Bidirectional Mendelian randomization analysis of shared genetic signals between coexisting neurodegenerative disorders to decipher underlying causal pathways

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Running head: Genetic etiology of neurodegeneration

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ABSTRACT

OBJECTIVE

To investigate whether coexistence of various neurodegenerative disorders is coincidental or biologically connected.

DESIGN

Two sample Mendelian randomization using summary effect estimates

SETTING

Genetic data taken on various neurodegenerative disorders from various cohorts comprising individuals predominantly of European ancestry.

PARTICIPANTS

International Genomics of Alzheimer's patients (IGAP), project MinE, International Age-related Macular Degeneration Consortium (IAMDGC), International Multiple Sclerosis Genetics Consortium (IMSGC), International Parkinson's Disease Genomics Consortium (IPDGC)

MAIN OUTCOME MEASURES

Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Age related macular degeneration (AMD), Multiple sclerosis (MS) and Parkinson's disease (PD).

RESULTS

A Bonferroni corrected threshold of P=0.005 was considered to be significant, and P<0.05 was considered suggestive of evidence for a potential association. I observed a risky effect of PD on ALS (OR = 1.126, 95% CI = 1.059-1.198, P = 0.005). Using AD as exposure and PD as outcome, I observed a risky effect of AD on PD using all the MR methods with strongest results using MBE method (OR = 2.072, 95% CI = 1.006-4.028, P = 0.0416). Genetic predisposition to AD was further observed to be a risky for AMD (OR = 1.759, 95% CI = 1.040-1.974, P = 0.0363). On the contrary, AMD was observed to be strongly protective towards MS (OR = 0.861, 95% CI = 0.776-0.955, P = 0.0059).

CONCLUSIONS

My findings are consistent with the previously observed relative occurrence of co-existing neurodegenerative diseases or overlapping symptoms among neurodegenerative diseases.

Introduction

It is not uncommon to see cases of neurodegeneration in clinical practice showing temporal development of one neurodegenerative disorder after another. For instance, observational studies have shown higher risk of Parkinson's disease (PD) and Alzheimers' disease (AD) among patients with a diagnosis of neovascular age-related macular degeneration (AMD)[1-4]. Occasional case reports of co-existence of Multiple sclerosis (MS) with Alzheimer's disease (AD) have also emerged in the literature[5]. Furthermore, the co-existence of Amyotrophic lateral sclerosis (ALS) with Frontotemporal dementia (FTD) had recently lead to revises consensus criteria for the diagnosis of FTD in ALS[6].

Not surprisingly, most neurodegenerative diseases share certain clinical and pathological features. Furthermore, a number of genetic studies have time and again have also shown existence of shared genetic aetiology[7-9]. It is common to see overlapping symptoms among various neurodegenerative disorders. For instance, up to 50% of AD cases exhibit aggregation of alpha-synuclein into Lewy bodies, a characteristic seen in PD cases[10]. Furthermore, degeneration of retinal layer, a characteristic of AMD has also been reported in cases with ALS and MS[11, 12]. Of all the co-existing neurodegenerative, presence of ALS, parkinsonism and dementia together is the most well characterized combination often reported in specific geographic locations and known by several name such as kii-ALS or Guam-ALS or ALS-PDC[13, 14].

It has been long debated whether co-existence of neurodegenerative disorders is purely coincidental or there is a causal relationship in between them. However, the varying latent phases of different neurodegenerative disorders make it difficult to interpret the exact relationship between the co-existing disorders. With age as a major confounding factor in observational studies, Mendelian randomization (MR) methodology could provide an alternative solution by providing life-long effect estimates using genetic variants as proxy pseudorandomized markers of neurodegenerative diseases[15]. Henceforth, the objective of the current study was to explore the causal relationships among different neurodegenerative disorders using MR approach.

Methods

A two-sample MR approach was applied to explore the relationship among six most commonly occurring neurodegenerative disorders namely Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Age-related macular degeneration (AMD), Frontotemporal dementia (FTD), Multiple sclerosis (MS) and Parkinson's disease (PD)[16-20]. I employed latest available summary GWAS datasets for the present study to prioritize genetic instruments for each of the neurodegenerative disorder. I used inverse variance weighted method as the main method to generate unconfounded estimates using the summary statistics from respective GWAS datasets to explore the relationship between each pair of neurodegenerative disorder. A Bonferroni corrected threshold of P=0.005 (as ten pairs of neurodegernative disorders were compared) was considered to be significant, and P<0.05 was considered suggestive of evidence for a potential association.

I also generated causal estimates adjusted for presence of potential pleiotropic variants by employing additional MR methods. The heterogeneity in the effect estimates were judged using MR-Egger, I2 and Cochrane-Q statistics. Lastly, sensitivity analysis was conducted to check reliability of estimates by excluding variants known to be directly involved in specific

neurodegenerative disorder as an outcome, and variants believed to be potential confounders between pair of neurodegenerative disorder under consideration.

Results

All the datasets used in the study have been shown in **Table 1**. In addition, complete summary statistics used for causal analysis is provided in **Supplementary table 1**. The results from direct and reverse causal estimate analysis have been provided in **Table 2a to 2e**. I observed a risky effect of PD on ALS (OR = 1.126, 95% CI = 1.059-1.198, P = 0.005). The risky effect was further retained using IVW, MR-Egger and WME method. Furthermore, a weak bidirectional relationship was observed between AD and PD. Using AD as exposure and PD as outcome, I observed a risky effect of AD on PD using all the MR methods with strongest results using MBE method (OR = 2.072, 95% CI = 1.006-4.028, P = 0.0416). A moderate risky effect of PD on AD was further observed using WME method (OR = 1.013, 95% CI = 1.006-1.019, P = 0.0606).

Genetic predisposition to AD was further observed to be a risky for AMD (OR = 1.759, 95% CI = 1.040-1.974, P = 0.0363). On the contrary, AMD was observed to be strongly protective towards MS using MR-Egger method in the presence of significant pleiotropy (MR-Egger intercept p-value = 0.0481, OR = 0.861, 95% CI = 0.776-0.955, P = 0.0059).

Discussion

The present study is the first study to comprehensively explore causal relationship among various neurodegenerative disorders. My results strongly confirm the genetic relationship between PD, ALS and PD as observed in the case of patients with kii-ALS or Guam-ALS or ALS-PDC. My results further suggest risky and protective effect of AMD towards AD and MS which is consistence with the relative prevalence of retinal degeneration seen in cases of AD and MS (See **Supplementary table 2**).

My study has several strengths and limitations. It is one of the most comprehensive study exploiting the genetics of neurodegenerative disorders to understand the relationship among different disorders. However, differential genomic coverage and different sample sizes of different datasets make it difficult to compare the results. It is quite possible that healthy controls used in different GWAS datasets may be overlapping, leading to the risk of bias in the findings. Nevertheless, I used improved version of IVW method which takes care of these biases. Another limitation could be my inability to explore causality using different types of dementias including Frontotemporal dementia (FTD) which is known to occur in combination with ALS, as it was observed that FTD dataset was highly underpowered with sample size <5000 individuals.

In future, it would be important to dissect different biological pathways using relevant genetic instrument for each pair of relationships. Nevertheless, my study shows utility of genetic data to unearth important biological findings and could enhance our understanding of interconnected etiopathologies of neurodegenerative disorders. Moreover, the finding could impact the diagnosis and management of neurodegenerative disorders.

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Table 1. Details of discovery GWAS datasets explored and prioritized instruments used for the main analysis in the present study.

S.No.	Exposure	Source study	Maximum sample size	GWAS study cohort	Number of SNPs analyzed	P	Number of significant SNPs (pre-clumping)	Number of significant SNPs (post-clumping)	Average F-statistics (median (range))
1	Alzheimer's disease (AD) (AD)	Jansen et al. 2018	71880 cases/ 383,378 controls	Discovery	133,672,99	5×10^{-8}	2357	26	42.2 (30.2-422.5)
2	Amyotrophic lateral sclerosis (ALS)	van Rheenen et al. 2016	12577 cases/ 23475 controls	Discovery	870, 945,2	5 x 10-8	125	4	37.2 (32.2-80.1)
3	Age-related macular degeneration (AMD)	Fritsche et al. 2016	16144 cases/17832 controls	Discovery	120,238,39	5×10^{-8}	7218	42	47.5 (29.2-382.5)
4	Multiple sclerosis (MS) (MS)	Patsopoulos et al. 2017	47351 cases/ 68284 controls	Discovery	859, 365,0	5×10^{-8}	26403	74	41.9 (29.8-561.9)
5	Parkinson's disease (PD) (PD)	Nalls et al. 2018	33,674 cases/ 449, 056 controls	Discovery	175,137,73	5×10^{-8}	3465	23	43.6 (30.0-181.5)

*Clumping was done using TwoSampleMR R package

Table 2a. Causal effect estimates exploring influence of various neurodegenerative disorders on Alzheimer's disaease (AD).

	MR methodology	Genetic Instruments	Causal effect estimates			Tests of heterogeneity	
		Number of SNPs	OR	95% CI	P		
Exposure		**Alzheimer's disease (Outcome)**					
Amyotrophic lateral sclerosis (ALS)	IVW	4	1,016	0.968-1.066	0.3729	MR-Egger intecept (p-value)	0.9244
	MR-Egger		1,022	0.799-1.308	0.7416	I square (IVW)	0.5325
	WME		1,018	1.004-1.032	0.2873	Cochrane Q-test (IVW) (p-value)	0.0930
	MBE		1,032	1.004-1.061	0.1101	Rucker's Q-test (p-value)	0.0409
						Rucker's test statistic/ Cochrane Q-statistics	0.9962
Age-related macular degneration (AMD)	IVW	40	1,032	0.994-1.072	0.9850	MR-Egger intecept (p-value)	0.4064
	MR-Egger		1,055	0.988-1.127	0.1055	I square (IVW)	0.8286
	WME		1,002	0.999-1.006	0.5548	Cochrane Q-test (IVW) (p-value)	0.0000
	MBE		1,003	0.995-1.010	0.4924	Rucker's Q-test (p-value)	0.0000
						Rucker's test statistic/ Cochrane Q-statistics	1.7613
Multiple sclerosis (MS)	IVW	69	0.999	0.996-1.004	0.9599	MR-Egger intecept (p-value)	0.4847
	MR-Egger		0.998	0.993-1.004	0.5790	I square (IVW)	0.1383
	WME		1,001	0.998-1.003	0.7979	Cochrane Q-test (IVW) (p-value)	0.1720
	MBE		1,000	0.995-1.005	0.8952	Rucker's Q-test (p-value)	0.1626
						Rucker's test statistic/ Cochrane Q-statistics	0.9924
Parkinson's disease (PD)	IVW	23	1,010	0.995-1.026	0.1762	MR-Egger intecept (p-value)	0.1165
	MR-Egger		1,039	1.000-1.079	0.0506	I square (IVW)	0.7311
	WME		1,013	1.006-1.019	**0.0606**	Cochrane Q-test (IVW) (p-value)	0.0000
	MBE		1,019	0.987-1.052	0.2598	Rucker's Q-test (p-value)	0.0000
						Rucker's test statistic/ Cochrane Q-statistics	0.8880

Table 2b. Causal effect estimates exploring influence of various neurodegenerative disorders on Amyotrophic lateral sclerosis (ALS).

	MR methodology	**Genetic Instruments**	**Causal effect estimates**			**Tests of heterogeneity**	
		Number of SNPs	OR	95% CI	P		
Exposure		**Amyotrophic lateral sclerosis (ALS) (Outcome)**					
Alzheimer's disease (AD)	IVW	25	0.996	0.623-1.591	0.9849	MR-Egger intecept (p-value)	0.3992
	MR-Egger		1,729	0.422-7.083	0.4299	I square (IVW)	0.0000
	WME		1,327	0.948-1.857	0.4087	Cochrane Q-test (IVW) (p-value)	0.6550
	MBE		1,584	0.497-5.043	0.4443	Rucker's Q-test (p-value)	0.6395
						Rucker's test statistic/ Cochrane Q-statistics	0.9670
Age-related macular degeneration (AMD)	IVW	42	0.986	0.945-1.030	0.5229	MR-Egger intecept (p-value)	0.4077
	MR-Egger		1,012	0.938-1.092	0.7495	I square (IVW)	0.1823
	WME		1,002	0.973-1.032	0.9539	Cochrane Q-test (IVW) (p-value)	0.1550
	MBE		1,015	0.948-1.086	0.6724	Rucker's Q-test (p-value)	0.1459
						Rucker's test statistic/ Cochrane Q-statistics	0.9857
Multiple sclerosis (MS)	IVW	72	1,008	0.984-1.033	0.4934	MR-Egger intecept (p-value)	0.3323
	MR-Egger		1,020	0.986-1.054	0.2464	I square (IVW)	0.0269
	WME		1,034	1.015-1.053	0.0786	Cochrane Q-test (IVW) (p-value)	0.4134
	MBE		1,023	0.992-1.056	0.1566	Rucker's Q-test (p-value)	0.4151
						Rucker's test statistic/ Cochrane Q-statistics	
Parkinson's disease (PD)	IVW	22	1,126	1.059-1.198	**0.0006**	MR-Egger intecept (p-value)	0.1318
	MR-Egger		1,280	1.068-1.533	**0.0099**	I square (IVW)	0.0000
	WME		1,111	1.064-1.161	**0.0239**	Cochrane Q-test (IVW) (p-value)	0.6965
	MBE		1,083	0.928-1.264	0.3248	Rucker's Q-test (p-value)	0.7844
						Rucker's test statistic/ Cochrane Q-statistics	0.8619

Table 2c. Causal effect estimates exploring influence of various neurodegenerative disorders on Age-related macular degeneration (AMD).

	MR methodology	**Genetic Instruments**	**Causal effect estimates**			**Tests of heterogeneity**	
		Number of SNPs	OR	95% CI	P		
Exposure		**Age-related macular degeneration (AMD) (Outcome)**					
Alzheimer's disease (AD)	IVW	26	1,759	1.040-2.974	**0.0363**	MR-Egger intecept (p-value)	0.2093
	MR-Egger		3,150	1.083-9.162	**0.0362**	I square (IVW)	0.3513
	WME		1,678	1.238-2.275	0.1010	Cochrane Q-test (IVW) (p-value)	0.0410
	MBE		1,683	0.791-3.581	0.1886	Rucker's Q-test (p-value)	0.0571
						Rucker's test statistic/ Cochrane Q-statistics	0.9295
Amyotrophic lateral sclerosis (ALS)	IVW	4	0.924	0.679-1.256	0.4717	MR-Egger intecept (p-value)	0.4079
	MR-Egger		1,209	0.369-3.959	0.5629	I square (IVW)	0.3516
	WME		0.985	0.900-1.078	0.8782	Cochrane Q-test (IVW) (p-value)	0.2013
	MBE		1,015	0.841-1.225	0.8879	Rucker's Q-test (p-value)	0.2119
						Rucker's test statistic/ Cochrane Q-statistics	0.6708
Multiple sclerosis (MS)	IVW	68	0.976	0.939-1.015	0.2239	MR-Egger intecept (p-value)	0.9725
	MR-Egger		0.978	0.870-1.099	0.7054	I square (IVW)	0.2083
	WME		0.968	0.943-0.993	0.2107	Cochrane Q-test (IVW) (p-value)	0.0717
	MBE		0.932	0.817-1.064	0.3023	Rucker's Q-test (p-value)	0.0608
						Rucker's test statistic/ Cochrane Q-statistics	1.0002
Parkinson's disease (PD)	IVW	23	0.953	0.901-1.007	0.0863	MR-Egger intecept (p-value)	0.7136
	MR-Egger		0.931	0.806-1.074	0.3098	I square (IVW)	0.0000
	WME		0.929	0.896-0.963	**0.0556**	Cochrane Q-test (IVW) (p-value)	0.7723
	MBE		0.927	0.836-1.028	0.1668	Rucker's Q-test (p-value)	0.7281
						Cochrane Q-staitics/Rucker's test statistic	0.9929

Table 2d. Causal effect estimates exploring influence of various neurodegenerative disorders on Multiple sclerosis (MS).

	MR methodology	Genetic Instruments	Causal effect estimates			Tests of heterogeneity	
		Number of SNPs	OR	95% CI	P		
Exposure		**Multiple sclerosis (MS) (Outcome)**					
Alzheimer's disease (AD)	IVW	26	1,597	0.257-9.908	0.6020	MR-Egger intecept (p-value)	0.7683
	MR-Egger		3,032	0.025-374.146	0.6388	I square (IVW)	0.7059
	WME		1,305	0.917-1.857	0.4577	Cochrane Q-test (IVW) (p-value)	0.0000
	MBE		1,445	0.563-3.708	0.4508	Rucker's Q-test (p-value)	0.0000
						Rucker's test statistic/ Cochrane Q-statistics	1.0094
Amyotrophic lateral sclerosis (ALS)	IVW	3	0.998	0.629-1.582	0.9860	MR-Egger intecept (p-value)	0.3454
	MR-Egger		1,822	0.016-204.153	0.3528	I square (IVW)	0.4493
	WME		0.976	0.888-1.072	0.8186	Cochrane Q-test (IVW) (p-value)	0.1627
	MBE		1,142	0.940-1.388	0.3138	Rucker's Q-test (p-value)	0.3285
						Rucker's test statistic/ Cochrane Q-statistics	0.2629
Age-related macular degeneration (AMD)	IVW	35	**0.939**	**0.884-0.997**	**0.0409**	MR-Egger intecept (p-value)	0.0481
	MR-Egger		**0.861**	**0.776-0.955**	**0.0059**	I square (IVW)	0.4715
	WME		0.966	0.930-1.004	0.3816	Cochrane Q-test (IVW) (p-value)	0.0013
	MBE		1,065	0.955-1.187	0.2652	Rucker's Q-test (p-value)	0.0055
						Cochrane Q-statistics/Rucker's test statistic	0.8898
Parkinson's disease (PD)	IVW	22	1,042	0.976-1.112	0.2030	MR-Egger intecept (p-value)	0.5749
	MR-Egger		1,087	0.918-1.287	0.3145	I square (IVW)	0.1214
	WME		1,049	1.005-1.095	0.2722	Cochrane Q-test (IVW) (p-value)	0.2978
	MBE		1,004	0.863-1.167	0.9627	Rucker's Q-test (p-value)	0.2655
						Rucker's test statistic/ Cochrane Q-statistics	0.9826

Table 2e. Causal effect estimates exploring influence of various neurodegenerative disorders on Parkinson's disease (PD).

	MR methodology	Genetic Instruments	Causal effect estimates			Tests of heterogeneity	
		Number of SNPs	OR	95% CI	P		
Exposure		**Parkinson's disease (PD) (Outcome)**					
Alzheimer's disease (AD)	IVW	26	2,189	0.996-4.812	**0.0510**	MR-Egger intecept (p-value)	0.3779
	MR-Egger		1,270	0.289-5.584	0.7418	I square (IVW)	0.5830
	WME		1,951	1.415-2.688	**0.0477**	Cochrane Q-test (IVW) (p-value)	0.0001
	MBE		2,072	1.066-4.028	**0.0416**	Rucker's Q-test (p-value)	0.0001
						Rucker's test statistic/ Cochrane Q-statistics	0.9961
Amyotrophic lateral sclerosis (ALS)	IVW	4	0.995	0.784-1.263	0.9514	MR-Egger intecept (p-value)	0.8013
	MR-Egger		1,053	0.425-2.606	0.8297	I square (IVW)	0.0000
	WME		0.998	0.915-1.089	0.9844	Cochrane Q-test (IVW) (p-value)	0.6030
	MBE		0.952	0.775-1.171	0.6749	Rucker's Q-test (p-value)	0.4118
						Rucker's test statistic/ Cochrane Q-statistics	0.9564
Age-related macular degeneration (AMD)	IVW	38	0.989	0.945-1.035	0.6427	MR-Egger intecept (p-value)	0.3854
	MR-Egger		0.962	0.887-1.042	0.3300	I square (IVW)	0.1454
	WME		0.976	0.947-1.005	0.4144	Cochrane Q-test (IVW) (p-value)	0.2205
	MBE		0.981	0.918-1.047	0.5647	Rucker's Q-test (p-value)	0.2139
						Rucker's test statistic/ Cochrane Q-statistics	0.9797
Multiple sclerosis (MS)	IVW	70	1,010	0.978-1.044	0.5289	MR-Egger intecept (p-value)	0.8676
	MR-Egger		1,014	0.958-1.074	0.6179	I square (IVW)	0.0776
	WME		0.984	0.961-1.007	0.4817	Cochrane Q-test (IVW) (p-value)	0.2954
	MBE		0.983	0.932-1.038	0.5438	Rucker's Q-test (p-value)	0.2673
						Rucker's test statistic/ Cochrane Q-statistics	0.9998