Supplementary Information for "Rare Copy Number Variants and Congenital Heart Defects in the 22q11.2 Deletion Syndrome"

Elisabeth E. Mlynarski,[1] Michael Xie,[2] Deanne Taylor,[2] Molly B. Sheridan,[1] Tingwei Guo,[3] Silvia E. Racedo,[3] Donna M. McDonald-McGinn,[1,4] Eva W.C. Chow,[5] Jacob Vorstman,[6] Ann Swillen,[7] Koen Devriendt,[7] Jeroen Breckpot,[7] Maria Cristina Digilio,[8] Bruno Marino,[9] Bruno Dallapiccola,[8] Nicole Philip,[10] Tony J. Simon,[11] Amy E. Roberts,[12] Małgorzata Piotrowicz,[13] Carrie E. Bearden,[14] Stephan Eliez,[15] Doron Gothelf,[16] Karlene Coleman,[17] Wendy R. Kates,[18] Marcella Devoto,[1,4,19,20] Elaine Zackai,[1,4] Damian Heine-Suñer,[21] Elizabeth Goldmuntz,[4,22] Anne S. Bassett,[5] Bernice E. Morrow,[3] Beverly S. Emanuel,[1,4,*] and the International Chromosome 22q11.2 Consortium

[1]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; [2]Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; [3]Department of Genetics, Albert Einstein College of Medicine, Bronx, NY 10461, USA; [4]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [5]Clinical Genetics Research Program, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, ON M5T 1R8, Canada; [6]Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht 3584, the Netherlands; [7]Center for Human Genetics, University of Leuven, Leuven 3000, Belgium; [8]Medical Genetics, Bambino Gesù Hospital, 00165 Rome, Italy; [9]Lorillard Spencer Cenci Foundation and Department of Pediatrics, La Sapienza University of Rome, Rome 00165, Italy; [10]Department of Medical Genetics, AP-HM and University of Mediterranee, Timone Children's Hospital, Marseille 13005, France; [11]M.I.N.D. Institute & Department of Psychiatry and Behavioral Sciences, University of California, Sacramento, CA 95817, USA; [12]Department of Cardiology and Division of Genetics, Boston Children's Hospital, Boston, MA 02115, USA; [13]Department of Genetics, Polish Mother's Memorial Hospital - Research Institute, 93-338 Łódź, Poland; [14]Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA 90095, USA; [15]Office Médico- Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, 1211 Geneva 8, Switzerland; [16]Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, and affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 52621, Israel; [17]Children's Healthcare of Atlanta and Emory University School of Nursing, Atlanta, GA 30322, USA; [18]Department of Psychiatry and Behavioral Sciences, and Program in Neuroscience, SUNY Upstate Medical University, Syracuse, NY 13210, USA; [19]Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [20]Department of Molecular Medicine, University of Rome La Sapienza, Rome 00185, Italy; [21]Genetics Department, Hospital Universitari Son Espases, Palma de Mallorca 07020, Spain; [22]Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

Contents

1. Mouse gene expression profiling of developing heart and pharyngeal arches at day E9.5 4
2. <0.1% Rare CNV Burden..... 6
3. The CNV map and rare CNV burden 7
4. References 9
5. Supplementary Figures 10

Fig. S1: All 22q11DS CNVs vs Inclusive CNV Map – by CN type 10

Fig. S2: All 22q11DS CNVs vs Inclusive CNV Map – all CNVRs 10

Fig. S3: All 22q11DS CNVs vs Stringent CNV Map – by CN type 11

Fig. S4: All 22q11DS CNVs vs Stringent CNV Map – all CNVRs..... 11

Fig. S5: qPCR validation of the *MYH11* deletion 12

Fig. S6: qPCR validation of the *CDH2* deletion..... 13

Fig. S7: Other previously reported CNVs detected in 22q11DS subjects with CHDs..... 14

Fig. S8: qPCR validation of the *LTBP1* duplication 15

6. Supplementary Tables 16

Table S1: <0.1% rare CNV burden..... 16

Table S2: Inclusive CNV map comparison – by CN type 17

Table S3: Inclusive CNV map comparison – all CNVRs..... 17

Table S4: Stringent CNV map comparison – by CN type 18

Table S5: Stringent CNV map comparison – all CNVRs..... 18

Table S6: Inclusive CNV map (by CN type) ultra-rare CNV burden..... 19

Table S7: Inclusive CNV map (all CNVRs) ultra-rare CNV burden 20

Table S8: Stringent CNV map (by CN type) ultra-rare CNV burden 21

Table S9: Stringent CNV map (all CNVRs) ultra-rare CNV burden 22

Table S10: qPCR validated Rare CNVs 23

Table S11: Mammalian Phenotype Analysis – ALL rare CNVs (<1.0%) 24

Table S12: Mammalian Phenotype Analysis – rare Deletions (<1.0%) 25

Table S13: Mammalian Phenotype Analysis – rare Duplications (<1.0%) 26

Table S14: Gene Ontology – ALL rare CNVs (<1.0%) 27

Table S15: Gene Ontology – rare Deletions (<1.0%) 28

Table S16: Gene Ontology – rare Duplications (<1.0%) 29

Table S17: GSEA/MSigDB – ALL rare CNVs (<1.0%) 30

Table S18: GSEA/ MSigDB – rare Deletions (<1.0%) 31

Table S19: GSEA/ MSigDB – rare Duplications (<1.0%) 32

Mouse gene expression profiling of developing heart and pharyngeal arches at day E9.5

Wild type mice maintained congenic in the Swiss Webster background were used for mouse expression studies. To obtain enough RNA for microarray hybridization experiments, micro-dissected pharyngeal arches and heart tubes from eighteen wild type embryos at E9.5 (19 - 21 somites pairs) were pooled in groups of six. At least three microarrays were performed per embryonic tissue. The tissue was homogenized in Buffer RLT (QIAGEN). Total RNA was isolated with the RNeasy Micro Kit according to the manufacturer's protocol. Quality and quantity of total RNA were determined using an Agilent 2100 Bioanalyzer (Agilent) and an ND-1000 Spectrophotometer (NanoDrop), respectively. Biotinylated single-stranded cDNA targets were amplified from 100 nanograms (ng) starting total RNA using the Ovation RNA Amplification System V2 and FLOvation cDNA Biotin Module V2 (NuGEN). A total of 3.75 mg of cDNA from the last step was hybridized to the GeneChip Test3 array (Affymetrix) to test the quality of the labeled target. Nucleic acid samples that passed quality control were then hybridized to the Affymetrix Mouse GeneST 1.0. Hybridization, washing, staining and scanning were performed in the Genomics Core at Einstein (http://www.einstein.yu.edu/genetics/CoreFacilities.aspx?id=23934) according to the Affymetrix manual.

The resulting microarray data was then analyzed with oligo and limma (Linear Models for Microarray Analysis), which are two libraries present in the R package. Briefly, the original Affymetrix GeneChip CEL files generated by the Genomics Core were imported and summarized at the probe set level or at the transcript cluster level using the oligonucleotide library. Robust multi-array average (RMA) method was used to normalize, background correct and summarize.

The data were converted to logarithmic scale and the significance analysis was performed using the two-sample t-test with a cut-off of unadjusted P-value of 0.05. The statistical analysis was performed using the Limma package.

Mouse transcripts were compiled by tissue type and converted to human gene designations. Genes were then ranked by expression level to identify the top 25% of genes with the highest expression in each tissue. The “Heart_High” list contains the top quartile of genes (n = 3,872) expressed in the developing mouse heart at day E9.5 (Supplementary appendix 1). The “PA_High” list contains the top quartile of genes (n = 3,873) expressed in the pharyngeal apparatus at day E9.5 (Supplementary appendix 2).

<0.1% Rare CNV Burden

Various frequency cutoffs have been used to define rare CNVs in other studies, therefore a more stringent CNV frequency threshold of <0.1% was also employed to further examine rare CNV burden in 22q11DS individuals. A total of 3,753 CNVs (28.20% of all 22q11DS CNVs), 3,280 deletions and 473 duplications, occurred at a frequency <0.1% in the healthy population control cohort (nstd100 (Coe et al. 2014)). The CNV burden analyses were repeated using this subset of rare CNVs (Table S1). There was no significant difference in the number (3.98±2.53 vs 3.94±2.37, p = 0.94), or the mean size (56.09±88.66 kb vs 56.78±89.24 kb, p = 0.64) of rare CNVs in 22q11DS individuals with CHDs compared to those with a normal heart and aortic arch (Table S1a). The results of the rare deletion (Table S1b) and rare duplication (Table S1c) analyses were consistent and showed that CNV burden, both in terms of number and size of <0.1% rare CNVs, was equivalent in CHD cases and controls with 22q11DS.

The CNV map and rare CNV burden

Since there was no difference in burden at either CNV frequency, the CNV map recently published by Zarrei et al. (Zarrei et al. 2015) was also utilized to fully assess rare CNV burden in 22q11DS. The CNV map contains the copy number variable regions (CNVRs) identified in healthy phenotypically normal individuals from 26 different studies, and thus can provide a comprehensive indication of CNV frequency in the general population (Zarrei et al. 2015). The CNV map does not contain the control cohort (nstd100 (Coe et al. 2014)) that was used to identify rare CNVs. All 13,310 autosomal CNVs detected in the 22q11DS cohort were included in the various CNV map analyses.

The 12,095 deletions and 1,215 duplications detected in the 22q11DS cohort were first compared to the inclusive CNV map by CN type. The majority of the 22q11DS deletions overlapped with CNVR losses, as only ~7% of deletions in CHD cases or controls were outside of the inclusive CNV map (Table S2). In contrast, ~45% of 22q11DS duplications were outside the inclusive CNV map (Table S2), indicating that over half of the duplications detected in 22q11DS subjects have not been seen in healthy controls. To address this possibility and determine if 22q11DS CNVs outside the CNV map were indeed rare, CNV frequency was assessed using the published control cohort (Coe et al. 2014). Nearly all deletions, as opposed to ~86% of duplications, outside of the CNV map were observed at a frequency <1.0% in the control cohort (Fig. S1; Table S2).

The discrepancies between deletions and duplications could be due to the paucity of CNVR gains in the CNV map (3,132 CNVR gains as opposed to 23,438 CNVR losses) (Zarrei et al.

2015). Therefore, the 22q11DS deletions and duplications were also analyzed with respect to all variants in the inclusive CNV map (CNVR gains and CNVR losses combined). The combination of all CNVRs had little effect on deletions, whereas the number of duplications outside the inclusive CNV map decreased to ~20% (Fig. S2; Table S3).

Additional CNV map analyses were performed using the stringent CNV map (Fig. S3-S4; Table S4-S5). The overall number of 22q11DS CNVs outside the CNV map increased since fewer 22q11DS CNVs overlapped with stringent CNVRs, the results of the stringent CNV map by CN type (Fig. S3; Table S4) and all CNVRs (Fig. S4; Table S5) analyses were proportionally consistent with the inclusive CNV map. Interestingly, the percentage of outside CNVs that were also rare in the published control cohort did not change even though the number of CNVs outside the stringent map was greater than the inclusive map.

The 22q11DS CNVs that were absent from the CNV map and rare in the published control cohort were classified as “ultra rare”. These CNVs were of particular interest and additional analyses were performed with the “ultra rare” CNVs from each CNV map comparison to investigate if perhaps 22q11DS individuals with CHDs carried a greater burden of “ultra rare” CNVs. The mean number and size of “ultra rare” CNVs carried in each subject was evaluated to assess the “ultra rare” CNV load. Separate burden analyses were performed using all “ultra rare” CNVs, the “ultra rare” deletions and “ultra rare” duplications; this process was repeated with the “ultra rare” CNVs from each of the four CNV map comparisons. The burden analyses revealed that there was no significant difference in the number or mean size of “ultra rare”

CNVs detected in 22q11DS individuals with CHDs compared to those with normal heart anatomy (Table S6-S9).

References

Coe BP et al. (2014) Refining analyses of copy number variation identifies specific genes associated with developmental delay Nature genetics 46:1063-1071 doi:10.1038/ng.3092

Zarrei M, MacDonald JR, Merico D, Scherer SW (2015) A copy number variation map of the human genome Nat Rev Genet 16:172-183 doi:10.1038/nrg3871

Figure S1

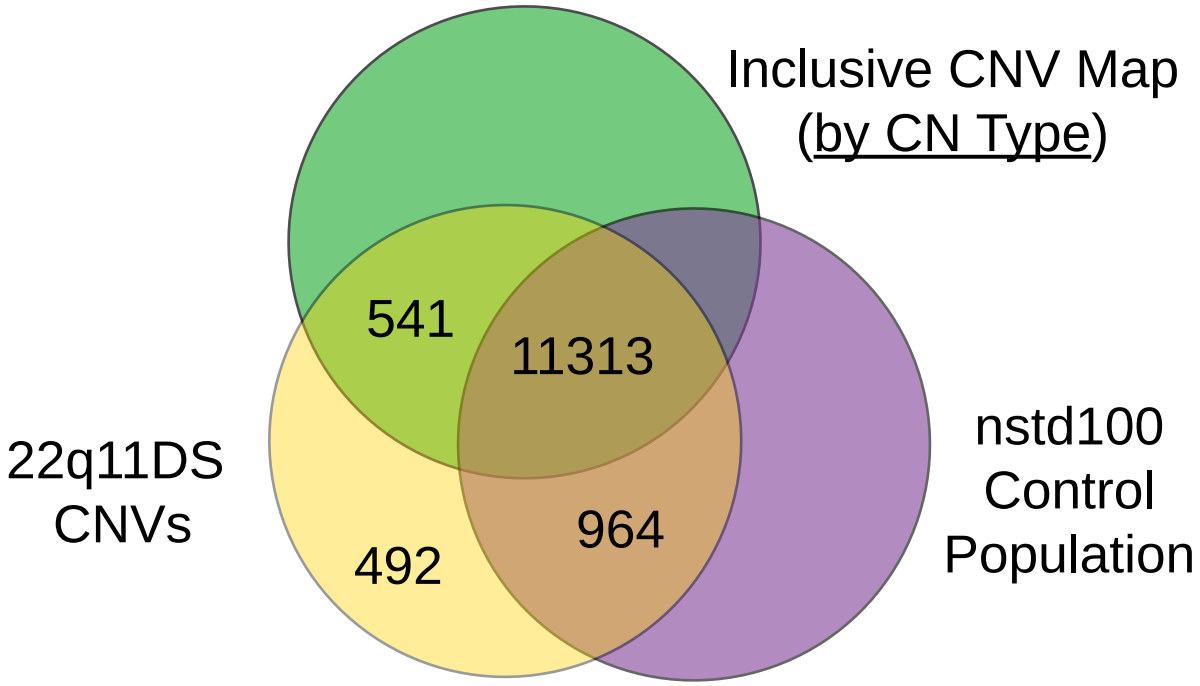


Figure S2

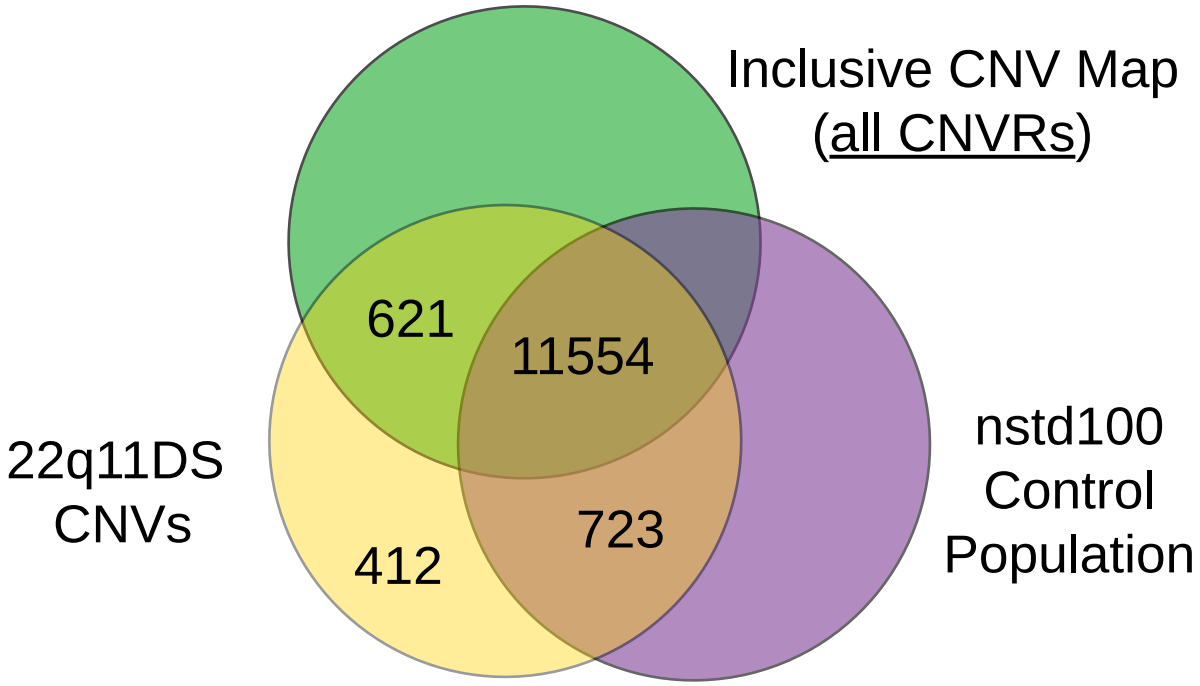


Figure S3

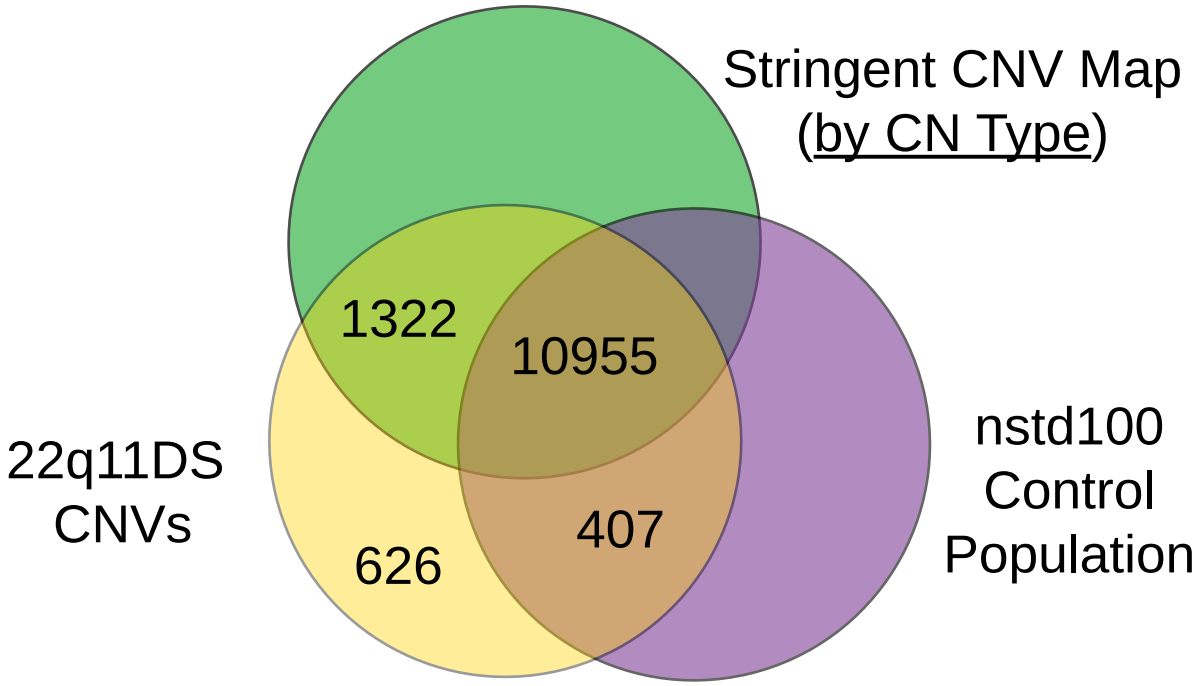


Figure S4

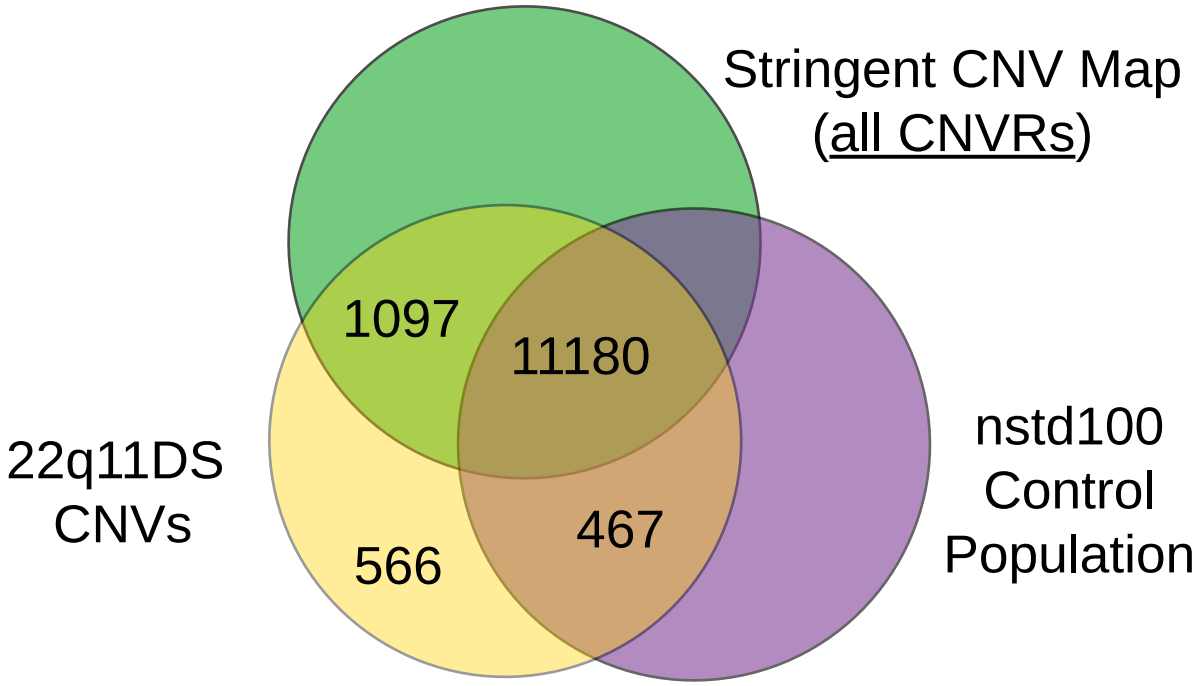
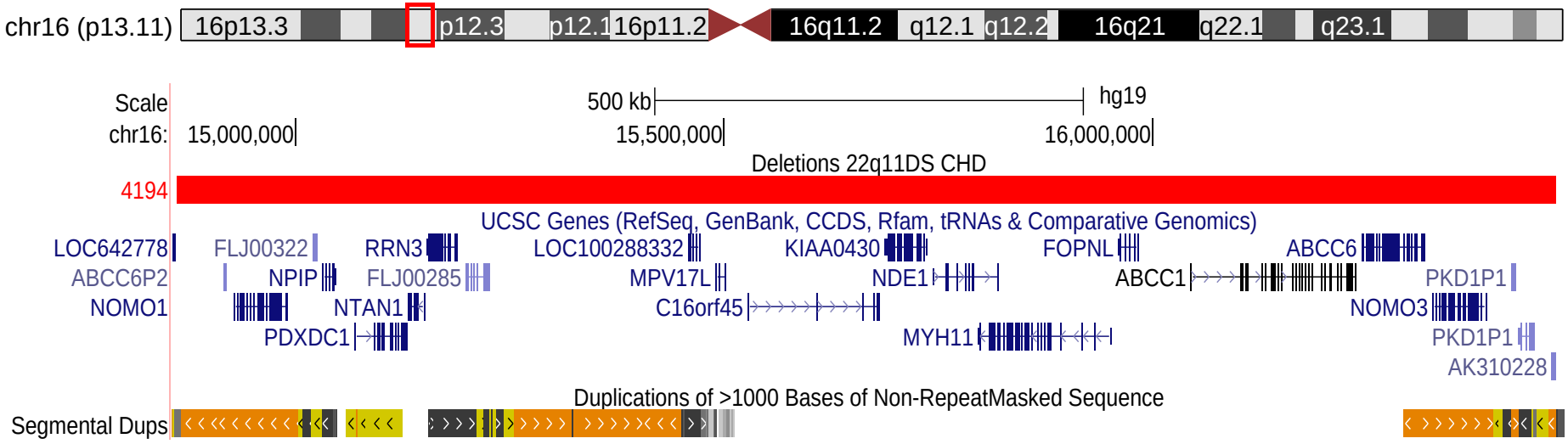


Figure S5


chr16 (p13.11)
16p13.3
p12.3
p12.1
16p11.2
16q11.2
q12.1
q12.2
16q21
q22.1
q23.1
Scale
chr16:
15,000,000
500 kb
15,500,000
hg19
16,000,000
Deletions 22q11DS CHD
4194
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
LOC642778
FLJ00322
RRN3
LOC100288332
KIAA0430
FOPNL
ABCC6
ABCC6P2
NPIP
FLJ00285
MPV17L
NDE1
ABCC1
PKD1P1
NOMO1
NTAN1
C16orf45
NOMO3
PDXDC1
MYH11
PKD1P1
AK310228
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups

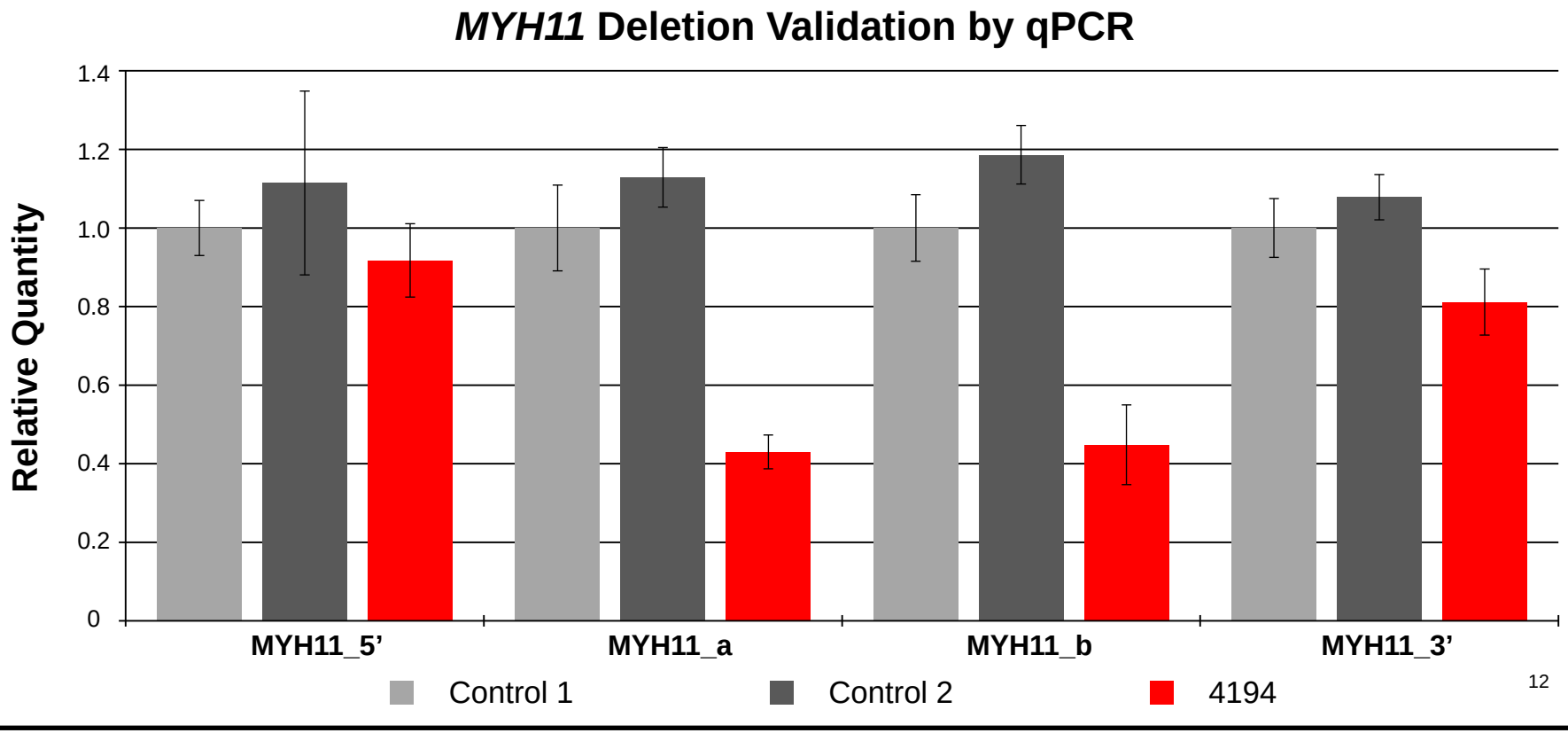
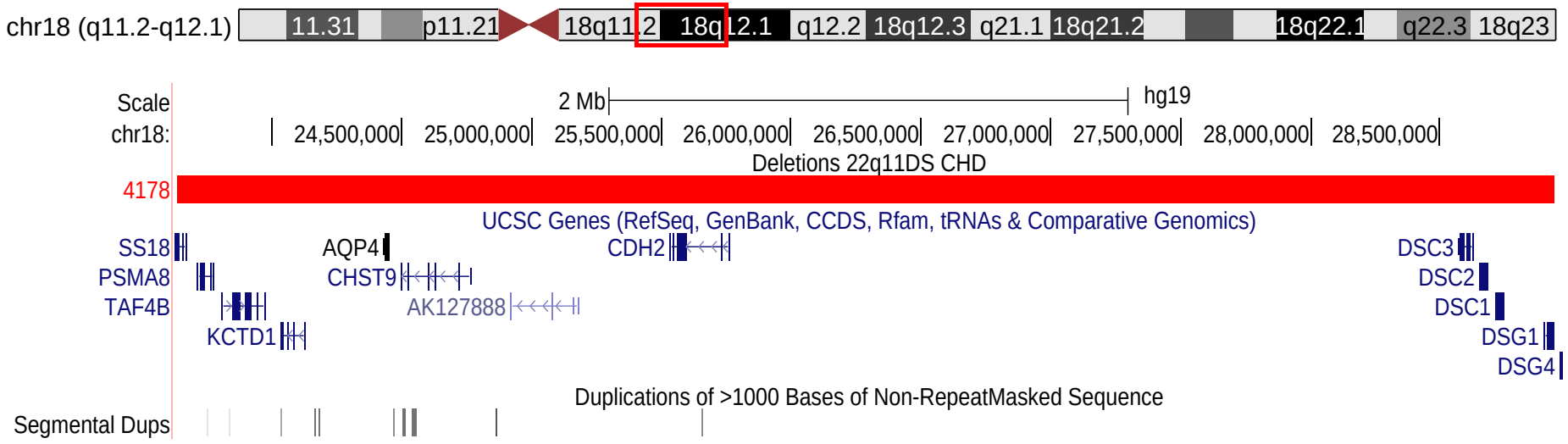

MYH11 Deletion Validation by qPCR
Relative Quantity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
MYH11_5'
MYH11_a
MYH11_b
MYH11_3'
Control 1
Control 2
4194

Figure S6


chr18 (q11.2-q12.1)
11.31
p11.21
18q11.2
18q12.1
q12.2
18q12.3
q21.1
18q21.2
18q22.1
q22.3
18q23
Scale
2 Mb
hg19
chr18:
24,500,000
25,000,000
25,500,000
26,000,000
26,500,000
27,000,000
27,500,000
28,000,000
28,500,000
Deletions 22q11DS CHD
4178
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
SS18
AQP4
CDH2
DSC3
PSMA8
CHST9
DSC2
TAF4B
AK127888
DSC1
KCTD1
DSG1
DSG4
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups

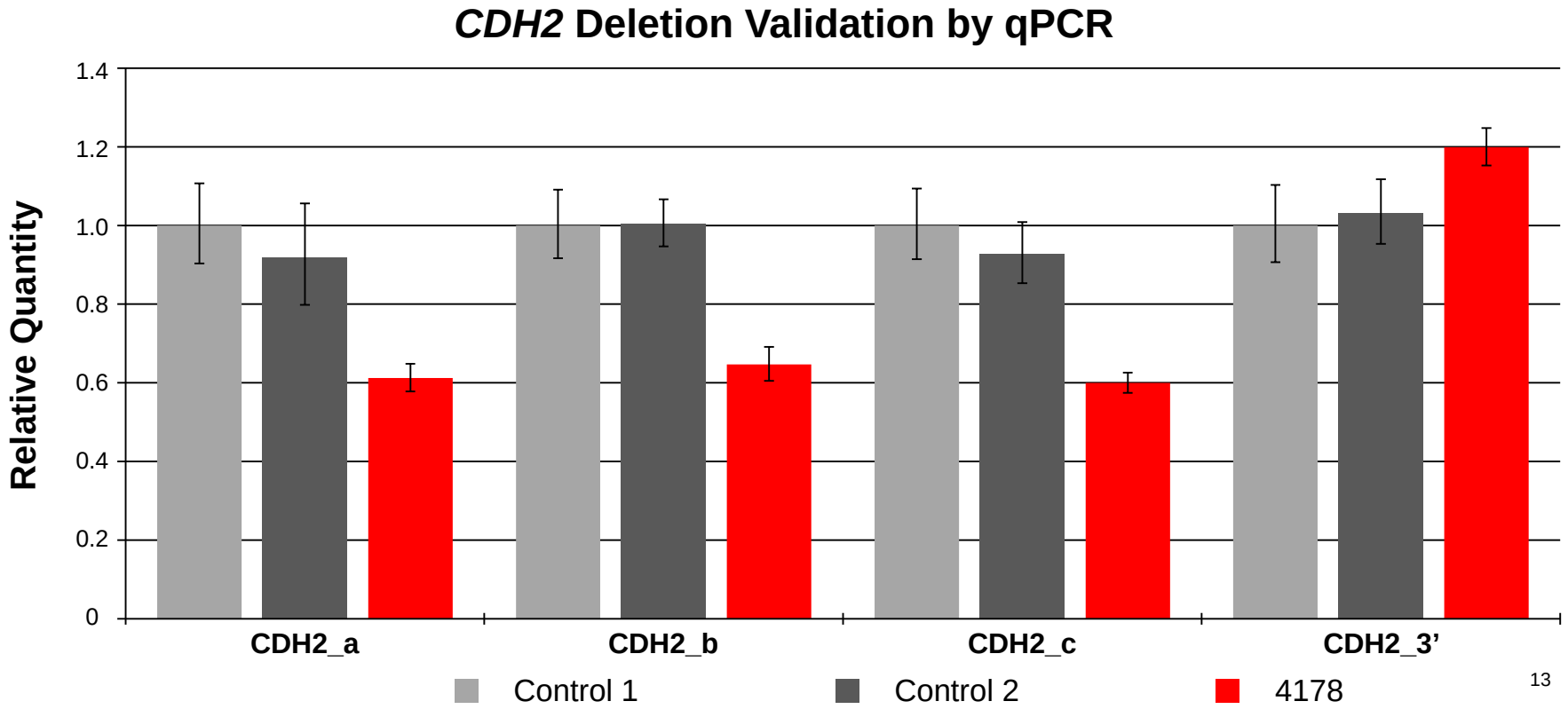

CDH2 Deletion Validation by qPCR
Relative Quantity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
CDH2_a
CDH2_b
CDH2_c
CDH2_3'
Control 1
Control 2
4178

Figure S7

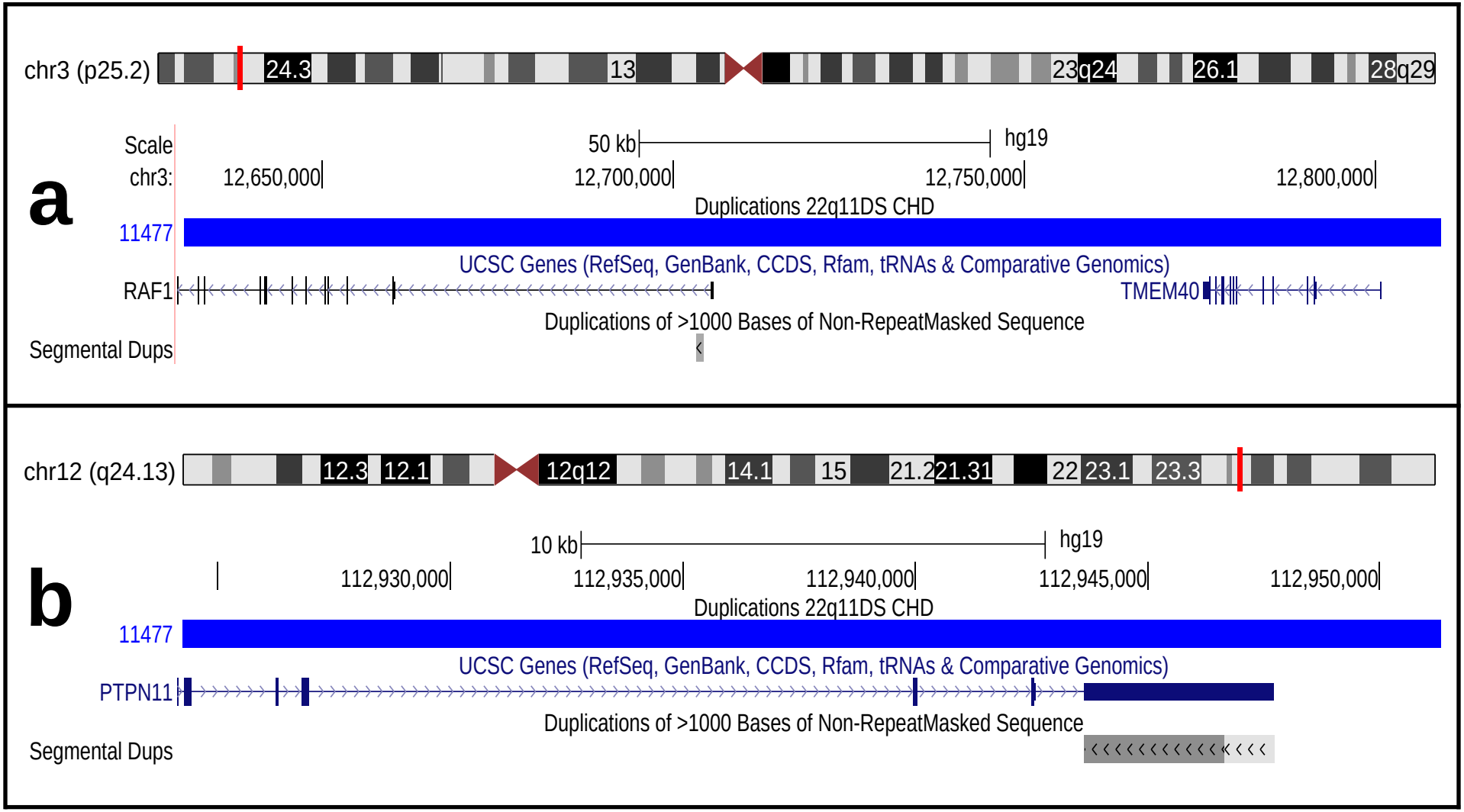

chr3 (p25.2)
24.3
13
23q24
26.1
28q29
a
Scale
chr3:
50 kb
hg19
12,650,000
12,700,000
12,750,000
12,800,000
Duplications 22q11DS CHD
11477
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
RAF1
TMEM40
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups
chr12 (q24.13)
12.3
12.1
12q12
14.1
15
21.2
21.31
22
23.1
23.3
b
10 kb
hg19
112,930,000
112,935,000
112,940,000
112,945,000
112,950,000
Duplications 22q11DS CHD
11477
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
PTPN11
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups

Figure S8

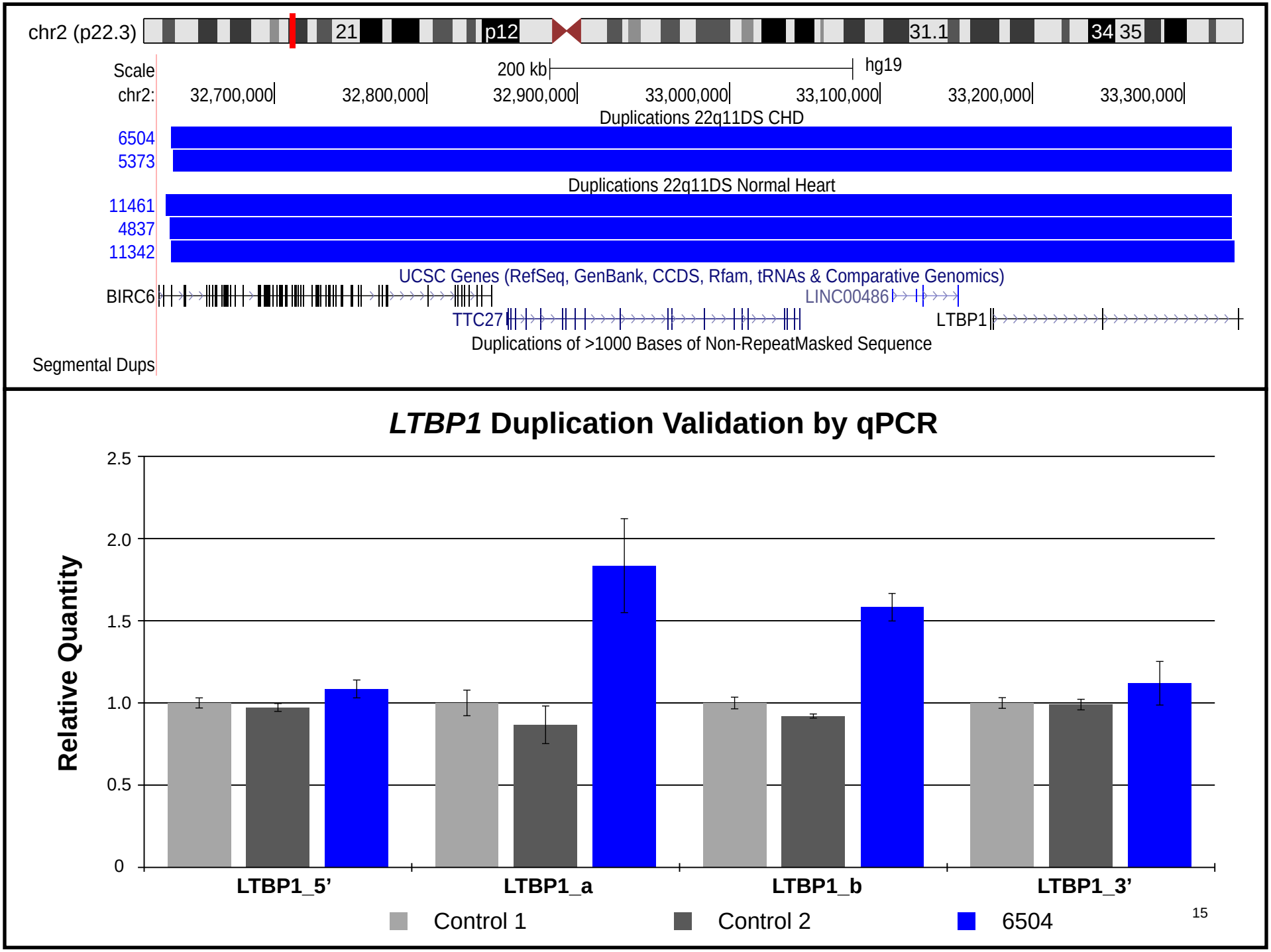

chr2 (p22.3)
21
p12
31.1
34
35
Scale
200 kb
hg19
chr2:
32,700,000
32,800,000
32,900,000
33,000,000
33,100,000
33,200,000
33,300,000
Duplications 22q11DS CHD
6504
5373
Duplications 22q11DS Normal Heart
11461
4837
11342
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
BIRC6
LINC00486
TTC27
LTBP1
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups
LTBP1 Duplication Validation by qPCR
Relative Quantity
2.5
2.0
1.5
1.0
0.5
0
LTBP1_5'
LTBP1_a
LTBP1_b
LTBP1_3'
Control 1
Control 2
6504
15

Table S1: <0.1% Rare CNV burden

A: ALL Rare CNVs (<0.1%)

	CHD	No CHD	pValue
# of subjects with Rare CNVs	586	330	0.57 [1]
% with Rare CNVs	96.54%	97.35%	
Mean # of Rare CNVs per subject	3.98	3.94	0.94 [2]
±StdDev	±2.53	±2.37	
Mean Rare CNV length (kb) per subject	56.09	56.78	0.63 [2]
±StdDev (kb)	±88.66	±89.24	
# with ≥1 Rare CNV ≥500 kb	44	24	1.00 [1]

B: Rare Deletions (<0.1%)

	CHD	No CHD	pValue
# of subjects with Rare CNVs	577	321	0.88 [1]
% with Rare CNVs	95.06%	94.69%	
Mean # of Rare CNVs per subject	3.46	3.48	0.52 [2]
±StdDev	±2.37	±2.17	
Mean Rare CNV length (kb) per subject	31.56	34.52	0.78 [2]
±StdDev (kb)	±55.41	±68.42	
# with ≥1 Rare CNV ≥500 kb	6	8	0.16 [1]

C: Rare Duplications (<0.1%)

	CHD	No CHD	pValue
# of subjects with Rare CNVs	224	116	0.44 [1]
% with Rare CNVs	36.90%	34.22%	
Mean # of Rare CNVs per subject	0.52	0.47	0.42 [2]
±StdDev	±0.79	±0.76	
Mean Rare CNV length (kb) per subject	90.11	67.10	0.33 [2]
±StdDev (kb)	±221.43	±152.17	
# with ≥1 Rare CNV ≥500 kb	38	16	0.38 [1]

CHD n=607; no CHD n=339

[1] two-tailed Fisher's exact test

[2] Wilcoxon Rank Sum

Table S2: 22q11DS CNVs outside Inclusive CNV map: by CN type *

		CNVs outside Inclusive CNV map		outside Inclusive CNV map & RARE (<1.0%)		
		#	% (of total)	#	% (of outside)	% (of all Rare)
All CNVs	Cohort Total	1456	10.94%	1338	91.90%	18.54%
	Cases	944	10.95%	870	92.16%	18.73%
	Controls	512	10.91%	468	91.41%	18.20%
Deletions	Cohort Total	905	7.48%	862	95.25%	13.28%
	Cases	588	7.52%	558	94.90%	13.39%
	Controls	317	7.42%	304	95.90%	13.09%
Duplications	Cohort Total	551	45.35%	476	86.39%	65.38%
	Cases	356	44.78%	312	87.64%	65.14%
	Controls	195	46.43%	164	84.10%	65.86%

* CNVR gains & CNVR losses analyzed separately

Table S3: 22q11DS CNVs outside Inclusive CNV map: all CNVRs ^

		CNVs outside Inclusive CNV map		outside Inclusive CNV map & RARE (<1.0%)		
		#	% (of total)	#	% (of outside)	% (of all Rare)
All CNVs	Cohort Total	1135	8.53%	1042	91.81%	14.44%
	Cases	724	8.40%	667	92.13%	14.36%
	Controls	411	8.76%	375	91.24%	14.59%
Deletions	Cohort Total	879	7.27%	836	95.11%	12.88%
	Cases	570	7.29%	540	94.74%	12.96%
	Controls	309	7.23%	296	95.79%	12.75%
Duplications	Cohort Total	256	21.07%	206	80.47%	28.30%
	Cases	154	19.37%	127	82.47%	26.51%
	Controls	102	24.29%	79	77.45%	31.73%

^ CNVR gains & CNVR losses combined

Table S4: 22q11DS CNVs outside Stringent CNV map: by CN type *

		CNVs outside Stringent CNV map		outside Stringent CNV map & RARE (<1.0%)		
		#	% (of total)	#	% (of outside)	% (of all Rare)
All CNVs	Cohort Total	1948	14.64%	1791	91.94%	24.82%
	Cases	1244	14.43%	1150	92.44%	24.75%
	Controls	704	15.01%	641	91.05%	24.93%
Deletions	Cohort Total	1279	10.57%	1225	95.78%	18.88%
	Cases	814	10.40%	776	95.33%	18.62%
	Controls	465	10.89%	449	96.56%	19.34%
Duplications	Cohort Total	669	55.06%	566	84.60%	77.75%
	Cases	430	54.09%	374	86.98%	78.08%
	Controls	239	56.90%	192	80.33%	77.11%

* CNVR gains & CNVR losses analyzed separately

Table S5: 22q11DS CNVs outside Stringent CNV map: all CNVRs ^

		CNVs outside Stringent CNV map		outside Stringent CNV map & RARE (<1.0%)		
		#	% (of total)	#	% (of outside)	% (of all Rare)
All CNVs	Cohort Total	1135	8.53%	1042	91.81%	14.44%
	Cases	724	8.40%	667	92.13%	14.36%
	Controls	411	8.76%	375	91.24%	14.59%
Deletions	Cohort Total	879	7.27%	836	95.11%	12.88%
	Cases	570	7.29%	540	94.74%	12.96%
	Controls	309	7.23%	296	95.79%	12.75%
Duplications	Cohort Total	256	21.07%	206	80.47%	28.30%
	Cases	154	19.37%	127	82.47%	26.51%
	Controls	102	24.29%	79	77.45%	31.73%

^ CNVR gains & CNVR losses combined

Table S6: ultra Rare CNV burden: <1.0% and outside Inclusive map (by CN type)

A: ALL ultra Rare CNVs

	CHD	No CHD	pValue
# of subjects with Rare CNVs	446	244	0.65 [1]
% with Rare CNVs	73.48%	71.98%	
Mean # of Rare CNVs per subject	1.43	1.38	0.55 [2]
±StdDev	±1.30	±1.27	
Mean Rare CNV length (kb) per subject	60.69	47.71	0.08 [2]
±StdDev (kb)	±102.03	±75.76	
# with ≥1 Rare CNV ≥500 kb	22	6	0.11 [1]

B: ultra Rare Deletions

	CHD	No CHD	pValue
# of subjects with Rare CNVs	347	196	0.89 [1]
% with Rare CNVs	57.17%	57.82%	
Mean # of Rare CNVs per subject	0.92	0.90	0.93 [2]
±StdDev	±1.09	±0.98	
Mean Rare CNV length (kb) per subject	22.60	20.37	0.83 [2]
±StdDev (kb)	±36.35	±30.24	
# with ≥1 Rare CNV ≥500 kb	0	0	1.00 [1]

C: ultra Rare Duplications

	CHD	No CHD	pValue
# of subjects with Rare CNVs	224	119	0.62 [1]
% with Rare CNVs	36.90%	35.10%	
Mean # of Rare CNVs per subject	0.51	0.48	0.61 [2]
±StdDev	±0.78	±0.76	
Mean Rare CNV length (kb) per subject	63.44	42.35	0.35 [2]
±StdDev (kb)	±151.52	±85.52	
# with ≥1 Rare CNV ≥500 kb	22	6	0.11 [1]

CHD n=607; no CHD n=339

[1] two-tailed Fisher's exact test

[2] Wilcoxon Rank Sum

Table S7: ultra Rare CNV burden: <1.0% and outside Inclusive map (all CNVRs combined)

A: ALL ultra Rare CNVs

	CHD	No CHD	pValue
# of subjects with Rare CNVs	393	216	0.78 [1]
% with Rare CNVs	64.74%	63.72%	
Mean # of Rare CNVs per subject	1.10	1.11	0.93 [2]
±StdDev	±1.13	±1.12	
Mean Rare CNV length (kb) per subject	29.28	25.82	0.47 [2]
±StdDev (kb)	±39.32	±35.44	
# with ≥1 Rare CNV ≥500 kb	0	0	1.00 [1]

B: ultra Rare Deletions

	CHD	No CHD	pValue
# of subjects with Rare CNVs	338	192	0.79 [1]
% with Rare CNVs	55.68%	56.64%	
Mean # of Rare CNVs per subject	0.89	0.87	0.87 [2]
±StdDev	±1.07	±0.97	
Mean Rare CNV length (kb) per subject	21.74	18.68	0.80 [2]
±StdDev (kb)	±35.40	±26.39	
# with ≥1 Rare CNV ≥500 kb	0	0	1.00 [1]

C: ultra Rare Duplications

	CHD	No CHD	pValue
# of subjects with Rare CNVs	110	66	0.60 [1]
% with Rare CNVs	18.12%	19.47%	
Mean # of Rare CNVs per subject	0.21	0.23	0.71 [2]
±StdDev	±0.47	±0.52	
Mean Rare CNV length (kb) per subject	13.38	13.31	0.81 [2]
±StdDev (kb)	±35.20	±36.43	
# with ≥1 Rare CNV ≥500 kb	0	0	1.00 [1]

CHD n=607; no CHD n=339

[1] two-tailed Fisher's exact test

[2] Wilcoxon Rank Sum

Table S8: ultra Rare CNV burden: <1.0% and outside Stringent map (by CN type)

A: ALL ultra Rare CNVs

	CHD	No CHD	pValue
# of subjects with Rare CNVs	493	271	0.67 [1]
% with Rare CNVs	81.22%	79.94%	
Mean # of Rare CNVs per subject	1.89	1.89	0.90 [2]
±StdDev	±1.57	±1.56	
Mean Rare CNV length (kb) per subject	67.83	62.25	0.17 [2]
±StdDev (kb)	±99.52	±92.86	
# with ≥1 Rare CNV ≥500 kb	29	15	0.87 [1]

B: ultra Rare Deletions

	CHD	No CHD	pValue
# of subjects with Rare CNVs	422	234	0.88 [1]
% with Rare CNVs	69.52%	69.03%	
Mean # of Rare CNVs per subject	1.28	1.32	0.56 [2]
±StdDev	±1.29	±1.26	
Mean Rare CNV length (kb) per subject	31.32	30.64	0.67 [2]
±StdDev (kb)	±43.72	±46.89	
# with ≥1 Rare CNV ≥500 kb	1	3	0.13 [1]

C: ultra Rare Duplications

	CHD	No CHD	pValue
# of subjects with Rare CNVs	254	132	0.41 [1]
% with Rare CNVs	41.85%	38.94%	
Mean # of Rare CNVs per subject	0.62	0.57	0.42 [2]
±StdDev	±0.86	±0.84	
Mean Rare CNV length (kb) per subject	74.18	57.71	0.21 [2]
±StdDev (kb)	±156.43	±125.54	
# with ≥1 Rare CNV ≥500 kb	28	12	0.50 [1]

CHD n=607; no CHD n=339

[1] two-tailed Fisher's exact test

[2] Wilcoxon Rank Sum

Table S9: ultra Rare CNV burden: <1.0% and outside Stringent map (all CNVRs combined)

A: ALL ultra Rare CNVs

	CHD	No CHD	pValue
# of subjects with Rare CNVs	468	258	0.75 [1]
% with Rare CNVs	77.10%	76.11%	
Mean # of Rare CNVs per subject	1.61	1.64	0.94 [2]
±StdDev	±1.39	±1.42	
Mean Rare CNV length (kb) per subject	41.06	39.73	0.39 [2]
±StdDev (kb)	±47.15	±51.26	
# with ≥1 Rare CNV ≥500 kb	0	2	0.13 [1]

B: ultra Rare Deletions

	CHD	No CHD	pValue
# of subjects with Rare CNVs	422	234	0.88 [1]
% with Rare CNVs	69.52%	69.03%	
Mean # of Rare CNVs per subject	1.26	1.31	0.56 [2]
±StdDev	±1.26	±1.25	
Mean Rare CNV length (kb) per subject	30.96	29.91	0.63 [2]
±StdDev (kb)	±42.25	±44.65	
# with ≥1 Rare CNV ≥500 kb	0	2	0.13 [1]

C: ultra Rare Duplications

	CHD	No CHD	pValue
# of subjects with Rare CNVs	163	91	1.00 [1]
% with Rare CNVs	26.85%	26.84%	
Mean # of Rare CNVs per subject	0.35	0.33	0.95 [2]
±StdDev	±0.64	±0.60	
Mean Rare CNV length (kb) per subject	26.15	21.99	0.80 [2]
±StdDev (kb)	±60.45	±50.47	
# with ≥1 Rare CNV ≥500 kb	0	0	1.00 [1]

CHD n=607; no CHD n=339

[1] two-tailed Fisher's exact test

[2] Wilcoxon Rank Sum

Table S10: Validated CNVs (GRCh37/hg19 genome build)

Sample	Phenotype	Chr	Start (bp)	End (bp)	Size	CNV Type	# of Probes	Freq in nstd100 Controls	Inherited	Gene(s) of Interest
3935	CHD	9	80,063,136	80,086,725	23,589	Deletion	23	0.009%	Yes	*GNA14*
3935	CHD	17	34,816,256	36,295,000	1,478,744	Duplication	996	0.009%	Yes	17q12
4160	CHD	3	7,617,670	8,156,424	538,754	Duplication	503	0.000%	Not tested	*GRM7*
4165	CHD	21	18,660,571	19,220,317	559,746	Duplication	374	0.027%	Not tested	*CXADR*
4178	CHD	18	23,640,045	28,940,607	5,300,562	Deletion	3360	0.000%	Not tested	*CDH2*
4194	CHD	16	14,861,832	16,470,166	1,608,334	Deletion	679	0.053%	Yes	*MYH11*
4212	No CHD	9	9,798,243	9,822,054	23,811	Deletion	57	0.320%	Yes	*PTPRD*
4251	No CHD	9	9,847,865	9,964,989	117,124	Deletion	144	0.044%	Yes	*PTPRD*
5387	No CHD	9	8,748,942	8,809,925	60,983	Deletion	61	0.009%	Not tested	*PTPRD*
5402	CHD	13	110,592,548	111,187,895	595,347	Duplication	570	0.009%	Not tested	*COL4A1*
5442	CHD	21	35,722,995	35,903,942	180,947	Duplication	109	0.187%	Yes	*RCAN1*
5456	No CHD	10	79,250,577	79,367,542	116,965	Deletion	98	0.000%	Not tested	*KCNMA1*
5471	CHD	2	27,263,122	27,650,213	387,091	Duplication	158	0.000%	Not tested	*EMILIN1, TRIM54*
5482	CHD	17	72,629,123	73,410,780	781,657	Duplication	382	0.000%	Not tested	*GRB2*
5496	No CHD	14	73,018,692	73,186,471	167,779	Duplication	125	0.000%	Not tested	*DPF3*
6501	CHD	5	179,615,422	179,877,247	261,825	Duplication	175	0.018%	Not tested	*MAPK9*
6501	CHD	16	82,714,047	82,764,168	50,121	Deletion	47	0.018%	Not tested	*CDH13*
6502	CHD	14	64,034,429	65,013,538	979,109	Duplication	184	0.000%	Not tested	*MTHFD1*
6504	CHD	2	32,631,641	33,331,779	700,138	Duplication	453	0.240%	Not tested	*LTBP1*
6516	CHD	9	119,413,509	119,659,873	246,364	Deletion	267	0.018%	Not tested	*ASTN2;TRIM32*
6700	CHD	16	83,308,001	83,349,855	41,854	Duplication	59	0.053%	Yes	*CDH13*
6963	CHD	21	18,735,222	19,133,564	398,342	Duplication	295	0.027%	Not tested	*CXADR*
7462	CHD	1	228,799,656	228,954,712	155,056	Duplication	86	0.009%	Not tested	*RHOU*
7542	No CHD	10	53,376,285	53,404,882	28,597	Deletion	18	0.009%	Yes	*PRKG1*

Table S11: Mammalian Phenotype - All rare CNVs (none are significant - top 25 are shown)

MP ID	MP Term Description	CHD	No CHD	p Value	FDR
MP:0003366	abnormal circulating glucocorticoid level	17	0	0.00059	1
MP:0003963	abnormal corticosterone level	17	0	0.00059	1
MP:0005345	abnormal circulating corticosterone level	17	0	0.00059	1
MP:0005437	abnormal glycogen level	28	3	0.00177	1
MP:0005438	abnormal glycogen homeostasis	28	3	0.00177	1
MP:0001186	pigmentation phenotype	27	3	0.00172	1
MP:0005559	increased circulating glucose level	25	3	0.00430	1
MP:0001944	abnormal pancreas morphology	20	2	0.00638	1
MP:0005291	abnormal glucose tolerance	23	3	0.00689	1
MP:0001560	abnormal circulating insulin level	26	4	0.01056	1
MP:0005440	increased glycogen level	16	1	0.00876	1
MP:0000559	abnormal femur morphology	22	3	0.01060	1
MP:0003856	abnormal hindlimb stylopod morphology	22	3	0.01060	1
MP:0004686	decreased length of long bones	22	3	0.01060	1
MP:0000062	increased bone mineral density	11	0	0.00968	1
MP:0002665	decreased circulating corticosterone level	11	0	0.00968	1
MP:0003368	decreased circulating glucocorticoid level	11	0	0.00968	1
MP:0005598	decreased ventricle muscle contractility	11	0	0.00968	1
MP:0003109	short femur	18	2	0.01642	1
MP:0002106	abnormal muscle physiology	138	55	0.01843	1
MP:0001194	dermatitis	10	0	0.01699	1
MP:0003383	abnormal gluconeogenesis	14	1	0.01485	1
MP:0005293	impaired glucose tolerance	14	1	0.01485	1
MP:0000849	abnormal cerebellum morphology	102	38	0.02181	1
MP:0002551	abnormal blood coagulation	26	5	0.02142	1

Table S12: Mammalian Phenotype - rare Deletions (none are significant - top 25 are shown)

MP ID	MP Term Description	CHD	No CHD	p Value	FDR
MP:0000003	abnormal adipose tissue morphology	33	15	0.54010	1
MP:0000008	increased white adipose tissue amount	1	0	1	1
MP:0000010	abnormal abdominal fat pad morphology	6	2	0.71851	1
MP:0000015	abnormal ear pigmentation	1	0	1	1
MP:0000018	small ears	1	0	1	1
MP:0000019	thick ears	1	0	1	1
MP:0000022	abnormal ear shape	1	0	1	1
MP:0000023	abnormal ear distance/ position	1	0	1	1
MP:0000024	lowered ear position	1	0	1	1
MP:0000026	abnormal inner ear morphology	11	8	0.63085	1
MP:0000031	abnormal cochlea morphology	11	7	0.80684	1
MP:0000032	cochlear degeneration	4	2	1	1
MP:0000034	abnormal inner ear vestibule morphology	2	1	1	1
MP:0000035	abnormal membranous labyrinth morphology	11	8	0.63085	1
MP:0000042	abnormal organ of Corti morphology	11	7	0.80684	1
MP:0000043	organ of Corti degeneration	4	2	1	1
MP:0000045	abnormal hair cell morphology	9	4	0.77997	1
MP:0000048	abnormal stria vascularis morphology	2	1	1	1
MP:0000049	abnormal middle ear morphology	1	0	1	1
MP:0000060	delayed bone ossification	1	1	1	1
MP:0000061	fragile skeleton	1	0	1	1
MP:0000062	increased bone mineral density	4	0	0.30302	1
MP:0000063	decreased bone mineral density	144	74	0.52067	1
MP:0000065	abnormal bone marrow cavity morphology	2	2	0.62080	1
MP:0000069	kyphoscoliosis	0	1	0.35835	1

Table S13: Mammalian Phenotype - rare Duplications (none are significant - top 25 are shown)

MP ID	MP Term Description	CHD	No CHD	p Value	FDR
MP:0002106	abnormal muscle physiology	41	6	0.00048	0.81827
MP:0000188	abnormal circulating glucose level	36	5	0.00075	0.81827
MP:0005620	abnormal muscle contractility	21	1	0.00110	0.81827
MP:0005406	abnormal heart size	28	3	0.00177	0.81827
MP:0002078	abnormal glucose homeostasis	46	9	0.00136	0.81827
MP:0003953	abnormal hormone level	43	8	0.00149	0.81827
MP:0005560	decreased circulating glucose level	24	2	0.00147	0.81827
MP:0000738	impaired muscle contractility	20	1	0.00190	0.81827
MP:0005418	abnormal circulating hormone level	37	6	0.00172	0.81827
MP:0002163	abnormal gland morphology	56	13	0.00171	0.81827
MP:0004087	abnormal muscle fiber morphology	23	2	0.00241	0.89450
MP:0005379	endocrine/exocrine gland phenotype	65	17	0.00249	0.89450
MP:0004857	abnormal heart weight	18	1	0.00314	1
MP:0000274	enlarged heart	24	3	0.00690	1
MP:0001186	pigmentation phenotype	20	2	0.00638	1
MP:0003921	abnormal heart left ventricle morphology	20	2	0.00638	1
MP:0005437	abnormal glycogen level	20	2	0.00638	1
MP:0005438	abnormal glycogen homeostasis	20	2	0.00638	1
MP:0005332	abnormal amino acid level	12	0	0.00566	1
MP:0002972	abnormal cardiac muscle contractility	16	1	0.00876	1
MP:0005140	decreased cardiac muscle contractility	16	1	0.00876	1
MP:0003795	abnormal bone structure	28	5	0.01489	1
MP:0002102	abnormal ear morphology	22	3	0.01060	1
MP:0003366	abnormal circulating glucocorticoid level	11	0	0.00968	1
MP:0003963	abnormal corticosterone level	11	0	0.00968	1

Table S14: Gene Ontology - All rare CNVs (none are significant - top 25 are shown)

GO ID	GO Term Description	GO Term Type	CHD	No CHD	p Value	FDR
GO:1901654	response to ketone	biological process	16	0	0.00101	1
GO:1902532	negative regulation of intracellular signal transduction	biological process	25	3	0.00430	1
GO:0012506	vesicle membrane	cellular component	37	7	0.00368	1
GO:0006091	generation of precursor metabolites and energy	biological process	28	4	0.00434	1
GO:0044070	regulation of anion transport	biological process	13	0	0.00588	1
GO:0044433	cytoplasmic vesicle part	cellular component	42	9	0.00630	1
GO:0030659	cytoplasmic vesicle membrane	cellular component	36	7	0.00538	1
GO:0043687	post-translational protein modification	biological process	29	5	0.00974	1
GO:0006487	protein N-linked glycosylation	biological process	22	3	0.01060	1
GO:0015081	sodium ion transmembrane transporter activity	molecular function	11	0	0.00968	1
GO:0040012	regulation of locomotion	biological process	106	39	0.01451	1
GO:0040013	negative regulation of locomotion	biological process	30	6	0.01314	1
GO:0006691	leukotriene metabolic process	biological process	10	0	0.01699	1
GO:0051896	regulation of protein kinase B signaling	biological process	10	0	0.01699	1
GO:0008238	exopeptidase activity	molecular function	14	1	0.01485	1
GO:0019318	hexose metabolic process	biological process	14	1	0.01485	1
GO:0051224	negative regulation of protein transport	biological process	14	1	0.01485	1
GO:0030336	negative regulation of cell migration	biological process	26	5	0.02142	1
GO:0051271	negative regulation of cellular component movement	biological process	26	5	0.02142	1
GO:2000146	negative regulation of cell motility	biological process	26	5	0.02142	1
GO:0030100	regulation of endocytosis	biological process	39	10	0.02147	1
GO:0008237	metallopeptidase activity	molecular function	23	4	0.02371	1
GO:0022412	cellular process involved in reproduction in multicellular organism	biological process	23	4	0.02371	1
GO:0060627	regulation of vesicle-mediated transport	biological process	46	13	0.02445	1
GO:0018196	peptidyl-asparagine modification	biological process	20	3	0.02564	1

Table S15: Gene Ontology - rare Deletions (none are significant - top 25 are shown)

GO ID	GO Term Description	GO Term Type	CHD	No CHD	p Value	FDR
GO:0030336	negative regulation of cell migration	biological process	17	1	0.00520	1
GO:0051271	negative regulation of cellular component movement	biological process	17	1	0.00520	1
GO:2000146	negative regulation of cell motility	biological process	17	1	0.00520	1
GO:0040013	negative regulation of locomotion	biological process	20	2	0.00638	1
GO:1902532	negative regulation of intracellular signal transduction	biological process	16	1	0.00876	1
GO:0006897	endocytosis	biological process	18	2	0.01642	1
GO:0043687	post-translational protein modification	biological process	18	2	0.01642	1
GO:0040012	regulation of locomotion	biological process	92	34	0.02805	1
GO:0002685	regulation of leukocyte migration	biological process	9	0	0.03060	1
GO:1901654	response to ketone	biological process	9	0	0.03060	1
GO:0030334	regulation of cell migration	biological process	90	34	0.04413	1
GO:2000145	regulation of cell motility	biological process	90	34	0.04413	1
GO:0031253	cell projection membrane	cellular component	15	2	0.04084	1
GO:0021987	cerebral cortex development	biological process	8	0	0.05630	1
GO:0010721	negative regulation of cell development	biological process	11	1	0.06535	1
GO:0051270	regulation of cellular component movement	biological process	90	36	0.07276	1
GO:0008238	exopeptidase activity	molecular function	7	0	0.05426	1
GO:0031396	regulation of protein ubiquitination	biological process	7	0	0.05426	1
GO:0032355	response to estradiol	biological process	7	0	0.05426	1
GO:1901681	sulfur compound binding	molecular function	7	0	0.05426	1
GO:0008233	peptidase activity	molecular function	31	9	0.09113	1
GO:0070011	peptidase activity, acting on L-amino acid peptides	molecular function	31	9	0.09113	1
GO:0008237	metallopeptidase activity	molecular function	16	3	0.08896	1
GO:0002221	pattern recognition receptor signaling pathway	biological process	21	5	0.09593	1
GO:0002758	innate immune response-activating signal transduction	biological process	21	5	0.09593	1

Table S16: Gene Ontology - rare Duplications (none are significant - top 25 are shown)

GO ID	GO Term Description	GO Term Type	CHD	No CHD	p Value	FDR
GO:0051051	negative regulation of transport	biological process	15	0	0.00177	1
GO:0032880	regulation of protein localization	biological process	26	3	0.00270	1
GO:0006091	generation of precursor metabolites and energy	biological process	25	3	0.00430	1
GO:0071705	nitrogen compound transport	biological process	25	3	0.00430	1
GO:0007005	mitochondrion organization	biological process	13	0	0.00588	1
GO:0044070	regulation of anion transport	biological process	12	0	0.00566	1
GO:0070201	regulation of establishment of protein localization	biological process	23	3	0.00689	1
GO:0005975	carbohydrate metabolic process	biological process	34	7	0.01163	1
GO:0055114	oxidation-reduction process	biological process	34	7	0.01163	1
GO:0032403	protein complex binding	molecular function	31	6	0.01322	1
GO:0008283	cell proliferation	biological process	28	5	0.01489	1
GO:0051223	regulation of protein transport	biological process	22	3	0.01060	1
GO:0030100	regulation of endocytosis	biological process	11	0	0.00968	1
GO:0000166	nucleotide binding	molecular function	72	23	0.01295	1
GO:1901265	nucleoside phosphate binding	molecular function	72	23	0.01295	1
GO:0009617	response to bacterium	biological process	15	1	0.01496	1
GO:0060627	regulation of vesicle-mediated transport	biological process	15	1	0.01496	1
GO:0016477	cell migration	biological process	33	7	0.01715	1
GO:0032787	monocarboxylic acid metabolic process	biological process	27	5	0.01448	1
GO:0012506	vesicle membrane	cellular component	24	4	0.01566	1
GO:0051346	negative regulation of hydrolase activity	biological process	10	0	0.01699	1
GO:0033157	regulation of intracellular protein transport	biological process	14	1	0.01485	1
GO:0042742	defense response to bacterium	biological process	14	1	0.01485	1
GO:0050863	regulation of T cell activation	biological process	14	1	0.01485	1
GO:0044723	single-organism carbohydrate metabolic process	biological process	29	6	0.01908	1

Table S17: GSEA/MSigDB Analysis - All rare CNVs (none are significant - top 25 are shown)

MSigDB Gene Set Name	CHD	No CHD	p Value	FDR
REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL	9	0	0.03060	1
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION	18	3	0.03906	1
REACTOME_GOLGI_ASSOCIATED_VESICLE_BIOGENESIS	8	0	0.05630	1
REACTOME_TRANS_GOLGI_NETWORK_VESICLE_BUDDING	8	0	0.05630	1
KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	25	6	0.05728	1
KEGG_HUNTINGTONS_DISEASE	17	3	0.05889	1
REACTOME_MEMBRANE_TRAFFICKING	11	1	0.06535	1
REACTOME_METABOLISM_OF_MRNA	11	1	0.06535	1
REACTOME_METABOLISM_OF_RNA	14	2	0.06397	1
KEGG_FOCAL_ADHESION	27	7	0.06844	1
REACTOME_EGFR_DOWNREGULATION	7	0	0.05426	1
REACTOME_MHC_CLASS_II_ANTIGEN_PRESENTATION	7	0	0.05426	1
KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	19	4	0.07740	1
REACTOME_NGF_SIGNALLING_VIA_TRKA_FROM_THE_PLASMA_MEMBRANE	19	4	0.07740	1
REACTOME_SIGNALLING_BY_NGF	26	7	0.09533	1
KEGG_PATHWAYS_IN_CANCER	44	15	0.09328	1
KEGG_INSULIN_SIGNALING_PATHWAY	23	6	0.11420	1
REACTOME_ADAPTIVE_IMMUNE_SYSTEM	50	18	0.11478	1
KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	25	7	0.13205	1
BIOCARTA_MTA3_PATHWAY	6	0	0.09367	1
REACTOME_LYSOSOME_VESICLE_BIOGENESIS	6	0	0.09367	1
REACTOME_METABOLISM_OF_NUCLEOTIDES	6	0	0.09367	1
REACTOME_AXON_GUIDANCE	27	8	0.10955	1
KEGG_GNRH_SIGNALING_PATHWAY	22	6	0.11436	1
REACTOME_RESPONSE_TO_ELEVATED_PLATELET_CYTOSOLIC_CA2_	9	1	0.10587	1

Table S18: GSEA/MSigDB Analysis - rare Deletions (none are significant - top 25 are shown)

MSigDB Gene Set Name	CHD	No CHD	p Value	FDR
REACTOME_DEVELOPMENTAL_BIOLOGY	18	4	0.11349	1
KEGG_CELL_ADHESION_MOLECULES_CAMS	15	3	0.13394	1
KEGG_CALCIUM_SIGNALING_PATHWAY	73	31	0.19393	1
REACTOME_PI3K_EVENTS_IN_ERBB2_SIGNALING	66	28	0.21385	1
REACTOME_SIGNALING_BY_ERBB2	66	28	0.21385	1
KEGG_GNRH_SIGNALING_PATHWAY	15	4	0.22915	1
KEGG_WNT_SIGNALING_PATHWAY	15	4	0.22915	1
REACTOME_PI3K_EVENTS_IN_ERBB4_SIGNALING	65	28	0.25531	1
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION	10	2	0.22967	1
KEGG_FOCAL_ADHESION	17	5	0.26154	1
KEGG_ERBB_SIGNALING_PATHWAY	74	33	0.28486	1
BIOCARTA_HER2_PATHWAY	64	28	0.30312	1
REACTOME_GRB2_EVENTS_IN_ERBB2_SIGNALING	64	28	0.30312	1
REACTOME_ADHERENS_JUNCTIONS_INTERACTIONS	12	3	0.27960	1
KEGG_ECM_RECEPTOR_INTERACTION	7	1	0.27102	1
REACTOME_ANTIGEN_PROCESSING_CROSS_PRESENTATION	7	1	0.27102	1
KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	14	4	0.32153	1
KEGG_PANCREATIC_CANCER	14	4	0.32153	1
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	14	4	0.32153	1
REACTOME_TOLL_RECEPTOR_CASCADES	14	4	0.32153	1
BIOCARTA_CTCF_PATHWAY	4	0	0.30302	1
REACTOME_POTASSIUM_CHANNELS	4	0	0.30302	1
REACTOME_SIGNALING_BY_EGFR_IN_CANCER	4	0	0.30302	1
REACTOME_SIGNALING_BY_ROBO_RECEPTOR	4	0	0.30302	1
REACTOME_SIGNALING_BY_THE_B_CELL_RECEPTOR_BCR	4	0	0.30302	1

Table S19: GSEA/MSigDB Analysis - rare Duplications (none are significant - top 25 are shown)

MSigDB Gene Set Name	CHD	No CHD	p Value	FDR
KEGG_ENDOCYTOSIS	10	0	0.01663	1
REACTOME_MEMBRANE_TRAFFICKING	9	0	0.03048	1
REACTOME_ADAPTIVE_IMMUNE_SYSTEM	31	8	0.04063	1
REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL	8	0	0.03064	1
REACTOME_SLC_MEDIATED_TRANSMEMBRANE_TRANSPORT	11	1	0.06531	1
KEGG_PENTOSE_PHOSPHATE_PATHWAY	7	0	0.05234	1
KEGG_SPLICEOSOME	7	0	0.05234	1
REACTOME_GOLGI_ASSOCIATED_VESICLE_BIOGENESIS	7	0	0.05234	1
REACTOME_TRANS_GOLGI_NETWORK_VESICLE_BUDDING	7	0	0.05234	1
KEGG_ERBB_SIGNALING_PATHWAY	10	1	0.06444	1
REACTOME_IMMUNE_SYSTEM	40	14	0.10999	1
BIOCARTA_MTA3_PATHWAY	6	0	0.09174	1
KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	6	0	0.09174	1
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	6	0	0.09174	1
KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	6	0	0.09174	1
REACTOME_LYSOSOME_VESICLE_BIOGENESIS	6	0	0.09174	1
REACTOME_METABOLISM_OF_NUCLEOTIDES	6	0	0.09174	1
REACTOME_MHC_CLASS_II_ANTIGEN_PRESENTATION	6	0	0.09174	1
REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA	6	0	0.09174	1
REACTOME_METABOLISM_OF_RNA	12	2	0.09777	1
REACTOME_METABOLISM_OF_MRNA	9	1	0.10331	1
REACTOME_NGF_SIGNALLING_VIA_TRKA_FROM_THE_PLASMA_MEMBRANE	16	4	0.15969	1
KEGG_FOCAL_ADHESION	11	2	0.14961	1
KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	11	2	0.14961	1
KEGG_PATHWAYS_IN_CANCER	18	5	0.18786	1