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Supplementary Data

Rare Deletions at the Neurexin 3 Locus in Autism Spectrum Disorder

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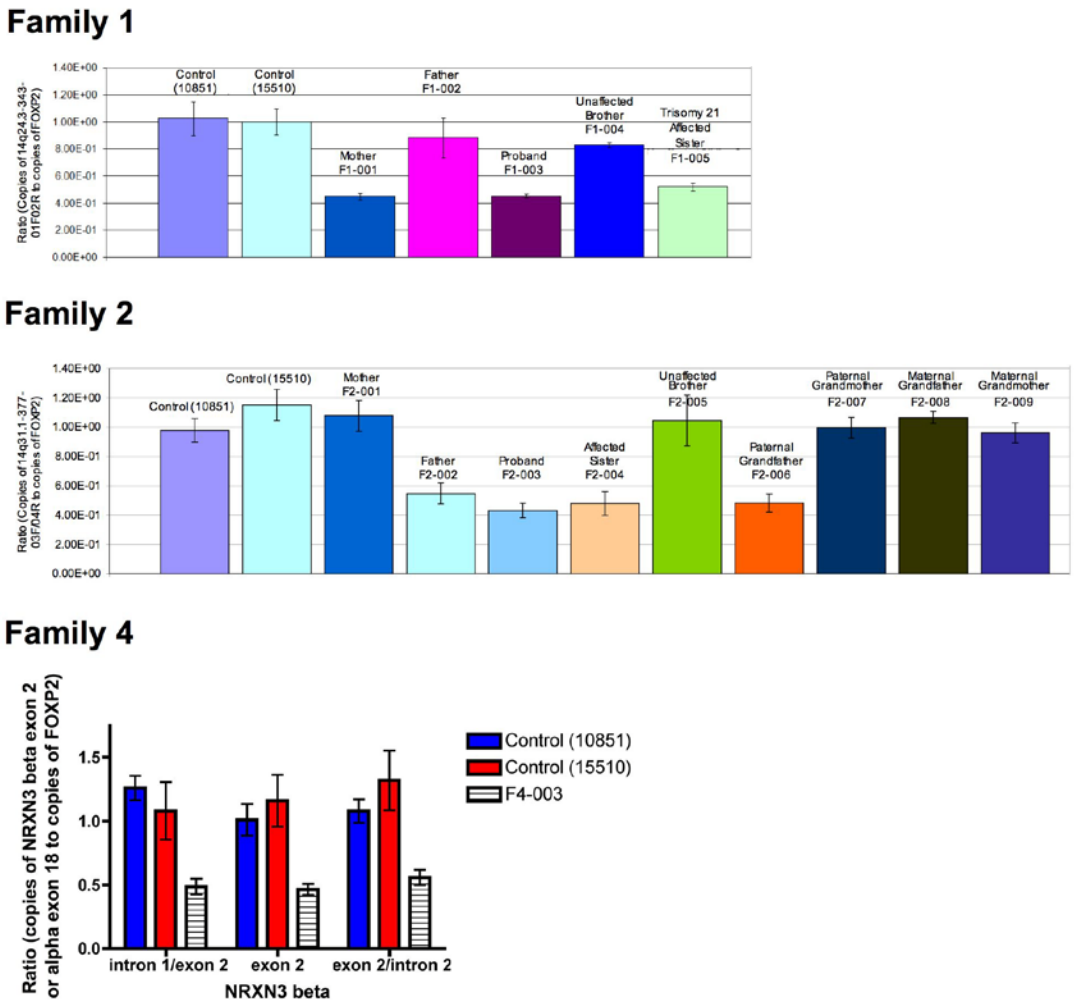

Figure S1. Quantitative polymerase chain reaction to detect copy number of 14q24.3 alleles in Family 1, 14q31.1 alleles in Family 2 and *NRXN3 alpha* exon 13 / *beta* exon 2 in Family 4 Extended family members were included when DNA samples were available. Error bars represent the standard error of three independent reactions for each sample. Assays were completed at two independent genomic loci within the region of the deletion; one assay for each region is shown.

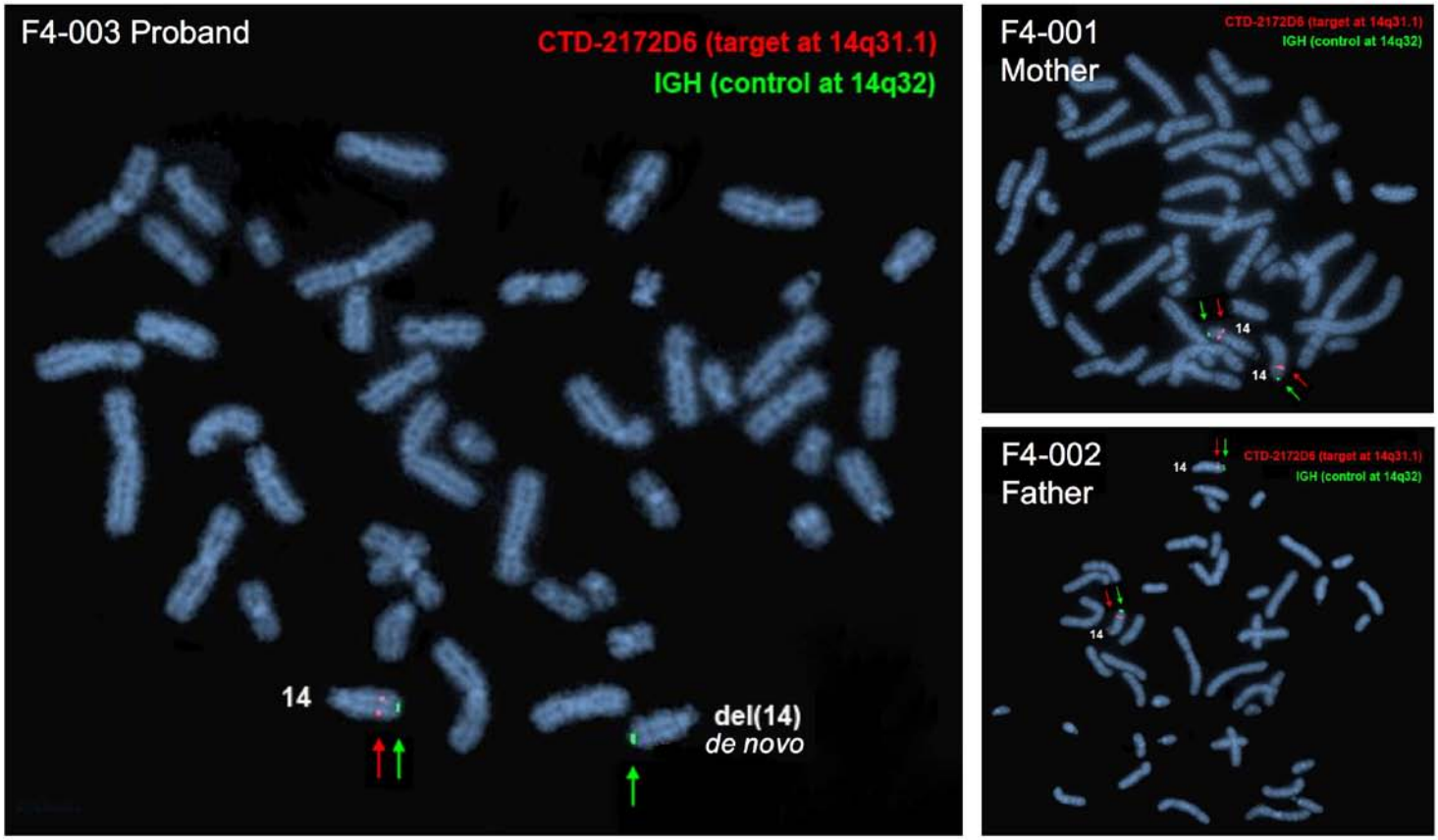

Figure S2. Fluorescence *in situ* hybridization (FISH) to detect copy number of 14q31.1 alleles in Family 4

The CTD-2172D6 probe was selected to overlap the deletion at 14q31.1, while the IGH probe at 14q32 was used as a control. Representative metaphase FISH for the proband (F4-003), mother (F4-001) and father (F4-002) are shown.

Table S1. Copy number variations detected by Affymetrix 6.0 and Illumina 1M Microarrays in proband F1-003

Number	Microarray	Chromosome and Band	Start (Build 36)	End (Build 36)	Estimated Size (bp)	CNV Type	Class[a]
1	Affymetrix 6.0	14q24.3	77,935,165	77,997,087	61,923	loss	likely pathogenic[b]
	Illumina 1M	14q24.3	77,936,279	77,994,370	58,092	loss	likely pathogenic[b]
2	Illumina 1M	13q33.1	102,690,014	102,700,873	10,860	gain	likely benign
3	Affymetrix 6.0	1p36.13	17,067,742	17,134,834	67,093	complex	normal
	Illumina 1M	1p36.13	17,086,470	17,140,083	53,614	loss	normal
4	Affymetrix 6.0	1p31.1	72,528,701	72,583,736	55,036	loss	normal
5	Affymetrix 6.0	1p13.3	110,025,907	110,044,476	18,570	gain	normal
6	Affymetrix 6.0	1q21.3	150,822,151	150,853,218	31,068	loss	normal
7	Affymetrix 6.0	2p22.3	34,552,819	34,590,561	37,743	gain	normal
8	Illumina 1M	3p11.1	90,390,913	90,576,572	185,660	loss	normal
9	Affymetrix 6.0	3q26.1	163,995,843	164,108,689	112,847	gain	normal
10	Illumina 1M	4p15.1	34,469,747	34,499,424	29,678	loss	normal
11	Illumina 1M	4p13	42,392,310	42,404,178	11,869	loss	normal
12	Affymetrix 6.0	4q13.2	70,162,233	70,273,689	111,457	loss	normal
	Illumina 1M	4q13.2	70,190,735	70,246,877	56,143	loss	normal
13	Affymetrix 6.0	5p15.2	8,755,522	8,800,142	44,621	loss	normal
	Illumina 1M	5p15.2	8,756,085	8,800,106	44,022	loss	normal
14	Illumina 1M	5q15	97,073,409	97,125,076	51,668	loss	normal
	Affymetrix 6.0	5q15	97,075,856	97,125,440	49,585	loss	normal
15	Affymetrix 6.0	5q35.3	180,311,316	180,350,709	39,394	loss	normal
16	Illumina 1M	6p21.32	32,546,520	32,641,450	94,931	gain	normal
17	Illumina 1M	6p21.32	32,643,872	32,654,432	10,561	loss	normal
18	Illumina 1M	6p21.32	32,656,281	32,666,924	10,644	gain	normal
19	Illumina 1M	6p21.32	32,713,045	32,768,921	55,877	loss	normal
20	Affymetrix 6.0	6q14.1	77,496,587	77,509,523	12,937	loss	normal
21	Affymetrix 6.0	6q16.3	103,844,669	103,868,754	24,086	loss	normal
22	Illumina 1M	7p12.1	52,700,785	52,711,270	10,486	gain	normal

23	Affymetrix 6.0	7q33	133,435,735	133,449,694	13,960	loss	normal
24	Affymetrix 6.0	7q34	141,693,868	141,712,586	18,719	loss	normal
25	Affymetrix 6.0	7q34	142,156,294	142,167,486	11,193	gain	normal
26	Illumina 1M	8p11.23	39,351,896	39,497,557	145,662	gain	normal
	Affymetrix 6.0	8p11.23 - p11.22	39,354,760	39,506,122	151,363	gain	normal
27	Affymetrix 6.0	9p21.3	24,487,680	24,507,682	20,003	loss	normal
	Illumina 1M	9p21.3	24,492,737	24,505,111	12,375	loss	normal
28	Affymetrix 6.0	9p11.2	44,667,855	44,777,523	109,669	gain	normal
29	Illumina 1M	9p11.2	44,844,429	45,270,306	425,878	gain	normal
29	Affymetrix 6.0	10q22.3	81,475,459	81,487,784	12,326	loss	normal
30	Affymetrix 6.0	12p13.31	9,525,137	9,619,559	94,423	gain	normal
31	Affymetrix 6.0	13q13.3	36,970,036	36,982,757	12,722	gain	normal
32	Affymetrix 6.0	14q32.33	105,950,876	105,989,153	38,278	loss	normal
33	Affymetrix 6.0	15q11.2	22,226,226	22,269,689	43,464	loss	normal
34	Illumina 1M	16p11.1	35,026,333	35,133,099	106,767	loss	normal
35	Affymetrix 6.0	17p11.2	18,296,117	18,405,946	109,830	loss	normal
36	Illumina 1M	17q12	31,462,326	31,499,244	36,919	gain	normal
	Affymetrix 6.0	17q12	31,464,091	31,559,764	95,674	gain	normal
37	Illumina 1M	17q21.31	41,521,621	41,562,443	40,823	gain	normal
38	Affymetrix 6.0	17q21.31- q21.32	41,756,832	42,107,479	350,648	loss	normal
	Illumina 1M	17q21.31-q21.32	41,792,236	41,914,286	122,051	loss	normal
39	Affymetrix 6.0	20q13.2	52,081,215	52,092,058	10,844	loss	normal
40	Illumina 1M	22q11.23	22,676,385	22,734,578	58,194	loss	normal
	Affymetrix 6.0	22q11.23	22,680,529	22,726,814	46,286	loss	normal
41	Illumina 1M	Xq21.31	88,349,201	88,416,721	67,521	gain	normal
	Illumina 1M	Xq21.31	88,956,094	89,138,513	182,420	gain	normal

[a]Classification based on Tsuchiya et al.[54]
[b]Inherited from mother as determined by qPCR

Table S2. Copy number variations detected by Illumina 2.5M Microarray in Down syndrome affected sister F1-005

Number	Chromosome and Band	Start (Build 36)	End (Build 36)	Estimated Size (bp)	CNV Type	Class[a]
1	21q11.2-q22.3	13,356,041	46,924,583	33,568,542	gain	pathogenic[b]
2	14q24.3	77,934,476	77,996,225	61,750	loss	likely pathogenic[c]
3	7p12.1	52,696,385	52,718,059	21,675	gain	normal
4	12q24.21	112,973,178	113,043,270	70,093	gain	normal
5	1p21.1	103,948,080	104,012,569	64,490	loss	normal
6	1q44	246,807,195	246,861,733	54,539	loss	normal
7	4p13	42,392,310	42,403,451	11,142	loss	normal
8	4p13.2	69,056,964	69,130,187	73,224	loss	normal
9	6q12	67,068,621	67,105,606	36,986	loss	normal
10	7q34	142,155,670	142,172,913	17,244	loss	normal
11	8p23.2	5,582,919	5,593,114	10,196	loss	normal
12	9p21.3	24,492,737	24,508,795	16,059	loss	normal
13	15q22.2	59,475,461	59,485,471	10,011	loss	normal
14	16q23.1	76,930,395	76,941,010	10,616	loss	normal
15	17q21.31	41,522,422	41,580,958	58,537	gain	normal
16	19p12	20,392,846	20,512,500	119,655	loss	normal

[a]Classification based on Tsuchiya et al.[54]

[b]Trisomy 21

[c]Inherited from mother as determined by qPCR

Table S3. Single nucleotide variants (SNVs) detected by exome sequencing of individuals with *NRXN3* deletions

Sample ID	Alignment with HuRef[a] (%)	Total SNVs	Exonic SNVs	Exonic novel SNVs	Exonic novel nonsynonymous SNVs	Exonic novel synonymous SNVs
F1-003	67	60,629	22,196	8,346	5,897	2,107
F2-003	72	102,743	38,934	22,858	16,690	5,386

[a]HuRef, human reference genome NCBI Build 37/hg19

Table S4. Nonsynonymous mutations within ASD-associated or neuronally-expressed genes detected by exome sequencing of families with *NRXN3* CNVs

ID	Chr	Position (NCBI 37/ hg19)	SNP	Substitution	Damaging or Tolerated[a]	Gene	Exon number	OMIM Identifier[b]	Inheritance
F1-003	3	74,334,560	C/T	R867Q	Tolerated	CNTN3	19	*601325	Paternal, not present in sibs
	9	39,171,471	C/T	G410S	Tolerated	CNTNAP3	8	-	Paternal, present in F1-005 (DS sister)
	22	41,513,727	G/A	G211S	Tolerated	EP300	2	*602700	Paternal, not present in sibs
F2-003	2	125,669,092	G/A	R1234Q	Tolerated	CNTNAP5	23	-	Paternal[c], present in F2-004 (AF sister)
	3	121,340,620	T/G	I115S	Damaging	FBXO40	3	*609107	Paternal[c], present in F2-004 (AF sister), F2-005 (UN brother)
	7	32,209,524	G/C	L61V	Damaging	PDE1C	3	*602987	Paternal[c], present in F2-005 (UN brother)
	9	79,324,017	T/C	E1058G	Damaging	PRUNE2	8	*610691	Paternal[c], not present in sibs
	15	80,847,464	G/A	R383H	Damaging	ARNT2	11	*606036	Paternal[c], not present in sibs

Abbreviations: Chr, chromosome; NCBI 37/hg19, NCBI Build 37/human genome 19; SNP, single nucleotide polymorphism; OMIM, On-line Mendelian Inheritance in Man gene locus identifier; - , unassigned; sibs, siblings; DS, Down's syndrome affected; AF, ASD affected; UN, ASD unaffected.

[a]Damaging amino acid substitutions were identified by SIFT
[b]In OMIM, * indicates a gene but no known phenotype
[c]Father (F2-002) inherited mutation from paternal grandfather (F2-006)

Table S5. Copy number variations detected by 1M Illumina and Agilent 1M Microarray in ASD-affected proband, F2-003

Number	Microarray	Chromosome and Band	Start (Build 36)	End (Build 36)	Estimated Size (bp)	CNV Type	Class[a]
1	Illumina 1M	14q31.1	79,194,519	79,484,830	290,312	loss	likely pathogenic[b]
	Agilent 1M	14q31.1	79,195,282	79,484,992	289,711	loss	likely pathogenic[b]
2	Agilent 1M	10q25.3	118,140,835	118,275,879	135,045	gain	uncertain clinical significance[c]
	Illumina 1M	10q25.3	118,146,973	118,273,902	126,930	gain	uncertain clinical significance[c]
3	Illumina 1M	1p36.11	25,470,863	25,537,253	66,391	loss	normal
4	Agilent 1M	1p31.1	72,538,943	72,579,511	40,569	loss	normal
5	Illumina 1M	1p21.1	103,969,301	104,094,454	125,154	loss	normal
6	Agilent 1M	1q21.3	150,822,873	150,851,639	28,767	loss	normal
7	Agilent 1M	2p11.2	88,913,881	88,939,755	25,875	loss	normal
8	Illumina 1M	2q37.3	242,568,437	242,597,673	29,237	loss	normal
	Agilent 1M	2q37.3	242,571,023	242,597,073	26,051	loss	normal
9	Agilent 1M	3q26.1	164,009,121	164,027,924	18,804	loss	normal
	Illumina 1M	3q26.1	164,037,547	164,101,579	64,033	loss	normal
10	Illumina 1M	3q26.31	176,555,296	176,570,084	14,789	loss	normal
11	Agilent 1M	3q29	196,835,213	196,961,438	126,226	gain	normal
12	Illumina 1M	4q13.1	64,378,106	64,392,223	14,118	loss	normal
13	Illumina 1M	4q13.2	69,064,675	69,186,276	121,602	gain	normal
	Agilent 1M	4q13.2	69,069,451	69,166,014	96,564	gain	normal
14	Illumina 1M	5p15.33	806,256	873,185	66,930	loss	normal
15	Illumina 1M	5q33.2	155,410,444	155,421,495	11,052	loss	normal
16	Agilent 1M	5q35.3	180,344,764	180,362,542	17,779	loss	normal
17	Agilent 1M	6p25.3	201,863	324,098	122,236	gain	normal
18	Illumina 1M	6p21.33	29,959,422	30,007,126	47,705	loss	normal
	Agilent 1M	6p21.33	29,962,649	30,022,108	59,460	loss	normal
19	Agilent 1M	6p21.32	32,563,052	32,601,162	38,111	loss	normal

20	Agilent 1M	6p21.32	32,716,055	32,731,272	15,218	gain	normal
	Illumina 1M	6p21.32	32,717,159	32,739,978	22,820	gain	normal
21	Illumina 1M	6p12.1	55,934,096	55,954,486	20,391	loss	normal
	Agilent 1M	6p12.1	55,934,616	55,950,698	16,083	loss	normal
22	Agilent 1M	6q14.1	79,024,357	79,085,447	61,091	loss	normal
	Illumina 1M	6q14.1	79,029,649	79,090,197	60,549	loss	normal
23	Illumina 1M	7p21.1	17,519,409	17,533,175	13,767	loss	normal
24	Agilent 1M	7q33	133,436,065	133,448,477	12,413	loss	normal
25	Illumina 1M	10q11.22	47,004,995	47,173,876	168,882	gain	normal
	Agilent 1M	10q11.22	47,021,215	47,172,734	151,520	gain	normal
26	Agilent 1M	10q23.1	82,869,226	82,881,404	12,179	loss	normal
27	Illumina 1M	11p15.4	7,774,010	7,785,071	11,062	loss	normal
28	Illumina 1M	11p11.12	49,669,405	49,701,670	32,266	loss	normal
29	Agilent 1M	14q32.33	105,314,054	105,416,596	102,543	gain	normal
30	Agilent 1M	14q32.33	105,607,372	105,632,368	24,997	loss	normal
31	Agilent 1M	14q32.33	105,951,199	105,989,360	38,162	loss	normal
32	Illumina 1M	15q26.2	95,616,714	95,633,191	16,478	loss	normal
33	Agilent 1M	16p11.2	32,378,926	33,559,407	1,180,482	gain	normal
34	Agilent 1M	16p11.1,16p11.2	34,325,301	34,602,518	277,218	gain	normal
35	Agilent 1M	16q22.1	68,732,167	68,753,409	21,243	gain	normal
36	Agilent 1M	16q23.1	76,929,398	76,940,418	11,021	loss	normal
37	Illumina 1M	18q22.1-q22.2	64,895,268	64,906,488	11,221	loss	normal
38	Agilent 1M	19q13.2	46,046,659	46,063,557	16,899	gain	normal
	Illumina 1M	19q13.2	46,047,894	46,073,380	25,487	gain	normal
39	Agilent 1M	19q13.42	59,420,997	59,434,402	13,406	loss	normal
	Illumina 1M	19q13.42	59,423,491	59,435,029	11,539	loss	normal
40	Agilent 1M	20p13	1,511,432	1,525,500	14,069	loss	normal
41	Agilent 1M	22p13	402,446	415,655	13,210	loss	normal
42	Illumina 1M	22q13.1	37,693,776	37,711,772	17,997	loss	normal
43	Illumina 1M	Xq21.31	88,597,748	89,049,558	451,811	gain	normal

[a]Classification based on Tsuchiya et al.[54]

[b]Inherited from the father as determined by qPCR
[c]Inherited from the mother as determined by SNP genotyping

Table S6. Copy number variations detected by Affymetrix 6.0 Microarray in ASD-affected sister, F2-004

Number	Chromosome and Band	Start (Build 36)	End (Build 36)	Estimated Size (bp)	CNV Type	Class[a]
1	14q31.1	79,194,993	79,486,637	291,645	loss	likely pathogenic[b]
2	10q25.3	118,146,569	118,277,144	130,576	gain	uncertain clinical significance[c]
3	Xq12	65,686,393	65,850,049	163,657	gain	uncertain clinical significance[c]
4	3p14.1	68,701,371	68,725,422	24,052	gain	likely benign
5	6q14.1	77,372,550	77,384,004	11,455	loss	likely benign
6	6q22.31	118,746,238	118,762,441	16,204	loss	likely benign
7	15q21.3	52,979,930	53,038,725	58,796	loss	likely benign
8	18q21.33	59,325,725	59,341,262	15,538	loss	likely benign
9	1p36.11	25,465,715	25,534,799	69,085	loss	normal
10	1p31.1	72,528,701	72,583,736	55,036	complex	normal
11	1q21.3	150,821,800	150,853,218	31,419	loss	normal
12	3q21.3	129,878,180	129,895,021	16,842	gain	normal
13	3q26.1	163,989,224	164,109,297	120,074	loss	normal
14	4p16.1	9,823,254	9,844,366	21,113	gain	normal
15	4q13.2	69,043,083	69,168,574	125,492	loss	normal
16	5q35.3	180,311,316	180,350,709	39,394	loss	normal
17	6p21.33	31,394,255	31,404,430	10,176	loss	normal
18	6p21.32	32,539,530	32,682,359	142,830	gain	normal
19	6q14.1	79,025,784	79,091,904	66,121	loss	normal
20	7q34	141,693,581	141,711,917	18,337	gain	normal
21	7q34	142,155,609	142,176,424	20,816	loss	normal
22	7q35	143,501,019	143,719,492	218,474	gain	normal
23	8p11.23-p11.22	39,354,760	39,506,122	151,363	loss	normal
24	9p21.3	23,353,115	23,363,484	10,370	loss	normal
25	10q11.22	46,337,321	46,467,605	130,285	gain	normal
26	10q11.22	46,482,317	47,012,099	529,783	gain	normal

27	10q11.22	47,012,100	47,173,619	161,520	gain	normal
28	11q11	55,130,608	55,209,585	78,978	loss	normal
29	14q11.2	19,270,023	19,493,212	223,190	gain	normal
30	14q32.33	105,601,409	105,638,145	36,737	loss	normal
31	14q32.33	105,950,876	105,989,694	38,819	loss	normal
32	15q26.2	95,618,796	95,634,656	15,861	loss	normal
33	16p12.3	19,853,151	19,874,863	21,713	loss	normal
34	16p11.1-p11.2	34,324,072	34,614,572	290,501	gain	normal
35	16q12.2	54,353,890	54,379,945	26,056	loss	normal
36	16q12.2	54,399,883	54,420,211	20,329	gain	normal
37	16q23.1	76,929,941	76,942,266	12,326	loss	normal
38	17q21.31-q21.32	41,563,921	42,120,174	556,254	loss	normal
39	19q13.12	40,541,333	40,553,688	12,356	loss	normal
40	19q13.31	48,394,873	48,448,077	53,205	loss	normal
41	19q13.41	58,210,559	58,244,245	33,687	gain	normal
42	21q11.2	13,374,733	13,463,240	88,508	loss	normal
43	22q13.1	37,693,565	37,705,253	11,689	loss	normal
44	Xq21.31	89,781,704	89,798,514	16,811	loss	normal

[a]Classification based on Tsuchiya et al.[54]

[b]Inherited from the father as determined by qPCR

[c]Inherited from the mother as determined by SNP genotyping

Table S7. Copy number variations detected by Agilent 244K Microarray in ASD-affected proband, F4-003

Number	Chromosome and Band	Start (Build 36)	End (Build 36)	Estimated Size (bp)	CNV Type	Class[a]
1	14q31.1	78,780,965	78,998,022	217,058	loss	likely pathogenic[b]
2	2q12.2-q12.3	106,244,482	107,899,060	1,654,579	loss	uncertain clinical significance[c]
3	7q35	143,515,304	143,694,327	179,024	loss	likely benign
4	14q11.2	19,287,128	19,491,517	204,390	gain	likely benign
5	Yq11.223-q11.23	22,926,984	26,611,063	3,684,080	gain	likely benign
6	1p36.13	16,746,296	16,857,821	111,525	loss	normal
7	1p36.13	16,926,444	16,996,364	69,920	loss	normal
8	1q21.1	144,323,050	144,651,248	328,199	loss	normal
9	1q21.1	147,098,951	147,134,234	35,283	loss	normal
10	1q21.1	147,307,637	147,490,646	183,010	loss	normal
11	1q44	246,794,552	246,857,555	63,004	loss	normal
12	2p12	82,059,920	82,159,192	99,273	gain	normal
13	2q37.3	242,514,593	242,677,125	162,533	loss	normal
14	3q12.2	101,830,256	101,928,155	97,900	gain	normal
15	3q26.1	163,996,796	164,101,835	105,040	loss	normal
16	4q13.2	69,057,324	69,173,429	116,106	loss	normal
17	5p15.33	794,369	894,992	100,624	loss	normal
18	6p25.3	181,142	238,493	57,352	loss	normal
19	6q27	168,081,602	168,324,063	242,462	gain	normal
20	7q22.1	100,757,569	100,925,126	167,558	gain	normal
21	7q22.1	101,915,687	102,107,694	192,008	gain	normal
22	8p23.1	7,103,471	7,843,639	740,169	loss	normal
23	10q11.21-q11.22	45,986,585	47,026,056	1,039,472	loss	normal
24	10q11.22	48,460,600	48,946,999	486,400	loss	normal
25	11q11	55,124,730	55,207,364	82,635	homo gain	normal
26	12q12	36,739,877	37,147,772	407,896	loss	normal

27	15q13.2	28,160,686	28,697,443	536,758	gain	normal
28	15q13.3	30,321,464	30,594,576	273,113	gain	normal
29	15q14	32,474,245	32,772,324	298,080	gain	normal
30	16p13.11-p12.3	16,611,886	16,755,263	143,378	gain	normal
31	16p12.3	18,150,085	18,695,395	545,311	gain	normal
32	17q12	31,541,821	31,574,772	32,952	gain	normal
33	17q21.31-q21.32	41,793,792	41,919,687	125,896	gain	normal
34	17q21.32	42,035,410	42,117,798	82,389	gain	normal
35	Xp22.33	17,768	102,197	84,430	homo loss	normal
36	Xq28	153,064,329	153,158,732	94,404	loss	normal

[a]Classification based on Tsuchiya et al. [54]

[b]*de novo* as determined by FISH

[c]Inherited from mother as determined by FISH

Table S8. Sanger sequencing of *NRXN3* variants in 350 ASD cases

Sample	Primer	Variant	Genomic Position[a]	Type	Inheritance	Comments
MMPro3-D11 (female proband)	FA/RA	*c19G>A(het), A7[T,A]*	g78,816,406	missense	*maternal;* also in UN sib	low conservation, Alanine (hydrophobic) → Threonine (polar neutral). Also rare 4.6 Mb 2q37.3 deletion.
MMPro2-D7 (male proband)	F2/R2	*c128G>A(het), R43[H,R]*	g78,245,338	missense	*paternal*, also in UN sib	highly conserved, Arginine (basic, polar) → histidine (basic, polar). No other rare CNVs.
MMPro3-E4 (male proband)	F6/R6	*c1219C>T(het), R407[R,W]*	g78,493,400	missense	*maternal*; also in matGF and 2 UN sibs	highly conserved, Arginine (basic,polar) → Tryptophan (hydrophobic, neutral, slightly polar). Also rare 260 kb 22q12.3 del and 37 kb 4q34.3 del.
SKPro4-E3 (female sibling)	F15/R15	*c3118G>A(het), E1040[E,K]*	g79,397,992	missense	*maternal*	dx changed to not-ASD, highly conserved, glutamic acid (acidic, polar) → Lysine (basic, polar). No other rare CNVs.

Abbreviations: UN, unaffected; matGF, maternal grandfather; dx, diagnosis. Primer3 software v. 0.4.0 (http://frodo.wi.mit.edu/primer3) was used to design PCR primers for standard PCR. Products were purified and sequenced directly using BigDye Terminator sequencing (Applied Biosystems, Foster City, CA, USA). Novel variants detected in the cases and controls, not previously reported in the Single Nucleotide Polymorphism Database (dbSNP) build 130, were validated by re-sequencing the proband and samples from both parents and siblings, when available.

[a]NCBI 36 (hg 18)