Supporting Information

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Table S1. Gene content of CNVs as defined and analyzed in this study

Locus	Genes included in deleted or duplicated regions	Refs
1q21.1	*PRKAB2, FMO5, CHDIL, BCL9, ACP6, GJA5,* ***GJA8***	1, figure 1*C* 2, figure 1 3, figure 1
15q13.3	*MTMR15*, *MTMR10*, *TRPM1, KLF13, OTUD7A,* ***CHRNA7***	1, figure 1*B* 4, figure 1*C*
16p11.2	***SEZ6L2****, ASPHD1, KCTD13, LOC124446, TAOK2, HIRIP3, CCDC95, DOC2A, FAM57B, ALDOA, PPP4C, TBX6, YPEL3, GDPD3, MAPK3*	5, table 1 6, table S2 7, figure 3 8, figure 1 9, table S3
16p13.1	*KIAA0430,* ***NDE1****, MYH11, ABCC1*	10, table S4 11, text 12, suppl table
17p12	***PMP22***	12, suppl table
22q11.21	*TSSK2,* ***DGCR14****, GSCL, SLC25A1, CLTCL1, HIRA, MRPL40,* ***UFD1L****, CDC45L,* ***CLDN5****, SEPT5, TBX1,* ***GNB1L****, c22orf29, TXNRD2,* ***COMT****, ARVCF, hsa-mir-185, c22orf25,* ***DGCR8****, HTF9C,* ***RANBP1****,* ***ZDHHC8****,* ***RTN4****R, DGCR6L*	1, table 1*A*
22q13.3	***SHANK3***	13, text

CNVs were defined to correspond to regions designated by the authors of previous studies, to the extent possible. Genes indicated in bold have been associated with autism or schizophrenia in functional studies, genetic-association studies, or both. For 1q21.1, 15q13.3, 16p11.2, and 16p13.1, these sets of genes served to define the CNVs in Table 1 of the main article. For 17p12 and 22q13.3, deletion or duplication of the single gene shown was used to define the CNV, due to heterogeneity in the size of the affected region and the relatively-high quality of information concerning the risk-association effects of the specific focal genes in each case. For 22q11.21, a 1.5-Mb region defined the CNV, and most CNVs also included flanking sequence.

Table S2. Data on ascertainment criteria for populations studied, numbers of cases and controls, and source populations

Study, ref.	Ascertainment	Cases	Controls	Sources
5	Autism	195	196	AGRE, NIMH
14	Autism	6,709	—	AGRE, 9 others
6	Autism	397	372	AGRE, NIMH
7	Autism	716	837	AGRE, NIMH
13	Autism	427	1,652+	Canada
11	Autism	182	—	Australia
15	Autism	2,195	2,519	AGRE, ACC
8	MR, AUT, ASD	2,252	20,688	AGRE, Boston, deCODE
3	MR, AUT	5,218	4,737	Multiple
16	MR, AUT, OTH	2,886	—	AGRE, Boston
2	MR, AUT, ANO	16,557	—	Baylor
17	MR, AUT, ANO	≈8,200	—	Baylor
18	MR/ANO	4,284	—	Europe, Australia
1	Schizophrenia	3,391	3,818	Multiple, incl Aberdeen
4	Schizophrenia	4,718	41,200	Multiple, incl Aberdeen
9	Schizophrenia	150/83	268/77	Wash. State, NIMH COS
19	Schizophrenia	359	—	Afrikaners
10	Schizophrenia	2,331	13,858	Multiple
12	Schizophrenia	471	2,792	WTCCC
20	Schizophrenia	4,566	6,391	Multiple
21	Schizophrenia	3,719	34,421	Multiple

MR, mental retardation; AUT, autism; ASD, autism spectrum disorder; OTH, other; ANO, congenital anomalies.

Table S3. Deletions and duplications of 1q21.1 in autism and schizophrenia

Disorder	Case data	CNV	Ref.
Autism	1 case, table 1, figure 1	Deletion	3
Autism	1 case, suppl. table 5	Deletion	14
Autism	3 cases, suppl. table 3, figure 1	Duplications	3
Autism	3 cases, text, suppl. tables 5, 6	Duplications	14
Autism	2 cases, table 2	Duplications	2
Autism	2 cases, suppl. table 2	Duplications	8
Schizophrenia	10 cases, table S7	Deletions	1
Schizophrenia	4 cases, table 1	Deletions	4
Schizophrenia	1 case, table 1	Deletion	9
Schizophrenia	3 cases, http://pngu.mgh.harvard.edu/isc/	Duplications	1
Schizophrenia	1 case, table 2	Duplication	12

Two of the schizophrenia cases with deletions in ref. 4 are the same patients (from the Aberdeen sample) as two of those reported in ref. 1 and in Need et al. (10). Stefansson et al. (4) reported two forms of the 1q21.1 deletion, one 1.35 Mb in length (seven cases) and the other 2.19 Mb (four cases), both of which include the seven genes. A partially overlapping deletion (144.6–146.3 Mb) in Need et al. (10) was not included. The deletion case in Walsh et al. (9) involves the 1.35-Mb deletion, and the deletion in ref. 14 involves a smaller 1.14-Mb region, as do the three duplication cases reported by these authors. The duplications and deletion in Mefford et al. (3) all involved the 1.35-Mb region, as did the two duplications in Brunetti-Pierri et al. (2) (referred to by these authors as Class 1). Brunetti-Pierri et al. (ref. 2, table 1) also reported a case of depression associated with the 1q21.1 deletion. The duplications in ref. 14 (suppl. table 5) were also detected in Weiss et al. (ref. 8, suppl. table 2). A deletion in Xu et al. (ref. 19, table 3) included only five of the seven genes and was not included. A statistical association between schizophrenia and deletions at 1q21.1 was reported by ISC (1) ($P = 0.046$), Stefansson et al. (4) ($P = 0.000029$), and Kirov et al. (ref. 12, $P = 9.6 \times 10^{-6}$) using an extended sample that included data from ISC, Stefansson et al. (4), and WTCCC. Based on the absence of duplications of this region in the ISC case ($N = 3391$) and control ($N = 3817$) datasets, an association of 1q21.1 duplications with schizophrenia appears unlikely. In a case population ascertained for autism (141 cases) or mental retardation, Mefford et al. (3) reported one individual with autism in 21 case individuals with deletions at 1q21.1, and three individuals with autism among the eight case individuals with duplications. Duplications were thus reported in three (2.1%) of 141 individuals with autism, and in one (0.02%) of 4,737 controls (Fisher's exact test, $P = 0.000092$). By contrast, deletions were reported in one (0.7%) of 141 individuals with autism, and in none of the control individuals, which suggests that the deletion may be associated with autism (Fisher's exact test, $P = 0.0289$), although a more robust test requires further data. The 1q21.1 region has been linked by genome-scan studies with risk of schizophrenia (22-24), bipolar disorder (25, 26), and autism or Asperger syndrome (27, 28). The *GJA8* gene was associated with schizophrenia risk by Ni et al. (29) using case-control and family-based analyses, and Brunetti-Pierri et al. (2) reported the presence of a paralog of the microcephaly-associated *HYDIN* gene in the 1q21.1 class 1 deletion/duplication region. Based on bioinformatic information, Allen et al. (ref. 30, suppl table 4) predicted that the *FMO5* gene was monoallelically expressed. These authors also predicted monoallelic expression in the *HYDIN* gene on chromosome 16, the gene from which the 1q21 paralog was apparently derived (31), and the *HYDIN* gene on chromosome 16 was disrupted by a CNV deletion breakpoint in a case of schizophrenia reported by Walsh et al. (ref. 9, table 2).

Table S4. Deletions and duplications of 15q13.3 in autism and schizophrenia

Disorder	Case data	CNV	Ref.
Autism	1 case in ″controls″ text	Deletion	4
Autism	2 cases	Deletions	17
Autism	2 cases, table 2	Duplications	16
Schizophrenia	2 cases, table 1	Deletions	4
Schizophrenia	8 cases, figure 1, table S7	Deletions	1
Schizophrenia	4 cases, http://pngu.mgh.harvard.edu/isc/	Duplications	1

The deletion and duplication cases included in the analysis for this region all comprise the genes *MTMR15*, *MTMR10*, *TRPM1*, *KLF13*, *OTUD7A*, and *CHRNA7*. One of the schizophrenia cases with a deletion in (4) represents the same case from the Aberdeen sample in ref. 1. The cases of 15q13.3 duplication and autism reported in Miller et al. (16) include patients with two size variants for the duplication, two cases with a 0.5-Mb duplication (that does not include the *CHRNA7* gene) and the other two cases with duplications 1.93 Mb and 1.98 Mb in length (that include the six genes noted above), and only the latter two cases are included here. Three autism duplication cases reported in Cuscó et al. (32) as encompassing only the *CHRNA7* gene were not included in the analyses, and an autism case in Christian et al. (6), which involved a 0.37-Mb duplication that included only the genes *TRPM1* and *KLF13* was also excluded. The schizophrenia cases in Stefansson et al. (4) involve deletions of about 1.5 Mb that share one endpoint with the duplications in Miller et al. (16). The four duplication cases reported in ref. 1 are all between 1.5 Mb and 2 Mb in length and include these six genes. Sebat et al. (5) reported a patient with autism and a 15q11-q13.3 duplication, which was not included here because it involves a much larger region than 15q13.3 (ref. 5, table 1 and Table S2). A statistical association between 15q13.3 deletions and schizophrenia was reported by Stefansson et al. (4) ($P = 0.00053$) and by Kirov et al. (12) in their pooled sample ($P = 3.34 \times 10^{-6}$). A statistical association between schizophrenia and duplications at 15q13.3 can be tested using the ISC data set; there were four duplications in 3,391 cases, and one duplication in 3,817 controls (Fisher's exact test, $P = 0.153$). Testing for a statistical association of autism with duplications or deletions at 15q13.3 is problematic due to the absence of designated control populations for both of the studies that reported CNVs in individuals with autism for this locus. Miller et al. (16) describes four cases of autism in five duplications detected at this locus and no cases of autism in five individuals with deletions, but the duplications varied in size as described above. A primary candidate gene for effects from copy-number variation at 15q13.3 is the cholinergic receptor gene *CHRNA7*, which has been linked with schizophrenia in six independent studies, with five other studies yielding negative results (33). Leonard and Freedman (34) reviewed the genetics of 15q13-q14 with regard to schizophrenia, describing the replicated linkages of *CHRNA7* and this region to the disorder. This gene and region have also been linked with a high incidence of cigarette smoking in schizophrenia (35, 36), and Bejerot and Nylander (37) reported evidence for a low prevalence of smoking in subjects with autistic spectrum disorders. A recent autism genome scan provided evidence of linkage at 15q13.3-q14 to autism, with the SNPs directly flanking *CHRNA7* exhibiting highly-significant LOD scores (38). Parent of origin effects in the linkages of one marker in the *CHRNA7* gene, and one marker 3 kb distal to this gene, with schizophrenia were described by Xu et al. (39), and Ma et al. (40) provided evidence of a parent of origin effect for a marker between TRPM1 and KLF13, also for association with schizophrenia. These effects may be related to the presence of a *CHRNA7* enhancer locus in the imprinted Prader-Willi/Angelman 15q11-q13 deletion region, as reported in a mouse model of these disorders (41). Tests for phenotypic differences between individuals with maternally derived versus paternally derived deletions or duplications at 15q13.3 have yet to be conducted.

Table S5. Deletions and duplications of 16q11.2 in autism and schizophrenia

Disorder	Case data	CNV	Ref.
Autism	7 cases, suppl. table 1	Deletions	8
Asperger	1 case, table 1	Deletion	5
Autism	2 cases, tables 2, 3, figure S5	Deletions	13
Autism	3 cases, table 1	Deletions	15
Autism	1 case, Text, tables I and II	Deletion	18
Autism	3 cases, suppl. table 1	Duplications	8
Autism	1 case, tables 2 and 3, figure S5	Duplication	13
Autism	1 case, table 1	Duplication	15
Schizophrenia	1 case, text	Deletion	8
Schizophrenia	2 cases, suppl. table 3	Deletions	4
Schizophrenia	1 case, http://pngu.mgh.harvard.edu/isc/	Deletion	1
Schizophrenia	1 case, table 1	Deletion	20
Schizophrenia	2 cases, text, table S3	Duplications	9
Schizophrenia	3 cases, http://pngu.mgh.harvard.edu/isc/	Duplications	1
Schizophrenia	19 cases, table 1	Duplications	20

The deletions and duplications for this region include about 0.5 Mb encompassing 20–28 genes between *BOLA2* and *MAPK3*, with some variation in the positions of the breakpoints, but the region including *SEZ6L* through *MAPK3* always deleted or duplicated. AGRE autism cases involving 16p11.2 deletions and duplications were independently genotyped and reported by multiple studies (6, 7, 8, 15), and each of these cases is included only once in the analysis; thus, Kumar et al. (7) and Christian et al. (6) each reported overlapping cases of 16p11.2 deletions in autism that are not listed in the table. Glessner et al. (15) kindly provided genomic coordinates for their samples. Kumar et al. (7) reported a patient with autism and a duplication of 16p11.2, as well as deletions at 7q31.2 and 16q22.1; this patient was excluded due to uncertainty regarding the nature and specificity of the causal variant. Kumar et al. (7) also noted two control subjects with 16p11.2 duplications, who exhibited ″generalized anxiety, specific phobias and panic attacks, but no mental health diagnosis.″ The two cases of 16p11.2 duplication in Walsh et al. (9) overlap with two of the 21 cases in McCarthey et al. (20). Kumar et al. (7) reported a significant association of autism with deletions at 16p11.2, with deletions found in 4 of 712 autism cases from AGRE and NIMH and no deletions in 837 controls (Fisher's exact test, $P = 0.044$). This finding is also supported by combining Kumar's data with data from the (nonoverlapping) ACC population of Glessner et al. (15) (Fisher's exact test, $P = 0.0295$). Kumar et al. (42) reported a significant association between markers in the *SEZ6L2* gene and autism in an SNP-based association study, although this relationship was not replicated in an independent data set. Deletions are also associated with autism in data from Weiss et al. (8), for their AGRE sample (5 of 1,441 cases, 3 of 4,234 controls, Fisher's exact test, $P = 0.029$), and their deCODE sample (3 of 299 cases, 2 of 18,832 unscreened controls, Fisher's exact test, $P = 0.000036$); their Children's Hospital Boston sample individuals were ascertained for mental retardation and developmental delay and could thus not be included. These results consistently support an association of 16p11.2 deletions with autism. Statistical association of 16p11.2 duplications with autism can be tested using data from Weiss et al. (8) and Glessner et al. (15). The AGRE sample of Weiss et al. (8) includes 7 of 1,441 cases and 2 of 4,234 controls with the duplications (Fisher's exact test, $P = 0.00147$). By contrast, their deCODE sample includes no duplications in 299 autism spectrum cases, compared to 5 duplications in 18,834 unscreened controls (Fisher's exact test, $P = 0.92$). Data from Glessner et al. (15) includes four duplications in 2,195 cases (three of which are the same as those in Weiss's AGRE sample) and three duplications in 2,519 controls (Fisher's exact test, $P = 0.425$). Data compiled by McCarthy et al. (20) cannot be used to test for association of 16p11.2 duplications with autism, because their analyses (ref. 20, table 2) combine autism with developmental delay. Taken together, these results can be interpreted as inconclusive. McCarthy et al. (ref. 20, table 1) provided strong evidence from a discovery data set ($P = 0.000014$), a replication data set ($P = 0.022$), and a meta-analysis ($P = 0.0000005$) for association of duplications at 16p11.2 with schizophrenia. The 16p11.2 region has also been linked in genome scans with schizophrenia (43, 44) and bipolar disorder (25, 26). Stefansson et al. (ref. 4, suppl. table 3) and McCarthy et al. (20) reported absence of statistical association of deletions at 16p11.2 with schizophrenia.

Table S6. Deletions and duplications of 16p13.1 in autism and schizophrenia

Disorder	Case data	CNV	Ref.
Autism	3 cases, text	Duplications	11
Schizophrenia	3 cases, text	Deletions	10
Schizophrenia	3 cases, http://pngu.mgh.harvard.edu/isc/	Deletions	1
Schizophrenia	2 cases, table 1	Deletions	21
Schizophrenia	13 cases, http://pngu.mgh.harvard.edu/isc/	Duplications	1
Schizophrenia	3 cases, text, table 2, suppl. table	Duplications	12
Schizophrenia	7 cases, table 1	Duplications	21

All of these duplications include the gene *NDE1*, which interacts with *DISC1* (45) and has been implicated in schizophrenia risk (46). The duplications in Ullmann et al. (11) are about 1.5 Mb in size; the deletions in Need et al. (10) are 1.2, 1.5, and 2.69 Mb in size; the duplications in Kirov et al. (12) are 0.79, 1.3 and 2.91 Mb in size; and the deletions and duplications in ISC (1) range in size from 0.7 to 3.0 Mb. All of these deletions and duplications include the genes *KIAA0430*, *NDE1, MYH11,* and *ABCC1* as a minimum deletion/duplication interval. Ullmann et al. (11) reported duplications in four severely autistic patients from three families, with two of the three index patients exhibiting "significantly-enlarged" head circumference; he also reported the reciprocal deletion in 3 patients with mental retardation. Hannes et al. (47) demonstrated that deletion of this region represents a risk factor for mental retardation ($P = 0.0048$), and that 3 of 4 adult patients with deletions exhibited microcephaly; they also noted that combining data from the three duplications in Ullman's cohort of 182 individuals with autism, with their data on presence of the duplication in five of 2,014 control individuals, leads to inference of statistical association of the duplication with autism (Fisher's exact test, $P = 0.023$). Feng and Walsh (48) describe the role of *NDE1* in mediating the development of cerebral cortex size in mice. In the ISC data set (1), deletions that include *NDE1* were reported in 3 of 3,391 cases and 1 of 3,818 controls (Fisher's exact test, $P = 0.27$), and duplications that include NDE1 were reported in 13 cases and 7 controls (Fisher's exact test, $P = 0.0825$). Kirov et al. (12) describe an "approximately two-fold" increased rate of the duplications in patients with autism, mental retardation, or schizophrenia. The deletion and duplication data reported in Ingason et al. (21) overlap with the data in Need et al. (10) for two deletion cases and with the data in ISC (1) for 1 deletion case and 6 duplication cases (from the Aberdeen sample). Ingason et al. (21) reported in their pooled data (from five samples) that duplications were found in 0.30% of schizophrenics, compared to 0.09% of controls ($P = 0.007$); this significant difference was due predominantly to the single, large, Icelandic sample. The *NDE1* region has been associated in genome scans with autism risk by IMGSAC (49) and Lamb et al. (50), and with schizophrenia risk by Williams et al. (51).

Table S7. Deletions and duplications of 17p12 in autism and schizophrenia

Disorder	Case data	CNV	Ref.
Autism	2 cases, text, suppl. table 5	Deletions	14
Autism	1 case, suppl. table 2	Deletion	8
Autism	1 case, table S2	Deletion	6
Autism	1 case, text, suppl. table 5	Duplication	14
Schizophrenia	4 cases, http://pngu.mgh.harvard.edu/isc/	Deletions	1
Schizophrenia	2 cases, suppl. table 3	Deletions	4
Schizophrenia	2 cases, text, table 2, suppl. table	Deletions	12

All of these CNVs include the *PMP22* gene, which causes Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) when deleted and Charcot-Marie-Tooth disease type 1a (CMT1a) when duplicated. Almost all of these CNVs are about 1–1.3 Mb in size, between genomic coordinates 14.0 and 15.4. This region is relatively gene-poor and *PMP22* is the only gene affected in all deletion or duplication cases. Kirov et al. (12) provide evidence, using a pooled sample of data from their study, ISC (1), and Stefansson et al. (4), that the 17p12 deletion is about 10 times more frequent in schizophrenia cases (0.15%) than in controls (0.015%) (Fisher's exact test, $P = 0.00005$). The *PMP22* gene shows lower expression in brain in schizophrenia (52), but the single genetic-association study conducted to date showed nonsignificant results (53).

Table S8. Deletions and duplications of 22q11.21 in autism and schizophrenia

Disorder	Case data	CNV	Ref.
Autism	1 case, suppl. tables 4 and 5	Deletion	14
Autism	1 case, suppl. tables 4 and 5	Duplication	14
Autism	2 cases, table S2	Duplications	6
Autism	2 cases, table 3, figure S5	Duplications	13
Autism	3 cases, table 1	Duplications	15
Schizophrenia	11 cases, text, suppl. table 7	Deletions	1
Schizophrenia	3 cases, table 1	Deletions	19
Schizophrenia	2 cases, table 2, suppl. table	Deletions	12
Schizophrenia	1 case, text	Duplication	10

Most of the deletions at 22q11.21 are about 3 Mb in length, and a smaller proportion of cases involve nested deletions of 1.5 Mb (ref. 1, figure 1a; ref. 54). Duplications at 22q11.21 usually involve regions about 3 Mb, 4 Mb, or 6 Mb in length, with a centromeric endpoint within the LCR (low copy repeat) near the gene *DGCR2* (refs. 55, 56; ref. 57, figure 1); this genomic location is shared with the 1.5-Mb and 3-Mb deletions. The 22q11.21 deletions and duplications in the analyses conducted here all included the 1.5-Mb region starting within this centromeric LCR; this region encompasses 15–20 genes including *TBX1* and *COMT*, which appear to play important roles in the phenotypes associated with velocardiofacial syndrome (58, 59). Cases involving alterations at 22q11.21 affecting regions smaller than this ≈1.5-Mb region were excluded from the analyses (e. g., ref. 13, one case in Table S2 involving three genes and one case in Table 3 involving seven genes), as were the two atypical deletions in ref. 1 and one duplication in ref. 14 that included *TBX1* and *COMT* but exhibited a proximal breakpoint about 0.5 Mb distal to *DGCR2*. A deletion case initially reported as involving autism in Marshall et al. (ref. 13, table 2, case number 25) was noted as losing the autism diagnosis upon re-examination. The data in ref. 1 (at http://pngu.mgh.harvard. edu/isc/) showed no cases of duplications that included the 1.5-Mb minimal region. Some schizophrenia studies (e.g., ref. 9) explicitly excluded 22q11.21 deletions from their case samples. The four deletions in schizophrenia cases in Need et al. (10) appear to overlap with cases in ISC (1) and were not included; Need et al. (10) also noted one duplication in a control individual, in addition to their duplication in an individual with schizophrenia. Weiss et al. (ref. 8, suppl. table 2) present data on two duplications of 22q11.21 in cases of autism from AGRE samples; these cases are not included because, based on the genomic coordinates of the duplications, they appear to be the same individuals as in the Autism Genome Project Consortium sample (14). Glessner et al. (15) kindly provided us with the genomic coordinates of their 22q11.21 cases and controls; three of their ACC duplications met the criteria for inclusion (spanning 17.2–19.79), two were much smaller (0.1–0.2 Mb) and were not included, and their two AGRE samples overlapped with those in Christian et al. (6). Statistical associations between 22q11.21 deletions and schizophrenia have been reported by ISC (1) ($P = 0.0046$), and by Kirov et al. (12) ($P = 0.02$), as well as in previous studies based on cytogenetic evidence. A hypothesis of statistical association of 22q11.2 duplications with autism can be tested using data from Glessner et al. (15), who reported a total of five duplications (meeting the 1.5Mb criterion) in 2,195 cases, compared to none in 2,519 controls (Fisher's exact test, $P = 0.0218$). The 1.5-Mb and 3-Mb deletions at 22q11.21 have been ascertained cytogenetically since the late 1990's and they represent well-documented highly-penetrant risk factors for schizophrenia, with about 25% of subjects exhibiting the disorder in adulthood (61, 62). Seventeen genes within the 3Mb 22q11.21 deletion region have been associated with schizophrenia risk in one or more studies (33), but no consensus has emerged concerning the genetic basis of elevated schizophrenia risk in this condition (62). Autistic spectrum disorders, mainly PDD-NOS, have been diagnosed in children with cytogenetically-ascertained 22q11.21 deletions in several studies (63-66). Ogilvie et al. (67) reported no cases of 22q11.21 deletion in a sample of 103 subjects diagnosed with autism by strict diagnostic criteria, Eliez (68) suggested that autism spectrum conditions in children with 22q11.21 deletions represent premorbidity for schizophrenia and related disorders rather than autism itself, and Feinstein and Singh (69) noted that social deficits are shared between autism and premorbidity for schizophrenia, making childhood diagnoses problematic. Brunet et al. (70) tested 190 patients with schizophrenia for 22q11.2 copy number alterations, reporting two cases of deletions, but no duplications. Ramelli et al. (71) and Mukaddes and Herguner (72) have each reported a single case of autism associated with cytogenetically-ascertained duplications at 22q11.21. Several genes in the 22q11.21 deletion region, including *TBX1*, *DGCR6*, and *SLC25A1*, have been predicted to exhibit imprinting in mice or humans from bioinformatic studies (73, 74), but there is no direct evidence of imprinting effects for any genes in this region.

Table S9. Deletions and duplications of 22q13.3 in autism and schizophrenia

Disorder	Case data	CNV	Ref.
Autism	1 case, table 1	Deletion	5
Autism	2 cases, table 2 and table S2	Deletions	13
Autism	2 cases, table 1	Deletions	15
Schizophrenia	4 cases, http://pngu.mgh.harvard.edu/isc/	Duplications	1

Cases for this locus were ascertained on the basis of deletion or duplication of the *SHANK3* gene. The deletion cases in Sebat et al. (5) (4.3-Mb), Marshall et al. (13) (3.2-Mb and 0.276-kb), and Glessner et al. (15) (1.3-Mb and 3.2-Mb) include notably larger regions, while the duplications involve smaller regions that include the *SHANK3* gene. Deletions and rare, nonsynonymous loss of function mutations in this gene have been implicated in autism by Durand et al. (75) and Moessner et al. (76), and large subtelomeric deletions at 22q13.3 are strongly associated with syndromic autism (77, 78). Marshall et al. (13) reported *SHANK3* deletions as autism-specific variants, but Glessner et al. (15) reported deletions of this gene in two control individuals and did not find statistical support for an association of *SHANK3* deletions with autism in their data. Inference of association of *SHANK3* deletions with autism is based on a combination of data from studies of loss of function mutations, deletions, and autism in 22q13.3 deletion syndrome. *SHANK3* duplications have been found in 4 of 3,391 schizophrenia cases compared to none of 3,818 controls (Fisher's exact test, $P = 0.0489$) (*1*), and schizophrenia was also reported in an individual with a 5.4-Mb subtelomeric duplication that included *SHANK3* (79). In addition, a case of Asperger syndrome was diagnosed in an individual with partial trisomy of 22q13.3 (including SHANK3), in association with a paternal translocation that also involved chromosome 14 (75).

Table S10. Combinations of associations of genes with autism and schizophrenia and their associated probabilities, under a null model of random association

A+S+	A−S+	A+S−	A−S−	Prob.	Cumu.
8	23	14	0	0.000	0.000
9	22	13	1	0.000	0.000
10	21	12	2	0.001	0.001
11	20	11	3	0.007	0.009
12	19	10	4	0.034	0.043
13	18	9	5	0.100	0.143
14	17	8	6	0.193	0.337
15	16	7	7	0.251	0.587
16	15	6	8	0.219	0.806
17	14	5	9	0.129	0.935
18	13	4	10	0.050	0.985
19	12	3	11	0.012	0.998
20	11	2	12	0.002	1.000*
21	10	1	13	0.000	1.000
22	9	0	14	0.000	1.000

Null-model probabilities are derived under the constraint that there are 45 total genes, 31 of which are S+ and 22 of which are A+.
*Observed data.

SI Text

Associations of Genes. Detailed information concerning associations of genes shown in the "Different alleles" column of Table 2. Information on genes in this category showing positive associations that were not replicated in one or both conditions is also provided.

***AHI1* Gene.** The protein product of the *AHI1* (Abelson Helper Integration Site 1) gene interacts with HapI (Huntingtin-associated protein 1) and functions in maintaining levels of the neurotrophic tyrosine kinase receptor B, which plays a critical role on brain development (80). Recessive loss of function of the gene *AHI1* causes Joubert syndrome, which involves autism spectrum disorders in up to 40% of cases (81). Anamm-Zalcenstein et al. (82) reported an association of haplotypes in the *AHI1* gene with schizophrenia, an association that was replicated in a different population by Ingason et al. (83). Retuerto et al. (81) reported an association of common variants in *AHI1* with autism, involving a large autism-associated haplotype block that contained the smaller schizophrenia-associated haplotypes, but represented different alleles. Ferland et al. (84) describe evidence of rapid adaptive amino acid evolution of the *AHI1* gene, along the human lineage.

***APC* Gene.** The protein product of the *APC* (Adenomatous Polyposis Coli) gene is a large multifunctional protein involved in Wnt/beta-catenin signaling and cytoskeletal dynamics, with a central role in early development of the cerebral cortex (85, 86). Zhou et al. (87) found that the common haplotype T-G-A-G for the tightly-linked SNPs rs2229992-rs42427-rs459552-rs465899 (LD of 0.86 to 0.98) was associated with increased autism risk ($P = 0.006$), and Cui et al. (88) reported that haplotype C-A-T for the overlapping SNP set rs2229992-rs42427-rs465899 was strongly associated with increased schizophrenia risk ($P < 0.001$).

***APOE* Gene.** The apolipoprotein E (*APOE*) gene codes for a protein that transports lipoproteins, fat-soluble vitamins, and cholesterol. The gene bears three major alleles, E2, E3 and E4 that exhibit notable physiological differences, including lower atherosclerosis risk associated with E2 and higher risk associated with E4, and well-documented effects on aspects of cognition, such as verbal fluency (89).

The E4 allele of *APOE* has been associated with higher risk of schizophrenia than the E3 allele, in a meta-analysis of 16 studies involving Caucasian populations (33) (OR = 1.16 (CI = 1.01–1.33), although this difference was nonsignificant in meta-analysis across all studies. This allele has also been associated with higher risk of early-onset bipolar disorder (90) and mediating age of onset in schizophrenia, with E4-bearing individuals showing earlier onset and E2-bearing individuals exhibiting later onset (91). The E2 allele has been linked with increased autism risk in an association study (92), although this result was not replicated in two more recent studies (93, 94). The influence of *APOE* alleles on schizophrenia risk may be related to association of the E4 allele with reduced hippocampus size and asymmetry (95, 96) and reduced white matter integrity (97). Such effects may also be related to the tendency for the E4 allele to provide less effective neuronal protection and repair than E2 and E3, leading to increased neurodegeneration (98).

Considerable evidence also indicates that *APOE* alleles have been subject to positive selection in the human lineage, although the context and causes of selection have yet to be clearly elucidated (99).

***DRD1* Receptor.** The dopamine *DRD1* receptor represents a key component of the dopaminergic system, via its functional interactions with *DRD2* and its high concentration in the prefrontal cortex (100). Meta-analysis of 10 studies showed a significant association of the G allele of the SNP rs4532 with higher schizophrenia risk (across all studies, OR = 1.18, CI = 1.01–1.38) (33), and alleles of this SNP have also been shown to influence response to clozapine (101), and neural function in a working-memory task (102). Hettinger et al. (103) found a significant association of the A allele for rs4532 with higher autism risk in multiplex-family males, both alone and in the tightly-linked haplotype combination rs265981-rs4532-rs686, with C-A-T overtransmitted in autism. Del Zompo et al. (104) found that the autism-associated haplotype was highly-significantly undertransmitted in bipolar I disorder, such that it was protective against this condition. Similarly, Dmitrzak-Weglarz et al. (105) and Severino et al. (106) found that the G allele and G/G genotype of rs4532 were significantly more frequent in bipolar patients compared with controls.

One case of a duplication encompassing the DRD1 gene has reported in a subject with autism (10) (duplication from 174,348,000–174,971,000)

***FOXP2* Gene.** *FOXP2* codes for a brain-expressed transcription factor that has been demonstrated to mediate the evolution and development of human speech and language (107). Gong et al. (108) reported preferential transmission of the C allele of the SNP rs1456031 to autistic offspring ($P < 0.05$), and Sanjuan et al. (109) found a lower proportion of the CC genotype at this locus in schizophrenics with auditory hallucinations, compared with controls ($P = 0.034$ for comparison of genotypes), although differences in allele frequency were non-significant ($P = 0.15$). Additional studies using this SNP, and the SNP rs2396753, which shows allelic and genotype association with schizophrenia (109), are required for robust interpretation.

***HLA-DRB1* Locus.** HLA alleles may mediate psychiatric conditions via some combination of neuroimmune system development and function, maternal-fetal interactions in pregnancy, and reactions to infectious disease during early development. Autism has been strongly associated with an increased frequency of DR4 alleles at the *HLA-DRB1* locus (110–114; but see also refs. 115 and 116), and it has also been associated with a significantly reduced frequency of DR13 alleles (112). There is evidence for a decreased frequency of the DR4 allele in schizophrenia in some populations (in patients and their mothers; refs. 117–119; reviewed in ref. 120) although some studies did not replicate this difference (121–123). One study also noted strong preferential transmission of the DR13 allele in schizophrenia (124), such that this allele is positively associated with the disorder. The *HLA-DRB1* locus also exhibits significantly differential expression in the central nervous system and in blood for schizophrenia patients versus controls (124). Interpretation of these findings is complicated by strong linkage in this region, and evidence that maternal genotype at this locus affects risk of autism in offspring (116). Further studies of both autism and schizophrenia that incorporate analyses of both maternal and offspring genotypes and extended haplotypes for the DRB1 region are required for strong inferences to be drawn.

***SHANK3* Gene.** Associations of *SHANK3* with autism and schizophrenia are described in Table S9.

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