REVIEW

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A narrative review on the role of genetics in children with acute recurrent pancreatitis and chronic pancreatitis

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ABSTRACT

The incidence of pancreatitis in children has increased over the past two decades. With advances in molecular biological techniques and clinical research, genetic variations have emerged as a pivotal etiological factor in pediatric pancreatitis. This review aims to summarize recent clinical research advancements in understanding pediatric pancreatitis caused by various gene mutations. As of the year 2020, researchers had identified 12 genes implicated in the pathogenesis of pancreatitis. These genes primarily contributed to the development of pancreatitis through three mechanisms. Pancreatitis resulting from these gene mutations exhibits several distinct characteristics, including early onset, a heightened risk of developing pancreatic duct stones, rapid disease progression, and a significantly increased risk of pancreatic endocrine and exocrine dysfunction, as well as pancreatic cancer in the future. Genetic sequencing is recommended for children with pancreatitis based on six indications. The sequencing not only assists in the clinical diagnosis but also enhances our understanding of the pathophysiology of pancreatitis.

KEYWORDS

Pancreatitis, Pediatric, Gene, Sequencing

INTRODUCTION

Pancreatitis is categorized as acute pancreatitis (AP), acute recurrent pancreatitis (ARP), and chronic pancreatitis (CP). Over the past two decades, studies have observed an overall increase in the incidence of pediatric pancreatitis, with the incidence of AP in children approaching 1/10 000,[1,2] and the incidence of CP estimated to be 0.5/100 000–2/100 000 per year.[3,4] Children with ARP or CP experience multiple acute episodes of pancreatitis, hospitalization, repeated endoscopy, and even surgical procedures during their lifetime, which not only costs substantial medical expenses but also seriously affects their quality of life. The research from the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) found that families with ARP or CP children had a severe burden of disease, costing an estimated average of $38 755 per person per year.[5] For most children, ARP

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or CP was not developed after one episode of AP.[1] The INSPPIRE registry study also found that AP in older children due to simple obesity or overweight was unlikely to progress to CP.[6] However, 15%–35% of children would develop ARP after the first idiopathic AP attack, which was a high-risk factor for further development of CP.[1,2,7] This suggests that other intrinsic risks are involved in developing ARP and CP in children. The first mutation in the *PRSS1* gene was identified as a cause of hereditary pancreatitis (HP) back in 1996.[8] Since then, an increasing number of genes have been recognized as potential contributors to pancreatitis. Previous studies have also suggested that these gene mutations were closely related to the clinical manifestations and prognosis in pediatric patients with ARP or CP. Therefore, genetic sequencing of the relevant genes is helpful in clarifying the etiological diagnosis, monitoring disease progression, and evaluating prognosis in children with ARP and CP. However, it is important to note that pediatricians often lack comprehensive knowledge about pancreatitis-related genes, as well as a clear understanding of the indications and significance of genetic testing in pediatric pancreatitis patients.

In this review, we summarized the role of relevant genetic variants in the pathogenesis of ARP and CP in children, the associated hotspot mutations, and the relationship between genotypes and phenotypes. In particular, we described the genetic aspects of Chinese children with ARP and CP in detail. The indications for genetic testing and the impact of test results on clinical prognosis and genetic counseling were also discussed.

METHODS

Literature published in English and Chinese was retrieved from Medline, Web of Science, China National Knowledge Infrastructure, and Wanfang Data from January 2000 to December 2022. “Genetics”, “acute recurrent pancreatitis”, and “chronic pancreatitis” were used as search terms. “From birth to 18 years”, “human species” and “original article” were added as filters. Two authors reviewed all the abstracts and identified articles associated with research on genotypes and phenotypes in pediatric pancreatitis. These selected articles were subjected to a thorough review by all authors involved in the study.

GENETIC FACTORS IN THE ETIOLOGY OF PEDIATRIC PANCREATITIS

Various factors have been recognized as etiologies of pediatric pancreatitis, including anatomical abnormalities and obstruction, environmental exposures, systemic diseases, autoimmune factors, heredity predisposition, and idiopathic factors. Idiopathic pancreatitis was previously considered the leading cause of pancreatitis in children, accounting for about 25% of all cases of childhood pancreatitis[9] and an even much higher proportion in pediatric CP, approximately 30%–60%.[10,11] In China, idiopathic CP (ICP) accounted for 65%–73% of CP in children.[12,13] However, advances in high-throughput sequencing technology have greatly improved the ability to detect genetic variants, which have become the most important risk factors for pancreatitis in children. Previous research has indicated that genetic factors contributed to about 50% and 75% of pediatric ARP and CP, respectively.[14] About 20%–50% of children with idiopathic pancreatitis were associated with gene mutations.[15,16] Our group conducted a study in China to sequence ten genes in 69 children with ARP or CP and found that 65.2% of children had relevant gene variations.[17] Even in children previously diagnosed with idiopathic pancreatitis, gene variations could be as high as 71.2%.[17] Another study from China also showed that the prevalence of pancreatitis-related gene variants in children with ICP was more than 50%, significantly higher than that in adult patients with ICP.[18] These results suggested that genetic variation has become the leading cause of ARP and CP in children. Therefore, molecular genetic detection may play an increasingly important role in the etiological investigation of pediatric ARP and CP.

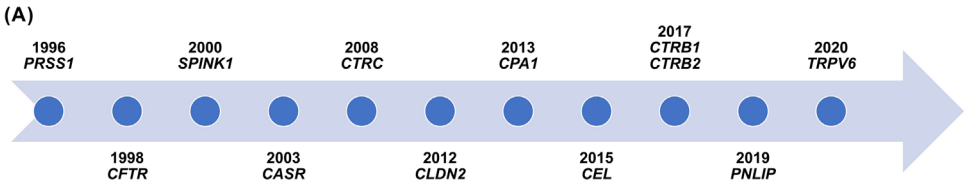
GENES ASSOCIATED WITH PEDIATRIC PANCREATITIS

Since Whitcomb et al.[8] first discovered in 1996 that mutation in the *PRSS1* gene could lead to HP, a total of 12 genes have been identified as associated with the pathogenesis of pancreatitis by the year 2020 (Figure 1A). In addition to *PRSS1*, the other genes are *CFTR* encoding cystic fibrosis (CF) transmembrane conductance regulator, *SPINK1* encoding serine protease inhibitor Kazal type 1, *CASR* encoding calcium-sensing receptor, *CTRC* encoding chymotrypsin C, *CLDN2* encoding claudin-2, *CPA1* encoding carboxypeptidase A1, *CEL* encoding carboxyl ester lipase, *CTRB1* and *CTRB2* encoding chymotrypsinogen B1 and B2, *PNLIP* encoding pancreatic lipase, and *TRPV6* encoding transient receptor potential cation channel subfamily V member 6. In several studies, *PRSS1*, *SPINK1*, *CFTR*, *CTRC*, and *CPA1* were closely associated with pediatric pancreatitis.[16,19,20] Among Chinese children, the most relevant genes were *PRSS1*, *SPINK1*, *CFTR*, and *CASR*, whereas *CTRC* and *CPA1* were not commonly identified as disease-causing genes[17,18,21]

GENETIC AND MOLECULAR MECHANISM OF PANCREATITIS

The above genes induce pancreatitis mainly through three mechanisms (Figure 1B):

I. Trypsin-dependent pathway: Premature activation of trypsinogen or failure to degrade it, which leads to



(B)

Pancreatitis-related genes and molecular mechanism
I. Trypsin-dependent pathway
PRSS1, SPINK1, CTRC, CTRB1, CTRB2
II. Protein misfolding
PRSS1, CPA1, PNLIP, CEL
III. Ductal abnormalities
CFTR, CLDN2, CASR, and TRPV6

FIGURE 1 Pathogenic genes associated with pancreatitis. (A) Chronological order of discovery of related genes. (B) Possible mechanisms by which different genes contribute to pancreatitis.

excessive pancreatic trypsin activation, will induce pancreatitis attack. *PRSS1*, *SPINK1*, *CTRC*, *CTRB1*, and *CTRB2* are involved in this mechanism.[22,23]

II. Protein misfolding: Mutant protein is misfolded due to genetic variation, which may cause endoplasmic reticulum stress and induce pancreatic acinar death. *PRSS1*, *CPA1*, *PNLIP*, and *CEL* are the central genes involved in this mechanism.[22–25]

III. Ductal abnormalities: Decreased water secretion from pancreatic ductal cells and associated electrolyte abnormalities (e.g., reduced sodium, chloride, bicarbonate, and increased calcium in the pancreatic fluid) cause calcification and protein stones, thus leading to pancreatitis. The critical genes involved are *CFTR*, *CLDN2*, *CASR*, and *TRPV6*.[22,23,26]

INHERITANCE OF DIFFERENT GENES IN PANCREATITIS

Although the above 12 genes are closely related to the pathogenesis of pancreatitis, only *PRSS1* and *SPINK1* can cause monogenic pancreatitis in the Online Mendelian Inheritance in Man (OMIM) database. Pathogenic variants in *PRSS1* can lead to both HP (MIM: 167800) and tropical calcifying pancreatitis (MIM: 608819). HP is an autosomal dominant (AD) disease, while tropical calcifying pancreatitis is an autosomal recessive (AR) disease. Although variants in *CFTR* and *CTRC* can also cause HP with AD inheritance, penetrance is very low (1%–4%) in heterozygotes and often in combination with other gene variants, especially with a mutation in *SPINK1*.[22,23] Most of the other genes act as susceptibility genes, involving gene–gene or gene–other risk factor interactions. Variations in these genes also significantly elevate the risk of ARP and CP in children. From this perspective, the development of most pediatric pancreatitis appears to be a consequence of a "second hit" with an oligogenic background.

GENETIC VARIANTS ASSOCIATED WITH PANCREATITIS IN CHILDREN

PRSS1

Gain of function mutations in *PRSS1* can cause hereditary CP. The penetrance of these mutations was more than 80%. In Caucasians, the top three hot spot variants were p.R122H (65%), p.N29I (25%), and p.A16V (4%).[22,27] However, p.G208A, rather than p.A16V, was more common in East Asian populations.[17] In Chinese pediatric pancreatitis cohort studies, the hotspot mutations in *PRSS1* were p.R122H, p.N29I, and p.G208A.[17,21] p.R122H increased the stability of the mutated trypsin, resulting in a high level of trypsin in the pancreas. The p.N29I mutation slowed down the degradation of the mutated trypsinogen, promoting its autonomous activation. p.A16V also enhanced CTRC-dependent autonomic activation of the mutated trypsinogen, while p.G208A caused misfolding of trypsinogen, resulting in endoplasmic reticulum stress.[22]

SPINK1

The serine protease inhibitor encoded by *SPINK1* is one of the critical proteins to prevent the premature autonomic activation of trypsinogen to protect the pancreas from self-digestion. Thus, the loss of function variants of *SPINK1* can cause ARP and CP. However, mutations of *SPINK1* had a significantly lower penetrance than those of *PRSS1*. The hot spots were p.N34S and c.194+2T>C. The former was a common mutation in Caucasians with pancreatitis, which could reach up to 21% in ICP, but only 5.7% of East Asian people with pancreatitis had the p.N34S mutation. The more common mutation in East

Asia was c.194+2T>C.[22,28] In a few cohort studies of Chinese children and adolescents with CP and ARP, only one case of p.N34S mutation was detected after using the target gene sequencing panel. Nevertheless, c.194+2T>C variation could be 23.2%–57.3%.[17,18,21] The exact mechanism by which the p.N34S mutation causes pancreatitis remains unclear. The splice site mutation c.194+2T>C can cause exon3 skipping, resulting in an unstable truncated protein with reduced expression, thus unable to effectively inhibit trypsinogen activation. Heterozygous mice that harbored this mutation also developed CP.[22,29,30] Although the frequency of these variants was much lower in individuals without pancreatitis compared to those with pancreatitis, they were still detected in the general population without pancreatitis.[22] In the mBiobank database (www.mbiobank.com) established by the China Metabolic Analytics Project (ChinaMAP), the proportion of people carrying p.N34S and c.194+2T>C variants was 0.23% and 0.54%, respectively.[31] This was consistent with the inheritance pattern of ARP and CP caused by *SPINK1* variation. When a patient has homozygous or compound heterozygous *SPINK1* mutations, it typically leads to AR-inherited pancreatitis. When a patient is heterozygous for these mutations, the role of p.N34S or c.194 +2T>C becomes more important as a risk factor with incomplete penetrance rather than as a causative pathologic mutation. Children with pancreatitis who have *SPINK1* variants may also have mutations in *CFTR*, *TRPV6*, *CTRC*, or other risk factors like anatomical abnormality.[17,22,26]

CFTR

CFTR can be defective in pancreatitis with or without CF. This gene has many pathologic variants, with over 2000 different mutations identified. These different variants can lead to various degrees of deterioration in protein function, resulting in a range of clinical manifestations.[32] The mutations in *CFTR* were categorized into six classes according to the degree of CFTR protein production and function. Grade I–III variants with severe functional impairment result in CF, a kind of AR disorder.[23] Grade IV–VI variants with less severe malfunction result in CFTR-related diseases, including ARP, CP, and exocrine pancreatic insufficiency (EPI). About 85% of patients with CF carry two severe functional impairment variants in the *CFTR* gene, either as homozygotes or compound heterozygotes. Approximately 1%–4% of CF patients may experience repeated episodes of pancreatitis.[22] Increased risk of ARP and CP had been also observed in the patients who carry one or two *CFTR* variants but do not meet the clinical criteria for diagnosis of CF. ARP and CP were regarded as CFTR-related diseases.[33–36] Biallelic variants that result in less severe function impairment are associated with atypical CF, recurrent pancreatitis, or CP, with a 40-fold increased risk of pancreatitis, compared to individuals without these variations.[23,33,37] In addition, numerous *CFTR* variants are also high-risk factors for pancreatitis and even a single variant can increase the risk of CP. Individuals with a heterozygous disease-causing mutation had an elevated risk for CP, about 3 to 4 times higher than individuals with wild-type *CFTR*.[38,39] However, although a single milder pathogenic mutation in *CFTR* may be more common in ICP patients compared to the general population, most carriers of such mutations remained healthy.[40] In other studies, the prevalence of CP was only slightly increased in the parents of patients with CF. These results suggested that milder pathogenic *CFTR* mutations likely interact with additional risk factors, such as other gene variants, environmental exposures, and structural malformation, to advance the risk of CP. Previous research showed that the risk of pancreatitis would increase by 900 times in individuals carrying both *CFTR* and *SPINK1* variants.[41] A Chinese single-center study of ARP and CP in children found that 47% (8/17) of children with pancreatitis and *CFTR* mutation also had additional mutations in *SPINK1*, *PRSS1*, or *CTRC*.[17]

Other genes

Chymotrypsin C, encoded by the *CTRC*, is the second line of defense against premature trypsinogen activation. In studies on adult CP, the prevalence of *CTRC* variations in patients was higher than in health control (2.9% *vs.* 0.7%).[42] In the INSPPIRE report, the proportion was even higher in children with CP. The prevalence of *CTRC* mutations was as high as 14% in children younger than six years of age with early-onset pancreatitis.[15,42]

The *CASR* encodes a calcium-sensitive receptor, which regulates calcium homeostasis. Genetic variants in *CASR* can lead to hereditary hypercalcemia. On the one hand, activating trypsinogen requires the participation of calcium ions, so the precise regulation of calcium concentration in acini and duct depends on CASR will affect the activation of trypsinogen. On the other hand, CASR expressed in pancreatic duct cells can promote pancreatic juice secretion and reduce the calcium level in the duct, thus keeping the pancreatic duct from stone formation. Some studies have found that mutations in *CASR* were associated with the development of CP. The proportion of homozygous p.A986S mutation significantly increased in ICP patients.[43] The p.A986S mutation was also identified in Chinese children, constituting 7.2% (5/69) of pediatric patients with ARP and CP. However, the homozygote for this mutation was only found in one case, while the remaining four cases were associated with mutations in other related genes.[17] In addition, the *CASR* variant (p.R990G) also increased the risk of alcohol-induced pancreatitis.[44]

Variants of *CPA1* have been associated with the development of non-alcoholic CP, particularly in cases of

early-onset pancreatitis.[22] A rare variant of *CPA1*, p.S282P, was identified in two families with CP, and another variant, p.N256K, was shown to impair the protein function.[45] It has been reported that individuals carrying the *CPA1* variant have an 84-fold higher risk of developing pancreatitis before the age of 10 years compared to those without the *CPA1* variant.[19,22] However, *CPA1* mutations were rarely found to be associated with early-onset pancreatitis in Chinese children. There was a case report of a 4-year-old Chinese boy with recurrent pancreatitis due to a homozygous *CPA1* variant; however, this patient also had variants in both the *PRSS1* and *SPINK1* genes.[46] Therefore it was difficult to determine whether this mutation in *CPA1* was the definitive cause of HP in this family pedigree. In another large case-control study involving Han Chinese, sequencing was performed on 1112 ICP patients and 1580 health controls. Despite the identification of 18 rare variants in *CPA1*, the frequency of these rare functionally impaired variants did not differ significantly between the patients and controls.[47] Therefore, it is concluded that *CPA1* mutations are not an essential factor contributing to pancreatitis in the Chinese population.

Other genes, including *CLDN2*, *CEL*, *CTRB1*, *CTRB2*, *PNLIP*, and *TRPV6*, have been studied in some animal experiments, revealing that some variants of these genes exhibit corresponding functional changes and can lead to pancreatitis phenotype. However, the frequency of these variants in pancreatitis is quite low. Their significance is most pronounced in increasing the risk of early-onset pancreatitis in carriers when combined with variants from other genes or other factors contributing to pancreatitis.[24,26,48–52]

THE RELATIONSHIP BETWEEN GENE VARIATIONS AND THE PHENOTYPE OF PANCREATITIS IN CHILDREN

There are apparent differences in the age of onset, disease progression, and prognosis of pancreatitis associated with different gene variations. For pancreatitis caused by *PRSS1* and *SPINK1* variants, the features include young age of onset, rapid disease progression, and high risk of pancreatic cancer.

Early onset of pancreatitis

The prevalence of gene variation in ARP and CP in children was significantly higher than in adults,[17,18,21] which indicated that carriers of the associated gene variant were at substantially higher risk of developing early-onset pancreatitis. The median age of onset of pancreatitis was 10, 14.5, 20.1, and 41.2 years in the *PRSS1* p.R122H mutation group, the *PRSS1* non-mutation group, the *SPINK1* mutation group, and the *SPINK1* non-mutation group, respectively.[27,53]

Rapid progression of pancreatitis

For pediatric pancreatitis onset before age 6 years, the median time from the first AP attack progressing to CP was 2.5 years in patients with *PRSS1* mutation and 3.79 years in patients without *PRSS1* mutation.[2] The median age of onset of EPI was 29 years, and the median age of diabetes was 38 years in patients with HP in a French study.[54] Results from the European HP Registry showed that the mean cumulative prevalence of EPI and diabetes at 50 years of age in patients with pancreatitis due to *PRSS1* mutation was 37.2% and 47.6%, respectively.[27] The report from a multicenter European cohort study of patients with *SPINK1*-related pancreatitis showed that the median age of EPI in patients with *SPINK1* mutation was younger than that in patients with ICP (49.5 years *vs.* 65.2 years); the cumulative prevalence of EPI in patients with *SPINK1* mutation was 5.3% and 52.4% at the age of 20 and 50 years, respectively; and the cumulative prevalence of diabetes due to *SPINK1*-related pancreatitis was 7.8% and 43.4% at the age of 30 and 50 years, respectively.[53] In a study from Japan, the cumulative prevalence of EPI and diabetes in patients with genetic variants (*PRSS1* or *SPINK1*) increased from 16.1% and 5.5% at age 20 to 45.3% and 28.2% at age 40, respectively.[55] The results of a Chinese study suggested that the clinical phenotypes were associated with genotypes in pediatric CP. In comparison to children without mutations, those with *CFTR* mutations had elevated serum amylase levels. Additionally, children with *SPNIK1* mutations had a significantly higher risk of developing pancreatic duct stones, with an odds ratio of 11.07.[17] The prevalence of pancreatic duct stones in children with multiple mutations in different genes was 83.3%, higher than that in children without or with only a single gene mutation.[17]

Increased risk of pancreatic cancer

Chronic inflammation in the pancreas can lead to hyperplasia and metaplasia of pancreatic ductal epithelial cells, increasing the risk of pancreatic cancer, particularly in patients with *PRSS1* and *SPINK1* mutations. The risk of pancreatic cancer was 53–78 times higher than that of individuals without these conditions, and the cumulative prevalence of pancreatic cancer reached 9.8%–18.7% at the age of 60.[53,55–57]

VALUE AND INDICATION OF GENE DETECTION IN CHILDREN WITH PANCREATITIS

The clinical value of genetic testing

Currently, the presence of relevant genetic variation in children with pancreatitis is not directly linked to their management. Usually, children with pancreatitis due to genetic abnormalities are managed similarly to patients with ARP

and CP of other etiologies.[22] Therapeutic endoscopic retrograde cholangiopancreatography was more frequently applied in patients with obstructive factors or pancreatic anatomical anomalies, regardless of the presence of genetic variants.[2,58] However, this is an evolving field. Two observational studies involving individuals with CF and ARP have demonstrated a reduction in AP attacks when CFTR modulator therapy is administered.[59,60] Ivacaftor is a CFTR potentiator that improves the function of the CFTR by increasing the open probability of the channel in individuals with specific *CFTR* mutations, such as p.G551D.[61] However, some case studies showed CFTR modulators may increase pancreatic acinar reserve. This may raise the risk of pancreatitis in CF patients with ductal obstruction.[62,63] These preliminary studies highlight the benefit of target gene therapy and bring hope for the management of patients with ARP who carry specific *CFTR* mutations.

For children with unexplained causes of ARP and CP, genetic testing can further clarify the underlying factors contributing to recurrent pancreatitis. This information gives physicians valuable insights that facilitate the early identification and treatment of pancreatitis-related complications during follow-up. In addition, an accurate etiological diagnosis also encourages children and their families to adhere to long-term treatment and follow-up, which may improve prognosis. Nonetheless, even in patients with HP, due to different penetrance and inheritance patterns, it is necessary to be cautious when interpreting genetic test results, especially non-*PRSS1* variants and heterozygous variants of *SPINK1* and *CFTR*. Many variants only increase the risk of disease rather than serving as the sole cause of illness. This information must be informed to the child and their parents before genetic testing. The physician who is familiar with HP should interpret the results after obtaining the sequencing data and provide accurate genetic counseling to ensure that the child and their family can correctly understand the test results.

Indications for gene sequencing

The Guidelines for Genetic Testing of Hereditary Pancreatitis outline six indications for gene sequencing.[64] If there is at least one indication, gene sequencing is recommended. The indications include the following:

I. Family history of idiopathic ARP, CP, or child-onset pancreatitis
II. Relatives with known mutations associated with HP
III. Unexpected pancreatitis in a child
IV. ICP occurring in patients younger than 25 years old
V. ARP of uncertain etiology
VI. Patients who fulfill the criteria for participation in approved research projects

According to these criteria, genetic testing is recommended for all children with idiopathic pancreatitis. Before testing, it is important to ensure that the child's guardian fully understands the significance of gene sequencing and provides informed consent.

Only sequencing of the *PRSS1* gene has been recommended in the INSPPIRE consensus.[65] However, with the progress of high-throughput next-generation sequencing technology, the sequencing cost has been significantly reduced, and the efficiency has been improved considerably. This allows for the simultaneous sequencing of all pancreatitis-related genes. It is suggested that pancreatitis-related genes can be sequenced by using a target gene sequencing panel that includes all 12 of the aforementioned genes or at least three essential genes: *PRSS1*, *SPINK1*, and *CFTR*.

CONCLUSIONS

So far, a total of 12 genes have been identified as playing a role in the pathogenesis of ARP and CP in children, especially *PRSS1*, *SPINK1*, and *CFTR*. Pancreatitis resulting from mutations in these genes has the characteristics of early onset, high risk of developing pancreatic duct stones, rapid disease progression, and significantly increased risk of pancreatic endocrine and exocrine dysfunction, as well as pancreatic cancer in the future. Genetic testing for children with specific indications is valuable in deepening our understanding of the pathophysiology of pancreatitis. It is also beneficial for children and their families to correctly understand the disease and adhere to regular treatment and follow-up protocols.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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