

Asparaginase-induced acute pancreatitis in children: unveiling predictive biomarkers for precision care

Evelin Cristine Mendonça de Senna^{1,3}, Lucas Rotella⁴, Daiane Keller Ceconello^{1,2}, Klerize Anecely de Souza Silva^{1,2}, Ciliana Rechenmacher^{1,2}, Andre Salim Khayat⁴, Alayde Vieira⁴, Liane Esteves Daudt^{1,2}, Mariana Bohns Michalowski^{1,2}

¹Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil, ²Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil, ³Universidade de São Paulo, São Paulo, SP, Brazil, ⁴Universidade Federal do Pará, Belém, PA, Brazil

Asparaginase (ASN) is a crucial drug in the treatment of acute lymphoblastic leukemia (ALL). However, it is associated with an important and unique toxicity profile compared to other types of chemotherapy. One of the most relevant toxicities is acute pancreatitis. Although it is frequently a reversible process, its severity may contraindicate the continued use of ASN, delay the entire chemotherapy regimen, and impact overall survival. So far, the pathophysiological mechanism that gives rise to this complication is not well defined. At the same time, some risk factors are being studied, mainly pharmacogenetic markers. This review will outline what is currently known about the main genetic polymorphisms associated with the risk of acute pancreatitis related to the use of asparaginase.

Keywords: Asparaginase. Acute lymphoblastic leukemia. Pancreatitis. Genetic factors.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and adolescents and its treatment has witnessed significant advancements, with asparaginase (ASN) playing a pivotal role in achieving therapeutic success, having generated cure rates close to 90% (Pui *et al.*, 2010; Hunger *et al.*, 2012).

ASN, a bacteria-derived enzyme that systematically depletes the non-essential amino acid asparagine, is

a key drug included in the induction phase of most protocols worldwide (Avramis *et al.*, 2002).

Through its mechanism, it selectively eliminates leukemic cells, as they have low levels of the enzyme asparagine synthetase, and preserves normal cells that have the ability to synthesize asparagine intracellularly (Pieters *et al.*, 2011). For these reasons, it presents low myelosuppressive effect and fewer gastrointestinal reactions when compared with other drugs (Pieters *et al.*, 2011).

There are currently three different forms of ASN. Two native formulations are initially derived from bacteria *Escherichia coli* or *Erwinia caratovari* (Hijiya *et al.*, 2016; Silverman *et al.*, 2001). Typically, *E. coli*-derived ASN is used as first-line therapy, with *Erwinia* ASN reserved for patients experiencing hypersensitivity reactions to the former. A third formulation, PEG-ASN, conjugates ASN with polyethylene glycol, resulting in reduced antibody formation, lower incidence of allergies, and longer half-life (Silverman *et al.*, 2001). PEG-ASN boasts a half-life of approximately one week, whereas *E. coli* and *Erwinia* ASN offer half-lives of 1.3

*Correspondence: M. B. Michalowski, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350 Bloco A, Av. Protásio Alves, 211 - Bloco B e C, CEP 90035-903, Santa Cecília, Porto Alegre, RS, Brasil, Phone: (51) 3359-8000, E-mail: mmichalowski@hcpa.edu.br, <https://orcid.org/0000-0002-9482-0776>, CV Lattes: <http://lattes.cnpq.br/3623764715432223>. E. Senna, evelinsenna3@gmail.com, <https://orcid.org/0009-0002-5149-3178>. L. Rotella, lucasrotella.lr@gmail.com, <https://orcid.org/0009-0007-4104-2310>. D. K. Ceconello, daia_ceconello@hotmail.com, <https://orcid.org/0000-0002-2796-6708>. K. A. S. Silva, klerize.anecely@gmail.com, <https://orcid.org/0000-0002-2424-0354>. C. Rechenmacher, cilianare@gmail.com, <https://orcid.org/0000-0002-1321-5807>. A. S. Khayat, khayatas@gmail.com, <https://orcid.org/0000-0002-3451-6369>. A. Vieira, alayde.viera@gmail.com. L. E. Daudt, ldaudt@hcpa.edu.br, <https://orcid.org/0000-0001-9495-6932>.

and 0.65 days, respectively (Asselin *et al.*, 2015).

However, the clinical use of ASN is not devoid of challenges. Drug toxicity is still a worrying factor that can lead to therapeutic failure and, consequently, reduce patient survival (Schmiegelow *et al.*, 2010; Lund *et al.*, 2014). Among these challenges lies the development of Acute Pancreatitis due to Asparaginase (AAP), a severe complication that can significantly affect treatment outcomes, reported in up to 7% of patients exposed to this medication, as detailed in the Dana-Farber Cancer Institute (DFCI) Protocol 91-01 (Silverman *et al.*, 2001). In numerous countries worldwide, PEG-ASN has taken precedence as a first-line option in ALL treatment (Avramis *et al.*, 2002). Given its paramount therapeutic significance, it becomes imperative to comprehend the associated adverse events, their management, and potential risk factors. While the genetic underpinnings of AAP continue to be a focus of active research, it is discernible that specific genetic polymorphisms can predispose patients to this adverse event (Liu *et al.*, 2016). This review aims to explore the genetic markers associated with AAP, shedding light on their clinical significance and the potential for personalized treatment strategies.

MATERIAL AND METHODS

This is a systematic review based on the requirements established by the international model PRISMA - Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) (Page *et al.*, 2021).

Articles were searched in SciELO and Pubmed, considering the relevance of the topic and searching for it through publications by different authors. Articles published between 2000 and 2023, in English and Portuguese, were included in this review. The inclusion criteria were articles in Portuguese or English that carried out research on the topic of acute pancreatitis, acute pancreatitis as an adverse event due to the use of asparaginase in children undergoing treatment for acute lymphoblastic leukemia, and genetic polymorphism of

acute pancreatitis.

RESULTS AND DISCUSSION

All selected articles addressed etiopathogenesis, clinical presentation, investigation diagnosis and management of Acute Pancreatitis in addition to genetic factors related to Acute Pancreatitis. 26 articles were found. Database searches found 23 articles in PubMed, and 3 articles in Scielo. Duplicate or articles unavailable for access were excluded, and only 24 articles were kept.

Pancreatitis and PEG ASN

Pancreatitis is defined by the histological presence of inflammation in the pancreatic parenchyma, interstitial edema, infiltration by inflammatory cells, and different levels of apoptosis, necrosis, and hemorrhage (Banks *et al.*, 2013).

ASN-associated pancreatitis (AAP) occurs in 2-18% of patients and can lead to short-term complications such as pancreatic necrosis and pseudocyst formation, as well as a systemic and multiorgan inflammatory response syndrome, and long-term complications such as the development of Diabetes Mellitus and chronic pancreatitis (Du *et al.*, 2022; Liu *et al.*, 2016).

These complications can be serious and may result in a definitive contraindication for the medication. AAP in its acute form is often considered a reversible process, but its pathophysiology is still not well defined, and one of the possible reasons is the sustained depletion of asparagine, which can trigger a reduction in protein synthesis in organs such as liver and pancreas (Knoderer *et al.*, 2007; Kearney *et al.*, 2009; Treepongkaruna *et al.*, 2009; Vrooman *et al.*, 2010; Samarasinghe *et al.*, 2013; Raja, Schmiegelow, Frandsen, 2012).

The diagnosis requires the presence of two of these criteria: typical and persistent abdominal pain, serum amylase and/or lipase levels increased by three times or more than normal values, and/or a typical image of pancreatitis shown by ultrasound or computed

tomography (Banks *et al.*, 2013).

The most frequent symptoms and clinical signs presented are abdominal pain, usually of severe intensity, associated with nausea and vomiting (Banks *et al.*, 2013).

To date, there is no specific classification of pancreatitis severity in Pediatrics (Banks *et al.*, 2013).

Thus, cases are classified according to the Atlanta Consensus (Table I) and/or according to the Common Terminology Criteria for Adverse Events (CTCAE) classification (Shah, 2022).

The Atlanta criteria, recently revised in 2013 by Banks *et al.* (2013), constitute a classification system for acute pancreatitis primarily designed for adults. It's important to note that adult patients typically differ from children in their predisposition to acute pancreatitis,

often stemming from other underlying comorbidities.

According to the study carried out by the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008, which evaluated the association of the use of Peg ASN with pancreatitis, forty-five patients (5.9%) developed AAP after a median of five doses (1-13) and 11 days (8-13 days) from the last administration of PEG ASN (Schmiegelow *et al.*, 2010). Of those, thirteen patients developed pseudocysts (30%), and 11 patients developed necrosis (25%). One patient died of pancreatitis. All patients had symptoms of AAP: abdominal pain in 41 patients (93%), nausea in 31 patients (71%), and vomiting in 28 patients (64%). Nine patients experienced back pain (21%), and six patients experienced shoulder pain (14%) (Schmiegelow *et al.*, 2010).

TABLE I - Atlanta Consensus classification for acute pancreatitis

Gravity	Criteria	Prognosis
Mild pancreatitis	Absence of organ failure and absence of local and systemic complications.	Great
Moderate pancreatitis	Presence of transient organ failure, resolved within 48 hours, and/or local or systemic complications without persistent organ failure	Low mortality
Severe pancreatitis	Presence of persistent organ failure >48 hours	High morbidity/high mortality

Adapted Acute Pancreatitis Classification Working Group (Banks *et al.*, 2013)

Although expert panel recommendations for adolescent and adult patients experiencing AAP do exist (Stock *et al.*, 2011), similar guidelines for children are not available.

Usually, the treatment of PEG ASN-related acute pancreatitis is supportive with the aim of reducing potential complications (Figure 1) (Gardner *et al.*, 2009).

Several randomized controlled trials of non-ASN pancreatitis in adults have shown that early enteral feeding reduces the incidence of complications (Petrov *et al.*, 2006; Wu *et al.*, 2010). Studies in children are limited, but early administration of adequate fluid resuscitation is generally recommended (Gardner *et al.*, 2009).

It's crucial to highlight that decreased exposure to L-ASN due to treatment discontinuation, often prompted by toxicity concerns, has been associated with reduced event-free survival in childhood ALL, as reported by Silverman *et al.* in 2001. This underscores the significance of addressing the possibility of re-exposure to L-ASN in post-acute pancreatitis treatment protocols.

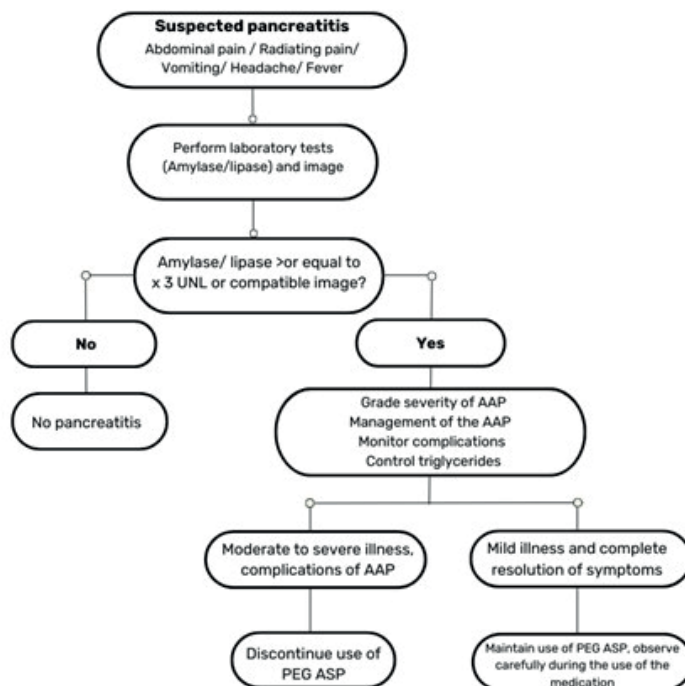


FIGURE 1 - Diagnosis and management of asparaginase-associated pancreatitis. Adapted from an article by Raja *et al.* Asparaginase-associated pancreatitis in children. British Journal of Hematology, 2012; 159 (1): 18-27.

Table II shows recent studies that described AAP in different clinical protocols for children with ALL. Three of them described the re-administration of ASN after the occurrence of AAP (Knoderer *et al.*, 2007; Kearney *et al.*, 2009; Schmidt *et al.*, 2021). AAP when L-ASN was reintroduced was reported to range from 7% (two of 26 patients) to 62.5% (10 of 16 patients), depending on the series (Knoderer *et al.*, 2007; Kearney *et al.*, 2009). Patients with mild illness and complete resolution of symptoms better respond to re-exposure to ASN (Knoderer *et al.*, 2007; Kearney *et al.*, 2009). The two studies had different criteria for reintroduction, which are mild or moderate AAP and complete

resolution of symptoms in one study (Knoderer *et al.*, 2007), whereas the other study required resolution of symptoms within 72h (Kearney *et al.*, 2009). Another more recent study (Schmidt *et al.*, 2021) observed the impact of re-administration of ASN; 3% of patients (five of 165 patients) presented a new AAP. Among the five patients with AAP after re-administration, 40% (n=2) were patients with severe conditions; 60% (n=3) were patients with mild conditions maintained therapy with ASN, none presented a new episode of AAP, which reinforces previous studies that stated that re-exposure to ASN in patients with mild conditions is possible (Schmidt *et al.*, 2021). These findings indicate d

TABLE II - Studies of Asparaginase-associated Pancreatitis in children

Reference	Lead Institution or Group	Period of Study	Chemotherapy Protocol	Number and % of Patients With AAP [n/N (%)]	ASN formulation and dosage	Definition of Pancreatitis Severity	Frequency of AAP Severity or AAP Complications
Samarasinghe <i>et al.</i> , 2013	Great North Children's Hospital, Newcastle, United Kingdom	2003-2011	UKALL 2003	48/3101 (1.5)	PEG Asn 1000 UI/m ² IM	CTCAE 4.03: Grade 3 and 4	Grade 3: 35/48 (73%) Grade 4: 13/48 (27%)
Raja, Schmiegelow, Frandsen, 2012	University Hospital Rigshospitalet, Kobenhaven, Denmark	2008-2012	NOPHO ALL 2008	45/786 (5.7)	PEG Asn 1000 UI/m ² IM	Only complications were described	19/45 (42%) had complications: 8 pseudocyst, 6 necrotizing pancreatitis, 5 pseudocysts +necrotizing pancreatitis, 30 SIRS
Kearney <i>et al.</i> , 2009	Dana-Farber Cancer Institute, Boston, USA	1987-2003	DFCI ALL Consortium protocols 87-01, 91-01, 95-01, 00-01	28/403 (7)	PEG Asn 2500 UI/m ² IM	Only complications were described	5/28 (18%) pseudocyst
Barry <i>et al.</i> , 2007	Dana-Farber Cancer Institute, Boston, USA	1991-2000	DFCI ALL Consortium protocols 91-01 and 95-01	34/844 (4)	PEG Asn 2500 UI/m ² IM	CTCAE v. 3	Not specified
Schmidt <i>et al.</i> , 2021	Sf.Maria Children's Hospital	2010-2019	ALL IC BFM 2002	5/165(3)	L-Asparaginase 5000 UI/M ²	CTCAE	2/5 (40%) Grade 3/4

These findings indicate that AAP can manifest after one or multiple asparaginase administrations, with likelihood of recurrence upon re-exposure, as noted by Raja, Schmiegelow, Frandsen, in 2012. Considering the currently available literature, the optimal approach seems to involve reintroducing asparaginase for patients with mild or moderate pancreatitis while conducting a case-specific assessment that balances the risk of pancreatitis against the risk of relapse (Knoderer *et al.*, 2007; Kearney *et al.*, 2009; Schmidt *et al.*, 2021).

However, if a subsequent episode of acute pancreatitis linked to asparaginase emerges, its use should be permanently discontinued (Knoderer *et al.*, 2007; Kearney *et al.*, 2009; Schmidt *et al.*, 2021).

Regarding potential risk criteria for the development of AAP, several factors have been implicated in the increase of this risk. These factors include older age, concurrent treatment with other anticancer drugs, usage of medications such as 6-mercaptopurine, glucocorticoids, and daunorubicin,

specific genetic polymorphisms, and the presence of hypertriglyceridemia (Knoderer *et al.*, 2007). While clinical factors are commonly investigated, there is a growing trend toward increased research into genetic factors (Knoderer *et al.*, 2007).

Within this context, some genes related to the pharmacokinetics of ASN have been studied to establish an association and risk stratification for the development of pancreatitis. In this review, the genes that are most frequently described and what is currently known about their clinical impact will be discussed.

Genetic Polymorphisms and AAP

CPA2 gene

The CPA2 gene encodes one of the three pancreatic procarboxypeptidases, procarboxypeptidase A2, which undergoes proteolytic activation in the duodenum by the action of chymotrypsin C (Szabó A *et al.*, 2016). When activated, it acts on residues of aromatic amino acids exposed by the action of chymotrypsin and elastases, hydrolyzing COOH-terminal peptide bonds in proteins and peptides (Szabó A *et al.*, 2016; Nakano *et al.*, 2015).

One of the variants of the CPA2 gene is rs199695765, which has a worldwide frequency of 0.01% and consists of the exchange of a cytosine base for thymine, leading to the formation of a stop codon, interrupting translation early in exon 2, codon 51 of a protein with 419 amino acids, rendering it non-functional (NIH, 2022). In a study by Liu *et al.*, 2016, 3469 control patients and 177 patients with AAP were evaluated. Among the several gene variants studied, rs199695765 was listed as high risk for the development of AAP, showing a frequency of 1.7% in the AAP group, with no occurrences in the control group (hazard ratio = 587). The mechanism by which this and other CPA2 variants increase the risk of developing AAP is still unclear, but the results of this study suggest that it possibly differs from what was previously described in other forms of pancreatitis (Liu *et al.*, 2016).

Furthermore, it is noteworthy that patients with

this variant developed AAP after the first dose of ASNase, showing that the drug is poorly tolerated, and a lower-dose approach may be recommended. Other CPA2 variants related to AAP are reported in the aforementioned study (Liu *et al.*, 2016). The analysis of the consequences of each alteration in this gene can be the target of future studies, which can broaden the understanding of the mechanism associated with AAP (Liu *et al.*, 2016). One of the interesting points to explore further is the regulatory aspect, as the consequence is the absence of the protein or its presence at a lower level, potentially generating an effect similar to that of rs199695765 (Liu *et al.*, 2016).

MYBBP1A gene

The MYBBP1A gene encodes protein 1A, which binds to the proto-oncogene c-MYB protein (George *et al.*, 2014; Felipe-Abrio *et al.*, 2020). It has a regulatory role in nucleolar transcription and is also important in several cellular processes such as nuclear stress response, ribosomal DNA synthesis, cell cycle control, early embryonic development, regulation of inflammation, tumor suppression via modulation of p53 activity, and cellular senescence (George *et al.*, 2014; Felipe-Abrio *et al.*, 2020).

In this gene, the rs3809849 variant was described. It has a worldwide frequency of 18.2% and consists of exchanging a guanine base for a cytosine base, changing the amino acid encoded by the codon (Abaji *et al.*, 2019). This variant is associated with the development of AAP, possibly by altering the function of MYBBP1A as a nuclear factor kappaB (NF-κB) co-repressor. The NF-κB transcription factor is activated early in acinar cells during acute pancreatitis and increases the expression of multiple genes involved in inflammatory and apoptotic responses (Abaji *et al.*, 2019). NF-κB pathways directly increase the severity of pancreatitis and are sufficient to produce chronic pancreatitis. Thus, in case this variant is present, NF-κB repression would not occur, leading to AAP (Abaji *et al.*, 2019; Huang *et al.*, 2013).

RGS6 gene

The RGS6 gene encodes a member of the RGS protein family (G protein signaling regulator), which is characterized by the presence of an RGS domain (Liu *et al.*, 2016; Ahlers *et al.*, 2016). This domain acts as regulator of the duration and magnitude of the signaling initiated by GPCRs - G protein-coupled receptors, and it modulates neuronal, cardiovascular, and lymphocytic activities. Furthermore, the RGS6 protein is also part of the R7 subfamily (RGS6, RGS7, RGS9, RGS11) of RGS proteins, characterized by the presence of DEP (disheveled/Egl-10/pleckstrin) and GGL (G gamma subunit-like) domains that allow interaction with membrane proteins to control cell targeting and association with G beta 5 (Liu *et al.*, 2016; Ahlers *et al.*, 2016). Moreover, the RGS6 gene has been found to be deregulated in some types of cancer, such as ovarian, breast, and pancreatic carcinoma (Liu *et al.*, 2016; Ahlers *et al.*, 2016).

A variant of RGS6 was associated with AAP by Wolthers *et al.*, 2017, specifically rs17179470, with worldwide frequency of 6.6%. This variant changes a base from guanine to cytosine within an intronic region. The hypothesis regarding the relationship between AAP and this alteration suggests that the presence of RGS6 protein in pancreatic acinar cells may be associated with a better outcome in pancreatitis (Wolthers *et al.*, 2017). However, the role of RGS6 in the pathophysiology of pancreatitis is not fully described (Wolthers *et al.*, 2017). There is a possibility that this variant negatively affects the gene, leading to a more severe inflammatory condition, as described by Jiang *et al.* (2014). A study conducted by Wolthers *et al.* (2017) also reported reduced expression of RGS6, both at the mRNA and protein level, in cases of pancreatic cancer patients, predicting a poor prognosis.

ULK2 gene

The ULK2 gene encodes a serine/threonine protein kinase, ULK2, which is important for astrocyte

transformation and tumor growth. Additionally, this protein is related to the p53 transcriptional gene network and plays a regulatory role in autophagy in response to starvation (Chaikuad *et al.*, 2019). This is due to its involvement in the regulated initiation of the mTOR metabolic pathway, where it regulates the formation of autophagophores, the precursors of autophagosomes (Chaikuad *et al.*, 2019; John Clotaire *et al.*, 2016).

This gene has several variants that are relevant in cases of AAP (Wolthers *et al.*, 2017). The first one is rs281366, which involves the exchange of a cytosine base for thymine and causes a non-coding exon variant. This variant was reported by Wolthers *et al.*, 2017. The association of ULK2 with AAP is speculated to be due to its role in autophagy in response to starvation. This process has been described in relation to inflammation, including pancreatitis. During the asparaginase treatment, it is speculated that asparagine depletion induces a state similar to starvation where autophagy is upregulated (Wolthers *et al.*, 2017).

Therefore, a higher incidence of pancreatitis may occur in patients with changes in autophagic function (Wolthers *et al.*, 2017). Another study targeting the ULK2 gene was conducted by Wang *et al.*, 2020; and focused on the rs281341 and rs281340 variants, both located in the promoter region of the gene. These variants may be the subject of future research to gain a greater understanding of their correlation with pancreatitis.

LINC01429/NFATC2 gene

The study by Wolthers *et al.*, 2017 reported new potential targets associated with AAP, including rs62228256, which is a variant of the LINC01429 gene that expresses a long non-coding RNA (lncRNA). LINC01429 acts as a quantitative trace expression site, explaining the expression variation in the NFATC2 gene in pancreatic tissue (Wolthers *et al.*, 2019). NFATC2 expresses a transcription factor essential for the development and function of the immune system, playing a central role in inducing the transcription of cytokine genes in T cells during the immune response

(Wolthers *et al.*, 2019). The rs62228256 variant involves the alteration of a cytosine to a thymine and showed strong association with AAP. However, this association was not found in the replication study, and there was also no association in studies involving adults with pancreatitis not associated with asparaginase. Therefore, while rs62228256 presented an interesting association, its reliability is low (Wolthers *et al.*, 2019).

PRSS1 and PRSS2 gene

The PRSS1 and PRSS2 genes encode cationic and anionic trypsinogen proteases, respectively, which are secreted by the pancreas and cleaved into their active form in the small intestine (Wolthers *et al.*, 2019). Changes in these genes are known to be correlated with hereditary pancreatitis. Two variants related to PRSS1/PRSS2 locus were found (Wolthers *et al.*, 2019). The first one is rs10273639, which involves an intronic variation of the exchange of a thymine for a cytosine. The second one is rs13228878, which, despite being located in the TRB gene, is associated with the PRSS1/PRSS2 locus (Wolthers *et al.*, 2019; Nielsen *et al.*, 2022). It consists of an intronic variation involving the exchange of a guanine for an adenine. The wild-type alleles, thymine and guanine, are associated with a reduced risk of AAP, while the variants have been associated with an increased expression of the PRSS1 gene, which is linked to alcoholic pancreatitis in adults (Wolthers *et al.*, 2019; Nielsen *et al.*, 2022). One of the possible effects of these variants is the cleavage and premature activation of proteases, which can lead to pancreatitis (NIH, 2022; Wolthers *et al.*, 2019; Nielsen *et al.*, 2022).

CLDN2 and MORC4 gene

The CLDN2 gene encodes the claudin-2 protein, which is found bound to the membrane in acinar, ductal, and islet cells in normal human pancreatic tissue. However, it exhibits aberrant expression in pre-malignant pancreatic cystic lesions (Wolthers *et al.*,

2019). The CLDN2 promoter has an NF- κ B binding site, and gene variants may play a role in activating this factor. On the other hand, MORC4 encodes a protein with an ATPase domain that suggests a functional requirement for ATP hydrolysis. It is widely expressed in normal tissues, including the pancreas (Wolthers *et al.*, 2019).

Both genes have variants associated with AAP. rs4409525 (CLDN2) involves the exchange of a guanine for a cytosine, and rs12688220 (MORC4) involves the exchange of cytosine for thymine (Wolthers *et al.*, 2019). These variants were described as being associated with AAP by Wolthers *et al.*, 2019, alcoholic and non-alcoholic chronic pancreatitis by Derikx *et al.*, 2015, and disease susceptibility in patients with chronic pancreatitis by Giri *et al.*, 2016. Another variant associated with CLDN2 and AAP is rs12853674, which involves the exchange of cytosine for thymine. This variant was described by Wolthers *et al.* (2019) and Nielsen *et al.* (2022).

New genes reported

Finally, there is a set of six variants also recently reported in the study by Nielsen *et al.*, 2022. They used the findings of the Wolthers *et al.*, 2019 study that are associated with AAP. Though not finding other studies in the literature that investigated these variants, the results were significant. The author of the study sought to analyze the possibility of predicting AAP through Machine Learning models based on these variants and on some others already described above, such as PRSS1/PRSS2.

The CTSC gene encodes the chymotrypsin C enzyme, which helps regulate the activation and degradation of trypsinogen, while SPINK1 encodes a trypsin inhibitor secreted by pancreatic acinar cells in the pancreatic juice (Mehandziska *et al.*, 2020). Both genes have been the subject of several works, such as Mehandziska *et al.*, 2020, who evaluated the genes as risk factors for the development of pancreatitis. They have variants with significant associations with

AAP, with rs10436957 (CTRC) as an intronic variant involving the exchange of guanine for adenine and rs17107315 (SPINK1) as the variant with a missense mutation involving the exchange of a thymine for a cytosine (Mehandziska *et al.*, 2020).

The second pair of genes are CASR and CFTR. CASR encodes a receptor coupled to the G protein on the plasma membrane responsible for detecting changes in the concentration of circulating calcium, while CFTR encodes a protein with a function similar to a chloride channel. It also controls the secretion and absorption of ions and water in epithelial tissues (Nielsen *et al.*, 2022). These two genes have variants that are part of the selected group among the 30 variants evaluated in the study by Nielsen *et al.*, 2022. They presented greater significance in the candidate genes for the occurrence of pancreatitis. Specifically, rs16832787 (CASR) and rs56296320 (CFTR) are intronic variants characterized by the exchange of guanine for adenine and thymine for cytosine, respectively (Nielsen *et al.*, 2022).

In addition, there is another pair of genes that, along with other variants, showed significance in several Machine Learning models. The first one is the EPHB2 gene, which encodes a transmembrane receptor capable of carrying out bidirectional signaling through binding to ephrin ligands in neighboring cells. This signaling is involved in developmental processes such as cell growth and cancers (Wolthers *et al.*, 2019; Nielsen *et al.*, 2022).

The second one is GALNTL6, which encodes a protein that catalyzes the initial reaction in the biosynthesis of oligosaccharides linked to protein O (Wolthers *et al.*, 2019; Nielsen *et al.*, 2022).

The variants of these genes are rs4655107 (EPHB2), an intronic variant involving the exchange of guanine for adenine, and rs1505495 (GALNTL6), a missense variant involving the exchange of cytosine for adenine (Wolthers *et al.*, 2019; Nielsen *et al.*, 2022).

A summary of the characteristics of the mentioned variants is provided in Table III.

TABLE III - Characteristics of Gene variants

Gene	Function	RS	Alteration	Consequence	Odds/Hazard ratio	Reference
<i>CPA2</i>	Carboxypeptidase	rs199695765	C>T	Stop Codon	HR: 587	Liu <i>et al.</i> , 2016
<i>MYBBP1A</i>	Nucleolar transcriptional regulator	rs3809849	G>C	Missense Variant	OR: 2.4%	Abaji <i>et al.</i> , 2019
<i>RGS6</i>	Regulator of GTPase activity	rs17179470	G>T	Intron Variant	OR: 7.3	Wolthers <i>et al.</i> , 2017
<i>ULK2</i>	Protein serine/threonine kinase	rs281366	C>T	Non-coding exon variant	OR: 6.7	Wolthers <i>et al.</i> , 2017
<i>LINC01429/NEATC2</i>	lncRNA/Transcription factors	rs62228256	C>T	Intron Variant	OR: 3.75	Wolthers <i>et al.</i> , 2019
<i>PRSS1/PRSS2</i>	Proteases	rs10273639 rs13228878	T>C G>A	Intron Variants	OR: 0.62 OR: 0.76	Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022
<i>CLDN2</i>	Regulator of tissue-specific physiologic properties	rs4409525 rs12853674	G>C C>T	Upstream Variants	OR: 1.41	Derikx <i>et al.</i> , 2015; Giri <i>et al.</i> , 2016; Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022

<i>MORC4</i>	Possible ATP hydrolyzer	rs12688220	C>T	Upstream Variant	OR: 2.26	Wolthers <i>et al.</i> , 2017; Derikx <i>et al.</i> , 2015; Giri <i>et al.</i> , 2016; Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022
<i>CTRC</i>	Regulator of trypsinogen activation and degradation	rs10436957	G>A	Intron Variant	OR: 0.66	Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022
<i>SPINK1</i>	Trypsin inhibitor	rs17107315	T>C	Missense Variant	OR: 2.87	Wolthers <i>et al.</i> , 2017
<i>CASR</i>	Responsible for detecting changes in circulating calcium concentration	rs16832787	G>A	Intron Variant	OR: 0.78	Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022
<i>CFTR</i>	Function as a chloride channel	rs56296320	T>C	Intron Variant	OR: 0.34	Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022
<i>EPHB2</i>	Transmembrane receptor	rs4655107	G>A	Intron Variant	OR: 0.55	Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022
<i>GALNTL6</i>	Initial reaction catalyst in oligosaccharide biosynthesis	rs1505495	C>A	Missense Variant	OR: 0.49	Wolthers <i>et al.</i> , 2019; Nielsen <i>et al.</i> , 2022

CONCLUSION

Acute pancreatitis is one of the adverse events more frequently associated with the use of Peg-ASN, and its potential complications can be severe, possibly leading to contraindications for drug usage and an increased rate of treatment failure. While the exact pathophysiology of pancreatitis in this context remains unclear, it is evident that specific genetic polymorphisms may increase the risk of developing Acute Asparaginase Pancreatitis.

The evaluation of genetic markers linked to metabolic pathways or drug action emerges as a crucial tool. It allows healthcare professionals to identify patients at increased risk of AAP, enabling necessary adjustments in their therapy. This proactive approach may not only decrease the incidence of complications but also reduce the rate of therapeutic failure, ultimately increasing the likelihood of a positive response to treatment.

From a clinical perspective, these findings hold

substantial promise. The ability to predict and preempt the occurrence of AAP through genetic screening can lead to personalized treatment strategies. Clinicians can tailor the asparaginase dosage and closely monitor high-risk patients, thus enhancing patient safety and treatment outcomes. Additionally, reducing the incidence of AAP-related complications may result in more successful and less disruptive treatment courses for pediatric patients battling leukemia. In conclusion, the exploration of genetic markers and their application in clinical practice holds promise for enhancing the safety and efficacy of Peg-ASN treatment, thereby advancing our ability to manage and mitigate the risks associated with acute pancreatitis in this context while improving the overall clinical experience for young patients.

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