The Role of Genetic Factors

Leyla Ozer

Many possible causes of idiopathic granulomatous mastitis (IGM) are thought to have a role in the formation of the disease. Several factors (autoimmunity, infections, hormonal abnormalities, breast trauma, and obesity) are blamed for the etiology of IGM [1, 2]. Autoimmune-mediated inflammatory response stands out among the possible mechanisms. Altintoprak et al. [1] hypothesized that ethnical differences and autoimmune responses are the main mechanisms of IGM [2]. In this review they searched articles related with IGM and they noticed that the patients originated from certain ethnic groups. In a literature search between 1995 and 2014, they found that the cases were frequently reported from Mediterranean and Asian countries [2]. The largest case series of IGM patients were reported in Iran (374 patients) and Turkey (>200 patients), respectively [2, 3]. The significant relationship between a particular ethnic group and the frequency of disease suggests that genetic differences between individuals may have an important role in the susceptibility to the disease. The underlying genetic causes are not fully understood and a limited number of studies were reported on genetic causes; however, genetic variations and gene expression changes potentially may be involved in causative factors.

1 Genetic Polymorphism Studies

In recent years, several studies have been reported analyzing the relationship between IGM susceptibility and the presence of certain types of genetic polymorphisms. Identification of SNPs (single-nucleotide polymorphisms) can help us to

L. Ozer (✉)
Department of Medical Genetics, Faculty of Medicine, Yuksek Ihtisas University, Ankara, Türkiye

Microgen Genetic Diagnostic Centers, Ankara, Türkiye

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understand the genetic basis of complex diseases. Bercot et al. [4] reported a case with granulomatous mastitis caused by *Corynebacterium kroppenstedtii* infection. They showed disrupted NOD2 protein (nucleotide-binding oligomerization domain-containing protein 2) function and the NOD2 gene sequencing revealed an SNP variant of the NOD2 gene (SNP13 Leu1007fsinsC) [4]. The SNP13 Leu1007fsinsC variant was reported as one of the most frequently observed polymorphisms in patients with Crohn's disease [4]. NOD2 plays an important role in the immune response. The NOD2 protein shows a significantly elevated level of expression in the peripheral blood leukocytes. It recognizes molecules containing muramyl dipeptide (MDP) which is found in some bacteria and which stimulates an immune reaction. Binding of NOD2 to its ligand stimulates the production and release of cytokines by activating the NF-κB protein. NOD2 also regulates processes like cell differentiation, proliferation, and apoptosis by activating the mitogen-activated protein kinase (MAPK) signaling pathway [5].

Some of the studies focused on common genetic polymorphisms such as MTHFR and ACE gene polymorphisms. Lei et al. [6] investigated the relationship between IGM and methylene tetrahydrofolate reductase (MTHFR) gene polymorphism (C677T and A1298C). They studied 55 IGM patients and found a significant relationship with C677T polymorphisms. The authors hypothesized that MTHFR C677T may have a role in the formation of idiopathic granulomatous mastitis. Destek et al. [7] also studied gene polymorphisms in a patient with IGM and they found the presence of MTHFR-C 677 TT, β-fibrinogen-455G/A, PA˙I-1 5 G/5 G, and ACE ˙I/D gene polymorphisms.

The human leukocyte antigen (HLA) region or complex localizes on chromosome 6 and includes several immune response genes. The HLA region is composed of 252 genes with different polymorphisms, which is the largest number of polymorphism within the genome. Human leukocyte antigen (HLA) genes are found to be associated with autoimmune disorders. The first known HLA association study on IGM was reported by Koksal [8]. Forty-eight IGM patients were compared with healthy controls in terms of HLA gene polymorphisms. The author observed that the prevalence of HLA-A * 10, HLA-A * 2403, HLA-B * 18, and HLA-DR * 17 were higher in IGM patients compared to the control group, whilst the prevalence of HLA-A * 29, HLA-B * 14, and HLA-DR * 1 were lower. The author hypothesized that increased incidence of both HLA-A*2403 and HLA-B*18 antigens may be related to the humoral immunity and autoimmunity in IGM pathogenesis [8]. Although the results of this study are valuable, it will be more meaningful with the increase in HLA association studies in IGM patients from different geographic regions and different ethnic groups.

Genome-wide association studies (GWAS) are used in genetic studies to identify inherited genetic risk variants associated with relevant diseases especially complex diseases. Although GWAS in autoimmune diseases and infectious diseases were reported, GWAS related to infectious mastitis were reported in animals, and according to the studies, DCK, SLC4A4, and EDN3 genes may play a role in response to pathogens. However, no GWAS related to IGM was found in literature [9].

Schelfout et al. [9] postulated that there might be a relationship between IGM and α1-antitrypsin (AAT) deficiency [10]. The authors reported the presence of IGM in a case of α1-antitrypsin deficiency. α1-Antitrypsin deficiency is a genetic disorder caused by SERPINA gene mutations. The primary function of AAT protein is to protect tissues from the harmful effects of proteases secreted by active neutrophils. Patients with AAT deficiency have risks of hepatic dysfunction, chronic obstructive lung disease (emphysema and/or bronchiectasis), panniculitis, and C-ANCA-positive vasculitis. They postulated that AAT deficiency may cause IGM but this was only reported in one patient and further studies should be designed to investigate SERPINA1 gene variations in IGM patients [10].

2 Gene Expression Studies

A limited number of gene expression studies were reported. Zhu et al. [11] designed a study to identify gene expression profiles of idiopathic granulomatous mastitis. They compared the differences between biopsy materials of granulomatous tissue and normal tissue in terms of differentially expressed RNAs. Gene expression analysis focused on immune system genes to enlighten the underlying immune mechanism and breast cancer genes to show the difference and relationship between IGM and breast cancer. Whole gene expression profiles detected 136 upregulated and 71 downregulated mRNAs between the IGM tissues and control tissues. In the study, DNAJC27-AS1 was reported as the highest unregulated mRNA and TRAV12-1 as the lowest downregulated mRNA. Although prednisone has been commonly used in the treatment of IGM; HSD11B1 mRNA, which was the drug target of prednisone, had lower expression in IGM tissues [11]. However, several studies demonstrated that prednisone treatment has an effective role in medical treatment at reducing the size and extent of the lesion and the recurrence risk. RNA-sequencing differential expression analysis revealed that the detected differentially expressed mRNAs take a significant part in the immune system. They compared gene expression profiles of two groups (IGM tissues and normal tissue) to define the gene-gene interaction related with IGM. The mRNAs related with immune system were classified into two groups: network A and B. Network A includes FCGR1A, TRIM29, GBP1, GBP5, LILRB4, HCK, C1QB, SLC7A7, IGSF6, and CD79A genes and network B includes TCN1, MMP9, TNFAIP6, CHIT1, LYZ, SLPI, CHI3L1, CTSC, PIGR, and MMP12 genes [11]. The hub gene (gene with high correlation in candidate modules) of network A was the FCGR1A gene which was associated with IgG and protein binding. The TCN1 was the hub gene in network B that was associated with cobalamin binding. FCGR1A is the drug target of methyl aminolevulinate, and TCN1 is the drug target of hydroxycobalamin [10]. These two networks contain immune system-related genes and represent the possible role of immune mechanisms in the pathogenesis of IGM. When the authors analyzed the gene expression profiles of breast cancer, they found that 73.6% of IGM gene expressions were high in both breast cancer and IGM tissues. According to the results of the study, they concluded that

IGM etiology is due to immune system dysfunction and they found a similarity between breast cancer and IGM in some previous studies [11].

Another gene expression study was reported by Aksan et al. [12]. Their study aimed to investigate the miR-155, let-7c, miR-21, and PTEN levels of patients with IGM and breast cancer [12]. MicroRNA (miRNA) is a short noncoding RNA molecule which has a role in gene silencing and the regulation of gene expression. In recent years, miRNAs have been accepted as a potential biomarker. Several studies have reported the use of miRNAs in the diagnosis of diseases. In the Aksan's study [12], the authors chose to analyze miR-21, miR-155, and let-7c levels because in previous studies, miR-21, miR-155, and let-7c expressions were used as potential biomarkers of breast cancer [11]. They also studied the PTEN expression levels due to the negative regulation of PTEN gene expression by miR-21. According to the results of this study, the authors concluded that miR-21 may be a potential biomarker for breast cancer in the differential diagnosis of IGM. They also found a negative correlation between miR-21 and PTEN in breast cancer. It was observed that miR-21 was overexpressed whilst PTEN expression decreased in breast cancer. MiR-21 expression and PTEN levels were concluded to be useful biomarkers in the differential diagnosis of IGM and breast cancer [12].

3 Human Microbiome Studies

Commensal and symbiotic microorganisms can be found in the human body. The microbiome includes the genome of microorganisms and their ecosystems. Environmental factors, nutrition habits, and host genetics may affect the occurrence of the wide microbial diversity. The microbiome and microbial products may have a role in the regulation of immune response in the host. The interaction between the human microbiome and immune system plays an important role in the etiopathogenesis of several diseases. Recently, several studies have concentrated on the role of the microbiome in the pathogenesis of autoimmune diseases [12]. With rapid developments in sequencing technology and bioinformatics methods, the number of metagenomic studies has increased. Clarifying the effect of the human microbiome on the host immune system enables the development of new therapeutic approaches. There are numerous studies investigating the relationship between intestinal microbiome and autoimmune diseases [13, 14]. The gut microbiome is composed of millions of microbes, and it plays a crucial role in host immunity and metabolism. Several studies have been reported to analyze the gut microbiome in autoimmune diseases, such as systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes but not in granulomatous mastitis [13, 14].

The microflora of IGM is still incompletely defined. The number of studies aimed to characterize the microbiome in IGM is very limited. The first study to use next-generation sequencing in this field was conducted by Yu et al. [15]. They studied the microbiome analysis of breast tissue in IGM patients and found

Corynebacterium in all patients (19/19). *Corynebacterium* was the most abundant taxon in 40% of patients. *Corynebacterium kroppenstedtii* is the predominant *Corynebacterium* species in these patients (11/19) [15]. Previous studies support Yu et al.'s [15] finding that *Corynebacterium*, especially *C. kroppenstedtii*, was commonly detected in IGM patients. Another study profiling the microbiota of IGM patients revealed that *Pseudomonas*, *Brevundimonas*, *Stenotrophomonas*, *Acinetobacter*, and *Aspergillus* were the most detected pathogens. In contrast to previous studies, *C. kroppenstedtii* was not the predominant pathogen of IGM patients according to this study [16]. Metagenomic studies with NGS technology are considered as a potential powerful technique to detect pathogenic microorganisms in the pathogenesis of granulomatous mastitis. Metagenomics will expand our knowledge regarding the microbial diagnosis of IGM and in order to find new treatment options, but further studies are needed due to the limited number of metagenomics studies on IGM.

4 The Future

Very little is known about genetic risk factors of IGM. With the rapid development of genetic technologies, studies reporting the detection of genetic factors that play a role in the formation of various diseases have attracted great interest. New investigations will be necessary to define the genetic factors in IGM susceptibility. Further genetic studies are required to discover the granulomatous mastitis risk loci and the role of microbiota in the pathogenesis of IGM.

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