REVIEW ARTICLE

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The Genetic Landscape of Hereditary Pancreatitis: A Review

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ABSTRACT: Hereditary pancreatitis, or HP, can be described as a rare genetic disorder that often presents with repeated occurrences of pancreatitis. This disorder is generally seen in children and adolescents. The genetic basis of HP has been studied in great detail, and as a result, researchers have discovered several important genes that are involved in the onset of the disease. Hereditary pancreatitis is mainly inherited through the autosomal dominant way, and the *PRSS1* gene is the one that has been most often pointed out as the gene that is linked to HP. The *PRSS1* gene is the one that codes for the trypsinogen enzyme. The mutations in the *PRSS1* gene are probably the main factor responsible for the increased trypsin activity that is found before the manifestation of pancreatitis. In addition to *PRSS1*, alterations in other genes have also been revealed to be associated with HP. For instance, the *SPINK1* gene, which produces the pancreatic secretory trypsin inhibitor, is also the frequently found partner with HP. Mutations found in *SPINK1* can turn into an uncontrolled trypsin activity that can lead to an increased risk of pancreatitis. Mutations that are present in the CFTR gene, which is well-known in terms of its relationship with cystic fibrosis, have been shown to have a modifying effect on the risk of getting pancreatitis in individuals with HP. Certain variations, such as ΔF508 and *G551D*, have been linked to the development of other clinical problems. Moreover, there are some other rare genetic variants that are implied for HP and could have connections as well. It is important to understand the genetic aspect of HP for the purpose of early identification, genetic counseling, and targeted therapy development. More studies are necessary to elaborate on the complex relationship between the genetic variables and environmental factors related to the development of hereditary pancreatitis. In order to give the most precise overview of the entire literature, the semantic parsimony and eigenfactor-based query search approach were utilized.

Keywords: Hereditary, Genetics, Mutations, Pancreatitis, Variants.

INTRODUCTION

General Overview of Hereditary Pancreatitis

Being one of the prominent rare conditions, the hereditary pancreatitis has been the subject of molecular research for understanding its molecular pathogenesis. The PRSS1 gene has been defined as the reason of this inherited disorder, with over 25 mutations linked to it (Felderbauer et al., 2008). It is clear noting that people with hereditary pancreatitis are more likely to acquire pancreatic cancer The syndrome is closely linked to a greatly increased overall likelihood of developing pancreatic cancer, which can approach 55% in afflicted persons (Harinck et al., 2010). Hereditary pancreatitis is part of a spectrum of hereditary tumor syndromes involving the pancreas, as shown by research (Mihaljevic et al., 2009).

Advances in the detection and therapy of hereditary pancreatitis and the associated pancreatic neoplasms are significantly done by the previous efforts. The implementation of well-organized screening programs can make it early for high-risk individuals such as those who have hereditary pancreatitis to notice the early symptoms of tumors in the pancreas (Benzel and Fendrich, 2018). The first step to start the right kind of physical examination and preventive measures is to establish individuals who have a genetic risk that is due to the presence of Peutz-Jeghers and Lynch syndromes. Vanek et al. (2022), who stress the significance of early detection, truly support this statement.

The advancements in molecular biology in the previous years shed light on the pathobiology of chronic pancreatitis and its transition to pancreatic cancer. The emphasis on the involvement of signaling pathways like the Hedgehog pathway in the fibrosis and tumorigenesis in the pancreas was made in different studies. Studies focusing on poly (ADP-ribose) polymerases (PARP) have clearly shown that they are a crucial element in the processes of pancreatitis and pancreatic cancer. This revolutionary finding has brought a promising breakthrough in using PARP inhibitors as a very effective targeted therapy (Martínez-Bosch et al., 2016).

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Pathogenesis of Hereditary Pancreatitis

Hereditary pancreatitis results from the mutations in the vital genes that are present including *PRSS1*, which is the gene that encodes for cationic trypsinogen which normally is used during digestion (Sahin-Tóth, 2022). The mutations that arise from these gene alterations result in abnormally elevated activity of trypsin within the pancreas which eventually leads to autodigestion of the organ and inflammatory lesions in pancreatic tissue (Masamune, 2014). A key issue here is the premature activation of trypsinogen since this is the main feature that marks the hereditary pancreatitis pathobiology leading to the destruction of pancreatic acinar cells and the initiation of a series of inflammatory responses (Masamune, 2014).

Hereditary pancreatitis is also associated with the variations in the other genes like *SPINK1* and *CFTR* that are responsible for trypsin activity and pancreatic ductal function. The dysregulation of those genes is the main factor leading to the chronic pancreatitis development in people under a hereditary risk factor (LaRusch and Whitcomb, 2011). The *CLDN2* and *PRSS1-PRSS2* loci were genotyped to be definite genetic risk factors for both alcohol-related and sporadic pancreatitis. This fact obliges the together of genetic susceptibility together with other factors as this disease process (Whitcomb et al., 2012). New generation sequencing techniques have produced insightful information of molecular pathways showing the hereditary pancreatitis. The in-depth examination of the genotypes and the ecological environments is critical in order to clarify the factors that are involved in the onset of hereditary pancreatitis (Masamune, 2014).

Additionally, hereditary pancreatitis management through just making lifestyle changes is smoking and alcoholism, which have been shown to act separately as individual risk factors for chronic pancreatitis (Yadav et al., 2009). The multifactorial nature of pancreatitis pathogenesis is highlighted by the involvement of alcohol and smoking. Therefore, the combination of these two factors in both prevention and treatment of disease becomes more significant (Yadav and Whitcomb, 2010).

Inheritance Patterns of Hereditary Pancreatitis

Hereditary pancreatitis follows an autosomal dominant mode of inheritance, which comes with variability in the penetrance and expression (Weber et al., 1999). Those who carry the altered gene have a 50% possibility of handing it down to their children, therefore, they are on the higher end of hereditary pancreatitis developing. Moreover, the presence of the particular gene change alone does not dictate the occurrence of the disease, since other determinants like the environment and additional genetic factors are responsible for its emergence (Rebours et al., 2008). The majority of hereditary pancreatitis cases derive from some specific mutations found in the cationic trypsinogen gene (*PRSS1*), located on the 7q35 band of the human chromosome, which, in turn, is the triggering factor to elevate pancreatic trypsin activity. Of these, the mutations increase trypsin activity in the pancreas, causing chronic inflammation and bringing back the pain. (Masamune, 2014). With the exemption of the *PRSS1* gene, hereditary pancreatitis is associated with variations in other chromosomal loci, such as *SPINK1* and *CFTR* have been associated with hereditary pancreatitis in both humans and animals. This illustrates the delicate interaction of the genetic risk factors in the etiology of the diseases (Hucl et al., 2007). Developments in genotyping technology have led to the provision of renewed opportunities to identify hereditary pancreatitis in individuals and families at risk with a high level of confidence. Also, genetic testing algorithms have been specifically developed to target mitochondrial DNA (introBiomes) which is autosomal associated. Thus, these algorithms are the most efficient to address diseases in autosomal dominant relatives relating to hereditary pancreatitis who have an association with other diseases in the family (Newrick et al., 2015).

Hereditary Pancreatitis in Animal Models

Animal models have been instrumental in not only clarifying the existing pathophysiological mechanisms and additional treatment modalities for hereditary pancreatitis but have also clarified existing pathophysiological mechanisms and additional treatment modalities. In an animal study, elevated intracellular trypsin levels were shown to worsen both the acute and the chronic forms of pancreatitis in mice, which simulates the situation seen in human beings with hereditary pancreatitis (Zhan et al., 2019). Animal research confirmed that cholecystokinin/gastrin-related compounds and their binding sites are implicated in exploratory pancreatitis. This emphasizes the complex connection between gastrointestinal hormones and pancreatic function (Jensen, 2002). Animal models play a vital role in accessing the molecular factors involved in pancreatic adenocarcinoma caused by genetic disorders such as Peutz-Jeghers syndrome and render an elemental connection between hereditary pancreatitis and pancreatic cancer progression (Yee et al., 2003). Inflammation of the pancreatic acinar cells, in addition to the enzyme activation, has been convincingly demonstrated in animal models of pancreatitis, as the accrescent early stages of the disease are shown. The researchers have achieved the ligation of the pancreatic duct, which triggers the pancreatitis in animal models (Boerma et al., 2003; Halangk and Lerch, 2004), developing an animal model dissolved resembling the main parameters of the disease and enabling the thorough study of its progression with confidence. Transgenic animal models were created by inserting mutated trypsinogen genes in order to control the doa line of animals that mimic the genetic mutations which are seen in the case of hereditary pancreatitis. These models are found to have offered useful insights into the presence of trypsinogen misfolding and activation, which may cause acute and chronic pancreatitis in animals (Selig et al., 2006).

REASONING, APPROACH AND METHODOLOGY

The principal objective of this article and the reasoning behind the study were to present concise yet indepht analysis of the genetic landscape of the hereditary pancreatitis specifically tailored to the field of medical genetics. The methodology applied involve the use of semantic query search to match and reveal the literature specifically relevant to the subject by utilizing parsimony and eigenfactor algorithms. In order to achieve this, the "Journal/Author Name Estimator" (JANE) semantic database search engine was put to use, which was created by Martin Schumie from The Biosemantics Group (Schumie, 2007). This engine is based on a parsimony algorithm that allows submitted queries to be analyzed semantically, and determine a specific hit by assessing its article influence score that is based on a complex network of varied parameters such as relevance, impact, trendline, and citations. In a more technical detail, JANE runs multi-algorithmic query search to construct pinpoint results according to defined parameters. It is a publicly available and free service accessible at https://jane.biosemantics.org in any browser.

The choice of JANE was based on its extensive indexing of the entirety of PubMED, MEDLINE, and DOAJ (Directory of Open Access Journals) databases, which enables the most extensive literature index for any subject.

In brief, the basic procedure is as follows: Keywords of ""Gene AND Genetics" AND "Hereditary Pancreatitis AND Pancreatitis"" were used as a query string encompassing entire database to obtain hits based on the article influence scores. First 200 hits that has article influence score above 5 (out of 10) were retrieved. Titles and Abstracts of the first 10 hits were queried again using semantic "Title Matching" and "Abstract Matching" options to curate database results with both relevancy and article influence to obtain eigenfactor values. Remaining results from the last 20 years were used as references for the study.

GENES AND MUTATIONS ASSOCIATED WITH HEREDITARY PANCREATITIS

PRSS1 Gene

Mutations of the *PRSS1* (Serine Protease 1) gene are probably the most significant factors in the genetic background of hereditary pancreatitis according to extensive research. Defects in the PRSS1 gene, which encodes cationic trypsinogen, are the main pathogenesis of hereditary pancreatitis. These mutations can greatly enhance the level of trypsin in the pancreas, which further leads to the autodigestion of pancreatic tissue and inflammation. However, the *R116C* mutation in the *PRSS1* gene is the one that induces cationic trypsinogen misfolding, which follows endoplasmic reticulum stress and intracellular retention, and ultimately causes hereditary pancreatitis (Cheng et al., 2021). The presence of combinations of mutations in *PRSS1* and mutations in other genes, especially SPINK1, has raised more aggressiveness of the disease, marking it with the earlier onset of symptoms and the more severe clinical course (Whitcomb, 2003). *N29I* and *R122H* are some of the specific *PRSS1* gene mutations that are often found in patients with chronic pancreatitis, indicating that these particular genetic variants have a unique role in the pathogenesis of the disease (Maruyama et al., 2010). Genetic analysis of *PRSS1* mutations is the primary screening and testing tool for diagnosing hereditary pancreatitis, especially in Japan, where it is particularly applicable in ambiguous cases of clinical presentation (Horitani et al., 2023).

The molecular frameworks of *PRSS1* defects are given in the pathogenesis of Hereditary Pancreatitis, where studies conducted on animal models have been particularly valuable for pinpointing associated mutations (Selig et al., 2006). *PRSS1* gene mutations can trigger several processes to turn trypsinogen into trypsin faster, such as trypsinogen-autoactivation. Abnormal trypsin activation can, thereby, precedently lead to fearsome digestive enzyme firing, which eventually leads to pancreatic autodigestion and the initiation of pancreatitis. *PRSS1* defects make it difficult to process and break down the protective trypsinogen and its inhibitor which leads to excess trypsin being produced in the pancreas. Mutated cationic trypsinogen forms can resist the usual degradation processes by accumulating the active trypsin that continues to cause pancreatic inflammation. The disruption of the trypsin inhibition ways may also contribute to the increase of the unconstrained trypsin levels, hence aggravating the inflammatory response in hereditary pancreatitis (Whitcomb, 2003; Cheng et al., 2021). Mutant folding of digestive enzymes, such as cationic trypsinogen variants encoded by *PRSS1* gene mutations, become very complex for the cases of chronic pancreatitis. They also cause endoplasmic reticulum stress, leading to intracellular retention and triggering the unfolded protein response. This entire process leads to the damage of pancreatic cells, inflammation, and the onset of disease (Cheng et al., 2021).

The *PRSS1* gene mutations are major candidates in the molecular pathobiology of hereditary pancreatitis. The activation of abnormal trypsinogen, the failure of protease-antiprotease, and endoplasmic reticulum stress are all caused by these mutations. The R122H mutation is the one that upsets the normal protein function which in turn causes trypsin to become more active and also makes inflammation of the pancreas occur more quickly. The N29I and N29T mutations lead to the same results by promoting trypsin to autoactivate quicker and in the end result in hereditary pancreatitis development (Whitcomb, 2003; Maruyama et al., 2010; Cheng et al., 2021).

SPINK1 Gene

The SPINK1 (Serine Peptidase Inhibitor Kazal Type 1) gene has important functions in hereditary pancreatitis through expression of pancreatic secretory trypsin inhibitor. *SPINK1* locus polymorphisms are related to hereditary pancreatitis, which results in less conversion of trypsinogen to trypsin in pancreatic effects. A considerable part of the *SPINK1* gene mutations in

trypsin activity regulation and protease inhibition disorders, pancreatic injury susceptibility increase, lead to the development of hereditary pancreatitis. *SPINK1* mutations lead to the secretion of pancreatic inflammation and tissue damage, which is due to the trypsin activity dysregulation (Whitcomb, 2003).

Most mutations that contribute substantially to the loss of *SPINK1* gene function, for instance, the common N34S mutation, are the ones that cause decrement in the pancreatic secretory trypsin inhibitor accumulation. This makes the trypsin inhibition weaker, which will lead to the unregulated trypsin in the pancreas. The surplus of trypsin activity and the lack of trypsin activity power the development of pancreatitis in people with *SPINK1* gene faults, especially when it is mixed with the *PRSS1* gene faults (Drenth, 2002; Whitcomb, 2003).

Cystic fibrosis-unrelated chronic pancreatitis cases have been found to have *CFTR* and *SPINK1* gene mutations together. Bicarbonate conductance is a problem in the *CFTR* variant, which along with the *SPINK1* defect will give an environment that is good for pancreatic injury and chronic inflammation to develop. The relationship between CFTR and SPINK1 mutations is what makes the hereditary pancreatitis multifactorial and the genetic interaction is the important factor in sickness development (Schneider et al., 2011). The missense mutations in *SPINK1* caused the Pancreatic Secretory trypsin Inhibitor to be retained intracellularly and thus degenerated. The decrease of *SPINK1* which is considered a classic defect has been associated with classic hereditary pancreatitis, indicating the significance of *SPINK1* in the prevention of pancreatic injury and the management of pancreatic homeostasis (Király et al., 2007). The discovery of the presence of *SPINK1* gene mutations in chronic pancreatitis that emerges from inheritable and those that are static is a clear evidence of the great significance of this gene in preserving pancreatic well-being (Whitcomb, 2003). The defects of *SPINK1* in chronic pancreatitis patients stress the importance of the effect of trypsin inhibition defects on disease causation. Chandak (2004) emphasizes that these mutations lower the level of protection against the early activation of trypsin, which is the main reason for injury to the pancreas and consequent chronic inflammation.

CFTR Gene

CFTR, which stands for Cystic Fibrosis Transmembrane Conductor Regulator, is the main gene that is involved in cystic fibrosis and represents the mutations of the gene in its development. The *CFTR* gene mutations in hereditary pancreatitis are the ones that have been shown to lead to disturbances in ion transport, bicarbonate secretion interference, as well as pancreatic inflammation and damage (Schneider et al., 2011). The *CFTR* gene variations can lead to the transportation deficiency of chloride and bicarbonate ions through the epithelial cell membranes. The impaired ionic transport is a risk factor for pancreatic inflammation, and this together with the ion regulation disturbance by the necessary enzyme first would lead to recurrent chronic enzymes-triggered inflammation and thus mostly be the cause of the hereditary pancreatitis (Maléth et al., 2015). CFTR gene mutations that are the cause of the imbalance in the secretion of the important substances by the pancreatic ductal cells can also increase the risk of pancreatitis. The *CFTR* channel dysfunction leads to a disturbed pancreatic microenvironment, which is accompanied by activation of trypsin and further damage to the pancreas (Maléth et al., 2015). However, this mechanism has a tendency to overshadow the hereditary character of the underlying disease without conducting genetic tests.

CFTR pancreatitis danger is very much associated with the occurrence of two *CFTR* defects that block the extrapancreatic *CFTR* functioning. The *CFTR* gene mutation ΔF508, which deletes phenylalanine at position 508, is connected to a more severe form of cystic fibrosis (CF) featuring the pancreas. Likewise, the G551D mutation, which substitutes glycine with aspartate at position 551, causes a defective CFTR protein that increases the risk of pancreatitis with other complications in CF patients. The presence of *CFTR* mutations further complicates the transport mechanism of ions and makes it difficult for the pancreas to secrete fluid and regulate the enzymes. The dysfunction of *CFTR*, which is the main factor contributing to the pathogenesis of hereditary pancreatitis, is the one that enhances the pancreatic inflammation susceptibility most (Noone et al., 2001). The *CFTR* gene mutations obstruct the bicarbonate conductance and pancreatic juice secretion is inhibited. This imbalance of pancreatic liquid leads to more trypsin and thus to pancreatitis. *CFTR* gene mutations set a pro-inflammatory state in the pancreatic microenvironment and therefore the pancreas is affected (Schneider et al., 2011). All in all, the present data gives a strong accent on the protective role of the *CFTR* mutations in Hereditary Pancreatitis, and it is quite obvious that acquiring the *CFTR* mutations will lead to the forms of the disease.

POTENTIAL GENES AND MUTATIONS FOR HEREDITARY PANCREATITIS

CPA1 Gene

The *CPA1* (Carboxypeptidase A1) gene is likely a significant factor in hereditary pancreatitis, contributing to its development. *CPA1* defects have been proposed for early-onset chronic pancreatitis, indicating that misfolding-induced endoplasmic reticulum stress is a key mechanism in pancreatitis susceptibility (Witt et al., 2013). Deletions in the *CPA1* significantly bring about pancreatitis. Although recently it was proposed that the relationships between *CPA1* polymorphisms and pancreatitis may vary across populations, it is important to explain that some individuals carrying these variants may not necessarily develop clinical pancreatitis (Piseddu et al., 2022). As a side note, *CPA1* variants, in conjunction with *CPB1* (Carboxypeptidase B1), increase

the risk of pancreatic carcinogenesis, underscoring the significant impact of these mutations on the development of pancreas neoplasms (Tamura et al., 2018).

The *CPA1* mutations in chronic pancreatitis have been heavilly worked in animal studies, and it has been obtained that mutant *CPA1* mice exhibit sudden and advanced chronic pancreatitis. The main characteristics are as the name suggests are acinar atrophy, acinar-to-ductal metaplasia, fibrosis, and macrophage infiltration. The *CPA1* gene's alterations have a distinctivity detrimental outcome on the pancreatic tissue proclaiming the development of chronic pancreatitis (Németh et al., 2022). SSA's disclosure of a considerable part, These animals have shown the evident differences in cholesterol absorption among the diets. It appears that *CPA1* plays the role of a pancreatic carcinogenesis marker in the regard it has excellent sensitivity to the normal and neoplastic differentiation of the pancreatic cells. It is regularly more *CPA1* in the neoplastic pancreatic cells thus showing the level of this molecule in the pathogenesis of pancreatic cancer (Xiao et al., 2023). However, even if there is a strong network with the inheritance of subfactor pancreatitis, the alterations of *CPA1* and *CPB1* are not yet truly seen as the main causes.

CTRC Gene

Hereditary pancreatitis may possibly involve the *CTRC* (Chymotrypsin C) gene as a causative candidate. Findings indicate that *CTRC* is a vital factor in the process of intracellular protein breakdown (proteolysis), mostly by keeping the trypsinogen and trypsin levels under control. *CTRC* has an important role to play in preventing the premature activation of trypsin and the consequent pancreatic damage by effectively blocking the pancreas trypsinogen conversion. The gene mutations lead to the dysfunction of *CTRC* and it can disrupt the balance of pancreatic protease activity, resulting in the increased levels of trypsinogen and eventually causing pancreatitis (Beer et al., 2012). The investigations of *CTRC* variants presented the particular ways in which loss-of-function mutations are connected to the augmented susceptibility to pancreatitis. *CTCR* alleles with poor activity and decreased secretion can cancel the normal inhibitory action of the *CTRC* on the levels of trypsin thus tripping the spillage of trypsin and causing inflammation (Rustgi, 2014).

CTRC variants have an impact on the signaling of trypsinogen and trypsin; thus, they also affect the susceptibility of individuals to this condition, as evidenced by the experimental studies. An unusual processing of trypsinogen activation peptides by the *CTRC*, which in turn leads to the enhancement of trypsin activity, promoted pancreatic inflammation and chronic pancreatitis (Szabó and Sahin–Tóth, 2012). *CTRC* idiopathic polymorphisms have been associated with idiopathic chronic pancreatitis, thus implying the genetic predisposition to pancreatic disorders. Rare variants of the *CTRC* were found in chronic pancreatitis, opening up the possibility of a link between *CTRC* polymorphisms and the manifestation of pancreatic diseases (Masson et al., 2008).

RARE MUTATIONS IMPLIED IN HEREDITARY PANCREATITIS

Various gene mutations discovered from medical genetics screening on different populations and some even not easily identified carry possibly direct or indirect associations with the development of hereditary pancreatitis. In addition to the aforementioned predominant gene mutations, these gene mutations are the same but still remain in the candidate state without stipulated connections to hereditary pancreatitis. Despite this, rare variants are imaginable avenues besides that are the first steps in the understanding of the disease.

To start briefly, these rare variants are as follows: *CASR*: Mutations in the *CASR* gene are known to be associated with the risk of pancreatitis, which signifies the central function of calcium-sensing receptors in the proper pancreatic condition (Sadiq et al., 2020). *CLDN2*: Variants in the *CLDN2* gene are connected with a high possibility of having pancreatitis, which in turn acts as the mechanism for claudin-2 to alter pancreatic function (Sadiq et al., 2020). *SBDS*: The identification of mutations in the SBDS gene in patients found with the hereditary variable runs out of a genetic necessity to the disease, while understanding far away (Sadiq et al., 2020). *TRPV6*: Among the newly identified mutations *TRPV6* gene is one of them responsible for the inherited disease. These are new to us, and they arise from individual molecular pathways possibly co-existing almost with the known ones (Piseddu et al., 2022). *AAT*: A detection of *AAT* gene mutations in patients with chronic and recurrent acute pancreatitis offers a suggestion that they might have a hereditary property (Grzybowska-Chlebowczyk et al., 2018). *CTSB*: The presence of variants in the *CTSB* gene among the patients suffering from recurring and chronic pancreatitis potentially indicates the edge of cathepsin B in terms of being involved in pancreatic disorders (Abu-El-Haija et al., 2019). *KRT8*: Changes in the *KRT8* paragenes could also be mentioned in the keratin 8 being implicated in the progress of pancreatitis in children (Abu-El-Haija et al., 2019). *ATP8B1*: A high occurrence of variants in the *ATP8B1* genetic region among the individuals with chronic and recurrent pancreatitis is an evidence of contemplated genetic alteration in disease evolution (Abu-El-Haija et al., 2019). These far less common genetic attach mutations emphasize the myriad genetic factors which underlie both the triggering and the progression of the disease. These will play a central role in the effort to create personal management strategies for those individuals who will be affected by the hereditary form.

GENE MUTATIONS IN DOMESTIC ANIMALS FOR HEREDITARY PANCREATITIS

Both the Hereditary Pancreatitis as a pathology and its genetic causes in domestic animal species are still unclear and are garnering attention from the field of veterinary genetics. Current understanding relies heavily on results in human medical genetics, yet no distinct gene or gene variants have been conclusively identified. Different research has revealed the prominence of *PRSS1* and *SPINK1* polymorphisms in rare cases of hereditary pancreatitis in domestic animals, particularly in house cats (Masamune, 2014). Rare genetic variants that were proposed to have association with hereditary pancreatitis are also implied for hereditary pancreatitis in domestic animal species with them being current targets for unveiling the complexity of the disease (Wu et al., 2022). Despite the presence of scarce literature, there's still an ongoing effort for establishing correlation between hereditary pancreatitis of humans and animal species. Aside from the mice models, the house cat is currently the only domestic animal species to provide a somewhat limited understanding for the genetics of hereditary pancreatitis in domestic animals.

CONCLUSION

The important progress has been done in determining key genes associated with hereditary pancreatitis. Alongside this, there are a few other tricky things and future objectives that are required to be covered. It is necessary to perform additional research to find out more of the genes responsible for hereditary pancreatitis. Using high-throughput sequencing technology, unique genes and pathways involved in inherited pancreatitis ought to be singled out. Ecological studies that are carried out among reference populations, with prevalent, or at risk, of hereditary pancreatitis are vital for the determination of the environmental and genetic factors that are implicated in the disease. The scope of forthcoming studies will be to explore the relationship between genetic mutations, protease regulation, and pancreatic inflammation with the aim of discovering the unique genetic patterns and risk factors which cause hereditary pancreatitis. Such endeavors will mainly not only promote progress in the particular field of hereditary pancreatitis, as well, it will provide one with diverse targets for treatment, for instance, populations from different ethnicity. The main aim of the research in the future should be the determination of the role of specific genetically determined factors in diease progression and treatment response, that will consequently allow individualized therapy (Masamune, 2014; Wu et al., 2022; Cheng et al., 2021).

All these variables are related to the hereditary pancreatitis pathophysiology that results from the overlapping of genetic mechanisms that predominantly express the individual's predisposition. Hereditary pancreatitis is due to a genetic mutation, the environment, and inflammatory processes that then develop into a chronic pancreatic inflammation. Animal models have been a critical tool in the research of hereditary pancreatitis, providing key insights into the underlying genetics and disease processes and potential therapies. Instead of simply dealing with the problems of today, we should also highlight the future directions related to the genetics of hereditary pancreatitis so we would comprehend the disorder more deeply, promote its early diagnosis, and make progress in the field of personalized treatments for those who are with the inherited pancreatitis.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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