

Data supplement

	rs7914558													
	Total sample				GG				AG				AA	
	Total	Patients	Controls	Total	Patients	Controls	Total	Patients	Controls	Total	Patients	Controls	Comparison	
Neurocognition sample														
<i>n</i>	560	400	160	89	66	23	258	174	84	213	160	53		
Gender, F:M		111:288	76:84		22:44	12:11		49:125	43:41		41:119	21:32	ns	
Age, years: mean (s.d.)		41.45 (12.25)	37.14 (12.70)		39.96 (10.45)	39.61 (14.14)		42.52 (11.86)	37.13 (12.33)		42.32 (11.79)	36.12 (13.02)	Controls < patients	
Years of education, mean (s.d.)		13.09 (2.55)	15.98 (2.42)		13.86 (2.47)	16.13 (2.63)		12.95 (2.45)	16.17 (2.60)		13.11 (2.71)	15.61 (2.00)	$F_{(1,537)} = 4.86, P < 0.05$ Controls > patients	
Age at onset, years: mean (s.d.)		22.79 (7.32)	n/a		21.57 (5.52)	n/a		23.28 (8.22)	n/a		21.87 (6.03)	n/a	$F_{(1,537)} = 105.61, P < 0.001$	
CPZeq, mg/day: mean (s.d.)		582.84 (543.76)	n/a		549.22 (478.55)	n/a		570.17 (511.79)	n/a		597.11 (618.99)	n/a	ns	
Irish imaging sample														
<i>n</i>	159			21			67			71			ns	
Gender, F:M			87:72			14:7			37:30			36:35	ns	
Age, years: mean (s.d.)			27.86 (12.42)			31.33 (16.19)			26.75 (10.91)			27.87 (12.51)	ns	
Years of education, mean (s.d.)			17.00 (2.30)			17.06 (3.06)			17.02 (2.11)			16.97 (2.26)	ns	
Italian imaging sample														
<i>n</i>	103	66	37	23	17	6	45	23	22	35	26	9	ns	
Gender, F:M		25:41	18:19		5:12	3:3		6:17	9:13		14:12	6:3	ns	
Age, years: mean (s.d.)		40.67 (11.67)	32.28 (12.58)		38.41 (10.83)	31.00 (17.54)		41.65 (12.01)	34.09 (12.89)		41.27 (12.15)	29.11 (7.89)	Controls < patients	
Years of education, mean (s.d.)		10.98 (4.02)	15.38 (3.20)		11.00 (3.93)	15.60 (4.93)		9.65 (3.14)	15.28 (3.10)		12.58 (4.59)	15.50 (2.26)	$F_{(1,97)} = 10.79, P = 0.001$ Controls > patients	
Age at onset, years: mean (s.d.)		24.11 (8.34)	n/a		24.00 (6.24)	n/a		23.05 (7.55)	n/a		25.42 (10.69)	n/a	ns	
Duration, years: mean (s.d.)		18.18 (10.41)	n/a		15.12 (8.85)	n/a		19.55 (10.21)	n/a		19.76 (11.76)	n/a	ns	
CPZeq, mg/day: mean (s.d.)		507.64 (606.42)	n/a		517.50 (297.92)	n/a		611.95 (912.49)	n/a		384.05 (309.31)	n/a	ns	

F, female; M, male; ns, not significant; n/a, not applicable; CPZeq, chlorpromazine equivalents.

Table DS2 Summary of performance on neuropsychological (cognitive and social cognitive) measures. Note: ** p<0.001; *p<0.05; LNS=letter number sequence; LM=logical memory; IDED=intradimensional/extradimensional set shifting task; HT = the hinting task; RME = reading the mind in the eyes; IPSAQ = internal, personal and situational attributions questionnaire; EB = externalising bias; PB = personalising bias.

Function	Test or Subscale	Cohort	N	GG (mean (sd))	AG (mean (sd))	AA (mean(sd))	Main effect of Group	Main effect of Genotype	Group x Genotype Interaction																																																																																																										
<i>IQ</i>	Abbreviated Full Scale IQ	Patients	305	94.6(20.5)	88.9(16.98)	90.2(17.7)	F=275.3**	F=0.246	F=1.835																																																																																																										
		Controls	158	119.7(13.4)	122.7(13.6)	121.8(16.8)				<i>Working Memory</i>	LNS	Patients	373	8.26(3.69)	7.6(3.3)	7.4(3.25)	F=220.1**	F=2.42	F=0.129	Controls	156	13.6(2.89)	12.8(3.08)	12.4(3.4)	CANTAB SWM	Patients	369	-.96(1.56)	-.86(1.26)	-1.06(1.25)	F=90.4**	F=0.268	F=0.807	Controls	151	.403(.72)	.169(.813)	.266(.742)	<i>Episodic Memory</i>	LM - Immediate	Patients	385	6.9(3.89)	6.3(3.27)	6.1(3.360)	F=309.2**	F=0.986	F=0.054	Controls	156	13.1(2.8)	12.6(2.89)	12.5(2.75)	LM – Delayed	Patients	382	8(3.42)	7.1(3.1)	7.03(3.2)	F=311.6**	F=0.864	F=0.449	Controls	156	13.4(2.74)	13.2(2.7)	13.3(2.3)	<i>Attentional Control</i>	IDED (8 shapes)	Patients	324	11.6(11.2)	12.4(10.7)	12.5(10.9)	F=11.9**	F=0.006	F=0.355	Controls	149	9.4(10.6)	8.9(9.3)	8(9.07)	IDED (6 shapes)	Patients	327	.94(1.8)	.77(1.51)	1.01(2.52)	F=0.307	F=0.914	F=1.24	Controls	148	1.25(2.42)	.67(2.3)	.41(.64)	<i>Social Cognition</i>	HT	Patients	276	15.6(3.3)	15.5(3.5)	15(3.41)	F=15.8**	F=1.58	F=0.055	Controls	132	17.2(1.4)	16.8(1.7)	16.3(2.1)	RME	Patients	151	25(4.7)
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	CANTAB SWM	Patients	369	-.96(1.56)	-.86(1.26)	-1.06(1.25)	F=90.4**	F=0.268	F=0.807																																																																																																										
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		Controls	132	17.2(1.4)	16.8(1.7)	16.3(2.1)					RME	Patients	151	25(4.7)	38(116.6)	24.3(4.8)	F=0.022	F=0.254	F=0.148																																																																																																
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		Controls	50	28.4(3.04)	26.3(4.1)	24.5(5.02)			
IPSAQ (EB)	Patients		256	1.6(2.9)	1.17(3.7)	.26(2.8)	F=0.167	F=5.72*	F=1.53
	Controls		131	3.2(3.8)	.78(4.25)	.38(3.6)			
IPSAQ (PB)	Patients		256	.48(.26)	.48(.29)	.51(.27)	F=2.17	F=2.17	F=2.27
	Controls		131	.61(.21)	.64(.25)	-1.4(13.2)			

Table DS3 Summary of group (patients vs. control) effects on gray matter and white matter volume in Italian sMRI analysis. In all clusters volume in patients < controls. Note: since a vast number of clusters were significantly different (i.e. patients < controls) at $p_{\text{CORRECTED}} < 0.05$, in the interests of simplicity only those clusters surviving at $p_{\text{CORRECTED}} < 0.001$, minimum cluster extent = 100 voxels are noted in the table (full list is available on request). *closest anatomical landmark.

Tissue Type	Region	Cluster Extent (voxels/mm ³)	MNI Co-ordinates			F (1,95)
			x	y	z	
Gray Matter	Left Insula	1001	-38	12	-6	49.76
	Right Medial Frontal Gyrus	235	4	47	14	46.87
	Left Inferior Frontal Gyrus	270	-36	5	25	46.54
	Left Anterior Cingulate	552	-6	39	17	44.73
	Right Cingulate Gyrus	1182	9	-12	36	44.28
	Right Insula	1703	34	19	7	43.75
	Right Middle Temporal Gyrus	451	58	-22	-4	42.28
	Left Middle Frontal Gyrus	105	-30	33	-10	41.03
	Right Cingulate Gyrus	459	8	20	27	41.01
	Left Middle Temporal Gyrus	534	-48	-32	0	40.80
	Right Fusiform Gyrus	287	48	-49	-14	40.51
	Left Posterior Cingulate	213	-6	-51	24	39.78
	Right Parahippocampal Gyrus	174	21	-39	-9	39.11
White Matter	Left Cingulate Gyrus*	478	-19	1	46	43.24
	Left Anterior Cingulate*	1224	-21	36	8	40.32
	Left Fusiform Gyrus*	129	-40	-6	-20	39.00

Online supplement

Bioinformatic analysis of rs7914558

rs7914558 is located on chromosome 10q24 in a large region of high and complex linkage disequilibrium (LD) that contains four RefSeq genes: C10orf32, AS3MT, CNNM2 and NT5C2. Analysis of three SNP x gene expression databases (mRNA by SNP Browserⁱ, SNPExpressⁱⁱ and Genevarⁱⁱⁱ) provides consistent evidence that the risk/major allele of rs7914558 is associated with increased expression of both the C10orf32 and AS3MT genes across multiple cell and tissue types including brain. C10orf32 and AS3MT are separated by a distance of just 5.24kb and are both encoded on the same strand. RefSeq does report a read-through transcript that combines C10orf32 and AS3MT together but it is noted as a candidate for nonsense-mediated mRNA decay (NMD), and is therefore unlikely to produce a protein product. Beyond rs7914558 and its multiple high-LD proxy SNPs (n=42) in this region, there is evidence for other SNPs that also have a cis-effect on transcription of C10orf32 and AS3MT. A group of 8 SNPs in complete LD ($r^2=1$), indexed by rs9537, also show consistent evidence of a cis-acting effect on expression of both C10orf32 and AS3MT and the effect is much stronger than for rs7914558. rs9537 and rs7914558 are in LD ($r^2=0.53$) and their respective major alleles that are associated with increased expression of C10orf32 and AS3MT are on the same haplotype. It's likely that the observation that rs7914558 is associated with differential expression of C10orf32 and AS3MT is a spurious one caused by LD and is indirectly due to the functional effect of rs9357 or one of its proxies. Teasing out the effect of either SNP on local gene expression would require data from a population with a different LD structure. Given that rs9357 (or proxy) was not reported to be more strongly associated with schizophrenia, these data do not prove that rs7914558 (or proxy) contributes to schizophrenia risk via increased expression of C10orf32 and/or AS3MT and thus all four genes in the large region remain candidate loci.

ⁱ <http://www.sph.umich.edu/csg/liang/asthma/>

ⁱⁱ <http://people.genome.duke.edu/~dg48/SNPExpress/>

ⁱⁱⁱ <http://www.sanger.ac.uk/resources/software/genevar/>