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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, while there is increased risk of pancreatic cancer in familial melanoma. The two cancers may share genetic susceptibility variants in common.

Methods—Three dbGaP-deposited GWAS 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% 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.

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Disclosure of Potential Conflicts of Interest
No potential conflict of interests was disclosed.

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.

Keywords

Shared etiology; pancreatic cancer; melanoma; association analysis

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 Genotypes and Phenotypes (dbGaP) were used: (i) MD Anderson Cancer Center melanoma GWAS (4), (ii) PanScan 1(5), and (iii) PanScan 2(6) (PanScan datasets). These datasets, quality control procedures, selection of candidate variants, gene 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 1 and 2). For candidate genes and pathway association analysis, SNPs were selected for each gene using a 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 (BMI), and long-standing diabetes. We performed a similar adjusted analysis of the melanoma data with publicly available covariates: age, sex, two significant PCs (4), family history of cancer, and sun exposure parameters (sunburn, nevi, moles, freckling, tanning, skin color, hair color, and eye color). Odds ratios (OR) and 95% confidence intervals (CI) were computed using Plink 1.07. Gene-based association analysis was conducted using logistic regression model fit for genotype trend effects (1 d.f.) adjusted for study, age, sex, self-described ancestry and PCs 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 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 LD (r^2>.05) (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 are shown in Supplementary Table 2. Examination of the 44 genes at chromosome 9p21, where *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's 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 ~3 kb regions of relatively high LD (r^2>0.5) (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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

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

					PanScan I		PanScan II		Combined PanScan I & II		Mayo Clinic combined subset	
Chr	**SNP**	**Gene Region**	**Melanoma OR (95% CI)**	**Minor / Ref All, MAF***	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**
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

					PanScan I		PanScan II		Combined PanScan I & II		Mayo Clinic combined subset	
Chr	**SNP**	**Gene Region**	**Melanoma OR (95% CI)**	**Minor / Ref All, MAF***	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**
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 with high LD (r^2>0.5)with susceptibility variants of interest												
9	rs935053 [rs10965127, rs7040895]#	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]#	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]#	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]#	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]#	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

*Minor and reference alleles and minor allele frequency (MAF) in Europeans

#Variant(s) within brackets are within LD of the targeted SNP and are used to represent the association between the targeted variant and pancreatic cancer risk

Table 2

Association of pancreatic cancer susceptibility variants with melanoma risk

					Melanoma	
Chromosome	**SNP**	**Gene Region**	**Pancreatic Cancer OR (95% CI)**	**Minor / Ref Allele, MAF***	**OR (95% C.I.)**	**p-value**
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 with high LD (r^2>0.5) with SNP of interest						
1	rs12029406 [rs17665538]#	NR5A2, 1q32.1	0.83 (0.78–0.89)	T/C 0.43	1.40 (1.01–1.93)	**0.04**
5	rs401681 [rs402710]#	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]#	ABO	1.20 (1.12–1.28)	C/T 0.37	0.96 (0.84–1.10)	0.57

*Minor and reference alleles and minor allele frequency (MAF) in Europeans

#Variant within brackets is within LD of the targeted SNP and is used to represent the association between the targeted variant and melanoma risk