A Meta-analysis of Overlapping Genes in Type 1 Diabetes and Pancreatic Cancer

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Type 1 diabetes (T1D) patients have a high vulnerability to pancreatic cancer, which is notoriously fatal. In particular, the symptoms of pancreatic cancer are not obvious at its early stage, which makes it more challenging to prevent the metastasis of tumors in patients. To understand the potential reasons behind the susceptibility of pancreatic cancer in T1D patients, this meta-analytical study investigates the genes that overlap between T1D and pancreatic cancer and the biological processes associated with the genes. The single-nucleotide polymorphism (SNP) and differentially expressed genes (DEG) of T1D patients from seven separate studies were compared to the copy number alteration (CNA) and mutated genes of pancreatic cancer patients from 14 studies using two bioinformatic tools. The results shed light on genes accountable for their immunological similarities and other biological processes. The prominent genetic functions associated with the identified genes include lymphocyte activation, STAT protein peptidyl-serine phosphorylation regulation, and JAK-STAT signaling pathway regulation. Some results suggested the diseases' associations with response to UV, mitotic cell division, and various other diseases such as autoimmune thyroid disease, bladder cancer, measles, and hepatitis C. The newly identified overlapping genes between T1D and pancreatic cancer can serve as genetic biomarkers for detecting these diseases at an early stage. Moreover, these genes can be targeted by CRISPR-Cas9 for genetic modification, which can potentially reverse the symptoms of T1D and pancreatic cancer in the future.

Introduction

T1D is a prevalent chronic autoimmune disease worldwide. The disease is autoimmune as the body's immune system destroys the insulin-producing beta cells and the insulin levels thus decrease. Insulin is a hormone that allows glucose to bind with the cellular insulin receptor of a cell. The supply of glucose to the cells is vital as it is their primary fuel source, enabling various metabolisms to take place. Increased insulin production helps decrease the blood glucose level in the body, while its counterpart glucagon does the opposite function to maintain blood glucose homeostasis. While the etiology of T1D remains unclear, there is evidence showing T1D can be a genetic disease since approximately 10 percent of people with T1D inherited the disease from their ancestors[1]. In the United States, the frequency of T1D is 10 to 20 people per 100,000 people in a year. The probabilities of having T1D are similar in the United Kingdom, Canada, New Zealand, and most European countries. The numbers differ in Asia and South America, with around one T1D case in one million people annually[2]. T1D is becoming a much more commonly encountered disease, with a report of roughly 8.4 million worldwide[3]. Pancreatic cancer is a disease arising from the formation of tumors in the pancreas. Since the early stages of pancreatic cancer are generally asymptomatic, patients discover their pancreatic tumors in their metastatic stage, at which complete removal of cancerous cells is challenging. Some research shows that increased cigarette smoking correlates with the occurrence of pancreatic cancer. Another crucial factor is aging. Many research points to the statistics that 90% of pancreatic cancer patients are above 55 years old, not to mention 70% of them being over 65 years old[4]. Research has shown that individuals with T1D are more likely to develop tumors, especially in the liver, pancreas, and kidney, compared to people without diabetes[5]. Pancreatic cancer is a significant complication of T1D, and hyperinsulinemia and insulin-deficient states can both play a role in triggering pancreatic cancer[6]. The recent innovation of the CRISPR-Cas9 technology can provide treatment that helps maintain normal levels of insulin in the body once the specificity and accuracy of the technology are reinforced[7]. CRISPR-Cas9, the newest genetic modification tool, can edit a specific genetic sequence and potential cure diseases with significant genetic factors, like sickle cell disease using CASGEVY, though the risk of potential side effects must be considered[8]. T1D and pancreatic cancer, which have shown strong genetic association via this research, can be treated in the future by targeting genetic sequences identified in this study as well as avoiding certain genetic sequences that would aggravate the disease progression of T1D and pancreatic cancer. Hence, understanding the genes associated with the pathogenesis of both diseases would be helpful for successful genetic modification.

This research proposes that T1D and pancreatic cancer will have multiple disease-specific genes that overlap since both diseases share a close association with the pancreas. The study aims to conduct a bioinformatic analysis of both diseases' overlapping genes to better understand their underlying mechanisms. This analysis will provide valuable insights into the molecular pathways involved in T1D and pancreatic cancer. The analyzed genes can become genetic biomarkers that enable more accurate early detection of T1D and pancreatic cancer. The research collected genomic data of pancreatic cancer and T1D patients. Using Google Sheets functions, the common genes among the two diseases were identified and analyzed using bioinformatics tools. The analysis shed light on the biological functions the genes are associated with, potentially explaining similarities and differences between pancreatic cancer and T1D.

Results

Genetic data from 1418 pancreatic cancer patients were collected from cBioPortal, disregarding their specific type of pancreatic cancer to establish a more holistic relationship between T1D and pancreatic cancer. Due to the vast number of genes collected from cBioPortal, three different boundaries (≥ 2, 30, and 50 patients) were set to distinguish the frequency of the genes among the total patients who have T1D and pancreatic cancer (Table 1). The boundary at more than 50 patients was considered most suitable since it eliminated genes that had a low frequency of incidence among studied patients to establish more reliable correlations and relationships when obtaining the results of genetic analysis. Hence, the list of altered genes found common in greater than or equal to 50 patients was considered most suitable for this meta-analytical study. Since there were more copy number alteration (CNA) genes than mutation genes in the table, the chromosomal changes due to the copy number alteration were considered more strongly linked to pancreatic cancer than the mutation genes.

Unlike cBioPortal, a public database for all types of cancers, a genetic database does not exist for T1D, so relevant data from articles about T1D were used. Different studies collected differentially expressed genes (DEG) or single-number polymorphism (SNP), so both types of data were analyzed. Two SNP and five DEG studies were used, among which there were two meta-analysis studies that broadened the range of genes that were used for our genetic analysis (Table 2). In addition, data from 2018 papers were used to conduct genetic analysis based on the most recent information about T1D. The discrepancy between Table 1 and Table 2 is that some studies about T1D investigated smaller numbers of patients than the data about pancreatic cancer from cBioPortal. Hence, the genes analyzed from the smaller set of patients can induce some inaccuracies in the final genetic analysis. The upregulated and downregulated genes were separated for DEG-based studies to accurately interpret the data and determine whether their gene

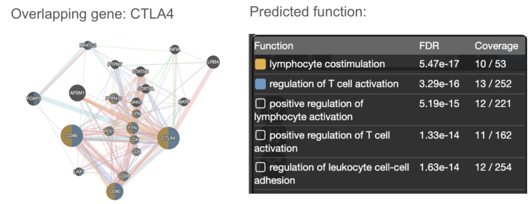

Fig. 1 The gene network analysis and function prediction of the overlapping genes of overall SNPs from T1D and CNA and mutated genes of pancreatic cancer.

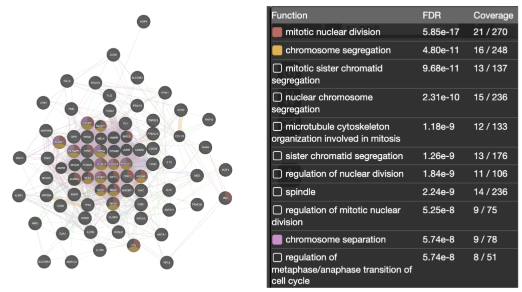

Fig. 2 The gene network analysis and function prediction of the overlapping genes of upregulated and downregulated DEGs from T1D and CNAs and mutated genes of pancreatic cancer using GeneMANIA.

functions are positively or negatively associated with disease occurrences of T1D and pancreatic cancer. For the two studies (January 2021 and January 2023) that did not explicitly provide the upregulation and regulation of the genes, the positivity and negativity of the logFC (log fold-change) values helped determine genes that were upregulated and downregulated.

The genes in T1D and pancreatic cancer were investigated by comparing the CNAs and mutated genes of pancreatic cancer patients and the overall SNPs of T1D patients (Figure 1). A single gene was found to overlap between the two diseases with key associated functions of lymphocyte costimulation and regulation of T cell activation.

After the analysis with SNP, the genes present in T1D and pancreatic cancer were investigated by comparing the CNAs and mutated genes characteristic of pancreatic cancer patients and the DEGs associated with T1D. Initially, the up and downregulated DEGs were subsequently analyzed to identify the chief functions of the overlapping genes between the two diseases, regardless of the direction of regulation in relation to the diseases. Sixty-three genes were found common in the two diseases, with critical functions associated with mitotic nuclear division, chromosome segregation, and chromosome separation (Figure 2). These findings can be used to potentially identify a new research area around the two diseases in the future.

The overlapping twenty-one upregulated genes were identified across T1D and pancreatic cancer (Figure 3). The genes were associated with cell cycle G1/phase transition, cell proliferation

Table 1. Genes associated with pancreatic cancer in 14 previous studies based on mutation and copy number alteration genes.

	Patient number	Total altered gene	Altered gene (# of patients $\geq$ 2)	Altered gene (# of patients $\geq$ 30)	Altered gene (# of patients $\geq$ 50)
cBioPortal Mutation (14 studies)	1418	15521 genes	12479 genes	49 genes	17 genes
cBioPortal Copy number alteration (14 studies)	1418	38245 genes	30279 genes	763 genes	193 genes

Table 2. Genes associated with T1D in seven previous studies based on analyzing SNP association studies and differentially expressed genes studies.

Published Year	Type of Study	Number of patient samples	Number of associated genes
NOV 2018[9]	Meta-analysis of SNP-based studies from 220 studies	N/A	166
JAN 2021[10]	DEG	4 patients, 12 controls (for T1D)	58 (34 upregulated; 24 downregulated)
APR 2021[11]	DEG	39 patients, 43 controls	284 (142 upregulated; 142 downregulated)
APR 2022[12]	DEG	N/A	85 (52 upregulated, 33 downregulated)
JUN 2022[13]	DEG	7 patients, 8 controls	952 (477 upregulated; 475 downregulated)
JAN 2023[14]	Meta-analysis of DEG	N/A	327 (199 upregulated; 128 downregulated)
MAY 2023[15]	SNP	4964 patients, 7497 controls	9

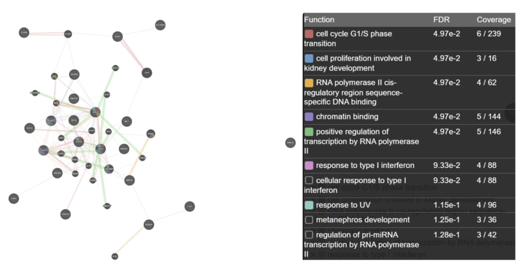

Fig. 3 The gene network analysis and function prediction of the overlapping genes of upregulated DEGs from T1D and CNAs and mutated pancreatic cancer genes.

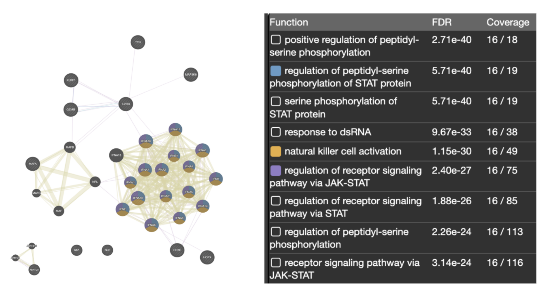

Fig. 4 The gene network analysis and function prediction of the overlapping genes of downregulated DEGs from T1D and CNAs and mutated pancreatic cancer genes.

involved in kidney development, chromatin binding, RNA polymerase II cis-regulatory region sequence-specific DNA binding, response to type 1 interferon, positive regulation of transcription by RNA polymerase II, and response to UV.

The 15 downregulated genes of T1D were shared in pancreatic cancer (Figure 4). The gene network shows the characteristic gene functions of regulating peptidyl-serine phosphorylation of STAT protein, natural killer cell activation, and regulation of the receptor signaling pathway via JAK-STAT.

This table generated by Enrichr-KG lists the functions relating to the input genes (Table 3). The most critical functions are indicated by the smallest q-value, down to the largest q-value for the least significant function related to the genes. The genetic functions showed high z-scores and combined scores, indicating a strong relevance to the mechanisms underlying T1D and pancreatic cancer.

In exploring the overlapping genes of upregulated DEGs in Type 1 diabetic patients and CNAs and mutations observed in pancreatic cancer, the Enrichr-KG program identified several significant associations. Notably, the analysis revealed connections to various types of cancer and specific biological processes. Key findings from the study include identifying bladder cancer, hepatitis C, endometrial cancer, and pancreatic cancer as related conditions, all sourced from the KEGG_2021_Human library with considerable combined

Table 3. The overlapping gene CTLA-4 of SNPs of type 1 diabetic patients and CNAs and mutated pancreatic cancer using Enrichr-KG program.

Term	Library	p-value	q-value	z-score	Combined score
negative regulation of regulatory T cell differentiation (GO:0045590)	GO_Biological_Process_2021	0.00025	0.0035	19995	165800
negative regulation of B cell proliferation (GO:0030889)	GO_Biological_Process_2021	0.0006	0.0035	19988	148300
negative regulation of T cell differentiation (GO:0045581)	GO_Biological_Process_2021	0.0007	0.0035	19986	145200
negative regulation of B cell activation (GO:0050869)	GO_Biological_Process_2021	0.0011	0.003656	19978	136100
regulation of regulatory T cell differentiation (GO:0045589)	GO_Biological_Process_2021	0.0013	0.003656	19974	132700
Autoimmune thyroid disease	KEGG_2021_Human	0.00265	0.006933	19947	118300
Rheumatoid arthritis	KEGG_2021_Human	0.00465	0.006933	19907	106900
T cell receptor signaling pathway	KEGG_2021_Human	0.0052	0.006933	19896	104600
Cell adhesion molecules	KEGG_2021_Human	0.0074	0.0074	19852	97400

Table 4. Overlapping genes of upregulated DEGs of type 1 diabetic patients, CNAs, and mutated pancreatic cancer using the EnrichR-KG program.

Term	Library	p-value	q-value	z-score	Combined score
Bladder cancer	KEGG_2021_Human	1E-05	0.001054	87.46	1004
Hepatitis C	KEGG_2021_Human	2E-05	0.001054	30.49	330.3
Endometrial cancer	KEGG_2021_Human	3E-05	0.001058	60.38	629.5
positive regulation of mesenchymal cell proliferation (GO:0002053)	GO_Biological_Process_2021	5E-05	0.009842	262.8	2619
Central carbon metabolism in cancer	KEGG_2021_Human	5E-05	0.001396	49.53	488.4
positive regulation of the production of miRNAs involved in gene silencing by miRNA (GO:1903800)	GO_Biological_Process_2021	6E-05	0.009842	233.6	2281
regulation of mesenchymal cell proliferation (GO:0010464)	GO_Biological_Process_2021	6E-05	0.009842	233.6	2281
Pancreatic cancer	KEGG_2021_Human	7E-05	0.001429	45.45	437
cellular response to cytokine stimulus (GO:0071345)	GO_Biological_Process_2021	0.0001	0.009842	12.78	115.6
positive regulation of gene expression (GO:0010628)	GO_Biological_Process_2021	0.0001	0.009842	12.78	115.6

scores suggesting robust associations (Table 4).

Additionally, the analysis showed significant biological processes, including the positive regulation of mesenchymal cell proliferation, central carbon metabolism in cancer, and the positive regulation of the production of microRNAs involved in gene silencing by miRNA, primarily sourced from the GO_Biological_Process_2021 library.

The functions of the overlapping genes of downregulated DEGs in Type 1 diabetic patients and CNAs and mutations observed in pancreatic cancer were explored (Table 5). Notably, the analysis revealed similar functions to those shown in GeneMANIA. Key findings from the analysis include the positive regulation of peptidyl-serine phosphorylation of STAT protein, activation of natural killer cells, lymphocyte activation

Table 5. Overlapping genes of downregulated DEGs of type 1 diabetic patients and CNAs and mutated pancreatic cancer using EnrichR-KG program.

Term	Library	p-value	q-value	z-score	Combined score
Autoimmune thyroid disease	KEGG_2021_Human	5.87E-08	2.817E-06	147.9	2463
positive regulation of peptidyl-serine phosphorylation of STAT protein (GO:0033141)	GO_Biological_Process_2021	2.77E-07	2.881E-05	332.8	5026
regulation of peptidyl-serine phosphorylation of STAT protein (GO:0033139)	GO_Biological_Process_2021	3.28E-07	2.881E-05	312	4658
natural killer cell activation involved in immune response (GO:0002323)	GO_Biological_Process_2021	4.50E-07	2.881E-05	277.3	4053
lymphocyte activation involved in immune response (GO:0002285)	GO_Biological_Process_2021	6.84E-07	2.984E-05	237.7	3374
response to dsRNA (GO:0043331)	GO_Biological_Process_2021	7.77E-07	2.984E-05	226.9	3191
Toll-like receptor signaling pathway	KEGG_2021_Human	9.01E-07	2.163E-05	72.31	1007
Natural killer cell-mediated cytotoxicity	KEGG_2021_Human	2.269E-06	3.448E-05	56.86	739
Measles	KEGG_2021_Human	2.874E-06	3.448E-05	53.47	682.3
JAK-STAT signaling pathway	KEGG_2021_Human	5.281E-06	5.07E-05	45.63	554.5

involved in immune response, and response to dsRNA, all sourced from the GO_Biological_Process_2021. These functions were also identified in GeneMANIA, showing a robust association between these mechanisms, T1D, and pancreatic cancer.

Additionally, the KEGG_2021_Human library showed significant biological mechanisms, such as the toll-like receptor signaling pathway, natural killer cell-mediated cytotoxicity, and the JAK-STAT signaling pathway. The toll-like receptor signaling pathway and cytotoxicity mediated by natural killer cells are new findings from Enrichr-KG.

When comparing GeneMANIA and Enrichr-KG analysis findings, a significant association with the immune system processes and cellular mechanisms was found in both T1D and pancreatic cancer. GeneMANIA highlighted the crucial roles of mitotic nuclear division, chromosome segregation, and chromosome separation, emphasizing increased proliferation of alpha, beta, and T cells in response to immune challenges. However, Enrichr-KG revealed broader immune-related pathways, including cytokine signaling and JAK-STAT pathways, and also noted associations with diseases like Hepatitis C and autoimmune thyroid disease (Table 6). Together, these results indicate a complex interplay of genetic and immunological factors that could inform future therapeutic strategies or diagnostic approaches in addressing the shared pathology of T1D and pancreatic cancer.

Discussion

The research findings unveil the relationship between T1D and pancreatic cancer by showing the commonalities in patients' genes with two different diseases. Results from GeneMANIA show that the genes present in both diseases are primarily associated with lymphocyte activation, mitotic nuclear division, the regulation of peptidyl-serine phosphorylation of STAT protein, and natural killer activation. Results from the Enrichr-KG bioinformatic program show that the diseases are more closely related immunologically, including the negative regulation of regulatory T cell differentiation and the negative regulation of B cell proliferation. Several other diseases are also shown to be linked to T1D and pancreatic cancer: autoimmune thyroid disease, measles, bladder cancer, and hepatitis C. In particular, other studies suggest that autoimmune thyroid disease commonly appears in people with T1D and pancreatic cancer.

Firstly, the validity of each genetic association is confirmed by drawing upon results from existing literature. With regards

Table 6. Overlapping genes of downregulated and upregulated DEGs of type 1 diabetic patients and CNAs and mutated pancreatic cancer using the Enrichr-KG program.

Term	Library	p-value	q-value	z-score	Combined score
cellular response to cytokine stimulus (GO:0071345)	GO_Biological_Process_2021	2.75E-09	3.231E-06	10.79	212.7
cytokine-mediated signaling pathway (GO:0019221)	GO_Biological_Process_2021	6.15E-09	3.612E-06	9.099	172
Hepatitis C	KEGG_2021_Human	3.24E-08	4.051E-06	19.32	333.1
JAK-STAT signaling pathway	KEGG_2021_Human	4.13E-08	4.051E-06	18.69	317.7
Measles	KEGG_2021_Human	2.69E-07	1.758E-05	18.75	283.7
Human cytomegalovirus infection	KEGG_2021_Human	5.15E-07	2.481E-05	13.22	191.4
Autoimmune thyroid disease	KEGG_2021_Human	6.74E-07	2.481E-05	35.72	507.6
type I interferon signaling pathway (GO:0060337)	GO_Biological_Process_2021	1.884E-06	0.0005534	28.56	376.5
cellular response to type I interferon (GO:0071357)	GO_Biological_Process_2021	1.884E-06	0.0005534	28.56	376.5
B cell proliferation (GO:0042100)	GO_Biological_Process_2021	3.008E-06	0.0007069	48.21	612.9

to Figure 1, a separate study states that CTLA4 and CD28 genes likely induce the proliferation of T cells. Thus, CTLA4 activation suggests T cell hyperactivation, which can damage organs in T1D patients. Comparing SNPs of T1D patients per se does not reveal whether CTLA4 is upregulated or downregulated in pancreatic cancer. However, it can be assumed that the increased inflammation in cancers from T cell activity is associated with T cell hyperactivation, which explains the presence of CTLA4 in pancreatic cancer.

Figure 2 suggests a strong relation between T1D, pancreatic cancer and cell mitosis. A study shows that alpha and beta cells undergo a notable increase in proliferation in Type 1 Diabetic people. Though the number of beta cells is reduced by 70-80% at diagnosis due to the predominant immune attack on beta cells, it suggests that they continue to increase as a defense against the persisting attack.

Another study sheds light on the proliferation of T cells in pancreatic cancer patients, following the finding in type 1 diabetic patients. Interleukin 6 (IL-6), which exists in all humans, is known to be promoted during inflammatory or acute phase responses[16]. Hence, IL-6 levels are significantly elevated in autoimmune diseases, including diabetes and rheumatoid arthritis, where the disease induces chronic inflammation. IL-6 is known to promote T cell proliferation.

Increased immune activity is raised to destroy the tumors of pancreatic cancer. The research found that CTLA-4 and CD28 induce T cell proliferation, a commonly found gene in T1D and pancreatic cancer, in the genetic analysis of SNPs of Type 1 Diabetic people. The proliferation of T cells hints at the overstimulated adaptive immune system. Relating to the cell cycle G1/phase transition identified in Figure 3, a study shows that the alpha and beta cells of the pancreatic islet cells undergo a notable increase in proliferation in recent-onset T1D adults during insulitis[17]. This suggests that islet cell proliferation initiates a response to the autoimmune attack in T1D. The study also found that increased islet cell proliferation was not markedly apparent in early-onset T1D and Type 2 Diabetes.

The diseases' relationship with kidney development is also noteworthy since diabetes is a leading cause of kidney diseases: around 1 in 3 diabetic adults have kidney disease. Acute and chronic kidney diseases experienced by T1D patients are due to the death of renal epithelial cells. The upregulation of cell proliferation in critical development may suggest that the body is trying to preserve the minimum number of kidney cells to retain some kidney functions. Acute kidney injury is also associated with acute pancreatitis (AP) patients, with around 70% of AP patients experiencing the disease[18]. The most tangible link between UV response genes and these conditions may lie in the broad mechanisms of cellular stress response, inflammation, and immune regulation. Some research shows that patients lacking vitamin D, which is synthesized from UV light, have reduced pancreatitis symptoms and risk of developing diabetes when taking vitamin D[19] .

In Figure 4, T1D and pancreatic cancer showed strong associations with natural killer cell activity. Natural killer cell (NK) activity is reduced in T1D patients. NK cells can destroy malignant cells and control cytotoxicity against the body's immune cells. They are accompanied by the production of pro-inflammatory cytokines that help restrict adaptive immune responses. The body is more susceptible to autoimmunity when NK activity is reduced. A study also shows that NK cell activity declined as pancreatic cancer progressed, which led to unsuccessful clinical outcomes[20]. Another takeaway is the relationship between beta cell survival and regulating the receptor signaling pathway via JAK-STAT[21] . A study predicted with computational modeling shows that regulating reactions upstream in the path can enhance STAT5 activation, increasing the survival of beta cells. The gene network shows a range of IFNA genes, which encode the most upstream proteins in the JAK-STAT pathway activation. Therefore, the downregulation of these genes will reduce the activation of the JAK-STAT pathway.

The gene network functions identified by GeneMANIA were further analyzed using Enrichr-KG. As shown in the SNP analysis in Figure 1, the T cell activation regulation was also determined with Enrichr-KG. Table 3, generated by Enrichr-KG, gave more details that the change in CTLA-4 will likely result in the negative regulation of regulatory T cell differentiation and negative regulation of B cell proliferation. Although the negative regulation functions are not congruent with the hyperactivated immune attack in autoimmune conditions, the results shown in Enrichr-KG can only be interpreted as the typical functions of CTLA-4. Since Enrichr-KG does not distinguish between SNP and DEGs based on our study, the results from Enrichr-KG are significant in a way that it shows more potential functions of CTLA-4 to T1D and pancreatic cancer, helping associate gene functions that may not seem related at first glance with the two diseases. Enrichr-KG also showed that the CTLA4 gene is highly associated with several autoimmune diseases, including rheumatoid arthritis and autoimmune thyroid disease.

In comparison to Table 4 of Enrichr-KG, earlier results from GeneMANIA highlighted mitotic cell division as a pivotal standard function between the two conditions. The Enrichr-KG results pointed more prominently towards immune activity and various cancer types, signaling potential differences in the underlying genetic interplay and biological significance between these datasets.

Based on the findings in Table 5, Autoimmune thyroid disease is the most relevant condition with downregulated genes, and measles also shows minor relevance. The collective emphasis on regulating STAT protein, natural killer cell activation, and JAK-STAT signaling pathway suggests that these downregulated genes would be heavily associated with the two diseases.

Our findings in Table 6 from using the Enrichr-KG program show a high association of these genes with autoimmune thyroid disease. Tables 3, 5, and 6 show the high relevance of autoimmune thyroid disease with the analyzed genes. A study shows that 17 to 30% of type 1 diabetic patients also have Hashimoto's thyroiditis and Graves' disease (types of autoimmune thyroid diseases)[22]. A separate study also suggests that thyroid dysfunction could increase the risk of pancreatic cancer, with around 24% of the investigated patients having anti-thyroglobulin anti-thyroid autoantibodies (ATA), characteristic symptoms of autoimmune thyroid disease[23]. The significant relevance of autoimmune thyroid disease, T1D, and pancreatic cancer suggests that the implications of this research may impact future research on autoimmune thyroid disease[24]. Identifying the genetic overlap between T1D and pancreatic cancer holds significant clinical implications, particularly for early diagnosis and treatment. Pancreatic cancer is often detected at late stages of disease progression as the disease barely causes observable symptoms in early stages. Thus, genetic analyses of patients to check the existence of overlapping genetic biomarkers can expedite the early detection of pancreatic cancer. This medical approach can enable relevant intervention for cancer therapy before pancreatic cancer can metastasize across the body, potentially improving survival rates. T1D patients, who are at a higher risk for pancreatic cancer, can also benefit from genetic analysis by monitoring any potential genetic predisposition or molecular pathway associated with pancreatic cancer. In the future, healthcare providers could develop self-diagnostic tools targeting these genetic biomarkers, enabling rapid intervention for at-risk individuals. Additionally, these biomarkers could help refine genetic therapies, such as CRISPR-Cas9, which can target the overlapping genetic factors to both T1D and pancreatic cancer and offer a dual approach to treatment.

While this analysis provides valuable insights by focusing on individual overlapping genes between T1D and pancreatic cancer, a deeper exploration of gene-to-gene interactions could significantly enhance our understanding of the shared molecular mechanisms of these conditions. Synergistic or antagonistic effects between genes might reveal complex pathways where certain gene combinations could amplify or mitigate disease progression. For example, interactions between immune-regulatory genes might exacerbate autoimmune responses in T1D or create a microenvironment conducive to cancer development. Exploring these interactions could help identify key regulatory networks or signaling cascades, like the JAK-STAT pathway, that may be influenced by multiple genes working together (Table 5 and 6). Understanding such cooperative or opposing gene interactions could lead to the development of more targeted therapeutic strategies and early diagnostic tools, facilitating a holistic review of patients in managing the risk and progression of both T1D and pancreatic cancer.

The genetic overlap observed between T1D and pancreatic cancer may be rooted in shared biological mechanisms involving immune regulation, chronic inflammation, and cellular stress responses. Both T1D and pancreatic cancer exhibit dysregulated immune activity, where genes involved in pathways like JAK-STAT signaling and lymphocyte activation play a central role

(Table 5 and 6). In T1D, the autoimmune destruction of pancreatic beta cells is mediated by hyperactive T cells and other immune cells, creating a pro-inflammatory environment in the pancreas. This chronic inflammatory state, characterized by the elevated levels of cytokines such as IL-6 and TNF-alpha, is observed in cancer progression and prolonged inflammation can induce DNA damage, promote cellular proliferation, and facilitate tumorigenesis (Figure 2). Additionally, dysregulation in cell cycle control mechanisms, including genes involved in mitosis and chromosome segregation, could link the regenerative attempts of the pancreas to repair beta cell loss in T1D with an increased risk of malignant transformation. Genes like CTLA4, which modulate immune checkpoints, could also play a dual role in T1D-associated inflammation and pancreatic cancer's evasion of immune surveillance (Table 3). Understanding these overlapping mechanisms not only highlights potential shared therapeutic targets but also underscores the importance of monitoring T1D patients for pancreatic cancer risk, as these pathways could drive both autoimmune and oncogenic processes. The limitations of the research include non-specificity of patient demographics and medical history, which does not allow accurate associations to be drawn about specific types of the two diseases or demographics. There is also a degree of bias within the methodology of this study. Since the study uses two bioinformatics tools (GeneMANIA, Enrichr-KG) and seven studies, the result of this study may not offer a comprehensive insight into different methodologies adopted by different scientists. To minimize the effect of bias, considering this research, widely acknowledged bioinformatics tools and the results from several of the most recent studies were used.

Despite certain limitations, the study successfully delineated the relationship between T1D and pancreatic cancer. The significant advantage of this meta-analytical research is that novel genes associated with the two diseases can be identified by analyzing various patient data from pre-established studies. The results from this research are also reliable since the different functions related to the overlapping genes were corroborated using two different bioinformatic programs (GeneMANIA and Enrichr-KG).

Using multiple genetic databases reduces the bias in the results obtained and helps discover a broader range of functions related to the analyzed genes. In addition, the same functions identified from two different programs reinforce the reliability of the results. For instance, the tasks that overlapped in both programs include lymphocyte activation, regulation of peptidyl-serine phosphorylation of STAT protein, natural killer activation, response to dsRNA, regulation of receptor signaling pathways via JAK-STAT, and response to type I interferon. There were also certain functions found only in each database. Notable functions identified in GeneMANIA include mitotic nuclear division, chromosome segregation, response to UV, and cell proliferation in kidney development. In Enrichr-KG, several functions and diseases associated with the genes were identified, including the negative regulation of regulatory T cell differentiation, negative regulation of B cell proliferation, autoimmune thyroid disease, measles, bladder cancer, and hepatitis C.

The wide range of genetic functions and diseases this research identified can act as biomarkers of the diseases in clinical diagnoses, allowing prevention of the diseases at an early stage. Since pancreatic cancer is difficult to diagnose from imaging and blood tests, this genetic biomarker can be effective in detecting pancreatic cancer more efficiently. Moreover, the overlapping genes of T1D and pancreatic cancer identified in this research can help target the sites of genetic modification with the implementation of CRISPR-Cas9 in the future to treat both diseases. A similar methodology can be adopted to understand several diseases at a genomic level. With much innovation in personalized medicine and genetic engineering treatment, a wet lab experiment on selection of the genes found most significant in this study's results can model a realistic impact a modification of those genes would have on a targeted tissue.

Conclusion

The genetic analyses of SNPs and DEGs of two separate groups of patients with T1D and pancreatic cancer shed light on important immunological and inflammatory pathways that link to the two diseases. The key biological pathways include T-cell hyperactivation, cell proliferation involved with kidney development, and reduced NK activity. The results of the research help understand the vulnerability of T1D patients to pancreatic cancer, twice as susceptible than the non-diabetic counterparts. The genetic biomarkers identified in this research may contribute towards the development of targeted treatments for T1D and pancreatic cancer.

Methods

This research is a meta-analytical study utilizing data established by published research to draw new implications surrounding pancreatic cancer and T1D. In this study, two bioinformatics tools, GeneMANIA and Enrichr-KG, were selected to analyze the genetic overlap between T1D and pancreatic cancer due to their complementary capabilities in gene function prediction and pathway analysis. GeneMANIA was used to map gene networks and predict interactions based on co-expression and co-localization, providing insights into functional connections among overlapping genes. Enrichr-KG, which integrates data from multiple databases, was employed to conduct detailed pathway and disease association analyses.

The search strategy involved a comprehensive review of available genetic studies on T1D and pancreatic cancer, with a focus on recent studies that reported SNPs and DEGs with methodological clarity. Studies were selected based on sample size, methodological rigor, and relevance of data to ensure high-quality input for the meta-analysis. Quality assessment was performed using standardized metrics, including publication date, impact factor of the journal, and clarity in reporting gene association methodologies.

Pancreatic cancer patient's genomic analysis using cBioPortal

A total of 14 studies on pancreatic cancer were analyzed using the cBioPortal database to identify the mutated genes with altered copy numbers. The analysis was based on the genomic information of 1418 patients[25]. The analyzed genes were selected for cases where the number of patients with alterations was greater than 50. cBioPortal relies on ethically collected data from published studies.

Collecting genes associated with T1D

Seven studies on T1D were collected to identify SNP associations and DEG. The list of genes was compiled in a Google Sheets document, with upregulated and downregulated genes separated into different categories, which enabled separate analyses for these genes.

Analysis of overlapping genes in T1D and pancreatic cancer using GeneMANIA

The bioinformatics tool GeneMANIA was used to produce gene networks and identify the functions of the overlapping genes between T1D and pancreatic cancer. These overlapping biological pathways and functions were examined to find potential molecular links between T1D and pancreatic cancer. The smaller the FDR value, the greater the significance of the function identified.

Gene function and biological pathway analysis using Enrichr-KG

Further analysis of the overlapping genes was performed using Enrichr-KG, another bioinformatics platform that integrates genetic information from multiple databases. KEGG (Kyoto Encyclopedia of Genes and Genomes) and GO Consortium (Gene Ontology Consortium funded by the National Human Genome Research Institute) were chosen as the two databases as they are prominently used in genetic analyses. This procedure enabled detailed insight into gene functions, pathways, and disease associations. The analysis of these overlapping genes successfully identified significant biological functions, deepening the understanding of the genetic interplay between T1D and pancreatic cancer. The smaller p-value indicates the greater significance of the function identified.

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