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Supplemental Data

DUF1220-Domain Copy Number Implicated in Human Brain-Size Pathology and Evolution

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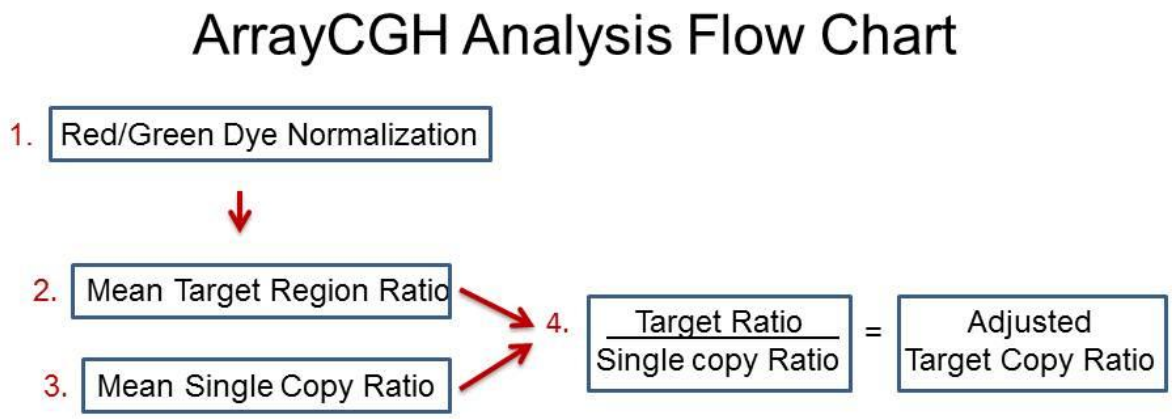

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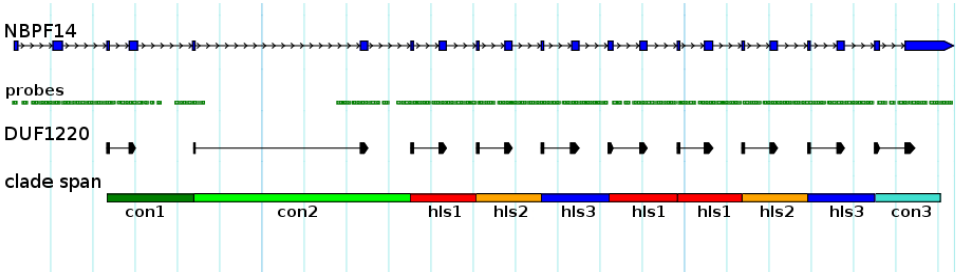

Figure S1. Flow Chart Describing Methods Used for Array Data Processing

(A) The array comparative genomic hybridization (aCGH) flow chart depicts the individual steps taken for the analysis of each sample tested on the custom 1q21 arrays. The following steps were applied to each array experiment (test individual/reference individual): (1) The dye normalized value for each probe on the array was calculated by the Feature Extraction software. (2) The mean test/reference ratio of all probes for a target region of interest was calculated. (3) The mean test/reference ratio of all of the single copy probes was calculated. (4) A normalized target copy ratio was calculated by dividing the target ratio calculated in step 2 by the single copy ratio calculated in step 3. A more detailed description of these procedures can be found in the Methods section.

(B) Diagram of *NBPF14* showing mapped probes, DUF1220 domains, and regions used for clade span analysis.

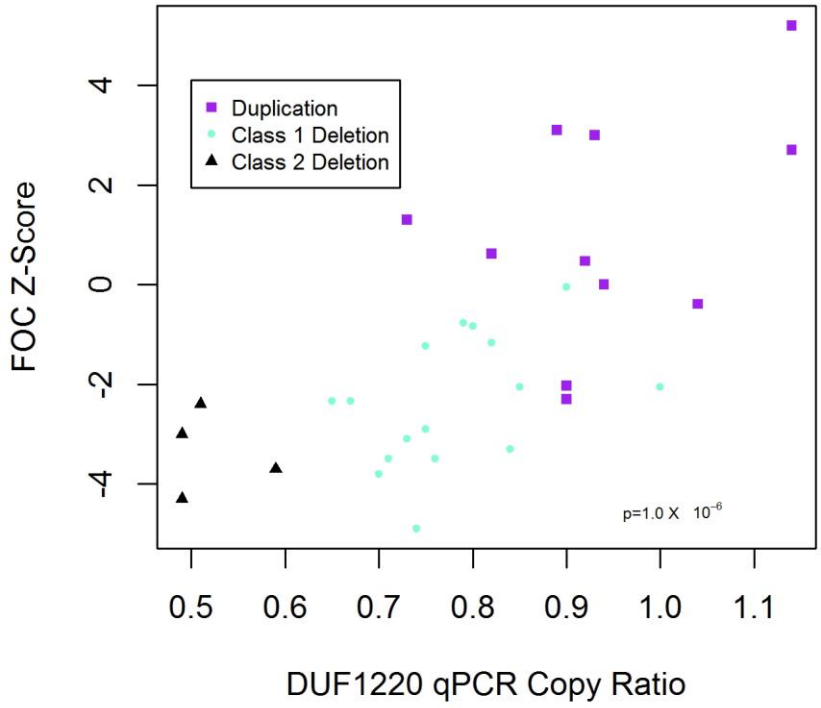

Figure S2. Correlation between FOC *Z* Score and qPCR-Predicted DUF1220 HLS Copy Number within the Disease Population

qPCR-predicted DUF1220 copy number and FOC *Z* scores are shown on *x* axis and *y* axis, respectively. Individuals with Class I deletions (aqua) Class II deletions (black), and duplications (purple) plotted against their FOC *Z* score.

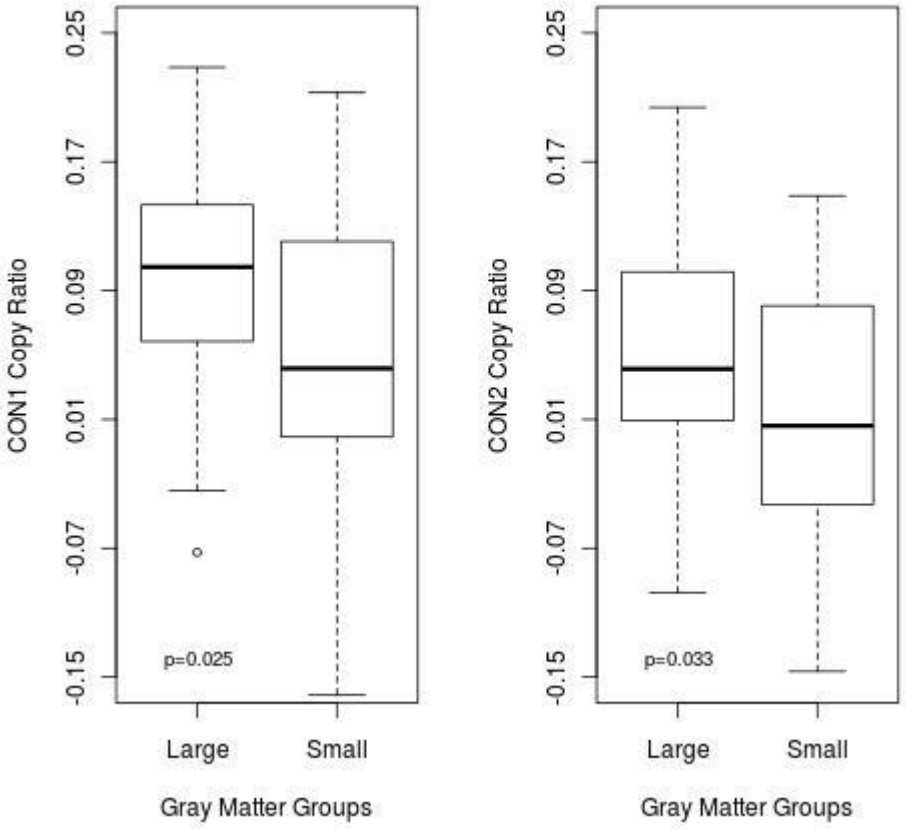

Figure S3. CON1 and CON2 Box Plots for the Nondisease Population

Box plots of CON1 and CON2 copy ratio in the nondisease population showing an increase in mean copy ratio in the large gray matter residual group over the small gray matter residual group. Copy ratio is defined as the relative copy number determined by aCGH in the test sample compared to the reference sample.

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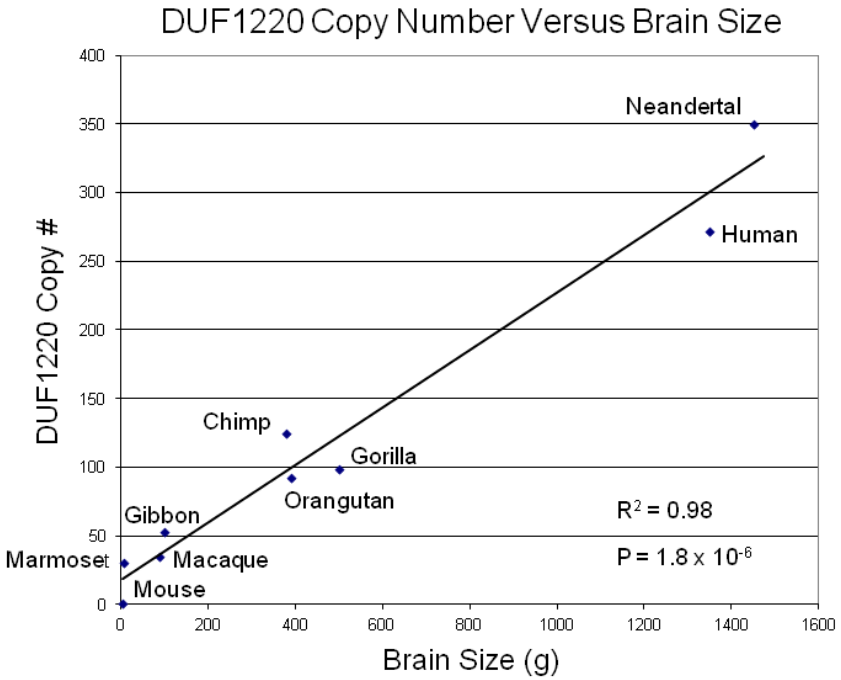

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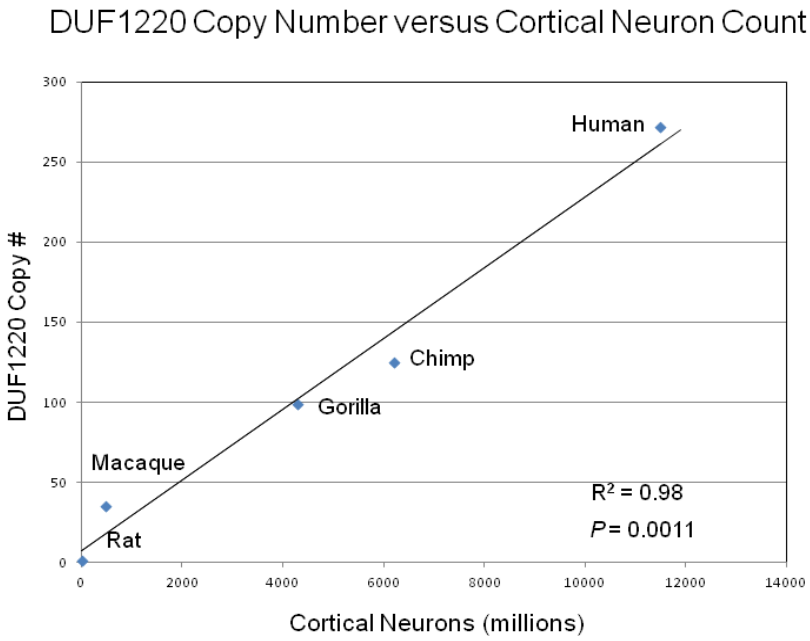

Figure S4. DUF1220 Copy Number Compared to Primate Brain Size and Cortical Neuron Count

(A) Graph showing correlation between brain size (g) versus DUF1220 copy number in multiple species. The DUF1220 copy number estimates were derived from the most recent genome assemblies for these species. The DUF1220 copy number for Neanderthal was estimated using read-depth coverage (Green et al. 2010).

(B) Graph showing correlation between cortical neuron counts (millions) versus DUF1220 copy number in five species.

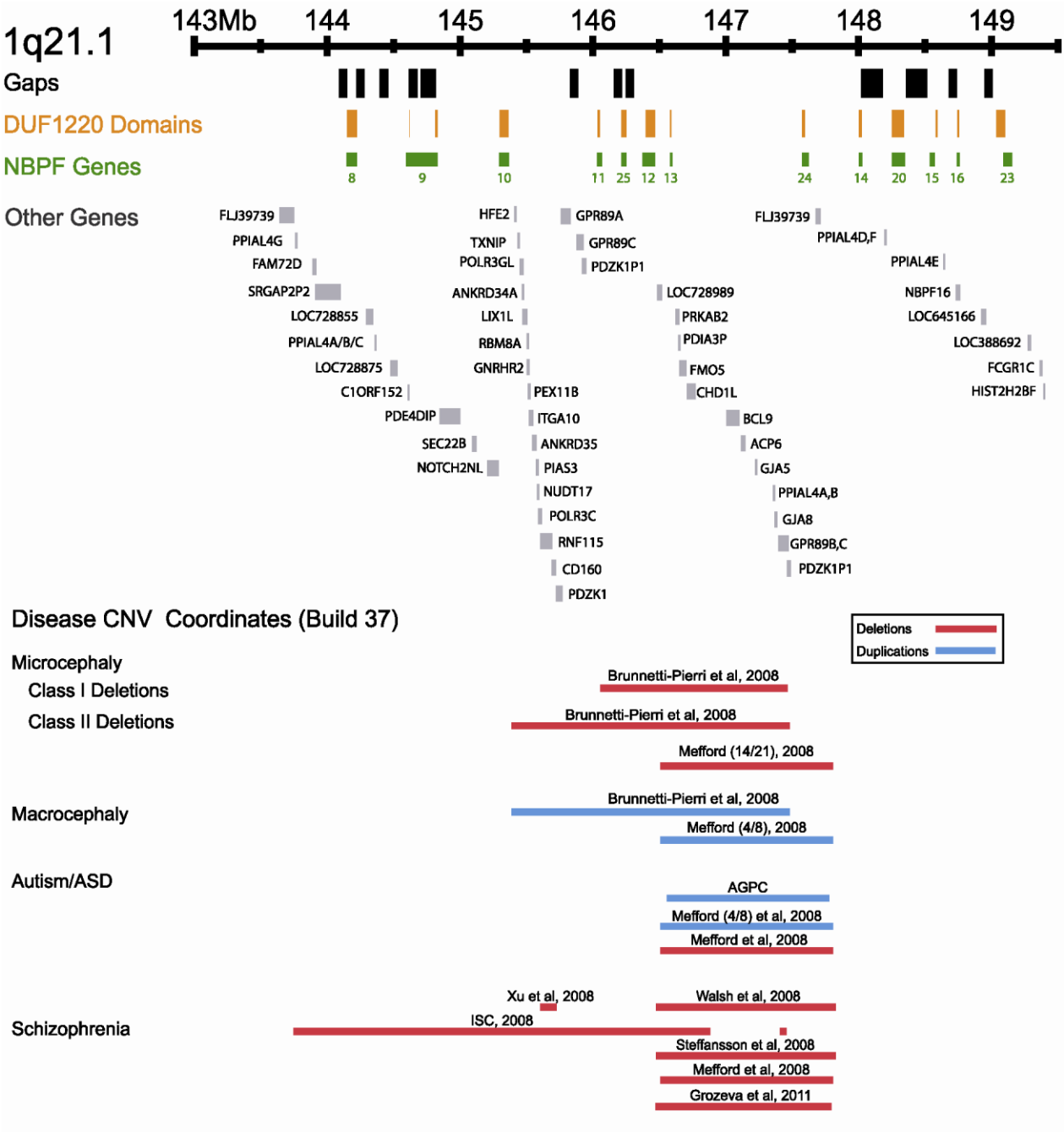

Figure S5. 1q21.1 Genome Map Showing Placement of Disease CNVs, DUF1220 Domains, *NBPF* Genes, Gaps, and Other Genes in the Region

Shown are gaps (black), DUF1220 domains (orange), *NBPF* genes (green), and genes other than *NBPF* genes (gray). Disease CNVs for microcephaly, macrocephaly, autism, and schizophrenia are shown at the bottom of the figure, with red lines representing deletions and blue lines representing duplications.

Table S1. List of Diseases that Have Been Associated with CNVs in the 1q21.1 Region and Their References

Disease	References
Autism [MIM 612475]	Autism Genome Project Consortium 2007 Xu et al. 2008 Mefford et al. 2008 Pinto et al. 2010
Congenital Heart Disease [MIM 121013]	Christiansen et al. 2004 Greenway et al. 2009
Congenital Anom. of Kidney/Urinary tract [MIM 612475]	Weber et al. 2011
Epilepsy [MIM 600669]	de Kovel et al. 2010
Intellectual Disability [MIM 612474; 612475]	Mefford et al. 2008 Jaillard et al. 2010
Intermittent Explosive Disorder [MIM 612474]	Vu et al. 2011
Macrocephaly [MIM 612475]	Mefford et al. 2008 Brunetti-Pierri et al. 2008
Mayer-Rokitansky-Kuster-Hauser Syn. [MIM 612474]	Ledig et al. 2011
Microcephaly [MIM 612474]	Mefford et al. 2008 Brunetti-Pierri et al. 2008 Velinov and Dolzhanskaya 2010
Neuroblastoma [MIM 613017]	Vandepoele et al. 2008 Diskin et al. 2009
Schizophrenia [MIM 612474]	International Schizophrenia Consortium 2008 Steffansson et al. 2008 Ikeda et al. 2010 Levinson et al 2011 Grozeva et al 2011
Thrombocytopenia-absent-radius Syn. [MIM 274000]	Klopocki et al. 2007 Houeijeh et al. 2011

Table S2. List of qPCR Primers and Probes

	Forward Primer Sequence (5'-3')	Reverse Primer Sequence (5'-3')	Probe Sequence (5'-3')
DufQ8IX62	GCTGGAGGTAGTAGAGCCTGAAGTC	GGAGTCAGGCTGTTCAAGACAA	[6-FAM]TGCAGGACTCACTGGATAGATGTTATTCAACTCC[TAMRA-6-FAM]
Hydin	TGTGAGCAGCATGTGGACTACA	TCAGGAGAGATGGTGAATTCTTTTG	[6-FAM]AAGACCATCTTGGACCAAGGAAGAAATATCCTC[TAMRA-6-FAM]
RP11-102F23	CCTTCCAGGCCAGCTTTTG	CGAAGCCTTTCAGATTACTCATGA	[6-FAM]CATGCTTCCCTTCTTTCCCTCTACCCTG[TAMRA-6-FAM]
PDE4DIP	GTCCGGGATGTTGGTATGAATT	CCAAGCCATTTGCTCTGTTGA'	[6-FAM]TCCTCTACTCCTGGCTCAGAAACGCCC[TAMRA-Q]
Class I-specific	CGAAACCACTTGGCCTTCAG	GCTTTCAGCTTTCGTAAATATTCAGTT	[6-FAM]CCCTGCCTCGGCCAGAGGTTTC[TAMRA-6-FAM]
Class II-specific	TGGCTTCTTCCTGCGAATTG	TCTGCTGGGCTACACTTCTCAA	[6-FAM]AAGGACACCGAGGGCCACCTGG[TAMRA-6-FAM]

Table S3. Phenotypic Information for Individuals in Disease Population

Individual	FOC Z Score	Class	Developmental Delay	Ethnicity	Phenotype
10F*	-3.5	del1	Yes	White	Seizures, feeding difficulties, precocious puberty
5F*	-3.3	del1	NA	Hispanic	Mild DF. Failure to thrive and microcephaly
CO16	-2.8	del1	NA	White	Microcephaly, Poor growth
CO18	-2.2	del1	NA	Hispanic	Failure to thrive, gastroesophageal reflux disease
1F(2)*	-2.34	del1	No	White	Intrauterine growth retardation, gastroesophageal reflux disease, 11 pairs of ribs, short stature
13m*	-0.77	del1	No	White	Aggressive behavior, ADHD, seizure disorder
14M*	-3.1	del1	Yes	White	Clubfeet, ankyloglossia, ADHD
15m*	-1.17	del1	Yes	African	Gastroesophageal reflux disease, inguinal hernia
8m*	-2.06	del1	No	Hispanic	Trigonocephaly
9m*	-0.05	del1	Yes	White	Autism spectrum behaviors, two- to three-toe syndactyly
CO10	-2.4	del1	NA	Hispanic	Microcephaly
CO12	-2.1	del1	Yes	African	Mild DD/MR
CO14	-1.1	del1	Yes	Hispanic	Failure to thrive and MCA
CO15	-3.6	del1	NA	White	Failure to thrive
CO17	-3.1	del1	yes	White	Moderate DD/MR, DF, short stature
4(11)*	-3.5	del1	Yes	White	Intrauterine growth retardation, chorioretinal and iris coloboma, lens subluxation, microphthalmia, laryngomalacia VUR grade 4/5, hydronephrosis, postaxial polydactyly, short stature
2(4)*	-3.8	del1	Yes	White	Ankyloglossia, behavioral problems, hallucinations, sleep disturbance
12(6)*	-2.9	del1	Yes	White	Failure to thrive, Hemangioma
17m*	-3.7	del2	Yes	White	Gestation complicated by maternal diabetes, cleft palate, preaxial polydactyly, sensorineural hearing loss, bicuspid aortic valve, congenital cystic adenomatoid malformation of the lung, pelvic kidney, short stature
18m*	-2.05	del2	Yes	White	Plagiocephaly, strabismus, MRI: brain asymmetry, enlargement of the lateral and III ventricles, increased subarachnoid space

19m*	-2.34	del2	Yes	White	Failure to thrive, frequent infections, pectus excavatum, small kidneys, hypospadias
20m*	-3	del2	Yes	White	Failure to thrive
21m*	-2.4	del2	Yes	White	Failure to thrive, speech delay, polyhydramnios, severe feeding difficulties, chronic vomiting
CO11	-2.8	del2	Yes	White	Mild developmental delay
CO6	-2.4	del2	NA	White	NA
16(12)*	-4.3	del2	Yes	White	NA
29F*	-2.03	dup	Yes	White	Failure to thrive, gastroesophageal reflux disease, lower limb hypertonicity
33F*	3	dup	Yes	White	Esotropia, hydrocephalus, advanced bone age
CO31	-0.02	dup	Yes	Hispanic	NA
34m*	-2.3	dup	Yes	Hispanic	Failure to thrive, Autism, spastic diplegia
CO21	-3.2	dup	Yes	White	Failure to thrive and hydrocephalus
CO23	0.9	dup	NA	White	Seizures, feeding difficulties, precocious puberty
CO27	-2.3	dup	NA	Hispanic	Autism, spastic diplegia,
22(13)*	2.7	dup	No	Hispanic	Complex congenital heart defect
23(14)*	1.3	dup	Yes	White	Failure to thrive, hypotonia, eczema
24(17)*	0	dup	Yes	East Indian	Speech delay, seizures
25(18)*	3.1	dup	Yes	White	Esotropia, VI and VII nerve paresis, hypotonia
26(19)*	0.47	dup	No	Hispanic	Lower limb hypertonicity
31(20)*	-0.39	dup	Yes	C-French	Arthrogryposis, fifth-finger clinodactyly, Psoriasis, right-sided hyperpigmentation
27(21)*	0.62	dup	Yes	Hispanic	Chiari malformation, hemihypertrophy
28(22)*	5.2	dup	Yes	White	Dysphagia, gastroesophageal reflux disease, lower limb hypertonicity
CO1	0.7	dup	NA	Hispanic	Pervasive Developmental Disorder

The FOC *Z* score, aberration class, and phenotype are shown. NA=not available; * denotes samples that were previously tested on low resolution arrays in Brunetti-Pierri et al, 2008.

Table S4. qPCR-Based Correlations between Copy Number and FOC *Z* Score for Six Genes/Regions for the Entire Disease Population

Probe	Beta	SE	p Value
DUF1220 (HLS)	9.99400	1.99500	1.0×10^{-6}
HYDIN	5.02200	2.00200	0.01757
Class II-specific	5.20700	2.00000	0.01403
RP11-102F23	3.43270	0.68570	1.0×10^{-5}
Class I-specific	6.46000	1.53400	0.00020
PDE4DIP	2.76200	2.72400	0.31900

In the following tables, common statistical nomenclature is used as follows: beta is the difference in mean copy ratio in the case of t-tests, or the slope of the fit line in the case of a linear regression; SE is the standard error of beta, and p value is the probability of obtaining a test statistic as extreme as the one observed given the null is true.

Table S5. Correlation of Average aCGH-Based Copy Ratio of Non-DUF1220 Genes in the 1q21.1-1q21.2 Region with FOC *Z* Score in the Whole Disease Population

Gene	Beta	SE	R^2	p Value
SRGAP2	**5.255**	**1.385**	**0.265**	**0.0005**
PDE4DIP*	**7.064**	**1.673**	**0.308**	**0.0001**
SEC22B	**5.255**	**1.385**	**0.265**	**0.0049**
II ***NOTCH2NL***	**5.879**	**1.292**	**0.341**	**4.88×10^{-5}**
HFE2	**3.217**	**1.185**	**0.156**	**0.0097**
TXNIP	**3.048**	**1.220**	**0.135**	**0.0166**
POLR3GL	**3.146**	**1.25**	**0.136**	**0.0164**
ANKRD34A	**3.462**	**1.479**	**0.120**	**0.024**
ANKRD35	**4.108**	**1.576**	**0.145**	**0.0128**
LIX1L	**2.847**	**1.205**	**0.122**	**0.0231**
RBM8A	**3.282**	**1.236**	**0.150**	**0.0113**
GNRHR2	**3.145**	**1.332**	**0.122**	**0.0235**
PEX11B	**3.434**	**1.294**	**0.150**	**0.0114**
ITGA10	**3.871**	**1.500**	**0.143**	**0.0134**
NUDT17	**4.617**	**1.977**	**0.120**	**0.025**
RNF115	**2.446**	**1.056**	**0.118**	**0.0260**
CD160	**3.480**	**1.362**	**0.140**	**0.0145**
I ***PDZK1***	**4.019**	**0.663**	**0.479**	**3.82×10^{-7}**
GPR89	**3.744**	**0.654**	**0.451**	**1.14×10^{-6}**
HYDIN	**2.9969**	**0.8220**	**0.2494**	**0.0008**
PRKAB2	**2.449**	**0.425**	**0.454**	**1.03×10^{-6}**
PDIA3P	**3.293**	**0.607**	**0.424**	**3.02×10^{-6}**
FMO5	**2.392**	**0.417**	**0.452**	**1.09×10^{-6}**
CHD1L	**2.392**	**0.454**	**0.415**	**1.02×10^{-6}**
BCL9	**2.484**	**0.429**	**0.456**	**9.28×10^{-7}**
ACP6	**2.733**	**0.478**	**0.450**	**1.17×10^{-6}**
GJA5	**2.933**	**0.517**	**0.446**	**1.36×10^{-6}**
GJA8	**2.626**	**0.459**	**0.450**	**1.19×10^{-6}**
FCGR1C	-0.209	1.803	0.000	0.909
SV2A	2.309	2.426	0.022	0.347
BOLA1	1.638	2.567	0.010	0.5271
MTMR11	3.206	3.434	0.021	0.3562
OTUD7B	5.271	7.468	0.012	0.4845
SF3B4	1.698	2.776	0.009	0.5442
VPS45	8.014	17.182	0.005	0.6434
PLEKHO1	6.233	4.455	0.047	0.1694
ANP32E	7.231	5.843	0.037	0.2231
PRPF3	7.231	7.698	0.022	0.3532
C1orf54	5.627	4.130	0.044	0.1807
MRPS21	10.401	8.408	0.037	0.2233

Genes with a significant association ($p \leq 0.05$) are in bold. Genes identified as Class I and Class II deletion groups are bracketed. *PDE4DIP* has an asterisk to indicate it encodes the ancestral DUF1220 domain copy.

Table S6. Correlation of Average aCGH-Based Copy Ratio of Non-DUF1220 Genes in the 1q21.1-1q21.2 Region with FOC *Z* Score for the Combined Class I and Class II Deletion Groups

Gene	Beta	SE	R^2	p Value
SRGAP2	2.819	1.707	0.102	0.113
PDE4DIP	2.273	1.198	0.131	0.070
SEC22B	1.529	0.982	0.092	0.132
NOTCH2NL	2.046	1.038	0.139	0.060
HFE2	1.018	0.658	0.091	0.135
TXNIP	1.006	0.662	0.088	0.141
POLR3GL	0.997	0.684	0.081	0.158
ANKRD34A	1.328	0.923	0.079	0.163
ANKRD35	1.403	0.922	0.088	0.141
LIX1L	0.973	0.640	0.088	0.141
RBM8A	1.062	0.703	0.087	0.144
GNRHR2	1.037	0.729	0.078	0.168
PEX11B	1.110	0.715	0.091	0.134
ITGA10	1.232	0.877	0.076	0.173
NUDT17	1.403	1.070	1.200	0.242
RNF115	0.813	0.556	0.082	0.157
CD160	1.138	0.747	0.088	0.141
PDZK1	1.725	1.029	0.105	0.107
GPR89	1.151	1.012	0.085	0.149
HYDIN	0.809	1.003	0.026	0.428
PRKAB2	-1.637	3.705	0.008	0.663
PDIA3P	-6.233	3.052	0.148	0.052
FMO5	-2.192	4.948	0.008	0.662
CHD1L	-2.142	3.557	0.015	0.553
BCL9	-0.399	3.296	0.006	0.905
ACP6	-0.556	2.370	0.002	0.817
GJA5	-0.440	1.558	0.003	0.780
GJA8	-1.504	2.764	0.012	0.591
FCGR1C	0.971	0.999	0.038	0.341
SV2A	-0.026	1.831	0.000	0.989
BOLA1	0.740	2.029	0.365	0.718
MTMR11	0.569	2.569	0.002	0.827
OTUD7B	0.787	5.306	0.001	0.883
SF3B4	1.209	2.007	0.015	0.553
VPS45	5.289	9.023	0.014	0.563
PLEKHO1	3.174	3.496	0.033	0.373
ANP32E	0.942	4.051	0.002	0.818
PRPF3	4.604	5.890	0.025	0.442
C1orf54	**4.846**	**2.251**	**0.162**	**0.042**
MRPS21	5.921	6.526	0.033	0.373

Significant ($p \leq 0.05$) associations are shown in bold, and beta is the slope of a fit line.

Table S7. aCGH-Predicted Correlation of DUF1220 Clade Copy Number versus Residual Gray Matter for the Nondisease Population

Clade	Beta	SE	p Value
CON1	**0.052**	**0.023**	**0.0246**
CON2	**0.042**	**0.019**	**0.0334**
CON3	0.019	0.020	0.3307
HLS1	0.001	0.030	0.9753
HLS2	0.017	0.035	0.6315
HLS3	0.014	0.035	0.6881

Significant ($p \leq 0.05$) associations are shown in bold. Beta is the difference in mean copy ratio between high and low gray matter volume groups.

Table S8. Correlation of Average aCGH-Based Copy Ratio of Non-DUF1220 Genes in the 1q21.1-1q21.2 Region with Residual Gray Matter Groups for the Nondisease Population

	Gene	Beta	SE	p Value
	SRGAP2	-0.022	0.018	0.238
	PDE4DIP*	**0.021**	**0.010**	**0.044**
	SEC22B	**0.018**	**0.009**	**0.045**
II	*NOTCH2NL*	0.050	0.032	0.127
	HFE2	-0.017	0.019	0.369
	TXNIP	-0.009	0.011	0.446
	POLR3	-0.014	0.015	0.351
	ANKRD34	-0.051	0.427	0.233
	ANKRD35	-0.030	0.020	0.131
	LIX1L	-0.010	0.008	0.182
	RBM8A	-0.021	0.026	0.424
	GNRHR2	-0.021	0.013	0.108
	PEX11B	-0.016	0.018	0.381
	ITGA10	-0.035	0.029	0.229
	NUDT17	**-0.037**	**0.017**	**0.034**
	RNF115	0.002	0.009	0.846
	CD160	-0.010	0.013	0.452
I	*PDZK1*	-0.011	0.008	0.218
	GPR89	0.006	0.005	0.298
	HYDIN	-0.063	0.127	0.623
	PRKAB2	-0.006	0.005	0.266
	PDIA3P	0.002	0.016	0.885
	FMO5	-0.002	0.008	0.782
	CHD1L	-0.003	0.005	0.554
	BCL9	-0.011	0.007	0.135
	ACP6	-0.016	0.012	0.185
	GJA5	-0.038	0.023	0.104
	GJA8	-0.014	0.014	0.319
	FCGR1	-0.005	0.056	0.936
	SV2A	**-0.067**	**0.033**	**0.048**
	BOLA1	-0.054	0.030	0.072
	MTMR11	-0.031	0.024	0.201
	OTUD7B	-0.010	0.007	0.148
	SF3B4	**-0.056**	**0.022**	**0.012**
	VPS45	0.001	0.007	0.856
	PLEKHO1	-0.021	0.022	0.329
	ANP32E	-0.016	0.012	0.163
	PRPF3	-0.002	0.009	0.832
	C1orf54	0.001	0.015	0.927
	MRPS21	-0.009	0.009	0.358

aCGH-predicted correlation of 1q21.1 gene copy number versus FOC *Z* score for nondisease populations is reported. Significant ($p \leq 0.05$) associations are shown in bold.

Table S9. Brain Size and Copy Number of DUF1220 Domains and 1q21 Genes in Multiple Species

	Human	Chimp	Orangutan	Macaque	Marmoset
Brain (g)	1,350	380	390	88	7
Copy #					
DUF1220	242(272)	105(125)	70(92)	13(35)	20(31)
SRGAP2	2*	0	0	0	0
PDE4DIP	3	3	4	1	1
SEC22B	1	1	1	1	1
NOTCH2NL	1	1	1	1	1
HFE2	1	1	1	1	1
TXNIP	1	1	1	1	1
POLR3	2	2	2	2	2
ANKRD34	1	1	1	1	1
ANKRD35	1	1	1	1	1
LIX1L	1	1	1	1	1
RBM8A	1	1	1	1	1
GNRHR2	1	1	1	1	1
PEX11B	1	1	1	1	1
ITGA10	1	1	1	1	1
NUDT17	1	1	1	1	1
RNF115	1	1	1	1	1
CD160	1	1	1	1	1
PDZK1	3	1	1	1	1
GPR89	3	1	1	1	1
HYDIN	1	0	0	0	0
PRKAB2	1	1	1	1	1
PDIA3P	1	1	1	1	1
FMO5	1	1	1	1	1
CHD1L	1	1	1	1	1
BCL9	1	1	1	1	1
ACP6	1	1	1	1	1
GJA5	1	1	1	1	1
GJA8	1	1	1	1	1
FCGR1	2	1	1	1	1
SV2A	1	1	1	1	1
BOLA1	1	1	1	1	1
MTMR11	1	1	1	1	1
OTUD7B	1	1	1	1	0
SF3B4	1	1	1	1	1
VPS45	1	1	1	1	1
PLEKHO1	1	1	1	1	1
ANP32E	1	1	1	1	1
PRPF3	1	1	1	1	1
C1orf54	1	1	1	1	1
MRPS21	1	1	1	1	1
CA14	1	1	1	1	1
C1orf51	1	1	1	1	1
APH1A	1	1	1	1	1

DUF1220 copy number in the 1q21 region is shown, with total DUF1220 genome counts listed in parenthesis. Genes that are in the Class I and Class II deletion and duplication regions identified by Brunetti-Pierri et al 2008 and Mefford et al 2008 are bracketed. *According to Dennis et al, 2012, two partial copies of SRGAP2 exist in the 1q21.1-1q21.2 region, although the current genome build (hg19) reports only 1 copy.

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