SUPPLEMENTAL MATERIAL

Table S1: Clinical Indications and Genetic Testing Results – Grouped by Disease Category

A) Connective Tissue Diseases

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
2	TAA/AAA (both)	65	M	*SMAD3* R243S	No	Yes (Nat Genet 2011;43(2):121-6	0	R243R in EXAC, personal history of TAA, AAA, tall, lanky, family history of TAA, AAA	Unknown Significance	PM2, PP3, PP4
27	TAA	62	M	*MYLK* R1232C	No	Yes (Am J Hum Genet 2010; 87(5):701-7	0	Actin-binding domain of gene, no curated	Unknown Significance	PM2, PP3 ,PP4,
29	TAA	45	M	*MYLK* R55W	No	Yes (Am J Hum Genet 2010; 87(5):701-8)	5.79E-5	Did not segregate in family; hot spot R55R, R55Q, R55L all in EXAC none have any ClinVar correlation	Unknown Significance	BS4
36	TAA	57	M							
47	TAA	46	F							
55	TAA	60	F							
58	TAA/family history TAA	63	M							
70	TAA	32	M							
74	TAA	52	M							
94	TAA; family history TAA	37	M							
139	TAA	61	M							
143	TAA	61	M							
148	TAA	54	M							
156	TAA	62	M							
159	TAA, Family history of TAAD	45	M							
173	TAA	54	M							
176	TAA	61	F	*MYH11 R1805W*	No	Yes (Nat Genet 2006; 38(3):343-9)	1.65E-05	Family history of valve replacement, brain aneurysm, family members unavailable for segregation	Unknown Significance	PP3, PP4
197	TAA	37	M	*SKI R489K*	No	For Sphrpintzen-Goldberg Craniosynostosis, Marfan Syndrome, or Loeys-Dietz (Nat Genet 2012;44(11):1249-54)	8.871E-06	Has aneurysm at Sinus of Valsalva, but no other features of other conditions.	Uncertain Significance	PP3, PP4
6	PVH; EDS	25	F	*FLNA* 4214delA; *COL5A1* D1771N; COL5A2 *G702R*	No; No; No	Yes (Neurology 2005;64(2):254-262;Yes(Am J Med Genet C Semin Med Genet 2005;139C(1):17-23); Yes(J Med Genet 1998;35:846-8)	0; 0; 1.663E-5	Family segregation done - Dad had *COL5A1*, but no phenotype, Mom has *COL5A2* with phenotype, *FLNA* de novo, sister has COL5A1/2 and phenotype, brother has COL5A2 and phenotype, maternal grandmother has COL5A2, history of aneursym; D1771G in EXAC 1 time; predicted benign	Pathogenic; Benign; Likely Pathogenic	PS2, PM2;BS2, BS4; PM2, PP1(family well-characterized), PP3
157	EDS	33	M	*ELN G3V*	No	No for Williams Syndrome (Cell 1993; 73:159-68), Cutis Laxa (Am J Med Genet 2008;146A:977-83), and Supravalvular Aortic Stenois (J Clin Invest 1994;93:1071-77.	0	G3G in EXAC	Unknown Significance	PM2, PP3

158	EDS	35	F							
160	EDS	62	F	*COL1A1 R763H*	No	Yes (Am J Hum Genet 2000;66:1398-1402)	4.954E-05	Sister has similar symptoms, but untested. G764 is a variant reported to cause osteogenesis imperfecta type 2. In triple helical region of gene	Unknown Significance	PP2, PP3, PP4
16	Marfan syndrome	26	F	*FBN1* IVS2+1G>A	Yes (http://www.umd.be/FBN1/4DACTION/W_DMDT1/1)	Yes (Proc Natl Acad Sci USA 1992;89(13):5917-22	0	Family has clinical phenotype: Brother, mother untested	Pathogenic	PVS1, PM2, PM3
20	Marfan syndrome	27	M							
31	Marfan syndrome	55	F	*FBN1* G77X	Yes(http://www.umd.be/FBN1/4DACTION/W_DMDT1/1)	Yes (Proc Natl Acad Sci USA 1992;89 (13):5917-21	0	Family has clinical phenotype, son was given Marfan clinical diagnosis as a child, but no genetic testing	Pathogenic	PVS1, PM2, PM4
34	Marfan syndrome	21	M	*TGFBR2* V387M	Yes (ClinVar, Hum Mutat 2006;27(8):760-9)	Yes(Hum Mutat 2006;27(8):760-9, Hum Mutat 2008; 29(11):E284-95)	0	Mild phenotype - tall lanky	Likely Benign	BS3, BP6
42	Marfan syndrome	64	F	*FBN2* D1485G	No	Yes (Nat Genet 1995; 11(4):456-8)	2.997E-4	D1485N also in EXAC, segregation in family; son has similar phenotype and same genotype	Unknown Significance	PP1, PP3
51	Marfan syndrome	53	F							
85	Marfan syndrome	57	F	*FBN1* R945C	No	Yes (Genomics 1993;17(2):468-75)	0	R954H in ClinVar as Pathogenic, son died of ruptured TAA, prompted testing	Likely Pathogenic	PM2, PM5, PP3, PP4
33	Noonan syndrome	24	M	*PTPN11* I309V; *MYH11* V87L	Yes (ClinVar);No	Yes(Am J Hum Genet 2002; 70(6):1555-63); Yes (Nat Genet 2006; 38(3):343-9	4.119E-4; 0	1 homozygous in EXAC for I309V; V87 in myosin motor domain of MYH11, Dad, sister has some features, but untested	Likely Benign; Unknown Significance	BS3, BP4, PB5, BP6; PM2
38	SCAD	60	F							
98	SCAD	28	M							
103	SCAD	63	M							
178	SCAD	43	F	*COL5A2 R1106W, FBN1 A2025S*	Yes (ClinVar); Yes (ClinVar)	For EDS (J Med Genet 1998;35:846-8); For SCAD (Heart 2016;102:878-881)	0.0004982; 0.0004622	Patient was post-partum with event and is hyperflexible, mother has similar symptoms (coronary stent w/o CAD and hyperflexible), patient also has had cerebral aneurysm <1 year post SCAD	Unknown Significance; Unknown Significance	PP3; PP3
186	SCAD	36	F							
188	SCAD	52	M	*FBN1 D2757N*	No	Yes (J Am Coll Cardiol 2016;67(23):2744-54, Heart 2016;102:878-881)	0	Patient also had splenic infarction, celiac artery aneurysm, renal artery aneurysm, has some flexibility, has family history of stroke and "heart attack". Variant in carboxyl terminal of gene	Uncertain Significance	PM2, PP3
190	SCAD	60	F							

B) Sudden Cardiac Death (SCD)

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
4	SCD (RCM)	54	F	*TNNI3* L198V	Yes(ClinVar)	Yes (Neth Heart J 2011; 19(7-8): 344-51)	0	Causes a change in splice site	Pathogenic	PM2, PM4, PP3, PP5
11	SCD	51	F							
12	SCD	66	F	*KCNH2* N33T	No	Yes (Circulation 2002; 105(7):794-9)	0	2 submissions in ClinVar - Gene DX pathogenic, NHS VUS, this mutation increased rate of deactivation several	Pathogenic	PS3, PM1, PM2, PP3, PP5

								papers; family segregation done unaffected do not have variant		
13	SCD	61	M	*DPP6* D801N	No	Yes (Am J Hum Genet 2009;84(4):468-76)	0	Segregation done on family, but since idiopathic VF, no phenotypic information	Unknown Significance	PM2, PP3
19	SCD (HCM)	58	M	*MYBPC3* IVS28+22T>G	No	Yes (Circulation 2003; 107(17):2227-32)	0	Family segregation done - children without phenotype and do not carry mutation	Pathogenic	PVS1, PM2, PP1, PP3
21	SCD (DCM)	47	F	*LMNA* S595R; *MYH6* R1636C	No; Yes (ClinVar)	Yes (Eur J Heart Fail 2013; 15(6):628-37;Yes (Circulation 2005;112(1):54-9)	0; 4.2E-4	EXAC also has R1636H	Unknown Significance; Likely Benign	PM2, PP3; BP4, BP6
26	SCD (Non-specific NICM)	47	F	*TTN* R18966X; *NEXN* E205K	No; Yes (ClinVar)	Yes (N Engl J Med 2012; 366(7): 619-28);Yes (Am J Hum Genet 2010; 87(5):687-93)	0; 1.9E-4	2 reports in ClinVar both unknown significance for NEXN variant, NEXN variant in Glu rich region.	Pathogenic; Unknown Significance	PVS1, PM2, PM4;PP3
30	SCD	21	M	*DSG2* V56M	Yes (ClinVar)	Yes for ARVC (Eur Heart J 2007; 28(5):581-8)	1.873E-3	Reported not likely pathogenic for ARVC (Nat Clin Cardiovasc Med 2008;5(12):E1)	Likely Benign	BS3, BP6,
32	SCD (HCM)	26	M							
44	SCD, TdP, LQTS	42	F	*SCN5A* L461V	Yes (ClinVar)	Yes (Heart Rhythm 2010;7(1):33-46)	0.01163	L461L in EXAC; Reported Polymorphism in Heart Rhythm 2010;7(1):33-46	Likely Benign	BS1, BP4, BP5
54	SCD (DCM)	47	F	*DSP* Q1672X	No	Yes for ARVC (Can J Cardiol 2014;30(12):1655-61), For DCM (Genet Med 2014; 16(8):601-8)	0		Pathogenic	PVS1, PM2, PM4
59	SCD (Non-Specific NICM)	24	F	*TTN* c.45689delG; *MYH6* R1270C	No; No	Yes (N Engl J Med 2012; 366(7):619-28, Sci Tranl Med 2015; 7(270):270ra6);Yes (Circulation 2005;112(1):54-9)	0; 5.766E-5	R1270H also in EXAC; segregation done on family - Dad carries *MYH6* only without disease; sister carries both mutations	Pathogenic; Benign	PVS1, PM2; BS2, BS4, BP5
63	SCD (Non-Specific NICM)	29	M							
65	SCD	47	F	*SCN5A* S216L; *DSG2* 12-2 A>G	Yes (ClinVar, Clin Transl Sci 2008;1(1):21-26); Yes(Circulation 2006;113:1171-1179)	Yes (Heart Rhythm 2010;7(1):33-46); Yes(Circulation 2006;113:1171-1179)	0.001;0	DSG2 mutation may not be sufficient to cause disease	Likely Pathogenic; Likely Benign	PS3, PP3, PP4; BS3, BP2
68	SCD	60	F							
75	SCD (DCM)	40	F	*TTN* c.29042-2A>C	Yes(Sci Tranl Med 2015; 7(270):270ra 6)	Yes (N Engl J Med 2012; 366(7):619-28, Sci Tranl Med 2015; 7(270):270ra6)	0	VF arrest, family unavailable for testing	Pathogenic	PVS1, PM2, PM4
77	SCD (LQTS)	78	M							
79	SCD (ARVC)	22	M	*SCN5A* V1951L; *PNN* I331(GAGdel)	Yes (ClinVar, Heart Rhythm 2004;1(5):60 0-7); No	Yes for BrS (Heart Rhythm 2010;7(1):33-46);	5.412E-3;0	V1951L has 6 homozygotes in EXAC, reported polymorphism, V1951M in EXAC and Pathogenic in ClinVar, most ClinVar reports for V1951L are benign likely benign;	Benign; Unknown Significance	BS2, BS3, BP4, BP6; PM2
83	SCD (LQTS)	60	F	*ANK2* V3634D; *AKAP9* R1285G; *GYG1* Y282S	Yes(ClinVar) ;No; No	Yes (Nature 2003;421:633-639, Proc Natl Acad Sci USA 2007;104(52):20990-5)	2.738E-4; 1.048e-5; 0	V3646I in EXAC, ClinVar reports V3634I as pathogenic;AKAP9 variant also known as R1246G; GYG1 Y282X in EXAC 8.238e-06, both heterozygous variants	Unknown Significance; Unknown Significance; Unknown Significance	PM5, PP3; BP4; PM2
84	SCD (DCM)	40	M	*TTN* W21280X	No	Yes (N Engl J Med 2012; 366(7):619-28)	0	Family segregation, Dad same phenotype and genotype	Pathogenic	PVS1, PM2, PM4, PP1
90	SCD (DCM)	19	M	*MYPN* L867I, *RBM20* F510S, *ACTN2* D475N	Yes (ClinVar); No; Yes (ClinVar)	Yes(Cardiovasc Res 2008;77(1):118-125); Yes(Clin Tranl Sci 2010; 3(3):90-7); Yes (Circ Cardiovac Genet 2014;7(6):741-50	3.296E-3; 9.39E-5; 7.229E-3	*MYPN* variant has 5 homozygous, 2 reports in ClinVar with no pathogenicity (uncertain significance); 45 homozygotes for *ACTN2* variant and 3 reports in ClinVar all benign	Unknown Significance; Unknown Significance; Likely Benign	PP3; PP3;BP4, BP5, BP6
127	SCD	52	F							
131	SCD (CPVT)	50	F	*RYR2* Y2553C; *AKAP9* G3816V	No; No	Yes(Heart Rhythm 2015;12(7):1636-43); Yes (Proc Natl Acad Sci USA 2007;104(52):20990-5)	0;0	Y2553Y in EXAC, segregation done on children; both have AKAP9 mutation and not RYR2	Unknown Significance; Unknown Significance	PM2, PP3, BS4; PM2, PP1, PP3

132	SCD	37	M	*NEXN* E407Q	No	Yes (Am J Hum Genet 2010; 87(5):687-93	0	In frame deletion in EXAC at E407, no clinical significance	Unknown Significance	PM2, BP4
136	SCD	34	F							
137	SCD (HCM)	40	F							
138	SCD	26	M	*TGFB3* Y390F	No	No for LDS/FTAAD (Am J Med Genet A 2013; 161A(8): 2040-6, J Am Col Cardiol 2015;65(13):1324-36)	0	No genotype/phenotype correlation known	Unknown Significance	PM2
140	SCD (LQTS)	32	F	*ANK2* D2445G	No	Yes (Nature 2003;421:633-639)	8.25E-6		Unknown Significance	PP3, PP4
144	SCD	23	M							
147	SCD	37	F							
152	Congenital hearing loss/TdP	34	F	*CACNA1D* R1902X	No	Homozygous Inframe insertion (Nat Neurosci 2011;14(1):77-84);	0	Possible dominant negative effect	Likely Pathogenic	PM2, PM4, PM6, PP4
163	SCD; TdP	57	M	*CACNA1D c.5827_5829 (F1943del)*	Yes (ClinVar)	Homozygous Inframe insertion (Nat Neurosci 2011;14(1):77-84)	0.002542	Patient also has bradycardia. Sister (unaffected) does not have variant. Reported benign in ClinVar	Likely Benign	BS1, BS4, BP6
165	SCD	18	M	*MYPN R955W*	Yes (ClinVar, Eur J Hum Genet 2013; 21(3):294-300	For cardiomyopathy (Cardiovasc Res 2008; 77(1):118-25 and J Am Col Cardiol 2014;64(25):2765-76).	0.0004287	ClinVar conflicting interpretations – 1 likely benign, 1 likely pathogenic, 2 uncertain significance, segregation in family – Dad has variant, but no cardiomyopathy and/or arrhythmia, patient had normal cMR. Eur J Hum Genet paper R955W suspected of being disease causing, variant in α-actinin binding region of gene	Uncertain Significance	PP3
170	SCD	25	F	*SCN5A A572D*	Yes (ClinVar, Genet Test 2003;7(1):57-61)	Yes (Genet Test 2003;7(1):57-61, Heart Rhythm 2010;7(7):912-9	0.004304	A572V in EXAC, did not segregate in family, ClinVAR 5 likely benign, 1 likely pathogenic	Benign	BS3, BS4, BP4
193	SCD	54	M	*RYR2 S3349L; TTN c.90223delG*	No; No	Yes(Circulation 2002;106:69-74); Yes(N Engl J Med 2012; 366(7): 619-28)	0; 0	Cardiac event was VF arrest, brother had cardiac arrest as well. RYR2 S3349T in EXAC no clinical information; TTN variant found in A band of gene	Uncertain Significance; Pathogenic	PM2, PP3; PVS1, PM2

C) Hypertrophic Cardiomyopathy (HCM)

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
7	HCM	46	M							
8	HCM	60	M	TPM1 *D175N*	Yes (Ann Med. 2013; 45(1):85-90)	Yes (Ann Med. 2013; 45(1):85-90)	0		Pathogenic	PS3, PP3, PP4, PP5
10	HCM (apical variant), syncope, bradycardia, conduction abnormality	73	F	TRPM4 *Q752X*	No	No, only missense mutations reported (J Clin Invest 2009; 119(9):2737-44, Circ Cardiovasc Genet 2010;3(4):374-85)	1.833E-3	Dominant negative mutations exist - D984A (J Biol Chem 2005;280(24):22899-906)	Pathogenic	PVS1, PS3
23	HCM	47	M	*MYH6* I753T	No	Yes (Circulation 2005;112(1):54-9)	3.30E-5	This has been segregated in family, son has variant and some LVH	Unknown Significance	PP3
37	HCM (apical variant)	57	M							
41	HCM	48	M							
46	HCM	57	M	*MYBPC3* c.2554_2555insT	No	Yes (Circulation 2003; 107(17): 2227-32)	1.69E-5	Family segregation done - son has genotype and clinical disease	Pathogenic	PVS1, PM4, PP1
50	HCM (Family history HCM)	33	F	*MYH6* V39M	Yes (ClinVar)	Yes (Circulation 2005;112(1):54-9)	9.06E-5	Family history of SCD with autopsy showing LVH	Unknown Significance	PP3
52	HCM	42	M	*TNNT2* c.477delCTC	No	Yes(N Engl J Med 1995;232(16):1058-64	0	Segregated with disease in NEJM paper	Pathogenic	PVS1, PM2, PM4
53	HCM	58	M	*MYH6* R34C; *MYBPC3* V219L	No; Yes (ClinVar)	Yes (Circulation 2005;112(1):54-9); Yes (Circulation 2003; 107(17):2227-32)	2.471E-5; 0	R34H also in EXAC, V219F in EXAC - considered pathogenic in ClinVar	Unknown Significance; Likely Pathogenic	PP3;PM2, PM5, PP1, PP3,

76	HCM	62	M	*MYBPC3* R820Q	Yes (ClinVar)	Yes (Circulation 2003; 107(17):2227-32, J Am Coll Cardiol 2003l 41(5):781-6)	1.66E-5	R820P and R820W also in ClinVar, both have uncertain significance, R820Q is pathogenic/likely pathogenic in ClinVar R820W also in EXAC	Pathogenic	PS3, PS4, PP5
86	HCM	56	M	*MYBPC3* V598S	No	Yes (Circulation 2003; 107(17):2227-32)	0	V598Sfs is pathogenic in ClinVar single submission with clinical assertion information	Likely Pathogenic	PM2, PP3, PP4
93	HCM	23	M	*TNNT2* A202T; *TCAP* S64L; *CALR3* R356L	No; Yes(ClinVar) ; No	Yes(Cell 1994; 77(5):701-12;Yes(Clin Tranl Sci 2010; 3(3):90-7);Yes(J Mol Cell Cardiol 2007;43(3):337-43)	0; 1.14E-3; 2.207E-	*TCAP* S64 has 2 homozygotes and multiple reports in ClinVar with a benign pathogenicity; R356 in *CALR3* hotspot R/H, R/C, R/G also seen, R365L has 6 homozygotes	Unknown Significance; Likely Benign; Unknown Significance	PM2; BP4, BP6; BP4
104	HCM	56	F	*TNNT2* A202T	No	Yes (Cell 1994; 77(5):701-12	0	Alternate isoform - intronic in canonical common alteration 0.01224 in EXAC (intronic mutation)	Unknown Significance	PM2, BP4
105	HCM	24	M	*MYBPC3* V189I	Yes(ClinVar)	Yes (Circulation 2003; 107(17):2227-32)	2.80E-03	4 homozygotes in EXAC, 4 total reports in ClinVar, 2 likely benign, 2 unknown significance	Likely Benign	BP4, BP6
112	HCM	65	F	*TNNT2* ΔGlu160	Yes(N Engl J Med 1995;232(16) :1058-64	Yes(N Engl J Med 1995;232(16):1058-64	0		Pathogenic	PVS1, PM2, PM4
117	HCM	52	M	*MYH7* T1377M; *MYBPC3* A522V; *AKAP9* D2381G; *TTN* R2262Q	Yes (Circulation 2003; 107(17):2227 -32, J Cardiovasc Med (Hagerstown) 2006;7(8):60 1-17, J Am Coll Cardiol 2004;44(3):6 02-10, J Med Genet 2011; 48(8):572-6); No; No; No	Yes(Circulation 2003; 107(17):2227-32, J Cardiovasc Med (Hagerstown) 2006;7(8):601-17, J Am Coll Cardiol 2004;44(3):602-10, J Med Genet 2011; 48(8):572-6);Yes (Proc Natl Acad Sci USA 2007;104(52):20990-5); No (N Engl J Med 2012; 366(7):619-28)	0; 2.94E-5; 0; 0	T1377M reported multiple cases of HCM without controls having mutations; A522T in ClinVar and called likely benign by all 5 reports	Pathogenic; Likely Benign; Unknown Significance; Likely Benign	PS4, PM2, PP2, PP3, PP4; BP4, BP5; BP5; BP1, BP5
118	HCM	61	M	*TNNT2* R285C	Yes (ClinVar, N Engl J Med 1995;332(16) :1058-64	Yes (N Engl J Med 1995; 232(16):1058-64	0	Did not segregate in family - brother has similar symptoms, but no other mutation found	Unknown Significance	PM2, PP5, BS4
119	HCM	56	F							
121	HCM	69	M							
123	HCM	39	F	*ABCC9* IVS17-1G>A	No	Yes for DCM, (Nat Genet 2004;36:382-387)	1.62E-3	Splice prediction loss of exon 17, radical mutations reported elsewhere, but closer to c-terminal of gene	Pathogenic	PVS1, PM4
145	HCM	53	M	*JPH2* A405T	No	Yes (J Mol Cell Cardiol 2007;42(6):1026-35	6.61E-5		Likely Pathogenic	PS3, PP3, PP4
168	LVH, TAA	48	M	*ACTN2 N170H*	No	For HCM (J Am Coll Cardiol 2010;55:1127-35)	3.29E-05	N170I and N170fs also in EXAC none have clinical correlation in ClinVar, Brother has similar phenotype (TAA with LVH) untested at this time	Uncertain Significance	PP3
177	HCM	28	M	*TPM1 D254G*	Yes (ClinVar)	Yes (Ann Med. 2013; 45(1):85-90)	0	Sister passed away at 13 – known HCM no genetic diagnosis, mother has variant and disease, ClinVar -2 submitters, likely pathogenic	Likely Pathogenic	PM2, PP1, PP3, PP4, PP5
179	HCM, syncope	29	M	*PRKAG2 T174M*	Yes (ClinVar)	Yes (Hum Molec Genet 2001;10:1215-20)	4.12E-05	Also has ventricular arrhythmias, family history of SCD. ClinVar – Uncertain significance 1 submission	Unknown Significance	PP4
182	HCM	54	M	*TNNT2 A28V*	Yes (Eur J Med Genet 2011;54(6):e5 70-5)	Yes for HCM (Cell 1994;77:701-12), For DCM (Eur J Med Genet 2011;54(6):e570-5)	0.0004868	ClinVar – 3 uncertain significance submissions, 1 likely benign submission, 1 pathogenic submission. All reports for are DCM	Unknown Significance	PP5, BP6
183	HCM	50	M							
184	HCM	27	M	*PRKAG2 R302P*	No	Yes (N Engl J Med 2001; 344(24):1823-31)	0	ClinVar has R302L – 5 submission all pathogenic, N Engl J Med reports R302Q as a segregating variant in a large family, reported binding site for ATP/AMP	Likely Pathogenic	PM1, PM2, PM5, PP3

D) Dilated Cardiomyopathy (DCM)

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
18	DCM	38	M							
22	DCM	30	M	DSP R866C	Yes (http://www.arvcdatabase.info/Default.aspx)	Yes for ARVC (Circulation 2011;123(23):2690-2700)	6.096E-4	Hotspot? R886H and R866L in EXAC; in clinical report of this mutation, several other mutations also found in LMNA, DES, MYBPC3, and MYH7, two independent labs call mutation likely benign	Likely Benign	BS3, BP6
39	DCM	32	F	RBM20 S1195Y	Yes (ClinVar)	Yes (Clin Tranl Sci 2010; 3(3): 90-7)	6.661E-4	No segregation, but family DCM	Unknown Significance	PP3, PP4
45	DCM	59	F	DSG2 V239A	Yes (ClinVar)	Yes for ARVC (Circulation 2011;123(23):2701-9)	9.14E-5		Unknown Significance	PP3
66	DCM	28	M							
88	DCM	29	F							
95	DCM	56	M	MYBPC3 V1139I	Yes(ClinVar)	Yes (Circulation 2003; 107(17):2227-32)	8.75E-5	2 reports in ClinVar with unknown significance	Unknown Significance	BP4
100	DCM, Afib, bradycardia	47	M	MYH6 S1917P; MYH6 L24P	No; No	Yes (Circulation 2005;112(1):54-9)	0;0	L24I in EXAC (with 1 homozygote) and ClinVar, Uncertain significance	Unknown Significance; Unknown Significance	PM2, PP4; PM2, PP4
102	DCM, Afib, bradycardia, VT	48	M							
106	DCM	56	F	PRDM16 A34T; BAG3 P23S	No; No	No related to 1p36 deletion (Am J Hum Genet 2013;93(1):67-77, PLoS One 2014;9(1):e85600); Yes (Am J Hum Genet 2011; 88(3):273-82	2.018E-3, 3.598e-5	1 homozygous in EXAC, Hot spot? A34V, A34G, and A34A all in EXAC, some debate about PRDM16 and disease - related to 1p36 deletion syndrome	Unknown Significance; Unknown Significance	PP3;PP3
107	DCM	54	F	HFE H63D	Yes (ClinVar, Gastroenterology 2002; 122(3): 646-51)	Yes (Am J Hum Genet 1997;61(3):762-4	0.1066	Family known to have hemochromatosis	Pathogenic	PS3, PP3, PP4, PP5
108	DCM	38	M	LMNA c.509 insC	No	Yes (Eur J Heart Fail 2013; 15(6):628-36	0	Other frameshifts reported to be deleterious	Pathogenic	PVS1, PM2, PM4
110	DCM	68	F	LMNA IVS3 - 10A>G	No	Yes (Eur J Heart Fail 2013; 15(6):628-37	0	Other frameshifts reported to be deleterious	Pathogenic	PVS1, PM2, PM4
130	DCM	38	F							
133	DCM	52	M							
134	DCM	67	M							
135	DCM	43	F							
150	DCM/family history SCD	57	M							
151	DCM/family history CHF	55	F							
155	DCM/CHF; family history CHF	64	F	TMPO S444C; LAMA4 N89S	Yes (Circ Cardiovasc Genet 2013;6(4):337-46);	Yes (Circ Cardiovasc Genet 2013;6(4):337-46); Yes(Circulation 2007;116(5);515-25)	1.73E-04; 8.242e-06	N89N in EXAC	Likely Benign; Unknown Significance	BS1, BP1; PM2, PP4

164	DCM	58	M	TTN c.48470delG; MYH7 V964L	No; Yes (ClinVar)	Yes (N Engl J Med 2012; 366(7): 619-28); Yes (Clin Transl Sci 2008;1(1):21-6)	0; 8.236E-06	TTN variant in A-band; father had heart transplant for cardiomyopathy; conflicting pathogenicity in ClinVar for MYH7 – 5 uncertain significance, one likely pathogenic; daughter has TTN variant	Pathogenic; Uncertain Significance	IVS1, PM2; PP3, PP5
180	DCM	57	M	PRDM16 I302T; SCN5A S216L	No; Yes(Clin Transl Sci 2008;1(1):21-6)	Yes(Am J Hum Genet 2013; 93:67-77);Yes for DCM (Clin Transl Sci 2008;1(1):21-6)	8.384E-06; 0.001	For SCN5A 1 homozygous person in EXAC, ClinVar – 5 submissions all uncertain significance, from Clin Transl Sci paper – 2 people with the same variant, no segregation, but highly conserved and changes charge, considered possible cause of disease, variant has been associated with LQTS and atrial fibrillation	Unknown Significance; Unknown Significance	BP4; PP3
185	DCM	62	F							
187	DCM	28	F	PRKAG2 R84W	Yes (ClinVar)	Yes (N Engl J Med 2001; 344(24):1823-31)	0.0002535	Family history of cardiomyopathy, sudden death. ClinVar 1 submission uncertain significance, 2 submissions likely benign, R84Q also in ClinVar, uncertain significance	Uncertain Significance	PP3, PP4, BP6

E) Familial Hypercholesterolemia (FH) and Lipo-dystrophy

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
1	FH	38	M							
89	FH	55	F							
91	FH	41	M							
92	FH	27	F	APOB R3500Q	Yes (ClinVar, Hum Biol 2005; 77(5):663-73)	Yes (Hum Biol 2005; 77(5):663-73)	2.311E-4	rs5742904, R3527Q, high total cholesterol, but no history of CAD	Likely Pathogenic	PS3, PP3, PP4, PP5
97	FH, DVT	45	M	PLAT Y413H						
99	FH	42	M							
101	FH	38	M	apoE V254E	Yes (ClinVar, Am J Hum Genet 1993;52(5)937-46)	Yes (Am J Hum Genet 1993;52(5)937-46)	1.35E-03	single submission in ClinVar - pathogenic	Pathogenic	PS3, PP3, PP5
124	FH	64	M							
141	FH/CAD	55	F	LDLR A431T	Yes (Annu Rev Genet 1990;24:133-70)	Yes (Annu Rev Genet 1990;24:133-70)	0	FH- Algeria	Pathogenic	PS3, PM1, PP3
154	FH/CAD	38	F	LDLR c.313+1G>A	Yes(Atherosclerosis 1994;111(2):175-82, Am J Med Genet 1996;65(2):149-54, Arterioscler Thromb Vasc Biol 1995; 15(2):219-27)	Yes (Atherosclerosis 1994;111(2):175-82, Am J Med Genet 1996;65(2):149-54, Arterioscler Thromb Vasc Biol 1995; 15(2):219-27)	4.12E-05	G>T also reported in EXAC	Pathogenic	PS1, PS3, PM1
166	FH, xanthomas	48	F							
169	FH	49	M							
171	FH	25	M							

172	FH	52	F							
191	FH; Family History of SCD	62	M							
192	FH	33	F	LDLR M1fs c.3delG	No	Yes (Cell 1985;41:735-43)	0	Maternal family history of hyperlipidemia without CAD	Pathogenic	PVS1, PM2, PM4
198	FH	22	M	LDLR I764fs c.2292delA	No	Yes (Cell 1985;41:735-43)	0	Paternal family history of premature CAD, hypercholesterolemia	Pathogenic	PVS1, PM2
5	Lipo-dystrophy	56	F							
71	Lipo-dystrophy	41	M	LMNA R644C	Yes (Am J Med Genet A 2008;146A(12):1530-42)	Yes (Am J Med Genet A 2008;146A(12):1530-42)	1.243E-3	Segregation in family, well-established mutation site with variable phenotypes	Likely Pathogenic	PS3, PP3, PP4
87	Lipo-dystrophy	33	M	PLIN1 R23W	No	No radical mutations only (N Engl J Med 2011;364(8):740-8, Diabetes 2015;64(1):299-310)	8.544E-4	Radical mutations only reported so far; brother has similar phenotype	Unknown Significance	BP1
149	Lipo-dystrophy	46	F	LMNA R582C	Yes (Eur J Endocrinol 2012;167(3):423-31)	Yes (Eur J Endocrinol 2012;167(3):423-31)	0	R582R in EXAC	Pathogenic	PS4, PM2, PP3, PP4, PP5

F) Long QT Syndrome

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC	Additional Information	Pathogenicity	ACMG criteria*
24	LQTS	56	F							
28	LQTS, syncope	56	F	AKAP9 Q3520H	No	Yes (Proc Natl Acad Sci USA 2007;104 (52):20990-5)	0	Q3520Q in EXAC	Unknown Significance	PM2, PP3
43	LQTS/AF	57	M							
81	LQTS, syncope	25	F							
82	LQTS, syncope	28	F	ANK2 V3634I	Yes (ClinVar, Heart Rhythm 2005;2(11):1218-23)	Yes (Heart Rhythm 2005;2(11):1218-23, Nature 2003;421:633-639)	3.30E-5	V3634I reported in ClinVar pathogenic -one report, V3634D has conflicting pathogenicity in ClinVar	Unknown Significance	PP4, PP5
96	LQTS, palpitations	35	F	RBM20 D996Y, TTN c.32562_insAGA	Yes(ClinVar) Yes (Eur Heart J 2014;35(32):2165-73)	Yes(Clin Tranl Sci 2010; 3(3):90-7); Yes (N Engl J Med 2012; 366(7):619-28)	0; 0	RBM20 Reported once in ClinVar with unknown significance; TTN reported twice with familial and non-familial DCM/PPCM	Unknown Significance; Pathogenic	PM2, PP3; PVS1, PM2, PM4
126	LQTS/AF/HCM	70	M							
129	LQTS	34	M							
142	LQTS, syncope	49	F							
153	LQTS	23	F							
162	LQTS; Family history of SCD	37	F	CTNNA3 H727R	No	Yes (Eur Heart J 2013;34(3):201-10	0	Brother drowned in ocean – military, patient had normal cMR	Unknown Significance	PM2, PP3
175	LQTS	24	F	CAV3 T78M	Yes (Circulation 2006; 114: 2104-2112).	Yes (Circulation 2006; 114: 2104-2112)	0.003038	1 Homozygote in EXAC, ClinVar 5 benign/likely benign, 2 uncertain significance, 2 pathogenic, no other family members available for testing	Unknown Significance	PP5, BP6
181	LQTS, syncope	52	F	ANK2 E1449G	Yes (Nature 2003;42(6923):634-9)	Yes (Nature 2003;42(6923):634-9 and Proc Natal Acad Sci 2004;101(24):9137-42)	0.0004222	ClinVar – 1 submussion likely benign, 5 submissions likely pathogenic/pathogenic, in Nature paper segregation in family	Pathogenic	PS1, PS3, PP4, PP5
196	LQTS, Family History SCD	67	M							

199	LQTS	57	M	KCNQ1 L266P	Yes (Heart Rhythm 2005;2:507-517, Circulation 2007;115(19):2481-9, Heart Rhythm 2009;6:1297-1303)	Yes (Heart Rhythm 2005;2:507-517; Circulation 2007;115(19):2481-9 Heart Rhythm 2009;6:1297-1303)	0	History of syncope in childhood (near drowning), VF arrest, family history of SCD. L266P is known/established cause of LQTS, transmembrane variant	Pathogenic	PS4, PM2, PP3, PP4, PP5

G) Atrial and/or Ventricular Arrhythmias

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
56	Atrial and Ventricular arrhythmias	43	F	CACNB2 V255L	No	Yes for BrS and SCD (J Mol Cell Cardiol 2009; 46(5):695-703,Heart Rhythm 2010;7(12):1872-82)	0		Unknown Significance	PM2, PP3
60	Atrial Arrhythmia	56	F							
62	Atrial Arrhythmia	66	F							
64	Atrial Arrhythmia	69	M	KCNE2 T8A	Yes (ClinVar)	Yes (Proc Natl Acad Sci U S A 2000;97(19):10613-18)	3.804E-3	May cause long QT when on antibiotic therapy (Proc Natl Acad Sci U S A 2000;97(19):10613-18) T8I in EXAC as well, all reports from ClinVar Benign	Unknown Significance	PS3, PP3, BP6
67	Atrial Arrhythmia (SVT)	41	F	ABCC9 I614T	No	Yes (Nat Clin Pract Cardiovasc Med 2007;4:110-116, Circ Res 2013; 112(7):1059-72)	0		Unknown Significance	PP3
73	Atrial Arrhythmia	22	M							
15	VT/Family History SCD	33	F	SYNE2 E497V	No	Yes (Hum Mol Genet 2007; 16(23): 2816-33)	0	GWAS identified SYNE2 loci for AF (Nat Genet 2012;44(6):670-5). Family history of SIDS, personal history of NSVT	Unknown Significance	PM2, PP3
57	Ventricular arrhythmia	23	F	GPD1L R220H	Yes (ClinVar)	Yes (Hum Mutat 2009;30(9):1256-66	3.484E-4	R220C also in EXAC 2.49E-5, both reports in ClinVar as Likely Benign	Likely Benign	BP4, BP6
167	VT, positive procainamide test, family history of VF	57	F							
189	VT/Family History of SCD	22	M							

H) Brugada syndrome

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
9	BrS	55	F							
48	BrS	63	F							
61	BrS, AF	53	M							
69	BrS	23	F	SCN5A S910L	Yes (Nat Rev Cardiol 2009;6(5):337-48)	Yes(Heart Rhythm 2010;7(1):33-46)	0	S910S in EXAC; known BrS variant	Likely Pathogenic	PS3, PM2, PP3, PP4
72	BrS	37	M	SCN5A I786V	No	Yes(Heart Rhythm 2010;7(1):33-46)	0	I786I in EXAC	Unknown Significance	PP3
78	BrS (Family history of SCD)	40	F	DSP V2388I	No	Yes for ARVC (Circulation 2011;123(23):2690-2700)	1.65E-05	Mom, Sister, Niece all have this variant, no one has cMRI indicative of CM, index case does not have ARVC, "low normal LVEF" on cMRI/echo, family hx of SCD, but autopsy shows no CM	Unknown Significance	PP3

115	BrS	64	F	SCN5A c.2551insTG; MYBPC3 V896M; CACNA1C G2022R	Yes(ClinVar) ; Yes(Am J Hum Genet 1999; 65(5):1308-1320; No	Yes (Heart Rhythm 2010;7(1):33-46); Yes (Proc Natl Acad Sci USA 2005;102(23):8089-96); Yes (Circulation 2003; 107(17):2227-32)	0; 0.1275; 0	F851L in ClinVar - Pathogenic; V896M - homozygote in EXAC	Pathogenic; Likely Benign; Unknown Significance	IVS1; BP5, BP6; PM2
146	BrS	51	M	RYR2 R1482H	Yes(ClinVar)	Yes for LQTS (Heart Rhythm 2005; 2(10):1099-1105); Yes for CPVT with and without Atrial Fibrillation (Can J Cardiol 2013;29(8):993-6, Heart Rhythm 2015;12(7):1636-43).	1.994E-4	R1482C in EXAC	Likely Pathogenic	PS3, PM5, BP4
194	BrS	49	M	RYR2 R1482H	Yes(ClinVar)	Yes for LQTS (Heart Rhythm 2005; 2(10):1099-1105); Yes for CPVT with and without Atrial Fibrillation (Can J Cardiol 2013;29(8):993-6, Heart Rhythm 2015;12(7):1636-43).	0.0001994	R1482C in EXAC. ClinVar – 3 submissions 1 likely benign, 2 uncertain significance	Uncertain Significance	BP4

I) Family History of SCD or LQTS

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
3	Family history SCD	59	M	TMEM43 V364M	No	Yes for ARVC (Eur Heart J 2013; 34(13): 1002-11)	8.24E-5	No ARVC phenotype - normal cMRI. Family history of SCD	Unknown Significance	PP2
14	Family history SCD	45	F							
49	Family history SCD; presyncope/palpitations	55	F	SCN5A R1192Q; SCN4B G8S	Yes (ClinVar);Yes (ClinVar)	Yes(Heart Rhythm 2010;7(1):33-46); Circulation 2007; 116(2):134-42	6.215E-3; 4.742E-4	R1192W and R1192R, R1192Q has 17 homozygotes, reports in ClinVar vary for SCN5A variant, SCN5A called polymorphism in 2 papers; SCN4B reported likely benign by one lab in ClinVar	Likely Benign; Unknown Significance	BP4, BP6; BP4, BP6
80	Family history of LQTS	45	M							
116	Family history of SCD, VT	67	M	DES K109N	No	Yes for myopathy with arrhythmias (Nat Genet 1998;19(4):402-3)	0	1st amino acid in the rod domain, E108K is reported to cause DCM (Circulation 2007;115(10):1244-51)	Likely Pathogenic	PM1,PM2, PP3, PP4
120	Family history SCD	45	M							
128	Family history SCD, TWI on EKG	60	F	CACNA1C W1612C; TNNI3 R141Q	No; Yes (Circulation 2003; 107(17):2227-32)	Yes (Proc Natl Acad Sci USA 2005;102(23):8089-96); Yes (Circulation 2003; 107(17):2227-32)	0; 0	CACNA1C W1612X in EXAC; TNNI3 R141W in EXAC and ClinVar - 1 report, predicted likely pathogenic, unclear if R141Q causes disease	Unknown Significance; Unknown Significance	PM2; PM2, PP3, PP5
161	Family history SCD/LQTS	60	M	ANK2 M3649V; DSG2 A308S	No; No	Yes (Nature 2003;421:634-9); Yes for ARVC (Circulation 2006;113:1171-9)	9.893E-05; 0	Brother has ANK2 variant and had SCD; DSG2 variant in Cadherin 3 domain, next to glycosylation site (N309), patient had normal cMR	Unknown Significance; Unknown Significance	PP1, BP4; PM2, PP3
174	Family history SCD	31	M	MYH6 R1398Q; VCL R502Q	Yes (ClinVar); No	For cardiomyopathy (Circulation 2005;112(1):54-9); For cardiomyopathy (Circulation 2002;105:431-7, Biophys Res Commun 2006;345:998-1003)	0.00003879;8.514E-05	VCL R502W and R502R in EXAC, patient had normal imaging studies	Unknown Significance; Unknown Significance	BP5;BP5

J) Non-specific NICM

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
111	Non-Specific NICM, primary conduction disease CM	58	F	LAMP2 T196S	Yes (ClinVar)	Yes (Neuromuscul Disord 2005;16(5):409-11)	2.393E-4	Two reports in ClinVar - one likely benign, one uncertain significance	Unknown Significance	BP6
114	Non-Specific NICM, VT	34	F	LDB3 c.287insC; TTN IVS100-2A>C; MYH6 A1004S	No; No; Yes(ClinVar)	No (Clin Transl Sci 2008;1(1):21-6); Yes (N Engl J Med 2012; 366(7):619-28); Yes (Circulation 2005;112(1):54-9)	0; 0; 9.801E-4	ClinVar has LDB3 c.287T>C likely benign, only missense reported in the literature. Unclear if radical mutation has an effect. MYH6 mutation reported in OMIM, but conflicting reports in ClinVar	Unknown Significance; Pathogenic; Unknown Significance	PM2; PVS1, PM2, PM4; PP5, BP6

122	Non-Specific NICM, Atrial Arrhythmias, Neuromuscular Disorder	33	M	RYR2 R3260W	No	Yes (Heart Rhythm 2015;12(7):1636-43)	4.15E-5	R3260Q in EXAC (with 1 homozygote)	Unknown Significance	PP4
125	Non-Specific NICM	23	M	MIB1 R676X	No	Yes for LVNC (Nat Med 2013;19(2):193-201	0	EXAC has c.2556delC (same location) and in ClinVar as well - reported pathogenic	Pathogenic	PVS1, PM2, PM4
195	Non-Specific NICM/LQT	45	F	PKP2 IVS6-1C>T(c.1379-1C>T; NEXN M540V; AKAP9 R3734P	Yes (ClinVar); Yes (ClinVar); Yes (ClinVar	Yes for ARVC(Nature Genet 2004;36:1162-4); Yes for DCM (Nature Med 2009;15:1281-8), Yes for HCM(Acta Biochm Biophys Sinica 2001;33:19-24); Yes for LQTS (Proc Nat Acad Sci 2007;104:20990-5)	0.0001499; 0.0004253; 0.0007003	PKP2 – ClinVar single submission uncertain significance, high confidence LoF variant EXAC; NEXN Clin Var – 2 submissions 1 likely benign, 1 uncertain significance; AKAP9 in ClinVar 3 submissions all benign/likely benign, R3742Q also in ClinVar 3 submission all benign/likely benign;	Likely Pathogenic; Uncertain Significance; Likely Benign	PVS1, PM4; BP4; BP4, BP6
200	Non-Specific NICM, VT	32	M	DSG2 L836V	No	Yes (Mol Genet Metab 2008;95:74-80)	0		Unknown Significance	PM2, PP3

K) Other

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
40	ARVC (family history of SCD)	60	M	DSP R1458G	Yes (http://www.arvcdatabase.info/Default.aspx)	Yes for ARVC (Circulation 2011;123(23):2690-2700)	1.737E-3	1 homozygous in EXAC, hotspot R1458R, R1458X, R1458Q all reported at least once in EXAC), Other reports of this mutation have people with other mutations compound heterozygous or other ARVC gene	Likely Benign	BP2, BP4, BP6
25	CPVT	48	F							
17	Heart Block (familial)	64	M							
35	PPCM	40	F	NDUFV2 Q31X	No	Yes for HCM (Hum Mutat 2003; 21(6): 582-6)	0	few reported mutations in ClinVar, similar mutation type with HCM	Likely Pathogenic	PM2, PM4,PP3, PP4
109	PPCM	56	F	EMD c.110_112del AGA	No	Yes for Emery-Dreifuss MD (Nat Genet 1994;8(4):323-327); mild features with DCM (BMC Med Genet 2014;15:77)	2.53E-05	No musculoskeletal features -- potentially very mild?	Likely Pathogenic	PVS1, PM4
113	RCM, VT/AF	15	M	*TNNT2* ΔGlu160; *SCN5A* R1027Q	Yes(N Engl J Med 1995;232(16) :1058-64;No	Yes(N Engl J Med 1995;232(16):1058-64;Yes(Heart Rhythm 2010;7(1):33-46)	0; 5.059E-5		Pathogenic; Unknown Significance	PVS1, PM2, PM4; PP5, PB5

* Abbreviations for the ACMG Criteria: PVS – Pathogenic Very Strong, PS – Pathogenic Strong, PM – Pathogenic Moderate, PP – Pathogenic Supporting, BS – Benign Strong, BP – Benign Supporting

Other Abbreviations: TAA – Thoracic Aortic Aneurysm, AAA – Abdominal Aortic Aneurysm, PVH – Periventricular Heterotopia, EDS – Ehlers Danlos Syndrome, SCAD – Spontaneous Coronary Artery Disease, SCD – Sudden Cardiac Death, RCM – Restrictive Cardiomyopathy, HCM- Hypertrophic Cardiomyopathy, DCM – Dilated Cardiomyopathy, Non-Specific NICM – Non-Ischemic Cardiomyopathy, TdP – Torsade Des Pointes LQTS – Long QT Syndrome, ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy, CPVT – Catecholaminergic Polymorphic Ventricular Tachycardia, LVH – Left Ventricular Hypertrophy, FH – Familial Hypercholesterolemia, CAD – Coronary Artery Disease, AF – Atrial Fibrillation, BrS – Brugada Syndrome, VT – Ventricular Tachycardia, VF- Ventricular Fibrillation, TWI on EKG – T-wave Inversion on Electrocardiogram, PPCM – Peripartum Cardiomyopathy

Table S2: Pathogenic Variants Found with American College of Medical Genetics Data

#	Reason for Referral	Age	Sex	Variant	Variant Previously Reported?	Disease Association	Freq. EXAC (January 2016)	Additional Information	Pathogenicity	ACMG criteria*
4	SCD (RCM)	54	F	TNNI3 L198V	Yes(ClinVar)	Yes (Neth Heart J 2011; 19(7-8): 344-51)	0	Causes a change in splice site	Pathogenic	PM2, PM4, PP3, PP5
6	EDS, PVH	25	F	FLNA 4214delA; COL5A2 G702R	No; No	Yes (Neurology 2005;64(2):254-262; Yes(J Med Genet 1998;35:846-8)	0; 1.663E-5	Family segregation done Mom has COL5A2 with phenotype, maternal grandmother has COL5A2 with phenotype, FLNA de novo, sister has COL5A2 and phenotype, brother has COL5A2 and phenotype	Pathogenic; Likely Pathogenic	PS2, PM2, PM2, PP1(family well-characterized), PP3
8	HCM	60	M	TPM1 D175N	Yes (Ann Med. 2013; 45(1):85-90)	Yes (Ann Med. 2013; 45(1):85-90)	0		Pathogenic	PS3, PP3, PP4, PP5
10	HCM (apical variant), syncope, bradycardia, conduction abnormality	73	F	TRPM4 Q752X	No	No, only missense mutations reported (J Clin Invest 2009; 119(9):2737-44, Circ Cardiovasc Genet 2010;3(4):374-85)	1.833E-3	Dominant negative mutations exist - D984A (J Biol Chem 2005;280(24):22899-906)	Pathogenic	PVS1, PS3
12	SCD	66	F	KCNH2 N33T	No	Yes (Circulation 2002; 105(7):794-9)	0	2 submissions in ClinVar - Gene DX pathogenic, NHS VUS, this mutation increased rate of deactivation several papers; family segregation	Pathogenic	PS3, PM1, PM2, PP3, PP5
16	Marfan syndrome	26	F	FBN1 IVS2+1G>A	Yes (http://www.umd.be/FBN1/4DACTION/W_DMDT1/1)	Yes (Proc Natl Acad Sci USA 1992;89(13):5917-22	0	Family has clinical phenotype… Brother, mother	Pathogenic	PVS1, PM2, PM3
19	SCD (HCM)	58	M	MYBPC3 IVS28+22T>G	No	Yes (Circulation 2003; 107(17):2227-32)	0	Family segregation done - children without phenotype and do not carry mutation	Pathogenic	PVS1, PM2, PP1, PP3
26	SCD (NICM)	47	F	TTN R18966X	No	Yes (N Engl J Med 2012; 366(7): 619-28	0		Pathogenic	PVS1, PM2, PM4
31	Marfan syndrome	55	F	FBN1 G77X	Yes(http://www.umd.be/FBN1/4DACTION/W_DMDT1/1)	Yes (Proc Natl Acad Sci USA 1992;89 (13):5917-21	0	Family has clinical phenotype	Pathogenic	PVS1, PM2, PM4
35	PPCM	40	F	NDUFV2 Q31X	No	Yes for HCM (Hum Mutat 2003; 21(6): 582-6)	0	few reported mutations in ClinVar, similar mutation type with HCM	Likely Pathogenic	PM2, PM4, PP3, PP4
46	HCM	57	M	MYBPC3 c.2554_2555insT	No	Yes (Circulation 2003; 107(17): 2227-32)	1.69E-5	Family segregation done - son has genotype and clinical disease	Pathogenic	PVS1, PM4, PP1
52	HCM	42	M	TNNT2 c.477delCTC	No	Yes(N Engl J Med 1995;232(16):1058-64	0	Segregated with disease in NEJM paper	Pathogenic	PVS1, PM2, PM4
53	HCM	58	M	MYBPC3 V219L	No; Yes (ClinVar)	Yes (Circulation 2003; 107(17):2227-32)	0	V219F in EXAC - considered pathogenic in ClinVar	Likely Pathogenic	PM2, PM5, PP1, PP3
54	SCD (DCM)	47	F	DSP Q1672X	No	Yes for ARVC (Can J Cardiol 2014;30(12):1655-61), For DCM (Genet Med 2014; 16(8):601-8)	0		Pathogenic	PVS1, PM2, PM4
59	SCD (NICM)	24	F	TTN c.45689delG;	No	Yes (N Engl J Med 2012; 366(7):619-28, Sci Tranl Med 2015; 7(270):270ra6);	0	Segregation done on family - Dad does not carry TTN and has no phenotype, sister sister carries and has phenotype	Pathogenic	PVS1, PM2, PM4

65	SCD	47	F	*SCN5A* S216L	Yes (ClinVar, Clin Transl Sci 2008;1(1):21-26);	Yes (Heart Rhythm 2010;7(1):33-46)	0.001		Likely Pathogenic	PS3, PP3, PP4
69	BrS	23	F	*SCN5A* S910L	Yes (Nat Rev Cardiol 2009;6(5):337-48)	Yes(Heart Rhythm 2010;7(1):33-46)	0	S910S in EXAC; known BrS variant	Likely Pathogenic	PS3, PM2, PP3, PP4
71	Lipo-dystrophy	41	M	*LMNA* R644C	Yes (Am J Med Genet A 2008;146A(12):1530-42)	Yes (Am J Med Genet A 2008;146A(12):1530-42)	1.243E-3	Segregation in family, well-established mutation site with variable phenotypes	Likely Pathogenic	PS3, PP3, PP4
75	SCD (DCM)	40	F	*TTN c.29042-2A>C*	Yes(Sci Tranl Med 2015; 7(270):270ra6)	Yes (N Engl J Med 2012; 366(7):619-28, Sci Tranl Med 2015; 7(270):270ra6)	0	VF arrest	Pathogenic	PVS1, PM2, PM4
76	HCM	62	M	*MYBPC3 R820Q*	Yes (ClinVar)	Yes (Circulation 2003; 107(17):2227-32, J Am Coll Cardiol 20031 41(5):781-6)	1.66E-5	R820P and R820W also in ClinVar, both have uncertain significance, R820Q is pathogenic/likely pathogenic in ClinVar R820W also in EXAC	Pathogenic	PS3, PS4, PP5
84	SCD (DCM)	40	M	*TTN W21280X*	No	Yes (N Engl J Med 2012; 366(7):619-28)	0	Family segregation, Dad same phenotype and genotype	Pathogenic	PVS1, PM2, PM4, PP1
85	Marfan syndrome	57	F	*FBN1 R945C*	No	Yes (Genomics 1993;17(2):468-75)	0	R954H in ClinVar as Pathogenic	Likely Pathogenic	PM2, PM5, PP3, PP4
86	HCM	56	M	*MYBPC3 V598S*	No	Yes (Circulation 2003; 107(17):2227-32)	0	V598Sfs is pathogenic in ClinVar single submission with clinical assertion information	Likely Pathogenic	PM2, PP3, PP4
92	FH	27	F	*APOB R3500Q*	Yes (ClinVar, Hum Biol 2005; 77(5):663-73)	Yes (Hum Biol 2005; 77(5):663-73)	2.311E-4	rs5742904, R3527Q, high total cholesterol, but no history of CAD	Likely Pathogenic	PS3, PP3, PP4, PP5
96	LQTS, palpitations	35	F	*TTN* c.32562_insAGA	Yes (ClinVar)	Yes (N Engl J Med 2012; 366(7):619-28)	0	TTN reported twice with familial and non-familial DCM/PPCM	Unknown Significance; Pathogenic	PVS1, PM2, PM4
101	FH	38	M	*apoE V254E*	Yes (ClinVar, Am J Hum Genet 1993;52(5)937-46)	Yes (Am J Hum Genet 1993;52(5)937-46)	1.35E-03	single submission in ClinVar - pathogenic	Pathogenic	PS3, PP3, PP5
107	DCM	54	F	*HFE H63D*	Yes (ClinVar, Gastroenterology 2002; 122(3): 646-51)	Yes (Am J Hum Genet 1997;61(3):762-4	0.1066	Family known to have hemochromatosis	Pathogenic	PS3, PP3, PP4, PP5
108	DCM	38	M	*LMNA c.509 ins C*	No	Yes (Eur J Heart Fail 2013; 15(6):628-36	0	Other frameshifts reported to be deleterious	Pathogenic	PVS1, PM2, PM4
109	PPCM	56	F	*EMD c.110_112del AGA*	No	Yes for Emery-Dreifuss MD (Nat Genet 1994;8(4):323-327); mild features with DCM (BMC Med Genet 2014;15:77)	2.53E-05	No musculoskeletal features -- potentially very mild?	Likely Pathogenic	PVS1, PM4
110	DCM	68	F	*LMNA IVS3 - 10A>G*	No	Yes (Eur J Heart Fail 2013; 15(6):628-37	0	Other frameshifts reported to be deleterious	Pathogenic	PVS1, PM2, PM4

112	HCM	65	F	*TNNT2 ΔGlu160*	Yes(N Engl J Med 1995;232(16):1058-64	Yes(N Engl J Med 1995;232(16):1058-64	0		Pathogenic	PVS1, PM2, PM4
113	RCM, VT/AF	15	M	*TNNT2 ΔGlu160*	Yes(N Engl J Med 1995;232(16):1058-64;No	Yes(N Engl J Med 1995;232(16):1058-64	0		Pathogenic	PVS1, PM2, PM4
114	NICM, VT	34	F	*TTN IVS100-2A>C;*	No	Yes (N Engl J Med 2012; 366(7):619-28	0		Pathogenic	PVS1, PM2, PM4; PP5
115	BrS	64	F	*SCN5A c.2551insTG*	Yes(ClinVar)	Yes (Heart Rhythm 2010;7(1):33-46	0	Pathogenic; V896M - homozygote in EXAC	Pathogenic	PVS1, PM2, PP5
116	Family history of SCD, VT	67	M	*DES K109N*	No	Yes for myopathy with arrhythmias (Nat Genet 1998;19(4):402-3)	0	1st amino acid in the rod domain, E108K is reported to cause DCM (Circulation 2007;115(10):1244-51)	Likely Pathogenic	PM1,PM2, PP3, PP4
117	HCM	52	M	*MYH7 T1377M*	Yes (Circulation 2003; 107(17):2227-32, J Cardiovasc Med (Hagerstown) 2006;7(8):601-17, J Am Coll Cardiol 2004;44(3):602-10, J Med Genet 2011; 48(8):572-6)	Yes (Circulation 2003; 107(17):2227-32, J Cardiovasc Med (Hagerstown) 2006;7(8):601-17, J Am Coll Cardiol 2004;44(3):602-10, J Med Genet 2011; 48(8):572-6)	0	T1377M reported multiple cases of HCM without controls having mutations	Pathogenic	PS4, PM2, PP2, PP3
123	HCM	39	F	*ABCC9 IVS17-1G>A*	No	Yes for DCM, (Nat Genet 2004;36:382-387)	1.62E-3	Splice prediction loss of exon 17, radical mutations reported elsewhere, but closer to c-terminal of gene	Likely Pathogenic	PVS1, PM4
125	NICM	23	M	*MIB1 R676X*	No	Yes for LVNC (Nat Med 2013;19(2):193-201	0	EXAC has c.2556delC (same location) and in ClinVar as well - reported pathogenic	Pathogenic	PVS1, PM2, PM4
141	FH/CAD	55	F	*LDLR A431T*	Yes (Annu Rev Genet 1990;24:133-70)	Yes (Annu Rev Genet 1990;24:133-70)	0	FH- Algeria	Pathogenic	PS3, PM1, PP3
145	HCM	53	M	*JPH2 A405T*	No	Yes (J Mol Cell Cardiol 2007;42(6):1026-35	6.61E-5		Likely Pathogenic	PS3, PP3, PP4
146	BrS	51	M	*RYR2 R1482H*	Yes(ClinVar)	Yes for LQTS (Heart Rhythm 2005; 2(10):1099-1105); Yes for CPVT with and without Atrial Fibrillation (Can J Cardiol 2013;29(8):993-6, Heart Rhythm 2015;12(7):1636-43).	1.994E-4	R1482C in EXAC	Likely Pathogenic	PS3, PM5, BP4

149	Lipo-dystrophy	46	F	*LMNA R582C*	Yes (Eur J Endocrinol 2012;167(3):423-31)	Yes (Eur J Endocrinol 2012;167(3):423-31)	0	R582R in EXAC	Pathogenic	PS4, PM2, PP3, PP4, PP5
152	Congenital hearing loss/TdP	34	F	*CACNA1D R1902X*	No	Homozygous Inframe insertion (Nat Neurosci 2011;14(1):77-84);	0	Possible dominant negative effect	Likely Pathogenic	PM2, PM4, PM6, PP4
154	FH/CAD	38	F	*LDLR c.313+1G>A*	Yes(Atherosclerosis 1994;111(2):175-82, Am J Med Genet 1996;65(2):149-54, Arterioscler Thromb Vasc Biol 1995; 15(2):219-27)	Yes (Atherosclerosis 1994;111(2):175-82, Am J Med Genet 1996;65(2):149-54, Arterioscler Thromb Vasc Biol 1995; 15(2):219-27)	4.12E-05	G>T also reported in EXAC	Pathogenic	PS1, PS3, PM1
164	DCM	58	M	*TTN c.48470delG;*	No	Yes (N Engl J Med 2012; 366(7): 619-28)	0	TTN variant in A-band; father had heart transplant for cardiomyopathy	Pathogenic	IVS1, PM2, PM4
177	HCM	28	M	*TPM1 D254G*	Yes (ClinVar)	Yes (Ann Med. 2013; 45(1):85-90)	0	Sister passed away at 13 – known HCM no genetic diagnosis, mother has variant and disease, ClinVar -2 submitters, likely pathogenic	Likely Pathogenic	PM2, PP1, PP3, PP4, PP5
181	LQTS, syncope	52	F	*ANK2 E1449G*	Yes (Nature 2003;42(6923):634-9)	Yes (Nature 2003;42(6923):634-9 and Proc Natal Acad Sci 2004;101(24):9137-42)	0.0004222	ClinVar – 1 submussion likely benign, 5 submissions likely pathogenic/pathogenic, in Nature paper segregation in family	Pathogenic	PS1, PS3, PP4, PP5
184	HCM	27	M	*PRKAG2 R302P*	No	Yes (N Engl J Med 2001; 344(24):1823-31)	0	ClinVar has R302L – 5 submission all pathogenic, N Engl J Med reports R302Q as a segregating variant in a large family, reported binding site for ATP/AMP	Likely Pathogenic	PM1, PM2, PM5, PP3
192	FH	33	F	*LDLR M1fs c.3delG*	No	Yes (Cell 1985;41:735-43)	0	Maternal family history of hyperlipidemia without CAD	Pathogenic	PVS1, PM2, PM4
193	SCD	54	M	*TTN c.90223delG*	No	Yes(N Engl J Med 2012; 366(7): 619-28)	0	Cardiac event was VF arrest, brother had cardiac arrest as well. TTN variant found in A band of gene	Pathogenic	PVS1, PM2, PM4

195	NICM/LQT	45	F	*PKP2 IVS6-1C>T(c.1379-1C>T*	Yes (ClinVar)	Yes for ARVC(Nature Genet 2004;36:1162-4	0.0001499	PKP2 – ClinVar single submission uncertain significance, high confidence LoF variant EXAC	Likely Pathogenic	PVS1, PM4
198	FH	22	M	*LDLR I764fs c.2292delA*	No	Yes (Cell 1985;41:735-43)	0	Paternal family history of premature CAD, hypercholesterolemia	Pathogenic	PVS1, PM2, PM4
199	LQTS	57	M	*KCNQ1 L266P*	Yes (Heart Rhythm 2005;2:507-517, Circulation 2007;115(19):2481-9, Heart Rhythm 2009;6:1297-1303)	Yes (Heart Rhythm 2005;2:507-517; Circulation 2007;115(19):2481-9 Heart Rhythm 2009;6:1297-1303)	0	History of syncope in childhood (near drowning), VF arrest, family history of SCD. L266P is known/established cause of LQTS, transmembrane variant	Pathogenic	PS4, PM2, PP3, PP4, PP5

* Abbreviations for the ACMG Criteria: PVS – Pathogenic Very Strong, PS – Pathogenic Strong, PM – Pathogenic Moderate, PP – Pathogenic Supporting, BS – Benign Strong, BP – Benign Supporting

Other Abbreviations PVH – Periventricular Heterotopia, EDS – Ehlers Danlos Syndrome, SCD – Sudden Cardiac Death, RCM – Restrictive Cardiomyopathy, HCM-Hypertrophic Cardiomyopathy, DCM – Dilated Cardiomyopathy, NICM – Non-Ischemic Cardiomyopathy, TdP – Torsade Des Pointes LQTS – Long QT Syndrome, FH – Familial Hypercholesterolemia, CAD – Coronary Artery Disease, AF – Atrial Fibrillation, BrS – Brugada Syndrome, VT – Ventricular Tachycardia PPCM – Peripartum Cardiomyopathy

Table S3: Gene represented by various commercially available arrhythmia panels:

Ambry – RhythmFirst and RhythmNext (From www.ambrygen.com on January 21, 2016)

GeneDX – Arrhythmia panel (From www.genedx.com on January 21, 2016)

Invitae – Comprehensive Arrhythmia Panel with Optional Limited Evidence Genes (Marked as O)

(from www.invitae.com on January 21, 2016)

Gene	Ambry	GeneDX	Invitae
ABCC9			X
ACTN2			X
AKAP9	X	X	O
ANK2	X	X	X
ANKRD1			O
CACNA1C	X	X	X
CACNA2D1	X		O
CACNB2	X	X	X
CALM1	X		X
CALM2			X
CALM3			X
CASQ2	X	X	X
CAV3	X	X	X
CTNNA3			O
DES			X
DSC2	X	X	X
DSG2	X	X	X
DSP	X	X	X
EMD			X
GPDL1	X	X	X
HCN4	X	X	X
JUP	X	X	X
KCND3	X		O
KCNE1	X	X	X
KCNE2	X	X	X
KCNE3	X	X	O
KCNE5			O
KCNH2	X	X	X
KCNJ2	X	X	X
KCNJ5		X	O
KCNJ8	X	X	O
KCNQ1	X	X	X
LDB3			O
LMNA	X		X
NKX2.5	X	X	X
PDLIM3			O
PKP2	X	X	X
PLN			X
PRKAG2			X
RANGRF		X	O

RBM20			X
RYR2	X	X	X
SCN1B	X	X	O
SCN2B			O
SCN3B	X	X	O
SCN4B	X	X	O
SCN5A	X	X	X
SCN10A			O
SLMAP			O
SNTA1	X	X	O
TBX5	X		
TGFB3	X		X
TMEM43	X	X	X
TNNI3			X
TNNT2			X
TRPM4	X		O
TRDN	X		X
TTN			X

Table S4: Genes represented by various commercially available cardiomyopathy panels

Ambry – CMNExt (From www.ambrygen.com on January 21, 2016)

GeneDX – Cardiomyopathy panel (From www.genedx.com on January 21, 2016)

Invitae – Comprehensive Cardiomyopathy Panel with Optional Limited Evidence Genes (Marked as O) and RASopathy genes for cardiomyopathy (Marked as R) (from www.invitae.com on January 21, 2016)

Gene	Ambry	GeneDX	Invitae
A2ML1			R
ABCC9	X	X	X
ACTC1	X	X	X
ACTN2	X	X	X
ALMS1			X
ANKRD1	X	X	O
BAG3	X	X	X
BRAF		X	R
CALR3			O
CAV3		X	X
CBL			R
CRYAB	X	X	X
CSRP3	X	X	X
CTF1			O
CTNNA3			O
DES	X	X	X
DMD	X	X	X
DSC2	X	X	X
DSG2	X	X	X
DSP	X	X	X
DTNA		X	O
ELAC2			X
EMD	X	X	X
EYA4	X		X
FHL1			X
FHL2			O
FKRP			X
FKTN	X	X	X
FXN	X		
GATA4			O
GATA6			O
GATAD1	X	X	O
GLA	X	X	X
HCN4			X
HRAS		X	R
ILK		X	O
JPH2	X	X	O
JUP	X	X	X

KRAS		X	R
LAMA4	X	X	O
LAMP2	X	X	X
LDB3	X	X	O
LMNA	X	X	X
MAP2K1		X	R
MAP2K2		X	R
MTND1		X	
MTND5		X	
MTND6		X	
MTTD		X	
MTTG		X	
MTTH		X	
MTTI		X	
MTTK		X	
MTTL1		X	
MTTL2		X	
MTTM		X	
MTTQ		X	
MTTS1		X	
MTTS2		X	
MTO1			X
MYBPC3	X	X	X
MYH6	X		O
MYH7	X	X	X
MYL2	X	X	X
MYL3	X	X	X
MYLK2			O
MYOM1			O
MYOZ2	X	X	O
MYPN	X	X	O
NEBL		X	O
NEXN	X	X	O
NRAS		X	R
NF1			R
NKX2.5	X		
NPPA			O
PDLIM3		X	O
PKP2	X	X	X
PLN	X	X	X
PRDM16			O
PRKAG2	X	X	X
PTPN11	X	X	R
RAF1	X	X	X
RASA1			R
RBM20	X	X	X
RIT1			R
RYR2	X	X	X
SCN5A	X	X	X
SDHA			X
SGCD		X	X
SHOC2			R

SOS1		X	R
SPRED1			R
TAZ	X	X	X
TBX20	X		
TCAP	X	X	X
TGFB3	X		X
TMEM43	X	X	X
TMPO	X	X	O
TNNC1	X	X	X
TNNI3	X	X	X
TNNT2	X	X	X
TPM1	X	X	X
TTN	X**	X	X
TTR		X	X
TXNRD2	X		O
VCL	X	X	X

*****TTN*** optional for Ambry CMNext

Table S5: The Actionable Incidental Pathological findings

Case	Reason for Referral	Incidental Finding	Mutation Previously Reported	Ref	Additional Information	Pathogenicity	ACMG criteria*
33	Noonan Syndrome	*MSH6* c.1352_1353insTCAG	No	1	Mother early onset CRC (40s) - no genetic testing	Pathogenic	PVS1, PM2, PM4
63	NICM	*BRCA2* R2505X	Yes (ClinVar)	2	No family history, but family is mostly males and small structure; index case is male	Pathogenic	PVS1, PP3, PP5
79	SCD (ARVC)	*LDLR* Q254P	Yes	3	LDLR variant - Reggio Emilia -2; family has known history of elevated LDL, not quantified, segregated with those known to have "high cholesterol"	Pathogenic	PS3, PM2, PP1, PP3, PP5
93	HCM	*BRCA2* IVS6-1delG	No	2	No family history, but family is mostly males; index case is male	Pathogenic	PVS1, PM2, PM4
107	DCM	*HFE* H63D	Yes	4	Family history of hemochromatosis	Pathogenic	PS3, PP1, PP3, PP4, PP5
133	DCM	*FBN1* P1009R	Yes (ClinVar)	5	No indication of Marfan syndrome	Likely Pathogenic	PS3, PP3, PP5
142	LQTS, syncope	*BRIP1/FANCJ* IVS3-2A>G	No	6	Maternal family history of disease - mother breast cancer and TAH at 30 years old	Pathogenic	PVS1, PM2, PM4
152	Hearing loss and Torsade	*APC* IVS11-2A>C	No	7	Maternal family history of disease - mother colon polyps and CRC	Pathogenic	PVS1, PM2, PM4
173	TAA	*LDLR G529E*	Yes (ClinVar)	8	Variant known a FH Sicily, known personal/family history of hypercholesterolemia	Pathogenic	PS3, PS4, PP3
183	HCM	*ATM Q1852X*	Yes (ClinVar)	9	Family history of female breast and pancreatic cancers and brain tumor	Pathogenic	PVS1, PS4, PM4
195	NICM	*SCNN1B T594M*	Yes (Lancet 1998;351(9113):1388-92)	10	Known variant for hypertension in individuals of African background	Pathogenic	PS3 PS4,PP3, PP5

* Abbreviations for the ACMG Criteria: PVS – Pathogenic Very Strong, PS – Pathogenic Strong, PM – Pathogenic Moderate, PP – Pathogenic Supporting, BS – Benign Strong, BP – Benign Supporting

References:

1. Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med. 2006;354:2751-2763
2. Hakansson S, Johannsson O, Johansson U, Sellberg G, Loman N, Gerdes AM, et al. Moderate frequency of brca1 and brca2 germ-line mutations in scandinavian familial breast cancer. Am J Hum Genet. 1997;60:1068-1078
3. Bertolini S, Cantafora A, Averna M, Cortese C, Motti C, Martini S, et al. Clinical expression of familial hypercholesterolemia in clusters of mutations of the ldl receptor gene that cause a receptor-defective or receptor-negative phenotype. Arterioscler Thromb Vasc Biol. 2000;20:E41-52
4. Melis MA, Cau M, Deidda F, Barella S, Cao A, Galanello R. H63d mutation in the hfe gene increases iron overload in beta-thalassemia carriers. Haematologica. 2002;87:242-245
5. Dietz HC, McIntosh I, Sakai LY, Corson GM, Chalberg SC, Pyeritz RE, et al. Four novel fbn1 mutations: Significance for mutant transcript level and egf-like domain calcium binding in the pathogenesis of marfan syndrome. Genomics. 1993;17:468-475
6. Seal S, Thompson D, Renwick A, Elliott A, Kelly P, Barfoot R, et al. Truncating mutations in the fanconi anemia j gene brip1 are low-penetrance breast cancer susceptibility alleles. Nat Genet. 2006;38:1239-1241
7. Fodde R, Smits R, Clevers H. Apc, signal transduction and genetic instability in colorectal cancer. Nature reviews. Cancer. 2001;1:55-67
8. Hobbs, H. H. , Brown M.S., Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Hum Mutat. 1992;1: 445-66
9. Chen, P.C., Lavin, M.F., Kidson C., Moss, D. Identification of ataxia telangiectasia heterozygotes, a cancer prone population. Nature. 1978;274: 484-6
10. Baker, E.H., Dong, Y.B., Sangella, G.A., Rothwell, M., Onipinla, A.K., Mankandu N.D., *et al.* Association of hypertension with T594M mutation in beta subunit of epithelial sodium channels in black people resident in London. Lancet. 1998; 351:1388-92.

Figure S1: (A) Amplified CACNA1D RNA from a human ventricular biopsy on agarose gel. (B) Relative mRNA expression of CACNA1D compared to housekeeping gene GAPDH.