Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Genes Critical to In Utero Survival
Supplemental Appendix

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Stillbirth Collaborative Research Network (SCRN) membership

The following institutions and researchers compose the Stillbirth Collaborative Research Network: University of Texas Health Science Center at San Antonio—Donald J. Dudley, Deborah L. Conway, Karen Aufdemorte, Angela Rodriguez, Monica Pina; University of Utah School of Medicine—Robert M. Silver, Michael W. Varner, Kristi Nelson; Emory University School of Medicine and the Rollins School of Public Health—Carol J. Rowland Hogue, Barbara J. Stoll, Janice Daniels Tinsley, Bahig Shehata, Carlos Abramowsky; Brown University—Donald Coustan, Halit Pinar, Marshall Carpenter, Susan Kubaska; University of Texas Medical Branch at Galveston—George R. Saade, Radek Bukowski, Jennifer Lee Rollins, Hal Hawkins, Elena Sbrana; RTI International—Corette B. Parker, Matthew A. Koch, Vanessa R. Thorsten, Holly Franklin, Pinliang Chen; Pregnancy and Perinatalogy Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health—Marian Willinger, Uma M. Reddy; Columbia University Medical Center—Robert L. Goldenberg.

IGM bioinformatics pipeline

DNA was extracted with the use of established methods. Concentrations for the samples and an estimated purity (260nm/280nm ratio) were determined by UV spectrophotometry (Nanodrop, Thermo Scientific, Wilmington, DE). Samples were analyzed by agarose gel electrophoresis to visualize sample integrity.

Exomes were captured using either the IDT xGen Exome Research Panel V1.0 (Integrated DNA Technologies, Coralville, IA, USA), the Agilent All Exon (65 MB; Agilent Technologies, Santa Clara, CA, USA) kit or the Nimblegen SeqCap EZ (version 2·0 or 3·0) Exome Enrichment kit (Roche NimbleGen, Madison, WI, USA) and sequenced according to standard protocols on Illumina's (Illumina, San Diego, CA, USA) NovaSeq 6000 and HiSeq2500 platforms. The sequence data from cases and controls were processed using the same Institute for Genomic Medicine's in-house Analysis Tool for Annotated Variants (ATAV)[1].

As detailed in earlier work, reads were aligned to the reference genome (Genome Reference Consortium build 37, human genome 19) using DRAGEN (Edico Genome, San Diego, CA, USA) and duplicates were marked with Picard (Broad Institute, Boston, MA, USA). Variant and genotype calling was performed using Genome Analysis Toolkit (GATK - Broad Institute, Boston, MA, USA) Best Practices recommendations v3.6. Finally, variants were annotated with ClinEff and ATAV[1].

Variants were further required to have: i) at least 10-fold coverage, ii) quality score (QUAL) of at least 50, iii) genotype quality (GQ) score of at least 20, iv) quality by depth (QD) score of at least 5, v) mapping quality (MQ) score of at least 40, vi) read position rank sum (RPRS) score greater than -3, vii) mapping quality rank sum (MQRS) score greater than -10, viii) indels were required to have a maximum Fisher's strand bias (FS) of 200, ix) for heterozygous genotypes, the alternative allele ratio was required to be ≥30%. Finally, variants were excluded if they were among a predefined list of known sequencing artifacts or if they were marked by EVS (http://evs.gs.washington.edu/EVS/) or ExAC (http://exac.broadinstitute.org/about) as being problematic variants.

Samples with >8% contamination according to VerifyBamID were also removed[2]. Lastly, samples were required to have >85% of 33.76 MB CCDS (release 20) protein coding sites covered at 10x[2,3].

Controlling for relatedness and population stratification

We used ATAV to create a PED and MAP pair on 7,947 samples (cases and controls) sequenced at the Institute for Genomic Medicine, Columbia University, and 12,840 SNPS of interest. ATAV uses a SNP set generated by taking intermediate MAF SNPs from a large set of exome samples of varied ancestry, restricted to the targeted regions of the Nextera 37 MB kit (as it is the smallest subset of targeted regions for all IGM samples), and finally LD-pruned[1]. We then ran KING to estimate pairwise kinship coefficients. We then produced a new pared down sample file, in which we removed at least one individual in every pair of samples related second-degree or greater favoring the inclusion of cases over controls (relatedness threshold = 0.0884). EIGENSTRAT was used to calculate the top 10 principal components (PCs) on 7,819 unrelated samples. As in other work, samples were removed as "ethnicity outliers" if they exceeded ±6 standard deviations across any principal component (Figure S4 in Supplmental Appendix)[4].

Stillbirth gene set curation

In order to generate an exhaustive list of genes previously implicated in stillbirth (Table S1 in Supplementary Appendix), we took the union of the following searches yielding 221 unique genes:

1. Clinical synopses in the Online Inheritance in Man (OMIM) database are highly variable and interchange closely related terms. In order to capture the greatest number of genes previously reported in stillbirth in OMIM, we first looked through all symptoms listed in the category 'prenatal Manifestations', 'prenatal Manifestations Delivery', 'prenatal Manifestations Maternal', 'prenatal Manifestations Placenta And Umbilical Cord', 'prenatal Manifestations Amniotic Fluid', and 'prenatal Manifestations Movement' and chose all symptoms that described stillbirth: "stillbirth", "stillborn", "embryonic lethality", "perinatal lethality", "neonatal lethality", "fetal lethality", "fetal demise", "embryonic demise", "perinatal demise", "neonatal demise", "perinatal death", "embryonic death", "fetal death", "neonatal death", "intrauterine death". We then scraped the full OMIM database for all genes associated with conditions that have one of these terms anywhere in the clinical synopsis regardless of inheritance pattern. This search yielding 52 unique genes.

2. We also considered 964 "high evidence" genes on the 'R21 Fetal Anomalies with a likely genetic cause' panel overseen by the NGS Genomic Medicine Service. The Fetal anomalies panel is based on a targeted virtual gene panel for developmental disorders developed by the Prenatal Assessment of Genomes and Exomes (PAGE) group. The PAGE gene list underwent expert review and curation to form the Fetal anomalies panel by the NGS Genomic Medicine Service. Genes were given a final "high evidence" rating only if the corresponding phenotype was likely to present in a fetus and the evidence was considered sufficient. Separately, we conducted a further literature review for 913 of the 964 genes on the panel that were not contained in the OMIM scrape results. We retained genes previously reported in at least one case of stillbirth (PMID provided; Table S1 in Supplementary Appendix). We did not include genes if the reported case died within the first few days of life or if it was unclear from the report whether the pregnancy resulted in stillbirth or termination. Our review yielded an additional 79 genes (Table S1 in Supplementary Appendix).

3. Certain cardiac channelopathies have been closely associated with sudden cardiac-related death in the setting of a morphologically normal heart and are known to account for a large portion of sudden infant death cases[5]. These include long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS). Additionally, cardiomyopathies, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic

cardiomyopathy (ACM), are potentially lethal and in certain cases can display minimal to no structural abnormalities in the heart. It has been suggested that a considerable portion of sudden infant death cases without morphological abnormalities in the heart may also be due to cardiomyopathy. Moreover, these channelopathy and cardiomyopathy disorders have each been reported in at least one instance of stillbirth. Thus, we include 94 cardiac-related sudden death-susceptibility genes curated by Narula *et al.* (2015).

Committee classification of diagnostic genotypes

Molecular diagnoses were classified as either "Pathogenic" or "Likely pathogenic" (P/LP) according to the American College of Medical Genetics (ACMG) criteria or "suggestive" by a multidisciplinary clinical and genetics team.

Committee classification of "suggestive" and not P/LP was based on the following flags:

1. Presence of greater than one allele of the exact variant in the gnomAD v2.1.1 control cohort (n=60,146).

2. Lack of convincing literature to substantiate the classification of the variant as P/LP in variant databases (it is well recognized that most variant databases are not well curated)[6,7].

3. Mismatch in predicted variant effect of observed variant and previously reported disease variants i.e. identification of a missense variant in a gene where the majority (80-85%) of previously reported variants are loss-of-function variants.

Gene-based collapsing analysis

We performed a standard gene-based collapsing analysis to identify individual genes with significant enrichment of qualifying variants (QV) in cases compared to healthy controls. As described in earlier work, the term QV refers to a subset of variation within the sequence data that meet criteria designed to enrich for pathogenic variants[8]. This analysis used established sets of criteria for selection of QV based on the variant effect annotation and minor allele frequency (Figure S5 in Supplementary Appendix)[8]. A two-tailed Fisher's exact test was performed across 18 653 consensus coding sequence protein-coding genes for 3 models (Figure S5 in Supplemental Appendix). Bonferroni-adjusted significance threshold was therefore $0.05/[18\ 654 \times 3] = 8.9 \times 10^{-7}$.

Q-Q plots were generated as previously described[2].To restate, using the in-house bioinformatics tool ATAV we generated a Q-Q plot based on 1,000 random permutations of case/control labels. The mean of each p-value rank is then calculated and plotted against the observed p-values. The plot also includes the 2.5th percentile and 97.5th percentile of expected p-values at each rank, which are displayed as green and yellow lines, respectively (Figure S5 in Supplementary Appendix). The lambda factor displayed on the plot is the slope of the regression line of the observed vs. expected points, after removing p-values of 1 (or -log10(p-value) of 0) and p-values of genome-wide significance after Bonferroni correction.

Enrichment analysis by permutation

The method partitions genes according to every possible intolerance division (gnomAD v2.1.1 loss-of-function observed/expected upper bound fraction; LOEUF[9]), maximizes the enrichment statistic over these divisions, and then assesses the significance of this maximum by permutation. In detail:

Assume there are n genes taking on p intolerance (LOEUF) values. Note that p is less than n as some genes have the same intolerance score. Let G_i be the intolerance score of the i^{th} gene. Let I_(1)>I_(2)>...>I_(p) be the ordered distinct intolerance scores found among all n genes.

Create p gene sets, S_j={ genes i | G_i>=I_(j) } such that the j^{th} gene set will contain all genes whose intolerance score is greater than or equal to the j^{th} most extreme intolerance score.

Compute an observed statistic by:

1. Test for loss-of-function case or control enrichment in each gene set using a logistic regression that controls for synonymous variation in the corresponding gene set. Denote the statistic for the j^{th} gene set by X_j

2. Minimize p-values over the X_j's. Call the min, T.

Assess the significance of T using permutation by:

3. Permute case-control labels and repeat steps 1 and 2.
4. Repeat 3 a large number of times b, so that you get a large sample from the permutation distribution of the procedure. Label the resulting mins from these permutations T_1, T_2, ..., T_b. In our application b = 10,000.

The empirical p-value is then the proportion of permuted mins that are as large or larger than the observed min T, i.e., p=sum 1(T_l >= T)/b, where the sum is taken for l = 1 to b and 1(.) is an indicator function.

To calculate the 95% confidence interval [CI] let X_b=1 if both the permuted minimum p-value is as small or smaller than the observed p-value (X_b=0 otherwise). Note that sum(X_b)/n is our empirical p-value estimate (0.0061) where n=10,000. Let p be the true proportion of permutations that lead to a p-value as extreme (i.e., p is our true p-value). Then X_b is a Bernoulli random variable and hence its variance is p*(1-p). From this we can deduce that the Var(sum(X_b)/n)=n*p*(1-p)/n^2=p*(1-p)/n. The central limit theorem can be applied in this case and we have that Dist(sum(X_b)/n) ~ Normal(p,p*(1-p)/n) and this implies (plugging in our empirical estimator for p) that the 95% CI for p can be given by 0.0061±1.96*sqrt(0.0061*(1-0.0061)/10000).

Table S1: Full set of genes previously described in stillbirth (n = 221). Source = indicates whether the gene came from (1) OMIM: keyword identified (2) the Fetal anomaly panel literature review with PMID provided or (3) Narula et al. (2015) cardiac-related sudden death-susceptibility gene set (see Methods in Supplementary Appendix for detail).

Gene	Source	Model Of Inheritance	Disease Association
ABCB4	OMIM:fetal death	BOTH BIALLELIC & MONOALLELIC	CHOLESTASIS, INTRAHEPATIC, OF PREGNANCY 3; ICP3
ACE	PMID:22095942	BIALLELIC	Renal tubular dysgenesis 267430
ACTB	PMID:29261186	MONOALLELIC	BARAITSER-WINTER SYNDROME;ACTB Haploinsufficiency syndtome
ACTC1	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
ACTN2	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
AKAP9	Narula et al. (2015)	MONOALLELIC	long QT syndrome
AKT1	PMID:28431992	MONOALLELIC	PROTEUS SYNDROME
ALPL	OMIM:stillborn	BIALLELIC	HYPOPHOSPHATASIA, INFANTILE
AMER1	PMID:19079258	MONOALLELIC	OSTEOPATHIA STRIATA WITH CRANIAL SCLEROSIS
ANK2	Narula et al. (2015)	MONOALLELIC	long QT syndrome
ANKRD1	Narula et al. (2015)	#N/A	dilated cardiomyopathy | hypertrophic cardiomyopathy
ARID1B	Kliegman RM, Bordini BJ. Undiagnosed and Rare Diseases in Children. Pediatr Clin North Am. 2017 Feb 1;64(1):i.	MONOALLELIC	MENTAL RETARDATION, AUTOSOMAL DOMINANT 12;COFFIN SIRIS SYNDROME
ARSE	PMID:9719382	X-LINKED	CHONDRODYSPLASIA PUNCTATA 1, X-LINKED
ARX	PMID:14722918	X-LINKED	PARTINGTON SYNDROME;MENTAL RETARDATION X-LINKED ARX-RELATED;LISSENCEPHALY X-LINKED TYPE 2;AGENESIS OF THE CORPUS CALLOSUM WITH ABNORMAL GENITALIA;EPILEPTIC ENCEPHALOPATHY EARLY INFANTILE TYPE 1
ATP8B1	OMIM:fetal death	BOTH BIALLELIC & MONOALLELIC	CHOLESTASIS, INTRAHEPATIC, OF PREGNANCY, 1; ICP1
B4GALT7	PMID:31278392	BIALLELIC	EHLERS-DANLOS SYNDROME PROGEROID TYPE
BAG3	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy
CACNA1C	Narula et al. (2015)	MONOALLELIC	brugada syndrome | long QT syndrome
CACNA2D1	Narula et al. (2015)	#N/A	brugada syndrome
CACNB2	Narula et al. (2015)	#N/A	brugada syndrome
CALM1	Narula et al. (2015)	MONOALLELIC	catecholiminergic polymorphic ventricular cardiomyopathy | long QT syndrome
CALM2	Narula et al. (2015)	MONOALLELIC	long QT syndrome
CALR3	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
CASQ2	Narula et al. (2015)	BIALLELIC	catecholiminergic polymorphic ventricular cardiomyopathy
CAV3	Narula et al. (2015)	MONOALLELIC	long QT syndrome
CC2D2A	PMID:26862157	BIALLELIC	JOUBERT SYNDROME 9;COACH SYNDROME;MECKEL SYNDROME, TYPE 6
CCBE1	PMID:19911200	BIALLELIC	HENNEKAM LYMPHANGIECTASIA-LYMPHEDEMA SYNDROME
CDKN1C	PMID:20484977	MONOALLELIC	BECKWITH-WIEDEMANN SYNDROME;IMAGe Syndrome
CEP120	OMIM:fetal death	BIALLELIC	SHORT-RIB THORACIC DYSPLASIA 13 WITH OR WITHOUT POLYDACTYLY; SRTD13

CEP290	PMID:24428858	BIALLELIC	JOUBERT SYNDROME TYPE 5;LEBER CONGENITAL AMAUROSIS TYPE 10;SENIOR-LOKEN SYNDROME TYPE 6;BARDET-BIEDL SYNDROME TYPE 14;MECKEL SYNDROME TYPE 4
CHRNA1	PMID:23037934	BIALLELIC	MULTIPLE PTERYGIUM SYNDROME LETHAL TYPE;Multiple pterygium syndrome, lethal type, 253290
CHRND	PMID:27245440	MONOALLELIC	MYASTHENIC SYNDROME, CONGENITAL, 3B, FAST-CHANNEL; CMS3B | MYASTHENIC SYNDROME, CONGENITAL, 3A, SLOW-CHANNEL; CMS3A | MYASTHENIC SYNDROME, CONGENITAL, 3C, ASSOCIATED WITH ACETYLCHOLINE RECEPTOR DEFICIENCY; CMS3C
CHRNG	PMID:27245440	BIALLELIC	MULTIPLE PTERYGIUM SYNDROME ESCOBAR VARIANT
CHST14	PMID:11370633	BIALLELIC	EHLERS-DANLOS SYNDROME MUSCULOCONTRACTURAL TYPE
CHUK	PMID:20961246	BIALLELIC	COCOON SYNDROME
CNTNAP1	PMID:28254648	BIALLELIC	LETHAL CONGENITAL CONTRACTURE SYNDROME 7
COG8	PMID:30690882	BIALLELIC	COG8-CDG
COL11A1	OMIM:stillborn	BIALLELIC	FIBROCHONDROGENESIS 1; FBCG1
COL11A2	PMID:28749478	BOTH MONOALLELIC & BIALLELIC	WEISSENBACHER-ZWEYMUELLER SYNDROME;DEAFNESS AUTOSOMAL RECESSIVE TYPE 53;AUTOSOMAL RECESSIVE OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA;DEAFNESS AUTOSOMAL DOMINANT TYPE 13;STICKLER SYNDROME TYPE 3
COL1A1	PMID:18412368	MONOALLELIC	COL1A1/2-RELATED OSTEOGENESIS IMPERFECTA;EHLERS-DANLOS SYNDROME, CLASSIC TYPE, COL1A1-RELATED;OSTEOGENESIS IMPERFECTA TYPE III;EHLERS-DANLOS SYNDROME TYPE VIIA;OSTEOGENESIS IMPERFECTA TYPE IIA;CAFFEY DISEASE;OSTEOGENESIS IMPERFECTA TYPE I
COL1A2	PMID:26147564	BOTH MONOALLELIC & BIALLELIC	Ehlers-Danlos syndrome;Osteogenesis imperfecta
COL2A1	OMIM:stillborn	MONOALLELIC	ACHONDROGENESIS, TYPE II; ACG2
COQ4	PMID:25658047	BIALLELIC	COENZYME Q10 DEFICIENCY, PRIMARY, 7
COQ9	PMID:29560582	BIALLELIC	COENZYME Q10 DEFICIENCY
CPT2	OMIM:sudden death within first days of life	BIALLELIC	CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, INFANTILE | CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, LETHAL NEONATAL
CRB2	PMID:28425981	BIALLELIC	VENTRICULOMEGALY WITH CYSTIC KIDNEY DISEASE
CREBBP	PMID:30633342	MONOALLELIC	CREBBP intellectual disability without typical RTS features;RUBINSTEIN-TAYBI SYNDROME TYPE 1
CRYAB	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	dilated cardiomyopathy
CSPP1	PMID:24360803	BIALLELIC	JOUBERT SYNDROME WITH OR WITHOUT JEUNE ASPHYXIATING THORACIC DYSTROPHY
CSRP3	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
CTF1	Narula et al. (2015)	#N/A	dilated cardiomyopathy
CTSA	PMID:28749478	BIALLELIC	GALACTOSIALIDOSIS
CTSD	PMID:16670177	BIALLELIC	NEURONAL CEROID LIPOFUSCINOSIS TYPE 10
CYP11A1	PMID:28425981	BIALLELIC	Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete 613743
DAG1	PMID:25934851	BIALLELIC	MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY LIMB-GIRDLE TYPE C7
DES	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	dilated cardiomyopathy
DHCR7	PMID:14735596; PMID:11078571	BIALLELIC	SMITH-LEMLI-OPITZ SYNDROME
DIS3L2	PMID:18780370	BIALLELIC	PERLMAN SYNDROME
DMD	Narula et al. (2015)	X-LINKED RECESSIVE, Other	dilated cardiomyopathy
DMPK	PMID:9856556	MONOALLELIC	DYSTROPHIA MYOTONICA TYPE 1
DOK7	OMIM:stillborn	BIALLELIC	FETAL AKINESIA DEFORMATION SEQUENCE 1; FADS1
DSC2	Narula et al. (2015)	MONOALLELIC	arrhymthmogenic cardiomyopathy
DSG2	Narula et al. (2015)	MONOALLELIC	arrhymthmogenic cardiomyopathy
DSP	OMIM:neonatal death; Narula et al. (2015)	BIALLELIC	SKIN FRAGILITY-WOOLLY HAIR SYNDROME; SFWHS | EPIDERMOLYSIS BULLOSA, LETHAL ACANTHOLYTIC; EBLA
EMD	Narula et al. (2015)	X-LINKED RECESSIVE	dilated cardiomyopathy
ESCO2	OMIM:stillborn	BIALLELIC	ROBERTS SYNDROME; RBS
ETFA	OMIM:neonatal death	BIALLELIC	MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD
ETFB	OMIM:neonatal death	BIALLELIC	MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD
ETFDH	OMIM:neonatal death	BIALLELIC	MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD

EVC2	PMID:23276573	BIALLELIC	ELLIS-VAN CREVELD SYNDROME;ACROFACIAL DYSOSTOSIS WEYERS TYPE
EXOSC3	PMID:24524299	BIALLELIC	PONTOCEREBELLAR HYPOPLASIA TYPE 1
EYA4	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy
FAM111A	PMID:23684011	MONOALLELIC	KENNY-CAFFEY SYNDROME
FAM20C	PMID:17924334	BIALLELIC	RAINE SYNDROME
FANCB	PMID:28425981	X-LINKED	FANCB-RELATED FANCONI ANEMIA
FBN1	PMID:16752434	BOTH MONOALLELIC & BIALLELIC	SHPRINTZEN-GOLDBERG CRANIOSYNOSTOSIS SYNDROME;MARFAN SYNDROME;MASS SYNDROME/OVERLAP CONNECTIVE TISSUE DISEASE
FBXL4	PMID:23993193	BIALLELIC	FATAL ENCEPHALOPATHY, LACTIC ACIDOSIS, AND SEVERE MTDNA DEPLETION IN MUSCLE
FCMD	Narula et al. (2015)	BIALLELIC	dilated cardiomyopathy
FGFR2	PMID:28425981	MONOALLELIC	BEARE-STEVENSON CUTIS GYRATA SYNDROME;LACRIMO-AURICULO-DENTO-DIGITAL SYNDROME;JACKSON-WEISS SYNDROME;ACROCEPHALOSYNDACTYLY TYPE V;FAMILIAL SCAPHOCEPHALY SYNDROME;ANTLEY-BIXLER SYNDROME;CROUZON SYNDROME;APERT SYNDROME
FGFR3	PMID:23551494	MONOALLELIC	LACRIMO-AURICULO-DENTO-DIGITAL SYNDROME;MUENKE SYNDROME;ACHONDROPLASIA;CROUZON SYNDROME WITH ACANTHOSIS NIGRICANS;CAMPTODACTYLY TALL STATURE AND HEARING LOSS SYNDROME;HYPOCHONDROPLASIA;THANATOPHORIC DYSPLASIA TYPE 2;THANATOPHORIC DYSPLASIA TYPE 1
FHL2	Narula et al. (2015)	BIALLELIC	dilated cardiomyopathy
FKTN	PMID:28749478	BIALLELIC	MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY CONGENITAL WITHOUT MENTAL RETARDATION TYPE B4;CARDIOMYOPATHY DILATED TYPE 1X;MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY LIMB-GIRDLE TYPE C4;MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY CONGENITAL WITH BRAIN AND EYE ANOMALIES TYPE A4
FLNA	OMIM:perinatal lethality | stillborn	X-LINKED	MELNICK-NEEDLES SYNDROME; MNS | OTOPALATODIGITAL SYNDROME, TYPE II; OPD2 | INTESTINAL PSEUDOOBSTRUCTION, NEURONAL, CHRONIC IDIOPATHIC, X-LINKED | PERIVENTRICULAR NODULAR HETEROTOPIA 1; PVNH1
FLNB	OMIM:neonatal death | stillborn	MONOALLELIC	ATELOSTEOGENESIS, TYPE I; AO1 | BOOMERANG DYSPLASIA; BOOMD
FLVCR2	OMIM:neonatal death | stillborn	BIALLELIC	PROLIFERATIVE VASCULOPATHY AND HYDRANENCEPHALY-HYDROCEPHALY SYNDROME; PVHH
FOXF1	PMID:23505205	MONOALLELIC	ALVEOLAR CAPILLARY DYSPLASIA WITH MISALIGNMENT OF PULMONARY VEINS
FOXP3	PMID:28425981	X-LINKED	IPEX SYNDROME
FRAS1	OMIM:stillborn	BIALLELIC	FRASER SYNDROME 1; FRASRS1
FREM2	OMIM:stillborn	BIALLELIC	FRASER SYNDROME 1; FRASRS1
FXN	Narula et al. (2015)	BIALLELIC	hypertrophic cardiomyopathy
GATA4	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
GATAD1	Narula et al. (2015)	BIALLELIC	dilated cardiomyopathy
GBA	PMID:12838552	BIALLELIC	GAUCHER DISEASE TYPE 3C;GAUCHER DISEASE TYPE 1;GAUCHER DISEASE PERINATAL LETHAL;GAUCHER DISEASE TYPE 3;GAUCHER DISEASE;GAUCHER DISEASE TYPE 2
GBE1	PMID:26147564	BIALLELIC	Glycogen storage disease IV;Polyglucosan body disease, adult form;Fetal akinesia deformation sequence
GDF5	OMIM:stillborn	BIALLELIC	CHONDRODYSPLASIA, GREBE TYPE
GLA	Narula et al. (2015)	Other	hypertrophic cardiomyopathy
GLDN	PMID:27616481	BIALLELIC	Lethal arthroogryposis
GLE1	OMIM:neonatal death	BIALLELIC	LETHAL CONGENITAL CONTRACTURE SYNDROME 1; LCCS1 | CONGENITAL ARTHROGRYPOSIS WITH ANTERIOR HORN CELL DISEASE; CAAHD
GPC3	PMID:29652239	X-LINKED	SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1

GPD1L	Narula et al. (2015)	#N/A	brugada syndrome
GPI	OMIM:neonatal death | stillbirth	BIALLELIC	HEMOLYTIC ANEMIA, NONSPHEROCYTIC, DUE TO GLUCOSE PHOSPHATE ISOMERASE DEFICIENCY
GRIP1	OMIM:stillborn	BIALLELIC	FRASER SYNDROME 3; FRASRS3
GUSB	PMID:28749478	BIALLELIC	MUCOPOLYSACCHARIDOSIS TYPE 7
HADHA	OMIM:neonatal onset | sudden infant death	BIALLELIC	MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY; MTPD
HADHB	OMIM:neonatal onset | sudden infant death	BIALLELIC	MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY; MTPD
HBA1	PMID:20301608	BIALLELIC	Fetal hydrops;Thalassemia, alpha-, 604131
HBA2	PMID:20301608	BIALLELIC	Fetal hydrops;Thalassemia, alpha-, 604131
HCN4	Narula et al. (2015)	MONOALLELIC	brugada syndrome
HNF1B	PMID:27297286	MONOALLELIC	RENAL CYSTS AND DIABETES SYNDROME
HRAS	PMID:20658932	MONOALLELIC	COSTELLO SYNDROME;CONGENITAL MYOPATHY WITH EXCESS OF MUSCLE SPINDLES
HSPG2	PMID:23836246	BIALLELIC	DYSSEGMENTAL DYSPLASIA SILVERMAN-HANDMAKER TYPE;SCHWARTZ-JAMPEL SYNDROME
HYLS1	OMIM:stillborn	BIALLELIC	HYDROLETHALUS SYNDROME 1; HLS1
ILK	Narula et al. (2015)	#N/A	dilated cardiomyopathy
INPPL1	PMID:25997753	BIALLELIC	OPSISMODYSPLASIA
INTU	OMIM:neonatal demise	BIALLELIC	SHORT-RIB THORACIC DYSPLASIA 20 WITH POLYDACTYLY; SRTD20
INVS	OMIM:neonatal death	BIALLELIC	NEPHRONOPHTHISIS 2; NPHP2
JAG1	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
JPH2	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
JUP	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	arrhymthmogenic cardiomyopathy
KCND3	Narula et al. (2015)	MONOALLELIC	brugada syndrome
KCNE1	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	long QT syndrome
KCNE2	Narula et al. (2015)	MONOALLELIC	long QT syndrome
KCNE3	Narula et al. (2015)	#N/A	brugada syndrome
KCNH2	Narula et al. (2015)	MONOALLELIC	long QT syndrome
KCNJ2	Narula et al. (2015)	MONOALLELIC	long QT syndrome
KCNJ5	Narula et al. (2015)	MONOALLELIC	long QT syndrome
KCNJ8	Narula et al. (2015)	#N/A	brugada syndrome
KCNQ1	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	long QT syndrome
KIAA1109	PMID:29290337	BIALLELIC	Brain atrophy, Dandy Walker and Contractures;Alkuraya-Kucinskas syndrome, 617822
KLHL24	OMIM:neonatal death	MONOALLELIC	EPIDERMOLYSIS BULLOSA SIMPLEX, GENERALIZED, WITH SCARRING AND HAIR LOSS; EBSSH
LAMA4	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy
LAMP2	Narula et al. (2015)	X-LINKED DOMINANT	hypertrophic cardiomyopathy
LBD3	Narula et al. (2015)	BIALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
LBR	OMIM:fetal death	BOTH BIALLELIC & MONOALLELIC	GREENBERG DYSPLASIA; GRBGD
LMNA	OMIM:stillbirth | Narula et al. (2015)	MONOALLELIC	MUSCULAR DYSTROPHY, CONGENITAL, LMNA-RELATED | RESTRICTIVE DERMOPATHY, LETHAL
MKS1	OMIM:perinatal death	BIALLELIC	MECKEL SYNDROME, TYPE 1; MKS1
MUSK	OMIM:stillborn	BIALLELIC	MYASTHENIC SYNDROME, CONGENITAL, 9, ASSOCIATED WITH ACETYLCHOLINE RECEPTOR DEFICIENCY; CMS9 | FETAL AKINESIA DEFORMATION SEQUENCE 1; FADS1
MYBPC3	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
MYH6	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
MYH7	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
MYL2	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
MYL3	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
MYLK2	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
MYOM1	Narula et al. (2015)	#N/A	hypertrophic cardiomyopathy
MYOZ2	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
MYPN	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
NDUFB11	OMIM:neonatal death	X-LINKED	MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 1; MC1DN1 | MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 30; MC1DN30
NEB	PMID:28749478; PMID:29274205	BIALLELIC	AUTOSOMAL RECESSIVE TYPICAL NEMALINE MYOPATHY
NEBL	Narula et al. (2015)	#N/A	dilated cardiomyopathy

NEXN	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
NIPBL	PMID:30890023; PMID:24189319	MONOALLELIC	CORNELIA DE LANGE SYNDROME TYPE 1
NKX2.5	Narula et al. (2015)	BIALLELIC	hypertrophic cardiomyopathy
OFD1	PMID:26147564	X-LINKED	JOUBERT SYNDROME TYPE 10;SIMPSON-GOLABI-BEHMEL SYNDROME TYPE 2;ORAL-FACIAL-DIGITAL SYNDROME TYPE 1
PADI6	OMIM:embryonic lethality	BIALLELIC	PREIMPLANTATION EMBRYONIC LETHALITY 2; PREMBL2
PDLIM3	Narula et al. (2015)	#N/A	dilated cardiomyopathy
PHGDH	OMIM:stillborn	BIALLELIC	NEU-LAXOVA SYNDROME 1; NLS1
PIEZO1	PMID:26333996; PMID:31028252	BOTH MONOALLELIC & BIALLELIC	hydrops fetalis gene 616843;Congenital lymphatic dysplasia with hydrops and/or lymphoedema
PKD2	OMIM:perinatal death	MONOALLELIC	POLYCYSTIC KIDNEY DISEASE 2 WITH OR WITHOUT POLYCYSTIC LIVER DISEASE; PKD2
PKHD1	PMID:19940839	BIALLELIC	POLYCYSTIC KIDNEY DISEASE, AUTOSOMAL RECESSIVE
PKP2	Narula et al. (2015)	MONOALLELIC	arrhymthmogenic cardiomyopathy
PKS	OMIM:stillborn	Somatic mosaicism	PALLISTER-KILLIAN SYNDROME; PKS
PLEC1	OMIM:onset: neonatal lethality	BIALLELIC	EPIDERMOLYSIS BULLOSA SIMPLEX WITH MUSCULAR DYSTROPHY; EBSMD | EPIDERMOLYSIS BULLOSA SIMPLEX WITH PYLORIC ATRESIA; EBSPA
PLN	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
PLOD2	PMID:29178448	BIALLELIC	BRUCK SYNDROME TYPE 2
POMT2	PMID:28815891	BIALLELIC	MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (CONGENITAL WITH MENTAL RETARDATION), TYPE B, 2; MDDGB2 | MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 2; MDDGC2
PRKAG2	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
PSEN1	Narula et al. (2015)	MONOALLELIC, Other	dilated cardiomyopathy
PSEN2	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy
PTEN	OMIM:neonatal death | stillbirth	BIALLELIC	VACTERL ASSOCIATION WITH HYDROCEPHALUS
PTH1R	PMID:9649554	BOTH MONOALLELIC & BIALLELIC	CHONDRODYSPLASIA BLOMSTRAND TYPE;EIKEN SKELETAL DYSPLASIA;JANSEN METAPHYSEAL CHONDRODYSPLASIA;PRIMARY FAILURE OF TOOTH ERUPTION
PTPN11	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
RAF1	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
RANGRF	Narula et al. (2015)	#N/A	brugada syndrome
RAPSN	OMIM:stillborn	BIALLELIC	MYASTHENIC SYNDROME, CONGENITAL, 11, ASSOCIATED WITH ACETYLCHOLINE RECEPTOR DEFICIENCY; CMS11 | FETAL AKINESIA DEFORMATION SEQUENCE 1; FADS1
RBM20	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy
REN	PMID:22095942	BIALLELIC	Renal tubular dysgenesis 267430
RET	PMID:18252215	BOTH MONOALLELIC & BIALLELIC	RENAL AGENESIS;MULTIPLE ENDOCRINE NEOPLASIA IIB
RIPK4	PMID:9738862	BIALLELIC	POPLITEAL PTERYGIUM SYNDROME, LETHAL TYPE
RNU4ATAC	OMIM:stillborn | stillbirth	BIALLELIC	MICROCEPHALIC OSTEODYSPLASTIC PRIMORDIAL DWARFISM, TYPE I; MOPD1
RPGRIP1L	OMIM:perinatal death	BIALLELIC	COACH SYNDROME | MECKEL SYNDROME, TYPE 5; MKS5
RYR2	Narula et al. (2015)	MONOALLELIC	catecholiminergic polymorphic ventricular cardiomyopathy | arrhymthmogenic cardiomyopathy
SBDS	PMID:17400792	BIALLELIC	SHWACHMAN-DIAMOND SYNDROME
SCN1B	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	brugada syndrome
SCN3B	Narula et al. (2015)	MONOALLELIC	brugada syndrome
SCN4B	Narula et al. (2015)	MONOALLELIC	long QT syndrome
SCN5A	OMIM:onset in utero | sudden infant death; Narula et al. (2015)	BIALLELIC	SUDDEN INFANT DEATH SYNDROME | SICK SINUS SYNDROME 1; SSS1

SEC23B	PMID:20381388	BIALLELIC	ANEMIA, DYSERYTHROPOIETIC CONGENITAL, TYPE II
SGCD	Narula et al. (2015)	BIALLELIC	dilated cardiomyopathy
SGPL1	OMIM:fetal demise	BIALLELIC	NEPHROTIC SYNDROME, TYPE 14; NPHS14
SLC17A5	PMID:28749478	BIALLELIC	SALLA DISEASE;INFANTILE SIALIC ACID STORAGE DISORDER
SLC26A2	OMIM:stillborn	BIALLELIC	ATELOSTEOGENESIS, TYPE II; AO2 | ACHONDROGENESIS, TYPE IB; ACG1B
SLC35D1	OMIM:stillborn	BIALLELIC	SCHNECKENBECKEN DYSPLASIA; SHNKND
SMN1	PMID:14968368	BIALLELIC	Spinal muscular atrophy 253550;Spinal muscular atrophy 271150;Spinal muscular atrophy 253400;Spinal muscular atrophy 253300
SNTA1	Narula et al. (2015)	MONOALLELIC	long QT syndrome
STE24	OMIM:stillbirth	BIALLELIC	RESTRICTIVE DERMOPATHY, LETHAL
STRA6	PMID:19839040; PMID:30204971	BIALLELIC	MICROPHTHALMIA SYNDROMIC TYPE 9
TAZ	OMIM:fetal demise; Narula et al. (2015)	X-LINKED	BARTH SYNDROME; BTHS
TBX1	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
TBX5	Narula et al. (2015)	MONOALLELIC	hypertrophic cardiomyopathy
TCAP	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
TCOF1	PMID:22729243	MONOALLELIC	TREACHER COLLINS SYNDROME TYPE 1
TGFB3	Narula et al. (2015)	MONOALLELIC	arrhymthmogenic cardiomyopathy
TLE6	OMIM:embryonic lethality	BIALLELIC	PREIMPLANTATION EMBRYONIC LETHALITY 1; PREMBL1
TMEM107	OMIM:perinatal death	BIALLELIC	MECKEL SYNDROME 13; MKS13
TMEM231	PMID:27449316	BIALLELIC	Joubert syndrome 20 614970;Meckel syndrome 11 615397
TMEM43	Narula et al. (2015)	MONOALLELIC	arrhymthmogenic cardiomyopathy
TMPO	Narula et al. (2015)	#N/A	dilated cardiomyopathy
TNNC1	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
TNNI3	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
TNNT2	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
TPM1	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
TRDN	Narula et al. (2015)	BIALLELIC	catecholiminergic polymorphic ventricular cardiomyopathy
TRIP11	OMIM:stillborn	BIALLELIC	ACHONDROGENESIS, TYPE IA; ACG1A
TTC21B	PMID:28749478	BIALLELIC	Short-rib thoracic dysplasia 4 with or without polydactyly 613819
TTN	Narula et al. (2015)	BOTH BIALLELIC & MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
TTR	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
TXNRD2	Narula et al. (2015)	BIALLELIC	dilated cardiomyopathy
UBR1	PMID:21711208	BIALLELIC	JOHANSON-BLIZZARD SYNDROME
VCL	Narula et al. (2015)	MONOALLELIC	dilated cardiomyopathy | hypertrophic cardiomyopathy
WT1	PMID:26882358	MONOALLELIC	FRASIER SYNDROME FRASIER SYNDROME FRASIER SYNDROME;DENYS-DRASH SYNDROME
ZMPSTE24	OMIM:stillbirth	BIALLELIC	RESTRICTIVE DERMOPATHY, LETHAL

Table S2: Autopsy and ultrasound in stillbirth cohort (n=246)

Analysis	**N=246 women**
Ultrasound available	233 (94.7)
Autopsy Consent	
• None	23 (9.3)
• Limited	47 (19.1)
• Full	176 (71.5)
Autopsy and Ultrasound	
• Neither	2 (0.8)
• Ultrasound only	21 (8.5)
• Autopsy only	11 (4.5)
• Both	212 (86.2)

Reporting: n (column percentage)

Table S3. Characteristics by completion of exome sequencing in the analysis among SCRN stillbirths (n=663)[a]

CHARACTERISTICS - unweighted %	SB sequenced and included in the analysis	SB not included in the analysis	p-value[b]
Unweighted sample size of stillborn babies [b] -	246	417	
Maternal age at delivery	246	417	0.9014
< 20	33 (13.4)	52 (12.5)	
20-34	176 (71.5)	294 (70.5)	
35-39	28 (11.4)	52 (12.5)	
40+	9 (3.7)	19 (4.6)	
Maternal race ethnicity	246	416	0.0170
Non-Hispanic White	105 (42.7)	129 (31.0)	
Non-Hispanic Black	48 (19.5)	94 (22.6)	
Hispanic	80 (32.5)	157 (37.7)	
Other	13 (5.3)	36 (8.7)	
Maternal education	228	384	0.1094
0-11 (none/primary/some secondary)	44 (19.3)	101 (26.3)	
12 (completed secondary)	66 (28.9)	111 (28.9)	
13+ (college)	118 (51.8)	172 (44.8)	
Insurance/method of payment	245	414	0.1513
No insurance	16 (6.5)	24 (5.8)	
Any public/private assistance	117 (47.8)	230 (55.6)	
VA/commercial health ins/ HMO	112 (45.7)	160 (38.6)	
Gestational age at delivery	246	417	0.7037
18 – 19 weeks	4 (1.6)	11 (2.6)	
20 – 23 weeks	84 (34.1)	132 (31.7)	
24 – 27 weeks	36 (14.6)	72 (17.3)	
28 – 31 weeks	32 (13.0)	63 (15.1)	
32 – 36 weeks	49 (19.9)	70 (16.8)	
37+ weeks	41 (16.7)	69 (16.5)	
Plurality of pregnancy	246	417	N/A
Multiple birth	0 (0.0)	43 (10.3)	
Singleton	246 (100.0)	374 (89.7)	
Parity	245	416	0.3163
nulliparous	105 (42.9)	195 (46.9)	
multiparous	140 (57.1)	221 (53.1)	

[a] SCRN defined stillbirth as Apgar scores of 0/0 at 1 and 5 minutes with no signs of life by direct observation. Results are presented here for pregnancies. A pregnancy is defined as a SCRN case if there were any stillbirths delivered.

Multiple births were not included in the analysis of the exome sequencing results.

[b] P-values from chi-square test for the comparisons of stillbirth included in the analysis compared to those who are not among those with INCODE analysis...

Table S4. Characteristics by completion of exome sequencing and inclusion in the analysis among SCRN stillbirths with consent for genetic study of the stillborn baby (n=639)[a]

CHARACTERISTICS - unweighted %	SB sequenced and included in the analysis	SB not included in the analysis	p-value[b]
Unweighted sample size of stillborn babies [b] -	246	393	
Maternal age at delivery	246	393	0.7839
< 20	33 (13.4)	46 (11.7)	
20-34	176 (71.5)	278 (70.7)	
35-39	28 (11.4)	50 (12.7)	
40+	9 (3.7)	19 (4.8)	
Maternal race ethnicity	246	392	0.0599
Non-Hispanic White	105 (42.7)	128 (32.7)	
Non-Hispanic Black	48 (19.5)	83 (21.2)	
Hispanic	80 (32.5)	149 (38.0)	
Other	13 (5.3)	32 (8.2)	
Maternal education	228	366	0.1161
0-11 (none/primary/some secondary)	44 (19.3)	97 (26.5)	
12 (completed secondary)	66 (28.9)	103 (28.1)	
13+ (college)	118 (51.8)	166 (45.4)	
Insurance/method of payment	245	390	0.1524
No insurance	16 (6.5)	21 (5.4)	
Any public/private assistance	117 (47.8)	217 (55.6)	
VA/commercial health ins/ HMO	112 (45.7)	152 (39.0)	
Gestational age at delivery	246	393	0.7391
18 – 19 weeks	4 (1.6)	9 (2.3)	
20 – 23 weeks	84 (34.1)	120 (30.5)	
24 – 27 weeks	36 (14.6)	68 (17.3)	
28 – 31 weeks	32 (13.0)	60 (15.3)	
32 – 36 weeks	49 (19.9)	68 (17.3)	
37+ weeks	41 (16.7)	68 (17.3)	
Plurality of pregnancy	246	393	N/A
Multiple birth	0 (0.0)	41 (10.4)	
Singleton	246 (100.0)	352 (89.6)	
Parity	245	393	0.4294
nulliparous	105 (42.9)	181 (46.1)	
multiparous	140 (57.1)	212 (53.9)	

[a] SCRN defined stillbirth as Apgar scores of 0/0 at 1 and 5 minutes with no signs of life by direct observation. Results are presented here for pregnancies. A pregnancy is defined as a SCRN case if there were any stillbirths delivered.

Multiple births were not included in the analysis of the exome sequencing results.

[b] P-values from chi-square test for the comparisons of stillbirth included in the analysis compared to those who are not among those with consent to genetic study of the baby..

Table S5 : Control cohort sources.

The controls used in this study were all individuals sequenced as healthy relatives to probands in various studies conducted at the Institute for Genomic Medicine.

No. Controls	Contributing individual or group
4	A Ponduri
7	R Buckley
105	A Gharavi
11	M Harms
413	R Wapner
9	S Berkovic
2	N Delanty
9	M Harms
114	ET Cirulli
1250	M Halvorsen
24	M Hauser
1	A Alkelai
2	Duke University Sequencing Clinic
7	Epilepsy Genetics Initiative
854	Epilepsy Phenome/Genome Project (EPGP)
126	epi4k Consortium
2	Duke Center for Human Genome Variation
10	Division of Personalized Genomic Medicine (PGM), Columbia University
3	Undiagnosed Disease Network Sequencing Clinic
9	Cold Spring Harbor Laboratory
2897	The Washington Heights, Inwood Columbia Aging Project
2	Johns Hopkins University
45	EpiGen Consortium
12	Neonatal Intensive Care Unit, Columbia University Irving Medical Center
1233	Institute for Genomic Medicine Sequencing Clinic (New York Presbyterian study)
88	Institute for Genomic Medicine external collaboration (MEDIN)
7239	**Total**

Table S6: Suggestive variants identified in a stillborn. Listed variants did not meet American College of Medical Genetics (ACMG) criteria for "pathogenic" or "likely pathogenic", but were considered "suggestive" by a multidisciplinary team (see Methods in Supplementary Appendix). Two variants were identified in genes previous reported in stillbirth and four were identified in genes that represent strong candidates for phenotype expansion. OMIM disease = Disease association according to the Online Mendelian Inheritance in Man database. Het = heterozygous. Chet = compound heterozygous. Hom = homozygous. Hemi = hemizygous. AF = allele frequency. VOUS = Variant of Uncertain Significance in ClinVar. HGMD = Human Gene Mutation Database. DM = "Disease Mutation" in HGMD. Suggestive = committee classification of "suggestive" and not P/LP based on flags (see Methods in Supplementary Appendix).

Body System	Gene	Evidence of Association	OMIM disease	Sample ID	DNA source	best gestational age at death	ultrasound	autopsy	Structural Anomalies	"probable" INCODE cause of death	IUGR	IUGR	Variant Effect Annotation	HGVS_c	HGVS_p	GT	gnomAD AF	Clinical Significance ClinVar | HGMD	Clinical Disease ClinVar | HGMD	Committee Classification
Heart	*KCNH2*	PMID: 23571586	Long QT syndrome 2 | Short QT syndrome 1 609620	stillborn389	placenta	38.71	yes	full	none	none	no		missense	c.3278C>T	p.Pro1093Leu	het	3.80E-05	DM | VOUS	Long_QT_syndrome | Congenital_long_QT_syndrome	suggestive
Multisystem	*PTPN11*	PMID: 25914815	Noonan syndrome 1	stillborn126	cord blood	35.57	yes	limited	none	none	yes	8.1%tile	missense	c.1232C>T	p.Thr411Met	het	1.22E-05	Pathogenic	Noonan_syndrome_1	suggestive
Kidney	*GREB1L*	NA	Renal hypodysplasia/aplasia 3	stillborn121	placenta	38.57	yes	full	none	none	no	11.8%tile	missense	c.5324G>A	p.Arg1775His	het	2.02E-05	DM	Renal_hypoplasia	suggestive
Multisystem	*BCOR*	NA	Microphthalmia syndromic 2	stillborn238	placenta	33.29	yes	full	none	none	no	84.79%tile	missense	c.904C>A	p.His302Asn	hemi	0	NA	NA	suggestive
Muscle	*DMD*	NA	Duchenne muscular dystrophy	stillborn365	placenta	28.43	yes	limited	none	none	yes	1.96%tile	missense	c.6571C>T	p.Arg2191Trp	hemi	3.82E-04; 0 hom	Conflicting interpretations of pathogenicity	Duchenne_muscular_dystrophy|not_specified|Cardiovascular_phenotype	suggestive
				stillborn093	placenta	37.00	yes	full	none	umbilical cord	no	57.21%tile	missense	c.1066C>T	p.Leu356Phe	hemi	2.24E-05; 0 hom	VOUS	Duchenne_muscular_dystrophy	suggestive

Table S7. GO enrichment analysis for known disease genes with diagnostic genotypes in a stillborn case. We provide the top 50 most enriched Gene-Ontology (GO) biological processes ranked by adjusted P value. Enrichr was used for all GO enrichment analyses.

Term	Genes	Overlap	P-value	Adjusted P-value	Odds Ratio
regulation of striated muscle contraction (GO:0006942)	HCN4;MYBPC3;RYR2	3/29	7.76E-07	0.001	159.151
regulation of cardiac muscle cell contraction (GO:0086004)	HCN4;RYR2;DSC2	3/26	5.53E-07	0.001	177.515
regulation of cardiac muscle cell action potential (GO:0098901)	HCN4;RYR2;DSC2	3/24	4.31E-07	0.002	192.308
regulation of ventricular cardiac muscle cell action potential (GO:0098911)	RYR2;DSC2	2/11	2.14E-05	0.027	279.720
cardiac muscle contraction (GO:0060048)	MYBPC3;RYR2	2/36	2.43E-04	0.124	85.470
regulation of cardiac muscle contraction (GO:0055117)	HCN4;RYR2	2/35	2.29E-04	0.130	87.912
regulation of heart rate by cardiac conduction (GO:0086091)	HCN4;DSC2	2/35	2.29E-04	0.146	87.912
positive regulation of ATPase activity (GO:0032781)	MYBPC3;RYR2	2/35	2.29E-04	0.167	87.912
heart contraction (GO:0060047)	MYBPC3;RYR2	2/44	3.63E-04	0.169	69.930
ventricular cardiac muscle tissue morphogenesis (GO:0055010)	MYBPC3;RYR2	2/34	2.16E-04	0.184	90.498
heart morphogenesis (GO:0003007)	MYBPC3;RYR2	2/50	4.69E-04	0.200	61.538
embryonic organ morphogenesis (GO:0048562)	FBN2;RYR2	2/33	2.04E-04	0.208	93.240
striated muscle contraction (GO:0006941)	MYBPC3;RYR2	2/61	6.98E-04	0.274	50.441
regulation of heart contraction (GO:0008016)	HCN4;RYR2	2/95	0.002	0.613	32.389
potassium ion import across plasma membrane (GO:1990573)	HCN4	1/9	0.006	0.677	170.940
regulation of cardiac muscle cell action potential involved in regulation of contraction (GO:0098909)	HCN4	1/8	0.005	0.679	192.308
sarcoplasmic reticulum calcium ion transport (GO:0070296)	RYR2	1/9	0.006	0.693	170.940
cellular response to purine-containing compound (GO:0071415)	RYR2	1/8	0.005	0.697	192.308
ventricular cardiac muscle cell action potential (GO:0086005)	RYR2	1/15	0.010	0.708	102.564
epithelial cell apoptotic process (GO:1904019)	RYR2	1/9	0.006	0.709	170.940
response to purine-containing compound (GO:0014074)	RYR2	1/17	0.011	0.710	90.498
embryonic eye morphogenesis (GO:0048048)	FBN2	1/11	0.007	0.713	139.860
positive regulation of DNA-templated transcription, initiation (GO:2000144)	HNF1B	1/16	0.010	0.714	96.154
response to epinephrine (GO:0071871)	RYR2	1/8	0.005	0.716	192.308
establishment of protein localization to endoplasmic reticulum (GO:0072599)	RYR2	1/15	0.010	0.718	102.564
positive regulation of glucose import in response to insulin stimulus (GO:2001275)	PTPN11	1/10	0.006	0.719	153.846
membrane depolarization during cardiac muscle cell action potential (GO:0086012)	HCN4	1/17	0.011	0.719	90.498
regulation of membrane depolarization (GO:0003254)	HCN4	1/16	0.010	0.724	96.154
sequestering of extracellular ligand from receptor (GO:0035581)	FBN2	1/7	0.005	0.724	219.780
regulation of sequestering of calcium ion (GO:0051282)	RYR2	1/9	0.006	0.726	170.940
import across plasma membrane (GO:0098739)	HCN4	1/11	0.007	0.728	139.860
sodium ion import across plasma membrane (GO:0098719)	HCN4	1/15	0.010	0.729	102.564
positive regulation of transcription initiation from RNA polymerase II promoter (GO:0060261)	HNF1B	1/17	0.011	0.729	90.498
calcium-mediated signaling using intracellular calcium source (GO:0035584)	RYR2	1/18	0.012	0.733	85.470
genitalia development (GO:0048806)	PTPN11	1/16	0.010	0.734	96.154
regulation of actin filament-based movement (GO:1903115)	MYBPC3	1/10	0.006	0.735	153.846
cellular response to epinephrine stimulus (GO:0071872)	RYR2	1/8	0.005	0.736	192.308
macromolecule biosynthetic process (GO:0009059)	COL1A1	1/19	0.012	0.737	80.972
positive regulation of calcium ion transmembrane transporter activity (GO:1901021)	RYR2	1/17	0.011	0.738	90.498
positive regulation of cell differentiation (GO:0045597)	FBN2;COL1A1	2/194	0.007	0.739	15.860
positive regulation of viral release from host cell (GO:1902188)	SMC3	1/15	0.010	0.739	102.564
regulation of transcription initiation from RNA polymerase II promoter (GO:0060260)	HNF1B	1/13	0.008	0.741	118.343
positive regulation by host of viral process (GO:0044794)	SMC3	1/11	0.007	0.742	139.860
regulation of cellular response to growth factor stimulus (GO:0090287)	FBN2	1/18	0.012	0.743	85.470
embryonic heart tube development (GO:0035050)	RYR2	1/16	0.010	0.744	96.154
response to muscle stretch (GO:0035994)	RYR2	1/9	0.006	0.745	170.940
cardiac left ventricle morphogenesis (GO:0003214)	RYR2	1/14	0.009	0.746	109.890
calcium ion transport into cytosol (GO:0060402)	RYR2	1/19	0.012	0.746	80.972
release of sequestered calcium ion into cytosol by endoplasmic reticulum (GO:1903514)	RYR2	1/7	0.005	0.748	219.780
regulation of cardiac muscle contraction by regulation of the release of sequestered calcium ion (GO:0010881)	RYR2	1/17	0.011	0.748	90.498

Table S8 : Results for the gene-based collapsing analysis of 246 stillborn cases and 7,239 healthy control exomes. The top 20 ranked genes from the "Known Pathogenic" model (i.e., variants that have been previously implicated as causing, when variant, disease). AD stillbirth gene = among the known dominant stillbirth genes aggregated by this group; Qualified case = number of cases carrying a qualifying variant under this model; Qualified Case Freq = proportion of cases carrying a qualifying variant; Qualified control = number of controls carrying a qualifying variant under this model; Qualified Case Freq = proportion of controls carrying a qualifying variant; Fet P = Fisher's exact test two-sided p-value.

Gene Name	AD stillbirth gene	Qualified Case	Qualified Case Freq	Qualified Ctrl	Qualified Ctrl Freq	Fet P
PTPN11	yes	3	0.0124	1	1.38E-04	1.29E-04
WDR72		2	0.0083	0	0	0.001
NPC1L1		2	0.0083	1	1.38E-04	0.003
NCF2		2	0.0083	1	1.38E-04	0.003
LAMA2		3	0.0124	9	0.0012	0.0059
SLCO2A1		2	0.0083	2	2.76E-04	0.0059
CRB1		3	0.0124	10	0.0014	0.0074
DARS2		2	0.0083	3	4.14E-04	0.0097
HNF1B	yes	2	0.0083	3	4.14E-04	0.0097
TK2		2	0.0083	3	4.14E-04	0.0097
AMT		2	0.0083	5	6.91E-04	0.0195
FAH		2	0.0083	7	9.67E-04	0.0321
C8B		1	0.0041	0	0	0.0322
SUN2		1	0.0041	0	0	0.0322
DCC		1	0.0041	0	0	0.0322
PRKAR1A		1	0.0041	0	0	0.0322
OGDHL		1	0.0041	0	0	0.0322
RTTN		1	0.0041	0	0	0.0322
HSPB1		1	0.0041	0	0	0.0322
GP6		1	0.0041	0	0	0.0322
RYR2	yes	1	0.0041	0	0	0.0322

Table S9: Samples (n=35) harboring at least one loss-of-function variant in a constrained (LOEUF ≤ 0.239) gene. LOEUF = gnomAD v2.1.1 loss-of-function observed/expected upper bound fraction. LOEUF threshold = AF = allele frequency; Passed IGV = Passed visual inspection in the Integrative Genomics Viewer (IGV); OMIM = Online Inheritance in Man database. GT = genotype.

Gene Name	Sample Name	HGVS_c	Effect	Passed IGV	GT	gnomAD Exome global AF	ClinVar Clinical Significance	OMIM Disease
ARID1B	stillborn280	c.2372-2A>C	splice acceptor	TRUE	het	0	Uncertain significance	Coffin-Siris syndrome 1
BRAF	stillborn282	c.2011C>T	stop gained	TRUE	het	0	NA	Adenocarcinoma of lung somatic | Cardiofaciocutaneous syndrome | Colorectal cancer somatic | LEOPARD syndrome 3 | Melanoma malignant somatic | Nonsmall cell lung cancer somatic | Noonan syndrome 7
CASZ1	stillborn015	c.3382C>T	stop gained	TRUE	het	0	NA	NA
CDH11	stillborn055	c.453delC	frameshift	TRUE	het	0	NA	NA
COG3	stillborn096	c.1333C>T	stop gained	TRUE	het	0	NA	NA
CTNND2	stillborn180	c.1669C>T	stop gained	TRUE	het	0	NA	NA
DCLK1	stillborn069	c.188_189insGAGATAG	frameshift	TRUE	het	0	NA	NA
DOCK9	stillborn258	c.2044-1G>C	splice acceptor	TRUE	het	0	NA	NA
E2F1	stillborn357	c.1017dupC	frameshift	TRUE	het	0	NA	NA
ESRP1	stillborn015	c.31delC	frameshift	TRUE	het	0	NA	NA
FBN2	stillborn316	c.2034delG	frameshift	TRUE	het	0	NA	Contractural arachnodactyly congenital | Macular degeneration early-onset
FMNL1	stillborn212	c.327+1G>A	splice donor	TRUE	het	0	NA	NA
FNBP4	stillborn088	c.2442_2443delTA	frameshift	TRUE	het	0	NA	NA
HCN4	stillborn144	c.1522dupA	frameshift	TRUE	het	0	NA	Brugada syndrome 8 | Sick sinus syndrome 2
HNF1B	stillborn064	c.1447C>T	stop gained	TRUE	het	0	NA	Diabetes mellitus noninsulin-dependent | Renal cysts and diabetes syndrome | {Renal cell carcinoma}
HNF1B	stillborn011	c.544+1G>A	splice donor	TRUE	het	0	NA	Diabetes mellitus noninsulin-dependent | Renal cysts and diabetes syndrome | {Renal cell carcinoma}
L3MBTL3	stillborn389	c.2284_2287delATTT	frameshift	TRUE	het	0	NA	NA
MAPK8IP3	stillborn185rep	c.440-1G>C	splice acceptor	TRUE	het	0	NA	NA
MAU2	stillborn077	c.1769_1775delGGACAGA	frameshift	TRUE	het	0	NA	NA
MSL1	stillborn321rep	c.270delA	frameshift	TRUE	het	0	NA	NA
MYT1L	stillborn077	c.2637-2A>G	splice acceptor	TRUE	het	0	NA	Mental retardation autosomal dominant 39
NCDN	stillborn310	c.828delG	frameshift	TRUE	het	0	NA	NA
NCOA6	stillborn425	c.1010delC	frameshift	TRUE	het	0	NA	NA
NDC1	stillborn297	c.455+1G>C	splice donor	TRUE	het	0	NA	NA
NOL6	stillborn348	c.2995_2998delACAG	frameshift	TRUE	het	0	NA	NA
NUP98	stillborn193	c.1497_1498delTC	frameshift	TRUE	het	0	NA	NA
PRMT5	stillborn202	c.1004delA	frameshift	TRUE	het	0	NA	NA
RNF2	stillborn334	c.72dupA	frameshift	TRUE	het	0	NA	NA
SPAG9	stillborn267	c.2965C>T	stop gained	TRUE	het	0	NA	NA
SRRM2	stillborn433	c.213_217delCGAGC	frameshift	FALSE	het	0	NA	NA
SRRM2	stillborn433	c.219_242+42delGGAGGAGATGATGGAAGAGCAGGGGTGAGGGAGAGCTGGGGGAGAGTCAAGCACTGAATGAGTGCA	splice donor	FALSE	het	0	NA	NA
STK40	stillborn440	c.1252C>T	stop gained	TRUE	het	0	NA	NA
TAOK1	stillborn266	c.1563delC	frameshift	TRUE	het	0	NA	NA
VPS54	stillborn327	c.646delG	frameshift	TRUE	het	0	NA	NA
ZNF236	stillborn186	c.3181C>T	stop gained	TRUE	het	0	NA	NA

Table S10. Comparison of loss-of-function signal in constrained (LOEUF≤ 0.239) genes across INCODE clinical characteristics. Comparison of burden of loss-of-function variants in constrained genes between unexplained cases (n=80) and those with "probable" INCODE obstetric/placental/umbilical cord abnormalities (n=161). Conf.low = lower 95% confidence. Conf.high = upper 95% confidence interval. FET = Fisher's exact test.

Gene-set	odds ratio	p.value	conf.low	conf.high	method	alternative
ALL	0.708	0.438	0.320	1.607	FET	two sided
OMIM	0.470	0.302	0.105	2.109	FET	two sided
NO_OMIM	1.062	1.000	0.411	2.985	FET	two sided

Table S11. GO biological processes enrichment analysis for stillbirth candidate disease genes. We provide the top 50 ranked Gene-Ontology (GO) biological processes from Enrichr. Enrichment for GO biological processes was ranked by adjusted P value. Overlap = the number of observed genes contained in the GO biological process / the total number of genes in the GO biological process.

Term	Genes	Overlap	P-value	Adjusted P-value	Odds Ratio
tRNA transport (GO:0051031)	NDC1;NUP98;NOL6	3/35	1.10E-05	0.014	68.571
tRNA export from nucleus (GO:0006409)	NDC1;NUP98;NOL6	3/33	9.18E-06	0.016	72.727
tRNA-containing ribonucleoprotein complex export from nucleus (GO:0071431)	NDC1;NUP98;NOL6	3/33	9.18E-06	0.023	72.727
positive regulation of JUN kinase activity (GO:0043507)	SPAG9;TAOK1;MAPK8IP3	3/50	3.25E-05	0.033	48.000
activation of JUN kinase activity (GO:0007257)	SPAG9;TAOK1;MAPK8IP3	3/30	6.85E-06	0.035	80.000
JNK cascade (GO:0007254)	SPAG9;TAOK1;MAPK8IP3	3/66	7.49E-05	0.055	36.364
nuclear pore complex assembly (GO:0051292)	NDC1;NUP98	2/10	6.71E-05	0.057	160.000
pore complex assembly (GO:0046931)	NDC1;NUP98	2/14	1.35E-04	0.086	114.286
nuclear pore organization (GO:0006999)	NDC1;NUP98	2/15	1.56E-04	0.088	106.667
RNA export from nucleus (GO:0006405)	NDC1;NUP98;NOL6	3/119	4.29E-04	0.199	20.168
RNA biosynthetic process (GO:0032774)	PRMT5;NCOA6	2/26	4.79E-04	0.204	61.538
activation of MAPK activity (GO:0000187)	SPAG9;TAOK1;MAPK8IP3	3/117	4.09E-04	0.208	20.513
regulation of generation of precursor metabolites and energy (GO:0043467)	NDC1;NUP98	2/46	0.002	0.306	34.783
nucleus organization (GO:0006997)	NDC1;NUP98	2/45	0.001	0.319	35.556
nuclear envelope disassembly (GO:0051081)	NDC1;NUP98	2/46	0.002	0.319	34.783
regulation of stress-activated MAPK cascade (GO:0032872)	TAOK1;MAPK8IP3	2/41	0.001	0.321	39.024
regulation of coenzyme metabolic process (GO:0051196)	NDC1;NUP98	2/39	0.001	0.324	41.026
neuron projection development (GO:0031175)	CTNND2;NCDN;DCLK1	3/167	0.001	0.326	14.371
protein complex subunit organization (GO:0071822)	NDC1;NUP98	2/45	0.001	0.333	35.556
mitotic nuclear envelope disassembly (GO:0007077)	NDC1;NUP98	2/44	0.001	0.334	36.364
regulation of ATP metabolic process (GO:1903578)	NDC1;NUP98	2/43	0.001	0.335	37.209
regulation of G0 to G1 transition (GO:0070316)	E2F1;RNF2	2/39	0.001	0.345	41.026
DNA damage checkpoint (GO:0000077)	TAOK1;E2F1	2/38	0.001	0.349	42.105
regulation of carbohydrate catabolic process (GO:0043470)	NDC1;NUP98	2/37	9.73E-04	0.355	43.243
regulation of posttranscriptional gene silencing (GO:0060147)	NDC1;NUP98	2/55	0.002	0.376	29.091
negative regulation of G0 to G1 transition (GO:0070317)	E2F1;RNF2	2/37	9.73E-04	0.382	43.243
regulation of gene silencing by RNA (GO:0060966)	NDC1;NUP98	2/55	0.002	0.390	29.091
transport of virus (GO:0046794)	NDC1;NUP98	2/54	0.002	0.390	29.630
regulation of glycolytic process (GO:0006110)	NDC1;NUP98	2/57	0.002	0.390	28.070
intracellular transport of virus (GO:0075733)	NDC1;NUP98	2/54	0.002	0.405	29.630
endosomal transport (GO:0016197)	SPAG9;VPS54;DCLK1	3/229	0.003	0.466	10.480
protein sumoylation (GO:0016925)	NDC1;NUP98	2/68	0.003	0.502	23.529
regulation of gene silencing by miRNA (GO:0060964)	NDC1;NUP98	2/67	0.003	0.503	23.881
regulation of cellular response to heat (GO:1900034)	NDC1;NUP98	2/78	0.004	0.638	20.513
retrograde transport, endosome to Golgi (GO:0042147)	SPAG9;VPS54	2/82	0.005	0.664	19.512
negative regulation of cell cycle process (GO:0010948)	E2F1;RNF2	2/81	0.005	0.667	19.753
regulation of JNK cascade (GO:0046328)	TAOK1;MAPK8IP3	2/90	0.006	0.775	17.778
viral life cycle (GO:0019058)	NDC1;NUP98	2/107	0.008	0.871	14.953
mRNA export from nucleus (GO:0006406)	NDC1;NUP98	2/105	0.008	0.878	15.238
cellular response to DNA damage stimulus (GO:0006974)	NCOA6;TAOK1;E2F1	3/329	0.008	0.880	7.295
glucocorticoid receptor signaling pathway (GO:0042921)	NCOA6	1/6	0.007	0.887	133.333
viral gene expression (GO:0019080)	NDC1;NUP98	2/110	0.008	0.899	14.545
histone H2A-K119 monoubiquitination (GO:0036353)	RNF2	1/8	0.010	0.907	100.000
viral transcription (GO:0019083)	NDC1;NUP98	2/113	0.009	0.908	14.159
corticosteroid receptor signaling pathway (GO:0031958)	NCOA6	1/6	0.007	0.909	133.333
peptidyl-lysine modification (GO:0018205)	NDC1;NUP98	2/115	0.009	0.920	13.913
Golgi organization (GO:0007030)	PRMT5;COG3	2/121	0.010	0.923	13.223
DNA replication (GO:0006260)	NCOA6;NUP98	2/120	0.010	0.925	13.333
mRNA-containing ribonucleoprotein complex export from nucleus (GO:0071427)	NDC1;NUP98	2/100	0.007	0.925	16.000

Figure S1: Flow diagram for case cohort. CCDS = consensus coding sequence. WES = whole exome sequence.

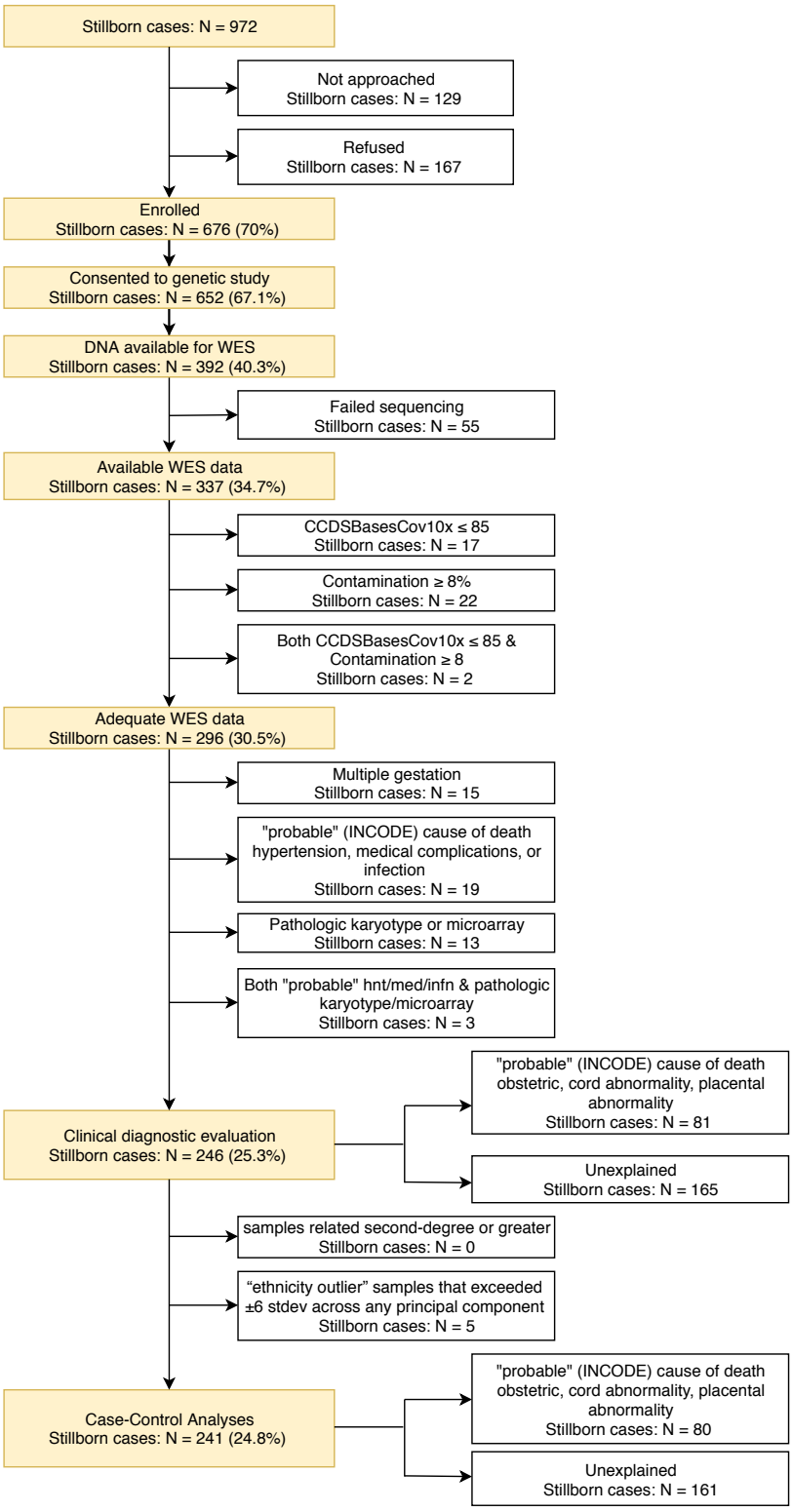


Figure S2: Case-level diagnostic pipeline. GATK = Genome Analysis Toolkit. Known pathogenic = previously reported as "Pathogenic" or "Likely pathogenic" in ClinVar or as "Disease Mutation" in the Human Gene Mutation Database. OMIM = Online Mendelian Inheritance in Man database. Novel = variant not previously reported as disease causing. PTV-intolerant = genes with a gnomAD 2.1 loss-of-function observed/expected upper bound fraction [LOEUF] < 0.35. HOM = homozygous variant. pCHET = possibly compound heterozygous variant. gnomAD hom = frequency of the homozygous genotype in gnomAD 2..1. Internal AF = allele frequency amongst internal cases and controls. External AF = allele frequency in external reference databases (gnomAD 2.1 & ExAC 3.0). IGV = Integrative Genome Viewer.

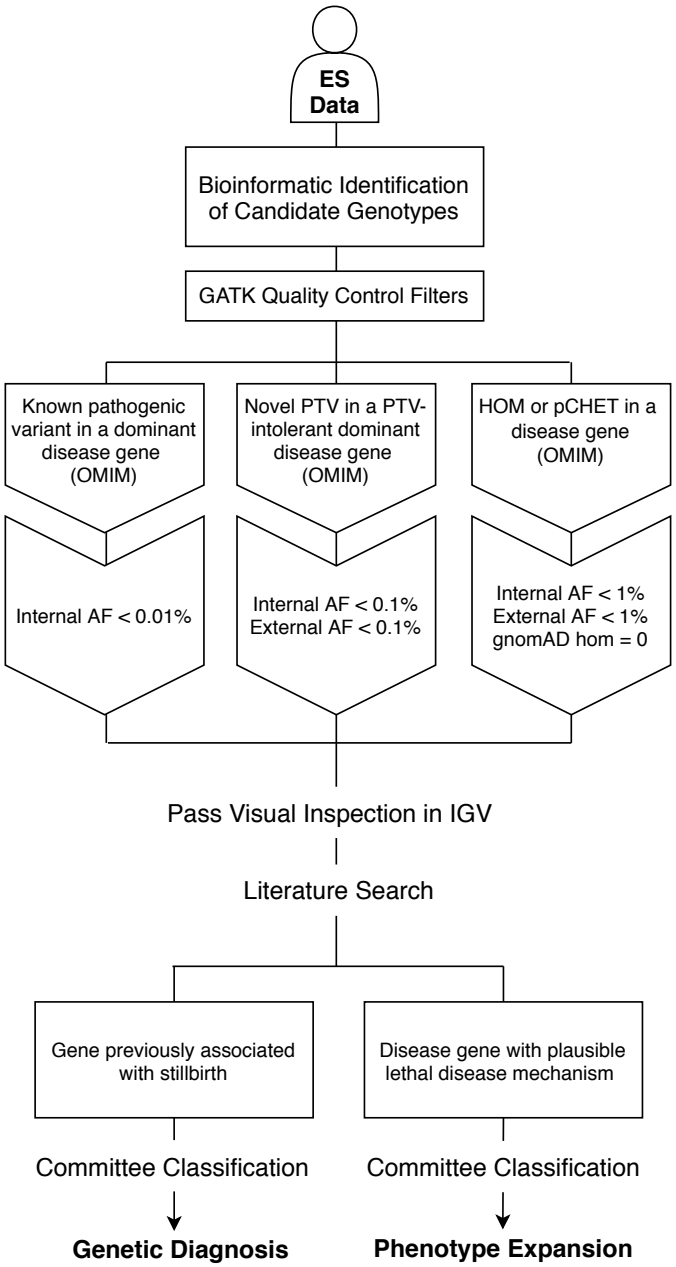


Figure S3. Cohort-level collapsing analysis work flow. CCDS = consensus coding sequence

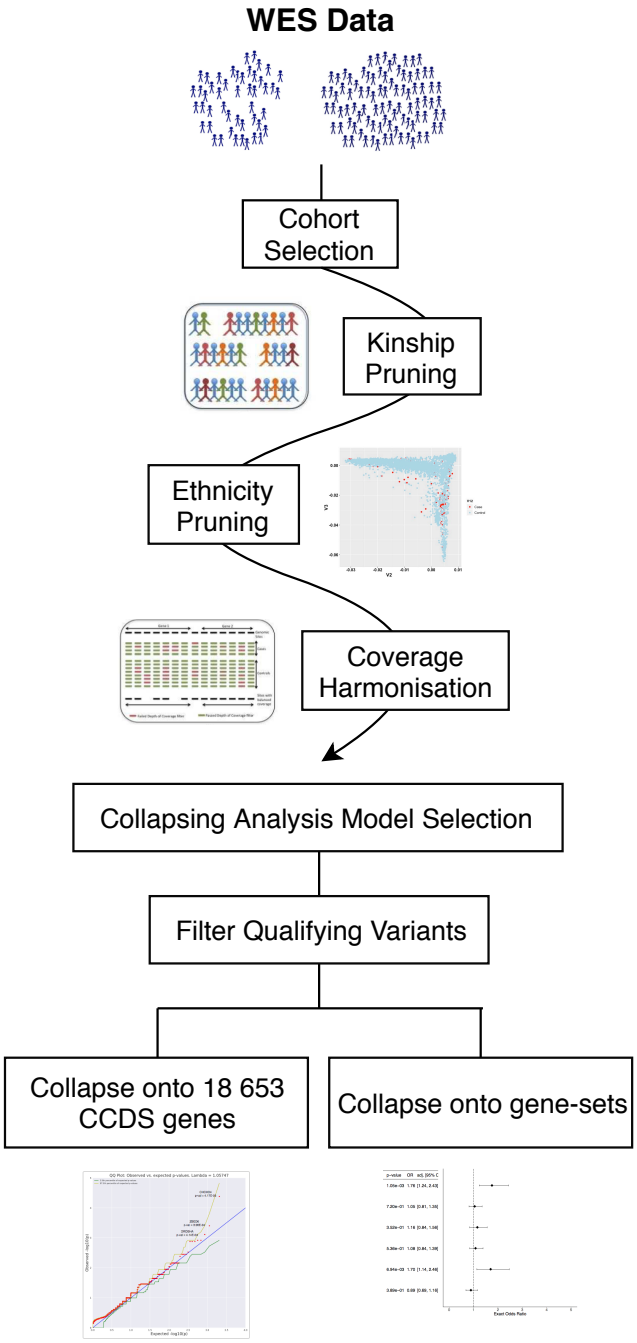


Figure S4 Principal components analysis for ancestry. (A) Principal component 1 vs 2, 2 vs 3 and 1 vs 3 for the case (red) and control (blue) cohort. (B) Cases and controls were retained only if they did not exceed 6 standard deviations along any principal component[4].

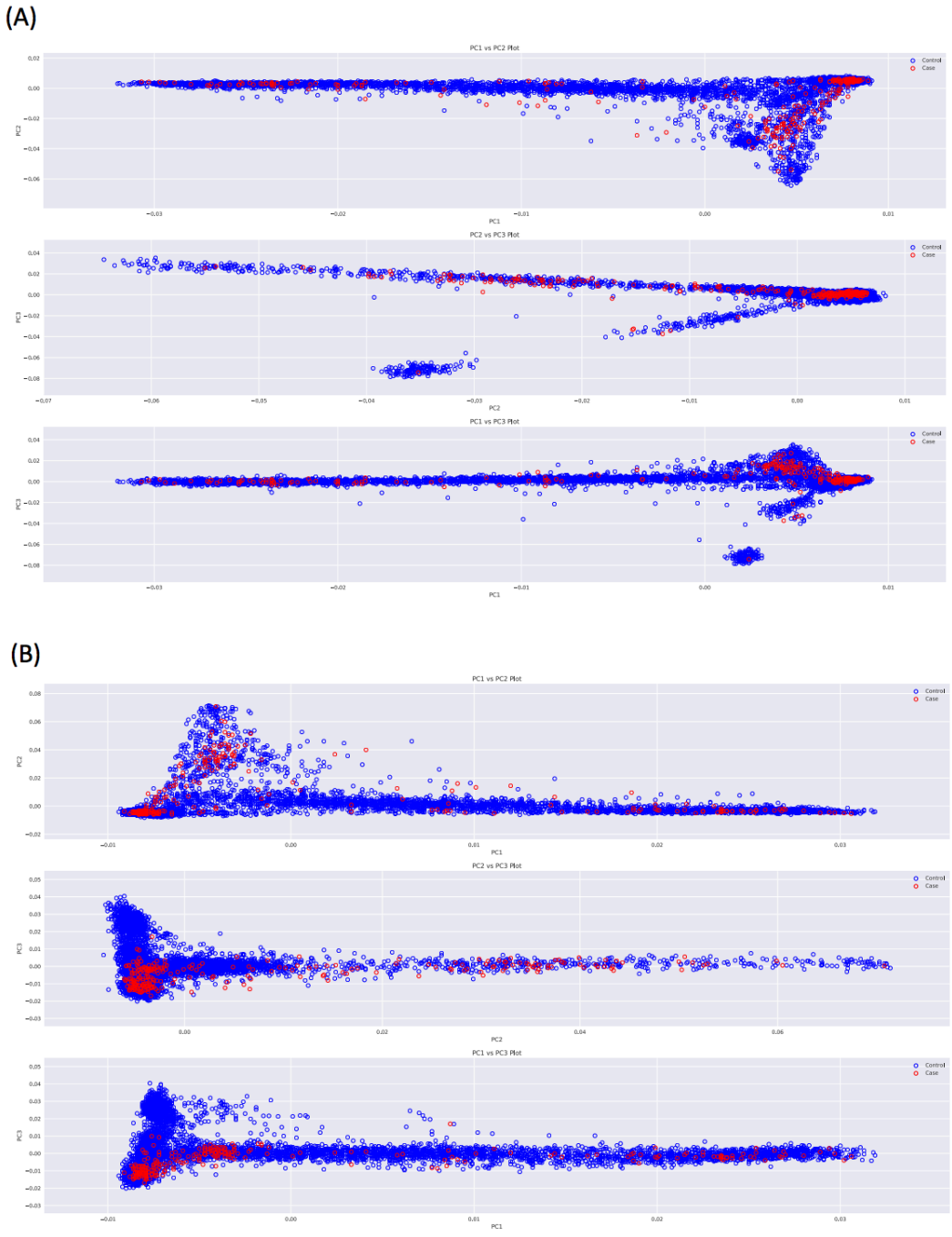
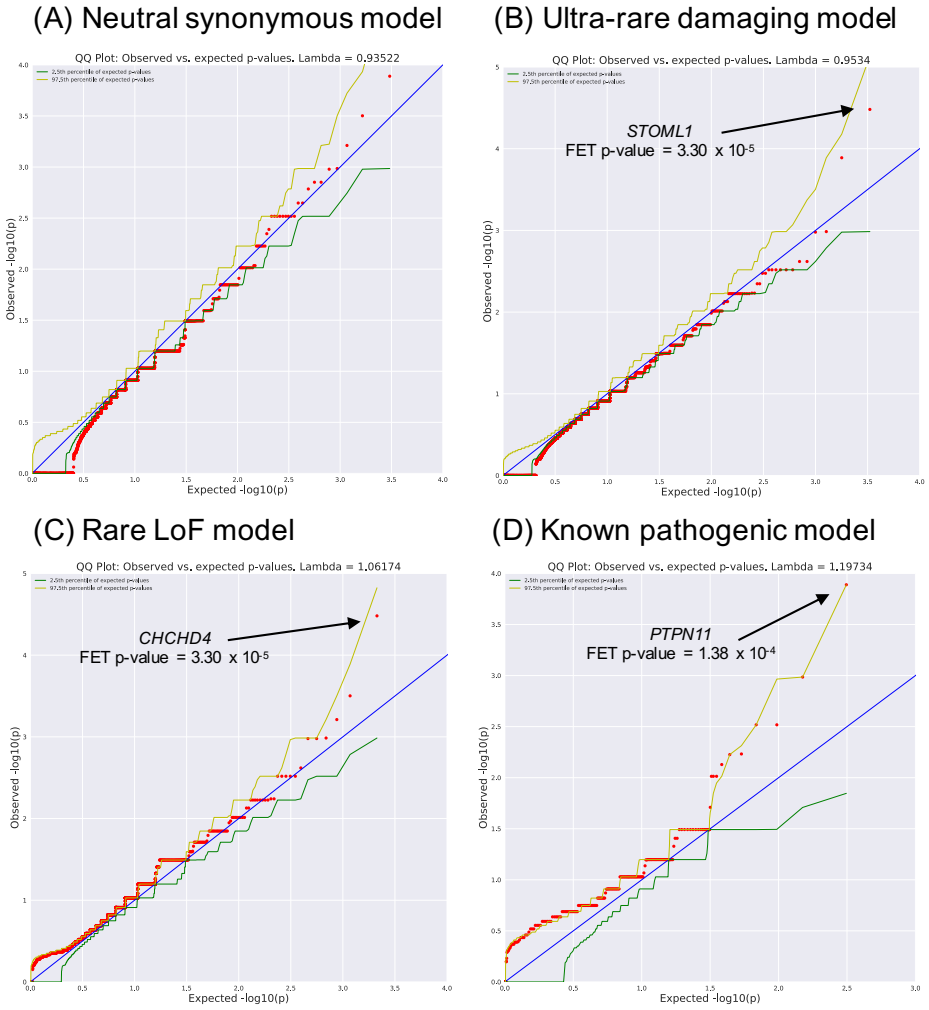


Figure S5. Quantile-quantile plots for the protein-coding genes that had at least one case or control qualifying variant per model. (A) Neutral synonymous model where qualifying variants are annotated as synonymous, have a minor allele frequency of less than 0·05% in internal case and control, and are absent in external reference cohorts (B) Ultra-rare damaging model where qualifying variants are annotated as loss-of-function, in-frame insertions or deletions, or missense variants predicted to be "probably" damaging by PolyPhen-2 (HumDiv) and have a minor allele frequency of less than 0.05% in internal case and control, and absent in external reference cohorts.(C) Rare loss-of-function model where qualifying variants are annotated as loss-of-function and have a minor allele frequency of less than 0.05% in internal case and control, and less than 0.01% in external reference cohorts (D) Known pathogenic model where qualifying variants are previously reported as "pathogenic" or "likely pathogenic" in ClinVar or "Disease Mutation" in HGMD and have a minor allele frequency of less than 0.01% in internal case and control. Bonferroni adjusted threshold of 0·05/[18 653 × 3]=8·9 × 10^{-7}. We did not correct for the neutral control model.



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