The Role of Genetic and Non-Genetic factors in Predicting Transition to Secondary-Progressive Multiple Sclerosis

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Background

- Most persons with multiple sclerosis (MS) present with relapsing remitting (RR) MS, characterized by exacerbation and remission cycles with modest increases in neurological deficits. At some point, most individuals with RRMS will **transition** to secondary progressive (SP) MS, which is characterized by the steady accumulation of disability a potentially increasing number of functional domains.
- The transition from RRMS to SPMS is a **critical** turning point in the disease course, as the available FDA-approved therapeutics have limited effect on preventing, slowing, or reversing disability accrual experienced in the SP phase.
- While several studies have identified factors influencing the transition, we are **yet unable to predict when** this critical transition might occur. Understanding risk for transition to SPMS is extremely valuable to individuals affected with MS, who must plan for long-term disease management in both clinical and personal life.

Objective: To identify predictors of the transition from RRMS to SPMS using information available at MS onset.

Materials & Methods

Study Population: The study population included 1,295 non-Hispanic white individuals with RRMS at onset who were participants in the Accelerated Cure Project for MS, a repository of biological and epidemiologic data from participants from 10 U.S. MS specialty clinics. All participants were ≥18 years of age at onset and met diagnostic criteria.

Outcome: We sought to identify baseline factors predictive of the transition from RRMS to SPMS within **10 years of onset** and **20 years of onset**. We explored binary outcomes (transition within time frame = 1, no transition = 0) and time-to-event outcomes (event = transition to SPMS, time measured in years).

Predictors: Predictors included sociodemographic factors, clinical variables, comorbid conditions, and symptoms at MS onset. Additionally, established genetic risk factors were incorporated into the models: *HLA-A*02*, *HLA-DRB1*15:01*, and a genetic risk score (GRS) based on 200 risk variants outside chromosome 6p21[1].

Statistical Models: Two models were conducted: **1. Predicting transition**. Logistic regression with LASSO variable selection, followed by Backwards Stepwise Elimination with a p-value threshold of 0.15, was used to identify non-genetic factors predictive of SPMS transition in 10 and 20 years (**Table 2**). **2. Identifying risk factors for transition.** Cox Proportional Hazards (PH) models with forward stepwise elimination (α=0.05) were used to identify non-genetic risk factors for time to SPMS transition **(Table 3)**. MS genetic risk factors were explored iteratively in the final models accounting for European genetic ancestry.

Table 1: Study Population Demographics

Variable Type	Variable	All Subjects	RRMS	SPMS
	N	1295	1098 (84.8%)	197 (15.2%)
Demographics	Age at RRMS Onset	32 (25, 39)	32 (26, 39)	30 (25, 39)
	Male	21.85% (283)	20.04% (220)	63 (31.98%)
	Smoker Within 5 Years of RRMS Onset	33.98% (440)	33.15% (364)	38.58% (76)
	History of Infectious Mononucleosis	29.73% (385)	30.33% (333)	26.40% (52)
	Years of Education	16 (14, 18)	16 (14, 18)	16 (14, 18)
Disease-Specific	Time Between First Two Relapses	2 (1, 5)	1.8 (1, 4)	3 (1, 6.75)
	Relapses Within 2 Years of MS Onset	2 (1, 3)	2 (1, 3)	2 (1, 3)
Symptoms	Total Number of Symptoms	2 (1, 4)	2 (1, 4)	1 (1, 3)
	Motor	46.56% (603)	46.99% (516)	44.16% (87)
	Cerebellar	32.20% (417)	32.33% (355)	31.47% (62)
	Spasticity	12.59% (163)	13.21% (145)	9.14% (18)
	Optic Nerve	27.88% (361)	27.23% (299)	31.47% (62)
	Facial (motor)	10.35% (134)	11.20% (123)	5.58% (11)
	Facial (sensory)	3.55% (46)	3.73% (41)	2.54% (5)
	Sensory	51.89% (672)	52.73% (579)	47.21% (93)
	Brainstem/Bulbar	30.73% (398)	31.88% (350)	24.37% (48)
	Cognitive	11.20% (145)	11.84% (130)	7.61% (15)
	Sexual	5.41% (70)	5.65% (62)	4.06% (8)
	Bladder/Bowel	11.58% (150)	12.39% (136)	7.11% (14)
	Affect Mood	10.27% (133)	11.11% (122)	5.58% (11)
	Fatigue	26.95% (349)	28.23% (310)	19.80% (39)
Comorbidities	Obesity	8.42% (109)	9.29% (102)	3.55% (7)
	High Cholesterol	7.88% (102)	7.56% (83)	9.64% (19)
	High Blood Pressure	5.87% (76)	6.10% (67)	4.57% (9)
	Type II Diabetes	0.77% (10)	0.64% (7)	1.52% (3)
	Neurological Diseases	24.02% (311)	25.96% (285)	13.20% (26)
	Other Physical Diseases	22.9% (296)	23.9% (262)	17.8% (35)
	Mental Disorders	16.9% (219)	17.9% (196)	12.2% (24)
	Cancer	2.78% (36)	2.82% (31)	2.54% (5)
	Autoimmune Diseases	18.9% (245)	20.0% (220)	13.2% (26)
Genetics	GRS	262 (256, 267)	261 (255, 267)	262.5 (257, 268)
	*HLA-A*02* (0 Alleles)	60.98% (711)	59.56% (589)	68.93% (122)
	*HLA-A*02* (1 Allele)	32.59% (380)	33.47% (331)	27.68% (49)
	*HLA-A*02* (2 Alleles)	6.43% (75)	6.98% (69)	3.39% (6)
	*HLA-DRB1*15:01* (0 Alleles)	53.44% (644)	52.54% (537)	58.47% (107)
	*HLA-DRB1*15:01* (1 Allele)	40.41% (487)	41.10% (420)	36.61% (67)
	*HLA-DRB1*15:01* (2 Alleles)	6.14% (74)	6.36% (65)	4.92% (9)

Table 1. Variables to which LASSO and Forward Stepwise Selection was applied for the Logistic and Cox PH models, respectively. Quantitative variables are described by median (IQR) within each disease subtype. Categorical and binary variables are described by % (n) per level within each disease subtype.

Results

Table 2: Logistic Model Predictors

	Transition Within 10 Years*			Transition Within 20 Years**		
Predictor	Odds Ratio	95% Confidence Interval	p-value	Odds ratio	95% Confidence Interval	p-value
Age of MS Onset	**1.08**	**1.05, 1.12**	***4.47E-06***	**1.15**	**1.12, 1.20**	***7.15E-15***
Sex (M)	**4.42**	**2.35, 8.39**	***4.32E-06***	1.58	0.89, 2.79	0.117
Years of Education				0.93	0.85, 1.02	0.123
Time to 2nd Relapse (2-5)	**0.50**	**0.26, 0.97**	***0.042***	0.94	0.51, 1.72	0.841
Time to 2nd Relapse (6+)	**0.20**	**0.07, 0.45**	***0.0004***	**0.43**	**0.23, 0.81**	***0.009***
Relapses within first two years (2-3)	0.53	0.20, 1.35	0.188			
Relapses within first two years (4+)	1.80	0.59, 5.20	0.284			
High Blood Pressure	2.20	0.69, 6.48	0.164			
Neurological Diseases				**0.31**	**0.14, 0.66**	***0.003***
Cancer	**7.36**	**1.80, 27.35**	***0.004***			
Spasticity				**0.41**	**0.16, 0.96**	***0.048***
Facial motor	0.31	0.05, 1.15	0.133			
Bladder/bowel				0.45	0.17, 1.10	0.089
GRS	1.03	0.98, 1.07	0.238	0.99	0.96, 1.03	0.647
*HLA-A*02*	0.57	0.30, 1.01	0.068	**0.50**	**0.30, 0.82**	***0.007***
*HLA-DRB1*15:01*	1.02	0.57, 1.78	0.939	1.17	0.74, 1.86	0.49

* Cases were defined as any individual who transitioned to SPMS within 10 years of RRMS onset. Controls were defined as any individual who had RRMS for at least 10 years before transition to SPMS.
** Cases were defined as any individual who transitioned to SPMS within 20 years of RRMS onset. Controls were defined as any individual who had RRMS for at least 20 years before transition to SPMS.

Table 3: Cox PH Model Predictors

	Transition at Any Time*			Transition Within 10 Years**			Transition Within 20 Years***		
Predictor	Hazard Ratio	95% Confidence Interval	p-value	Hazard Ratio	95% Confidence Interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
Age of MS Onset	**1.07**	**1.06, 1.09**	***<0.001***	**1.06**	**1.03, 1.09**	***<0.001***	**1.07**	**1.05, 1.09**	***<0.001***
Sex (M)	**1.96**	**1.45, 2.65**	***<0.001***	**2.93**	**1.75, 4.91**	***<0.001***	**1.86**	**1.30, 2.67**	***0.001***
Time to 2nd Relapse (2-5)	1.08	0.77, 1.50	0.67	0.65	0.37, 1.14	0.1345	0.86	0.59, 1.27	0.45
Time to 2nd Relapse (6+)	**0.64**	**0.45, 0.92**	***0.017***	**0.31**	**0.14, 0.72**	***0.006***	**0.54**	**0.35, 0.85**	***0.007***
Obesity							0.37	0.14, 0.99	0.05
Neurological Diseases	**0.58**	**0.38, 0.88**	***0.010***				**0.44**	**0.26, 0.76**	***0.003***
Cancer				**3.03**	**1.17, 7.86**	***0.02***			
Spasticity	**0.57**	**0.35, 0.94**	***0.026***						
Brainstem/bulbar				**0.46**	**0.23, 0.91**	***0.026***			
GRS	1.00	0.98, 1.02	0.990	1.03	1.00, 1.06	0.089	1.00	0.98, 1.03	0.706
*HLA-A*02*	**0.73**	**0.55, 0.97**	***0.027***	0.60	0.35, 1.03	0.065	**0.55**	**0.39, 0.79**	***0.001***
*HLA-DRB1*15:01*	1.02	0.78, 1.33	0.912	0.83	0.51, 1.36	0.460	0.95	0.69, 1.30	0.728

* Censoring occurred if an individual did not transition to SPMS before participating in the Accelerated Cure Project for MS.
** Censoring occurred if an individual did not transition to SPMS within 10 years of RRMS onset.
*** Censoring occurred if an individual did not transition to SPMS within 20 years of RRMS onset.

Figure 1

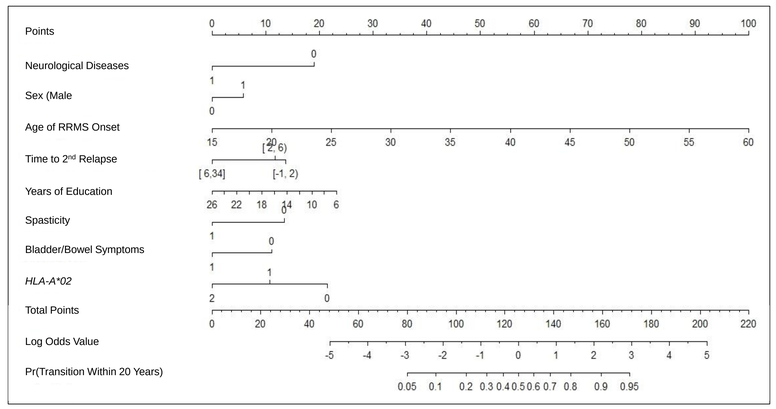

Figure 1. Nomogram for SPMS transition within 20 years (Table 2), with *HLA-A*02* allele counts adjusted for genetic ancestry. Each variable value can be ascribed a specific amount of points, which, when summed, can calculate an overall probability of transitioning to SPMS within 20 years.

Figure 2

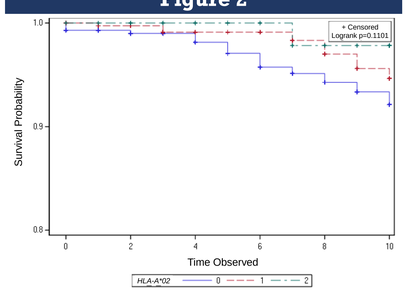

Figure 2. Kaplan Meier survival curves for *HLA-A*02* Non-Carriers (0 alleles), Heterozygotes (1 allele), and Homozygotes (2 alleles) within 10 years of RRMS onset.

Figure 3

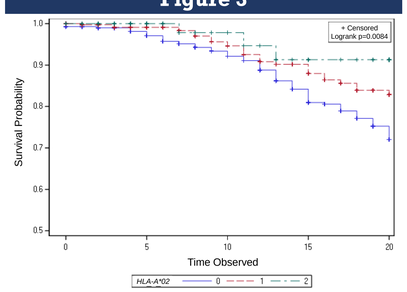

Figure 3. Kaplan Meier survival curves for *HLA-A*02* Non-Carriers (0 alleles), Heterozygotes (1 allele), and Homozygotes (2 alleles) within 20 years of RRMS onset.

1. Predicting transition (Table 2)

- The transition to SP within 10 years was predicted (α = 0.05) by comorbid cancer, being male, later age of MS onset, and shorter time to 2nd relapse.
- The transition to SP within 20 years (**Figure 1**) was predicted by comorbid neurological diseases, later age of MS onset, and shorter time to 2nd relapse. RRMS cases with spasticity or had a *HLA-A*02* allele were 60% and 50% less likely to transition, respectively.

2. Identifying risk factors for transition (Table 3)

- Risk for transitioning within 10 years was increased for having had cancer (3-fold), being male (3-fold), older age of MS onset (6% per year in age). Risk was decreased 70% for those with time to 2nd relapse >5years and 54% for those with brainstem/bulbar symptoms at onset.
- Risk for transitioning within 20 years was increased for males (86% greater) and older age at MS onset (7% per year in age). Risk was decreased for those with other neurological diseases (56% reduction), took >5 years to 2nd relapse (46% reduction), and carriers of the *HLA-A*02* variant (45% reduction per allele).
- Risk for ever transitioning was significantly greatly for males (Hazard Ratio[HR]=1.96) and those who were older at MS onset (HR=1.07 per year). Risk was decreased for those with a neurological disease (HR=0.58), took >5 years to 2nd relapse (HR=0.64), presented with spasticity (HR=0.57), or are carriers of *HLA-A*02* (HR=0.73 per allele).

Overall

- **Being male** significantly increased risk for SPMS, but interestingly was a stronger predictor of **earlier** transition to SPMS than later transition. ***HLA-A*02*** was strongly **protective** against transition to SPMS later versus earlier in the disease course (**Figure 2**) (**Figure 3**). **Neurological diseases** were **protective** against transition to SPMS – this effect was **driven** by those reporting migraines (85.5%). Six or more years between first two relapses consistently conferred decreased risk of transition and later transition across time frames.

Conclusions

- Our results demonstrate males have a higher risk of transition to SP closer to MS onset, which is consistent with prior findings[2].
- We are among the **first** to demonstrate that ***HLA-A*02***, which is protective against MS risk, appears to be protective against transition to SPMS.
- One interesting finding is the apparent protective effect of comorbid neurological disease. The neurological disease variable was defined as having at least one of a list of various neurological diseases, including Epilepsy, Bell's Palsy, Dementia, Parkinson's Disease, Amyotrophic Lateral Sclerosis, Trigeminal Neuralgia and Migraines. The **majority of subjects** (85.5%) in our sample with a comorbid neurological disease presented with migraines at MS onset. It is possible that some of these individuals might have been misdiagnosed with MS [3], as Migraines are not a traditional MS symptom.
- **Future directions** will investigate the roles of the 200 individual risk variants outside chromosome 6p21 on MS progression, and the role that comorbid conditions developed post-MS onset play in transition to SPMS

1. Patsopoulos, N. et al. 2017. doi: https://doi.org/10.1101/143933; 2. Manouchehrinia, A. et al. 2017. doi: https://doi.org/10.1177/1352458518783667; 3. Kaisey, M. et al. 2019. doi: https://doi.org/10.1016/j.msard.2019.01.048