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Genetic Determinants of Autoimmune Gastritis

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Abstract
Autoimmune gastritis (AIG) is an immuno-mediated disease characterized by the production of antibodies to the parietal cells of the stomach, which leads to the loss of the internal Castle factor and decrease in the production of hydrochloric acid. Diagnosis of AIG remains difficult due to the lack of symptoms at early stages, ineffective or costly screening strategies, and incomplete established etiology. Patients with AIG are at high risk of developing malignant neoplasms and neuroendocrine tumors, and they would greatly benefit from any means to predict the likelihood of developing and the severity of a possible disease. Here, we aim to summarize data on the genetic nature of AIG. We will also describe the clinical picture of AIG, *Helicobacter pylori* association with it, and elaborate on the pathogenesis of the disease.

Keywords Autoimmune gastritis · Genetic risk score · Prediction

1 Introduction

Autoimmune diseases (AIDs) are a group of pathologies with different clinical manifestations that develop as a result of the body's loss of tolerance to its own antigens. AIDs result in a steady activation of immune cells, leading to tissue damage [1]. Current prevalence of AIDs is 10%, but there is a trend towards an increase in the incidence in the world [2]. In the structure of AIDs, the autoimmune thyroiditis (AIT) ranked first, accounting for 20% of the prevalence among the population [3]; the second place is taken by celiac disease, the prevalence of which is 1.4% according to the results of blood tests and 0.7% according to the results of biopsy screening [4]; prevalence of rheumatoid arthritis (RA) ranges from 0.5 to 1% [5], and vitiligo has an estimated prevalence of 0.5–2% [6]. AIG is one of the least studied AIDs, with a global prevalence ranging from 0.5 to 4.5%. However, given the complexity of diagnosis,

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the incidence of this pathology can be much higher [7, 8]. AIG is more often detected among female patients [9] older than 60 years [10] and characterized by the production of autoantibodies to parietal cells (AT to PC) and intrinsic factor of Castle (IFK), which in all cases leads to atrophic gastritis [7]. The particular importance of early diagnosis of the disease lies in a significantly increased risk of developing neuroendocrine tumors (NET) and gastric cancer (GC) in patients with AIG [11–14]. The level of risk of developing gastric cancer and neuroendocrine tumors of the stomach in patients with AIG has not been fully studied. According to the analysis of the literature, the risk of developing in this cohort of patients increases by 3–7 once. Also, AIG is often combined with other AIDs and develops as part of the so-called autoimmune polyglandular syndrome. Despite the rapid development of diagnostic methods, the detection of AIG at the early stages is difficult, which significantly worsens the prognosis and the risk of complications. This may be due to the lack of awareness among specialists about the disease, as well as the lack of specific symptoms and markers. Molecular genetic studies, being the basis of modern personalized medicine, often allow solving the problem of not only establishing diagnosis and selecting an individual treatment, but also predicting the course of a disease and the development of undesirable consequences. Currently, the possibilities of genetic testing in the management of patients with AIG are not widely used due to the small number of studies and the relatively low prevalence of the disease. However, the introduction of molecular diagnostics will increase the prospects for developing a strategy for the personalized management of patients with AIG.

2 Etiology and Prevalence

The prevalence of AIG is probably underestimated due to the high incidence of asymptomatic or oligosymptomatic disease. Various diagnostic criteria, ethnic, and demographic characteristics lead to the lack of a single screening strategy, which also does not allow obtaining reliable data on the incidence of AIG in the population. Thus, according to various studies, the prevalence of AIG is up to 10% [15–18]. The etiology of AIG is characterized by a multifactorial nature, including genetic, which can be common to several autoimmune pathologies (the principle of pleiotropy), or specific to one disease [19]. A possible genetic predisposition is indicated by the presence of familial forms of AIG and the detection of antibodies to PC in the blood in 20–30% of relatives of patients with pernicious anemia (PA, B12 deficiency anemia). However, AIG and PA may be underdiagnosed due to the treatment of almost all forms of micro- and macrocytic anemia with iron, folic acid, and cobalamin preparations without identifying the etiology of anemia. Therefore, patients with chronic anemia should be screened for AIG [20]. The relationship of AIG and *Helicobacter pylori* (HP) infection is confirmed by the detection of antibodies to PC in 20–30% of patients with HP infection and the presence of IgG to HP in patients with AIG [21, 22]. A characteristic feature of AIG is the predominant lesion of the body and fundus of the stomach, in contrast to HP-associated gastritis. There is a specific form of AIG that can develop in genetically predisposed individuals when infected with HP [23], suggesting HP as a predictor of the development of AIG. Thus, the lack of case-finding strategies for diagnosing AIG, the lack of epidemiological studies, and the often-indolent course of the disease may contribute to a lack of knowledge about the true prevalence of AIG.

3 Genetic Aspects of AIG

Genetic risk factors predisposing to AIG are not well understood. In particular, no gene highly associated with AIG has yet been described. However, there are genes associated to other AIDs like diabetes mellitus type 1 (DM1) and AIT. In some cases, one molecular genetic marker is a risk factor for two or more AIDs. Considering that the combination of several AIDs occurs in many patients and can lead to a more severe course of disease, it is important to identify predisposing risk factors. The genes that are associated with the development of AIG are shown in Fig. 1. To date, it is planned to introduce this panel into practical use.

The high frequency of occurrence and high concordance in monozygotic twins, ranging from 15 to 57%, confirms the role of genetic factors in the pathogenesis of many AIDs and the existence of several genes that contribute to the emergence of an autoimmune phenotype [24].

Some studies, using mouse models, found several genes of predisposition to autoimmune gastritis: *Gasa1*, *Gasa2*, *Gasa3*, and *Gasa4* (gastritis type A susceptibility) [25, 26]. An association between AIG and DM1 has been suggested, as three of these genes are located at the same locus as genes for DM1 susceptibility in non-obese mice [27]. This discovery opened up prospects for diagnosing AIG at the molecular genetic level; however, since homologues of the *Gasa1*, *Gasa2*, *Gasa3*, *Gasa4* genes have not been found in humans, it is not yet possible to conduct clinical studies in this area.

AIG occurs as part of autoimmune polyglandular syndrome (APS) types 2 and 3, accompanying DM1, thyroid AID, adrenal insufficiency, celiac disease, and pernicious anemia [28].

Analysis of variants in the *AIRE*, *CTLA4*, *PTPN22*, and HLA genes makes it possible to determine the risk of developing APS, as well as AIG, which occurs up to 4 times more often in patients with DM1 relative to the risk in the general population [29, 30].

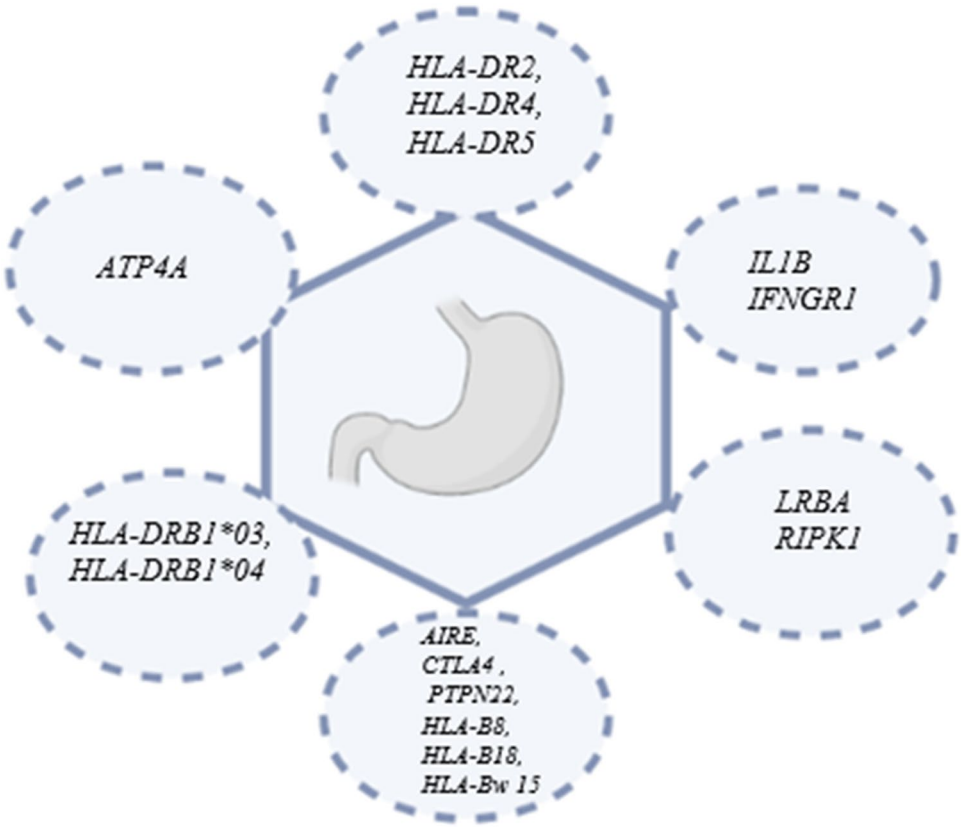

Fig. 1 Genes associated with AIG

Currently, associations of various AIDs with the genes of the HLA system are being searched [31, 32]. In patients with autoimmune endocrine diseases, *HLA-B8*, *HLA-B18*, and *HLA-Bw 15* occur, while in those who do not have these diseases, the *HLA-B7* and *HLA-B12* genotypes are more common. It is currently unknown whether these serotypes risk developing AIG or have a protective effect [7]. Some studies describe an increased frequency of *HLA-DRB1*03* and *HLA-DRB1*04* alleles in patients with thyroid AID and *HLA-DR2*, *HLA-DR4*, and *HLA-DR5* in patients with B12 deficiency anemia [33]. In a study of the Italian population, *HLA-DRB1*03* and *HLA-DRB1*04* alleles were detected significantly more often than in patients without AIG [34]. In the Finnish population, *HLA-DRB1*04* and *HLA-DQB1*03*, but not *HLA-DRB1*03*, were identified as a marker of an increased risk of AIG development [35]. In a study by Ungar and Mathews, a weak relationship between AIG and *HLA-DR5* was reported [33]. The diversity of HLA haplotypes in different clinical subgroups reflects the genetic heterogeneity of various autoimmune diseases, including AIG [36, 37].

Given the relationship between HP and AIG, researchers are focusing on identifying individual risk factors for HP infection, which may further trigger AIG. Thus, it is assumed that genetic variants of the *IL1B* gene can affect the expression of cytokines and create favorable conditions for hypoacidity, which contributes to the survival and colonization of HP. The study of the *IL1B* gene revealed 5 nucleotide variants associated with HP infection: − 338, − 155, + 38, *rs16944*(− 511) and *rs1143627*(− 31) [38].

The literature mentions cases of increased susceptibility to HP in patients with mutations in the interferon gamma receptor (*IFNGR*) gene, which are known to be an important part of the signaling system in the immune response to pathogens. In a study by Thye et al., as a result of a genome-wide analysis, patients who had IgG antibodies to HP were found to have the 56C-T variant in the *IFNGR1* gene [39]. However, the exact role of the contribution of *IFNGR1* gene variants in susceptibility to HP requires further research, since patients with identified mutations had a positive effect on eradication therapy.

4 AIG as Part of a Hereditary Syndrome

To determine the molecular genetic markers of AIG and study etiopathogenesis, in addition to studying comorbid diseases with AIG, attention should be paid to hereditary syndromes, one of the clinical symptoms of which is AIG.

These pathologies include a case of cystic fibrosis syndrome, HP-associated gastritis, folic acid deficiency, megaloblastic anemia, and mental disorders in consanguineous

children with presumably autosomal recessive inheritance, the molecular genetic association of which is unknown [40].

Early onset of gastrointestinal autoimmune disorders (severe refractory autoimmune gastritis), recurrent infections, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and inflammatory bowel disease are characteristic of type 8 primary immunodeficiency associated with mutations in the *LRBA* gene [41].

Gastritis may be one of the clinical manifestations in patients with type 57 immunodeficiency associated with mutations in the *RIPK1* gene. Cuchet-Lourenco et al. reported on 4 patients with primary immunodeficiency that were diagnosed with recurrent infections, developmental delay during the first year of life, gastritis, and signs of chronic inflammatory bowel disease up to 4 years [42].

These cases highlight the importance of molecular genetic diagnosis in patients with early forms of AID, which can improve the prognosis of the course of the disease.

5 Pathogenesis

The mechanism of AIG development is complex, but its understanding allows developing diagnostic algorithms and determining the tactics of patient management. The development of AIG is based on immune-mediated reactions, as a result of which sensitized CD4 + T lymphocytes are triggered and autoantibodies are produced. Despite the upward trend in the incidence of AIG, the pathogenesis has not been fully elucidated to date. With AIG, antibodies to PC and IFK are produced. The destruction of PK leads to a decrease in the production of hydrochloric acid and an increase in the level of gastrin in the serum, which in turn, by the mechanism of negative feedback, is accompanied by hypergastrinemia. Hypergastrinemia resulting from PC breakdown and hypochlorhydria increases the risk of developing adenocarcinoma and neuroendocrine tumors (NETs). This highlights the need for early diagnosis of AIG and follow-up [43]. IFK is a glycoprotein synthesized by the PC of the stomach, which ensures the absorption of vitamin B12 in the intestine. As mentioned above, with AIG, antibodies are produced, including against IFK, and the absorption of vitamin B12 is impaired, which leads to pernicious anemia (PA). Recently, the relationship of HP infection in the development of AIG has been discussed. In HP-induced atrophic gastritis, activated CD4 + -Th1 cells that enter the gastric mucosa cross-recognize the proton pump of these cells and various HP proteins. However, it is not clear whether HP is an activating factor for Th1 cells leading to inflammation and apoptosis. In many cases, patients with AIG may also have HP infection at the same time. First of all, it should be remembered that AIG affects the body and fundus of the stomach, while HP-induced gastritis is predominantly localized in the antrum. As atrophy progresses, HP can migrate into the body and fundus of the stomach or disappear from the gastric mucosa, and therefore, such a cohort of patients is likely to get a false negative result. In some patients, antibodies to PC develop, as a result of which the disease becomes similar to classic AIG. It is important to differentiate between AIG and HP-associated gastritis [44]. Current epidemiological data suggest a decrease in HP infections and an increase in the incidence of autoimmune diseases such as AIG.

Diagnosis of AIG involves a comprehensive assessment of clinical, serological, and histopathological data. AIG is often detected at a late stage — atrophic changes in the gastric mucosa. The importance of timely diagnosis of AIG is especially emphasized by the need for constant monitoring of such patients in order to timely detect malignant neoplasms. The gold standard is to conduct a morphological study. Serological methods include GastroPanel, which is a blood test for assessing the condition of the gastric mucosa and atrophy. The GastroPanel includes such indicators as pepsinogen-1 (Pg-I), pepsinogen-2 (Pg-II), gastrin-17 (G-17), and anti-HP IgG antibodies [45]. According to the available data, pepsinogens are precursors of the main digestive enzyme, pepsin. In turn, hydrochloric acid converts pepsinogen into pepsin. With AIG, the acid production of PC is reduced, which disrupts enzyme formation. The study of the level of pepsinogens in the blood serum and the calculation of their ratio are used to assess the state of the gastric mucosa. Pg-1 is synthesized by the chief cells of the gastric mucosa, with the loss of these cells, in the case of atrophic gastritis with lesions of the gastric corpus, the level of Pg-1 in the serum decreases, suggesting atrophy [46]. G-17 is secreted by G cells located in the antrum of the stomach. Secretion is examined using a protein stimulation test. If the serum level of G-17 does not rise after stimulation, this is a sign of atrophy. HP infection causes an inflammatory response in the stomach, which over time can lead to atrophic gastritis [47]. Also, the presence of HP IgG antibodies helps to identify patients with past or current HP infection. Thus, serological screening using biomarkers, gastropanels can serve as an indicator of precancerous pathology and early detection of gastric cancer [48]. Recently, with the development of technologies, especially molecular genetic diagnostics, it has become possible to personalize the approach to patients with AID, including those that make it possible to determine the prognosis and assess its risks at the early stages of the development of the disease.

6 Clinical Manifestations

Most patients with AIG have no symptoms. In some cases, dyspeptic symptoms occur, such as bloating, rapid satiety, and nausea. It is worth paying attention to patients with

iron deficiency due to reduced secretion of hydrochloric acid (in 25–50% of patients) and vitamin B 12 deficiency, found in 15–25% of patients with AIG [49]. Malabsorption of vitamin B 12 from the terminal ileum due to AIG can lead to irreversible hematological and neurological consequences, such as paresthesia, numbness of the extremities, mood disorders, and memory impairment. The Pernicious Anaemia Society (PAS) showed that 44% of patients with AIG were initially misdiagnosed, while for 14 to 22% of patients, it took from 5 to 10 years to get a correct diagnosis [50]. Despite the availability of safe and effective therapy for PA, establishing a diagnosis can be difficult due to the variability of clinical manifestations and the presence of comorbidities. For example, the case of a 34-year-old woman who went to the doctor with a complaint of progressive fatigue, weakness and numbness of the limbs, and impaired gait. The examination revealed anemia, ataxia, and reduced sensitivity of the lower extremities. Babinski's sign was positive. In laboratory tests, an increase in the level of antibodies to Castle's internal factor was noted. According to instrumental examinations, esophagogastroduodenoscopy revealed a gastric polyp, according to histology — NET the background of severe atrophic gastritis. After vitamin B12 treatment, the patient's symptoms gradually disappeared [51].

7 Prognosis and Treatment Tactics

For the majority of AIDs, immunosuppressive and glucocorticosteroid therapy remain the best treatment options. In patients with AIG, these therapies did not show a positive effect. To date, no etiopathogenetic treatment has been developed. In a number of patients with low stomach acid, it is recommended to take intestinal antiseptics in order to prevent bacterial overgrowth syndrome. Paramount in the management of patients with AIG is the prevention and treatment of vitamin B12 deficiency, as well as the timely diagnosis of gastric adenocarcinoma and NETs. The prognosis of the disease depends on possible comorbidities and complications, such as other AIDs, NETs, and GC. As noted above, patients with AIG are at an increased risk of developing GC, so gastric atrophy should be assessed using histological staging systems. To determine the personalized risk of carcinogenesis, and assess the severity of gastric atrophy and intestinal metaplasia, a biopsy is performed according to the operative link on gastritis assessment (OLGA) staging system. Patients with advanced AIG (stage III/IV OLGA) should undergo endoscopic follow-up every 3 years, and patients with AIG (stage I/II OLGA) every 3 to 5 years [52].

8 Association of AIG with Other Autoimmune Diseases

AIG is accompanied by other AIDs in 40 to 60% of cases. The most common among them are autoimmune thyroiditis (AIT), type 1 diabetes mellitus (DM1), celiac disease, and rheumatoid arthritis (RA) [53].

In a study by Kalkan and Soykan, of 320 patients with AIG, 53.4% had an autoimmune comorbidity. The most frequent was AIT diagnosed in 116 patients (36.2%) [54].

AIT and AIG are the result of an association between genetic susceptibility and several environmental factors, and patients with these diseases have lesions in PC and thyroid follicular cells. The exact mechanism leading to damage to PC and/or thyrocytes is not well understood. Perhaps this is due to the common embryological origin of GM cells and follicular cells of the thyroid gland, which develop from the endoderm and have some functional and morphological similarities.

According to another study, a higher incidence of AIG in patients with DM1 was found in 5–10% of individuals [55]. A feature of the syndromes is that at first, one autoimmune disease appears, and subsequent ones join during life [56]. In patients with one autoimmune disease, the development of the second during life occurs in 25% of cases [57–62].

The relationship of AIG with other AIDs such as celiac disease, vitiligo, and rheumatoid arthritis is being actively researched and discussed.

9 AIG and Stomach Cancer

Patients with AIG have an increased risk of developing GC. The overall annual incidence of gastric carcinoma in patients with AIG remains less than 1% with the following identified risk factors: disease duration, severity of atrophy, pernicious anemia, and age over 50 years [63]. A systematic review by Vannella et al. reported an annual incidence of gastric adenocarcinoma of about 0.27% per person per year with an overall relative risk of 6.8 [64]; in one of the mentioned studies, among 877 patients with gastric cancer, 12 (1.3%) had a history of AIG.

As described above, in patients with AIG, hypergastrinemia is observed for a long time, which, due to the stimulation of proliferation, increases the risk of somatic mutations, ultimately leading to GC. PA, which occurs in patients with gastric atrophy due to HP or AIG, is associated with an approximately sevenfold increase in the risk of GC [65]. According to several studies, 5% of patients with AIG and without concomitant HP infection may

develop GC. However, the prevalence of AIG in patients with GC has not yet been studied. Thus, the characterization and early identification of patients at increased risk of GC, especially those resulting from AIG, is of great importance for early diagnosis and reduction of mortality from GC [66].

10 Conclusion

Understanding the development of the disease is essential for its detection and prevention of complications. Also, we can conclude that the timely diagnosis of one AID allows you to determine the prognosis and prevention for another. It is worth noting that patients with AIG should be screened for other autoimmune diseases and micronutrient deficiencies, including iron and vitamin B12 deficiencies. A multidisciplinary approach is essential to reduce risk.

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Declarations

Research Involving Humans and Animals None.

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Data are presented only in this review.