Title: Pancreatic cancer and autoimmune diseases: An association sustained by computational and epidemiological case-control approaches

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Short tile: Autoimmune diseases and pancreatic cancer risk

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Key words: Pancreatic cancer risk; Autoimmune diseases; Multimorbidity; Genetic network; Gene-disease associations; Case-control study.

Abbreviations: Autoimmune disease (AID), Biological Process (BP), Disease Specificity (DSI), Gene-disease association (GAD), Pancreatic cancer (PC), Disease Pleiotropy (DPI).

Article category: Research article

Novelty and impact: Using a bioinformatics approach we show that autoimmune diseases share genetic components with pancreatic cancer and further corroborate this association in a European case-control study population. Some of these results are confirmatory of the mechanisms of pancreatic carcinogenesis while others might point to novel mechanisms. This information could open new venues to explore and increase our understanding of PC risk, potentially impacting the prevention and treatment strategies for this deadly cancer.

Deaths from pancreatic cancer are increasing making it a public health emergency to define the molecular causes of this deadly disease. Here the authors show that autoimmune diseases share genetic components with pancreatic cancer and further corroborate this association in a case-control study. This could bring new mechanistic understanding of pancreatic cancer, potentially impacting its prevention and treatment in the future.

Abstract

Deciphering the underlying genetic basis behind pancreatic cancer (PC) and its associated multimorbidities will enhance our knowledge towards PC control. The study investigated the common genetic background of PC and different morbidities through a computational approach and further evaluated the less explored association between PC and autoimmune diseases (AIDs) through an epidemiological analysis. Gene-disease associations (GDAs) of 26 morbidities of interest and PC were obtained using the DisGeNET public discovery platform. The association between AIDs and PC pointed by the computational analysis was confirmed through multivariable logistic regression models in the PanGen European case-control study population of 1,705 PC cases and 1,084 controls. Fifteen morbidities shared at least one gene with PC in the DisGeNET database. Based on common genes, several AIDs were genetically associated with PC pointing to a potential link between them. An epidemiologic analysis confirmed that having any of the nine AIDs studied was significantly associated with a reduced risk of PC (Odds Ratio (OR)=0.74, 95% Confidence Interval (CI) 0.58-0.93) which decreased in subjects having ≥2 AIDs (OR=0.39, 95%CI 0.21-0.73). In independent analyses, polymyalgia rheumatica and rheumatoid arthritis were significantly associated with low PC risk (OR=0.40, 95%CI 0.19-0.89, and OR=0.73, 95%CI 0.53-1.00, respectively). Several inflammatory-related morbidities shared a common genetic component with PC based on public databases. These molecular links could shed light into the molecular mechanisms underlying PC development and simultaneously generate novel hypotheses. In this study, we report sound findings pointing to an association between AIDs and a reduced risk of PC.

Introduction

Pancreatic cancer (PC) is a deadly disease[1] and projected to become the second cause of cancer-related death in Europe by 2030[2], supporting its consideration as a public health emergency[3]. Patients with chronic pancreatitis, type 2 diabetes (T2D), or obesity have an increased risk of PC[4–6] while those with nasal allergies and asthma have a reduced risk[7]. Multiple morbidities are common in ageing, a main risk factor of PC, but they are seldom studied in a contextual frame, which is important since multiple conditions can share adverse lifestyle and/or genetic susceptibility. In this respect, a higher risk of PC has been reported among subjects having ≥3 metabolic syndrome-related disorders or gastric conditions versus those having none of them[8,9]. Understanding the mechanisms shared between multimorbidities and PC could help improve primary prevention, early-diagnosis, prognosis and/or treatment of PC. Therefore, the combined use of well-annotated epidemiological and clinical datasets with bioinformatics tools becomes ideal to systematically explore the genetic complexity underlying the associations between different multimorbidities and PC.

Autoimmune diseases (AIDs) are characterized by an immune dysregulation in which immune cells react against self-antigens resulting in cell and tissue damage. AIDs are classified into organ-specific and systemic depending on whether the autoimmune response is directed against a single or multiple tissues[10]. Cancer is thought to result from the accumulation of genetic alterations and the evasion of the immune response against neoantigens; therefore, it is conceivable that AIDs and cancer share genetic mechanisms. Studies have reported positive associations between overall cancer risk and AIDs such as celiac disease, Crohn's disease, rheumatoid arthritis, or systemic lupus erythematosus [11–13]. However, contrary associations have been reported for specific types of cancer, e.g. positive associations have been observed for Non-Hodgkin's lymphoma with Crohn's disease,

rheumatoid arthritis, and lupus erythematosus, or liver cancer with celiac disease, ulcerative colitis, or inflammatory bowel disease [12,14–17], while other studies have reported negative associations between breast cancer with celiac disease, rheumatoid arthritis, and lupus erythematosus, or colorectal cancer with rheumatoid arthritis[18–21]. However, to date, limited and conflicting information exists regarding the association between autoimmunity and the risk of PC, which could be partly explained by the relatively low prevalence of both conditions in the population [12,17,18,22,23].

In this study, we examine the genetic background shared between 26 candidate medical conditions and PC to identify underlying common genes using DisGeNET, a platform that integrates information on gene-disease associations from different public resources including the literature. Our aim was to generate novel genetic-based hypothesis regarding multimorbidities associated with PC as well as to obtain insight into their underlying molecular mechanisms. Finally, we sustain these observations through an epidemiological approach using the resources of a large international case-control study.

Material and Methods

The bioinformatics analysis was performed with disgenet2r version 3.1.2 (https://bitbucket.org/ibi_group/disgenet2r), an R package that explores the molecular basis of comorbidities based on DisGeNET[24] (version 3.0), a knowledge platform on human diseases and their association with gene alterations reported in UniProt, ClinVar, and CTD datasources.

Disease vocabulary. To interrogate the DisGeNET database, diseases were defined as Concept Unique Identifiers (CUIs) from the Unified Medical Language Systems Metathesaurus. The CUIs for PC and 26 candidate morbidities were selected from three semantic types (disease or syndrome, sign or symptom and neoplastic process) by two

members of the group (PG and NM). A mean of 4 (range 1 to 12) CUIs were used to define each disease (Additional file 1: Table S1). All 26 candidate morbidities were included in the bioinformatics analysis based on their availability of epidemiological information in the PanGenEU study.

DisGeNET query. For all but four conditions, the curated subset of DisGeNET was queried. Polymyalgia rheumatica, mumps, pernicious anaemia, and Addison's disease were not found in the curated data sources and thus were queried from all sources that include data automatically extracted from the literature using text mining approaches. The obtained genes were manually curated by a member of the group (PG).

Disease association on the basis of shared genes. The number of common genes between disease pairs was used to determine disease "genetic" similarities. The Jaccard index (JI) was calculated to estimate the association among diseases accounting for variation in gene findings due differentially studied morbidities, i.e. diseases with more versus less total number of genes identified. The JI is defined as: $|Genesdis1 \cap Genesdis2| / |Genesdis1 \cup Genesdis2|$, where Genesdis1 and Genesdis2 are the genes associated with disease 1 and 2, respectively, $\cap$ is the intersection operator, and $\cup$ is the union operator between the two sets of genes. An empirical P value was calculated for each JI using 50,000 bootstrapped samples from a pool of the 7,878 disease genes available in DisGeNET (curated data set). Additionally, the Disease Specificity (DSI) and Pleiotropy (DPI) indexes were calculated (www.disgenet.org/web/DisGeNET/menu/dbinfo#specificity) to characterize all disease genes. Both indexes range from 0 to 1, where DSI = 1 implies high disease specificity (genes associate only with one disease) and DPI = 1 implies high disease pleiotropy (the gene is associated with several diseases and these belong to different classes).

Gene Ontology analysis. The Gene Ontology terms, restricted to the Biological Process (BP) branch, were identified through an enrichment analysis performed with the common genes between disease pairs with GO.db and GOstats packages in R.

Pathway analysis. An enrichment analysis was performed using the ReactomePA package in R to identify pathways shared between morbidities based on common genes between disease pairs.

The epidemiological analysis was performed using resources from the PanGenEU case-control study conducted in Spain, United Kingdom, Germany, Ireland, Sweden, and Italy, between 2009-2014 (Additional file 1: Annex S1).

Study population. Potentially eligible pancreatic ductal adenocarcinoma patients, men and women ≥18 years of age, were approached for participation. Subjects with diagnosis not confirmed by the physician were excluded from the study. Eligible controls did not have previous history of PC and their primary diagnosis for hospital admission was not associated with known risk factors of PC (Supplementary Table S1 and S2) when recruited in a hospital-based setting; controls from Ireland and Sweden were population-based. Subjects without information in the entire medical section of the questionnaire were excluded (N=268, 8.8%) leaving 1,705 PC cases and 1,084 controls for analyses. Age, sex, and smoking distributions were similar between included and excluded subjects (P >0.05). An overall response rate of 86.3% was observed for cases and 77.8% for controls. IRB ethical approval and written informed consent was obtained by all participating centers and study participants, respectively.

Study variables. Demographics, lifestyle, and medical history were gathered through in-person interviews applying standardized questionnaires. Subjects reported "yes/no" to "Has your doctor ever told you that you had any of the following illnesses, health problems or procedures?" for 26 candidate morbidities including 9 AIDs further categorized as

systemic (rheumatoid arthritis, lupus erythematosus, scleroderma, and polymyalgia rheumatica), hematologic (pernicious anaemia), gastrointestinal (Crohn's disease, ulcerative colitis, and celiac disease), and endocrine (Addison's disease). Regular consumption of anti-inflammatory/pain killer medication (aspirin, paracetamol, NSAIDs and corticosteroids) was defined as subjects reporting ever taking one of these treatments at least once a week, on average, for 3 months or more.

Statistical analysis. Imputation of missing values (3.7% in cases and 2.9% in controls) was performed with random forest (missForest R package). Missing values were assumed to be missing at random. Variables used for imputation (% missings) included case-control status, country, age (2.3%), sex (0.2%), smoking (pack/years, 9.4%), alcohol status (1.5%), medication (6.1- 7.9%), and morbidities and time since diagnosis (0.8%-21.7%). Imputation was performed with no maximum number of iterations and 100 trees. An imputation test introducing the same proportions of missing values to a complete-case dataset resulted in a concordance mean between imputed and real data >90% and out of bag errors < 0.35 (0= good imputation performance, 1= bad imputation performance). Multivariable logistic regression models were used to test the association between PC risk and AIDs, individually and by defined groups. Adjustment variables were selected based on the 10% change in estimate, the likelihood ratio tests and the Akaike Information Criterion (AIC). Potential confounders considered were smoking, alcohol, T2D, obesity, family history of PC, years of education, and treatment. Multicollinearity between variables was discarded based on variance-inflation factor threshold <2. Interactions with age, sex, smoking, alcohol and treatments were explored by including the interaction terms in the models.

Results

The gene-disease association analysis based on publicly available information showed that all diseases except hypothyroidism, were connected through shared genes with at least one other morbidity (Additional file 1: Figure S1). The total number of genes associated with the 26 non-cancer medical conditions averaged 41.3 ranging from 1 in heartburn to 185 in hypertension (Table 1). The strongest associations based on common genes were found between mumps and polymyalgia, Crohn's disease and ulcerative colitis, asthma and nasal allergies, and diabetes and hypertension (average JI= 0.124, range, 0.10–0.14) (Additional file 1: Table S3). The average number of biological processes and pathways shared between morbidities was 147.2 (range 9-386) and 29.7 (range 4-96).

DisGeNET curated subset showed 73 genes associated with PC; half of these had disease specificity >0.75 and disease pleiotropy <0.30 (Additional file 1: Table S4). Twenty-two out of the 73 genes (range 0-10) were also associated with other morbidities (Tables 1 and 2), with *ABO*, *SPINK1*, *PDX1*, *TFPI2*, and *STK11* showing the highest disease specificity and the lowest disease pleiotropy (DSI > 0.73 and DPI < 0.41).

Fifteen morbidities were associated with PC through at least one gene, including peptic ulcer (JI=0.055), hypertension (JI=0.04), and ulcerative colitis (JI=0.04) that showed the most robust genetic relationship with PC (Table 1 and Figure 1). PC and hypertension had the highest number of shared biological processes (N=69); 125 unique biological processes were shared between PC and seven morbidities (Table 3). The biological process that was shared between PC and more morbidities was 'negative regulation of fat cell differentiation'. Twenty-one unique pathways were shared between PC and at least one morbidity with peptic ulcer sharing the highest number of pathways (N=16) (Table 3). 'TNF signalling' and 'TNFR1-mediated proapoptotic signalling' pathways were shared between PC, T2D, peptic ulcer, and rheumatoid arthritis.

Giving the unexpected genetic link observed between AIDs and PC in DisGeNET and the existing scarce literature regarding this relationship [4,9,25], we decided to focus on these conditions in the PanGenEU epidemiological study and assessed the association with PC risk of nine AIDs with enough available data in the study population. Overall, 16.2% of controls reported having any AID in comparison to 13% reported by PC cases (Table 4). Multivariable logistic regression models showed that having any AID was associated with a significant reduced risk of PC (OR=0.74, 95%CI 0.58-0.93). Furthermore, the number of AIDs was significantly associated with a reduced PC risk trend (*P* trend = 0.002). Having any systemic or organ-specific AID was significantly associated with lower PC risk (OR=0.74, 95%CI: 0.55-0.99, and OR=0.71, 95%CI 0.52-0.97, respectively). Among organ-specific diseases, having any one or more gastrointestinal AID was borderline associated with a low risk of PC (OR= 0.51, 95%CI 0.26-1.00). Analysis of individual AIDs showed significant and borderline significant associations with polymyalgia rheumatica and rheumatoid arthritis, respectively (OR=0.4, 95%CI: 0.18-0.89, and OR=0.73, 95%CI: 0.53-1.00). The association with any AID and $\geq$2 AIDs was maintained after inflammatory/pain killer treatment adjustment. No significant interactions were observed.

Discussion

We used a systems medicine approach to unravel the shared genetic background of PC and its associated co-morbidities. We show that out of the 26 morbidities of interest 15, including five AIDs, share a genetic background with PC according to the available data in DisGeNET, a fact that points to the involvement of immune dysregulation processes in PC pathogenesis. We confirmed the AID-PC association first observed in DisGeNET with the results from a large European case-control study population.

We observed that some morbidities previously associated with PC risk in the literature[9,26] were also sustained at a genetic level sharing 22 genes with PC according to DisGeNET. Many of the genes highlighted in these explorations are relevant in pancreatic carcinogenesis (e.g. *KRAS*, *ABO*, *BRCA2*, *STK11*), while others are important players in inflammatory process (e.g. *PTGS2, TGFB1, CXCL8)*[27,28]. Likewise, many of the biological processes and pathways shared between these morbidities and PC are essential in inflammation and carcinogenesis.

Disentangling the underlying mechanisms behind multimorbidities could improve disease prevention and patient management. Growing evidence suggests that integrative approaches help to better grasp disease complexity. New bioinformatics tools such as DisGeNET that generate multimorbidity networks based on gene-disease associations available from public datasets have become ideal for this purpose. A main limitation of this approach is that we can only consider gene-disease associations that have been published, curated and registered in databases. In our study, the few or lack of genetic associations between some morbidities may result from either a real absence of a genetic association or due to the incomplete knowledge about the genetic basis of human diseases. Therefore, we cannot rule out that some associations could have been missed due to the still limited spectrum of the information available. In this respect, we relied on the JI to overcome problems due to differences in how well studied some diseases are over others. Conversely, we cannot exclude the possibility that other morbidities not included in our bioinformatics analysis could be also genetically associated with PC. Assessing the common genetic background of other autoimmune morbidities and PC might help us to gather an even broader view of this malignancy and further increase our understanding of PC.

Applying a systems approach to explore PC-associated multimorbidities has the potential to generate new hypotheses. Among the 15 morbidities found genetically associated

with PC, rheumatoid arthritis, lupus erythematosus, ulcerative colitis, Crohn's disease, and scleroderma have been vaguely studied as risk factors of PC (Additional file 1: Figure S2). Previous work suggested that AIDs could predispose individuals to cancer. Additionally, paraneoplastic autoimmune syndromes have been described[29]. Current studies point to an association between certain AIDs and an increased risk of different types of cancers such as small intestine and oesophageal cancers with celiac disease, or haematological neoplasms with rheumatoid arthritis, systemic lupus erythematous, and scleroderma[11,17,19,30]. Yet, some of these AIDs have been associated with a decreased risk of other cancers such as breast and colorectal[18,19,31], suggesting that the association may not be the same for all cancer types. For PC, the information is limited and conflicting.

The association with pernicious anaemia seems to be the only one that has been purposely analysed in the context of PC, but no significant association was reported [32]. Other studies exploring the association between specific AIDs and cancer overall mainly relying on registry data and reporting on PC, appear inconclusive[22,33–35]. The retrospective nature of most of these studies limits the adjustment for potential confounders. Moreover, to our knowledge, no study explored the association between PC and scleroderma. Our study design allowed us to account for confounding and interaction of a broad set of factors.

We report a significant negative association between suffering one or more of the nine AIDs under study and PC risk. We observed that the estimate further decreased in subjects reporting $\geq$2 AIDs, with a significant negative trend. Independent analysis of each AID showed a significant association between polymyalgia rheumatica and rheumatoid arthritis with lower PC risk. However, these analyses were limited by sample size. Other studies have reported a lack of significant association between lupus or Addison's disease and PC [13,17,20,22,23,31,36]. Contradictory results have been published regarding pernicious anaemia, Crohn's disease, and ulcerative colitis with some studies reporting no significant

association[16,22,32,33,35] while others showing a significant increased PC risk[12,15,34]. For celiac disease, studies have reported both significantly reduced and increased risk of PC[18,22], but a recent meta-analysis showed no significant association[11]. Furthermore, most studies have described a lack of association between rheumatoid arthritis and PC risk[22,37–39]. However, a study performed with the Scottish Cancer Registry reported a significant negative association between rheumatoid arthritis and PC among women but not among men[21]; in our study, no interaction was observed with gender. Other studies evaluating ulcerative colitis, Crohn's disease, rheumatoid arthritis, polymyalgia and giant cell arthritis, and pernicious anaemia by time since diagnosis reported significantly increased PC risk mostly restricted to subjects reporting <1 year difference between AIDs and cancer diagnoses; when >1 year between diagnoses is reported, loss of significance is commonly observed [12,15,34,40,41]. Comparison with the existing literature is challenging since, to our knowledge, this is the first study incorporating confounders and combining different AIDs into single variables. Although the epidemiological literature is inconclusive regarding their link, atopy and autoimmunity are known hypersensitive reactions of the immune system[42]. Accordingly, our enrichment analyses showed that atopic and autoimmune diseases share several immune-related biological processes and pathways (Additional file 1: Figure S3). The importance of the immune environment in which tumours develop is further strengthened by the emerging evidence of the role of immune checkpoint inhibition as a potent therapeutic strategy in a wide variety of tumours. However, only a fraction of patients respond to such therapies and there is an urgent need to identify predictors of response[43]. These results, and our previous findings of a reduced PC risk among subjects with atopic conditions[7], strongly suggest that immune recognition of neoantigens, its quantity and quality could contribute to modulate the immune response to emerging preneoplastic clones[44].

Conversely, while autoimmune pancreatitis is an AID suggested to develop into chronic pancreatitis, its link with PC risk has not been established[45,46]. Moreover, it is reasonable to expect a different type of association in AIDs that result in localized damage to the pancreas. Moreover, one could hypothesize that the decreased risk of certain cancers and AIDs could be the consequence of confounding by particular treatments. However, we lacked information about treatment for AIDs. *In vivo* studies suggest that anti-TNF therapy could inhibit pancreatic tumour growth and metastasis[47,48], though its link with carcinogenesis is not completely elucidated[49,50]. Combination of gemcitabine with TNF inhibitors at doses approved for AID treatment does not seem to significantly improve gemcitabine treatment in PC patients[51]. We show that further adjusting for anti-inflammatory/pain relief treatment results in the loss of significance for some associations. While these results could suggest a potential confounding effect, additionally supporting common pathways between PC and AID, we cannot completely rule out chance findings giving the small effect of the treatment adjustment on the estimates and the sustained significance of the main variables.

The interpretation and generalization of these results must be done carefully. While the combination of AIDs into categories helped us to overcome the problem of statistical power, our study size is limited for the inquiry of specific disorders and stratified analysis. Additionally, considering that our information is self-reported, some degree of disease misclassification might have occurred resulting in a lower rate of false positive than false negative reports, probably those with less severe conditions, which would attenuate the risk estimates. It remains necessary to replicate these associations; in this context register-based information and electronic Medical Records could be an ideal setting to gather a longitudinal view of the assicuation between AIDs and PC.

Conclusion

To our knowledge this is the first study exploring in depth the association between several autoimmune diseases and PC risk. This report highlights the importance of multimorbidities in PC risk. Many of these results are confirmatory of the mechanistic notions about pancreatic carcinogenesis. Importantly, common genetic association between PC and AIDs was identified through a bioinformatics approach, which was further characterized in an epidemiological setting as a negative association between AIDs and PC risk, opening new venues to explore and increase our understanding of PC risk potentially impacting the prevention and treatment strategies for this deadly cancer.

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Conflict of interests. The authors declare none.

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Table 1. Number of concept unique identifiers, total genes, common genes with pancreatic cancer and respective Jaccard indexes for diseases under study.

Disease1	Number of CUIs	$Genes_{dis1}$	Common Genes	JI	*P* val[a]
Peptic ulcer	3	23	5	0.0549	$< 10^{-5}$
Hypertension	9	185	10	0.0403	$< 10^{-5}$
Ulcerative colitis	1	57	5	0.04	$< 10^{-5}$
Acid regurgitation	2	5	2	0.0263	$< 10^{-5}$
Asthma	6	83	5	0.0331	0.0001
Obesity	10	156	7	0.0315	0.0001
Type 2 diabetes	3	124	6	0.0314	0.0002
H.pylori	2	5	1	0.013	0.0009
Rheumatoid arthritis	1	123	5	0.0262	0.001
Chronic pancreatitis	1	6	1	0.0128	0.0013
Periodontitis	4	9	1	0.0123	0.0032
Hyperthyroidism	4	10	1	0.0122	0.0037
Scleroderma	12	11	1	0.012	0.0048
Crohn's disease	3	41	2	0.0179	0.0065
Lupus erythematosus	6	68	2	0.0144	0.0250
Nasal allergies	3	17	0	0	-
Skin allergies	9	43	0	0	-
Hypercholesterolemia	12	40	0	0	-
Heartburn	1	1	0	0	-
Hypothyroidism	2	3	0	0	-
Mumps	1	9	0	0	-
Pernicious anaemia	1	2	0	0	-
Gallstones	3	6	0	0	-
Celiac disease	1	28	0	0	-
Polymyalgia	3	7	0	0	-
Addison disease	1	11	0	0	-

[a]Empirical p value calculated after performing 50,000 bootstraps

CUI: Concept unique identifier, JI= Jaccard index

Note: pancreatic cancer CUIs = 3, Genes = 73.

Table 2. Common genes between pancreatic cancer and other diseases in DisGeNET.

Gene	N_{dis}	Diseases
TNF	9	Asthma, obesity, type 2 diabetes, hypertension, peptic ulcer, rheumatoid arthritis, scleroderma, Crohn's disease, ulcerative colitis
MMP9	6	Asthma, obesity, peptic ulcer, periodontitis, lupus erythematosus, ulcerative colitis
PTGS2	6	Obesity, hypertension, peptic ulcer, acid regurgitation, rheumatoid arthritis, lupus erythematosus
SOD2	5	Obesity, type 2 diabetes, hypertension, hyperthyroidism, rheumatoid arthritis,
PPARG	4	Obesity, type 2 diabetes, hypertension, Crohn's disease
TGFB1	4	Asthma, type 2 diabetes, hypertension, peptic ulcer
AHR	2	Hypertension, rheumatoid arthritis
CDH1	2	Ulcerative colitis, *H. pylori* infection
CXCL8	2	Acid regurgitation, Ulcerative colitis
PTEN	2	Asthma, hypertension
ABO	1	Peptic ulcer
BCL2L1	1	Type 2 diabetes
CNR1	1	Obesity
DPYD	1	Obesity
HIF1A	1	Hypertension
PDX1	1	Type 2 diabetes
PLAU	1	Asthma
SPINK1	1	Chronic pancreatitis
STAT3	1	Ulcerative colitis
STK11	1	Hypertension
TFPI2	1	Rheumatoid arthritis
TP53	1	Hypertension

Table 3. Number of unique biological processes and pathways shared between each disease and any other diseases and number of processes shared between the diseases and pancreatic cancer.

Disease	N unique processes annotated	N processes shared with PC	N unique pathways annotated	N pathways shared with PC
Hypertension	386	69	96	0
Type 2 diabetes	340	18	54	10
Asthma	278	14	46	0
Rheumatoid arthritis	277	13	36	7
Crohn's disease	266	0	36	0
Obesity	251	31	37	0
Ulcerative colitis	195	18	30	0
Peptic ulcer	177	31	37	16
Lupus erythematosus	169	0	32	0
Skin allergies	139	0	26	0
Pancreatic cancer	125	-	21	-
Hyperthyroidism	50	0	12	0
Hypercholesterolemia	36	0	16	0
Celiac disease	30	0	12	0
Mumps	24	0	4	0
Addison disease	17	0	14	0
Polymyalgia	17	0	16	0
Scleroderma	10	0	6	0
Nasal allergies	9	0	0	0

PC: pancreatic cancer

Note: Only diseases for which biological processes and/or pathways were found through enrichment analyses are presented.

Table 4. Odds ratios for the association between autoimmune diseases and pancreatic ductal adenocarcinoma.

	Cases		Controls							
	N=1705	**%**	**N=1084**	%	**OR[a]**	**95%CI**	**OR[b]**	**95%CI**	**OR[c]**	**95%CI**
Autoimmune diseases										
No	1483	86.9	908	83.8	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any	222	13.0	176	16.2	**0.78**	**[0.62;0.98]**	**0.74**	**[0.58;0.93]**	**0.78**	**[0.61;0.99]**
Number of AID										
No	1483	86.9	908	83.8	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	201	11.8	146	13.5	0.85	[0.66;1.08]	0.81	[0.63;1.04]	0.85	[0.66;1.09]
≥2	21	1.2	30	2.8	**0.45**	**[0.25;0.83]**	**0.39**	**[0.21;0.73]**	**0.44**	**[0.24;0.81]**
P trend[d]						0.009		0.002		0.01
Type of AID										
None	1483	86.9	908	83.8	Ref.	Ref.				
Systemic only	120	7.0	86	7.9	0.85	[0.62;1.16]	0.78	[0.58;1.08]	0.83	[0.60;1.15]
Organ-specific only	88	5.2	73	6.7	0.77	[0.55;1.08]	0.76	[0.54;1.07]	0.78	[0.55;1.11]
Hematologic	65	3.8	53	4.9	0.82	[0.56;1.21]	0.80	[0.54;1.18]	0.82	[0.55;1.21]
Gastrointestinal	20	1.2	15	1.4	0.58	[0.25;1.32]	0.60	[0.26;1.37]	0.64	[0.28;1.46]
Endocrine	2	0.1	1	0.1	1.84	[0.16;2.11]	2.65	[0.23;3.07]	2.91	[0.25;3.34]
Mixed organ-specific	1	0.1	4	0.4	0.28	[0.03;2.64]	0.29	[0.03;2.74]	0.29	[0.03;2.85]
Both systemic and localized	14	0.8	17	1.6	0.50	[0.24;1.07]	**0.42**	**[0.19;0.90]**	0.48	[0.22;1.05]
Systemic AID										
No	1571	92.1	981	90.5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any	134	7.9	103	9.5	0.81	[0.60;1.08]	**0.74**	**[0.55;0.99]**	0.79	[0.59;1.07]
Organ-specific AID										
No	1603	94	994	91.7	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any	102	6	90	8.3	0.73	[0.53;0.99]	**0.71**	**[0.52;0.97]**	0.74	[0.54;1.02]
Gastrointestinal AID										
No	1679	98.5	1059	97.7	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any	26	1.5	25	2.3	0.51	[0.26;0.99]	0.51	[0.26;1.00]	0.55	[0.28;1.09]
Lupus										
No	1696	99.5	1081	99.7	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	9	0.5	3	0.3	1.91	[0.48;7.53]	2.08	[0.51;8.44]	2.04	[0.49;8.39]
Scleroderma										
No	1697	99.5	1080	99.6	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	8	0.5	4	0.4	0.91	[0.23;3.54]	0.81	[0.20;3.20]	0.83	[0.21;3.25]
Polymyalgia										
No	1692	99.2	1065	98.3	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

Yes	13	0.8	19	1.8	**0.42**	**[0.20;0.92]**	**0.40**	**[0.18;0.89]**	0.46	[0.21;1.04]
Pernicious anemia										
No	1630	95.6	1014	93.5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	75	4.4	70	6.5	0.75	[0.53;1.06]	0.72	[0.51;1.02]	0.75	[0.53;1.07]
Crohn's disease										
No	1701	99.8	1079	99.5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	4	0.2	5	0.5	0.26	[0.05;1.46]	0.32	[0.05;1.94]	0.36	[0.58;2.24]
Celiac disease										
No	1698	99.6	1078	99.5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	7	0.4	6	0.6	0.54	[0.15;1.95]	0.63	[0.18;2.17]	0.62	[0.18;2.19]
Addison's disease										
No	1698	99.6	1078	99.5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	7	0.4	6	0.6	0.89	[0.30;2.68]	0.91	[0.29;2.81]	0.96	[0.31;2.99]
Rheumatoid arthritis										
No	1597	93.7	1000	92.3	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	108	6.3	84	7.8	0.81	[0.59;1.11]	0.73	[0.53;1.00]	0.78	[0.56;1.08]
Ulcerative colitis										
No	1690	99.1	1068	98.5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	15	0.9	16	1.5	0.55	[0.24;1.30]	0.49	[0.21;1.16]	0.54	[0.23;1.30]

[a] Adjusted for age (continuous), sex and country

[b] Model adjusted for age (continuous), sex, country, smoking (pack/years, tertiles based on the population distribution and alcohol status (never, former, current)

[c] Model adjusted for age (continuous), sex, country, smoking (pack/years, tertiles based on the population distribution, alcohol status (never, former, current), and treatment (no treatment, aspirin only, NSAIDs only, paracetamol only, corticosteroids only, and more than one treatment type)

[d] Trend was calculated using number of AID as a continuous variable (range from 0 to 4)

Figure 1. Gene network of medical conditions associated with PC through common genes. A) Network of diseases that share genes with pancreatic cancer and all corresponding connections; B) Network of diseases that share genes with pancreatic cancer, only connections with pancreatic cancer shown. Edge width represents the Jaccard index for each disease pair; Jaccard indexes were multiplied by 100 in order to allow better visualization. Node size represents the number of genes obtained through DisGeNET for each medical condition.