Supplementary Table 2. Demographic and clinical characteristics of the COURAGE-PD cohort.

Principal Investigators	Country	Ancestry	Cases (N)	Controls (N)	Total (N)	Female cases (%)	Female controls (%)	Case age at enrolment (mean, SD in years)	Control age at enrolment (mean, SD in years)
Aasly	Norway	European	510	509	1019	40%	45.2%	77.7(11.6)	NA
Bardien/Carr	South Africa	European	170	85	255	38.8%	43.5%	68.7(10.6)	51.1(12.7)
Annesi	Italy	European	93	94	187	35.5%	54.3%	66.5(9.0)	58.2(20.3)
Brice	France	European	851	280	1131	41.6%	43.6%	60.7(10.9)	62.4(10.7)
Brighina	Italy	European	48	40	88	20.8%	40%	66.3(9.8)	66.7(5.3)
Carmine	Sweden	European	286	629	915	38.5%	44.8%	67.4(10.3)	NA
Chartier-Harlin	France	European	370	228	598	45.7%	60.1%	64.3(9.0)	59.9(12.6)
Deutschlander	Germany	European	285	46	331	38.2%	69.6%	69.4(9.9)	66.0(10.3)
Elbaz	France	European	455	1066	1521	40.2%	40.8%	70.1(7.4)	69.8(7.6)
Farrer	USA	European	389	409	798	34.4%	68.2%	67.7(10.3)	69.4(12.4)
Ferreira	Portugal	European	415	67	482	42.9%	74.6%	69.0(10.1)	47.1(17.8)
Gasser/Sharma	Germany	European	681	549	1230	36.4%	56.6%	64.9(10.9)	61.9(7.8)
Goldwurm	Italy	European	1391	1370	2761	40.8%	66.3%	65.8(10.8)	61.9(10.9)
Hadjigeorgiou	Greece	European	283	314	597	51.6%	52.9%	67.9(10.3)	69.8(8.7)
Koks	Estonia	European	216	170	386	60.2%	58.2%	73.0(8.2)	72.3(10.2)
Krainc	USA	European	59	16	75	25.4%	81.2%	64.7(10.7)	61.4(11.7)
Mellick	Australia	European	480	508	988	36.0%	54.7%	68.3(9.3)	66.9(9.6)
Pchelina	Russia	European	15	5	20	46.7%	80%	60.7(6.4)	59.8(20.0)
Puschmann	Sweden	European	110	105	215	37.3%	70.5%	68.8(10.6)	66.7(8.9)
Rogaeva	Canada	European	215	153	368	34.0%	62.1%	63.6(12.4)	73.8(8.6)
Stefanis	Greece	European	242	181	423	38.4%	64.1%	67.1(13.5)	67.0(9.6)
Valente	Italy	European	326	54	380	37.7%	61.1%	67.0(12.1)	78.4(9.6)
Wirdefeldt	Sweden	European	147	176	323	44.2%	54.5%	72.2(9.3)	73.5(9.7)
Zimprich	Austria	European	598	184	782	36.6%	59.2%	66.8(11.3)	NA
Kruger	Luxembourg	European	333	360	693	32.7%	44.2%	67.4(11.2)	58.1(11.9)
TOTAL	-	**European**	**8968**	**7598**	**16566**				

Supplementary Table 3. Demographic and clinical characteristics of the AMP-PD cohort.

Study	Cases (N)	Controls (N)	Total (N)	Female cases (%)	Female control (%)	Case age at onset (mean, SD in years)	Control age at last exam (mean, SD in years)
BIOFIND	75	56	131	38.7	48.2	67.5(6.2)	65.4(7.2)
HBS	524	392	916	36.3	64.0	61.5(10.6)	68.5(10.3)
LBD	-	1759	1759	-	49.5	-	71.9(13.5)
SURE-PD3	227	-	227	49.3	-	62.3(9.5)	-
PDBP	767	437	1204	35.6	55.1	59.6(10.6)	62.8(10.8)
PPMI	381	173	554	35.7	34.1	62.0(9.6)	61.0(10.4)
STEADY-PD3	274	-	274	30.7	-	62.7(9.2)	-
TOTAL	**2248**	**2817**	**5065**				

NA: Not Applicable

Supplementary Table 4. PD cases and controls in each quantile of polygenic risk scores per cohort.

Quantiles	IPDGC		COURAGE-PD		UKBB		AMP-PD	
	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases
1 (0 - 25%)	2353	926	1900	1520	3575	507	704	389
2 (26 - 50%)	2353	1396	1899	1961	3575	606	704	475
3 (51- 75%)	2353	1869	1899	2384	3575	678	704	585
4 (76- 100%)	**2353**	**3011**	**1900**	**3102**	**3576**	**847**	**705**	**798**
Total	9412	7204	7598	8968	14301	2639	2817	2248

Supplementary Table 5. Meta-GWAS summary statistics for the sub-top loci associated with PD resilience.

SNP	CHR	BP	Nearest Gene	Variant type	Effect allele	Other allele	Frequency	Beta (SE)	*P* value	I^2	Beta(SE) in Risk GWAS	P value in Risk GWAS
rs62325099	4	190552831	*LINC01262*	Intergenic	T	C	0.569	-0.328(0.061)	1.03e-07	NA	0.089(0.069)	0.206
rs2652202	5	77095148	*TBCA*	Intergenic	T	C	0.645	0.127(0.024)	1.64e-07	0	-0.023(0.022)	0.303
rs12245509	10	91752990	*LINC01375*	Intergenic	A	G	0.940	-0.248(0.049)	5.21e-07	0	0.016(0.045)	0.721
rs292289	18	5198809	*C18orf42*	Intergenic	C	A	0.144	-0.301(0.056)	9.85e-08	NA	-0.020(0.043)	0.641

SNP: single nucleotide polymorphism, CHR: chromosome, BP: base pair, SE: standard error. NA: not applicable. rs62325099 and rs292289 were only present in the discovery dataset (IPDGC). Risk GWAS means the Mike Nalls *et al.* 2019 PD GWAS.

Supplementary Table 6. Pearson correlation between risk and resilience scores in four groups of genetic cohorts.

Cohort	Group	Pearson's r	95%CI	P
IPDGC	Control	0.132	0.111, 0.151	**2.20E-16**
IPDGC	PD	-0.092	-0.115, -0.069	**2.20E-16**
IPDGC	Resilient-control	-0.027	-0.100, 0.0457	0.464
IPDGC	Risk-matching-PD	-0.001	-0.067, 0.065	0.970
COURAGE-PD	Control	0.022	-0.001, 0.044	0.058
COURAGE-PD	PD	-0.013	-0.033, -0.008	0.226
COURAGE-PD	Resilient-control	0.005	-0.040, 0.050	0.823
COURAGE-PD	risk-matching-PD	-0.021	-0.057, -0.014	0.233
AMP-PD	Control	0.0004	-0.036, 0.037	0.982
AMP-PD	PD	-0.004	-0.045, 0.037	0.843
AMP-PD	Resilient-control	-0.028	-0.102, 0.045	0.451
AMP-PD	Risk-matching-PD	-0.018	-0.087, 0.052	0.615
UKBB	Control	0.006	-0.010, 0.022	0.471
UKBB	PD	-0.012	-0.051, 0.026	0.523
UKBB	Resilient-control	0.009	-0.023, 0.042	0.571
UKBB	Risk-matching-PD	-0.011	-0.078, 0.056	0.745

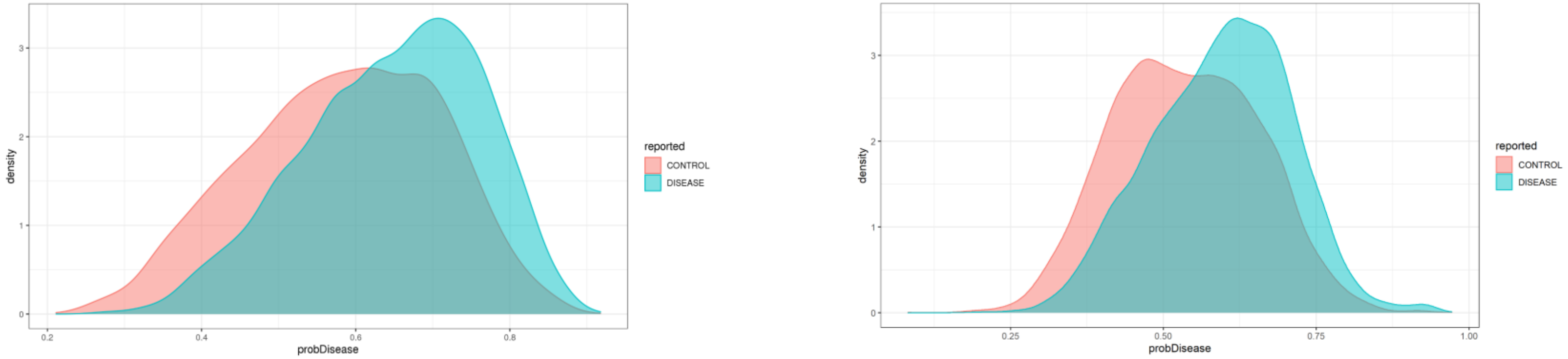
Significant values are highlighted in bold.

Supplementary Table 7. Top ten ranked pathways associated with PD resilience.

Gene Set	N Genes	Beta	Beta STD	SE	P value	Pbon
GO_bp:go_histone_h3_k9_dimethylation	5	1.370	0.024	0.292	1.36e-06	**0.021**
Curated_gene_sets:burton_adipogenesis_7	40	0.582	0.028	0.137	1.16e-05	0.18
GO_mf:go_selenium_binding	7	1.446	0.026	0.326	5.25e-05	0.81
GO_cc:go_vcb_complex	6	1.500	0.028	0.390	5.98e-05	0.92
Curated_gene_sets:davicioni_pax_foxo1_signature_in_arms_up	48	0.473	0.025	0.130	0.000128	1
GO_bp:go_protein_localization_to_membrane	515	0.128	0.022	0.036	0.000169	1
GO_mf:go_calcium_channel_regulator_activity	45	0.444	0.023	0.126	0.000214	1
GO_bp:go_positive_regulation_of_voltage_gated_calcium_channel_activity	12	0.812	0.022	0.233	0.000242	1
GO_cc:go_microbody_membrane	53	0.336	0.019	0.097	0.000260	1
Curated_gene_sets:torchia_targets_of_ewsr1_fli1_fusion_dn	268	0.183	0.023	0.053	0.000290	1

MAGMA gene-set analysis is performed for curated gene sets and gene ontology (GO) terms obtained from MsigDB. GO_bp: GO biological process, GO_mf: GO molecular function, GO_cc: GO cellular component, N Genes: the number of genes in the data that was in the set, BETA: the regression coefficient of the variable, BETA STD: the semi-standardized regression coefficient, corresponding to the predicted change in Z-value given a change of one standard deviation in the predictor gene set/gene covariate (i.e., BETA divided by the variable's standard deviation), SE: the standard error of the regression coefficient, P_{bon}: Bonferroni adjusted p-value.

Supplementary Figure 1. Density plots displaying genetic risk profiling for PD cases and controls.

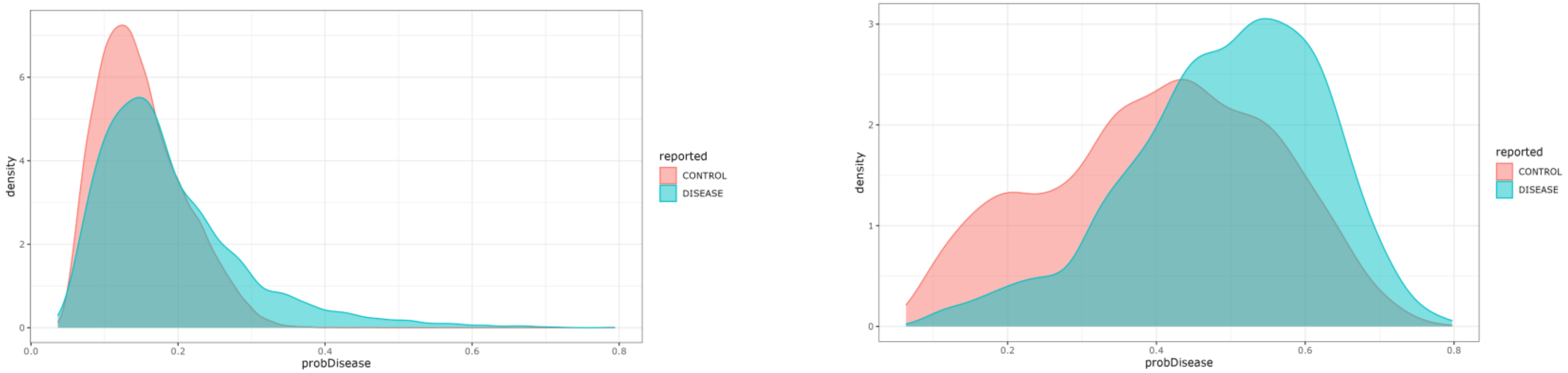


A. IPDGC

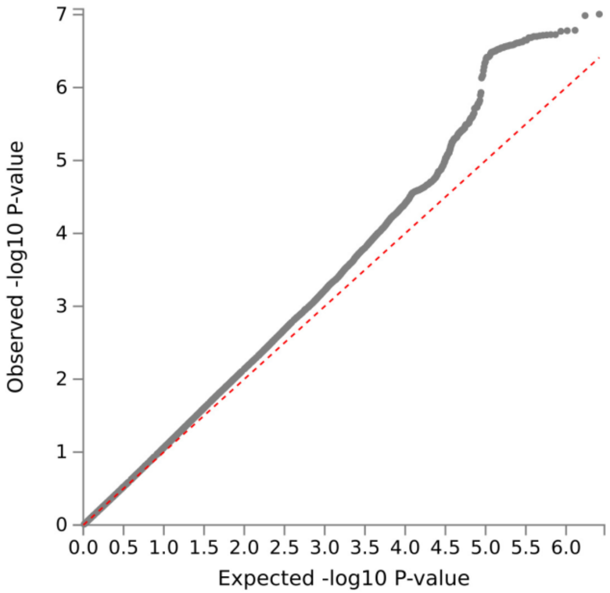
B. COURAGE-PD

C. UKBB

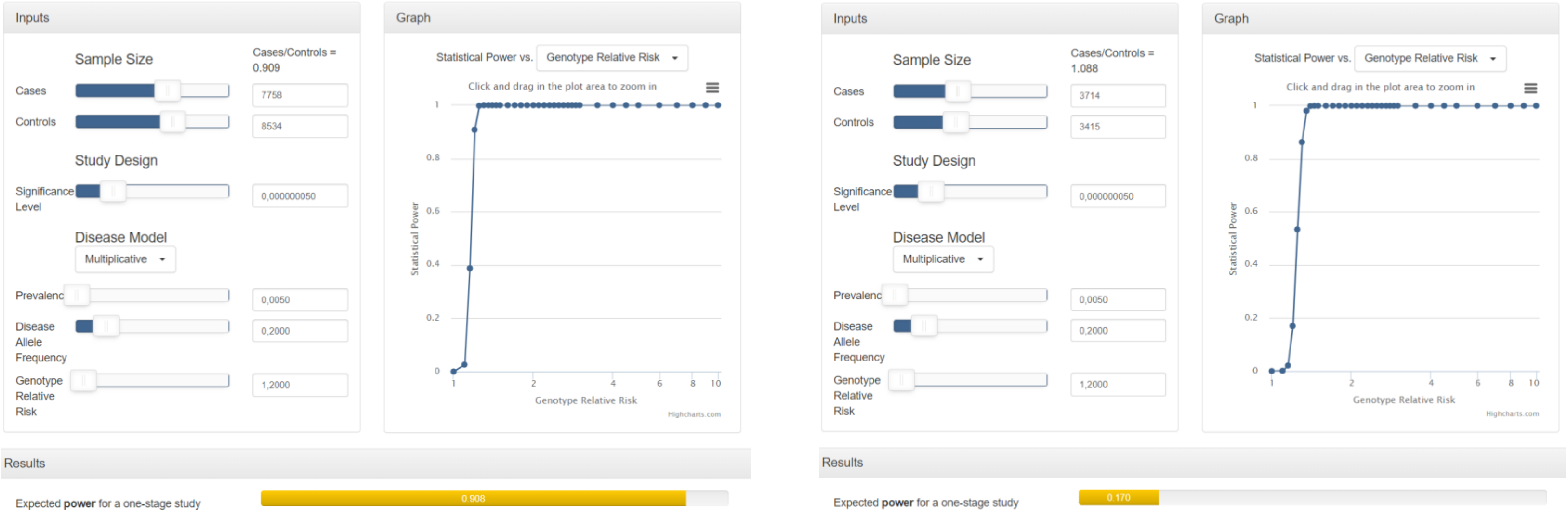
D. AMP-PD



Supplementary Figure 2. Quantile-quantile (QQ) plot showing the distribution of p-values from the genome-wide association study meta-analysis of resilience to PD (grey dots) compared to a theoretical distribution of p-values for an equivalent number of variants (red dashed line).



Supplementary Figure 3. Power calculations at meta-GWAS sample size.



A. Top-25% of the data

Inputs

Sample Size

Cases/Controls = 0.909

Cases 7758

Controls 8534

Study Design

Significance Level 0,000000050

Disease Model

Multiplicative

Prevalenc 0,0050

Disease Allele Frequency 0,2000

Genotype Relative Risk 1,2000

Results

Expected **power** for a one-stage study 0.908

B. Top-10% of the data

Inputs

Sample Size

Cases/Controls = 1.088

Cases 3714

Controls 3415

Study Design

Significance Level 0,000000050

Disease Model

Multiplicative

Prevalenc 0,0050

Disease Allele Frequency 0,2000

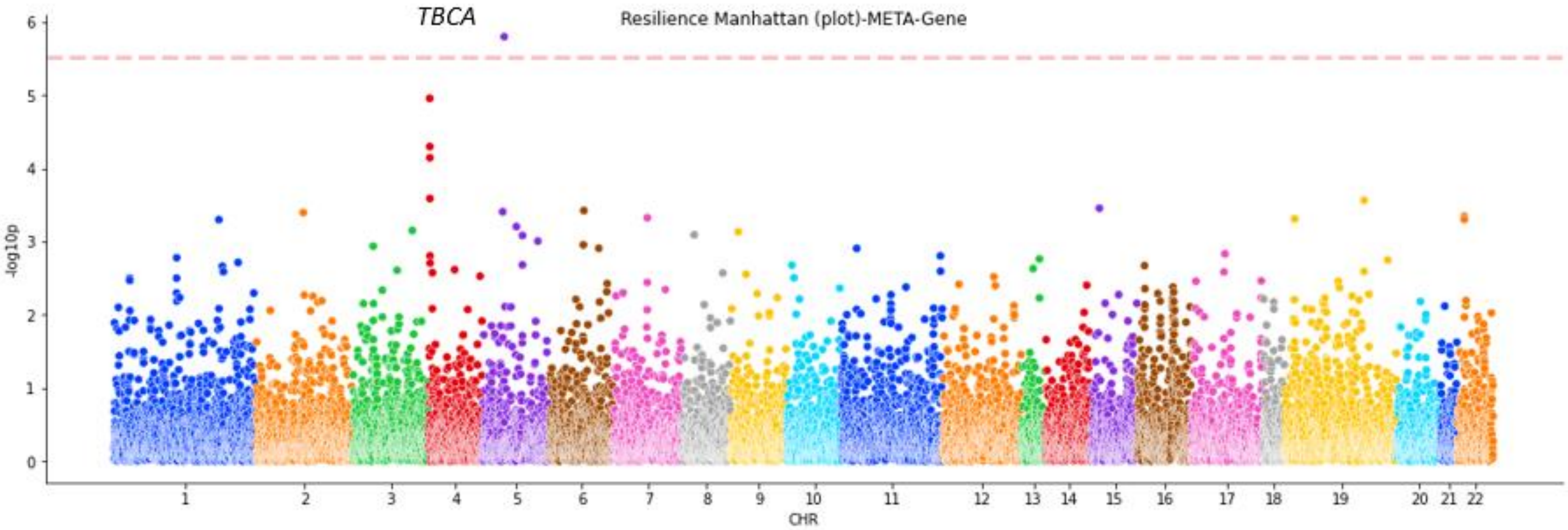
Genotype Relative Risk 1,2000

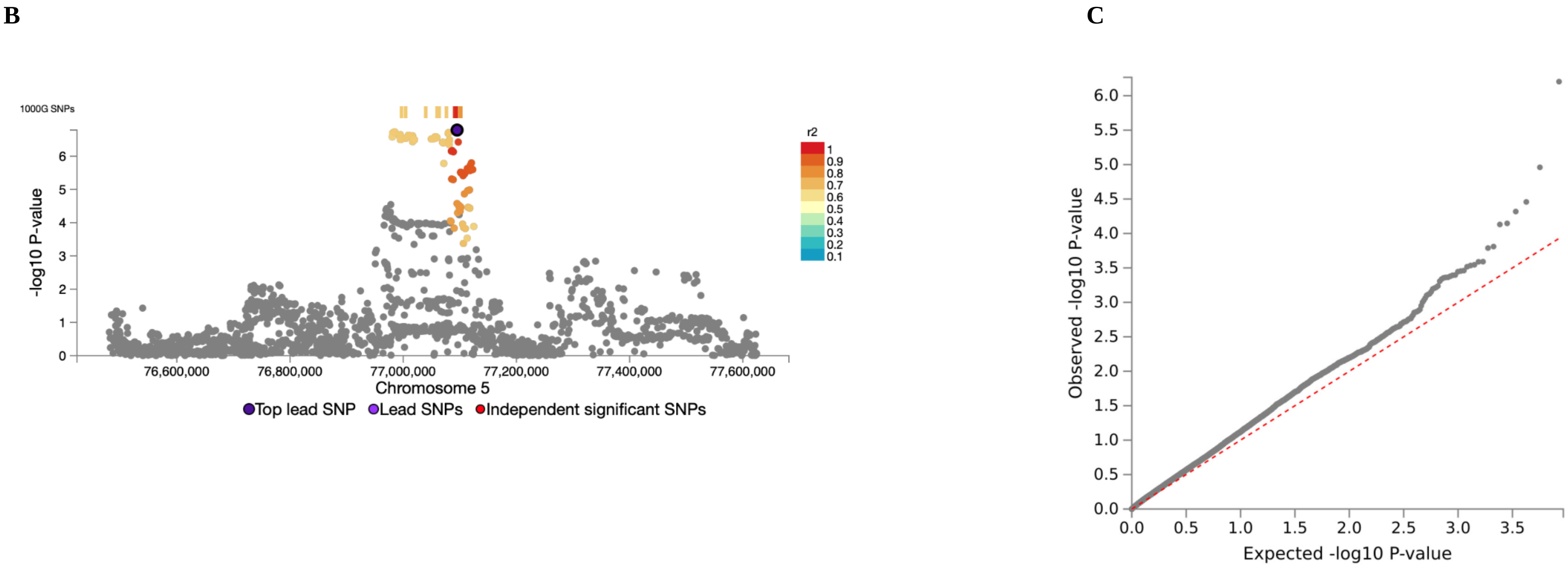
Results

Expected **power** for a one-stage study 0.170

Supplementary Figure 4. Gene-based MAGMA analysis.

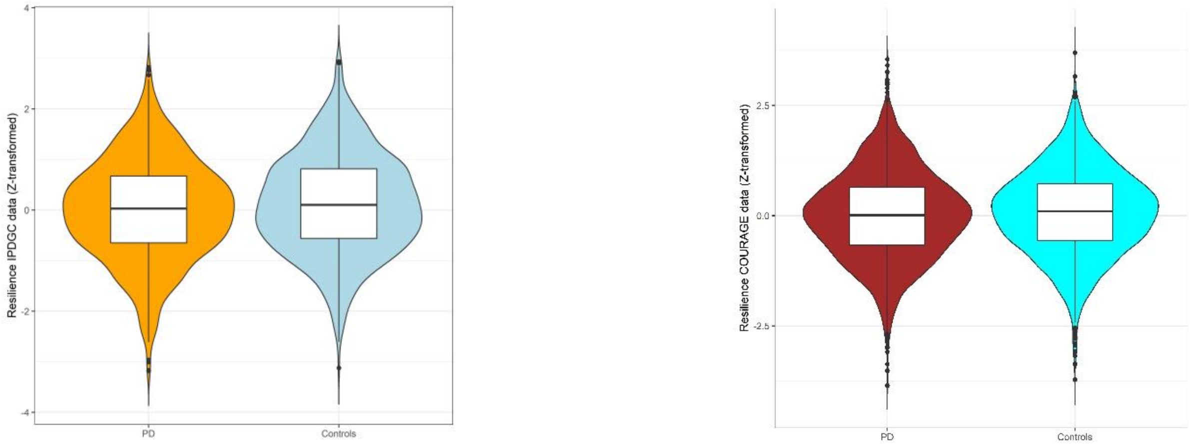
A



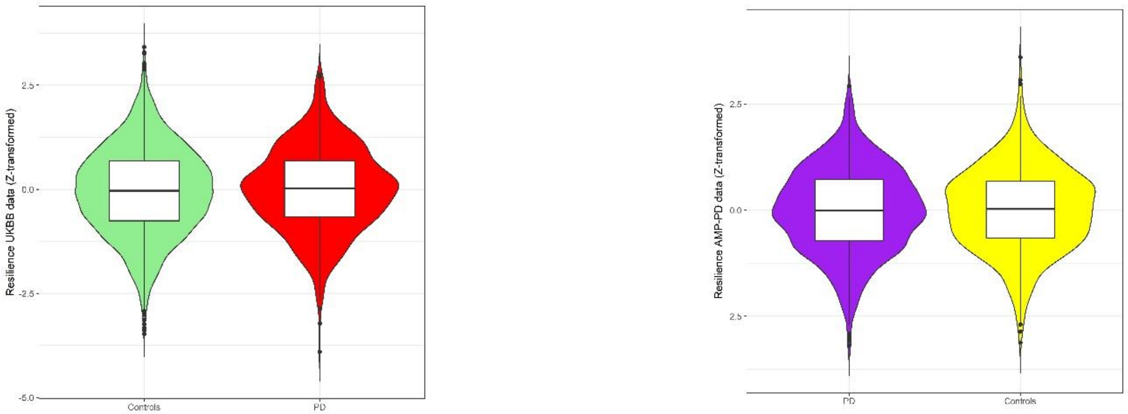


A) Gene-based Manhattan plot. B) Locus zoom plot of the TBCA region nominated through MAGMA gene-based analyses. Each SNP is color-coded based on the highest r2 to one of the independent significant SNPs if that is greater or equal to the user-defined threshold. Other SNPs (i.e. below the user-defined r^2) are colored in grey. The top lead SNPs in genomic risk loci, lead SNPs, and independent significant SNPs are circled in black and colored in dark-purple, purple and red, respectively. C) Quantile-quantile (QQ) plot showing the distribution of p-values from MAGMA gene-based GWAS of resilience to PD (grey dots) compared to a theoretical distribution of p-values for an equivalent number of variants (red dashed line).

Supplementary Figure 5. Polygenic resilience score of resilient controls and risk-matching cases.

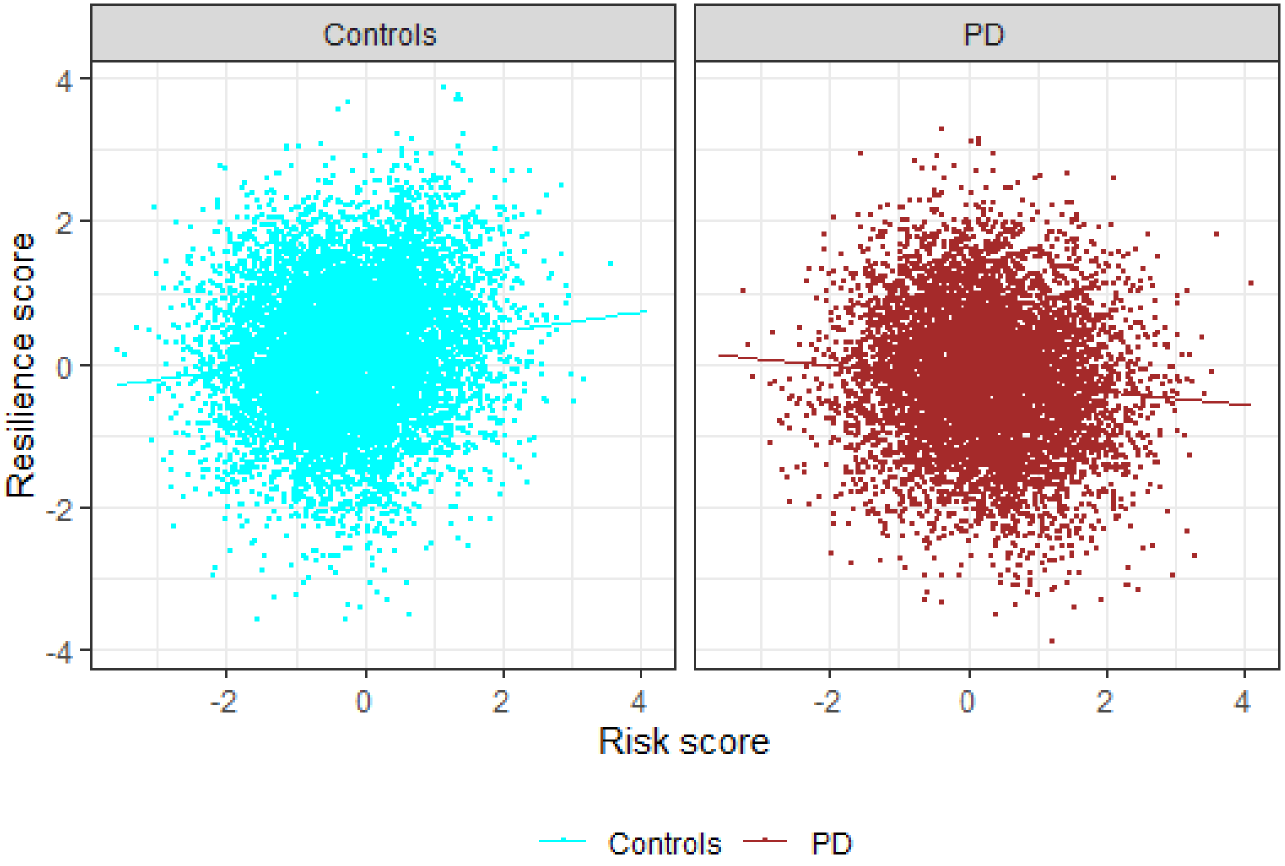

A. IPDGC

B. COURAGE-PD

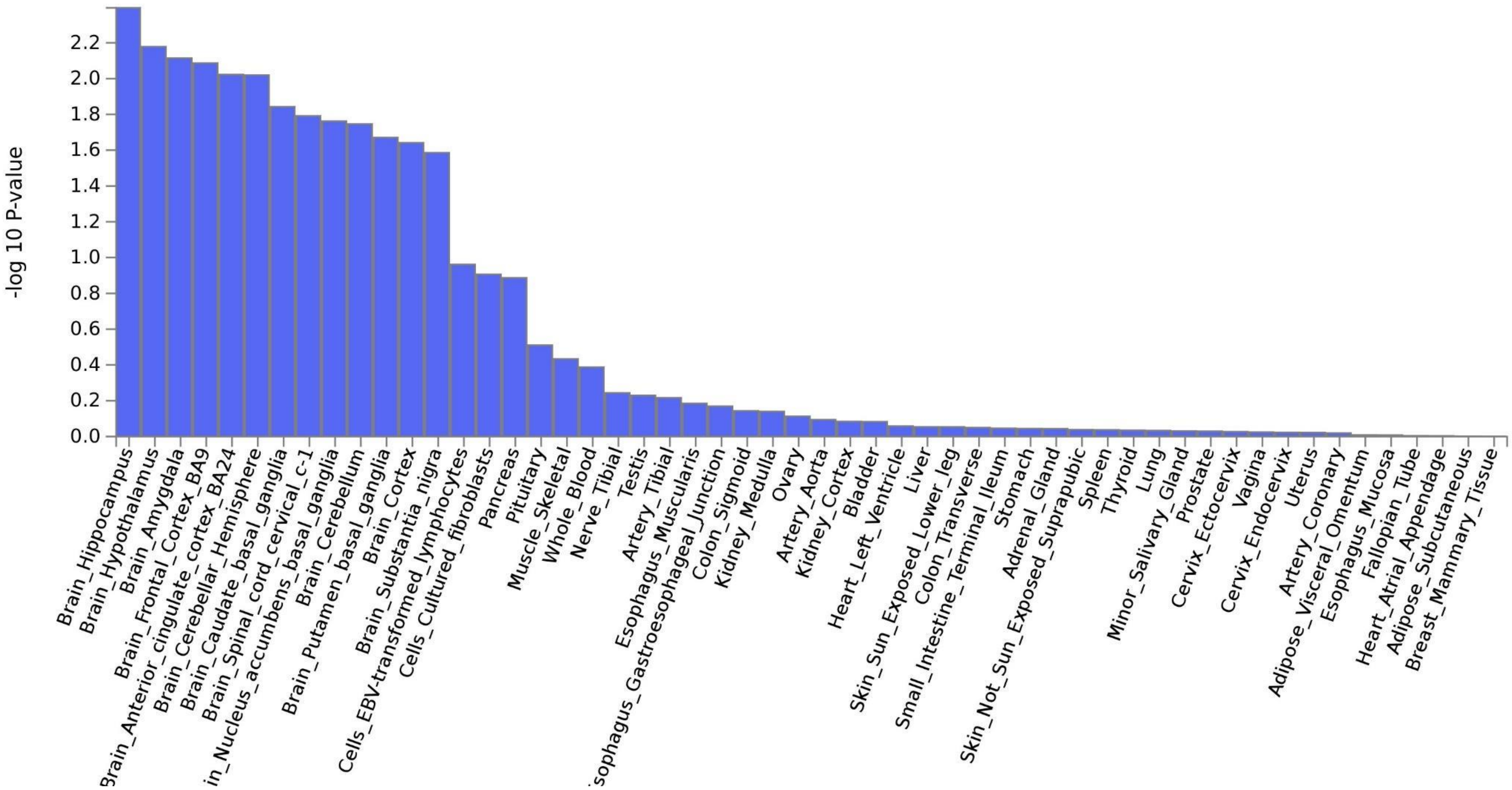

C. UKBB

D. AMP-PD

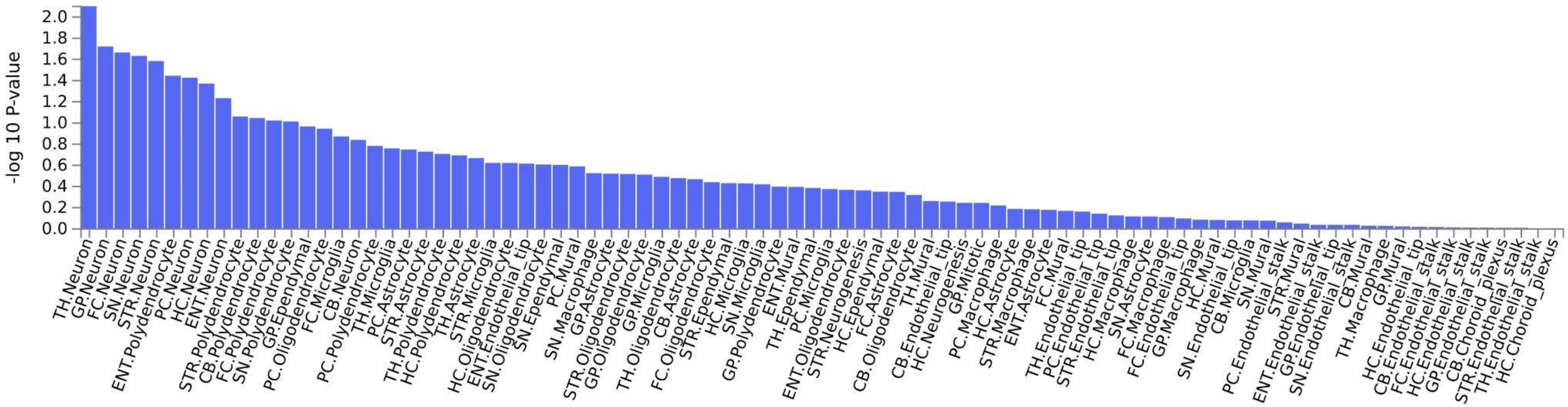
Supplementary Figure 6. Correlation between risk and resilience scores in the discovery IPDGC cohort, including 7,204 PD cases and 9,412 controls.



Supplementary Figure 7. Tissue specific expression enrichment analyses for PD resilience variants.



Supplementary Figure 8. Cell type expression enrichment analyses for PD resilience variants.



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