has been reported, highlighting the importance of carefully evaluating patients with AIP to rule out an underlying neoplasm [7, 90, 91].

IDCP or AIP with GEL

In parallel with the new classification of AIP in Japan based on a pathological background of LPSP [1, 4, 5, 7, 50, 92-95], many reports from Western countries have described a pancreatitis that may have been caused by autoimmunity [35, 96-98]. At the American Pancreatic Association meetings in 2002, descriptions of AIP by American, Japanese, and Italian researchers were discussed [83]. As described above, in the section on Pathological findings, the Italian and Japanese descriptions of AIP were quite different [19, 83]. Furthermore, researchers at the Mayo Clinic in the USA presented pathological findings of IDCP as another type of AIP [17, 83], with a European group later presenting similar pathological findings as AIP with GEL [18]. The clinical features of AIP described by the Italian group may partly reflect the pathological background of IDCP or AIP with GEL [16, 19, 83], which may explain the distinct differences in AIP observed in Italy and Japan. The Japanese, Korean, HISORt, and Asian diagnostic criteria defined AIP on a pathological background of LPSP [9, 16, 79, 99, 100], whereas the European criteria defined AIP as including two types of pathologies, LPSP and IDCP/AIP with GEL [16].

IDCP is characterized by ductal epithelial granulocytic infiltration, which frequently results in the destruction of duct epithelium. Due to inflammatory involvement, the duct lumens appear tortuous and irregular and are sometimes obliterated. These characteristic ductal lesions are also called granulocyte epithelial lesions (GEL) [18]. These findings are not present in LPSP. Similarly, typical findings of LPSP, including obliterative phlebitis and infiltration of numerous IgG4 bearing plasma cells, are uncommon in IDCP. Thus, it has been proposed that the IDCP/AIP with GEL pathological subtype be called type 2 AIP, and the LPSP subtype be called type 1 AIP [16, 101]. The clinical features of type 2 AIP are unclear, but include the following: on average, patients are a decade or more younger than patients with type 1 AIP, there is no gender bias, no association with systemic involvement, no elevation of serum IgG4, no or minimal tissue infiltration of IgG4 bearing plasma cells, and 30% of patients show an association with inflammatory bowel disease [16].

Ordinary Chronic Pancreatitis

In general, it is not difficult to differentiate between AIP and ordinary chronic pancreatitis, including alcoholic chronic pancreatitis. The latter condition is characterized by irregular dilatation of the MPD with severe abdominal pain, impaired exocrine and endocrine functions, and pancreatic stone formation over the long-term. In contrast, AIP is characterized by irregular narrowing of the MPD with mild or no pain, mild or moderate exocrine or endocrine dysfunctions that is sometimes ameliorated after corticosteroid therapy, and no pancreatic stone formation [1, 4-6]. Other useful findings indicative of AIP include high serum IgG4 concentrations [2], CT or MRI detection of a capsule-like, low density rim in pancreatic lesions [43], and infiltration into pancreatic tissue of numerous IgG4 bearing plasma cells [3]. However, pancreatic stone formation is sometimes observed in the chronic stages of AIP [102], indicating that AIP may either transform into or represent an early stage of ordinary chronic pancreatitis [23, 102].

TREATMENT

The first report on successful corticosteroid therapy of a patient with suspected AIP was published in 1978; this patient, who had Sjoegren's syndrome, showed disappearance of an abdominal mass after corticosteroid treatment [103]. Thereafter, many reports have shown that a favorable response to corticosteroids was a characteristic feature of AIP [1, 4, 5]. An extensive survey of AIP treatments was recently conducted by the Research Committee of Intractable Pancreatic Diseases in Japan. Their report, called "Consensus for a Treatment of Autoimmune Pancreatitis", was presented as shown in Table **1** [104]. Patients treated with corticosteroids showed good results, with a high complete remission rate and a low recurrence rate compared with patients who received non-corticosteroid therapy, indicating that steroid treatment should be a standard therapy for patients with AIP [104, 105]. Most patients with obstructive jaundice, diffuse enlargement of the pancreas, associated extra-pancreatic involvement, and abdominal pain are good candidates for steroid therapy [105], though spontaneous remission has been observed in patients with low activity. However, there is no established method for predicting spontaneous remission.

Patients receiving corticosteroid therapy may also require biliary drainage to control obstructive jaundice and control of blood glucose to improve impaired glucose tolerance. In general, patients are started on 30~40mg, or 0.6mg/kg, per day of prednisolone for 2~4 weeks with careful assessment of clinical findings, and laboratory and imaging results [86, 104, 105]. Drastic amelioration of the clinical features of AIP are usually observed within 2 weeks [71], with clinical remission usually observed within 4 weeks. Thereafter, the dosage is reduced by 5 mg/day every 2 weeks over 2-3 months to 2.5~7.5mg per day, which is maintained for 6 months to 3 years [86, 104, 105], because most recurrences are observed within 3 years of treatment [21, 86, 104, 105]. Maintenance therapy may be stopped after 6 months, however, for patients with low disease activity, including those with low serum IgG4 concentrations or no systemic lesions. In contrast, some patients with high activity may continue maintenance therapy for 3 years.

Although most patients show amelioration of endocrine function after corticosteroid treatment [27, 104], others show no change or even deterioration [26, 104-106]. Increased age is associated with increased rates of newly developed or exacerbated diabetes mellitus [26]. Exocrine function is generally ameliorated or shows no deterioration after corticosteroid therapy [29, 104, 106], indicating that dysfunctions of the exocrine and endocrine systems of the pancreas are, to some extent, reversible by steroid therapy. Pancreatic tissue obtained by needle biopsy after corticosteroid therapy showed marked histological improvements, including amelioration of fibrosis, reduced

Table 1. Consensus on the Treatment for Patients with AIP in Japan[a]

1. Administration of an oral steroid should be a standard therapy for AIP
2. Consider performing biliary drainage for patients with jaundice
3. Consider controlling blood glucose concentrations in patients with diabetes mellitus
4. For patients with jaundice or bile-duct stricture, or cases in which the clinical manifestations do not improve (e.g., abdominal pain), consider administration of an oral steroid. However, for patients that have not been diagnosed with AIP, steroid therapy should be used with extreme caution. In addition, when a course of steroid therapy does not have the desired result, perform a re-evaluation, taking into consideration pancreatic carcinoma
5. Start the oral administration of a steroid with an initial dose of 30–40 mg per day
6. Maintain the initial dose of steroid for 2–4 weeks, while carefully monitoring the patient's clinical manifestations, laboratory data, and imaging findings. Then, gradually reduce the amount of steroid to a maintenance dose over a period of 2–3 months
7. In principle, continue steroid maintenance treatment (2.5–5 mg per day) after remission
8. The length of time that maintenance treatment should be continued is not yet clear, but it can probably be stopped after a predetermined period (about 6–12 months), as long as an improvement in the clinical manifestations can be observed. In addition, the patient should be followed-up to monitor for recurrences
9. In order to evaluate the effectiveness of steroid therapy, in addition to follow-up observations for recurrence, use repeated biochemical examinations of blood findings, including serum γ-globulin, IgG, and IgG4, repeat imaging findings, and check for clinical manifestations, including jaundice and abdominal discomfort

[a]Reference [104].

infiltration of inflammatory lymphocytes, and a substantial increase in the number of pancreatic acinar cells [29, 107].

Other therapies have been attempted for patients with AIP, particularly those with highly active disease. Steroid pulse therapy has been shown effective in patients intractable to standard corticosteroid therapy and in patients with conditions that may need future surgical treatment and require a prompt steroid response [108]. Immunosuppressive therapy with azathioprine or 6-mercaptopurine has also been tested in patients with recurrent AIP [109-113], though azathioprine may induce acute pancreatitis [114]. Rituximab treatment of a patient with AIP and IgG4-associated cholangitis refractory to steroids and 6-mercaptopurine resulted in an improvement of biliary stricture and the removal of a biliary stent [115]. Although azathioprine or rituximab may be effective in patients with refractory or recurrent AIP, future improvements in corticosteroid treatment regimens may provide an effective alternative.

PROGNOSIS

Because lymphoplasmacytic inflammation of the pancreatic parenchyma represents an acute stage of AIP, it likely does not persist for long periods of time. The features of chronic stage disease may therefore differ from those generally recognized [1, 4, 5, 50]. Long-term follow-up of patients with AIP showed that 41% experienced AIP recurrence and 18% showed pancreatic stone formation, findings previously considered uncommon in AIP [1]. Pancreatic stone formation was significantly more frequent in patients with than without AIP recurrence, suggesting an association between stone formation and recurrence and that some forms of AIP may transform into ordinary chronic pancreatitis after several recurrences [102]. Other reports have also shown a close association between pancreatic stone formation and atrophy of the parenchyma [116]. The exact mechanisms that underlie pancreatic stone formation in AIP are obscure, but pancreatic stones are regarded as resulting from incomplete obstruction of the main pancreatic duct system due to irregular narrowing and stasis of pancreatic juices. In addition, recurrent attacks may intensify an incomplete obstruction of the duct system and facilitate pancreatic juice stasis. In contrast, we found that 7% of patients with ordinary chronic pancreatitis had high serum IgG4 concentrations [23]. Because high serum IgG4 concentration is specifically found in AIP [2] and persists even after remission in over 60% of patients [117], ordinary chronic pancreatitis may include an advanced stage of AIP with high serum IgG4 concentrations. That is, some forms of AIP may constitute an early stage of ordinary chronic pancreatitis, such as alcoholic chronic pancreatitis [23]. In agreement with our results, a Korean study reported that 12% of patients with ordinary chronic pancreatitis had elevated serum IgG4 [118].

Various serum markers and genetic, including circulating immune complex (CIC) [119] and polymorphisms in the human leukocyte antigen (HLA) [120] and cytotoxic T lymphocyte antigen 4 (CTLA4) genes [121], have been reported to predict the recurrence of AIP. A Japanese report showed that patients with recurrent AIP frequently had high serum IgG concentrations, diffuse pancreatic swelling, and lower bile duct stenosis, with logistic regression analysis showing that diffuse pancreatic swelling was a predictor of recurrence [122]. Early detection of recurrences with these markers may facilitate prompt treatment and prevent disease progression.

AIP is generally found in elderly people with suppressed immunosurveillance systems who may therefore be susceptible to various malignant diseases. Many reports have found that various malignancies were accompanied by AIP [106, 116, 123-128]. The lymphoid hyperplasia in AIP or IgG4-related disease may provide a substrate for the emergence of lymphoma, and a close association between IgG4-related disease and non-Hodgkin lymphoma has been reported [123, 125-127]. Most patients showed evidence of extranodal involvement, including of the ocular adnexa, liver, adrenal glands, kidneys and lungs [125]. Although it is unclear whether these patients had lymphoma complicating IgG4-related disease or de novo IgG4+ MALT lymphoma, B-cell lymphoma can arise on a background of IgG4-related chronic inflammation, and IgG4-producing cells can be transformed to IgG4-producing marginal zone B-cell lymphoma [126, 127]. Pancreatic cancer has also been reported to be complicated with AIP, mainly by researchers in Japan [90, 91, 122, 129-131]. Some of these patients had

pancreatic cancer simultaneous with AIP, whereas others developed pancreatic cancer several years after the diagnosis of AIP. Many of these pancreatic cancers were located in the body and tail of the pancreas, suggesting that this may be a characteristic of pancreatic cancer associated with AIP (Tanaka S *et al.*, Suizo 2007; 22: 663-71 in Japanese). Pancreatic malignancies may be evoked by the combination of an immunosuppressed state with a chronic inflammatory process similar to ordinary chronic pancreatitis [132]. K-ras mutations have been reported in significant numbers of AIP tissues [133]. Because we had no age-matched controls, we could not conclude that AIP represents a significantly higher risk for malignant diseases. However, a careful follow-up with tumor markers is mandatory.

CHARACTERISTIC IMMUNOLOGICAL FEATURES

Efficacy of IgG4

IgG4 is a minor subclass of IgG, comprising only 4~7% of total IgG, which is elevated only under restricted conditions, including various forms of atopy [134], parasitic infestations [135], and pemphigus vulgaris and pemphigus foliaceus [136]. However, high serum concentrations of IgG4 were observed in 90% of patients with AIP [2] but rarely in other conditions, including pancreatic cancer, chronic pancreatitis, and other autoimmune diseases [2]. In differentiating between AIP and pancreatic cancer, IgG4 showed a sensitivity of 90%, a specificity of 98%, and an accuracy of 95% [2]. After corticosteroid therapy, serum IgG4 content and IgG4 to IgG ratio decreased significantly, suggesting that IgG4 levels reflect the activity of AIP [2]. Sequential serum IgG4 measurements in patients with multiple AIP recurrences demonstrated that IgG4 may be elevated several months before a clinical recurrence, suggesting that IgG4 may be a sensitive marker for predicting recurrence [23]. Accordingly, IgG4 is considered the most reliable serum marker for a diagnosis of AIP [2, 23]. At present, elevated IgG4 is included in various diagnostic criteria for AIP [9, 79, 82, 100]. Furthermore, infiltration of IgG4-bearing plasma cells, a characteristic finding in patients with AIP, has been recognized as a histological hallmark for diagnosing AIP and other IgG4-related diseases [3, 15].

The role of IgG4 in the pathogenesis of AIP remains unclear; it may be beneficial or harmful. In contrast to pemphigus, where IgG4 recognition of skin autoantigens (desmogleins) is at the origin of the disease process [136], there is little evidence showing that IgG4 autoantibodies play a direct role in the pathogenesis of AIP. IgG4 of patients with AIP has been reported to react with duct cells from a healthy pancreas [137]. Recent studies have shown that IgG4 has two outstanding characteristics: Fab-arm exchange [138] and rheumatoid factor-like activity [139], properties that may confer on IgG4 activities that defend against disease progression. For example, Fab arm exchange results in bi-specific antigen binding, which interferes with the formation of IgG4-associated immune complexes [138]. In addition, *via* Fc-Fc interactions, IgG4 binds to other IgG4 and to conformationally altered IgG1 [139, 140]; this rheumatoid factor-like activity may promote the formation of large circulating immune complexes that are easily eliminated from the circulation.

Other Autoantibodies

Several studies have showed that carbonic anhydrase II (CA II) and lactoferrin may be the candidate target antigens for pathogenic autoantibodies in AIP [141]. For example, neonatally thymectomized BALB/c mice immunized with CA II or lactoferrin showed evidence of discrete inflammatory changes in pancreatic tissue; moreover, transfer of whole, CD4+, or CD8+ spleen cells from these mice into nude mice caused the appearance of these inflammatory changes in the latter [142]. Furthermore, the *Helicobactor pylori* derived HLA DRB1 0405 molecule, with a peptide structure mimicking that of CA II, was found to be closely associated with AIP, suggesting that infection with *H. pylori* may trigger an autoimmune response leading to AIP [143, 144]. Other candidate target antigens include pancreatic secretory trypsin inhibitor (PSTI) [145], amylase alpha-2A [146], HSP 10 [147], and the plasminogen-binding protein (PBP) peptide of *Helicobacter pylori* [148]. However, it is unclear whether these autoantibodies belong to the IgG4 subclass and are involved in both systemic and pancreatic lesions.

HLA and Immunogenetic Findings

Common autoimmune diseases are multifactorial; thus, pathogenesis involves a complex interplay between multiple genetic and environmental factors. Several genes have been found to contribute to autoimmune diseases, including HLA complex genes [144, 149, 150], the Fc receptor-like 3 (FCRL3) gene [151], and the CTLA4 gene [121]. The proteins encoded by these genes may play key roles in antigen presentation, B cell immunity, and T cell recognition/activation.

We reported an association between HLA alleles and susceptibility to AIP in the Japanese population. Indeed, the frequency of the DRB1*0405-DQB1*0401 haplotype was significantly higher in patients with AIP than in controls, suggesting that the DRB1*0405 and/or DQB1*0401 alleles play a functional role in autoantigen presentation and, therefore, autoimmunity [150]. These findings also suggests the involvement of other non-HLA alleles that are in linkage disequilibrium with these polymorphic HLA genes [144]. Genes that confer susceptibility or resistance to a significant number of autoimmune diseases are considered to be located elsewhere in the major histocompatibility complex (MHC); i.e., within non-HLA genes. In our study of genes widely associated with the MHC, we mapped AIP susceptibility to two regions: the HLA-DRB1 to -DQB1 region in the centromeric part of the MHC and the telomeric MHC, near C3-2-11, between HLA-E and HLA-A in the class I region [149]. The neighboring C3-2-11 region also contains the 121 kb centromerically located ATP-binding cassette sub-family F (ABCF1) gene, which is regulated by TNF-α, a major cytokine in inflammatory and auto-immune reactions. Thus, ABCF1 may also be a susceptibility gene for AIP [149]. Although AIP responds well to corticosteroid therapy, relapse is not uncommon during maintenance therapy or after the cessation of corticosteroids. Although another study

found that DQβ1 mutations with substitutions in an aspartic acid at residue 57 were significantly associated with AIP relapses [120], this finding could not be confirmed [152].

Polymorphisms in Fc receptor-like genes (FCRLs) have been associated with various autoimmune diseases in Japanese populations [153]. These polymorphisms alter the binding affinity of nuclear factor κB and regulate FCRL3 expression. An analysis of genotype distribution frequencies of FCRL3-110 polymorphisms revealed a significant association between the -110A/A genotype and AIP [151]. In patients with AIP, serum IgG4 concentrations were significantly positively correlated with the number of susceptibility alleles [151].

One characteristic pathological feature of AIP is lymphoplasmacytic infiltration, including CD4+ and CD8+ T lymphocytes, into the pancreatic parenchyma and other involved organs. Thus, factors that regulate T-cell function may also influence the development of AIP. The CTLA4 (or CD152) gene product is an inhibitory receptor expressed on the cell surface of activated memory T cells and CD4+ CD25+ regulatory T cells that acts largely as a negative regulator of T-cell responses [154]. CTLA4 +49A/G single nucleotide polymorphisms (SNPs) have been associated with susceptibility to autoimmune diseases. We found that the +6230 G/G genotype was significantly higher in Japanese patients with than without AIP, and that the +49A/A and +6230A/A genotypes were associated with an enhanced risk of AIP relapse [121]. The CTLA-4 49A polymorphism and -318C/+49A/CT60G haplotype have also been associated with AIP in a Chinese population [155].

Toll-like receptor-4 (TLR-4) is an important mediator in both innate and adaptive immunity, and polymorphisms in the TLR4 gene have been linked to several autoimmune diseases. However, an analysis of allelic frequencies in patients with AIP revealed no statistical associations between TLR4 polymorphisms and either AIP susceptibility or relapse [156].

EXTRA-PANCREATIC LESIONS

A variety of extra-pancreatic involvements have been associated with AIP [10-12, 30]. Similar to pancreatic lesions, these extra-pancreatic lesions may exhibit IgG4-positive plasma cell infiltration [3] and show a favorable response to corticosteroid therapy [10-12], similarities suggesting a common background associated with IgG4. However, it is not certain that all of these reported extra-pancreatic lesions are closely associated with or share the same background as pancreatic lesions. Pathological studies have confirmed that pancreatic lesions are closely associated with lachrymal and salivary gland lesions, respiratory lesions, sclerosing cholangitis, renal lesions, retroperitoneal fibrosis, and prostate hypertrophy. Because an extra-pancreatic lesion can be erroneously diagnosed as an inherent disease of the corresponding organ, the identification of the AIP-related characteristics of each extra-pancreatic lesion may provide a means to distinguish the true underlying disease.

Hypophysitis

Hypophysitis has been reported to be associated with AIP [14, 157]. Patients with AIP have presented with compressive optic neuropathy, panhypopituitarism, pituitary hypothyroidism, adrenocortical insufficiency, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). MRI analysis revealed pituitary gland and pituitary stalk swelling that produced a high signal on T1-weighted images and early enhancement on dynamic studies; all of these findings disappeared after corticosteroid treatment [157].

Lachrymal and Salivary Gland Lesions

Symmetrical lachrymal and salivary gland lesions have been observed in 14~39% of patients with AIP, making it important to differentiate AIP from Sjögren's syndrome [31, 103, 158, 159]. Compared with Sjögren's syndrome, AIP was associated with milder exocrine dysfunction of lachrymal and salivary gland lesions, and patients with AIP were negative for anti SS-A/Ro and SS-B/La autoantibodies [158] and a preponderance of submandibular gland lesions [30].

Hypothyroidism

Hypothyroidism, indicated by high TSH (27%), low T4 (15%), and positive anti-thyroid peroxidase (TPO) autoantibody (37%), has been reported as a complication in patients with AIP [87]. Serum IgG4 concentrations were similar in hypothyroid and euthyroid patients, suggesting that the hypothyroid state or thyroiditis represents a burnout after thyroid injury. Patients with Hashimoto's thyroiditis could be classified based on immunostaining of IgG4 into patients with IgG4 thyroiditis (IgG4-related thyroiditis, rich in IgG4-positive plasma cells) and non-IgG4 thyroiditis (non-IgG4-related thyroiditis, poor in IgG4-positive plasma cells) [160]. Hypothyroidism associated with AIP may be included in IgG4 thyroiditis.

Respiratory Lesions

A variety of respiratory lesions are associated with AIP, including interstitial pneumonia [30, 32, 34, 161-163], inflammatory pseudotumor [30, 164], and hilar or mediastinal lymphadenopathy [30, 33]. Interstitial pneumonia has been observed in 8~13% of patients with AIP, presenting as dry cough, high serum KL-6 concentrations, and appearance on CT of a ground glass appearance in the middle and lower lung fields and honeycombing in the lower lung field [162]. Inflammatory pseudotumor, corresponding to plasma cell granuloma [164, 165], is frequently misdiagnosed as a lung tumor. CT, Gallium scintigraphy, and FDG-PET revealed hilar and mediastinal lymphadenopathy in 60~70% of patients with AIP [30, 33, 67]. AIP-related central airway stenosis and hilar lymphadenopathy should be differentiated from sarcoidosis [33, 163], and the absence of angiotensin-converting enzyme (ACE) may help differentiate between these conditions.

Gastric Ulcers

Gastric ulcers may be a complication of AIP. These ulcers typically have a linear presentation, with the long axis perpendicular to the incisura on the lesser curvature of the stomach, and they occur independently of NSAID medication or *Helicobacter pylori* infection [166, 167].

Numerous IgG4-bearing plasma cells infiltrate these gastric lesions [166].

Main Duodenal Papilla Lesions

Swelling of the main duodenal papilla is observed in 40~65% of patients with AIP, and these lesions respond to corticosteroid therapy [168, 169]. Similar to pancreatic lesions, significant numbers of IgG4-positive plasma cells have been detected in this lesion [169], suggesting that assays of these tissues may provide an alternative to pancreatic tissue biopsy.

Sclerosing Cholangitis

Sclerosing cholangitis has been observed in 60~70% of patients with AIP [7, 35, 36, 51, 52, 170-172] and should be differentiated from primary sclerosing cholangitis (PSC) and biliary malignancies [51, 52, 173, 174]. PSC is usually observed in young and middle-aged patients and may accompany inflammatory bowel disease [51]. Its characteristics on cholangiography include a band-like stricture, beaded or pruned tree appearance, and diverticulum-like outpouching [48, 51, 52]. In contrast, cholangiography of sclerosing cholangitis associated with AIP showed evidence of lower bile duct stenosis and relatively long strictures from the hilar to intrahepatic biliary systems with simple distal dilatation [48, 51, 52].

Hepatic Lesions

Hepatic lesions associated with AIP display a variety of histological changes, including portal inflammation, interface hepatitis, large bile-duct obstructive features, portal sclerosis, lobular hepatitis, and canalicular cholestasis; these are collectively designated IgG4 hepatopathy [175]. Some of these lesions mimic those observed in autoimmune hepatitis (AIH), with similar clinical presentation; thus, some patients with AIP that display these symptoms may be misdiagnosed with AIH [176].

Renal Lesions

Most renal lesions affect the uriniferous tubules, with few being glomerular. These patients present with tubulointerstitial nephritis indicative of hypocomplementemia, and deposits of immune complexes and C3 in tubular basement membranes [39, 76, 177-181]. Renal cortical lesions show decreased enhancement and appear as small peripheral cortical nodules, round or wedge-shaped lesions, or with diffuse patchy involvement [30, 182, 183].

Retroperitoneal Fibrosis

Retroperitoneal fibrosis, observed in about 10-20% of patients with AIP, may affect the urinary system [3, 184-188] or accompany periaortitis or aortic aneurysma [189]. Patients with renal lesions sometimes complain of lumbago or back pain due to hydronephrosis, which may result in renal atrophy and renal failure with elevated serum BUN and creatinine concentrations [3, 186, 187]. Aortic lesions consist of dense soft tissue masses along the abdominal aorta [30, 184, 187]. Thickening of the aortic wall or aneurysms are sometimes observed, giving rise to the concept of IgG4-related periaortitis [189].

Prostatitis

Prostatitis that responds well to corticosteroid therapy is another complication of AIP [63, 190, 191]. Patients with prostatitis complain of pollakiuria, dysuria, and nocturia, and display a symmetrical, non-tender, swollen prostate. Imaging has shown severe inflammatory lesions, mainly in the central and transition zones [191].

Thrombocytopenic Purpura

AIP-related thrombocytopenic purpura has been reported [157, 192, 193]. Patients complain of petechia, and blood tests show thrombocytopenia, positive platelet associated IgG (PA IgG), and hypocomplementemia. Platelet counts recover promptly after corticosteroid therapy.

DIAGNOSTIC CRITERIA

Diagnostic Criteria in Japan

AIP was first described in 1992 as an unusual type of chronic pancreatitis with diffuse irregular narrowing of the entire main pancreatic duct on ERCP [8]. The entity AIP was proposed in 1995 by the same researchers who proposed the concept of chronic pancreatitis caused by an autoimmune abnormality; AIP was characterized by 11 clinical features (Table **2**) [1]. Thereafter, many patients were diagnosed with AIP based on these clinical features, providing new information for the development of AIP diagnostic criteria in Japan and other countries. For example, imaging showing irregular narrowing of the MPD and pancreatic swelling were cardinal features of AIP, and these were adopted as diagnostic criteria in Japan. Histopathologically, however, AIP showed massive infiltration of lymphoplasmacytes with storiform fibrosis and obliterating phlebitis, findings consistent with lymphoplasmacytic sclerosing pancreatitis (LPSP), which was proposed in 1991 as being associated with AIP [7].

In 2002, the Japan Pancreas Society (JPS) became the first in the world to propose diagnostic criteria for AIP [83, 194]. The original criteria were updated in 2006 (Table **3**) [9]. The original criteria required that the irregular narrowing of the MPD cover more than one third of the length of the entire pancreas, a criterion intended to strictly differentiate between AIP and pancreatic cancer. Furthermore, the original criteria did not include elevated serum IgG4. Although many patients had been diagnosed with AIP based on these original criteria, the latter were criticized since; 1) many patients with AIP were excluded because the extent of MPD narrowing was less than one-third the length of the entire pancreas, and 2) elevated IgG4 was not included as a useful serum marker [2, 83, 195]. Therefore, the Research Committee of Intractable Pancreatic Diseases (RCIPD), provided by the Ministry of Health, Labor, and Welfare of Japan, and the JPS issued revised clinical diagnostic criteria for AIP in 2006 (Table **3**) [9]. These revised criteria deleted the extent of MPD involvement and introduced elevated serum IgG4 levels as a serological criterion.

Table 2. Characteristic Features of Autoimmune Pancreatitis[a]

1. Increased serum γ-globulin or IgG levels.
2. Presence of autoantibodies.
3. Diffuse enlargement of the pancreas.
4. Diffuse irregular narrowing of the main pancreatic duct on ERP.
5. Fibrotic change with lymphocyte infiltration observed with histopathology.
6. No symptoms or only mild symptoms, usually without acute attacks of pancreatitis.
7. Common bile duct in the pancreas is constricted with dilation of the upstream bile duct, and cholestatic liver dysfunction and hyperbilirubinemia.
8. No pancreatic calcification.
9. No pancreatic cysts.
10. Occasional association with other autoimmune diseases.
11. Effectiveness of steroid therapy.

[a]Reference [1].

Diagnostic Criteria of Other Countries and Asian Criteria

The concept of AIP has been widely recognized in Asian [196] and Western [83, 197, 198] countries. Several other diagnostic criteria for AIP have been proposed by researchers from Korea [79], Japan and Korea [100], the US [99], and Italy [19]. Most of the differences among these criteria are due to differences in the methods first used to detect the disease, consisting primarily of imaging findings in Japan [8, 43, 50] and pathological findings in Western countries [17, 18, 199]. In addition, there were differences in pathological backgrounds, with LPSP being predominant in Japan, Korea [7], and the US [99], while LPSP+IDCP/AIP with GEL was prevalent in European countries [17, 18]. Moreover, the recognition of extra-pancreatic involvement

Table 3. Japanese Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006[a]

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas detected in imaging studies, including abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI).
2. High serum γ-globulin, IgG, or IgG4, or the presence of autoantibodies, including antinuclear antibodies and rheumatoid factor.
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.
Diagnosis of autoimmune pancreatitis is established when criterion 1, together with criterion 2 and/or 3, are fulfilled. However, it is necessary to exclude malignant diseases, particularly pancreatic or biliary cancers.

[a]Reference [9].

Table 4. Korean Diagnostic Criteria for AIP[a]

Criterion I. Imaging (both required)
Imaging (US, CT, MRI) of pancreatic parenchyma
Diffusely/segmentally/focally enlarged gland, occasionally with a mass and/or hypoattenuated rim
Imaging (ERCP or MRCP) of pancreaticobiliary ducts
Diffuse/segmental/focal pancreatic ductal narrowing, often with stenosis of the bile duct
Criterion II. Serology (one required)
Elevated level of serum IgG or IgG4
Detection of autoantibodies
Criterion III. Histopathology of pancreatic/extrapancreatic lesions (one required)
Lymphoplasmacytic infiltration and fibrosis, often with obliterative phlebitis
Presence of abundant [10 cells/HPF] IgG4-positive plasma cells
Criterion IV. Response to steroids
Resolution/marked improvement of pancreatic/extrapancreatic lesions with steroid therapy
Diagnosis of AIP is made when criterion I and at least one other criterion are satisfied
Definite diagnosis (one required)
1. Criterion I together with any other criterion (II to IV)
Before establishing the preoperative diagnosis of AIP, a thorough work-up should be performed to exclude pancreatobiliary malignancies
When it is still uncertain whether pancreatic cancer is present, short-interval imaging (CT and ERCP/MRCP) at 2 weeks after the initiation of steroid therapy must be used to confirm whether there is resolution/marked improvement of the main pancreatic duct stricture
2. A full spectrum of changes in lymphoplasmacytic sclerosing pancreatitis and abundant IgG4-positive cell infiltrations identified in pancreatic resection specimens
Probable diagnosis
Unexplained pancreatic disease without pancreatic enlargement, but associated with other organ involvement or elevated serum IgG4 levels

[a]Reference [79].

changed the concept of AIP to a systemic disease [3, 7, 13, 15]; thus, extra-pancreatic lesions were considered characteristic findings of this disease and were incorporated into some diagnostic criteria [19, 99].

Korean criteria for AIP, modified from the Japanese criteria, were proposed in 2006 [79, 80] and modified by the Korean Society of Pancreatobiliary Diseases in 2007 [21, 80] (Table **4**). Although the Korean diagnostic criteria emphasize the use of imaging methods, the Korean criteria include response to steroid. This type of diagnostic test is prohibited in Japan due to the possibility for delays in diagnosis and treatment for patients later found to have pancreatic or biliary malignancies. Other items have also been incorporated into the Korean criteria, together with recent advances in AIP studies. These include 1) the use of magnetic resonance cholangiopancreatography (MRCP) as an alternative to ERCP, 2) omission of high serum γ-globulin concentration, 3) inclusion of abundant IgG4-positive plasma cells in pancreatic or extra-pancreatic lesions, and 4) inclusion of histopathologic evaluation of extra-pancreatic lesions and response to steroids.

Due to differences among these criteria, it became difficult after 2007 to compare data in studies from different countries and to elucidate the general characteristics of AIP. Thus, the RCIPD and the Korean Society of Pancreatobiliary Diseases held three Japan-Korea symposia on AIP to reach a consensus [100, 200, 201] and establish Asian criteria for the diagnosis of AIP (Table **5**). The major points in this consensus were: 1) MRCP could not replace ERCP in diagnosing AIP because the imaging resolution of MRCP is too low; 2) γ-globulin concentration is not necessary as a serological criterion because its sensitivity is lower than that of IgG and IgG4; 3) AIP should be diagnosed on the basis of pancreatic, not extra-pancreatic, lesions; 4) LPSP, when confirmed by surgical resection of specimens, can establish the diagnosis of AIP; 5) histological criteria based on pancreatic biopsy specimens can include findings of lymphoplasmacytic infiltration in fibrosis together with abundant IgG4-positive cell infiltration; and 6) response to steroid therapy may be diagnostic. The diagnosis of AIP should be based on satisfaction of criterion I and one of the other two criteria, or when histology shows the presence of lymphoplasmacytic sclerosing pancreatitis in the resected pancreas. The criteria recommend that a diagnostic trial of steroid therapy be performed by expert pancreatologists only in patients who fulfill criterion I and show negative results in a diagnostic work-up for pancreatobiliary cancer.

In 2006, a group from the Mayo clinic proposed diagnostic criteria for AIP known as the HISORt criteria, which consisted of 5 items, including histology, pancreatic imaging, serology, other organ involvement, and response to steroid therapy (Table **6**) [88, 99]. According to these criteria, AIP diagnosis is established when (a) a review of histology shows a full spectrum of LPSP changes or immunostaining shows abundant IgG4-positive cells; (b) imaging shows a diffusely enlarged pancreas and diffusely irregular narrowing of the MPD, and serology shows elevated IgG4 levels; or (c) the patient has elevated IgG4 and/or extra-pancreatic manifestations, with the latter resolving with steroid therapy. The HISORt criteria focus on histological findings, but, in practice, it is difficult to obtain a specimen large enough to assess the full spectrum of LPSP changes. Like the Korean criteria, the HISORt criteria recommend a diagnostic trial of steroid therapy. Of note, the HISORt criteria cover a diverse spectrum of disease conditions, from acute to post-acute stages, including pancreatic atrophy and calcification [99, 102]. A revised version of the HISORt criteria included IDCP or AIP with GEL as type 2 AIP, with LPSP defined as type 1 AIP [202, 203].

Authorized European criteria for AIP have not been established, although Italian diagnostic criteria have been proposed (Table **7**) [19]. These combine the clinical features of LPSP and IDCP/AIP with GEL. AIP is diagnosed following surgery by assessment of resected pancreatic specimens, including periductal lymphoplasmacytic infiltration, and fibrosis that includes granulocytic epithelial lesions (GEL) [18]. In non-operated patients, AIP is diagnosed based on at least three of the criteria reported in Table **7**. In contrast to other criteria, the Italian criteria stress the close association between AIP and inflammatory bowel diseases [19].

Comparison of Diagnostic Criteria and Towards the Construction of an International Consensus

A comparison of the diagnostic criteria for AIP is shown in Table **8**. Several differences are apparent.

Table 5. Asian Diagnostic Criteria for Autoimmune Pancreatitis

Criterion I. Imaging (Both Required)
1. Imaging of pancreatic parenchyma: Diffuse/segmental/focal enlargement of the gland, occasionally with a mass and/or hypoattenuated rim
2. Imaging of pancreaticobiliary ducts: Diffuse/segmental/focal pancreatic ductal narrowing, often with stenosis of the bile duct
Criterion II. Serology (One Required)
1. High levels of serum IgG or IgG4
2. Detection of autoantibodies
Criterion III. Histopathology of Pancreatic Biopsy Lesions
Lymphoplasmacytic infiltration with fibrosis and abundant IgG4-positive cell infiltrations
AIP should be diagnosed when criterion I and one of the other two criteria are satisfied or when the histology shows lymphoplasmacytic sclerosing pancreatitis in the resected pancreas
Optional criterion: Response to steroid therapy
Diagnostic trials of steroid therapy should be conducted carefully by pancreatologists and only in patients that fulfill criterion I and have negative results in a work-up for pancreatobiliary cancer

Proposed by the Research Committee of Intractable Pancreatic Diseases, provided by the Ministry of Health, Labor, and Welfare of Japan and the Korean Society of Pancreatobiliary Diseases [100].

Table 6. HISORt Diagnostic Criteria for Autoimmune Pancreatitis[a]

Category	Criteria
A. Histology	1. Diagnostic (any one)
	(a) Pancreatic histology showing lymphoplasmacytic sclerosing pancreatitis (LPSP)
	(b) Lymphoplasmacytic infiltrate with abundant (>10cells/HPF) IgG4-positive cells in the pancreas
	2. Supportive (any one)
	(a) Lymphoplasmacytic infiltrate with abundant (>10cells/HPF) IgG4-positive cells in an extrapancreatic organ
	(b) Lymphoplasmacytic infiltrate with fibrosis in the pancreas
B. Imaging	Typical imaging features
	1. CT/MRI: diffusely enlarged gland with delayed (rim) enhancement
	2. ERCP: diffusely irregular, attenuated main pancreatic duct
	Atypical imaging features
	Pancreatitis, focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy, pancreatic calcification
C. Serology	Elevated serum IgG4 levels
D. Other organ involvement	Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
E. Response to Diagnosis	Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
	1. Group A: diagnostic histology alone
	2. Group B: typical imaging features and elevated serum IgG4
	3. Group C: unexplained pancreatic disease with serology or other organ involvement and response to steroid therapy

MRI, magnetic resonance imaging.
[a]Reference [88, 89].

Table 7. Italian Diagnostic Criteria for AIP[a]

Suggestive radiological features (CT or MR)
• Diffuse or focal involvement of the pancreas
• Delayed enhancement in the involved parenchyma
• No dilation of the main pancreatic duct in diffuse form
• No extra-pancreatic or vascular involvement
Association with autoimmune diseases
Ulcerative colitis, Crohn's disease, Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, retroperitoneal fibrosis, autoimmune thyroiditis, tubulointerstitial nephritis, uveitis, and Mikulicz's disease
Consistent cytological or histological features
• Periductal lymphoplasmacytic infiltration
• Presence of granulocytic epithelial lesions
• Negative for epithelial atypia
Response to steroid therapy
• Clinical: resolution of symptoms/signs of AIP
• Radiological (CT or MRI): disappearance/significant reduction in the size of the involved pancreas, normalization of the main pancreatic duct

[a]Reference [193].

First, these criteria define at least two distinct histological types of AIP, LPSP and IDCP/AIP with GEL. The Japanese, Korean, original HISORt, and Asian criteria are based on LPSP, whereas the Italian criteria are based on a mixture of LPSP and IDCP/AIP with GEL. There are also differences in clinical stages. The Japanese, Korean, and Asian criteria refer to an acute stage of LPSP, whereas the HISORt criteria refer to both acute and post-acute or chronic stages of LPSP. Accordingly, the term AIP likely refers to more than one distinct disease or clinical stage [16, 99]. To reach an international consensus, we should clearly define the type of AIP identified by the diagnostic criteria.

Second, the Japanese, Korean, and Asian criteria stress imaging findings, while the HISORt and Italian criteria stress pathological findings. In practice, it is difficult to obtain specimens from AIP tissues large enough for full pathological assessment; moreover, pathological analyses may be available only for surgical specimens. Therefore, it seems appropriate to regard imaging findings and serology as most important for diagnostic criteria. There are no controversies in the clinical utility of IgG4 [2, 89, 118]. Because the diagnostic use of ERCP has been recently restricted, it is necessary to confirm useful findings by non-invasive imaging methods, including US, CT, and MRI. A capsule-like low-density rim apparent on CT or MRI is a specific indication of AIP and some criteria have adopted this indication, although its sensitivity is not high [43].

Other criteria, but not the Japanese criteria, include response to corticosteroid therapy. The major reason the Japanese criteria exclude response to steroid is that treatment

Table 8. Comparison of Diagnostic Criteria for AIP

	Japanese Criteria (Revised in 2006)	Korean Criteria	Asian Consensus Criteria	Mayo Clinic HISORTs Criteria	Italian Criteria
Disease type	LPSP Acute stage	LPSP Acute stage	LPSP Acute stage	LPSP Acute and post-acute stage	LPSP/AIP with GEL Acute and Post-acute stage
I. Image findings	Mandatory ERCP irregular narrowing CT, MRI swelling	Mandatory ERCP/MRCP irregular narrowing CT, MRI swelling	Mandatory ERCP irregular narrowing CT, MRI swelling	Not mandatory Typical : irregular narrowing swelling Atypical: pancreatitis focal mass focal duct stricture atrophy calcification	Not mandatory
II. Serology	γ-globulin IgG, IgG4 autoantibodies	IgG, IgG4 autoantibodies	IgG, IgG4 autoantibodies	IgG4	Not included
III. Histology	LPSP	LPSP IgG4 positive plasma cell infiltration	LPSP IgG4 positive plasma cell infiltration	LPSP IgG4 positive plasma cell infiltration	Periductal lymphocyte infiltration GEL
IV. Extra-pancreatic lesions	Not included	IgG4 positive plasma cell infiltration steroid response	Not included	IgG4 positive plasma cell infiltration steroid response	IBD Autoimmune diseases
V. Steroid response	Not included	Included	Option	Included	Included
Diagnosis	I+II I+III	I+II I+III I+IV I+V	I+II I+III	Group A: III Group B: I+II Group C: I (atypical) +II or IV +V	Operation: III Non-operation: Any 3 of I, III, IV, and V

may delay the diagnosis and treatment of potential pancreatic or biliary malignancies. However, the Asian criteria have adopted the steroid trial as an option that should be applied carefully and only by pancreatologists familiar with AIP [100]. Prompt assessment is crucial for its clinical use. In the clinical setting of suspected AIP, there is a continuous need for differentiation from pancreatic cancer due to atypical imaging for AIP. Thus, "a 2-week steroid trial and subsequent assessment of its response" may be helpful in confirming the diagnosis of AIP without negative consequences for patients with resectable pancreatic cancer [204]. Steroid pulse therapy may contribute to the prompt assessment of a diagnostic trial [108]. In addition, FDG-PET may also prove effective for evaluating response to steroid therapy within one week [70, 71]. However, a steroid trial should be performed carefully and only by pancreatologists.

Unlike the Japanese and Asian criteria, other criteria include the presence of extra-pancreatic lesions. A variety of extra-pancreatic lesions may complicate AIP, and they may exhibit pathological characteristics similar to those observed in AIP tissues, including abundant IgG4-positive plasma cell infiltration [3, 10, 11]. The recognition of these extra-pancreatic lesions and their response to steroid may be useful for the diagnosis of AIP. However, it is necessary to define the extent of extra-pancreatic lesions before including them with the diagnostic criteria, because it is difficult to perform a whole body check for each patient. The response to corticosteroid therapy is markedly different for each extra-pancreatic lesion, so the targets of a steroid trial should be strictly defined. In addition, the incorporation of extra-pancreatic lesions into the diagnostic criteria of AIP is controversial, because in principle, the diagnosis of AIP should be based on findings from the pancreatic lesion [100].

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Polymorphism in the *KCNA3* gene is associated with susceptibility to autoimmune pancreatitis in the Japanese population

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Abstract. Autoimmune pancreatitis (AIP), characterized by irregular narrowing of the main pancreatic duct, swelling of the pancreas, and histological evidence of lymphoplasmacytic inflammation by high serum immunoglobulin G4, is distinct from ordinary pancreatitis. However, genetic factors involved in the etiology and pathophysiology of AIP remain unclear. Sixty-four patients with autoimmune pancreatitis (53 men, 11 women; mean age, 62.4 years) and 104 healthy Japanese controls were enrolled in this study. We performed an association analysis using 400 microsatellite markers with an average spacing of 10.8 cM in the genome. We also evaluated the association of AIP with seven single nucleotide polymorphisms (SNPs) within the 20-kb region around the potassium voltage-gated channel, shaker-related subfamily, member 3 gene (*KCNA3*). We identified six statistically significant markers (D1S2726, D5S410, D6S460, D10S548, D15S128, and D20S186; $P < 0.05$) related to susceptibility. The surrounding region showing the strong association ($P = 7.4 \times 10^{-7}$ Pc = 0.0015) contained the *KCNA3* gene. Further analysis by SNP genotyping in *KCNA3* gene revealed that four SNPs (rs2840381, rs1058184, rs2640480, rs1319782) were significantly associated with the AIP susceptibility ($P < 0.007$). *KCNA3* is known to be involved in immunomodulation of autoreactive effector and memory T cell–mediated autoimmune diseases. Our findings provide the first evidence that *KCNA3* is associated with AIP and suggest that *KCNA3* may influence the risk for AIP.

Keywords: AIP autoimmune pancreatitis, SNPs, KCNA3, disease susceptibility

Abbreviations

AIP,	autoimmune pancreatitis;
HWE,	Hardy-Weinberg equilibrium;
HWP,	Hardy-Weinberg proportion;
KCNA3,	potassium voltage-gated channel, shaker-related subfamily, member 3;
LD,	linkage disequilibrium;
SNP,	single nucleotide polymorphism;
Pc-value,	corrected *P*-value.

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1. Introduction

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by minimal abdominal pain, irregular narrowing of the pancreatic duct, swelling of the pancreatic parenchyma, and predominance in elderly males. It has been referred to by various designations [1–7] and is now generally termed AIP based on clinical features, various serum autoantibodies, hypergammaglobulinemia, histological evidence of lymphoplasmacytic inflammation and fibrosis, and a favorable response to glucocorticoid treatment [3].

Awareness of AIP is a matter of clinical importance because this disease has been frequently misdiagnosed as pancreatic cancer [8]. Furthermore, this disease is

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associated with a variety of extra-pancreatic complications such as sclerosing cholangitis [2,5] sialoadenitis [9,10], hypothyroidism [11], hilar lymphadenopathy [10], retroperitoneal fibrosis [7], interstitial pneumonia [12], and tubulointerstitial nephritis [13], and frequently has been designated as primary sclerosing cholangitis, Sjogren's syndrome, Hashimoto's thyroiditis, sarcoidosis, or primary retroperitoneal fibrosis. Because patients with AIP respond to corticosteroid treatment, the correct diagnosis should be made in order that timely and effective treatment can be implemented.

The etiology and pathogenesis of AIP remain unclear. Previous studies have shown that T-lymphocytes infiltrate the pancreatic tissues and that carbonic anhydrase II and lactoferrin are candidate target antigens [14]. However, there have been conflicting reports regarding the role of cellular immunity and effector cells, and anti-carbonic anhydrase II and anti-lactoferrin autoantibodies have not been proven specific to this condition [15]. The most characteristic feature of AIP is a specific augmentation of serum IgG4 concentration, which was found in over 90% of patients and is indicative of disease activity [6]. Histological findings of abundant IgG4-positive plasma cells are a hallmark of this disease [7,9,16]. These results suggest that IgG4 plays a major role in the pathogenesis of AIP

The development of AIP is likely influenced by multiple interactions between genetic and environmental factors. Our previous report suggested that genetic factors for susceptibility to the disease were premier immune loci, such as the HLA *DRB1*0405-DQB1*0401* haplotype [17], the Fc receptor-like gene 3 (*FCRL3*) [18], and cytotoxic T-lymphocyte antigen 4 gene (*CTLA4*) [19]. However, the genetic factors underlying AIP have not been elucidated conclusively. Moreover, there are numerous candidate genes for AIP susceptibility. Recent progress in molecular genetics has enabled direct approaches for identifying genetic determinants. Here, we aimed to identify potential AIP susceptibility gene regions by performing a genome-wide scan and single nucleotide polymorphism (SNP) genotyping around candidate susceptibility genes.

2. Materials and methods

2.1 Patients

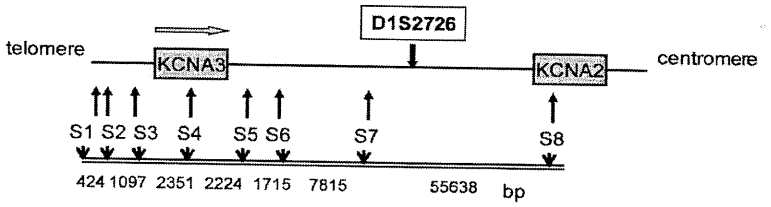
Between September 1994 and October 2004, we treated and followed 64 patients with AIP The 53 men and 11 women were 38-79 years of age (median age, 62.4 years). Diagnostic criteria for AIP included (1) enlarged pancreas on ultrasonography, computed tomography, or magnetic resonance imaging, and irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangio-pancreatography; (2) increased serum gammaglobulin levels, high serum IgG or IgG4 concentrations, or the presence of autoantibodies; and (3) characteristic histological findings of lymphoplasmacytic infiltration and fibrosis [20]. Thirtynine (61%) had concurrent autoimmune diseases, including hypothyroidism (12 patients; 22%) and sclerosing cholangitis (34 patients; 74%), whose diagnosis was described in our prior study [21]. Eight patients had a pathological diagnosis. In western countries, AIP is classified in type 1 and type 2, in which type 1 corresponds to LPSP (lymphoplasmacytic sclerosing pancreatitis; IgG4-related disease) and type 2 to IDCP or AIP with GEL(granulocyte epithelial lesion). The clinical features of type 2 AIP include the following; on average, patients are a decade or more younger in age than patients with type 1 AIP, there is no gender bias, no association with systemic involvements, no elevation of serum IgG4, no or minimal tissue infiltration of IgG4 bearing plasma cells, and there is an association with inflammatory bowel disease in almost 30% of patients. Clinical findings of Japanese AIP definitely different from type 2. All of our patients showed clinical findings of type 1 AIP or LPSP

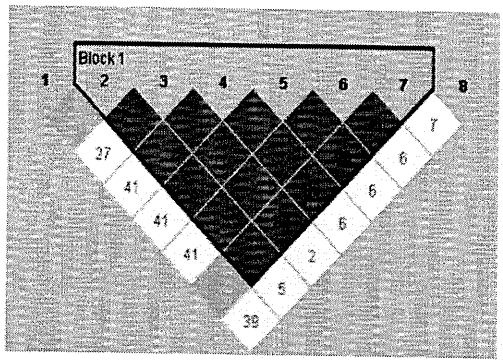
One hundred and four individuals (56 men and 48 women, median age, 54.5 years) for controls were enrolled in this study. The control subjects are all healthy volunteers having regular medical check-ups and they reside in Nagano prefecture.

The institutional ethics committee granted permission for this study; all patients and control subjects provided written performed consent to participate in this study.

2.2. Microsatellite genotyping

The genome scan was carried out using 400 microsatellite markers (ABI Linkage Mapping Set v.2.5 – MD10; Applied Biosystems, Foster City, CA) with an average heterozygosity of 79% and an intermarker distance of 9.4 ± 2.9 cM (mean ± SD). The entire marker set consisted of 28 panels, each containing markers pooled together according to size and fluorescent tag (6-FAM, VIC, NED). The markers were amplified by polymerase chain reaction (PCR) in 10-μl reactions each containing 40 ng of genomic DNA, according to the manufacturer's protocol. After PCR, the pooled





Estimated haplotype frequencies in control

Haplotype	S2	S3	S4	S5	S6	S7	Frequency (n=104)
1	T	A	C	A	T	A	0.428
2	C	G	A	C	C	G	0.389
3	C	A	C	A	T	G	0.130
4	C	G	C	A	T	G	0.029
6	C	G	A	C	C	A	0.019

Estimated haplotype frequencies in patients

Haplotype	S2	S3	S4	S5	S6	S7	Frequency (n=64)
1	C	G	A	C	C	G	0.554
2	T	A	C	A	T	A	0.352
3	C	A	C	A	T	G	0.039
4	C	G	C	A	T	G	0.016
5	C	G	C	A	T	A	0.016
6	C	A	C	A	T	A	0.015

Fig. 1. Structures of linkage disequilibrium (LD) and the haplotype block from rs3762379 to rs3887820 on chromosome 1p13.3. The pairwise LD (D') diagram was delineated using the solid spine method with D' > 0.8 for the 104 Japanese control samples. Haplotype frequencies were estimated by the maximum-likelihood method, with an expectation-maximization algorithm. S1. rs3762379, S2: rs2821557, S3: rs2840381, S4: rs1058184, S5: rs2640480, S6: rs1319782, S7:rs2821548, S8: rs3887820. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/DMA-2011-0820)

panels were electrophoresed on an ABI 3130 DNA Analyzer. Semi-automated genotyping was performed using GeneMapper v 3.5 (Applied Biosystems). DNA samples from all patients were collected before steroid therapy.

2.3. *Singlel nucleotide polymorphism genotyping*

We identified one locus located on chromosome 1p13.3 (microsatellite marker D1S2726) as potentially associated with AIP The gene encoding potassium voltage-gated channel, shaker-related subfamily, member 3 (*KCNA3*) lies 31 kb telomeric of the D1S2726 microsatellite marker and was therefore targeted as a candidate susceptibility gene.

Eight SNPs distributed around *KCNA3* were selected from the National Center for Biotechnology Information (NCBI) dbSNP database (build 36), the JSNP database, and the SNP database of Applied Biosystems (Fig. 1) based on the following criteria: (a) location within the 20-kb region around the candidate microsatellite marker; (b) greater than 10% minor allele frequency in the Japanese population; (c) 0.3 average heterozygosity; (d) marker density of at least one SNP per 8 kb; and (e) availability for validation assays. SNP genotyping was performed using TaqMan® SNP Genotyping Assays, according to manufacturer's instructions.

2.4. *Statistical analysis*

Frequencies of alleles in each microsatellite marker were estimated by direct counting. To estimate the statistical significance of comparisons between patients with AIP and healthy control subjects, we used the χ^2-test and Fisher's exact probability test for 2×2 contingency tables. We defined a P-value of less than 0.05 as statistically significant. The P-values were corrected by multiplying by the number of different alleles observed in each locus (Pc), and also by multiplying the 400 markers typed in the study. The pairwise relationships between microsatellites, SNPs, and haplotypes were estimated by calculating odds ratios (ORs) and 95% confidence intervals (CIs). The Hardy-Weinberg proportion (HWP) for multiple alleles was calculated by the Markov chain method within the GENEPOP software package (http://wbiomed.curtin.edu.au/genepop/index.html). The linkage disequilibri-

Table 1
Statistically significant STR markers by association for AIP

Chromosome	locus	allele	patient (%) $n = 64$	control (%) $n = 104$	OR	95%CI	c2	P	Pc	Pc*
1	D1S2726	280	27 (42.2)	9 (8.7)	7.70	3.31–17.92	24.507	0.00000074	0.0000037	0.00030
		292	6 (9.4)	27 (26.0)	0.30	0.11–0.76	5.895	0.015	0.076	
	D1S0655i	266	47 (73.4)	47 (45.2)	3.35	1.71–6.59	12.825	0.00034	0.0014	
5	D5S410	331	38 (59.4)	32 (30.8)	3.29	1.72–6.30	13.340	0.00026	0.0067	
6	D6S460	289	23 (35.9)	17 (16.3)	2.87	1.39–5.95	8.383	0.0038	0.0010	
10	D10S548	188	60 (93.8)	69 (66.3)	7.61	2.56–22.65	16.691	0.000097	0.00039	0.039
15	D15S128	203	37 (57.8)	33 (31.7)	2.95	1.55–5.62	11.089	0.00087	0.0070	
20	D20S186	127	35 (54.7)	32 (30.8)	2.72	1.43–5.17	9.450	0.0021	0.021	

Pc was calculated by multiplying the numbers of alleles in the locus.
Pc* was calculated by multiplying the 400 markers typed in the study.

um (LD) patterns, haplotype block structure, and haplotype frequency analysis for SNPs were identified using the block definition of Gabriel et al. [22] and were based on the 95% CI of pairwise LD (D'), as determined with Haploview software [23].

3. Results

Genome-wide linkage association analysis using 400 microsatellite markers identified seven markers as new candidate loci for AIP (Table 1). Strong evidence of positive association was detected for the marker D1S2726 (42.2% vs. 8.7%, $Pc = 0.0000037$) on chromosome (chr) 1p13.1, D5S410 (59.4% vs. 30.8%, $Pc = 0.0067$) on chr 5q31-33, D6S460 (35.9% vs. 16.3%, $Pc = 0.0010$) on chr 6q14, D10S548 (93.8% vs. 66.3%, $Pc = 0.00039$) on chr 10p12, D15S128 (57.8% vs. 31.7%, $Pc = 0.007$) on chr 15q15, and D20S186 (54.7% vs. 30.8%, $Pc = 0.021$) on chr 20p12.2. The observed and expected frequencies of each genotype for the seven markers in both case and control subjects were within Hardy-Weinberg equilibrium (HWE; data not shown).

D1S2726 was identified as a marker of interest for further analysis. To further validate the association of the D1S2726 marker with AIP, we examined the association of AIP with an additional marker located 30.7 kb centromeric of D1S2726, D1S0655i. Allele 266 of D1S0655i was also indicated a positive association with AIP (73.4% vs. 45.2% OR = 3.35, $Pc = 0.0014$, Table 1).

To predict novel susceptibility genes within 100-kb of significant markers, we used the NCBI Map Viewer (http://www.ncbi.nlm.nih.gov/mapview/; Table 2). Two genes, *KCNA3 and KCNA2*, were identified within the candidate region around D1S2726. We characterized *KCNA3* as a candidate gene by performing an association analysis using seven SNPs (Fig. 1). Four SNPs (rs2840381 allele G, rs1058184: allele A, rs2640480: allele C, rs1319782: allele C) showed statistically significant association (Table 2). All SNPs were screened in all AIP cases and control subjects. The frequencies of the SNPs for both patients and controls were within HWE. Pairwise LD mapping confirmed that the haplotype structure including*KCNA3* was divided into three blocks (rs3762379, major block; rs2821557 to rs2821548, and rs3887820, Fig. 1). The CGACCG haplotype of the major block was significantly more prevalent in the patient group than in the control group ($P = 0.04$, OR = 1.93).

4. Discussion

Despite recent progress in its clinical, immunological, radiological, and morphological characterization [24], the etiology of AIP still remains unclear. Genetic factors including the HLA DRB1*0405-DQB1*0401 haplotype [17] and polymorphisms of the *FCRL3* and *CTLA4* genes [18,19] have been implicated in the etiology of AIP However these risk factors are identified during analyses performed in a limited region of the genome. A more comprehensive understanding of how the genetic background influences the outcome of AIP requires genome-wide association analyses [25].

This is the first case-control genome-wide association study aimed at identifying candidate genes for AIP pathogenesis, even though the number of enrolled subjects was too small to overcome type I error. Four hundred microsatellite markers were used for this study, providing 10.8-cM genome-wide resolution. This approach is not as efficient as using tens of thousands of microsatellite markers at 100 kb intervals across the human genome [26]; therefore, there are likely to be many undetected genes involved in susceptibility to

Table 2

Association of 8 SNPs around KCNA3 gene with AIP

SNP rs	Observed Allele (1/2)	Frequency		Genotype distribution						P value (1/2)	OR 95% CI (1/2)	P value (11/12+22)	P value (11+12/22)	HWE	
		Allele 1		Allele 1/1		Allele 1/2		Allele 2/2							
		Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls					Patients	Controls
rs3762379	C/T	0.922	0.856	55	75	8	28	1	1	0.0692	1.99 (0.94–4.22)	0.038	0.727	0.290	0.355
rs2821557	C/T	0.648	0.567	27	39	29	40	8	25	0.1407	1.14 (0.89–2.22)	0.546	0.068	0.961	0.027
rs2840381	G/A	0.594	0.438	22	24	32	43	10	37	0.0054	1.88 (1.20–2.94)	0.111	0.005	0.771	0.103
rs1058184	A/C	0.563	0.409	21	22	30	41	13	41	0.0061	1.86 (1.19–2.90)	0.093	0.010	0.703	0.060
rs2640480	C/A	0.563	0.409	21	22	30	41	13	41	0.0061	1.86 (1.19–2.90)	0.093	0.010	0.703	0.060
rs1319782	C/T	0.563	0.409	21	22	30	41	13	41	0.0061	1.86 (1.19–2.90)	0.093	0.010	0.703	0.060
rs2821548	G/A	0.609	0.553	24	37	30	41	10	26	0.3091	1.26 (0.81–1.97)	0.801	0.150	0.902	0.039
rs3887820	C/A	0.586	0.457	25	22	25	51	14	31	0.0214	1.68 (1.08–2.63)	0.012	0.260	0.119	0.904

SNPrs: public reference SNP number from the dbSNP database.
95% CI: 95% confidence interval; OR: odds ratio.
P value was calculated by c2 test 2 × 2 contingency table.
HWE: Hardy-Weinberg Equilibrium.

Table 3
Estimated haplotype frequencies from 3 SNPs in four different populations

SNP	rs1058184	rs2640480	rs1319782	Frequency
Pop				
CEU	C	A	T	0.70
	A	C	C	0.30
CHB	C	A	T	0.56
	A	C	C	0.44
YRI	C	A	T	0.65
	A	C	C	0.34
	C	A	C	0.01
JPA (Cont)	C	A	T	0.59
	A	C	C	0.41
JPA(AIP)	C	A	T	0.44
	A	C	C	0.56

Haplotye frequencies in CEU, CHB, and YRI populations were calculated by HapMap database data.
CEU: Utah residents with ancestry from northern and western Europe.
CHB: Han Chinese in Beijine, China.
YRI: Yoruba in Ibadan, Nigeria.
JAP (Cont): Control group in this study, Japanese.
JAP (AIP): Patients group in this study, Japanese.

AIP Nonetheless, this approach identified seven statistically significant makers (Table 1). In the regions surrounding these markers, we noted interesting genes that might be linked to AIP susceptibility, including *KCNA3*.

KCNA3 is located 30 kb telomeric of D1S2726 and encodes the voltage-gated potassium channel Kv1.3 [27]. Kv1.3 regulates membrane potential and Ca^{2+}-signaling in human T cells and plays an essential role in T-cell proliferation and activation [28–30]. This molecule is expressed in a variety of tissues and hematopoietic cells, particularly in effector memory T cells (T_{EM}). Terminally differentiated T_{EM} cells enter inflamed tissues rapidly and produce copious amount of IFN-γgnd IL-4 [31]. Therefore, suppressing the function of these cells by selectively blocking the Kv1.3 channel offers a potential therapeutic strategy for T cell-mediated autoimmune diseases [32]. Interestingly, Kv1.3 blockers preferentially suppress the proliferation of late memory B cells (CD27+IgG+IgD-) [33], which play an important role in production of IgG antibodies. Consequently, Kv1.3 serves a critical function in modulating immune responses. Thus, the high level production of IgG4 in patients with AIP could be caused by the proliferation of late memory B cells and the elevated expression of Kv1.3 molecules.

Association analysis using eight SNPs in the region of *KCNA3* identified four SNPs (rs2840381, rs1058184, rs2640480, rs1319782) significantly associated with susceptibility to AIP ($P < 0.007$). SNPs in the promoter region of the Kv1.3 gene were examined whether they were associated with impaired glucose tolerance and reduced insulin sensitivity in patients with diabetes mellitus [34]. One of these, rs2821557 (T-1645C) was shown to exhibit differential transcription activity. However, rs2821557 SNP in our analysis was not associated with disease susceptibility to AIP The haplotype (GACC) frequency of these four SNPs involved in the one haplotype block (rs2821557 to rs2821548: CGACCG) was significantly higher in the patient group than in the control group ($P = 0.014$, OR $= 2.45$). This haplotype locates at 6.29 kb upstream of the promoter/5'-untranslated region (UTR) to downstream of the 3'-UTR in *KCNA3* and includes the full length of the *KCNA3* coding region. This result highlights the need to investigate haplotype frequencies in different populations. When comparing the distribution of haplotype frequencies constructed by three of these SNPs (rs1058184, rs2640480, rs1319782) using HapMap data (http://www/hapmap.org/) in three different populations (northern and western Europe, Han Chinese, Yoruba in Ibadan, Nigeria) and in our control group, the CAT haplotype was the most frequent (Table 3). These results provide further support that *KCNA3* is a general susceptibility gene for AIP

Currently, we are searching for candidate susceptibility genes by performing high-resolution microsatellite analysis around the positive markers identified in this study. Future studies also need to focus in the identification of therapy-effectiveness- or disease-severity-related genes. These types of studies could aid in the identification and development of specific therapies for patients with AIP

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Competing interests

The authors declare that they have no competing interests.