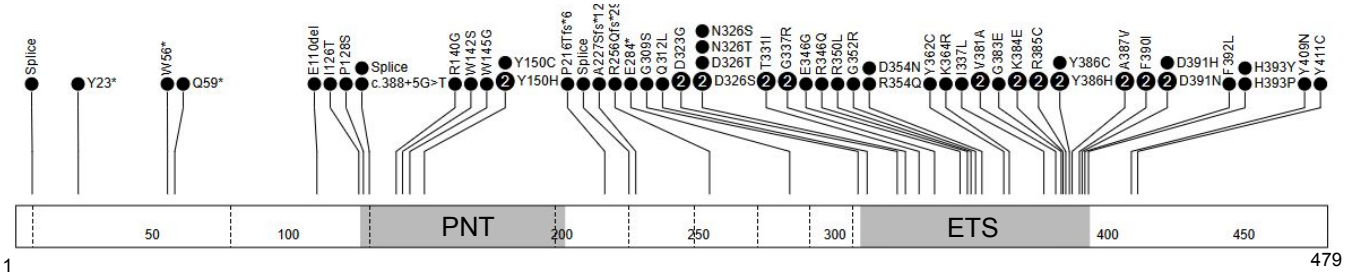
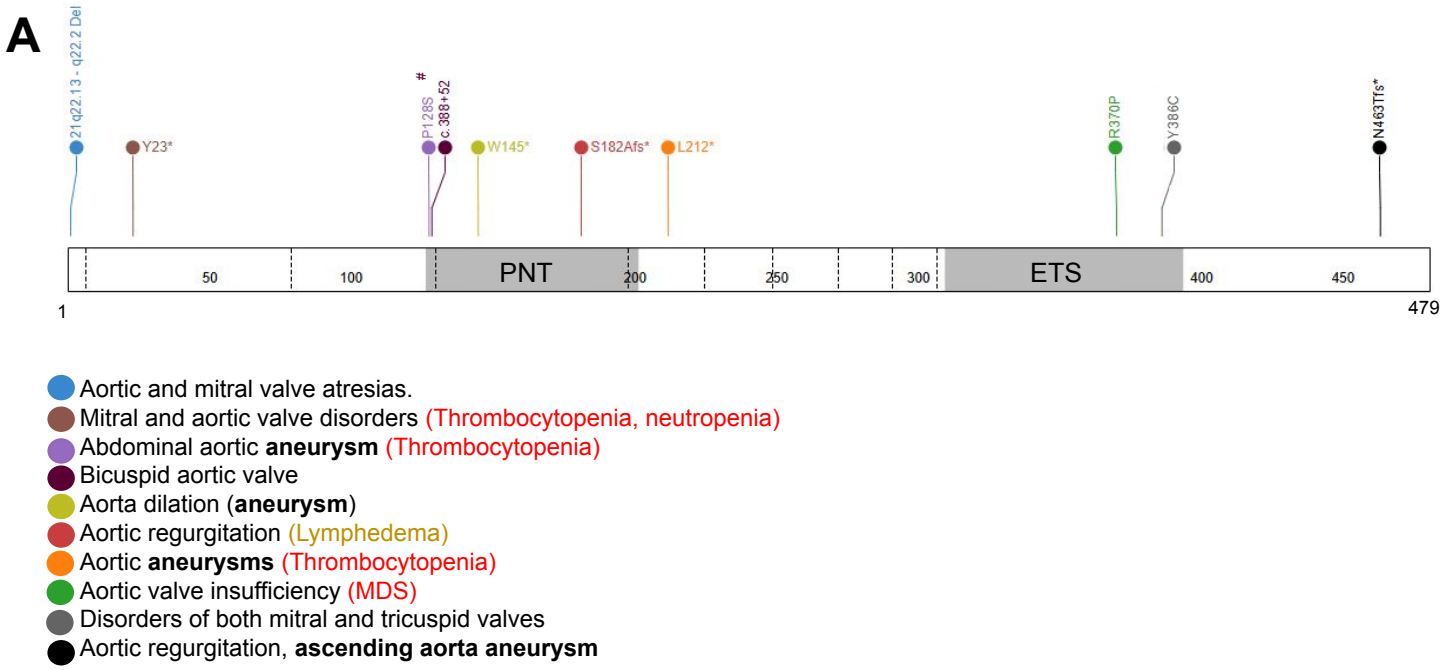
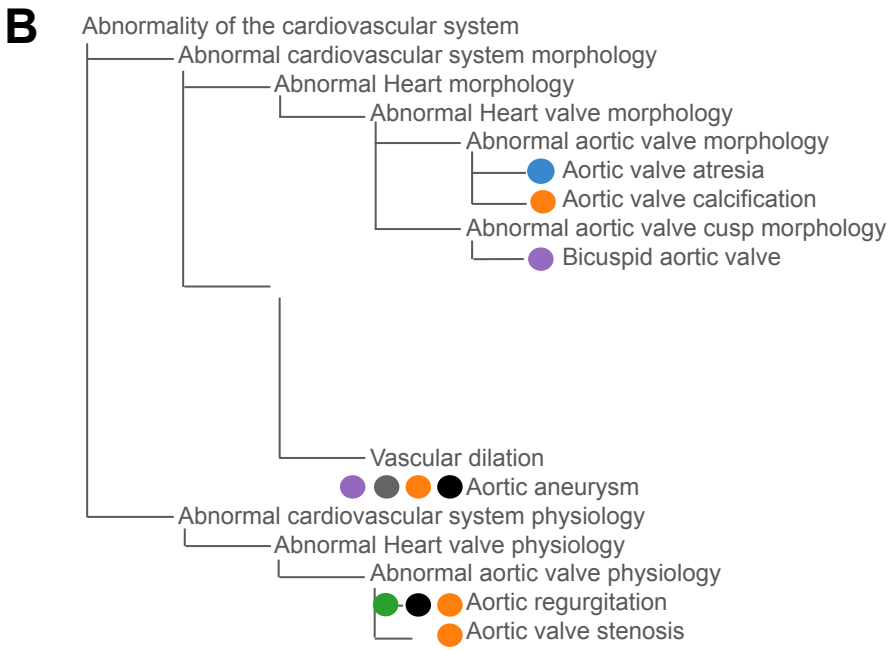
Supplemental Figures

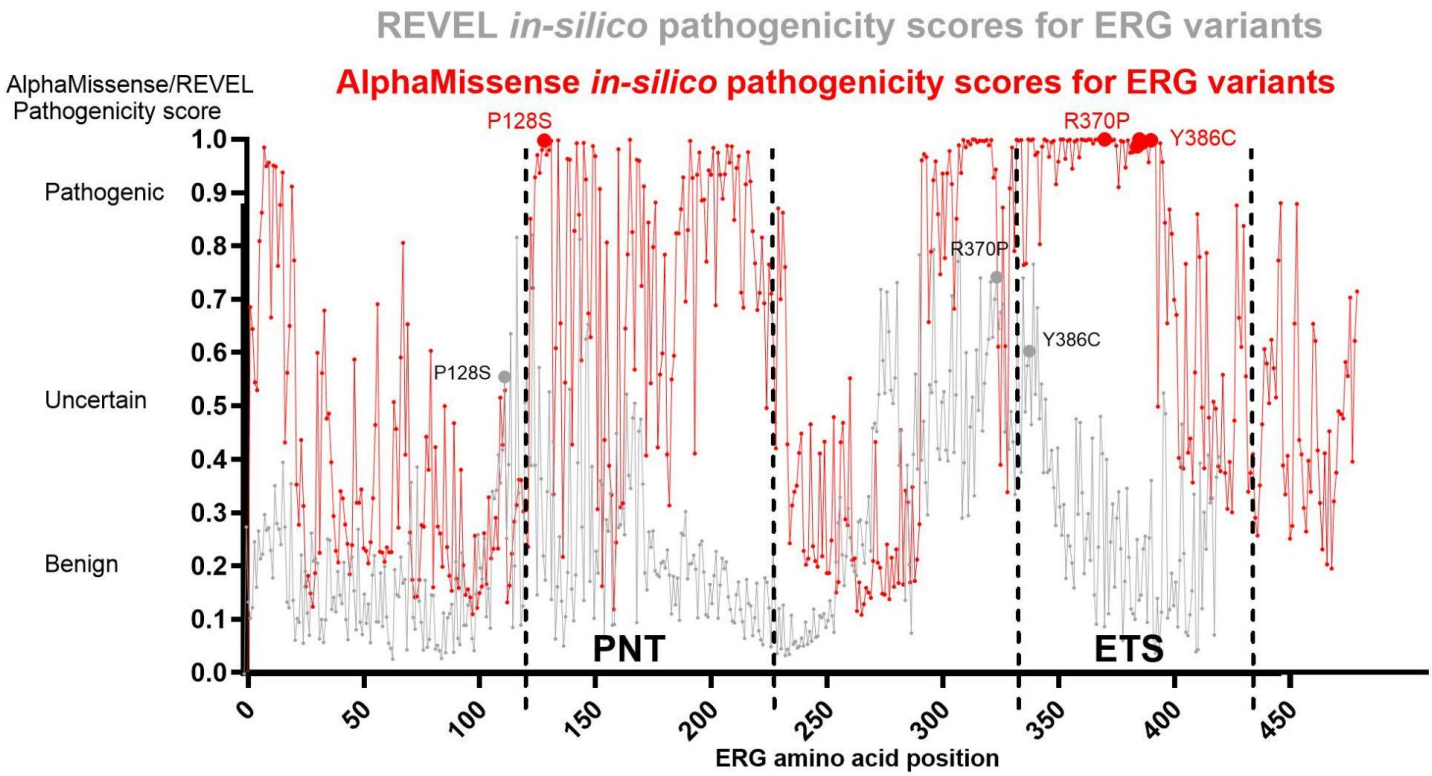


Supplemental Figure 1. Identification of high confidence rare ERG variants from population databases. Rare *ERG* variants from population databases (UK Biobank, All of Us, RGC) that passed a filtering strategy based on (i) variant type, (ii) ultra-rare allele frequency in population and (iii) *in silico* pathogenicity predictions using established algorithms (*i.e.* REVEL) and/or location (functional domain).

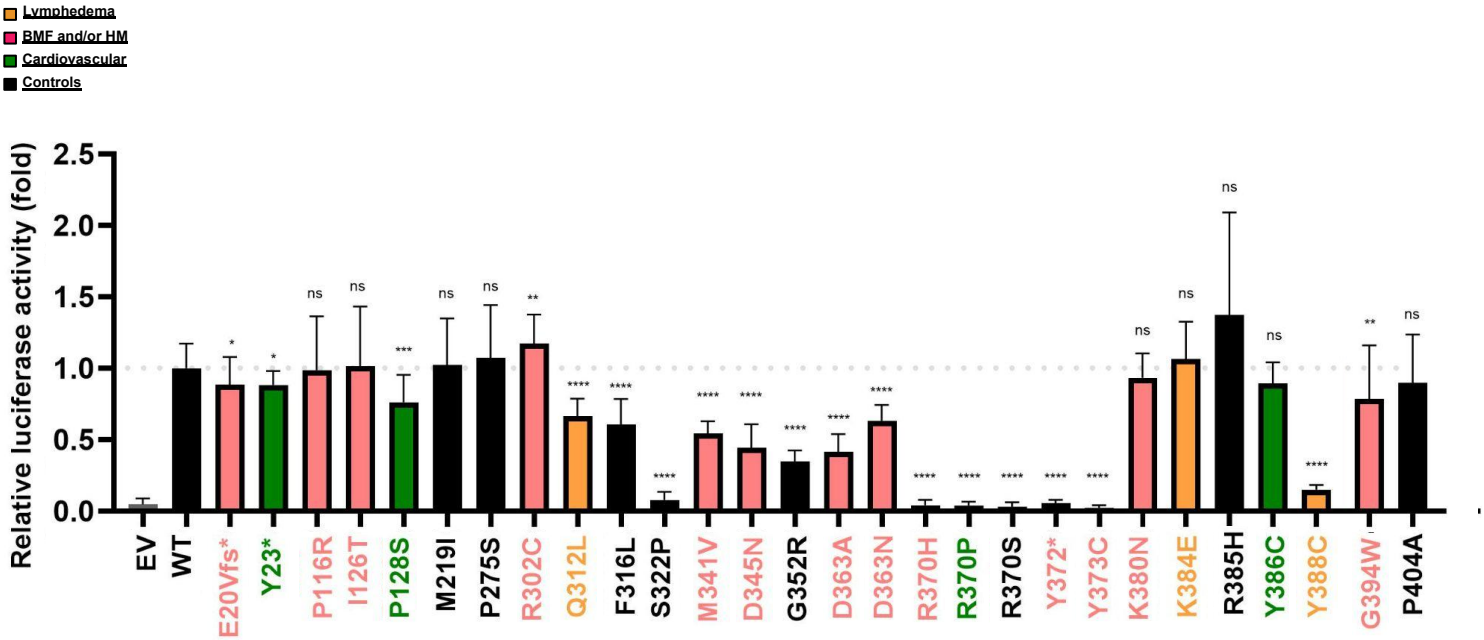




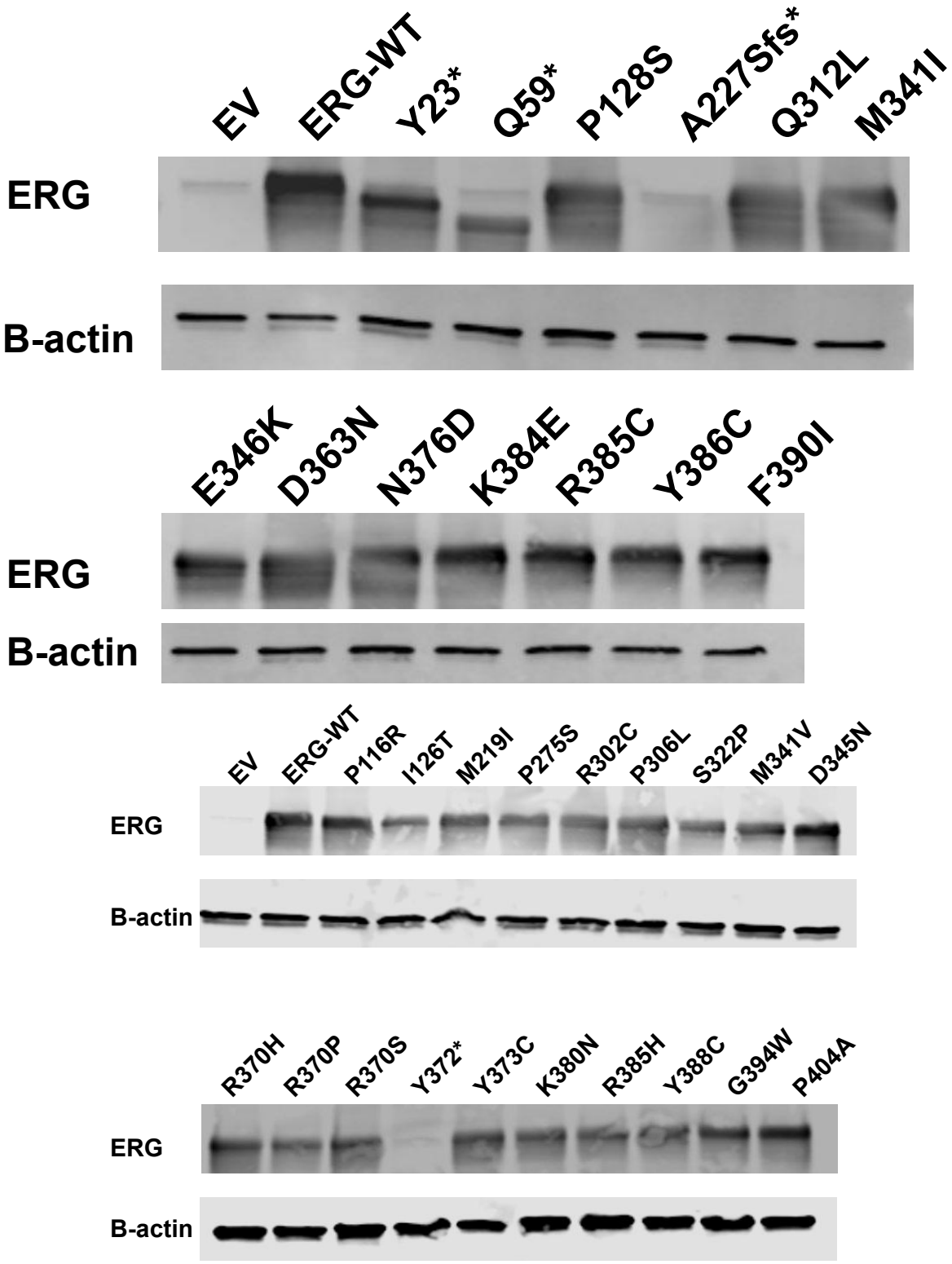
Supplemental Figure 2. Phenotypic breakdown of rare germline *ERG* variants identified in patients with aortic/mitral valve morphology and/or physiology and/or aortic aneurysm. A) Rare germline *ERG* variants from patients carrying aortic/mitral valve morphology and/or physiology and/or aortic aneurysm phenotypes are mapped onto the ERG protein (isoform, NP_891548.1; transcript, NM_182918.4). Previously reported ERG deficiency syndrome phenotypes (blood-related and lymphatic) included (brackets). ETS DNA binding domain (ETS); Pointed domain (PNT); exon junctions (black dotted lines). **B)** Patients with aortic valve dysfunction phenotypes mapped onto HPO term tree stemming from *abnormality of the cardiovascular system*. Variants (Y23*, P128S) could not be mapped due to unavailable clinical diagnosis information.



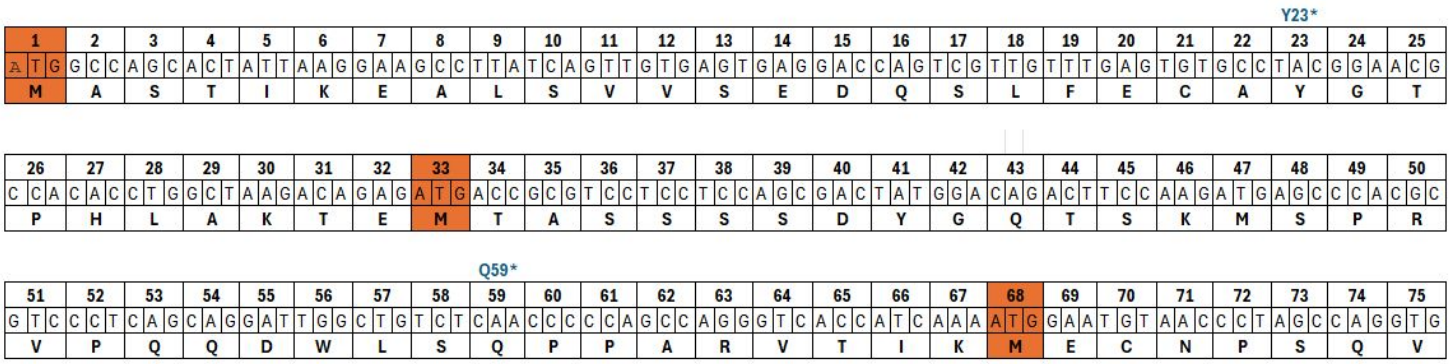
Supplemental Figure 3. ***In silico*** **pathogenicity predictor scores for** ***ERG*** **variants.** REVEL (grey) and AlphaMissense (red) scores of every possible variation at each amino acid position in NP_891548.1 were averaged and plotted. Average REVEL and AlphaMissense scores indicate pathogenicity (0.6-1.0), variants of uncertain significance (0.3-0.6) and likely benign (0.0-0.3). ETS DNA binding domain (ETS) and Pointed domain (PNT) indicated by broken black lines. Missense variants from study indicated by larger dot.



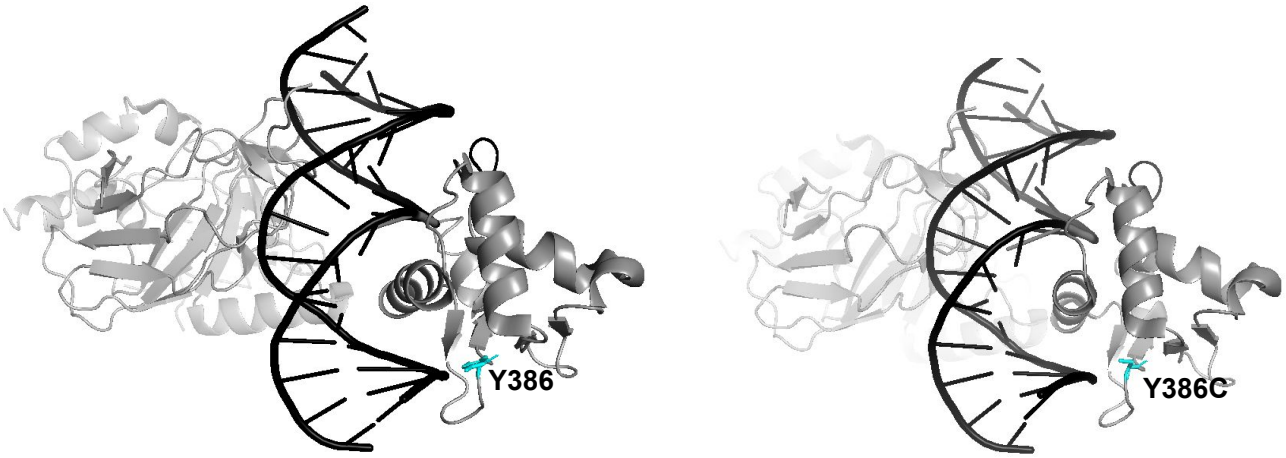
Supplemental Figure 4. Functional validation of ERG variants. K562 cells were transfected with pcDNA3 empty vector (EV) or pcDNA3-ERG (WT or variants) and co-transfected with a luciferase reporter plasmid driven by a ITGA2B promoter-Luc using lipofectamine 2000 and incubated for 20 hours before collection (quadruplicate replicates, repeated 3 times). Fold change (mean ± SEM) compared to the ERG is plotted. Pairwise comparisons are shown (* $P < 0.05$, ** $P < 0.01$, *** $P<0.001$, **** $P < 0.0001$ compared to ERG WT).



Supplemental Figure 5. Western blot of ERG-mutant lysates. Western blot of ERG-mutant lysates (previously published and novel variants). All ERG variants produced protein, except for A227Sfs*12 and Y372* (unstable). ERG early termination lysates demonstrates re-initiation and expression of smaller protein. Western blots were performed according to standard protocols probing with anti-ERG (ab92513, Abcam 1:1000) and a fluorescent secondary anti-rabbit antibody (LCR-925-68071, LI-COR 1:10,000) and anti-Bactin (3700S, CST 1:1000) and a fluorescent secondary anti-mouse antibody (LCR-925-32210, LICOR 1:10,000).

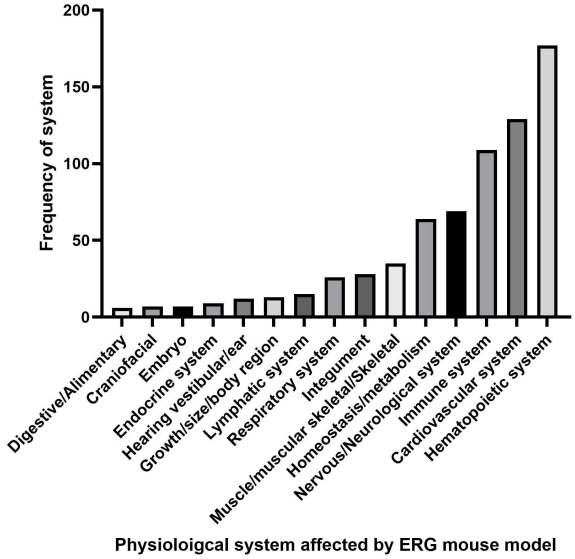


Supplemental Figure 6. ERG early terminations likely re-initiate translation. Early termination variants have inframe translation initiation sites immediately downstream, red.

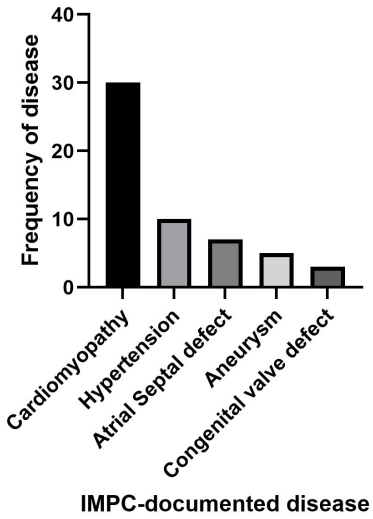


Supplemental Figure 7. Predicted modelling of Y386 missense variant. Predicted effect of ERG ETS domain variants on DNA binding - no predicted polar contacts (any hydrogen bonds) were identified. DNA (black double helix), indicated amino acid (cyan). 3D protein modelling performed on an ERG-DNA X-ray crystallography model (PDB ID: 6VGE A chain) obtained from UNIPROT online database. PyMOL was used to visualise the predicted structural impact of each variant.

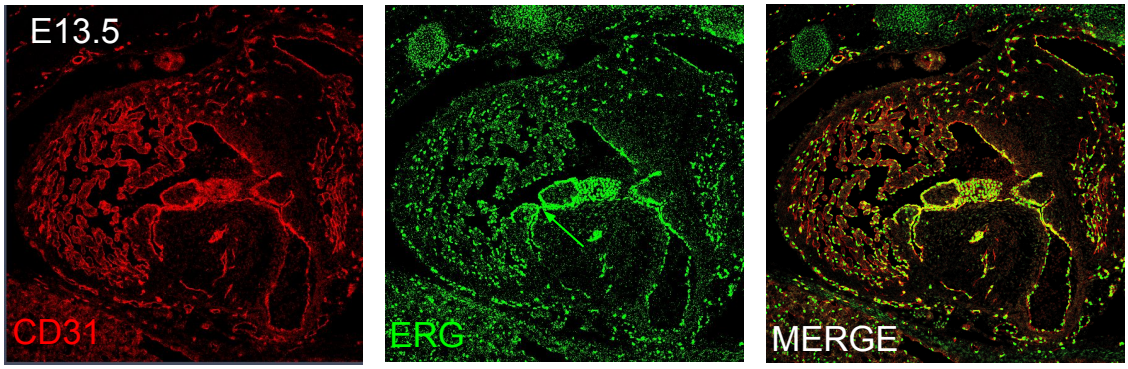
A



B



Supplemental Figure 8. Assessing the phenotypic similarity between *Erg* mouse models and human diseases revealed the two most frequently affected systems were the hematopoietic and cardiovascular systems. A) PhenoDigm scores were used to assess phenotypic similarity between human diseases and multiple Erg mouse models, including International Mouse Phenotyping Consortium (IMPC) and previously described targeted alleles ($Erg^{em1(IMPC)Bay}$, Erg^{mld2}/Erg^{+}, $Erg^{tm1.1Path}/Erg^{tm1.1Path}$ and $Erg^{tm2Poet}/Erg^{tm2Poet}$). Each IMPC documented disease was categorized into a physiological system, allowing for a system-wide analysis of *ERG*-linked phenotypes. The frequency of each physiological system was quantified, and only high-confidence associations (PhenoDigm scores >50) were included. Frequencies are shown for physiological systems observed more than five times. **B)** Top 5 most frequent IMPC diseases documented in the cardiovascular system.



Supplemental Figure 9. ERG expression in developing mitral valve. Coronal sections through the mitral valve of E13.5 wild type mouse embryos, immunostained for CD31 and ERG. ERG is highly expressed in the mitral valve (indicated by green arrow).

Supplemental Tables

Supplemental Table 1: Summary of all new and reported *ERG* variants in patients/families with ERG deficiency syndrome (SGR of pathogenic ERG variant and/or aortic/mitral valve morphology and/or physiology and/or aortic aneurysm, HM/BMF and/or lymphedema phenotypes). Variant Allele frequency (VAF); Aortic aneurysm (AA); Aortic valve dysfunction (AV); Mitral valve dysfunction (MV); tricuspid valve dysfunction (TV); Thrombocytopenia (Thr); Neutropenia (Neu); Pancytopenia (Pan); Inherited bleeding disorder (IBD); Myelodysplastic syndrome (MDS); Acute Myeloid Leukemia (AML); Acute lymphoblastic leukemia (ALL); Chronic lymphocytic leukemia (CLL); American College of Medical Genetics and Genomics (ACMG); Pathogenic (P); Likely Pathogenic (LP); Variant of Uncertain Significance (VUS); Variant of Uncertain Significance favoring pathogenicity (VUS-A). Families highlighted within black box.

Source/Reference	Family	Individual	p.HGVS (NM_182918.4) (NP_891548.1)	Germline ERG (inherited/de novo) *VAF = 40-60%	Sex	Age of diagnosis (yr)	Aortic Aneurysm	Valve dysfunction	Other Cardiovascular dysfunction	Bone Marrow Failure	Hematological malignancy	Lymphatic phenotype	Somatic Gene Rescue	ACMG classification	ACMG criteria (Modified - see Supplemental Table
International collaboration (GeneMatcher)	Family	I.I	Whole gene deletion (+2 other genes KCNJ15, KCNJ6)	Unknown	M									LP	PVS1, PM2
		II.I		Yes (inherited)	M	<18		AV MV TV							
Previously reported (Zerella et al. 2024)	Individual	I.I	p.E20Vfs*13	Yes (inherited)	M	38					MDS AML			VUS-A	PVS1_Moderate, PM2
Population database (UK Biobank)	Individual	I.I	p.Y23*	Yes*	M			MV AV		Thr Neu				VUS-A	PVS1_Moderate, PM2
Previously reported (Zerella et al. 2024)	Individual	I.I	p.P116R		F	73				Thr				VUS	BS3_Supporting
Previously reported (Zerella et al. 2024)	Individual	I.I	p.I126T	Yes (unknown)		<14				Thr	AML			VUS	BS3_Supporting, PM2_Supporting
Previously reported (Zerella et al. 2024)	Individual	I.I	p.V127Efs*82	Yes (unknown)		<18					ALL			VUS-A	PVS1, PM2
Population database (UK Biobank)	Individual	I.I	p.P128S	Yes*	M		AA			Thr				LP	PS3, PP3_Supporting, PM2_Supporting
National collaboration	Individual	I.I	c.388+52C>G	Unknown	M			AV						VUS-A	PVS1, PM2
International collaboration (GeneMatcher)	Individual	I.I	p.W145*	Yes *(de novo)*		0	AA							P	PVS1, PS2, PM2
Previously reported (Greene et al. 2023)	Family	I.I	p.S182Afs*22	Unknown	F									P	PVS1, PM2, PM3
		II.I	p.S182Afs*22	Yes (inherited)	M			AV							
Previously reported (Erhart et al. 2025)	Family	I.I	p.L212*	Unknown	M	49	AA	AV MV		Thr				LP	PVS1, PM2
		I.II	p.L212*	Yes (inherited)	M	18									
Previously reported (Greene et al. 2023)	Individual	I.I	p.T224Rfs*15	Yes (*de novo*)	M	<1								P	PVS1, PS2, PM2
Previously reported (Zerella et al. 2024)	Individual	I.I	p.R302C	Yes (unknown)	M						CLL			VUS	PS3_Supporting, PP3
Population database (UK Biobank)	Individual	I.I	p.Q312L	Yes*										LP	PS3, PP3_Moderate, PM2_Supporting
Population database (UK Biobank)	Individual	I.I	p.F316L	Unknown	F									LP	PS3, PP3, PM2_Supporting, PM3
Previously reported (Zerella et al. 2024)	Family	I.I	p.M341V	Unknown	M									LP	PS3, PM5, PM2_Supporting
		I.II	p.M341V	Yes (inherited)	F	0				BMF					
Previously reported (Zerella et al. 2024)	Individual	I.I	p.M341V	Unknown	F	56				BMF	MDS			LP	PS3, PM5, PM2_Supporting

Previously reported (Zerella et al. 2024)	Individual	I.I	p.D345N	Likely Somatic							MDS			LP	PS3, PP3_Supporting, PM1, PM2_Supporting	
Population database (UK Biobank)	Individual	I.I	p.G352R	Unknown	F									LP	PS3, PP3_Strong, PM2_Supporting, PM3	
Previously reported (Zerella et al. 2024)	Individual	I.I	p.D363A	Likely Somatic							MDS			LP	PS3, PM2_Supporting, PM1_Supporting, PM5	
International collaboration	Individual	I.I	p.D363N	Yes*							MDS			P	PS3, PM3, PP3_Supporting, PM1_Supporting, PM2_Supporting, PM5	
Previously reported (Zerella et al. 2024)	Family	II.I	p.R370H	Yes (inherited)	M	0				Neu Pan	AML			P	PS3, PM1, PM2-Supporting, PM3, PM5, PP3	
		II.II	p.R370H	Yes (inherited)	F	NA										
		II.III	Unknown													
Previously reported (Zerella et al. 2024)	Individual	I.I	p.R370P	Yes (inherited)	M	29		AV		Thr Leu	MDS			P	PS3, PM1, PM2-Supporting, PM5, PP3	
Previously reported (Zerella et al. 2024)	Individual	I.I	p.Y372*	Yes (*de novo*)	M	0				BMF Pan				P	PVS1, PS2, PM2	
Previously reported (Zerella et al. 2024)	Family	I.I	p.Y373C	Unknown	F	27				Thr Neu	MDS AML			P	PS3, PM1, PM2_Supporting, PM3, PP1, PP3_Strong	
		II.I	p.Y373C	Yes (Inherited)	M	19				Thr Neu						
		II.II	p.Y373C	Yes (Inherited)	M	21				Thr Neu						
Previously reported (Zerella et al. 2024)	Individual	I.I	p.K380N	Yes (*de novo*)		>18				Pan Thr				LP	PS2, PS3_Supporting, PM1_Supporting, PM2_Supporting, PP3_moderate	
Population database (UK Biobank)	Individual	I.I	p.K384E	Yes*	M					Thr				VUS-A	PS3_Supporting, PM1_Supporting, PM2_Supporting, PP3_Moderate	
Population database (All of us)	Individual	I.I	p.Y386C	Yes*				MV TV						LP	PS3_Moderate, PM1_Supporting, PM2_Supporting, PP3_Moderate	
Previously reported (Zerella et al. 2024)	Family	I.I	p.Y388C	Unknown	F	8								P	PS3, PM1_Supporting, PM2_Supporting, PM3, PP3_Strong	
		II.I	p.Y388C	Yes (inherited)	F	~50										
Previously reported (Zerella et al. 2024)	Individual	I.I	p.G394W	Yes (unknown)							AML			VUS	PS3_Supporting, PM2_Supporting, PP3_Moderate	
International collaboration	Individual	I.I	p.F446Lfs*59	Yes (*de novo*)	M	9				IBD				LP	PVS1_Moderate, PM2, PS2	
Previously reported (Greene et al. 2023)	Family	I.I	p.N463Tfs*42	Unknown	M									VUS-A	PS3, PM2	
		II.I	p.N463Tfs*42	Yes (inherited)	F			AV								
		II.II	p.N463Tfs*42	Yes (inherited)	M	~13	AA	AV TV								

Supplemental Table 2: High confidence rare *ERG* variants are hidden in population/phenotype databases. *ERG* variants from allele frequency browsers of All of Us, Regeneron Genetics center, UK Biobank, Geno2MP and Decipher were pulled down and filtered using (i) Variant type, (ii) ultra-rare allele frequency in population and (iii) in silico pathogenicity predictions using established algorithms (i.e., REVEL ≥0.6) and location (functional domain). Variants that passed these criteria below. Variants that progressed to functional validation are highlighted with black boxes. Not applicable, NA.

Database	g.HGVS (GRCh38/hg38) (Chr21)	ERG p.HGVS (NP 891548.1) (ENSP298319.7) (479 aa)	Variant Type	Allele frequency (gnomAD v 4.0.0)	Situated in PNT/ETS domain	REVEL score	GENEie	Metadome tolerance to variation score	ERG deficiency syndrome phenotype	Phenotype
Decipher	21:38546420-40477677 Del	NA	Partial deletion (deletes promoter of some ERG transcripts and not others)	NA	NA	NA	NA	NA	None reported	
All of Us	21:38584842 AC>A	c.-48+1del	Splice donor	0	NA	NA	Uncertain	NA	None reported	Cataract: 2; Nicotine dependence: 1; Arthritis of shoulder region joint: 1; Premature beats: 1; Iron deficiency anemia: 1; Inflammatory disorder of digestive tract: 1; Kidney stone: 1; Depressive disorder: 1; Sciatica: 1; Myopia: 1
All of Us	21:38575697 T>TCATG	p.Ile2HisfsTer21 (I2Hfs*21)	Frameshift	0	NA	NA	NA	NA	None reported	Depressive disorder: 1
All of Us	21:38575661 C>T	c.39+1G>A	Splice donor	0	NA	NA	Uncertain	NA	None reported	Hemorrhage of rectum and anus: 1; Adrenocortical hyperfunction: 1
All of Us	21:38445622 C>T	c.19-1G>A	Splice acceptor	0	NA	NA	Splice altering (95% probability)	NA	None reported	Bipolar affective disorder, currently manic, mild: 1
UK Biobank	21:38445571 G>T	p.Tyr23Ter (Y23*)	Termination	1	NA	NA	NA	NA	Yes Disorders of both mitral and aortic valves	D70 Agranulocytosis, E87.1 Hypo osmolality and hyponatraemia, G47.3 Sleep apnoea, I08.0 Disorders of both mitral and aortic valves, I10 Essential (primary) hypertension, I25.1 Atherosclerotic heart disease, I26.9 Pulmonary embolism without mention of acute cor pulmonale, I44.0 Atrioventricular block, first degree, I80.0 Phlebitis and thrombophlebitis of superficial vessels of lower extremities, L97 Ulcer of lower limb, not elsewhere classified, M41.96 Scoliosis, unspecified (Lumbar region), M43.16 Spondylolisthesis (Lumbar region), M47.86 Other spondylosis (Lumbar region), M48.06 Spinal stenosis (Lumbar region), M51.2 Other specified intervertebral disk displacement, M51.3 Other specified intervertebral disk degeneration, M54.5R Low back pain (Sacral and sacrococcygeal region), M54.59 Low back pain (Site unspecified), M54.9R Dorsalgia, unspecified (Sacral and sacrococcygeal region), M54.99 Dorsalgia, unspecified (Site unspecified), M79.69 Pain in limb (Site unspecified), N18.3 Chronic kidney disease, stage 3, N19 Unspecified renal failure, R06.0 Dyspnoea, R07.3 Other chest pain, R07.4 Chest pain, unspecified, R41.0 Disorientation, unspecified, Y83.1 Surgical operation with implant of artificial internal device, Z51.2 Other chemotherapy, Z86.7 Personal history of diseases of the circulatory system, Z87.2 Personal history of diseases of the skin and subcutaneous tissue, Z87.3 Personal history of diseases of the musculoskeletal system and connective tissue, Z92.1 Personal history of long term (current) use of anticoagulants
All of Us	21:38445473 C>T	p.Trp56Ter (W56*)	Termination	0	NA	NA	NA	NA	None reported	Closed fracture proximal tibia, bicondylar: 1
UK Biobank	21:38445465 G>A	p.Glu59Ter (Q59*)	Termination	1	NA	NA	NA	NA	None reported	D25.9 Leiomyoma of uterus, unspecified, D35.1 Parathyroid gland, K44.9 Diaphragmatic hernia without obstruction or gangrene, N85.2 Hypertrophy of uterus, N92.0 Excessive and frequent menstruation with regular cycle, Z30.2 Sterilisation
RGC Million Exome Variant Browser	21:38425405 C>A	c.388+5G>T	Splice	1	NA	NA	Splice altering (75% probability)	NA	Unknown	
All of Us	21:38423467 TCTC>T	p.Glu110del (E116del)	In frame deletion	2	PNT	NA	NA	NA	None reported	Obstructive sleep apnea syndrome: 1
UK Biobank	21:38423416 G>A	p.Pro128Ser (P128S)	Missense	2	PNT	0.598	NA	0.35 (intolerant)	Yes Thrombocytopenia, Abdominal aortic aneurysm	D64.9 Anaemia, unspecified, D69.6 Thrombocytopenia, unspecified, I10 Essential (primary) hypertension, I48 Atrial fibrillation and flutter, I48.0 Paroxysmal atrial fibrillation, I48.9 Atrial fibrillation and atrial flutter, unspecified, I67.8 Other specified cerebrovascular diseases, I70.00 Atherosclerosis of aorta (without gangrene), I71.4 Abdominal aortic aneurysm, without mention of rupture, I80.3 Phlebitis and thrombophlebitis of lower extremities, unspecified, K25.9 Unspecified as acute or chronic, without haemorrhage or perforation, K29 Gastritis and duodenitis, K29.7 Gastritis, unspecified, K30 Dyspepsia, K59.0 Constipation, K76.8 Other specified diseases of liver, L03.1 Cellulitis of other parts of limb, M17.9 Gonarthrosis, unspecified, M47.86 Other spondylosis (Lumbar region), M79.8 Other specified soft tissue disorders, N40 Hyperplasia of prostate, R00.1 Bradycardia, unspecified, R07.2 Precordial pain, R63.4 Abnormal weight loss, S00.8 Superficial injury of other parts of head, S06.50 Traumatic subdural haemorrhage (without open intracranial wound), S36.80 Injury of other intra abdominal organs (without open wound into cavity), S62.00 Fracture of navicular [scaphoid] bone of hand (closed), S62.30 Fracture of other metacarpal bone (closed), S62.80 Fracture of other and unspecified parts of wrist and hand (closed), S70.9 Superficial injury of hip and thigh, unspecified, S89.9 Unspecified injury of lower leg, V13.4 Driver injured in traffic accident, Z03.8 Observation for other suspected diseases and conditions, Z50.1 Other physical therapy, Z87.1 Personal history of diseases of the digestive system, Z92.1 Personal history of long term (current) use of anticoagulants, Z92.2 Personal history of long term (current) use of other medicaments
RGC Million Exome Variant Browser	21:38403673 C>G	p.Trp142Ser (W142S)	Missense	0	PNT	0.936	NA	0.53 (slightly intolerant)	Unknown	Unknown
RGC Million Exome Variant Browser	21:38403665 A>C	p.Trp145Gly (W145G)	Missense	0	PNT	0.656	NA	0.65 (slightly intolerant)	Unknown	Unknown
All of Us	21:38403649 T>C	p.Tyr150Cys (Y150C)	Missense	0	PNT	0.653	NA	0.97 (slightly intolerant)	None reported	
All of Us	21:38403650 A>G	p.Tyr150His (Y150H)	Missense	1	PNT	0.587	NA	0.97 (slightly intolerant)	None reported	Depressive disorder: 1
RGC Million Exome Variant Browser	21:38403650 A>G	p.Tyr150His (Y150H)	Missense	1	PNT	0.587	NA	0.97 (slightly intolerant)	Unknown	
All of Us	21:38403710 C>A	c.389-1G>T	Splice acceptor	0	NA	NA	Splice altering (99% probability)	NA	None reported	Disorder of intestine: 1; Genitourinary tract hemorrhage: 1; Uterine scar from previous surgery in pregnancy, childbirth and the puerperium: 1
All of Us	21:38402583 GGA>G	p.Pro216Thrfs*6 (P216Tfs*6)	Frameshift	1	NA	NA	NA	NA	None reported	Patent ductus arteriosus: 1
UK Biobank	21:38400638 TGC>T	p.Ala227Serfs*12 (A227Sfs*12)	Frameshift	1	NA	NA	NA	NA	None reported	null
All of Us	21:38392428 G>GT	p.Arg256Glnfs*29 (R256Qfs*29)	Frameshift	2	NA	NA	NA	NA	None reported	
All of Us	21:38392377 T>C	c.813A>G	Splice	0	NA	NA	Splice altering (75% probability)	NA	None reported	Hyperlipidemia: 1
All of Us	21:38391680 C>A	p.Glu284Ter (E284*)	Termination	0	NA	NA	NA	NA	None reported	Melanocytic nevus of trunk: 1; Neoplasm of uncertain behavior of skin: 1
UK Biobank	21:38383908 T>A	p.Gln312Leu (Q312L)	Missense	1	ETS	0.73	NA	0.28 (intolerant)	Yes localized edema	A09.9 Gastroenteritis and colitis of unspecified origin, A41.9 Septicaemia, unspecified, B95.1 Streptococcus, group B, as the cause of diseases classified to other chapters, B95.6 Staphylococcus aureus as the cause of diseases classified to other chapters, B96.2 Escherichia coli [E. coli] as the cause of diseases classified to other chapters, C90.0 Multiple myeloma, D18.0 Haemangioma, any site, D70 Agranulocytosis, E83.5 Disorders of calcium metabolism, E87.6 Hypokalaemia, F41.9 Anxiety disorder, unspecified, I26.9 Pulmonary embolism without mention of acute cor pulmonale, I27.2 Other secondary pulmonary hypertension, I51.7 Cardiomegaly, I84.5 External haemorrhoids without complication, J10.0 Influenza with pneumonia, influenza virus identified, J10.1 Influenza with other respiratory manifestations, influenza virus identified, J12.1 Respiratory syncytial virus pneumonia, J18.0 Bronchopneumonia, unspecified, J18.1 Lobar pneumonia, unspecified, J22 Unspecified acute lower respiratory infection, J45.9 Asthma, unspecified, J90 Pleural effusion, not elsewhere classified, J96.9 Respiratory failure, unspecified, J96.91 Respiratory failure unspecified; Type II [hypercapnic], K20 Oesophagitis, K44.9 Diaphragmatic hernia without obstruction or gangrene, K59.0 Constipation, K83.0 Cholangitis, M19.9 Arthrosis, unspecified, M41.9 Scoliosis, unspecified, M48.54 Collapsed vertebra, not elsewhere classified (Thoracic region), M94.0 Chondrocostal junction syndrome [Tietze], N39.0 Urinary tract infection, site not specified, R06.0 Dyspnoea, R09.2 Respiratory arrest, R10.1 Pain localised to upper abdomen, R10.3 Pain localised to other parts of lower abdomen, R11 Nausea and vomiting, R50.9 Fever, unspecified, R60.0 Localised oedema, Z02.8 Other examinations for administrative purposes, Z51.1 Chemotherapy session for neoplasm, Z51.2 Other chemotherapy, Z53.8 Procedure not carried out for other reasons, Z73.9 Problem related to life management difficulty, unspecified, Z86.0 Personal history of other neoplasms, Z86.4 Personal history of psychoactive substance abuse, Z86.7 Personal history of diseases of the circulatory system, Z92.1 Personal history of long term (current) use of anticoagulants, Z92.6 Personal history of chemotherapy for neoplastic disease, Z99.8 Dependence on other enabling machines and devices
RGC Million Exome Variant Browser	21:38383875 T>C	p.Asp323Gly (D323G)	Missense	1	ETS	0.676	NA	0.06 (highly intolerant)	Unknown	Unknown
UK Biobank	21:38383875 T>C	p.Asp323Gly (D323G)	Missense	1	ETS	0.676	NA	0.06 (highly intolerant)	Essential (primary) hypertension	I10 Essential (primary) hypertension, R55 Syncope and collapse, S00.8 Superficial injury of other parts of head, S50.9 Superficial injury of forearm, unspecified, W01.0 Home
UK Biobank	21:38383834 C>G	p.Gly337Arg (G337R)	Missense	1	ETS	0.66	NA	0.25 (intolerant)	Unknown	
RGC Million Exome Variant Browser	21:38383834 C>T	p.Gly337Arg (G337R)	Missense	1	ETS	0.66	NA	0.25 (intolerant)	Unknown	
All of Us	21:38383806 T>C	p.Glu346Gly (E346G)	Missense	0	ETS	0.59	NA	0.5 (intolerant)	None reported	
All of Us	21:38383758 T>C	p.Tyr362Cys (Y362C)	Missense	0	ETS	0.854	NA	0.22 (intolerant)	None reported	Bite wound: 1
RGC Million Exome Variant Browser	21:38383701 A>G	p.Val381Ala (V381A)	Missense	2	ETS	0.681	NA	0.13 (highly intolerant)	Unknown	Unknown
UK Biobank	21:38383701 A>G	p.Val381Ala (V381A)	Missense	2	ETS	0.681	NA	0.13 (highly intolerant)	None reported	Patient 1: F31.9 Bipolar affective disorder, unspecified, M72.0 Palmar fascial fibromatosis [Dupuytren], R69 Unknown and unspecified causes of morbidity Patient 2: K04.8 Radicular cyst
RGC Million Exome Variant Browser	21:38383695 C>T	p.Gly383Glu (G383E)	Missense	0	ETS	0.862	NA	0.12 (highly intolerant)	Unknown	Unknown
UK Biobank	21:38383693 T>C	p.Lys384Glu (K384E)	Missense	2	ETS	0.687	NA	0.11 (highly intolerant)	Yes Thrombocytopenia, Localized edema	A09.9 Gastroenteritis and colitis of unspecified origin, C17.0 Duodenum, C18.7 Sigmoid colon, D12.3 Transverse colon, D12.5 Sigmoid colon, D37.4 Colon, D50.9 Iron deficiency anaemia, unspecified, D69.6 Thrombocytopenia, unspecified, E11.9 Without complications, E87.6 Hypokalaemia, H35.0 Background retinopathy and retinal vascular changes, H53.8 Other visual disturbances, H81.1 Benign paroxysmal vertigo, H90.3 Sensorineural hearing loss, bilateral, I891.9 Hearing loss, unspecified, I893.1 Tinnitus, I10 Essential (primary) hypertension, I48.1 Persistent atrial fibrillation, I48.9 Atrial fibrillation and atrial flutter, unspecified, I50.0 Congestive heart failure, I50.9 Heart failure, unspecified, I51.7 Cardiomegaly, I67.9 Cerebrovascular disease, unspecified, I70.9 Generalised and unspecified atherosclerosis, I84.2 Internal haemorrhoids without complication, I84.9 Unspecified haemorrhoids without complication, I86.8 Varicose veins of other specified sites, J96.90 Respiratory failure, unspecified; Type I [hypoxic], K21.9 Gastro oesophageal reflux disease without oesophagitis, K22.2 Oesophageal obstruction, K30 Dyspepsia, K44.9 Diaphragmatic hernia without obstruction or gangrene, K58.9 Irritable bowel syndrome without diarrhoea, K63.8 Other specified diseases of intestine, K76.0 Fatty (change of) liver, not elsewhere classified, K80.2 Calculus of gallbladder without cholecystitis, K85.1 Biliary acute pancreatitis, M10.9 Gout, unspecified, M13.9 Arthritis, unspecified, M47.9 Spondylosis, unspecified, M79.86 Other specified soft tissue disorders (Lower leg), N17.9 Acute renal failure, unspecified, N18.1 Chronic kidney disease, stage 1, N18.3 Chronic kidney disease, stage 3, N39.0 Urinary tract infection, site not specified, N40 Hyperplasia of prostate, N48.5 Ulcer of penis, R10.1 Pain localised to upper abdomen, R11 Nausea and vomiting, R18 Ascites, R55 Syncope and collapse, R60.0 Localised oedema, R63.4 Abnormal weight loss, R93.3 Abnormal findings on diagnostic imaging of other parts of digestive tract, R94.5 Abnormal results of liver function studies, Y83.2 Surgical operation with anastomosis, bypass or graft, Y83.6 Removal of other organ (partial) (total), Z03.8 Observation for other suspected diseases and conditions, Z09.0 Follow up examination after surgery for other conditions, Z12.1 Special screening examination for neoplasm of intestinal tract, Z50.1 Other physical therapy, Z53.0 Procedure not carried out because of contraindication, Z72.1 Alcohol use, Z85.0 Personal history of malignant neoplasm of digestive organs, Z86.4 Personal history of psychoactive substance abuse, Z86.6 Personal history of diseases of the nervous system and sense organs, Z87.1 Personal history of diseases of the digestive system, Z90.4 Acquired absence of other parts of digestive tract, Z92.1 Personal history of long term (current) use of anticoagulants, Z92.2 Personal history of long term (current) use of other medicaments
RGC Million Exome Variant Browser	21:38383693 T>C	p.Lys384Glu (K384E)	Missense	2	ETS	0.687	NA	0.11 (highly intolerant)	Unknown	Unknown
UK Biobank	21:38383690 G>A	p.Arg385Cys (R385C)	Missense	2	ETS	0.619	NA	0.15 (highly intolerant)	No	A09.9 Gastroenteritis and colitis of unspecified origin, D27 Benign neoplasm of ovary, I10 Essential (primary) hypertension, K07.3 Anomalies of tooth position, M17.9 Gonarthrosis, unspecified, N83.2 Other and unspecified ovarian cysts, R07.3 Other chest pain, R07.4 Chest pain, unspecified, R10.4 Other and unspecified abdominal pain, R20.2 Paraesthesia of skin, Z72.1 Alcohol use, Z82.4 Family history of ischaemic heart disease and other diseases of the circulatory system
RGC Million Exome Variant Browser	21:38383690 G>A	p.Arg385Cys (R385C)	Missense	2	ETS	0.619	NA	0.15 (highly intolerant)	Unknown	Unknown
All of Us	21:38383686 T>C	p.Tyr386Cys (Y386C)	Missense	0	ETS	0.735	NA	0.19 (intolerant)	Yes Disorders of both mitral and tricuspid valves	Disorder of intestine: 1; Disorders of both mitral and tricuspid valves: 1
UK Biobank	21:38383687 A>G	p.Tyr386His (Y386H)	Missense	1	ETS	0.698	NA	0.19 (intolerant)	No	NA
RGC Million Exome Variant Browser	21:38383687 A>G	p.Tyr386His (Y386H)	Missense	1	ETS	0.698	NA	0.19 (intolerant)	Unknown	Unknown
All of Us	21:38383683 G>A	p.Ala387Val (A387V)	Missense	0	ETS	0.6996	NA	0.16 (highly intolerant)	None reported	Disorder of thyroid gland: 1
RGC Million Exome Variant Browser	21:38383675 A>T	p.Phe390Ile (F390I)	Missense	1	ETS	0.821	NA	0.2 (intolerant)	Unknown	Unknown
UK Biobank	21:38383675 A>T	p.Phe390Ile (F390I)	Missense	1	ETS	0.821	NA	0.2 (intolerant)	No	E11.9 Without complications, E66.9 Obesity, unspecified, E78.0 Pure hypercholesterolaemia, H26.9 Cataract, unspecified, I10 Essential (primary) hypertension, I25.1 Atherosclerotic heart disease, I25.2 Old myocardial infarction, I25.9 Chronic ischaemic heart disease, unspecified, I48.9 Atrial fibrillation and atrial flutter, unspecified, L40.9 Psoriasis, unspecified, Y83.2 Surgical operation with anastomosis, bypass or graft, Z50.1 Other physical therapy, Z86.4 Personal history of psychoactive substance abuse, Z87.4 Personal history of diseases of the genito urinary system
UK Biobank	21:38383672 C>G	p.Asp391His (D391H)	Missense	0	ETS	0.648	NA	0.25 (intolerant)	Unknown	
UK Biobank	21:38383669 A>G	p.Phe392Leu (F392L)	Missense	1	ETS	0.512	NA	0.24 (intolerant)	Unknown	
UK Biobank	21:38383618 A>T	p.Tyr409Asn (Y409N)	Missense	1		0.593	NA	0.45 (intolerant)	None reported	C43.5 Malignant melanoma of trunk, E78.0 Pure hypercholesterolaemia, I10 Essential (primary) hypertension, K21.9 Gastro oesophageal reflux disease without oesophagitis, L21.9 Seborrhoeic dermatitis, unspecified, L90.5 Scar conditions and fibrosis of skin, M10.99 Gout, unspecified (Site unspecified), M13.99 Arthritis, unspecified (Site unspecified), M16.1 Other primary coxarthrosis, N35.9 Urethral stricture, unspecified, N36.0 Urethral fistula, N40 Hyperplasia of prostate, R31 Unspecified haematuria, R33 Retention of urine, R79.8 Other specified abnormal findings of blood chemistry, S63.0 Dislocation of wrist, S63.3 Traumatic rupture of ligament of wrist and carpus, T83.0 Mechanical complication of urinary (indwelling) catheter, W10.9 Unspecified place, Y83.1 Surgical operation with implant of artificial internal device, Y84.6 Urinary catheterisation, Z46.6 Fitting and adjustment of urinary device, Z53.8 Procedure not carried out for other reasons, Z85.8 Personal history of malignant neoplasms of other organs and systems, Z87.4 Personal history of diseases of the genito urinary system, Z96.6 Presence of orthopaedic joint implants
UK Biobank	21:38383611 T>C	p.Tyr411Cys (Y411C)	Missense	0		0.609	NA	0.46 (intolerant)	None reported	D26.1 Corpus uteri, N81.2 Incomplete uterovaginal prolapse

Supplemental Table 2. Rare heterozygous *ERG* variants associated with aortic/mitral valve morphology and/or physiology and/or aortic aneurysm. Patients 6-8, 10-11 have been previously published (7–9,27). Information unknown (blank); Peripheral blood (PB); Not applicable (NA); Not performed (NP).

Patient ID	Family member	g.HGVS (GRCh38/hg38) (Chr21)	ERG c.HGVS (NM_182918.4)	ERG p.HGVS (NP_891548.1) (ENSP00000288319.7) (479 aa)	Variant Class	VAF (%)	Sex	Sample analyzed	gnomAD (v 4.0.0)	COSMIC (v99)	CADD Score (Raw rank score)	REVEL Score (Rank score)	Ages onset of phenotypes (yr)	Germline ERG cVAF is within germline range (40-60%)	Chr21q cnLOH	ERG deficiency syndrome Phenotype	Other phenotype/s
1	1	Minimum deletion chr21:37,994,184-38,423,616 (hg38) ERG, KCNJ15 Maximum deletion chr21:37,916,342-38,445,595 (hg38) ERG, KCNJ15, KCN26	NA	NA	Whole gene deletion (+2 other genes KCNJ15, KCN26)		Male	Blood	NA	NA	NA	NA	<1ß	paternally inherited	No	Aortic and mitral valve atresias Mild to moderate tricuspid valve insufficiency.	Hypoplastic left heart syndrome, with severe left ventricular hypoplasia, unrestrictive atrial shunt. Severe long segment coarctation of the aorta. Sinus rhythm with 1:1 AV conduction
2	1	21:38445571G>T	c.69C>A	p.Tyr23Ter (Y23*)	Termination	40-60	Male	PB	1	1	38 (0.976)	NA		Yes#	No	Disorders of both mitral and aortic valves, low platelet count (130), low neutrophil count (1.8)	D70 Agranulocytosis, E87.1 Hypo-osmolality and hyponatraemia, G47.3 Sleep apnoea, I08.0 Disorders of both mitral and aortic valves, I10 Essential (primary) hypertension, I25.1 Atherosclerotic heart disease, I26.9 Pulmonary embolism without mention of acute cor pulmonale, I44.0 Atrioventricular block, first degree, I80.0 Phlebitis and thrombophlebitis of superficial vessels of lower extremities, L97.1 Ulcer of lower limb, not elsewhere classified, M41.96 Scoliosis, unspecified (Lumbar region), M43.16 Spondylolisthesis (Lumbar region), M47.86 Other spondylosis (Lumbar region), M48.06 Spinal stenosis (Lumbar region), M51.2 Other specified intervertebral disk displacement, M51.3 Other specified intervertebral disk degeneration, M54.5K Low back pain (Sacral and sacrococcygeal region), M54.59 Low back pain (Site unspecified), M54.98 Dorsalgia, unspecified (Sacral and sacrococcygeal region), M54.99 Dorsalgia, unspecified (Site unspecified), M79.69 Pain in limb (Site unspecified), N18.3 Chronic kidney disease, stage 3, N19 Unspecified renal failure, R06.0 Dyspnoea, R07.3 Other chest pain, R07.4 Chest pain, unspecified, R41.0 Disorientation, unspecified, Y83.1 Surgical operation with implant of artificial internal device, Z51.2 Other chemotherapy, Z86.7 Personal history of diseases of the circulatory system, Z87.2 Personal history of diseases of the skin and subcutaneous tissue, Z87.3 Personal history of diseases of the musculoskeletal system and connective tissue, Z92.1 Personal history of long-term (current) use of anticoagulants
3	1	21:38423416G>A	c.382C>T	p.Pro128Ser (P128S)	Missense	40-60	Male	PB	2	2	25.9 (0.83)	0.598 (0.841)		Yes#	No	Abdominal aortic aneurysm, low platelet count	E21.3 Hyperparathyroidism, unspecified. E66.9 Obesity, unspecified, F10.1 Harmful use, F10.2 Dependence syndrome, G56.0 Carpal tunnel syndrome, I10 Essential (primary) hypertension, I48 Atrial fibrillation and flutter, I48.9 Atrial fibrillation and atrial flutter, unspecified, I71.4 Abdominal aortic aneurysm, without mention of rupture, I72.3 Aneurysm of iliac artery, J06.9 Acute upper respiratory infection, unspecified, J44.9 Chronic obstructive pulmonary disease, unspecified, J46 Status asthmaticus, K20 Oesophagitis, K21.9 Gastro-oesophageal reflux disease without oesophagitis, K29 Gastritis and duodenitis, K44.9 Diaphragmatic hernia without obstruction or gangrene, M19.9 Arthrosis, unspecified, T81.0 Haemorrhage and haematoma complicating a procedure, not elsewhere classified, T82.3 Mechanical complication of other vascular grafts, Z13.3 Special screening examination for mental and behavioural disorders, Z13.6 Special screening examination for cardiovascular disorders, Z50.1 Other physical therapy, Z86.4 Personal history of psychoactive substance abuse, Z86.7 Personal history of diseases of the circulatory system, Z87.1 Personal history of diseases of the digestive system, Z92.1 Personal history of long-term (current) use of anticoagulants Atherosclerosis of aorta , Aneurysm of iliac artery,
4	1	21:38423358G>C	c.388+52C>G	Intronic	Splice Donor gain		Male		0	0	NA	NA		unknown (WES conducted on singleton)	No	Bicuspid aortic valve	congenital cleft digestive, congenital genital, congenital musculoskeletal. ASD. Primary Congenital heart disease: perimembranous ventricular septal defects. Secondary Congenital heart disease: Secundum atrial septal defect, Patent Ductus Arteriosus
5	1	21:38403664C>T	c.434G>A	p.Trp145* (W145*)	Termination	22		amniocytes	0	2 (Malignant melanoma)	40 (0.983)	NA	fetus	de novo		Ascending aorta dilatation.	diagnosed in utero with non-immune hydrops fetalis, cystic hygroma, congenital heart defect: membranous ventricular septal effect
6	1	21:38403555del	c.543del	p.Ser182Alafs*22 (S182Afs*22)	Frameshift	4	Male		1	0 (1x S182(6*26)	NA	NA	Unknown	Unknown	Yes	Lymphoedema. Aortic regurgitation.	Hypertension.
7	2	21:38403555del	c.543del	p.Ser182Alafs*22 (S182Afs*22)	Frameshift		Female		1	0 (1x S182(6*26)	NA	NA	Unknown	inherited		Lymphoedema.	Hypertension. Transient ischemic attack.
8	1	21:38402595A>T	c.635T>A	p.Leu212* (L212*)	Termination		Male	PB	0	0	39 (0.984)	NA	49	Unknown	NP	Aortic Aneurysm. Thrombocytopenia. abnormal platelet functionr abnormal platelet aggregation. Moderate to severe aortic valve calcification and stenosis, mild mitral valve insufficiency.	ASPI-Heradin and ADP-Heradin pathologic, Antiphospholipid syndrome, hypercholesterinemia, thrombosis of left V. femoralis (07/2020), retinal vein occlusions of both eyes (2020?), Multiple arterial aneurysms (aorta, and multiple vessels of larger caliber including an intracranial aneurysm). Arterial hypertension. Coronary heart disease without major artery stenoses
9	1	21:38383734C>G	c.1109G>C	p.Arg370Pro (R370P)	Missense	44	Male	PB Hair	0	1 (1x R370G, 3x R370C, 2x R370L)	33 (0.854)	0.888 (0.968)	29	Yes	No	Severe aortic valve insufficiency. Myelodysplastic syndromes (asymptomatic thrombocytopenia and leukopenia)	an inguinal hernia on both sides, deformation (avascular necrosis) of the femoral head, Groin hernia, Bilateral vascular necrosis of the femoral head,
10	1	21:38383686T>C	c.1157A>G	p.Tyr386Cys (Y386C)	Missense	40-60		PB	0	0	30 (0.881)	0.735 (0.908)		Inherited		Disorders of both Mitral and tricuspid Valve	
11	1	21:38383455del	c.1388del	p.Asn463Thrfs*42 (N463Tfs*42)	Frameshift		Female		0	0	NA	NA		Inherited		Lymphoedema. Aortic regurgitation. Ascending tubular aorta aneurysm.	Hypertension.Cerebral ischemia. Cerebral ischemia. Carotid artery dilation
12	2	21:38383455del	c.1388del	p.Asn463Thrfs*42 (N463Tfs*42)	Frameshift		Male		0	0	NA	NA		Inherited		Lymphoedema. Aortic regurgitation. Tricuspid regurgitation.	

Supplemental Table 4: Expanding the known variants associated with ERG deficiency syndrome. Information unknown (blank).

Patient ID	Source	g.HGVS (GRCh38/hg38) (Chr21)	ERG c.HGVS (NM_182918.4)	ERG p.HGVS (NP_891548.1) (ENSP288319.7) (479 aa)	Variant Class	VAF (%)	Sex	Sample analysed	gnomAD (v 4.0.0)	COSMIC (v99)	CADD Score (Raw rank score)	REVEL Score (Rank score)	ERG deficiency syndrome Phenotype	Ages onset of phenotypes (yr)	Germline ERG (inherited/de novo) #VAF = 40-60%	Chr21q cnLOH	Somatic mutations	Other phenotype/s
A	Population database (UK Biobank)	21:38383908 T>A	c.935A>T	p.Gln312Leu (Q312L)	Missense	40-60		Blood	1	0	29.7 (0.878)	0.73 (0.905)	Localized edema		inherited#			A09.9 Gastroenteritis and colitis of unspecified origin, A41.9 Septicaemia, unspecified, B95.1 Streptococcus, group B, as the cause of diseases classified to other chapters, B95.6 Staphylococcus aureus as the cause of diseases classified to other chapters, B96.2 Escherichia coli [E. coli] as the cause of diseases classified to other chapters, C90.0 Multiple myeloma, D18.0 Haemangioma, any site, D70 Agranulocytosis, E83.5 Disorders of calcium metabolism, E87.6 Hypokalaemia, F41.9 Anxiety disorder, unspecified, I26.9 Pulmonary embolism without mention of acute cor pulmonale, I27.2 Other secondary pulmonary hypertension, I51.7 Cardiomegaly, I84.5 External haemorrhoids without complication, J10.0 Influenza with pneumonia, influenza virus identified, J10.1 Influenza with other respiratory manifestations, influenza virus identified, J12.1 Respiratory syncytial virus pneumonia, J18.0 Bronchopneumonia, unspecified, J18.1 Lobar pneumonia, unspecified, J22 Unspecified acute lower respiratory infection, J45.9 Asthma, unspecified, J90 Pleural effusion, not elsewhere classified, J96.9 Respiratory failure, unspecified, J96.91 Respiratory failure unspecified; Type II [hypercapnic], K20 Oesophagitis, K44.9 Diaphragmatic hernia without obstruction or gangrene, K59.0 Constipation, K83.0 Cholangitis, M19.9 Arthrosis, unspecified, M41.9 Scoliosis, unspecified, M48.54 Collapsed vertebra, not elsewhere classified (Thoracic region), M94.0 Chondrocostal junction syndrome [Tietze], N39.0 Urinary tract infection, site not specified, R06.0 Dyspnoea, R09.2 Respiratory arrest, R10.1 Pain localised to upper abdomen, R10.3 Pain localised to other parts of lower abdomen, R11 Nausea and vomiting, R50.9 Fever, unspecified, R60.0 Localised oedema, Z02.8 Other examinations for administrative purposes, Z51.1 Chemotherapy session for neoplasm, Z51.2 Other chemotherapy, Z53.8 Procedure not carried out for other reasons, Z73.9 Problem related to life management difficulty, unspecified, Z86.0 Personal history of other neoplasms, Z86.4 Personal history of psychoactive substance abuse, Z86.7 Personal history of diseases of the circulatory system, Z92.1 Personal history of long term (current) use of anticoagulants, Z92.6 Personal history of chemotherapy for neoplastic disease, Z99.8 Dependence on other enabling machines and devices
B	International collaboration	21:38383756C>T	c.1087G>A	p.Asp363Asn (D363N)	Missense	42	Male		0	5	33 (0.799)	0.41 (0.722)	Pancytopenia	6	inherited#	UPD21q confirmed	SETBP1, ASXL1, CSF3R	hypocellular bone marrow (without fibrosis), macrocytosis. Progression to hypercellular bone marrow with significantly increased dysplastic megakaryopoiesis and marrow fibrosis (Monosomy 7). (Received HSCT). Echocardiogram in the 1st year of life: small muscular ventricular septal defect (VSD) without relevant shunt. Echocardiogram at age 13: unremarkable, and no abnormal cardiac findings
C	Population database (UK Biobank)	21:38383693 T>C	c.1150A>G	p.Lys384Glu (K384E)	Missense	2		Blood	2	0	28.6 (0.842)	0.687 (0.886)	Thrombocytopenia, Localised edema		inherited#			A09.9 Gastroenteritis and colitis of unspecified origin, C17.0 Duodenum, C18.7 Sigmoid colon, D12.3 Transverse colon, D12.5 Sigmoid colon, D37.4 Colon, D50.9 Iron deficiency anaemia, unspecified, D69.6 Thrombocytopenia, unspecified, E11.9 Without complications, E87.6 Hypokalaemia, H35.0 Background retinopathy and retinal vascular changes, H53.8 Other visual disturbances, H81.1 Benign paroxysmal vertigo, H90.3 Sensorineural hearing loss, bilateral, H91.9 Hearing loss, unspecified, H93.1 Tinnitus, I10 Essential (primary) hypertension, I48.1 Persistent atrial fibrillation, I48.9 Atrial fibrillation and atrial flutter, unspecified, I50.0 Congestive heart failure, I50.9 Heart failure, unspecified, I51.7 Cardiomegaly, I67.9 Cerebrovascular disease, unspecified, I70.9 Generalised and unspecified atherosclerosis, I84.2 Internal haemorrhoids without complication, I84.9 Unspecified haemorrhoids without complication, I86.8 Varicose veins of other specified sites, J96.90 Respiratory failure, unspecified; Type I [hypoxic], K21.9 Gastro oesophageal reflux disease without oesophagitis, K22.2 Oesophageal obstruction, K30 Dyspepsia, K44.9 Diaphragmatic hernia without obstruction or gangrene, K58.9 Irritable bowel syndrome without diarrhoea, K63.8 Other specified diseases of intestine, K76.0 Fatty (change of) liver, not elsewhere classified, K80.2 Calculus of gallbladder without cholecystitis, K85.1 Biliary acute pancreatitis, M10.9 Gout, unspecified, M13.9 Arthritis, unspecified, M47.9 Spondylosis, unspecified, M79.86 Other specified soft tissue disorders (Lower leg), N17.9 Acute renal failure, unspecified, N18.1 Chronic kidney disease, stage 1, N18.3 Chronic kidney disease, stage 3, N39.0 Urinary tract infection, site not specified, N40 Hyperplasia of prostate, N48.5 Ulcer of penis, R10.1 Pain localised to upper abdomen, R11 Nausea and vomiting, R18 Ascites, R55 Syncope and collapse, R60.0 Localised oedema, R63.4 Abnormal weight loss, R93.3 Abnormal findings on diagnostic imaging of other parts of digestive tract, R94.5 Abnormal results of liver function studies, Y83.2 Surgical operation with anastomosis, bypass or graft, Y83.6 Removal of other organ (partial) (total), Z03.8 Observation for other suspected diseases and conditions, Z09.0 Follow up examination after surgery for other conditions, Z12.1 Special screening examination for neoplasm of intestinal tract, Z50.1 Other physical therapy, Z53.0 Procedure not carried out because of contraindication, Z72.1 Alcohol use, Z85.0 Personal history of malignant neoplasm of digestive organs, Z86.4 Personal history of psychoactive substance abuse, Z86.6 Personal history of diseases of the nervous system and sense organs, Z87.1 Personal history of diseases of the digestive system, Z90.4 Acquired absence of other parts of digestive tract, Z92.1 Personal history of long term (current) use of anticoagulants, Z92.2 Personal history of long term (current) use of other medicaments
D	International collaboration	21:38383504CA>C	c.1338del	p.Phe446Leufs*49 (F446Lfs*49)	Frameshift	36	Male	Blood	0	6	NA	NA	Slow blood clotting (50 sec aPTT)		de novo			Right and leg-emphasized spastic movement disorder with progressive course, neurogenic hollow foot, hypotonia and strength deficit (DD: infantile spastic cerebral paresis)

Supplemental Table 5: Rare ERG heterozygous variants found in patients with cnLOH across the ERG locus.

Source	Family member	g.HGVS (GRCh38/hg38) (Chr21)	ERG c.HGVS (NM_182918.4)	ERG p.HGVS (NP_891548.1) (ENSP288319.7) (479 aa)	Variant Class	VAF (%)	Sex	Sample analysed	gnomAD (v 4.0.0)	COSMIC (v99)	CADD Score (Raw rank score)	REVEL Score (Rank score)	Ages onset of phenotypes (yr)	Germline ERG (inherited/ *de novo*)	Chr21q cnLOH	ERG deficiency syndrome Phenotype	Other phenotype/s
Population database (UK Biobank)	1	21: 38383897A>G	c.946T>C	p.Phe316Leu (F316L)	Missense	25	Female	Blood	1	0	29.7 (0.87)	0.853 (0.955)		likely inherited	Yes	None reported	C44.7 Skin of lower limb, including hip, C50.9 Breast, unspecified, D22.3 Melanocytic naevi of other and unspecified parts of face, E78.0 Pure hypercholesterolaemia, F32.9 Depressive episode, unspecified, F41.9 Anxiety disorder, unspecified, H11.4 Other conjunctival vascular disorders and cysts, H21.8 Other specified disorders of iris and ciliary body, H25.8 Other senile cataract, I10 Essential (primary) hypertension, I83.9 Varicose veins of lower extremities without ulcer or inflammation, I97.8 Other postprocedural disorders of circulatory system, not elsewhere classified, J34.8 Other specified disorders of nose and nasal sinuses, J44.9 Chronic obstructive pulmonary disease, unspecified, K21.0 Gastro-oesophageal reflux disease with oesophagitis, K21.9 Gastro-oesophageal reflux disease without oesophagitis, K31.7 Polyp of stomach and duodenum, K40.9 Unilateral or unspecified inguinal hernia, without obstruction or gangrene, K44.9 Diaphragmatic hernia without obstruction or gangrene, L90.5 Scar conditions and fibrosis of skin, L98.9 Disorder of skin and subcutaneous tissue, unspecified, M13.9 Arthritis, unspecified, M21.24 Flexion deformity (Hand), M24.54 Contracture of joint (Hand), M79.86 Other specified soft tissue disorders (Lower leg), R06.0 Dyspnoea, S01.2 Open wound of nose, S02.20 Fracture of nasal bones (closed), S09.9 Unspecified injury of head, S61.0 Open wound of finger(s) without damage to nail, S63.1 Dislocation finger, T92.3 Sequelae of dislocation, sprain and strain of upper limb, W01.9 Unspecified place, W10.5 Trade and service area, Y48.3 Local anaesthetics, Y86 Sequelae of other accidents, Z09.8 Follow-up examination after other treatment for other conditions, Z85.0 Personal history of malignant neoplasm of digestive organs, Z85.3 Personal history of malignant neoplasm of breast, Z85.8 Personal history of malignant neoplasms of other organs and systems, Z87.1 Personal history of diseases of the digestive system, Z88.5 Personal history of allergy to narcotic agent, Z88.6 Personal history of allergy to analgesic agent, Z92.2 Personal history of long-term (current) use of other medicaments
Population database (UK Biobank)	1	21: 38383789C>T	c.1054G>A	p.Gly352Arg (G352R)	Missense	19	Female	Blood	0	1	32 (0.82)	0.939 (0.987)		likely inherited	Yes	Hypertension	B95.6 Staphylococcus aureus as the cause of diseases classified to other chapters, C50.9 Breast, unspecified, C77.3 Axillary and upper limb lymph nodes, D12.2 Ascending colon, D12.3 Transverse colon, E66.9 Obesity, unspecified, H90.3 Sensorineural hearing loss, bilateral, I10 Essential (primary) hypertension, K57.3 Diverticular disease of large intestine without perforation or abscess, K63.5 Polyp of colon, L03.3 Cellulitis of trunk, M19.91 Arthrosis, unspecified (Shoulder region), M75.4 Impingement syndrome of shoulder, R00.2 Palpitations, R19.5 Other fecal abnormalities, T85.7 Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts, Z85.3 Personal history of malignant neoplasm of breast, Z88.0 Personal history of allergy to penicillin, Z88.2 Personal history of allergy to sulphonamides, Z88.3 Personal history of allergy to other anti-infective agents, Z88.8 Personal history of allergy to other drugs, medicaments and biological substances, Z90.1 Acquired absence of breast(s)

Supplemental Table 6: ERG-specific ACMG-AMP guidelines developed for variant classification. The framework incorporates pathogenic variant–defining features (e.g., SGR [PM3]), curated phenotypic evidence, and expert consensus on the weighting of functional and computational data.

Criteria	When to apply	Up/downgrade	Why	Other notes
Terminations (PVS1)	Terminations removing DNA binding domain	PVS1	Literature and functional studies suggest this is the most important domain to do ERGs TF role.	To apply this we are assuming clinical validity classification of gene is STRONG or DEFINITIVE. ClinGene curation panel in Dec/Jan
	If termination is after 400 aa	PVS1_Moderate	Although the termination does not remove the DNA binding domain, functional studies suggest a functional consequence for N-terminal terminations	
	If termination is before 68 aa	PVS1_Moderate	Re-initiation sites at position 33 and 68. Although just cDNA constructs, we have shown these do re-initiate here.	
De novo (PS2)	Proven de novo	PS2	Variants identified as de novo in patients with ERG deficiency syndrome, confirmed by parental testing, provide strong evidence of pathogenicity.	
Functional data (PS3)	Complete LOF in any functional assay (transactivation, DNA binding and subcellular localisation)	PS3	Complete LOF in any assay indicates loss of ERG's ability to act as a transcription factor.	
	Partial loss (~50% loss in transactivation assay)	PS3	A reduction of ~50% in transactivation activity has been called to represent the functional threshold that results in pathogenicity	
	Significant changes in any functional assay	PS3_Supporting	Significant alterations in any functional assay demonstrates impaired ERG function and supports pathogenicity	
	LOF in one assay WT like in another	PS3_Moderate	LOF in one assay, (even if WT activity is retained in another) still supports pathogenicity, as disruption of a single critical ERG function (e.g., DNA binding or transactivation) is sufficient to impair its role as a transcription factor.	
Hot spot (PM1)	Between amino acids 340-365	PM1_Supporting	Variants clustered between amino acids 340–365 occur within a mutational hot spot critical for ERG function and often result in patrial LOF shown by functional assays. Variants 365 - 370 (although no functional data has been accumulated so far, would predict to also be PM1_Supporting)	
	Between amino acids 370-375	PM1	Variants clustered between amino acids 370–375 occur within a mutational hot spot critical for ERG function, often resulting in complete LOF in functional assays	
	Between amino acids 380-390	PM1_Supporting	Variants clustered between amino acids 380–390 occur within a mutational hot spot critical for ERG function and often result in patrial LOF shown by functional assays. Variants 375 - 380 (although no functional data has been accumulated so far, would predict to also be PM1_Supporting)	
Absence in general population (PM2)	LOF variants (i.e. premature termination stops and frameshifts, and splice site variants) seen <5 times in gnomAD	PM2	LOF variants are markedly rarer in the general population compared with missense variants, and no variant observed more than five times has been associated with pathogenicity or functional impact.	
	Missense variants seen < 5 times in gnomAD	PM2_Supporting	No missense variant observed more than five times has been associated with pathogenicity or functional impact.	
Surrogate for SGR (PM3)	cnLOH across 21q present through SNP array/B-allele frequency plot	PM3	To date, SGR has only been present in patients harboring LP/P ERG variants and therefore we are calling this an indicator of pathogenicity	
Seen before at same residue (PM5)	variant affecting the same amino acid residue as a previously established pathogenic or likely pathogenic	PM5	A novel variant affecting the same amino acid residue as a previously established pathogenic or likely pathogenic variant provides moderate evidence for pathogenicity.	
Multiple affected family members (PP1)	The variant is observed in multiple affected family members.	PP1	Co-segregation of the variant with disease in multiple affected family members provides supporting evidence for pathogenicity.	
Computational evidence (PP3)	REVEL > 0.8 (CADD ~ 30)	PP3_Strong	All such variants to date have been pathogenic and demonstrated functional consequences.	Based on observations to date, REVEL scores are weighted more heavily than CADD. Computational predictions should be considered alongside functional data to avoid false positives. For example, variants with high REVEL/CADD scores but no demonstrable functional consequence should not be overcalled as pathogenic.
	REVEL > 0.6 (CADD ~25)	PP3_Moderate	Most variants to date have been LP/P and demonstrated functional consequences	
	REVEL > 0.3 (CADD ~20)	PP3_Supporting	Some variants to date have been LP/P and demonstrated functional consequences	