Utilizing Genetic and Clinical Factors to Predict Depression Risk after the Onset of Multiple Sclerosis

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BACKGROUND

- Persons with multiple sclerosis (PwMS) are disproportionately diagnosed with clinical depression compared to both the general population and those with other chronic diseases.
- Clinical factors predisposing PwMS for depression are poorly characterized.
- Although several genetic variants, including the apolipoprotein (*APOE*) alleles, have been associated with depressive disorders, their roles in assessing depression outcomes for PwMS have not been investigated.

OBJECTIVE

To determine genetic and non-genetic factors conferring risk for depression after onset of MS and to assess the ability of these risk factors to predict development of depression in PwMS who were depression naïve prior MS onset.

METHODS

Study Population

- Accelerated Cure Project for Multiple Sclerosis: 883 PwMS of European ancestry, recruited across 10 neurology centers across the United States with complete epidemiologic and genetic variables of interest, and did not have a history of depression prior MS onset.

Data Collection

- Clinical data were collected through a detailed survey administered by certified neurologists and trained ACP staff.
- Genomic data was collected through blood-derived biospecimens at baseline.

Statistical analyses

- An optimized depression-risk survival model generated with non-genetic variables was selected using a 150-replication bootstrap resampling validated AUC. The final model used was from a backwards stepwise regression.
- The genetic model was constructed to include APOE alleles and a genetic risk score (GRS) derived from 30 established depression risk variants, adjusted for population stratification.
- The final predictive model for depression was generated by combining the clinical and genetic risk factors in a Cox proportional hazards model.

RESULTS

- The non-genetic risk factors for depression were having a mother with history of depression, obesity, hypertension, mononucleosis, obstructive pulmonary disease, and facial motor, sensory, physical, and affect/mood symptoms at onset (**Figures 2 & 3**, **Table 3**).
- For the genetic variables, the Depression GRS and APOE alleles alone produced a significant model for predicting depression (p= 0.03; **Table 2**).
- Having *APOE* E4/E4 genotype was a risk factor for depression while being an *APOE* E2 carrier was protective in PwMS (**Figure 1**, **Tables 2 & 3**).
- The strongest predictors of depression were APOE, reported a mother with history of depression, hypertension, and obstructive pulmonary disease.

LIMITATIONS

- Non-racially diverse population of only white individuals
- SNPs used to construct the GRS were general risk variants for depression, not specific to PwMS

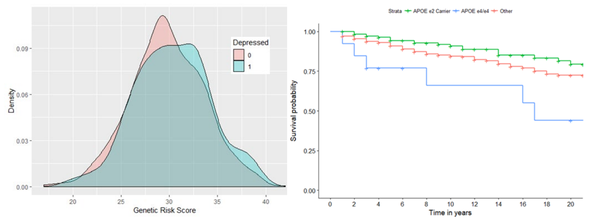
References used to create the Depression GRS

1. Howard DM, Adams MJ, Shirali M, Clarke TK, Marioni RE, Davies G, et al. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat Commun. 2018;9(1):1470.
2. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668-81.

TABLE 1. Baseline Characteristics

Number of Subjects		Total 883	No Depression 705	Depression 178	p
Female (%)		210 (23.8)	171 (24.3)	39 (21.9)	0.577
Age (median [IQR])		48.00 [39.00, 55.00]	47.00 [38.00, 54.00]	50.00 [42.25, 56.00]	<0.001
Disease Duration (median [IQR])		12.00 [6.00, 20.50]	11.00 [6.00, 19.00]	18.00 [9.25, 26.00]	<0.001
Age of MS Onset (median [IQR])		32.87 (9.56)	33.39 (9.69)	30.81 (8.75)	0.001
Primary Progressive Subtype (%)		65 (7.4)	51 (7.2)	14 (7.9)	0.899
Years of Education (median [IQR])		16.00 [14.00, 18.00]	16.00 [14.00, 18.00]	16.00 [14.00, 17.00]	0.043
Smoker within 5 Years of Onset (%)		313 (35.4)	229 (32.5)	84 (47.2)	<0.001
Pre-Existing Conditions at MS Onset					
Vascular Disease (%)		128 (14.5)	96 (13.6)	32 (18.0)	0.175
Pre-Diagnosed Obesity (%)		48 (5.4)	33 (4.7)	15 (8.4)	0.074
Hypercholesterolemia (%)		70 (7.9)	55 (7.8)	15 (8.4)	0.904
Chronic Obstructive Pulmonary Disease (%)		48 (5.4)	31 (4.4)	17 (9.6)	0.012
Hypertension (%)		38 (4.3)	29 (4.1)	9 (5.1)	0.729
Heart Disease (%)		2 (0.2)	1 (0.1)	1 (0.6)	0.363
Non-depressive Mental Disorder(s) (%)*		12 (1.4)	8 (1.1)	4 (2.2)	0.434
Neurological Disorder(s) (%)		186 (21.1)	154 (21.8)	32 (18.0)	0.304
Physical Disorder(s) (%)		184 (20.8)	140 (19.9)	44 (24.7)	0.186
Infectious Mononucleosis (%)		259 (29.3)	200 (28.4)	59 (33.1)	0.247
Family History					
Multiple Sclerosis (%)		172 (25.3)	140 (25.5)	32 (24.8)	0.968
Any Autoimmune Disease (%)		632 (75.9)	504 (75.3)	128 (78.0)	0.531
Depression (%)		373 (42.2)	279 (39.6)	94 (52.8)	0.002
Genetic Variables					
Genetic Risk Score (Mean (SD))		29.91 (3.83)	29.80 (3.82)	30.35 (3.87)	0.087
APOE Category (%)	E2 Carrier	699 (79.2)	144 (20.4)	27 (15.2)	0.022
	E4/E4	171 (19.4)	7 (1.0)	6 (3.4)	
	Other	13 (1.5)	554 (78.6)	145 (81.5)	

FIGURE 1. Genetic Variables and Depression Outcome



CONCLUSIONS

- We presented a framework for including genetic information with clinical information to improve prognostication of depression in PwMS. Several readily accessible factors available at MS onset confer increased risk of downstream depression and can be used to identify PwMS at high risk for depression (**Figure 2**). Interestingly, genetic risk variants for depression risk variants significantly improved predicting depression in PwMS.

FIGURE 2. Clinical Nomogram for Predicting Depression Risk

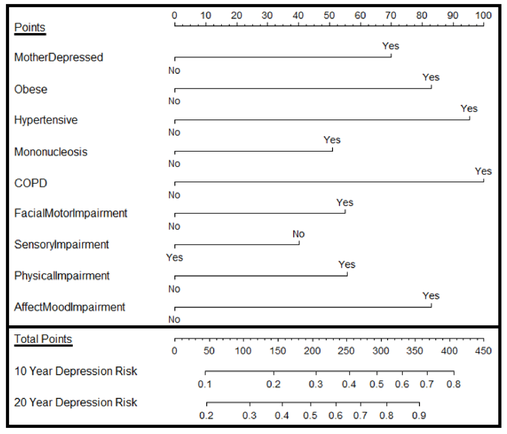


FIGURE 3. Hazards Ratios for Depression in Clinical Risk Factor Model

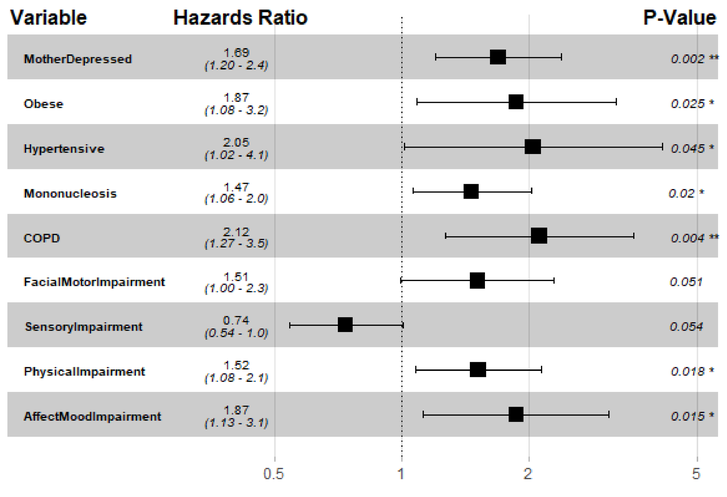


TABLE 2. Genetic Variables and Risk of Depression

Variable	Crude Hazards Ratio*	Adjusted Hazards Ratio**	P-Value
Genetic Risk Score	1.24 (0.98, 1.57)	1.27 (1.00, 1.62)	0.05
APOE E2 Carrier	0.64 (0.42, 0.99)	0.62 (0.43, 1.01)	0.06
APOE E4/E4	2.25 (0.99, 5.13)	2.35 (1.02, 5.41)	0.04

*Adjusted for ancestry, **Adjusted for ancestry and other genetic variables

TABLE 3. Risk Factors for Developing Depression

Risk Factor	Hazards Ratio	P	10-Year HR*	P
Mother Depressed	**1.71 (1.21, 2.44)**	0.003	**1.99 (1.28, 3.10)**	0.002
Pre-existing Medical Conditions				
Physical Disorder	**1.53 (1.08, 2.17)**	0.016	**1.64 (1.07, 2.52)**	0.024
Obese	**1.89 (1.08, 3.30)**	0.025	1.75 (0.88, 3.48)	0.113
Hypertension	**2.08 (1.03, 4.21)**	0.043	2.11 (0.97, 4.57)	0.059
Infectious Mononucleosis	**1.46 (1.05, 2.03)**	0.024	1.26 (0.83, 1.92)	0.272
COPD	**2.09 (1.24, 3.52)**	0.006	1.75 (0.92, 3.35)	0.089
Impaired Domains				
Facial Motor	1.36 (0.89, 2.10)	0.156	0.84 (0.45, 1.57)	0.578
Sensory	0.77 (0.56, 1.05)	0.094	0.79 (0.53, 1.18)	0.250
Affect Mood	1.73 (1.03, 2.90)	0.037	**2.22 (1.22, 4.03)**	0.009
Genetic Factors				
Genetic Risk Score	1.15 (0.90, 1.47)	0.274	1.12 (0.82, 1.53)	0.481
APOE E2 Carrier	**0.67 (0.43, 1.03)**	0.065	**0.47 (0.26, 0.88)**	0.017
APOE E4/E4	**2.23 (0.96, 5.19)**	0.063	**2.81 (1.00, 7.90)**	0.05

All hazards ratios are adjusted for other risk factors listed and ancestry, *105 events