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ORIGINAL ARTICLE

Genetic determinants of immune-related adverse events in patients with melanoma receiving immune checkpoint inhibitors

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Abstract

Background Immune checkpoint inhibitors (ICIs) can cause profound immune-related adverse events (irAEs). The host genetic background is likely to play a role in irAE susceptibility because the presentation of toxicity varies among patients and many do not develop irAEs despite continued ICI use. We sought to identify potential genetic markers conferring risk for irAEs.

Methods We conducted a pilot exploratory study in 89 melanoma patients who received ICIs (44 with irAEs, and 45 without irAEs after at least 1 year from starting treatment). Genotyping was performed using the Infinium Multi-Ethnic Global-8 v1.0 Bead Chip. The genotype data were extracted using PLINK (v1.90b3.34) and processed for quality control. Population structure-based clustering was carried out using IBS matrix, pairwise population concordance test ($p < 1 \times 10^{-3}$), and phenotype distribution for all study participants, resulting in seven population structure-based clusters. In the analytical stage, 599,931 variants in autosomal chromosomes were included for the association study. The association test was performed using an additive genetic model with exact logistic regression, adjusted for age, sex, and population cluster.

Results A total of 30 variants or single-nucleotide polymorphisms with $p < 1 \times 10^{-4}$ were identified; 12 were associated with an increased risk of irAEs, and the remaining 18 were associated with a decreased risk. Overall, nine of the identified single-nucleotide polymorphisms mapped to eight unique genes that have been associated with autoimmunity or inflammatory diseases.

Conclusion Several genetic variants associated with irAEs were identified. Additional larger studies are needed to validate these findings and establish their potential functional relevance.

Keywords Checkpoint inhibitors · Immune-related adverse events · Genetics

Abbreviations

CI	Confidence interval
CTLA-4	Cytotoxic T-cell lymphocyte-associated protein-4
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
OR	Odds ratio
PD-1/PD-L1	Programmed cell death-1/programmed cell death-ligand 1
SNP	Single-nucleotide polymorphism

Introduction

The development of immune checkpoint inhibitors (ICIs) targeting cytotoxic T-cell lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1/programmed cell

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Sanjay S. Shete and Maria E. Suarez-Almazor contributed equally to this work.

The is the first pilot genome-wide study to identify genetic variants that may be associated with the risk of developing immune-related adverse events in melanoma patients treated with checkpoint inhibitors.

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Extended author information available on the last page of the article

death-ligand 1 (PD-1/PD-L1) has led to a major breakthrough in the treatment of cancer [1–3]. Nevertheless, the therapeutic benefits of ICIs are limited by toxicity arising from off-target inflammatory and/or autoimmune responses that can be life threatening and may require high-dose immunosuppressive therapies and permanent discontinuation of ICIs. The presentation of toxicity varies widely among patients; although many patients develop immune-related adverse events (irAEs) in multiple organs, some develop irAEs limited to one organ and others never develop irAEs despite continued ICI use. Notably, onset of well-defined autoimmune diseases has also been reported in some patients following initiation of ICI therapy; these diseases include rheumatoid arthritis, myasthenia gravis, cryoglobulinemic vasculitis, and Sjogren syndrome, among others [4–7]. Conceivably, the genetic background of patients receiving ICIs could play a role in susceptibility to irAEs, contributing to the observed variation. Elucidating which individual genetic determinants may predispose patients to the development of irAEs can contribute to understanding of the pathogenesis of irAEs, support clinical decision-making, and improve the management of cancer patients receiving ICIs.

We conducted a pilot genome-wide study of patients with melanoma who received ICIs, comparing the genotypes of those who developed irAEs with the genotypes of those who did not, using a comprehensive, multi-ethnic microarray. Our objective was to agnostically interrogate the entire genome to identify genetic markers conferring risk for irAEs, to inform future, larger studies on the choice of potential candidate genes.

Materials and methods

Study design

We designed a case–control study with a convenience sample of cancer patients who received ICIs at The University of Texas MD Anderson Cancer Center between January 2012 and September 2017 identified from melanoma and specialty clinics for diagnosis and management of irAEs. Patients who developed irAEs after initiation of ICI therapy were considered cases, and those who did not develop irAEs for at least 1 year after initiating ICI therapy were considered controls. Common inclusion criteria for both cases and controls were as follows: (1) age > 18 years; (2) histologic diagnosis of melanoma; and (3) treatment with a US Food and Drug Administration-approved ICI. The study was approved by The Institutional Review Board at The University of Texas MD Anderson Cancer Center.

Specific inclusion criteria for cases included the following: (1) ≥ grade 2 irAEs occurring at any time during ICI therapy, or within 1 month of the last ICI infusion; (2) use of corticosteroids or other immunosuppressive therapy for a minimum of 2 weeks for treatment of an irAE (except for endocrinopathies); (3) no other conditions (e.g., infection) that could potentially cause similar symptoms, as per medical record; and (4) no prior history of inflammatory or autoimmune disease in the same affected organs. Specific organ irAEs were identified based on the Common Terminology Criteria for Adverse Events [8]. Patients who developed irAEs in multiple organs and those who had irAEs limited to one organ were included. Skin irAEs are the most common ICI-related toxicity, typically mild, and do not require systemic immunosuppressive therapy making diagnosis sometimes difficult, so patients with isolated rash were excluded from the study.

Specific inclusion criteria for controls included the following: (1) for ipilimumab-treated patients: at least 12 weeks of treatment without any irAEs during therapy and within the 9 months subsequent to the last treatment dose; and (2) for patients treated with anti-PD-1/PD-L1: at least 1 year of treatment without irAEs. To maximize similarities between cases and controls other than the presence or absence of irAEs, controls were matched to the cases by type of ICI agent. Eligible patients were approached during their follow-up visits in the melanoma clinic and those who agreed to participate in the study signed an informed consent form. Patients were interviewed to evaluate past medical history and their medical records were reviewed for additional pertinent information (patient demographics, prior autoimmune diseases, type of ICI agent, duration of ICI treatment, and occurrence of toxicity). The final inclusion of patients as cases or controls was agreed upon by two investigators (N.A. and A.D.).

Genotyping

Genotyping was performed at the Sequencing and Microarray Facility at MD Anderson using the Infinium Multi-Ethnic Global-8 v1.0 Bead Chip, which covers all five supercontinental populations, account for subtle genetic variations that exist even among Caucasians, is based on the most current genomic information (phase 3 of the 1000 Genomes Project), and is augmented with significant clinical database content and functional content. Briefly, genomic DNA was isolated from whole blood samples and was assessed for quality and quantified; 200 ng of dsDNA was denatured, neutralized, and isothermally amplified. The amplified DNA was enzymatically fragmented, precipitated, and resuspended in hybridization buffer before being loaded to the chip, which was incubated overnight. Following hybridization, the chip was washed to remove unhybridized and non-specifically hybridized DNA and then stained by single-base extension of the primers, which uses the captured DNA as a template and incorporates a fluorescently labeled

complementary nucleotide. Chips were scanned on the Illumina iScan, which uses a laser to excite the incorporated fluorophore and records high-resolution images of the light emitted from the fluorophores.

The genotype data were processed using PLINK (v1.90b3.34). The initial set of 1,523,415 raw variants on autosomal chromosomes (1 through to 22) and sex chromosomes (23 and 24) was processed for quality control, including call rate (> 99%), non-missing genotyping rate (> 95%), minor allele frequency (no less than 5%), and Hardy–Weinberg equilibrium ($p < 1 \times 10^{-6}$). Then, the pairwise genetic distance was calculated using identity-by-state (IBS matrix) implemented in the genome option of PLINK, and the population structure-based clustering was carried out using IBS matrix, pairwise population concordance test ($p < 1 \times 10^{-3}$), and phenotype distribution for all patients, resulting in seven structure groups.

Statistical analysis

This is a pilot study and our sample size included 44 cases and 45 controls selected from the populations described above. Based on the proposed sample size, we have more than 80% power to detect odds ratios (OR) of 3.58, 3.38, 3.66 or above as significant, depending on the prevalence of the single-nucleotide polymorphisms (SNPs) in the population (50, 30, and 20%, respectively). Descriptive statistics were used to summarize the data, with median and range for continuous variables and frequencies and percentages for categorical variables. Chi-square and Fisher exact tests were used to compare categorical variables, and Wilcoxon or Kruskal–Wallis tests were used to compare continuous variables between groups.

A total of 599,931 variants in autosomal chromosomes remained after quality control processes were complete, and these chromosomes were included in the analysis. Testing was performed using an additive genetic model with exact logistic regression adjusting for sex, age, and seven population clusters identified from the identity-by-state analyses to account for race/ethnicity. Population cluster analyses identify homogeneous groups to account for underlying subpopulations beyond the self-reported race and ethnicity. Because this was a pilot study and the aims were primarily hypothesis generating, within a small sample of patients, we were interested in identifying only a small subset of SNPs that are suggestive of association. Therefore, we used $p \leq 1 \times 10^{-4}$ as the threshold for selecting SNPs, and testing for multiple comparisons was not possible.

Literature search

To highlight the most up-to-date evidence in the literature, we conducted a comprehensive Medline search from inception to December 2019 and identified previous studies that evaluated the association between autoimmune SNPs or variants and occurrence of irAEs and/or tumor response to ICI therapy. We then recognized the full list of SNPs within these previously reported genes and evaluated their potential association with irAEs in our sample.

Results

Patient characteristics

A total of 90 melanoma patients were included in our analysis; 45 were cases (i.e., patients who developed irAEs) and 45 were controls (i.e., no irAEs). However, one patient with both melanoma and renal cell carcinoma was excluded from the case group in our final analysis because the patient was receiving ICI therapy for renal cell carcinoma and did not have active melanoma. Patient demographics and baseline characteristics, including the distribution of age, sex, population clusters, and class of ICI therapy, are provided in Table 1. The overall median age of the patients was 64 years (range 23–92 years); 63 (71%) were male and 85 (96%) were white. Eighty-four patients (94%) had unresectable stage III/IV metastatic melanoma and the remaining five were receiving adjuvant ICI after surgical resection. Single-agent anti-PD-1/PD-L1 therapy was the most frequently used ICI therapy, in 49 patients (55%). Colitis (10%) and pneumonitis (9%) were the most frequently reported irAEs in our sample population. Other irAEs included hypophysitis, thyroiditis, arthritis, and multiple irAEs (≥ 2 irAEs). Among the cases, the median duration of follow-up after initiation of ICI therapy was 2.0 years (range 0.31–4.3 years). In the control group, the median duration of follow-up for patients treated with ipilimumab was 2.5 years (range 1–3 years), and for those receiving anti-PD-1/PD-L1 therapy, 1.5 years (range 1–5 years).

Association of SNPs with irAEs

The full list of all SNPs or variants from chromosome 1–22 for our sample is shown in Supplemental Table 1. We identified a total of 30 variants or SNPs that were significantly associated ($p \leq 1 \times 10^{-4}$) with irAEs development.

Twelve SNPs were associated with significantly increased odds of developing irAEs (Table 2). Four of these were mapped to genes that have been previously associated with inflammatory and autoimmune diseases. Carriers of at least one copy of a minor allele A for rs11743438 were more likely to develop irAEs (OR 4.3; 95% confidence interval [CI] 2.3–8.0; $p = 5.56 \times 10^{-6}$). rs11743438 was mapped to the *GABRP* (gamma-aminobutyric acid type A receptor subunit pi) gene, which has been associated with autoimmune

Table 1 Patient demographic and baseline characteristics among cases ($n=44$) and controls ($n=45$)

Patient characteristic	No. (%)			p value
	Total	Cases	Controls	
Median age (range)	64 years (23–92 years)	62 years (23–92 years)	66 years (23–82 years)	0.6427
Sex				0.8689
Male	63 (71)	32 (73)	31 (69)	
Female	26 (29)	12 (27)	14 (31)	
Ethnicity				0.6251
Not Hispanic or Latino	85 (96)	43 (98)	42 (93)	
Hispanic or Latino	4 (4)	1 (2)	3 (7)	
Race				0.2614
White or Caucasian	85 (96)	43 (98)	42 (93)	
Black or African American	1 (1)	0	1 (2)	
Others	2 (2)	0	2 (4)	
Unknown	1 (1)	1 (2)	0	
Checkpoint inhibitor				0.029
Ipilimumab	17 (19)	12 (27)	5 (11)	
Anti-PD-1/PD-L1 agents	49 (55)	20 (45)	29 (64)	
Nivolumab	11 (12)	3 (7)	8 (18)	
Pembrolizumab	37 (42)	16 (36)	21 (47)	
Atezolizumab	1 (1)	1 (2)	0	
Combination ICI[a]	4 (4)	4 (9)	0	
Sequential ICI[b]	19 (21)	8 (18)	11 (24)	
Immune-related adverse events	44 (49)	44 (100)	0	< 0.0001
Colitis	9 (10)	9 (20)		
Pneumonitis	8 (9)	8 (18)		
Thyroiditis	7 (8)	7 (16)		
Hypophysitis	6 (7)	6 (14)		
Arthritis	7 (8)	7 (16)		
Multiple[c]	7 (8)	7 (16)		
No immune-related adverse events	45 (51)	0	45 (100)	

Numbers are rounded to the nearest whole number

[a]Two patients received a combination of ipilimumab and nivolumab, and two others received a combination of ipilimumab and pembrolizumab

[b]Consecutive use of checkpoint inhibitors (switch to a different agent or re-induction with the same agent) was reported in 19 patients

[c]Seven patients were reported to have multiple immune-related adverse events, including hypophysitis, hepatitis, thyroiditis, colitis, pneumonitis, adrenal insufficiency, and/or myositis

movement disorders [9]. Carriers of at least one copy of a minor allele A for JHU_20.57183980 were more likely to develop irAEs (OR 6.9; 95% CI 2.7–17.6; $p=8.85\times10^{-6}$). JHU_20.57183980 was mapped to the *DSC2* (desmocollin 2) gene, which has been associated with autoimmune bullous disorders of the pemphigus group [10]. Carriers of at least one copy of a minor allele G for rs56328422 were more likely to develop irAEs (OR 4.2; 95% CI 2.1–8.4; $p=4.14\times10^{-5}$). rs56328422 was mapped to *BAZ2B* (bromodomain adjacent to zinc finger domain 2B) gene, which has been associated with Murray Valley encephalitis. Carriers of at least one copy of a minor allele T for rs3026321 were more likely to develop irAEs (OR 19.8; 95% CI 2.6–152.7; $p=6.31\times10^{-5}$). rs3026321 was mapped to the *SEMA5A* (semaphorin 5A) gene, which has been associated with systemic lupus erythematosus, rheumatoid arthritis, and idiopathic thrombocytopenic purpura [11–13]. The other eight variants or SNPs associated with increased risk of developing irAEs along with their base-pair position, gene location (when available) and associated odds ratios with confidence intervals are listed in Table 2 top panel.

We also identified 18 SNPs that were associated with significantly reduced odds of developing irAEs (Table 2). Five of these SNPs were mapped to four genes that were

Table 2 Top variants or single-nucleotide polymorphisms associated with immune-related adverse events

Single-nucleotide polymorphism	Chromosome position	Base-pair position	Minor allele	Gene (description)	Odds ratio (95% confidence interval)	Ranking p value	Possible associated diseases reported in the literature
Variants associated with increased odds of developing immune-related adverse events							
rs11743438	5	170,218,232	A	*GABRP* (gamma-aminobutyric acid type A receptor subunit pi)	4.3 (2.3–8.0)	5.56×10^{-6}	Immune-mediated movement disorders
rs11743735	5	170,213,256	A	*GABRP*	4.5 (2.3–8.8)	8.34×10^{-6}	
JHU_20.57183980	20	58,608,925	A	*DSC2* (desmocollin 2)	6.9 (2.7–17.6)	8.85×10^{-6}	Autoimmune bullous disorders of the pemphigus group
rs56328422	2	159,529,709	G	*BAZ2B* (bromodomain adjacent to zinc finger domain 2B)	4.2 (2.1–8.4)	4.14×10^{-5}	Corneal dystrophy, Lisch epithelial, Murray Valley encephalitis, phlebotomus fever, and narcissistic personality disorder
rs35807769	3	102,737,107	G		4.9 (2.2–11.1)	6.07×10^{-5}	
rs3026321	5	9,241,576	T	*SEMA5A* (semaphorin 5A)	19.8 (2.6–152.7)	6.31×10^{-5}	Systemic lupus erythematosus, idiopathic thrombocytopenic purpura, rheumatoid arthritis, Parkinson disease, Cri-du-Chat syndrome, Charcot–Marie–Tooth disease, autism, autism spectrum disorders, glioma
rs1276216	5	30,927,091	A		6.4 (2.3–17.6)	8.18×10^{-5}	
rs919682	2	178,263,102	G	*OSBPL6* (oxysterol binding protein-like 6)	4.6 (2.1–10.1)	8.29×10^{-5}	
JHU_2.179128562	2	178,263,836	G	*AGPS*	4.6 (2.1–10.1)	8.29×10^{-5}	
rs239731	21	27,331,808	A	LOC102724355 (uncharacterized LOC102724355)	11.3 (2.5–50.4)	8.56×10^{-5}	
JHU_5.9269447	5	9,269,336	G	*SEMA5A*	3.5 (1.9–6.5)	8.61×10^{-5}	
rs359975	2	219,012,933	G	Near genes *CFAP65* (cilia and flagella associated protein 65) and LOC100129175 (uncharacterized LOC100129175)	8.5 (2.4–29.9)	9.41×10^{-5}	
Variants associated with decreased odds of developing immune-related adverse events							
rs11711517	3	65,112,627	G	LOC105377125	0.16 (0.07–0.37)	2.39×10^{-6}	
JHU_15.93602126	15	93,058,898	A		0.24 (0.13–0.46)	8.89×10^{-6}	
JHU_15.93604000	15	93,060,772	G		0.24 (0.13–0.46)	8.89×10^{-6}	
rs470753	18	65,315,670	G		0.16 (0.07–0.40)	1.65×10^{-5}	
rs4778080	15	93,060,296	C	*RGMA* (repulsive guidance molecule BMP co-receptor a)	0.24 (0.12–0.47)	1.92×10^{-5}	Hemochromatosis type 2

Table 2 (continued)

Single-nucleotide polymorphism	Chromosome position	Base-pair position	Minor allele	Gene (description)	Odds ratio (95% confidence interval)	Ranking p value	Possible associated diseases reported in the literature
rs2117997	12	29,143,428	G	*ANKRD42* (ankyrin repeat domain 42)	0.22 (0.10–0.45)	2.44×10^{-5}	Systemic inflammatory response syndrome or sepsis
rs55733913	6	163,155,093	G	*PACRG* (parkin coregulated)	0.16 (0.06–0.42)	3.98×10^{-5}	Autoimmune thyroid disease, adult astrocytic tumor, leprosy, testicular diseases, hydrocephalus, late-onset Parkinson disease
rs7954686	12	29,211,874	G	*FAR2* (fatty acyl-CoA reductase 2)	0.16 (0.06–0.42)	3.98×10^{-5}	Familial amyloidosis, renal, Ostertag type (lysozyme deposit)
rs6440251	3	144,415,631	A	LOC105374140	0.13 (0.04–0.40)	5.15×10^{-5}	
JHU_14.101799748	14	101,333,412	A		0.11 (0.03–0.38)	5.20×10^{-5}	
rs4800887	18	28,670,714	A		0.25 (0.13–0.50)	5.74×10^{-5}	
rs162263	3	78,907,054	C	*ROBO1* (roundabout guidance receptor 1)	0.24 (0.12–0.49)	5.88×10^{-5}	Autoimmune diabetes, pituitary stalk interruption syndrome, reading disorder, dyslexia, breast cancer
rs10814859	9	4,180,887	G	*GLIS3* (GLIS family zinc finger 3)	0.24 (0.12–0.49)	5.88×10^{-5}	Autoimmune diabetes, possible association with rheumatoid arthritis, congenital hypothyroidism, hypothyroidism, 1ry angle-closure glaucoma
kgp3960064	3	78,962,516	A	*ROBO1*	0.28 (0.15–0.53)	6.76×10^{-5}	Autoimmune diabetes
rs2062059	3	98,978,545	G		0.28 (0.15–0.53)	7.37×10^{-5}	
rs12548560	8	129,094,808	G	*PVT1* (Pvt1 oncogene)	0.28 (0.14–0.53)	8.95×10^{-5}	
rs66502444	6	163,133,717	T	*PACRG* (parkin coregulated)	0.16 (0.06–0.43)	9.11×10^{-5}	
rs6993547	8	68,061,465	G	*PREX2* (phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 2)	0.16 (0.06–0.43)	9.11×10^{-5}	Corneal dystrophy, endothelial x-linked posterior polymorphus

previously associated with inflammatory and autoimmune diseases. rs2117997 was mapped to the *ANKRD42* (ankyrin repeat domain 42) gene, associated with systemic inflammatory response syndrome [14]. rs55733913 was mapped to the *PACRG* (parkin coregulated) gene, associated with autoimmune thyroid diseases [15]. rs162263 and kgp3960064 were both mapped to the *ROBO1* (roundabout guidance receptor 1) gene, associated with autoimmune diabetes [16]. rs10814859 was mapped to the *GLIS3* (GLIS family zinc finger 3) gene, which has also been associated with autoimmune diabetes, and possibly with rheumatoid arthritis [17, 18]. These variants or SNPs associated with decreased risk of developing irAEs along with their base-pair position, gene location (when available) and associated odds ratios with confidence intervals are listed in Table 2 bottom panel.

In addition, our literature search identified a list of 36 genes that were previously evaluated in selected studies of irAEs and/or for tumor response with ICI therapy [19–22] (Supplemental Table 2). The full list of SNPs within these genes (n = 296) and their association parameters with irAEs in our sample is shown in Supplemental Table 3. Six SNPs showed nominal statistical significance ($p < 0.05$), although above the value we predetermined for cutoff (Table 3). The carriers of at least one copy of a minor allele A for exm1425699 were more likely to develop irAEs (OR 2.643; 95% CI 1.3–5.3; $p = 0.0067$); this SNP maps to the *TYK2* (tyrosine kinase 2) genes, which encode for tyrosine kinases that are instrumental in the coding of various inflammatory cytokines associated with autoimmune diseases. The other five SNPs were mapped to the *HLA* (human leukocyte antigen), *TNFAIP3* (TNF alpha induced protein 3), and *TYK2* genes, and all were associated with significantly reduced odds of developing irAEs.

Discussion

The current study, to the best of our knowledge, is the first exploratory genome-wide study to identify genetic variants that may be associated with the risk of developing irAEs in melanoma patients treated with ICIs. Our objective was to agnostically examine a broad array of genetic markers to evaluate their possible association with immune toxicity in patients with irAEs, to provide information on potential candidate genes to be examined in subsequent larger studies. Because the current study was exploratory, we did not aim to ascertain genetic associations with specific organ toxicity and included patients with various irAEs.

We identified 12 SNPs that were associated with an increased risk of developing an irAE, and 18 others appeared to be protective. Overall, nine of the identified SNPs were mapped to eight unique genes that have previously been associated with inflammatory and autoimmune diseases. Our data suggest that patients harboring at least one variant allele A in the *GABRP* SNP rs11743438, one variant allele A in the *DSC2* SNP JHU_20.57183980, one variant allele G in the *BAZ2B* SNP rs56328422, or one variant allele T in the *SEMA5A* SNP rs3026321 have an increased risk of developing irAEs. Our findings align with earlier studies that identified the association between these genes and susceptibility to autoimmune diseases, which share some clinical features with ICI-induced irAEs such as rheumatoid arthritis, lupus erythematosus, and blistering skin diseases, among others [9–13]. Although the functional consequences of the identified SNPs need to be elucidated, one could speculate that the use of ICI therapy in patients harboring these SNPs triggered the autoimmune phenotypes to clinically manifest in patients with the predisposing genotype. Several other SNPs were associated with a reduced risk of immune toxicity; five of these SNPs map to genes that are known to be

Table 3 Variants or single-nucleotide polymorphisms associated with autoimmune genetic loci reported in literature as biomarkers for immune-related adverse events or tumor response to checkpoint inhibitor therapy

Single-nucleotide polymorphisms	Chromosome position	Base-pair Position	Minor allele	Gene (description)	Odds ratio (95% confidence interval)	Ranking p value
rs3830135	6	32580687	A	*HLA-DRB1* (major histocompatibility complex, class II, DR beta 1)	0.2108 (0.08–0.59)	0.002048
rs28654242	6	32641284	A	*HLA-DQA1* (major histocompatibility complex, class II, DQ alpha 1)	0.2251 (0.08–0.63)	0.003645
rs17500468	6	32743401	G	*HLA-DQA2* (major histocompatibility complex, class II, DQ alpha 2)	0.3142 (0.12–0.84)	0.02402
JHU_6.138190532	6	137869396	A	*TNFAIP3* (TNF alpha induced protein 3)	0.2821 (0.09–0.90)	0.0389
exm1425699	19	10364976	A	*TYK2* (tyrosine kinase 2)	2.643 (1.3–5.3)	0.00671
rs12720250	19	10369138	A	*TYK2*	0.2535 (0.07–0.94)	0.0481

associated with autoimmune diseases, including systemic inflammatory response syndrome, autoimmune thyroid disease, and type I diabetes [14–18]. Our analysis reported a "protective" effect, which may indicate that these SNPs may have a regulatory role in the underlying gene transcription and, thus, help suppress the target immune-adverse event. Whether these variants help gene expression or suppression depends on the biological pathways, which are beyond the scope of this study but provide the suggestive information for scientific community to carry out further investigation to better understand underlying biological etiology. The small number of patients in this pilot study does not allow for definitive inferences, and larger studies are warranted to validate our findings.

The pathogenesis of irAEs in patients receiving ICI therapy is thought to be driven by increased inflammation and/or autoimmunity [23–25]. Whether germline genetic variants that are known to contribute to susceptibility to autoimmune diseases [26] could also play a role in susceptibility to irAEs remains an intriguing question. Preclinical studies have shown that mice deficient in CTLA-4 die from massive lymphoproliferative disorders, and those with genetic deletion of PD-1/PD-L1 have an increased risk of autoimmunity [27–30]. In humans, selected polymorphisms in CTLA-4- and PD-1-related alleles have been linked to a number of autoimmune diseases such as thyroiditis, neurologic disorders, inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, and type I diabetes [28, 31–37].

Queirolo and colleagues evaluated the association between six SNPs associated with the *CTLA-4* gene (−1661A > G, −1577G > A, −658C > T, −319C > T, +49A > G, and CT60G > A) and the occurrence of endocrine irAEs in 173 melanoma patients treated with ipilimumab; only the *CTLA-4* gene variant −1661A > G (rs4553808) appeared to predispose patients to endocrinopathies following treatment initiation [38]. Similarly, Bins and colleagues assessed the association between seven SNPs in four genes involved in the PD-1 pathway, including programmed cell death 1 (*PDCD1*), zeta chain of T cell receptor-associated protein kinase 70 (*ZAP70*), interferon gamma (*IFNG*), and *PTPN11*, and occurrence of irAEs in 161 patients with non-small cell lung cancer treated with nivolumab [19]. In that study, carriers with at least one copy of a minor allele G in the *PTPN11* 333–223A > G SNP (rs2301756) had increased odds of developing elevated transaminases, and those with a homozygous variant for the *IFNG* −1616 T > C SNP had an increased risk for rheumatologic irAE. They also found that patients with the TT genotype in the *PDCD1* 804C > T SNP (rs2227981) had decreased odds of developing any grade treatment-related adverse events. However, these findings could not be replicated in their validation cohort that included another 161 patients. In our sample of melanoma patients, genetic variants in *CTLA-4*, *PDCD1*, or *PD-L1* were not associated with irAE risk.

Genetic variations in human leucocyte antigens (HLA) have previously been associated with a number of autoimmune diseases such as rheumatoid arthritis and type 1 diabetes. Recently, Cappelli and colleagues evaluated whether HLA class I and II alleles were more prevalent among patients with ICI-induced arthritis ($n = 26$) compared with the general population ($n = 726$) [20]. In that study, HLA DRB1*04:05 was increased in patients with ICI-induced arthritis (OR 8.6; 95% CI 1.7–43.4; $p = 0.04$). Nonstatistically significant associations with other alleles were also reported including an increase in HLA A*03:01, and HLA C*12:02 and a decrease in DQB1*03:01 (OR 0.4; 95% CI 0.1–1.1; $p = 0.06$). Patients with ICI-induced arthritis were compared with patients with primary rheumatoid arthritis ($n = 220$) and no differences were observed in the probability of having at least one HLA shared epitope allele (which confers risk for rheumatoid arthritis), but rheumatoid arthritis patients were more likely to be homozygous. A single-center prospective cohort study of rheumatic syndromes induced by ICI therapy reported two patients with ICI-induced arthritis harboring HLA-DRB1*01:01; both instances of irAEs manifested as arthritis resembling rheumatoid arthritis, and one of the patients had positive antibodies against citric citrullinated peptide [39]. Another small series reported that four of five melanoma patients with type I diabetes diagnosed following initiation of anti-PD-1 therapy were found to have HLA DRB01*03 or 04, which are known to be associated with an increased risk of type I diabetes in the general population [40]. In our sample population, which included patients with different irAE phenotypes, carrying a specific genetic variant within the HLA region—HLA DRB1 (rs3830135), HLA-DQA1 (rs28654242), and HLA-DQA2 (rs17500468)—conferred reduced odds of developing irAEs.

Specific SNPs within the *PTPN22* (protein tyrosine phosphatase non-receptor type 22) gene have been associated with several autoimmune diseases [41]; however, no significant association with irAEs was identified in our sample population.

As our sample was small, we did not attempt to evaluate genetic associations with specific organ irAE. Our goal was to identify signals for potential genetic markers associated with developing any irAE, as many patients present with immune toxicity across various organs.

Growing evidence suggests that patients who develop irAEs could have better tumor response to ICI therapy [42–44], raising a question about the possibility of shared genetic associations between treatment-related toxicity and efficacy. HLA genotyping was recently performed in 1535 patients with melanoma and non-small cell lung cancer treated with ICIs; extended survival was observed in patients with HLA-B44, whereas those with HLA-B62, including

(HLA-B*15:01), had worse disease outcomes [45]. Another study evaluated the association between autoimmune germline genetic variants and tumor response to ICI therapy in 436 patients with melanoma, but that study did not examine the association of the genetic variants with irAEs [22]. In that study, the authors performed a comprehensive search of the published literature to select genetic variants associated with autoimmune diseases in genome-wide association studies. The authors considered 25 variants; each variant is known to be associated with at least three autoimmune traits that could manifest clinically as part of irAEs, and at least one of these associations exceeded the genome-wide association study level of significance ($p = 1E-07$). The authors reported that rs17388568 (*IL2* and *IL21* genes) was associated with an increased response to anti-PD-1 therapy. In the current study, no attempt was made to evaluate tumor response, as our study had a case–control design and controls were chosen on the basis of continuing their ICI therapy, and therefore were likely to be responders, so it was not adequate for such an aim.

Our study was exploratory and preliminary in nature. It was limited by the small sample size; therefore, it was powered only to evaluate large ORs given the set threshold for statistical significance at $p \leq 1 \times 10^{-4}$, and smaller effect sizes were unlikely to be detected. Because of the exploratory nature of our study, we did not use the genome-wide threshold of 5.0×10^{-8} for significance. Additionally, because of the small sample, we included all types of irAEs as one group which could have lowered the statistical power of detecting an association, and we were not able to evaluate if differing associations exist among specific organ irAEs which are thought to have different underlying mechanisms. Although colitis was the most frequent irAE in our sample population, we did not identify any SNPs that were previously known to be associated with colitis [46, 47]. This could be partially explained by the small sample size (only nine patients had colitis) and the fact that ICI-related colitis represents a distinct form of colitis, which has similarities and differences with ulcerative colitis and Crohn's disease [48–51]. Moreover, the small sample size did not allow for testing or adjusting for other factors that could affect the occurrence of irAEs such as the recent use of cancer vaccines. However, our study provides the first exploratory genome-wide evaluation in melanoma patients who have various irAEs compared with other patients who have received ICI therapy without developing irAEs. Larger number of patients received ipilimumab and ICI combination among the case group (12 out of 44 cases = 27%; 95% CI 15–43%); however, the difference among cases and controls (5 out of 45 controls = 11%; 95% CI 2–24%) did not reach statistical significance (overlapping confidence intervals). Future larger studies should include cases and controls matched by therapy received and other relevant factors. Since ipilimumab and anti-PD-1/PD-L1 agents target different immune regulatory mechanisms, conducting a study specifically focused on the anti-PD-1/PD-L1 treated cases will further clarify the etiology of irAEs.

In conclusion, in our exploratory study, we identified 30 genetic variants associated with the risk of irAEs in patients with melanoma receiving ICIs; 12 SNPs were associated with an increased risk, and 18 others seemed to be protective. The genes associated with some of these SNPs were previously known to be associated with inflammatory and autoimmune diseases. Our findings suggest a contributing role of polygenic predisposition in the occurrence of ICI-induced irAEs. Our study was exploratory, and as our next step we plan a prospective validation cohort study of melanoma patients initiating anti-PD1 agents to further evaluate the association between the identified autoimmune SNPs, immune toxicity, and efficacy of ICI therapy. Given the large number of potential alleles that may be associated with immune toxicity, the wide variation in clinical phenotypes, and the increasing number of cancer types for which ICIs are used, it will be necessary to establish large prospective registries to further define risk profiles. Understanding the effect of germline genetic variants on the risk of irAEs may lead to the development of polygenic risk scores that could be implemented in clinical settings to identify patients who are at risk and who require additional surveillance and prompt treatment when receiving ICI therapy, primarily those who receive treatment in the adjuvant setting.

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Data availability Not applicable.

Compliance with ethical standards

Ethics approval and consent to participate The study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. IRB number: PA16-0928. All patients signed an informed consent prior to study participation.

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