Supplementary Appendix

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

Supplement to: Herman DS, Lam L, Taylor MRG, et al. Truncation of titin causing dilated cardiomyopathy. N Engl J Med 2012;366:619-28.

Truncations of Titin Causing Dilated Cardiomyopathy

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SUBJECT COHORTS

Study subjects with dilated cardiomyopathy (DCM) were recruited from 3 independent groups. Group A was recruited from among DCM patients clinically evaluated at the Brigham and Women's Cardiovascular Genetics Center and subjects referred directly for research genetic evaluation. Group B was recruited from UK patients undergoing evaluation for cardiac transplantation with sufficient DNA samples for genetic analyses. Group C was recruited from subjects prospectively recruited in Colorado or Italy into a Familial Dilated Cardiomyopathy Registry. Ischemic heart disease was assessed in subjects from groups A and groups C by non-invasive studies and/or cardiac catheterization. All subjects in group B had coronary arteriography. Subjects who were found to have significant coronary artery disease or who were diagnosed with DCM in infancy were excluded from study. Groups A and C were enriched for subjects with a known family history of DCM. Concurrent genetic studies of other previously identified DCM genes[1-10] in subjects recruited from the Brigham and Women's Cardiovascular Genetics Center, led to the identification of likely pathogenic mutations in 40 subjects. These 40 group A subjects did not undergo TTN sequencing or phenotypic analyses reported here. However, to avoid untended inflation of the frequency of TTN truncating mutations in DCM, we increased the size of group A by 40 subjects for comparisons of mutation frequencies.

The hypertrophic cardiomyopathy (HCM) cohort consisted of 136 subjects recruited from the Brigham and Women's Cardiovascular Genetics Center, subjects referred directly for research genetic studies and 100 HCM subjects who underwent septal myectomy at the Mayo Clinic, Rochester, MN.

DCM and HCM subjects were diagnosed according to standard guidelines[11,12] without knowledge of genotype. Control samples (n=249) are from de-identified subjects, recruited from multiple sites, with no known history of idiopathic cardiomyopathy. There were no significant differences in the frequencies of TTN truncating variants amongst control samples from different sites.

All studies were performed in accordance with institutional guidelines and with the approval of the local ethics committees. Subjects in DCM groups A and C, all HCM, and all control subjects provided written informed consent. Within the proband cohorts, no subjects had a known familial relationship.

SEGREGATION ANALYSES

For linkage studies, unknown affection status was assigned to family members of age ≤40 years who lacked criteria for DCM and/or had confounding clinical diagnoses. Logarithm of the odds scores were calculated using FASTLINK (http://www.ncbi.nlm.nih.gov/CBBresearch/Schaffer/fastlink.html)[13]

Kaplan-Meier curves (Fig. 2D) of freedom from cardiac transplant, left ventricular assist device implantation, and death in male and female mutation carriers remained significantly different when family was used as a covariate ($P=1.4X10^{-5}$).

DNA SEQUENCING

Targets for filter-based hybridization capture were defined as *TTN* exons in the UCSC hg18 refGene table (NM_003319, NM_133437, NM_133378, NM_133432, NM_133379) or the hg18 knownGene table (uc002umr.1, uc002ums.1, uc010frc.1, uc010frd.1, uc010fre.1, uc002umz.1, uc002unb.1) +/- 10 bp and genomic intervals in the UCSC hg18 phastConsElements28wayPlacMammal and hg18 phastConsElements28way tables that were within 2kb of *TTN* and had conservation scores >= 350. Target regions within 180 bp of one another were merged and primers were designed using ExonPrimer (http://ihg.gsf.de/ihg/ExonPrimer.html) or Primer3 (http://frodo.wi.mit.edu/primer3) with a 28 bp target gap, an optimal annealing temperature of 62°C and an optimal primer length of 22-24 bp. Filter traps were generated as previously described[14], except that PCR amplimers were not confirmed by dideoxy sequencing and all DNA cleanups were performed with AmpureXP beads (Agencourt). Target amplimers, including three autosomal, three X-chromosome, and three Y-chromosome amplimers that were added at one quarter the molarity of the *TTN* amplimers, as a control for capture and copy-number, are listed in Table 1 of the Supplementary Appendix.

Genomic DNA libraries were made from 0.5 to 3 µg of genomic DNA and captured largely as previously described[14]. However, most samples were sheared using a Covaris E200 in single tubes (10% duty cycle, 5 intensity, 200 cycles/burst for 13 m) with a sample volume of 120 µl and most subject libraries were barcoded with a 3bp + 'T' sequence (Supplementary Appendix, Table 2), pooled in groups of 10–21, and hybridized as a pool of 2 to 4 µg.

For dideoxy sequencing, *TTN* targets were defined as all coding exons in refseq transcripts NM_133378, NM_00319, and NM_133379.

NEXT-GENERATION DNA SEQUENCE ANALYSIS

For next-generation sequence data, short-read sequences and quality scores were generated with Illumina Genome Analyzer Pipeline Software v1.0 to v.1.80, mapped with Novoalign V2.07.05 (http://www.novocraft.com/), using full Needleman-Wunsch alignment, to the hg19 human reference genome. Sequence read base quality scores were recalibrated using the genome analysis toolkit (GATK) v1.0.4418[15]. Sequence reads were realigned (using GATK) and duplicate masked with Picard (http://picard.sourceforge.net/). Single-nucleotide variants (SNV) and small indels were detected using GATK UnifiedGenotyper. Shorter single-end sequencing read lengths (32-46 bp) in 56 HCM subjects and 2 control subjects may have limited detection of insertions/deletions (especially those with sizes greater than 3 bp) in these subjects. Reported comparisons remain significant if these subjects or larger mutations are excluded (data not shown). The quality of identified nonsense, frameshift, and splicing variants was assessed using additional GATK tools and visual inspection using the Integrative Genomics Viewer[16]. The quality of missense variants (excluding nonsense and frameshift variants) was assessed using automated GATK tools alone.

The effect of each variant on titin RNA and protein was predicted using transcript definitions from the UCSC hg19 refGene table, with slight adaptations (see below). To identify variants likely to affect splicing, for each variant within the splice-donor or splice–acceptor sites, the

difference between the log2(maximum-entropy) of the mutant allele and that of the wild-type allele was calculated using an existing maximum entropy model[17]. Twenty-seven variants were identified with a maximum-entropy difference less than -2. Twenty-three of these variants were seen either in a single subject or in subjects with the same diagnosis and were absent from the 1000 Genomes Project[18,19] Phase I data (629 samples; 20100804 genotypes) (1KG). However, variant c.40160-10A>G was identified in subjects with different diagnoses and present in 1KG, variant c.3100G>A was present in a subject with DCM and one with HCM, and variants c.10114+5G>A and c.30811+5G>A were present in 1KG. Excluding these four variants left 23 variants likely to substantially affect splicing (Supplementary Table 7).

In all subjects studied by next-generation sequencing, we assessed the copy-number of *TTN* amplimers by visual inspection of heat maps and quantile-quantile plots of normalized median read depths (Supplementary Fig. 4). The median read depths of each amplimer in each subject were median-normalized by both amplimer and sample. Newly identified variants were confirmed by the presence of sequence reads spanning likely DNA breakpoints and by breakpoint PCR (Supplementary Appendix, Table 8 and Fig. 5).

Forty-five TTN variants identified by next-generation sequencing in subjects with DCM from groups A and B, including 15 frameshifts, 17 nonsense, 12 splice, and one duplication, were assessed by independent dideoxy genomic sequencing and/or RNA sequencing and/or by restriction enzyme digest analyses (Supplemental Fig. 3 and data not shown). All were confirmed (100% validation).

TTN TRANSCRIPT DEFINITIONS USED FOR VARIANT ANALYSES

The *TTN* consensus transcript sequence (Q8WZ42.nt) used to describe most variants was constructed to correspond to the protein sequence UniProtKB Q8WZ42 version 88. This transcript was defined as the combination of the UCSC hg19 alignments of RefSeq transcripts NM_003319 (N2B) and NM_133378 (N2A). The protein product predicted by the genomic sequence differs from Q8WZ42 at positions 17036-17043, because of a likely insertion of 'C' at position 51,102 of the cDNA sequence encoding Q8WZ42, and at several scattered single amino acids encoded by polymorphic nucleotides. The few exons (identified by black carets in Fig. 1 of the manuscript and defined in Supplementary Appendix, Table 15), with the least evidence for cardiac expression (Illumina Human Body Map 2.0 Project and unpublished) were excluded from analyses. Variants falling outside of this transcript are described using transcript definitions that include the corresponding alternatively spliced exon (novex-3, NM_133379; novex-1, NM_133432; novex-2, NM_133437).

TTN VARIANTS IN dbSNP

In dbSNP version 132, there are nine TTN nonsense SNPs (rs72646813, rs72646828, rs72646831, rs72646837, rs72646846, rs72648222, rs72648224, rs72648249, rs72648250) and two TTN frameshift variants (rs72647879, rs72648265) that were found by dideoxy sequencing of DCM subjects in group C (see the Methods, DNA Sequencing and Genotyping). For all other nonsense or frameshift TTN variants in dbSNP version 132, population frequencies are not provided and these have not been validated.

Previous studies have reported structural mutations within the M-band portion of titin in

subjects with recessive, early-onset skeletal and cardiac myopathy or tibial muscular dystrophy (Supplementary Table 14). Carmignac et al.[22] showed that truncated titin peptides lacking part of the M-band were incorporated into the sarcomere. We identified no TTN truncating mutations within the M-band portion in subjects with DCM, implying that M-band TTN truncating mutations may not cause isolated DCM. As such, in addition to assessing the uniformity of *TTN* truncating mutations in DCM subjects across all of titin, we also assessed the spatial uniformity of mutations when excluding the portion of titin distal to the previously reported carboxy-terminal titin truncations that do not appear to cause dominant DCM. With this exclusion the associations remained significant (data not shown).

Supplementary Appendix Table 1: *TTN* and Control amplimer PCR primers*

Amplimer	Forward primer	Reverse primer	Chr	Start	End
TTN_1#1	TTTGAACTTGAGTTGCCTTATCTATC	GATGTTTGCATTTACCCTCCTG	chr2	179390615	179391238
TTN_3#7	ACCTCAGGCGTTCCACTTGTAG	ACCAGAATTTACCCTGCCTCTC	chr2	179397970	179398571
TTN_7#4	TGTATTTTCCAGCATCGTACCG	GAGCAATAATGCCTTTGTGAGTC	chr2	179408621	179409331
TTN_10#4	GGTTCACCAACTCCATTTTCTATTG	CTTGGCTGGAGTAAGCCTGTC	chr2	179417865	179418475
TTN_13#5	CAAGCATGGTAGATTTTGTGGC	GAGTGCCAGTAATTGCAAGGG	chr2	179426342	179427007
TTN_13#16	GGAAATGGCTGTGGCAAATG	CCAAAGATCTGGTAATTGAGCC	chr2	179432850	179433487
TTN_13#27	GCCAGCTAATTGTCATTGAATCC	GTCAAGGAGCAGACAATGCTTC	chr2	179439317	179439989
TTN_18#1	TCCGAGATTTAAATGTGCCTCC	TGGAGAAGTGTGATGTAAGCCG	chr2	179448936	179449578
TTN_1#2	TGGCCGTTACACTTTGCTCTG	GATCCATTTAAGAGGGCCTGTG	chr2	179391128	179391749
TTN_3#8	TTACTCCAAACCGGACATTTTC	AGCACCCATGGTTGAAGCAG	chr2	179398504	179399136
TTN_8#1	GATTGTGTGTTGGAAAATTATCTGTC	GAATGCCCAACCCTATCCTATG	chr2	179410041	179410682
TTN_10#5	TCTTCCTCTCCTTGTCTTATCTCG	TCTTGGAAAGAATGCGAACATC	chr2	179418396	179419027
TTN_13#6	CATTGAAAGTATGGAAAGGAAGCTC	TCCAAAACAGCTTTTGTTAACGTC	chr2	179426939	179427599
TTN_13#17	ATCTTGGCCAACCTGTACACTG	CTGTGAGAGTTCTGGACACGCC	chr2	179433417	179434075
TTN_13#28	CTTTGGCAATGACCAGTTTCTG	AAAGTGGCTTTGTGAACGTCAG	chr2	179439920	179440588
TTN_18#2	CTTTCCAACCCTGCAGGAAG	TGCACCAGTATAGCTCTCCACC	chr2	179449499	179450149
TTN_1#3	TTCAGAAAGATTAGTCCGTGTGAAAC	TCCAGCAGCTTTATGGGAATATC	chr2	179391664	179392251
TTN_3#10	CAAAAGCACTTGTGTTAATGCG	CGAGATTCTGTCAACTTAACATGG	chr2	179399614	179400235
TTN_8#2	TACTGCCCTCACTCGGAATATG	GAACTGGATGCCCGATTACAC	chr2	179410608	179411215
TTN_11#1	AAAGCATATGCACAGGTTAGCG	GGTGCTGAATACAGACCACTGTC	chr2	179419104	179419588
TTN_13#7	TATGGTCAAATTCACAGGGGC	GTGCGTGTGATGCCTTGTATC	chr2	179427534	179428171
TTN_13#18	TGTGACTTTCAGGTTAACAGGTGG	CTTCTGCTTACCAAAAGGCTTG	chr2	179434026	179434681
TTN_13#29	ATGTCTGTAGGCCGCAGGTTG	TTGTTTCTTTCTCAGATCCTCCAG	chr2	179440519	179441158
TTN_19	CATGTGTTTGAAAGCCACTGTTC	TTCTATGTACATTGGAGCAAATCC	chr2	179451093	179451640
TTN_1#4	CCTCTACCAGTAATTTTATTGCTCACC	TGCCGTGTAACATTTATTTGCAG	chr2	179392147	179392788
TTN_3#11	TTTGCTGCCACCATCAGAGG	GATGCCACAGTTTACCAAGTCAG	chr2	179400182	179400784
TTN_8#3	TCAGAACCTGCTCTGATGGTAAC	CGAAGCTTCAAGACCTATAATGGC	chr2	179411163	179411767
TTN_11#2	GTGGGCCTGGTTTGTCTATCAG	TGCATAGAATTATAATGATGGTGTGTG	chr2	179419465	179420011
TTN_13#8	AGTGTCCGTCACTTTTGGATTG	TCAGCAATGTTGGTGGTACAAAG	chr2	179428113	179428807
TTN_13#19	TGGTTATGTCTATGACTTTGGGG	TCAAGGTTCTTGACAGACCAGG	chr2	179434604	179435263
TTN_13#30	TGGTAGTATCAGTGACATGCGG	CATGTGGCAACCAAACTTATCC	chr2	179441099	179441767
TTN_20#1	TTTTAGTATGGATTTGCTCCAATG	GGATGCCCTATTCGTCTCTTTG	chr2	179451608	179452471
TTN_2#1	GTTTTCTGTGCTTGAAAGAGAGG	CAGCGATCAGACCCTAACCATC	chr2	179392920	179393507
TTN_4#2	GCTGGACTTTGTATTTCCCAGC	TGTGCTCATTGAATCCCTATTTACC	chr2	179402120	179402834
TTN_8#5	GCGCTTGACACTGGAATTGAC	GTTGAAGCTGGTCACACCAAAC	chr2	179412258	179412872
TTN_12#1	GGAAAAGGTATGCGGAAATACTG	GCTGGAGTTGGAAAACCTAGCC	chr2	179421510	179422037
TTN_13#9	CTCCAGTAACTTTCAGAGGCCC	CAGAATGCTTTGTTGCTCGTG	chr2	179428715	179429374
TTN_13#20	TATGATGTCACTCCCACCATCC	GGCAAGCCGAGTAAAGTATCAG	chr2	179435145	179435885
TTN_13#31	CAGGTTCTCCTTTGCCATAGTG	TTGCAAGGATGAATACGGTAGG	chr2	179441686	179442345
TTN_20#2	GGTAGAATTGGGGATGACAAGG	AGCAACTCTTAATCTCAAGCACAG	chr2	179452325	179453234
TTN_2#2	TTGCTTATGCAGGTGAGGATTC	CAAAAGTGGAACTGAGAAAGTATTAGG	chr2	179393439	179394100
TTN_5#1	CCAGGGTTCTACTTAGTATAGAGGGG	CACAGAATGATGTTGGCCTGAG	chr2	179403182	179403741
TTN_8#6	CATTCTTGGCCTTCACACGG	ACCCTCACTGTGGAAAACTGC	chr2	179412782	179413415
TTN_12#2	CATCAATTGCCAAGACTGGTTC	GTTGCAAGAACCATGATGAAAG	chr2	179421986	179422507
TTN_13#10	CATTTCAGTGTGACATTGTTTCTTG	TCGTTTTAGAAAAGCCTGGACC	chr2	179429287	179429956
TTN_13#21	ACCGTCATAGGTGGGTTTCTTC	TATCGTTCTTGACAAACCAGGG	chr2	179435757	179436450

TTN_14#1	ACATGTTCAACTGTTCTCAGGG	TGGCACCAAGGAAGGAACTATC	chr2	179443260	179443870
TTN_21#1	TTTATCGAATACTTCTGTGCTTGAG	AGCCTGGTCCTGTGAGAAATC	chr2	179453197	179453861
TTN_3#2	TAAAGGCTTGCCCCATAAATTG	CACCAAGTGACCACCACAAAG	chr2	179395204	179395819
TTN_5#2	GGATCTTTGCAAACAACTGGTTC	GGTGGTAAAAGGCCTCAAAGAG	chr2	179403678	179404227
TTN_8#7	ACCACTGTTGTTTTCCACAGTAAG	GAAAATGCTGCAGGAGTTGGAC	chr2	179413344	179413961
TTN_12#4	ACTTTGGGAAGTGGTTTTCCAG	TGGTTCAGAAGCAAAATGGG	chr2	179422854	179423522
TTN_13#11	GAGGTTCCCAAGATATGACTACAAAG	TGAAAGCTGCTGAACCTCCTTC	chr2	179429870	179430535
TTN_13#22	CTTCCACCATCATACTTGGGTG	AAGCATCAGAACGACCTCTTCC	chr2	179436343	179437024
TTN_14#2	AAATTTGATTGGTCCAGTGGG	GAATATACCTTCAGAGTGAGTGCTGAG	chr2	179443798	179444372
TTN_21#2	TCTGGTGGATCCCAGCAAAC	TAAAGTGGCGGAGGCCTGAC	chr2	179453786	179454392
TTN_3#3	ATCGGAAGCCTGGACTGAAGAG	AGTCCTCACCCTGGAAATTCTG	chr2	179395757	179396357
TTN_5#4	GTCTGATGACGCCACCTTGC	GGTGGCACAGCTAATTTTCAAC	chr2	179404622	179405162
TTN_8#8	GACCACTGTGGGAGGACCTG	TTGTGCTCCCATAACCCACTAC	chr2	179413869	179414505
TTN_13#1	GAATAGTTTGGGGTGTGAAGGG	CCCAGTGATAGCTCTGACCCTC	chr2	179423908	179424653
TTN_13#12	ATAAGTGATGCACTGGTCTGGG	GTGAGGCTACATCAGTTCCTGG	chr2	179430460	179431144
TTN_13#23	CTAGAATTCGGCTGCCTCCATC	TGGAACTCCAAAGGCTGAAGAC	chr2	179436911	179437617
TTN_14#3	AACATCATCCCTTGCCACAAC	CCCATTATTGATGGCGGAAG	chr2	179444289	179444882
TTN_21#3	ATGACAGATTTGGACTGCCACC	GGCAGACCTGAACCAGACATAAC	chr2	179454345	179454948
TTN_3#4	CGGTAGGTTCCACTGTCATCAG	AAATCAAGGCGACAAAGAGAAG	chr2	179396304	179396938
TTN_7#1	GGTTTAGAAACCTGAGAAAAGGAGG	ACAATGCCTCAGAAGACCATCC	chr2	179406827	179407653
TTN_9	TACCATTTTACAGGCCAGGGG	TCCATGGATGATTAAGACCTGG	chr2	179415608	179416052
TTN_13#2	CAATCAAGGTCTTCCTCATTTCAC	GGCACTAGATCCATTTACAGTTCC	chr2	179424563	179425230
TTN_13#13	CAAGGTCAAGTTCAGGTGCTTC	AATCCATTTGTGCTTCCTGGAC	chr2	179431076	179431715
TTN_13#24	GTAACAACTTTGCGCAGGTCAG	TTGCAGTGAATCCTTATGGACC	chr2	179437543	179438215
TTN_14#4	ACCAGGATTTCCTCTCTGCATC	ATTTTAGGAGTGACAAGGCCAG	chr2	179444810	179445419
TTN_21#4	CTCGGACCAATACTTTGCCTTC	GGAACGTCGAGAAGTAACTGGC	chr2	179454894	179455528
TTN_3#5	TAGACGCAGATGAGGATGATTC	AAATGGCGTATTCCTAAACTGTCC	chr2	179396839	179397490
TTN_7#2	CAACTGTGACACGCTCTGATTC	TATGGCATTGGAGAACCTTGTG	chr2	179407515	179408147
TTN_10#2	TGCTGTAACAAGTAATTTCTCCTCC	AAAGGTGAACAGACGTGGTCC	chr2	179416843	179417413
TTN_13#3	GAAGTAATTTCCAAAGACGTGGG	CCACTGGGCCTATTATAGTTAAAGATG	chr2	179425177	179425834
TTN_13#14	ACAGACGGTCATGGAGTCTTTG	AGGATGAGGTTGAACTCCCAAG	chr2	179431641	179432305
TTN_13#25	CCAGCAGACAACCATCGAATC	GCTATCACTTGCAGGGATGATG	chr2	179438130	179438810
TTN_15#1	TCTTGGAGTTACCAGCTCTACACC	CTCACCCATCACTGGCTATTTG	chr2	179446106	179446844
TTN_21#5	TGAACTTCAGGTCAGCGATAGG	TGAGCACTACACAGTTGAAACAGAC	chr2	179455461	179456086
TTN_3#6	GGTCGGTAGTAAAAGTCATAATCAGG	GAGTCACAGCCACTAACACAGC	chr2	179397393	179398038
TTN_7#3	TCGACCACTTCTAGCTTTGCAG	AAGACCACCTCCTGTCATAACG	chr2	179408062	179408751
TTN_10#3	GGCTAACCTCAATTTCACATGTCTTAC	CACCATTCCTCAAGTTACTCGC	chr2	179417353	179417936
TTN_13#4	AACGTCTCGGAACTTGACATCC	TCAGCTGTTGTTGCAGAGTATCC	chr2	179425761	179426429
TTN_13#15	TCAAGTCTGAATGTTTCTCCAGC	CTACAAAGAACCAGGCCCTCC	chr2	179432218	179432898
TTN_13#26	GCTTCACCTGCTTTTAATATAACCG	TGCCAACTATCCATTTAAGGTTCC	chr2	179438722	179439402
TTN_16	TGAATGTCTTCTCCCACATTATTC	GAAGCAGCATATGAATTTCCCAC	chr2	179447576	179448044
TTN_21#6	GCCCAGGAACATCAAGAACAG	TTGGATCCTCTCCGTAAGTTGC	chr2	179455932	179456717
TTN_21#7	CTAGGGAGACTTCAGTCTTGTCAAC	TGAAGATGGTGGAATTTATTCTTTAAC	chr2	179456557	179457185
TTN_29#4	TGGTTCATTCCATTTCACTAGCATAC	CCACAAATCATGTCAGAGGAGC	chr2	179473128	179473732
TTN_34#1	TTGTATGGCATCCCAACCTTC	CACTGCAAACTCATTAACTTTTCTTC	chr2	179481130	179481773
TTN_44#1	GCTGCTTTCATGCAATATAACACTTAG	AGGAACCCAGGAAATCACAGG	chr2	179496767	179497407
TTN_54	GAGCAAGGAGTCAGGTAAAGGG	CAAAGCTTGGTTTTGATTCTTGG	chr2	179509215	179509435
TTN_85#1	GGAGATGAACAAAAGGATGGG	GTGATCACAGAATATTTGCCTTTC	chr2	179542272	179542740
TTN_109	CCTTCCTTCACCCTCCACTG	CCTGAAAGCATTTTAGTTACTTACACC	chr2	179563485	179563709

TTN_121#2	CTACAATTGTTGCAGGCTCTGG	TTATCACTAGTTTGATTCCCGGC	chr2	179578885	179579394
TTN_21#9	TCATCTCCAACTTTCTGGTACTCAAC	TGAAAGCCAAAGATCGTTTCAG	chr2	179457672	179458315
TTN_30#1	TGCTGAAGCTATGTCCCATTTC	GAGTTGCCACTTTCCCATTTTG	chr2	179473832	179474393
TTN_34#2	GGCCTTGGATAGCCTGTACTTG	TTTTAGAAACCCAGACTGTGCCTAC	chr2	179481641	179482380
TTN_44#2	AAAAGCAGCTGACTTGATCACC	GAGGGGTTGCTTGGTTGTGTAG	chr2	179497320	179497884
TTN_56	CCACAGTTGACATGAGAGAAACAG	TGCATCAATGTGAAATTTGTATGAG	chr2	179511025	179511367
TTN_88#1	CTCACCAAGTTATGCTGCATGG	AGTGGTGCCAGTGATACCAGTC	chr2	179544001	179544646
TTN_110-111	AGGGCCAATGCGTTGTATTAAG	TTCTGCCATTAGATATGCCTGAC	chr2	179565760	179566430
TTN_122	GATAAGACTGGGCTGGGGTG	TCTCTCTGATGGAGTGGAAGATTG	chr2	179579626	179580077
TTN_23	TCTCATGATGTGAAATGGTCAGC	CAAAGCTATGCTGTATGCTGTGTAAC	chr2	179461750	179462205
TTN_30#2	GGGGCATCTATAGTGATCATAACC	TTTTGTTTTAAGAAGGTGGTTTTCC	chr2	179474291	179474768
TTN_35#2	TCAACTCCTCCTTTCTGTAGACCAG	GCATAATAACATGATGTAGCTTGGC	chr2	179483005	179483650
TTN_44#3	TGTTTGGAGTGAGGGTTAGAAGG	GACAAAACTGCAGTGGAGAAGG	chr2	179497773	179498371
TTN_60	ATGCAACAACAATGAGGACAAC	ACTTTGGACCCACAGAATTTGG	chr2	179514192	179514745
TTN_88#2	AGTAAGCAATCATTGGTGCTGC	TGAAGCTCAGAATCCTTTCCAC	chr2	179544515	179545232
TTN_112	CTAGCATCAGCTGAGTGAGACC	CCCAGACGATGAAGGTGATTTC	chr2	179566543	179567194
TTN_123	AAGAATCAATCTTCCACTCCATCAG	CATTTAACTCTTCTTCCTTGAACTGC	chr2	179580048	179580645
TTN_24	TTGTTACACAGCATACAGCATAGC	GGAAGCCATTAAAGCAAGAAGC	chr2	179462178	179462853
TTN_30#3	ACATCTACAGGTGGATCAGGGG	AGCCCCACTTAGAGACAAGTGC	chr2	179474689	179475195
TTN_36#1	GAAATGAAAGACCCTCACAAGG	TTGCAAGCTAACTGATAATCCAATG	chr2	179484246	179484874
TTN_44#4	TCACCATCTTTGAACCATTTCAC	AATGGGTCCCTTTTACTCAGGC	chr2	179498286	179498899
TTN_61	TTCTGTGGGTCCAAAGTTTTATG	CAAAGAAGTCAGTGCAAATGAGATAG	chr2	179514729	179515164
TTN_89#1	GGCTAACAGGCTATGGATGTATTTAG	AAGTGCTGAAGAAAGCTGTCCC	chr2	179545599	179546180
TTN_113	TGAGCGCATACAGGGTAGAAATAC	GCTACATTCGACCAGCATGAATAC	chr2	179567101	179567608
TTN_124#1	CTCTCTCTCAAGCACACCCACC	GTGTCTTGGTACAAGGATGGGG	chr2	179581738	179582430
TTN_25#1	ACAGAAGTTAATGGGATTGAGAATAAC	AGAGCCAGAATATGATGGAGGC	chr2	179463151	179463719
TTN_31#1	GCACTGCAAAGTTAACTAATTTCCTC	GATGCTGGGAGAAAACACATTG	chr2	179475652	179476369
TTN_36#2	ACTCATCATCCAGCCTGCAATC	GAAGACCTTAGGATTGTTGAGCC	chr2	179484772	179485350
TTN_47#1	TGTAATACTGGGAAACGAGGTCC	AAGACCTCCACGGCTAAACTTG	chr2	179500607	179501155
TTN_72	AAAGGTGGTCCTTTCTATCGCC	GTGGAACAAAGGGAGGATGGAG	chr2	179529124	179529775
TTN_91	GGAACTAGAAGGCAAAGAGCCAG	TGTCTTTGTCCTTGAATTGTTTG	chr2	179547873	179548111
TTN_114#1	CACAACATTTGCCATTGACC	CAACTTAAAGACCAGGGCAATTATC	chr2	179568815	179569309
TTN_124#2	ATACTGCCCTATGTGGCTCTGG	GCCTGATAGAAAATGAGGCTGG	chr2	179582311	179583105
TTN_25#3	CCATCATCTTTAGGTGGAAACC	TCTGCCTACAGTGGATCCAAAC	chr2	179464082	179464680
TTN_31#2	TCCATTTCTCAGTGCCTACTGG	TATTTTCAGCCACTCCTGGACC	chr2	179476258	179476898
TTN_36#4	TTTTCTGAAAGCAACCGACAAG	CGGAAGAGAATCCTGGTCATTC	chr2	179485717	179486304
TTN_47#2	TGCAAGTTGCTACTAAGGTTTGTTAC	TGCTTTACGGCTGGTTTTATCC	chr2	179501056	179501622
TTN_74	TTGGTTGAGCTTCTACTTGGGG	CCAAGAAAGTCAAGTCCCACAC	chr2	179531407	179531802
TTN_94	CCACCAACATATAAACAGTATGACCC	AAAAGTGAATGCTAAGCCCCAC	chr2	179549295	179549796
TTN_114#2	TAGCGCTAGCGATGTGTGGAC	ACCTAACCAGCATCCAGAATGG	chr2	179569252	179569791
TTN_124#3	TCAGTCATGCCATGTAAAAGAGG	GAATGAGCCTCACATTCACCAG	chr2	179582978	179583652
TTN_26#2	CTGGATTGACTTTGGTCCAGG	GGAATTTGATGGAAAGGCAAAG	chr2	179466130	179466762
TTN_31#3	TCGTTTTGTCACATCAACCAC	TTCTAATATCTGCCTGTGAGCTACG	chr2	179476840	179477464
TTN_37	AAGTAAAGTGGTGACCAGAGAAGTTG	GGCAGCTTCAAGTGATTTCAAAG	chr2	179487281	179487643
TTN_48	TTCCCCTTGAATATGAACTTTGG	TTTATAATGGAGCATGACTCACCC	chr2	179502023	179502241
TTN_77	TGTGGCATTGAGAAGAGAAAGG	TGTTTATATCTCTCATGCTCTGCTTG	chr2	179534856	179535101
TTN_96	TGGTAGATGTTCACTGAATTTGTGTC	CCATGAAGCTATGTCCTAAGCAG	chr2	179552714	179553069
TTN_117	AGCCTACAAATTGCAGATGAGC	TTGTCTTTAGAGAGGAATAAACCAGG	chr2	179572120	179572698
TTN_124#4	GCTGCCTTTAAACCACTTGACC	GCACTGTATCCGTCCATGTTTC	chr2	179583582	179584304

TTN_26#3	TCCATCCTATTAGAAAAGGAGACAG	AAGACTCCAGCACTTCATCAGC	chr2	179466636	179467380
TTN_31#4	TCATTAAGAAGTAATGTAGCCAGGAGG	AAAATAAACATAGGCTTCTTCTGCTTC	chr2	179477377	179478069
TTN_40	GCAGGAGCTAGTTATTTACCAAAGC	GTTTGATTAACCAGAAGGCAGG	chr2	179493364	179493745
TTN_49-50	GGGCTTGAATTTTAATCAAGTGTG	CGTGGGCTTAATTTTAGTTTTGAC	chr2	179504344	179504919
TTN_78	TTGGTAGAACTTCCCTTGGACC	ATGTGTAATATGAAGGAATGTGTGTG	chr2	179535641	179536121
TTN_97	TGTGGAAGAAGAAGAGACTTTGAGG	GGTGTACTGTGCAACTCTTCCC	chr2	179553335	179553595
TTN_120#1	GGATTACTTAAGCAGAATTTTAAGCC	CCCATTTCGGTTACCTGGAAG	chr2	179576548	179577231
TTN_124#5	ATGTGGGGAAGGGTAGTTTTGC	TGATAACATTGCAACCCTCCAG	chr2	179584181	179584828
TTN_29#1	AGACTGTTGGGAGTTTGAAGCC	GAGCTGGATAAAGACCGTGTTG	chr2	179471654	179472281
TTN_32#2	TCTGCAGCAACTCTGAAGATG	TTGAAAATGTCCCTAAGAAATCCAC	chr2	179478841	179479321
TTN_41	GCGGAAAGAGAAAGGCAAAG	GAACCCTTAAAGACCACTTCCC	chr2	179493903	179494675
TTN_51	GAGTGAGATGGTAAAGAAAATTAAGCC	GGGAGTGGAAGATAAGTGGATGG	chr2	179505125	179505561
TTN_80	GAGGGATCCATTGCTATGTGTATAAG	CACCTCTAGGGTTCCTACTCCAC	chr2	179538078	179538596
TTN_99	GGGTGGACAGACACTTTTGTTC	GATTTGTGCATGTGCCTATGTTC	chr2	179554401	179554699
TTN_120#2	TGTCCTGCATCCTCTACTGTGC	TCCCATGGATGTTTTAACTGGG	chr2	179577107	179577674
TTN_124#6	AATTAGATGCTTCTGGACTCCCC	TTTCTTGTGTCAGCATGTATTGTC	chr2	179584782	179585513
TTN_29#2	GCCATGGTCTTTTCGCAGTG	GGGGAAATTGTTGGCTATTTTG	chr2	179472195	179472719
TTN_32#3	AAGACGTTCACTTCCACCACAG	CTGCTGAATGTACTGCCTGCTC	chr2	179479195	179479895
TTN_42	TTTGAACCACTTCTGTATTGGAATG	GTTTCATCACCATTTATTTGTTGC	chr2	179494801	179495205
TTN_52	AGAAAGCAGACAATGGAAAACAG	TCGGTGTAAATGCTTACTTTCCAG	chr2	179505816	179506188
TTN_81	GCTACTGAGAAAGATTTGGAACACC	TTTACACAAGCGTTTCGAAGG	chr2	179538978	179539242
TTN_106	TTACGCACAACTTTGAACTCTGG	CTGCTTGATCCTGCTTCAAATC	chr2	179559807	179560310
TTN_120#3	TCACTGCTACCTTTGAACCAGC	AAAAGAGCCAAATGGATCTAGGG	chr2	179577579	179578223
TTN_126#1	TGTTGCCTCCAACACTAATACAC	ATTAAATGGCTCTGCACCCATC	chr2	179586434	179587191
TTN_29#3	CATTTGTGCCAACCAACTGC	ATGCACCAGATAAGCCCATTG	chr2	179472671	179473195
TTN_33	TTAAATTTTCCCCAACAAAGCC	CTGCAGTTTGTATCCCTGGTC	chr2	179479959	179480608
TTN_43	TCCTGCATCCACTCTGACTTTC	TTCCAAGAGATTGTCATTTCCC	chr2	179495447	179496092
TTN_53	GCGAACCAATTCAAAGAAAACC	TGCAGCGAAAATTGTTACTTAATG	chr2	179506859	179507164
TTN_83	TGAGTGTCCTGTGTGGATAGAACC	ACAGACCTGTCTTGAGCGACTG	chr2	179540324	179540838
TTN_108	GAGGAGACTCCACAACTTTCAATAAG	GGAAGGGCTGGTGTATGAGTAG	chr2	179561734	179562024
TTN_121#1	TTGCTGATTCAGAAGATGTCGG	CAGATACAAGGCACACACTCACC	chr2	179578499	179578994
TTN_126#2	GTGGGTTGGAAGCTGAGCAAG	TTCCTTAGAACCGCCTTATTTTG	chr2	179587025	179587672
TTN_126#3	CTCCAGAGGTTCCAGTTCCG	AGTGGGGAATACACCTGTGTGG	chr2	179587627	179588217
TTN_129#9	TGGGTGGTTCTGAAGAAGGG	TTGCCCAGCTCAAATTTTATTC	chr2	179597437	179598076
TTN_134#4	GAAATGCTCATTTGGTGTACCG	AATCACTTCAATGGAGGTGGAAG	chr2	179611683	179612325
TTN_136#2	TCTGCAATTTGTGAAAGGGATG	AAGGAACCAGATACTGCATGGC	chr2	179621275	179621770
TTN_147#5	CAACTTCAACATTTACTTTGCATCTTG	GATTCTGGGGAATGGACTGTG	chr2	179641643	179642222
TTN_170	CTACCCCATGGCTCTGTG	CTGCAAAGCAGCTCCAGAGT	chr2	179668899	179669447
TTN_17b	TTTTTATTAGGAAAAATGACCATCA	CAGGGATGATAATGTGAAATATGGA	chr2	179448264	179448712
TTN_3#9b	GCTGGAGAGCCTCCGATG	CACAAGTGCTTTTGAACTTAATGAAAG	chr2	179399134	179399627
TTN_126#4	AAACCTTTCACAAAGAGACGGG	TCATCACCTATTTCAGTTGCCTG	chr2	179588141	179588778
TTN_130#1	TTCTTCCATGGGGTAAGAAAGC	TCATGTGAAGCAGTGAATGACG	chr2	179598987	179599494
TTN_134#5	GTGGACGACCTAGTGATTCCTG	TTGTCCTCTAGAAAATGGAGGC	chr2	179612240	179612871
TTN_137	CAGTATGCAATAAAACAAACAGCAG	AAGGACAAGGCAGTAGGAGTGG	chr2	179622171	179622775
TTN_148#1	GCCATTTTAGCCCTCGATTTTC	TCATAGCTCCTTGCCACAGTAAAG	chr2	179643495	179643937
TTN_13#32b	ATGGACCTACCGTATTCATCCTT	TGTATAAATAATTTGGGCAACACA	chr2	179442319	179442993
TTN_90b	TTGGGTATCCAAATTTTTATCTTG	GCAAAAGAATAAAATCAAAGCACATT	chr2	179547323	179547722
TTN_163	AGAAAATCTATTCAAATGCGAGGTG	TCAAGGTAGGAAGGCAAAGAGTG	chr2	179658624	179658861
TTN_126#5	GTGGTTTGGTACTTTGCTCCAC	CCATCTCACTGGGAGAAACAATC	chr2	179588708	179589360

TTN_130#2	TGAAAGCATTGTGTAAGTAATGGG	TGTGTGTTGGGTCTCTTTGTTG	chr2	179599345	179599813
TTN_134#6	AAAGGCTTTTCCTCACTTGCTG	CCTGCAATTTCTAAAAGAGCTGAAC	chr2	179612800	179613449
TTN_139	TTGTGATGGAGGAGAAGCTGAC	CTACATGCTCCCTTCTGTGAGG	chr2	179628817	179629099
TTN_38b	TCTTTAAACACATAAAGGATCAGGT	AAAGTTGAGAAGGTACCAAAACTCT	chr2	179489030	179489529
TTN_175	TAGAATTAGTAAACTAGTCTTGTGGAAACC	CATTGAATATTGTGCTTAAAGAGAGAA	chr2	179674426	179674625
TTN_153	GAAACTGATCTTTGCAAACGTGTAT	CATGAGCTAAGAGTTTATGAGATTTCC	chr2	179648366	179648583
TTN_154	CACCTGGCCCTGCTCAAT	GGGCTAGCCATCGGAGGAT	chr2	179648740	179649136
TTN_127#2	GATTGTCCAGATCATGCGAGAG	GTGCTGGACTCTACTTACCCATTAG	chr2	179590412	179590896
TTN_131	AAAGTGTACTGACTGAATTGTTTGCC	CTTAACTCATCTTTTCTCTGTCTTGG	chr2	179600146	179600893
TTN_134#7	TGTGTTTTATTTGAGTGTGAAACTGC	CCAAGCAGAGGGTACTGTTTATCC	chr2	179613371	179614008
TTN_140	CACTGGGAAAGGACAAAAGCC	GAGTTTTGCATGCTCTCTTGTG	chr2	179629186	179629604
TTN_164	TGAGTTAATGTGCACTGAAGGA	GGTGGCTCAGTTTTCCAGT	chr2	179659065	179659364
TTN_87	AAAGAGTTGCATCCCAAAGAG	ATTGCCAGCCTTAAAATCTTAGC	chr2	179543376	179543625
TTN_100b	GGCAGCATAGTACATATGAAGATCG	TGTAATCTTAGATGTCTCAGAAGGTGA	chr2	179556658	179556894
TTN_10#1c	AGCATTCCTTGATATATTTGTTTCTAA	ACCTGAAGATAATGGAGGAGGAGA	chr2	179416284	179416883
TTN_128#1	TAATACCCAGGGGAGAAGGTGG	TTTCTGTCTGACTGTGTCTTTGG	chr2	179591757	179592287
TTN_132	TTTCCCACACATGTACAGAAAGC	CACCAATTTCAACTGTTTTACTCC	chr2	179602728	179603198
TTN_134#8	CATTTTCCTTTTCTGATCTACCAAG	AGAGAAGGGGATTCCATCATTC	chr2	179613899	179614616
TTN_144#2	TGGACTTTCCTTTCTGAGACCAG	CAGGACTTCTTTTCCTTGATGATG	chr2	179634882	179635466
TTN_128#2b	ACCAAAGACACAGTCAGACAGAA	AATGTCCATAAAACTGTCACAATAAT	chr2	179592264	179592663
TTN_79#1b	TCTTCCAAACTGAACACAAAATTTAC	TAGATGCTCTTTCAGGGAGAACT	chr2	179536612	179537009
TTN_141b	TTACAAGAATTTAGTGACTTAAACAGGA	GGGAGGAAACCAGAGCTTCAA	chr2	179631029	179631404
TTN_102c	GTATGCACACTGTGACTAAATCTATTATT	TCATTTCATGTTTGTCTCTGTTTTC	chr2	179558225	179558524
TTN_129#1	ACAAAGGCAAGAGTGATACATTTAAG	ATGACCTTGGAATGTGTTGTGG	chr2	179592766	179593449
TTN_133#1	AAGTGAAAATTTAAGTGATGCAAGC	AACAAGTTTGCAAGAAGAAATGG	chr2	179603784	179604460
TTN_134#9	CAACTGCCCCTGAATTGTTTTC	ACATGCCAATCCCACGTAATC	chr2	179614406	179615185
TTN_146#2	CTTCGTCTGAAGCATGAGTTCG	GAGGGTGACATTGTTCAGCTTG	chr2	179638246	179638790
TTN_166	AGAGACATGTGCTTTTAAGTTTCAC	GATTTTTGTTGTAGAGTAAGGCAAAC	chr2	179661384	179661659
TTN_92b	GATTAGTTTTAGTGTCTGGATGCTT	TGTCAAGTGTTTATGTTTGGGCTAC	chr2	179548664	179548904
TTN_39b	TGGCATTGTTCATGAGCCTCT	AAATGCACCCATATACTAGATTGC	chr2	179489942	179490180
TTN_104c	ATGTTTTGATCTATAGGGACAAACAATGC	ATTAGTAGTTTGCTAACTTCACTATGC	chr2	179558889	179559085
TTN_129#2	TGGGAACTATTTGTTTCCCGTC	TTGCCCTGAAAGGTCAGTTATAC	chr2	179593371	179594026
TTN_133#2	AACTTCTGGTTCAGTAATGGGTTC	AGAATTGAGGAAGGCAAGTCC	chr2	179604388	179604999
TTN_134#10	TTCCATATTGGTTAAATAGCACACAAG	AGCCAAGAAGCACTGGTAAAGG	chr2	179615057	179615702
TTN_146#3	CACAATGTGAACCCTGTCACTG	GGGGAGATAAAAGACATACAAGACATC	chr2	179638683	179639296
TTN_101b	GATGCTATTTTGTTAATACACAGATCTTA	ACAACAACATATGCCTTGTCAAA	chr2	179557138	179557367
TTN_12#3b	AACTGTTGCAGACACTTCAGTCC	TGACCTTATCAAGAGATGGTGTC	chr2	179422505	179422854
TTN_73b	GAAACCATAGTTTTAAGAGCAGAGGAC	AAATATCACTTTGGTTCAGCTCATTT	chr2	179530037	179530270
TTN_115c	TTCTGGTAATTCAAAGGGAATATGTG	TTGAATGATGATAGACAATTAAAAATAAG	chr2	179569822	179570156
TTN_129#3	AATGAATGATGGTGGTTCTGTG	AAGCCCAGTCCAGTCTTAGTGC	chr2	179593880	179594652
TTN_133#3	CAGTACCTGCTTTTCTTCAAGTGC	GGGAATTTCTTTGCATCAATGG	chr2	179604940	179605574
TTN_134#11	TGTCCTCTTGCTTGGGTATTTTC	GAGGCTTTAGTTGAAAGGGGAG	chr2	179615614	179616266
TTN_147#1	TTTTACCACATGCTAAGGGTGAC	TGGTCATAAGAGATGTGACTGCTG	chr2	179639582	179640184
TTN_5#3b	CAGAGATGTACCTCGGACTCTG	CAGACTTACCATACCAATCAAAGG	chr2	179404227	179404626
TTN_129#5b	TTTGACTGTCAGATGCCCACT	GCAGCTGCAAGGCTAGAAT	chr2	179595233	179595681
TTN_169	TCCCAATTTGCTGGAGATGT	GCAGTGAACATGATGGGACAG	chr2	179666803	179667147
TTN_119#1c	CACCTTCAGGCTATACTACAAAATGA	AATCAAATATGAACTTAGGGAGAAAT	chr2	179575298	179575744
TTN_129#6	CAGCTGCTCCTCCCAACATC	GTTGGTTCCAGTGAGGGACTG	chr2	179595675	179596413
TTN_133#4	AGGTTGGGAGATGGTTCCTTG	AATTCGCTGTGCTCAAGGGC	chr2	179605511	179606122

TTN_135#1	AAGTCCATGCCAAACAAACTATTG	CAGGATACCACGTGGACTGAAG	chr2	179618041	179618540
TTN_147#2	GACTGGAGGTTTCTCCAGCTATG	TGTTGACACCACTGAAACCAAAG	chr2	179640104	179640690
TTN_93b	GCCCCCATAACCAGTGTATT	TCTAAAATCACAGTACTTTCTGGCTAGT	chr2	179548982	179549223
TTN_103b	GACAACAAGAGGGATAAAAATCTGC	TCTAAATACTTGAGTATAAAATCCATGTG	chr2	179558578	179558824
TTN_162b	GGTAAAGGTGATTATCTGTGTTGACC	CGAGGCTGGTCTTGAACTAATTT	chr2	179658061	179658340
TTN_125c	CTCATAACTTTGCTAAGAGCCCAAA	ATGGGATCTTCAGCTACAAAAACAA	chr2	179585581	179586011
TTN_129#7	GGGAGCTGGTACTCTCGATCTTC	GAGAAATTAAGGAGAGCAGCAAAC	chr2	179596269	179596951
TTN_134#2	TTGATAAACCTGGGAGGCCC	TCAAGAAATTGTCCTGGAAGTTG	chr2	179610574	179611206
TTN_135#2	TTCCACAAGGAATATGCACAGC	GAATGTCAAACCCCTGGAAGTC	chr2	179618431	179618938
TTN_147#3	TTTCATGGGTAATTCTTTCAGCC	TGAGAAAAGTCTTGTGGAAGAATCC	chr2	179640626	179641203
TTN_84b	TTTTCCTAAAACCCAGTTTCATCA	GTTTGTGGTCTTATCCTCACG	chr2	179541847	179542119
TTN_160	TGATGAAAATGTAGGTGATTTGC	CATCCTGTATTTTCCTGAGTGTTTC	chr2	179655364	179655663
TTN_21#10b	CATACTGAAACGATCTTTGGCTTT	CCTGGTTCAAAGATGAAGCTGAT	chr2	179458290	179458864
TTN_127#1c	GCCAGTAACTCTTAGTAATTCATTCCA	CATGATCTGGACAATCTTTTCAAC	chr2	179590028	179590427
TTN_129#8	ACCACTGTCTTCGATGCCAAC	TCATCTTCCCTTAGATCAACCCTC	chr2	179596860	179597507
TTN_134#3	CGGGAACTGTCACTATTTTCACC	TCCTACTGGAGGACCAAACCC	chr2	179611124	179611770
TTN_136#1	TTGAATTTGCATGGCAGAAAAG	CTCAAAGTTCCATCCACACAGC	chr2	179620872	179621353
TTN_147#4	TTCTCTGTAAGCCTTTCCTCCC	TCTGCCTGGTATACTGCGACTG	chr2	179641145	179641718
TTN_118b	GCTCATGGATATATAACAGGCAGTG	AGTTGGTTAGCCTTGATTTTTAAC	chr2	179574228	179574697
TTN_143b	CCCACATTTTATTTATCCATTCATT	CCTCAACAGACGCACTAAAAACA	chr2	179633304	179633769
TTN_155	AATCCTCCATTGGCCTACCC	CATCTGCCTGTCCTGATGC	chr2	179650252	179650951
TTN_129#10c	AAAATTTGAGCTGGGCAACAT	AAAACTCTTAAATATAGATGGTGTTGAAAG	chr2	179598059	179598694
TTN_134#12c	CCTTTCAACTAAAGCCTCCACA	TAAACAGAGCATGGTGTTGC	chr2	179616249	179616939
TTN_158c	ATTTCACATGATATGTGGTATTAATGT	GGAAGGGGGAAGGGTCATACTA	chr2	179654019	179654299
TTN_27c	AAGGCAGAATTATCCATTTAGTGA	TACAGTCATCCCTCCCAAAATAAGTT	chr2	179468534	179469129
TTN_79#2c	GACAGTTCTCCCTGAAAGAGCAT	GTAATGTTGGCGTTGTCTCTGG	chr2	179536984	179537516
TTN_21#11b	CATCTTTGAACCAGGAAACCTTAG	GGAATATTCACTACATCCTACTACATTCTT	chr2	179458850	179459449
TTN_3#1b	TCAAATGTGTGTTTCTGCTTTGG	ATTTATGGGGCAAGCCTTTAAGA	chr2	179394524	179395223
TTN_134#1c	GAGTCCATTCCACTGAAACACTTT	GGTTTATCAAAGGTATTTCTGACTG	chr2	179609984	179610583
TTN_159c	AGGGATTTTAAAAGGCAAATACA	GCCTCCTTTCTTTTTGACTTACG	chr2	179654593	179654928
TTN_28#1c	ATGGCATCAAACCAGAGTCATGTA	ACAGGCCTTCCAATGCCTAAGA	chr2	179469373	179469933
TTN_36#5c	TCCGTCCTTCAGTCAGTATTTCAT	TTTCTTAAGGACACCTGTGTGA	chr2	179486301	179486800
TTN_4#1b	TTAAAAGAATTTTATGCAAAGATGG	AAAGTCCAGCTCAGCAATGTTTT	chr2	179401599	179402129
TTN_105c	TTTTGGTCGTTTCAGATTTGTGAG	AAGTTGTGCGTAAAGGTCAAAG	chr2	179559220	179559819
TTN_138c	TTGTTACAGACATTGTTAAGATTCGAT	GTGTTTGCAGGTAAATTGTAAAAATCC	chr2	179623645	179623970
TTN_161c	TGCAGCTGGCTGTAATGTGAT	GAAAAGGGATTTTACATCTTCAAA	chr2	179656737	179657033
TTN_35#1c	TTTATTTTAATTGATAGGCCTAATATCTG	GGTCTACAGAAAGGAGGAGTTGA	chr2	179482436	179483027
TTN_107c	TGCAAATCAGGTTCATAGCA	TAGTGAAGCAGTTGGATGGAT	chr2	179560505	179561054
TTN_134#13b	TGCATGCTACAGATCTCACAAATC	AAAATAGACAATAACCTAGCTGTCATTC	chr2	179616858	179617497
TTN_116c	GTTGACTGTGGATGCGGAAC	AGGCTTATTTTACAAAGGGGGATA	chr2	179571110	179571759
TTN_145c	TTTTAAAACGATAACGATCAAGATT	TACTTCTGCAAAGATTTTCCCATT	chr2	179635874	179636270
TTN_165c	GAGTTTCATGGCAGAAATCCAG	TTAAAGCACTTCCAGCTTTTCATC	chr2	179659575	179660069
TTN_36#3c	TAAGGTCTTCCTCTGTTGTAAAGG	CTTGTCGGTTGCTTTCAGA	chr2	179485341	179485738
TTN_146#1c	AGGAATTTTGGGGGAAATGAATA	AGACGAAGGACCTTACAAGCTG	chr2	179637754	179638253
TTN_98b	AGAATTTAACACACTCGAAGATTTTT	TGTCCACCCGTCTGCTTTC	chr2	179553710	179554409
TTN_167#1c	ATGATACATGATCACCTTCTAAAATACTTC	CCCTCCTCCCGTGTAAGTTTC	chr2	179663135	179663832
TTN_148#c	ACTGTGGCAAGGAGCTATGAT	TCTCCCAGCTAAAAACTTCAAC	chr2	179643918	179644293
TTN_167#3c	CTTTCTCGTTTCAAAACCTAGTTCC	TCTTTTAAAATGGGTCATTGTGC	chr2	179664150	179664694
TTN_45c	TTAGAACTTGGCGTCCTATCTT	AAATTTGTATCTGAAACACTTCTCCT	chr2	179499013	179499651

TTN_129#4c	GACTGGACTGGGCTTCTTAAT	GGTTGGCAAATTTTATTTCCACTTA	chr2	179594638	179595232
TTN_89#2b	GACAGCTTTCTTCAGCACTTCAAA	CCTACTTCAATAGGCTATGGCTATACT	chr2	179546161	179546592
TTN_46b	TAGATCCTGAATATTGGATGTGGT	TCCTGAAATTTACTAAGGAAGCTATGTA	chr2	179499827	179500520
TTN_149c	CCGAGCTCATCACTTGAA	TTATCAACTTTCCCCAGTGTAGAG	chr2	179644635	179645031
TTN_168c	TGGCCCCATTTAGACACAAAC	TTTAAAAATACCTTGTAGGGAGCAC	chr2	179665057	179665474
TTN_55c	TCATTTCAGATGGCTGGATAGA	TGTTTTATGTTGGATACTGGTATTACG	chr2	179510581	179510928
TTN_134#14c	AGCTAGGTTATTGTCTATTTTCAATGTAAT	AAAAATGTTTTAAATCTTTCTGTCAAC	chr2	179617477	179618113
TTN_32#1b	TCCCAAGGAATACTAAAGAGTAAACA	AGTTGCTGCAGAAAACATGTATGG	chr2	179478404	179478852
TTN_95b	AGACAGTTATGCAAATGTGAAGGTATTATT	AGGGGTTTGGCAAGGGTTA	chr2	179549902	179550446
TTN_15#2c	TGAGCCCCCATCATCTGC	GGTCTCCAGACCTCTACTCTATACTCAT	chr2	179446841	179447388
TTN_171c	AACCAGCTTAAATTGATCTTACATTCC	TTCACTTAATATTCTAAAAGTTGAGGTC	chr2	179671302	179671696
TTN_59c	TTTCTGTGCAATATGGTTTTAACATAAAT	TGCTGCTCCAATAAATACAGGTTT	chr2	179513858	179514147
TTN_142e	GGTTAGAAAATGTAAAAGGGAAACATT	TGAATTATATCTCAATAAAGCTGTTAAAAA	chr2	179632393	179632941
TTN_21#8b	TCATGGGCAGCATTACGAA	ATGAAGAGTGGAGAAGAGCCAATC	chr2	179457183	179457675
TTN_62-63	GGAAGGAAGAAGAACAAAGCTTAAAT	TCCAATTCCTCTGCTGTATATTTTG	chr2	179515402	179518121
TTN_150c	CAGCAAACGGACAGCACT	TCACAGATAAGTCCAATTATTTTACCC	chr2	179645773	179646068
TTN_172c	TCCAGAGCCAGAGATCAATAA	CAACACAGTTATTCTTTAAATACAGTTCTA	chr2	179671876	179672375
TTN_82c	AATATGTTGATTTCCTGGGGTAAA	TCATCTTGTGTATGTGCCTTG	chr2	179539659	179539958
TTN_152c	GCACAGAAACCATATTGTGGAAAAG	GCATAAGTTCAAACTCTACATTTGTT	chr2	179647451	179647881
TTN_6b	CAAAAAGGTGAATTTTCCCACATA	CCAACCAAAACCTAAGGAAAACAC	chr2	179405941	179406402
TTN_67-69	CCAGAGCACAAGAGATAGATCA	TGATGTGCTGCTGGAAAA	chr2	179522175	179524056
TTN_151c	CTACTCTAGGCTTCATGCACGTAT	TCAGTGCTAAGCAGGGGTCACT	chr2	179646873	179647391
TTN_173c	CACTTGTGGGCAGTCATACAAAA	TGGATTCTGGAGAATGTAGGTAG	chr2	179672451	179672681
TTN_85#2c	ATGAAGAAGCTTATGAAAGGCAAAT	TTTCATATCTATTGCTCTAAGACATTTT	chr2	179542703	179543002
TTN_26#1c	TGTGAACTATTATTGAACACCTAGGAAG	AAGCCTGGACCAAAGTCAA	chr2	179465509	179466153
TTN_8#9b	GAGCACAACCGTCATTGAGTG	TGGCCTTGTGATATGGCACTAC	chr2	179414498	179415092
TTN_71	CCAGAGCAGAAGAGATACATCA	TGGGTGGGGCGATAGAAA	chr2	179528304	179529152
TTN_156c	TGATTCCCTAAGGGTAAGATTGT	TTGTTTCATTCTTTGCTTTAACTCTCC	chr2	179651422	179651624
TTN_174c	ATGCTTAAATCATCCATAAGGTTCC	ACAAGACAATTTTCCTCCCTCTAAG	chr2	179672888	179673125
TTN_86c	TGTAATGGGGAAATTTGTATGTGAG	CTTAATCTTTTGAAACTATGCTTGG	chr2	179543061	179543301
TTN_22c	GAATGAAATGTACGGCATTTATACACA	TCAAAACAACATTTTTGTCTCCTTT	chr2	179460134	179460633
TTN_8#4b	GCTTCGCTGGCCTTGCTA	GCGCACTCAAATTAAAGTCACTCAT	chr2	179411762	179412261
TTN_147#6c	TCCCCAGAATCACTGGGTGT	TGTTTTGCTGAGTTTTCTTTATGCC	chr2	179642212	179642759
TTN_157c	GGAGGATGGACTGAATCTAACCA	AAAATCTGCTGAACCAGCCACA	chr2	179652753	179652997
TTN_25#2c	CTGGCTCTTCCCAGTTGACAG	TGATGGTGGGTCTAAGATTACAAAC	chr2	179463712	179464087
TTN_76c	AAAAGACAAACATAGTGAATTTAAGGA	TCATCTTGTTAGATGCCCCTTC	chr2	179534030	179534491
TTN_119#2c	ATTTCTCCCTAAGTTCATATTTGATT	ATTGCATATATACGTGCGTTTG	chr2	179575719	179576167
TTN_3#12b	TAGCTCTGACTTGGTAAACTGTGG	CCAATTTCATCTTTCTGGAATAGC	chr2	179400757	179401435
MYBPC3_8	GGGCTGGGGATGATTTG	GGGACACTAGCCAGATTGG	chr11	47369117	47369331
MYL2_2	CACCCAGAGTAGGGGCCTGACCTA	TTCAGGCCGAATTTGGGATTGTTT	chr12	111356770	111357073
MYH7_12	GGGAGTCTCAGAACCCACAG	TGAGCAGACATGGCCCTCC	chr14	23898925	23899240
GLA_2	GTGAAATCCCAAGGTGCCTA	AGAAGTGCTTACAGTCCTCTGAA	chrX	100658747	100659058
LAMP2_4	GGGTAGGGCAGGCAGAGA	CAGATAATGACTTCAATGAAAGCTA	chrX	119582741	119583087
G6PDe11	TAGCTCCACCCTCACCCCG	GTGGCCTTTGCCCTCCCT	chrX	153760338	153760557
G6PDe10	GGTCCAGCTCCGACTCCT	GGTGCCCTTCATCCTGCG	chrX	153760804	153761016
SRYc	TGGCTGTAGCGGTCCCGT	TCGTCGGAAGGCGAAGAT	chrY	2655045	2655252
SRYb	ATCCTGGACGTTGCCTTTACTG	AAATAAGTTTCGAACTCTGGCACCT	chrY	2655470	2655702

* Positions correspond to hg19. MYBPC3, MYL2, MYH7, GLA, LAMP, G6PD, and SRY

primers were used as controls for CNV analyses.

Supplementary Appendix Table 2: Genomic library adaptor oligonucleotides

Name	Sequence
Solexa_PE_Fh_AACT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTAAC*T
Solexa_5'AACT	/5Phos/GTTAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_AGGT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTAGG*T
Solexa_5'AGGT	/5Phos/CCTAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_ATGT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTATG*T
Solexa_5'ATGT	/5Phos/CATAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_CACT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTCAC*T
Solexa_5'CACT	/5Phos/GTGAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_CGAT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTCGA*T
Solexa_5'CGAT	/5Phos/TCGAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_GGAT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTGGA*T
Solexa_5'GGAT	/5Phos/TCCAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_GTCT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTGTC*T
Solexa_5'GTCT	/5Phos/GACAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_TCGT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTTCG*T
Solexa_5'TCGT	/5Phos/CGAAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_TGAT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTTGA*T
Solexa_5'TGAT	/5Phos/TCAAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_Fh_TTCT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTTTC*T
Solexa_5'TTCT	/5Phos/GAAAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_PE_5'ACGT	/5Phos/CGTAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_ACGT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTACG*T

Solexa_PE_5'AGCT	/5Phos/GCTAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_AGCT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTAGC*T
Solexa_PE_5'TGGT	/5Phos/CCAAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_TGGT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTTGG*T
Solexa_PE_5'TCCT	/5Phos/GGAAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_TCCT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTTCC*T
Solexa_PE_5'GACT	/5Phos/GTCAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_GACT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTGAC*T
Solexa_PE_5'CGTT	/5Phos/ACGAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_CGTT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTCGT*T
Solexa_PE_5'GTGT	/5Phos/CACAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_GTGT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTGTG*T
Solexa_PE_5'CTCT	/5Phos/GAGAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_CTCT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTCTC*T
Solexa_PE_5'CAGT	/5Phos/CTGAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_CAGT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTCAG*T
Solexa_PE_5'GCAT	/5Phos/TGCAGATCGGAAGAGCGGTTCAGCAGGAATGCCGAG
Solexa_Fh_GCAT	ACACTCTTTCCCTACACGACGCTCTTCCGATCTGCA*T

* = phosphorothioate linkage; /5Phos/ = 5’ phosphate

Supplementary Appendix Table 3: Summary of cohort characteristics*

	DCM			HCM	Control
	Group A	**Group B**	**Group C**		
Subjects, no.	92	71	149	231	249
Women, no. (%)	28 (30)	16 (23)	60 (40)	NA	NA
Age, yr*	37.2±14.0	40.6±12.7	39.4±12.5	NA	NA
LVEF (%)*	29.4±12.2	24.8±11.5	31.2±11.5	NA	NA
Sequencing Methodology^	Next-gen	Next-gen	Dideoxy	Next-gen	Next-gen
Mutation Positive, no.(%)	37 (40)	17 (24)	13 (9)	3	7
Family History, no.(%)				NA	NA
Yes	78 (89)	9 (21)	102 (68)		
No	10 (11)	30 (70)	47 (32)		
NA	4	29	0		
Mutation Positive Family History, no.(%)				NA	NA
Yes	33 (88)	3 (21)	11 (85)		
No	3 (12)	11 (79)	2 (15)		
NA	1	3			

No., number; * Values are means ±SD. ^Sequencing methods were Next-gen, filter-based hybridization capture of TTN and next-generation sequencing or Dideoxy, conventional Sanger dideoxy sequencing. Age and left ventricular ejection fraction (LVEF) are taken at the time of initial diagnosis of DCM. Percent of subjects with family history excludes subjects in whom family history was not available. Across all DCM groups, TTN truncating mutations were found in 25% of subjects with and 18% of subjects without a family history of DCM (P=0.3).

Supplementary Appendix Table 4: Sequencing data for *TTN* truncating mutations

Chr position	Ref base	Var base	Nucleotide change	Quality	Filter	Allele balance	# Reads			Subject	Cohort
							Major allele	Minor allele	Total		
179659280	TA	T	c.1246-3delT	23585.55	PASS	0.14	1146	6989	8135	pv-75	Control
179647331	T	A	c.3101-2A>T	7728.48	FDRtranche10.00to50.00+	0.58	348	250	598	N-50	Control
179604949	CT	C	c.12059delA	10405.56	PASS	0.43	1155	1551	2706	pv-1	Control
179604264	G	A	c.12745C>T	1962.07	PASS	0.57	136	103	239	HFA-42	DCM-A
179591957	TC	T	c.19183delG	2609.57	PASS	0.54	120	104	224	HFA-9	DCM-A
179583071	ACAGATATCTTGAC	A	c.23798_23810delGTCAAGATATCTG	1797.98	PASS;StrandBias	0.22	124	451	575	PA-1	HCM
179558736	C	T	c.30476-1G>A	2380.12	FDRtranche10.00to50.00+;PASS	0.58	155	113	268	D13KD-1	DCM-A
179535816	C	A	c.34186+1G>T	833.79	PASS	0.49	38	39	77	SS-333	HCM
179516991	C	A	c.34690G>T	1122.33	PASS	0.10	109	955	1064	12s-C11	Control
179506963	C	T	c.35635+1G>A	7327.23	PASS	0.54	65	55	120	HFA-26	DCM-A
179506963	C	T	c.35635+1G>A	7327.23	PASS	0.55	263	217	480	HFA-41	DCM-A
179506964	C	G	c.35635G>C	6450.31	PASS	0.43	55	75	131	UK-B12	DCM-B
179498055	T	C	c.38024-2A>G	1440.31	FDRtranche10.00to50.00+	0.58	288	207	495	MIY-11	DCM-A
179497076	T	TA	c.38621_38622insA	2339.05	PASS	0.20	145	595	740	MDT-11	DCM-A
179485012	G	T	c.41313C>A	12126.6	PASS	0.52	421	383	804	UK-H11	DCM-B
179478864	CT	C	c.44336delA	4754.46	PASS	0.56	240	187	427	HFA-68	DCM-A
179477885	TA	T	c.44725+2delT	5928.55	PASS	0.48	90	98	188	MDD-22	DCM-A
179477885	TA	T	c.44725+2delT	5928.55	PASS	0.48	90	98	188	MIV-14	DCM-A
179477004	TA	T	c.45322delT	4088.96	PASS	0.52	178	166	344	UK-G1	DCM-B
179472127	C	A	c.48364+1G>T	3132.58	FDRtranche10.00to50.00+;PASS	0.57	215	159	374	HFA-71	DCM-A
179471841	C	A	c.48565G>T	17194.16	PASS	0.48	479	516	995	UK-A3	DCM-B
179467006	T	C	c.50197+3A>G	4964.76	PASS	0.55	226	183	409	12s-G11	Control
179458075	AG	A	c.53935delC	4133.57	PASS	0.51	179	172	351	HFA-63	DCM-A
179457392	A	T	c.54422-5T>A	6168.22	PASS	0.54	215	186	401	UK-B1	DCM-B
179457005	C	T	c.54704-1G>A	1273.14	PASS	0.49	56	59	115	UK-B12	DCM-B
179456704	C	T	c.55003+1G>A	7835.09	PASS	0.53	310	276	586	MGR-11	DCM-A
179455162	A	T	c.56367T>A	5790.41	PASS	0.58	228	167	395	MEH-11	DCM-A
179454957	G	A	c.56572C>T	8250.03	PASS	0.52	269	253	522	MDJ-21	DCM-A
179454576	G	A	c.56953G>A	5819.28	PASS	0.52	197	184	381	MEW-11	DCM-A
179452435	G	A	c.58678C>T	3233.06	PASS	0.58	198	146	344	MAO-92	DCM-A
179447207	TG	T	c.60147delC	1144.41	StrandBias	0.23	165	552	717	SS-201	HCM

179444661	C	T	c.62425+5G>A	9756.67	FDRtranche10.00to50.00+;PASS	0.24	8	25	33	MAM-12	DCM-A
179444429	G	A	c.62572C>T	18928.38	PASS	0.57	572	428	1000	UK-A10	DCM-B
179443339	T	C	c.63405A>G	1427.03	PASS	0.55	224	187	411	MIS-11	DCM-A
179442324	C	G	c.63901+5G>C	7488.06	FDRtranche10.00to50.00+	0.55	343	286	629	MCL-15	DCM-A
179441649	C	T	c.64489+1G>A	6822.3	PASS	0.52	255	234	489	UK-B2	DCM-B
179441015	CT	C	c.64920delA	5378.99	PASS	0.66	395	201	596	UK-H2	DCM-B
179440067	CT	C	c.65867delA	2395.82	PASS	0.13	117	798	915	UK-C8	DCM-B
179438874	ATATGC	A	c.67057_67063delGCATATGinsTA	4467.51	PASS	0.23	165	559	724	MHG-23	DCM-A
179434160	CAA	C	c.71774_71775delTT	7059.09	PASS	0.54	306	262	568	A-15	Control
179433758	G	GT	c.72178_72179insT	4981.24	PASS	0.55	244	197	441	HFA-57	DCM-A
179433213	G	GGTTTATCTATCT	c.72723_72739delinsAGA	945.03	PASS	0.33	125	254	379	SS287-15	DCM-A
179428871	G	A	c.77065C>T	21554.16	FDRtranche10.00to50.00+;PASS	0.61	188	119	307	MID-1	DCM-A
179428871	G	A	c.77065C>T	21554.16	FDRtranche10.00to50.00+;PASS	0.61	188	119	307	SS725	DCM-A
179425091	G	A	c.80845C>T	1841.18	PASS	0.14	127	784	911	MGW-11	DCM-A
179424496	C	T	c.81440G>A	1670.2	PASS	0.14	148	898	1046	MIP-13	DCM-A
179424398	CAG	C	c.81536_81537delCT	6212.74	StrandBias	0.57	283	214	497	UK-C6	DCM-B
179424036	A	T	c.81898+2T>A	10097.32	PASS	0.47	266	300	566	MIA-1	DCM-A
179422457	G	T	c.82701C>A	2923.47	PASS	0.59	219	153	372	UK-B6	DCM-B
179417723	ATAAT	A	c.84977_84980delATTA	8795.62	PASS	0.62	230	142	372	UK-E12	DCM-B
179413187	G	A	c.88242C>T	2808.37	PASS	0.54	150	126	276	UK-C10	DCM-B
179412902	C	A	c.88528G>T	1639	FDRtranche10.00to50.00+;PASS	0.53	87	76	163	MBG-121	DCM-A
179412245	CTTTAA	C	c.89180_89184delAAATT	10083.39	PASS	0.54	140	117	257	HFA-46	DCM-A
179410799	G	A	c.90241C>T	1584.39	PASS	0.12	107	782	889	MHQ-12	DCM-A
179410544	T	TGGG	c.90493+2insCCT	41982.72	PASS	0.58	862	621	1483	SS723	DCM-A
179408239	G	GT	c.91537_91538insA	3613	PASS	0.62	220	136	356	UK-E4	DCM-B
179406990	C	G	c.92569+1G>C	8827.13	FDRtranche10.00to50.00+;PASS	0.51	180	173	353	HFA-83	DCM-A
179406990	C	G	c.92569+1G>C	8827.13	FDRtranche10.00to50.00+;PASS	0.51	289	274	563	HFA-66	DCM-A
179404491	CCT	C	c.93376_93377delAG	12491.23	PASS	0.61	562	361	923	UK-G7	DCM-B
179404286	G	A	c.93583C>T	8470.72	PASS	0.55	364	299	663	UK-G9	DCM-B
179403522	T	A	c.94111A>T	7746.65	PASS	0.50	250	250	500	MHX-11	DCM-A
179402067	A	G	c.94942+2T>C	7331.01	PASS	0.50	269	265	534	pv-35	Control
179401029	G	T	c.95522C>A	2296.56	PASS	0.58	158	115	273	UK-C9	DCM-B

Supplementary Appendix Table 5. Numbers of *TTN* missense variants* and truncating mutations in cohorts.

Cohort		Cohort size (no.)	Missense variants	Avg. / subject^	Truncating mutations	Avg. / subject^
DCM	Group A	92	117	1.27	37	0.40
	Group B	71	103	1.45	17	0.24
	Group C	149	136	0.91	13	0.087
HCM		231	263	1.14	3	0.013
Control		249	332	1.33	7	0.027

*Missense variants and truncating mutations with a minor allele frequency less than 0.01.

^Average number of missense variants or truncating mutations per subject.

Supplementary Appendix Table 6: *TTN* nonsense and frameshift mutations*

Chr 2 Position	Nucleotide	Amino Acid	Pedigree	ID	Diagnosis
179640342	c.6247delG	p.Arg2083fs	TSSDC011	450	DCM
179604949	c.12059delA	p.Lys4020fs	pv	1	Control
179604264	c.12745C>T	p.Gln4249X	HFA	42	DCM
179591957	c.19183delG	p.Ser6395fs	HFA	9	DCM
179583071	c.23798_23810delGTCAAGATATCTG	p.Gly7933fs	PA	1	HCM
179497076	c.38621_38622insA	p.Ala12873fs	MDT	11	DCM
179485012	c.41313C>A	p.Cys13771X	UK	H11	DCM
179478864	c.44336delA	p.Glu14779fs	HFA	68	DCM
179477004	c.45322delT	p.Phe15108fs	UK	G1	DCM
179471841	c.48565G>T	p.Gly16189X	UK	A3	DCM
179469903	c.49077G>A	p.Trp16359X	DNFDC144	05-0444	DCM
179463630	c.51883G>A	p.Arg17295X	DNFDC116	04-1545	DCM
179462477	c.52408C>T	p.Arg17470X	TSFDC050	115	DCM
179459153	c.53145_53146insG	p.Glu17715fs	TSFDC017	253-2	DCM
179458849	c.53347G>T	p.Glu17783X	DNFDC103	03-0941	DCM
179458075	c.53935delC	p.Glu17978fs	HFA	63	DCM
179455162	c.56367T>A	p.Cys18789X	MEH	11	DCM
179454957	c.56572C>T	p.Arg18858X	MDJ	21	DCM
179454575	c.56953C>T	p.Arg18985X	DNFDC142 MEW	05-0569 11	DCM DCM
179452435	c.58678C>T	p.Arg19560X	MAO	92	DCM
179449211	c.60147delC	p.Pro20049fs	SS	201	HCM

179444429	c.62572C>T	p.Arg20858X	UK	A10	DCM
179441015	c.64925delT	p.Lys21640fs	UK	H2	DCM
179440067	c.65867delA	p.Glu21956fs	UK	C8	DCM
179438874	c.67057_67063delGCATATGinsTA	p.Ala22353fs	MHG	23	DCM
17943819	c.67745delT	p.Pro22582fs	MEK	111	DCM
179434160	c.71774_71775delTT	p.L23925fs	A	015	Control
179433758	c.72178_72179insT	p.Gln24059fs	HFA	57	DCM
179433213	c.72723_72739delinsAGA	p.Ser24241fs	SS	287-15	DCM
179428871	c.77065C>T	p.Gln25689X	MID	1	DCM
			SS	725	DCM
179426039	c.79896G>A	p.Trp26632X	DNFDC088	02-1900	DCM
179425091	c.80845C>T	p.Arg26949X	MGW	11	DCM
179424889	c.81046A>T	p.Lys27016X	DNFDC081	02-1564	DCM
179424496	c.81440G>A	p.Trp27147X	MIP	13	DCM
179424398	c.81536_81537delCT	p.Ser27179fs	UK	C6	DCM
179422457	c.82701C>A	p.Tyr27567X	UK	B6	DCM
179417723	c.84977_84980delATTA	p.Tyr28326fs	UK	E12	DCM
179413476	c.87953G>A	p.Trp29318X	TSSDC019	268	DCM
179413187	c.88242C>T	p.Arg29415X	UK	C10	DCM
			TSFDC002	23	DCM
179412902	c.88528G>T	p.Glu29510X	MBG	121	DCM
179412245	c.89180_89184delTTAAA	p.Thr29725fs	HFA	46	DCM
179410799	c.90241C>T	p.Gln30081X	MHQ	12	DCM
179408989	c.91043delA	p.Asn30348fs	TSFDC033	434	DCM
179408239	c.91537_91538insA	p.Thr30513fs	UK	E4	DCM
179404491	c.93376_93377delAG	p.Arg31126fs	UK	G7	DCM

179404286	c.93583C>T	p.Arg31195X	UK	G9	DCM
179403522	c.94111A>T	p.Lys31371X	MHX	11	DCM
179401029	c.95522C>A	p.Ser31841X	UK	C9	DCM

*Mutations are annotated using Human Genome Variation Society guidelines: http://www.hgvs.org/mutnomen/.

Supplementary Appendix Table 7: *TTN* splicing mutations

Chr 2 Position	Nucleotide	Position in splice site 5′	3′	Splicing score change	Amino Acid	Pedigree	ID	Diagnosis
179659280	c.1246-3delT	-	-3	-2.2	p.Val416	pv	75	Control
179647331	c.3101-2A>T	-	-2	-8.37	p.Val1034	N	050	Control
179558736	c.30476-1G>A	-	-1	-8.75	p.Gly10159	D13KD	1	DCM
179535816	c.34186+1G>T	+1	-	-8.5	p.Val11396	SS	333	HCM
179516991	c.34690G>T	+1	-	-11.03	p.Val11564Phe	12s	C11	Control
179506964	c.35635G>C	-1	-	-14.19	p.Val11879	UK	B12	DCM
179506779	c.35635+1G>A	+1	-	-8.18	p.Val11879	HFA HFA	26 41	DCM DCM
179498055	c.38024-2A>G	-	-2	-7.95	p.Ala12675	MIY	11	DCM
179477885	c.44725+2delT	+2	-	-12.92	p.Asp14909	MDD MIV	22 14	DCM DCM
179472127	c.48364+1G>T	+1	-	-8.5	p.Asp16122	HFA	71	DCM
179467006	c.50197+3A>G	+3	-	-5.04	p.Glu16733	12s	G11	Control
179466858	c.50346+3A>G	+3	-	-3.42	p.Lys16782	TSFDC023	300	DCM
179457392	c.54422-5T>A	-	-5	-2.34	p.Glu18141	UK	B1	DCM
179457005	c.54704-1G>A	-	-1	-8.75	p.Asp18235	UK	B12	DCM
179456704	c.55003+1G>A	+1	-	-8.18	p.His18335	MGR	11	DCM
179444661	c.62425+5G>A	+5	-	-12.17	p.Gln20809	MAM	12	DCM
179443339	c.63405A>G	-2	-	-2.67	p.Thr21135	MIS	11	DCM
179442324	c.63901+5G>C	+5		-5.38	p.Tyr21301	MCL	15	DCM
179441649	c.64489+1G>A	+1	-	-8.18	p.Gly21497	UK	B2	DCM
179424036	c.81898+2T>A	+2	-	-8.18	p.Glu27300	MIA	1	DCM
179410544	c.90493+2insCCT	+2	-	-32.13	p.Thr30165	SS	723	DCM
179406779	c.92569+1G>C	+1	-	-8.27	p.Arg30857	HFA HFA	66 83	DCM DCM

179402067	c.94942+2T>C	+2	-	-7.75	p.Asp31648	pv	35	Control

*Mutations are annotated using Human Genome Variation Society guidelines: http://www.hgvs.org/mutnomen/. Amino acid indicated is the residue juxtaposed to the aberrant splice signal.

Supplementary Appendix Table 8: CNV validation primers

Name	Sequence
TTN_37_intF1	TGAGGAGCTGTAAGAGAATGTCATCAGA
TTN_i21_R1	AGTGCTGGCATTACCACTCCTAGTT

Supplementary Appendix Table 9: Clinical characteristics of DCM Group A probands

Subject	Sex	BSA (m2)	Current age (yr) or death†	Age of Dx (yr)	Family Hx	LVEF (%)‡	FS (%)‡	LVEDD (mm)‡	NYHA class¶	Age at VAD, Tx, Death (yr)^	Comments‖	Gene	Mutation(s)※
HFA-42	M	1.84	66	54	No	47.5	27.9	61	4		CHF, Embolic CVA, ICD	TTN	p.Gln4249X
HFA-9	M	1.89	55	42	Yes	15	15.5	84	3		CHF, ICD(50) NSVT	TTN	p.Ser6394fs
D13KD-1	F	1.99	51	39	Yes	15	24.3	70	4		NI Cors	TTN	p.Gly10159
MIY-11	M	2.14	42	41	Yes	20	15.8	65	3			TTN	p.Ala12675
HFA-26	F	1.56	51	45	No	40	29.2	48	2			TTN	p.Val11879
HFA-41	M	2.14	60	57	No	45	24	58	1		Episodic severe dypsnea	TTN	p.Val11879
MDT-11	F	1.66	30	19	Yes	20	11	52	3		ICD(28)	TTN	p.Ala12873fs
MEQ-132	M	1.6	25	22	Yes	45	19.3	57	1		Familial Screening	TTN	p.Pro13298_ Thr17642dup
HFA-68	F	1.83	40	37	Yes	45	21.4	56	1		CHF, ICD(38) NSVT	TTN	p.Glu14779fs
MDD-22	F	1.88	73	57	Yes	20	18	58	2		ICD(70)	TTN	p.Asp14909
MIV-14	M	1.9	50	26	Yes	20	9.5	63	3	49	AF, CHF (35), ICD(47)	TTN	p.Asp14909
HFA-71	M	2.05	61	40	Yes	15	11.3	80	4		CHF,ICD(56), NSVT	TTN	p.Asp16122
HFA-63	M	2.25	32	29	Yes	15	15.9	63	4		CHF, ICD, NSVT	TTN	p.Glu17978fs
MGR-11	F	1.58	59	53	Yes	20	9.7	62	2.5		CHF(53)	TTN	p.His18335
MEH-11	M	2.36	28†	25	Yes	11	NA	NA	4	28	CHF, NSVT	TTN	p.Cys18789X
MDJ-21	M	2.13	35	NA	NA	40	21	64	3		ICD, NSVT	TTN	p.Arg18858X
MEW-11	M	1.97	37†	20	Yes	25	NA	50	4	31, 37		TTN	p.Arg18985X
MAO-92	F	1.6	36	17	Yes	37.5	22.4	63	2		ICD(33)	TTN	p.Trp976Arg/ p.Arg19560X
MAM-12	M	1.79	23	23	Yes	32.5	25	68	4	23	ICD, NSVT, SMD	TTN	p.Gln20809*
MIS-11	F	1.8	62	59	Yes	20	25.5	61	2		AF, CHF	TTN	p.Thr21135
MCL-15	F	1.53	54	24	Yes	28	18	51	3		ICD(35)	TTN	p.Tyr21301
MHG-23	M	1.98	52	31	Yes	29	14.3	77	4	52	AF, CHF, ICD(46)	TTN	p.Ala22353fs
MEK-111	M	1.94	24†	15	Yes	NA	17	77	4	15,24	CHF	TTN	p.Pro22582fs
HFA-57	F	1.98	55	48	Yes	22.5	13.7	51	2	55	AF, CHF, NI Cors	TTN	p.Gln24059fs
SS287-15	F	1.97	54	45	Yes	45	36	55	1		Familial Screening; RVD, SVT	TTN	p.Ser24241fs
MID-1	M	1.83	40	37	Yes	34	15.7	51	2		Familial Screening	TTN	p.Gln25689X
SS725	M	2.28	62	51	Yes	20	9.5	63	4		CHF, ICD(61)	TTN	p.Gln25689X
MGW-11	M	NA	40†	35	Yes	12.5	13.3	98	4	40	CHF, ICD	TTN	p.Arg26949X
MIP-13	M	2.33	41	33	Yes	30	16.5	51	2		CHF, ICD(33) NSVT; NI Cors	TTN	p.Trp27147X
MIA-1	M	2.35	30	14	Yes	32.5	25	68	2		ICD, NSVT	TTN	p.Glu27300

MBG-121	M	2.21	34	35	Yes	20	NA	NA	3		CHF, ICD	TTN	p.Glu29510X
HFA-46	M	1.9	66	53	Yes	20	57	62	3		AF, AI, ICD	TTN	p.Thr29725fs
MHQ-12	M	2.07	42	38	Yes	17.5	9.7	72	1		CHF, ICD(41)	TTN	p.Gln30081X
SS723	M	NA	56	51	Yes	15	38	67	3		AF, ICD(52)	TTN	p.Thr30165
HFA-83	M	1.98	45	40	Yes	20	15.2	66	4		AF, CHF, ICD	TTN	p.Arg30857
HFA-66	M	2.04	29	28	Yes	22.5	13	77	3	29,32	ICD(29), NSVT	TTN	p.Arg30857
MHX-11	M	2.24	58†	52	Yes	32.5	8.2	61	3.5	58	CHF	TTN	p.Lys31371X
HFA-10	M		64	57	NA	15	5.9	84	2	64	ICD(58)		
HFA-30	M		62	55	No	25	22.6	62	2	60	IC(54) NSVT		
HFA-37	M		38	18	No	35	22.6	53	1		NSVT		
HFA-43	M		47	37	No	45	22.2	54	1				
HFA-50	M		51	47	No	20	16.7	60	3		ICD(49)		
HFA-51	M		43	33	No	30	18.3	71	2		ICD		
HFA-53	F		51	47	Yes	55	25	44	1		Familial Screening; Abn LV wall motion; Nl Cors; NSVT; ICD(47)		
HFA-56	M		37	33	Yes	35	20.4	54	1				
HFA-61	F		63	47	Yes	37.5	8.8	57	4		ICD(62)		
HFA-67	M		49	43	NA	15	14.5	69	4	45	CAD, ICD(41)		
HFA-70	F		74	58	Yes	25	12.7	71	3		AF, ICD, NSVT		
JG-32	F		51	43	Yes	45	38	60	3		ICD(45) SM, Nl Cors		
MAB-17	F		31	22	Yes	27	21.2	66	3	33	ICD(33)		
MAE-3111	M		35	34	Yes	25	57	15.8	3	58	AF, ICD(35), NSVT		
MAG-3	F		69	50	Yes	35	18	56	3				
MAK-13	M		38	61	Yes	40	22	70	3		ICD(39)		
MBS-1	M		65	65	Yes	42.5	30.8	65	1		AF		
MCH-123	M		12	12	Yes	30	15.4	65	1	13	ICD(12)		
MDK-11	M		53	NA	Yes	52	NA	NA	NA				
MDU-111	F		43	31	Yes	NA	NA	NA	NA				
MDX-11	F		40	37	Yes	40	36	61	1		Family Screening		
MEE-11	M		44	32	Yes	40	22.6	62	2		ICD(34) VT		
MEI-112	M		27	17	Yes	NA	NA	NA	NA				
MEM-11	M		18	10	Yes	NA	NA	NA	4	12	CHF		
MEN-111	M		31	12	Yes	42.5	22.6	62	1		AF,ICD, NSVT		
MEP-111	M		46	23	Yes	45	22	61	NA				
MER-11	M		54	38	Yes	18	NA	60	3		ICD(38)		
MEX-1	M		53	NA	Yes	9	NA	70	NA		VT, CAD		
MGL-11	F		27	25	Yes	30	16.1	62	2	27	SMD		
MGM-1	F		73	36	Yes	30	14	50	2		AF, ICD, NSVT		
MGP-1	M		58	57	Yes	44	29.7	64	2		ICD(58)		

MGS-111	M		30	25	No	50	NA	59	1		NI Cors; Syncope		
MGU-111	M		41	NA	Yes	NA	NA	NA	NA	32			
MGY-123	M		35	34	Yes	15	12.3	65	NA				
MHA-145	F		37	34	Yes	40	31.5	54	3	34	ICD(34) NSVT		
MHE-113	M		54	NA	Yes	22.5	12.5	64	4	54	ICD, AVB		
MHF-11	F		43	40	Yes	15	8.9	56	1		AF, ICD(41)		
MHI-11	M		70†	56	Yes	NA	NA	NA	3	70	AF		
MIF-14	M		42	42	Yes	35	30.6	62	2				
MIJ-1	M		49	29	Yes	15	5.2	77	4	47	ICD(40) NSVT		
MIK-111	F		38	NA	Yes	40	27.6	58	1	37	SCD; ICD(37)		
MIM-11	F		49	33	Yes	20	13.2	68	4	46	ICD(45)		
MI0-13	M		28	25	Yes	30	NA	55	2		Familial Screening		
MJ-11	M		26	17	Yes	NA	NA	69	4	26	WPW, RVF		
MT13	M		48	18	Yes	30	31	56	1		Familial Screening; AVB; SVT; LV biopsy, myocarditis negative		
MW-11	M		61	43	Yes	20	12.5	64	2		ICD(56)		
MYC-11	M		53	43	Yes	15	9.9	71	1		AF, ICD(50)		
SS126	M		38	28	Yes	38	18.8	64	1		ICD		
SS705	F		42	33	Yes	15	5	59	4	41	MR		
SS719	F		60	45	Yes	20	6.3	64	4		CHF; NI Cors		
SS720	M		67	52	NA	25	10.3	68	2		ICD(66), NSVT		
SS731	M		65	65	No	25	16.6	66	3		AF, MR, NI Cors		
MHM-22	M		29	19	Yes	40	28.8	59	1				
HFA-65	F		54	51	Yes	42.5	14.8	54	1		ICD(50)		
MHO-4	M		60	54	Yes	20	13.6	66	1		ICD(54), NSVT, mild CAD		

BSA, body surface area (m2) is provided for subjects with TTN mutations; Age of Dx, age of diagnosis; Family Hx, Familial history of DCM.

‡ Echocardiographic measurements of left ventricular ejection fraction (EF), fractional shortening (FS) and left-ventricular end-diastolic diameter (LVEDD) obtained at time of diagnosis. NA, not available.

¶ New York Heart Association classifications (NYHA) range from 1 to 4.

^ Earliest ages at which subject received a ventricular assist device (VAD) or a cardiac transplant (Tx), or age at death.

‖ Clinical data are denoted by: Abn LV wall motion, abnormal left ventricular wall motion identified by echocardiography**;** AF, atrial fibrillation; AI, aortic insufficiency; AVB, atrio-ventricular block; CHF, hospitalized for congestive heart failure; CVA, cerebral vascular accident; Familial screening, clinical evaluations were prompted by overt DCM in a first-degree relative; ICD, implanted cardiac defibrillator implanted at age (parentheses); MR, mitral regurgitation; PCM, pacemaker; Nl cors, normal coronary artery anatomy defined by cardiac angiography; NSVT, non-sustained ventricular tachycardia; WPW, Wolf Parkinson White; RVD, right ventricular dilation; RVF, right ventricular heart failure, SMD, skeletal muscle disease.

※ TTN mutations are detailed in Supplementary Tables 6 and 7. * denotes homozygous mutation.

Supplementary Appendix Table 10: Clinical characteristics of DCM Group B probands

Subject	Sex	BSA (m2)	Current age (yr) or death†	Age of Dx (yr)	Family Hx	LVEF (%)‡	LVEDD (mm) ‡	NYHA Class¶	Age at VAD, Tx, Death (yr)^	Comments‖	Gene	Mutation(s)※
UK-H11	F	1.74	40	32	No	20	68	3	32		TTN	p.Cys13771X
UK-G1	M	1.9	49†	46	NA	35	74	4	49		TTN	p.Phe15108fs
UK-A3	M	1.67	30	18	No	24	79	2	19		TTN	p.Gly16189X
UK-B1	M	2.1	71	50	No	50	55	4	60	RVF RVEF=14%	TTN	p.Glu18141
UK-B12	M	1.78	39	30	No	6	81	4	31		TTN	p.Val11879 p.Asp18235
UK-A10	M	1.88	55†	49	No	29	64	4	55		TTN	p.Arg20858X
UK-B2	M	NA	42†	37	No	23	70	4	42		TTN	p.Gly21497
UK-H2	M	2.09	51	39	Yes	18	80	3	41		TTN	p.Lys21640fs
UK-C8	M	NA	55†	37	NA	11	76	4	55		TTN	p.Glu21956fs
UK-C6	M	1.83	41	31	No	29	67	3	31		TTN	p.Ser27179fs
UK-B6	M	2.19	38†	30	NA	38	82	4	38		TTN	p.Tyr27567X
UK-E12	M	1.8	57	49	No	21	78	4	51	ICD	TTN	p.Tyr28326fs
UK-C10	M	NA	38	29	No	34	73	4	30		TTN	p.Arg29415X
UK-E4	M	NA	42	32	No	18	61	4	32		TTN	p.Thr30513fs
UK-G7	F	1.78	63	53	Yes	14	59	3	54		TTN	p.Arg31126fs
UK-G9	M	2.2	50†	43	No	17	70	3	50		TTN	p.Arg31195X
UK-C9	M	NA	62	49	Yes	32	66	4	54		TTN	p.Ser31841X
UK-A2	M		60	49	NA	44	69	3	49			
UK-A4	M		40	29	No	15	87	3	29	AVR		
UK-A5	M		40	30	No	16	72	3	31			
UK-A7	M		26	17	NA	NA	NA	3	17			
UK-A8	M		50	40	No	17	81	3	45			
UK-A9	M		69	48	No	20	69	3	60			
UK-A12	M		58	48	NA	18	78	2				
UK-B3	M		44†	32	NA	33	72	4	44			
UK-B7	M		52†	41	NA	19	80	4	52			
UK-B8	M		63	50	NA	8	90	3	54	AF		
UK-B9	F		50†	49	NA	26	66	4	50	ICD		
UK-B10	M		67	53	NA	18	57	3	59	PCM		

UK-B11	F		57	51	Yes	34	62	3	52	PCM		
UK-C1	F		64	51	Yes	31	61	3	53			
UK-C3	M		46	29	NA	27	79	3	35			
UK-C4	F		66	55	NA	32	69	2				
UK-C5	M		57	46	NA	24	66	3	47			
UK-C7	M		60	43	NA	32	78	4	59			
UK-C12	F		28†	28	NA	15	64	3	28			
UK-D1	M		62	46	No	37	78	3	51			
UK-D3	F		44	33	Yes	44	69	3	34			
UK-D4	M		47	36	No	35	63	3				
UK-D6	M		59†	57	NA	44	75	4	59	AF		
UK-D8	M		43†	38	NA	9	98	4	43			
UK-D9	M		32	13	NA	20	54	3	23		TTN	
UK-D10	M		28	18	No	5	59	3	20			
UK-D11	F		65	54	NA	6	74	3	57			
UK-D12	M		44†	39	Yes	12	76	3	39,44			
UK-E3	F		43	27	No	20	71	3	32			
UK-E6	M		69	58	NA	11	74	3	59	PCM		
UK-E9	M		50	17	NA	21	65	3	41	PCM		
UK-E7	M		32†	26	NA	10	91	4	32			
UK-E10	M		61†	56	NA	30	88	4	61	AF		
UK-E11	M		60	52	YES	18	80	3	52			
UK-F1	M		71	59	Yes	27	71	3	60	PCM		
UK-F3	M		42†	29	NA	13	62	4	42			
UK-F4	M		57†	52	No	45	71	4	57			
UK-F5	F		27	13	No	20	94	3	16	PCM		
UK-F6	M		55	21	NA	20	87	3	45			
UK-F7	F		64	54	No	49	57	2				
UK-F9	M		51†	50	NA	23	77	3	51			
UK-F10	M		50	36	NA	21	91	2		AF, ICD		
UK-F11	M		52†	52	NA	23	73	4	52			
UK-G2	F		44	31	NA	30	63	2				
UK-G3	M		58†	56	NA	40	76	4	58			
UK-G5	F		17†	16	No	44	77	4	17			

UK-G6	M		46†	45	NA	34	67	4	46			
UK-G8	F		61	47	No	30	61	3	57			
UK-G11	M		67	56	No	28	80	3	59			
UK-H3	M		62	51	No	17	72	3	52			
UK-H4	M		57	47	No	11	78	3	47			
UK-H8	F		66	56	No	30	71	3	57			
UK-H9	M		64	54	No	48	93	3				
UK-H12	M		46†	46	No	10	NA	4	46			

Footnotes for symbols (†‡¶^‖※) and abbreviations are defined in Supplementary Appendix Table 9.

Additional abbreviations used: AVR, aortic valve replacement; RVEF, right ventricular ejection fraction.

Supplementary Appendix Table 11: Clinical characteristics of DCM Group C probands

Subject	Sex	BSA (m2)	Current age (yr) or death†	Age of Dx (yr)	Family Hx	LVEF (%)‡	FS (%)‡	LVEDD (mm)‡	NYHA class¶	Age at VAD, Tx, Death (yr)^	Comments‖	Gene	Mutation(s)※
TSSDC011-450	M	2.1	53	45	No	37	12	82	2			TTN	p.Arg2083fs
DNFDC144-05-0444	F	2.18	54	32	Yes	45	NA	57	2			TTN	p.Trp16359X
TSFDC023-300	F	1.75	38	20	Yes	26	15	60	1			TTN	p.Lys16782
DNFDC116-04-1545	M	1.96	33	21	Yes	40	15	54	1			TTN	pArg17295X
TSFDC050-115	M	1.74	53	35	Yes	24	13	70	3			TTN	p.Arg17470X
TSFDC017-253-2	M	2.13	72	65	Yes	40	22	59	1			TTN	p.Glu17715fs
DNFDC103-03-0941	M	2.48	57	45	Yes	30	10	74	2.5			TTN	p.Glu17783X
DNFDC142-05-0569	M	1.79	30	23	Yes	20	15	69	2.5			TTN	p.Arg18985X
DNFDC088-02-1900	F	2.04	40	38	Yes	25	NA	50	2			TTN	p.Trp26632X
DNFDC081-02-1564	M	2.13	45	43	Yes	20	13	63	4	45		TTN	p.Lys27016X
TSSDC019-268	F	1.45	67	60	No	21	13	70	4			TTN	p.Trp29318X
TSFDC002-23	M	1.79	57	43	Yes	29	10	72	1			TTN	p.Arg29415X
TSFDC033-434	M	2.0	40	19	Yes	24	10	72	4			TTN	p.Asn30348fs
TSFDC004-118	M		41	37	Yes	18	10	57	3	41			
DNFDC050-02-2210	F		36	29	Yes	43	22	56	2				
DNFDC096-03-0005	F		37	36	No	37	NA	NA	NA				
TSFDC049-4	M		64	45	Yes	29	18	79	2				
TSXLC002-22	M		38	19	Yes	25	7	83	2				
TSFDC007-28	F		42	20	Yes	20	11	73	2				
TSFDC047-120	M		35	30	Yes	39	12	52	4	35			
TSXLC001-131	M		31	31	Yes	28	15	60	4	42			
TSFDC010-134	M		46	36	No	29	15	71	3				
TSFDC003-136	F		51	54	Yes	34	NA	62	1				
TSLVN002-156	M		24	18	Yes	17		74	1				
TSLVN001-172	F		57	41	Yes	35	18	56	1				
TSFDC013-206	F		26†	25	Yes	NA		51	4	26			
TSFDC014-208	F		60	43	No	41	21	62	1				
TSFDC015-230-2	M		49	34	Yes	38	24	63	1				
TSFDC016-254-2	M		59	44	Yes	32	20	66	2				
TSFDC026-311	M		27	14	Yes	27	16	53	4	27			
TSFDC029-409	F		59	46	Yes	42	20	56	2				
TSFDC027-419	M		52†	35	Yes	22	17	69	4	52			
TSFDC032-430	M		39	22	Yes	23	8	76	3				
TSFDC031-438	M		48†	44	Yes	17	5	75	4	48			
DNFDC020-99-0824	M		60	55	Yes	45	20	59		3			
DNFDC010-01-0045	M		58	56	Yes	45	NA	71	3				

DNFDC053-01-0081	M		42	41	Yes	60	34	60	1		Abn LV wall motion		
DNFDC058-01-0341	F		37	31	Yes	32	NA	NA	2				
DNFDC055-01-0439	F		39	38	Yes	10	5	90	2				
TSFDC036-01-0729	M		50	40	Yes	48	27	63	4	50			
TSFDC039-01-0731	F		55	54	Yes	23	26	69	4	55			
DNFDC054-01-0937	M		70	56	Yes	28.5	NA	NA	2				
DNFDC004-01-1624	M		35	21	Yes	NA	NA	NA	2				
DNFDC065-01-2260	M		66	55	Yes	37	18	55	2				
DNFDC066-01-2393	F		39	34	Yes	50	23	57	1				
DNFDC068-02-0053	M		47	45	Yes	50	18	67	4	47			
TSFDC040-02-0169	M		37	28	Yes	52	25	61	1				
TSFDC041-02-0176	M		NA	45	Yes	24	6	63	2				
TSFDC042-02-0191	F		60	46	Yes	22	15	72	4	46			
TSFDC038-02-0225	F		62	48	Yes	46	20	58	1				
DNFDC071-02-0394	F		76	58	Yes	45	29	41	2				
DNFDC073-02-0502	M		19	18	Yes	25	11	56	2				
DNFDC072-02-0503	M		44†	32	No	19	12	89	4	44			
DNFDC069-02-0646	F		36	28	Yes	30	22	62	2				
DNFDC074-02-0911	F		53	46	Yes	35	NA	NA	2				
DNFDC077-02-0954	M		46†	44	Yes	10	NA	NA	46				
TSFDC018-02-1027	M		74	33	Yes	40	19	61	2				
TSFDC045-02-1089	M		60	49	Yes	40	20	64	2				
TSFDC025-02-1092	M		41	28	Yes	22	21	70	2				
TSFDC044-02-1097	M		34	26	Yes	43	18	56	1				
DNFDC078-02-1192	M		48†	39	Yes	20	NA	NA	3	48			
DNFDC079-02-1517	F		34	33	Yes	20	15	55	3				
DNFDC029-02-1532	F		76	62	Yes	25	13	NA	2				
DNFDC083-02-1566	F		69	38	Yes	30	20	74	2				
DNFDC030-02-1612	M		40	29	Yes	21	9	75	3				
DNFDC087-02-1758	F		48	22	Yes	11	9	81	3				
DNFDC013-02-1902	F		44	37	Yes	37	11	62	2				
DNFDC042-02-2037	F		53	52	Yes	20	11	64	4	53			
DNFDC034-02-2053	M		64	53	No	35	NA	74	3				
DNFDC090-02-2104	M		47	47	Yes	41	22	84	2				
DNFDC089-02-2151	F		38	31	Yes	25	14	80	3				
TSFDC009-02-2276	M		67	44	Yes	26	13	83	1				
TSFDC022-02-2304	F		60	44	No	40	28	56	1				
DNFDC092-02-2349	F		39	38	Yes	45	NA	NA	2				
DNFDC091-02-2555	M		43	35	Yes	31	20	54	2.5				
DNFDC099-03-0432	F		32	30	Yes	17	16	66	3				
DNFDC100-03-0433	M		49	39	Yes	27	13	80	3	49			
DNFDC108-03-2056	F		61	49	Yes	29	14	NA	2				
DNFDC016-04-0243	F		38	36	Yes	15	15	60	3				

DNFDC109-04-0326	F		59	58	Yes	30	13	67	2				
DNFDC014-04-0567	M		50	34	Yes	17	NA	NA	3				
DNFDC114-04-0871	F		42	41	Yes	40	23	47	2				
DNFDC112-04-0906	F		55	38	Yes	19	12	66	3				
DNFDC117-04-1674	M		60	50	Yes	15	11	55	2.5				
DNFDC123-05-0110	F		65	63	Yes	30	26	49	2.5				
DNFDC133-05-0199	M		50	47	No	17	5	66	2				
DNFDC039-05-0234	M		54	50	Yes	34	17	64	2.5				
DNFDC131-05-0381	F		28	24	Yes	25	11	64	3				
DNFDC139-05-0394	M		45	30	No	33	NA	NA	3				
DNFDC147-05-0548	F		36	33	Yes	25	NA	64	2				
DNFDC155-05-0698	F		49	43	Yes	47	21	50	2				
DNFDC141-05-0716	F		22	18	Yes	18	14	64	2.5				
TSAR004-6	M		73	53	Yes	50	32	61	1				
TSAR003-35-2	M		14	12	Yes	31	7	56	2	14			
TSAR005-125	M		37	19	Yes	37	18	65	1				
TSFDC001-98-38	M		51	29	Yes	21	11	87	1				
TSSDC128-220	M		42	38	No	37	24	59	4	42			
TSSDC012-273	M		69	53	Yes	38	19	64	2				
TSSDC116-292	M		24	23	No	18	13	61	4	24			
TSSDC020-395	F		56	39	No	33	20	59	2				
TSSDC009-398-2	F		59	46	Yes	18	16	89	4	59			
TSSDC024-401	M		50†	38	No	17	15	89	4	50			
TSSDC026-433	F		71	51	No	25	10	68	2				
TSSDC027-435	M		50†	44	No	29	9	78	2				
TSSDC028-436	M		32	25	No	22	10	79	2	32			
TSSDC030-439	M		61	44	No	28	10	79	3				
TSSDC031-441	M		69†	56	No	29	19	67	2	69			
TSSDC032-442	M		74	57	Yes	37	11	77	2				
TSSDC033-443	M		58	46	No	26	9	64	1				
TSSDC002-445-2	M		51	39	No	17	6	77	4	51			
TSFDC005-127	F		52	34	Yes	35	16	60	4				
TSFDC012-148-2	M		58	41	Yes	61	24	50	1		Familial Screening; NSVT, AF		
TSSDC004-447	M		76	55	No	45	16	83	3				
TSSDC005-448	M		65†	53	No	NA	12	67	4	65			
TSSDC007-449	M		72	53	No	25	13	70	2				
TSSDC014-451	M		72†	48	No	42	14	65	3	72			
TSSDC015-452	M		48	48	No	40	30	63	1				
DNFDC052-01-0131	M		21	17	Yes	NA	27	57	2	21			
DNFDC057-01-0987	F		59	48	Yes	30	25	NA	2	59			
DNFDC084-02-1567	F		52	42	No	10	NA	69		2			
DNFDC095-02-2523	M		54	44	Yes	10	6	78	2				

DNFDC113-04-0881	F		45	44	Yes	25	NA	NA	NA	NA			
DNFDC138-05-0395	F		27	21	No	20	5	53	3				
DNFDC080-02-1405	M		52	33	Yes	30	7	53	3	52			
DNFDC094-02-2524	M		68	52	yes	21	20	63	1				
DNFDC101-03-0942	F		61	50	No	25	14	60	2				
DNFDC104-03-2029	F		37	27	No	30	16	60	2				
DNFDC110-04-0347	M		59	58	No	28	12	58	2				
DNFDC119-04-1877	M		55	49	Yes	15	23	70	2				
DNFDC127-05-0160	M		55	44	No	18	NA	NA	3				
DNFDC140-05-0355	F		39	31	No	40	25	60	2				
DNFDC075-02-0970	M			31	Yes	52							
DNFDC136-05-0301	F			23	No	50							
TSSDC010-01-0745-2	M			56	No	49							
DNFDC102-03-2097	F			27	No	48							
TSFDC067-02-2315	M			13	No	47							
DNFDC093-03-0646	M			58	No	47							
DNFDC047-02-0952	F			49	No	46							
TSFDC054-03-0818	M			27	No	46							
DNFDC107-03-1827	F			40	Yes	42							
DNFDC026-02-1565	M			63	No	36							
TSFDC069-02-2322	F			50	No	35							
DNFDC059-01-2291	M			58	No	33							
TSSDC058-03-0817	M			20	No	30							
DNFDC118-04-1787	M			22	No	29							
TSSDC056-02-0174	F			47	No	28							
TSSDC060-01-0725	M			49	No	13							
DNFDC008-02-2451	F		66	61	Yes	55	29	NA	4	66	Rapid Progression		
DNFCD003-02-01704	F		59	41	Yes	56	35	NA			Familial Screening		

Footnotes for symbols (†ǂ¶^‖※) and abbreviations are defined in Supplementary Appendix Table 9.

Additional abbreviations used: AVR, aortic valve replacement; RVEF, right ventricular ejection fraction.

Supplementary Appendix Table 12: Clinical findings in DCM families with *TTN* truncating mutations*

Pedigree	ID	Sex	Current age (yr) or death†	Age at diag-nosis (yr)	FS (%)‡	LVEDD (mm)‡	NYHA class¶	Age of VAD/ Tx/Death (yr)^	Comment‖	Clinical Status	TTN Genotype(s)※
DNFDC081	02-1564	M	45	43	13	63	4	Tx(45)	EF=20%	A	p.Lys27016X
	02-1663	M	33	33	30.2	53	1		IVCD	A	+
DNFDC088	02-1900	F	40	38	16	50	2		EF=25%	A	p.Trp26632X
	2395	M	70	61	39	54	1			I	-
	1901	F	58	58	33	55	1		Diastolic Dysfunction, TWA	I	+
	05-0427	M	47	45	NA	NA	4	Tx(47)	ST, RBBB, LAFB	A	+
DNFDC103	03-0941	M	57	45	10	74	2.5		TWA, 1AVB EF=30%	A	p.Glu17783X
	05-1266	M	51	48	NA	NA	2		EF=10%	A	+
DNFDC142	05-0569	M	30	23	15	69	2.5		TWA, LAFB, IVCD, EF=20%	A	p.Arg18985X
	0568	F	53	53	NA	NA	2			I	+
MAO	92	F	36	17	22.4	63	2		EF=37% ICD(33)	A	p.Trp976Arg p.Arg19560X
	9	M	49†	47	32	50	1	49	Septic Shock†	U	p.Trp976Arg

	90	F	49	NA	NA	NA	NA			I	p.Arg19560X
	91	F	40	40	35.3	51	1			I	p.Arg19560X
	93	M		19			1			I	pArg19560X
MDD	22	F	73	57	18	58	2		EF=20% ICD(70)	A	p.Asp14909
	21	M	31†	31					CHF	A	NA
	23	F	72	58					EF=20%	A	NA(+)
	231	M	45	45					AF(39)	I	+
	2311	M	18	18	35.7	56	1		AF(16)	I	+
	2312	M	16	16	33.3	48			NSR	I	-
MEK	111	M	24†	17	17	77	4	15,24	Tx(15)	A	p.Pro22582fs
	1	F	72	50	34	50	NA		STTWA; Q-waves,CHF	A	+
	11	M	41†	25	8	75	4	36	1AVB, LAFB, TWA Tx(36)	A	+
	110	F	43	NA	NA	NA	NA			U	-
	112	F	19	NA	NA	NA	NA			I	+
	12	M	33†	30	NA	NA	4	33	CHF(33)	A	NA
MEQ	132	M	25	22	19.3	57	1		SB, EF=45%	A	p.Pro13298_Thr17642dup
	12	M	56	33	NA	NA	4	50	NSVT, CHF(49) Tx(50)	A	NA
	13	M	46†	41	NA	NA	NA	42	SCD(46)	A	NA(+)
	131	M	33	33	38.8	54				I	-
MEW	11	M	37	20	NA	50	4	31	EF=25% Tx(30)	A	p.Arg18985X

	1	M	63	62	NA	NA	4	43	Tx(43)	A	NA(+)
	21	M	32	23	NA	NA	NA		ICD	A	+
MHG	23	M	52	31	14.3	77	4	52	AF, EF=29% ICD(46)	A	p.Ala22353fs
	1	F	57†	NA	NA	NA	NA	58	Lung Ca	U	NA
	12	M	65	62	43.2	44	1		SB	U	-
	15	F	57	41	32.8	61	2		Morbid Obesity Type II DM, PCM	I	-
	152	F	27	27	50	46				I	-
	2	F	66†	59	NA	NA	NA	66	CHF	A	NA(+)
	21	F	63	48	31.9	38.3	2		LBBB, ICD	A	+
	211	M	41	37	28.2	44.7				I	+
	212	M	41	37	32.8	45.4				I	+
	22	F	61	42	30.1	55.2	2		1AVB, LBBB EF=22%	A	+
	221	F	35	32	30.1	52.2	1		NSR	I	+
	222	M	32	29					NSR	I	-
	231	M	33	33					NSR	I	-
	3	F	25†						Leukemia†	I	NA
	31	M	52	52	46.4	48.1	1		IVCD	U	-
	311	F	28	28	38	47	1			I	-
	4	F	55†	50	NA	NA	NA	54	CHF	A	NA(+)

	41	F	56	NA	NA	NA	NA			I	-
	43	F	50	46	12.2	57.3	3		NSVT, STTWA ICD(50)	A	
	46	F	48	48	32	50	1			I	-
	47	M	42	NA	26	53.5	1		NSR	A	+
	48	M	42	43	16.7	72	NA		ICD(42)	A	NA
	6	M	41†	37	NA	NA	3	41	NSVT, CHF(37)	A	NA
	61	M	49	49	30.5	40.6	NA		NSR	U	-
	62	F	47	47	41.7	34.3	NA		TWA	U	-
	63	F	45	45	24.7	38.1	NA		TWA	I	-
	64	M	42	NA	38.1	40.4	NA		NSR	U	-
	7	M	61†	56	NA	68	NA	61	ST, CHF	A	NA(+)
	70	F	65	NA	NA	NA	NA			U	-
	71	F	45	45	34.9	47	1		NSR	U	-
	72	M	44	44	30.9	57.2	1		NSR	A	+
	73	F	43	NA	36.3	38.6	1		SB, long QTc, TWA	I	-
	74	M	42	NA	19.2	49.9	NA		SB	I	+
	8	F	63†	59	NA	NA	2	63	Long QTc, TWA, CHF NI Cors	A	+
	82	M	40	31	9.6	55.3	2		LVH, LAFB, TWA	A	+
	83	F	42	38	43.2	45.5	2			I	+

	84	F	48	44	40.6	43.3	2		SB, TWA	I	+
	9	F	66	62	41.6	39.9	1		NSR	U	-
	98	M	53†	NA	NA	NA	NA	53	SCD(53)	I	NA
	981	F	42	39	33	43				U	-
	99	F	59	56	33.8	41.7	1		PVC, MR	I	+
MHQ	12	M	42	38	9.7	72	3		EF=17.5% CHF, NSR ICD(41)	A	p.Gln30081X
	1	F	64	64	37.2	43	1		PAC	A	NA(+)
	11	F	44	38	26.5	49	1			U	-
MHX	11	M	58†	52	8.2	61	3.5		EF=32.5% CHF, IVCD	A	p.Lys31371X
	1	M	59†	50	NA	NA			DCM CHF	A	NA(+)
	10	F	90	90						U	-
	12	F	59	NA	41.3	46	1		TWA	U	-
	13	M	51	50	27	63	NA		PVC, LVH, RBBB, ICD(51)	A	+
	14	M	53	NA	36	50	NA		NSR	U	-
	15	F	61	54	40	48			ICD(56) MRI:GdE	I	+
	16	M	63						NI Echo	U	-
	17	M	61†	56	34	58	4	61	CHF SCD	A	NA
	18	F	66	52	NA	NA	NA		CHF;ICD	A	NA
MID	1	M	40	37	15.7	51	2		PVC, TWA, EF=34%	A	p.Gln25689X

	2	M	48	41	19.6	56	1			A	+
	21	M	19	19	25.5	55	1		JR	A	+
	22	M	17	NA	38.3	60	1			A	+
MIP	13	M	41	33	16.5	51	2		EF=25% CHF, NSVT, ICD(33)	A	p.Trp27147X
	1	M	65	42	19.7	76	4	50 (Tx)	ST, 1AVB, ICD	A	+
	11	M	45	44	9	64	2		STTWA, ICD	A	+
	111	M	27	27			1			I	_
	112	M	15	15	27.1	48	1		NSR	I	+
	113	M	12	12	33.3	48	1		LVH, long QTc	I	+
	12	F	44	44	27.7	47	1		STTWA, PVC	I	+
	121	M	19	19	34.6	52	1		NSR	I	-
	122	M	18	18	30.8	52	1		NSR	I	_
	123	M	16	16	38	50	1		NSR	I	-
	131	M	10	10	45.2	42	1		NSR	I	+
	132	M	7	7	43.6	39	1		NSR	I	-
	14	F	40	40	40	50	1		NSR	U	-
	141	F	14	14	30.2	43	1		NSR	I	-
	142	F	10	10	37.8	45	1		NSR	I	-
	2	M	60	60	32.1	53	1		IVCD	U	-

	3	M	63	56	5.6	54	4		AF	A	+
MIS	11	F	62†	59	25.5	61	2	62	EF=20% AF, CHF	A	p.Thr21135
	1	F	65†	65					CHF, ICD	A	NA(+)
	2	F	79	79						U	-
	3	F	85	85						U	-
	12	M	61	55	18	57	1			A	+
	13	M	59	59	19	48.9			CAD/MI PCIX3	I	-
	132	M	35	35	28	51.6	1			I	-
	14	M	37†	27	13	76	4		Tx(37)	A	NA
	141	M	30	30	32.6	52	1		EF=60%	I	-
	142	M	29	29	27	46.7	2		Epilepsy	I	-
	19	M	50						DCM reported	A	NA
MIV	14	M	50	26	9.5	63	3	49	EF=20% CHF, AF, ICD(47)	A	p.Asp14909
	11	M	56	54	31.1	54.3	1		NSR, CAD	I	-
	12	F	53	52	22.3	54.3	1		Long QTc, VT ablation X2	A	+
	121	M	22	20	13	76	4		VAD(20)	A	+
	13	F	52	52	34.2	44.7	1		NRS	U	-
	16	M	43	43	25.8	53.5	1		NSVT, RV dilated (55mm)	A	+
	2	F	81	81	12.4	49.2	1			A	+

	21	F	51	51	35	53.2	1		AVR/MVR	I	+
	23	F	48	48	33.3	55.5	1		NSR	I	-
	24	M	46	46	34	54.5	1			I	-
TSFDC002	23	M	57	43	10	72	1	57	PVC, LAFB, EF=29%	A	p.Arg29415X
	116	M	51	42	8.6	70	1		TWA, LAFB	A	+
	190	F	72	66	22.4	58	3		TWA, PVC, RBBB, LAFB	A	+
	205	F	52	47	NA	NA	3		LAFB, ST	A	+
	26	F	18	13	32	50	1		NSR, Abn LV wall motion, MR	I	+
TSFDC017	253-2	M	72	65	22	59	1		EF=40%	A	p.Glu17715fs
	318	M	54	34	15	75	2	54	AF, EF=17%	A	+
TSFDC033	434	M	40	19	10	72	4		AF, TWA, ICD EF=24%	A	p.Asn30348fs
	0173	M	35	26	16.2	68	1	35	NSR	A	+
TSFDC050	115	M	53	35	13	70	3		NSR, ICD EF=24%	A	p.Arg17470X
	1	M	50	48	NA	NA	3	50		A	NA(+)
	113	F	21	18	31	48	1			I	_
	114	F	61	40	10.3	68	2		1AVB, TWA ICD	A	+

* Pedigrees are provided in Supplementary Fig. 1. Probands and the *TTN* truncating mutation are listed first among family

members. Footnotes for symbols (ǂ¶^‖) are defined in Supplementary Appendix Table 9. † Non-cardiac causes of death are indicated. Clinical status is denoted: A, affected; U, unaffected; I, indeterminate. ※ TTN genotypes are +, mutation present; -, mutation absent; NA, genotype not available; NA(+), obligate carrier based on pedigree position, but genotype not available.

Abbreviations used are defined in Supplementary Appendix Table 9. Additional abbreviations used to describe electrophysiology are: NSR, normal sinus rhythm, LVH, electrocardiographic criteria for left ventricular hypertrophy; ST, sinus tachycardia; SB, sinus bradycardia; Q, Q waves; STTWA, ST and T-wave abnormality; TWA: T-wave abnormality; 1AVB, first degree atrioventricular block; LAFB, left anterior fasicular block; IVCD, intraventricular conduction delay; JR, junctional rhythm; RBB, right bundle branch block; LBBB, left bundle block; VT, ventricular tachycardia; PAC, premature atrial contractions; PVC, premature ventricular contractions; long QTc, prolonged corrected QT interval. Additional abbreviations to denote clinical findings are: Abn LV wall motion; abnormal left ventricular wall motion identified by echocardiography; CAD/MI, coronary artery disease/myocardial infarction; Diastolic Dysfunction, physician reported abnormal LV relaxation parameters; DM, diabetes mellitus; EF, ejection fraction; PCI, percutaneous coronary intervention SCD, sudden cardiac death; MRI:GdE, LV fibrosis identified by gadolinium enhance-MRI ; RV, right ventricle; VT ablation, ventricular tachycardia treated by ablation.

Supplementary Appendix Table 13: Likelihood of the odds (LOD) scores reflecting linkage between *TTN* mutation and DCM in individual families*

Family	TTN variant	LOD score (pen=0.95)	LOD score (pen=0.80)
MEK	Frameshift	0.29	0.29
MEW	Nonsense	0.17	0.17
MHQ	Nonsense	0.16	0.12
MIP	Nonsense	1.16	1.04
MID	Nonsense	0.59	0.59
MHG	Frameshift	3.57	3.21
MEQ	Duplication	0.00	0.00
DNFDC081	Nonsense	0.17	0.17
DNFDC088	Nonsense	0.84	0.84
DNFDC103	Nonsense	0.17	0.17
DNFDC142	Nonsense	0.00	0.00
TSFDC002	Nonsense	0.59	0.59
TSFDC017	Frameshift	0.00	0.00
TSFDC033	Frameshift	0.17	0.17
TSFDC050	Nonsense	0.30	0.30
TSSDC019	Nonsense	0.00	0.00
MHX	Nonsense	1.14	0.96
MDD	Splice	0.17	0.17
MIV	Splice	1.47	1.40
MIS	Splice	0.14	0.09
	total	11.1	10.3

*LOD score for each family calculated at θ=0 and indicated penetrance. Pedigrees and clinical data are provided in Supplementary Fig. 1 and Table 13. See Methods for details on the assignment of affection status.

Supplementary Appendix Table 14 Previously published *TTN* truncation mutations*

AA position	NT name	AA name	Mutation Type	Genotype^	Diagnosis	Source
2484	c.7450G>A	p.Gln2484X	nonsense	Hetero	Cancer	Greenman 2007[20]
4053	c.12156C>T	p.Gln4053X	nonsense	Hetero	Heart failure	Itoh-Satoh 2002
15465	c.46395C>T	p.Trp15465X	nonsense	Somatic	Cancer	Greenman 2007[20]
15700	c.47098G>A	p.Arg15700X	nonsense	Somatic	Cancer	Greenman 2007[20]
21924	c.65766_65767insAT	p.Thr21924fs	frameshift	Hetero	DCM	Gerull 2002[1]
28388	c.85161delG	p.Glu28388fs	frameshift	Hetero	DCM	Gerull 2006[21]
33534	c.100601_100608 delACCAAGTG	p.His33534fs	frameshift	Homo	Congenital Myopathy	Carmignac 2007[22]
33915	c.101744delA	p.Lys33915fs	frameshift	Homo	Congenital Myopathy	Carmignac 2007[22]
34242	c.102723delT	p.Ser34242fs	frameshift	Hetero	Severe tibial muscular dystrophy	Hackman 2008[23]
34322	c.102965delA	p.Lys34322fs	frameshift	Hetero	Severe tibial muscular dystrophy	Hackman 2008[23]
34323	c.102967G>A	p.Gln4322X	nonsense	Hetero	Severe tibial muscular dystrophy	Hackman 2008[23]

*Positions are for UniProt titin (Q8WZ42); ^ Subjects are reported to have germline (hetero, heterozygous or homo, homozygous) or somatic *TTN* mutations.

Supplementary Appendix Table 15: *TTN* exons comprising the standard UniProt titin protein (Q8WZ42) that have minimal or no evidence for cardiac expression

Chrom	hg19 start	hg19 end	Q8WZ42 start	Q8WZ42 end
2	179,535,817	179,537,208	11245	11396
2	179,540,648	179,542,644	11029	11139
2	179,544,066	179,545,898	10766	10931
2	179,549,057	179,549,716	10507	10591

Supplementary Appendix Figure Legends

Supplementary Appendix Figure 1: Kaplan-Meier curves displaying (A) age of clinical diagnosis and (B) freedom cardiac transplantation, ventricular assist device and/or death among subjects with DCM from group A (black lines), group B (blue lines) and group C (red lines).

Supplementary Appendix Figure 2: Pedigrees of families with *TTN* truncation mutations. Probands (arrow) and family members are from group A or group C of the DCM cohort. Clinical status defined by cardiac evaluations and/or medical records is indicated: black, DCM; white, unaffected; grey, status uncertain due to age ≤ 40 years, and/or confounding cardiac diagnoses; slash, deceased. Genotypes (+, *TTN* mutation present; -, mutation absent) are indicated.

Supplementary Appendix Figure 3: Confirmation that *TTN* mutation (c.44725+2delT) disrupts normal splicing. The consequences of a single A/T basepair deletion at chr2:179477886 (identified in genomic DNA from subject MIV-14) on splicing was assessed by sequencing RNA from the subject's explanted left ventricular tissue. (A): IGV (Integrated Genomics View) screenshot of ~950 bp of genomic sequence from subject MIV-14. Eight read are displayed. Among the 188 50-basepair reads aligned at residue chr2:179477886, 98 reads predicted the A/T deletion (Supplementary Appendix Tables 4, 6). (B) IGV screenshot of aligned sequences derived from RNA sequence of left ventricular tissue. Reads were aligned using TOPHAT. A BAM file of RNA sequences corresponding to genomic region in A is displayed. Ten of 11 sequences

show normal RNA splicing. One read (denoted as exon skip) omitted exon 204. Six other reads that were not aligned by TOPHAT (not shown) also indicate abnormal splicing. (C) IGV screenshot of TTN exons and introns in the 950 bp region flanking chr2:179477886. Note that normal splicing (indicated in panel B) includes exon 204. Primers (denoted pF and pR) designed to correspond to sequences in exon 203 and 205 are:
pF:CCATCATGTTCTGGTTTTGTCCAATTCAACCTTACT and pR:
CAATCACAGGATACTGGGTTGAAAGACTGGA. (D) MIV-14 RNA was RT-PCR amplified using primer pF and pR and size fractionated by gel electrophoresis (3% agarose). Lanes (left to right) are: 50bp ladder, control A, control B, and MIV14. PCR products corresponding to WT-splicing and MIV-14 exon skip splicing were analyzed by dideoxy sequencing (data not shown).

Supplementary Appendix Figure 4: *TTN* copy-number analysis. The color of each box represents the log base-2 copy-ratio of a subject's target amplimer. Copy-ratios are iteratively median-normalized by amplimer and subject

Supplementary Appendix Figure 5: Confirmation of a large *TTN* tandem-insertion in MEQ-132. Primer pairs TTN_21_3F and TTN_21_3R (amplimer TTN_21), TTN_155F and TTN_155R (amplimers TTN_155), and TTN_37+intF1 and TTN_i22_R1 (predicted break-point) were used for PCR amplification of genomic DNA from proband MEQ-132, unaffected relatives (MEQ-130, MEQ-131) and an unrelated control sample (CTL). The lane denoted by '-' contained no genomic DNA. The predicted size of the PCR product

was 292 bp.

Supplementary Appendix Figure 6: Transmission electron micrograph of a cardiac left ventricular free wall specimen, derived at autopsy, from DCM-A subject MGW-11 who carries a TTN nonsense mutation (p.Arg26949X). Sarcomere structure is normal. The myocyte nucleus is highly lobulated.

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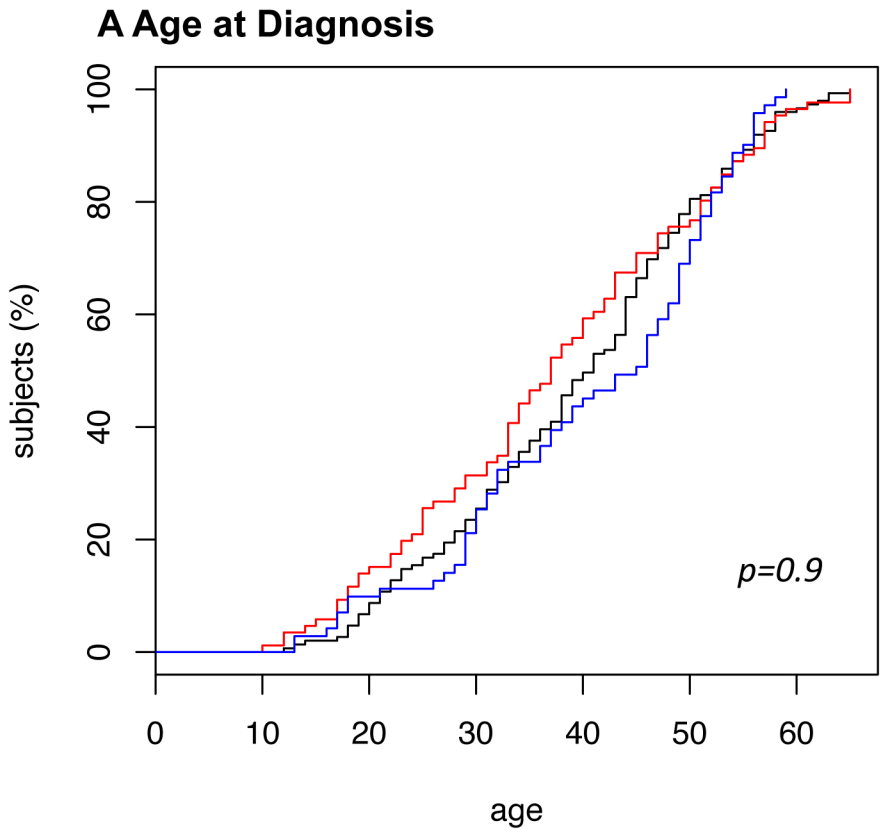
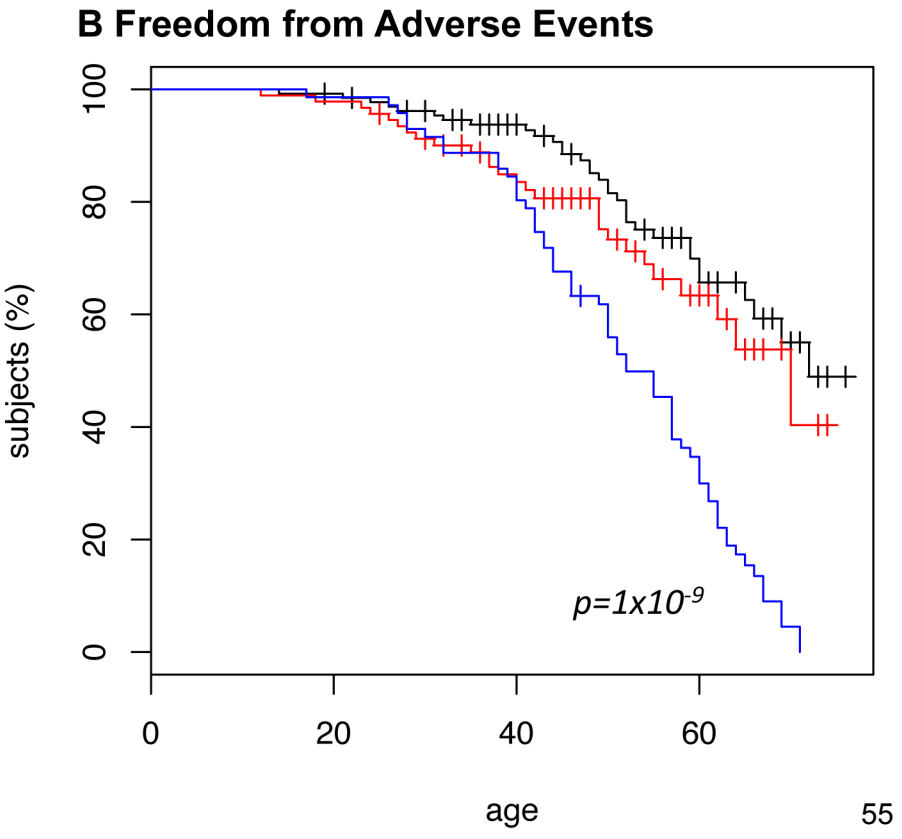
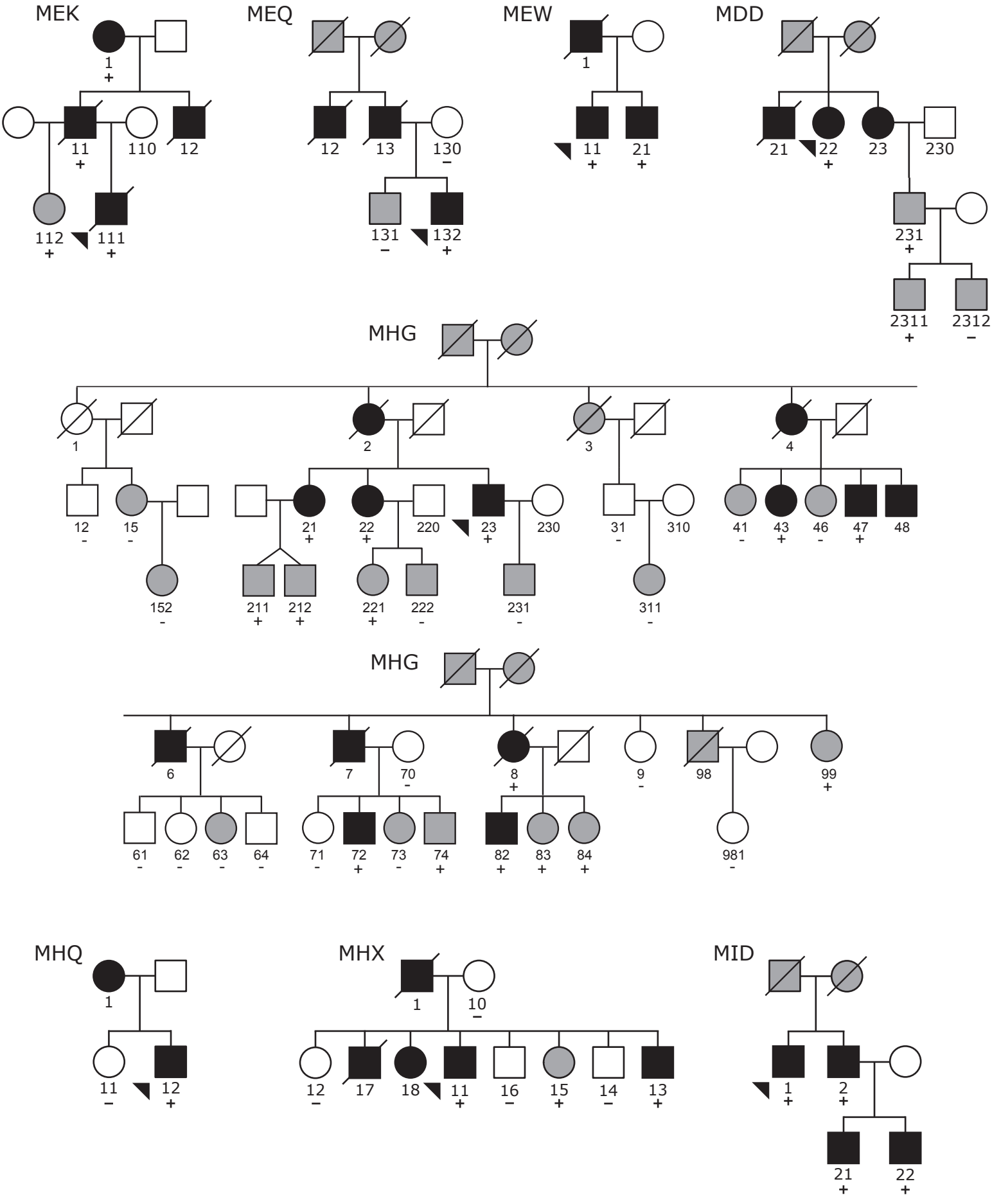
Supplementary Appendix Figure 1

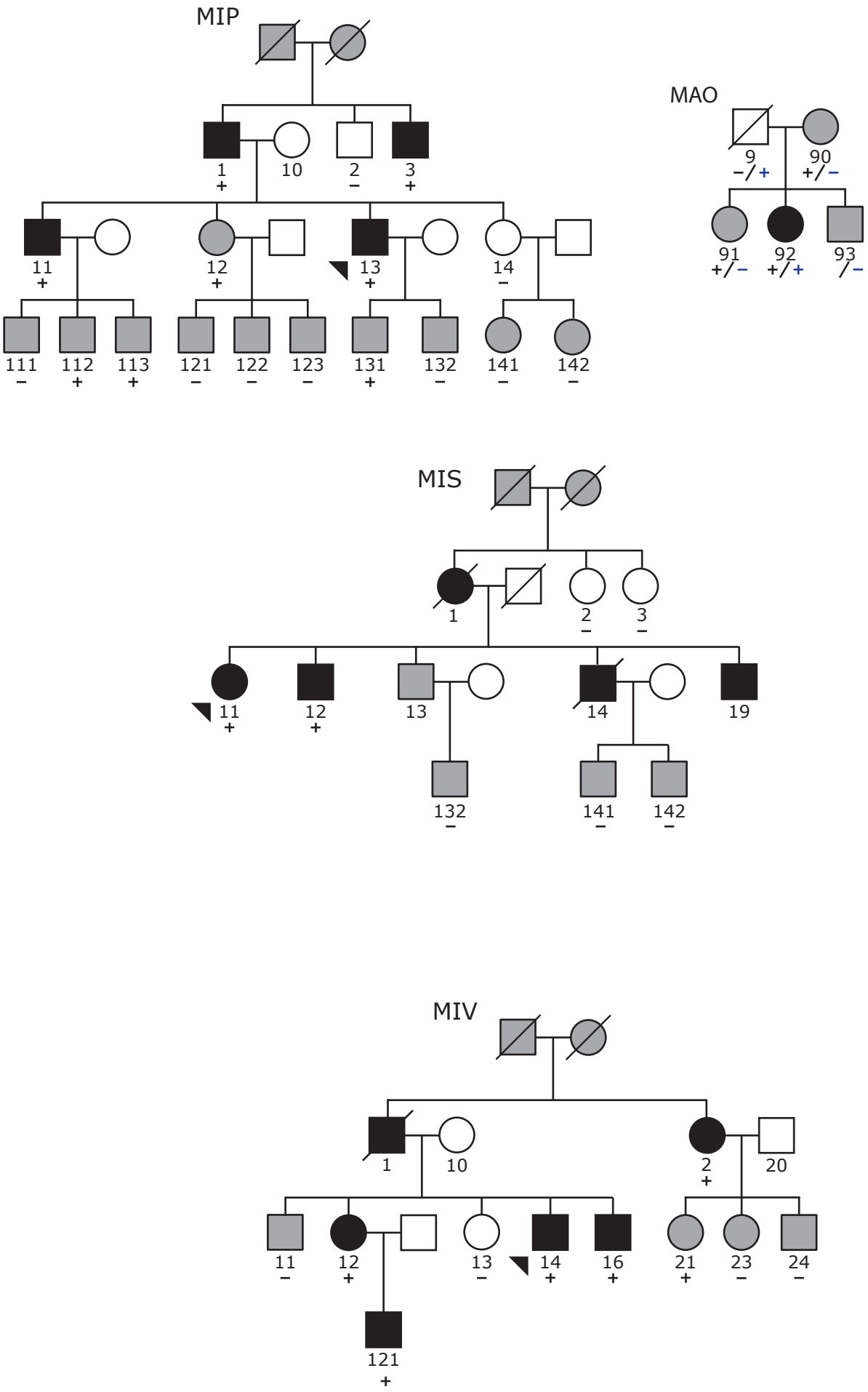




Supplementary Appendix Figure 2



Supplementary Appendix Figure 2 (continued)



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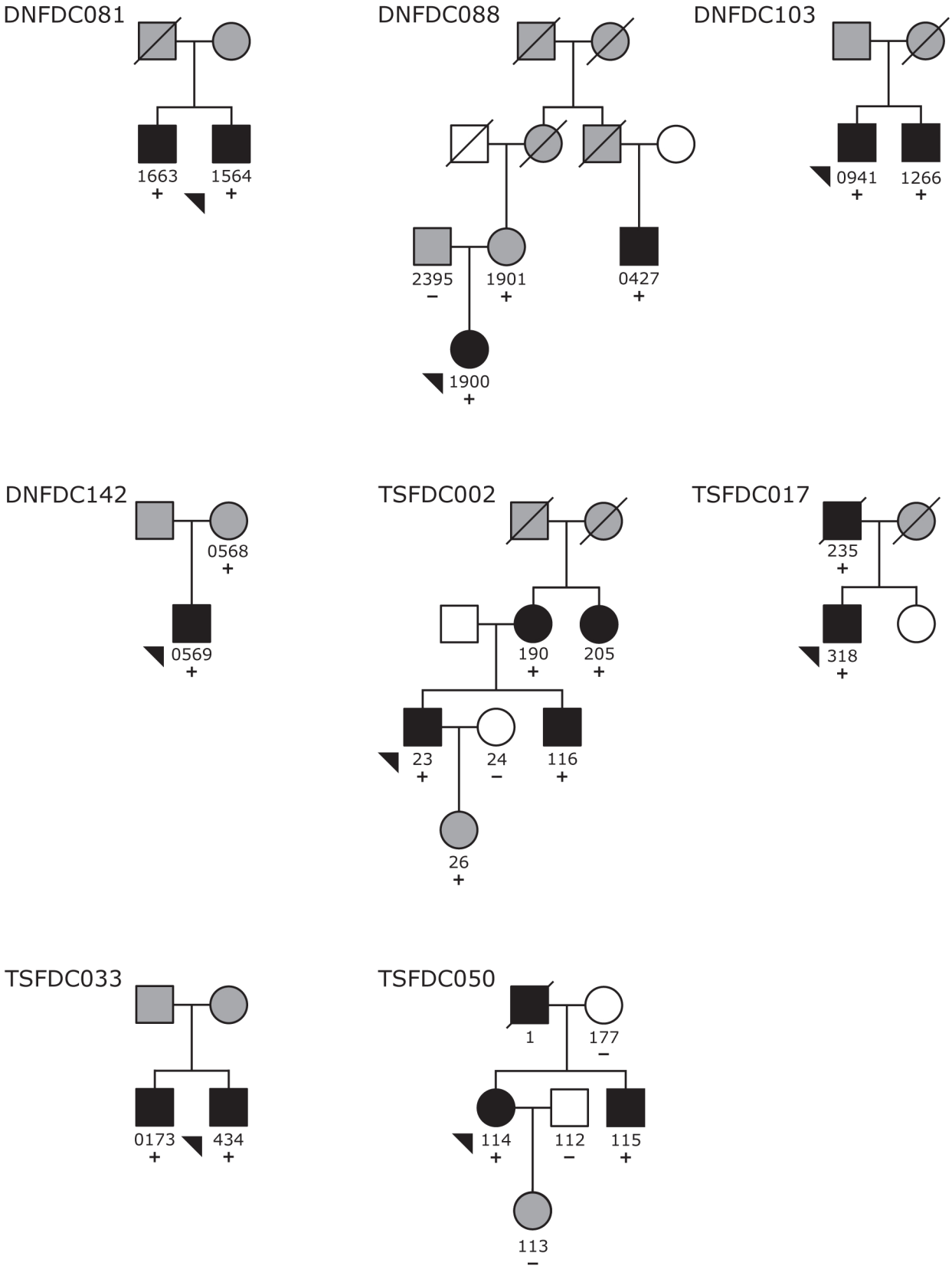
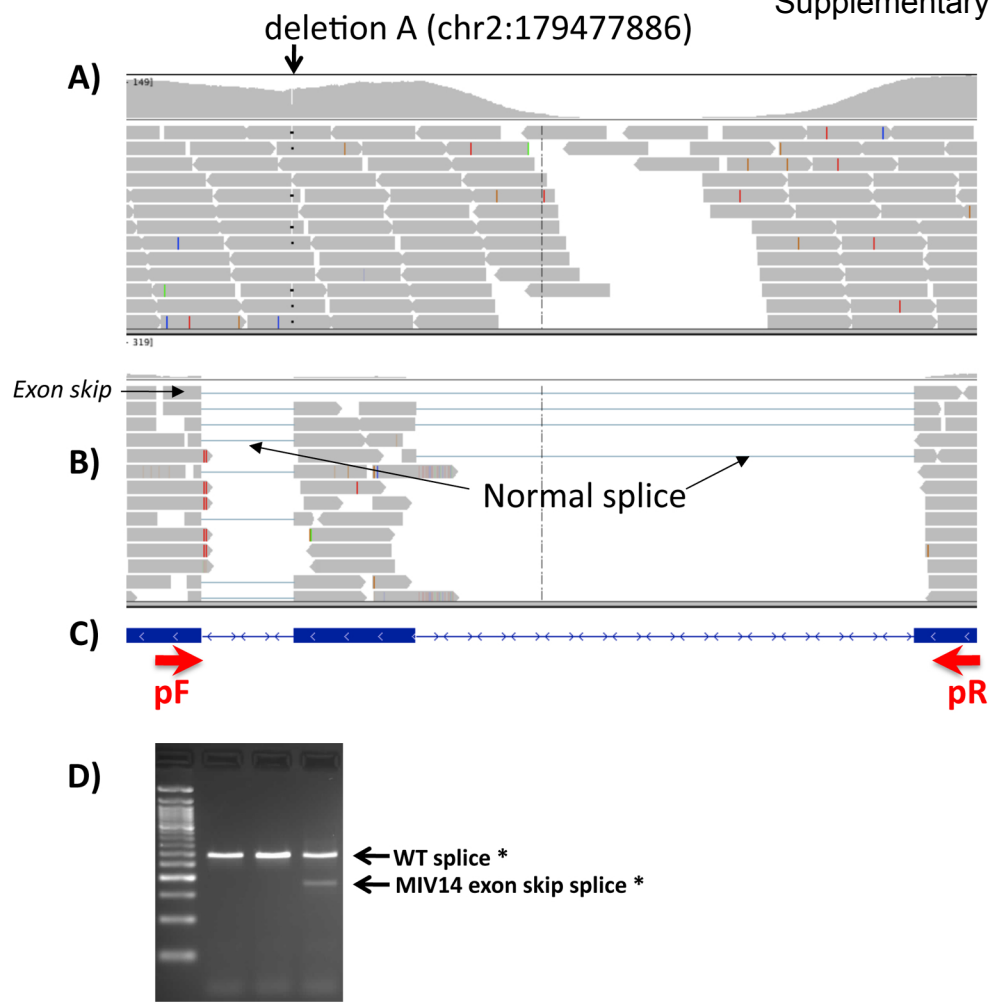
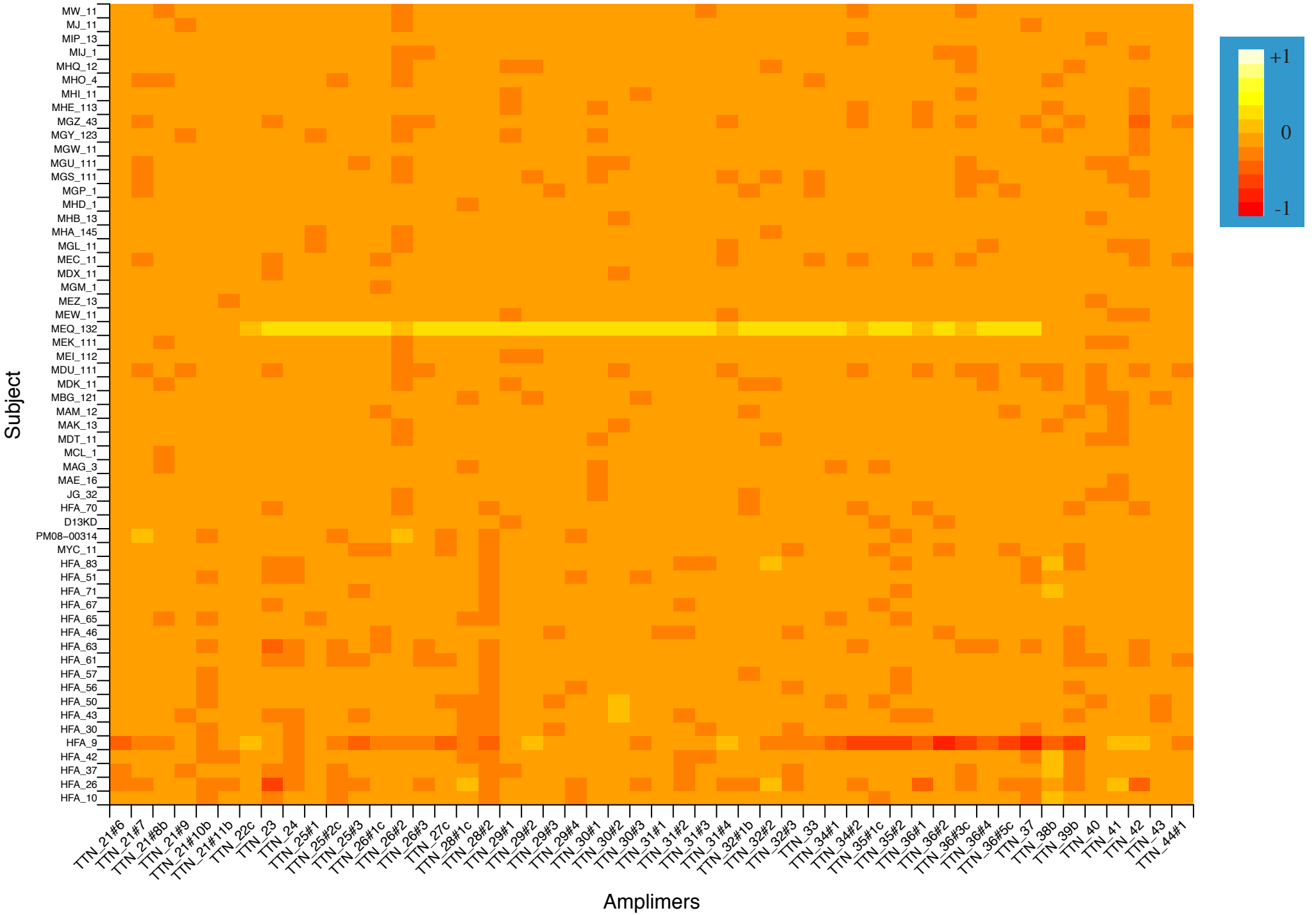
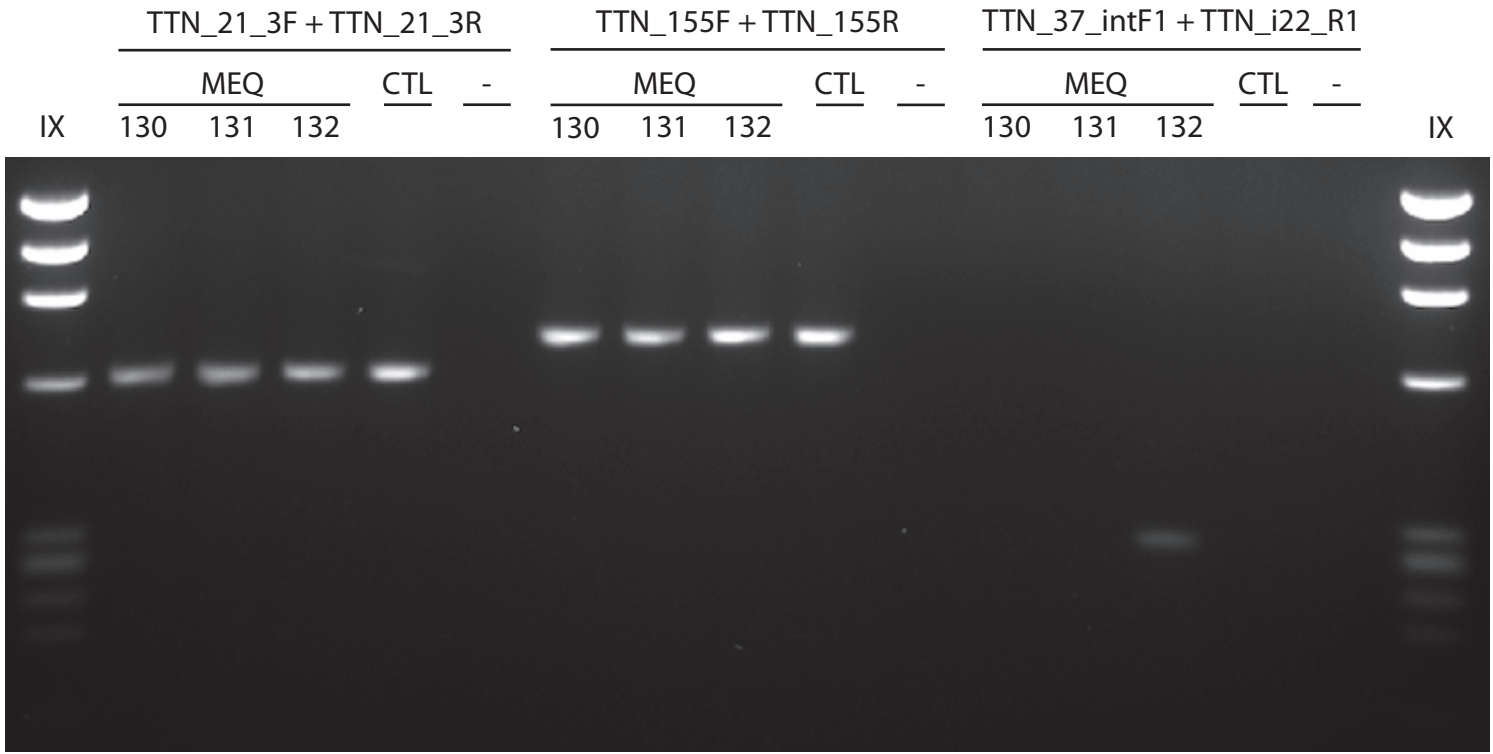



deletion A (chr2:179477886)
A)
149]
319]
Exon skip
B)
Normal splice
C)
pF
pR
D)
WT splice *
MIV14 exon skip splice *

Supplementary Appendix Figure 4



Supplementary Appendix Figure 5



Supplementary Appendix Figure 6