Characterizing polyautoimmunity and familial autoimmunity in a U.S. multiple sclerosis population.

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Background

There is overlap in the genetic and non-genetic risk components across several autoimmune diseases (ADs). However, it is unclear whether polyautoimmune persons with MS (PwMS) or those with familial autoimmunity differ from sporadic PwMS. Differences may highlight distinct etiologic mechanisms and processes.

Objective

To characterize a U.S. population of PwMS with comorbid ADs and those with a familial history of autoimmunity.

Materials & Methods

Study population. The Accelerated Cure Project Repository is an open-access resource of data from PwMS recruited at 10 U.S. MS clinics (www.acceleratedcure.org). PwMS met diagnostic criteria and were ≥18 years of age at onset. There were **1,507 unrelated PwMS** for this analysis.

Polyautoimmunity and familial autoimmunity. Participants completed structured questions on **31 ADs** (excluding MS). They reported whether they had a comorbid AD and whether their parents, siblings, or other family members had an AD. PwMS were classified as polyautoimmune if they reported having a second AD. Variables for family history of autoimmunity were determined for 1st degree relatives (parents, siblings) and for any familial history (1st degree and extended relatives).

Predictors of interest. Participants provided information on MS subtype at onset, birth year, sex, race (white, black, other), years of education, being obese, smoking history, and history of MS among relatives. A subset of the participants who identified as non-Hispanic whites were genotyped by the International Multiple Sclerosis Genetics Consortium[1]. After removing genetic outliers and cases with cryptic relatedness there were **1,074 cases**. *HLA-DRB1*15:01* was determined by the tagging variant rs3135388A and *HLA-A*02* was determined by the tagging variant rs2394250T. The 200 putative risk variants outside chromosome 6p21 were directly genotyped on this platform and in Hardy Weinberg equilibrium. The GRS was derived by summing the risk alleles across the 200 variants for **1,045 cases**.

Early clinical presentation of MS. We investigated if four aspects of the early clinical presentation of MS differed in PwMS by polyautoimmunity status and by familial autoimmunity status. The outcomes of interest were age of onset, number of impaired functional domains at onset, time to second relapse from onset, and early relapse activity in the first two years after onset. Our prior work in this same study sample, investigated the contribution of genetic and non-genetic MS risk factors on these onset traits[2]. We took the final models for each onset trait and further adjusted for polyautoimmunity status and familial autoimmunity.

Statistical analysis. The backward stepwise variable selection of non-genetic predictors using logistic regression was conducted to investigate the primary questions: **Q1. What factors are associated with polyautoimmunity in PwMS?** and **Q2. What factors are associated with a PwMS reporting a family history of autoimmunity (Any AD, non-MS ADs, or MS)?** We retained non-genetic predictors with p-values ≤0.1. The final models were sequentially adjusted for HLA variants and the GRS, accounting for ancestry. We investigated individual ADs with a frequency of at least 1%, as well. AOO was natural log transformed to meet normality assumptions. The NIFDs, TT2R, and ERA were event counts with negative binomial distributions and coefficients can be interpreted as relative ratios. Our published models[2] (**Models 3-6**) for these outcomes were adjusted for polyautoimmunity status and familial autoimmunity. A two-sided alpha of 0.05 was considered significant.

Table 1: Study Population

Variable (Mean; %)		All	Poly-autoimmune		Family history of autoimmunity			
					1st degree relative		Any relative	
			Yes	No	Yes	No	Yes	No
N		1507	28%	72%	64%	36%	87%	13%
Age at interview (years)		46.3	47.8	45.7	47.0	45.7	46.3	45.4
Male		22.0	14.6	24.8	19.6	26.1	19.1	34.6
Disease duration (years)		12.8	14.0	12.4	13.6	12.0	13.1	12.2
Birth year		1962	1960	1962	1961	1962	1962	1963
Years of education (years)		15.8	16.1	15.7	15.8	16.0	15.9	15.8
Ever smoker		47.1	50.0	45.9	48.2	45.3	46.9	47.4
History of obesity		11.5	15.4	9.9	11.8	10.7	11.5	11.2
Race	White	90.2	92.2	89.5	92.4	87.3	91.1	89.4
	Black	7.4	5.9	8.0	6.3	8.6	6.9	6.7
	Other	2.3	1.9	2.5	1.3	4.2	2.0	3.9
MS among 1st degree relative	No	83.2	79.0	84.8	78.4	100	82.6	100
	Yes	9.4	10.9	8.9	15.3	0	10.9	0
MS family history	No	60.5	54.7	62.8	54.1	77.9	54.7	100
	Yes	27.1	29.3	26.3	35.4	15.2	34.8	0
Non-MS AD among 1st degree relative	No	37.3	25.0	42.1	5.2	100	24.7	100
	Yes	52.1	65.8	46.7	92.9	0	66.3	0
Non-MS familial autoimmunity	No	23.4	15.6	26.5	3.1	62.0	7.0	100
	Yes	71.3	80.9	67.6	95.7	38.0	90.9	0
***HLA-DRB1*15:01* alleles**	0	53.4	53.5	53.3	55.0	53.6	54.6	49.0
	1	40.2	39.8	40.3	38.7	40.6	39.0	45.6
	2	6.5	6.7	6.4	6.3	5.8	6.4	5.4
***HLA-A*02:01* alleles**	0	61.0	58.7	62.0	61.9	58.8	61.8	57.8
	1	32.8	33.5	32.5	32.2	34.8	32.3	34.0
	2	6.2	7.8	5.6	5.9	6.3	5.9	8.2
Genetic risk score		263.1	263.5	262.9	263.5	262.3	263.2	262.2
Age of MS onset (years)		33.5	33.7	33.4	33.4	33.8	33.2	33.2
Primary progressive		7.4%	6.1%	7.8%	6.5%	9.2%	6.8%	7.3%
No. of impaired domains at onset (median, IQR)		2 (1,4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 3)
No. of relapses in the 1st two years (median, IQR)		2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Time to 2nd relapse (years)		3.59	3.86	3.49	3.79	3.40	3.70	3.44

Table 2: Factors associated polyautoimmunity and familial autoimmunity in PwMS

Predictors		Polyautoimmunity (self)		Familial history of autoimmunity					
				Any AD		Non-MS AD		MS	
		OR	p	OR	p	OR	p	OR	p
Age		1.02	0.0024						
Female		1.83	0.00014	2.10	$2.6x10^{-5}$	2.13	$9.4x10^{-8}$		
Race	White			Ref		Ref		Ref	
	Black			0.98	0.95	0.54	0.0063	1.47	0.092
	Other			0.47	0.091	0.45	0.035	0.90	0.79
PP									
Education		1.05	0.015						
Ever smoker		1.25	0.060						
Ever obese		1.61	0.0056						
Any family history of any AD		2.36	0.00011						
Polyautoimmune		NA	NA	2.36	$9.6x10^{-5}$	1.88	$4.2x10^{-5}$	1.29	0.055
HLA-DRB1*15:01		1.03	0.76	0.85	0.27	1.00	0.97	1.16	0.16
HLA-A*02:01		1.18	0.11	0.81	0.15	0.80	0.043	1.02	0.89
GRS		1.01	0.29	1.02	0.18	1.02	0.09	1.00	0.66

Table 3: The relationships of AD family history on comorbid AD status

Comorbid AD	Frequency	Family history of autoimmunity among 1st degree relatives						*Models for Any AD family hx further adjusted for specific AD fam hx			
		MS		Non-MS		Any AD		Any AD		Specific AD	
		OR	P	OR	P	OR	P	OR	P	OR	P
Polyautoimmune (any)	28.1%	1.20	0.38	**2.28**	$5.6x10^{-10}$	**2.43**	$5.3x10^{-10}$				
Eczema	10.7%	0.91	0.76	**2.01**	0.00052	**1.87**	0.0027	1.33	0.21	**3.46**	$2.9x10^{-8}$
Hashimoto's thyroiditis	8.3%	1.17	0.64	**2.38**	0.00021	**2.55**	0.00021	1.45	0.19	**4.70**	$8.8x10^{-11}$
Psoriasis	3.9%	0.43	0.24	**3.14**	0.0011	**3.52**	0.0015	2.23	0.054	**4.19**	$1.2x10^{-5}$
Graves disease	2.9%	1.49	0.61	1.59	0.40	1.90	0.27	1.20	0.40	**4.22**	0.00054
Ulcerative Colitis	1.2%	0.65	0.68	0.62	0.33	0.62	0.36	0.45	0.18	**5.20**	0.028
Celiac disease	1.1%	1.65	0.52	**4.66**	0.04	3.77	0.08	3.58	0.10	2.52	0.39
Rheumatoid arthritis	1.1%	2.44	0.17	2.80	0.11	3.64	0.09	2.34	0.30	**4.15**	0.013
Rheumatic fever	1.0%	1.65	0.52	1.72	0.36	1.96	0.31	1.96	0.32	1.53	0.60

1. All models were adjusted for age, sex, history of smoking, history of obesity, and years of education

* The models including family history for any AD among first degree relatives were further adjusted for first degree family histories for the specific ADs. For example, the model investigating the relationship of family history of AD on presence of comorbid Graves disease was further adjusted for family history of Graves disease among first degree relatives. **These models suggest that a family history of OTHER ADs do not contribute to a PwMS having a specific ADs.**

Table 4: The influence of comorbid AD or family history of AD on MS presentation

	Age of MS onset		No. of impaired domains at onset		Time to 2nd relapse		No. of relapses in the 1st two years	
	% change	p	% change	P	% change	p	% change	p
Polyautoimmunity	-1.6%	0.26	7.5%	0.09	11.5%	0.14	1.8%	0.77
Family history of any AD	-1.4%	0.49	11.1%	0.08	5.2%	0.64	1.3%	0.87
Family history of non-MS AD	-3.6%	0.014	8.1%	0.09	3.5%	0.69	1.9%	0.78
Family history of MS	-1.4%	0.34	-1.5%	0.75	5.4%	0.50	-4.6%	0.46

Results & Conclusions

- **Polyautoimmunity** (having a comorbid AD) in PwMS was greater among women, those of older age, with higher education, reported being ever obese and those with a family history of autoimmunity (**Table 2**).
- PwMS were more likely to report a **family history of autoimmunity** if they were female and if they had a second AD themselves (**Table 2**). Interestingly, non-white PwMS were >50% less likely to report a history of a non-MS AD than white PwMS. There were **no differences** in PwMS who reported a family history of MS and those who did not.
- Among PwMS with a comorbid AD (polyautoimmune), they were more likely to report a history of non-MS ADs (**Table 3**). These results at first glance, might suggest the clustering of various ADs in families may increase the prevalence of polyautoimmunity in PwMS. However, when we account for family histories for specific ADs, **a family history of other ADs are not associated with the presence of a specific ADs**. For example, PwMS are 4.7 times more likely to report Hashimoto's thyroiditis if they reported having a first degree relative with Hashimoto's as well; reporting a family member with another AD did not make a difference (p=0.19)
- Notable is the lack of strong associations between established MS genetic risk factors and polyatuoimmunity and familial autoimmunity (**Table 2**).
- Also noteworthy, is that PwMS did not differ in their presentation at/near onset based on polyautoimmunity and familial autoimmunity (**Table 4**).
- **Collectively, these results do not suggest that polyautoimmune PwMS differ from those who are not, nor do they suggest that PwMS differ by familial autoimmunity history. These analyses also do not provide evidence that the clustering of varied ADs in families predisposed PwMS for nonspecific ADs.**

1. Patsopoulos N, Baranzini SE, Santaniello A, et al. The Multiple Sclerosis Genomic Map: Role of peripheral immune cells and resident microglia in susceptibility. bioRxiv. 2017.
2. Briggs FBS, Justin J, et al. Multiple sclerosis risk factors contribute to onset heterogeneity. Mult Scler Relat Disord. https://doi.org/10.1016/j.msard.2018.12.007