

SHORT COMMUNICATION

Causal relationships between cathepsins and psychiatric disorders: A Mendelian randomization study

Supplementary Files
Table S1. Additional information about genome-wide association study in the exposure groups

Exposure	GWAS ID	Sample size	Number of SNPs	PubMed ID
Cathepsin B	prot-a-718	3,301	10,534,735	29875488
Cathepsin E	prot-a-720			
Cathepsin F	prot-a-722			
Cathepsin G	prot-a-723			
Cathepsin H	prot-a-725			
Cathepsin O	prot-a-726			
Cathepsin S	prot-a-727			
Cathepsin L2	prot-a-728			
Cathepsin Z	prot-a-729			

Abbreviations: GWAS: Genome-wide association study;
 SNP: Single-nucleotide polymorphism.

Table S2. Overview of the genome-wide association study data sources for outcome groups

Outcome	Case	Control	Web source
Schizophrenia	6,515	364,160	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_F5_SCHZPHR.gz
Bipolar disorder	7,006	329,192	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_F5_BIPO.gz
Depression	43,280	329,192	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_F5_DEPRESSIO.gz
Anorexia nervosa	1,897	366,876	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_F5_ANOREX.gz
Attention-deficit hyperactivity disorder	2,340	371,117	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_F5_ADHD.gz
Autism spectrum disorder	564	277,526	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_KRA_PSY_AUTISM_EXMORE.gz
Anxiety disorders	40,191	277,526	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_KRA_PSY_ANXIETY_EXMORE.gz
Panic disorder	4,801	337,577	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_F5_PANIC.gz
Obsessive-compulsive disorder	1,962	337,577	https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_F5_OCD.gz

Table S3. Cochran's Q test and Mendelian randomization-Egger intercept results in univariable Mendelian randomization analysis

Outcome	Exposure	IVW-Q test		Mendelian randomization-Egger intercept analysis		
		Q-statistic	Q-p-value	Intercept	SE	p-value
Schizophrenia	Cathepsin B	13.996	0.667	0.015	0.028	0.595
	Cathepsin E	9.23	0.323	0.012	0.023	0.632
	Cathepsin F	5.07	0.828	0.008	0.033	0.814
	Cathepsin G	11.187	0.343	-0.047	0.036	0.228
	Cathepsin H	13.666	0.135	0.032	0.020	0.145
	Cathepsin O	9.612	0.566	-0.006	0.028	0.832
	Cathepsin S	16.122	0.810	-0.030	0.015	0.056
	Cathepsin L2	9.512	0.484	-0.036	0.037	0.364
	Cathepsin Z	7.925	0.791	0.005	0.017	0.794
Bipolar disorder	Cathepsin B	18.379	0.365	0.014	0.020	0.482
	Cathepsin E	3.989	0.858	-0.001	0.015	0.965
	Cathepsin F	17.346	0.044	-0.041	0.031	0.228
	Cathepsin G	12.351	0.262	0.070	0.025	0.121
	Cathepsin H	2.907	0.968	-0.010	0.012	0.450
	Cathepsin O	9.934	0.536	-0.005	0.019	0.813
	Cathepsin S	15.078	0.859	-0.001	0.011	0.951
	Cathepsin L2	4.871	0.900	0.044	0.026	0.127
	Cathepsin Z	11.720	0.468	-0.008	0.012	0.528
Depression	Cathepsin B	16.868	0.463	0.014	0.008	0.089
	Cathepsin E	11.439	0.178	0.007	0.007	0.389
	Cathepsin F	9.886	0.360	0.020	0.010	0.070
	Cathepsin G	10.774	0.375	0.012	0.010	0.261
	Cathepsin H	4.709	0.859	0.002	0.005	0.694
	Cathepsin O	13.450	0.265	-0.001	0.009	0.883
	Cathepsin S	17.782	0.719	-0.002	0.004	0.608
	Cathepsin L2	7.429	0.684	0.006	0.011	0.606
	Cathepsin Z	14.967	0.243	0.002	0.005	0.705
Anorexia nervosa	Cathepsin B	16.119	0.515	-0.035	0.034	0.320
	Cathepsin E	7.628	0.471	-0.020	0.026	0.478
	Cathepsin F	5.476	0.791	0.006	0.042	0.881
	Cathepsin G	9.278	0.506	-0.065	0.044	0.173
	Cathepsin H	11.728	0.229	0.010	0.026	0.715
	Cathepsin O	7.005	0.799	0.027	0.034	0.450
	Cathepsin S	28.123	0.172	0.032	0.020	0.131
	Cathepsin L2	14.757	0.141	-0.085	0.052	0.136
	Cathepsin Z	8.705	0.728	0.032	0.021	0.146
Attention-deficit hyperactivity disorder	Cathepsin B	7.635	0.974	0.043	0.031	0.189
	Cathepsin E	13.265	0.103	-0.020	0.032	0.541
	Cathepsin F	11.084	0.270	0.044	0.042	0.329
	Cathepsin G	14.765	0.141	0.016	0.051	0.763

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Table S3. (Continued)

Outcome	Exposure	IVW-Q test		Mendelian randomization-Egger intercept analysis			
		Q-statistic	Q-p-value	Intercept	SE	p-value	
Autism spectrum disorder	Cathepsin H	6.656	0.673	-0.028	0.020	0.198	
	Cathepsin O	16.797	0.114	0.025	0.040	0.543	
	Cathepsin S	25.965	0.253	-0.015	0.019	0.436	
	Cathepsin L2	6.838	0.741	0.035	0.042	0.423	
	Cathepsin Z	9.662	0.646	0.013	0.019	0.520	
	Cathepsin B	16.836	0.466	0.127	0.069	0.085	
	Cathepsin E	20.614	0.008*	-0.028	0.088	0.760	
	Cathepsin F	17.324	0.144	-0.073	0.120	0.558	
	Cathepsin G	12.202	0.272	0.071	0.101	0.500	
	Cathepsin H	5.922	0.748	-0.047	0.044	0.318	
	Cathepsin O	11.852	0.375	-0.046	0.075	0.552	
	Cathepsin S	24.866	0.304	-0.046	0.040	0.259	
	Anxiety disorders	Cathepsin L2	7.816	0.647	-0.010	0.092	0.920
Cathepsin Z		7.483	0.824	0.001	0.042	0.999	
Cathepsin B		27.234	0.055	0.017	0.010	0.118	
Cathepsin E		8.148	0.419	0.008	0.006	0.247	
Cathepsin F		12.621	0.181	0.004	0.013	0.738	
Cathepsin G		11.920	0.290	0.031	0.011	0.020	
Cathepsin H		5.149	0.821	0.001	0.005	0.962	
Cathepsin O		15.393	0.165	0.018	0.009	0.063	
Cathepsin S		24.884	0.302	-0.007	0.005	0.179	
Cathepsin L2		19.394	0.136	0.012	0.016	0.471	
Cathepsin Z		10.831	0.543	-0.005	0.005	0.384	
Panic disorder		Cathepsin B	9.902	0.908	-0.011	0.022	0.637
		Cathepsin E	3.330	0.912	0.011	0.017	0.511
	Cathepsin F	15.465	0.079	0.026	0.036	0.481	
	Cathepsin G	8.278	0.602	0.003	0.028	0.914	
	Cathepsin H	14.222	0.115	-0.009	0.018	0.639	
	Cathepsin O	12.670	0.315	-0.018	0.024	0.464	
	Cathepsin S	30.141	0.115	-0.026	0.013	0.062	
	Cathepsin L2	11.738	0.303	-0.039	0.031	0.238	
	Cathepsin Z	12.518	0.405	-0.011	0.014	0.543	
	Obsessive-compulsive disorder	Cathepsin B	19.489	0.301	0.005	0.038	0.905
		Cathepsin E	6.831	0.555	0.025	0.026	0.359
		Cathepsin F	7.659	0.569	-0.032	0.041	0.469
		Cathepsin G	13.711	0.187	-0.057	0.051	0.290
Cathepsin H		6.418	0.698	0.025	0.022	0.290	
Cathepsin O		13.556	0.259	-0.034	0.039	0.400	
Cathepsin S		24.565	0.318	-0.012	0.020	0.554	
Cathepsin L2		6.520	0.770	0.065	0.046	0.196	
Cathepsin Z		14.640	0.262	-0.005	0.024	0.851	

Note: Asterisk (*) represents $P < 0.05$.

Abbreviations: IVW: Inverse-variance weighted; SE: Standard error.

Table S4. Results of inverse-variance weighted method in univariable Mendelian randomization analysis

Outcome	Exposure	SNPs	OR	95% CI	p-value
Schizophrenia	Cathepsin B	18	0.992	0.908 – 1.082	0.851
	Cathepsin E	9	1.047	0.940 – 1.165	0.406
	Cathepsin F	9	1.020	0.924 – 1.126	0.696
	Cathepsin G	11	0.995	0.883 – 1.121	0.931
	Cathepsin H	10	0.937	0.871 – 1.009	0.086
	Cathepsin O	12	1.020	0.905 – 1.150	0.746
	Cathepsin S	23	1.019	0.945 – 1.099	0.619
	Cathepsin L2	11	1.024	0.890 – 1.177	0.744
	Cathepsin Z	13	0.975	0.895 – 1.062	0.566
Bipolar disorder	Cathepsin B	18	0.973	0.913 – 1.037	0.405
	Cathepsin E	9	1.014	0.945 – 1.088	0.700
	Cathepsin F	10	0.974	0.885 – 1.072	0.592
	Cathepsin G	11	1.097	1.004 – 1.197	0.040*
	Cathepsin H	10	0.968	0.928 – 1.009	0.127
	Cathepsin O	12	0.957	0.880 – 1.041	0.303
	Cathepsin S	23	1.004	0.952 – 1.059	0.880
	Cathepsin L2	11	1.052	0.954 – 1.160	0.308
	Cathepsin Z	13	1.007	0.949 – 1.068	0.823
Depression	Cathepsin B	18	0.994	0.969 – 1.019	0.625
	Cathepsin E	9	1.008	0.974 – 1.044	0.633
	Cathepsin F	10	1.019	0.989 – 1.049	0.220
	Cathepsin G	11	1.008	0.975 – 1.042	0.650
	Cathepsin H	10	0.997	0.980 – 1.015	0.761
	Cathepsin O	12	0.978	0.942 – 1.016	0.256
	Cathepsin S	23	1.025	1.003 – 1.047	0.025*
	Cathepsin L2	11	0.981	0.943 – 1.021	0.350
	Cathepsin Z	13	0.996	0.970 – 1.024	0.795
Anorexia nervosa	Cathepsin B	18	1.030	0.924 – 1.149	0.591
	Cathepsin E	9	0.964	0.850 – 1.093	0.565
	Cathepsin F	10	0.988	0.874 – 1.118	0.852
	Cathepsin G	11	1.125	0.978 – 1.294	0.100
	Cathepsin H	10	1.030	0.945 – 1.122	0.503
	Cathepsin O	12	0.986	0.849 – 1.145	0.854
	Cathepsin S	23	1.030	0.926 – 1.145	0.591
	Cathepsin L2	11	1.038	0.840 – 1.282	0.730
	Cathepsin Z	13	0.878	0.790 – 0.976	0.015*
Attention-deficit hyperactivity disorder	Cathepsin B	18	0.944	0.855 – 1.043	0.257
	Cathepsin E	9	0.961	0.829 – 1.115	0.604
	Cathepsin F	10	0.985	0.870 – 1.116	0.816
	Cathepsin G	11	1.070	0.916 – 1.249	0.395
	Cathepsin H	10	0.991	0.926 – 1.062	0.803
	Cathepsin O	12	1.152	0.974 – 1.364	0.099

(Cont'd...)

Table S4. (Continued)

Outcome	Exposure	SNPs	OR	95% CI	p-value
Autism spectrum disorder	Cathepsin S	23	1.063	0.968 – 1.167	0.202
	Cathepsin L2	11	0.887	0.757 – 1.040	0.139
	Cathepsin Z	13	1.076	0.977 – 1.184	0.136
	Cathepsin B	17	0.871	0.700 – 1.083	0.213
	Cathepsin E	9	0.914	0.610 – 1.370	0.662
	Cathepsin F	10	0.953	0.677 – 1.342	0.784
	Cathepsin G	11	1.220	0.892 – 1.668	0.213
	Cathepsin H	10	1.012	0.872 – 1.175	0.875
	Cathepsin O	12	1.277	0.934 – 1.747	0.126
	Cathepsin S	23	0.900	0.737 – 1.100	0.305
Anxiety disorders	Cathepsin L2	11	1.113	0.786 – 1.577	0.545
	Cathepsin Z	13	0.862	0.696 – 1.068	0.174
	Cathepsin B	18	0.987	0.954 – 1.021	0.446
	Cathepsin E	9	0.998	0.968 – 1.030	0.925
	Cathepsin F	10	1.019	0.984 – 1.056	0.290
	Cathepsin G	11	1.026	0.988 – 1.065	0.178
	Cathepsin H	10	0.997	0.979 – 1.016	0.755
	Cathepsin O	12	0.979	0.937 – 1.022	0.337
	Cathepsin S	23	1.018	0.993 – 1.044	0.154
	Cathepsin L2	11	0.994	0.936 – 1.055	0.836
Panic disorder	Cathepsin Z	13	0.987	0.962 – 1.013	0.331
	Cathepsin B	18	1.003	0.936 – 1.075	0.925
	Cathepsin E	9	0.963	0.889 – 1.044	0.361
	Cathepsin F	10	1.062	0.958 – 1.176	0.252
	Cathepsin G	11	0.955	0.874 – 1.044	0.316
	Cathepsin H	10	1.020	0.960 – 1.083	0.526
	Cathepsin O	12	0.966	0.873 – 1.070	0.512
	Cathepsin S	22	1.034	0.964 – 1.109	0.349
	Cathepsin L2	11	0.955	0.847 – 1.076	0.452
	Cathepsin Z	13	1.004	0.938 – 1.074	0.917
Obsessive-compulsive disorder	Cathepsin B	18	1.018	0.906 – 1.143	0.768
	Cathepsin E	9	1.006	0.888 – 1.140	0.922
	Cathepsin F	10	0.996	0.881 – 1.126	0.946
	Cathepsin G	11	1.011	0.858 – 1.191	0.896
	Cathepsin H	10	0.940	0.872 – 1.013	0.106
	Cathepsin O	12	0.947	0.803 – 1.118	0.521
	Cathepsin S	23	0.960	0.869 – 1.060	0.417
	Cathepsin L2	11	0.990	0.832 – 1.177	0.908
	Cathepsin Z	13	1.032	0.919 – 1.159	0.599

Note: Asterisk (*) represents $p < 0.05$.

Abbreviations: CI: Confidence interval; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

Table S5. Results of inverse-variance weighted method in reverse Mendelian randomization analysis

Outcome	Exposure	SNPs	OR	95% CI	p-value
Cathepsin B	Bipolar disorder	15	1.190	0.967 – 1.463	0.100
Cathepsin E		15	1.007	0.874 – 1.160	0.927
Cathepsin F		15	0.868	0.675 – 1.115	0.267
Cathepsin G		15	0.910	0.766 – 1.081	0.282
Cathepsin H		15	1.051	0.912 – 1.212	0.489
Cathepsin O		15	1.060	0.872 – 1.289	0.559
Cathepsin S		15	1.186	0.968 – 1.453	0.101
Cathepsin L2		15	0.971	0.831 – 1.135	0.715
Cathepsin Z		15	1.052	0.913 – 1.212	0.480
Cathepsin B		Depression	36	1.157	0.945 – 1.417
Cathepsin E	36		0.856	0.700 – 1.046	0.128
Cathepsin F	36		1.093	0.866 – 1.380	0.453
Cathepsin G	36		0.943	0.769 – 1.156	0.572
Cathepsin H	36		1.025	0.839 – 1.252	0.809
Cathepsin O	36		1.079	0.883 – 1.318	0.457
Cathepsin S	36		0.904	0.740 – 1.105	0.324
Cathepsin L2	36		1.048	0.853 – 1.288	0.655
Cathepsin Z	36		1.047	0.856 – 1.279	0.656
Cathepsin B	Anorexia nervosa		7	1.040	0.977 – 1.107
Cathepsin E		7	0.984	0.924 – 1.047	0.602
Cathepsin F		7	1.058	0.988 – 1.133	0.104
Cathepsin G		7	1.016	0.955 – 1.081	0.616
Cathepsin H		7	0.970	0.910 – 1.030	0.305
Cathepsin O		7	0.964	0.906 – 1.026	0.250
Cathepsin S		7	1.003	0.942 – 1.067	0.929
Cathepsin L2		7	1.010	0.949 – 1.075	0.753
Cathepsin Z		7	1.002	0.941 – 1.066	0.950

Abbreviations: CI: Confidence interval; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

Table S6. Results of multivariable Mendelian randomization analysis

Outcome	Exposure	SNPs	OR	95% CI	p-value
Schizophrenia	Cathepsin B	94	1.020	0.933 – 1.114	0.665
	Cathepsin E		0.995	0.904 – 1.096	0.924
	Cathepsin F		1.027	0.916 – 1.151	0.654
	Cathepsin G		0.950	0.852 – 1.059	0.355
	Cathepsin H		0.985	0.862 – 1.126	0.830
	Cathepsin O		1.045	0.898 – 1.216	0.570
	Cathepsin S		0.998	0.921 – 1.081	0.954
	Cathepsin L2		0.968	0.843 – 1.111	0.644
	Cathepsin Z		0.941	0.845 – 1.048	0.269
Bipolar disorder	Cathepsin B	94	0.972	0.917 – 1.031	0.351
	Cathepsin E		1.023	0.960 – 1.091	0.479
	Cathepsin F		0.958	0.889 – 1.033	0.269
	Cathepsin G		1.079	1.004 – 1.160	0.038*
	Cathepsin H		0.981	0.941 – 1.022	0.351
	Cathepsin O		0.962	0.870 – 1.063	0.447
	Cathepsin S		1.028	0.975 – 1.084	0.308
	Cathepsin L2		1.048	0.956 – 1.149	0.315
	Cathepsin Z		1.036	0.966 – 1.111	0.323
Depression	Cathepsin B	94	0.993	0.968 – 1.019	0.592
	Cathepsin E		0.999	0.971 – 1.027	0.949
	Cathepsin F		1.026	0.993 – 1.060	0.125
	Cathepsin G		0.998	0.967 – 1.030	0.911
	Cathepsin H		1.001	0.983 – 1.019	0.916
	Cathepsin O		0.984	0.942 – 1.028	0.464
	Cathepsin S		1.028	1.004 – 1.052	0.020*
	Cathepsin L2		1.015	0.976 – 1.057	0.454
	Cathepsin Z		0.983	0.953 – 1.013	0.257
Anorexia nervosa	Cathepsin B	94	1.024	0.913 – 1.149	0.685
	Cathepsin E		1.016	0.895 – 1.153	0.808
	Cathepsin F		1.041	0.898 – 1.207	0.595
	Cathepsin G		1.058	0.918 – 1.218	0.439
	Cathepsin H		1.063	0.981 – 1.153	0.138
	Cathepsin O		0.925	0.760 – 1.127	0.440
	Cathepsin S		1.023	0.921 – 1.135	0.675
	Cathepsin L2		1.083	0.904 – 1.297	0.386
	Cathepsin Z		0.878	0.765 – 1.008	0.065
Attention-deficit hyperactivity disorder	Cathepsin B	94	0.975	0.880 – 1.080	0.622
	Cathepsin E		0.978	0.874 – 1.094	0.694
	Cathepsin F		0.934	0.819 – 1.065	0.309
	Cathepsin G		1.045	0.922 – 1.185	0.494
	Cathepsin H		0.998	0.929 – 1.072	0.955
	Cathepsin O		1.046	0.878 – 1.246	0.617

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Table S6. (Continued)

Outcome	Exposure	SNPs	OR	95% CI	p-value
Autism spectrum disorder	Cathepsin S	94	1.053	0.959 – 1.155	0.279
	Cathepsin L2		0.879	0.749 – 1.032	0.116
	Cathepsin Z		1.165	0.948 – 1.433	0.172
	Cathepsin B		0.845	0.672 – 1.062	0.148
	Cathepsin E		0.997	0.775 – 1.283	0.981
	Cathepsin F		0.930	0.692 – 1.251	0.633
	Cathepsin G		1.166	0.879 – 1.548	0.286
	Cathepsin H		1.037	0.884 – 1.217	0.654
	Cathepsin O		0.946	0.638 – 1.403	0.783
	Cathepsin S		0.919	0.746 – 1.131	0.424
Anxiety disorders	Cathepsin L2	94	1.244	0.868 – 1.782	0.235
	Cathepsin Z		0.929	0.703 – 1.228	0.606
	Cathepsin B		0.984	0.953 – 1.016	0.329
	Cathepsin E		0.997	0.962 – 1.033	0.851
	Cathepsin F		1.013	0.972 – 1.056	0.543
	Cathepsin G		1.011	0.971 – 1.052	0.602
	Cathepsin H		1.001	0.979 – 1.025	0.898
	Cathepsin O		0.983	0.930 – 1.039	0.535
	Cathepsin S		1.021	0.991 – 1.051	0.174
	Cathepsin L2		1.020	0.969 – 1.073	0.452
Panic disorder	Cathepsin Z	94	0.985	0.947 – 1.024	0.436
	Cathepsin B		1.010	0.937 – 1.090	0.790
	Cathepsin E		0.974	0.896 – 1.058	0.535
	Cathepsin F		0.989	0.898 – 1.090	0.828
	Cathepsin G		0.978	0.891 – 1.073	0.634
	Cathepsin H		1.025	0.972 – 1.081	0.363
	Cathepsin O		0.943	0.829 – 1.074	0.379
	Cathepsin S		1.002	0.935 – 1.073	0.954
	Cathepsin L2		0.971	0.862 – 1.093	0.626
	Cathepsin Z		1.040	0.951 – 1.138	0.391
Obsessive-compulsive disorder	Cathepsin B	94	1.065	0.951 – 1.193	0.275
	Cathepsin E		1.035	0.914 – 1.171	0.587
	Cathepsin F		0.922	0.797 – 1.067	0.276
	Cathepsin G		1.040	0.904 – 1.196	0.585
	Cathepsin H		0.945	0.872 – 1.023	0.162
	Cathepsin O		0.977	0.804 – 1.187	0.816
	Cathepsin S		0.981	0.885 – 1.087	0.710
	Cathepsin L2		1.104	0.924 – 1.319	0.276
	Cathepsin Z		1.057	0.922 – 1.212	0.425

Note: Asterisk (*) represents $p < 0.05$.

Abbreviations: CI: Confidence interval; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

Table S7. Cochran's Q test and Mendelian randomization-Egger intercept results in multivariable Mendelian randomization analysis

Outcome	IVW-Q test		Mendelian randomization-Egger		
	Q-statistic	Q-p-value	Intercept	SE	p-value
Schizophrenia	85.490	0.465	0.001	0.005	0.845
Bipolar disorder	76.520	0.733	0.007	0.004	0.146
Depression	87.607	0.402	-0.002	0.002	0.126
Anorexia nervosa	93.430	0.249	-0.009	0.007	0.172
Attention-deficit hyperactivity disorder	88.600	0.373	0.003	0.006	0.649
Autism spectrum disorder	91.850	0.287	0.014	0.013	0.281
Anxiety disorders	97.822	0.105	-0.001	0.002	0.663
Panic disorder	100.273	0.123	-0.005	0.005	0.259
Obsessive-compulsive disorder	91.366	0.299	0.001	0.007	0.859

Abbreviations: IVW: Inverse-variance weighted; SE: Standard error.