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Supplemental Data

Copy-Number Disorders Are a Common Cause of Congenital Kidney Malformations

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Supplemental Material and Methods

Matching Cases to Controls for Burden Analysis

In order to match a representative set of controls based on ancestry of our case cohort, we used 29,856 high quality (genotype call rates > 99.5%) and independent SNPs ($r^2 < 0.05$ with all other SNPs) that were overlapping between all 192 cases and 15,323 controls analyzed in this study (total 15,516). The ethnic composition of this cohort includes the following ancestries: 12,753 (82.2%, including 442 Ashkenazi Jewish) White, 2,083 (13.4%) Asian, and 680 (4.4%) African. The overall genotyping rate of this dataset was 99.8%. This set was utilized for eigenvector decomposition and spectral embeddings analysis. We selected a spectral graph approach as it is more flexible, less sensitive to outliers, and offers improved performance compared to the traditional principal component analysis. Based on the genotype data, we calculated a graph Laplacian matrix, derived its eigenvectors, and tested their significance using the eigengap heuristic (SPECTRAL-GEM)[1]. The eigenvalues were normalized and the Euclidean distances were calculated between all subjects. We defined homogenous ancestry clusters of individuals using *k*-means Ward's clustering algorithm. The plots of principal components and the distributions of minimal distances between cases and controls (and *vice versa*) were examined visually. Based on these distributions, we excluded outliers and unmatchable cases and controls. After each round of sample exclusions, we re-run eigenvector decomposition and re-examined case-control distances.

The full dataset was decomposed into 33 significant eigenvectors and clustered into 86 homogenous clusters. In order to achieve optimal case-control matching, we eliminated over 80% of outlier and unmatchable controls in five rounds of sample exclusions (Table S4). Each round was followed by a new eigenvector and clustering analyses. The final matched dataset included 179 cases and 2,264 controls. There were only 3 significant principal components that captured most of the genetic variance in this dataset (Figure S1). This reduced set of closely matched cases and controls was used in the downstream CNV burden analyses. To assure no residual effect of population stratification, selected burden tests were also controlled for the strata defined by the cluster solution and, as a confirmatory procedure, adjusted for the three significant eigenvectors using a regression-based approach.

Reference

1. Lee AB, Luca D, Klei L, Devlin B, Roeder K. Discovering genetic ancestry using spectral graph theory. Genet Epidemiol; 2010:34:51-9.

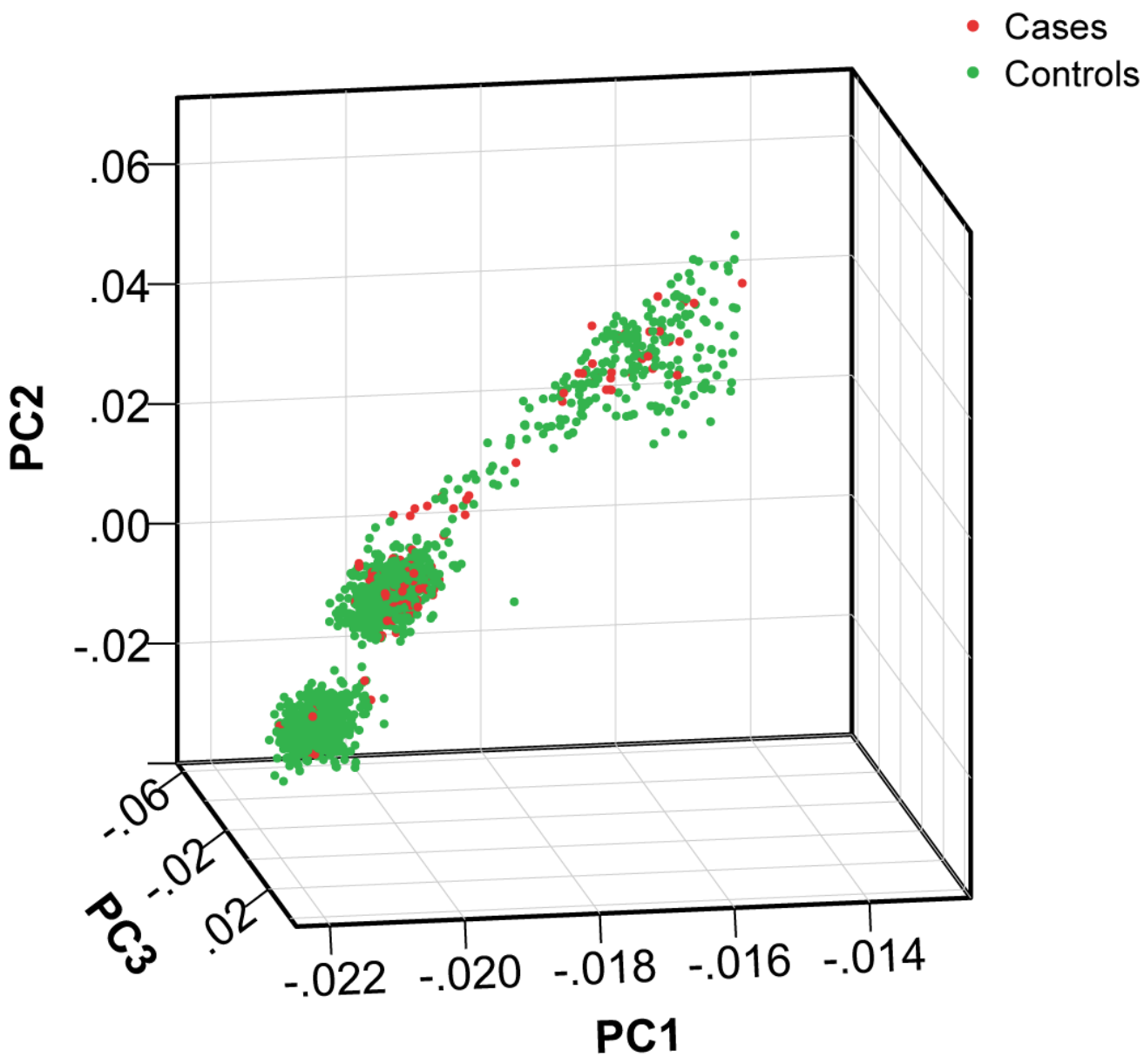

Figure S1. Distribution of the Final Dataset of 178 RHD Cases and 1,993 Matched Controls along the Three Axes of Significant Principal Components

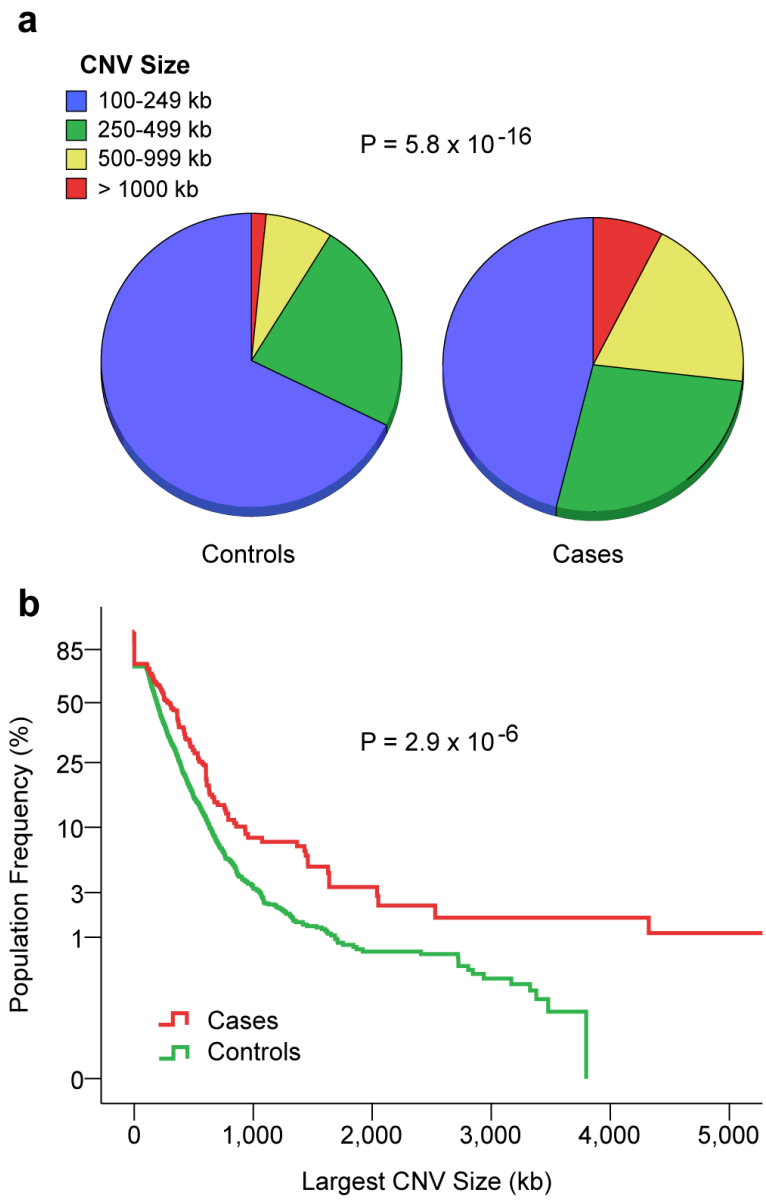

Figure S2. Adjusted Comparison of the Largest CNV per Genome Shows Enrichment of Larger Events among RHD Cases

(A) Distribution of large (>100 kb) rare (<1%) CNVs by size in RHD cases and genetically-matched controls.

(B) Global Differences in the largest CNV size distributions between cases and genetically-matched controls.

Repeated analysis using Cox Proportional Hazards model after adjustment for the three significant principal components and homogenous ancestry clusters yielded nearly identical results ($P = 1.1 \times 10^{-6}$ and $P = 2.6 \times 10^{-6}$, respectively).

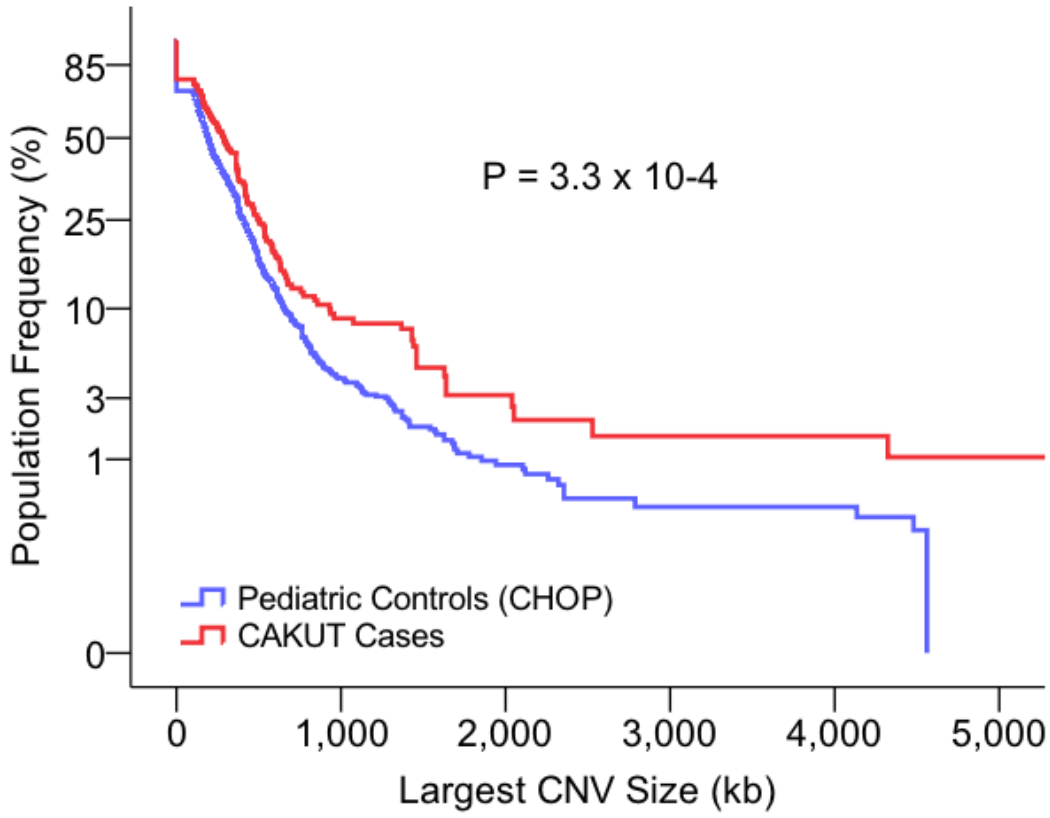

Figure S3. Global Differences in the Largest CNV Size Distributions between Cases and Pediatric Controls from the CHOP Study

Table S1. Clinical Characteristics of the Cases Cohort Genotyped for the CNV Study

	Discovery (n = 192)	Replication 1 (n = 196)	Replication 2 (n = 134)	Combined (n = 522)
Males (%)	123 (64)	119 (61)	71 (53)	313 (60)
Ethnicity (%)				
……White European	192 (100)	196 (100)	84 (63)	472 (90)
……African American	-	-	32 (24)	32 (6)
……Admixed	-	-	14 (10)	14 (3)
……Other/not reported	-	-	4 (3)	4 (1)
Positive family history of nephropathy (%)	51 (27)	45 (23)	NA	96 (25)*
Renal agenesis/solitary kidney (%)	107 (56)	92 (47)	47 (35)	246 (47)
Renal hypodysplasia (%)	85 (44)	104 (53)	87 (65)	276 (53)
Complex urinary tract malformations (%)	59 (31)	54 (27)	55 (41)	168 (32)
Extra-urinary tract malformations (%)	48 (25)	41 (21)	53 (40)	142 (27)
Cases source (%)				
……CRO	-	26 (13)	-	26 (5)
……CZE	-	12 (6)	-	12 (2)
……ITA	126 (66)	44 (22)	-	170 (33)
……MCD	23 (12)	63 (32)	-	86 (16)
……POL	43 (22)	51 (26)	-	94 (18)
……USA	-	-	134 (100)	134 (26)

NA= not available. *Percentage for family history of nephropathy calculated based on 388 samples for which these data were available. Complex uri1nary tract malformations defined as individuals with kidney parenchymal defects *and* additional defects in the urinary tract such as vesicoureteral reflux, posterior urethral valve, duplicated ureters or ureteropelvic junction obstruction.

Centers

CRO= University Hospital Split, Croatia
CZE= Palacky University, Olomouc, Czech Republic
ITA= Gaslini Institute, Genoa, University of Brescia, Brescia, Italy, University of Parma, Parma, Italy, University of Foggia, Foggia, Italy, and University of Milan, Milan, Italy
MCD= University Children's Hospital, Skopje, Macedonia
POL= Polish Registry of Congenital Malformations, Poznan, Poland
USA= Children's Hospital of Philadephia, USA

Table S2. Controls Cohorts

Study	Illumina Platform	WE	AA	ASIAN	TOTAL	After QC
Hypergenes[1]	1M-Duo	3,640	0	0	3,640	3,102
Glasgow HTN [2]	610-Quad	3,910	0	0	3,910	3,220
CHOP CNV[3]	550v1-v3	1,320	694	12	2,026	1,972
NIA[4]	610-Quad	2,921	136	4	3,061	2,748
IgAN[5]	610-Quad	541	0	2,096	2,637	2,360
PD AJ[6]	610-Quad/660W	447	0	0	447	437
TOTAL		12,779	830	2,112	15,721	13,839

WE = White European. AA= African American. Two cohorts (CHOP Control CNV Study, phs000199.v1.p1; NIA, phg000049.v1.p1) were obtained from the dbGaP repository (http://www.ncbi.nlm.nih.gov/gap/).

References

1. Salvi E, Kutalik Z, Glorioso N, et al. Genomewide association study using a high-density single nucleotide polymorphism array and case-control design identifies a novel essential hypertension susceptibility locus in the promoter region of endothelial NO synthase. Hypertension 2012;59:248-55.
2. Padmanabhan S, Melander O, Johnson T, et al. Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. PLoS Genet 2010;6:e1001177.
3. Shaikh TH, Gai X, Perin JC, et al. High-resolution mapping and analysis of copy number variations in the human genome: a data resource for clinical and research applications. Genome Res 2009;19:1682-90.
4. Lee JH, Cheng R, Graff-Radford N, Foroud T, Mayeux R. Analyses of the National Institute on Aging Late-Onset Alzheimer's Disease Family Study: implication of additional loci. Arch Neurol 2008;65:1518-26.
5. Gharavi AG, Kiryluk K, Choi M, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet 2011;43:321-7.
6. Liu X, Cheng R, Verbitsky M, et al. Genome-wide association study identifies candidate genes for Parkinson's disease in an Ashkenazi Jewish population. BMC Med Genet 2011;12:104.

Table S3. Illumina Genotyping Platforms Used for the Three RHD Cohorts

Study	N Cases	Hap 550v1	Hap 550v3	610-Quad	660W	Omni1-Quad
Discovery	192	0	0	155	37	0
Replication 1	196	0	0	0	0	196
Replication 2	134	19	71	44	0	0
Total	522	19	71	199	37	196

Table S4. Ancestry-Based Matching of Cases and Controls for CNV Burden Tests

	N. of Individuals entered in the analysis	N. of Significant Eigenvectors	N. of Homogenous Clusters	N. of Individuals Excluded
PCA Round 1	15,332 (193 cases and 15,321 controls)	33	86	8,610
PCA Round 2	6,722 (193 cases and 6,600 controls)	8	34	3,244
PCA Round 3	3,478 (186 cases and 3,290 controls)	6	18	797
PCA Round 4	2,681 (180 cases and 2,499 controls)	5	12	236
PCA Round 5	2,445 (179 cases and 2,264 controls)	3	11	0

Table S5. Differences in Global CNV Counts between RHD Cases and Genetically Matched Controls

Global CNV Metrics	RHD Cases (n = 178)	Genetically Matched Controls (n = 1,993)	p Value (Exact Test)
Total number of rare CNVs	N_{cnv} = 291	N_{cnv} = 4,330	
Size Distribution of All CNVs			
100-250 kb	134 (46.0%)	2,934 (67.8%)	5.8×10^{-16}
250-500 kb	79 (27.1%)	1,015 (23.4%)	
500-1000 kb	56 (19.2%)	313 (7.2%)	
>1000 kb	22 (7.6%)	68 (1.6%)	
Size Distribution of Deletions			
100-250 kb	74 (56.6%)	2,105 (74.3%)	9.6×10^{-14}
250-500 kb	27 (20.6%)	585 (20.6%)	
500-1000 kb	16 (12.2%)	123 (4.3%)	
>1000 kb	14 (10.7%)	20 (0.7%)	
Size Distribution of Duplications			
100-250 kb	60 (37.5%)	829 (55.4%)	8.4×10^{-6}
250-500 kb	52 (32.5%)	430 (28.7%)	
500-1000 kb	40 (25.0%)	190 (12.7%)	
>1000 kb	8 (5.0%)	48 (3.2%)	
Size Distribution of Gene-Disrupting CNVs			
100-250 kb	87 (42.4%)	2,112 (66.8%)	1.8×10^{-15}
250-500 kb	53 (25.9%)	748 (23.7%)	
500-1000 kb	45 (22.0%)	248 (7.8%)	
>1000 kb	20 (9.8%)	53 (1.7%)	
Size Distribution of Intergenic CNVs			
100-250 kb	47 (54.7%)	822 (70.3%)	0.0043
250-500 kb	26 (30.2%)	267 (22.8%)	
500-1000 kb	11 (12.8%)	65 (5.6%)	
>1000 kb	2 (2.3%)	15 (1.3%)	

Table S6. Differences in the Per-Genome CNV Metrics between RHD Cases and 1,993 Genetically Matched Controls

Per-Genome CNV Metrics	Cases n = 178	Controls n = 1,993	Asymptotic p Value[#]	Empiric p Value[##]
Average CNV Size [kb] (Median)	380.2 (230.7)	192.6 (164.8)	9.5×10^{-6}	1.2×10^{-5}
Average Largest CNV Size [kb] (Median)	533.8 (288.7)	279.4 (190.5)	5.6×10^{-4}	5.6×10^{-4}
Average Total CNV Span [kb] (Median)	852.1 (402.7)	565.4 (275.1)	5.7×10^{-2}	5.8×10^{-2}

[#] **Non-parametric (Mann-Whitney U) test.**
[##] **1,000,000 permutations.**

Table S7. Differences in Global CNV Counts between RHD Cases and Pediatric Controls from the CHOP Study

Global CNV Metrics	CAKUT Cases (n = 192)	Pediatric Controls (n = 1,235)	p Value (Exact Test)
Total number of rare CNVs	N_{cnv} = 351	N_{cnv} = 2,717	
Size Distribution of All CNVs			
100-250 kb	168 (47.9%)	1,745 (64.2%)	6.9×10^{-13}
250-500 kb	107 (30.5%)	732 (26.9%)	
500-1000 kb	52 (14.8%)	188 (6.9%)	
> 1000 kb	24 (6.8%)	52 (1.9%)	
Size Distribution of Deletions			
100-250 kb	77 (56.2%)	1,525 (70.1%)	6.4×10^{-16}
250-500 kb	28 (20.4%)	546 (25.1%)	
500-1000 kb	16 (11.7%)	94 (4.3%)	
> 1000 kb	16 (11.7%)	11 (0.5%)	
Size Distribution of Duplications			
100-250 kb	91 (42.5%)	220 (40.7%)	0.262
250-500 kb	79 (36.9%)	186 (34.4%)	
500-1000 kb	36 (16.8%)	94 (17.4%)	
> 1000 kb	8 (3.7%)	41 (7.6%)	
Size Distribution of Gene-Disrupting Deletions			
100-250 kb	41 (47.1%)	1,305 (68.0%)	2.2×10^{-16}
250-500 kb	20 (23.0%)	516 (26.9%)	
500-1000 kb	11 (12.6%)	88 (4.6%)	
> 1000 kb	15 (17.2%)	11 (0.6%)	
Size Distribution of Gene-Disrupting Duplications			
100-250 kb	65 (43.9%)	186 (39.6%)	0.235
250-500 kb	44 (29.7%)	161 (34.3%)	
500-1000 kb	32 (21.6%)	83 (17.7%)	
> 1000 kb	7 (4.7%)	40 (8.5%)	

Table S8. Known Diagnostic Genomic Disorders Identified in 522 RHD Cases

Chr.	CNV Type	Start (Mb)	End (Mb)	Size (Mb)	Syndrome	N. of genes	Segm. Dup.	Discovery Cohort (n = 192)	Repli. Cohort 1 (n = 196)	Repli. Cohort 2 (n = 134)	All cohorts (n = 522)	Controls (n = 13,839)	p Value	Sample	Extrarenal Phenotypes	De Novo or Inherited?	Prior Reported Association with Urinary Tract / Neuropsychiatric Phenotypes	Candidate Genes with mouse orthologs implicated in RHD
1p36	Dup	2.91	3.65	0.74	1p36 duplication[1,2]	13	None	0	0	2	2	0	1.3×10^{-3}	CHOP_2 CHOP_11	N N	NA NA	N/Y	
1p22	Dup	89.50	89.97	0.47	1p22.2-31.1 duplication[3]	4	Within-3'	0	1	1	2	0	1.32×10^{-3}	MCD_14 CHOP_12	Y N	NA NA	N/Y	
1q21	Del	144.11	144.63	0.52	1q21 TAR deletion[4]	26	5'-3'	1	0	0	1	1	0.07	POL_6	Y	NA	Y/Y	
1q21	Del	144.80	145.86	1.06	1q21 distal deletion[5]	15	5'-3'	1	3	0	4	4	1.1×10^{-4}	POL_6 MCD_16 POL_15 POL_20	Y N N N	NA Inherited[j] NA NA	Y/N	
1q43-q44	Del	240.61	245.67	5.06	1q43-q44 deletion[6]	41	5'-3'	1	0	0	1	0	0.036	MCD_1	Y	De novo	Y/Y	SDCCAG8, KIF26B, NLRP3
2q37	Dup	240.99	242.44	1.45	2q37 deletion[7]	40	None	0	1	0	1	0	0.036	POL_13	Y	NA	Y/Y	
3p26	Dup	1.35	2.18	0.83	3pter-p25 deletion[8]	2	5'-3'	2	0	0	2	8	0.049	MCD_19 ITA_33	Y Y	NA Inherited[i]	N/Y	
4p16[a]	Del	0.06	17.29	17.23	Wolf-Hirschorn[9]	186	5'-within	0	1	1	2	0	1.32×10^{-3}	POL_18 CHOP_14	Y Y	NA NA	Y/Y	FGFRL1, FGFR3, SLC2A9
5p15	Dup	0.11	10.96	10.85	5p distal duplication[10-12]	78	5'-within	0	0	1	1	0	0.036	CHOP_14	Y	NA	Y/Y	
5q14-q23	Del	91.46	114.55	23.09	5q interstitial deletion[13]	89	Within-3'	0	0	1	1	0	0.036	CHOP_8	Y	NA	N/Y	MAN2A1, APC
6q13-q14	Dup	70.29	70.76	0.47	6q13-q14 deletion[14]	2	Within	1	0	0	1	0	0.036	ITA_2	N	NA	Y/Y	
7p22	Dup	6.82	7.27	0.45	7p interstitial duplication[15]	3	5'-within	0	0	1	1	0	0.036	CHOP_18	Y	NA	Y/Y	C1GALT1
7p21	Dup	16.80	17.71	0.91	7p interstitial duplication[15]	3	Within	0	0	1	1	1	0.071	CHOP_1	Y	NA	Y/Y	
7p15	Del	23.68	27.43	3.75	7p15.1-21.1 deletion[16]	43	5'-3'	0	1	0	1	0	0.036	POL_9	N	NA	Y/N	HOXA11, HOXA13
7q34-q36[b]	Del	141.53	158.81	17.28	7q36 deletion[17]	255	Within	1	0	1	2	0	1.32×10^{-3}	MCD_3 CHOP_9	Y Y	De novo NA	Y/Y	GSTK1, NOS3, SHH
8p23	Dup	8.13	11.94	3.81	8p23.1 duplication[18]	42	5'-3'	1	0	0	1	1	0.071	ITA_27	Y	NA	Y/Y	BLK
9p22	Del	14.81	14.97	0.17	9p22.3 deletion[19]	3	Within-3'	0	1	0	1	0	0.036	ITA_1	N	NA	N/N	FREM1[k]
16p13	Dup	0.04	15.09	15.04	16p subtelomeric duplication[20]	323	5'-3'	0	1	0	1	0	0.036	POL_21	Y	NA	Y/Y	AXIN1, IFT140, TSC2, PKD1, PDPK1
16p13	Dup	15.03	15.80	0.77	16p13.11 duplication[21]	15	5'-3'	1	0	0	1	5	0.199	ITA_32	N	NA	N/Y	MYH11
16p11[c]	Del	29.55	31.86	2.31	16p11.2 distal deletion [22,23]	53	5'-3'	0	2	0	2	0	1.32×10^{-3}	MCD_5 POL_16	N Y	NA NA	Y/Y	TBX6
16p11	Dup	29.50	30.05	0.55	16p11.2 distal duplication[24]	43	5'-3'	0	0	1	1	3	0.138	CHOP_19	N	NA	N/Y	TBX6
17p11-p12	Dup	16.41	20.23	3.82	Potocki-Lupski syndrome[25]	96	5'-3'	1	0	1	2	0	1.32×10^{-3}	POL_3 CHOP_4	N Y	NA NA	Y/Y	FLCN, TOM1L2, B9D1
17q11-q12	Del	31.89	33.35	1.46	RCAD (renal cysts and diabetes)[26]	19	5'-3'	5	5	1	11	0	1.32×10^{-16}	ITA_7 ITA_40 POL_10 ITA_34 ITA_21 MCD_17 ITA_36[e] POL_17 POL_19 ITA_30 CHOP_3	N Y N N N N N N N Y Y	NA De novo De novo NA NA NA NA NA NA NA NA	Y/Y	HNF1B
17q11-q12	Dup	31.89	33.25	1.36	17q12 duplication[26]	18	5'-3'	1	0	0	1	1	0.071	ITA_39	Y	NA	Y/Y	
17q21	Del	40.94	41.41	0.47	17q21.31 deletion[27]	11	5'-3'	1	0	0	1	2	0.105	POL_4	N	NA	Y/Y	LHX1
20p11-p13	Dup	0.11	24.77	24.66	20p partial trisomy[28]	224	NA	0	1	0	1	0	0.036	MCD_14	Y	NA	Y/Y	JAG1, PAX1, THBD
21q22	Del	40.51	46.91	6.40	21q partial monosomy[29]	134	Within-3'	0	0	1	1	0	0.036	CHOP_6	Y	NA	N/Y	CBS, SLC19A1
22q11	Dup	15.29	18.61	3.32	22q11.2 duplication (VCFS region)[30]	77	5'-3'	0	1	0	1	0	0.036	POL_13	Y	NA	Y/Y	

22q11	Del	17.27	19.79	2.52	DiGeorge/VCFS deletion[31]	71	5'-3'	3	1	0	4	0	1.73 x 10^{-6}	ITA_35 ITA_25[f] ITA_13[f] CZEC_1[f]	Y N N N	NA Inherited[i] Inherited[j] De Novo	Y/Y	
22q13[g]	Del	42.94	49.52	6.58	Phelan-McDermid[32]	102	5'-3'	0	1	1	2	0	1.32 x 10^{-3}	POL_21 CHOP_3	Y Y	NA NA	Y/Y	UPK3A, WNT7B
X	Gain	XXY	XXY	--	Klinefelter's syndrome[33]	--	NA	1	0	0	1	0	0.044	ITA_4	N	NA	Y/Y	
Xp22	Del	6.46	8.10	1.64	Xp22.31 deletion[34]	6	5'-3'	2	0	0	2	0	1.92 x 10^{-3}	ITA_17 POL_12	N N	NA NA	Y/Y	
Xp22	Dup	8.19	8.67	0.48	Kallman's syndrome region (KAL1)[35]	3	5'-3'	2	1	0	3	4	2.58 x 10^{-3}	ITA_43 ITA_6 POL_14[h]	N N N	NA NA NA	Y/Y	
Xq27	Dup	139.36	139.91	0.55	Mental Retardation with panhypopituitarism syndrome[36]	4	5'-3'	1	0	0	1	0	0.044	MCD_13[d]	Y	NA	N/Y	

ITA=Italy; MCD=Macedonia; POL=Poland; CRO=Croatia; CRHF=Czech Republic; CHOP=Children Hospital of Philadelphia. Segm. Dup=Segmental Duplications. [a]The CNV in case CHOP_14 spans 5.81 Mb and is included in the larger 17.23 MB deletion. [b]The CNV in case CHOP_9 spans 7.3 Mb and is included in the larger 17.28 deletion. [c]The CNV in case MCD_5 spans 690 Kb and is included in the larger 2.31 deletion. [d]This case was found to have XX caryotype with male phenotype and hypospadia. [e]This case was found to have a small 90 Kb deletion involving DDX52 and TCF2 genes at the RCAD locus. [f]These three individuals shared smaller 370-410 kb deletions included in the larger 2.52 deletion. [g]Cases POL_21 and CHOP_3 harbor overlapping deletions of 6.39 Mb and 5.04 Mb, respectively. [h]This case carries a smaller 100 Kb duplication affecting the KAL1 gene. [i]Segregating CNVs; [j]No family history of nephropathy. [k]homozygous mutations in *FREM1* produce Bifid Nose with or without Anorectal and Renal Anomalies (BNAR; OMIM 608980), but heterozygous mutations are only associated with craniosynostosis (ref 19 below).

References

1. Gajecka M, Mackay KL, Shaffer LG. Monosomy 1p36 deletion syndrome. Am J Med Genet C Semin Med Genet 2007;145C:346-56.
2. Garcia-Heras J, Corley N, Garcia MF, Kukolich MK, Smith KG, Day DW. De novo partial duplications 1p: report of two new cases and review. Am J Med Genet 1999;82:261-4.
3. Lo IF, Cheung LY, Ng AY, Lam ST. Interstitial Dup(1p) with findings of Kabuki make-up syndrome. Am J Med Genet. 1998 ;78(1):55-7.
4. Klopocki E, Schulze H, Strauss G, et al. Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. Am J Hum Genet 2007;80:232-40.
5. Brunetti-Pierri N, Berg JS, Scaglia F, et al. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet 2008;40:1466-71.
6. Beemer FA, Klep-de Pater JM, Sepers GJ, Janssen B. Two cases of interstitial deletion of the long arm of chromosome 1: del(1)(q21----q25) and del(1)(q41----q43). Clin Genet 1985;27:515-9.
7. Galasso C, Lo-Castro A, Lalli C, Nardone AM, Gullotta F, Curatolo P. Deletion 2q37: an identifiable clinical syndrome with mental retardation and autism. J Child Neurol 2008;23:802-6.
8. Schwyzer U, Binkert F, Caflisch U, Baumgartner B, Schinzel A. Terminal deletion of the short arm of chromosome 3, del(3pter-p25): a recognizable syndrome. Helv Paediatr Acta 1987;42:309-15.
9. Bergemann AD, Cole F, Hirschhorn K. The etiology of Wolf-Hirschhorn syndrome. Trends Genet 2005;21:188-95.
10. Harrison KJ, Teshima IE, Silver MM, et al. Partial tetrasomy with triplication of chromosome (5) (p14-p15.33) in a patient with severe multiple congenital anomalies. Am J Med Genet 1998;79:103-7.
11. Chia NL, Bousfield LR, Johnson BH. A case report of a de novo tandem duplication (5p) (p14----pter). Clin Genet 1987;31:65-9.
12. Cervera M, Sanchez S, Molina B, et al. Trisomy of the short arm of chromosome 5 due to a de novo inversion and duplication (5)(p15.3 p13.3). Am J Med Genet A 2005;136A:381-5.
13. Garcia-Minaur S, Ramsay J, Grace E, Minns RA, Myles LM, FitzPatrick DR. Interstitial deletion of the long arm of chromosome 5 in a boy with multiple congenital anomalies and mental retardation: Molecular characterization of the deleted region to 5q22.3q23.3. Am J Med Genet A 2005;132:402-10.
14. McNeal RM, Skoglund RR, Francke U. Congenital anomalies including the VATER association in a patient with del(6)q deletion. J Pediatr 1977;91:957-60.
15. Reish O, Berry SA, Dewald G, King RA. Duplication of 7p: further delineation of the phenotype and restriction of the critical region to the distal part of the short arm. Am J Med Genet 1996;61:21-5.
16. Hoover-Fong JE, Cai J, Cargile CB, et al. Facial dysgenesis: a novel facial syndrome with chromosome 7 deletion p15.1-21.1. Am J Med Genet A 2003;117A:47-56.
17. Caselli R, Mencarelli MA, Papa FT, et al. Delineation of the phenotype associated with 7q36.1q36.2 deletion: long QT syndrome, renal hypoplasia and mental retardation. Am J Med Genet A 2008;146A:1195-9.
18. Barber JC, Maloney VK, Huang S, et al. 8p23.1 duplication syndrome; a novel genomic condition with unexpected complexity revealed by array CGH. Eur J Hum Genet 2008;16:18-27.

19. Vissers LE, Cox TC, Maga AM, et al. Heterozygous mutations of FREM1 are associated with an increased risk of isolated metopic craniosynostosis in humans and mice. PLoS Genet 2011;7:e1002278.
20. Digilio MC, Bernardini L, Capalbo A, et al. 16p subtelomeric duplication: a clinically recognizable syndrome. Eur J Hum Genet 2009;17:1135-40.
21. Nagamani SC, Erez A, Bader P, et al. Phenotypic manifestations of copy number variation in chromosome 16p13.11. Eur J Hum Genet 2011;19:280-6.
22. Hernando C, Plaja A, Rigola MA, et al. Comparative genomic hybridisation shows a partial de novo deletion 16p11.2 in a neonate with multiple congenital malformations. J Med Genet 2002;39:E24.
23. Hanson E, Nasir RH, Fong A, et al. Cognitive and behavioral characterization of 16p11.2 deletion syndrome. J Dev Behav Pediatr 2010;31:649-57.
24. Fernandez BA, Roberts W, Chung B, et al. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11.2 in individuals ascertained for diagnosis of autism spectrum disorder. J Med Genet 2010;47:195-203.
25. Potocki L, Bi W, Treadwell-Deering D, et al. Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. Am J Hum Genet 2007;80:633-49.
26. Mefford HC, Clauin S, Sharp AJ, et al. Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes, and epilepsy. Am J Hum Genet 2007;81:1057-69.
27. Shaw-Smith C, Pittman AM, Willatt L, et al. Microdeletion encompassing MAPT at chromosome 17q21.3 is associated with developmental delay and learning disability. Nat Genet 2006;38:1032-7.
28. Oppenheimer S, Dignan P, Soukup S. Partial trisomy 20p: familial occurrence. Am J Med Genet 2000;95:316-9.
29. Roberson ED, Wohler ES, Hoover-Fong JE, et al. Genomic analysis of partial 21q monosomies with variable phenotypes. Eur J Hum Genet 2011;19:235-8.
30. Lo-Castro A, Galasso C, Cerminara C, et al. Association of syndromic mental retardation and autism with 22q11.2 duplication. Neuropediatrics 2009;40:137-40.
31. Shprintzen RJ. Velocardiofacial syndrome and DiGeorge sequence. J Med Genet 1994;31:423-4.
32. Bonaglia MC, Giorda R, Beri S, et al. Molecular mechanisms generating and stabilizing terminal 22q13 deletions in 44 subjects with Phelan/McDermid Syndrome. PLoS Genet 2011;7:e1002173.
33. Polani PE, Bishop PM, Lennox B, Ferguson-Smith MA, Stewart JS, Prader A. Colour vision studies and the x-chromosome constitution of patients with Klinefelter's syndrome. Nature 1958;182:1092-3.
34. Ballabio A, Bardoni B, Carrozzo R, et al. Contiguous gene syndromes due to deletions in the distal short arm of the human X chromosome. Proc Natl Acad Sci U S A 1989;86:10001-5.
35. Franco B, Guioli S, Pragliola A, et al. A gene deleted in Kallmann's syndrome shares homology with neural cell adhesion and axonal path-finding molecules. Nature 1991;353:529-36.
36. Lagerstrom-Fermer M, Sundvall M, Johnsen E, et al. X-linked recessive panhypopituitarism associated with a regional duplication in Xq25-q26. Am J Hum Genet 1997;60:910-6.

Table S9. CNV Burden Analysis in 167 RHD Cases in the Discovery Cohort after Exclusion of 25 Cases with Known Genomic Disorders

	Cases (n = 167)	Controls (n = 4,733)	Asymptotic p Value[a]	Empiric p Value[b]
Average CNV rate	1.54	1.68	0.18	0.77
Average CNV size [kb] (median)	317.4 (198.8)	197.1 (161.1)	8.0×10^{-3}	7.9×10^{-3}
Average largest CNV size [kb] (median)	380.8 (248.4)	260.4 (178.5)	1.4×10^{-2}	1.4×10^{-2}
Average total CNV span [kb] (median)	547.8 (362.0)	476.1 (234.2)	3.3×10^{-2}	3.3×10^{-2}

[a]Non-parametric (Mann-Whitney U) test for quantitative variables; Poisson rate ratio test for rates, and Fisher exact test for proportions.
[b]Based on 1,000,000 permutations.

Table S10. Novel or Rare Genomic Disorders in RHD

Chr.	CNV Type	Start (Mb)	End (Mb)	Size (Mb)	N. of genes	Segm. Dup.	Discov. Cohort (n = 192)	Repli 1 Cohort (n = 196)	Repli 2 Cohort (n = 134)	All Cohorts (n = 522)	Controls (n = 13,839)	p Value	Sample	Extrarenal Phenotypes	De Novo or Inherited?	Candidate Genes with Mouse Orthologs Implicated in RHD
1p36	Del	12.78	13.25	0.47	10	5'-3'	1	0	0	1	0	0.036	ITA_38	N	NA	
1p32	Del	57.97	58.44	0.47	4	Within	0	1	0	1	0	0.036	ITA_22	Y	Inherited[e]	
1q32	Del	162.68	163.19	0.51	3	5'-Within	0	1	0	1	0	0.036	CRO_2	N	De novo	PBX1
1q42	Del	223.78	224.08	0.30	6	5'-3'	1	0	0	1	0	0.036	POL_4	N	NA	
2p25[a]	Dup	0.02	3.65	3.63	33	5'-3'	1	0	1	2	0	1.32 x 10^{-3}	ITA_2 CHOP_3	N Y	NA NA	
2p11	Dup	88.16	89.24	1.08	17	5'-3'	0	0	1	1	0	0.036	CHOP_15	N	NA	
2p11	Del	89.39	89.88	0.49	3	5'-3'	0	0	1	1	1	0.071	CHOP_5	N	NA	
2q12	Del	104.97	105.19	0.22	1	None	1	0	0	1	0	0.036	ITA_5	N	NA	
2q32	Dup	190.87	191.31	0.44	4	Within	1	0	0	1	0	0.036	POL_8	N	NA	
3q13-q22	Del	118.15	133.11	14.96	186	Within-3'	1	0	0	1	0	0.036	POL_1	Y	De novo	GSK3B, GPR156, FSTL1, GATA2, HGD
3q29	Dup	199.17	199.32	0.15	3	5'-3'	1	1	0	2	3	0.012	ITA_45 MCD_12	Y N	NA NA	
4p16	Dup	7.27	7.76	0.49	2	Within	0	1	0	1	0	0.036	MCD_18	N	NA	
4p13	Dup	44.12	44.75	0.63	4	Within-3'	1	0	0	1	0	0.036	ITA_8	N	De novo	
4q28	Dup	141.35	141.81	0.46	9	Within	0	1	0	1	0	0.036	ITA_44	N	Inherited[b]	
5q34	Dup	159.53	160.58	1.05	10	3'	0	2	0	2	0	1.32 x 10^{-3}	MCD_8 MCD_9	N N	NA NA	
7p12	Del	47.76	48.52	0.76	8	Within	0	1	0	1	0	0.036	CRO_1	N	NA	
7q21	Del	79.33	80.91	1.58	4	Within	0	1	0	1	0	0.036	MCD_10 CRO_4	N N	NA Inherited[c]	CD36
7q22	Del	104.41	104.81	0.40	5	Within	0	0	1	1	0	0.036	CHOP_7	Y	NA	
9q33	Dup	115.20	116.61	0.41	0	Within	0	0	1	1	0	0.036	CHOP_13	Y	NA	
10p11	Dup	42.10	42.71	0.61	13	5'-3'	2	0	0	2	0	1.32 x 10^{-3}	POL_10 MCD_7	N Y	NA NA	
11p11	Dup	49.58	50.52	0.94	8	5'-Within	0	2	0	2	1	3.86 x 10^{-3}	ITA_23 CRO_3	N N	NA NA	
12q21	Del	83.69	84.31	0.62	5	None	1	0	0	1	2	0.105	ITA_17	N	NA	
12q24	Del	120.38	120.83	0.46	14	None	0	0	1	1	0	0.036	CHOP_9	Y	NA	
12q24	Dup	124.67	132.29	7.52	65	Within	1	0	0	1	0	0.036	MCD_3	Y	De novo	
13q11	Del	22.44	23.80	1.36	14	5'-3'	1	0	0	1	3	0.138	ITA_46	Y	De novo	
13q12	Dup	28.14	28.77	0.63	3	5'-3'	1	0	0	1	0	0.036	ITA_47	Y	NA	
13q12	Dup	36.28	37.51	1.23	11	None	1	0	0	1	0	0.036	MCD_3	Y	Inherited[d]	
13q13	Dup	38.70	39.44	0.74	3	5'-3'	0	0	1	1	0	0.036	CHOP_16	N	NA	
13q32	Del	99.39	99.82	0.43	3	None	0	0	1	1	0	0.036	CHOP_7	Y	NA	PCCA
15q13[>]	Del	40.90	41.33	0.43	7	5'-3'	1	0	0	1	0	0.036	ITA_9	N	Inherited[c]	
16p12[#]	Dup	21.51	21.66	0.15	3	5'-3'	1	0	0	1	8	0.283	ITA_18	N	NA	
16q22	Del	73.39	73.90	0.51	9	Within	1	0	0	1	0	0.036	POL_7	N	De novo	
17p13	Dup	0.15	0.25	0.10	3	5'-3'	1	0	0	1	0	0.036	ITA_19	N	NA	
17q25	Dup	71.00	78.63	7.63	222	Within	0	0	1	1	0	0.036	CHOP_9	Y	NA	ITGB, JMJD6, TK1, SGSH, STRA13, ARHGDIA
20q13	Dup	60.32	60.81	0.49	11	None	0	0	1	1	0	0.036	CHOP_11	N	NA	LAMA5,

																GATA5
21p11	Dup	9.81	10.21	0.40	5	Within	0	1	0	1	0	0.036	ITA_31	N	Inherited[b]	
21p11	Dup	13.52	14.20	0.68	4	5'-3'	0	0	1	1	2	0.105	CHOP_10	N	NA	
21q22	Del	36.33	37.14	0.81	14	Within	0	0	1	1	0	0.036	CHOP_17	N	NA	

ITA = Italy; MCD = Macedonia; POL = Poland; CRO = Croatia; CRHF = Czech Republic; CHOP = Children Hospital of Philadelphia. Segm. Dup.=Segmental Duplications.
[a]The CNV in case ITA_2 spans 770 Kb and is included in the larger 3.63 Mb duplication. [b]Segregating CNVs; [c]No family history of nephropathy; [d]inherited in a case where family history was unknown, [e]non-discernible.

Table S11. Individuals with Multiple Diagnostic or Novel Large CNVs

Case ID (Cohort)	Extrarenal Defects	Locus	CNV Type	Name	Chr.	Start	End	Size	N. Gene	Inheritance
ITA_17	N	Xp22	Del	Xp22.31 deletion	X	6.46	8.1	1.64	6	NA
(Disc)	N	12q21	Del	Novel	12	83.69	84.31	0.62	5	NA
ITA_2	N	6q13-q14	Dup	6q13-q14 deletion	6	70.29	70.76	0.47	2	NA
(Disc)	N	2p25	Dup	Novel	2	0.02	3.65	3.63	33	NA
MCD_3	Y	7q34-q36	Del	7q36 deletion17	7	141.53	158.81	17.28	255	De novo
(Disc)	Y	12q24	Dup	Novel	12	124.67	132.29	7.52	65	De novo
	Y	13q12	Dup	Novel	13	36.28	37.51	1.23	11	Inherited
POL_10	N	17q11-q12	Del	RCAD (renal cysts and diabetes	17	31.89	33.35	1.46	19	De novo
(Disc)	N	10p11	Dup	Novel	10	42.1	42.71	0.61	13	NA
POL_4	N	17q21	Del	17q21.31 deletion (MAPT)	17	40.94	41.41	0.47	11	NA
(Disc)	N	1q42	Del	Novel	1	223.78	224.08	0.3	6	NA
POL_6	Y	1q21	Del	1q21 TAR deletion	1	144.11	144.63	0.52	26	NA
(Disc)	Y	1q21	Del	1q21 distal deletion	1	144.8	145.86	1.06	15	NA
MCD_14	Y	1p22	Dup	1p22.2-31.1 deletion	1	89.5	89.97	0.47	4	NA
(Repli 1)	Y	20p11-p13	Dup	20p partial trisomy	20	0.11	24.77	24.66	224	NA
POL_13	Y	2q37	Dup	2q37 deletion	2	240.99	242.44	1.45	40	NA
(Repli 1)	Y	22q11	Dup	22q11.2 duplication (VCFS region)	22	15.29	18.61	3.32	77	NA
POL_21	Y	16p13	Dup	16p subtelomeric duplication	16	0.04	15.09	15.04	323	NA
(Repli 1)	Y	22q13	Del	Phelan-McDermid	22	42.94	49.52	6.58	102	NA
CHOP_11	N	1p36	Dup	1p36 duplication	1	2.91	3.65	0.74	13	NA
(Repli 2)	N	20q13	Dup	Novel	20	60.32	60.81	0.49	11	NA
CHOP_14	Y	4p16	Del	Wolf-Hirschhorn	4	0.06	17.29	17.23	186	NA
(Repli 2)	Y	5p15	Dup	5p distal duplication	5	0.11	10.96	10.85	78	NA
CHOP_3	Y	17q11-q12	Del	RCAD (renal cysts and diabetes)	17	31.89	33.35	1.46	19	NA
(Repli 2)	Y	22q13	Del	Phelan-McDermid	22	42.94	49.52	6.58	102	NA
	Y	2p25	Dup	Novel	2	0.02	3.65	3.63	33	NA
CHOP_7	Y	7q22	Del	Novel	7	104.41	104.81	0.4	5	NA
(Repli 2)	Y	13q32	Del	Novel	13	99.39	99.82	0.43	3	NA
CHOP_9	Y	7q34-q36	Del	7q36 deletion	7	141.53	158.81	17.28	255	NA
(Repli 2)	Y	12q24	Del	Novel	12	120.38	120.83	0.46	14	NA
	Y	17q25	Dup	Novel	17	71.00	78.63	7.63	222	NA

Disc = Discovery cohort; Repli 1= Replication cohort 1; Repli 2 = Replication cohort 2.

Table S12. Intergenic CNVs Identified in the Discovery Cohort and Absent in 13,839 Controls

Chr.	CNV Type	Start (Mb)	End (Mb)	Size (Mb)	5' Gene	Dist (Kb)	3' Gene	Dist (Kb)	Segm. Dup.	Cases (n = 192)	Controls (n = 13,839)	p	Sample/ Ethnicity	Extrarenal Phenotypes
2p16	Del	55.82	55.90	0.08	PNPT1	48.6	EFEMP1	41.4	3'	1	0	0.014	ITA_42	N
4p16	Del	12.52	12.65	0.13	BC042433	658.8	HSP90Bb	297.8	None	1	0	0.014	ITA_29	N
4q26	Del	115.60	115.67	0.07	ARSJ	479.0	UGT8	61.4	None	1	0	0.014	ITA_48	Y
4q28	Del	131.30	131.54	0.24	BC041448	206.8	BC041865	1361.0	None	1	0	0.014	ITA_32	N
4q32	Del	171.43	171.58	0.15	AADAT	181.6	BC047077	620.9	None	1	0	0.014	ITA_12	N
7p22	Del	10.41	10.45	0.04	NR_002790	771.3	NDUFA4	491.2	3'	1	0	0.014	ITA_20	N
7p21	Dup	13.27	13.36	0.09	ARL4A	575.0	ETV1	535.3	None	1	0	0.014	ITA_24	N
7p21	Del	17.05	17.08	0.03	AGR3	159.5	AHR	222.1	None	1	0	0.014	POL_2	N
7p15	Dup	22.06	22.11	0.05	CDCA7L	112.7	RAPGEF5	15.2	None	1	0	0.014	ITA_41	Y
7q11	Dup	61.68	62.34	0.66	L37717	3978.3	NR_003952	52.7	5'-3'	1	0	0.014	POL_11	N
7q21	Del	79.72	79.78	0.06	GNAI1	38.3	CD36	61.0	None	1	0	0.014	ITA_26	Y
7q33	Dup	135.41	135.47	0.06	MTPN	100.4	CHRM2	731.7	None	1	0	0.014	ITA_18	Y
8q21	Dup	88.51	88.62	0.11	CNBD1	45.3	WDR21C	333.2	5'	2	0	1.7×10^{-4}	MCD_2 MCD_6	Y Y
8q24	Del	138.32	138.41	0.09	SALP	1594.5	C8orfK32	802.2	None	1	0	0.014	ITA_3	N
8q24	Del	142.65	142.95	0.30	FLJ43860	60.5	TSNARE1	344.3	5'-within	1	0	0.014	POL_4	Y
9p24	Del	3.68	3.71	0.03	RFX3	166.9	GLIS3	103.8	None	1	0	0.014	POL_5	N
9p23	Del	11.10	11.85	0.75	PTPRD	498.5	TYRP1	831.4	Within-3'	1	0	0.014	ITA_17	N
9p13	Del	29.74	29.93	0.19	LINGO2	1034.1	ACO1	2444.2	None	1	0	0.014	MCD_11	N
9q34	Dup	136.52	136.59	0.07	RXRA	43.3	COL5A1	85.7	5'-3'	2	0	1.7×10^{-4}	MCD_4 MCD_15	N N
10q21	Del	59.21	59.52	0.31	ZWINT	1424.1	IPMK	100.2	3'	1	0	0.014	POL_2	N
11p14	Del	26.80	26.96	0.16	SLC5A12	102.3	FIBIN	8.3	None	1	0	0.014	ITA_10	N
12q21	Del	76.40	76.56	0.16	E2F7	414.1	NAV3	189.6	None	1	0	0.014	ITA_11	N
15q15	Del	51.02	51.40	0.38	ONECUT1	149.6	WDR72	189.2	5'	1	0	0.014	ITA_16	N
21q21	Del	26.87	26.95	0.08	CYYR1	1.5	ADAMTS1	182.1	None	1	0	0.014	ITA_29	N
Xp22	Dup	6..20	6.43	0.23	NLGN4X	48.0	VCX3A	33.6	3'	1	0	0.014	ITA_37	N
Xp22	Del	22.71	22.77	0.06	ZNF645	509.9	DDX53	156.9	None	1	0	0.014	ITA_14	N
Xp22	Dup	25.52	25.89	0.37	ARX	577.0	MAGEB18	176.6	Within	1	0	0.014	ITA_28	N

ITA = Italy; MCD = Macedonia; POL = Poland; CRO = Croatia; CRHF = Czech Republic; CHOP = Children Hospital of Philadelphia. Segm. Dup.=Segmental Duplications.

Table S13. Single-Gene CNVs Detected in the Discovery Cohort with No Overlap with 13,839 Controls

Chr.	CNV Type	Start (Mb)	End (Mb)	Size (Mb)	Gene	Sample	Extrarenal Phenotypes	Human Phenotype	Mouse Model	Expression in Urinary Tract
2p23	Dup	29.38	29.49	0.11	ALK	ITA_12	N	Neuroblastoma[1]	Behavioral phenotype[2]	+
2p16	Del	55.88	56.02	0.13	EFEMP1	ITA_27	Y	Doyne honey comb retinal dystrophy[3]	AMD-like deposits[4]	+
2q12	Dup	102.48	102.50	0.02	SLC9A4	ITA_24	N	-	Metabolic acidosis[5]	+
2q12	Del	104.96	105.19	0.23	MRPS9	ITA_5	N	-	-	+
2q22	Dup	139.25	139.36	0.11	NXPH2	MCD_1	Y	-	-	+
3q21	Dup	127.33	127.34	0.01	ALDH1L1	ITA_24	N	-	Low reproductive efficiency[6]	+
10p15	Del	3.01	3.12	0.11	PFKP	POL_12	Y	-	-	+
11q22	Del	99.44	99.54	0.10	CNTN5	MCD_7	Y	-	Neuronal auditory system impairment[7]	-
11q25	Dup	130.24	130.66	0.42	SNX19	MCD_15	N	-	-	+
12q24	Dup	112.83	113.04	0.21	RBM19	POL_7	N	-	Preimplantation embryonic lethality[8]	+
13q12	Del	34.58	34.92	0.34	NBEA	ITA_17	N	Candidate for autism[9]	Neuro-muscular paralysis[10]	+
16q11	Dup	47.83	47.92	0.09	CBLN1	ITA_49	Y	-	Ataxia[11]	-
Xq11	Dup	63.38	63.92	0.54	MTMR8	ITA_15	N	-	-	-

ITA=Italy; MCD=Macedonia; POL=Poland; CRO=Croatia; CRHF=Czech Republic; CHOP=Children Hospital of Philadelphia. Expression in urinary tract from GUDMAP microarray data.

References

1. Mosse, Y.P. et al. Identification of ALK as a major familial neuroblastoma predisposition gene. *Nature* 455, 930-5 (2008).
2. Bilsland, J.G. et al. Behavioral and neurochemical alterations in mice deficient in anaplastic lymphoma kinase suggest therapeutic potential for psychiatric indications. *Neuropsychopharmacology* 33, 685-700 (2008).
3. Stone, E.M. et al. A single EFEMP1 mutation associated with both Malattia Leventinese and Doyne honeycomb retinal dystrophy. *Nat Genet* 22, 199-202 (1999).
4. Fu, L. et al. The R345W mutation in EFEMP1 is pathogenic and causes AMD-like deposits in mice. *Hum Mol Genet* 16, 2411-22 (2007).
5. Bourgeois, S. et al. NHE4 is critical for the renal handling of ammonia in rodents. *J Clin Invest* 120, 1895-904 (2010).
6. Champion, K.M., Cook, R.J., Tollaksen, S.L. & Giometti, C.S. Identification of a heritable deficiency of the folate-dependent enzyme 10-formyltetrahydrofolate dehydrogenase in mice. *Proc Natl Acad Sci U S A* 91, 11338-42 (1994).
7. Li, H. et al. Aberrant responses to acoustic stimuli in mice deficient for neural recognition molecule NB-2. *Eur J Neurosci* 17, 929-36 (2003).
8. Zhang, J., Tomasini, A.J. & Mayer, A.N. RBM19 is essential for preimplantation development in the mouse. *BMC Dev Biol* 8, 115 (2008).
9. Castermans, D. et al. The neurobeachin gene is disrupted by a translocation in a patient with idiopathic autism. *J Med Genet* 40, 352-6 (2003).
10. Su, Y. et al. Neurobeachin is essential for neuromuscular synaptic transmission. *J Neurosci* 24, 3627-36 (2004).
11. Hirai, H. et al. Cbln1 is essential for synaptic integrity and plasticity in the cerebellum. *Nat Neurosci* 8, 1534-41 (2005).