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***Association of genetic polymorphisms with survival of pancreatic ductal adenocarcinoma patients***

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**Abstract**

Germline genetic variability might contribute, at least partially, to the survival of pancreatic ductal adenocarcinoma (PDAC) patients. Two recently performed genome-wide association studies (GWAS) on PDAC overall survival (OS) suggested (p<10-5) the association between 30 genomic regions and PDAC OS. With the aim to highlight the true associations within these regions, we analyzed 44 single-nucleotide polymorphism’s (SNPs) in the 30 candidate regions in 1722 PDAC patients within the PANcreatic Disease ReseArch (PANDoRA) consortium. We observed statistically significant associations for five of the selected regions. One association in the *CTNNA2* gene on chromosome 2p12 (rs1567532, HR=1.75, 95% CI 1.19-2.58, p=0.005) and one in the last intron of the *RUNX2* gene on chromosome 6p21 (rs12209785, HR=0.88, 95% CI 0.80-0.98, p=0.014) are of particular relevance. *In silico* analysis strongly suggested a direct, mechanistic link between these two SNPs and pancreatic cancer survival. Functional studies are warranted to confirm the link between these genes (or gene mapping in those regions) and PDAC prognosis in order to understand whether these variants may have the potential to impact treatment decisions and design of clinical trials.

**Introduction**

Pancreatic cancer, particularly pancreatic ductal adenocarcinoma (PDAC), the most common form of the disease, is one of the leading causes of cancer deaths in the European Union and in the USA, with a five-year survival of less than 5% ([Ferlay, Soerjomataram et al. 2013](#_ENREF_12)). There is a certain degree of variability in the survival of patients, which is not entirely explained by the traditional prognostic factors such as tumor grade, lymph node and distal metastasis and tumor size ([Hidalgo 2010](#_ENREF_15)). There are growing evidences that germline genetic variability may play a role in the prognosis. Several *loci* have been proposed by candidate gene studies, in pathways such as mitotic regulation ([Asomaning, Reid et al. 2008](#_ENREF_1), [Couch, Wang et al. 2010](#_ENREF_6)), DNA repair ([Li, Liu et al. 2006](#_ENREF_17)), insulin metabolism ([Dong, Javle et al. 2010](#_ENREF_8)) and gemcitabine metabolism ([Okazaki, Javle et al. 2010](#_ENREF_20)). Furthermore a single-nucleotide polymorphism (SNP) associated with cancer risk was found to be weakly associated with overall survival (OS) ([Rizzato, Campa et al. 2011](#_ENREF_23)). In addition two genome-wide association studies (GWAS) on PDAC OS have identified several additional *loci* ([Willis, Olson et al. 2012](#_ENREF_31), [Wu, Kraft et al. 2012](#_ENREF_32)).

The largest of the two studies was performed by Wu and colleagues in 1005 PDAC cases ([Wu, Kraft et al. 2012](#_ENREF_32)). The study design was a two-phase GWAS with the first stage comprising 642 cases of European descent (from prospective cohort studies) and the second stage 363 cases of Chinese descent (from a retrospective case-control study). In the first stage, based on the subjects of European descent, twenty-eight genomic regions showed association with OS, with a statistical significance of at least p<10-5. Among these, three regions, 11p15.4, 18p11.21 and 1p36.13 were identified as particularly interesting (p<5x10-7), but still not reaching genome-wide significance level. The joint analysis of all 1005 pancreatic cancer cases identified two variants in the *SBF2* gene locus on chromosome 11p15.4. In particular rs10500715 in *SBF2* showed the strongest association with OS, (HR=0.76; 95% CI 0.68-0.84; p=1.72×10−7). In another earlier study Willis and colleagues have identified, through a GWAS on 252 PDAC cases, two *loci* that showed suggestive association with pancreatic cancer OS (p<10-5) ([Willis, Olson et al. 2012](#_ENREF_31)).

Finding genetic variants associated with PDAC survival may lead to the identification of therapeutic targets and/or the development of new strategies for treatment of pancreatic cancer. Thus, it is important to carry forward the work started by the published GWAS with independent, large-scale studies, such as the PANcreatic Disease ReseArch (PANDoRA) consortium ([Campa, Rizzato et al. 2012](#_ENREF_5)), a multi-centric study conducted mainly in Europe. We selected all the polymorphic variants found in the two GWAS studies to be associated with survival of PDAC patients with a threshold of p<10-5, and genotyped them in 1722 PDAC cases, constituting by far the largest effort on the topic to date. By doing so, we aimed at clarifying if some of the candidate SNPs found by the two GWASs are true survival *loci* for pancreatic cancer.

**Matherial and methods**

**Study population**

1722 PDAC cases have been retrospectively collected in 7 European countries in the context of the PANDoRA consortium, which has been extensively detailed elsewhere ([Campa, Rizzato et al. 2012](#_ENREF_5)). Briefly, all cases were collected between 1996 and 2012. The cases were defined by a confirmed diagnosis of PDAC through histology or, for patients who were not operated, through clinical symptoms, imaging results and/or physical examination. For each patient, data on gender, age at diagnosis, date of diagnosis, date of death or date of last known contact, as well as clinical information (such as disease stage and surgical resection) were collected. The stage of the disease was assessed by TNM classification and categorized as stage 1 (T1-2, N0, M0), stage 2 (T1-3, N0-1, M0), stage 3 (T4, any N, M0), stage 4 (any T, any N, M1). Relevant characteristics of patients are provided in table 1. For each subject, informed consent to collect biological samples and perform DNA extraction for research purposes was obtained.

**SNP selection**

We selected the polymorphisms starting from a list of 131 SNPs in 28 *loci* that were identified, through a GWAS, to be associated with pancreatic cancer at a significance threshold of p<10-5 ([Wu, Kraft et al. 2012](#_ENREF_32)). We defined independent regions as mapping to different chromosomes, or spaced by more than 1Mb. In each region, the SNP with the lowest reported p-value for association with survival ([Wu, Kraft et al. 2012](#_ENREF_32)) has been chosen. HapMap data have been analyzed with Haploview, and within each region, tagSNPs have been selected with Tagger (pairwise tagging, r2>0.8, force include the SNP with the lowest p-value for association with survival in PanScan). This resulted in a list of 43 SNPs which effectively tag the 28 regions emerging from the GWAS. In addition we added two SNPs identified by a small-scale GWAS on survival of pancreatic cancer ([Willis, Olson et al. 2012](#_ENREF_31)), and the rs9350 SNP, situated in the *EXO1* gene that was identified, through a candidate gene study, by Dong and colleagues ([Dong, Jiao et al. 2009](#_ENREF_9)) and that was also replicated by Willis and colleagues ([Willis, Olson et al. 2012](#_ENREF_31)).

**DNA extraction and genotyping**

DNA was extracted from whole blood or from frozen or paraffin-embedded pancreatic tissues of patients using the Qiagen-mini kit (Qiagen, Hilden, Germany) or the AllPrep Isolation Kit (Qiagen, Hilden, Germany) according to the manufacturer’s protocols. All the genotyping was carried out using the TaqMan assay. The MGB TaqMan probes and primers were synthesized by Applied Biosystems (Foster City, CA, USA). PCRs were performed according to the manufacturer’s instructions. PCR plates were read on an Applied Biosystems ViiA™ 7 Real-Time PCR System. Assays for two SNPs (rs1391315 and rs4382459) did not work, thus 44 SNPs were available for statistical analysis.

**Statistical analysis**

For survival analysis, the median follow-up time was computed with censored observations only, whereas the median survival time was calculated using data from all patients. OS was defined as the time interval between diagnosis and death (uncensored observation) or the last date when the patient was still alive (censored observation, mean follow-up time 20.3 months).

OS was evaluated using methods for censored survival time. In particular, risk of dying was estimated by hazard ratios (HR) and 95% confidence intervals (CI) in Cox proportional hazard models under different genetic models (i.e. allelic, dominant, recessive) with adjustment for factors that might influence patient survival, including age (continuous), sex and the stage of the disease defined by TNM status. Given the significant differences in survival among patients from different PANDoRA centers, we performed all analyses by stratifying the population by country of origin and then meta-analyzing the HR obtained for each population to estimate the HR for the whole PANDoRA population.

The heterogeneity assumption was assessed by the Chi-square-based Q-test. If there was evidence for heterogeneity, indicated by P<0.05 in the Q-test, the random-effects model was used to calculate the meta-analysis ORs. Otherwise, the fixed-effects model was adopted.

To assess the cumulative effect of the SNPs that were individually associated with pancreatic cancer OS we created a genetic score by multiplying the number of alleles weighted by the associated hazard ratio. We coded each SNP according to the genetic model for which it showed the association with survival. More in detail for the SNPs associated with the recessive model the homozygotes for the common allele and the heterozygotes were coded equal to one and the homozygotes for the minor allele were coded equal to their hazard ratio. For the SNPs that were associated with the dominant model the homozygotes for the common allele were coded equal to one and the heterozygotes and the homozygotes for the minor allele were coded as their hazard ratio. More details on this method are given elsewhere ([Husing, Canzian et al. 2012](#_ENREF_16)). The effect of the score on OS of PDAC patients was analyzed by Cox regression adjusting by age, gender, stage of disease and country of origin on quartiles of the score distribution.

Since the SNPs under investigation were previously reported to show suggestive associations with PDAC OS and thus had a high prior probability of association, we considered the threshold for significance to be p<0.05.

All the analyses were performed with STATA software (StataCorp, College Station, TX, USA).

**Bioinformatics analysis**

We used HaploReg v2 ([Ward and Kellis 2012](#_ENREF_30)), and RegulomeDB ([Boyle, Hong et al. 2012](#_ENREF_4)) to evaluate the genomic regions surrounding the SNPs that showed statistical significant associations with OS in our study population. The analyzed SNPs and the SNPs in linkage disequilibrium (LD) with them can be visualized along with their predicted chromatin state, their sequence conservation across mammals, and their effect on regulatory motifs, enhancer annotations, and eQTLs.

In addition, we used Genevar ([Yang, Beazley et al. 2010](#_ENREF_33)) to evaluate the *cis* associations between the selected SNPs and the expression of nearby genes in subjects of European descent from three publicly available data sets ([Dimas, Deutsch et al. 2009](#_ENREF_7), [Grundberg, Small et al. 2012](#_ENREF_13), [Stranger, Montgomery et al. 2012](#_ENREF_27)).

**Results**

The median survival time (MST) of the patients enrolled in this study was 11.5 months for the patients that died (N=1325, 77%) and 16 months for those still alive at the time of the last follow-up (N=397, 23%). The relevant characteristics of the patients enrolled in this study are shown in table 1.

Age (analyzed as continuous variable) and gender had no statistically significant effect on OS of PDAC patients. The stage of the disease, as expected, was strongly associated with OS (p<10-8). We also observed a significant difference in survival time for the patients recruited from different countries. This difference persisted even when adjusting by stage. Table 2 and figure 1 report the results of these analyses.

**Data filtering and quality control**

We excluded from the analysis all the samples with a genotyping call rate <75% (75 individuals). After this exclusion, the average call rate per SNP was 97.4% (range 91.3%-99.4%). Approximately 10% of the samples were analyzed in duplicate, and the concordance rate of their genotypes was higher than 99%. The genotype distributions at all SNPs were in Hardy-Weinberg equilibrium in healthy controls (n=1200 that were genotyped to check for HWE), with non-significant chi square values (using a threshold of p<0.05, data not shown).

**Effect of the SNPs on OS of PDAC patients**

To take into account the difference in survival in the various PANDoRA centers, we analyzed the polymorphisms separately by country of origin and then we performed a meta-analysis combining the HRs (supplementary table 1). We also performed pooled analysis by Cox regression, whose results are reported in supplementary table 2 and 3. We observed statistically significant associations with OS of PDAC patients for three polymorphisms (2p12-rs1567532, 9p33-rs10818020 and 10q26-rs10764826) with a recessive model of inheritance (figure 2). The most statistically significant association was for the homozygous carriers of the minor allele of 2p12-rs1567532 with a worse survival, with a MST of 10.37 months compared with 13.07 months for the carriers of the major allele (HRhomozygous=1.75, 95% CI 1.19-2.58; p=0.005); The homozygotes for the minor allele of 9p33-rs10818020 had longer survival time (13.03 months) compared with the carriers of the major allele (12.95 months) (HRhomozygous=0.85; 95% CI 0.73-0.99; p=0.033). Another significant association with OS was found for homozygotes for the minor allele of the SNP 10q26-rs10764826 (HRhomozygous=3.37; 95% CI 1.04-10.92; p=0.043) with a worse MST of 7.08 months compared with 12.92 months for carrier of the major allele. Furthermore we observed that the carriers of the minor allele (G) of the 6p21-rs12209785 SNP had a better survival compared to carriers of the major (A) allele (HRallelic=0.88; 95% CI 0.80-0.98; p=0.014) while the carriers of the minor allele (C) of the 2p11-rs13431245 SNP showed a worse survival than the major allele carriers (T) (HRallelic=1.14; 95% CI 1.03-1.27; p=0.011) (figure 3). Among the three top SNPs reported by Wu and colleagues as associated with OS in pancreatic cancer patients we observed an association close to statistical significance for rs16861827 (HR=1.70; 95% CI 0.95-3.03; p=0.074), but did not confirm the other two.

Finally, with the aim of analyzing the impact of the combination of the five SNPs significantly associated with OS and the SNP reported in Wu and colleaguesfor which we observed a borderline association with OS of PDAC patients, we constructed a variable "score" and analyzed it in relation with OS. Each SNP was weighted for the correspondent hazard ratio as described in the material and methods section.

We found that PDAC survival was, as expected, inversely correlated with the number of genotypes that were individually associated with shorter survival (table 3). In particular we observed that individuals who belonged to the last quartile of the distribution were associated with worse OS and had an HR of 1.41 (95% CI 1.17-1.69). This correlation was statistically significant (p=2.97x10-4).

**Biological inferences for survival-associated *loci***

We analyzed with the HaploReg software the possible functional consequences of the *loci* showing a statistically significant association with OS of patients in at least one of the performed analyses (2p12-rs1567532, 9p33-rs10818020, 10q26-rs10764826, 6p21-rs12209785 and 2p11-rs13431245) (supplementary table 4). For three *loci* (6p21, 9q33, and 10q26), either the index SNP or a highly correlated one (r2≥0.8) mapped to a DNase I hypersensitivity region in one or more cell types. The *loci* overlapped with active regulatory elements or transcription binding sites. The RegulomeBD software assigned a low score (6) to all the SNPs with the exception of 6p21-rs12209785 to which it assigned a score of "1f" or "likely to affect binding and linked to expression of a gene target (*RUNX2*)".

Using Genevar to detect *cis*-eQTLs revealed that the minor allele of the 6p21-rs12209785 SNP is consistently associated with a decreased expression of the (*RUNX2*) gene in monocytes, supporting the data of RegulomeDB.

**Discussion**

There is no effective cure for pancreatic cancer yet and often surgery offers the only treatment option that significantly improves survival. The strongest factors that affect PDAC prognosis are the presence of lymph-node metastases, a high tumor grade, a large tumor, high pre- and postoperative levels of CA-19-9, and positive margins of resection. Additionally there are growing evidences of the involvement of the genetic variability in the disease prognosis ([Li, Liu et al. 2006](#_ENREF_17), [Asomaning, Reid et al. 2008](#_ENREF_1), [Dong, Jiao et al. 2009](#_ENREF_9), [Dong, Javle et al. 2010](#_ENREF_8), [Okazaki, Javle et al. 2010](#_ENREF_20), [Avan, Pacetti et al. 2013](#_ENREF_2), [Bournet, Muscari et al. 2013](#_ENREF_3), [Ellsworth, Eckloff et al. 2013](#_ENREF_10), [Hackert and Buchler 2013](#_ENREF_14), [Reid-Lombardo, Fridley et al. 2013](#_ENREF_22), [Sivaprasad, Govardhan et al. 2013](#_ENREF_26), [Uzunoglu, Kolbe et al. 2013](#_ENREF_29)). Finding genetic variants associated with survival is of the utmost importance because it could help in identifying new targets for therapeutic interventions, in stratifying patients and in the longer term in moving towards a personalized approach for each patient.

In this study we report a large-scale analysis of 44 SNPs suggested to be associated with OS of PDAC patients in recent GWASs ([Willis, Olson et al. 2012](#_ENREF_31), [Wu, Kraft et al. 2012](#_ENREF_32)). We were able to confirm association of five SNPs at P<0.05 (2p12-rs1567532, 9p33-rs10818020, 10q26-rs10764826, 6p21-rs12209785, 2p11-rs13431245) and one more showed an association that approached statistical significance (rs16827275). We could not replicate the other reported associations, although the allelic frequencies in our study subjects were comparable to those obtained in the previous studies and we had more than 98% of power to detect an HR of 1.26 (which was the smallest HRs observed in the papers by Wu and Willis).

The most statistically significant association we observed in the PANDoRA populationwas between the rare allele of 2p12-rs1567532 and a decreased survival time in pancreatic cancer patients. This SNP is located in the proximity of the catenin (cadherin-associated protein), alpha 2 (*CTNNA2*) on chromosome 2p12. Alpha N-catenin is a cadherin-binding protein that plays a crucial role in cadherin-mediated cell-cell adhesion and that has been proposed as a tumour suppressor gene in laryngeal squamous cell carcinoma and in gastric cancer ([Uemura and Takeichi 2006](#_ENREF_28)). Functional studies revealed an increase in the migration and invasive ability of head and neck squamous cell carcinoma cells producing mutated forms of *CTNNA2* that are also associated with poor prognosis in laryngeal squamous cell carcinoma ([Fanjul-Fernandez, Quesada et al. 2013](#_ENREF_11)). We used Genevar to test for any possible *cis*-eQTLs for 2p12-rs1567532, but the software did not highlight any. Similarly RegulomeDB assigned to the SNP a score of 6, which indicates no strong functional importance. The variation from C to T of the 2p12-rs1567532, according to Haploreg might possibly alter the binding of several regulatory motifs to the *CTNNA2* gene, which in turn may lead to a down-regulation of the gene that could, as in the case of gastric and laryngeal cancer, lead to a poor prognosis. This remains a very speculative hypothesis that needs to be tested in functional studies, however, the mechanism suggested is in agreement with what found for the other two cancer types, i.e. a down-regulation of the *CTNNA2* gene that is associated with a poor survival of the patients.

Another suggestive finding is the association of the minor allele (G) of the 6p21-rs12209785, which is situated in the last intron of the *RUNX2* gene, with longer survival. The *in silico* analysis strongly suggested a direct functionality of the SNP since the minor allele (G) is associated with the down-regulation of the Runt-related transcription factor 2 (*RUNX2*) gene, while the over-expression of the *RUNX2* gene is associated with increased cellular proliferation, increased invasiveness and poor survival in several cancer types ([Onodera, Miki et al. 2010](#_ENREF_21), [Sadikovic, Thorner et al. 2010](#_ENREF_24), [Li, Xu et al. 2012](#_ENREF_19), [Sase, Suzuki et al. 2012](#_ENREF_25), [Li, Zhou et al. 2013](#_ENREF_18)). It is, therefore, plausible that rs12209785-G could decrease *RUNX2* expression and thus improve survival of patients. The results found by Wu and colleagues (the original GWAS) taken together with our results and the indication from the bioinformatic tools make 6p21-rs12209785 a worthy candidate to follow up in functional studies.

To analyze the impact of the combination of the associated variants we used a genetic score and we found that the number of "worse survival" genotypes was correlated with shorter survival. Even if this result was expectable it is worth noting that implementing a "survival score" with the additional variants that will be uncovered by future studies, rather than using the information provided by individual SNPs, will be beneficial to stratify the patients with the aim of a personalized treatment.

This study has a number of important strengths. First of all, with over 1700 PDAC patients it is the largest study on pancreatic cancer survival performed so far. Additionally, the tagging SNPs approach that we used provides an extensive coverage of genetic diversity in the regions of interest. Finally the selected SNPs had already a strong *a priori* epidemiological evidence to be related to pancreatic cancer survival, but they needed additional analysis to be confirmed or disproven as PDAC survival *loci*.

A possible limitation is that all subjects included were of European origin and therefore we cannot extend the findings to other populations.

To achieve the ultimate goal of a personalized medicine it is essential to further our knowledge on the biologic mechanisms underlying pancreatic cancer initiation and progression. To this end the associations between 2p12-rs1567532, 6p21-rs12209785 and PDAC survival seem to have a biologic explanation that directly links the genetic variation to the effect on pancreatic cancer survival. In conclusion, in this study we could clearly confirm several associations suggested by recent GWAS confirming the evidence that germline genetic polymorphisms, alone or in combination, affect OS of PDAC patients. For two of the SNPs (2p12-rs1567532 and 6p21-rs12209785) we also propose an explanation of the association based on *in silico* analysis. Functional studies are warranted to confirm the link between these genes (or gene mapping in those regions) and PDAC prognosis in order to understand whether these variants may have the potential to impact treatment decisions and design of clinical trials.

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**Table 1.** Characteristics of 1722 PDAC cases from PANDoRA used in this study.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **PANDoRA** |  | **Male** | **Female** |  |  |  |  |
| Gender | 1005 | 704 |  |  |  |  |
|  | **Median** | **25%** | **75%** | **Median** | **25%** | **75%** |
| Age (yrs) | 62 | 50 | 70 |  |  |  |
|  | **Dead** | | | **Alive** | | |
| N | 1325 |  |  | 397 |  |  |
| Survival in months | 11.5 | 6.0 | 20.3 | 16 | 7.4 | 34.9 |
| **Czech Republic** | N | 177 |  |  | 28 |  |  |
|  | Survival in months | 10.4 | 3.8 | 15.4 | 88.4 | 68.7 | 94.8 |
| **United Kingdom** | N | 90 |  |  | 9 |  |  |
|  | Survival in months | 9.8 | 5.2 | 15.7 | 12.1 | 6 | 23.4 |
| **Germany** | N | 456 |  |  | 128 |  |  |
|  | Survival in months | 11.8 | 6.9 | 22.6 | 14.9 | 4 | 44.2 |
| **Greece** | N | 26 |  |  | 6 |  |  |
|  | Survival in months | 9 | 5 | 14 | 28 | 22 | 47 |
| **Italy** | N | 523 |  |  | 139 |  |  |
|  | Survival in months | 12.8 | 7.0 | 21.6 | 19.1 | 7.03 | 31.8 |
| **Lithuania** | N | 22 |  |  | 34 |  |  |
|  | Survival in months | 4.63 | 2.36 | 16.2 | 10.8 | 7.6 | 20.7 |
| **Poland** | N | 31 |  |  | 53 |  |  |
|  | Survival in months | 9.8 | 6.3 | 14.4 | 11.4 | 9.5 | 16.1 |

**Table 2.** Cox regression analysis for association between OS and age, gender, stage and country of origin.

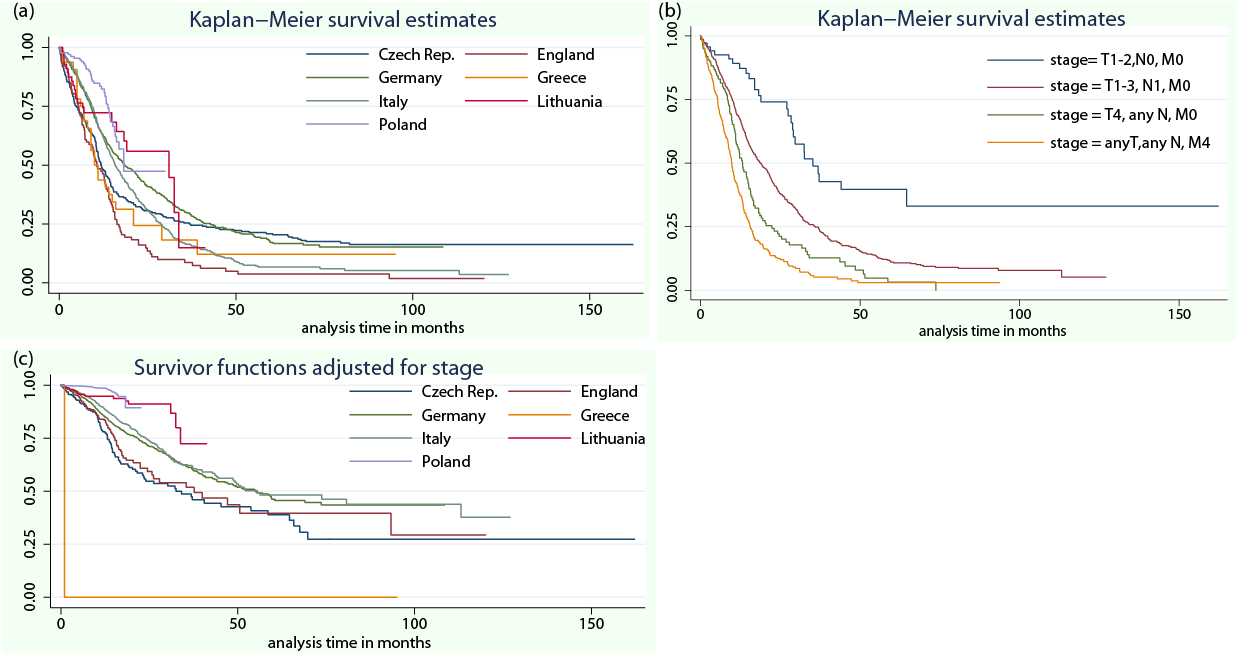
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **N (%)** | **MST** | **HR** | **95% CI** | **P** |
| Age (continuous) |  |  | 1 | (0.99-1.00) | 0.184 |
| Gender |  |  | 1 | (0.87-1.13) | 0.944 |
| Stage 1 (T1-2, N0, M0) | 86 (5.8%) | **16.98** | **ref** |  |  |
| Stage 2 (T1-3, N1, M0) | 868 (58.2%) | 15.33 | 2.26 | (1.49-3.41) | 1.12x10-4 |
| Stage 3 (T4, any N, M0) | 163 (10.9%) | 11.03 | 3.71 | (2.37-5.83) | 1.11x10-8 |
| Stage 4 (any T, any N, M1) | 374 (25.1%) | 10.98 | 5.75 | (3.76-8.81) | 6.66x10-16 |
| Italy | 662 (38.4%) |  | **ref** |  |  |
| Germany | 584 (33.9%) |  | 1.07 | (0.89-1.29) | 0.487 |
| Czech Republic | 205 (11.9%) |  | 1.44 | (1.13-1.84) | 3.00x10-3 |
| Poland | 84 (4.9%) |  | 0.87 | (0.59-1.26) | 0.451 |
| United Kingdom | 99 (5.8%) |  | 2.10 | (1.62-2.73) | 2.68x10-8 |
| Lithuania | 56 (3.3%) |  | 0.58 | (0.37-0.91) | 0.017 |
| Greece | 32 (1.9%) |  | 2.18 | (1.45-3.28) | 1.82x10-4 |

**Table 3.** Cox regression analysis for association between score in PDAC cases and OS. This analysis was performed by adjusting for age, gender, stage of disease and country of origin. Associations showing p<0.05 are reported in bold.

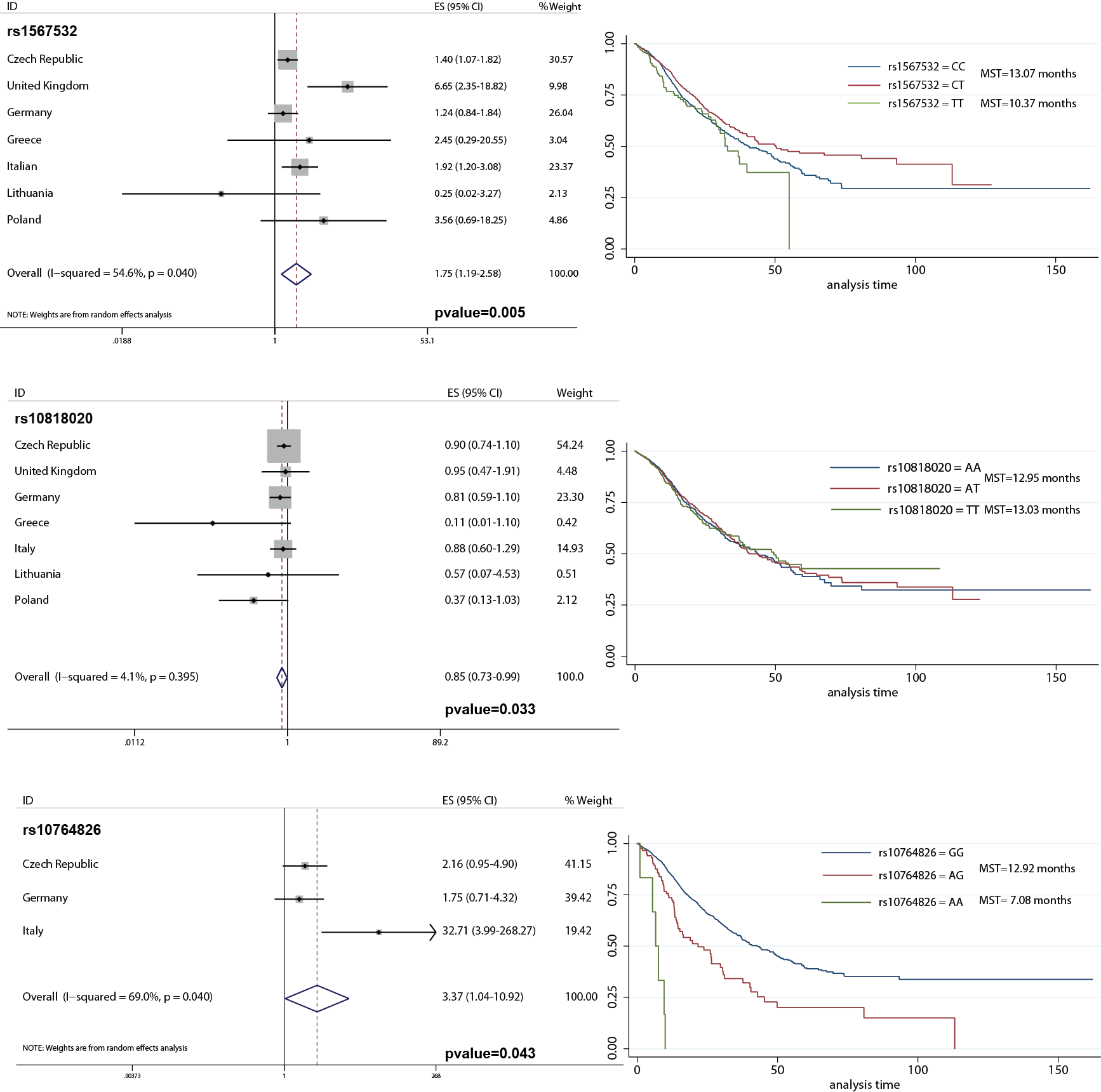
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Score** | **Alivea** | **Deada** | **MST** | **HR (95%CI)** | **P-value** |
| 1st quartile | 162 | 382 | 12.7 | 1.00 |  |
| 2nd quartile | 16 | 24 | 11.3 | 0.93 (0.58-1.51) | 0.775 |
| 3rd quartile | 186 | 500 | 12.9 | 1.10 (0.94-1.29) | 0.241 |
| 4th quartile | 90 | 303 | 11.6 | 1.41 (1.17-1.69) | **2.97x10-4** |

a Numbers may not add up to 100% of subjects due to genotyping failure.

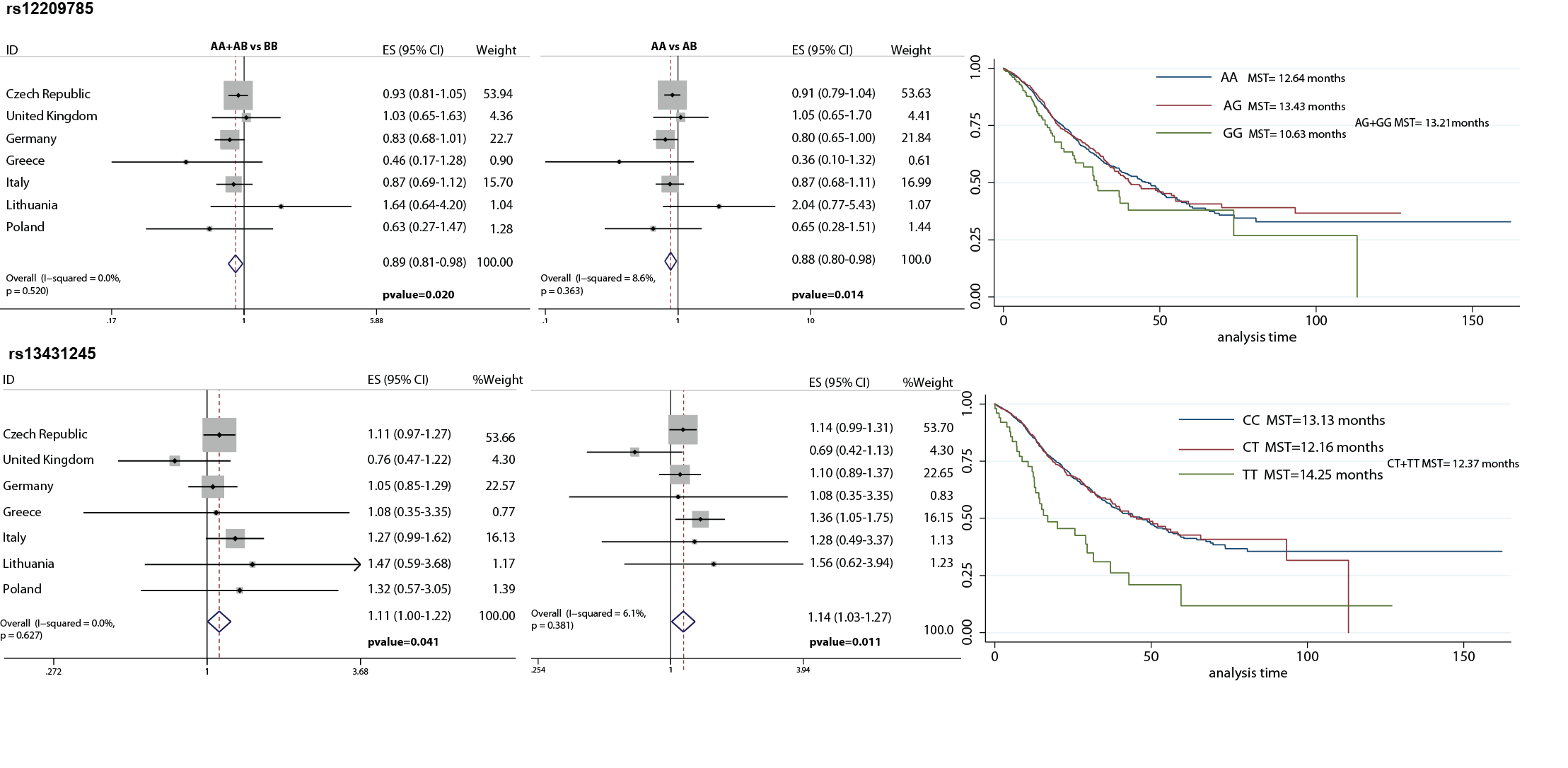
**Figure 1.** Kaplan-Meier curves by country of origin (a), stage of disease (b) country of origin adjusting for stage (c).



**Figure 2.** Kaplan-Meier curves and meta-analyses of SNPs associated with OS of PDAC patients.



**Figure 3.** Kaplan-Meier curves and meta-analyses of SNPs associated with OS of PDAC patients.

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**Supplementary table 1.** Meta-analysis of Cox regression results for SNPs genotyped in PDAC cases and OS. This analysis was performed by adjusting for age, gender, TNM stage and country of origin. Meta-analysis was performed with fixed effect if the p-value for heterogeneity test was p>0.05 and with a random-effects model if the p-value for heterogeneity test was p<0.05 (marked with \* in the table). Associations showing p<0.05 are reported in bold.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | allelic | | AAvsAB | | recessive | | AAvsAB+BB | |
| Study | ES (95%CI) | Ptest | ES (95%CI) | Ptest | ES (95%CI) | Ptest | ES (95%CI) | Ptest |
| rs10500715 | 0.97 (0.91-1.04) | 0.349 | 0.93 (0.84-1.03) | 0.173 | 0.95 (0.83-1.09) | 0.492 | 0.94 (0.85-1.03) | 0.193 |
| rs10736390 | 1.04 (0.97-1.11) | 0.261 | 0.98 (0.88-1.10) | 0.768 | 1.09 (0.95-1.25) | 0.219 | 1.01 (0.91-1.13) | 0.822 |
| rs10764826 | 1.05 (0.89-1.24) | 0.574 | 0.95 (0.79-1.15) | 0.613 | 3.37 (1.04-10.92) | **0.043\*** | 1.00 (0.84-1.20) | 0.974 |
| rs10788473 | 0.96 (0.90-1.03) | 0.256 | 1.00 (0.90-1.10) | 0.935 | 0.92 (0.79-1.06) | 0.229 | 0.97 (0.88-1.07) | 0.574 |
| rs10817611 | 1.06 (0.97-1.17) | 0.193 | 1.07 (0.96-1.20) | 0.244 | 1.10 (0.83-1.46) | 0.493 | 1.07 (0.96-1.20) | 0.201 |
| rs10818020 | 0.93 (0.87-0.99) | **0.027** | 0.94 (0.85-1.04) | 0.225 | 0.85 (0.73-0.99) | **0.033** | 0.91 (0.83-1.01) | 0.066 |
| rs10835187 | 0.98 (0.91-1.04) | 0.481 | 1.01 (0.91-1.13) | 0.822 | 0.95 (0.83-1.09) | 0.482 | 0.99 (0.90-1.10) | 0.880 |
| rs10835188 | 1.00 (0.92-1.08) | 0.979 | 1.01 (0.91-1.12) | 0.870 | 1.00 (0.79-1.26) | 0.982 | 1.00 (0.91-1.10) | 0.981 |
| rs10983614 | 0.94 (0.88-1.01) | 0.077 | 0.98 (0.89-1.09) | 0.732 | 0.86 (0.74-1.01) | 0.060 | 0.95 (0.86-1.04) | 0.276 |
| rs11639759 | 1.01 (0.90-1.13) | 0.901 | 1.04 (0.92-1.19) | 0.520 | 1.19 (0.43-3.29) | 0.738\* | 1.02 (0.90-1.16) | 0.711 |
| rs12101726 | 1.14 (1.00-1.31) | 0.059 | 1.15 (0.99-1.33) | 0.067 | 1.31 (0.62-2.75) | 0.484 | 1.15 (0.99-1.32) | 0.062 |
| rs12209785 | 0.93 (0.86-1.01) | 0.074 | 0.88 (0.80-0.98) | **0.014** | 0.97 (0.80-1.18) | 0.759 | 0.89 (0.81-0.98) | **0.020** |
| rs1225 | 1.00 (0.94-1.07) | 0.970 | 0.99 (0.89-1.10) | 0.828 | 1.00 (0.88-1.15) | 0.982 | 0.99 (0.89-1.09) | 0.821 |
| rs12362504 | 0.98 (0.91-1.05) | 0.555 | 0.99 (0.90-1.09) | 0.808 | 0.95 (0.79-1.14) | 0.577 | 0.98 (0.89-1.08) | 0.661 |
| rs12620038 | 1.04 (0.97-1.12) | 0.252 | 1.05 (0.95-1.16) | 0.329 | 1.08 (0.93-1.25) | 0.323 | 1.05 (0.96-1.16) | 0.274 |
| rs13431245 | 1.06 (0.97-1.15) | 0.182 | 1.14 (1.03-1.27) | **0.011** | 0.94 (0.73-1.22) | 0.639 | 1.11 (1.00-1.22) | **0.041** |
| rs1352757 | 1.03 (0.97-1.10) | 0.362 | 1.07 (0.96-1.19) | 0.210 | 1.05 (0.92-1.20) | 0.498 | 1.06 (0.96-1.17) | 0.229 |
| rs1414153 | 1.01 (0.93-1.10) | 0.808 | 0.99 (0.89-1.09) | 0.783 | 1.08 (0.86-1.37) | 0.512 | 1.00 (0.90-1.10) | 0.928 |
| rs1567532 | 1.08 (1.00-1.17) | 0.060 | 0.96 (0.87-1.06) | 0.422 | 1.75 (1.19-2.58) | **0.005\*** | 1.02 (0.93-1.12) | 0.691 |
| rs16827275 | 1.13 (0.99-1.30) | 0.069 | 1.11 (0.95-1.28) | 0.184 | 1.71 (0.96-3.05) | 0.067 | 1.12 (0.97-1.30) | 0.111 |
| rs16861827 | 0.93 (0.83-1.05) | 0.227 | 0.91 (0.80-1.02) | 0.719\* | 1.70 (0.95-3.03) | 0.074 | 0.91 (0.81-1.03) | 0.808\* |
| rs17077369 | 1.06 (0.95-1.18) | 0.312 | 1.08 (0.96-1.22) | 0.205\* | 1.09 (0.71-1.67) | 0.701 | 1.07 (0.95-1.21) | 0.240\* |
| rs17124276 | 1.02 (0.94-1.10) | 0.658 | 0.99 (0.90-1.10) | 0.892 | 1.15 (0.93-1.42) | 0.191 | 1.01 (0.91-1.11) | 0.916 |
| rs17275283 | 0.98 (0.92-1.05) | 0.606 | 0.97 (0.87-1.07) | 0.490 | 0.98 (0.84-1.15) | 0.820 | 0.97 (0.88-1.06) | 0.484 |
| rs361052 | 0.94 (0.86-1.02) | 0.135 | 0.92 (0.83-1.02) | 0.094 | 0.95 (0.75-1.20) | 0.678 | 0.92 (0.83-1.01) | 0.094 |
| rs4536164 | 1.03 (0.96-1.11) | 0.443 | 1.02 (0.92-1.12) | 0.733 | 1.09 (0.90-1.31) | 0.375 | 1.03 (0.94-1.13) | 0.577 |
| rs4596 | 0.97 (0.91-1.04) | 0.420 | 0.93 (0.83-1.04) | 0.178 | 0.94 (0.82-1.08) | 0.404 | 0.94 (0.84-1.04) | 0.238 |
| rs4757645 | 0.97 (0.91-1.04) | 0.427 | 1.02 (0.92-1.13) | 0.705 | 0.94 (0.82-1.08) | 0.394 | 0.99 (0.90-1.09) | 0.858 |
| rs6479073 | 0.92 (0.83-1.01) | 0.086 | 0.90 (0.81-1.01) | 0.067 | 0.95 (0.69-1.30) | 0.730 | 0.91 (0.81-1.01) | 0.076 |
| rs6662005 | 0.91 (0.80-1.03) | 0.147 | 0.97 (0.85-1.11) | 0.675 | 0.48 (0.22-1.08) | 0.077 | 0.93 (0.81-1.06) | 0.272 |
| rs7202041 | 1.03 (0.92-1.15) | 0.588 | 1.10 (0.98-1.25) | 0.113 | 0.73 (0.41-1.30) | 0.287 | 1.08 (0.95-1.21) | 0.237 |
| rs7330800 | 0.96 (0.89-1.03) | 0.255 | 1.03 (0.94-1.14) | 0.525 | 0.84 (0.71-1.00) | 0.054 | 0.98 (0.90-1.08) | 0.744 |
| rs770996 | 0.97 (0.90-1.03) | 0.321 | 0.95 (0.85-1.07) | 0.418 | 0.93 (0.81-1.06) | 0.283 | 0.94 (0.85-1.05) | 0.298 |
| rs7853844 | 1.02 (0.93-1.11) | 0.680 | 1.01 (0.91-1.13) | 0.817 | 1.05 (0.80-1.37) | 0.727 | 1.02 (0.92-1.14) | 0.666 |
| rs823918 | 0.97 (0.89-1.07) | 0.547 | 0.92 (0.82-1.02) | 0.114 | 1.23 (0.93-1.61) | 0.146 | 0.94 (0.85-1.04) | 0.251 |
| rs9517906 | 1.04 (0.97-1.12) | 0.241 | 1.01 (0.91-1.12) | 0.835 | 1.11 (0.96-1.27) | 0.163 | 1.04 (0.94-1.14) | 0.487 |
| rs9539806 | 1.00 (0.93-1.06) | 0.912 | 1.06 (0.96-1.18) | 0.249 | 0.96 (0.83-1.11) | 0.556 | 1.03 (0.93-1.13) | 0.603 |
| rs9593831 | 0.95 (0.87-1.03) | 0.195 | 0.97 (0.87-1.08) | 0.534 | 0.86 (0.67-1.10) | 0.215 | 0.96 (0.87-1.06) | 0.435 |
| rs981621 | 0.99 (0.93-1.06) | 0.811 | 1.00 (0.90-1.10) | 0.923 | 0.98 (0.84-1.14) | 0.794 | 0.99 (0.90-1.09) | 0.794 |
| rs9946524 | 0.99 (0.92-1.07) | 0.847 | 0.94 (0.85-1.04) | 0.217 | 1.11 (0.79-1.57) | 0.552 | 0.96 (0.87-1.05) | 0.371 |
| rs9954359 | 0.99 (0.92-1.06) | 0.704 | 0.93 (0.84-1.03) | 0.181 | 1.03 (0.88-1.22) | 0.695 | 0.94 (0.86-1.04) | 0.221 |
| rs1482426 | 0.95 (0.82-1.10) | 0.5 | 0.50 (0.94-0.79) | 0.501 | 1.05 (0.66-1.66) | 0.843 | 0.94 (0.79-1.11) | 0.459 |
| rs4285214 | 1.03 (0.94-1.14) | 0.51 | 0.51 (0.96-0.81) | 0.599 | 1.08 (0.89-1.31) | 0.449 | 0.99 (0.85-1.16) | 0.920 |
| rs9350 | 1.00 (0.87-1.15) | 0.98 | 0.98 (0.97-0.83) | 0.742 | 1.82 (0.66-5.03) | 0.098\* | 0.98 (0.84-1.15) | 0.842 |

**Supplementary table 2.** Cox regression analysis for SNPs genotyped in PDAC cases and OS. This analysis was performed by adjusting for age, gender, TNM stage and country of origin. Associations showing p<0.05 are reported in bold.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **N of subjectsa** | **N of failuresa** | **Per allele** | | **AA *vs.* ABb** | | **AA *vs.* BB** | | **AA *vs.* AB+BB** | |
| **HR (95% CI)c** | **Pvalue** | **HR (95% CI)** | **Pvalue** | **HR (95% CI)** | **Pvalue** | **HR (95% CI)** | **Pvalue** |
| rs10500715 | 1223 | 940 | 0.96 (0.88-1.06) | 0.415 | 0.91 (0.79-1.05) | 0.209 | 0.94 (0.78-1.14) | 0.547 | 0.92 (0.80-1.05) | 0.231 |
| rs10736390 | 1226 | 946 | 1.05 (0.95-1.15) | 0.338 | 0.99 (0.85-1.16) | 0.909 | 1.11 (0.92-1.33) | 0.283 | 1.03 (0.89-1.19) | 0.729 |
| rs10764826 | 1178 | 899 | 1.03 (0.82-1.30) | 0.780 | 0.94 (0.72-1.22) | 0.635 | 2.14 (0.94-4.86) | 0.069 | 0.99 (0.77-1.27) | 0.922 |
| rs10788473 | 1182 | 908 | 0.96 (0.88-1.05) | 0.396 | 1.01 (0.88-1.16) | 0.892 | 0.90 (0.73-1.09) | 0.276 | 0.98 (0.86-1.12) | 0.776 |
| rs10817611 | 1228 | 947 | 1.04 (0.91-1.18) | 0.595 | 1.04 (0.89-1.22) | 0.611 | 1.05 (0.71-1.55) | 0.806 | 1.04 (0.90-1.21) | 0.586 |
| rs10818020 | 1150 | 872 | 0.93 (0.85-1.02) | 0.143 | 0.92 (0.80-1.06) | 0.227 | 0.88 (0.72-1.08) | 0.210 | 0.91 (0.80-1.04) | 0.149 |
| rs10835187 | 1200 | 922 | 0.98 (0.90-1.08) | 0.703 | 1.01 (0.87-1.17) | 0.915 | 0.96 (0.80-1.16) | 0.661 | 0.99 (0.86-1.14) | 0.929 |
| rs10835188 | 1178 | 911 | 1.00 (0.90-1.12) | 0.943 | 1.00 (0.87-1.15) | 0.984 | 1.02 (0.74-1.40) | 0.923 | 1.00 (0.88-1.15) | 0.963 |
| rs10983614 | 1214 | 934 | 0.95 (0.87-1.05) | 0.296 | 0.96 (0.84-1.11) | 0.603 | 0.89 (0.73-1.10) | 0.290 | 0.95 (0.83-1.08) | 0.420 |
| rs11639758 | 1213 | 934 | 1.04 (0.88-1.22) | 0.638 | 1.07 (0.89-1.28) | 0.463 | 0.88 (0.44-1.77) | 0.721 | 1.06 (0.89-1.26) | 0.534 |
| rs12101726 | 1202 | 924 | 1.13 (0.94-1.37) | 0.198 | 1.13 (0.92-1.38) | 0.248 | 1.37 (0.51-3.68) | 0.528 | 1.13 (0.93-1.38) | 0.216 |
| rs12209785 | 1200 | 926 | 0.93 (0.84-1.04) | 0.219 | 0.88 (0.77-1.01) | 0.073 | 0.98 (0.75-1.29) | 0.902 | 0.90 (0.78-1.02) | 0.101 |
| rs1225 | 1209 | 930 | 1.00 (0.91-1.10) | 0.971 | 1.01 (0.87-1.16) | 0.944 | 1.00 (0.83-1.21) | 0.980 | 1.00 (0.87-1.15) | 0.950 |
| rs12362504 | 1217 | 937 | 0.98 (0.88-1.08) | 0.653 | 0.98 (0.85-1.13) | 0.785 | 0.95 (0.74-1.22) | 0.671 | 0.98 (0.86-1.11) | 0.711 |
| rs12620038 | 1197 | 918 | 1.05 (0.96-1.16) | 0.291 | 1.06 (0.93-1.22) | 0.386 | 1.10 (0.89-1.35) | 0.373 | 1.07 (0.94-1.22) | 0.306 |
| rs13431245 | 1216 | 935 | 1.04 (0.92-1.16) | 0.539 | 1.10 (0.95-1.27) | 0.189 | 0.89 (0.62-1.29) | 0.548 | 1.07 (0.94-1.23) | 0.301 |
| rs1352757 | 1223 | 941 | 1.03 (0.94-1.13) | 0.533 | 1.08 (0.93-1.24) | 0.329 | 1.04 (0.87-1.26) | 0.656 | 1.07 (0.93-1.22) | 0.359 |
| rs1414153 | 1212 | 933 | 1.00 (0.90-1.13) | 0.932 | 0.99 (0.86-1.14) | 0.887 | 1.05 (0.77-1.44) | 0.756 | 1.00 (0.87-1.14) | 0.968 |
| rs1567532 | 1212 | 935 | 1.07 (0.96-1.20) | 0.197 | 0.95 (0.82-1.09) | 0.441 | **1.53 (1.17-2.00)** | **0.002** | 1.01 (0.88-1.15) | 0.899 |
| rs16827275 | 1218 | 942 | 1.18 (0.99-1.42) | 0.067 | 1.16 (0.95-1.42) | 0.148 | 1.67 (0.79-3.53) | 0.183 | 1.18 (0.97-1.43) | 0.095 |
| rs16861827 | 1216 | 938 | 0.91 (0.78-1.07) | 0.258 | 0.88 (0.74-1.04) | 0.128 | 1.62 (0.72-3.65) | 0.240 | 0.89 (0.76-1.05) | 0.174 |
| rs17077369 | 1208 | 930 | 1.08 (0.93-1.25) | 0.333 | 1.12 (0.94-1.33) | 0.217 | 0.95 (0.52-1.74) | 0.871 | 1.10 (0.93-1.30) | 0.255 |
| rs17124276 | 1196 | 918 | 1.01 (0.91-1.13) | 0.849 | 0.99 (0.86-1.14) | 0.898 | 1.07 (0.80-1.43) | 0.654 | 1.00 (0.88-1.14) | 0.988 |
| rs17275283 | 1213 | 934 | 0.98 (0.89-1.08) | 0.663 | 0.97 (0.85-1.12) | 0.691 | 0.96 (0.78-1.19) | 0.740 | 0.97 (0.85-1.10) | 0.654 |
| rs361052 | 1222 | 942 | 0.92 (0.82-1.04) | 0.182 | 0.91 (0.79-1.05) | 0.221 | 0.88 (0.64-1.22) | 0.444 | 0.91 (0.79-1.04) | 0.179 |
| rs4536164 | 1208 | 932 | 1.04 (0.94-1.15) | 0.472 | 1.02 (0.89-1.17) | 0.770 | 1.11 (0.86-1.43) | 0.413 | 1.03 (0.91-1.18) | 0.612 |
| rs4596 | 1231 | 949 | 0.98 (0.89-1.08) | 0.696 | 0.96 (0.82-1.12) | 0.585 | 0.97 (0.80-1.17) | 0.728 | 0.96 (0.83-1.11) | 0.589 |
| rs4757645 | 1153 | 891 | 0.99 (0.90-1.09) | 0.849 | 1.05 (0.91-1.22) | 0.476 | 0.96 (0.79-1.16) | 0.661 | 1.03 (0.90-1.18) | 0.693 |
| rs6479073 | 1215 | 938 | 0.93 (0.82-1.07) | 0.320 | 0.91 (0.78-1.06) | 0.245 | 0.98 (0.63-1.53) | 0.930 | 0.92 (0.79-1.07) | 0.260 |
| rs6662005 | 1194 | 918 | 0.92 (0.77-1.09) | 0.346 | 0.98 (0.81-1.18) | 0.795 | 0.39 (0.12-1.21) | 0.104 | 0.94 (0.79-1.14) | 0.547 |
| rs7202041 | 1227 | 948 | 1.06 (0.92-1.24) | 0.418 | 1.12 (0.94-1.32) | 0.195 | 0.78 (0.39-1.58) | 0.493 | 1.10 (0.93-1.29) | 0.275 |
| rs7330800 | 1223 | 940 | 0.97 (0.87-1.07) | 0.480 | 1.06 (0.92-1.21) | 0.428 | 0.83 (0.65-1.05) | 0.124 | 1.01 (0.89-1.15) | 0.899 |
| rs770996 | 1209 | 931 | 0.98 (0.89-1.07) | 0.599 | 0.96 (0.82-1.12) | 0.591 | 0.95 (0.79-1.15) | 0.603 | 0.96 (0.82-1.11) | 0.553 |
| rs7853844 | 1211 | 931 | 1.01 (0.89-1.15) | 0.849 | 1.00 (0.86-1.17) | 0.985 | 1.06 (0.74-1.52) | 0.766 | 1.01 (0.87-1.17) | 0.916 |
| rs823918 | 1217 | 941 | 0.98 (0.86-1.11) | 0.773 | 0.93 (0.80-1.08) | 0.358 | 1.18 (0.80-1.73) | 0.401 | 0.95 (0.83-1.10) | 0.514 |
| rs9517906 | 1218 | 938 | 1.02 (0.93-1.12) | 0.630 | 1.00 (0.87-1.16) | 0.976 | 1.06 (0.87-1.28) | 0.572 | 1.02 (0.89-1.16) | 0.817 |
| rs9539806 | 1203 | 926 | 1.00 (0.91-1.09) | 0.961 | 1.08 (0.93-1.24) | 0.315 | 0.95 (0.78-1.16) | 0.635 | 1.04 (0.91-1.19) | 0.548 |
| rs95933831 | 1208 | 929 | 0.97 (0.86-1.09) | 0.585 | 1.01 (0.87-1.16) | 0.946 | 0.85 (0.60-1.19) | 0.341 | 0.98 (0.85-1.13) | 0.816 |
| rs981621 | 1174 | 905 | 1.00 (0.91-1.09) | 0.928 | 1.01 (0.88-1.16) | 0.914 | 0.98 (0.80-1.21) | 0.861 | 1.00 (0.88-1.14) | 0.980 |
| rs9946524 | 1200 | 923 | 0.99 (0.90-1.09) | 0.863 | 0.95 (0.83-1.10) | 0.507 | 1.03 (0.82-1.28) | 0.819 | 0.97 (0.85-1.10) | 0.625 |
| rs9954359 | 1189 | 917 | 0.99 (0.90-1.09) | 0.850 | 0.95 (0.83-1.10) | 0.516 | 1.03 (0.82-1.29) | 0.830 | 0.97 (0.85-1.10) | 0.632 |
| rs1482426 | 1155 | 895 | 0.92 (0.79-1.06) | 0.246 | 0.88 (0.74-1.05) | 0.171 | 0.96 (0.62-1.51) | 0.875 | 0.89 (0.76-1.06) | 0.185 |
| rs4285214 | 1046 | 807 | 1.02 (0.93-1.13) | 0.648 | 0.95 (0.81-1.12) | 0.547 | 1.06 (0.87-1.28) | 0.568 | 0.99 (0.85-1.15) | 0.852 |
| rs9350 | 1093 | 830 | 0.97 (0.85-1.11) | 0.624 | 0.96 (0.82-1.13) | 0.657 | 0.95 (0.62-1.45) | 0.796 | 0.96 (0.83-1.12) | 0.626 |

a Numbers may not add up to 100% of subjects due to genotyping failure.

b A = major allele; B = minor allele.

c HR: hazard ratio; CI: confidence interval.

**Supplementary table 3.** Cox regression analysis for SNPs genotyped in PDAC cases and OS. This analysis was performed by adjusting for age, gender and country of origin. Associations showing p<0.05 are reported in bold.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **N of subjectsa** | **N of failuresa** | **Per allele** | | **AA *vs.* ABb** | | **AA *vs.* BB** | | **AA *vs.* AB+BB** | |
| **HR (95% CI)c** | **Pvalue** | **HR (95% CI)** | **Pvalue** | **HR (95% CI)** | **Pvalue** | **HR (95% CI)** | **Pvalue** |
| rs10500715 | 1616 | 1259 | 0.95 (0.88-1.03) | 0.22 | 0.90 (0.80-1.02) | 0.114 | 0.92 (0.78-1.08) | 0.319 | 0.91 (0.81-1.02) | 0.111 |
| rs10736390 | 1621 | 1268 | 1.05 (0.97-1.14) | 0.261 | 0.99 (0.87-1.13) | 0.872 | 1.11 (0.94-1.31) | 0.206 | 1.02 (0.90-1.16) | 0.72 |
| rs10764826 | 1565 | 1215 | 1.11 (0.91-1.35) | 0.314 | 1.06 (0.85-1.33) | 0.611 | 1.63 (0.77-3.45) | 0.199 | 1.09 (0.88-1.35) | 0.434 |
| rs10788473 | 1574 | 1227 | **0.92 (0.84-0.99)** | **0.033** | 0.95 (0.84-1.07) | 0.402 | **0.82 (0.69-0.97)** | **0.024** | 0.92 (0.82-1.03) | 0.139 |
| rs10817611 | 1622 | 1267 | 0.97 (0.87-1.08) | 0.582 | 0.97 (0.85-1.12) | 0.687 | 0.93 (0.67-1.30) | 0.674 | 0.97 (0.85-1.10) | 0.617 |
| rs10818020 | 1519 | 1167 | 0.98 (0.91-1.06) | 0.664 | 1.00 (0.89-1.13) | 0.998 | 0.95 (0.80-1.13) | 0.589 | 0.99 (0.88-1.11) | 0.84 |
| rs10835187 | 1595 | 1243 | 1.02 (0.94-1.10) | 0.697 | 1.02 (0.89-1.16) | 0.797 | 1.03 (0.88-1.21) | 0.702 | 1.02 (0.90-1.15) | 0.736 |
| rs10835188 | 1562 | 1222 | 1.06 (0.96-1.17) | 0.214 | 1.09 (0.97-1.24) | 0.146 | 1.05 (0.79-1.39) | 0.747 | 1.09 (0.97-1.22) | 0.154 |
| rs10983614 | 1609 | 1254 | 0.98 (0.91-1.07) | 0.687 | 1.03 (0.91-1.16) | 0.661 | 0.94 (0.78-1.12) | 0.466 | 1.01 (0.90-1.13) | 0.926 |
| rs11639758 | 1598 | 1244 | 0.97 (0.85-1.12) | 0.71 | 0.99 (0.85-1.16) | 0.89 | 0.84 (0.45-1.56) | 0.579 | 0.98 (0.84-1.14) | 0.795 |
| rs12101726 | 1599 | 1246 | 1.16 (0.99-1.36) | 0.064 | 1.14 (0.97-1.35) | 0.115 | 1.75 (0.72-4.21) | 0.215 | 1.16 (0.98-1.37) | 0.085 |
| rs12209785 | 1592 | 1243 | 0.97 (0.89-1.07) | 0.542 | 0.92 (0.82-1.04) | 0.177 | 1.05 (0.83-1.32) | 0.689 | 0.94 (0.84-1.05) | 0.278 |
| rs1225 | 1605 | 1252 | 1.02 (0.94-1.10) | 0.645 | 1.05 (0.92-1.19) | 0.483 | 1.03 (0.88-1.21) | 0.724 | 1.04 (0.92-1.17) | 0.504 |
| rs12362504 | 1607 | 1254 | 0.96 (0.88-1.04) | 0.317 | 0.95 (0.84-1.07) | 0.394 | 0.92 (0.75-1.14) | 0.449 | 0.95 (0.84-1.06) | 0.327 |
| rs12620038 | 1587 | 1235 | 1.04 (0.96-1.12) | 0.387 | 1.05 (0.93-1.18) | 0.418 | 1.06 (0.89-1.27) | 0.5 | 1.05 (0.94-1.18) | 0.365 |
| rs13431245 | 1612 | 1257 | 1.06 (0.96-1.17) | 0.26 | 1.10 (0.98-1.24) | 0.119 | 0.99 (0.73-1.34) | 0.943 | 1.09 (0.97-1.22) | 0.153 |
| rs1352757 | 1620 | 1263 | 1.03 (0.96-1.12) | 0.403 | 1.04 (0.91-1.17) | 0.578 | 1.07 (0.91-1.25) | 0.418 | 1.05 (0.93-1.18) | 0.46 |
| rs1414153 | 1602 | 1248 | 0.98 (0.89-1.08) | 0.637 | 1.02 (0.90-1.15) | 0.757 | 0.86 (0.65-1.13) | 0.278 | 1.00 (0.89-1.12) | 0.955 |
| rs1567532 | 1606 | 1255 | 1.03 (0.94-1.13) | 0.523 | 0.99 (0.88-1.12) | 0.931 | 1.12 (0.90-1.40) | 0.296 | 1.01 (0.91-1.14) | 0.796 |
| rs16827275 | 1608 | 1259 | **1.23 (1.06-1.44)** | **0.008** | **1.20 (1.02-1.42)** | **0.029** | 2.06 (0.98-4.36) | 0.058 | **1.22 (1.04-1.44)** | **0.015** |
| rs16861827 | 1607 | 1256 | 0.98 (0.86-1.12) | 0.769 | 0.98 (0.85-1.13) | 0.777 | 0.97 (0.46-2.04) | 0.928 | 0.98 (0.85-1.13) | 0.77 |
| rs17077369 | 1596 | 1244 | 1.05 (0.92-1.19) | 0.496 | 1.05 (0.90-1.22) | 0.523 | 1.08 (0.63-1.83) | 0.785 | 1.05 (0.91-1.21) | 0.498 |
| rs17124276 | 1584 | 1235 | 0.97 (0.89-1.07) | 0.582 | 0.95 (0.84-1.07) | 0.383 | 1.01 (0.79-1.29) | 0.944 | 0.96 (0.85-1.07) | 0.441 |
| rs17275283 | 1609 | 1255 | 0.95 (0.87-1.03) | 0.23 | 0.96 (0.85-1.07) | 0.446 | 0.90 (0.74-1.08) | 0.264 | 0.94 (0.84-1.05) | 0.304 |
| rs361052 | 1609 | 1255 | 1.01 (0.92-1.11) | 0.832 | 1.02 (0.91-1.15) | 0.732 | 0.99 (0.74-1.32) | 0.95 | 1.02 (0.91-1.14) | 0.766 |
| rs4536164 | 1603 | 1254 | 1.07 (0.98-1.17) | 0.142 | 1.06 (0.95-1.20) | 0.294 | 1.15 (0.92-1.43) | 0.215 | 1.08 (0.96-1.20) | 0.191 |
| rs4596 | 1628 | 1271 | 0.95 (0.88-1.03) | 0.236 | 0.92 (0.81-1.05) | 0.231 | 0.91 (0.77-1.07) | 0.271 | 0.92 (0.81-1.04) | 0.186 |
| rs4757645 | 1534 | 1201 | 1.02 (0.94-1.11) | 0.622 | 0.99 (0.88-1.12) | 0.902 | 1.05 (0.89-1.24) | 0.542 | 1.01 (0.9-1.130) | 0.901 |
| rs6479073 | 1609 | 1258 | 0.94 (0.84-1.05) | 0.291 | 0.95 (0.83-1.08) | 0.423 | 0.86 (0.58-1.26) | 0.436 | 0.94 (0.83-1.07) | 0.339 |
| rs6662005 | 1589 | 1238 | 0.89 (0.77-1.03) | 0.13 | 0.97 (0.83-1.14) | 0.742 | **0.30 (0.11-0.80)** | **0.016** | 0.93 (0.79-1.09) | 0.341 |
| rs7202041 | 1622 | 1269 | 1.00 (0.87-1.14) | 0.982 | 1.04 (0.90-1.21) | 0.559 | 0.67 (0.35-1.30) | 0.238 | 1.02 (0.89-1.18) | 0.764 |
| rs7330800 | 1615 | 1260 | 0.95 (0.87-1.03) | 0.241 | 1.04 (0.93-1.17) | 0.486 | **0.80 (0.64-0.98)** | **0.035** | 0.99 (0.89-1.11) | 0.873 |
| rs770996 | 1573 | 1228 | 0.99 (0.92-1.08) | 0.865 | 1.01 (0.89-1.16) | 0.845 | 0.99 (0.84-1.16) | 0.854 | 1.00 (0.88-1.14) | 0.943 |
| rs7853844 | 1606 | 1253 | 1.01 (0.91-1.12) | 0.838 | 1.02 (0.90-1.17) | 0.727 | 0.98 (0.72-1.35) | 0.924 | 1.02 (0.90-1.15) | 0.768 |
| rs823918 | 1611 | 1264 | 0.99 (0.89-1.10) | 0.797 | 0.96 (0.85-1.09) | 0.533 | 1.07 (0.77-1.48) | 0.678 | 0.97 (0.86-1.10) | 0.635 |
| rs9517906 | 1601 | 1253 | 1.02 (0.95-1.11) | 0.557 | 1.06 (0.94-1.20) | 0.325 | 1.03 (0.87-1.22) | 0.73 | 1.06 (0.94-1.19) | 0.366 |
| rs9539806 | 1595 | 1244 | 0.97 (0.90-1.05) | 0.508 | 1.06 (0.94-1.20) | 0.324 | 0.90 (0.76-1.07) | 0.223 | 1.02 (0.91-1.14) | 0.763 |
| rs95933831 | 1599 | 1246 | 0.94 (0.85-1.04) | 0.256 | 0.95 (0.84-1.07) | 0.407 | 0.87 (0.64-1.18) | 0.373 | 0.94 (0.83-1.06) | 0.309 |
| rs981621 | 1556 | 1214 | 1.00 (0.92-1.09) | 0.949 | 1.03 (0.91-1.16) | 0.679 | 0.99 (0.82-1.18) | 0.875 | 1.02 (0.91-1.14) | 0.774 |
| rs9946524 | 1591 | 1241 | 0.96 (0.88-1.05) | 0.354 | 0.96 (0.85-1.08) | 0.521 | 0.92 (0.76-1.12) | 0.412 | 0.95 (0.85-1.07) | 0.406 |
| rs9954359 | 1582 | 1236 | 0.98 (0.90-1.07) | 0.682 | 0.99 (0.88-1.11) | 0.831 | 0.96 (0.78-1.17) | 0.682 | 0.98 (0.88-1.10) | 0.746 |
| rs1482426 | 1529 | 1199 | 0.99 (0.88-1.12) | 0.878 | 1.00 (0.86-1.16) | 0.987 | 0.95 (0.65-1.39) | 0.780 | 0.99 (0.86-1.15) | 0.941 |
| rs4285214 | 1392 | 1085 | 1.00 (0.92-1.09) | 0.989 | 0.90 (0.78-1.04) | 0.140 | 1.02 (0.86-1.20) | 0.839 | 0.94 (0.82-1.07) | 0.325 |
| rs9350 | 1445 | 117 | 0.97 (0.86-1.08) | 0.575 | 0.92 (0.80-1.05) | 0.231 | 1.12 (0.80-1.56) | 0.508 | 0.94 (0.82-1.07) | 0.346 |

a Numbers may not add up to 100% of subjects due to genotyping failure.

b A = major allele; B = minor allele.

c HR: hazard ratio; CI: confidence interval.