Supplement. Detailed description of samples.

A total of 2,977 schizophrenia patients and 33,746 controls from six European populations were examined for CNVs at the three loci studied here, *NRXN1, NRXN2*, and *NRXN3*; 1,439 schizophrenia patients and 28,551 control individuals from Iceland, Scotland, Germany, England, Italy and Finland (The SGENE sample; http://www.SGENE.eu), an additional 493 affected and 871 controls from Bonn, Germany, 245 cases and 272 controls from Norway, and 806 cases and 4039 controls from the Netherlands. The full geographic breakdown is shown in supplementary table 1.

The Icelandic sample consists of 648 schizophrenics and 27,747 controls. Patients and controls were all Icelandic and diagnoses were assigned according to Research Diagnostic Criteria (RDC) (35) through the use of the lifetime version of the Schizophrenia and Affective Disorders Schedule (SADS-L) (36). The Icelandic controls were chosen from persons who have participated in other genetic studies at deCODE Genetics. A further 5,630 genotyped samples were examined but excluded from association analysis due to other psychiatric disorders (autism, bipolar disorder, ADHD, dyslexia and alcoholism) and/or first degree relationships to schizophrenic patients.

The Scottish sample is comprised of 211 schizophrenia cases and 229 controls. All participants self-identified as born in the British Isles (95% in Scotland) and met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition and ICD-10 (37,38) criteria for schizophrenia. Diagnosis was made by OPCRIT (39). Controls were volunteers recruited through general practices in Scotland, and subjects with major mental illness were excluded.

The German sample (Munich) consisted of 195 Caucasian cases and 192 Caucasian controls. Cases diagnosed with DSMIV schizophrenia were ascertained from the Munich area in Germany. Diagnosis was made according to DSMIV criteria using the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (40). The controls were unrelated volunteers randomly selected from the general population of Munich.

The Finnish sample consisted of 191 schizophrenics and 200 regionally selected controls that had no medical history of schizophrenia. Diagnosis was according to DSMIV criteria (DSM-

IV) (37).

The sample from the UK consisted of cases (n = 104) and controls (n = 95) who were unrelated white European Caucasians. All patients were interviewed with the Schedule for Affective Disorders and Schizophrenia Lifetime Version or the Item Group Checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (38) and diagnosed according to ICD-10 RDC. UK controls were unrelated individuals with no history of major mental illness.

Diagnosis of the 86 Italian cases from the local population of South Verona was also by IGC and ICD-10 RDC for schizophrenia, and the 91 controls were unrelated healthy volunteers randomly selected from the same population.

The German sample (Bonn) is comprised of 491 patients and 881 controls. Patients were recruited from consecutive hospital admissions and were all of German descent. In patients, lifetime best estimate diagnoses according to DSM-IV criteria were based on multiple sources of information including structured interview with the SCID (40) or SADS-L (41), OPCRIT data (39), medical records, and the family history. Best estimate diagnoses were obtained from at least two experienced psychiatrists/psychologists. Controls were derived from two German population-based cohorts, PopGen (N=495) (42) and Heinz Nixdorf Recall (N=386) (43). Ethical approval was obtained from the local Ethics Committees. All participants gave written informed consent.

The Norwegian sample included 245 patients who had been recruited to the TOP study from all the psychiatric hospitals in the Oslo area. The patients were diagnosed according to Structural Clinical Interview for DSM-IV (SCID) as schizophrenia (N=153) schizoaffective (N=34), schizophreniform disorder (N=10), psychosis NOS (N=42) and delusional disorder (N=6). The healthy control subjects (N=272) were randomly selected from statistical records of persons from the same catchment area as the patient groups. Only subjects born in Norway, all of Caucasian origin, were contacted by letter and invited to participate. All subjects have given written informed consent prior to inclusion into the project and the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency approved the study.

The Dutch sample consisted of 806 patients and 706 controls from Utrecht and additional 3,333 control individuals from Nijmegen in the Netherlands. Inpatients and outpatients were recruited from different psychiatric hospitals and institutions throughout the Netherlands, coordinated via academic hospitals in Amsterdam, Groningen, Maastricht and Utrecht. Detailed medical and psychiatric histories were collected, including the Comprehensive Assessment of Symptoms and History (CASH) (45), an instrument for assessing diagnosis and psychopathology. To exclude related patients and controls, all subjects were fingerprinted (Illumina DNA panel, 400 SNPs). Only patients with a DSM-IV diagnosis of schizophrenia were finally included as cases (295.xx). All patients and controls were of Dutch descent, with at least three out of four grandparents of Dutch ancestry. The controls were volunteers and were free of any psychiatric history. Ethical approval was obtained from the local Ethics Committees. All participants gave written informed consent.

The additional Dutch controls consisted of 3,333 samples, collected by the Radboud University Nijmegen Medical Centre (RUNMC) for genetic studies (cancer and control samples). All 3,333 participants used in the present study are of self-reported European descent. The study protocol was approved by the Institutional Review Board of Radboud University and all study subjects gave written informed consent.

The SGENE samples were typed on the HumanHap300 BeadArrayTM (Illumina, San Diego, USA) at deCODE genetics. The samples from Bonn were typed at Bonn University on the HumanHap550v3 BeadArrayTM (Illumina, San Diego, USA). The Dutch samples from Utrecht University were genotyped at the University of California, Los Angeles, on HumanHap550v3 BeadArrayTM (Illumina, San Diego, USA). The remaining Dutch samples were genotyped at deCODE genetics on HumanHap300 BeadArrayTM (Illumina, San Diego, USA). The Norwegian samples were genotyped on Affymetrix GeneChip(r) GenomeWide SNP 6.0 array and analyzed using the Affymetrix Power Tools 1.8.0. Samples with Contrast QC below 0.4 were excluded as recommended by the manufacturer.

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Supplementary table 1: Breakdown of sample by population

Population	**Aff**	**Ctrl**
Finland*	191	200
Germany	686	1073
Holland	806	4039
Italy	86	91
Scotland	211	229
UK	104	95
Iceland	648	27747**
Norway	245	272
Total	2977	33746

* Part of the Finnish sample comes from a genetic isolate with increased incidence of schizophrenia, we have accordingly analyzed the Finnish sample as two groups in the Cochran-Mantel-Haenszel analysis.

** A further 5,630 genotyped samples were examined but excluded from association analysis due to other psychiatric disorders (autism, bipolar disorder, ADHD, dyslexia and alcoholism) and/or first degree relationships to schizophrenic patients.

Supplementary table 2. Identified CNVs at the *NRXN1* locus on 2p16.3

CNV	Population	Phenotype	Sex	Exons disrupted in NRXN1-α	Boundaries (Build 36)	First SNP in CNV	Last SNP in CNV
Duplication	Italy	Schizophrenia	Female	e19-e20	chr2:50,071,499-50,208,992	rs1421567	rs2060885
Deletion	Holland	Control	Female	No	chr2:50,438,401-50,493,827	rs2037387	rs10181522
Deletion	Iceland	Control	Female	e5-e15	chr2:50,558,547-50,977,187	rs7595040	rs1544690
Deletion	Germany	Schizophrenia	Male	e5	chr2:50,711,199-50,756,435	rs11691013	rs2194390
Deletion	Holland	Control	Male	No	chr2:50,718,838-50,756,435	rs2194385	rs2194390
Deletion	Iceland	Alcoholism	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Alcoholism	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion[1]	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Holland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Holland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Holland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Holland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940

Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Male	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Iceland	Control	Female	No	chr2:50,735,657-50,799,203	rs1518551	rs858940
Deletion	Germany	Control	Female	No	chr2:50,735,657-50,800,548	rs1518551	rs17501747
Deletion	Holland	Schizophrenia	Female	No	chr2:50,735,657-50,800,548	rs1518551	rs17501747
Deletion	Iceland	Control	Female	No	chr2:50,786,446-50,882,166	rs1518548	rs2352077
Deletion	Iceland	Control	Female	No	chr2:50,786,446-50,882,166	rs1518548	rs2352077
Duplication	Holland	Control	Female	No	chr2:50,786,446-50,900,862	rs1518548	rs9309203
Duplication	Holland	Control	Male	No	chr2:50,786,446-50,900,862	rs1518548	rs9309203
Duplication	Holland	Control	Male	No	chr2:50,786,446-50,900,862	rs1518548	rs9309203
Duplication	Holland	Schizophrenia	Male	No	chr2:50,786,446-50,900,862	rs1518548	rs9309203
Deletion	Iceland	Control	Female	e3-e4	chr2:50,786,446-51,082,210	rs1518548	rs10195460
Deletion	Italy	Schizophrenia	Female	No	chr2:50,822,312-50,948,557	rs10184594	rs1558799
Deletion	Holland	Control	Male	No	chr2:50,822,312-50,990,306	rs10184594	rs2193412
Deletion	Germany	Schizophrenia	Female	No	chr2:50,836,690-50,936,258	rs17041014	rs10490175
Deletion	Holland	Control	Male	No	chr2:50,839,632-50,936,258	rs10445932	rs10490175
Deletion	Holland	Control	Male	No	chr2:50,839,632-50,936,258	rs10445932	rs10490175
Deletion	Holland	Control	Female	No	chr2:50,839,632-50,936,258	rs10445932	rs10490175
Deletion	Germany	Schizophrenia	Female	e1-e4	chr2:50,850,456-51,225,851	rs3892750	rs10490158
Deletion	Germany	Schizophrenia	Female	No	chr2:50,856,110-50,900,862	rs3850332	rs9309203
Deletion	Scotland	Control	Male	No	chr2:50,867,151-50,985,170	rs9309199	rs2352540
Deletion	Holland	Control	Male	No	chr2:50,872,736-50,900,862	rs9751737	rs9309203
Deletion	Germany	Control	Female	No	chr2:50,878,545-50,932,986	rs3850336	rs2193225
Deletion	Holland	Control	Male	No	chr2:50,890,216-50,990,306	rs9750635	rs2193412
Deletion	Germany	Schizophrenia	Male	e1-e4	chr2:50,890,216-51,116,653	rs9750635	rs1995584
Deletion	Holland	Control	Female	No	chr2:50,912,249-50,948,557	rs10167695	rs1558799
Deletion[2]	Iceland	Autism	Male	e1-e4	chr2:50,947,040-51,164,471	rs11884918	rs11896803
Deletion	Finland	Control	Male	e1-e4	chr2:50,985,170-51,211,406	rs2352540	rs7602156
Deletion	Holland	Schizophrenia	Male	e1-e4	chr2:51,002,576-51,250,922	rs7423296	rs10490156
Deletion	Holland	Schizophrenia	Female	e1-e2	chr2:51,0249,62-51,251,873	rs4971709	rs10490155

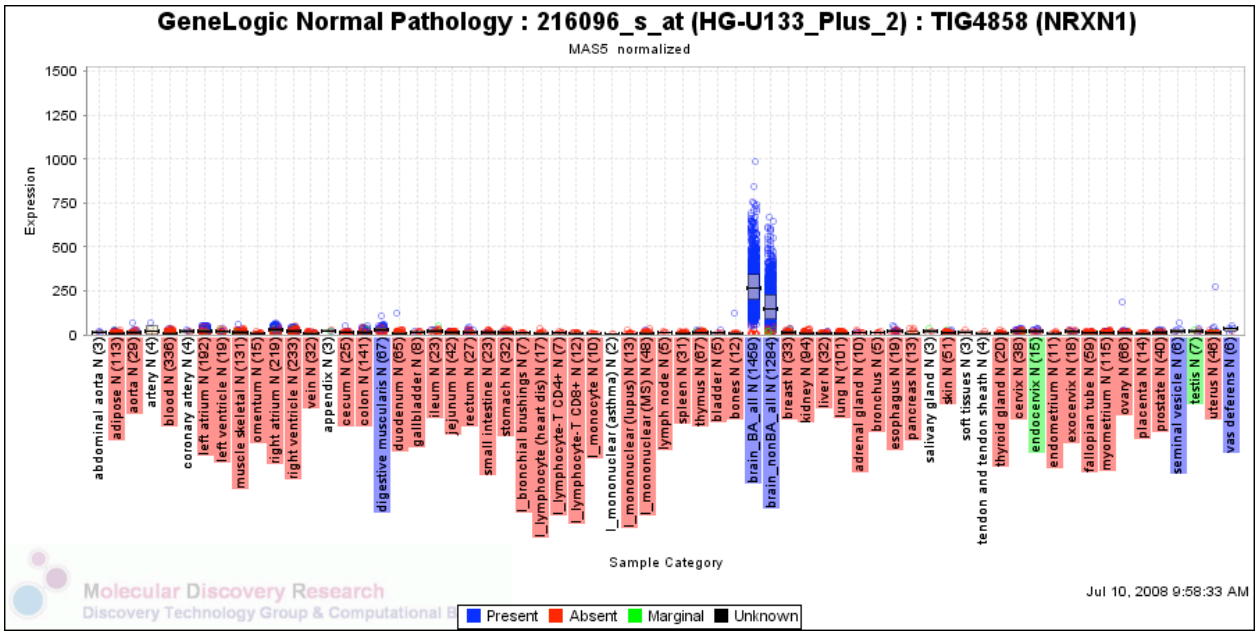
Deletion	Iceland[3]	Alcoholism, Dyslexia	Male	e1-e2	chr2:51,082,210-51,225,851	rs10195460	rs10490158
Deletion	Iceland[3]	Control	Male	e1-e2	chr2:51,082,210-51,225,851	rs10195460	rs10490158
Deletion	Iceland	Control	Female	e1-e2	chr2:51,082,210-51,225,851	rs10195460	rs10490158
Deletion	Finland	Schizophrenia	Male	e1-e2	chr2:51,101,161-51,344,213	rs10490162	rs9309208
Deletion	Holland	Control	Female	No	chr2:51,132,898-51,189,362	rs4971724	rs2195477
Deletion	Germany	Control	Female	No	chr2:51,132,898-51,225,851	rs4971724	rs10490158
Deletion	Germany	Schizophrenia	Female	No	chr2:51,147,600-51,225,851	rs988982	rs10490158
Deletion	Iceland	Control	Female	No	chr2:51,147,600-51,419,724	rs988982	rs1008618
Deletion	Iceland	First degree relative to schizophrenia	Male	No	chr2:51,211,406-51,299,436	rs7602156	rs10490153
Deletion	Iceland	Control	Female	No	chr2:51,211,406-51,299,436	rs7602156	rs10490153
Deletion	Iceland	Control	Female	No	chr2:51,211,406-51,299,436	rs7602156	rs10490153
Deletion	Iceland	Schizophrenia	Male	No	chr2:51,211,406-51,299,436	rs7602156	rs10490153
Deletion	Iceland	Control	Male	No	chr2:51,250,505-51,352,966	rs10490157	rs1016387
Deletion	Iceland	Control	Female	No	chr2:51,250,505-51,352,966	rs10490157	rs1016387

[1]homozygous deletion

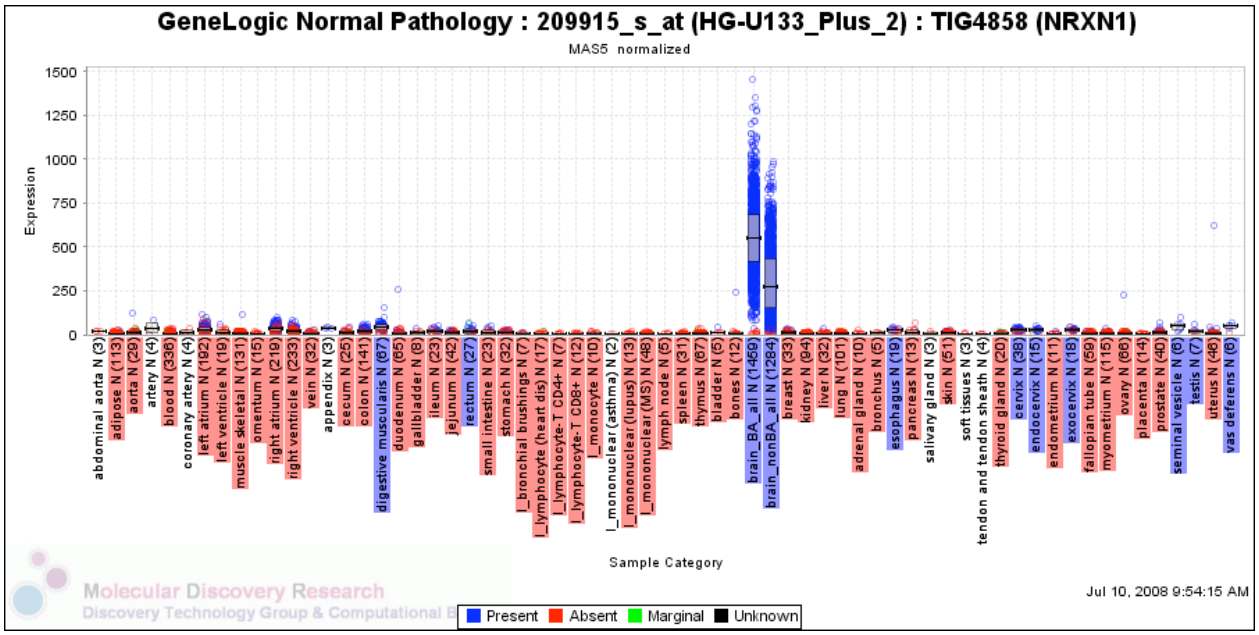
[2] previously identified as a *de novo* deletion in Stefansson et al. (2008)

[3] the control individual is the father of the subject diagnosed with alcoholism and dyslexia

Supplementary figure 1a: NRXN1a expression in normal tissues (216096_s_at)



Supplementary figure 1b: NRXN1b expression in normal tissues (209915_s_at)



Supplementary figure 1c: NRXN1a-2 expression in normal tissues (1558708_at)