American Research Journal of Biosciences

Volume 8, Issue 1, 7-10 Pages
Research Article | Oen Access
ISSN (Online)- 2379-7959
DOI : 10.21694/2379-7959.23002

AMERICAN RESEARCH JOURNALS
An Academic Publishing House

Association of Genetic Polymorphisms with Pancreatic Adenocarcinoma Progression

Helen Yang
Harvard-Westlake School, CA.

ABSTRACT

Pancreatic cancer (PC) is one of the most malignant types of cancer. It is characterized by insidious onset, aggressive tumor growth, and early metastasis. Advances in treatment strategies are critically needed. In this research project, it is hypothesized that single nucleotide polymorphisms (SNPs) in Chromosome 17 may play a role in the development and progression of metastatic pancreatic cancer.

Method: *Blood samples from a total of 229 individuals were previously collected from various clinical cohorts, including patients with primary pancreatic cancer (n=61), metastatic pancreatic cancer (n=47), as well as healthy control (n=121). DNA sequencing in Chromosome 17 from all the samples was also obtained previously. The research work started by obtaining a source database from the National Library of Medicine. The bioinformatics analysis programs Binary Variant Call Format (BCFtools), Sequences Alignment Map Tools (SAMtools), and Burrows-Wheeler Aligner (BWA) were then downloaded and used to analyze and sort the sequences into data tables. Finally, the Entrez Molecular Sequence Database system was used to identify mutations found as SNPs.*

Results: *153 mutations were identified. Among them, 10 SNPs were unique and frequent to the metastasized pancreatic cancer samples studied. Specifically, 87-94% of the samples from the metastasized pancreatic cancer patients carry at least one of these 10 SNPs, whereas none of these SNPs were identified in the primary pancreatic cancer patients or in the control.*

Conclusion: *Overall, the finding may provide insight into the mutations that spur the growth and spread of pancreatic cancer cells, and may help inform the future development of new cancer treatments.*

KEYWORDS: *pancreatic, cancer, SNPs, adenocarcinoma*

INTRODUCTION

Cancer has and will continue to be a serious health issue in the modern world. In 2022 alone, the North American Association of Central Cancer Registries (NAACCR) reported 1,918,030 new cancer cases in the United States (1). Furthermore, cancer continues to be the fourth most common cause of death in the US (2). In 2022, the United States is projected to have 609,360 cancer-related deaths based on The National Center for Health and Statistics (NCHS) (1). Economically, cancer is costly as well: in 2019, cancer-related economic burden was reported to be $21.09 billion (3).

Pancreatic cancer is one of the most aggressive and deadly types of cancer. It is a malignant tumor that arises from the cells of the pancreas, which is an organ located deep in the abdomen that produces enzymes that aid in digestion and hormones that regulate blood sugar levels. Pancreatic cancer is ranked 4th in leading causes of death among all types of cancer in the United States and is ranked 7th worldwide. Furthermore, pancreatic cancer is known for its high mortality rate, with a 5-year survival rate of only around 10%, according to the American Cancer Society report in 2022 (4).

Although the cancer originates in the pancreas, the disease is usually diagnosed after metastasis as early pancreatic cancer is often insidious, and early development of the disease is difficult to detect (5). Tools to diagnose pancreatic cancer are also limited. Moreover, the location of the pancreas, its resistance to chemotherapy and lack of effective targeted therapies make pancreatic cancer one of the most difficult cancer types to treat. The complexity of the disease underscores the need for more research and innovative approaches to develop effective treatments.

Pancreatic cancer is a genetically complex disease, with many different mutations and changes in gene expression.

Accumulating evidence has shown that genetics play an essential role in PC carcinogenesis (6,7). The CTCF (CCCTC-binding factor, also known as 11-zinc finger protein) gene is a transcription factor that plays a crucial role in gene expression regulation, chromatin structure, and DNA replication (8). Recent research has suggested that alterations in the CTCF gene may contribute to the development and progression of pancreatic cancer. Specifically, studies have shown that mutations or deletions in the CTCF gene can lead to altered chromatin structure, aberrant gene expression, and increased genomic instability in pancreatic cancer cells (9). Additionally, changes in CTCF expression levels have been associated with poor prognosis in pancreatic cancer patients (10). While further research is needed to fully understand the role of CTCF in pancreatic cancer, these studies suggest that CTCF alterations may contribute to the genetic complexity of the disease and could be a potential target for therapeutic intervention.

Single nucleotide polymorphisms (SNPs) are genetic mutations of single nucleotides that are commonly found in humans. We hypothesized that SNPs affecting CTCF binding might contribute to pancreatic cancer susceptibility to metastasis. In this study, we first genome-widely screened candidate SNPs via bioinformatics analysis. Then we tested their associations with pancreatic cancer metastasis risk in an independent case-control study. The goal of the study is to contribute to further understanding of (1) biomarkers that can be used to predict the pancreatic cancer susceptibility to metastasis early; (2). to develop personalized treatment plans that target these specific mutations, potentially improving treatment outcomes.

METHODS

Study Clinical cohort

The study cohorts consisted of 112 patients with pancreatic cancer and 117 healthy patients who were recruited at several tertiary care centers. All patients provided written informed consent to participate in the study, which was approved by the institutional review board and conducted in accordance with the principles of the Declaration of Helsinki. Clinical and pathological data were collected prospectively, including tumor location, tumor stage, histological grade, treatment received, and outcomes such as recurrence and overall survival. To protect patient privacy, all data were de-identified before analysis, and access was restricted to authorized personnel only.

In addition, a portion of the tissue samples collected during surgery was stored in a biorepository for future molecular studies. Patients were informed of the biorepository and provided separate written consent for tissue banking. The use of tissue samples for research was also approved by the institutional review board. Overall, this study was conducted with strict adherence to ethical guidelines, and all patients were treated with respect and confidentiality.

SNP Genotyping

Genomic DNA was extracted from whole blood samples collected from the 108 (47 metastatic, 61 primary) pancreatic cancer patients and 121 control mentioned above. From the SRA repository, samples were downloaded using program Fastq-dump and run through quality control with Fastqc. The Fastqc tool transformed raw sequence data into graphical representations of reads. From that, nucleotides with assigned Phred quality scores of 40 or lower were removed by Trimmomatic. Fastqc was run a second time to ensure all faulty data was trimmed. Sequence mapping tool, Bowtie2, was then used to organize data in the correct order.

Whole genome sequencing was performed for all samples. This data had already been available at the time of this research work. No statistical analysis was performed on data prior to research work, providing raw DNA sequence data for experimentation

Statistical Analysis of Mutations

Mapped DNA sequences were analyzed using several bioinformatics tools: Binary Variant Call Format (BCFtools), Sequences Alignment Map Tools (SAMtools), and Burrows-Wheeler Aligner (BWA). Data were organized into comprehensive tables which displayed mutations common to at least 70% of primary, metastasized, and control samples. A final merge was conducted by comparison of mutations in metastasized samples to primary and control samples. Common mutations between these experimental groups were removed so that only mutations unique to metastasized pancreatic cell samples remained.

Selection of Candidate SNPs

Mutations found in final merge entered in the Entrez Molecular Sequence Database System in the National Center for Biotechnology Information (NCBI) to find candidate SNPs specific to metastasized pancreatic cancer samples. This ensures that mutations found are known SNPs with assigned Reference SNP cluster ID (rsID) numbers.

RESULTS

Selection of candidate SNPs

Using Entrez Molecular Sequence Database System from the NCBI database, mutated positions located on Chromosome 17 solely unique to metastasized pancreatic cancer went through SNP identification.

Identification of SNPs in pancreatic cancer metastasis susceptibility

The 153 identified variants from the NCBI database were then applied to the genomic data from the clinical cohorts, including 61 samples of primary pancreatic cancer, 47 samples of metastatic pancreatic cancer, and 121 samples of healthy control.

Prespecified criterium was applied, in that the SNPs of interest

would be of high frequency (>85%). These SNPs would exist only in the metastatic pancreatic cancer samples and would exist neither in the samples of primary pancreatic cancer without metastasis nor in the healthy control samples. Based on this criterium, 10 SNPs with Chromosome 17 were further identified that reside uniquely in metastatic pancreatic cancer patients (Table 1). Among them, two SNPs reside in as high as 94% of metastatic pancreatic cancer patients.

Table 1. SNPs of interest (in percentage) only in metastasized pancreatic cancer patients, as compared to primary pancreatic cancer or healthy control

SNPs	Position	Reference	Mutation	Metastatic pancreatic cancer (n=47)	Primary pancreatic cancer (n=61)	Healthy control (n=121)
#1: rs1364594065	21990949	C	A	94%	0%	0%
#2: rs1418119660	21969284	G	T	94%	0%	0%
#3: rs1442151552	26702166	G	T	89%	0%	0%
#4: rs1906095433	26671574	T	C	89%	0%	0%
#5: rs1906596072	26691266	C	A	87%	0%	0%
#6: rs1324698886	26702121	C	T	87%	0%	0%
#7: rs1420855545	26697866	T	A	87%	0%	0%
#8: rs1905340017	26643343	A	T	87%	0%	0%
#9: rs1905425870	26643343	C	G	87%	0%	0%
#10: rs1427320931	26691477	A	C	87%	0%	0%

DISCUSSION

Pancreatic cancer is a complex and heterogeneous disease, and the prognosis can vary significantly depending on various genetic factors. Genetic polymorphisms, the variations in the DNA sequence that occur within a population, are one type of genetic factor that is commonly studied. Identifying the SNPs that influence the prognosis of pancreatic cancer can help clinicians tailor diagnosis and treatment strategies and provide more personalized care to the patients.

Our study identified 10 SNPs in large percentages in the patient cohort of metastasized pancreatic cancers, while the patients in the nonmetastatic pancreatic cancer or noncancerous control do not pertain to any of the SNPs. It suggests that the SNPs identified may play a role in the development or progression of pancreatic cancer metastasis. The candidate SNPs in our study were selected only in Chromosome 17 in which the CTCF gene existed. CTCF is a well-known transcription factor that plays an essential role in gene expression regulation, chromatin structure, and DNA replication. Alterations in CTCF expression and function by SNPs may affect a specific pathway or mechanism that is involved in the metastatic process, such as cancer cell invasion, migration, or adhesion. The importance of CTCF gene expression guided us to focus on SNPs located in Chromosome 17.

The identification of the SNPs in Chromosome 17 that are unique to metastatic pancreatic cancer cells may help identify molecular targets. Interventions through these targets may potentially impact specific pancreatic cancer cells that are prone to metastasis while sparing normal healthy cells. Therefore, SNP identification provides a promising strategy for the treatment of metastatic pancreatic cancer.

One of the holy grails in pancreatic cancer management is to identify biomarkers that can be used to predict pancreatic cancer susceptibility to metastasis early. Since the SNPs are only associated with the metastatic samples, they may potentially provide diagnostic evidence. Therefore, our study is also in alignment with the important clinical goal.

However, a few caveats are worth mentioning, and further research is needed to fully evaluate its clinical utility.

First, it is necessary to confirm the association between the SNP and pancreatic cancer metastasis in larger and more diverse patient populations. The sample size, patient selection criteria, and study design can all influence the results and limit the generalizability of the findings.

Second, the clinical usefulness of an SNP as a biomarker depends on its sensitivity, specificity, and predictive value. A biomarker with high sensitivity and specificity can accurately identify patients who are at risk of developing metastasis, while a biomarker with high predictive value can help guide treatment decisions and improve patient outcomes. A stringent criteria with specific clinical utility should be applied.

Lastly, it is important to consider the limitations of using a single biomarker to predict pancreatic cancer metastasis, as it is a complex and multifactorial process involving interactions between cancer cells and their microenvironment. Therefore, a comprehensive approach that incorporates multiple biomarkers and clinical factors may be necessary to accurately predict pancreatic cancer metastasis.

CONCLUSION

Using various computational programs and databases, we were able to identify 10 common SNPs that are uniquely

associated with the risk of pancreatic cancer metastasis. The results suggest that certain genetic variations may increase the likelihood of metastasis in patients with pancreatic cancer. However, it is important to note that this study has some limitations, including a relatively small sample size and potential confounding factors. Nonetheless, the findings from this study suggest that genetic testing for these SNPs could help identify patients who are at increased risk of metastasis and inform treatment decisions. Further research is needed to confirm and expand upon these findings, with the ultimate goal of improving outcomes for patients with pancreatic cancer.

ACKNOWLEDGEMENTS

This research study was conducted with the guidance of Dr. Robert Aguilar. I'd like to thank him for his instruction on the study objective, methodology, and data analysis.

REFERENCES

1. 1. Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: a cancer journal for clinicians*, *72*(1), 7–33. https://doi.org/10.3322/caac.21708
2. 2. Castillo, C. F.-D., & Jimenez, R. E. (2023, January 23). *Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer*. UpToDate. Retrieved March 2, 2023, from https://www.uptodate.com/contents/epidemiology-and-nonfamilial-risk-factors-for-exocrine-pancreatic-cancer
3. 3. *Annual Report to the Nation Part 2: Patient economic burden of cancer care more than $21 billion in the United States in 2019*. (2021, October 26). National Cancer Institute. Retrieved March 2, 2023, from https://www.cancer.gov/news-events/press-releases/2021/annual-report-nation-part-2-economic burden#:~:text=In%202019%2C%20the%20national%20patient,time%20costs%20of%20%244.87%20billion
4. 4. *Survival Rates for Pancreatic Cancer*. (2023, March). American Cancer Society. Retrieved March 2, 2023, from https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/survival-rates.html
5. 5. *Signs and Symptoms of Pancreatic Cancer*. (2019, February 11). American Cancer Society. Retrieved March 2, 2023, from https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging.html
6. 6. Hidalgo M. (2010). Pancreatic cancer. *The New England journal of medicine*, *362*(17), 1605–1617. https://doi.org/10.1056/NEJMra0901557
7. 7. Canela-Xandri, O., Rawlik, K., & Tenesa, A. (2018). An atlas of genetic associations in UK Biobank. *Nature genetics*, *50*(11), 1593–1599. https://doi.org/10.1038/s41588-018-0248-z
8. 8. Phillips, J. E., & Corces, V. G. (2009). CTCF: master weaver of the genome. *Cell*, *137*(7), 1194–1211. https://doi.org/10.1016/j.cell.2009.06.001
9. 9. Peng, W. X., He, R. Z., Zhang, Z., Yang, L., & Mo, Y. Y. (2019). LINC00346 promotes pancreatic cancer progression through the CTCF-mediated Myc transcription. *Oncogene*, *38*(41), 6770–6780. https://doi.org/10.1038/s41388-019-0918-z
10. 10. Umer, H. M., Cavalli, M., Dabrowski, M. J., Diamanti, K., Kruczyk, M., Pan, G., Komorowski, J., & Wadelius, C. (2016). A Significant Regulatory Mutation Burden at a High-Affinity Position of the CTCF Motif in Gastrointestinal Cancers. *Human mutation*, *37*(9), 904–913. https://doi.org/10.1002/humu.230

Citation: Helen Yang, "Association of Genetic Polymorphisms with Pancreatic Adenocarcinoma Progression", American Research Journal of Biosciences, Vol 8, no. 1, 2023, pp. 7-10.