>	KP and LP LOF
Lynch syndrome	<i>MLH1</i>	KP and LP LOF
	<i>MSH2</i>	
	<i>MSH6</i>	
	<i>PMS2</i>	
Familial adenomatous polyposis	<i>APC</i>	KP and LP LOF
MYH-associated polyposis; adenomas, multiple colorectal, FAP type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	<i>MUTYH</i>	KP and LP LOF
Juvenile polyposis	<i>BMPR1A</i>	KP and LP LOF
	<i>SMAD4</i>	
Von Hippel–Lindau syndrome	<i>VHL</i>	KP and LP LOF
Multiple endocrine neoplasia type 1	<i>MEN1</i>	KP and LP LOF
Multiple endocrine neoplasia type 2	<i>RET</i>	KP
Familial medullary thyroid cancer	<i>RET</i>	KP
PTEN hamartoma tumor syndrome	<i>PTEN</i>	KP and LP LOF
Retinoblastoma	<i>RB1</i>	KP and LP LOF
Hereditary paraganglioma pheochromocytoma syndrome	<i>SDHD</i>	KP and LP LOF
	<i>SDHAF2</i>	KP
	<i>SDHC</i>	KP and LP LOF
	<i>SDHB</i>	
Tuberous sclerosis complex	<i>TSC1</i>	KP and LP LOF
	<i>TSC2</i>	
WT1-related Wilms tumor	<i>WT1</i>	KP and LP LOF
Neurofibromatosis type 2	<i>NF2</i>	KP and LP LOF
Ehlers-Danlos syndrome, vascular type	<i>COL3A1</i>	KP and LP LOF
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	<i>FBN1</i>	KP and LP LOF
	<i>TGFBR1</i>	

	<i>TGFB2</i>	
	<i>SMAD3</i>	
	<i>ACTA2</i>	
	<i>MYH11</i>	
Hypertrophic cardiomyopathy, dilated cardiomyopathy	<i>MYBPC3</i>	KP and LP LOF
	<i>MYH7</i>	KP
	<i>TNNT2</i>	KP and LP LOF
	<i>TNNI3</i>	KP
	<i>TPM1</i>	
	<i>MYL3</i>	
	<i>ACTC1</i>	
	<i>PRKAG2</i>	
	<i>GLA</i>	KP and LP LOF
	<i>MYL2</i>	KP
	<i>LMNA</i>	KP and LP LOF
Catecholaminergic polymorphic ventricular tachycardia	<i>RYR2</i>	KP
Arrhythmogenic right ventricular cardiomyopathy	<i>PKP2</i>	KP and LP LOF
	<i>DSP</i>	
	<i>DSC2</i>	
	<i>TMEM43</i>	KP
	<i>DSG2</i>	KP and LP LOF
Long QT and Brugada Syndrome	<i>KCNQ1</i>	KP and LP LOF
	<i>KCNH2</i>	
	<i>SCN5A</i>	
Familial hypercholesterolemia	<i>LDLR</i>	KP and LP LOF
	<i>APOB</i>	KP
	<i>PCSK9</i>	
Wilson disease	<i>ATP7B</i>	KP and LP LOF
Ornithine transcarbamylase deficiency	<i>OTC</i>	KP and LP LOF
Malignant hyperthermia susceptibility	<i>RYR1</i>	KP
	<i>CACNA1S</i>	

Abbreviations: KP, known pathogenic variants that were previously reported to cause the disease; LP LOF, likely pathogenic loss of function variants, that are previously not reported, and the loss of function is a known disease-causing mechanism in the gene.

Supp. Table S2 | Phenotypic data for Qatar genome program participants, available in Qatar biobank.

Disease category	Phenotypic information extracted from QBB
Cardiovascular diseases	ECG records measured by the Atria 6100 automated system (ECG; Mortara Eli 350 automated system, Skaneateles Falls, NY, USA) (Goloba, Nelson, & MacFarlane, 2010).
	The ECG test was repeated three times for each participant and the report was written by trained technician.
	The result of the ECG was obtained as; Normal ECG, Borderline ECG (with borderline ECG statement), or Abnormal ECG (with abnormal ECG statement).
	Participants self-reported information from the nurse questionnaire include medical history of; Heart revascularization, heart attack, or Angina.
	Participants self-reported information from the main questionnaire include: <ul style="list-style-type: none"> • Have any of your brothers or sisters been diagnosed with heart attack?
Cancer	Participants self-reported information of parent history of heart diseases from the main questionnaire include: <ul style="list-style-type: none"> • Father and /or Mother history of heart disease.
	Participant self-reported information about having any type of cancer (cancer type) from the nurse questionnaire.
	Participant self-reported information about having any type of surgical procedures (surgery type) from the nurse questionnaire.
	Father and/ or Mother history of cancer (cancer type) from the nurse questionnaire.
Familial Hypercholesterolemia	Father and/ or Mother cause of death was cancer (cancer type) from the nurse questionnaire.
	Lipid profile including total cholesterol, and LDL.
	Participants self-reported information from the main questionnaire include:

	<ul style="list-style-type: none">• Has a doctor ever told you that you have or had high cholesterol?• Are you being treated for high cholesterol? (if “Yes” specify; Diet only, Tablets only, or diet and tablets).
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Abbreviations: QBB, Qatar Biobank; ECG, electrocardiogram; LDL, low-density lipoprotein.

Supp. Table S3 | ACMG classification criteria of novel loss of function variants.

						ACMG pathogenicity evidence		
Gene	CHR	Locus	Transcript	cDNA name	Protein name	PVS1	PM2	ACMG classification
BRCA1	17	412314 18	ENST000004711 81	c.4358- 2A>T	NA	Null variants in this gene are known cause of Breast-ovarian cancer, familial 1	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
BRCA1	17	412434 51	ENST000004711 81	c.4096+1 G>C	NA	Null variants in this gene are known cause of Breast-ovarian cancer, familial 1	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
BRCA1	17	412461 82	ENST000004711 81	c.1365du pT	p.Ile45 6Tyrfs* 2	Null variants in this gene are known cause of Breast-ovarian cancer, familial 1	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
BRCA2	13	328905 58	ENST000003801 52	c.-39- 1G>C	NA	Null variants in this gene are known cause of Breast-ovarian cancer, familial 2	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic

BRCA2	13	32911202	ENST00000380152	c.2711_2714dupG AAA	p.Asn905Lysfs*4	Null variants in this gene are known cause of Breast-ovarian cancer, familial 2	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
COL3A1	2	189858982	ENST00000404636	c.1218del IT	p.Pro407Leufs*3	Null variants in this gene are known cause of Ehlers-Danlos syndrome, type 4	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
DSC2	18	28669534	ENST00000280904	c.497del A	p.Asn166Thrfs*8	Null variants in this gene are known cause of Arrhythmogenic right ventricular cardiomyopathy, type 11	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
KCNQ1	11	2482945	ENST00000335475	c.5+1G>A	NA	Null variants in this gene are known cause of Long QT syndrome 1	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
LDLR	19	11201365	ENST00000252444	c.67+1074C>A	NA	Null variants in this gene are known cause of Familial hypercholesterolemia	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
MUTYH	1	45799181	ENST00000450313	c.252C>A	p.Tyr84*	Null variants in this gene are known cause of MYH-associated	Absent from the annotated databases despite a good coverage of >30 reads at this	Likely pathogenic

						polyposis, and Pilomatrixoma	position and had MAF ≤ 0.001 in QGP data.	
PKP2	12	330308 78	ENST000000708 46	c.925_93 5delGCC GTGGAT TC	p.Ala30 9Glnfs* 23	Null variants in this gene are known cause of Arrhythmogenic right ventricular cardiomyopathy, type 9	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
TNNT2	1	201331 147	ENST000004584 32	c.610G>T	p.Glu2 04*	Null variants in this gene are known cause of Left ventricular noncompaction 6	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
TNNT2	1	201335 964	ENST000004584 32	c.239+2T >C	NA	Null variants in this gene are known cause of Left ventricular noncompaction 6	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
WT1	11	324380 88	ENST000003323 51	c.951- 2A>G	NA	Null variant in this gene cause Wilms' tumor	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic
WT1	11	324520 75	ENST000003790 79	c.10+1G> A	NA	Null variant in this gene cause Wilms' tumor	Absent from the annotated databases despite a good coverage of >30 reads at this position and had MAF ≤ 0.001 in QGP data.	Likely pathogenic

Determination of very strong criteria (PVS1): We determine these variants as stop gained, start lost, stop lost, splice donor, splice acceptor, and frameshift for prediction of Loss of Function (LOF). We checked whether LOF is the main cause of disease for that gene manually. Determination of moderate criteria (PM2): All variants were not reported in Population datasets like dbSNP, ClinVar, Human Genome Mutation Database, 1000 Genome Project, gnomAD Exome and WGS, and the Greater Middle East data. Additionally, the selected variants should have minor allele frequency less than or equal to 0.001 in the Qatar Genome Program data to be selected. Abbreviations: CHR, chromosome; NA, not applicable; MAF, minor allele frequency; QGP, Qatar Genome Program.

Supp. Table S4| Distribution of ACMG disease-causing, pathogenic and likely pathogenic variants in the Human Gene Mutation and ClinVar using 6045 whole-genome sequencing from Qatar genome program.

Gene	HGMD DM	ClinVar P/LP
<i>APC</i>	5	0
<i>APOB</i>	8	1
<i>FBN1</i>	4	1
<i>KCNH2</i>	10	1
<i>LMNA</i>	7	1
<i>COL3A1</i>	1	0
<i>DSC2</i>	3	0
<i>DSG2</i>	5	0
<i>DSP</i>	4	0
<i>MLH1</i>	5	1
<i>PKP2</i>	7	1
<i>PMS2</i>	2	1
<i>RET</i>	12	1
<i>SCN5A</i>	37	2
<i>SDHB</i>	3	1

<i>MSH2</i>	5	0
<i>MSH6</i>	5	0
<i>TNNI3</i>	3	1
<i>VHL</i>	5	1
<i>MYH11</i>	3	0
<i>BRCA1</i>	6	2
<i>PCSK9</i>	6	0
<i>BRCA2</i>	10	2
<i>KCNQ1</i>	14	2
<i>PTEN</i>	1	0
<i>RB1</i>	4	0
<i>MYBPC3</i>	18	3
<i>MYH7</i>	6	2
<i>RYR2</i>	4	1
<i>MUTYH</i>	10	4
<i>RYR1</i>	20	4
<i>SMAD4</i>	1	0
<i>STK11</i>	2	0
<i>TGFBR1</i>	1	0

<i>ATP7B</i>	26	6
<i>TNNT2</i>	4	0
<i>TP53</i>	3	0
<i>TPM1</i>	1	0
<i>TSC2</i>	4	0
<i>LDLR</i>	22	9
<i>WT1</i>	1	0
Total	298	48

Abbreviations: HGMD, Human Gene Mutation Database; DM, Disease-causing variants; P/LP, pathogenic and/or likely pathogenic variants.

Supp. Table S5 | Supported phenotypic data for pathogenic and Likely pathogenic cancer variants

Gene	HGVS_C	HGVS_P	Zygosity	How many brothers and sisters you have?	Gender /Age	Medical history of personal cancer	History of personal surgical procedure	Parents history of cancer (cancer type)
BRCA1	c.4850C>A	p.Ser1617*	Heterozygous	B:3, S:3	M/39	No	No	Mother (breast cancer)
			Heterozygous	B:2, S:1	M/59	No	Appendix	Mother (endometrium cancer)
			Heterozygous	B:3, S:3	F/19	No	No	No
			Heterozygous	B:7, S:3	M/57	No	Hemorrhoids	Father (bowel cancer)
	c.4065_4068delTCAA	p.Asn1355fs	Heterozygous	B:4, S:6	F/49	No	Tonsil's adenoids	Mother (endometrium cancer)
	c.4358-2A>T	NA	Heterozygous	B:4, S:3	M/43	No	No	No
			Heterozygous	B:4, S:5	M/41	No	No	No
			Heterozygous	B:5, S:4	F/35	No	No	No
	c.4096+1G>C	NA	Heterozygous	B:6, S:0	F/32	No	No	Father (stomach cancer)
			Heterozygous	B:5, S:5	M/36	No	No	No
			Heterozygous	B:6, S:4	F/43	No	No	No
	c.1365dupT	p.Ile456Tyrfs*2	Heterozygous	B:0, S:6	M/22	No	Fracture or dislocation	No

			Heterozygous	B:9, S:5	M/60	No	Kidney stones and fracture or dislocation	No
			Heterozygous	B:1, S:5	F/28	No	No	No
			Heterozygous	B:1, S:5	F/19	No	No	No
BRCA2	c.4211_4215delCAAAT	p.Ser1404*	Heterozygous	B:2, S:5	M/30	No	No	No
			Heterozygous	B:3, S:4	F/40	No	No	No
			Heterozygous	B:9, S:6	M/36	No	No	No
			Heterozygous	B:3, S:1	M/66	No	No	No
	c.9382C>T	p.Arg3128*	Heterozygous	B:3, S:8	M/33	No	No	No
	c.-39-1G>C	NA	Heterozygous	B:1, S:5	F/39	No	No	No
			Heterozygous	B:2, S:5	F/44	No	No	No
	c.2711_2714dupGAAA	p.Asn905Lysfs*4	Heterozygous	B:6, S:7	M/67	No	Gallbladder, hernia and male genital organs	Father (cancer type not specified)
			Heterozygous	B:3, S:2	M/30	No	Tonsil's adenoids and hemorrhoids	Mother (breast cancer)
MLH1	c.306G>T	p.Glu102Asp	Heterozygous	B:3, S:1	F/46	No	No	Mother (colon cancer)
PMS2	c.1376C>G	p.Ser459*	Heterozygous	B:6, S:4	M/38	No	No	No
			Heterozygous	B:5, S:5	M/44	No	No	Father (lung cancer)
			Heterozygous	B:8, S:7	F/34	No	No	Father (lung cancer)
RET	c.2410G>A	NA	Heterozygous	B:2, S:3	F/32	No	Breast tissue	No
SDHB	c.143A>T	p.Asp48Val	Heterozygous	B:3, S:3	F/29	No	Breast tissue	No
VHL	c.548C>G	p.Ser183Trp	Heterozygous	B:4, S:3	F/27	No	No	No

			Heterozygous	B:4, S:4	F/62	No	Tonsil's adenoids and gallbladder	Mother (breast cancer)
WT1	c.951-2A>G	NA	Heterozygous	B:2, S:4	M/31	No	No	No
	c.10+1G>A	NA	Heterozygous	B:3, S:6	F/35	No	No	No
			Heterozygous	B:2, S:6	F/44	No	Other surgery (not specified).	No

Abbreviations: B, brothers; S, sisters; F, female; M, male; NA, not available/applicable.

Supp. Table S6 | Supported phenotypic data for pathogenic and Likely pathogenic cardiovascular variants.

Gene	HGVS_C	HGVS_P	Zygosity	Gender /Age	ECG clinical report	ECG statement reason	Medical history of heart attack or Angina	Sibling history of heart disease	Parents history of heart disease
KCNH2	c.23C>T	p.Ala8Val	Heterozygous	M/46	Abnormal	Sinus rhythm with prolonged PR interval, incomplete right bundle branch block.	Prefer not to answer	No	No
KCNQ1	c.569G>A	p.Arg190Gln	Heterozygous	F/43	Normal	NA	No	No	Mother
	c.914G>T	p.Trp305Leu	Heterozygous	F/25	Normal	NA	No	No	No
			Heterozygous	M/35	Borderline	Possible right ventricular conduction delay [RSR (QR) in V1/V2].	No	No	No
			Heterozygous	F/32	Borderline	Sinus rhythm with occasional ventricular premature complex.	No	No	No
			Heterozygous	F/38	Normal	NA	No	No	No
			Heterozygous	F/46	Normal	NA	No	No	Father
	c.5+1G>A	NA	Heterozygous	F/30	Normal	NA	No	No	No
			Heterozygous	F/29	Normal	NA	No	No	No
			Heterozygous	M/69	Abnormal	Sinus rhythm with occasional ventricular premature complex with occasional supraventricular premature complex, left anterior fascicular block, QRS axis ≤ -45 , QR in I, RS in II.	No	Sibling diagnosed with heart attack.	No

			Heterozygous	M/45	Borderline	Incomplete right bundle branch block, 90+ ms QRS duration, terminal R in V1/V2, 40+ ms S in I/aVL/V4/V5/V6, ST elevation probably early polarization.	No	No	No
			Heterozygous	F/59	Normal	NA	No	No	No
			Heterozygous	M/34	Normal	NA	No	No	No
			Heterozygous	F/34	Normal	NA	No	No	No
			Heterozygous	M/45	Normal	NA	No	No	Father
SCN5A	c.1127G>A	p.Arg376His	Heterozygous	F/29	Normal	NA	No	No	No
			Heterozygous	F/28	Normal	NA	No		No
			Heterozygous	F/48	Borderline	Nonspecific T wave abnormality	No	No	No
	c.2893C>T	p.Arg965Cys	Heterozygous	F/41	Abnormal	Moderate ST depression [0.05+ mV ST depression], sinus arrhythmia.	No	No	Father
			Heterozygous	M/46	Borderline	Early repolarization [ST elevation with normally inflected T wave].	No	No	Father
LMNA	c.1444C>T	p.Arg482Trp	Heterozygous	F/36	Borderline	Nonspecific ST and T wave abnormality	No	No	Father and mother
MYBPC3	c.2449C>T	p.Arg817Trp	Heterozygous	F/48	Borderline	Possible left atrial enlargement	No	No	Mother
	c.2311G>A	p.Val771Met	Heterozygous	F/48	Normal	NA	Prefer not to answer	No	No
	c.495G>C	p.Glu165Asp	Heterozygous	F/28	Borderline	Nonspecific T wave abnormality	No	No	Father and mother
			Heterozygous	F/27	Normal	NA	No	No	No
			Heterozygous	M/60	Normal	NA	No	No	No

			Heterozygous	F/33	Abnormal	Sinus rhythm with first degree AV block.	No	No	No
			Heterozygous	M/46	Borderline	Sinus rhythm with sinus arrhythmia, moderate voltage criteria for LVH, consider normal variant.	No	No	Father and mother
MYH7	c.4066G>A	p.Glu1356Lys	Heterozygous	F/51	Abnormal	Sinus bradycardia, inferior myocardial infarction, of indeterminate age [40+ ms Q wave and/or ST/T abnormality in II/aVF].	No	No	No
	c.2608C>T	p.Arg870Cys	Heterozygous	F/33	Normal	NA	No	No	No
TNNI3	c.422G>A	p.Arg141Gln	Heterozygous	F/32	Borderline	Sinus bradycardia with sinus arrhythmia	No	No	No
TNNT2	c.610G>T	p.Glu204*	Heterozygous	M/29	Borderline	Sinus rhythm with sinus arrhythmia, minimal ST depression, 0.025+ mV ST depression	No	No	No
	c.239+2T>C	NA	Heterozygous	F/44	Normal	NA	No	No	Father
PKP2	c.148_151delACAG	p.Thr50Serfs*61	Heterozygous	F/24	Normal	NA	No	No	Father
			Heterozygous	F/32	Normal	NA	No	No	No
			Heterozygous	M/40	Borderline	ST elevation with normally inflected T wave	No	No	No
			Heterozygous	F/39	Normal	NA	No	No	No
			Heterozygous	F/61	Abnormal	Right bundle branch block, 120+ ms QRS duration, upright V1, 40+ ms S in I/aVL/V4/V5/V6.	No	No	No
	c.925_935delGCC	p.Ala309Glnfs*23	Heterozygous	F/31	Abnormal	Sinus bradycardia with sinus arrhythmia, marked	No	No	Father

	GTGGAT TC					right axis deviation [QRS axis > 100].			
DSC2	c.497del A	p.Asn166fs	Heterozygous	M/39	Borderline	Sinus bradycardia.	No	No	Father
			Heterozygous	M/42	Borderline	Sinus bradycardia with sinus arrhythmia	No	No	Father

Abbreviations: M, male; F, female; ECG, electrocardiogram; ms, millisecond; AV, atrioventricular; LVH, left ventricular hypertrophy; NA, not available/applicable.

Supp. Table S7 | Supported phenotypic data for pathogenic and Likely pathogenic variants associated with familial hypercholesteremia.

Gene	HGVS_C	HGVS_P	Number of QGP participants	Zygosity	Total cholesterol (mmol/L)		LDL (mmol/L)		Number of participants with medical diagnosis of HC	Number of participants on treatments for HC
					Borderline high (5.17 - 7.4)	High (≥ 7.5)	Borderline high (3.36 - 4.8)	High (≥ 4.9)		
<i>APOB</i>	c.10700C>T	p.Thr35667Met	9	Heterozygous	0	0	0	0	3	3
<i>LDLR</i>	c.-135C>G	NA	1	Heterozygous	0	1	0	1	0	0
	c.269A>G	p.Asp90Gly	3	Heterozygous	1	1	0	1	3	3
	c.1691A>G	p.Asn564Ser	1	Heterozygous	0	1	0	1	1	1
	c.1774G>A	p.Gly592Arg	2	Heterozygous	1	0	1	0	1	1
	c.91G>A	Glu31Lys	1	Heterozygous	1	0	1	0	1	0
	c.1145G>T	p.Gly382Val	1	Heterozygous	0	0	0	0	1	1
	c.1154T>G	p.Leu385Arg	1	Heterozygous	0	0	0	0	1	1
	c.67+1074C>A	NA	2	Heterozygous	0	0	0	0	1	1

Abbreviations: QGP, Qatar genome program; LDL, Low-density lipoprotein; HC, Hypercholesterolemia.

References:

Goloba, M., Nelson, S., & MacFarlane, P. (2010). The electrocardiogram in pregnancy. In *Computing in Cardiology* (Vol. 37, pp. 693–696). <https://doi.org/10.1097/00000441-191308000-00057>