HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2019 January 15.

Published in final edited form as:

J Invest Dermatol. 2017 January ; 137(1): 251–253. doi:10.1016/j.jid.2016.07.038.

IRF4 Polymorphism Is Associated with Cutaneous Squamous Cell Carcinoma in Organ Transplant Recipients: A Pigment-Independent Phenomenon

Maryam M. Asgari[1], **Amanda E. Toland**[2], and **Sarah T. Arron**[3,*]

[1]Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts, USA;

[2]Department of Cancer Biology and Genetics and the Division of Human Genetics, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA;

[3]Department of Dermatology, University of California, San Francisco, California, USA

TO THE EDITOR

Cutaneous squamous cell carcinoma (cSCC) is the most common cancer in solid organ transplant recipients (OTRs), with a U.S. incidence of 1,355 per 100,000 (Garrett et al., unpublished data) and a 65- to 100-fold increased risk over the general population (Hartevelt et al., 1990; Jensen et al., 1999; Zwald and Brown, 2011). Primary risk factors for posttransplantation cSCC are white race, male sex, older age at transplantation, and extent and duration of immunosuppression (Gogia et al., 2013; Mansh et al., 2016; Singer et al., 2012; Zwald and Brown, 2011). An additional risk factor is Fitzpatrick skin type, a scale that describes patient ability to suntan versus sunburn (Fitzpatrick, 1988; Gogia et al., 2013).

Recently, a genome-wide association study (GWAS) was performed for cSCC (Asgari et al., 2016). This study reported increased cSCC risk associated with polymorphisms in six pigment-related loci and found that these influenced cSCC risk independent of pigment-related phenotypes. In this study, we investigated the association between pigment-related single-nucleotide polymorphisms (SNPs) and hazard for cSCC in organ transplant recipients (OTRs), independent of Fitzpatrick skin type.

Methods

Subjects in this study were white OTRs drawn from a previously described cohort and enrolled from patient-targeted outreach between 2004 and 2008 (Gogia et al., 2013). Subjects consented for a cross-sectional survey and medical record review. Of the 694 subjects in the cohort, 639 (92%) were white; 453 gave blood for genotyping (71%). Subjects provided written informed consent according the procedures approved by the University of California, San Francisco Institutional Review Board.

*Corresponding author sarah.arron@ ucsf.edu.

CONFLICT OF INTEREST

The authors state no conflict of interest.

Samples were genotyped using the Axiom Genome-Wide Human Array system, with the EUR array (Affymetrix, Santa Clara, California) used for the Kaiser Permanente Research Program on Genes, Environment and Health (Asgari et al., 2016; Hoffmann et al., 2011). Of 453 subjects, 44 (9.7%) failed quality control checks based on a call rate of less than 97%; 13 were removed on the basis of chromosome X heterozygosity requiring males to be less than 20% and females greater 10%; five were excluded for cSCC before transplantation (left-censoring), leaving 388 for analysis. We excluded 8,529 SNPs with greater than 5% missing geno-typing data, 4,154 SNPs with a minor allele frequency less than 1%, and 17,499 SNPs on the sex chromosomes, resulting in a total of 544,820. The potential for population stratification was assessed via principle components analysis and the EIGENSTRAT method (Price et al., 2006).

We screened our genotype dataset for previously reported genes of pigmentation associated with cSCC development, based on systematic review of the literature (Binstock et al., 2014) and the recently published GWAS for cSCC (Asgari et al., 2016). Eight candidate SNPs were identified for investigation.

We conducted Cox proportional hazards models to assess the association of each SNP with time to cSCC. We evaluated the effect of genotype by extending our previously reported Cox regression model of male sex, age at transplantation older than 50 years, type of organ transplanted (abdominal vs. thoracic), and Fitzpatrick skin type (Gogia et al., 2013). The SNP variables were coded as a continuous count of the number of minor alleles based on the additive genetic model. Per-allele hazard ratio (HR) and 95% confidence interval were obtained for each SNP, adjusted for the described covariates. Statistical significance was assessed with the Wald test, and proportional hazards assumption for these SNPs was tested using the Schoenfeld residuals.

Results

Of our previously reported OTR cohort, 388 subjects had genotype data, and 177 subjects (59.8%) developed cSCC during the follow-up period (Table 1). Most subjects were male and received abdominal transplants (kidney, liver, and pancreas), with a normal distribution of Fitzpatrick skin types.

Eight candidate SNPs in genes of pigmentation were available for analysis (Table 2). In univariate analysis, the *IRF4* rs12203592 Tallele was associated with a significantly increased hazard for time to first cSCC (HR = 1.36, $P = 0.02$); this association was maintained when adjusted for sex, age, organ transplanted, and Fitzpatrick skin type (HR = *1.34*, $P = 0.04$). The *SLC45A2* rs16891982 C allele was associated with a decreased hazard for cSCC in univariate analysis (HR = 0.58, $P = 0.04$), and the effect was similar but not significant in the multivariate model (HR = 0.74, $P = 0.06$). None of these candidates achieved a Bonferroni-adjusted P-value threshold for multiple tests ($P < 0.00625$ for eight SNPs).

Six other SNPs did not show a significant association with hazard for cSCC by univariate or multivariate regression. These included two that were identified in the prior GWAS, *TYR* rs1126809 and *HERC2* rs12916300.

Discussion

This study investigates the association between genetic polymorphism in pigmentation genes with cSCC risk in OTRs. We have confirmed a significant role for *IRF4* rs12203592 and *SLC45A2* rs16891982, with effect sizes similar to those observed by Asgari et al. (2016). The modest effect sizes observed in the GWAS study for the TYR rs1126809 and *HERC2* rs12916300 SNPs were similar to those observed in our OTR cohort; these may have achieved significance with a larger sample size.

IRF4 is involved in activation of melanin synthesis via tyrosinase. rs12203592 falls within an enhancer region of *IRF4*; the T allele impairs transcription factor binding, leading to reduced expression of IRF4 and tyrosinase (Praetorius et al., 2013).

In a recent meta-analysis, the association between rs12203592 polymorphism and SCC was significant in dominant, recessive, and codominant models (Wu et al., 2016). The additive genetic model was selected a priori for our study, but exploration of the codominant model confirmed the association between SCC risk and the TT versus CC genotype (HR = 2.24, 95% confidence interval = 1.22–4.09, $P = 0.009$).

Previous studies investigating genetic risks for cSCC in OTRs have been limited by small sample sizes and candidate gene approach; the recent GWAS for cSCC has informed our candidate gene selection in this cohort. Our study design enabled investigation of these genes in the context of Fitzpatrick skin type, an important risk factor. Our data show that genotype data can improve risk stratification for post-transplantation cSCC beyond the clinical pigmentation phenotype.

Strengths of this study include a well-characterized cohort with Fitzpatrick type and histopathologic confirmation of cSCC outcomes. The genotyping array is the same as that used in Asgari et al. (2016), allowing direct validation of SNPs reported in that publication. The primary limitation is small sample size, but this pilot data supports development of cohort studies to generate genetic risk prediction models for posttransplantation cSCC.

ACKNOWLEDGMENTS

This work was supported in part by NIH R01CA166672 (MMA) and NIH/NCRR/OD UCSF/CTSI grant number KL2 RR024130 (STA).

Abbreviations:

cSCC	cutaneous squamous cell carcinoma
GWAS	genome-wide association study
HR	hazard ratio

OTR	organ transplant recipient
SNP	single-nucleotide polymorphism

REFERENCES

Asgari MM, Wang W, Ioannidis NM, Itnyre J, Hoffmann T, Jorgenson E, et al. Identification of Susceptibility Loci for Cutaneous Squamous Cell Carcinoma. J Invest Dermatol 2016;136:930–7. [PubMed: 26829030]

Binstock M, Hafeez F, Metchnikoff C, Arron ST. Single-nucleotide polymorphisms in pigment genes and nonmelanoma skin cancer predisposition: a systematic review. Br J Dermatol 2014;171:713–21. [PubMed: 25319428]

Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988;124:869–71. [PubMed: 3377516]

Gogia R, Binstock M, Hirose R, Boscardin WJ, Chren MM, Arron ST. Fitzpatrick skin phototype is an independent predictor of squamous cell carcinoma risk after solid organ transplantation. J Am Acad Dermatol 2013;68:585–91. [PubMed: 23107311]

Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation 1990;49:506–9. [PubMed: 2316011]

Hoffmann TJ, Kvale MN, Hesselson SE, Zhan Y, Aquino C, Cao Y, et al. Next generation genome-wide association tool: design and coverage of a high-throughput European-optimized SNP array. Genomics 2011;98:79–89. [PubMed: 21565264]

Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 1999;40:177–86. [PubMed: 10025742]

Mansh M, Binstock M, Williams K, Hafeez F, Kim J, Glidden D, et al. Voriconazole exposure and risk of cutaneous squamous cell carcinoma, Aspergillus colonization, invasive aspergillosis and death in lung transplant recipients. Am J Transplant 2016;16:262–70. [PubMed: 26372838]

Praetorius C, Grill C, Stacey SN, Metcalf AM, Gorkin DU, Robinson KC, et al. A polymorphism in IRF4 affects human pigmentation through a tyrosinase-dependent MITF/TFAP2A pathway. Cell 2013;155:1022–33. [PubMed: 24267888]

Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 2006;38:904–9. [PubMed: 16862161]

Singer JP, Boker A, Metchnikoff C, Binstock M, Boettger R, Golden JA, et al. High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients. J Heart Lung Transplant 2012;31:694–9. [PubMed: 22484291]

Wu M, Cao Y, Liu YL, Ma LL, Yang XH. Meta-analysis of the correlation netween interleukin-6 promoter polymorphism p-174G/C and interferon regulatory factor 4 rs12203592 polymorphism with skin cancer susceptibility [e-pub ahead of print]. Am J Ther 2016; 10.1097/MJT.0000000000000429.

Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011;65:253–61. [PubMed: 21763561]

Table 1.

Demographics of genotyped patient cohort (N = 388)

Characteristic	n (%)
Sex	
Female	138 (35.6)
Male	250 (68.4)
Age at transplantation, years	
<50	208 (54.0)
≥50	177 (46.0)
Organ transplanted	
Kidney, liver, pancreas	319 (82.2)
Heart, lung (including heart-lung, heart-kidney)	69 (17.8)
Fitzpatrick skin type	
I: Always burns easily	26 (6.9)
II: Always burns easily, tans a little	74 (19.7)
III: Burns moderately, tans gradually	122 (32.45)
IV: Burns a little, tans well	94 (25.0)
V: Rarely burns, tans profusely	49 (13.0)
VI: Never burns	11 (2.93)
Hair color	
Brown/black	286 (75.1)
Red/blond	95 (24.9)
Eye color	
Brown/hazel/green	187 (49.21)
Blue/gray	193 (59.79)
Developed posttransplantation cSCC	
No	119 (40.2)
Yes	177 (59.8)

Table 2.

Hazard of developing squamous cell carcinoma after organ transplantation based on genotype

Gene	SNP	Minor Allele	Minor Allele Frequency	Univariate HR	*P*	95% Cl	Multivariate HR[1]	*P*	95% CI
IRF4[2]	rs12203592	T	0.232	**1.36**	**0.02**	**1.04–1.77**	**1.34**	**0.04**	**1.02–1.77**
SLC45A2[2]	rs16891982	C	0.043	**0.58**	**0.04**	**0.35–0.96**	0.74	0.06	0.55–1.01
TY[2]	rs1126809	A	0.274	1.04	0.81	0.78–1.38	0.87	0.34	0.66–1.15
HERC2[2]	rs12916300	C	0.263	0.88	0.33	0.68–1.14	0.90	0.36	0.71–1.13
ASIP	rs1015362	T	0.286	0.94	0.59	0.73–1.20	0.79	0.05	0.62–1.00
TYR	rs1042602	A	0.381	1.05	0.64	0.85–1.31	1.07	0.53	0.87–1.32
MC1R	rs4408545	T	0.472	0.89	0.38	0.69–1.15	0.83	0.17	0.64–1.08
OCA2	rs916977	T	0.176	0.91	0.46	0.72–1.16	0.87	0.31	0.68–1.13

Abbreviations: CI, confidence interval; HR, hazard ratio; SNP, single nucleotide polymorphism.

Boldface type highlights SNPs achieving statistical significance.

[1]Multivariate Cox regression model is adjusted for sex, age at transplantation, abdominal vs. thoracic organ transplanted (heart, lung, heart-lung, and heart-kidney vs. kidney, liver, and pancreas), and Fitzpatrick skin type.

[2]Indicates SNPs meeting genome-wide significance in Asgari et al. (2016).