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Null Results in Brief

Variants Associated with Susceptibility to Pancreatic Cancer and Melanoma Do Not Reciprocally Affect Risk

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Abstract

Background: Melanoma cases may exist in pancreatic cancer kindreds, whereas there is increased risk of pancreatic cancer in familial melanoma. The two cancers may share genetic susceptibility variants in common.

Methods: Three dbGaP (datasets in Genotypes and Phenotypes)-deposited GWAS (genome-wide association study) datasets (MD Anderson melanoma, PanScan 1, and PanScan 2 for pancreatic cancer) were used. Thirty-seven melanoma susceptibility variants in 22 genomic regions from published GWAS, plus melanoma-related genes and pathways were examined for pancreatic cancer risk in the PanScan datasets. Conversely, nine known pancreatic cancer susceptibility variants were examined for melanoma risk in the MD Anderson dataset.

Results: In the PanScan data, initial associations were found with melanoma susceptibility variants in *NCOA6* [rs4911442; OR, 1.32; 95% confidence interval (CI), 1.03–1.70; $P = 0.03$], *YWHAZP5* (rs17119461; OR, 2.62; 95% CI, 1.08–6.35; $P = 0.03$), and *YWHAZP5* (rs17119490; OR, 2.62; 95% CI, 1.08–6.34; $P = 0.03$), *TYRP1* ($P = 0.04$), and *IFNA13* ($P = 0.04$). In the melanoma dataset, two pancreatic cancer susceptibility variants were associated: *NR5A2* (rs12029406; OR, 1.39; 95% CI, 1.01–1.92; $P = 0.04$) and *CLPTM1L-TERT* (rs401681; OR, 1.16; 95% CI, 1.01–1.34; $P = 0.04$). None of these associations remained significant after correcting for multiple comparisons.

Conclusion: Reported variants of melanoma genes and pathways do not play a role in pancreatic cancer predisposition. Reciprocally, pancreatic cancer susceptibility variants are not associated with melanoma risk.

Impact: Known melanoma-related genes and pathways, as well as GWAS-derived susceptibility variants of melanoma and pancreatic cancer, do not explain the shared genetic etiology of these two cancers. *Cancer Epidemiol Biomarkers Prev; 23(6); 1121–4. ©2014 AACR.*

Introduction

Certain subsets of pancreatic cancer kindreds have members with increased risk of melanoma (1); in parallel, there is increased risk for pancreatic cancer in melanoma kindreds (2, 3). Hypothesizing that these two cancers have common genetic susceptibility, we examined whether known melanoma-related genes and pathways, or susceptibility variants of melanoma and pancreatic cancer found in previous genome-wide association studies (GWAS), have shared genetic etiology.

Materials and Methods

Three public GWAS datasets in the database of Genotypes and Phenotypes (dbGaP) were used: (i) the MD Anderson Cancer Center melanoma GWAS (4), (ii) PanScan 1(5), and (iii) PanScan 2 (PanScan datasets; ref. 6). These datasets, quality control procedures, selection of candidate variants, genes and pathways, and methods are provided in Supplementary Materials and Methods. Candidate susceptibility variants from existing GWAS and known melanoma-related genes were selected. Pathways included genes known to be related to melanoma (26 genes), chromosome 9p21 (44 genes), cell cycle (8 genes), eye color (7 genes), freckling (5 genes), nevi (3 genes), pigmentation (12 genes), and sun sensitivity (8 genes; Supplementary Tables S1 and S2). For candidate genes and pathway association analysis, single-nucleotide polymorphisms (SNP) were selected for each gene using a

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Table 1. Associations of melanoma susceptibility variants, genes, and pathways with pancreatic cancer risk

Chromosome	SNP	Gene region	Melanoma OR (95% CI)	Minor/ref. alleles, MAF[a]	PanScan I		PanScan II		Combined PanScan I and II		Mayo clinic combined subset	
					OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Susceptibility variants observed in GWAS												
1	rs3219090	*PARP1*	0.91 (0.85–0.97)	T/C 0.35	0.94 (0.85–1.03)	0.20	1.02 (0.91–1.14)	0.76	0.98 (0.91–1.05)	0.52	1.17 (0.99–1.38)	0.07
1	rs7412746	*ARNT/CYCSP51*	0.89 (0.85–0.95)	C/T 0.47	0.98 (0.89–1.08)	0.66	1.03 (0.93–1.15)	0.54	1.02 (0.95–1.09)	0.66	0.94 (0.80–1.10)	0.43
2	rs13016963	*ALS2CR12*	1.11 (1.06–1.18)	A/G 0.40	1.07 (0.97–1.18)	0.16	1.01 (0.91–1.13)	0.87	1.05 (0.98–1.13)	0.20	1.007 (0.85–1.19)	0.94
9	rs10757257	*MTAP*	0.83 (0.76–0.91)	A/G 0.39	1.04 (0.94–1.14)	0.45	1.06 (0.96–1.18)	0.25	1.05 (0.97–1.12)	0.21	1.03 (0.88–1.22)	0.69
9	rs1335510	Near *MTAP*	0.84 (0.77–0.92)	G/T 0.39	1.05 (0.96–1.16)	0.30	1.05 (0.95–1.17)	0.35	1.05 (0.98–1.12)	0.20	1.08 (0.91–1.27)	0.37
9	rs1408799	Near *TYRP1*	0.87 (0.81–0.94)	T/C 0.34	1.05 (0.95–1.16)	0.36	1.08 (0.97–1.21)	0.18	1.08 (0.998–1.16)	0.06	0.98 (0.82–1.17)	0.78
9	rs2218220	Near *MTAP*	1,15 (1.09–1.22)	C/T 0.51	0.99 (0.91–1.09)	0.85	0.95 (0.86–1.06)	0.35	0.97 (0.91–1.04)	0.47	0.96 (0.82–1.13)	0.62
9	rs7023329	*MTAP*	0.85 (0.80–0.91)	G/A 0.47	1.02 (0.93–1.12)	0.72	1.06 (0.95–1.17)	0.30	1.03 (0.96–1.11)	0.36	1.05 (0.89–1.23)	0.58
10	rs17119434	Near *YWHAZP5*	6.8 (3.3–14.2)	G/A 0.01	1.04 (0.67–1.62)	0.86	0.97 (0.59–1.60)	0.90	1.05 (0.76–1.45)	0.78	2.12 (0.91–5.03)	0.08
10	rs17119461	Near *YWHAZP5*	8.4 (4.2–17.0)	C/T 0.01	0.99 (0.63–1.55)	0.96	1.03 (0.63–1.70)	0.90	1.05 (0.75–1.46)	0.78	2.62 (1.08–6.35)	0.03
10	rs17119490	Near *YWHAZP5*	8.4 (4.2–17.0)	A/G 0.01	1.02 (0.65–1.59)	0.95	1.04 (0.63–1.72)	0.87	1.07 (0.77–1.49)	0.69	2.62 (1.08–6.34)	0.03
11	rs1042602	*TYR*	0.92 (0.87–0.98)	A/C 0.37	1.03 (0.94–1.14)	0.53	1.03 (0.93–1.15)	0.55	1.04 (0.97–1.12)	0.28	0.97 (0.82–1.14)	0.71
11	rs1393350	*TYR*	1.29 (1.21–1.38)	A/G 0.23	1.11 (0.99–1.23)	0.08	0.92 (0.81–1.03)	0.16	1.008 (0.93–1.09)	0.85	1.008 (0.83–1.22)	0.94
11	rs1801516	*ATM*	0.87 (0.81–0.94)	A/G 0.16	1.02 (0.89–1.16)	0.81	0.95 (0.82–1.10)	0.50	0.99 (0.90–1.09)	0.86	1.15 (0.92–1.44)	0.21
11	rs1806319	*TYR/NOX4*	1.24 (1.13–1.35)	C/T 0.35	1.07 (0.97–1.18)	0.19	0.90 (0.80–1.00)	0.06	0.98 (0.92–1.06)	0.68	0.99 (0.83–1.17)	0.88
16	rs258322	*CDK10*	1.67 (1.52–1.83)	A/G 0.27	0.94 (0.81–1.10)	0.46	1.02 (0.85–1.23)	0.82	0.98 (0.87–1.10)	0.70	1.01 (0.78–1.33)	0.92
16	rs4785763	*AFG3L1*	1.36 (1.28–1.45)	A/C 0.29	1.07 (0.97–1.19)	0.16	0.98 (0.87–1.09)	0.67	1.03 (0.95–1.11)	0.49	1.12 (0.94–1.34)	0.19
20	rs1015362	*RPS2P1/XPOTP1*	0.69 (0.61–0.78)	T/C 0.28	0.99 (0.89–1.10)	0.78	1,08 (0.96–1.21)	0.21	1.02 (0.95–1.11)	0.56	1.04 (0.87–1.24)	0.66
20	rs4911414	*RPS2P1/XPOTP1*	1.45 (1.29–1.64)	T/G 0.31	1.01 (0.92–1.12)	0.83	1.09 (0.97–1.22)	0.15	1.03 (0.96–1.11)	0.44	1.14 (0.96–1.35)	0.13
20	rs4911442	*NCOA6*	1.51 (1.33–1.7)	G/A 0.09	1.04 (0.84–1.20)	0.65	0.997 (0.85–1.17)	0.97	0.998 (0.90–1.11)	0.97	1.32 (1.03–1.70)	0.03
21	rs45430	*MX2*	0.91 (0.86–0.96)	C/T 0.37	0.98 (0.89–1.08)	0.67	0.99 (0.89–1.11)	0.88	0.99 (0.92–1.07)	0.80	0.98 (0.83–1.16)	0.85
22	rs2284063	*PLA2G6*	0.83 (0.78–0.88)	G/A 0.34	0.93 (0.85–1.03)	0.15	1.04 (0.93–1.16)	0.48	0.98 (0.91–1.05)	0.60	1.02 (0.86–1.20)	0.86
22	rs6001027	*PLA2G6*	0.83 (0.78–0.89)	G/A 0.34	0.93 (0.84–1.02)	0.12	1.04 (0.93–1.16)	0.53	0.98 (0.91–1.05)	0.49	1.01 (0.85–1.20)	0.90
SNPs in high LD ($r^2 > 0.5$) with susceptibility variants of interest												
9	rs935053 [rs10965127, rs7040895][b]	Near *MTAP*	0.81 (0.74–0.89)	A/G 0.50	0.91 (0.78–1.07)	0.25	0.95 (0.85–1.05)	0.33	0.97 (0.91–1.04)	0.41	0.93 (0.71–1.21)	0.58
11	rs10830253 [rs1393350, rs1939255][b]	*TYR*	1.26 (1.14–1.39)	G/T 0.30	1.11 (0.99–1.23)	0.08	0.84 (0.66–1.06)	0.14	0.90 (0.77–1.06)	0.20	0.92 (0.65–1.30)	0.64
11	rs1847142 [rs1393350, rs1939255][b]	*TYR*	1.31 (1.21–1.41)	A/G 0.30	1.11 (0.99–1.23)	0.08	0.84 (0.66–1.06)	0.14	0.90 (0.77–1.06)	0.20	0.92 (0.65–1.30)	0.64
15	rs12913832 [rs7183877][b]	*HERC2*	0.69 (0.61–0.79)	A/G 0.29	1.13 (0.94–1.37)	0.20	1.06 (0.87–1.28)	0.58	1.11 (0.97–1.27)	0.13	0.81 (0.57–1.15)	0.24
20	rs1885120 [rs11906160, rs6058154][b]	*MYH7B*	1.78 (1.54–2.04)	C/G 0.05	1.003 (0.91–1.10)	0.95	0.97 (0.82–1.15)	0.73	0.98 (0.88–1.10)	0.76	1.09 (0.93–1.28)	0.29

[a]Minor and reference alleles and minor allele frequency (MAF) in Europeans.

[b]Variant(s) within brackets are in LD with the targeted SNP and are used to represent the association between the targeted variant and pancreatic cancer risk.

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boundary of 20 kb upstream and 10 kb downstream of the transcriptional sites. Data from genotyping and imputation were analyzed using unconditional multivariable logistic regression assuming an additive model. For the PanScan data, covariates in the model included age, sex, study site, genotypic race from EIGENSTRAT analysis (principal components PC1 and PC2), and other significant principal components (PC4 and PC9 for PanScan1, and PC3 for PanScan 2). In the Mayo Clinic subset, we also included additional covariate data: smoking status, family history of cancer (first degree), body mass index, and long-standing diabetes. We performed a similar adjusted analysis of the melanoma data with publicly available covariates: age, sex, two significant principal components (4), family history of cancer, and sun exposure parameters (sunburn, nevi, moles, freckling, tanning, skin color, hair color, and eye color). ORs and 95% confidence intervals (CI) were computed using Plink 1.07. The gene-based association analysis was conducted using the logistic regression model fit for genotype trend effects (1 degree of freedom) adjusted for study, age, sex, self-described ancestry and principal components as previously described (6). The gene-based *P* value was evaluated through a bootstrap procedure using the minP test statistic. We then conducted the pathway analysis based on the adaptive rank truncated product (ARTP) method, which combines gene-level *P* values within a pathway into the test statistic and uses a bootstrap procedure to estimate its *P* value (7). The *P* value for both the gene-based and pathway analyses was estimated by 30,000 parametric bootstrap steps.

Results

Of 37 melanoma susceptibility variants included in this analysis, 28 were present in the PanScan GWAS data ($n = 23$) or were represented by SNPs in high linkage disequilibrium (LD) ($r^2 > 0.5$; ref. 8) as determined by Haploview ($n = 5$). Nine variants could not be tagged (rs16891982, rs17305573, rs1805006, rs1805007, rs28777, rs35391, rs35391, rs1129038, and rs1805008). Several SNPs were shown to be associated with pancreatic cancer risk in the Mayo Clinic subset with covariate adjustment: *NCOA6* (rs4911442; OR, 1.32; 95% CI, 1.03–1.70; $P = 0.03$), *YWHAZP5* (rs17119461; OR, 2.62; 95% CI, 1.08–6.35; $P = 0.03$), and *YWHAZP5* (rs17119490; OR, 2.62; 95% CI, 1.08–6.34; $P = 0.03$; Table 1). The association analysis of melanoma pathways and genes in the PanScan data is shown in Supplementary Table S2. Examination of the 44 genes at chromosome 9p21, in which *CDKN2A* is located, revealed marginal evidence for significant associations with pancreatic cancer risk: *IFNA13* ($P = 0.044$) and *IFNA6* ($P = 0.059$). Evaluation of all 9p21 SNPs showed that the top three SNPs with the lowest *P* values were observed in *LINGO2*, which is associated with Parkinson disease and essential tremor disorder. Although the gene-based *P* value of *LINGO2* is 0.13, this gene had several SNPs (including those with the lowest *P* values) with $P < 0.001$ located in two approximately 3-kb regions of relatively high LD ($r^2 > 0.5$; ref. 8) within this large gene (total number of SNPs evaluated = 294). Evaluation of the 26 melanoma candidate genes produced only one nominally significant gene, *TYRP1*. The top five SNPs with the lowest *P* values were in *PTPRD*, located at 9p. *CDKN2A* and *CDKN2B* were not significant in this analysis ($P = 0.60$ and 0.45, respectively). Of the nine known pancreatic cancer susceptibility variants, one SNP showed moderate association with melanoma risk: *NR5A2* (rs12029406; OR, 1.40; 95% CI, 1.01–1.93; $P = 0.04$; Table 2). None of the detected associations were significant after adjusting for multiple comparisons.

Table 2. Association of pancreatic cancer susceptibility variants with melanoma risk

Chromosome	SNP	Gene region	Pancreatic cancer OR (95% CI)	Minor/ref. allele, MAF[a]	Melanoma OR (95% CI)	Melanoma *P*
SNPs observed in GWAS						
1	rs10919791	*NR5A2*, 1q32.1	0.77 (0.71–0.84)	A/G 0.24	1.01 (0.85–1.19)	0.95
1	rs3790843	*NR5A2*, 1q32.1	0.81 (0.75–0.87)	T/C 0.31	1.05 (0.91–1.22)	0.49
1	rs3790844	*NR5A2*, 1q32.1	0.77 (0.71–0.84)	G/A 0.26	1.01 (0.86–1.18)	0.94
1	rs4465241	*NR5A2*, 1q32.1	1.25 (1.14–1.37)	T/C 0.18	1.00 (0.83–1.21)	0.97
13	rs9543325	Near *FABP5L1*, 13q22.1	1.26 (1.18–1.35)	C/T 0.39	1.05 (0.91–1.21)	0.54
13	rs9564966	Near *FABP5L1*, 13q22.1	1.21 (1.13–1.30)	A/G 0.34	1.04 (0.90–1.21)	0.60
SNPs in high LD ($r^2 > 0.5$) with SNP of interest						
1	rs12029406 [rs17665538][b]	*NR5A2*, 1q32.1	0.83 (0.78–0.89)	T/C 0.43	1.40 (1.01–1.93)	0.04
5	rs401681 [rs402710][b]	*CLPTM1L-TERT*, 5p15.33	1.19 (1.11–1.27)	T/C 0.46	1.15 (1.00–1.33)	0.06
9	rs505922 [rs630014][b]	*ABO*	1.20 (1.12–1.28)	C/T 0.37	0.96 (0.84–1.10)	0.57

[a]Minor and reference alleles and minor allele frequency (MAF) in Europeans.

[b]Variant within brackets is in LD with the targeted SNP and is used to represent the association between the targeted variant and melanoma risk.

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Discussion

Genetic variants associated with risk for pancreatic cancer and melanoma and known melanoma-related pathways and genes do not account for the shared genetic etiology between melanoma and pancreatic cancer. The shared etiology of these cancers, clearly involves factors beyond SNPs.

Conclusion

Reported variants of melanoma genes and pathways do not play a role in pancreatic cancer predisposition. Conversely, pancreatic cancer susceptibility variants are not associated with melanoma risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Wu, A.M. Goldstein, L.T. Amundadottir, G.M. Petersen
Development of methodology: L. Wu, G.M. Petersen
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Wu, A.M. Goldstein, K. Yu, L.T. Amundadottir, G.M. Petersen
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.A. Arslan, R. Stolzenberg-Solomon, G.M. Petersen
Study supervision: L.T. Amundadottir, G.M. Petersen

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