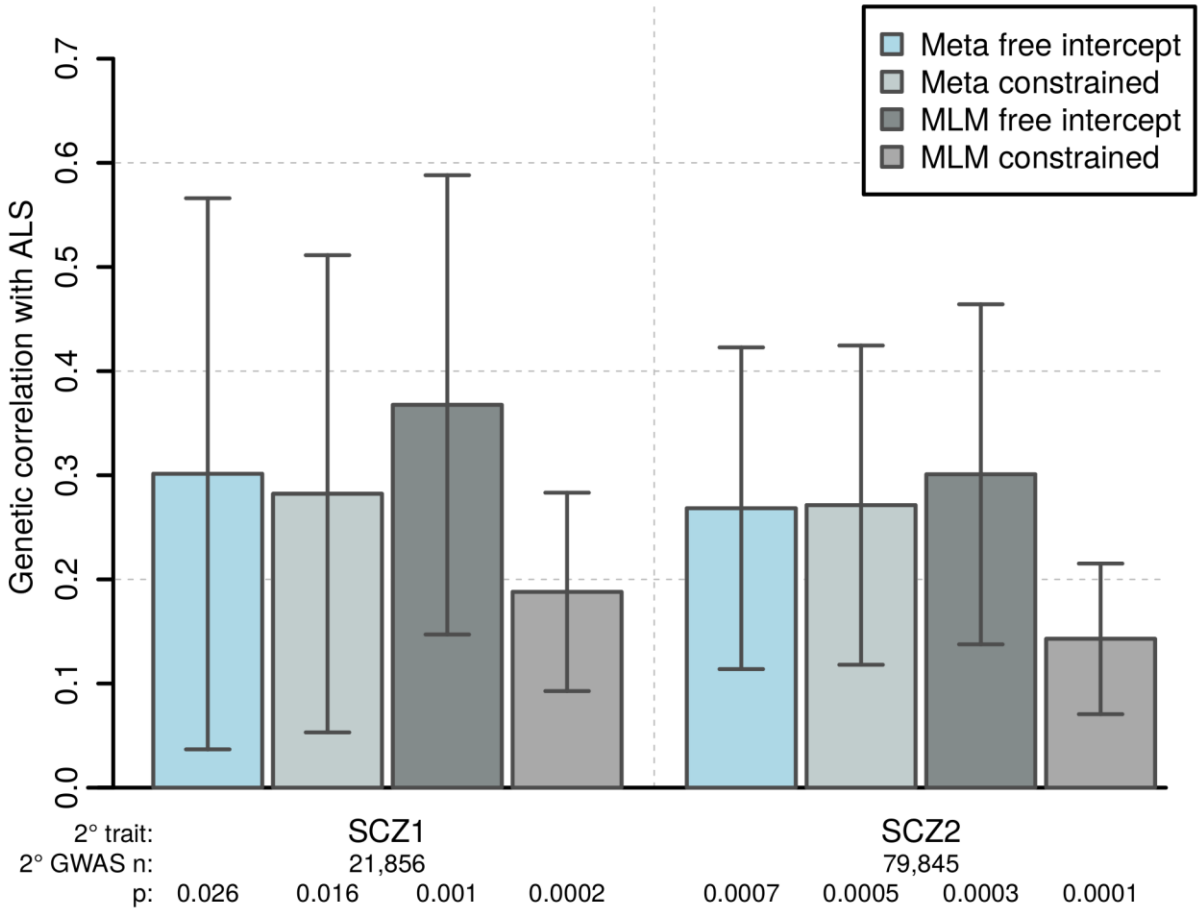
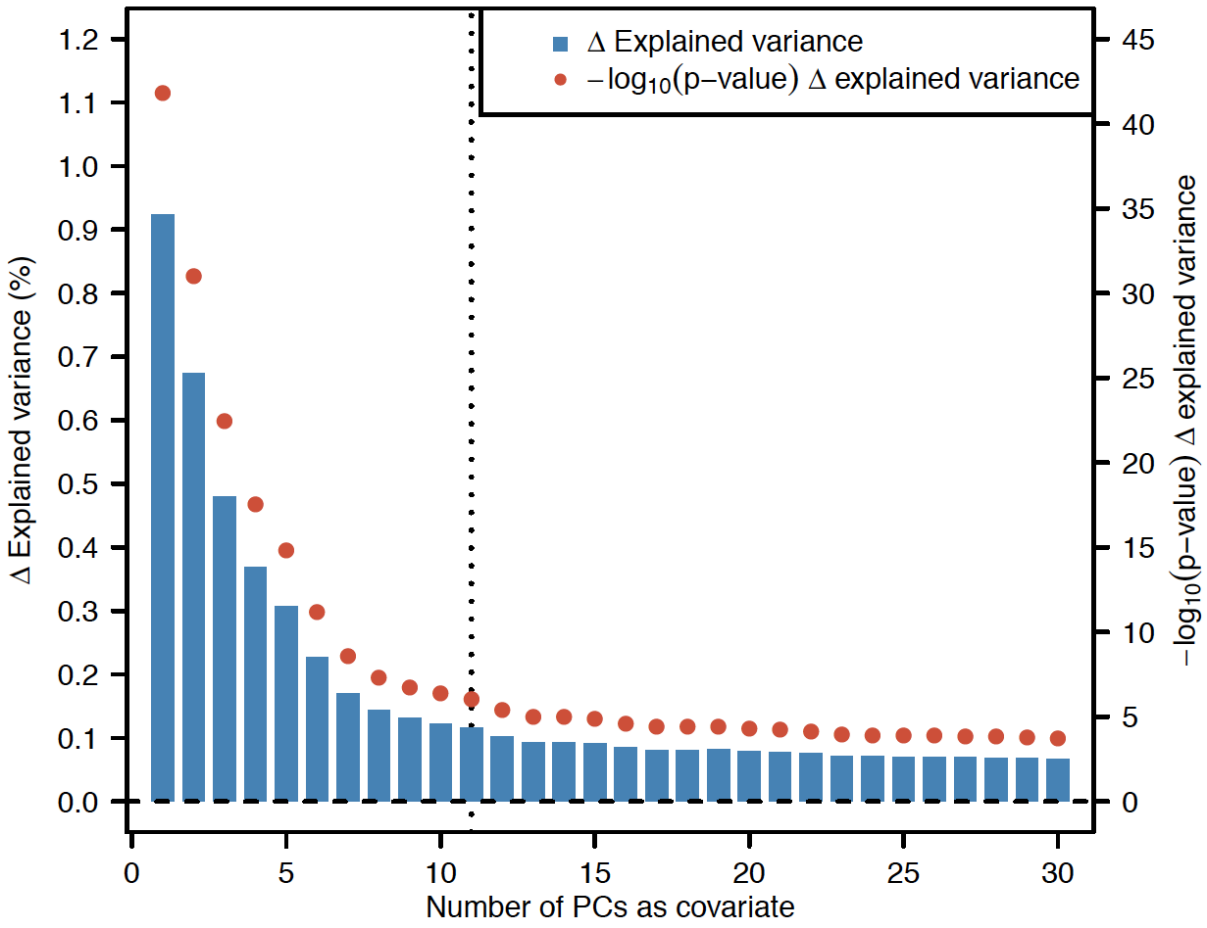
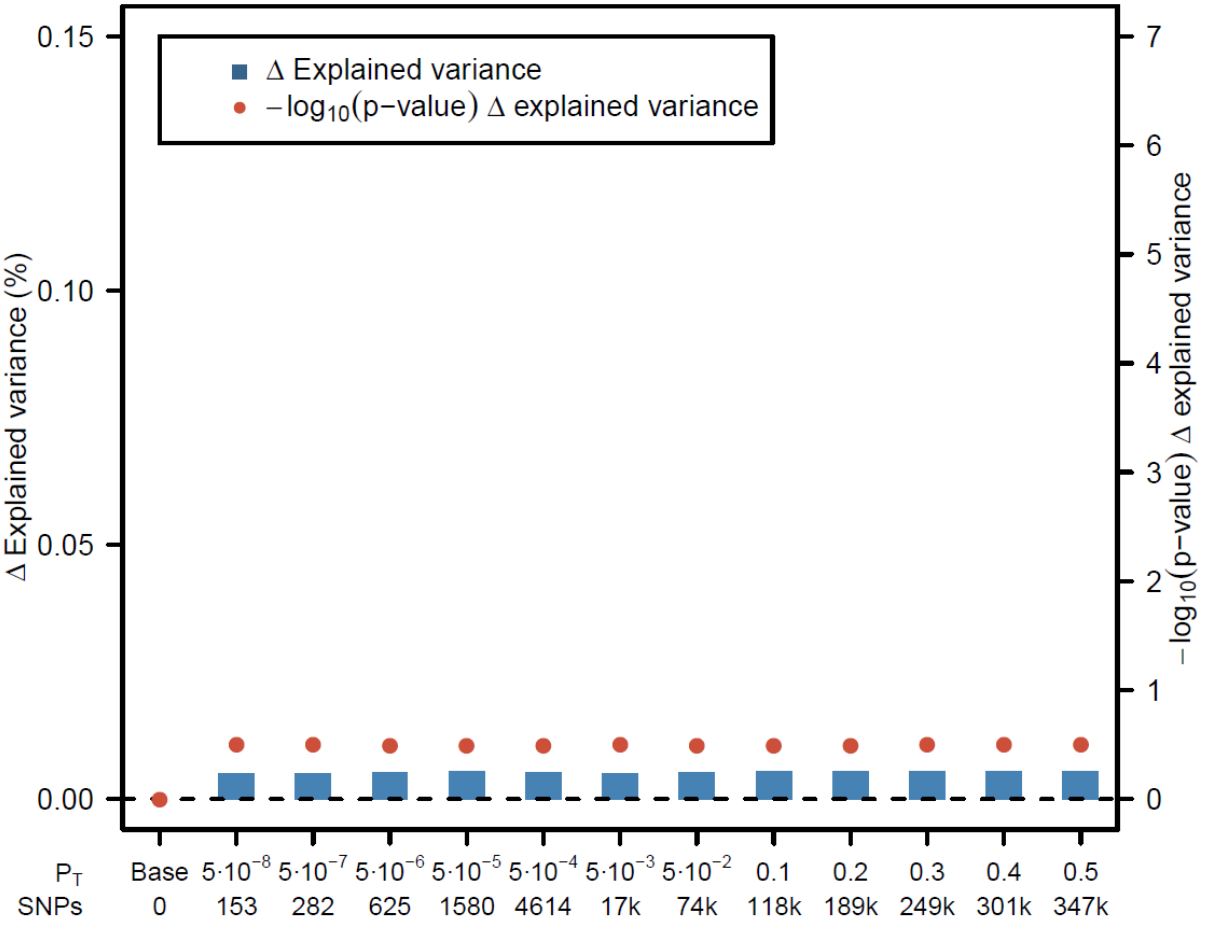


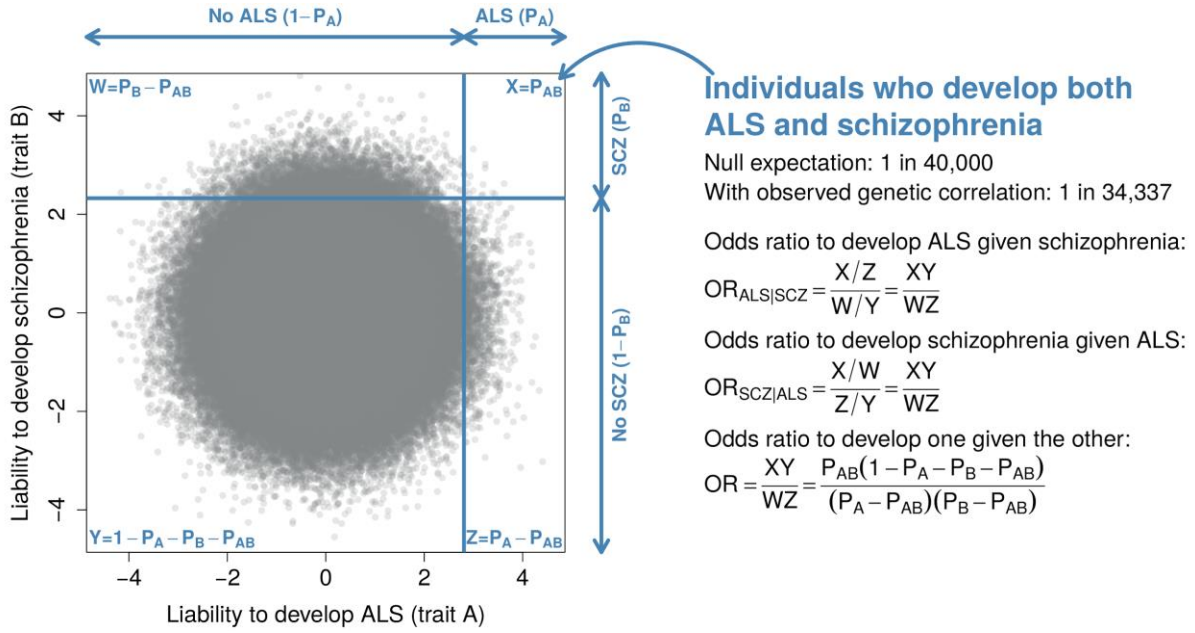
Supplementary figure 1 Comparison of genetic correlation estimates for two schizophrenia cohorts. SCZ1 denotes data from the 2011 study by the Schizophrenia Psychiatric Genome-Wide Association Study Consortium (European ancestry cohort); SCZ2 indicates data from the 2014 study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (European and Asian ancestry cohort). Error bars indicate 95% confidence intervals.



Supplementary figure 2 Effect of increasing the number of PCs as covariates in generalized linear model on explained variance in ALS and -log(p-values) attributable to polygenic risk scores (Δ explained variance) at schizophrenia P_T = 0.2. The dotted line indicates the 11 most significant PCs ($p < 0.0005$) used in the main analysis.



Supplementary figure 3 Effect of 1000 permutations of case-control labels, with conservation of case:control ratio, on analysis of polygenic risk scores (PRS) for schizophrenia in the ALS dataset. The schizophrenia P_T and associated number of SNPs are similar to the main analysis. Blue bars show the averaged **Δ** explained variance of a linear model containing PRS compared to a baseline model with only covariates. Red dots indicate averaged -$\log_{10}$ p-values of **Δ** explained variance.



Supplementary figure 4 Simulated example of the bivariate distribution of liability for two traits with a genetic covariance (liability-scale) of 1.88% in a population of 500,000 individuals (grey dots). P_A and P_B represent the proportions of the population that carry above-threshold liabilities for traits A and B (defined by the lifetime risks for these traits). Individuals in sector X in the plot carry above-threshold liability for both traits A and B (P_{AB} of the population).

Supplementary table 1 LD score regression heritability estimates for amyotrophic lateral sclerosis

Method	h_S^2 (%)	95% CI
MLM constrained intercept	8.17	7.21-9.13
MLM free intercept	1.54	0.13-2.95
Meta constrained intercept	1.34	0.61-2.07
Meta free intercept	1.61	0.67-2.55
Permuted constrained intercept	-0.7	-1.50-0.18
Permuted free intercept	0.09	-1.09-1.27

h_S^2, SNP-based heritability; CI, confidence interval; MLM, mixed linear model summary statistics; meta, meta-analysis summary statistics

Supplementary table 2 Genetic correlation between amyotrophic lateral sclerosis and 8 secondary traits

	2° Trait	AD	ADHD	ASD	BPD	HEIGHT	MDD	MS	SCZ
	GWAS n	54,162	5,422	10,263	16,731	253,288	18,759	17,597	79,845
	K	0.15	0.05	0.01	0.01	n/a	0.15	0.0029	0.01
	h_S^2 **% (s.e.)**	8.1 (1.6)	9.5 (6.7)	17.0 (2.3)	17.1 (2.1)	27.4 (1.6)	13.4 (3.1)	19.1 (7.8)	19.7 (1.0)
MLM cons	ρ_g **% (s.e.)**	0.5 (0.8)	-0.7 (1.9)	-1.0 (1.0)	-0.2 (0.8)	-0.7 (0.4)	0.02 (1.0)	0.3 (0.6)	1.8 (0.5)
MLM cons	r_g **% (s.e.)**	6.3 (9.6)	-8.3 (21.9)	-8.6 (8.7)	-1.9 (6.6)	-4.5 (2.9)	0.2 (9.8)	2.1 (4.7)	14.3 (3.7)
MLM cons	**p**	0.51	0.71	0.32	0.78	0.11	0.98	0.65	**0.0001**
MLM free	ρ_g **% (s.e.)**	1.5 (1.8)	-1.6 (4.0)	-3.1 (2.2)	-0.3 (1.6)	-1.4 (1.0)	-0.3 (1.9)	0.9 (1.4)	3.8 (1.1)
MLM free	r_g **% (s.e.)**	18.8 (22.4)	-18.4 (44.7)	-25.8 (19.0)	-2.9 (13.4)	-9.2 (6.7)	-2.8 (18.3)	6.9 (11.0)	30.1 (8.3)
MLM free	**p**	0.40	0.68	0.18	0.83	0.18	0.88	0.53	**0.0003**
Meta cons	ρ_g **% (s.e.)**	1.9 (1.8)	-0.9 (3.2)	-2.3 (2.1)	-0.9 (1.5)	-0.2 (0.9)	0.1 (2.0)	1.0 (1.2)	3.4 (1.0)
Meta cons	r_g **% (s.e.)**	23.3 (21.8)	-10.0 (36.3)	-19.1 (18.0)	-8.0 (12.6)	-1.3 (6.0)	1.3 (18.9)	8.3 (9.8)	27.1 (7.8)
Meta cons	**p**	0.28	0.78	0.29	0.52	0.83	0.94	0.40	**0.0005**
Meta free	ρ_g **% (s.e.)**	2.0 (1.8)	-0.9 (3.6)	-2.4 (2.2)	-1.1 (1.7)	-0.2 (0.9)	0.1 (2.2)	1.2 (1.3)	3.4 (1.0)
Meta free	r_g **% (s.e.)**	24.5 (21.6)	-10.4 (40.5)	-20.1 (19.0)	-9.1 (14.2)	-1.4 (6.3)	0.9 (21.1)	9.2 (10.5)	26.8 (7.9)
Meta free	**p**	0.26	0.80	0.27	0.52	0.83	0.97	0.38	**0.0007**

AD, Alzheimer's disease; ADHD, attention deficit-hyperactivity disorder; ASD, autism spectrum disorder; BPD, bipolar disorder; MDD, major depressive disorder; MS, multiple sclerosis; SCZ, schizophrenia; n, sample size; K, population prevalence (lifetime risk) for binary traits; h_S^2, SNP-based heritability; ρ_g, genetic covariance; r_g, genetic correlation; s.e., standard error; MLM, mixed linear model summary statistics for ALS; Meta, meta-analysis summary statistics for ALS; cons, constrained-intercept LD score regression for primary trait (ALS) h_S^2 estimation

p-values are emboldened if they are significant at (conservative) Bonferroni-corrected $\alpha = 0.0016$

h_S^2 and ρ_g estimates are liability-scale for binary traits

h_S^2 estimates for secondary traits used free-intercept LD score regression

Supplementary table 3 Number of individuals in the ALS dataset excluded from PRS analysis due to (suspected) sample overlap with the schizophrenia dataset

Stratum	Name	Total individuals	Excluded individuals	Percentage
1	NL1	843	5	0.6
2	BE1	616	1	0.2
3	NL2	5027	25	0.5
4	SW1	556	82	14.7
5	FR1	809	0	0.0
6	UK1	327	0	0.0
7	US1	1937	4	0.2
8	IR1	639	16	2.5
9	UK2	3301	2555	77.4
10	US2	779	4	0.5
11	IT1	626	0	0.0
12	FIN1	756	756	100.0
13	NL3	2781	86	3.1
14	GER1	776	776	100.0
15	IT2	383	0	0.0
16	IB1	225	0	0.0
17	SWISS1	424	0	0.0
18	BE2	447	1	0.2
19	SW2	467	60	12.8
20	FIN2	232	232	100.0
21	IR2	707	299	42.3
22	US3	2562	3	0.1
23	FR2	1332	0	0.0
24	UK3	3534	2433	68.8
25	GER2	2047	2047	100.0
26	IT3	2790	0	0.0
27	NL4	1129	8	0.7
	Total	**36052**	**9393**	**26.1**

NL, Netherlands; BE, Belgium; SW, Sweden; FR, France; UK, United Kingdom; US; United States of America; IR, Ireland; IT, Italy; FIN, Finland; GER, Germany; IB, Iberia (Spain and Portugal); SWISS, Switzerland.

Supplementary table 4 Genomic regions with high LD removed prior to polygenic risk score calculation

Chromosome	Basepair start	Basepair end
1	48000000	52000000
2	86000000	100500000
	183000000	190000000
3	47500000	50000000
	83500000	87000000
5	44500000	50500000
	129000000	132000000
6	25500000	33500000
	57000000	64000000
	140000000	142500000
7	55000000	66000000
8	8000000	12000000
	43000000	50000000
	8135000	12000000
	112000000	115000000
10	37000000	43000000
11	87500000	90500000
12	33000000	40000000
17	40900000	45000000
20	32000000	34500000

Positions refer to human genome build GRCh37

Supplementary table 5 Estimated explained variances and p-values of polygenic risk scores through generalized linear model

SCZ P_T	n SNPs	Explained variance (Nagelkerke R^2, %)	Δ Explained variance (Nagelkerke R^2, %)	p-value	$-\log_{10}$(p-value)
Baseline	0	9.050	-	-	-
5×10^{-8}	153	9.051	0.001	6.90E-01	0.16
5×10^{-7}	282	9.056	0.006	2.73E-01	0.56
5×10^{-6}	625	9.053	0.002	5.10E-01	0.29
5×10^{-5}	1,580	9.057	0.007	2.36E-01	0.63
5×10^{-4}	4,614	9.081	0.030	1.15E-02	1.94
5×10^{-3}	17,042	9.126	0.075	7.15E-05	4.15
0.05	74,036	9.143	0.093	1.01E-05	4.99
0.1	118,335	9.163	0.112	1.27E-06	5.90
0.2	189,492	9.166	0.116	8.43E-07	6.07
0.3	249,452	9.162	0.111	1.41E-06	5.85
0.4	301,405	9.164	0.114	1·06E-06	5.97
0.5	346,683	9.161	0.111	1·50E-06	5.82

SCZ, schizophrenia; P_T, p-value threshold

Supplementary table 6 ALS case-control ratio for schizophrenia polygenic risk score deciles

Decile	Cases	Controls	OR vs decile 1	95% CI	Z value	p-value
1	732	1,934	-	-	-	-
2	801	1,865	1.02	0.90-1.15	0.27	7.6×10^{-1}
3	882	1,784	1.11	0.98-1.25	1.60	9.4×10^{-2}
4	910	1,756	1.10	0.97-1.24	1.47	1.3×10^{-1}
5	967	1,698	1.13	1.00-1.27	1.89	4.8×10^{-2}
6	982	1,685	1.10	0.97-1.24	1.39	1.3×10^{-1}
7	1,056	1,610	1.16	1.03-1.31	2.26	1.7×10^{-2}
8	1,103	1,562	1.15	1.02-1.30	2.06	2.6×10^{-2}
9	1,224	1,442	1.25	1.10-1.41	3.35	3.9×10^{-4}
10	1,375	1,291	1.30	1.15-1.48	3.84	5.1×10^{-5}

OR, odds ratio; CI, confidence interval

Supplementary table 7 Misdiagnosis rates (M_{TA}) of ALS as schizophrenia required to yield genetic correlation estimates assuming true genetic correlation of 0

Method	r_g (%)	95% CI	$\rho_{g,l}$ (%)	95% CI	M_{TA} (%)	95% CI
MLM constrained	14.3	7.08-21.6	1.88	0.92-2.83	4.86	2.47-7.13
MLM free	30.1	13.8-46.4	3.95	1.81-6.09	9.70	4.70-14.2
Meta constrained	27.1	11.8-42.4	3.55	1.55-5.56	8.82	4.04-13.1
Meta free	26.8	11.4-42.2	3.52	1.50-5.53	8.73	3.91-13.1

r_g, genetic correlation between ALS and schizophrenia; CI, confidence interval; $\rho_{g,l}$, liability-scale genetic covariance; M_{TA}, misdiagnosis rate

Supplementary table 8 Genomic loci associated with ALS at $cFDR_{ALS|SCZ} < 0.05$

Index SNP	Chromosome	Position (GRCh37)	GWAS p_{ALS}	GWAS p_{SCZ}	$cFDR_{ALS\|SCZ}$	Closest gene
rs63535762	1	233663807	4.0882×10^{-6}	0.1232	0.02914227	*KCNK1*
rs11124852	2	42131864	5.6779×10^{-6}	0.04953	0.03113055	*C2orf91*
rs149853584	3	1728150	3.5418×10^{-8}	0.03095	0.00038322	*CNTN6*
rs2625891	3	9541761	2.763×10^{-6}	0.03099	0.01459386	*LHFPL4*
rs616147	3	39534481	5.7276×10^{-8}	0.6211	0.00133118	*MOBP*
rs1817362	3	147770849	8.3621×10^{-6}	0.009266	0.03495604	*AGTR1*
rs71308531	3	171681860	2.0263×10^{-6}	0.5228	0.02195072	*FDNC3B*
rs13164762	5	83141157	4.5304×10^{-6}	0.07264	0.02709394	*EDIL3*
rs34384833	5	91238155	9.9144×10^{-6}	0.0399	0.04847741	*ARRDC3*
rs189841212	5	117878641	6.5395×10^{-6}	0.02757	0.02927102	*DTWD2*
rs10463311	5	150410835	3.645×10^{-7}	0.1378	0.00317718	*TNIP1*
rs116946806	7	131682571	2.5608×10^{-6}	0.3095	0.02134998	*PLXNA4*
rs17070492	8	2420855	4.0231×10^{-6}	0.01049	0.01994008	*MYOM2*
rs7814166	8	143370923	6.8943×10^{-5}	1.373×10^{-10}	0.0427745	*TSNARE1*
rs10965525	9	22936164	5.0503×10^{-6}	0.006832	0.02977711	*DMRTA1*
rs2484319	9	27563755	2.0583×10^{-17}	0.007078	2.8215×10^{-12}	*C9orf72*
rs76794160	9	71621214	1.5665×10^{-6}	0.1176	0.01059827	*PIP5K1B*
rs11146348	10	133772553	7.1712×10^{-7}	0.0113	0.00453269	*PPP2R2D*
rs143276647	11	118299359	8.2063×10^{-6}	0.06059	0.03712072	*KMT2A*
rs79676202	12	50180558	4.5475×10^{-8}	0.369	0.00070155	*NCKAP5L*
rs113247976	12	57975700	4.1051×10^{-6}	0.1964	0.03831843	*KIF5A*
rs116900480	12	58656105	1.4775×10^{-6}	0.1303	0.01195632	*XRCC6BP1*
rs76805704	12	64532377	1.5297×10^{-6}	0.1331	0.01220552	*SRGAP1*
rs74654358	12	64881967	1.5956×10^{-7}	0.02022	0.00103714	*TBK1*
rs179552	14	31225831	9.8359×10^{-7}	0.1131	0.01156173	*SCFD1*
rs3097439	15	27871229	7.5601×10^{-6}	0.1372	0.0401236	*GABRG3*
rs35714695	17	26719788	3.1748×10^{-9}	0.7655	0.00023563	*SARM1*
rs78549703	19	17749542	1.6827×10^{-9}	0.1015	1.4414×10^{-5}	*UNC13A*
rs6015322	20	57206540	1.3812×10^{-6}	0.4992	0.03610187	*APCDD1L-AS1*
rs117635456	21	43460912	4.377×10^{-7}	0.3587	0.00546115	*ZNF295-AS1*
rs2176039	22	45585032	9.1138×10^{-6}	0.02482	0.04064275	*NUP50*

SNP, single nucleotide polymorphism; GWAS, genome-wide association study; ALS, amyotrophic lateral sclerosis; SCZ, schizophrenia; cFDR, conditional false discovery rate

Supplementary note 1: IGAP data

This study made use of data from the International Genomics of Alzheimer's Project (IGAP), a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

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Supplementary methods 1: estimation of diagnostic misclassification

A positive genetic correlation between ALS and schizophrenia could derive from misdiagnosis of cognitive- or behavioural-onset FTD-ALS as schizophrenia. For traits A and B, Wray et al[1] describe the relationship between the misdiagnosis rate of trait A as trait B (M_{TA}) and the number of cases diagnosed with trait A (N_{caseDA}), the genetic variance of trait A (σ^2_{uDA}) and the genetic covariance of traits A and B ($\sigma_{\mathrm{uDA,uDB}}$) as

$$N_{\mathrm{caseDA}} = (1 - M_{\mathrm{TA}})N_{\mathrm{caseTA}} + M_{\mathrm{TB}}N_{\mathrm{caseTB}}\,,$$

(Equation 4)

$$\sigma^2_{\mathrm{uDA}} = \frac{(1 - M_{\mathrm{TA}})^2 N^2_{\mathrm{caseTA}}\sigma^2_{\mathrm{uTA}} + M^2_{\mathrm{TB}}N^2_{\mathrm{caseTB}}\sigma^2_{\mathrm{uTB}} + 2(1 - M_{\mathrm{TA}})M_{\mathrm{TB}}N_{\mathrm{caseTA}}N_{\mathrm{caseTB}}\sigma_{\mathrm{uTA,uTB}}}{N^2_{\mathrm{caseDA}}},$$

(Equation 5)

and

$$\sigma_{\mathrm{uDA,uDB}} = \frac{[\big((1 - M_{\mathrm{TA}})(1 - M_{\mathrm{TB}}) + M_{\mathrm{TA}}M_{\mathrm{TB}}\big)N_{\mathrm{caseTA}}N_{\mathrm{caseTB}}\sigma_{\mathrm{uTA,uTB}} + (1 - M_{\mathrm{TA}})M_{\mathrm{TA}}N^2_{\mathrm{caseTA}} + (1 - M_{\mathrm{TB}})M_{\mathrm{TB}}N^2_{\mathrm{caseTB}}\sigma^2_{\mathrm{uTB}}]}{N_{\mathrm{caseDA}}N_{\mathrm{caseDB}}},$$

(Equation 6)

where N_{caseTA} and N_{caseTB} are the total numbers of "true" cases of traits A and B respectively, M_{TB} is the misdiagnosis rate of trait B as trait A, σ^2_{uTA} and σ^2_{uTB} are the genetic variances of true cases of traits A and B respectively, $\sigma_{\mathrm{uTA,uTB}}$

is the genetic covariance of true cases of traits A and B and N_{caseDB} is the number of cases diagnosed with trait B. For consistency with Wray et al[1] we have used their symbols in these derivations; in the main text of this study the symbol M is used for M_{TA}, ρ_g for $\sigma_{\mathrm{uDA,uDB}}$, N_{ALS} for N_{caseDA} and N_{SCZ} for N_{caseDB}.

Assigning ALS as trait A and schizophrenia as trait B, and reasoning that misdiagnosis of schizophrenia as ALS is highly unlikely ($M_{\mathrm{TB}} = 0$), our specific interest is in cases where FTD-ALS (trait A) has been misdiagnosed as schizophrenia (trait B) under a true genetic correlation of 0 (ie $\sigma_{\mathrm{uTA,uTB}} = 0$). Equations 1-3 therefore simplify to

$$N_{\mathrm{caseDA}} = (1 - M_{\mathrm{TA}})N_{\mathrm{caseTA}}\,,$$

(Equation 7)

$$\sigma^2_{\mathrm{uDA}} = \frac{(1 - M_{\mathrm{TA}})^2 N^2_{\mathrm{caseTA}} \sigma^2_{\mathrm{uTA}}}{N^2_{\mathrm{caseDA}}}$$

(Equation 8)

and

$$\sigma_{\mathrm{uDA,uDB}} = \frac{(1 - M_{\mathrm{TA}}) M_{\mathrm{TA}} N^2_{\mathrm{caseTA}}}{N_{\mathrm{caseDA}} N_{\mathrm{caseDB}}}.$$

(Equation 9)

The assumption $M_{\mathrm{TB}} = 0$ implies that the genetic variance estimate of diagnosed cases of trait A (σ^2_{DA}) accurately reflects the genetic variance of true cases of trait A (σ^2_{TA}); this is confirmed by substituting equation 7 into equation 8:

$$\sigma^2_{\mathrm{DA}} = \frac{(1 - M_{\mathrm{TA}})^2 N^2_{\mathrm{caseTA}} \sigma^2_{\mathrm{uTA}}}{(1 - M_{\mathrm{TA}})^2 N^2_{\mathrm{caseTA}}},$$

which simplifies to $\sigma^2_{\mathrm{uDA}} = \sigma^2_{\mathrm{uTA}}$. The misdiagnosis rate of trait A (M_{TA}) can be established by rearranging equation 7 in terms of the unknown term N_{caseTA}:

$$N_{\mathrm{caseTA}} = \frac{N_{\mathrm{caseDA}}}{(1 - M_{\mathrm{TA}})},$$

and substituting this into equation 9 to give the relationship between genetic covariance ($\sigma_{\mathrm{uDA,uDB}}$) and M_{TA}, N_{caseDA} and N_{caseDB}:

$$\sigma_{\mathrm{uDA,uDB}} = \frac{(1 - M_{\mathrm{TA}}) M_{\mathrm{TA}} \frac{N^2_{\mathrm{caseDA}}}{(1 - M_{\mathrm{TA}})^2}}{N_{\mathrm{caseDA}} N_{\mathrm{caseDB}}}.$$

Simplifying this,

$$\sigma_{\mathrm{uDA,uDB}} = \frac{M_{\mathrm{TA}} N_{\mathrm{caseDA}}}{(1 - M_{\mathrm{TA}}) N_{\mathrm{caseDB}}},$$

and expressing in terms of M_{TA} yields the relationship

$$\frac{\sigma_{\mathrm{uDA,uDB}} N_{\mathrm{caseDB}}}{N_{\mathrm{caseDA}}} = \frac{M_{\mathrm{TA}}}{(1 - M_{\mathrm{TA}})}.$$

(Equation 10)

Substituting $C = \sigma_{\mathrm{uDA,uDB}} N_{\mathrm{caseDB}} / N_{\mathrm{caseDA}}$ (the left-hand term) and solving for M_{TA} gives the relationship

$$M_{\mathrm{TA}} = \frac{C}{C + 1}.$$

(Equation 11)

Using mixed linear model GWAS association statistics for ALS and constrained intercept LD score regression, the genetic correlation (r_g) estimate for ALS and schizophrenia was 14.3% (7.05-21.6). Using the relationship $\rho_{g,l} = r_g \sqrt{h^2_{\mathrm{ALS},l} h^2_{\mathrm{SCZ},l}}$ (ref 11) where subscript l denotes liability-scale, this corresponds to a liability-scale genetic covariance of 1.88% (0.92-2.83). With GWAS case cohort sizes of $N_{\mathrm{caseDA}} = 12{,}577$ and $N_{\mathrm{caseDB}} = 34{,}241$, M_{TA} evaluates to 4.86% (2.47-7.13). Supplementary table 7 shows M_{TA} estimates for the study's other $\rho_{g,l}$ estimates.

Supplementary methods 2: Modelling expected comorbidity

Under a positive genetic correlation between two binary phenotypes, an increased number of individuals exhibiting both phenotypes would be expected. To determine the required cohort size to observe a significant excess of comorbidity, we modelled the bivariate distribution in liability for pairs of traits as $N_2(0, \Sigma)$ given the covariance matrix $\Sigma = \begin{bmatrix} 1 & \rho_{g,l} \\ \rho_{g,l} & 1 \end{bmatrix}$, where $\rho_{g,l} = r_g \sqrt{h^2_{\mathrm{ALS},l} h^2_{\mathrm{SCZ},l}}$ is the liability-scale genetic covariance. We calculated the liability thresholds t_{A} and t_{B} for traits A and B as the Normal quantiles above which proportions P_{A} and P_{B} of liability lie, corresponding to lifetime risks for traits A and B, respectively. We then calculated the expected proportion P_{AB} of cases that pass these thresholds from the bivariate cumulative distribution of liability using the algorithm of Genz et al[2] implemented in the mvtnorm package in R 3.0.2. The odds ratio for developing ALS given a diagnosis of schizophrenia is (supplementary figure 3)

$$OR_{\mathrm{ALS|SCZ}} = \frac{P_{\mathrm{AB}} / (P_{\mathrm{B}} - P_{\mathrm{AB}})}{(P_{\mathrm{A}} - P_{\mathrm{AB}}) / (1 - P_{\mathrm{A}} - P_{\mathrm{B}} - P_{\mathrm{AB}})}.$$

(Equation 12)

The odds ratio for developing schizophrenia given a diagnosis of ALS is

$$OR_{\mathrm{SCZ|ALS}} = \frac{P_{\mathrm{AB}} / (P_{\mathrm{A}} - P_{\mathrm{AB}})}{(P_{\mathrm{B}} - P_{\mathrm{AB}}) / (1 - P_{\mathrm{A}} - P_{\mathrm{B}} - P_{\mathrm{AB}})}.$$

(Equation 13)

Cross-multiplying, both equations become

$$OR = \frac{P_{\mathrm{AB}}(1 - P_{\mathrm{A}} - P_{\mathrm{B}} - P_{\mathrm{AB}})}{(P_{\mathrm{A}} - P_{\mathrm{AB}})(P_{\mathrm{B}} - P_{\mathrm{AB}})}.$$

(Equation 14)

Under no genetic correlation the expected proportion P_0 of individuals passing liability thresholds t_{A} and t_{B} for traits A and B is the bivariate cumulative distribution function for $N_2(0, \mathbf{I})$ at t_{A} and t_{B}, which is equivalent to $P_{\mathrm{A}}P_{\mathrm{B}}$ ($\mathbf{I}$ is the identity matrix). This was used to calculate the size of population n required to achieve 80% power ($\beta = 0.2$) to observe a significant ($\alpha = 0.05$) excess of co-occurrences of the two traits using the two-tailed binomial power equation,

$$n = P_{\mathrm{AB}}(1 - P_{\mathrm{AB}})\left(\frac{\phi^{-1}_{1-\frac{\alpha}{2}} + \phi^{-1}_{1-\beta}}{P_{\mathrm{AB}} - P_0}\right)^2,$$

(Equation 15)

where ϕ is the cumulative distribution function of the Normal distribution. Multiplying n by the lifetime risk for developing ALS (1/400) gives the required size of incident ALS cohort to observe this excess.

References

1. Wray NR, Lee SH, Kendler KS. Impact of diagnostic misclassification on estimation of genetic correlations using genome-wide genotypes. Eur J Hum Genet. 2012 Jun;20(6):668–74.

2. Genz A. Numerical Computation of Multivariate Normal Probabilities. J Comput Graph Stat. 1992 Jun;1(2):141–9.