MEDICAL UNIVERSITY-PLEVEN
Faculty of Pharmacy

Department of „Chemistry and Biochemistry“

Borislav Tsvetanov Dimitrov

ANALYSIS OF THE ROLE OF GENETIC VARIANTS OF THROMBOPHILIC FACTORS IN THE PATHOLOGY OF PSORIASIS VULGARIS

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Scientific supervisors:

Prof. Regina Komsa-Penkova, PhD, DBs

Prof. Dr. Dimitar Konstantinov Gospodinov, MD, PhD, DSc.

Official Reviewers:

Prof. Tatyana Ivanova Vlaikova, PhD

Prof. Maria Atanasova Radanova, PhD

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The PhD student works as a teacher in the "Biochemistry" section at the Medical University - Pleven.

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Abbreviations used

MS - Metabolic Syndrome
BP- Arterial pressure
CVD - Cardiovascular disease
DVT - Deep vein thrombosis
PTE - Pulmonary thromboembolism
SD - Standard deviation
Cl - Confidence interval
OR - Odds ratio
IL-6 - Interleukin-6
TNF-α - Tumor necrosis factor-α
SNP - Single nucleotide polymorphism
PASI - Psoriasis Area and Severity Index
BMI - Body mass index
CRP - C-reactive protein
PAI-1 - Plasminogen activator inhibitor type 1
SND - Single nucleotide deletion
tPA - Tissue plasminogen activator
uPA - Urokinase
GP - Glycoprotein
FV - Factor V
FVL - Factor V Leiden
FII - Prothrombin/Factor II
MTHFR - Methylene Tetrahydrofolate Reductase
THF - Tetrahydrofolate
MI - Myocardial infarction
PCR - Polymerase Chain Reaction
GPIIb/IIIa - Glycoprotein IIb/IIIa
GPIIb - Glycoprotein IIb
SAM - S-adenosylmethionine
HDL - High Density Lipoprotein
ADP - Adenosine diphosphate
HWE - Hardy-Weinberg equation
NAFLD - Non-alcoholic fatty liver disease
VWF - Von Willebrand Factor

1. INTRODUCTION

Psoriasis is a widespread chronic relapsing-remitting dermatosis that affects about 1-5% of the population in developed countries. Pathological epidermal hyperproliferation and parakeratosis are the main histological features of psoriasis. Increased release of pro-inflammatory cytokines and chronic activation of the innate and adaptive immune system result in long-term damage to multiple tissues and organs of patients. Psoriasis is a systemic process associated with multiple comorbidities, such as psoriatic arthritis, Crohn's disease, cancer, hypertension, cardiovascular disease (CVD), chronic obstructive pulmonary disease, non-alcoholic fatty liver disease (NAFLD), depression, etc.

A growing number of clinical studies confirm that psoriasis is often associated with cardiometabolic factors such as obesity, diabetes mellitus, hyperlipidemia, insulin resistance, and metabolic syndrome (MS). These cardiometabolic factors directly increase the risk of CVD, arterial and venous thrombosis and lead to premature mortality in patients with psoriasis, thereby significantly reducing their life expectancy. It is therefore crucial to understand the mechanisms and factors underlying the relationship between psoriasis and comorbidities. Although a definitive causal relationship has not been established, a combination of genetic factors, common signaling pathways, and environmental factors could lead to metabolic abnormalities in patients with psoriasis. As an immunoinflammatory disease, psoriasis is characterized by T helper type 1 and T helper type 17-mediated inflammation, with marked overlap with inflammatory markers and mediators of atherosclerosis. Furthermore, pathological angiogenesis, endothelial dysfunction, and impaired coagulation are common in both psoriasis and cardio-metabolic diseases, suggesting a link in their pathogenesis. These data may explain, in part, the psoriasis-associated risk of atherothrombotic cardiovascular events, e.g., acute myocardial infarction (MI) and cardiovascular mortality. Atherothrombotic events are accompanied by increased markers of hypercoagulability, including platelet activation and hyperhomocysteinemia.

Data on the potential impact of psoriasis on the risk of venous thrombotic events and venous thromboembolism (VTE) in particular are limited.

There is evidence that the risk of venous thrombosis and other adverse cardiovascular events increases in patients with psoriasis. A meta-analysis of five studies from 2021 suggests that the risk for VTE in patients with psoriasis is elevated, albeit nonsignificantly compared with healthy controls. Chronic inflammation in autoimmune diseases has been shown to promote the coagulation cascade, disrupt the anticoagulation pathway, and inhibit the fibrinolytic process (the components of the Virchow triad). Endothelial dysfunction has been documented in patients with psoriasis. Despite these data, it is unclear why patients with psoriasis have a higher risk of comorbidities of inflammatory and prothrombotic origin. More research is needed to identify risk subgroups (e.g., younger patients, carriers of certain genetic factors, lifestyle and metabolic indicators) for the development of comorbidities.

At the same time, psoriasis has a multifactorial genetic basis evidenced by epidemiological studies and family histories involving different polymorphic alleles.

These facts suggest that specific polymorphisms associated with risk of proinflammatory and prothrombotic conditions may also contribute to a higher risk of developing comorbidities in the course of psoriatic disease.

2. AIM AND OBJECTIVES

2.1. Aim

To investigate the role of the polymorphisms PAI-1 (*-675* ID, (*4G/5G*), PL *A1/A2(rs5918ITGB3)*, *MTHFR C667C>T* (*rs1801133*), *FVL* (*rs 6025*) and *FII 20210 G>A* (*rs179996*) as risk factors for the development of Psoriasis vulgaris and comorbidities.

2.2. Objectives

1. To genotype patients with plaque psoriasis and a control group of healthy volunteers for a polymorphism *(-675 ID, (4G/5G)*, in the plasminogen activator inhibitor type 1 (PAI-1) gene and to investigate the association between carrying this polymorphism and determining the risk of developing this disease, as well as its relevance to possible comorbidities, i.e. CVD, type 2 diabetes, hyperlipidemia, obesity and MS manifesting in carriers of this polymorphism.
2. To genotype patients with plaque psoriasis and a control group of healthy volunteers for the *C667C>*T polymorphism in the Methylene Tetrahydrofolate Reductase (MTHFR) gene and to investigate the association between carrying this polymorphism and determining the risk of developing this disease, as well as its relevance to possible comorbidities, including CVD, type 2 diabetes, hyperlipidemias, obesity and MS manifesting in carriers of this polymorphism.
3. To genotype patients with plaque psoriasis and a control group of healthy volunteers for the *PLA1/A2 (rs5918ITGB3)* polymorphism in the platelet integrin 3B gene and to investigate the association between carrying this polymorphism and determining the risk of developing this disease and its relevance to possible comorbidities, including CVD, type 2 diabetes, hyperlipidemias, obesity and MS manifesting in carriers of this polymorphism.
4. Genotyping of patients with plaque psoriasis and a control group of healthy volunteers for the Factor V Leiden *(FVL)* polymorphism *(rs6025)* in the Factor V (FV) gene and investigating the association between carriage of this polymorphism and determining the risk of developing this disease, as well as its relevance to possible comorbidities, incl. CVD, type 2 diabetes, hyperlipidemias, obesity and MS manifested in carriers of this polymorphism.
5. To genotype patients with plaque psoriasis and a control group of healthy volunteers for the *FII 20210 G>A (rs179996)* polymorphism in the Factor II/prothrombin (FII) gene and to investigate the association between carrying this polymorphism and determining the risk of developing this disease and its relevance to possible comorbidities, incl. CVD, type 2 diabetes, hyperlipidemias, obesity and MS manifesting in carriers of this polymorphism.

3. MATERIALS AND METHODS

3.1. Groups of individuals studied. Selection and clinical criteria for inclusion in the study.

3.1.1. Selection of patients with psoriasis

The subject of the study were patients with psoriasis of Caucasian race, aged 18 years and older, undergoing inpatient treatment at the Clinic of Skin and Venereal Diseases, Dr. Georgi Stransky University Hospital in Pleven, Bulgaria from 2015 to2021.

The study was a clinical-laboratory study carried put in hospital settings and included 82 men and 27 women, 109 patients in total (Table 3.1).

Patients with dermatosis were hospitalized according to the NHIF regulations on clinical pathways. Selection of eligible patients with plaque psoriasis for the study was performed by the attending physicians in the clinic from a total of 940 patients hospitalized with dermatological disease during the same time period.

The selection was based on the patients' records and specially designed questionnaires containing information on the type of psoriasis, age of onset, presence of risk factors, family history, dietary habits, and physical activity. There was no consanguinity between the patients. Specialists in the fields of dermatology, biochemistry and medical genetics were involved in the preparation of the questionnaires using the most recent published data on the problem.

3.1.2. Control group selection

The control group included 181 healthy individuals aged 18 years and older (77 males and 104 females) (Table 3.1). Individuals in the control groups were not related by blood and were of the Caucasian race. All control group participants signed an informed consent form.

Table 3.1. Number and demographic characteristics of psoriasis patients and control group of healthy individuals

Individuals studied	**Psoriasis patients**	**Controls**
Nuimber (n)	109	181
Males n (%)	82 (75)	77 (42.55)
Females n (%)	27 (25)	104 (57.45)
Age ($\bar{X}$ ± SD) Range	53.87 (± 12.60) (20-87)	41.14 (± 12.01) (17-71)
Age males ($\bar{X}$ ± SD) Range	54.67 (± 11.68) (30-87)	39.62 (±11.95) (21-71)
Age females ($\bar{X}$ ± SD) Range	51.48 (± 15.02) (20-77)	42.21 (±11.98) (17-71)

3.2. Clinical method

Data on the medical history, physical and dermatological status, laboratory investigations, data on heredity, stress, infections and other provoking factors; past and present

diseases; and therapy underway (methotrexate, systemic and topical steroids, retinoids, phototherapy et al.); harmful habits - smoking, stimulant intake, alcohol abuse were taken from the patient records (case histories) and plotted on an form designed for the study. Clinical data were provided by the Clinic of Skin and Venereal Diseases, Dr. Georgi Strensky University Hospital - Pleven.

Anthropometric data were taken from the patients' clinical charts: height (cm) and weight (kg) and body mass index (BMI) was calculated as weight (kg) over height (m) squared (kg/m^2).

The following biochemical parameters were tested in the clinical laboratory of the University Hospital - Pleven: fasting blood glucose (mmol/l), triglycerides (mmol/l), high-density lipoprotein (HDL)-cholesterol (mmol/l), total cholesterol (mmol/l), C-reactive protein (CRP) (mg/l), and uric acid.

(The clinical laboratory of the University Hospital - Pleven is certified every two weeks according to the certification rules.)

The patients with hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, high CRP were statistically analyzed by groups.

The patients' disease severity data included Psoriasis Area Severity Index (PASI). This index ranges from zero to seventy-two, and reflects the degree of involvement of the skin surface. Also it defines the severity of the disease. According to the PASI score, the disease severity was differentiated as follows: mild psoriasis (PASI < 3), moderate psoriasis (PASI 3-10), severe psoriasis (PASI 10-20) and very severe psoriasis (PASI > 20) The following data on comorbidities were taken from the patients' clinical records for statistical analysis: the presence of comorbidities such as hypertension, type 2 diabetes, psoriatic arthritis, CVD without hypertension, CVD + hypertension, liver disease, thrombosis, MS, MS + BMI > 30. Some patients had charts with incomplete data on comorbidities and were not included in the analysis of comorbidities.

3.2.1. Criteria for the diagnosis of MS

The presence of MS was diagnosed according to IDF (International Diabetes Federation) and NCEP: ATPIII (National Cholesterol Education Program: Adult Treatment Panel III) criteria . The diagnosis was made in the presence of the first criterion, which is obesity, and two of the next 4 criteria.

1. Obesity grade III - IV. Defined by the waist circumference size according to the European norms for central obesity (mandatory component) - for the Europid race - waist circumference ≥ 94 cm in men and ≥ 80 cm in women, and BMI greater than 30 kg/m^2 for both sexes.
2. Elevated triglyceride levels ≥ 1.7 mmol/l (≥ 150 mg/dl) or specific treatment due to this lipid disorder.
3. Low HDL-cholesterol (HDL) ≤1.04 mmol/l (40 mg/dl) in men and 1.30 mmol/l in women.
4. Hyperglycemia > 6.1 mmol/l or previously diagnosed type 2 diabetes.

Hypertension, elevated blood pressure (BP) - systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85

mm Hg, or treatment of previously diagnosed hypertension.

3.3. DNA analysis

This section includes: extraction methods and characterization of the quantity and quality of extracted DNA, DNA amplification and analysis.

3.3.1. Extraction of genomic DNA by the salt extraction method

For the extraction of genomic DNA from venous blood, white blood cells with nuclei were lysed and histone and non-histone proteins associated with genomic DNA were removed. DNA yield is ~30-60 μg/ml.

3.3.2. Use of Polymerase Chain Reaction (PCR) to analyze the carriage of SND *-675 ID 4G/5G* polymorphisms in PAI-1 gene, *677 C>T* variant in *MTHFR(rs1801133), PLA1/A2* in platelet glycoprotein IIb/IIIa gene *(rs5918ITGB3), FVL (rs6025), FII 20210 G>A (rs1799963)* mutation in prothrombin gene.

Polymerase chain reaction is the in vitro replication of a selected region of DNA using primers (short DNA sequences) recognizing the region of interest. The synthesis of the DNA copies was carried out by Taq polymerase, which is a thermostable DNA polymerase. PCR results in millions of copies of DNA from the region of interest, which were then used in qualitative reactions to detect polymorphisms. The PCR reaction itself can also be used directly as an allele-specific diagnostic method to detect genetic polymorphisms.

3.3.3. Diagnostic DNA analysis. Methods for detection of known polymorphisms.

Three methodologies were used for direct DNA analysis of polymorphisms: allele-specific PCR, restriction analysis, and strip assay.

3.3.3.1. Restriction analysis

This methodology was used to confirm or reject the presence of a mutation where PCR products were incubated with restriction endonuclease. The enzyme was selected to recognize a specific DNA sequence and cut it into two smaller fragments. The presence of a mutation in the DNA region analyzed creates/removes the specific sequence recognized by the restrictase. The PCR product containing the polymorphism differs in length compared to the PCR product without the polymorphism, resulting in a different electrophoretic mobility.

Restriction analysis was used in this dissertation to confirm the recessive allele *677 T* of the *677 C>T* polymorphism in the MTHR gene, the dominant allele *1691A* of the *FVL* polymorphism of factor FV, and the dominant allele *20210A* of the polymorphism (FII 20210 G>A) of the coagulation FII gene.

3.3.3.2. Allele-specific PCR

Allele-specific PCR is a modification of standard PCR in which an allele-specific primer that hybridises only in the presence or absence of a mutation in the DNA is used to achieve high specificity.

For each DNA sample, two parallel PCRs were performed: one with a primer for the normal allele and the other - with a primer for the mutant allele. In both reaction mixtures, so-called constitutive primers were inserted to amplify the DNA sequence outside the region of interest. The product resulting from the hybridization of constitutive primers is a guarantee that the PCR reaction has proceeded. The amplified products of the two parallel reactions were tested simultaneously on gel electrophoresis. The presence of a product in the respective PCR reaction indicated the carriage of the respective allele (mutant or normal). The presence of product in both PCR reactions indicated heterozygous carriage.

Allele-specific PCR was used to determine the carrier status of the 4G recessive allele of SND -*675 ID 4G/5G* in the PAI-1 gene.

3.3.3.3. Visualization of allele-specific PCR and restriction analysis results by agarose gel electrophoresis

Agarose gel electrophoresis was used to separate DNA sequences on agarose gel, due to their different electrophoretic mobility depending on their length, when a direct current of 140-160 V is passed. The mobility of the DNA fragments in the gel was maintained by an electrophoretic buffer. In order to confine the dropped DNA in the wells of the agarose gel, mixing with the dye xylene cyanol, which also served as a visual marker for the movement of DNA in the gel (2 μl of xylene cyanol mixed with 10-15 μl of the DNA product) was applied. Ethidium bromide (an intercalating dye in the DNA helix) was added to the cooled agarose prior to polymerisation. As it moved through the agarose gel, the DNA was labeled with ethidium bromide and could be observed under UV light. Screening of the separated DNA sequences was performed using a UV transilluminator.

3.3.3.4. Using Strip Assay kit (Cardiovascular diseases (CVD) of Vienna Lab Diagnostics) analysis of the carriage of polymorphism *1298A>C* variant in MTHFR

ViennaLab Diagnostics' Strip Assay kit for Cardiovascular diseases (CVD) was used for determining the carrier status of the following polymorphisms: Factor V Leiden, H1299R in the Factor V gene, V34L in the Factor XIII gene, 20210 G>A (*rs179996*) in the prothrombin gene, A1/A2 (*rs5918ITGB3*) in the GPIIb/IIIa gene, SND -675 ID 4G/5G polymorphism in the PAI- 1 gene, A1298C polymorphism in the MTHFR gene, polymorphism 677 in the MTHFR gene, R3500Q in the Apolipoprotein B gene, Apolipoprotein E (Apo E) E2/E3/E4, -455 G>A in the Beta-Fibrinogen gene, insertion/deletion (I/D) at position 287 bp in the Angiotensin-Converting Enzyme gene. It consisted of multiplex PCR and precise selective hybridization of specific sequences (southern blot test form).

3.4. Carriage analysis of polymorphisms SND - *675 ID 4G/5G* in the PAI-1 gene, PL *A1/A2 (rs5918ITGB3)* in the platelet integrin B3 gene, *677C>T* in *MTHFR((rs5918ITGB3)* in the MTHFR gene, *FII 20210 G>A (rs1799963)* in the coagulation FII gene, and *FVL (rs6025)* in the FV gene in the psoriasis patients and controls.

An association analysis was performed between heterozygous and homozygous genotypes for the variant (mutant) alleles [odds ratio (OR), 95% confidence interval (CI) and p were determined], which were evaluated against homozygous genotypes for the more common allele perceived as the reference genotype, respectively the reference allele, whose OR was 1 (Additive model). Thus, for each polymorphism, the risk or protective role of the variant allele and the genotypes, including the variant allele, were clearly visible.

For the recessive model, the analysis performed was on [NN] vs. [MM+MN (ref)]. It was used to analyze the 4G allele of SND *-675 ID 4G/5G* in the PAI-1 gene and the *677* T allele in the MTHFR gene.

For the dominant allele, the analysis was performed on [NN+MN] vs. [MM (ref)]; the remaining three polymorphisms: *PL A1/A2 (rs5918ITGB3),* FII 20210 G>A (rs1799963) and *FVL (rs6025)* were calculated for the dominant allele.

3.4.1. Analysis of the association between the carriage of the five thrombophilic polymorphisms and clinical and laboratory data for patients with psoriasis

To assess the significance of 4G/4G genotype carriage on clinical and laboratory data of patients with psoriasis, carriers of this genotype were initially compared with a group of non-carriers of the 4G/4G genotype in the PAI-1 gene.

In the second stage, the association of 4G/4G genotype carriage with the clinical and laboratory data of patients with psoriasis was examined against a group of non-carriers of both this genotype and non-carriers of other thrombophilic polymorphisms studied in this thesis as follows: SND *-675 ID 4G/5G*; *677 C>T in MTHFR*, (*rs1801133*) polymorphism in MTHFR gene, (*rs5918ITGB3*) PL A1/A2 polymorphism in integrin β3 gene, FVL polymorphism (rs6025) in factor V gene and (*rs179996*) *FII 20210 G>A* polymorphism. After subtracting the patients carrying the above five risk polymorphisms for arterial or venous thrombosis, a group of 44 patients was obtained, which was used as a reference for analysing the comorbidities of carriers of each polymorphism versus non-carriers of thrombophilic mutations.

Similarly, the association of the remaining four thrombophilic polymorphisms with clinical and laboratory data of psoriasis patients with mutant allele carriers and non-carriers of the five polymorphisms was examined.

3.5. Determination of serum PAI-1 levels by ELISA (enzyme-linked immunosorbent assay)

PAI-1 concentration in serum was measured by enzyme-linked immunosorbent assay (ELISA) using a BioVendor R&D kit.

3.6. Statistical methods

The data collected were entered and processed using the Statistical Package for Social Sciences (SPSS) version 23.0. and EXCEL. A significance level of $p < 0.05$ was chosen to reject the null hypothesis.

The results are described by tables, graphs and numerical values: percentages, coefficients, means, standard deviation (SD), etc.

The assessment of statistical significance in the study groups was carried out by means of the "p" value for the chi-square ($\chi 2$) value found, with differences considered significant at a significance level of $p < 0.05$.

Analysis of variance

The following descriptive numerical characteristics were used to measure the variation: range (range) of the variation series - the difference between the extreme values (maximum and minimum), SD - the mean deviation of the results from the arithmetic mean.

Parametric methods for hypothesis testing

Applicable only to quantitative quantities with normal or near-normal distribution

ANOVA test was used to analyze parametric data.

Non-parametric hypothesis testing methods - applicable to quantitative and qualitative variables, regardless of the shape of the distribution.

Pearson $\chi 2$ criterion and Kruskall-Wallis criterion were used to analyze non-parametric data.

4. RESULTS

4.1. Anthropometric and clinical data

The primary anthropometric and clinical data of patients (n=109) and controls (n=181) are presented in Table 4.1.

The mean age of te patients and the controls had similar values. Body mass index was higher in patients 28.97 kg/m^2 compared with controls 24.35 ± 3.9. The patient group was generally overweight, close to obese. The mean PASI value of the entire patient group was 26.62 (>20), placing it in the "very severe psoriasis" category. The patients had the following comorbidities: hypertension 58.7.0%, MS 45.0%, CVD 31.19%, psoriatic arthritis 36.0% and Type 2 Diabetes 18.34%.

Table 4.1. Anthropometric and clinical data: BMI, PASI, CVD, hypertension, Type 2 Diabetes, CVD, psoriatic arthritis and MS of the patients included in the study. Mean age and BMI of controls.

Parameters	**Paients** $\bar{X}$ **± SD**	**Controls** $\bar{X}$ **± SD**	
Number of individuals	109	181	
Mean age (years)	54.07 ± 12.70	52.40 ± 14.82	P > 0.05
Age at diagnosis (years)	36.56 ± 15.80		
BMI (kg/m^2)	28.97 ± 5.56	24.35 ± 3.90	P > 0.05
PASI	26.62 ± 9.69		
Hypertension (n, %)	64 (58.7)		
Diabetes type 2 (n, %)	20 (18.34)		
CVD (n, %)	34 (31.19)		
MS (n, %)	49 (45.0)		
Psoriatic arthritis (n, %)	39 (36.0)		
Liver diseases, including (NAFLD) (n, %)	13 (11.9)		
Thromboses (DVT), Pulmonary thromboembolism (n, %)	6 (5.50)		

4.2. Carriage of SND *-675 ID, 4G/5G* in the PAI-1 gene in patients with psoriasis

The results of DNA analysis for 4G/4G, 4G/5G 5G/5G genotype carriage and allele frequencies, OR, χ2, 95% CI and Fisher's exact test are presented in Table 4.2 and and Figure 4.1.

Table 4.2 Carriage of the 4G/4G, 4G/5G and 5G/5G genotypes of SND *-675 ID, 4G/5G* in the PAI-1 gene, ancestry for both models (additive and recessive), allele distribution, OR, χ2, 95% CI and Fisher's exact test of patients and controls.

PAI-1 4G/5G	**Patients with psoriasis109 n (%)**	**Контроли 181 n (%)**	**OR**	**95 % CI**	**χ2**	**P**
Additive model						
5G/5G (Ref.)	21 (19.26)	38(21)	1	0.446-1.787	0.101	0.750
4G/5G	50 (45.87)	108(59.66)	0.838	0.448-1.564	0.304	0.581
4G/4G	38(35)	35(19.33)	1.956	0.976-3.953	3.577	0.059
Recessive model						
5G/5G +4G/5G (Ref)	71 (65)	146 (80.67)	1	0.230-0.842	6.287	0.013
4G/4G	38(35)	35(19.33)	2.232	1.301-3.830	8.705	0.003*
Allele distribution						
5G	92(42.20)	184(50.83)	1	0.412-1.264	1.299	0.254
4G	126 (57.80)	178 (49.17)	1.415	0.009-1.986	4.059	0.043*

Significant values are marked with*

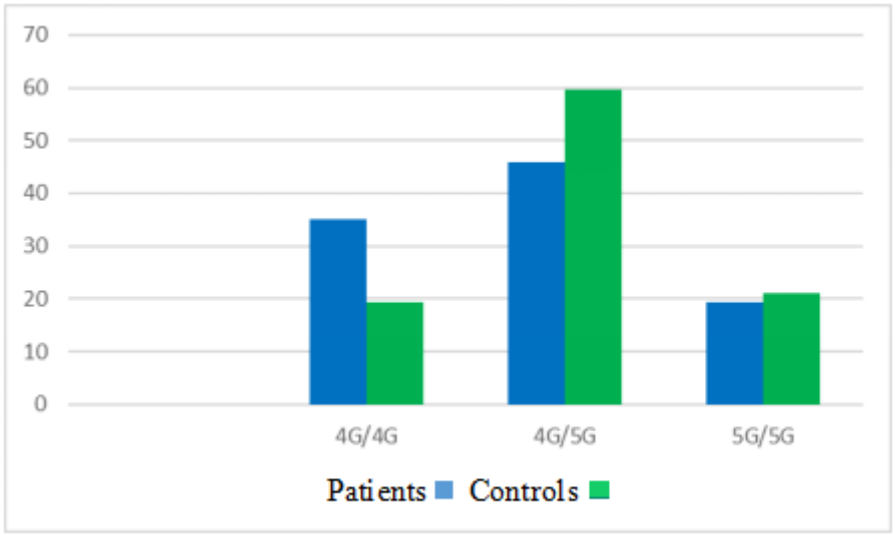

Figure 4.1. Carriage of 4G/4G, 4G/5G and 5G/5G genotypes of SND *-675* ID, 4G/5G in the PAI-1 gene, anterior recessive, for patients and controls.
* Statistical data are presented in Table 4.2.

The frequency of 4G/4G genotype carriage was significantly higher in psoriasis patients compared to controls: 35.0% vs 19.3%, OR = 2.32 and $\chi 2$ = 8.705, had very high values, indicating that the risk of developing the disease is significantly higher in carriers. The allele frequencies for the 4G allele were 57.80% for patients and 49.17% for controls. The allele frequencies in the 5G allele in the patients were 42.20% and for controls were 50.83%. These frequencies (p = 0.043) were significantly different for the patients than in the controls. (Table 4.2)

4.2.1. Clinical and laboratory data for psoriasis patients carrying SND *-675 ID* 4G/4G genotype

The carriers and non-carriers of the *-675 ID*, 4G polymorphism in the PAI-1 genotype 4G/4G gene had very high and almost identical BMI (29.25 kg/m^2 versus 28.82 kg/m^2, p > 0.05), similar mean age (53.6 vs 54.32, p > 0.05), but the age at first incident of psoriasis differed significantly in favour of the polymorphism carriers.

The number of patients with high blood glucose levels was significantly higher in the carriers of the 4G/4G genotype studied compared with noncarriers (41.2% vs 16.2%, p < 0.05), as was the number of patients with type 2 diabetes (32.4% vs 11.8%, p < 0.05). Fasting blood glucose levels (6.28 vs 5.59, p = 0.059) were higher in carriers of the studied genotype compared with noncarriers, but not significantly so.

The number of patients carrying the 4G/4G genotype with high triglycerides was higher (32.4%), but not significantly, compared to that of noncarriers (23.5%). The number of patients with dyslipidemia was also nonsignificantly higher among carriers of the genotype studied. Significantly low HDL levels were found among 14.7% of genotype carriers compared with 2.9% of noncarriers (Figure 4.2 and Table 1D) (Tables 1D-10D are presented in the supplementary materials of the dissertation). High total cholesterol was found in over 57% of carriers and 60% of non-carriers. The incidence of metabolic syndrome was not significantly higher among 4G/4G genotype carriers compared to non-carriers as were hypertension, ischemic heart disease, heart failure and psoriatic arthritis.

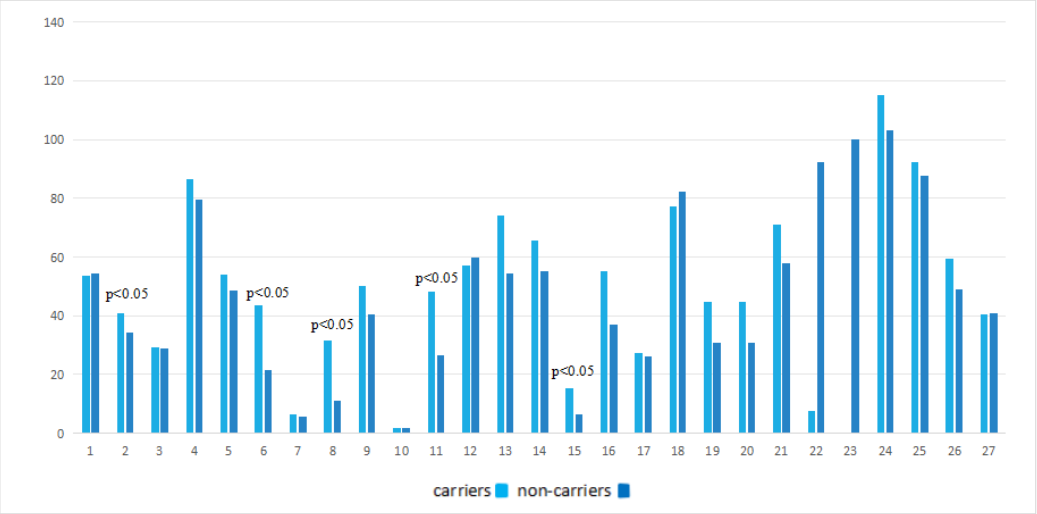

Figure 4.2. Clinical and laboratory data and comorbidities in psoriasis patients carrying genotype 4G/4G of SND *-675 ID*, *4G/5G* in the PAI-1 gene compared to non-carriers.
1. Mean age (years); 2. Mean age at first onset (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 25 (kg/m^2) (%); 5. Patients with BMI ≥ 30 (kg/m^2) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l);

8. Patients with type 2 diabetes (%); 9. Patients with triglyceridemia (%); 10. Triglycerides (mmol/l); 11. Patients with low HDL (%); 12. Patients with hypercholesterolemia (%); 13. Patients with dyslipidemia (%); 14. Patients with hypertension (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with psoriatic arthritis (%); 20. Patients with CVD without hypertension (%); 21. Patients with CVD + hypertension (%); 22. Patients with liver disease (%); 23. Patients with thromboses (%); 24. PAI-1 ng/ml; 25. Patients with high PAI-1 values (%); 26. Patients with MS (%); 27. Patients with MS + BMI > 30 (%);

* Statistical data are presented in Table 1D

* Reference values used for statistical analysis: fasting glucose 3.60-6.20 mmol/L, cholesterol 2.50-5.20 mmol/L, triglycerides: 0.50-1.7 mmol/L, CRP 0-5.0 mg/L, uric acid 80-420 mmol/L, HDL-cholesterol men > 0.75 mmol/L, women > 0.91 mmol/L, PAI-1 2-46 ng/ml

The PASI values (28.74 versus 24.90, $p > 0.05$) were nonsignificantly higher (Figure 4.2), and the number of patients with high PASI (> 20) was higher among 4G/4G genotype carriers as compared with non-carriers (92.9% vs73.3%). CRP values were significantly higher in 4G/4G genotype carriers compared with non-carriers (15.14 mg/L versus 6.40 mg/L, $p > 0.05$). PAI-1 values were very high in all psoriasis patients, with higher values in patients carrying the 4G/4G genotype compared to non-carriers (115.2 mg/l versus 103.7 mg/l, $p > 0.05$).

To assess the significance of 4G/4G genotype carriage on clinical and laboratory data of psoriasis patients carrying this genotype, a group of forty-four patients, both non-carriers of the 4G/4G genotype and non-carriers of other thrombophilic polymorphisms, were compared with the group of forty-four patients studied in this work: (*rs1801133*) polymorphism in the MTHFR gene, (*rs5918ITGB3*) *PL A1/A2* polymorphism in the integrin β3 gene, *FVL* polymorphism (*rs6025*) and *FII 20210 G>A* polymorphism (*rs179996*) (The group was formed after excluding patients carrying procoagulants and risk polymorphisms for arterial and venous thrombosis). Data on the frequency of the comorbidities obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, high CRP, PASI > 20, CVD, MS, and common comorbidities in patients with psoriasis carrying the 4G/4G genotype versus non-carriers of the five thrombophilic polymorphisms are presented in Figure 4.3. and Table 2D were not significantly different from those analyzed against 4G/4G genotype carriers alone (Figure 4.2. and Table 1D). Significant difference in psoriasis carriers versus non-carriers was found only for blood glucose values, number of patients with hyperglycemia and type 2 diabetes, patients with low HDL dyslipidemia and high CRP (mg/l) values. A relatively high percentage of carrier patients had hepatic steatosis (30.8%), but these were fewer than the non-carriers.

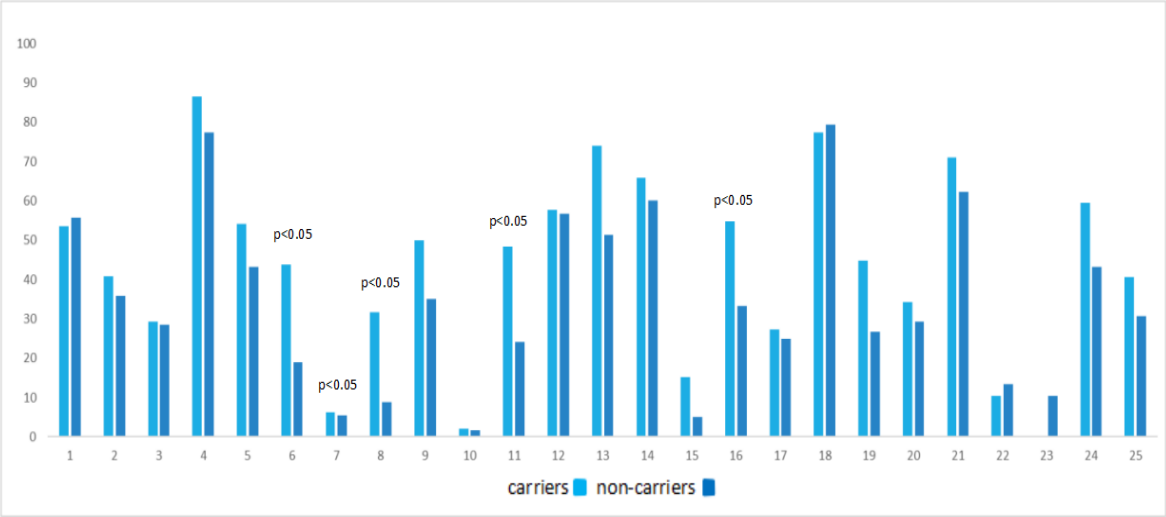

Figure 4.3 Clinical and laboratory data and comorbidities in psoriasis patients carrying, SND -*675 ID* genotype 4G/4G, *4G/5G* in the PAI-1 gene versus non-carriers of the five thrombophilic polymorphisms.
1. Mean age (years); 2. Mean age at first presentation (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 25 (kg/m^2) (%); 5. Patients with BMI ≥ 30 (kg/m^2) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l); 8. Patients with type 2 diabetes (%); 9. Patients with triglyceridemia (%); 10. Triglycerides (mmol/l); 11. Patients with low HDL (%); 12. Patients with hypercholesterolemia (%); 13. Patients with dyslipidemia (%); 14. Patients with hypertension (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with psoriatic arthritis (%); 20. Patients with CVD without hypertension (%); 21. Patients with CVD + hypertension (%); 22. Patients with liver disease (%); 23. Patients with thromboses (%); 24. Patients with MS (%); 25. Patients with MS + BMI > 30 (%);
* Statistical data are presented in Table 2D

4.3. Carriage of *MTHFR 677C>T* polymorphism *(rs1801133)* in patients with psoriasis

The results of DNA analysis for *MTHFR 677C>T* polymorphism carriage for both models (additive and recessive) and allele frequencies, OR, χ2, 95% CI and Fisher's exact test versus controls are presented in Table 4.3 and Figure 4.4.

Table 4.3. Carriage of the *MTHFR 677 C>T* genotypes T/T, C/T and C/C in the *MTHFR* gene, ancestry for the two models (additive and recessive), allele distribution, OR, χ2, 95%, CI and Fisher's exact test in psoriasis patients versus controls.

Carriage of *MTHFR 677C>T*	**Patients 109 n (%)**	**Controls 181 n (%)**	**OR**	**95 % CI**	**χ2**	**p**
Additive model						
T/T	15(13.76)	20(11.06)	1.284	0.627-2.629	0.471	0.492
C/T	38 (34.87)	87 (48.06)	0.578	0.354 - 0.944	4.836	0.027*
C/C (Ref)	56 (51.37)	74 (40.88)	1	0.856-2.619	2.012	0.155

Recessive model						
T/T	15(13.76)	20(11.06)	1.317	0.566-3.061	0.411	0.522
C/T + C/C (Ref.)	94 (86.24)	161 (88.94)	1	0.326-1.764	0.411	0.522
Allele distribution						
T	68 (31.20)	127(35.08)	0.838	0.586 -1.200	0.922	0.337
C	150 (68.80)	235(64.92)	1	0.664-2.162	0.361	0.547

Significant values are marked with *

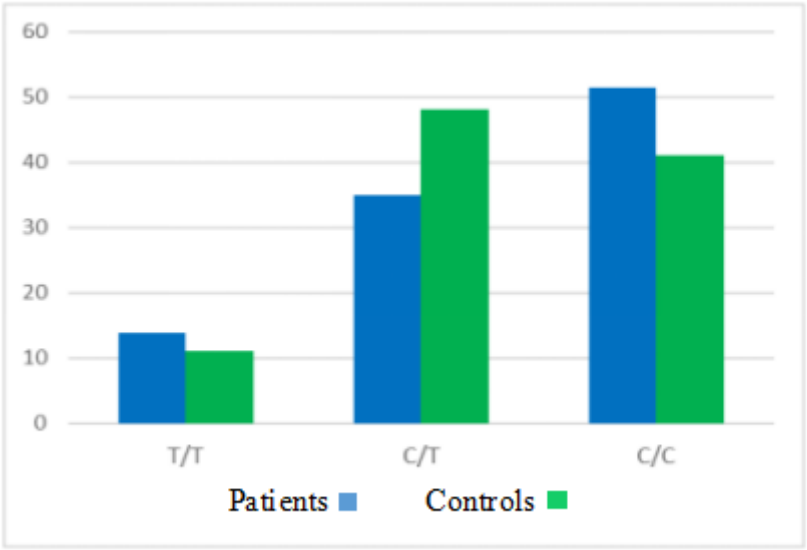

Figure 4.4. Carriage of genotypes T/T, C/T, C/C polymorphism *MTHFR 677 C>T* (*rs1801133*) in the MTHFR gene of psoriasis patients vs controls.
*Statistical data are presented in Table 4.3.

Carriage of genotype T/T in the MTHFR gene with polymorphism *677 C>T* (*rs1801133*) was significantly higher in the psoriasis patients compared with controls: 13.76% vs 11.06%, p > 0.05 (Table 4.3), indicating that carriage of this genotype is not a risk factor for developing the disease. It is noteworthy that heterozygous genotype carriage was significantly lower in tha patients than in the controls. The frequencies of the (C) and (T) alleles in the patient group compared with those in the control group were calculated using the Hardy-Weinberg equation (HWE) and were found in patients (*rs1801133*) (T) 31.20%, and in 35.08% in the controls, while for (*rs1801133*)(C) it was 68.80% in the patients and 64.92% in the controls (Table 4.3). These results confirmed that *MTHFR 677* T allele carriage is not a risk factor for psoriasis. According to the Gnom database ID information (1-11856378-G-A), the total SNP frequency was 0.3085 (30.85%); European (Non-Finnish) frequency was 0.3380 (33.80%); ClinVar (3520); ClinGen Allele Registry (CA170990).

4.3.1. Clinical and laboratory data

The results of laboratory and clinical data for the patients carrying the polymorphism (*rs1801133*) genotype T/T compared to the results of patients non-carriers are presented in Figure 4.5 and Table 3D. The carriers and non-carriers of the *677C>T* polymorphism (*rs1801133*) in the MTHFR gene had significantly higher BMI values compared with noncarriers, (31.92 kg/m^2 vs 28.75 kg/m^2; $p < 0.05$). Of note, they had the highest BMI compared to all other carrier groups (Figure 4.5 and Table 3D). The number of obese patients in the two groups differed significantly - 73.3% in the carrier group versus 46.7% in the non-carrier group ($p < 0.05$).

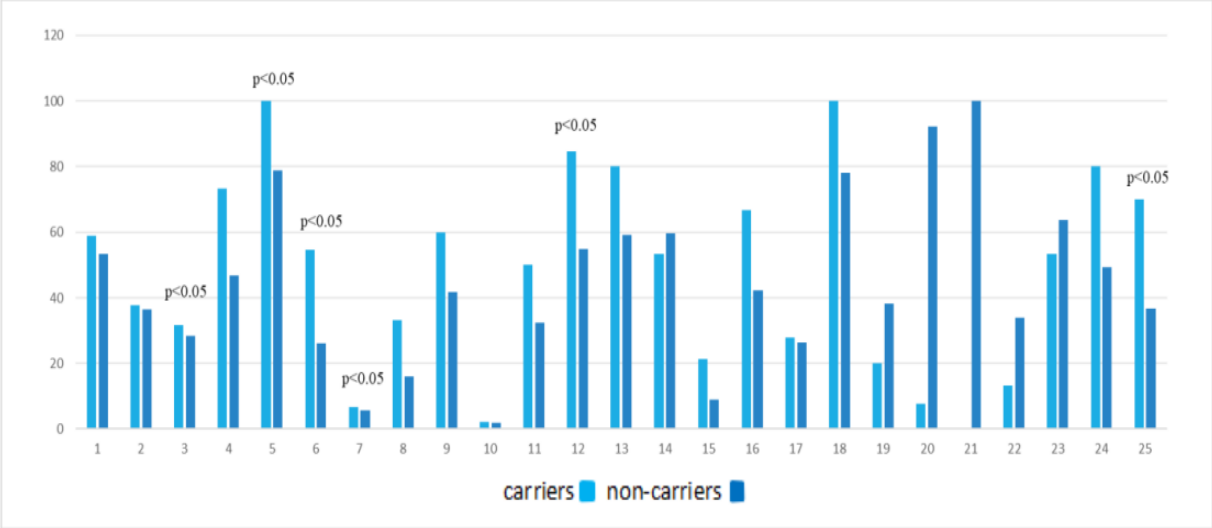

Figure 4.5 Clinical and laboratory data and comorbidities in psoriasis patients carrying the T/T genotype of the *MTHFR 677C>T* polymorphism in the MTHFR gene versus non-carriers.
1. Mean age (years); 2. Mean age at first presentation (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 30 (kg/m^2) (%); 5. Patients with BMI ≥ 25 (kg/m^2) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l); 8. Patients with type 2 diabetes (%); 9. Patients with triglyceridemia (%); 10. Triglycerides (mmol/l); 11. Patients with low HDL (%); 12. Patients with hypercholesterolemia (%); 13. Patients with dyslipidemia (%); 14. Patients with hypertension (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with psoriatic arthritis (%); 19. Patients with liver disease (%); 20. Patients with thromboses (%); 22. Patients with CVD without hypertension (%); 23. Patients with CVD + hypertension (%); 24. Patients with MS (%); 25. Patients with MS + BMI > 30 (%);
* Statistical data are presented in Table 3D.

The patients in the two groups had relatively similar mean age and age at first disease presentation. They were higher in carriers though not significantly.

Fasting blood glucose levels of T/T genotype carriers were significantly higher than those of non-carriers (6.76 mM vs 5.7 mM, $p < 0.05$). The number of patients with high blood glucose levels was significantly higher (54.54% vs 20.26%, $p < 0.05$). The number of patients with type 2 diabetes (33.3% vs 16.7%, $p > 0.05$) was higher, but not significantly so.

Total cholesterol was significantly high: it was found in 84.6% of carriers and 55.0% of non-carriers. The number of patients with dyslipidemia was significantly but non-significantly higher among carriers of the polymorphism studied (80.0% vs 59.3%), as were HDL level: 50.0% in carriers of the polymorphism vs 32.3% in non-carriers (Figure 4.5 and Table 3D). The number of patients carrying the T/T genotype with high triglycerides was higher (32.4%), but not significantly so, compared with that of non-carriers (23.5%). The incidence of metabolic syndrome was significantly higher among polymorphism carriers

(80.4%) compared with noncarriers (49.4%), whereas hypertension, ischemic heart disease, heart failure, and psoriatic arthritis were elevated but non-significantly. The PASI values (27.96 vs 26.44, $p > 0.05$) were non-significantly higher (Figure 4.5 and Table 3D). The percentage of patients with high PASI was higher among T/T genotype carriers compared with non-carriers (100% vs 78.0%). It is noteworthy that all carriers of this mutation had PASI > 20. To assess the significance of carrying the *677C>T* polymorphism in our gene with the group of 44 patients without polymorphisms, both noncarriers of genotype T/T and noncarriers of other thrombophilic polymorphisms were studied in this work: SND (-675*ID, (-) 4G/5G* polymorphism in the PAI-1 gene, MTHFR polymorphism (*rs5918I* on clinical and laboratory data of patients with psoriasis, including comorbidities carriers of genotype T/T, we compared *TGB3*) *PL A1/A2* in the integrin β3 gene, *FVL* polymorphism (*rs 6025*) and (*rs179996*) polymorphism of FII *20210 G>A*. (This group was obtained after excluding patients carrying procoagulants and risk polymorphisms for arterial and venous thrombosis). The clinical and laboratory data for psoriasis patients carrying the T/T genotype versus non-carriers of thrombophilic polymorphisms are presented in Figure 4.6 and Table 4D. The carriers of genotype T/T analyzed against non-carriers of the five thrombophilic mutations (Figure 4.6 and Table 4D) had similar results to those analyzed against non-carriers of genotype T/T (Figure 4.5 and Table 3D). There was a significant difference for obesity (BMI ≥ 30), hyperglycaemia, number of obese, hyperglycaemic and diabetic patients, triglyceridaemia, low HDL, hypercholesterolaemia, dyslipidaemia and MS. Also, CRP values were significantly higher in patients carrying the T/T genotype compared with non-carriers of the five thrombophilic polymorphisms (21.29 mg/L vs 5.05 mg/L, $p > 0.05$).

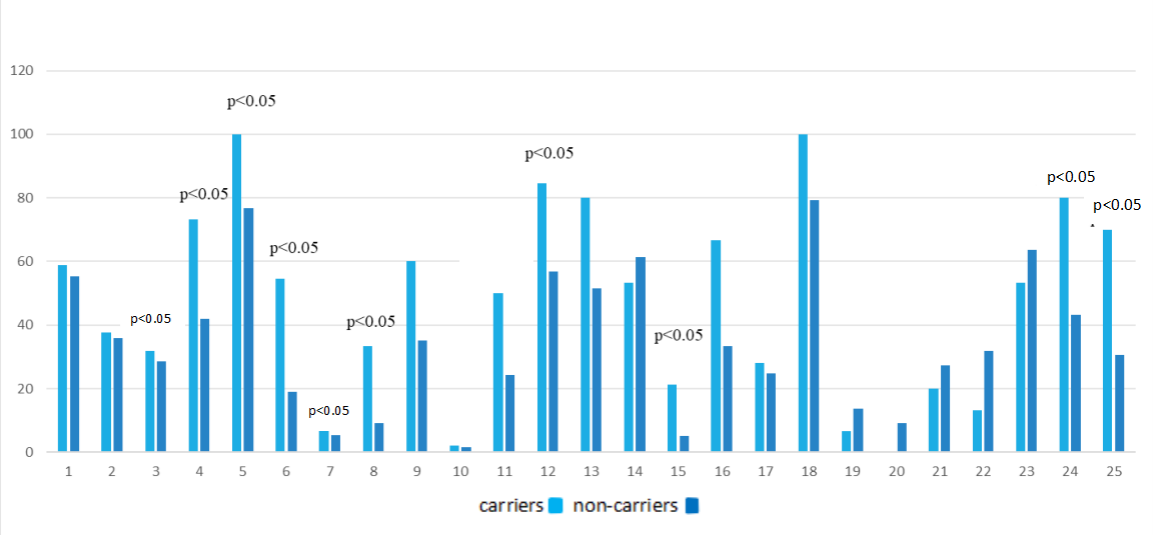

Figure 4.6. Clinical and laboratory data and comorbidities in patients with psoriasis carrying the T/T genotype of the *MTHFR 677C>T* polymorphism in the MTHFR gene compared with noncarriers of the five thrombophilic polymorphisms

1. Mean age (years); 2. Mean age at first presentation (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 30 (kg/m^2) (%); 5. Patients with BMI ≥ 25 ((kg/m^2) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l); 8. Patients with type 2 diabetes (%); 9. Patients with triglyceridemia (%); 10. Triglycerides (mmol/l); 11. Patients with low HDL (%); 12. Patients with hypercholesterolemia (%); 13. Patients with dyslipidemia (%); 14. Patients with hypertension (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with liver disease (%); 20. Patients with thromboses (%); 21. Patients with psoriatic arthritis (%); 22. Patients with CVD without hypertension (%); 23. Patients with CVD + hypertension (%); 24. Patients with MS (%); 25. Patients with MS + BMI > 30 (%);

*The statistical data are presented in Table 4D.

The data for hypertension, PASI > 20, CVD, and common comorbidities in psoriasis patients carrying the T/T genotype are presented in Figure 4.6 and Table 4D. The data showed no significant difference from non-carriers of the five thrombophilic polymorphisms and were not significantly different from those analyzed only against non-carriers of the T/T genotype (Figure 4.5 and Table 3D). We found only one patient with liver disease among genotype T/T carriers and none with thrombosis.

4.4. Carriage of the *PLA1/A2* polymorphism genotypes C/C, C/T and T/T (*rs5918(C)* in the ITGB3 gene and allelic distribution, OR, χ2, 95% CI and Fisher's exact test in patients with psoriasis versus controls

The results of the DNA analysis for polymorphism *rs5918 (C)* in the ITGB3 gene carriage and allele frequencies, OR, χ2, 95% CI and Fisher's exact test vs controls are presented in Table 4.4 and Figure 4.7.

Table 4.4. Carriage of the genotypes (C/C, C/T and T/T) of the PLA1/A2 polymorphism (*rs5918(C)*) in the ITGB3 gene and allele distributions, OR, χ2, 95% CI and Fisher's exact test in psoriasis patients versus controls.

Genotypes and allele distribution of ITGB3 *T>C*	**Patients N (%) 109**	**Controls N (%) 181**	**OR**	**95% CI**	**χ2**	**p**
Additive model						
C/C	2(1.83)	1(0.55)	3.364	0.301 - 37.549	1.092	0.295
C/T	20(18.34)	36(19.88)	0.905	0.493 -1.660	0.103	0.747
T/T(Ref.)	87(19.26)	144(21)	1			
Dominant model						
C/T + C/C	22 (20.6)	18 (18.6)	0.245	0.570 -2.325	1.246	p > 0.05
T/T (Ref.)	87(19.26)	144(21)	1	0.592-1.957	0.058	0.808
Allele distribution						
rs5918 C	24 (11.1)	38 (10.5)	1.054	0.614 -1.812	0.037	0.846
rs5918T	194 (88.9)	324 (89.5)	0.948	0.551 - 1.628	0.037	0.846

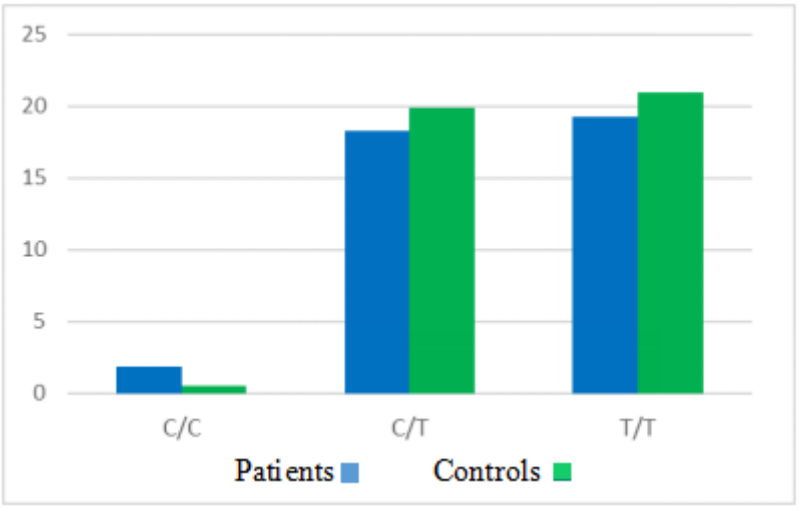

Figure 4.7 Carriage of genotypes (C/C, C/T and T/T) of the PLA1/A2 (*rs5918(C)*) polymorphism in the ITGB3 gene in psoriasis patients versus controls.
*Statistical data are presented in Table 4.4.

The homozygous mutant genotype is rare in the general population; it is less than 1%. In our study, DNA analysis results revealed two homozygous patients with the mutant version of the allele and one in the controls. This was the reason why the carriage of the *rs5918(C)* polymorphism was also calculated as the sum (20.6%) of the prevalence of homozygous *rs5918(C)* (1.96%) and heterozygous *rs5918(T>C)* genotypes (18.8%) and presented as a common group of C allele carriers. We found no difference in carriage of this polymorphism in the patients and controls.

The frequencies of the (C) and (T) alleles in the patient group compared to those in the control group were calculated using the HWE equation and were 11.1% and 10.5% for *rs5918(C)* patients and controls, respectively, 89.5% for *rs5918(T)* patients and 88.9% in controls (Figure 4.7 and Table 4.4). The frequency of the *rs5918(C)* allele according to the gnomAD database for the general population was 0.1223 (12.23%).

4.4.1. Clinical and laboratory data

Results of laboratory and clinical data for this polymorphism are presented in Figure 4.8, Figure 4.9, Tables 5D and 6D.

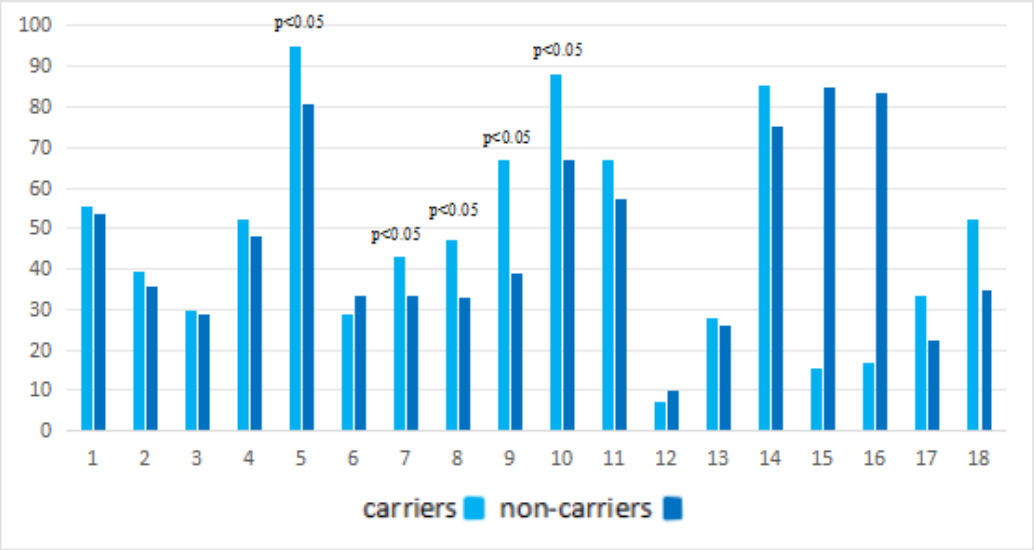

Figure 4.8. Clinical and laboratory data and comorbidities in psoriasis patients carrying the mutant *A2* allele of the *PLA1/A2* (*rs5918(C)*) polymorphism in the ITGB3 gene compared to non-carriers. 1. Mean age (years); 2. Mean age at first presentation (years); 3. BMI ($^{kg/m2}$); 4. Patients with BMI ≥ 30 ($^{kg/m2}$) (%); 5. Patients with BMI ≥ 25 ($^{kg/m2}$) (%); 6. Patients with hyperglycemia (%); 7. Patients with triglyceridemia (%); 8. Patients with low HDL (%); 9. Patients with hypercholesterolemia (%); 10. Patients with dyslipidemia (%); 11. Patients with hypertension (%); 12. CRP (mg/l); 13. PASI; 14. Patients with PASI > 20 (%); 15. Patients with liver disease (%); 16. Patients with thromboses (%); 17. Patients with CVD (%); 18. Patients with MS(%); * Statistical data are presented in Table 5D.

The carriers and non-carriers of the *ITGB3 rs5918(C)* polymorphism did not differ significantly in age at diagnosis, fasting blood glucose levels (Figure 4.8 and Table 5D) and BMI (29.94 kg/m^2 versus 28.97 kg/m^2, p > 0.05). Patients carrying the *ITGB3 rs5918(C)* allele showed nonsignificantly elevated PASI (28.03 versus 25.90, p > 0.05) (Figure 4.8 and Table 5D). The number of patients with high PASI (>20) was higher among *ITGB3 rs5918(C)* allele carriers compared to non-carriers (85.5% versus 75.3%). Liver disease occurred in only two carriers and thrombosis in only one. The number of patients with hyperlipidemia was significantly higher among carriers of the studied polymorphism. The number of patients carrying *rs5918(C)* with high triglycerides was significantly higher (42.9%) than that of non-carriers (33.3%). High total cholesterol was found in 66.7% of carriers vs 45.0% of non-carriers. Low HDL was detected in 47.2% of *rs5918(C*) polymorphism carriers vs 32.8% of the non-carriers (Figure 4.8 and 5D). The total number of patients with dyslipidemia was significantly higher in the *rs5918(C)* carriers versus the non-carriers (88.0% versu 63.6%). The incidence of metabolic syndrome was not significantly higher in the polymorphism carriers (52.4%) compared with the non-carriers (34.6%). Hypertension, ischemic heart disease, heart failure, and psoriatic arthritis were not significantly also nonsignificantly higher. To assess the significance of the *ITGB3 rs5918T>C* polymorphism on comorbidities, especially cardiovascular risk and metabolic syndrome, clinical and laboratory data of patients with psoriasis carrying the *ITGB3 rs5918T>C* allele were compared with a group of forty-four patients not carrying the five polymorphisms studied. (The group was obtained after subtracting the patients carrying the five studied polymorphisms for thrombosis). Clinical and

laboratory data for psoriasis patients carrying the *ITGB3 rs5918(C)* allele versus noncarriers of the five thrombophilic polymorphisms (including *ITGB3 rs5918(C))* are presented in Figure 4.9 and Table 6D.

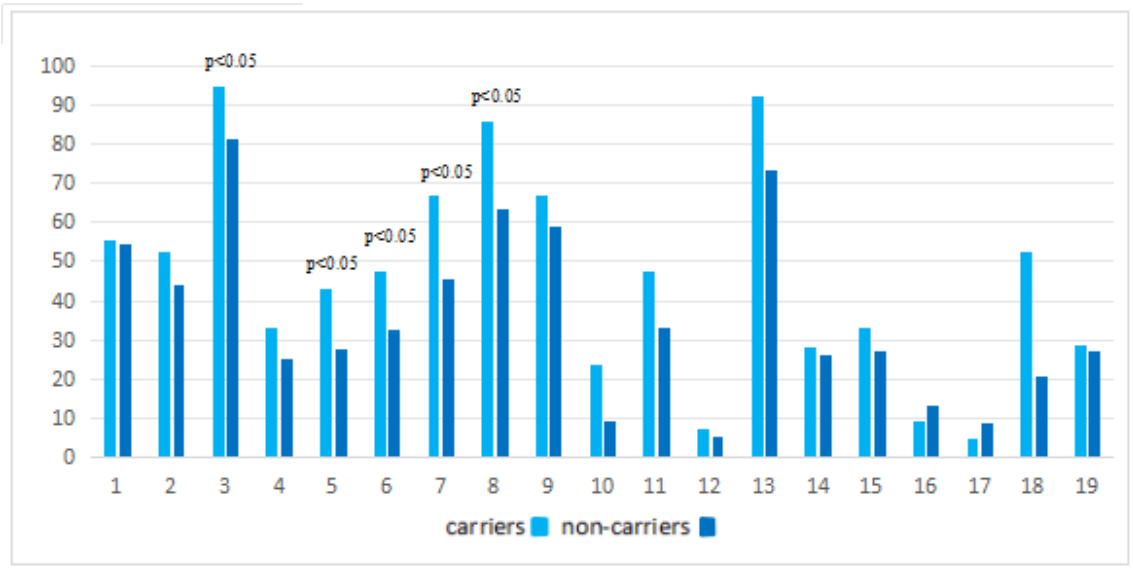

Figure. 4.9. Clinical and laboratory data and comorbidities in psoriasis patients carrying the A2 mutant allele of the *PLA1/A2* polymorphism *(rs5918(C)*) in the ITGB3 gene compared to non-carriers.non-carriers of the five thrombophilic polymorphisms.
1. Mean age (years); 2. Patients with BMI ≥ 30 ($^{kg/m2}$) (%); 3. Patients with BMI ≥ 25 ($^{kg/m2}$) (%); 4. Patients with hyperglycemia (%); 5. Patients with triglyceridemia (%); 6. Patients with low HDL (%); 7. Patients with hypercholesterolemia (%); 8. Patients with dyslipidemia (%); 9. Patients with hypertension (%); 10. Patients with type 2 diabetes (%); 11. Patients with high CRP (%); 12. CRP (mg/l); 13. Patients with PASI > 20 (%); 14. PASI; 15. Patients with CVD (%); 16. Patients with liver disease (%); 17. Patients with thromboses (%); 18. Patients with MS (%); 19. Patients with psoriatic arthritis (%);
* Statistical data are presented in Table 6D.

Data on the incidence of comorbidities and laboratory data: Obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, high CRP, PASI > 20, CVD, MS, and common comorbidities in psoriasis patients carrying the *ITGB3 rs5918(C)* allele vs non-carriers of the five thrombophilic polymorphisms presented in Figure 4. 9. and Table 6D, and for the most part were not significantly different from those analyzed against *ITGB3 rs5918(C)* allele carriers alone (Figure 4.8. and Table 5D). A significant difference in psoriasis carriers versus non-carriers was observed only for patients with triglyceridaemia, low HDL dyslipidaemia, hypercholesterolaemia and the number of comorbidities associated with CVD.

4.5. Carriage of the *FVL 1691(G>A)* polymorphism *(rs6025)* in patients with psoria

The results of DNA analysis for heterozygous *FVL 1691(G>A)* carriage and allele frequencies of *1691(G)* and *1691(A)*, OR, χ2, 95% CI and Fisher's exact test against controls are presented in Table 4.5 and Figure 4.10.

The frequency of heterozygous *FVL 1691(G>A)* polymorphism carriage was marginally higher in psoriasis patients compared to controls: 10.10% versus 7.73%, indicating that *FVL*

1691(G>A) carriage is not a risk factor for disease development. It should be noted that no homozygous carrier was found in the patient group, in contrast to the control group, in which there was one carrier.

Table 4.5 Frequency of genotypes A/A, A/G and G/G of polymorphism *FVL 1691(G>A)* (*rs6025*) in the factor V gene, allele distribution, OR, χ2, 95% CI and Fisher's exact test in patients with psoriasis versus controls.

Carriage of Factor V Leiden	**Patients n (%) 109**	**Controls n (%) 181**	**OR**	**95% CI**	**χ2**	**P**
Additive model						
A/A	0(0)	1(0.55)				
A/G	11 (10.10)	14 (7.73)	1.338	0.584-3.064	0.479	0.488
G/G (Ref.)	98 (89.90)	166 (91.72)	0.805	0.355-1.822	0.602	0.271
Dominant model						
A/A + A/G	11 (10.10)	15 (8.28)				
G/G (Ref.)	98 (89.90)	166 (91.72)				
Allele distribution						
A	11 (5.05%)	16 (4.42%)	1.149	0.523 - 2.523	0.120	0.729
G	207 (94.95%)	346 (95.58%)	0.870	0.396-1.911	0.120	0.729

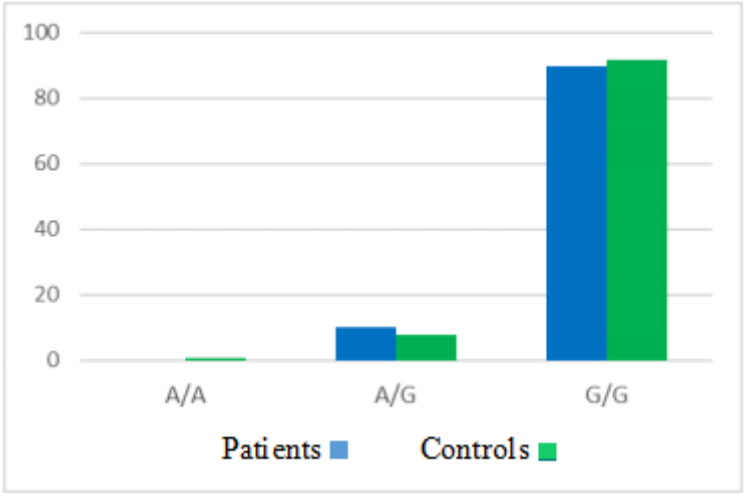

Figure 4.10. Carriage of the genotypes of (A/A, A/G and G/G) of polymorphism *FVL 1691(G>A)* (*rs6025*), in the factor FV gene in patients with psoriasis compared to controls.
* Statistical data are presented in Table 4.5.

Carriage of the (A) and (G) alleles in the patient group compared to those in the control group, calculated using the HWE equation, was not significantly different in the patients and controls: carriage of *1691(A)* was 5.05% in patients and 4.42% in controls. Carrigae of *1691(G)* was 94.95% in the patients and 95.58% in the controls (Table 4.5). According to Gnom, database ID information (1-11856378-G-A), the total frequency for the wild-type allele was 0.98070 (98.07%). According to European (Non-Finnish) database, the frequency was 0.974; ClinVar (226007).

4.5.1. Clinical and laboratory data

There was no significant difference from the non-carriers of this polymorphism in regard to the following clinical parameters: obesity (BMI ≥ 30), hyperglycaemia, triglyceridaemia, low HDL, dyslipidaemia, hypertension, high CRP, PASI > 20, CVD, MS and common comorbidities in psoriasis patients carrying *FVL* (*rs6025*) (Figure 4.11 and Table 7D). A significant difference was observed only for the mean age of patients and the number of patients with hypercholesterolemia. It is interesting to note that hypercholesterolaemia was found in more patients carrying this polymorphism. Since *FVL* (*rs6025*) carriage is relatively rare, data with higher OR did not yield a significant difference, e.g., high OR values were obtained for triglyceridemia and hyperglycemia, CRP and thromboses. However, they were not significantly higher ($p > 0.05$) (Figure 4.11 and Table 7D). Comparison of carriers wit non-carriers of thrombophilic mutations showed significantly higher CRP levels in the carriers. (Figure 4.12. and Table 8D).

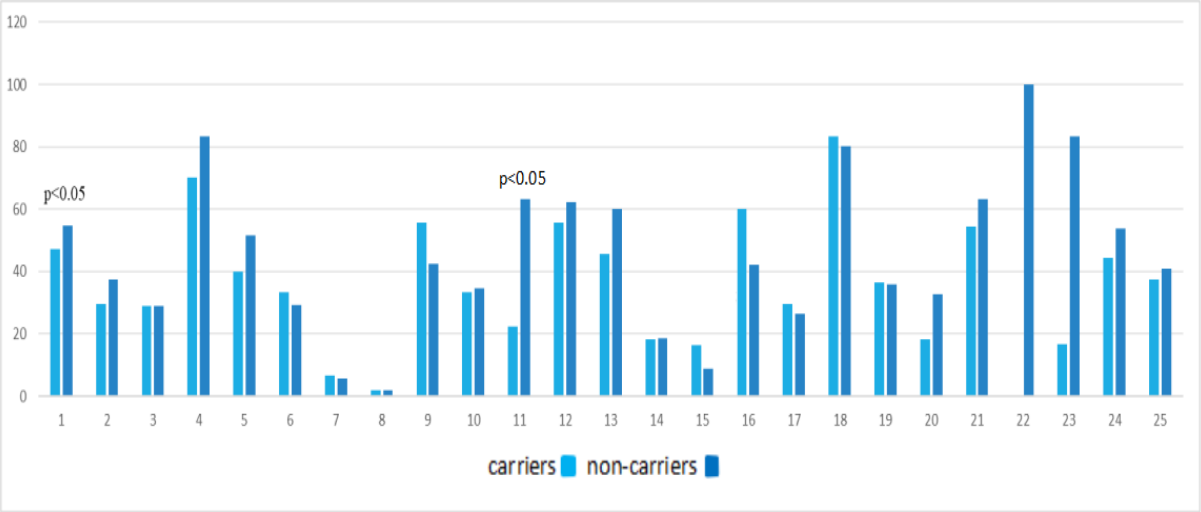

Figure 4.11. Clinical and laboratory data and comorbidities in psoriasis patients carrying the mutant allele of the *FVL* polymorphism (*rs6025*) vs noncarriers
1. Mean age (years); 2. Mean age at first presentation (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 25 (kg/m^2) (%); 5. Patients with BMI ≥ 30 ($^{kg/m2}$) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l); 8. Triglycerides (mmol/l); 9. Patients with triglyceridemia (%); 10. Patients with low HDL (%); 11. Patients with hypercholesterolemia (%); 12. Patients with dyslipidemia (%); 13. Patients with hypertension (%); 14. Patients with type 2 diabetes (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with psoriatic arthritis (%); 20. Patients with CVD without hypertension (%); 21. Patients with CVD + hypertension (%); 22. Patients with liver disease (%); 23. Patients with thromboses (%); 24. Patients with MS (%); 25. Patients with MS + BMI > 30 (%);
* Statistical data are presented in Table 7D.

Clinical and laboratory data of psoriasis patients carrying the *FVL* mutant allele *(rs6025)* were also analyzed against non-carriers of the five thrombophilic mutations studied. The results were similar to those obtained when analysed against non-carriers of the *FVL (rs6025*) allele alone. A close to significant difference was observed between the mean age of patients. A significant difference was observed for the CRP values, and a close to significant difference was found between the hypercholesterolemia values (Figure 4.12 and Table 8D), as well as the high OR values of patients with hyperglycemia, type 2 diabetes, and patients with triglyceridemia.

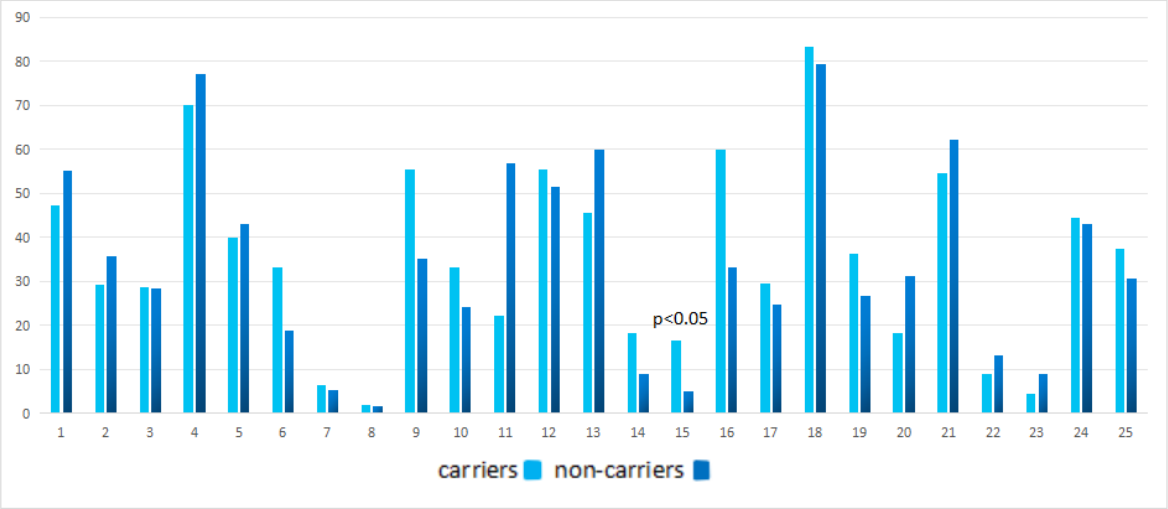

Figure 4.12. Clinico-laboratory data and comorbidities in psoriasis patients carrying the *FVL* mutant allele (*rs6025*) versus non-carriers of thrombophilic polymorphisms.
1. Mean age (years); 2. Mean age at first presentation (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 25 (kg/m^2) (%); 5. Patients with BMI ≥ 30 (kg/m^2) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l); 8. Triglycerides (mmol/l); 9. Patients with triglyceridemia (%); 10. Patients with low HDL (%); 11. Patients with hypercholesterolemia (%); 12. Patients with dyslipidemia (%); 13. Patients with hypertension (%); 14. Patients with type 2 diabetes (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with psoriatic arthritis (%); 20. Patients with CVD without hypertension (%); 21. Patients with CVD + hypertension (%); 22. Patients with liver disease (%); 23. Patients with thromboses (%); 24. Patients with MS (%); 25. Patients with MS + BMI > 30 (%);
* Statistical data are presented in Table 8D.

4.6. Carriage of *FII 20210 (G>A)* SNP: *rs1799963* polymorphism in patients with psoriasis

The results from the DNA analysis for *FII 20210 G>A* polymorphism mutant allele carriage and allele frequencies, OR, χ2, 95%, CI and Fisher's exact test against controls are presented in Table 4.6 and Figure 4.13. The frequency of heterozygous carriage of the *FII 20210A* mutant allele was higher in psoriasis patients compared to controls: 4.58% versus 2.21%, OR higher than 2, indicating a definite importance of this polymorphism in disease development, however the association was nonsignificant. Of note is the fact that carriage is rare, the low numbers of patients make the data non-significant. No homozygous carrier was found in the patient group, nor in the control group.

Table 4.6. Carriage of G/G, G/A and A/A genotypes of the *FII 20210 G>A* polymorphism in the FII gene (*rs179996*), allele frequency, OR, χ2, 95% CI and Fisher's exact test in psoriasis patients vs controls.

Cariage of *rs179996 FIIG20210G>A*	**Patients n (%)109**	**Controls n (%)181**	**OR**	**95% CI**	**χ2**	**p**
Additive model						
A/A	0(0)	0(0)				
G/A	5 (4.58)	4 (2.21)	2.127	0.558-8.099	1.278	0.258
G/G (Ref.)	104 (95.42)	177(97.79)	1			
Dominant model						
G/A + GG	5 (4.58)	4 (2.21)				
G/G (Ref.)	104 (95.42)	177(97.79)	1			
Allele distribution						
A	5(2.30)	4(1.10)	2.100	0.558 - 7.909	1.258	0.272
G	213(97.70)	358(98.90)	1			

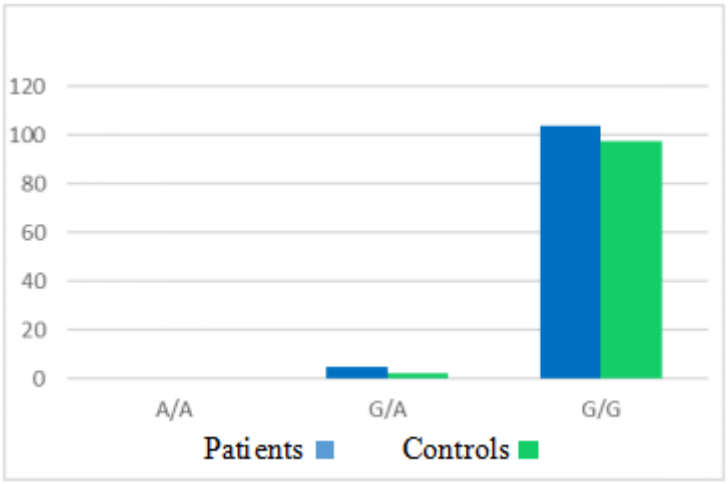

Figure 4.13. Carriage of G/G, G/A and A/A genotypes of the *FII 20210 G>A* polymorphism (*rs179996*) in the FII gene in psoriasis patients versus controls.
* Statistical data are presented in Table 4.6.

The frequencies of the (A) and (G) alleles in the patient group compared to those in the control group were calculated using the HWE equation and were 2.30% and 1.10% for *20210A* patients and controls, respectively, and 97.70% and 98.90% for *20210 G* patients and controls, respectively (Table 4.6). According to GnomAD database ID information, total incidence was

0.008441; European (Non-Finnish) incidence was 0.01245; ClinGen Allele Registry (CA325636). Results of DNA analysis to calculate *FII 20210 G>A* , (SNP: *rs1799963*) allele frequencies are presented in Table 4.6.

4.6.1. Clinical and laboratory data

Clinical and laboratory data for obesity (BMI ≥ 30), hyperglycaemia, triglyceridaemia, low HDL, dyslipidaemia, hypertension, CRP, PASI > 20, type 2 diabetes, CVD, MS and common comorbidities of psoriasis patients carrying *FII 20210 A* showed no significant difference from those in non-carriers of this polymorphism (Figure 4.14 and Table 9D**)**.

Carriage of *FII 20210 A* is very rare and the number of carrier patients was small. For this reason, when comparing the results with the group of non-carriers of this allele only, we obtained data with higher OR values (1.9 - 2.4) but no significant difference. For example, these were the results for patients with low HDL, patients with dyslipidemias, type 2 diabetes, and high PASI values (Figure 4.14 and Table 9D**)**.

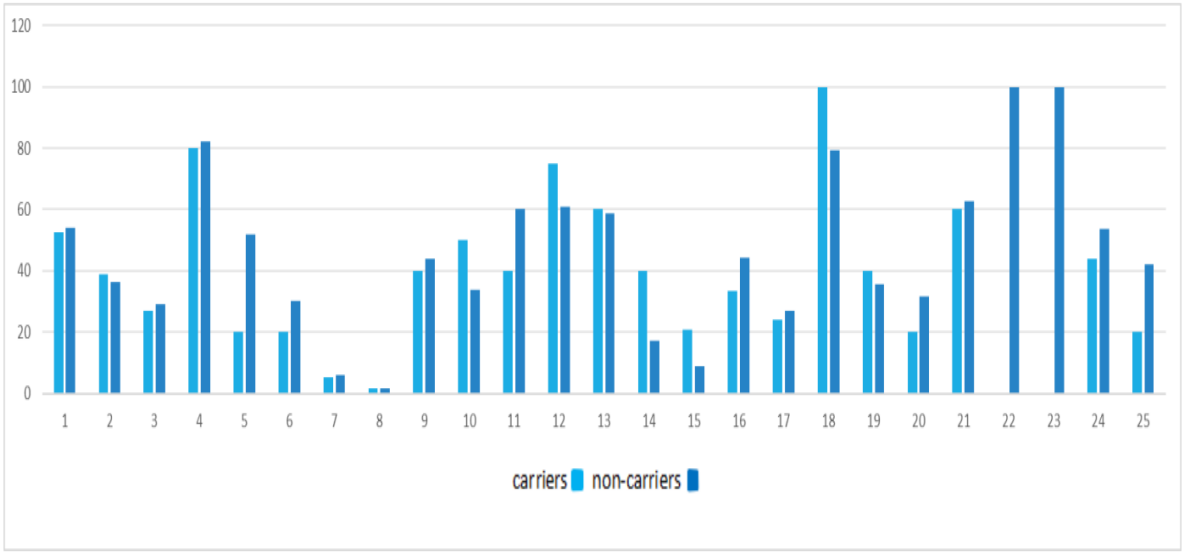

Figure 4.14. Clinical and laboratory data and comorbidities in patients with psoriasis carrying the *FII 20210A* mutant allele of the *FII 20210 G>A* polymorphism (*rs179996*) compared with noncarriers of this allele.
1. Mean age (years); 2. Mean age at first appearance (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 25 (kg/m^2) (%); 5. Patients with BMI ≥ 30 (kg/m^2) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l); 8. Triglycerides (mmol/l); 9. Patients with triglyceridemia (%); 10. Patients with low HDL (%); 11. Patients with hypercholesterolemia (%); 12. Patients with dyslipidemia (%); 13. Patients with hypertension (%); 14. Patients with type 2 diabetes (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with psoriatic arthritis (%); 20. Patients with CVD without hypertension (%); 21. Patients with CVD + hypertension (%); 22. Patients with liver disease (%); 23. Patients with thromboses (%); 24. Patients with MS (%); 25. Patients with MS + BMI > 30 (%);
* Statistical data are presented in Table 9D.

Clinical and laboratory data of psoriasis patients carrying the *FII 20210 A* mutant allele of the *FII 20210 G>A* polymorphism were analyzed and compared to non-carriers of all thrombophilic mutations tested (*FII 20210 G>A* (*rs1799963*), SND -675*ID*, *4G/5G* in the PAI-1 gene, *677C>T* variant in the MTHFR gene, *PLA1/A2* in the platelet glycoprotein IIb/IIIa gene *(rs5918ITGB3*) and *FVL* (*rs6025*)). The results were similar to those obtained when analysed

against non-carriers of the *FII 20210 A* allele alone (Figures 4.14, 4.15 and Tables 9D and 10D). However, in this analysis, we found significant differences for patients with type 2 diabetes and CRP, whereas differences between the other parameters (patients with low HDL, dyslipidemias and high PASI values and psoriatic arthritis remaned non-significant (Figure 4.15. and Table 10D).

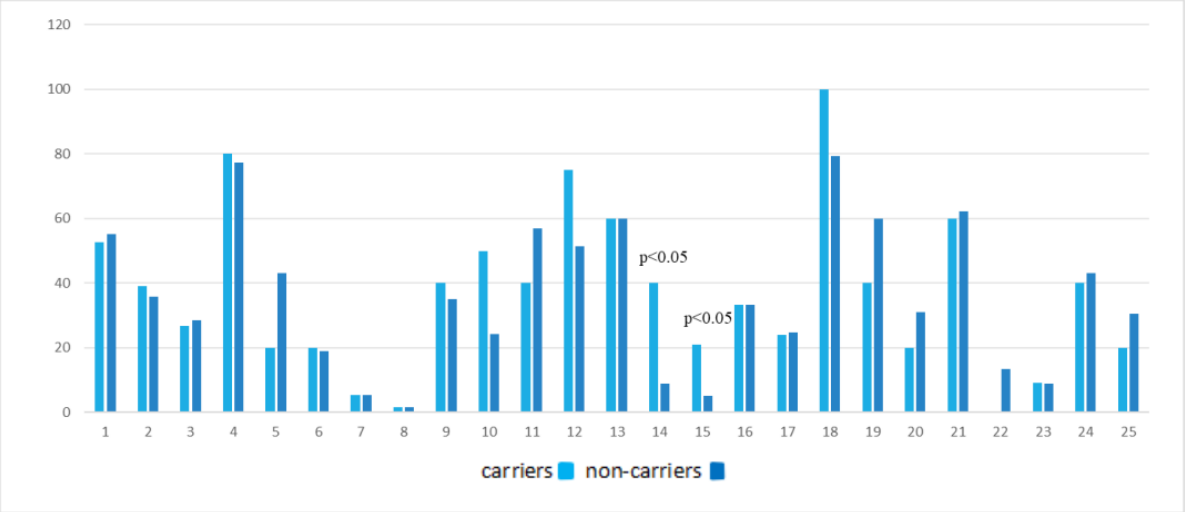

Figure 4.15. Clinical and laboratory data and comorbidities in psoriasis patients carrying the *FII 20210A* mutant allele of the *FII 20210 G>A* polymorphism (*rs179996*) versus noncarriers of the five thrombophilic polymorphisms
1. Mean age (years); 2. Mean age at first presentation (years); 3. BMI (kg/m^2); 4. Patients with BMI ≥ 25 kg/m^2) (%); 5. Patients with BMI ≥ 30 (kg/m^2) (%); 6. Patients with hyperglycemia (%); 7. Fasting blood glucose (mmol/l); 8. Triglycerides (mmol/l); 9. Patients with triglyceridemia (%); 10. Patients with low HDL (%); 11. Patients with hypercholesterolemia (%); 12. Patients with dyslipidemia (%); 13. Patients with hypertension (%); 14. Patients with type 2 diabetes (%); 15. CRP (mg/l); 16. Patients with high CRP (%); 17. PASI; 18. Patients with PASI > 20 (%); 19. Patients with psoriatic arthritis (%); 20. Patients with CVD without hypertension (%); 21. Patients with CVD + hypertension (%); 22. Patients with liver disease (%); 23. Patients with thromboses (%); 24. Patients with MS (%); 25. Patients with MS + BMI > 30 (%);
* Statistical data are presented in Table 10D.

5. DISCUSSION

Psoriasis vulgaris is a complex multifactorial dermatologic disease with various genetic and environmental factors involved in its triggering and progression agravated by comorbidities.

Epidemiological and genetic studies confirm that psoriasis is a disease caused by polygenic interactions between different genomic loci and environmental risk factors that contribute not only to disease development but also to specific comorbidities of psoriasis. These are associated with the inflammatory component and endothelial dysfunction leading to cardiometabolic pathologies.

It has been shown in numerous studies that, besides the classical comorbidities of psoriasis, such as psoriatic arthritis, non-alcoholic fatty liver steatosis and Crohn's disease,

which share genetically based pathomechanisms, patients with psoriasis are at higher risk of developing cardiometabolic diseases - coronary artery disease, acute MI, stroke, diabetes and MI with characteristic hypertension, dyslipidaemia, hypercholesterolaemia, obesity and insulin resistance.

The etiology of cardiometabolic disease risk in patients with psoriasis continues to be the subject of numerous studies. A potential mechanism of this association may be compromised metabolic status, which activates inflammatory mediators and procoagulant factors involved in psoriasis development and vascular pathogenesis, contributing to comorbid conditions in these patients. This study aimed to investigate the carriage of thrombophilic factors contributing to proinflammatory and prothrombotic states and the cause of arterial and venous thromboses in patients with psoriasis in an attempt to shed light on their impact on the development of psoriasis and its comorbidities associated with cardiovascular risk, diabetes and metabolic syndrome.

We set out to understand to what extent the carriage of thrombophilic procoagulant mutations influences the development of psoriasis and the manifestation of comorbidities. Investigating thrombophilic genetic markers could contribute to improve the understanding of the relationship between psoriasis comorbidities, such as diabetes, CVD and MS, and also pave the way for refining existing and potentially new approaches to prevention and treatment.

We examined Five prothrombotic polymorphisms in 109 patients diagnosed with psoriasis and 181 healthy controls of Caucasion origin to accomplish this task.

5.1. Carriage of SND -*675 ID, 4G/5G* in the PAI-1 gene polymorphism among patients with psoriasis

One of the first genetic factors that were investigated was the *4G/5G* polymorphism in the PAI-1 gene, a major physiological inhibitor of tissue-type plasminogen activators (tPA) and urokinase-type plasminogen activators (uPA), and therefore an important inhibitor of the plasminogen/plasmin system. Plasminogen activator inhibitor type 1 is a fast-acting inhibitor of tPA and serves as an important regulator of fibrinolysis. By inhibiting uPA and interacting with biological ligands, such as vitronectin and cell surface receptors, the functions of PAI-1 extend to pericellular proteolysis, tissue remodeling, and other processes, including cell migration.

Significantly fewer studies have investigated the contribution of elevated PAI-1 levels to the development of psoriasis, and data on the association of this polymorphism with psoriasis are lacking in the literature. A) Our results showed that carriage of *SND -675 ID*, genotype 4G/4G in the PAI-1 gene was significantly higher in patients with psoriasis compared to controls: 35.0% versus 19.3%; (OR 2.32; $\chi^2 = 8.705$) (Table 4.2). The high OR and χ^2 values indicated that the risk of developing the disease was significantly higher in carriers of the 4G/4G genotype. Allele frequencies were significantly different in patients compared to controls (for 4G allele they were 57.80% for

patients and 49.17% for controls)(Table 4.2.). This is one of the most significant results of the study. B) Plasminogen activator inhibitor type 1 (PAI-1) is synthesized by various cells including endothelial cells, hepatocytes, adipocytes and platelets. Its synthesis is influenced by factors such as inflammation. Cytokines - interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), directly increase PAI-1 levels. Insulin also has a direct impact on PAI-1 synthesis, linking metabolic pathways to regulation. Cells that carry the SND *-675 ID*, 4G allele in the PAI-1 gene produce up to 6-fold more iRNA in vitro. In vivo, elevated PAI-1 levels are associated with various pathological conditions: a hypofibrinolytic state that contributes to thrombotic complications, with increased fibrosis and inflammation, impaired tissue regeneration, and function. In skeletal muscle, high levels of PAI-1 can lead to reduced muscle mass and impaired regeneration, contributing to conditions such as muscular dystrophy, diabetes, and age-related muscle pathology. Significantly fewer studies have investigated the role of i elevated PAI-1 levels in the development of psoriasis.

5.1.1. Association of 4G/4G genotype with metabolic parameters and comorbidities

When analysing the comorbidities of 4G/4G genotype carriers versus 4G/5G+5G/5G carriers, we found definite differences in both metabolic parameters and comorbidities.

a. The significance of carrying the 4G/4G genotype in the PAI-1 gene on clinical and laboratory data of patients with psoriasis was determined in two ways. Carriers of this genotype were compared with a group of non-carriers, and with another group of forty-four patients including both non-carriers of (*SND-675 ID*, 4G/4G genotype in the PAI-1 gene and non-carriers of other thrombophilic polymorphisms studied in this work: (*rs1801133*) polymorphism in the MTHFR gene, *(rs5918ITGB3) PL A1/A2* polymorphism in the integrin β3 gene, *FVL* polymorphism (*rs6025*), and *(rs179996*) *FII 20210 G>A* polymorphism (The group was obtained after subtraction of patients carrying procoagulant and thrombophilic polymorphisms).

b. Of the metabolic parameters examined in the two groups analyzed (4G/4G carriers versus noncarriers of this genotype, and versus noncarriers of the five thrombophilic polymorphisms), the significant difference was obtained for fasting blood glucose levels, and the number of patients with high blood glucose and the number of patients with type 2 diabetes (32.4% versus 11.8%) (Table. 1D.). were significantly higher in carriers. All the three parameters yielded a significant association between psoriasis and diabetes in carriers of this genotype, indicating that carrying this genotype contributes to insulin resistance and type 2 diabetes in patients with psoriasis.

c. In a study of lipid metabolic indices, we found significantly lower HDL levels among homozygous carriers compared with noncarriers, as well as compared with non-carriers of the five thrombophilic mutations. High total cholesterol was found in carriers and non-carriers of the 4G/4G genotype in the PAI-1 gene. Similar abnormalities in lipid profiles have been noted in psoriatic patients in other studies that did not analyze the genetic factor.

d. CRP values were significantly higher in patients carrying the 4G/4G genotype in the PAI-1 gene compared with non-carriers (15.14 mg/L versus 6.40 mg/L, $p < 0.05$) (Table 1D). PAI-1 is known to influence inflammatory processes, smooth muscle cell proliferation, cell migration, and keratinocyte migration in particular, increase angiogenesis, and extracellular

matrix remodeling towards increased risk of thrombosis. All these are factors that are also present in the pathology of psoriasis.

e. PAI-1 values were very high in all patients with psoriasis. However, patients carrying the 4G/4G genotype in the PAI-1 gene had higher values compared with non-carriers (115.2 mg/L vs 103.7 mg/L, $p > 0.05$) (Table 1D). Increased CRP and PAI-1 levels are markers of higher inflammatory level in patients carriers of 4G/4G genotype.

f. PAI-1 levels were higher in the psoriasis patients compared with the healthy controls. This increase in PAI-1 expression is probably related to hyperproliferation of keratinocytes, inflammatory cell migration, and angiogenesis –i.e. processes that play critical roles in the pathogenesis of psoriasis. The morphological results obtained by Rubina et al. showed that uPA, urokinase-type plasminogen activator receptor, tPA and PAI-1 are present in the epidermis of psoriatic skin, whereas in normal epidermis they are undetectable in most cases, or are present in negligible amounts. It should be noted that plasma PAI-1 levels decrease after treatment for psoriasis and during the recovery period.

g. Numerous studies have demonstrated that inheritance of the 4G/4G genotype results in an increased risk of stroke incidents and ischemic heart disease, including an increased risk for coronary heart disease. In our study, patients with psoriatic arthritis, hypertension, ischemic heart disease, heart failure, and MS had a higher, though insignificant incidence among the 4G/4G genotype carriers compared with non-carriers. This is a logical consequence of the more severe inflammasome status of this patient group. Disease severity, measured as PASI index, was also higher in carriers of this genotype.

Interestingly, 59.4% of the carriers of the 4G/4G genotype in the PAI-1 gene had MS, but because it also had a high frequency in non-carriers of thrombophilic mutations (43.2%), no significant difference was observed despite the relatively high OR value (1.92) (Table 2D). Individual components of the metabolic syndrome such as hyperglycemia in diabetic patients, and lipidemia (low HDL) were significantly increased, but obesity- a major component of the metabolic syndrome was not.

The comorbidities of psoriasis patients carrying the 4G/4G genotype were significantly more expressed as compared to those in the group of patients without thrombophilic mutations than when compared with non-carriers of the 4G/4G genotype alone, as this eliminated the contribution of the other mutations to the comorbidities.

Elevated levels of PAI-1 are associated with various pathological conditions, such as abdominal obesity, insulin resistance, hypertriglyceridemia, thrombosis, and CVD, frequent comorbidities of psoriasis.

In our patients, the percentage of CVDs without hypertension was relatively lower –it was similar to that in carriers and non-carriers of the 4G/4G genotype (34.2% versus 29.2%, $p > 0.05$) (Table 2D), i.e., the contribution of carrier status was not significant. Regarding the hypertensive patients, the number was much higher: 71.1% in 4G/4G genotype carriers versus 62.2% in non-carriers. However, the difference was not significant ($p > 0.05$)(Table. 2D).

On the other hand, obesity, type 2 diabetes, and MS are often associated with a chronic inflammatory state characterized by overexpression of inflammatory adipokines, such as IL-6 and TNF-α, which induce PAI-1 expression in adipose tissue. These increased levels of PAI-1 further contribute to the development of inflammation in adipose tissue by increasing the number of inflammatory macrophages that infiltrate the tissue.

5.2. MTHFR 677C>T polymorphism as a risk factor for psoriasis and comorbidities

Methylenetetrahydrofolate reductase (MTHFR*)* is a key enzyme for the processes of one-carbon metabolism involving folate and homocysteine metabolism. This enzyme catalyzes the irreversible conversion of 5,10-methyl tetrahydrofolate (THF) to 5-methyl THF via the reduction of the methylene to methyl group, which is involved generating S-adenosyl methionine (SAM) in the methionine cycle from homocysteine and the release of THF from the methyl group. S-adenosyl methionine is required for the synthesis of biologically important molecules such as adrenaline, choline, betaine, thymine. It is also involved in biotransformation processes in the inactivation of endo- and xeno-biotics, and THF for the transfer of one-carbon atom groups in the metabolism of amino acids and nucleotides. Another important function of SAM and the methionine cycle is involvement in genome methylation processes, which is part of a regulatory system of gene expression and epigenetic adaptive patterning - processes that influence cell development and cellular functions. The multiple functions suggest that disruption of one of the components in the methylation system induce certain functional disorders and disease processes. The *MTHFR 677C>T* polymorphism, resulting in a valine to alanine substitution at codon 222, decreases the activity of this enzyme by up to 50-70% in homozygous carriers of this mutation (*677* TT) and, correspondingly, higher homocysteine levels, while heterozygous carriage (*677* CT) yields slightly elevated homocysteine levels compared with (*677* CC) in healthy controls.

Hyperhomocysteinemia is a risk factor for CVD and tumor disease. There are studies showing the association of this polymorphism with obesity, diabetes mellitus, neurodegenerative and other disorders.

5.2.1. Association of psoriasis with the *677C>T* polymorphism (*rs1801133*) TT genotype in patients with plaque psoriasis

a. The investigation of MTHFR polymorphism *677C>T (rs1801133)* TT genotype carriage in the MTHFR gene showed that carriage of this genotype was significantly higher in patients with psoriasis compared with the control group: 13.76% vs 11.06%, (OR 1.24, $p > 0.05$) (Table 4.3). This finding proves that carrying genotype *677* TT is not a risk factor for the development of the disease in the patient group. Interestingly, heterozygous C/T carriage was significantly lower in patients with psoriasis ($p = 0.027$). b. The data on the association of genotype *677* T T carrier status in the MTHFR gene with psoriasis in different regions of the world are quite controversial. A significant association between MTHFR *677* TT genotype carriage and psoriasis was found in earlier reports on Chinese populations by Baiqiu et al. (2000) and in a study on psoriasis patients of Turkish ethnic groups by Izmirli M. Their data showed a significant increase in TT genotype carriage in psoriasis patients (CC 35.4%, CT 47.9%, and TT 16.7%) whereas the distribution in the control group was as follows: CC 50.6%, CT 45.5%, and TT 3.9%. c. The Weger study on the Austrian population showed that the homozygous TT genotype was not more frequent in psoriasis patients (15.2% vs. 11.7%, p=0.24). Carriage of the *MTHFR* TT genotype was less frequent among patients with plaque psoriasis (10.5%) from the Czech Republic (Vasku, 2009) compared to controls (11.8%). The results found for the Caucasian race are consistent with our finding for the Bulgarian population,, namely that the difference between the homozygous *677* TT genotype carriage in psoriasis patients and controls was not significant.

Similar results were also found by Liew et al. for the Malaysian population.

A recently published study in the Arab region reconfirmed the association between *MTHFR 677* TT genotype carriage and psoriasis in Saudi patients, suggesting that the difference in ethnicity explains these conflicting findings regarding the role of *MTHFR 677* TT genotype and psoriasis.

5.2.2. Association of *MTHFR 677C>T (rs1801133*) polymorphismcarriage with metabolic parameters and comorbidities

Our studies on the association of *MTHFR 677* TT genotype carriage with metabolic indices and comorbidities showed significant changes in both the metabolic index values and comorbidities.

To assess the severity of *MTHFR* genotype *677* TT genotype carriage on clinical and laboratory data of patients with psoriasis, including comorbidities, carriers of MTHFR genotype *677* TT genotype were compared with the group of non-carriers of this genotype in the MTHFR gene and the group of 44 patients without other thrombophilic polymorphisms. The group of non-carriers of the thrombophilic polymorphisms had higher OR values, more significant in the studied parameters.

5.2.3. Carriage of *MTHFR 677C>T* TT genotype and diabetes mellitus, dyslipidemias and MS

a. Fasting blood glucose levels, the number of patients with hyperglycemia and type 2 diabetes were significantly higher in carriers of the *677* TT genotype of the *677C>T* polymorphism (*rs1801133*) in the MTHFR gene and were characterized by high OR values ($OR \geq 5.0$, $p < 0.05$).

b. Although the association between *MTHFR 677* TT genotype and the risk of type 2 diabetes has been extensively studied, conclusions are still rather controversial. Carriage of the mutant allele is significantly correlated with diabetes in the Arab population, and according to Zhang et al. (2014) in the Chinese population as well. In a meta-analysis by Meng et al.(2019), including data for Caucasian, African and Asian populations, the authors establishe an association between the *677* TT genotype and type 2 diabetes only in the Arab population studued. A correlation between *677* TT genotype carriage in psoriatics with diabetes was noted by Vasku in the Czech population. Some other recent publications have reported the association between *MTHFR 677* TT genotype carriage, insulin resistance and diabetes in subjects without psoriasis. Some studies have also reported correlations with dyslipidemias.

This study demonstrated a significant association between *677* TT genotype carriage and type 2 diabetes in patients with psoriasis.

c. Another important factor that has been commented in *MTHFR 677* TT genotype carriers is the presence of dyslipidemias. In our study, total cholesterol, HDL cholesterol, total lipids were examined. We found a significantly higher number ($p < 0.05$) of patients with hypercholesterolemia (84.6%) in carriers, compared to non-carriers (55.0%). The number of patients with hyperlipidemia was higher, but nonsignificantly, among carriers of genotype *677* TT (80.0%) versus noncarriers (59.3%) (Table 3D). HDL levels were low in 50.0% of genotype carriers versus 32.3% in noncarriers (Table 3D). The OR values of all lipid parameters were high - between 2.7 - 4.2, but the values were significant only for cholesterol, ($p < 0.05$) (Table.

3D). d. All the patients studied who were carriers of the *677* TT genotype were obese (BMI > 30 kg/m^2) and, as a consequence, the incidence of metabolic syndrome was significantly higher among carriers of the polymorphism (80.4%) compared with noncarriers (49.4%) (Table. 3D). Obesity, hyperglycaemia/type 2 diabetes and hypercholesterolaemia were the three most relevant parameters to define the metabolic syndrome. e. The metabolic syndrome is a complex of interrelated risk factors for the development of diabetes mellitus and CVD. These factors include hyperglycemia, dyslipidemia, hypertension, and visceral obesity. In the present study, the number of patients with obesity, hyperglycemia, diabetes, and hypercholesterolemia was significantly higher in *MTHFR 677* TT genotype carriers. These observations led to revealing a significant association between TT genotype carriers and metabolic syndrome. f. CRP, known as a marker of systemic inflammation in obesity and type 2 diabetes values had were significantly higher levels in TT genotype carriers compared with non-carriers (Table. 4D). It is well known that tissue inflammation plays a critical role in insulin resistance, which underlies the development of type 2 diabetes, as well as MS. g. Hyperhomocysteinemia, which is seen in homozygous carriers of TT alleles in the MTHFR gene, is a risk factor for various CVDs, such as coronary heart disease. It is also associated with an increased risk of developing ischemic stroke in European and Asian populations. There is evidence that, carrying the *677* TT genotype is associated with an increased risk of (MI) in various populations presented in a recent meta-analysis by Samii et al. To our surprise, the pathologies most frequently commented for this recessive mutation, such as hypertension, coronary heart disease, heart failure, and psoriatic arthritis, were not significantly increased in the study group, which has been found in other studies. h.Such results are probably due to the protective anticoagulant and anti-aggregant therapy and alsothe supplementation with folic acid (vitamin B9) and vitamin B12 in our patients. These dietary recommendations, with the addition of vitamins B9 and B12 adjusted the plasma homocysteine level, which is higher in individuals with *MTHFR 677C>T* TT genotype and determines a significantly higher risk of coronary heart disease and other comorbidities.

DNA methylation is essential for the regulation of MTHFR gene expression and cell function. When analyzing epithelial tissues from psoriasis patients and healthy controls, and comparing the methylation patterns of the tumor suppressor gene promoter, it was found that hypomethylation was more frequent in the homozygous *MTHFR 677C>T* TT genotype than in the wild-type variant.

Conflicting data on the severity of psoriasis and its association with *MTHFR 677* TT genotype carriage are found in the literature. Karabacak et al. reported a correlation of the *MTHFR 677C>T* polymorphism with psoriasis severity in carriers of the CC genotype versus TT. In our study, PASI values [27.96 for TT versus 26.44 (TT+TT), $p > 0.05$] were not significantly different (Table 3D), and the percentage of patients with high PASI was higher among TT genotype carriers compared with noncarriers (100% vs 78.0%). It sould be oted that all carriers of this mutation had PASI > 20.

Patients in the two groups analyzed for this carrier had relatively close mean ages, as well as age of first incident.

The relationships and causes of increased metabolic and cardiovascular risk in patients

with psoriasis are the subject of intensive research, indicating that chronic inflammatory processes and high metabolic parameters such as hyperglycemia and hyperlipidemia lead to premature atherosclerosis through shared immunopathogenic mechanisms in patients with psoriasis.

Despite large-scale studies on the association between genetic and extrinsic risk factors, the mechanisms underlying the association between psoriasis and diabetes, dyslipidemias, and metabolic syndrome remain unspecified, both in the general population and among carriers of the *677* TT genotype. Psoriasis has a multifactorial genetic basis evidenced by epidemiological studies and familial recurrences involving different polymorphic alleles of inherited predisposition.

5.3. Carriage of the *ITGB3 rs5918(C)* polymorphism in patients with psoriasis

One other cardiometabolic polymorphism, a vital element of platelet aggregation and blood coagulation, is *rs5918T > C* in the ITGB3 gene. Integrin B3 (ITGB3) is the beta subunit of glycoprotein αIIbβ3, which is found in a large quantity on the platelet membrane surface (~80,000 copies), serving as a receptor for fibrinogen and the VonWillebrand factor (VWF). Initial adhesive interaction with extracellular surfaces, such as a fibrin clot, induces platelet activation via the αIIbβ3 integrin receptor.

Platelet activation by external stimuli (ADP, thrombin, adrenaline, and VWF) results in the expression of a greater number of αIIbβ3 molecules on the cell surface and conformational changes that increase its affinity for binding to fibrinogen.

5.3.1. Carriage of *ITGB3 rs5918(C)* polymorphism in patients with psoriasis

Carriage of the mutant allele of the *rs5918* (CC+CT) polymorphism, as homozygous and heterozygous variants, is occurs in approximately 15% in a healthy population. This polymorphism is due to a thymine to cytosine (T>C) substitution at position 1565 in exon 2 of the ITGB3 gene, resulting in the substitution of leucine with. Even in the heterozygous state, the *rs5918(C)* polymorphism alters ITGB3 conformation and orientation of the ligand-binding region and contributes to the increased risk of CVD. ITGB3, as a subunit of glycoprotein IIb/IIIa, is a key platelet receptor associated with fibrinogen-mediated platelet aggregation and blood coagulation. We found no difference in the carriage of the mutant allele of the *ITGB3 rs5918(C)* polymorphism between patients with psoriasis and controls, indicating its lack of influence on disease development.

5.3.2. Association of *ITGB3 rs5918* (*C)* polymorphism with metabolic parameters and comorbidities

We next investigated the impact of the *ITGB3 rs5918(C)* mutant allele on metabolic parameters and the presence of comorbidities in patients with psoriasis. In the 109 patients studied, we found a statistically significant association of the polymorphism with the following metabolic parameters: a. Statistical analysis showed an association of carrying the *rs5918(C*) mutant allele with the

incidence of triglyceridemia, hypercholesterolemia, and low HDL values - factors contributing to the development of CVD and MS, in patients with psoriasis. b. The number of *rs5918(C)* carriers with triglyceridemia (42.9%) was significantly higher ($p < 0.05$) than the non-carriers (27.5%) (Table 6D). The large number of patients with hypercholesterolemia was found in 66.7% of the mutant allele carriers, compared with 45.0% of th non-carriers (Table. 6D). Low HDL was found in 47.2% of *rs5918(C*) mutant allele carriers versus 32.8% of non-carriers (Table 6D). The total number of patients with dyslipidemia was significantly higher in *rs5918(C)* carriers, compared to non-carriers (85.7% and 63.6%, respectively). (Table 6D).

c. Although the number of patients with hyperglycemia and hypertension did not reach the level of statistical significance, the combination of these factors with hyperlipidemic and dyslipidemic factors and BMI resulted in a higher but not significant risk of MS in carriers of the *rs5918(C)* allele compared with the non-carriers in our patient group.

d. High triglyceridemia, hypercholesterolemia, and hyperglycemia deserve special attention because they are risk factors for other diseases besides metabolic syndrome, namely CVD, type 2 diabetes, neurodegenerative diseases, pregnancy complications, and others.

e. The incidence of metabolic syndrome was not significantly higher among polymorphism carriers (52.4%) compared with non-carriers (20.5%). The same was true of hypertension, ischemic heart disease, heart failure, and psoriatic arthritis (Table 6D).

f. The nonsignificant increase in cardiovascular events in patients carrying the *rs5918(C)* mutant allele was unexpected because the scientific literature shows a high incidence of CVD in patients with psoriasis and from the presence of this polymorphism in patients with CVD (Table 5D and Table 6D). The association between *ITGB3 rs5918(C)* carriage and cardiometabolic risk has been investigated in multiple studies with conflicting results. For example, the prevalence of this polymorphism in MI patients has been found with OR values ranging from 0.570 to 5.935. Carriage of the *rs5918* mutant genotype (CC+CT) contributes to an increased risk of coronary artery disease, coronary stent thrombosis, MI, stroke, and is more resistant to the antithrombotic effects of aspirin. Carriage of the *PlA2* mutant allele (*rs5918*(C)) in the ITGB3 gene has been found to be significantly associated with acute coronary thrombosis, particularly in patients diagnosed with sudden cardiac death, with an increased correlation seen in patients younger than 60 years of age.

These data suggest that *rs5918(C)* carriage has an increased association with platelet-mediated, thrombotic cardiac events. This assumption proves of significant importance in our patient group: the majority (70%) of our patient were under 60 years of age. We should consider that patients with psoriasis face a higher risk of dyslipidemia and MS. The risk of CVD is non-significantly higher in patients carrying *ITGB3 rs5918(C)*. Carriers of the *ITGB3 rs5918(C)* allele presented higher PASI values (Table 5D and Table 6D) compared with non-carriers, but not significantly higher. In the present study on carriage of the *ITGB3 rs5918(C)* allele, some results (triglyceridemia, hypercholesterolemia, hyperglycemia, MS, etc. (Table 5D Table 6D) did not reach statistical significance and it is impossible to conclusively say whether they matter. We believe that awareness of CVD and

MS risk factors and their genetic background are important in the management of patients with psoriasis.

5.4. Role of *FVL* in the development of psoriasis and comorbiditie

Factor V Leiden *(FVL)* is thought to be a major thrombophilic factor associated with the risk of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE**)**. Research on the mutation began after the first report of an association of this mutation with DVT and BTE back in 1994.

5.4.1. Carriage of the *FVL* polymorphism among patients with psoriasis

In our study group, the frequency of *FVL 1691(A)* mutant allele carriage was higher in patients with psoriasis compared to the control group (10.10% vs 7.73%, $p > 0.05$), but not significantly so (Table 4.5). The calculated relative risk was low: (OR 1.38, $p > 0.05$) indicating that carrying the mutant *FVL* allele was not a risk factor for the disease development. Carriage of the mutant *FVL* allele varies widely (from 0.7 to 7%) between races, in the Bulgarian population it is about 7-9%. We found no homozygous carrier in the patient group.

5.4.2. Relationship of *FVL* polymorphism with metabolic parameters and comorbidities

Clinical data for obesity, hyperglycaemia, triglyceridaemia, HDL, dyslipidaemia, hypertension, CRP and PASI in carriers of the *FVL* mutant allele showed no significant difference from non-carriers of this polymorphism, and from non-carriers of the five thrombophilic mutations (Figure 4.11 and Table 7D and Figure 4.12 Table 8D).

a. The findings concerning the comorbidities: hypertension, CVD, diabetes, psoriatic arthritis, liver disease, and MS in patients with psoriasis – carriers of the *FVL* mutant allele were similar, because no significant difference was found between them and the non-carrers of the mutant allele and the other thrombophilic mutaions (Figure 4.11 and Table 7D, Figure 4.12 and Table 8D). There was only one case of thromboembolism: a patient with psoriasis carrying *FVL*. The association between psoriasis, DVT and venous thromboembolism (VTE) has been presented as significant in the literature. The study by Ogdie et al. on VTE in patients with psoriasis and psoriatic arthritis showed that the risk was significantly elevated and remained elevated after adjustment for age, sex, and established risk factors for VTE (general surgery, major trauma, immobilization, or oral contraceptives). Isolated clinical cases of pulmonary embolism and psoriasis have also been described. A meta-analysis examining the risk of VTE in patients with psoriasis compared with healthy controls done by Hillari et al. in 2021 confirmed that the risk was increased but did not reach significance. Inconsistency between different studies suggests that psoriasis severity, age, sex and/or comorbidities may influence the risk of VTE in subgroups of the psoriasis population. b. The high OR values and significant difference ($p < 0.05$) (Table 8D) obtained for CRP in patients with psoriasis indicate a more significant proinflammatory and prothrombotic state of these patients.

c. High OR values were also obtained for hyperglycemia and lipidemia, however they were nonsignificant (Table 8D). Since

FVL (rs6025A) carriage is relatively rare, and the cohort was limited (109 patients), our data are nonsignificant and did not allow to draw a conclusion about risk. Also of note is the fact that the mean age of the patients was significantly lower (the difference was close to significant). Over the last decade, many studies have been done on the importance of *FVL* polymorphism in the development of VTE. Evidence has been presented for a 3- to 10-fold higher risk of VTE in *FVL* carriers (OR 9.7, 95% CI: 3.4-27.3) compared with non-carriers of the mutation. It should be noted that one of the two patients with pulmonary embolism was a heterozygous carrier of *FVL*.

5.5. *FII 20210 G>A SNP* polymorphism *(rs1799963)* in patients with psoriasis

The *20210 G>A* single nucleotide substitution in the prothrombin gene is the second most important thrombophilic factor associated with an increased risk of venous thromboses.

5.5.1. Carriage of the *FII 20210 G>A* polymorphism among patients with psoriasis

The frequency of the mutant 20210 A allele of the *FII 20210 G>A* polymorphism was higher, albeit nonsignificantly, in patients with psoriasis compared to the control group: 4.58% versus 2.21%, an OR higher than 2 (OR 2.13), indicating a definite importance of this polymorphism in the development of the disease (Table 4.6). Of note is the fact that carriage is rare, and probably the small number of patients carrying this allele makes our data non-significant. No homozygous carriers were found in the patient group, nor in the control group.

The first study of the *FII 20210 G>A* polymorphism on an association of the development of thromboses and VTE in carriers of the mutation was presented by Poort et al. in 1996. The same authors found that carriage of the *20210A* mutant allele resulted in almost twice the prothrombin levels in plasma compared to prothrombin levels in non-carriers of the mutation. A meta-analysis of studies on Indo-European patients found an approximately four-fold higher risk of developing VTE in *FII 20210A* carriers (OR 3.8 95% CI: 3.0 - 4.9). Homozygous carriage of the *20210 A* allele is very rare (Bosler et al.)

5.5.2. Association of *FII 20210 G>A* polymorphism with metabolic parameters and comorbidities

Clinical and laboratory data of psoriasis patients carrying the *FII 20210A* mutant allele of the *FII 20210 G>A* polymorphism were analysed relative to non-carriers of this allele, as well as to non-carriers of other thrombophilic mutations (Table 9D and Table 10D).

a. The results of the statistical analysis showed that carrying the *FII 20210A* mutant allele significantly increased the risk of developing type 2 diabetes (OR 6.83, $p < 0.05$) (Table 10D).

b. Significantly high CRP values in psoriasis patients carrying the *FII 20210A* allele ($p < 0.05$) (Table 10D) indicated the contribution of the carriage to the patients' proinflammatory state. Elevated CRP levels were associated with chronic inflammation, including cardiovascular risk. C-reactive protein (CRP) is an acute phase protein that is synthesized in the liver in response to inflammation. Chronic inflammation (elevated CRP) can contribute to endothelial dysfunction and promote a prothrombotic state, further enhancing this prothrombotic tendency of the *FII 20210G>A* mutation. c. We obtained high OR values (between 2 and 3). However, they were not significant for patients with low HDL

and patients with dyslipidemias, high PASI values, and psoriatic arthritis, and in carriers of the *FII20210A* mutant allele of prothrombin (Table 10D). These data demonstrated the contribution (non-significant) of carrying the mutant allele of *FII20210A* to the disease development and comorbidities. The results of the statistical analysis proved significantly higher when comparing carriers of the *FII20210A* allele with the group of non-carriers of the thrombophilic mutations than with the non-carriers of the mutant allele alone. Data on the association of this polymorphism and psoriasis are lacking in the literature.

5.6. Relationship of investigated prothrombotic mutations to metabolic parameters and comorbidities in patients with psoriasis.

Extensive data on psoriasis and its comorbidities already exists in the scientific literature. However, it is not yet clear how this knowledge can translate into routine clinical practice for the prevention and treatment of psoriasis comorbidities. It has been shown in several studies that patients with psoriasis and at risk for CVD are less likely to receive cardioprotective therapy compared with patients at typical risk for CVD and MS alone. Given this, it is critical for patients with psoriasis, especially at younger ages, to be screened for CVD risk with a broad panel of polymorphisms to assess potential risk factors that could contribute to a higher incidence of comorbidities. The etiology of CVD risk and metabolic syndrome in patients with psoriasis continues to be the subject of numerous studies. A potential mechanism of this association may be compromised metabolic status, which activates inflammatory mediators and procoagulant factors involved in psoriasis and vascular pathogenesis, contributing to comorbid conditions in such patients. There is evidence for the presence of systemic inflammation in psoriasis and the association of psoriasis with early coronary artery disease. Psoriasis has a multifactorial genetic basis, evidenced by epidemiological studies and familial recurrences involving various polymorphic alleles of inherited predisposition. These facts have stimulated our interest in the role of specific polymorphisms associated with risk of proinflammatory and prothrombotic conditions that may contribute to a higher risk of developing psoriasis and also influence its comorbidities.

One of the significant comorbidities in carriers of prothrombotic mutations turned to be type 2 diabetes. Diabetes disrupts the physiological balance between coagulation and fibrinolysis, leading to a prothrombotic state characterized by platelet hypersensitivity, coagulation factor disorders, and hypofibrinolysis. Hyperglycaemia and insulin resistance increase platelet number and aggregation by increasing vWF factor levels and inhibiting the anti-aggregation efficiency of nitric oxide and prostaglandin I 2. Diabetes also slows fibrinolysis by decreasing tPA as well as by increasing PAI-1 and the fibrinolysis inhibitor thrombin activator.

In addition to hyperglycemia and insulin resistance, comorbid metabolic disorders such as hypoglycemia, obesity, dyslipidemia, and NAFLD also contribute to the proinflammatory state of patients with diabetes mellitus.

In many studies, including this one, some of the results do not reach statistically significant and it is then virtually impossible to decide definitively whether a particular association of psoriasis with type 2 diabetes, cardiovascular comorbidity and metabolic syndrome is significant. However, such results should not

necessarily be ignored. In our opinion, these data should be thoroughly analysed to determine their biological significance. The importance of comorbidities should be emphasized, and awareness and efforts to search for their risk factors and their genetic origins should be a key factor for dermatologists and other medical professionals involved in the treatment and care of patients with psoriasis.

6. CONCLUSION AND IMPLICATIONS

1. Significance of carrying the 4G/4G genotype of SND-675 *ID, 4G/5G* in the PAI-1 gene

1.1. There was a significant difference in the carriage of genotype 4G/4G of the *-675 ID, 4G/5G* polymorphism in the PAI-1 gene in psoriasis patients compared to controls, defining this polymorphism as a risk factor for the development of psoriasis disease ($p < 0.05$).

1.2. A significant difference was demonstrated for fasting blood glucose levels between the number of patients with high blood glucose and the number of patients with type 2 diabetes in carriers versus non-carriers of the *-675 ID* 4G/4G genotype of the *4G/5G* polymorphism in the PAI-1 gene, indicating that carriage of this genotype contributes to insulin resistance and type 2 diabetes in patients with psoriasis.

1.3. There was a significant difference in HDL levels, the number of patients with dyslipidaemia among carriers of the 4G/4G genotype of the *-675 ID, 4G/5G* polymorphism compared to the non-carriers, and the non-carriers of the five thrombophilic mutations.

1.4. No significant association was found between CVD manifestation and MS in psoriasis patients carrying genotype 4G/4G of *-675 ID, 4G/5G* polymorphism.

2. Significance of carrying the TT genotype of the *677C>T* polymorphism *(rs1801133)* in the MTHFR gene

2.1. The present study of the *677C>T (rs1801133*) polymorphism in the MTHFR gene in patients with psoriasis showed that carriage of the 677 TT genotype was marginally higher compared to the control group, therefore not contributing to the risk of disease development.

2.2. A significant difference was found in fasting blood glucose levels, the number of patients with high blood glucose, the number of patients with type 2 diabetes carrying the *677* TT genotype, indicating that this carriage contributes to insulin resistance and type 2 diabetes in patients with psoriasis.

2.3. A significant difference was found in dyslipidemia and obesity rates in psoriasis patients carrying the *677 TT* genotype compared to non-carriers and non-carriers of other thrombophilic polymorphisms.

2.4. There was a significant difference regarding genotype *677 TT (rs1801133*) carriage and the development of MS in patients with psoriasis.

3. Significance of carrying the *rs5918(C)* polymorphism in the ITGB3 gene

3.1. No significant difference was found for carriage of the mutant allele of the *rs5918(C)* polymorphism in the ITGB3 gene in patients with psoriasis compared to controls, indicating that this carriage does not increase the risk of developing psoriasis.

3.2. Carriage status for the *rs5918*(C) mutant allele showed an association of the carriage with the incidence of triglyceridaemia, hypercholesterolaemia and low HDL values in patients with psoriasis - factors contributing to the development of CVD and MS.

4. Significance of carrying the FVL mutant allele *(rs6025)*

4.1. Carriage for the mutant *FVL* allele (*rs6025*) in patients with psoriasis does not contribute to the risk of developing psoriasis.

4.2 High OR values and a significant difference for CRP in psoriasis patients carrying the mutant allele of *FVL* (*rs6025*) indicated a more significant proinflammatory and prothrombotic state of these patients.

5. Значение на носителството на мутантния алел FII 20210 A

5.1. Carriage of the *FII 20210 G>A* polymorphism was higher in psoriasis patients compared to the control group, but not significant. Therefore, no conclusion can be drawn about the risk of disease development in carriers.

5.2. Carriage of the *FII 20210A* mutant allele significantly increases the risk of developing type 2 diabetes.

5.3. Significantly high CRP values in psoriasis patients carrying the *FII 20210A* allele suggest that this mutant allele contributes to proinflammatory processes.

5.4. Nonsignificantly elevated HDL levels, number of patients with dyslipidemias, number of patients with high PASI values and psoriatic arthritis were found among carriers of the mutant allele compared with noncarriers, as well as noncarriers of other thrombophilic mutations.

Contributions

Original scientific contributions

1. For the first time, the carriage of *PLA1/A2* polymorphism (-675 ID, (4G/5G), in the PAI-1 gene, *PLA1/A2* polymorphism (*rs5918ITGB3*) in the platelet integrin 3B gene, 667C>T polymorphism in the MTHFR gene, *FVL* polymorphism (*rs6025*) in the FV gene, and *FII 20210 G>A* polymorphism (*rs179996*) in the FII gene were investigated in patients with psoriasis vulgaris as risk factors for the development of dermatosis.
2. This was the first study on the association between patients with psoriasis carrying the above polymorphisms and the development of comorbid conditions CVD, type 2 diabetes, hyperlipidemia, obesity and MS in a Bulgaria population .

Scientific and theoretical contributions

1. Carriage of the 4G/4G genotype of the *-675 ID, 4G/5G* polymorphism of the PAI-1 gene is a risk factor for the development of psoriatic disease.
2. Carriage of genotype *677* TT *(rs1801133)* in the MTHFR gene, the *PLA2* mutant allele (*rs5918ITGB3*) in the platelet integrin 3B gene, the FVL mutant allele (rs6025) in the FV gene, and the *FII 20210A* mutant allele (*rs179996)* in the FII gene in patients with psoriasis do not pose a risk for the development of dermatosis.

Scientific and confirmatory contributions

1. In patients with psoriasis, carrying the 4G/4G genotype of the *-675 ID, 4G/5G* polymorphism in the PAI-1 gene contributes to insulin resistance and the development of type 2 diabetes.
2. Patients carrying genotype *677* TT in the MTHFR gene have been found to have significantly high rates of dyslipidemia, obesity and MS.
3. Carriage of the *rs5918*(C) mutant allele in the ITGB3 gene showed an association with triglyceridemia, hypercholesterolemia and low HDL values - factors in the development of CVD and MS.
4. High CRP values in psoriasis patients carrying the *FVL* mutant allele (*rs6025*), indicates a more significant proinflammatory and prothrombotic state of these patients.

5. A significantly increased risk of developing type 2 diabetes also exists in psoriatic patients carrying the *FII 20210A* mutant allele .

LIST OF SCIENTIFIC PRODUCTION RELATED TO THE THESIS

Publications:

1. Dimitrov BT, Gincheva VH, Simeonova IG, Ivanova AI, Petkova MP, Gospodinov DK, Komsa-Penkova R. Recurrent arterial and venous thrombotic events in a patient with psoriasis. Impact of PAI-1 Polymorphism: A case report. J Biomed Clin Res, 2016; 9 (2): 163 – 168. ISSN: 1313-9053(online)
2. Dimitrov B, Ilieva K, Gospodinov D, Komsa-Penkova R. Impact of carriage of 4G/5G PAI-1 and Glycoprotein IIb/IIIa polymorphism on development of Chronic Obstructive Pulmonary Disease in a patient with псориазис вулгарис. Clinical Case. Journal of IMAB - Annual Proceeding (Scientific Papers), 2019, 25(2): 2537-2543; ISSN: 1312-773X. *Web of Science*
3. Dimitrov B, Gospodinov D, Gincheva V, Komsa-Penkova R. Prevalence of MTHFR gene 677c>t polymorphism in the patients with псориазис вулгарис. Journal of IMAB - Annual Proceeding (Scientific Papers), 2021, 27(2): 3707-3711; ISSN: 1312-773X. *Web of Science*
4. Dimitrov B, Georgieva G, Gospodinova K, Tonchev P, Gospodinov D, Stavreva G, Komsa-Penkova R. Platelet polymorphism RS5918T > C in the Integrin B3 Gene modulates comorbidities in patients with psoriasis. Biotechnology & Biotechnological Equipment, 2023; 37:1, 2212083, ISSN: 1310-2818. *Web of Science, Scopus.*

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1. Dimitrov B, Simeonova I, Ivanova A, Petkova M, Gospodinov D, Komsa-Penkova R. Recurrent arterial and venous thrombotic events in patient with psoriasis. Impact of PAI-1 polymorphism. Clinical Case. XIV Международна медицинска научна конференция за студенти и млади лекари. МУ-Плевен, 10-15 октомври 2016.

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3. Dimitrov B, Gospodinov D, Komsa-Penkova R.Носителство на полиморфизма PL(A1)/PL(A2) при пациенти с псориазис. XVI Международна медицинска научна конференция за студенти и млади лекари. МУ-Плевен. 8-13 октомври 2018.

4. Dimitrov B, Ilieva K, Gospodinov D, Komsa-Penkova R. Carriage of PAI-1 and glycoprotein IIb/IIIa polymorphism on development of chronic obstructive pulmonary disease in patient

with псориазис вулгарис. Clinical case. 29-th Annual Assembly of IMAB and with the satellite 6-th Meeting of Alumni Club at Medical University Varna, 9 - 12 May 2019.

5. Komsa-Penkova R, Dimitrov B, Tonchev P, Gospodinova K, Gospodinov D. Place of MTHFR gene polymorphism C677T as a risk factor in obese male patients with psoriasis. Clinical Nutrition ESPEN 40(2020).

Additional materials of dissertation

„Analysis of the role of genetic variants of thrombophilic factors in the pathology of psoriasis vulgaris“

of Borislav Dimitrov

Table 1D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, high CRP, PASI > 20, cardiovascular disease, metabolic syndrome and common comorbidities in psoriasis patients, carriers of 4G/4G genotype of the SND -*675* ID polymorphism in the PAI-1 gene versus non-carriers.

Parameters PAI-1 4G/4G -675 ID, (-)	Carriers $\bar{X}$± SD	Non-carriers $\bar{X}$ ± SD	OR	95% CI	χ2	p
Number of patients (n)	38	71				
Average age (years)	53.60 ± 12.41	54.32 ±12.94				0.780
Average age of onset (years)	40.86 ±15.17	34.29 ± 15.75				0.043
BMI kg/m²	29.25 ± 5.62	28.82 ± 5.56				0.704
Patients with BMI ≥ 25 kg/m² (n, %)	32 (86.48)	54 (79.41)	1.659	0.546 - 5.038	0.809	0.368
Patients with BMI ≥ 30 kg/m² (n, %)	20 (54.05)	33 (48.52)	1.247	0.559 - 2.784	0.293	0.589
Patients with hyperglycemia (n, %)	14 (43.75)	12 (21.42)	2.851	1.107-7.346	4.874	0.027
Fasting blood sugar level mmol/l	6.28 ± 2.207	5.59 ± 1.172				0.059
Patients with Diabetes type 2 (n, %)	12 (31.57)	8 (11.26)	3.634	1.331- 9.924	6.815	0.009
Patients c triglyceridemia (n, %)	16 (50)	23(40.35)	1.478	0.618 - 3.535	0.775	0.378
Triglycerides mmol/l	1.966 ± 1.197	1.795 ± 1.047				0.485
Patients with low HDL (n, %)	15 (48.4)	14 (26.4)	2.611	1.028 - 6.634	4.177	0.041
Patients with hypercholesterolemia (n, %)	19 (57)	36 (60)	0.904	0.382 - 2.142	0.051	0.819
Patients with dyslipidemia (n, %)	23 (74)	30 (54.5)	2.395	0.913 - 6.281	3.236	0.072
Patients with hypertension (n, %)	25 (65.78)	39 (55)	1.577	0.696 - 3.572	1.204	0.272
CRP (mg/L)	15.141 ± 21.86	6.403 ± 9.061				0.042
Patients with high CRP (n, %)	11(55)	13(37.1)	0.483	0.158-1.476	1.650	0.199
PASI	27.290 ± 9.12	26.306 ± 10.4				0.699
Patients with PASI scores > 20 (n, %)	17 (77.3)	37 (82.2)	1.360	0.387- 4.778	0.231	0.630
Patients with psoriatic arthritis (n, %)	17 (44.73)	22 (31)	1.803	0.799 - 4.067	2.037	0.154
Patients with CVD without hypertension (n, %)	13 (44.73)	21 (31)	1.238	0.533 - 2.873	0.248	0.619
Patients with CVD + hypertension (n, %)	27 (71.05)	41 (57.74)	1.796	0.771 - 4.179	1.867	0.171
Patients with liver diseases (n, %)	1 (7.7)	12 (92.3)	0.488	0.059 - 4.055	0.458	0.498
Patients with thrombosis (n, %)	0 (0)	6 (100)	1.092	1.018 - 1.172	3.398	0.065
PAI-1 ng/ml	115.2 ± 21.68	103.0 ± 17.55				
Patients with high PAI-1 levels (%)	92.5	87.5				
Patients with metabolic syndrome (n, %)	19 (59.4)	28 (49.1)	1.513	0.630 - 3.634	0.864	0.352
Patients with metabolic syndrome + BMI > 30 kg/m² (n, %)	13 (40.6)	22 (40.7)	0.995	0.408 - 2.423	0.001	0.991

Table 2D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, high CRP, PASI > 20, cardiovascular disease, metabolic syndrome and common comorbidities in psoriasis patients, carriers of 4G/4G genotype of the SND -*675* ID polymorphism in the PAI-1 gene versus non-carriers of the five thrombophilic polymorphisms.

Parameters -*675* ID, PAI-1 4G/4G	Carriers $\bar{X}$ ± SD	Non-carriers $\bar{X}$ ± SD	OR	95% CI	χ2	p

Number of patients (n)	38	44				
Average age (years)	53.60 ±12.41	55.08 ± 13.46				0.606
Average age of onset (years)	40.86 ± 15.17	35.77 ± 16.75				0.163
BMI kg/m²	29.25 ± 5.62	28.54 ± 5.63				0.571
Patients with BMI ≥ 25 kg/m² (n, %)	32 (86.48)	34 (77.3)	1.882	0.580 - 6.108	1.131	0.288
Patients with BMI ≥ 30 kg/m² (n, %)	20 (54.1)	19 (43.2)	1.548	0.642 - 3.731	0.952	0.329
Patients with hyperglycemia (n, %)	14 (43.8)	7 (18.9)	3.333	1.132 - 9.807	4.997	0.025
Fasting blood sugar level mmol/l	6.27 ± 2.20	5.42 ± 0.93				0.036
Patients with Diabetes type 2 (n, %)	12 (31.6)	4 (8.9)	4.730	1.377 - 16.244	6.815	0.009
Patients with triglyceridemia (n, %)	16 (50)	13 (35.13)	1.846	0.701 - 4.857	1.556	0.212
Triglycerides mmol/l	1.96 ± 1.19	1.64 ± 0.86				0.201
Patients with low HDL (n, %)	15 (48.4)	8 (24.2)	2.929	1.011-8.482	4.047	0.044
Patients with hypercholesterolemia (n, %)	19 (57.6)	21 (56.8)	1.034	0.400 - 2.669	0.005	0.945
Patients with dyslipidemia (n, %)	23 (74)	18 (51.4)	2.715	0.957 - 7.700	3.621	0.057
Patients with hypertension (n, %)	25 (65.8)	27 (60)	1.282	0.522 - 3.144	0.295	0.587
CRP (mg/L)	15.14 ± 21.86	5.05 ± 5.04				0.025
Patients with high CRP (n, %)	11 (55)	9 (33.3)	2.444	0.743 - 8.035	2.206	0.137
PASI scores	27.29 ± 9.12	24.81 ± 8.17				0.314
Patients with PASI scores > 20 (n, %)	17 (77.3)	23 (79.3)	1.127	0.295 - 4.315	0.031	0.861
Patients with psoriatic arthritis (n, %)	17 (44.7)	12 (26.7)	2.226	0.887 - 5.583	2.959	0.085
Patients with CVD without hypertension (n, %)	13 (34.2)	14 (29.2)	1.262	0.506 - 3.151	0.251	0.617
Patients with CVD + hypertension (n, %)	27 (71.05)	28 (62.2)	1.490	0.591 - 3.756	0.719	0.397
Patients with liver diseases (n, %)	4 (10.5)	6 (13.3)	0.764	0.199 - 2.938	0.153	0.696
Patients with thrombosis (n, %)	0 (0)	4 (10.5)	0.119	0.006 - 2.298	3.549	0.060
Patients with metabolic syndrome (n, %)	19 (59.4)	16 (43.2)	1.918	0.734 - 5.007	1.787	0.181
Patients with metabolic syndrome + BMI > 30 (n, %)	13 (40.6)	11 (30.6)	1.555	0.571 - 4.228	0.752	0.386

Table 3D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, CRP, PASI > 20 and comorbidities cardiovascular disease, metabolic syndrome and common comorbidities in patients with psoriasis, carriers of genotype *677* TT in the MTHFR gene versus non-carriers.

Parameters **MTHFR 677C>T**	**Carriers** $\bar{X}$ ± SD	**Non-carriers** $\bar{X}$ ± SD	**OR**	**95% CI**	χ^2	**p**

Number of patients (n)	15	94				
Average age (years)	58.86 ± 6.17	53.30 ± 13.32				0.116
Average age of onset (years)	37.71 ± 13.48	36.38 ± 16.18				0.772
BMI kg/m^2	31.76 ± 4.95	28.51 ± 5.54				0.035
Patients with BMI ≥ 30 kg/m^2 (n, %)	11 (73.3)	42 (46.7)	3.143	0.931 -10.614	3.657	0.055
Patients with BMI ≥ 25 kg/m^2 (n, %)	15 (100)	71 (78.9)	8.454	0.484 - 147.685	3.866	0.049
Patients with hyperglycemia (n, %)	6 (54.54)	20 (26)	3.420	0.940 - 12.443	3.774	0.052
Fasting blood sugar level mmol/l	6.76 ± 1.48	5.70 ± 1.12				0.045
Patients with Diabetes type 2 (n, %)	5 (33.3)	15(16)	2.633	0.788 - 8.806	2.607	0.106
Patients with triglyceridemia (n, %)	6 (60%)	33 (41.77)	2.090	0.546 - 8.000	1.198	0.273
Triglycerides mmol/l	2.091	1.827				0.480
Patients with low HDL (n, %)	5 (50.0)	24 (32.43)	2.083	0.550 - 7.890	1.203	0.273
Patients with hypercholesterolemia (n, %)	11 (84.61)	44 (55)	4.500	0.936 - 21.624	4.059	0.044
Patients with dyslipidemia (n, %)	8 (80.0)	45 (59.21)	2.755	0.547 - 13.863	1.615	0.204
Patients with hypertension (n, %)	8 (53.3)	56 (59.6)	0.776	0.259 - 2.318	0.208	0.648
CRP (mg/L)	21.29 ± 29.87	8.90 ± 14.43				0.179
Patients with high CRP (n, %)	2 (66.7)	22 (42.3)	2.727	0.232 - 32.008	0.684	0.408
PASI scores	27.96 ± 7.23	26.44 ± 10.01				0.682
Patients with PASI scores > 20 (n, %)	8 (100)	46 (78.0)	4.935	0.267 - 91.133	2.187	0.139
Patients with psoriatic arthritis (n, %)	3 (20)	36 (38.3)	0.403	0.106 - 1.526	1.885	0.170
Patients with liver diseases (n, %)	1 (7.7)	12 (92.3)	0.488	0.059 - 4.055	0.458	0.498
Patients with thrombosis (n, %)	0 (0)	6 (100)	0.936	0.888 - 0.987	1.013	0.314
Patients with CVD without hypertension (n, %)	2 (13.3)	32 (34)	0.298	0.063 - 1.402	2.585	0.108
Patients with CVD + hypertension (n, %)	8 (53.3)	60 (63.8)	0.648	0.216 - 1.942	0.607	0.436
Patients with metabolic syndrome (n, %)	8 (80)	39 (49.4)	4.103	0.819 - 20.546	3.342	0. 068
Patients with metabolic syndrome + BMI > 30 kg/m^2 (n, %)	7 (70)	28 (36.8)	4.000	0.957 - 16.724	4.026	0 .045

Table 4D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridaemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, CRP, PASI > 20 and comorbidities cardiovascular disease, metabolic syndrome and common comorbidities in patients with psoriasis, carriers of genotype *677* TT in the MTHFR gene, compared to non-carriers of the five thrombophilic polymorphisms.

Parameters ***MTHFR 677C>T***	**Carriers** **$\bar{X}$ ± SD**	**Non-carriers** **$\bar{X}$ ± SD**	**OR**	**95% CI**	**χ2**	**p**

Number of patients (n)	15	44				
Average age (years)	58.86 ± 6.17	55.18 ± 13.60				0.317
Average age of onset (years)	37.71± 13.48	35.77 ± 16.75				0.695
BMI kg/m^2	31.76 ± 4.95	28.51 ± 5.69				0.054
Patients with BMI ≥ 30 kg/m^2 (n, %)	11 (73.3)	18 (41.9)	3.819	1.046 - 13.943	4.406	0.036
Patients with BMI ≥ 25 kg/m^2 (n, %)	15 (100)	33 (76.7)	9.716	0.534 - 176.635	4.215	0.040
Patients with hyperglycemia (n, %)	6 (54.54)	7 (18.9)	5.143	1.214 - 21.795	5.450	0.020
Fasting blood sugar level mmol/l	6.76 ± 1.58	5.42 ± 0.93				p < 0.001
Patients with Diabetes type 2 (n, %)	5 (33.3)	4 (9.1)	5.000	1.131 - 22.102	5.086	0.024
Patients with triglyceridemia (n, %)	6 (60)	13 (35.13)	2.769	0.660 - 11.617	3.882	0.144
Triglycerides mmol/l	2.09 ± 1.21	1.64 ± 0.86				0.190
Patients with low HDL (n, %)	5 (50.0)	8 (24.2)	3.125	0.716 - 13.635	2.414	0. 120
Patients with hypercholesterolemia (n, %)	11 (84.61)	21 (56.8)	4.190	0.812 - 21.625	3.241	0.048
Patients with dyslipidemia (n, %)	8 (80)	18 (51.4)	3.778	0.700 - 20.378	2.603	0.107
Patients with hypertension (n, %)	8 (53.3)	27 (61.4)	0.720	0.221- 2.347	0.299	0.585
CRP (mg/L)	21.29 ± 29.87	5.05 ± 5.04				0.008
Patients with високо CRP (n, %)	2 (66.7)	9 (33.3)	4.000	0.319 - 50.229	1.292	0.256
PASI scores	27.96 ± 7.23	24.81 ± 8.17				0.332
Patients with PASI scores > 20 (n, %)	8 (100)	23 (79.3)	4.702	0.238 - 92.718	1.976	0.160
Patients with liver diseases (n, %)	1 (6.7)	6 (13.6)	0.452	0.050 - 4.099	0.520	0.471
Patients with thrombosis (n, %)	0 (0)	4 (9.1)	0.290	0.014 - 5.715	1.463	0.226
Patients with psoriatic arthritis (n, %)	3 (20)	12 (27.3)	0.667	0.160 - 2.782	0.312	0.576
Patients with CVD without hypertension (n, %)	2 (13.3)	14 (31.8)	0.330	0.065 - 1.663	1.934	0.164
Patients with CVD + hypertension (n, %)	8 (53.3)	28 (63.6)	0.653	0.200 - 2.138	0.499	0.480
Patients with metabolic syndrome (n, %)	8 (80)	16 (43.2)	5.250	0.978 - 28.182	4.256	0.039
Patients with metabolic syndrome + BMI > 30 kg/m^2 (n, %)	7 (70)	11 (30.6)	5.303	1.152 - 24.420	5.112	0.024

Parameters ***ITGB3 rs5918*** **(CT + CC)**	**Carriers** $\bar{X}$ **± SD**	**Non-carriers** $\bar{X}$ **± SD**	**χ2**	**OR**	**P**
Number of patients	21	81			
Average age (years)	55.65 ± 9.96	53.71 ±13.26			p > 0.05

Average age of onset (years)	39.21 ± 15.23	35.58±15.62			p > 0.05
BMI kg/m^2	29.94 ± 5.49	28.97±5.71			p > 0.05
Patients with BMI ≥ 30 kg/m^2 (n, %)	11 (52.38)	39 (48.15)		1.158	p > 0.05
Patients with BMI ≥ 25 kg/m^2 (n, %)	19 (95)	63 (80.8)	4.524	2.360	p < 0.05
Patients with hyperglycemia (n, %)	6 (28.6)	26 (33.3)			p > 0.05
Patients with triglyceridemia (> 1.7) (n, %)	9 (42.9)	25 (33.3)	0.601	1.505	p < 0.05
Patients with low HDL (n, %)	47.2	32.8	1.195	1.818	p < 0.05
Patients with hypercholesterolemia (n, %)	14 (66.7)	48.2 (39.0)	2.29	2.167	p ≅ 0.05
Patients with dyslipidemia (n, %)	19 (88.0)	63 (66.7)	6.806		p < 0.05
Patients with hypertension (n, %)	14 (66.7)	46 (57.5)	0.701	1.447	p > 0.05
CRP (mg/L)	7.18 ± 7.27	10.11 ± 16.71			p > 0.05
PASI scores	28.03 ± 12.36	25.90 ± 8.33			p > 0.05
Patients with PASI > 20 (n, %)	18 (85.5)	62 (75.3)	0.659	1.950	p > 0.05
Patients with liver diseases (n, %)	2 (15.4)	11 (84.6)	0.211	0.691	p > 0.05
Patients with thrombosis (n, %)	1 (16.7)	5 (83.3)	0.049	0.781	p > 0.05
Patients with CVD (n, %)	7 (33.3)	24 (22.2)		1.790	p > 0.05
Patients with metabolic syndrome (n, %)	11 (52.4)	28 (34.6)	4.896		p > 0.05

Table 5D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, high CRP, PASI > 20, cardiovascular disease, metabolic syndrome and common comorbidities in psoriasis patients, carriers of *ITGB3 rs5918(C)* allele versus non-carriers.

Table 6D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, high CRP, PASI >20 and comorbidities cardiovascular disease, metabolic syndrome and common comorbidities in patients with psoriasis, carriers of the *ITGB3 rs5918(C)* allele versus non-carriers of the five thrombophilic polymorphisms

Parameters *ITGB3 rs5918* **(CT + CC)**	**Carriers** $\bar{X}$ **± SD**	**Non-carriers** $\bar{X}$ **± SD**	**χ^2**	**(OR)**	**p**
Number of patients	21	44			
Average age (years)	55.65 ± 9.96	54.27 ± 18.41			p > 0.05
Patients with BMI ≥ 30 kg/m^2 (n, %)	11 (52.4)	19 (44.2)	0.9	1.4	p > 0.05
Patients with BMI ≥ 25 kg/m^2 (n, %)	19 (95)	35 (81.4)	2.1	4.3	p < 0.05
Patients with hyperglycemia (n, %)	7 (33.3)	11 (25.0)	1.1	1.50	p > 0.05
Patients with triglyceridemia (> 1.7) (n, %)	9 (42.9)	11 (27.5)	1.98	1.5	p < 0.05
Patients with low HDL (n, %)	10 (47.6)	13 (32.8)	3.8	3.4	p < 0.05
Patients with hypercholesterolemia (n, %)	15 (66.7)	20 (45.5)	2.29	2.167	p ≅ 0.05
Patients with dyslipidemia (n, %)	18 (85.7)	28 (63.6)	3.4	2.7	p < 0.05
Patients with hypertension (n, %)	14 (66.7)	26 (59.1)	0.701	1.4	p > 0.05
Patients with Diabetes type 2 (n, %)	5 (23.8)	4 (9.1)	2.582	3.125	p > 0.05
Patients with високо CRP (n, %)	10 (47.6.)	14 (33.3)		1.8.0	p > 0.05
CRP (mg/L)	7.18 ± 7.27	5.05 ± 16.71			p > 0.05
Patients with PASI scores > 20 (n, %)	19 (92.5)	32 (73.3)	1.97	4.3	p > 0.05
PASI scores	28.03 ± 12.36	25.90 ± 8.33			p > 0.05
Patients with CVD (n, %)	7 (33.3)	12 (27.3)		1.20	p > 0.05
Patients with liver diseases (n, %)	2 (9.1)	6 (13.3)	0.650	0.615	p > 0.05
Patients with thrombosis (n, %)	1 (4.5)	4 (8.9)	0.488	0.525	p > 0.05
Patients with metabolic syndrome (n, %)	11 (52.4)	9 (20.5)	6.8	4.3	p > 0.05
Patients with psoriatic arthritis (n, %)	6 (28.7)	12 (27.3)		1.00	p > 0.05

Table 7D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, CRP, PASI > 20 and comorbidities cardiovascular disease, metabolic syndrome and general comorbidities in patients with psoriasis, carriers of the mutant polymorphism *FVL* (*rs6025*) allele versus non-carriers.

Parameters Factor V Leiden	Carriers $\bar{X}$ ± SD	Non-carriers $\bar{X}$ ± SD	(OR)	95% CI	$\chi 2$	p
Number of patients	11	98				
Average age (years)	47.18 ± 13.99	54.84 ± 12.3				0.05
Average age of onset (years)	29.40 ± 14.72	37.32 ± 15.79				0.132
BMI kg/m²	28.84 ± 7.19	28.99 ± 5.41				0.938
Patients with BMI ≥ 25 kg/m² (n, %)	7 (70)	79 (83.2)	0.472	0.110 - 2.025	1.057	0.304
Patients with BMI ≥ 30 kg/m² (n, %)	4 (40.0)	49 (51.6)	0.625	0.165 - 2.360	0.485	0.486
Patients with hyperglycemia (n, %)	3 (33.3)	23 (29.1)	1.217	0.280 - 5.287	0.069	0.793
Fasting blood sugar level mmol/l	6.49 ± 3.63	5.76 ± 1.27				0.210
Triglycerides mmol/l	1.86 ± 1.16	1.85 ± 1.10				0.980
Patients with triglyceridemia (n, %)	5 (55.55)	34 (42.5)	1.691	0.422 - 6.773	0.454	0.560
Patients with low HDL (n, %)	3 (33.3)	26 (34.7)	0.942	0.217 - 4.078	0.006	0.937
Patients with hypercholesterolemia (n, %)	2 (22.2)	53 (63.1)	0.167	0.032 - 0.855	5.620	0.018
Patients with dyslipidemia (n, %)	5 (55.6)	48 (62.3)	0.755	0.187 - 3.042	0.156	0.692
Patients with hypertension (n, %)	5 (45.5)	59 (60)	0.550	0.157 - 1.930	0.888	0.346
Patients with Diabetes type 2 (n, %)	2 (18.2)	18 (18.4)	0.988	0.196 - 4.967	0.0001	0.988
CRP (mg/L)	16.49 ± 19.49	8.89 ± 15.02				0.298
Patients with high CRP (n, %)	3 (60)	21 (42)	2.071	0.318 - 13.511	0.599	0.439
PASI scores	29.63 ± 13.05	26.33 ± 9.38				0.431
Patients with PASI scores > 20 (n, %)	5 (83.3)	49 (80.3)	1.224	0.131 - 11.478	0.032	0.859
Patients with psoriatic arthritis (n, %)	4 (36.4)	35 (35.7)	1.029	0.281 - 3.759	0.002	0.966
Patients with CVD without hypertension (n, %)	2 (18.2)	32 (32.7)	0.458	0.093 - 2.246	0.965	0.325
Patients with CVD + hypertension (n, %)	6 (54.5)	62 (63.3)	0.696	0.198 - 2.446	0.320	0.571
Patients with liver diseases (n, %)	0 (0)	13 (100)	0.275	0.015 - 4.950	1.657	0.198
Patients with thrombosis (n, %)	1 (16.7)	5 (83.3)	1.860	0.197 - 17.540	0.303	0.582
Patients with metabolic syndrome (n, %)	4 (44.4)	43 (53.8)	0.688	0.172 - 2.753	0.281	0.596
Patients with metabolic syndrome + BMI > 30 kg/m² (n, %)	3 (37.5)	32 (41.0)	0.862	0.192 - 3.868	0.037	0.847

Table 8D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, CRP, PASI > 20 and comorbidities cardiovascular disease, metabolic syndrome and general comorbidities in psoriasis patients, carriers of the mutant *FVL (rs6025*) allele versus non-carriers of the five thrombophilic polymorphisms.

Parameters Factor V Leiden	Carriers $\bar{X}$ ± SD	Non-carriers $\bar{X}$ ± SD	OR	95% CI	$\chi 2$	p
Number of patients	11	44				
Average age (years)	47.18 ± 13.99	55.08 ± 13.46			0.050	0.089
Average age of onset (years)	29.40 ± 14.72	35.77 ± 16.75				0.273
BMI kg/m²	28.84 ±7.19	28.54 ± 5.63				0.885
Patients with BMI ≥ 25 kg/m² (n, %)	7 (70)	34 (77.3)	0.686	0.149 - 3.154	0.236	0.627
Patients with BMI ≥ 30 kg/m² (n, %)	4 (40.0)	19 (43.2)	0.877	0.217 - 3.553	0.034	0.854
Patients with hyperglycemia (n, %)	3 (33.3)	7 (18.9)	2.143	0.428 - 10.738	0.884	0.347
Fasting blood sugar level mmol/l	6.49 ± 3.63	5.42 ± 0.93				0.110
Triglycerides mmol/l	1.86 ± 1.16	1.64 ± 0.86				0.519
Patients with triglyceridemia (n, %)	5 (55.55)	13 (35.13)	2.307	0.526 - 10.116	1.267	0.260
Patients with low HDL (n, %)	3 (33.3)	8 (24.2)	1.563	0.316 - 7.726	0.302	0.582
Patients with hypercholesterolemia (n, %)	2 (22.2)	21 (56.8)	0.218	0.040 - 1.192	3.453	0.063
Patients with dyslipidemia (n, %)	5 (55.6)	18 (51.4)	1.181	0.271 - 5.147	0.049	0.825
Patients with hypertension (n, %)	5 (45.5)	27 (60)	0.556	0.147 - 2.097	0.764	0.382
Patients with Diabetes type 2 (n, %)	2 (18.2)	4 (8.9)	2.278	0.360 - 14.405	0.798	0.372
CRP (mg/L)	16.49 ± 19.49	5.05 ± 5.04				0.010
Patients with high CRP (n, %)	3 (60)	9 (33.3)	3.000	0.423 - 21.297	1.280	0.258
PASI scores	29.63 ± 13.05	24.81 ± 8.17				0.246
Patients with PASI scores > 20 (n, %)	5 (83.3)	23 (79.3)	1.304	0.127 - 13.372	0.050	0.823
Patients with psoriatic arthritis (n, %)	4 (36.4)	12 (26.7)	1.571	0.390 - 6.340	0.407	0.523
Patients with CVD without hypertension (n, %)	2 (18.2)	14 (31.1)	0.492	0.094 - 2.580	0.724	0.395
Patients with CVD +hypertension (n, %)	6 (54.5)	28 (62.2)	0.729	0.192 - 2.758	0.218	0.640
Patients with liver diseases (n, %)	2 (9.1)	6 (13.3)	0.650	0.120 - 3.518	0.253	0.615
Patients with thrombosis (n, %)	1 (4.5)	4 (8.9)	0.488	0.051 - 4.647	0.404	0.525
Patients with metabolic syndrome (n, %)	4 (44.4)	16 (43.2)	1.050	0.242 - 4.552	0.004	0.948
Patients with metabolic syndrome + BMI > 30 kg/m² (n, %)	3 (37.5)	11 (30.6)	1.364	0.276 - 6.737	0.146	0.703

Table 9D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridaemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, CRP, PASI > 20 and comorbidities cardiovascular diseases, metabolic syndrome and common comorbidities in patients with psoriasis, carriers of *FII 20210A* allele versus non-carriers.

Parameters *FII 20210A*	Carriers $\bar{X} \pm SD$	Non-carriers $\bar{X} \pm SD$	(OR)	95% CI	$\chi 2$	p
Number of patients	5	104				
Average age (years)	52.60 ± 16.93	54.14 ± 12.57				0.792
Average age of onset (years)	39.00 ± 19.86	36.44 ± 15.68				0.726
BMI kg/m²	26.80 ± 3.27	29.08 ± 5.64				0.374
Patients with BMI ≥ 25 kg/m² (n, %)	4 (80)	82 (82)	0.878	0.093 - 8.330	0.013	0.910
Patients with BMI ≥ 30 kg/m² (n, %)	1 (20.0)	52 (52)	0.231	0.024 - 2.138	1.951	0.163
Patients with hyperglycemia (n, %)	1 (20)	25 (30.1)	0.580	0.0617 - 5.453	0.232	0.630
Fasting blood sugar level mmol/l	5.21 ± 1.27	5.87 ± 1.66				0.389
Triglycerides mmol/l	1.63 ± 0.719	1.87 ± 1.12				0.643
Patients with triglyceridemia (n, %)	2 (40)	37 (44.04)	0.846	0.134 - 5.334	0.031	0.859
Patients with low HDL (n, %)	2 (50)	27 (33.8)	1.963	0.262 - 14.709	0.445	0.505
Patients with hypercholesterolemia (n, %)	2 (40)	53 (60.2)	0.440	0.070 - 2.770	0.801	0.371
Patients with dyslipidemia (n, %)	3 (75)	50 (61)	1.920	0.191 - 19.271	0.317	0.573
Patients with hypertension (n, %)	3 (60)	61 (58.7)	1.057	0.169 - 6.600	0.004	0.952
Patients with Diabetes type 2 (n, %)	2 (40)	18 (17.3)	3.185	0.496 - 20.459	1.640	0.200
CRP (mg/L)	20.84 ± 30.17	8.93 ± 14.43				0.196
Patients with high CRP (n, %)	1 (33.3)	23 (44.2)	0.630	0.053 - 7.394	0.137	0.711
PASI scores	23.90 ± 1.92	26.80 ± 9.96				0.565
Patients with PASI scores > 20 (n, %)	4 (100)	50 (79.4)	2.405	0.121 - 47.503	1.024	0.312
Patients with psoriatic arthritis (n, %)	2 (40)	37 (35.6)	1.207	0.193 - 7.553	0.041	0.840
Patients with CVD without hypertension (n, %)	1 (20)	33 (31.7)	0.538	0.058 - 5.002	0.306	0.580
Patients with CVD + hypertension (n, %)	3 (60)	65 (62.5)	0.900	0.144 - 5.626	0.013	0.910
Patients with liver diseases (n, %)	0 (0)	13 (100)	0.616	0.032 - 11.783	0.710	0.400
Patients with thrombosis (n, %)	0 (0)	6 (100)	0.942	0.899 - 0.988	0.305	0.581
Patients with metabolic syndrome (n, %)	2 (44)	45 (53.6)	0.577	0.091 - 3.637	0.349	0.555
Patients with metabolic syndrome + BMI > 30 kg/m² (n, %)	1 (20)	34 (42.0)	0.346	0.037 - 3.231	0.942	0.332

Table 10D. Frequency of clinical data: obesity (BMI ≥ 30), hyperglycemia, triglyceridaemia, low HDL, hypercholesterolemia, dyslipidemia, hypertension, CRP, PASI > 20 and comorbidities cardiovascular disease, metabolic syndrome and common comorbidities in patients with psoriasis, carriers of *FII 20210A* allele versus non-carriers of the five thrombophilic polymorphisms.

Parameters *FII rs179996*	Carriers $\bar{X}$ ± SD	Non-carriers $\bar{X}$ ± SD	(OR)	95% CI	$\chi 2$	p
Number of patients	5	44				
Average age (years)	52.60 ± 16.93	55.08 ± 13.46				0.704
Average age of onset (years)	39.00 ± 19.86	35.77 ± 16.75				0.690
BMI kg/m^2	26.80 ± 3.27	28.54 ± 5.63				0.504
Patients with BMI ≥ 25 kg/m^2 (n, %)	4 (80)	34 (77.3)	1.176	0.118 - 11.757	0.019	0.890
Patients with BMI ≥ 30 kg/m^2 (n, %)	1 (20.0)	19 (43.2)	0.329	0.034 - 3.187	0.999	0.318
Patients with hyperglycemia (n, %)	1(20)	7 (18.9)	1.071	0.103 - 11.130	0.003	0.954
Fasting blood sugar level mmol/l	5.21 ± 1.27	5.42 ± 0.93				0.662
Triglycerides mmol/l	1.63 ± 0.71	1.64 ± 0.86				0.983
Patients with triglyceridemia (n, %)	2 (40)	13 (35.13)	1.230	0.1818 - 8.330	0.045	0.831
Patients with low HDL (n, %)	2 (50)	8 (24.2)	3.125	0.377 - 25.918	1.200	0.273
Patients with hypercholesterolemia (n, %)	2 (40)	21 (56.8)	0.508	0.076 - 3.409	0.499	0.480
Patients with dyslipidemia (n, %)	3 (75)	18 (51.4)	2.833	0.268 - 29.955	0.803	0.370
Patients with hypertension (n, %)	3 (60)	27 (60)	1.000	0.152 - 6.593	0.000	1.000
Patients with Diabetes type 2 (n, %)	2 (40)	4 (8.9)	6.833	0.868 - 53.766	4.125	0.042
CRP (mg/L)	20.84 ± 30.17	5.05 ± 5.04				0.010
Patients with high CRP (n, %)	1 (33.3)	9 (33.3)	1.000	0.080 - 12.557	0.000	1.000
PASI scores	23.90 ± 1.92	24.81 ± 8.17				0.827
Patients with PASI scores > 20 (n, %)	4 (100)	23 (79.3)	2.489	0.118 - 52.467	1.011	0.315
Patients with psoriatic arthritis (n, %)	2 (40)	3 (60)	1.833	0.272 - 12.347	0.397	0.529
Patients with CVD without hypertension (n, %)	1 (20)	14 (31.1)	0.554	0.057 - 5.414	0.265	0.607
Patients with CVD + hypertension (n, %)	3 (60)	28 (62.2)	0.911	0.138 - 6.016	0.009	0.923
Patients with liver diseases (n, %)	0(0)	6 (13.3)	0.264	0.0138 - 5.050	1.643	0.200
Patients with thrombosis (n, %)	1 (9.1)	4 (8.9)	1.025	0.103 - 10.201	0.000	0.983
Patients with metabolic syndrome (n, %)	2 (40)	16 (43.2)	0.875	0.130 - 5.872	0.019	0.891
Patients with metabolic syndrome + BMI > 30 kg/m^2 (n, %)	1 (20)	11 (30.6)	0.568	0.057 - 5.685	0.236	0.627