Immunoglobulin KM and GM Gene Polymorphisms Modify the Clinical Presentation of Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** To investigate whether polymorphism of immunoglobulin (Ig) genes affects susceptibility to or severity of primary Sjögren's syndrome (pSS).

Methods. Ig gene kappa (KM) and gamma (GM) polymorphisms were analyzed by a polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) based method in 65 Finnish Caucasian patients with pSS and in 66 healthy controls matched for sex, ethnic origin, and area of residence. Clinical and immunological data on the pSS patients were analyzed in relation to Ig genotypes.

Results. The genotype frequencies of Ig KM and GM genes did not differ between pSS patients and controls. Anti-SSB antibodies were encountered significantly more frequently in pSS patients carrying the KM1 allele than in those without (100% vs 48%, p = 0.016). The pSS patients with the KM1 allele had several signs of immunologically active disease: they had significantly higher erythrocyte sedimentation rate, serum IgA, serum ß$_2$-microglobulin (ß$_2$-m), and plasma IgG1 concentrations than patients without this allele. The pSS patients carrying the GM z allele had a milder form of pSS than those without this determinant. They had less severe labial salivary gland histological findings (grade 3-4 in 60% vs 93%, p = 0.004) and lower plasma IgG3 and serum ß$_2$-m concentrations than those without GM z allele.

Conclusions. Ig KM and GM genes do not contribute to susceptibility to pSS. The Ig KM1 allele is associated with several markers of immunologically active disease, whereas the Ig GM z allele is associated with milder pSS. (J Rheumatol 2004;31:2175–80)

Key Indexing Terms:
IMMUNOGLOBULIN GENE POLYMORPHISM PRIMARY SJÖGREN'S SYNDROME

Primary Sjögren's syndrome (pSS) is a chronic autoimmune exocrinopathy causing symptoms of dry eyes and mouth but also various extraglandular symptoms. Hypergammaglobulinemia and abundant autoantibody production, including rheumatoid factor (RF), antinuclear antibody (ANA), and anti-SSA and anti-SSB antibodies are characteristic features of the disease. The etiology of pSS is largely unknown, but an interaction between genetic and environmental factors is thought to lead to autoimmunity in SS[1]. HLA class II genes are known to affect susceptibility and autoantibody production in pSS[2] , but non-HLA genes, e.g., the genes encoding for cytokines, have also been found to influence susceptibility[3,4], clinical presentation[5,6], and autoantibody production in pSS[7].

Immunoglobulin (Ig) genes are polymorphic, and their polymorphism has been found to have an effect on various autoimmune and infectious diseases. The Ig kappa (KM) and gamma (GM) genes are located on human chromosomes 2 and 14, respectively. Allelic variation at the KM and GM loci results in amino acid differences in the constant regions of the kappa and gamma 1, 2, and 3 polypeptide chains, respectively[8]. The role of constant region allotypes in antibody response could be explained by possible linkage disequilibrium with particular variable region determinants or by effects on antibody affinity or idiotype formation[9]. An association between anti-SSB antibodies and serologically detected Ig KM allotypes has been observed[10]. However, it was recently reported that KM light chain alleles detected by a polymerase chain reaction (PCR)

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and restriction fragment length polymorphism (RFLP)-based method were not associated with pSS in an Australian population; moreover, the KM gene polymorphism was not associated with anti-SSA or anti-SSB antibody production[11]. The association of KM or GM allotypes with the clinical presentation and severity of pSS has not been previously investigated.

Our aim was to establish in a well-characterized group of Finnish Caucasian patients with pSS whether polymorphism of the Ig genes (KM and GM) affects susceptibility, clinical presentation, or autoantibody production in pSS.

MATERIALS AND METHODS

Patients. All patients fulfilling 3 or more modified California criteria for pSS[12] (salivary flow determinations were not performed, histological findings were graded on the Chisholm-Mason scale[13], grades 3 and 4 being regarded as diagnostic) were selected from the records of patients with sicca symptoms examined in the Department of Internal Medicine, Section of Rheumatology, at Tampere University Hospital, Finland, during the years 1977 to 1992 (n = 111). Those alive were invited by letter to attend for gene polymorphism determinations. Samples for genotyping were collected after obtaining informed consent from 65 pSS patients (63 female, 2 male, mean age 60 ± 12 years). Sixty-two of the patients fulfilled the revised American-European consensus group criteria for SS[14]. Demographic and clinical data are presented in Table 1.

Clinical methods. A careful clinical examination together with an in-depth interview covering previous and concurrent diseases and duration of pSS had recently been conducted with these patients[15]. Special emphasis was laid on possible extraglandular symptoms of pSS (dermatological, endocrine, gastrointestinal, lymphoproliferative, musculoskeletal, neurological, renal, respiratory, and vascular symptoms). Purpura was defined as a history of typical episodic palpable purpura lesions in the lower limbs or skin biopsy histology. Lymphadenopathy was defined as lymph node enlargement so persistent as to have indicated a nodal biopsy. Arthritis was defined as articular swelling observed by a clinician. Peripheral and central neurological symptoms were recorded from the history given by the patients as well as from data on possible neurological investigations from case histories. Diagnosis of pulmonary fibrosis was based on findings in chest radiographs; the diagnosis of alveolitis had been established by thorough investigations in a pulmonary unit. Urinary total protein excretions had been measured[15] and proteinuria was defined as urinary total protein excretion ≥ 0.15 g/24 h. Labial salivary gland biopsies had been taken from all 65 patients and the histological grade according to Chisholm-Mason scale was 0 in one, 1 in 2, 2 in 14, 3 in 15, and 4 in 33 of the patients.

Table 1. Demographic, clinical, and immunological characteristics of 65 patients with pSS. The values indicate numbers of patients, unless otherwise indicated, and the numbers in parentheses are percentages of cases.

Characteristic	Value or Frequency
Demographic	
Females: males	63:2
Age, mean ± SD (yrs)	60 ± 12
Disease duration, mean ± SD (yrs)	9 ± 4
Clinical	
Labial salivary gland histological grade 3–4*	48 (74)
Arthralgia	43 (66)
Raynaud's syndrome	36 (55)
Recurrent salivary gland swelling	29 (45)
Proteinuria (≥ 0.15 g/24h)	26 (43)
Arthritis	14 (22)
Purpura	12 (19)
Peripheral nervous system symptoms	12 (19)
Alveolitis or pulmonary fibrosis	8 (12)
Pleuritis	7 (11)
Lymphadenopathy	7 (11)
Central nervous system symptoms	5 (8)
Myositis	0
Immunological	
ANA positive	55/64 (86)
RF positive	46/63 (73)
Anti-SSA antibody positive	44/63 (70)
Anti-SSB antibody positive	33/63 (52)

* Chisholm-Mason scale[10]. ANA: anti-nuclear antibodies; RF: rheumatoid factor.

Controls. Sixty-six healthy Finnish Red Cross Transfusion Service blood donors matched for sex (64 female, 2 male), ethnic origin (Finnish Caucasian), and area of residence (Tampere, Finland) served as a control group for DNA studies of pSS patients. The mean age of the control subjects was 53 ± 7 years.

GM and KM genotyping. DNA samples were typed for G3M b/5 and g/21 alleles using a PCR-RFLP method as described[16]. For the determination of G1M f/3 and z/17 alleles, the CH1 region of the γ1 chain was amplified by PCR, using primers described by Balbin, *et al*[17], and purified double-stranded PCR product was subjected to automatic DNA sequencing on an ABI PRISM 377. κ chain determinants KM1 and 3 were characterized by a PCR-RFLP technique using the following primers: 5´TAG GGG GAA GCT AGG AAG AAA 3´and 5´AAA AAG GGT CAG AGG CCA AA 3´. After digestion of the amplified product (538 bp) with the restriction enzyme Acc1, products corresponding to the 3 genotypes were detected: KM1 (538 bp), KM1/3 (538 bp, 390 bp, 148 bp), and KM3 (390 bp, 148 bp).

The Ig KM, GM (b,g), and GM (f,z) genotypes were successfully determined in 62, 59, and 62 patients with pSS, respectively. KM and GM (f,z) genotyping was successfully performed in all 66 control subjects, and GM (b,g) genotyping in 63 of them.

Statistical analysis. Mann-Whitney U-test and chi-square test were used in comparisons of continuous and dichotomous variables, respectively. Findings were considered statistically significant at $p < 0.05$. P values were not corrected for multiple comparisons. Statistical analyses were performed with SPSS 10.1 for Windows.

Ethical approval. The study protocol was approved by the Ethical Committee of Tampere University Hospital.

RESULTS

Ig KM gene polymorphism. The Ig KM genotype frequencies in pSS patients and controls were not different (Table 2). The pSS patients carrying the rare KM1 allele yielded several laboratory findings suggestive of a more active form of the disease (Table 3). Anti-SSB antibodies were encountered significantly more frequently in pSS patients with the KM1 allele than in patients without this allele (100% vs 48%, p = 0.016). The titer of anti-SSB antibodies was higher in KM1 carriers compared to non-carriers, albeit not significantly (Table 3). The KM1 allele carriers had significantly higher mean erythrocyte sedimentation rate, serum IgA, serum beta-2 microglobulin ($ß_2$-m), and plasma IgG1 subclass concentrations than patients not carrying this allele.

No differences were observed in the frequencies of such

extraglandular manifestations of pSS as a history of arthralgia, arthritis, salivary gland swelling, Raynaud's symptoms, purpura, lymphadenopathy, pleuritis, alveolitis or pulmonary fibrosis, or peripheral or central nervous system symptoms (data not shown). Neither the histological grade in labial salivary gland biopsies nor the number of diagnostic criteria for pSS differed between pSS patients with or without KM1 allele (Table 3).

Ig GM gene polymorphism. The Ig GM genotype frequencies in pSS patients and controls did not differ (Table 2). A strong, but not absolute, linkage between the GM b,g and GM f,z allotypes was observed in both pSS patients and controls. The GM g allele occurred more frequently in both controls and pSS patients carrying the GM z allele compared to non-carriers of z (94% vs 0, $p < 0.0001$, and 76% vs 16%, $p < 0.0001$, in the respective groups).

Patients with pSS carrying the GM allele z had findings suggestive of a milder form of the disease than patients without this determinant. They had less severe labial salivary gland histological findings (grade 3-4 in 60% vs 93%, $p = 0.004$) and lower plasma IgG3 and serum $ß_2$-m concentrations than those without GM z allele (Table 4).

The pSS patients with GM allele g had proteinuria significantly more frequently than those not carrying allele g. They had lower plasma IgG3 concentrations than those without this allele (Table 5).

Pulmonary fibrosis or alveolitis occurred less frequently in both Ig GM z carriers (3% vs 22%, $p = 0.017$) and Ig GM g carriers (3% vs 21%, $p = 0.049$) compared with respective non-carriers. Purpura occurred less frequently (10% vs 31%, $p = 0.045$) in Ig GM g carriers compared with g non-carriers. No differences were observed in the frequencies of other extraglandular manifestations of pSS between Ig GM z or g carriers and corresponding non-carriers (data not shown).

Table 2. The frequencies of immunoglobulin kappa (KM) and gamma (GM) b,g and f,z genotypes in patients with pSS and controls. The numbers in parentheses are percentages of cases. Statistical analysis was performed using the chi-square test.

Genotype	pSS Patients	Controls	p
KM 1	0	0	
KM 1, 3	6 (10)	6 (9)	
KM 3	56 (90)	60 (91)	0.909
GM b	29 (49)	32 (51)	
GM b,g	24 (41)	24 (38)	
GM g	6 (10)	7 (11)	0.954
GM f	27 (44)	30 (46)	
GM f, z	30 (48)	28 (42)	
GM z	5 (8)	8 (12)	0.672

DISCUSSION

The main findings in our study were that Ig KM genes contribute to the severity of pSS and to anti-SSB antibody pro-

Table 3. Demographic, clinical, and immunological characteristics of patients with pSS carrying or not carrying the Ig kappa (KM) 1 allele. The values indicate numbers of patients, unless otherwise indicated, and the numbers in parentheses are percentages of cases. Statistical analysis was performed using the Mann-Whitney U-test or chi-square test. P values were not corrected for multiple comparisons.

Characteristic	Genotype KM 1,3 n = 6	Genotype KM 3 n = 56	p
Age, yrs, mean ± SD	58 ± 13	60 ± 11	0.789
Disease duration, yrs, mean ± SD	7 ± 4	9 ± 4	0.553
Proteinuria	3 (50)	21 (40)	0.624
LSG histological grade 3-4[13]	5 (83)	40 (71)	0.534
4/4 of diagnostic criteria[12]	2 (33)	25 (45)	0.595
ESR, mm/h, mean ± SD	49 ± 20	30 ± 20	0.040
S-IgA, g/l, mean ± SD	5.2 ± 2.1	3.0 ± 1.7*	0.002
S-IgG, g/l, mean ± SD	23.1 ± 6.4	18.5 ± 7.0*	0.093
S-IgM, g/l, mean ± SD	1.7 ± 0.6	1.4 ± 0.8*	0.218
P-IgG1, g/l, mean ± SD	20.1 ± 5.8	15.4 ± 7.0*	0.049
P-IgG2, g/l, mean ± SD	2.48 ± 0.79	2.80 ± 1.22*	0.546
P-IgG3, g/l, mean ± SD	0.63 ± 0.27	0.60 ± 0.50*	0.247
P-IgG4, g/l, mean ± SD	0.24 ± 0.20	0.24 ± 0.36*	0.485
S-ß2m, mg/l, mean ± SD	4.1 ± 1.6	2.8 ± 0.9*	0.021
RF positivity	5 (83)	39 (72)**	0.559
ANA positivity	6 (100)	46 (84)*	0.283
Anti-SSA positivity	6 (100)	37 (69)**	0.104
Anti-SSB positivity	6 (100)	26 (48)**	0.016
Anti-SSA titer, U/l, mean ± SD	86 ± 32	68 ± 53**	0.418
Anti-SSB titer, U/l, mean ± SD	88 ± 57	62 ± 76**	0.239

LSG: labial salivary gland biopsy; ESR: erythrocyte sedimentation rate; ß2m: beta-2 microglobulin; RF: rheumatoid factor; ANA: antinuclear antibodies. * n = 55. ** n = 54.

Table 4. Demographic, clinical, and immunological characteristics of patients with pSS carrying or not carrying the Ig gamma (GM) z allele. Values indicate numbers of patients, unless otherwise indicated; numbers in parentheses are percentages of cases. Statistical analysis was by Mann-Whitney U-test or chi-square test. P values were not corrected for multiple comparisons.

Characteristic	GM z+ n = 35	GM z- n = 27	p
Age, yrs, mean ± SD	59 ± 10	62 ± 14	0.170
Disease duration, yrs, mean ± SD	9 ± 4	10 ± 5	0.568
Proteinuria	16 (49)	7 (28)	0.114
LSG histological grade 3-4[13]	21 (60)	25 (93)	0.004
4/4 of diagnostic criteria[12]	15 (43)	13 (48)	0.678
ESR, mm/h, mean ± SD	28 ± 19	36 ± 23	0.112
S-IgA, g/l, mean ± SD	3.1 ± 1.6*	3.5 ± 2.0	0.338
S-IgG, g/l, mean ± SD	18.1 ± 5.8*	19.3 ± 8.6	0.885
S-IgM, g/l, mean ± SD	1.4 ± 0.5*	1.5 ± 1.0	0.942
P-IgG1, g/l, mean ± SD	14.8 ± 5.4*	16.3 ± 8.5	0.733
P-IgG2, g/l, mean ± SD	2.80 ± 1.13*	2.72 ± 1.28	0.885
P-IgG3, g/l, mean ± SD	0.43 ± 0.26*	0.83 ± 0.59	0.002
P-IgG4, g/l, mean ± SD	0.26 ± 0.44*	0.21 ± 0.18	0.541
S-ß2m, mg/l, mean ± SD	2.7 ± 0.9*	3.2 ± 1.1	0.024
RF positivity	24 (71)*	20 (77)†	0.582
ANA positivity	29 (85)*	23 (85)	0.990
Anti-SSA positivity	26 (79)**	16 (59)	0.101
Anti-SSB positivity	19 (58)**	12 (44)	0.311
Anti-SSA titer, U/l, mean ± SD	72 ± 44**	65 ± 73	0.561
Anti-SSB titer, U/l, mean ± SD	65 ± 73**	58 ± 75	0.549

GM z+: carrier of Ig GM z allele; GM z-: non-carrier of Ig GM z allele. For additional definitions see Table 3. * n = 34. ** n = 33. † n = 26.

Table 5. Demographic, clinical, and immunological characteristics of patients with pSS carrying or not carrying the Ig gamma (GM) g allele.Values indicate numbers of patients, unless otherwise indicated; numbers in parentheses are percentages of cases. Statistical analysis was by Mann-Whitney U-test or chi-square test. P values were not corrected for multiple comparisons.

Characteristic	GM g+ n = 30	GM g- n = 29	p
Age, yrs, mean ± SD	61 ± 11	58 ± 13	0.383
Disease duration, yrs, mean ± SD	10 ± 4	9 ± 4	0.256
Proteinuria	16 (57)	8 (29)	0.031
LSG histological grade 3-4[13]	20 (67)	23 (79)	0.275
4/4 of diagnostic criteria[12]	12 (40)	13 (45)	0.708
ESR, mm/h, mean ± SD	32 ± 24	31 ± 17	0.452
S-IgA, g/l, mean ± SD	3.1 ± 1.8*	3.5 ± 2.0	0.384
S-IgG, g/l, mean ± SD	18.7 ± 6.5*	19.2 ± 7.8	0.901
S-IgM, g/l, mean ± SD	1.3 ± 0.5*	1.6 ± .0.9	0.384
P-IgG1, g/l, mean ± SD	15.8 ± 6.5*	16.2 ± 7.7	0.870
P-IgG2, g/l, mean ± SD	2.78 ± 0.88*	2.73 ± 1.35	0.414
P-IgG3, g/l, mean ± SD	0.43 ± 0.26*	0.79 ± 0.59	0.019
P-IgG4, g/l, mean ± SD	0.26 ± 0.35*	0.24 ± 0.36	0.852
S-ß2m, mg/l, mean ± SD	2.9 ± 1.2*	2.8 ± 1.0	0.882
RF positivity	22 (76)*	20 (71)**	0.704
ANA positivity	25 (86)*	25 (86)	1.000
Anti-SSA positivity	22 (79)**	19 (66)	0.273
Anti-SSB positivity	15 (54)**	15 (52)	0.889
Anti-SSA titer, U/l, mean ± SD	71 ± 45**	67 ± 57	0.987
Anti-SSB titer, U/l, mean ± SD	64 ± 75**	65 ± 74	0.987

GM g+: carrier of Ig GM g allele; GM g-: non-carrier of Ig GM g allele. For additional definitions see Table 3. * n = 29. ** n = 28.

duction and that the GM z allele seems to be a protective factor in respect of pSS severity. Ig gene polymorphism does not affect susceptibility to pSS in Finnish Caucasian patients. Previously, the association of KM or GM allotypes with the clinical presentation and severity of pSS has not been investigated, except for the presence of anti-SSA and anti-SSB antibodies.

We found anti-SSB antibodies significantly more frequently in pSS patients with the KM1 allele than in patients without this allele. The titer of anti-SSB antibodies also tended to be higher in KM1 carriers compared to non-carriers. This finding is analogous to original findings of an association of serologically detected KM allotypes with anti-SSB antibodies[10], but is in contrast to a recent report from Australia, in which KM alleles were not associated with anti-SSA or anti-SSB antibody responses in patients with pSS[11]. The difference between those results and ours is probably explained by different genetic backgrounds of study populations. Frequencies of GM and to a lesser extent KM allotypes vary widely among racial groups. Within a race, GM allotypes show strong linkage disequilibrium[18]. KM and GM markers are located on the constant region of the Ig, but there is a growing body of evidence for involvement of these regions in antibody specificity usually associated with the variable region of the Ig molecule. The underlying mechanisms are not completely understood, but there are several well-documented examples of constant domains influencing the specificity of antibodies to various antigens[19-21]. Previously, associations have been found with KM alleles and production of various autoantibodies such as anti-DNA antibodies in systemic lupus erythematosus (SLE)[22], anti-fibrillin antibodies in scleroderma[23], and anti-Mi antibodies in inflammatory myositis[24]. Ig GM f,z genotypes and interleukin 6 –174 genotypes have recently been shown to exert an epistatic effect on the production of autoantibodies to heat-shock protein[25].

The pSS patients with the KM1 allele had several other laboratory findings uniformly suggesting immunologically active disease: they had significantly higher mean erythrocyte sedimentation rate, serum IgA, and serum $ß_2$-m concentrations than patients not carrying the KM1 allele. Increased levels of serum $ß_2$-m have been associated with lymphoproliferative and renal complications of pSS[6,26,27]. The association of serum $ß_2$-m concentrations with KM or GM allotypes in pSS has not previously been investigated. However, in hematological malignancies the phenotype facilitating $ß_2$-m shedding from cell surface has been found to be independent of specific IgG heavy chain allotypes[28].

IgG1 levels were associated with KM allotypes, and IgG3 levels were lower in patients with GM z or GM g than in patients with GM f or GM b, respectively. These findings are in agreement with previously observed strong associations of IgG subclasses with Ig gene loci[29,30].

For the first time, GM z was found to constitute a protective factor with respect to the severity of pSS. The pSS patients carrying GM allele z had less severe labial salivary gland histological findings and lower serum $ß_2$-m concentrations than those without this allele.

Pulmonary fibrosis or alveolitis occurred less frequently in both Ig GM z carriers and Ig GM g carriers compared with the corresponding non-carriers. Purpura occurred less frequently in Ig GM g carriers compared with g non-carriers. Patient numbers in these subgroups were very small and therefore reliable conclusions cannot be drawn. It is nonetheless of interest that in a family study with 12 subjects with clinical evidence of pulmonary fibrosis, all affected siblings were carrying the Ig haplotype GM1, and based on this observation a dominantly inherited gene located on chromosome 14 close to the loci of GM was suggested to be associated with familial fibrosing alveolitis[31].

The pSS patients with GM allele g had proteinuria significantly more frequently than those not carrying allele g. In an earlier study no difference was observed in the distribution of GM and KM alleles among patients with IgA nephropathy and controls[32] or between SLE patients with or without nephritis[33], but contrasting results regarding GM allotypes and renal manifestations in patients with SLE have been found[34].

Neither the Ig KM nor GM genotype frequencies in pSS patients and controls differed. This is similar to findings reported in the recent Australian study[11]. No association with disease susceptibility and KM or GM allotypes has been found in rheumatoid arthritis[35,36] or in scleroderma[23]. KM genotypes have been found to affect susceptibility to SLE, but conflicting associations have been reported[22,37]. A strong association between the KM1 allele and susceptibility to SLE was observed in one study[22] but in contrast, in a population-based case-control study the KM3,3 was associated with an increased risk, whereas KM1,3 with a lower relative risk of SLE in Caucasians[37].

Recently HLA class II markers were reported to confer genetic susceptibility to Sjögren's syndrome only in patients with anti-SSA and anti-SSB antibodies[38]. Hence, the role of KM allotypes in the pathogenesis of pSS appears to be similar to that of HLA antigens; neither genetic system is strongly associated with the disease itself, but both contribute significantly to the generation of particular autoimmune responses.

In conclusion, Ig allotypes were found to be responsible for many determinants of the clinical presentation and severity of pSS as well as for anti-SSB antibody production, but did not affect disease susceptibility.

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