

## Genome-Wide "Pleiotropy Scan" Identifies HNF1A Region as a Novel Pancreatic Cancer Susceptibility Locus

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### Abstract

In genome-wide association (GWA) studies, hundreds of thousands of single-nucleotide polymorphisms (SNP) are tested for association with a disease trait. Typically, GWA studies give equal consideration to all SNPs tested, regardless of existing knowledge of an SNP's functionality or biological plausibility of association. Because many tests are conducted, very low statistical significance thresholds ( $P < 5 \times 10^{-8}$ ) are required to identify true associations with confidence. By restricting GWA analyses to SNPs with enhanced prior probabilities of association, we can reduce the number of tests conducted and relax the required significance threshold, increasing power to detect association. In this analysis of existing GWA data on pancreatic cancer cases ( $n = 1,736$ ) and controls ( $n = 1,802$ ) of European descent (the PanScan study), we conduct a GWA scan restricted to SNPs that have been reported to associate with human phenotypes in previous GWA studies (with  $P < 5 \times 10^{-8}$ ). Using this method, we drastically reduce the number of tests conducted (from  $\sim 550,000$  to 1,087) and test only SNPs that are known to be (or tag) variants that influence human biological processes. Of the 1,087 SNPs tested, the strongest association observed was for HNF1A SNP rs7310409 ( $P = 3 \times 10^{-5}$ ;  $P_{\text{Bonferroni}} = 0.03$ ), an SNP known to associate with circulating C-reactive protein. This association was replicated in an independent sample of 1,094 cases and 1,165 controls ( $P = 0.02$ ), producing a highly significant association in the combined data sets ( $P = 2 \times 10^{-6}$ ;  $P_{\text{Bonferroni}} = 0.002$ ). The HNF1A region also harbors variants that influence several human traits, including maturity-onset diabetes of the young, type 2 diabetes, low-density lipoprotein cholesterol, and N-glycan levels. This novel "pleiotropy scan" method may be useful for identifying susceptibility loci for other cancer phenotypes. *Cancer Res*; 71(13); 4352–8. ©2011 AACR.

### Introduction

Recently, genome-wide associations (GWA) studies have identified common single-nucleotide polymorphisms (SNP) in 4 genomic regions that are associated with pancreatic cancer risk (1, 2). These SNPs show associations with pancreatic cancer that are statistically significant at a "genome-wide" significance level ( $\sim P < 5 \times 10^{-8}$ ; ref. 3). This stringent significance threshold accounts for the fact that many statistical tests are being conducted and ensures that the majority of the significant associations identified will be true positives. However, as a consequence of this threshold, variants with very weak associations may not be detectable, even in large GWA studies of pancreatic cancer, because the resulting  $P$  values do not surpass the genome-wide significance threshold.

Reducing the number of tests conducted in an association study will relax the required significance threshold, thereby increasing statistical power to detect associations with pancreatic cancer for each SNP. One strategy for reducing the number of tests is to only test SNPs with heightened prior probabilities of association. The vast majority of the SNPs tested in a GWA study have no known consequences for human biology. However, recent GWA studies have identified thousands of loci harboring variants that are robustly associated with human phenotypes (3, 4). By testing only these variants, we can conduct a more hypothesis-based analysis, reduce the number of tests conducted, relax the significance thresholds, and increase power for each test.

In this analysis of existing GWA data on pancreatic cancer cases and controls, we conducted a GWA scan using only SNPs reported to associate with human phenotypes (other than pancreatic cancer) in previous GWA studies. Because these SNPs are markers of human biological processes, we argue that they are more likely, on average, to associate with pancreatic cancer risk than SNPs that have no known effects on human biology. We tested these SNPs for association with pancreatic cancer risk using data from cases and controls of European descent participating in the PanScan-I GWA study. We attempted to replicate our findings in an independent data set, the PanScan-II GWA study. By design, all observed associations arise from SNPs that have

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doi: 10.1158/0008-5472.CAN-11-0124

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implications for other human traits; thus, we call this approach a "pleiotropy scan."

## Materials and Methods

The Cancer Genetic Markers of Susceptibility (CGEMS) PanScan-I and PanScan-II GWA studies have been previously described (1, 2). Briefly, cases and controls were drawn from 12 cohort studies and 8 case-control studies. All cases were diagnosed with primary adenocarcinoma of the exocrine pancreas. Controls were matched to cases based on birth year, sex, and race/ethnicity and were free of pancreatic cancer at the time of diagnosis of the matched case. Sample quality control and genotyping was conducted at the National Cancer Institute (NCI) Core Genotyping Facility, using Illumina HumanHap550 and HumanHap550-Duo SNP arrays (PanScan-I) and Illumina Human 610-Quad arrays (PanScan-II; refs. 1, 2). In total, CGEMS provided high-quality genotype data for 1,895 cases and 1,937 controls from PanScan-I and for 1,478 cases and 1,534 controls from PanScan-II (after excluding duplicate samples). All data were downloaded from the database of Genotypes and Phenotypes (5).

This analysis was restricted to PanScan participants of European ancestry. We assessed population structure in both PanScan-I and PanScan-II using approximately 12,000 SNPs with low pair-wise linkage disequilibrium ( $r^2 < 0.05$  for any pair) and high call rates (<1% missing) in PanScan and HapMap3 founders (from CEU, YRI, and CHB + JPT data sets). Because PanScan-I and PanScan-II contain a substantial number of individuals of non-European ancestry, the EIGENSTRAT principal-components analysis (PCA) program was used to identify and exclude participants who did not cluster tightly with the CEU HapMap samples (253 in PanScan-I; 753 in PanScan-II). Based on identity-by-descent estimates, 1 individual from each suspected first- or second-degree relative pair was removed (14 in PanScan-I; 1 in PanScan-II). The resulting sample size for PanScan-I was 1,763 cases and 1,802 controls, and PanScan-II had 1,094 cases and 1,165 controls. PCA was used to generate principal components of ancestry in the PanScan-I, PanScan-II, and combined data sets.

SNPs included in this "pleiotropy scan" were selected using the National Human Genome Research Institute's (NHGRI's) catalogue of published GWA studies (6) that contains descriptive information on SNPs reported to be associated with a human phenotype in a GWA study at a significance level of  $P < 1.0 \times 10^{-5}$ . The catalogue data was downloaded on December 20, 2010, including SNP identifiers and  $P$  values for the reported associations. The catalogue contained 3,554 unique SNPs after excluding the 5 established pancreatic cancer susceptibility loci (rs9543325, rs3790844, rs401681, and rs505922) and 7 SNPs in linkage disequilibrium (LD;  $r^2 > 0.3$ ) with either rs401681 [telomerase reverse transcriptase (TERT) region] or rs505922 (ABO region).

Approximately 57% of the 3,554 catalogue SNPs ( $n = 2,043$ ) did not show prior evidence of association at a genome-wide significance level ( $P > 5 \times 10^{-8}$ ), and we excluded these SNPs to ensure that the vast majority of the SNPs in our analysis were truly associated with human traits. Of the remaining

1,511 catalogue SNPs, 883 were present in the PanScan-I data set. For the 628 SNPs not present, the GLIDERS program (7) was used to identify appropriate tagSNPs ( $r^2 > 0.9$  in HapMap3 CEU). By incorporating an additional 211 tagSNPs into our data set of 883 SNPs (1,094 SNPs total), we were able to tag 291 of the 628 catalogue SNPs that were missing from the PanScan-I data set (some tagSNPs tagged multiple catalogue SNPs). The remaining 337 catalogue SNPs were not included in this analysis; thus, we captured 78% of the 1,511 SNPs with reported significance level of  $P < 5 \times 10^{-8}$  in GWA studies. The 7 nonautosomal SNPs present in our data set were excluded, resulting in a final data set of 1,087 SNPs eligible for analysis. No individual was missing >5% of SNP data and no SNP was missing >5% of genotypic data.

Our general analytic strategy was to test all 1,087 SNPs for association with pancreatic cancer in the larger PanScan-I data set, attempt to replicate the top 10 hits in the PanScan-II data set, and assess their overall statistical significance based on the combined PanScan-I and PanScan-II data set. Logistic regression adjusted for 5 principal components, sex, and 10-year age groups (categorical) was used to generate ORs, 95% CIs, and  $P$  values for each of the 1,087 SNPs selected from the PanScan-I GWA data set. All SNPs were coded as 0, 1, or 2 minor alleles (a log-additive model).

In addition to Bonferroni-corrected  $P$  values, permutation-based  $P$  values were calculated to obtain less conservative, empirical significance measures that account for the LD structure of the SNPs in the GWA catalogue. Permutation-based  $P$  values were generated for the combined PanScan-I/II data set by conducting the pleiotropy scan on 10,000 data sets in which each subject's phenotypic data were randomly reassigned to another subject's genotypic data. The test statistics observed in the original analysis were compared with the distribution of maximum test statistics from each simulated data set to determine how often the observed  $P$  value occurred by chance.

To characterize the statistically significant association signals, we examined associations for all SNPs in the region of interest, using all SNPs present in the combined PanScan data sets. Statistical analyses were conducted using PLINK (8). Figures were generated using R (9) and LocusZoom (10).

## Results

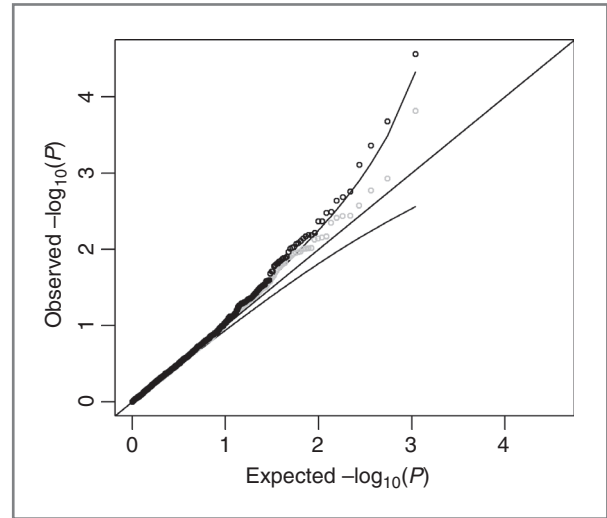
After PCA-based exclusions, PanScan-I had a slightly higher percentage of females (49%) than PanScan-II (46%). The age distributions categorized in <51, 51 to 60, 61 to 70, 74 to 80, and >80 age groups were 3%, 14%, 39%, 37%, and 7% for PanScan-I and 11%, 25%, 34%, 25%, and 4% for PanScan-II.

The vast majority of the  $P$  values for the 1,087 SNPs included in the PanScan-I pleiotropy scan did not show systematic departure from the expected uniform distribution ( $\lambda = 1.01$ ), suggesting that population stratification had been adequately accounted for using to PCA methods. The 10 most significantly associated SNPs from PanScan-I are shown in Table 1. Only rs7310409 showed a significant association with pancreatic cancer after Bonferroni correction ( $P_{\text{Bonferroni}} = 0.03$ ). Two additional HNF1A SNPs, rs735396 and rs2650000,

**Table 1.** Association estimates for the 10 most significant associations observed in PanScan pleiotropy scan

SNP	Chrom.	Gene region	MAF (MA)	PanScan-I (1,763 cases; 1,802 controls)		PanScan-II (1,094 cases; 1,165 controls)		PanScan-I + II (2,857 cases; 2,967 controls)			
				OR	95% CI	P	$P_{\text{Bonferroni}}$	OR	95% CI	P	$P_{\text{Bonf}}$
<b>rs7310409</b>	<b>12</b>	<b>HNF1A</b>	<b>0.40 (A)</b>	<b>1.11-1.35</b>	<b>0.00003</b>	<b>0.03</b>	<b>1.02-1.30</b>	<b>0.02</b>	<b><math>2 \times 10^{-6}</math></b>	<b>0.002</b>	<b>0.0008</b>
rs3748816	1	MME1	0.33 (C)	1.09-1.33	0.0002	0.21	0.78-1.00	0.05	0.66	1.00	1.00
<b>rs735396</b>	<b>12</b>	<b>HNF1A</b>	<b>0.38 (G)</b>	<b>1.08-1.31</b>	<b>0.0005</b>	<b>0.51</b>	<b>0.97-1.24</b>	<b>0.14</b>	<b>0.0003</b>	<b>0.33</b>	<b>0.07</b>
rs7202877	16	Intergenic	0.11 (G)	1.11-1.48	0.0009	1.00	0.99-1.43	0.07	0.0003	0.32	0.19
<b>rs2650000</b>	<b>12</b>	<b>HNF1A</b>	<b>0.37 (T)</b>	<b>1.06-1.28</b>	<b>0.002</b>	<b>1.00</b>	<b>1.02-1.30</b>	<b>0.03</b>	<b>0.0001</b>	<b>0.11</b>	<b>0.04</b>
rs2736990	4	SNCA	0.45 (C)	0.79-0.95	0.002	1.00	0.88-1.11	0.86	0.01	1.00	1.00
rs727957	21	KCNE1	0.18 (T)	1.07-0.36	0.003	1.00	0.94-1.28	0.23	0.001	1.00	0.95
rs2126259	8	PPP1R3B	0.09 (A)	0.67-0.92	0.003	1.00	0.75-1.14	0.46	0.005	1.00	0.98
rs9989419	16	CETP	0.40 (A)	0.79-0.96	0.004	1.00	0.89-1.13	0.99	0.03	1.00	1.00
rs9368699	6	SNORD52	0.04 (C)	0.53-0.88	0.004	1.00	0.82-1.48	0.53	0.07	1.00	1.00

NOTE: The three correlated HNF1A SNPs are shown in bold. Abbreviations: MAF, minor allele frequency; MA, minor allele.



**Figure 1.** A Q-Q plot of  $-\log_{10}(P)$  for associations of 1,087 trait-associated SNPs with pancreatic cancer (PanScan-I data). Data are shown both before (black) and after (gray) exclusion of all SNPs in the HNF1A region of association. The curved lines represent the 95% confidence envelope.

were ranked third and fifth among the top 10 associations and were in LD with lead SNP rs7310409 ( $r^2 = 0.77$  and  $0.55$ , respectively).

Interestingly, there were more SNPs contained in the low end of the  $P$ -value distribution than expected under null hypothesis of a uniform  $P$ -value distribution. In other words, the  $-\log_{10}(P)$  at the high end of the distribution were higher than expected according to the 95% confidence envelope of the quantile-quantile (Q-Q) plot (Fig. 1). After exclusion of SNPs in the HNF1A region, there was still suggestive evidence of departure from the null distribution, indicating that additional trait-associated SNPs may have true associations with pancreatic cancer.

In the PanScan-II replication analysis of the 10 most significant associations from PanScan-I, only the lead SNP from PanScan-I (HNF1A SNP rs7310409) and a correlated HNF1A SNP rs2650000 showed a nominally significant association with pancreatic cancer risk ( $P = 0.02$  and  $P = 0.03$ , respectively). On combining the PanScan-I and PanScan-II data sets, the association for rs7310409 reached a  $P$  value =  $2 \times 10^{-6}$  ( $P_{\text{Bonferroni}} = 0.002$ ; Table 1). The other 2 HNF1A SNPs showing associations with pancreatic cancer (rs735396 and rs2650000) had  $P$  values of 0.0002 ( $P_{\text{Bonferroni}} = 0.22$ ) and 0.0001 ( $P_{\text{Bonferroni}} = 0.11$ ) in the combined data set.

After all SNPs in the HNF1A region were analyzed in the combined PanScan-I and PanScan-II data set, including all noncatalogue SNPs included on the Illumina platforms, the strongest association was still rs7310409 (Fig. 2A), with several nearby correlated SNPs showing weaker associations. When rs7310409 was included as a covariate in the logistic regression analyses, all associations arising from the HNF1A region were essentially eliminated (Fig. 2B), indicating that there is most likely a singular association signal arising from the HNF1A region in this data set.

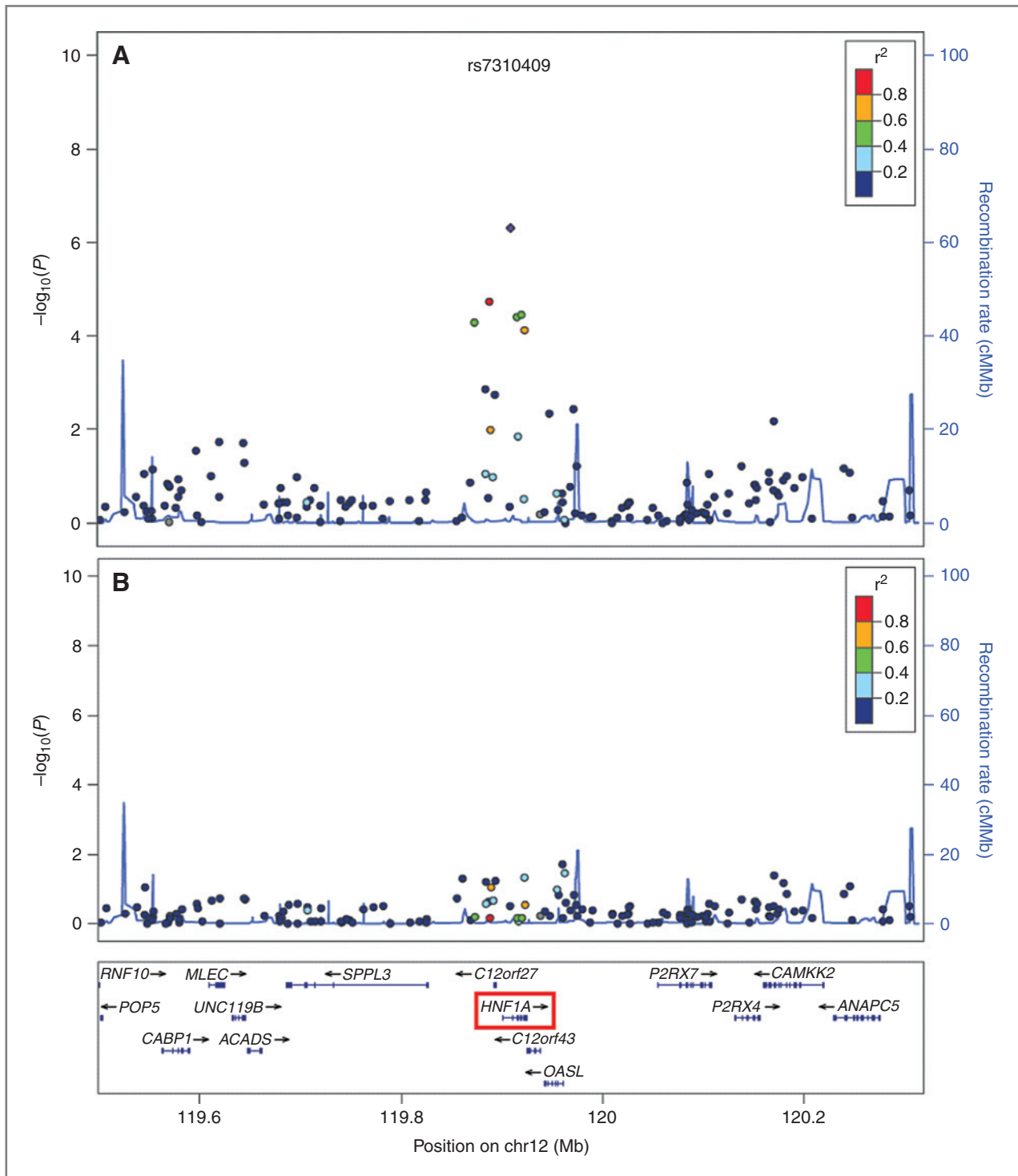


Figure 2. Association results for all genotyped SNPs in the HNF1A region (PanScan-I + II data).  $P$  values for each SNP are plotted both before (A) and after (B) adjusting each logistic regression for lead SNP rs7310409. Color coding of plotted  $P$  values represents correlation with rs7310409 (in HapMap CEU population). This figure includes all genotyped SNPs, including SNPs not contained in the NHGRI GWA study catalogue.

In the PanScan-I + II combined data set of 900 independent catalogue SNPs (excluding HNF1A SNPs and SNPs with pairwise  $r^2 > 0.5$  with other SNPs), 5.3% of SNPs had a  $P < 0.05$  and

1.6% of SNPs had  $P < 0.01$ , providing evidence for mild enrichment of non-HNF1A catalogue SNPs for association with pancreatic cancer.

## Discussion

In this study, we tested 1,087 SNPs with known implications for human phenotypes for association with pancreatic cancer risk using data from a large 2-stage GWA study of pancreatic cancer. By focusing on SNPs that represent genetic variation with effects on human biology, we have drastically reduced the number of tests typically conducted in a GWA study, while focusing on SNPs that are likely to have increased prior probabilities of association with human phenotypes, including pancreatic cancer. The 1,087 SNPs we interrogated were selected based on their strong evidence of association with human phenotypes in prior GWA studies.

We have identified an association signal in the HNF1A region. SNP rs7310409, an intronic SNP that lies <2 kilobases (kb) upstream of exon 2 of the HNF1A gene, showed convincing evidence of association with pancreatic cancer in the PanScan-I study, even after a conservative Bonferroni correction for multiple testing. This finding was replicated in PanScan-II, producing combined Bonferroni *P* value of 0.002. All associated SNPs in this region are in substantial LD with rs7310409, indicating that there is a singular association signal for pancreatic cancer in this region. Evidence for additional associations outside of the HNF1A regions was suggestive.

Several previous studies have considered integrating biological information, such as gene expression data (11), into GWA studies to improve gene discovery. However, to our knowledge, this is the first study to leverage biological information drawn from previous GWA studies. A recent study showed that trait-associated SNPs are more likely to be expression quantitative trait loci (eQTLs) than other SNPs on GWA platforms (12), suggesting that incorporating eQTL information into GWA studies may facilitate the discovery of new associations and provide a better understanding of dis-

ease mechanisms. In a similar fashion, our results suggest that SNPs identified in GWA studies may be more likely to show associations with other human traits than SNPs with no prior evidence of association. Although this theory warrants further evaluation in independent data sets, there is emerging evidence for pleiotropy in the cancer GWA literature, as several susceptibility loci [e.g., 8q24 (13), TERT (14), CDKN2A/2B (15–17)] have been linked to multiple cancers and other complex traits.

HNF1A (12q24.31) codes for hepatocyte nuclear factor 1 homeobox A (TCF1), a transcription factor expressed in the human liver, pancreas, kidney, and gut (18). HNF1A is known to be a critical member of a regulatory transcription factor circuit in the developing and mature pancreas (19). Common variants in the HNF1A region have been implicated by GWA studies in several human phenotypes, including circulating levels of the acute-phase inflammatory marker C-reactive protein (CRP; refs. 20–22), liver enzyme  $\gamma$ -glutamyl transferase (GGT; ref. 23), low-density lipoprotein (LDL) cholesterol (24), coronary heart disease (25), type 2 diabetes (26), and N-glycan levels in plasma (27; Table 2). However, this is the first study to link HNF1A variants to risk for any type of cancer. Although the lead SNP from this analysis (rs7310409) is in the NHGRI catalogue due to its reported associations with CRP, based on HapMap3 CEU LD estimates for nearby SNPs, rs7310409 would also be expected to associate with GGT levels, LDL cholesterol, coronary heart disease, and N-glycan levels in European populations (Table 2).

Interestingly, the lead SNP rs7310409 is not strongly correlated with the type 2 diabetes-risk variant rs7957197 ( $r^2 = 0.11$ ). Although rs7957197 is not present in our data set, its best tagSNP, rs7965349 ( $r^2 = 0.82$ ), is not associated with pancreatic cancer ( $P = 0.53$ ; Table 2), suggesting that the diabetes and pancreatic cancer association signals are independent. Type 2 diabetes is a well-established risk factor for pancreatic cancer

**Table 2.** A description of SNPs in the HNF1A region with associations reported in the NHGRI GWA study catalogue

SNP	$r^2$ with rs7310409 <sup>a</sup>	Associations reported in GWA catalogue				PanScan-I + II			
		Associated trait	Risk (or increaser) allele	Reported <i>P</i> value	Ref.	Best tagSNP ( $r^2$ )	OR	95% CI	<i>P</i>
rs7310409	N/A	C-reactive protein	A	$7 \times 10^{-17}$	(22, 31)	SNP present	1.19	1.11–1.19	$2 \times 10^{-6}$
rs1169310	0.71	C-reactive protein	A	$2 \times 10^{-8}$	(21)	rs735396 (1.00)	1.15	1.07–1.24	0.0003
rs1183910	0.64	C-reactive protein	T	$1 \times 10^{-30}$	(20)	rs2650000 (0.88)	0.16	1.07–1.25	0.0001
rs1169313	0.64	$\gamma$ -Glutamyl transferase	C	$2 \times 10^{-10}$	(23)	rs735396 (1.00)	1.15	1.07–1.24	0.0003
rs2650000	0.45	LDL cholesterol	A	$2 \times 10^{-8}$	(24)	SNP present	0.16	1.07–1.25	0.0001
rs7957197	0.11	Type 2 diabetes	T	$2 \times 10^{-8}$	(26)	rs7965349 (0.82)	0.97	0.88–1.07	0.52
rs2259816	0.64	Coronary heart disease	T	$5 \times 10^{-7}$	(25)	rs735396 (1.00)	1.15	1.07–1.24	0.0003
rs7953249	0.79	N-Glycan levels	G	$2 \times 10^{-8}$	(27)	rs7310409 (0.89)	1.19	1.11–1.19	$2 \times 10^{-6}$
rs735396	0.64	N-Glycan levels	G	$4 \times 10^{-8}$	(27)	SNP present	1.15	1.07–1.24	0.0003

<sup>a</sup>All  $r^2$  values are derived from HapMap3 CEU data.

(28), although the potential causality of this association is not well understood. Rare variants HNF1A are also known to cause maturity-onset diabetes of the young (MODY; ref. 29). Furthermore, it is worth noting that, in the combined Pan-Scan-I + II data set, the strongest non-HNF1A association observed was for the type 1 diabetes-associated SNP rs7202877 ( $P = 0.0003$ ,  $P_{\text{Bonferroni}} = 0.32$ ; ref. 30). Further investigation of this result is warranted.

Additional research is needed to identify the causal variant for pancreatic cancer in this region. Lead SNP rs7310409 is intronic and is in moderate LD with nonsynonymous coding HNF1A SNPs rs1169288 ( $r^2 = 0.62$ ) and rs2464196 ( $r^2 = 0.55$ ) and HNF1A 5'-untranslated region (UTR) SNPs rs1169310 ( $r^2 = 0.71$ ) and rs1169312 ( $r^2 = 0.73$ ). Furthermore, it is possible that the causal variant is untyped, potentially with a low minor allele frequency. Additional genes within approximately 100 kb of the HNF1A signal include C12orf27, C12orf43, OASL, SPPL3, and P2RX7.

This study was limited by our inability to test all SNPs of interest for association with pancreatic cancer. A total of 337, out of 1,511, eligible SNPs in the GWA catalogue (~22%) were neither present in our data set nor strongly correlated with any SNP in our data set. Thus, we may have missed additional regions with pleiotropic effects on pancreatic cancer risk. Furthermore, we acknowledge that secondary analyses of GWA data have the potential to generate false-positive associations. Thus, for secondary GWA analyses that integrate biological information, we emphasize the importance of clear hypotheses, careful treatment of multiple testing issues, and, ideally, a strategy for replication. Multiple testing issues are particularly important when multiple hypotheses are evalu-

ated and/or multiple analyses are carried out in relation to multiple traits.

In summary, this study has used a novel "pleiotropy scan" approach to identify HNF1A as a pancreatic cancer-risk locus. In this GWA-based approach, we have interrogated only SNPs that have been shown, in previous GWA studies, to associate with human traits. This approach increases the statistical power of GWA approaches by reducing the number of tests conducted and focusing on SNPs with heightened prior probabilities of association with disease risk. The central findings of this study further emphasize the importance of variation in the HNF1A gene region in relation to pancreatic function and related disease phenotypes, including type 2 diabetes, MODY, and pancreatic cancer.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Acknowledgments

The authors thank all researchers and study participants for contributing to the PanScan study and making this genetic data available to the research community. The authors also thank Lin Tong for her assistance in preparing the data sets.

### Grant Support

This work was supported by the NIH (grant nos. CA122171 and CA102484 to H. Ahsan) and the Department of Defense (grant no. W81XWH-10-1-0499 to B. Pierce).

Received January 12, 2011; revised March 18, 2011; accepted April 5, 2011; published OnlineFirst April 15, 2011.

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*Cancer Res* 2011;71:4352-4358. Published OnlineFirst April 15, 2011.

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