

Polygenic and multifactorial scores for pancreatic ductal adenocarcinoma risk prediction

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Abstract

Background Most cases of pancreatic ductal adenocarcinoma (PDAC) are asymptomatic in early stages, and the disease is typically diagnosed in advanced phases, resulting in very high mortality. Tools to identify individuals at high risk of developing PDAC would be useful to improve chances of early detection.

Objective We generated a polygenic risk score (PRS) for PDAC risk prediction, combining the effect of known risk SNPs, and carried out an exploratory analysis of a multifactorial score.

Methods We tested the associations of the individual known risk SNPs on up to 2851 PDAC cases and 4810 controls of European origin from the PANcreatic Disease ReseArch (PANDoRA) consortium. Thirty risk SNPs were included in a PRS, which was computed on the subset of subjects that had 100% call rate, consisting of 839 cases and 2040 controls in PANDoRA and 6420 cases and 4889 controls from the previously published Pancreatic Cancer Cohort Consortium I–III and Pancreatic Cancer Case-Control Consortium genome-wide association studies. Additional exploratory multifactorial scores were constructed by complementing the genetic score with smoking and diabetes.

Results The scores were associated with increased PDAC risk and reached high statistical significance (OR=2.70, 95% CI 1.99 to 3.68, $p=2.54 \times 10^{-10}$ highest vs lowest quintile of the weighted PRS, and OR=14.37, 95% CI 5.57 to 37.09, $p=3.64 \times 10^{-8}$, highest vs lowest quintile of the weighted multifactorial score).

Conclusion We found a highly significant association between a PRS and PDAC risk, which explains more than individual SNPs and is a step forward in the direction of the construction of a tool for risk stratification in the population.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and represents about 85% of total cases.¹ Due to the lack of early symptoms for most patients,² the lack of reliable biomarkers and the difficulty in imaging its initial development,³ PDAC is typically detected in advanced stages,¹ when there is a shortage of effective therapies. Surgical removal is considered the most effective treatment for localised disease.³ Pancreatic cancer shows a multifactorial aetiology⁴ and the main epidemiological risk factors are tobacco smoking, heavy alcohol consumption, type 2 diabetes mellitus, obesity and chronic pancreatitis.⁵ Family history of pancreatic cancer is another risk factor, with about 5%–10% of patients reporting affected first-degree relatives, suggesting a contribution of inherited genetic variation in risk.⁶ As for other complex diseases, PDAC is affected both by rare highly penetrant mutations associated with high risk and common low-penetrance variants. Both genome-wide association studies (GWAS) and candidate gene studies have identified several SNPs associated with the risk of developing PDAC.^{7–17} Several SNPs with a

genome-wide level of statistical significance ($p < 5 \times 10^{-8}$) have been identified and many others are considered potentially interesting since they are very close to this threshold. Moreover, many studies showed a connection between blood groups and the risk of several malignancies including pancreatic cancer, in particular increased risk for non-O blood group subjects.^{18–22} A viable approach to reduce PDAC mortality would be to implement early detection. The overall incidence of the disease is relatively low, thus screening is not suggested for the general population. It would therefore be useful to have tools to stratify the general population and to identify a subgroup at higher risk among whom a regular screening could bring benefits. Genetic variants can be useful for such risk stratification. Common variants, taken individually, are associated with a small increase in risk and therefore are not applicable for risk prediction. However, the combination of different SNPs increases the cumulative effect on risk. Thus, the establishment of a multigenic score could lead to a better estimation of individual risk. This approach has already been successfully attempted for other cancers such as prostate,²³ breast^{24–27} and endometrial.²⁸ For pancreatic cancer a first attempt has been made, however it was based on a very small number of SNPs.²⁹ The aim of this work was to generate a polygenic risk score (PRS) for PDAC risk prediction combining the effects of known risk SNPs, including the *ABO* alleles. In addition, as an exploratory analysis, we have included two well-known risk factors, smoking and diabetes, to construct a multifactorial score.

Materials and methods Study population

The study was conducted on 3619 patients with PDAC and 5790 controls from nine European countries within the PANcreatic Disease ReseArch (PANDoRA) consortium.³⁰ Cases were defined by an established diagnosis of PDAC and controls were individuals of the general population without a pancreatic disease at recruitment, individuals that were hospitalised for non-tumour related causes, or blood donors. For each subject, information on country of origin, sex and age (age at diagnosis for cases and age at recruitment for controls) was also available. In addition, for a subset of individuals, smoking (expressed as ever (current+former)/never smokers) and diagnosis of type 2 diabetes (before the diagnosis of PDAC for the cases) were retrospectively collected. In accordance with the Declaration of Helsinki, written informed consent was obtained from each participant. Finally, we also used as a validation step genotyping data of 8769 PDAC cases and 7055 controls downloaded from the database of Genotypes and Phenotypes (dbGaP, <https://www.ncbi.nlm.nih.gov/gap/>) (study accession numbers phs000206.v5.p3 and phs000648.v1.p1; project reference number 12644). The genotyping data were obtained from previously published GWAS on PDAC risk: the Pancreatic Cancer Cohort Consortium (PanScan I–III)^{7–9} and the Pancreatic Cancer Case-Control Consortium (PanC4).¹⁰

SNP selection In order to generate a PRS, we selected polymorphisms belonging to the chromosomal regions identified through previous studies to be associated with PDAC risk at genome-wide significance level ($p < 5 \times 10^{-8}$, 18 SNPs) or close to that threshold ($p < 10^{-7}$, 11 SNPs). In regions with multiple risk-associated SNPs, only SNPs not in high LD ($r^2 < 0.7$) were selected. The selection

was made based on the lowest p value with PDAC risk reported in the original study. We also included SNPs necessary to infer the ABO blood groups from genotypes, in order to use the blood groups in the computation of the score. Namely, we selected rs505922, which discriminates O from non-O and rs8176746 that distinguishes between ABO A and B alleles.^{18 21 22} The combination of these two SNPs allows to reconstruct ABO blood groups. The final selection resulted in 30 SNPs as described in online supplementary table I.

Genotyping Genotyping of the PANDoRA cases and controls was performed at German Cancer Research Center in Heidelberg, Germany, using TaqMan or KASP (Kompetitive Allele-Specific PCR) technology, according to the manufacturer protocol, in 384-well plates. In addition to the samples, no-template controls and duplicated samples (8%), used for quality control purposes, were included on each plate and genotyped under the same conditions. The endpoint fluorescence reading of the plates and the assignment of the genotype were performed using a ViiA 7 Real-Time PCR System (Thermo Fisher Applied Biosystems, Waltham, MA, USA).

Data filtering, statistical analysis and score computation For PANDoRA we started from a total of 9409 subjects (3619 cases and 5790 controls). Pearson χ^2 test was used to verify that the genotype frequencies of the controls were in Hardy-Weinberg equilibrium (HWE). We eliminated one genotyping plate filled with 330 controls because it systematically showed a deviation from HWE, leaving 5460 controls. The breakdown of cases and controls by countries is shown in table 1. After exclusion of subjects with missing covariates and genotypes we used up to 2851 cases and 4810 controls to test whether the associations of the single risk variants replicated. The samples used had an average call rate of 97.6%, and a concordance rate between duplicated samples higher than 99%. Considering only samples with call rate of 100%, 2879 subjects (839 cases and 2040 controls) remained for the PRS in PANDoRA, consisting of the 30 variants (28 loci each identified by an individual SNP and two SNPs for the ABO locus, see below). For the PanScan I–III and PanC4 data sets obtained from dbGaP, genotyping procedures, genotyping quality control checks and data collection were thoroughly reported in the original publications.^{7–10} We removed individuals with gender mismatches, call rate <0.9 , minimal or excessive heterozygosity (>3 SDs from the mean) or cryptic relatedness ($PI_HAT >0.2$). We performed imputation using IMPUTE4³¹ and the 1000 Genomes version 3 reference panel.³² The different GWAS data sets were each imputed separately. We discarded SNPs with a minor allele frequency $<0.5\%$, completion rate $<90\%$, evidence for violations of HWE ($p < 10^{-6}$) or low-quality imputation score (INFO score <0.7). The number of SNPs available in the final data set was 7 509 345. Principal component analysis was carried out including genotypes from all the populations of phase 3 of the 1000 Genomes Project (<http://www.internationalgenome.org/>). Individuals not clustering with the 1000 Genomes subjects of European descent were excluded from further analysis. Unconditional logistic regression was used to validate the associations between the individual SNPs and PDAC risk. ORs, 95% CIs and p values were calculated. The SNPs were analysed according

to the codominant and allelic inheritance models, using the most common allele in controls as reference. The association between genotype-derived ABO blood groups and PDAC risk was also tested with unconditional logistic regression using the O group as the reference category. To validate the associations between the risk factors assessed as dichotomous variables and PDAC risk, logistic regression was used. All analyses were adjusted for: sex, age and country of origin (PANDoRA) or sex, age and the top eight principal components (PanScan and PanC4). Associations showing a p value less than 0.05 were considered significant since all these associations have been extensively studied and replicated elsewhere. The genetic score was computed on the subset of subjects that had 100% call rate, consisting of 839 cases and 2040 controls in PANDoRA and 6420 cases and 4889 controls in PanScan I–III and PanC4, for a total of 14 188 subjects. Score quintiles were calculated based on their distribution in the controls. Details on score computation have been give elsewhere¹⁴ and in the online supplementary material. We built two types of PRS, a simple unweighted score and a weighted score. We generated the unweighted score for each subject by summing the total number of risk alleles (attributing the value of 1 to each risk allele) and adding the value associated with the ABO groups, with a value of 0 for the OO group, 1 for OA/OB and 2 for AB group. We generated the weighted score assigning to each genotype the relative OR, using the OR reported in the literature by GWAS on PDAC, and the same was done for the ABO groups. Subsequently, from the product of all the ORs, we obtained the weighted score of each individual. Online supplementary table II shows an example of how the scores were generated. The computed score was used as a categorical variable, calculating the quintiles based on the distribution in controls. We validated the genetic scores in 6420 PDAC cases and 4889 controls (subjects from PanScan I–III and PanC4 with 100% call rate) using the same statistical models used for the PANDoRA data set and adjusting for the top eight principal components to avoid confounding due to population stratification.

We also computed multifactorial scores (for PANDoRA only) complementing the genetic weighted score with variables for tobacco smoking and type 2 diabetes, using 101 PDAC cases and 250 controls. The computed scores were analysed for their association with PDAC risk with logistic regression, adjusting for sex, age and country of origin. Given the limited number of subjects in PANDoRA who had 100% call rate and complete data for the covariates, we also included in the multifactorial score subjects without all the genetic variants (call rate >80%, 243 cases and 511 controls) and normalised the scores of each subject, in order to make them comparable, by multiplying them for (total number of variables)/(number of available variables) obtaining a ‘scaled’ score. Receiver operating characteristic curves were constructed and the related areas under the curve (AUC) were calculated, to determine the performance of scores in discriminating individuals with the disease from individuals without the disease.

Results

Main effects of SNPs, ABO blood groups and epidemiological risk factors Most of the associations between the GWAS-identified SNPs and ABO blood groups and PDAC risk were replicated in PANDoRA, using up to 2851 cases and 4810 controls (tables 2 and 3). As expected, we observed statistically significant associations between smoking (with 1472 cases and 1865 controls), diabetes (with 1028 cases and 1906 controls) and PDAC risk (OR=2.66, 95% CI 2.20 to 3.21, $p=2\times 10^{-22}$ for smoking, and OR=1.46, 95% CI 1.14 to 1.86, $p=0.003$ for diabetes) (online supplementary table III).

Risk scores The PRS (which includes the genetically predicted ABO blood groups) showed very significant associations. For the highest versus lowest quintile of the unweighted score we observed in PANDoRA an OR=2.64 (95% CI 1.97 to 3.54, $p=8.76\times 10^{-11}$) and for the highest versus lowest quintile of the weighted score,

OR=2.70 (95% CI 1.99 to 3.68, $p=2.54\times 10^{-10}$), using 839 cases and 2040 controls. The results are shown in table 4. The validation analysis performed in the PanScan and PanC4 data sets, using 6420 cases and 4889 controls, showed similar results. For the unweighted score, we observed an OR=3.22 (95% CI 2.86 to 3.64, $p=1.20\times 10^{-71}$) for the highest versus lowest quintile and OR=3.24 (95% CI 2.86 to 3.67, $p=1.20\times 10^{-63}$) for the weighted score comparing the highest versus lowest quintile. When we restricted the analyses to the extreme tails of the distribution, we observed substantially larger risks, with good agreement between PANDoRA and the PanScan+PanC4 data set. Namely, when we compared the top versus the bottom 5% of the distributions. We observed OR=4.56 (95% CI 2.50 to 8.35, $p=1.19\times 10^{-6}$) in PANDoRA and OR=4.63 (95% CI 3.63 to 5.91, $p=6.16\times 10^{-32}$) in PanScan+PanC4. The results are shown in table 4. The exploratory analysis of different multifactorial risk scores, using 101 PDAC cases and 250 controls, showed significant associations as well. The results are summarised in table 5. The weighted score complemented with smoking and diabetes showed OR=14.37 (95% CI 5.57 to 37.09, $p=3.64\times 10^{-8}$) for the highest versus lowest quintile. Similar statistically significant results were observed with the scaled score (OR=6.01, 95% CI 3.48 to 10.39, $p=1.28\times 10^{-10}$), which includes a larger number of individuals (243 cases and 511 controls). The results of the scaled score are reported in table 6.

Evaluation of prediction performance results The AUC value for the unweighted PRS is 0.59 (95% CI 0.57 to 0.61) in PANDoRA and 0.61 (95% CI 0.60 to 0.63) in the PanScan I–III and PanC4 combined data set. The highest AUC value for the multifactorial scores is 0.63 (95% CI 0.59 to 0.67).

Discussion

A promising way to decrease PDAC mortality is to improve early detection, which can be achieved by identifying subjects at high risk of developing the disease. The International Cancer of the Pancreas Screening consortium recommends regular screening for subjects with at least a fivefold increased risk.³³ This level of risk determination can be obtained by integrating genetic and epidemiological risk factors. In recent years a number of SNPs convincingly associated with PDAC risk have been reported.^{7–13} They generally show a small effect on risk (OR <1.5), therefore individually are not very useful in risk prediction. Yet, combining them in a PRS may lead to a significant improvement in risk prediction,^{34 35} as already demonstrated for other diseases.^{36–38} The PRS reached high statistical significance both when unweighted and weighted, with similar ORs in PANDoRA and in the combined PanScan I–III+PanC4 data set, with an approximately threefold increase in risk for the 20% of subjects with the highest score values if compared with the subjects with the 20% lowest. The level of risk becomes more pronounced when looking only at the extremes of the distribution, with approximately fivefold differences in risk between the top and the bottom 5%. This level of risk is in the same order of magnitude as reported for rare, highly penetrant mutations in familial pancreatic cancer syndromes (eg, for mutations in *BRCA1*, *BRCA2* or *ATM*).⁴ The substantial concordance between PANDoRA and the combined PanScan I–III+PanC4 data set, based on data of about 7000 PDAC cases and 7000 controls, makes us confident in the stability of these predictions. In spite of the clear discrimination of risk level and the strong statistical significance, the values of the AUC based on the SNPs alone (ranging from 0.59 to 0.61) are not satisfactory. However, theoretical predictions³⁹ and previous studies on cancer types for which a much larger number of risk SNPs are known^{23 24 36 37} have shown that the addition of risk variants increases the predictive power of PRS, to the point of envisaging their implementation in screening of the general population.²⁵ Thus, it is foreseeable that continued efforts for discovery of novel pancreatic cancer risk SNPs will enable us in the middle/long term to build scores with a much larger number of genetic variants, which will lead to much improved risk prediction. Furthermore, it is useful to combine the genetic score with non-genetic risk factors obtaining a multifactorial score. This has already been done for other cancers and has shown slightly better prediction performances.^{23 37 40} The idea is to build a score that includes all known genetic variants associated with risk and all known epidemiological risk factors. The exploratory results we observed in our data set are encouraging because they showed a large increase in the ORs. It should, however, be noted that the data of the covariates in PANDoRA are largely incomplete and currently this prevents us from including all known non-genetic risk factors in the score. Moreover, as retrospective data, they may be subjected to recall bias. Data available from dbGaP for PanScan I–III and PanC4 do not include any variable about known risk factors; thus we could not evaluate the multifactorial score in the replication data set. For these reasons, we need to use caution in interpreting the results, but the combination of genotypes and data on risk factors seems a suitable

way for the construction of a score that leads to the identification of a subgroup of subjects with very high risk. Indeed, subjects in the highest quintile of the multifactorial score including both smoking and diabetes reached an OR=14.37, which is comparable to effect of rare high-penetrance disease causing mutations. Strengths of this study are the sample size, since it is the largest study of this type conducted on PDAC to date, and the number of polymorphisms included in the computation of the genetic score, since all the known *loci* have been included in the score, unlike what was previously done. In addition, another clear advantage of this study is the external validation of the score using PanScan and PanC4 data. The limitations are the possible bias deriving from the inclusion of subjects that come from different countries and the fact that in PANDORA the information on epidemiological and lifestyle factors is limited. In addition, it is possible that the OR that we observe in the multifactorial risk score is inflated, given the relatively small sample size (101 cases and 250 controls) that we could use for running that exploratory analysis. In conclusion, in this study, we found a highly significant association between a PRS and the risk of PDAC onset, which explains more than individual SNPs and is a step forward in the direction of the construction of a tool for risk stratification. Furthermore, the exploratory analysis of a multifactorial score was encouraging. In perspective, the implementation of the score with new genetic risk variants, which are continuously discovered, and with complete data on epidemiological risk factors can lead to the achievement of a tool for risk stratification of clinical utility. Such an instrument, if perfected, could be conceived as a tool for risk stratification in the population, which in turn can contribute to improved early diagnosis. A test with relatively low predictive power as the score could be used to define groups of subjects at increased risk on which to apply screening tools and, lastly, the expensive and invasive imaging on the subjects that are positive.

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Tables

Country	Cases	Controls	Total
Czech Republic	386	450	836
Germany	1375	1791	3166
Greece	239	192	431
Hungary	260	353	613
Italy	968	1681	2649
Lithuania	56	185	241
The Netherlands	117	164	281
Poland	107	333	440
UK	111	311	422
Total	3619	5460	9079
Sex (%)			
Male	56.6	53.1	54.5
Female	43.4	46.9	45.5
Median age	64.3	56.0	59.6

PANDoRA, PANcreatic Disease ReseArch.

SNP	Nearest gene(s)	Alleles (M/m)	Codominant model				Allelic model		
			M/M versus M/m		M/M versus m/m		M versus m		
			OR (95% CI)	P value	OR (95% CI)	P value	P trend	OR (95% CI)	P value
rs13303010	<i>NOC2L</i>	A/G	1.34 (1.18 to 1.53)	1.3×10⁻⁵	1.95 (1.32 to 2.90)	0.001	5.7×10⁻⁸	1.42 (1.26 to 1.59)	7.8×10⁻⁹
rs351365	<i>WNT2B</i>	G/A	0.97 (0.87 to 1.08)	0.523	0.83 (0.66 to 1.04)	0.099	0.072	0.92 (0.84 to 1.00)	0.056
rs2816938	<i>NR5A2</i>	T/A	1.11 (0.99 to 1.24)	0.077	1.08 (0.86 to 1.36)	0.515	0.151	1.09 (0.99 to 1.19)	0.076
rs3790844	<i>NR5A2</i>	T/C	0.93 (0.83 to 1.05)	0.226	0.94 (0.74 to 1.19)	0.607	0.049	0.93 (0.84 to 1.02)	0.1
rs1486134	<i>ETAA1</i>	T/G	1.10 (0.99 to 1.21)	0.080	1.11 (0.92 to 1.33)	0.291	0.058	1.06 (0.98 to 1.15)	0.124
rs9854771	<i>TP63</i>	G/A	0.88 (0.80 to 0.98)	0.019	0.81 (0.69 to 0.95)	0.010	0.003	0.91 (0.85 to 0.98)	0.016
rs2736100	<i>CLPTM1L TERT</i>	G/T	0.97 (0.86 to 1.09)	0.614	1.21 (1.05 to 1.39)	0.008	0.012	1.09 (1.01 to 1.17)	0.018
rs2853677	<i>CLPTM1L TERT</i>	A/G	0.78 (0.69 to 0.87)	2.47×10⁻⁵	0.77 (0.66 to 0.89)	6.3×10⁻⁴	2.5×10⁻⁴	0.85 (0.79 to 0.92)	9.1×10⁻⁵
rs2736098	<i>CLPTM1L TERT</i>	G/A	0.90 (0.81 to 1.00)	0.050	0.85 (0.69 to 1.05)	0.123	0.004	0.85 (0.78 to 0.93)	3.6×10⁻⁴
rs35226131	<i>CLPTM1L TERT</i>	G/A	0.81 (0.64 to 1.03)	0.085	0.41 (0.12 to 1.34)	0.139	0.012	0.89 (0.71 to 1.11)	0.296
rs401681	<i>CLPTM1L TERT</i>	C/T	1.20 (1.07 to 1.35)	0.002	1.31 (1.14 to 1.50)	1.3×10⁻⁴	5.1×10⁻⁶	1.14 (1.07 to 1.23)	1.7×10⁻⁴
rs17688601	<i>SUGCT</i>	C/A	0.97 (0.88 to 1.08)	0.628	0.73 (0.60 to 0.90)	0.003	0.051	0.91 (0.84 to 0.99)	0.028
rs73328514	<i>TNS3</i>	A/T	1.11 (0.97 to 1.26)	0.142	0.52 (0.31 to 0.89)	0.016	0.690	1.00 (0.88 to 1.13)	0.962
rs6971499	<i>LINC-PINT</i>	A/G	0.86 (0.76 to 0.97)	0.012	0.71 (0.49 to 1.04)	0.079	0.001	0.84 (0.75 to 0.93)	0.002
rs172310	<i>SHH</i>	C/A	1.02 (0.92 to 1.14)	0.636	0.94 (0.78 to 1.12)	0.462	0.964	1.01 (0.93 to 1.09)	0.848
rs2941471	<i>HNF4G</i>	A/G	0.95 (0.84 to 1.07)	0.396	0.79 (0.68 to 0.92)	0.003	0.013	0.89 (0.82 to 0.96)	0.004
rs10094872	<i>MYC</i>	A/T	1.16 (1.03 to 1.29)	0.011	1.40 (1.20 to 1.64)	2.6×10⁻⁵	2.9×10⁻⁵	1.18 (1.09 to 1.28)	2.4×10⁻⁵
rs1561927	<i>MIR1208</i>	T/C	0.83 (0.75 to 0.93)	0.001	0.81 (0.66 to 1.00)	0.044	3.4×10⁻⁴	0.86 (0.79 to 0.94)	0.001
rs8176746	<i>ABO</i>	C/A	1.10 (0.96 to 1.26)	0.171	1.11 (0.68 to 1.80)	0.674	0.235	1.04 (0.92 to 1.17)	0.546
rs505922	<i>ABO</i>	T/C	1.39 (1.24 to 1.55)	7.2×10⁻⁹	1.39 (1.20 to 1.61)	1.6×10⁻⁵	1.4×10⁻⁷	1.19 (1.10 to 1.28)	4.0×10⁻⁶
rs10991043	<i>SMC2</i>	T/C	1.05 (0.94 to 1.17)	0.403	1.02 (0.87 to 1.19)	0.793	0.353	1.01 (0.94 to 1.09)	0.709
rs7310409	<i>HNF1A</i>	G/A	1.02 (0.91 to 1.14)	0.709	1.21 (1.05 to 1.40)	0.010	0.051	1.08 (1.01 to 1.16)	0.033
rs9581943	<i>PDX1</i>	G/A	0.95 (0.85 to 1.07)	0.431	1.17 (1.01 to 1.36)	0.043	0.052	1.07 (0.99 to 1.16)	0.092
rs9543325	13q22.1	T/C	1.18 (1.05 to 1.32)	0.005	1.43 (1.23 to 1.66)	3.2×10⁻⁶	4.1×10⁻⁶	1.18 (1.10 to 1.28)	1.3×10⁻⁵
rs8028529	15q14	T/C	1.00 (0.90 to 1.11)	0.966	1.15 (0.92 to 1.45)	0.229	0.907	1.05 (0.96 to 1.15)	0.291
rs7190458	<i>BCAR1</i>	C/T	1.26 (1.04 to 1.53)	0.017	1.67 (0.56 to 4.94)	0.355	0.025	1.20 (0.99 to 1.45)	0.068
rs4795218	<i>HNF1B</i>	G/A	0.93 (0.84 to 1.04)	0.211	0.77 (0.60 to 0.98)	0.037	0.018	0.091 (0.83 to 0.99)	0.036
rs11655237	<i>LINC00673</i>	C/T	1.25 (1.10 to 1.41)	2.6×10⁻⁴	1.60 (1.08 to 2.39)	0.021	2.9×10⁻⁵	1.24 (1.12 to 1.39)	8.0×10⁻⁵
rs1517037	<i>GRP</i>	C/T	0.88 (0.79 to 0.99)	0.026	0.64 (0.48 to 0.86)	0.002	0.001	0.84 (0.77 to 0.93)	3.6×10⁻⁴
rs16986825	<i>ZNRF3</i>	C/T	1.11 (1.00 to 1.25)	0.057	1.28 (0.97 to 1.68)	0.080	0.004	1.19 (1.08 to 1.31)	3.7×10⁻⁴

All analyses were adjusted for age, sex and geographic region of origin.

Text in bold indicates associations with $p \leq 0.05$.

m, minor allele; M, major allele; PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.

Table 3 Association between the ABO blood groups and PDAC risk in 2361 PDAC cases and 4418 controls from PANDoRA

Cases	Controls	rs505922	rs8176746	Blood group	OR (95% CI)	P value
780	1785	T/T	Any	OO	Reference	–
885	1474	T/C	C/C	AO	1.40 (1.24 to 1.59)	6.41×10⁻⁸
242	370	C/C	C/C	AA	1.53 (1.27 to 1.85)	1.09×10⁻⁵
281	481	T/C	A/A	BO	1.40 (1.18 to 1.67)	1.70×10⁻⁴
27	52	C/C	A/A	BB	1.34 (0.82 to 2.20)	0.245
146	256	T/C or C/C	C/A	AB	1.27 (0.82 to 2.20)	0.042

All analyses were adjusted for age, sex and geographic region of origin.

Text in bold indicates associations with $p \leq 0.05$.

PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.

Table 4 Associations between the genetic scores and PDAC risk

	PANDoRA				PanScan I–III+PanC4			
	Controls	Cases	OR (95% CI)	P value	Controls	Cases	OR (95% CI)	P value
Unweighted polygenic score								
First quintile	529	131	1.00 (reference)	–	1220	908	1.00 (reference)	–
Second quintile vs first quintile	395	148	1.60 (1.19 to 2.17)	2.13E-03	994	980	1.31 (1.16 to 1.49)	1.92E-05
Third quintile vs first quintile	437	185	1.94 (1.45 to 2.58)	7.07E-06	1025	1384	1.83 (1.62 to 2.06)	1.24E-21
Fourth quintile vs first quintile	355	176	2.19 (1.63 to 2.94)	2.24E-07	870	1291	2.00 (1.77 to 2.26)	2.34E-26
Fifth quintile vs first quintile	324	199	2.64 (1.97 to 3.54)	8.76E-11	780	1857	3.22 (2.86 to 3.64)	1.20E-71
95th vs 5th centile			3.81 (2.15 to 6.77)	6.36E-06			5.67 (4.50 to 7.14)	9.72E-45
95th vs 50th centile			1.76 (1.11 to 2.81)	1.67E-02			3.14 (2.72 to 3.64)	1.33E-48
Weighted polygenic score								
First quintile	410	94	1.00 (reference)	–	977	675	1.00 (reference)	–
Second quintile vs first quintile	408	145	1.66 (1.20 to 2.30)	2.48E-03	980	923	1.37 (1.2 to 1.57)	1.91E-06
Third quintile vs first quintile	408	155	1.79 (1.29 to 2.47)	4.24E-04	976	1240	1.86 (1.63 to 2.12)	5.44E-14
Fourth quintile vs first quintile	408	204	2.28 (1.67 to 3.12)	2.50E-07	977	1402	2.09 (1.84 to 2.38)	2.32E-21
Fifth quintile vs first quintile	406	241	2.70 (1.99 to 3.68)	2.54E-10	979	2180	3.24 (2.86 to 3.67)	1.20E-63
95th vs 5th centile			4.56 (2.50 to 8.35)	1.19E-06			4.63 (3.63 to 5.91)	6.16E-32
95th vs 50th centile			2.70 (1.72 to 4.22)	1.76E-05			3.15 (2.73 to 3.65)	5.87E-49

All analyses were adjusted for age, sex and geographic region of origin (PANDoRA) or the top eight principal components (PanScan I–III+PanC4).

Text in bold indicates associations with $p \leq 0.05$.

PanC4, Pancreatic Cancer Case-Control Consortium; PANDoRA, PANcreatic Disease ReseArch; PanScan, Pancreatic Cancer Cohort Consortium; PDAC, pancreatic ductal adenocarcinoma.

Table 5 Associations between scores with genetic and non-genetic variables and PDAC risk in PANDoRA

Quintile	Controls	Cases	OR (95% CI)	P value
Unweighted multifactorial score				
First quintile	63	13	1.00 (reference)	–
Second quintile vs first quintile	50	12	1.09 (0.45 to 2.63)	8.53E-01
Third quintile vs first quintile	51	27	2.55 (1.19 to 5.47)	1.60E-02
Fourth quintile vs first quintile	47	17	1.70 (0.75 to 3.88)	2.05E-01
Fifth quintile vs first quintile	39	32	3.89 (1.81 to 8.37)	5.05E-04
Weighted multifactorial score				
First quintile	60	6	1.00 (reference)	–
Second quintile vs first quintile	58	12	2.02 (0.71 to 5.75)	1.90E-01
Third quintile vs first quintile	51	13	2.54 (0.89 to 7.19)	8.00E-02
Fourth quintile vs first quintile	46	20	4.21 (1.55 to 11.4)	4.71E-03
Fifth quintile vs first quintile	35	50	14.37 (5.57 to 37.09)	3.64E-08

All analyses were adjusted for age, sex and geographic region of origin.

Text in bold indicates associations with $p \leq 0.05$.

PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.

Table 6 Associations between scores scaled (call rate >80%) with genetic and non-genetic variables and PDAC risk in PANDoRA

Quintile	Controls	Cases	OR (95% CI)	P value
Unweighted multifactorial score				
First quintile	113	29	1.00 (reference)	–
Second quintile vs first quintile	116	41	1.17 (0.65 to 2.11)	5.91E-01
Third quintile vs first quintile	116	62	2.17 (1.25 to 3.76)	5.96E-03
Fourth quintile vs first quintile	79	29	1.34 (0.71 to 2.54)	3.63E-01
Fifth quintile vs first quintile	87	82	3.66 (2.11 to 6.33)	3.62E-06
Weighted multifactorial score				
First quintile	116	38	1.00 (reference)	–
Second quintile vs first quintile	121	35	0.83 (0.46 to 1.50)	5.43E-01
Third quintile vs first quintile	98	48	1.75 (0.99 to 3.10)	5.40E-02
Fourth quintile vs first quintile	100	35	1.10 (0.61 to 2.00)	7.50E-01
Fifth quintile vs first quintile	76	87	6.01 (3.48 to 10.39)	1.28E-10

Scaled scores obtained by multiplying the score for (total number of variables)/ (number of available variables), in subjects with call rate >80%. All analyses were adjusted for age, sex and geographic region of origin.

Text in bold indicates associations with $p \leq 0.05$.

PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.