Vitiligo Age of Onset and PRS Association

Genevieve HL Roberts

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Introduction

In this study, we aim to investigate the association between a vitiligo Polygenic Risk Score (PRS) excluding MHC Class II region SNPs and the age of onset. Our hypothesis posits a correlation wherein a higher PRS (excluding MHC Class II) is linked to an earlier age of onset, indicating a potential association with elevated genetic risk.

Moreover, we extend our hypothesis to carriers of the extreme risk/early age of onset MHC Class II haplotype. In this subgroup, we anticipate that the impact of a high PRS without MHC Class II may be diminished due to the substantial genetic risk conferred by the haplotype (haplotype OR=8.1). We believe there may be an interaction effect, suggesting that the slope of the regression line for age of onset ~ PRS is smaller in individuals carrying the high-risk haplotype compared to non-carriers.

Results

Categorizing Age of Onset into Early- and Late- Onset Groups

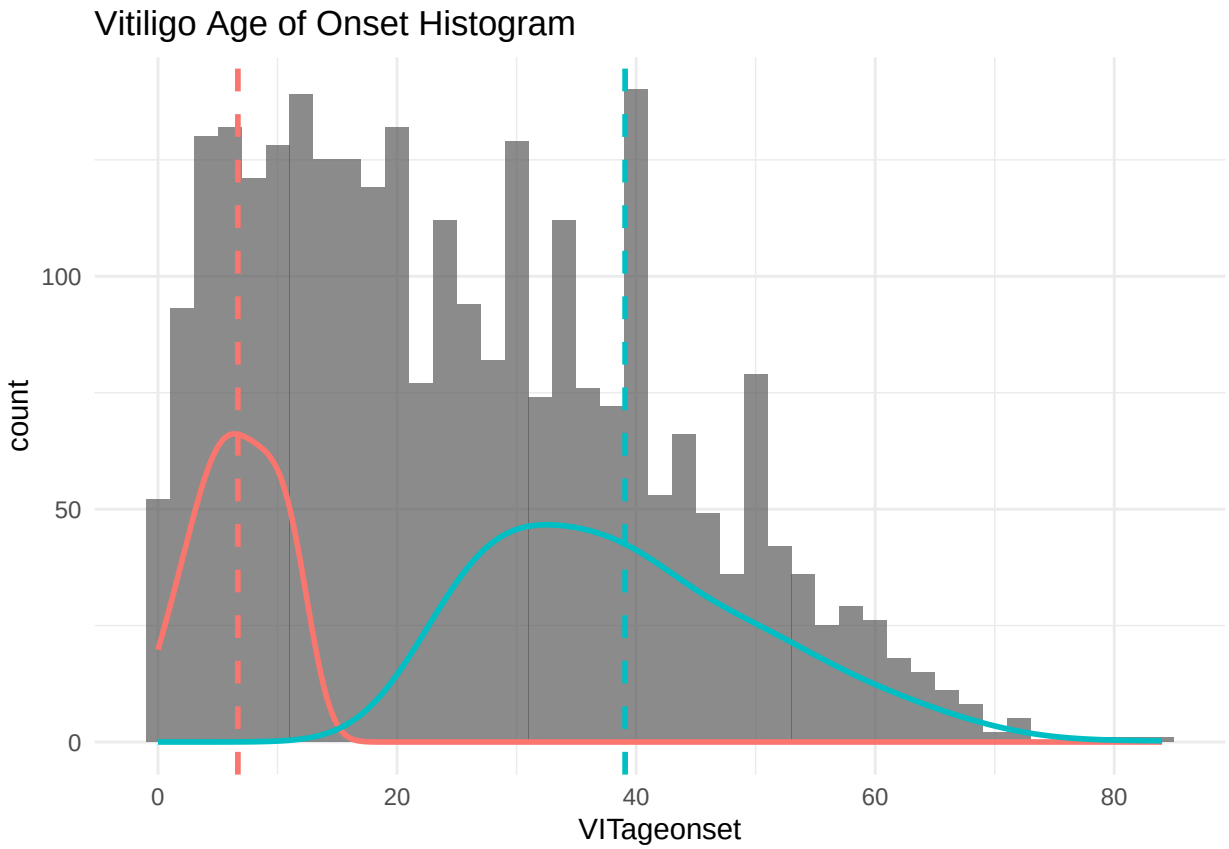
I no longer have the AOO classifications that we created previously, so I have re-fit the finite mixture model to categorize GWAS123 cases as either early onset or late onset. I have used the same methods here.

In the eAOO paper, we report that for GWAS123, "After subgroup assignment and control matching, the combined early-onset subgroup contained 704 cases and 9,031 controls and the combined late-onset subgroup contained 1,467 cases and 19,156 controls.

number of iterations= 94

AOO_category	n	min_aoo	median_aoo	mean_aoo	max_aoo	sd_aoo
early_onset	719	0	7	6.684	12	3.394
late_onset	1431	23	37	39.08	84	11.4
NA	617	12.5	17	17.19	22	2.817

As shown in the table above, you can see that we achieve similar sample sizes for early and late onset (719 early here vs. 704 in our earlier analysis and 1,431 late here vs. 1,467 in our earlier analysis); however, the mean age of onset for each group is rather different: we find mean eAOO of 6.7 here versus 10.3 for GWAS123 + Rep in our earlier analysis and mean lAOO of 39 years here versus 34.0 for GWAS123 + Rep in our earlier analysis.


Vitiligo Age of Onset Histogram
count
100
50
0
0
20
40
60
80
VITageonset

Association of each PRS with vitiligo risk

Next, I wanted to verify that the associations looked as I would expect for each of the PRSs. So, I checked the association with overall vitiligo risk (i.e. in all cases and controls in GWAS123):

Phenotype	PRS or SNP	pval	OR	lower_ci	upper_ci
vitiligo	CONFIRMED	0.00e+00	2.71	2.6	2.82
vitiligo	eA00_rs145954018	1.74e-49	2.35	2.1	2.64
vitiligo	generic_rs9271597	1.90e-97	1.84	1.74	1.95
vitiligo	mhc_class2_only	6.12e-110	1.46	1.42	1.51
vitiligo	no_mhc_classII	0.00e+00	2.59	2.48	2.7
late_onset_vitiligo	CONFIRMED	3.61e-230	2.46	2.33	2.6
late_onset_vitiligo	eA00_rs145954018	9.05e-08	1.61	1.35	1.92
late_onset_vitiligo	generic_rs9271597	1.26e-31	1.59	1.47	1.71
late_onset_vitiligo	mhc_class2_only	1.08e-27	1.3	1.24	1.36
late_onset_vitiligo	no_mhc_classII	2.25e-222	2.51	2.37	2.66
early_onset_vitiligo	CONFIRMED	4.93e-192	3.06	2.84	3.3
early_onset_vitiligo	eA00_rs145954018	2.38e-75	4.7	3.99	5.55
early_onset_vitiligo	generic_rs9271597	4.00e-51	2.31	2.08	2.58
early_onset_vitiligo	mhc_class2_only	4.99e-92	1.82	1.72	1.93
early_onset_vitiligo	no_mhc_classII	1.61e-127	2.55	2.36	2.75

These results look generally as I would expect, with the CONFIRMED risk score having the highest performance with respect to OR per standard deviation of PRS. The pvals = 0 mean that the p-value is lower than the numerical precision in R, which I believe is something like $p < 1e\text{-}300$.

Note that the scaling is different for SNPs and for PRS, so the estimates are not directly comparable (for PRS, the OR is per standard deviation of PRS, whereas for SNPs, it is per SNP risk allele).

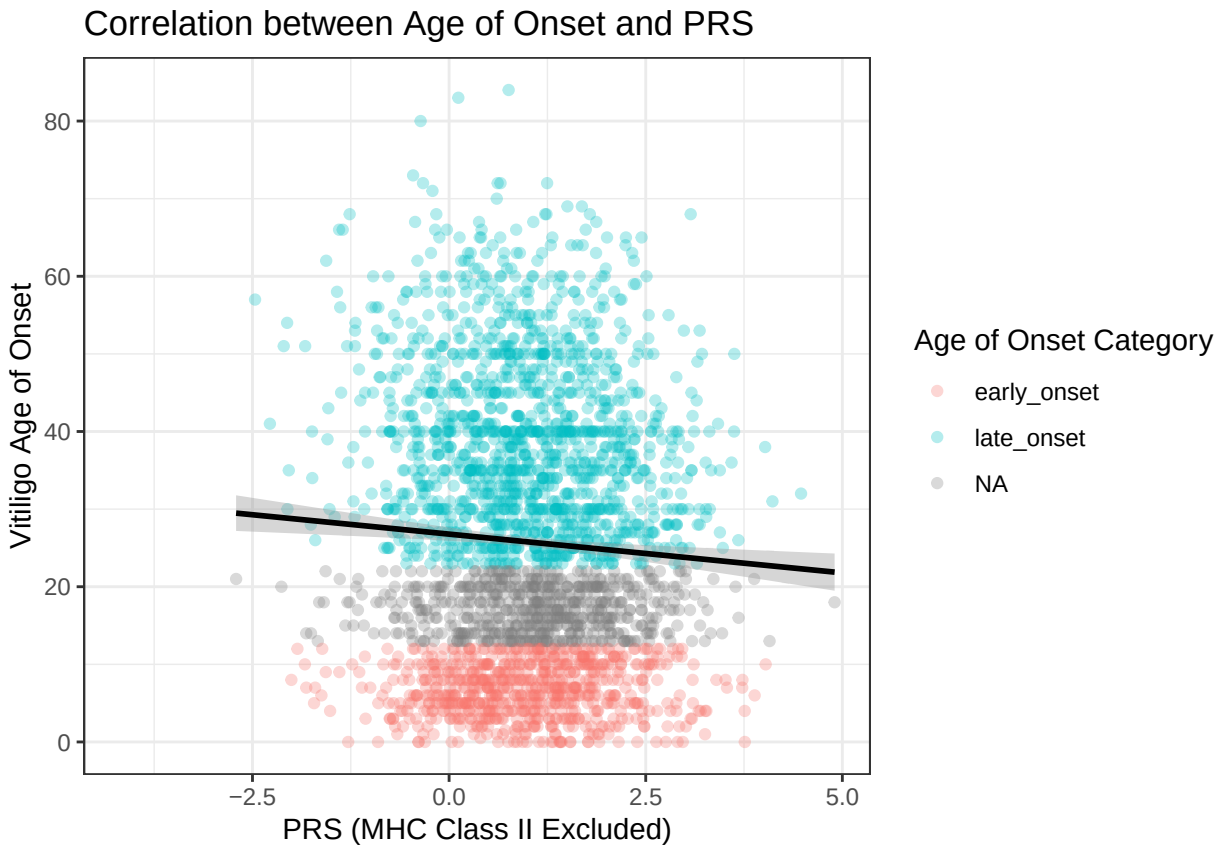
Association of each PRS with vitiligo Age of Onset

I also checked the association with vitiligo age-of-onset risk (i.e. cases with non-missing age-of-onset in GWAS123):

Phenotype	PRS or SNP	pval	estimate	lower_ci	upper_ci
VITageonset	no_mhc_classII	7.30e-04	-1.03	-1.63	-0.43
VITageonset	mhc_class2_only	2.94e-22	-2.59	-3.11	-2.07
VITageonset	CONFIRMED	1.59e-15	-2.37	-2.96	-1.79
VITageonset	eA00_rs145954018	9.74e-18	-7.29	-8.94	-5.64
VITageonset	generic_rs9271597	6.32e-11	-2.91	-3.78	-2.04

Again, these results look about as I would expect: the MHC class 2 only PRS is more strongly associated than the confirmed PRS. Nevertheless, there is modest association between the non-MHC Class II PRS and lower vitiligo age-of-onset, as we hypothesized (P=7.30e-04).

Note that the scaling is different for SNPs and for PRS, so the estimates are not directly comparable (for PRS, the estimate is interpreted as years per standard deviation of PRS, whereas for SNPs, it is interpreted as years per copy of SNP risk allele).

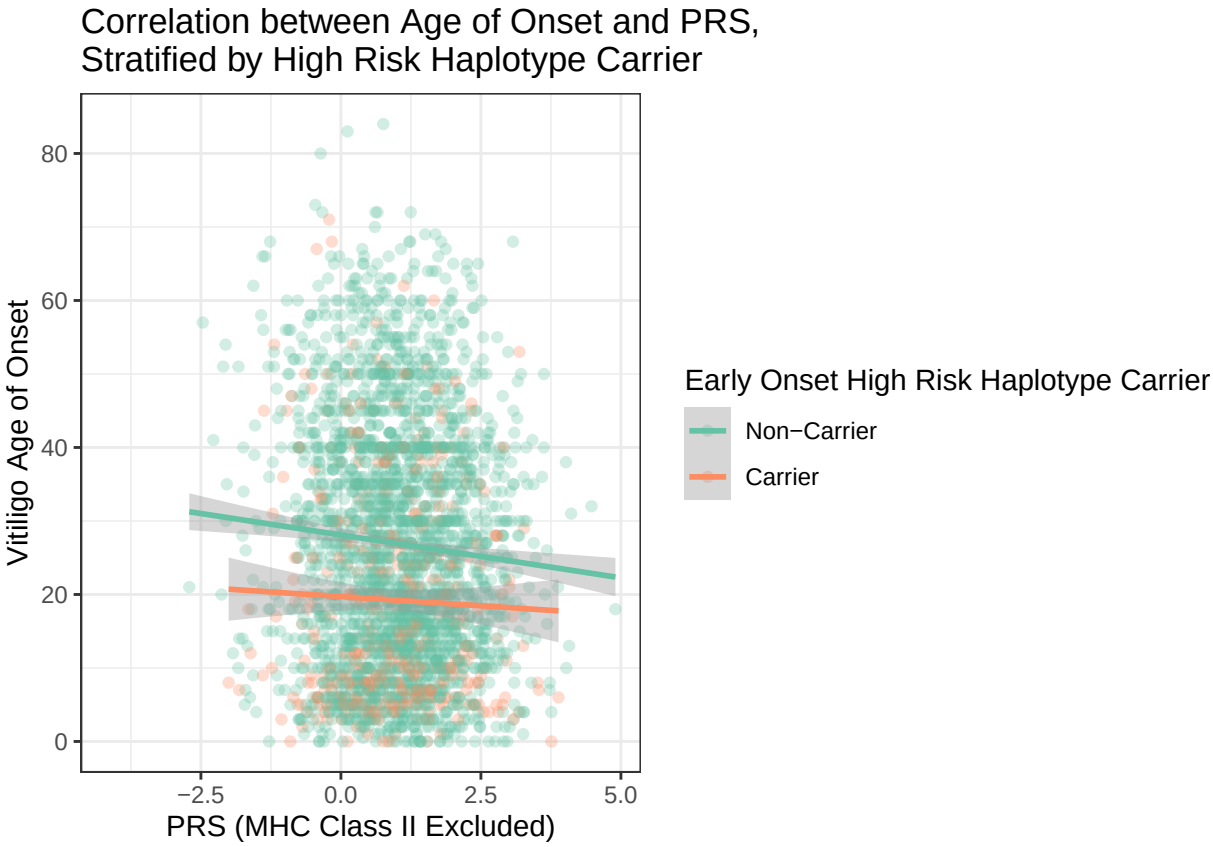

Correlation between Age of Onset and PRS
Vitiligo Age of Onset
80
60
40
20
0
−2.5
0.0
2.5
5.0
PRS (MHC Class II Excluded)
Age of Onset Category
early_onset
late_onset
NA

Interaction Test Between eAOO SNP and PRS (excluding MHC Class II SNPs)

Table 4: Table continues below

outcome	predictor	term
VITageonset	no_mhc_classII_prs_scaled	no_mhc_classII_prs:eAOO_hap_carrier

pval	estimate	std_error	lower_ci	upper_ci
0.38	28.29	0.83	26.33	30.25



Although there is a trend towards a stronger negative slope for those that do not carry the high-risk eAOO haplotype relative to those that do carry the haplotype (consistent with our hypothesis), the difference is not significant (interaction P = 0.38).