Supplementary material: A large replication study and meta-analysis in European samples provides further support for association of AHI1 markers with schizophrenia.

Supplement 1: Sample description.

Munich sample

Healthy volunteers

Unrelated volunteers of German descent (i.e., both parents German) were randomly selected from the general population of Munich, Germany, and contacted by mail. To exclude subjects with central neurological diseases and psychotic disorders or subjects who had first-degree relatives with psychotic disorders, several screenings were conducted before the volunteers were enrolled in the study.

First, subjects who responded were initially screened by phone for the absence of neuropsychiatric disorders. Second, detailed medical and psychiatric histories were assessed for both themselves and their first-degree relatives by using a semi-structured interview. Third, if no exclusion criteria were fulfilled, they were invited to a comprehensive interview including the Structured Clinical Interview for DSM-IV (SCID[1] and SCID-II[2]) to validate the absence of any lifetime psychotic disorder. Fourth, the Family History Assessment Module[3] was conducted to exclude psychotic disorders among first-degree relatives. Finally, a neurological examination was conducted to exclude subjects with current CNS impairment. In the case that the volunteers were older than 60 years, the Mini Mental Status Test[4] was performed to exclude subjects with possible cognitive impairment.

Following the screening assessments, 1 272 control subjects (588 men and 684 women) were included. Further sample details are described elsewhere[5].

Schizophrenic patients

We ascertained 495 individuals with schizophrenia (322 men and 173 women) from the Munich area in Germany. Of them, 66.3% were of German descent (i.e., both parents were German), and 33.7% were Caucasian of European descent. No evidence for ethnic stratification was observed after testing with the software STRUCTURE[6]. Subjects had a DSM-IV and ICD-10 diagnosis of schizophrenia of four subtypes: paranoid (78.2%), disorganized (15.4%), catatonic (2.0%), and undifferentiated (4.4%). Detailed medical and psychiatric histories were collected, including a clinical interview using the Structured Clinical Interview for DSM-IV (SCID), to evaluate lifetime Axis I and II diagnoses[1,2]. Four physicians and one psychologist rated the SCID interviews and all measurements were double-rated by a senior researcher. Exclusion criteria included a history of head injury or neurological diseases. All subjects were out-patients or stable in-patients. Further details are described elsewhere[7].

A large part of the Munich sample has also been genotyped genome-wide, one part through the SGENE collaboration, and another part by Duke University on behalf of GlaxoSmithKline, made available to us through the extended SGENE+ consortium, see further details below.

SCOPE sample

The Danish sample comprised 456 patients and 995 controls; 408 patients were affected with schizophrenia and 48 were affected with related psychoses. Patients were recruited to Danish Psychiatric Biobank from the psychiatric departments at the six hospitals in the Copenhagen region. The healthy controls subjects were recruited through the Danish Blood Donor Corps in the Copenhagen area. All subjects were of Caucasian origin with >0.9 probability determined by microsatellite genotypes[8].

The Norwegian sample comprised 264 patients, affected with schizophrenia and related psychoses, and 181 controls. Patients were recruited from all the psychiatric hospitals in the Oslo area and diagnosed according to Structural Clinical Interview for DSM-IV (SCID). The healthy control subjects 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.

Detailed description of the SCOPE sample is provided elsewhere[9].

SGENE+ sample

The SGENE sample is composed of 1 433 schizophrenia patients and 33 250 control individuals from Iceland, Scotland, Germany, England and Wales, Italy, and Finland (http://www.SGENE.eu). The extended SGENE+ consortium includes, in addition to the SGENE sample, further samples from Aberdeen, Scotland and Munich, Germany, collected with support from GSK, as well as samples from Bonn, Germany, and Utrecht, Holland, in total 3 417 patients and 35 100 controls.

The Munich German part of the SGENE+ sample, 615 patients and 612 controls, overlaps to a large extent the Munich sample described above. We therefore omit the Munich part of the SGENE+ sample entirely from the analysis of *AHI1* markers.

The 589 Icelandic patients of the SGENE+ sample are essentially the same as reported in Ingason *et al.*[11], while the Icelandic SGENE+ controls are not the same. For the meta-analysis of the seven markers reported by Amann-Zalcenstein et al.[10] we choose to use the results from the Icelandic SGENE+ sample, as this includes many more controls (although, in this study we only use the 11 491 Icelandic controls that were typed on the HumanHap300 array out of the total of 32 443 Icelandic controls in the SGENE+ sample, this is done to avoid a systematic array effect as all the Icelandic patients are typed on the HumanHap300 array).

The remaining part of the SGENE+ sample includes 182 affected and 197 control individuals from Finland (part of the Finnish sample comes from a genetic isolate, and we therefore treat the Finnish sample as two separate samples in the meta-analysis); 84 and 89 from Italy; 93 and 88 from England and Wales; 658 and 661 from Aberdeen, Scotland; 483 and 367 from Bonn, Germany (the Bonn controls were derived from the German population-based Heinz Nixdorf Recall cohort); and 713 and 643 from Utrecht, Holland.

Thus, the SGENE+ sample investigated in the current study includes 2 802 patients and 13 536 controls. Detailed description of the SGENE+ samples is provided elsewhere[12]. Ethical approval was obtained from the local Ethics Committees. All participants gave written informed consent.

Cardiff University sample

The case sample consisted of 642 unrelated subjects with schizophrenia (436 male and 206 female) of which 479 were used in the GWA study. All were white and born in the British Isles. All patients had a consensus diagnosis of schizophrenia according to DSMIV criteria made by two independent raters following a semi-structured interview by trained psychiatrists or psychologists using the Present State Examination[13] or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview[14] and review of case records. Cases were screened to exclude substance-induced psychotic disorder or psychosis due to a general medical condition. The mean age at first psychiatric contact was 23.8 (SD 7.9) years and the mean at ascertainment was 44.8 (SD 13.1) years. Multicentre and Local Research Ethics Committee approval were obtained, and all subjects gave written informed consent to participate.

The control sample used by the Wellcome Trust Case Control Consortium is described in detail elsewhere[15]. Briefly, controls (n= 2936) came from two sources, the 1958 British Birth Cohort (58C) and UK blood donors. At a genome wide level, the two groups do not significantly differ with respect to allele frequencies justifying their use as a single control group. Individuals included in the study were living within England, Scotland and Wales. Individuals (n=26) with non-Caucasian ancestry as determined by Multidimensional Scaling (MDS) were previously removed by the WTCCC from the sample.

Supplementary references

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Supplementary Table 1: Surrogate alleles typed in different samples and their correlation with original alleles

Original study[1]	Munich		SCOPE		SGENE+		Cardiff	
Allele	Allele	R^2	Allele	R^2	Allele	R^2	Allele	R^2
rs9321501-A	rs9321501-A	-	rs9321501-A	-	rs2064430-C	1	rs2757649-A	0.96
rs11154801-C	rs11154801-C	-	rs7750586-A	0.96	rs11154801-C	-	rs7750586-A	0.96
rs7750586-A	rs7750586-A	-	rs7750586-A	-	rs11154801-C	0.96	rs7750586-A	-
rs9647635-A	rs9647635-A	-	rs7750586-A	1	rs11154801-C	0.96	rs7750586-A	1
rs7739635-C	rs12196952-A	0.85	rs9494335-A	0.81	rs9321521-G	0.96	rs9494322-C	0.83
rs9494332-A	rs9494332-A	-	rs9494335-A	1	rs10223338-C	0.92	rs9494322-C	0.91
rs1475069-A	rs1475069-A	-	rs9399158-C	1	rs1475069-A	-	rs9389329-C	0.96

The table shows correlation of surrogate alleles with original alleles in the Hapmap CEU population (http://www.hapmap.org)

[1]*The family study of Amann-Zalcenstein et al. (2006)*

Supplementary Table 2: Surrogate markers and allele counts for sub-samples in the meta-analysis of alleles reported by Amann-Zalcenstein et al. (2006).

					Affected		Controls	
Study	**Sub-sample**	**Allele**	**Marker**	**R^2**	**Allele count**	**Other allele count**	**Allele count**	**Other allele count**
Munich	Germany - Munich	**A**	**rs9321501**	-	565	425	1407	1137
SCOPE	Denmark	**A**	**rs9321501**	-	479	433	1055	935
SCOPE	Norway	**A**	**rs9321501**	-	277	251	191	171
SGENE+	Iceland	C	rs2064430	1	659	517	12 076	10 832
SGENE+	England/Wales	C	rs2064430	1	110	72	92	80
SGENE+	Finland I[1]	C	rs2064430	1	68	50	178	116
SGENE+	Finland II[1]	C	rs2064430	1	145	97	54	44
SGENE+	Italy	C	rs2064430	1	94	74	111	67
SGENE+	Holland	C	rs2064430	1	819	607	669	613
SGENE+	Scotland	C	rs2064430	1	752	562	736	586
SGENE+	Germany – Bonn	C	rs2064430	1	525	441	378	356
Cardiff	England/Wales	A	rs2757649	0.96	555	403	3275	2597
Munich	Germany – Munich	**C**	**rs11154801**	-	643	347	1643	901
SCOPE	Denmark	A	rs7750586	0.96	593	319	1253	737
SCOPE	Norway	A	rs7750586	0.96	333	195	229	133
SGENE+	Iceland	**C**	**rs11154801**	-	807	371	15 222	7760
SGENE+	England/Wales	**C**	**rs11154801**	-	123	63	115	61
SGENE+	Finland I[1]	**C**	**rs11154801**	-	79	39	201	93
SGENE+	Finland II[1]	**C**	**rs11154801**	-	181	65	69	31

SGENE+	Italy	**C**	**rs11154801**	-	106	62	121	57
SGENE+	Holland	**C**	**rs11154801**	-	950	476	794	492
SGENE+	Scotland	**C**	**rs11154801**	-	860	456	850	472
SGENE+	Germany – Bonn	**C**	**rs11154801**	-	624	342	457	275
Cardiff	England/Wales	A	rs7750586	0.96	627	329	3727	2143
Munich	Germany – Munich	**A**	**rs7750586**	-	641	349	1638	906
SCOPE	Denmark	**A**	**rs7750586**	-	593	319	1253	737
SCOPE	Norway	**A**	**rs7750586**	-	333	195	229	133
SGENE+	Iceland	C	rs11154801	0.96	807	371	15 222	7760
SGENE+	England/Wales	C	rs11154801	0.96	123	63	115	61
SGENE+	Finland I[1]	C	rs11154801	0.96	79	39	201	93
SGENE+	Finland II[1]	C	rs11154801	0.96	181	65	69	31
SGENE+	Italy	C	rs11154801	0.96	106	62	121	57
SGENE+	Holland	C	rs11154801	0.96	950	476	794	492
SGENE+	Scotland	C	rs11154801	0.96	860	456	850	472
SGENE+	Germany – Bonn	C	rs11154801	0.96	624	342	457	275
Cardiff	England/Wales	**A**	**rs7750586**	-	627	329	3727	2143
Munich	Germany – Munich	**A**	**rs9647635**	-	641	349	1639	905
SCOPE	Denmark	A	rs7750586	1	593	319	1253	737
SCOPE	Norway	A	rs7750586	1	333	195	229	133
SGENE+	Iceland	C	rs11154801	0.96	807	371	15 222	7760
SGENE+	England/Wales	C	rs11154801	0.96	123	63	115	61
SGENE+	Finland I[1]	C	rs11154801	0.96	79	39	201	93

SGENE+	Finland II[1]	C	rs11154801	0.96	181	65	69	31
SGENE+	Italy	C	rs11154801	0.96	106	62	121	57
SGENE+	Holland	C	rs11154801	0.96	950	476	794	492
SGENE+	Scotland	C	rs11154801	0.96	860	456	850	472
SGENE+	Germany – Bonn	C	rs11154801	0.96	624	342	457	275
Cardiff	England/Wales	A	rs7750586	1	627	329	3727	2143
Munich	Germany – Munich	A	rs12196952	0.85	674	316	1676	868
SCOPE	Denmark	A	rs9494335	0.81	612	300	1327	663
SCOPE	Norway	A	rs9494335	0.81	340	188	245	117
SGENE+	Iceland	G	rs9321521	0.96	828	342	15 045	7509
SGENE+	England/Wales	G	rs9321521	0.96	124	58	111	65
SGENE+	Finland I[1]	G	rs9321521	0.96	97	21	227	63
SGENE+	Finland II[1]	G	rs9321521	0.96	195	47	79	19
SGENE+	Italy	G	rs9321521	0.96	107	61	120	58
SGENE+	Holland	G	rs9321521	0.96	950	472	781	499
SGENE+	Scotland	G	rs9321521	0.96	856	444	873	441
SGENE+	Germany – Bonn	G	rs9321521	0.96	604	362	447	285
Cardiff	England/Wales	C	rs9494322	0.83	683	275	3968	1902
Munich	Germany – Munich	**A**	**rs9494332**	-	670	320	1647	897
SCOPE	Denmark	A	rs9494335	1	612	300	1327	663
SCOPE	Norway	A	rs9494335	1	340	188	245	117
SGENE+	Iceland	C	rs10223338	0.92	859	319	16 016	6940
SGENE+	England/Wales	C	rs10223338	0.92	131	55	124	52

SGENE+	Finland I[1]	C	rs10223338	0.92	98	20	232	62
SGENE+	Finland II[1]	C	rs10223338	0.92	198	46	81	19
SGENE+	Italy	C	rs10223338	0.92	119	49	132	46
SGENE+	Holland	C	rs10223338	0.92	1019	407	855	429
SGENE+	Scotland	C	rs10223338	0.92	927	385	931	391
SGENE+	Germany – Bonn	C	rs10223338	0.92	653	309	492	242
Cardiff	England/Wales	C	rs9494322	0.91	683	275	3968	1902
Munich	Germany – Munich	**A**	**rs1475069**	-	711	279	1719	825
SCOPE	Denmark	C	rs9399158	1	621	291	1373	617
SCOPE	Norway	C	rs9399158	1	355	173	251	111
SGENE+	Iceland	**A**	**rs1475069**	-	871	303	15 955	6883
SGENE+	England/Wales	**A**	**rs1475069**	-	136	50	126	50
SGENE+	Finland I[1]	**A**	**rs1475069**	-	97	19	230	62
SGENE+	Finland II[1]	**A**	**rs1475069**	-	200	46	81	19
SGENE+	Italy	**A**	**rs1475069**	-	122	46	119	53
SGENE+	Holland	**A**	**rs1475069**	-	1029	395	861	423
SGENE+	Scotland	**A**	**rs1475069**	-	918	392	933	389
SGENE+	Germany - Bonn	**A**	**rs1475069**	-	658	308	501	227
Cardiff	England/Wales	C	rs9389329	0.96	654	298	3926	1942

The original alleles/markers of Amann-Zalcenstein et al. (2006) are designated in bold; rs7739635 is not directly typed in any sub-sample. The R^2 column shows the correlation (R^2) of surrogate markers with the original markers in the Hapmap CEU sample (http://www.hapmap.org).

[1]Part of the Finnish SGENE+ sample comes from a genetic isolate, we therefore treat it as a separate sample in the meta-analysis; Finland I = general population, Finland II = genetic isolate.

Supplementary table 3: Probabilities for Hardy-Weinberg distribution of genotypes in subsamples.

Munich

	Affected genotypes (N=495)					Controls genotypes (N=1272)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs9321501	152	261	83	2.7	0.10	403	601	268	2.5	0.11
rs11154801	55	237	204	1.3	0.26	162	574	534	0.2	0.69
rs7750586	203	237	56	1.1	0.29	529	578	163	0.1	0.79
rs9647635	203	237	56	1.1	0.29	531	577	164	0.1	0.71
rs12196952	229	218	49	0.1	0.78	548	580	144	0.3	0.61
rs9494332	226	220	50	0.1	0.74	530	585	156	0.1	0.78
rs1475069	251	188	42	0.6	0.43	549	519	115	0.2	0.63

SCOPE – Denmark

	Affected genotypes (N=456)					Controls genotypes (N=995)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs9321501	130	214	108	1.2	0.28	276	498	210	0.3	0.60
rs7750586	195	200	57	0.3	0.61	384	474	126	1.2	0.28
rs9494335	205	172	59	5.4	0.02	436	395	119	3.9	0.048
rs9399158	213	178	53	2.7	0.10	477	405	103	1.5	0.22

SCOPE – Norway

	Affected genotypes (N=264)					Controls genotypes (N=181)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs9321501	68	129	59	0	0.88	53	75	42	2.2	0.14
rs7750586	93	104	34	0.3	0.58	67	57	25	4.2	0.039

rs9494335	108	111	38	1.2	0.28	81	66	20	1.3	0.26
rs9399158	119	100	34	3	0.083	88	62	20	2.9	0.086

SGENE+ - Scotland

	Affected genotypes (N=662)					Controls genotypes (N=670)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	322	283	51	1.1	0.30	337	257	67	2.9	0.087
rs11154801	71	314	273	1.9	0.17	99	274	288	6.2	0.013
rs1475069	319	280	56	0.2	0.62	345	243	73	8.7	0.0031
rs2064430	215	322	120	0.0	0.98	212	312	137	1.3	0.26
rs9321521	72	300	278	0.4	0.51	85	271	301	3.7	0.054

SGENE+ - Germany (Bonn)

	Affected genotypes (N=491)					Controls genotypes (N=383)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	219	215	47	0.3	0.58	169	154	44	0.9	0.33
rs11154801	58	226	199	0.3	0.61	59	157	150	2.7	0.10
rs1475069	225	208	50	0.0	0.85	175	151	38	0.4	0.52
rs2064430	147	231	105	0.6	0.43	109	160	98	5.9	0.015
rs9321521	64	234	185	0.6	0.46	60	165	141	1.0	0.32

SGENE+ - the UK

	Affected genotypes (N=104)					Controls genotypes (N=95)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	49	33	11	2.0	0.15	46	32	10	1.4	0.24
rs11154801	9	45	39	0.6	0.44	7	47	34	2.8	0.093

rs1475069	52	32	9	1.4	0.23	46	34	8	0.2	0.64
rs2064430	34	42	15	0.1	0.74	24	44	18	0.1	0.79
rs9321521	14	30	47	5.3	0.022	12	41	35	0.0	1

SGENE+ - Finland (General Population)

	Affected genotypes (N=63)					Controls genotypes (N=150)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	40	18	1	0.4	0.52	91	50	6	0.1	0.79
rs11154801	5	29	25	0.7	0.40	14	65	68	0.1	0.79
rs1475069	40	17	1	0.3	0.59	94	42	10	2.9	0.091
rs2064430	18	32	9	0.7	0.40	52	74	21	0.4	0.52
rs9321521	1	19	39	0.6	0.44	7	49	89	0.0	0.94

SGENE+ - Finland (Genetic Isolate)

	Affected genotypes (N=128)					Controls genotypes (N=50)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	81	36	5	0.2	0.69	31	19	0	2.8	0.097
rs11154801	7	51	65	0.5	0.46	4	23	23	0.3	0.59
rs1475069	83	34	6	1.0	0.31	31	19	0	2.8	0.097
rs2064430	44	57	20	0.0	0.83	14	26	9	0.3	0.61
rs9321521	5	37	79	0.1	0.80	0	19	30	2.8	0.092

SGENE+ - Iceland

	Affected genotypes (N=612)					Controls genotypes (N=11492)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	308	243	38	1.2	0.28	5655	4706	1117	9.0	0.0026

rs11154801	54	263	272	0.7	0.40	1339	5082	5070	1.5	0.23
rs1475069	318	235	34	1.2	0.27	5612	4731	1076	3.0	0.085
rs2064430	184	291	113	0.0	0.91	3186	5704	2564	0.0	0.91
rs9321521	46	250	289	0.6	0.43	1294	4921	5062	3.5	0.062

SGENE+ - Italy

	Affected genotypes (N=86)					Controls genotypes (N=91)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	43	33	8	0.2	0.65	51	30	8	1.3	0.26
rs11154801	12	38	34	0.1	0.79	11	35	43	0.8	0.36
rs1475069	46	30	8	0.9	0.35	43	33	10	0.9	0.35
rs2064430	26	42	16	0.0	0.90	36	39	14	0.4	0.53
rs9321521	12	37	35	0.2	0.66	11	36	42	0.6	0.45

SGENE+ - Holland

	Affected genotypes (N=713)					Controls genotypes (N=643)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P
rs10223338	359	301	53	0.9	0.35	275	305	62	2.9	0.086
rs11154801	66	344	303	5.1	0.024	87	318	238	1.4	0.23
rs1475069	368	293	51	0.5	0.48	286	289	67	0.2	0.63
rs2064430	229	361	123	0.9	0.34	164	341	136	2.8	0.095
rs9321521	74	324	313	0.5	0.46	94	311	235	0.3	0.59

Cardiff

	Affected genotypes (N=479)					Controls genotypes (N=2937)				
Marker	1-1	1-2	2-2	X2	P	1-1	1-2	2-2	X2	P

rs2757649	167	221	91	1.4	0.24	914	1447	575	0.0	0.96
rs7750586	211	205	62	1.2	0.27	1189	1349	397	0.2	0.64
rs9494322	250	183	46	2.1	0.14	1329	1310	296	1.0	0.31
rs9389329	225	204	47	0.0	0.94	1297	1332	305	1.9	0.17