Table S1. Fosmid Clones Used for FISH Experiments, Related to Figure 1

Probe	Fosmid clone	Genomic coordinates (NCBI36/hg18)	Target Sequence Description
1	WIBR2-2926C23_G248P88292B12	chr1: 204,575,058-204,618,304	duplicated *SRGAP2* sequence (predicted copy number 6 in human) from intron 2 to intron 3
2	WIBR2-2044O01_G248P86756H1	chr1: 205,518,260-205,556,982	region telomeric to 1q32.1 *SRGAP2A* contig
3	WIBR2-3685H16_G248P801507D8	chr1: 204,455,995-204,491,660	region slightly beyond 5' end of 1q32.1 *SRGAP2A* contig (5' of 1q32.1 paralog)
4	WIBR2-2212C22_G248P86986B11	chr1: 204,976,699-205,015,867	region slightly beyond 3' end of 1q32.1 *SRGAP2A* contig (3' of 1q32.1 paralog)
5	WIBR2-3549F23_G248P802137C12	chr1: 119,969,004-120,006,662	region telomeric to 1p12 *SRGAP2C* contig
6	WIBR2-1864B19_G248P86489A10	chr1: 147,506,053-147,549,258	region within 1p12 *SRGAP2C* contig, near the 5' end (5' of 1p12 paralog)
7	WIBR2-1489L21_G248P83865F11	chr1: 120,931,054-120,966,849	region slightly beyond 3' end of 1p12 *SRGAP2C* contig (3' of 1p12 paralog)
8	WIBR2-2397J12_G248P82711E6	chr1: 120,697,113-120,735,077	region just outside of original 258 kbp duplicated sequence (targets sequence where the original duplication landed)
9	WIBR2-3738J10_G248P802587E5	chr1: 204,285,032-204,323,561	duplicated *SRGAP2* sequence (predicted copy number 8 in human) from upstream of the gene to intron 1

Table S2. Maximum-Likelihood Estimates of Selection of *SRGAP2* Orthologs, Related to Figure 2

Model comparison	Model 1	Model 2	p-value*	dN/dS
Purifying selection	dN/dS = 1	one dN/dS	6.95E-126	All = 0.01221
Lineage heterogeneity	one dN/dS	free dN/dS	1.16E-05	Human *SRGAP2A* = 0.0001 Human *SRGAP2B* = 0.6302 Human *SRGAP2C* = ∞
Primate specific	one dN/dS	primate dN/dS	1.46E-03	Primates = 0.0415 Rest = 0.00542
Human specific	one dN/dS	human dN/dS	3.05E-10	Human = 0.7358 Rest = 0.0044
Human *SRGAP2B/C* specific	**one dN/dS**	**duplicate dN/dS**	**1.32E-11**	**Human *SRGAP2B/C* = 2.2310** **Rest = 0.0044**
Human *SRGAP2B* specific	one dN/dS	1q21.1 dN/dS	1.79E-03	Human *SRGAP2B* = 0.62909 Rest = 0.01000
Human *SRGAP2C* specific	one dN/dS	1p12 dN/dS	2.53E-09	1p12 = 999 Rest = 0.00662
Site-specific positive selection	model 1a	model 2	0.999	n/a
	model 7	model 8	1	n/a
	model 8a	model 8	1	n/a

* A likelihood ratio test (chi-squared test of the log-likelihood ratio of two models) was used to compare model 1 (null model) and model 2 (alternative model). Significant p-values reflect a higher fit of the data to the alternative model over the null model.

Table S3. Sequence Analysis of Human *SRGAP2* mRNA Transcripts from Neuronal Cells, Related to Figure 3

Variant	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Exon	**1**			**2**		**3**	**5**			**6**			**8**	**9**	**Intron 9 extension**	
ANCESTRAL *SRGAP2A*																
***SRGAP2A* contig (CH17)**	**C**	**G**	**G**	**G**	**C**	**C**	**G**	**C**	**C**	**G**	**T**	**G**	**G**	**T**	**a**	**g**
SH-SY5Y Cell Line [3]	C	G	G	G	C	C	G	C	C	G	T	G	G	T	n/a	n/a
Pooled Fetal Brain [8]	C	G	G	G	C	C	G	C	C	G	T	G	G	T	n/a	n/a
DUPLICATE *SRGAP2C*																
***SRGAP2C* contig (CH17)**	**T**	**G**	**G**	**A**	**C**	**T**	**C**	**T**	**C**	**A**	**C**	**A**	**G**	**T**	**A**	**A**
I.M.A.G.E. cDNA clone (Accession:BC112927)*	T	A	G	A	C	T	C	T	C	A	C	A	G	T	A	A
Pooled Fetal Brain [1]	T	G	G	A	C	T	C	T	C	A	C	A	G	T	A	A
SH-SY5Y Cell Line [2]	T	A	G	A	C	T	C	C	T	G	C	A	G	T	A	A
Single Adult Brain [14]			G	A	C	T	C	C	T	G	C	A	G	T	A	A
Single Fetal Brain [17]	T	A	G	A	C	T	C	C	T	G	C	A	G	T	A	A
Single Fetal Brain [3]	T	A	G	A	C	T	C	A	T	G	C	A	G			
Single Fetal Brain [1]^				G	C	T	C	C	T	G	C	A	G			A
Pooled Fetal Brain [8]	T	A	G	A	C	T	C	C	T	G	C	A	G	T	A	A
Pooled Fetal Brain [1]^	T	A	G	A	C	T	C	C	T	G	C	A	G	C	A	A
Pooled Fetal Brain [2]	T	A	G	A	C	n/a	C	C	T	G	C	A	G	T	A	A
DUPLICATE *SRGAP2B/D*																
***SRGAP2B* contig (CH17)**	**T**	**G**	**G**	**G**	**T**	**C**	**C**	**C**	**C**	**G**	**C**	**G**	**C**	**C**	**G**	**G**
***SRGAP2D* contig (CH17)**													**C**	**C**	**A**	**G**
SH-SY5Y Cell Line [1]	T	G	G	G	T	C	C	C	C	G	C	G	C	C	G	G
Single Fetal Brain [1]				G	T	C	C	C	C	G	C	G	C	C	G	G
Pooled Fetal Brain [2]*	T	G	G	G	T	C	C	C	C	G	C	G	C	C	G	G
SH-SY5Y Cell Line [2]	T	G	A	n/a	n/a	n/a	C	C	C	A	C	G	C	C	A	G
Single Adult Brain [3]	T	G	A	n/a	n/a	n/a	C	C	C	A	C	G	C	C	G	G
Single Fetal Brain [6]	T	G	G	n/a	n/a	n/a	C	C	C	A	C	G	C	C	A	G
Pooled Fetal Brain [8]	T	G	A	n/a	n/a	n/a	C	C	C	G	C	G	C	C	A	G
Pooled Fetal Brain [11]	T	G	A	n/a	n/a	n/a	C	C	C	A	C	G	C	C	A	G
Pooled Fetal Brain [1]^	T	G	A	n/a	n/a	n/a	n/a	C	C	G	C	G	C	C	A	G
UNKNOWN																
Pooled Fetal Brain [1]^	T	G	G	G	T	C	C	C	C	G	C	G	G	T	A	A

Total clones sequenced: Ancestral *SRGAP2A*: SH-SY5Y = 3 clones; pooled fetal brain = 8 clones; Duplicates *SRGAP2B/C/D*: SH-SY5Y = 5 clones; pooled fetal brain = 35 clones; single fetal brain = 28; single adult brain = 17.

Colored boxes represent types of substitutions compared to the ancestral state (from chimpanzee sequence): red = nonsynonymous; blue = synonymous; yellow = noncoding. The green boxes including "n/a" represent variants not represented in transcript due to splicing and/or deleted exons. The empty gray boxes are variants that did not have high-quality coverage during sequencing of clones. The numbers in brackets are the total transcripts observed from the tissue source.

*These cDNA clones were used in functional assays in the accompanying manuscript (Charrier et. al., 2012 [this issue of *Cell*]).

^ Transcript only observed once in any tissue type.

Table S4. Copy Number Variants Detected in Cases with Developmental Delay and Controls, Related to Table 2

ID	Sex	Age	Cytoband	Human reference genomic coordinates (NCBI36)	Size (bp)	Type	Phenotype	Inheritance	Notes
9906627 Signature Genomics	Female	23 months	1q32.1 - 1q32.2	chr1:203,821,004-208,526,029	4,705,025	Deletion	Developmental delay, dysmorphic features, and multiple congenital anomalies	*De novo*	No other large CNVs in the genome
GC21416 Signature Genomics	Female	3 years	1q32.1 - 1q41	chr1:203,845,072-215,071,039	11,225,967	Deletion	Developmental delay, growth delay, hypotonia, and carnitine deficiency	*De novo*	No other large CNVs in the genome
9881737 Signature Genomics	Male	6 months	1q32.1 - 1q32.2	chr1:204,164,223-205,670,688	1,506,465	Deletion	Marked hypertelorism in both baby and father. Also, father has neurocognitive defects (may be from serious traumatic brain injury at age 11)	Paternal	No other large CNVs in the genome
9900886 Signature Genomics	Female	10 years	1q32.1 - 1q41	chr1:204,650,122-213,516,382	8,866,260	Duplication	MRI showed asymmetry: stable, abnormal left hippocampus, prominence of the left anterior temporal horn, probable mild left periventricular leukomalacia, and stable hypoplasia of the posterior body of the corpus callosum. The patient has a history of seizures, ADHD, behavior problems, and learning disabilities	Unknown	Patient also has a 283 kbp duplication at 1q32.1 (2 Mbp proximal to described duplication) including *KISS1*, *GOLT1A*, *PLEKHA6*, *PPP1R15B*, and *PIK3C2B*, and a 7.7 kbp *NRG3* intronic deletion
9896507 Signature Genomics	Male	Newborn	1q21.1-1q44	chr1:143,793,178-247,169,918	103,376,741	Duplication	Patient exhibits multiple congenital abnormalities	Unknown	Mosaic (18/50 uncultured cells)
9885509 Signature Genomics	Female	3 weeks	1q31.1-1q32.2	chr1:184,399,825-208,376,099	23,976,275	Duplication	Patient exhibits multiple congenital abnormalities	Unknown	No other large CNVs in the genome.
02753 Intellectual Disability	Male	3 years and 10 months	1p12-1p11.2	chr1:120,498,679-121,186,957	688,278*	Duplication	Patient shows regression of speech and behavior. Psychological evaluation led to the diagnosis of intellectual disability and generalized development disturbance	Unknown	No other large CNVs in the genome
12523.p1 SSC Autism	Male	6 years and 1 month	1p12-1p11.2	chr1:120,498,679-121,186,957	688,278*	Duplication	Patient is cognitively normal but his adaptive behavior skills fall in the low range; he reportedly shows significant hyperactivity and inappropriate speech. ADOS score = 9 (on 1-10 scale; >4 clinical; 10 most impaired)	Paternal	Patient also has 1.8 Mbp deletion at 11p14.3 including *AN05*, *SLC17A6*, *FANCF*, *GAS2*, and *SVIP*
13398.p1 SSC Autism	Male	8 years and 7 months	1p12-1p11.2	chr1:120,498,679-121,186,957	688,278*	Duplication	Patient shows attentional deficits, anxiety/depression, and aggression. ADOS score = 9 (on 1-10 scale; >4	Maternal	Maternal side has history of migraines, eating disorder,

							clinical; 10 most impaired)		obsessive compulsive disorder, and post-traumatic stress syndrome. No other large CNVs in the genome
150-10596 NIMH control	Male	73 years	1p12-1p11.2	chr1:120,498,679-121,186,957	688,278*	Duplication	This control is self-reported as neurologically normal	Unknown	No other large CNVs in the genome

*Due to several gaps and incorrect annotations of the human reference 1p12.1-1p11.2 genomic region (e.g., inversion and a gap within *SRGAP2C*; see **Figure 1C** in main text), there is uncertainty in these size estimates. They are likely greater than reported here and, notably, include numerous genes.

Table S5. *SRGAP2* Paralog-Specific BAC Clones, Related to Experimental Procedures

***SRGAP2* Contig**	**GenBank Accession number**	**Clone**	**Sequence status at time of publication**
SRGAP2A	AC244035	CH17-84K15	complete
SRGAP2A	AC244158	CH17-67I7	complete
SRGAP2A	AC244017	CH17-255A18	complete
SRGAP2A	AC244016	CH17-251H16	complete
SRGAP2A	AC244023	CH17-465H19	complete
SRGAP2A	AC244018	CH17-286M8	complete
SRGAP2A	AC244024	CH17-67D14	complete
SRGAP2A	AC244019	CH17-397E23	complete
SRGAP2A	AC244159	CH17-94O18	complete
SRGAP2A	AC244034	CH17-76K2	complete
SRGAP2B	AC243754	CH17-61O17	fragmented working draft
SRGAP2B	AC241585	CH17-195P21	complete
SRGAP2B	AC244020	CH17-400H17	complete
SRGAP2B	AC242498	CH17-254B7	complete
SRGAP2B	FP700111	CH17-164J11	contiguous working draft
SRGAP2C	AC241377	CH17-118O6	complete
SRGAP2C	FP700108	CH17-465D18	complete
SRGAP2C	AC244453	CH17-469K7	complete
SRGAP2C	AC240103	CH17-366F13	complete
SRGAP2C	AC243994	CH17-219N22	complete
SRGAP2C	AC244021	CH17-437K3	complete
*SRGAP2D**	AC244015	CH17-248H7	complete

* An additional *SRGAP2D* BAC clone (CH17-266P3; GenBank Accession Number AC246680), not included in our analysis, was sequenced after acceptance of the manuscript. This clone verifies the *SRGAP2D* deletion spanning across exons 2 and 3.

Table S6. *SRGAP2* Primers, Related to Experimental Procedures

Experiment	Forward Primer		Reverse Primer	
	***SRGAP2* Target**	**Sequence**	***SRGAP2* Target**	**Sequence**
Validate discordant *SRGAP2*-containing BACs	Intron 2	GGATTGGCTTTGATTGCTGT	Intron 3	TGGGGGTCTGGTGTACAGAT
	Intron 1	CATGTTTGCATGTGGTAGGC	Intron 1	CTCAGAGCAACCAGGGAGTC
SRGAP2B paralog-specific qPCR	Intron 2	AGACCTCTACTTCTCAATGCCTCA	Intron 2	TGTGCACACATTTTAACACTTGG
SRGAP2C paralog-specific qPCR	Intron 6	GTAAGTGCCGTGTACATGTATGG	Intron 6	AAATGGGTGTTTCACAGTTCAGG
	Intron 7	CGGACCACTGTCAAAGCATA	Intron 7	GGCAGAAGAGTGAGCTAGCAG
SRGAP2D paralog-specific qPCR	Intron 6	GACAACACCAGATAAACCTGAAAAC	Intron 6	TTCAACGGTTAAACACACCCTAC
SRGAP2A paralog-specific qPCR	Intron 12	TCAGTTCCTTGGCTGAAACC	Intron 12	TGCCAAACTGATGTCTCTGG
Sequencing *SRGAP2A* transcripts	Exon 1	CATGTTGTGCGGAAGGACT	Exon 10	TGCCCTCCAGGTACTCTTTC
Sequencing *SRGAP2* duplicate transcripts	Exon 1	(same as above)	Intron 9 extension	TCTGAGTATGCCCACATTCG
	Exon 5	CCAGTCAACTGCTGGAATCTC		
SRGAP2A-specific RT-PCR	Exon 8	TCCACTCTAAAGATTGAAAACGAA	Exon 10	(same as above)
	Exon 21	CGGCTGGATAGTCCACAGAT	Exon 22	TGCCGTTCTAGTTCCCGTAG
SRGAP2-duplicate-specific RT-PCR	Exon 8	(same as above)	Intron 9 extension	(same as above)
SRGAP2C-specific RT-PCR	Exon 7*	AAGGCCATCAAAGCCCA	Exon 8	TGCACCAGATTCCTGAACAA
SRGAP2D NMD assay	Exon 1	(same as above)	Exon 5	CCGAGTAGAGCTCGTTCAGG
	Exon 1/4 junction	CGATACTCAGGTCAAAGAGTAA	Exon 5b	CCAATTTGCTTCTCCTCCTG
ALB qPCR control	n/a	GTGGGCTGTAATCATCGTCT	n/a	TGCTGGTTCTCTTTCACTGAC
GAPDH RT-PCR control	n/a	AGCCACATCGCTCAGACACC	n/a	GTACTCAGCGCCAGCATCG

* This oligonucleotide contains a *SRGAP2C* PSV.