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Keywords: skin aging; polymorpysms; laboratory analysis

Article

Genetical Signature–An Example of Personalized Skin Aging Investigation with Possible Implementation to Clinical Practice

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Abstract: We conducted a research study to create groundwork for personalized solutions within skin aging segment. This test utilises genetic and general laboratory data to predict individual susceptibility of weak skin characteristics, leveraging on the research on genetic polymorphisms related to skin functional properties. A cross-sectional study was conducted in collaboration between the Private Clinic Medicina Practica Laboratory (Vilnius, Lithuania) and the Public Institution Lithuanian University of Health Sciences (Kaunas, Lithuania). 370 participants agreed to participate in the project. The median age of respondents was 40, with a range of 19 to 74 years. After the literature search, we selected 15 polymorphisms of the genes related to skin aging subsequently distributed for different skin functions: *SOD2*(rs4880), *GPX1*(rs1050450), *NQO1*(rs1800566), *CAT* (rs1001179), *TYR* (rs1126809), *SLC45A2* (rs26722), SLC*45A2* (rs16891982), *MMP1*(rs1799750), *ELN* (rs7787362), *COL1A1*(rs1800012), AHR (rs2066853), *IL6 (rs1800795), IL1Beta* (rs1143634), *TNF-α* (rs1800629), *AQP3*(rs17553719). RT genotyping, blood count and immunochemistry results have been analysed using statistical methods. Obtained results showed significant associations among genotyping models and routine blood screens. These findings demonstrate the personalized medicine approach for aging segment and further add onto the growing field of literature. Further investigation is warranted to fully understand the complex interplay between genetic factors, environmental influences, and skin aging.

Keywords: skin aging; polymorphisms; laboratory analysis; personalized medicine

1. Introduction

"Aging and beauty" – two frequently juxtaposed concepts, when "healthy and beautiful" serve as synonyms. Over the ages doctors and scientists were focused on creating the elixir of youth or a formula for immortality which would work for all of humankind. The past century has witnessed significant advancements in genetic discoveries and elucidation of molecular secrets, which have recently culminated in a transformative impact on the field of medicine, particularly in the realms of treatment advancements and personalized approaches [1,2]. Moreover, the comprehensive understanding of intrinsic and extrinsic factors impacting the body played the crucial role for interesting findings of genetic pleiotropy and clear mechanisms of skin aging, which is an inevitable process, and all attempts to search for individualised diagnostics and treatment procedures could give the best results [3]. When examining variations in biological and social age across different racial or ethnic groups, investigators found that the influence of intrinsic factors supported the concept of a personalized medicine approach to aging, without exceptions for skin aging [4].

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Considering the current trends toward longevity and the prioritization of a precision medicine approach, research studies are ongoing on a very wide spectrum of medicine topics, such as genomic correlation with cardiovascular and neurogenerative disease [5], as well as various prediction models in cancer or rare disease treatment [6]. Highly successful examples of personalized medicine implementation include the discovery of genetically mediated pharmacokinetics of drug-metabolizing enzymes [7] and treatment of chronic myelogenous leukaemia with Imatinib [8]. The progress and availability of genotyping and sequencing techniques for individuals, particular imaging technologies, blood-based clinical assays combined with its accessibility and inexpensiveness allows to continuously monitor an individual's health status or health-related concerns [9].

Last decade, significant advancements in Genome wide association studies (GWAS) focusing on skin aging made considerable progress in analysing various mechanisms and identifying the underlying reasons for skin aging [3,10,11]. Building upon these works, we conducted a collaborative cross-sectional research study to create groundwork for personalized solutions and developing a reference skin. This test utilises genetic and general laboratory data to predict individual susceptibility of weak skin characteristics, leveraging on the research on genetic polymorphisms related to skin functional properties.

2. Materials and methods

2.1. Study design

Between 2019 and 2021, a cross-sectional study was conducted in collaboration between the Private Clinic Medicina Practica Laboratory (Vilnius, Lithuania) and the Public Institution Lithuanian University of Health Sciences (Kaunas, Lithuania). Informed consent was obtained from each participant recruited into the study. The study protocol was approved by the Regional Medical Research Bioethics Committee: BE-2-53 (2019-06-10).

2.2. Study population and exclusion criteria

The study population was comprised of healthy individuals aged ≥ 18 years who signed a written informed consent, which resulted in 370 participants. SNPs had been selected for laboratory analysis with respect to possible PCR limitations and information collected from studies which have been published within the last 10 years.

Blood samples were collected using standard venepuncture procedure, which involved obtaining two tubes (1 EDTA tube for complete blood count and DNA extraction; 1 tube with gel to accelerate separation of serum for immunochemical assays). Subjects who had concomitant medical illness or anyone with ongoing ailments such as viral or bacterial infections that could potentially affect results were excluded. A skin condition self-assessment form was filled out by all participants. 15 questions were grouped to 5 different groups presenting skin reaction or resistance to most common environmental and individual factors: Hydration, Inflammation, Elasticity [11], Mechanical Resistance and Other (skin pigmentation, food supplemental use and regular beauty treatments). The assessment of the skin condition of the study participants was subjective, they answered the standard questions based on their complaints, changes in the appearance of the skin and their subjective opinion related to their perceives and notes. We did not find any significant associations for self-assessment data with all laboratory results. Thus, this part has been excluded from further analysis. To assess the objective appearance and condition of the skin, a different study design would have had to be chosen, i.e., dermatologist would have had to provide standardized conclusions and evaluation results by objective means (dermatoscope, histological examination or etc.). This is the first stage of the study to obtain initial results to explore further research with extended team of investigators.

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2.3. Single nucleotide polymorphisms detection

Genomic DNA was extracted from whole blood samples using a commercial PureLink Genomic DNA kit (Invitrogen, Thermo Fisher Scientific, Bleiswijk, The Netherlands) according to manufacturer's recommendation and quantified by NanoDrop 2000 (Thermo Fisher Scientific, Bleiswijk, The Netherlands) spectrophotometer. SNP genotyping was performed on 7900 HT Real-Time PCR system using TaqMan (Life Technologies, Thermofisher Scientific, Bleiswijk, The Netherlands) chemistry under standard conditions. Primary SNPs selection was obtained using scientific literature search with the keywords: "GWAS, polymorphisms, skin aging, personal skin care" on 2016.02.10 in PubMed NCBI data basis website (https://www.ncbi.nlm.nih.gov/pmc) with filters for "full text, author manuscript, open access, not older than 5 years". A total of 67 articles were found. Sequencing-only studies were excluded from the analysis, and instead, SNPs were selected for analysis using Real-Time genotyping. To ensure the selection of relevant SNPs, a search was conducted in the SNP database (https://www.snpedia.com/). The aim was to identify SNPs that were most found in European populations, with a minimum occurrence of 1,00% for the minor genotype. Based on these criteria, 16 SNPs were chosen for final laboratory analysis. However, one SNP (rs35652124) was excluded from further investigation due to primer synthesis defects that rendered it unsuitable for analysis. All 15 SNPs investigated and analysed are presented in Table 1. This part of the study has been performed in Laboratory of Molecular Cardiology at Lithuanian University of Health Sciences.

2.4. Complete blood count and biochemical analysis

Clinical Laboratory testing was performed in a certified Clinical Diagnostics Laboratory "Medicina Practica Laboratorija" (Vilnius, Lithuania). Complete blood count was determined on Sysmex XT-1800 analyser using a Roche Diagnostic kit according to standard procedures. Biochemical and serological blood testing was performed on a Cobas 6000 analyser and included: C reactive protein (CRP), aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, pancreatic amylase, lipid panel (total cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL)), blood urea test, creatinine, sodium, potassium, magnesium, chloride, ionised calcium, immunoglobulin E (IgE), thyroid stimulating hormone (TSH).

2.5. Statistical analysis

The participants' gender is presented as a number and percentage, age described with median and minimum-maximum values. The distribution of analyzed blood results was tested using the Kolmogorov-Smirnov test. Since some indicators significantly deviated from the normal distribution, to simplify the presentation, all results of the complete blood count and biochemical analysis for all genotypes were presented as median, minimal, and maximal values. The Mann–Whitney U-test was used to detect significant genetic models. A difference was considered statistically significant if $p < 0.05$. Statistical data analysis was performed using the statistical package IBM SPSS Statistics for Windows, Version 20.0

3. Results

3.1. Initial grouping and screening

Out of the 370 participants, there were 83 males (22.4 %) and 287 females (77.6 %). The median age was 40, with a range of 19 to 74 years.

Rs polymorphisms (SNPs) were grouped based on their main qualities and functions related to the skin for further structured evaluation (Table 1).

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Table 1. Grouped polymorphisms and their skin related functions, (see „Single nucleotide polymorphism detection ") and data reference source.

Antioxidative	Protective	Elasticity and support	Immune response	Skin hydration
SOD2 (rs4880) [11]	*TYR* (rs1126809) [38]	*MMP1* (rs1799750) [11]	*IL1Beta* (rs1143634) [17]	*AQP3* (rs17553719) [11]
GPX1 (rs1050450) [11]	*SLC45A2* (rs26722) [39]	*ELN* (rs7787362) [35]	*TNF-α* (rs1800629) [29]	
NQO1 (rs1800566) [11]	*SLC45A2* (rs16891982) [38]	*COL1A1*(rs1800012) [32]		
CAT (rs1001179) [11]	*AHR* (rs2066853) [37]			
IL6 (rs1800795) [11]				

The SNP frequencies for *AHR* (rs2066853) and *SLC45A2* (rs26722) gene minor variants (MT) were found to be less 1,00 %, respectively (Table 2), similar findings were published by De Sousa with colleagues [12]. 368 subjects were tested for (rs2066853), because two samples have been excluded from genotyping due to preanalytical errors.

Table 2. Calculated genotype frequency within tested Lithuanian population.

Function	Corresponding gene with investigated polymorphism	WT	HT	MT	N
Antioxidative	SOD2 (rs4880)	24,86%	49,46%	25,68%	370
	GPX1 (rs1050450)	53,51%	38,65%	7,84%	370
	NQO1 (rs1800566)	65,41%	30,27%	4,32%	370
	CAT (rs1001179)	59,73%	35,95%	4,32%	370
Protective	TYR (rs1126809)	60,82%	34,86%	4,32%	370
	SLC45A2 (rs26722)	96,22%	3,78%	0%	370
	SLC45A2 (rs16891982)	94,05%	5,95%	0%	370
Elasticity and support	MMP1 (rs1799750)	34,32%	46,49%	19,19%	370
	ELN (rs7787362)	32,97%	46,76%	20,27%	370
	COL1A1 (rs1800012)	75,95%	22,70%	1,35%	370
	AHR (rs2066853)	85,05%	14,68%	0,27%	368
	IL6 (rs1800795)	28,90%	45,00%	26,10%	370
Immune response	IL1Beta (rs1143634)	54,32%	36,49%	9,19%	370
	TNF-α (rs1800629)	78,11%	20,27%	1,62%	370
Hydration	AQP3(rs17553719)	49,19%	41,89%	8,92%	370

WT- wild type genotype, HT – heterozygous genotype, MT – minor genotype, N- number of samples investigated.

3.2. Genetic model analysis

The multiple associations of blood count and immunochemical laboratory parameters with different genotyping models of various polymorphisms were further evaluated for clinical significance related to the reference range of each subsequent parameter (Tables A1 and A2) considering the calculated median range of each parameter. The significance with $p < 0.05$ are only presented for demonstration and further analysis.

3.3. Associations of routine laboratory findings with different genotypes

Calculated associations among different parameters of blood count and immunochemistry with corresponding polymorphisms are present in Tables 5 and 6. Associations with $p \geq 0.05$ are excluded from analysis as considered not statistically significant. Green colours show an association of corresponding genotype with lower or normal concentration of analyte, purple colour – with elevated concentration of analyte, all coloured associations are statistically significant ($p < 0.05$).

Table 5. Associations of complete blood count results with different genotypes.

Function	Antioxidative				Protective				Elasticity			Immune response		Hydration
CBC parameter	rs4880	rs1050450	rs1800566	rs1001179	rs1126809	rs26722	rs16891982	rs1799750	rs7787362	rs1800012	rs2066853	rs1800795	rs1143634	rs1800629	rs17553719
RBC												HT		MT	
WBC, total				HT								HT		HT	
LYPH (N)															HT
LYMPH, (%)	MT			MT						MT			MT	HT	HT
EO (N)													HT		
EO (%)		HT											HT		
Baso (N)			MT HT						MT						
Baso (%)			MT HT						MT						
MONO (N)				HT											HT
MONO (%)		HT									HT		MT		
NEUT (N)		HT		MT								HT		HT	
NEUT (%)		HT		MT						HT			MT		HT
PCT					HT										
MPV					HT					HT				HT	

RBC – red blood cell, WBC – white blood cell, N – absolute count, % - relative count, LYMPH – lymphocyte, EO – eosinophil, Baso – basophil, MONO – monocyte, NEUT – neutrophil, PCT – plateletcrit, MPV – mean platelet volume, HT – heterozygous genotype, MT – minor genotype.

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Table 6. Associations of immunochemistry results with different genotypes.

Function	Antioxidative					Protective			Elasticity			Immune response		Hydration
Immunochemistry parameter	rs4880	rs1050450	rs1800566	rs1001179	rs1126809	rs26722	rs16891982	rs1799750	rs7787362	rs1800012	rs2066853	rs1800795	rs1143634	rs1800629	rs17553719
Potassium						HT									
Calcium	HT					HT	HT*		HT						HT
Calcium, ionized	HT														
Chloride						HT	HT			HT					
Alkaline phosphatase	HT								HT						
Urea	HT									MT^		MT			
Pancreatic Amylase				HT									MT		
Creatine			HT					HT							
CRP		HT	HT					MT HT		MT HT			HT	HT	
LDL			HT								HT		HT		
HDL					HT							HT			
Cholesterol											HT	HT			
AST						HT	HT						MT		HT
ALT		HT	MT	MT	HT			HT					MT		
GGT						HT							MT HT		
IgE								MT				MT	MT		

HT – heterozygous genotype, MT – minor genotype, CRP – C reactive protein, LDL – low density lipoprotein, HDL – high density lipoprotein, AST – aspartate aminotransferase, ALT – alanine transaminase, GGT – gamma-glutamyl transferase.

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4. Discussion

We carried out a study to examine for possible associations between specific genotypes and health parameters, with focus on skin aging. Recently performed genome-wide association studies (GWAS) studies, other original research works lay the groundwork for personalized approach to healthcare, where a niche for more effective skin care approaches certainly exists [13–15]. In the literature, there are different types of investigations with different objectives, some of them are orientated to a thorough pathophysiological and genetical analysis [3,15], others are focused on more practical approach, trying to find the best way how to utilize scientific findings for clinical use [6,10,11]. Our work stands out from both categories by combining routine laboratory investigations with molecular genotyping results offering regular blood tests that would depend on individual skin-associated genotypes.

We found significant correlations with liver and pancreatic enzymes, lipoproteins, electrolytes, and blood counts parameters with various polymorphisms of genes, thought to be involved in the skin aging pathogenesis. These results highlight some possible pathways and mechanisms that would explain the resulting phenotypes. 15 different genotypes had different associations with blood results, but some tendencies were noticed. Certain genetic variants, namely CAT (rs1001179), GPX1 (rs1050450), NQO1 (rs1800566), IL1Beta (rs1143634), and COL1A1 (rs1800012), which are primarily associated with antioxidant functions, exhibit significant correlations with liver enzymes ALT and AST, as well as white blood cell counts, particularly with respect to Neutrophils (Neu), Eosinophils (Eo), Lymphocytes (Lymph), Basophils (Baso), and Monocytes (Mono). These associations highlight their potential roles in maintaining liver health and immune system support. These findings showed no objections with other studies, where genes functions and relations within different pathways had been described [11,16,17].

CAT (Catalase gene) known as important antioxidant enzyme which breaks down hydrogen peroxide to oxygen and water lowering impact of ROS (Reactive Oxygen Species) supporting negative effect to carcinogenesis and skin protection against radiation and UV [18]. Rs1001179 polymorphism is related to oxidative stress and observed in chronic hepatitis patients [19]. Our results confirmed the elevated AST concentration is associated with rs1001179 minor homozygous genotype, and this finding probably supports negative effect for skin by lowering protection against oxidative stress.

GPX1 (Glutathione peroxidase) enzyme is related to antioxidative capacity. *GPX1* rs1050450 minor homozygous genotype has been implicated in reduced skin antioxidative capacity [11], and has been found related to various breast, lung, prostate, and colorectal cancers [20]. Its heterozygous and homozygous combination of alleles is associated with elevated Leu, Mo, Eo level within inflammation or hyperreactivity pathways. This effect is possibly related to GPX1 role to remove intracellular hydrogen peroxide, which protects endothelial stability. A *GPX1* mutation with lowered activity was found to accelerate thrombosis and has been associated with stent stenosis [21]. This mechanism probably could work not only in suppressing antioxidative function, but also in stiffening endothelial structure in derma [22]. We could speculate that this might have a positive effect on skin sculpture, by supporting a stronger base for all epidermic layers. Similar effect is seen after PRP (Plasma Rich Platelets) injections, releasing cumulative effect for skin, besides the stimulation of growth factor release, where indirect NO (Nitric Oxide) stability and stiffened endothelial are a result of thrombocyte activation [23,24].

Similar effect is seen with *Il1β* rs1143634, known for its responsibility in skin immunity, which was also found to be involved in cancer development, where it stimulates activated blood monocytes and tissue macrophages [17]. Proinflammatory cytokine Il1β affects cell proliferation, differentiation and apoptosis, and oxidative stress stimulates excess release of Il1β, and subsequently, affects pancreatic beta cells, which has been implicated in pancreatic cancer development [17]. Based on our findings, we have identified a strong association between elevated Pancreatic amylase levels and several other factors, which all together support the theory of inflammation having an overall impact. Interleukins are involved in pyroptosis and inflammasome pathway regulation by transcriptional

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and translational mechanisms, balancing the normal activity of inflammation, while undue activation influences inflammatory, metabolic, and oncogenic disbalance [25]. Rs1143634 heterozygous genotype was reported to be positively associated with modulation of inflammasomes, which probably has a protective effect on lung fibroblasts [26] and was found to be associated with dermal fibrosis, explaining how chronic collagen overexpression might be involved to skin aging pathogenesis [27].

NQO1 (NADPH oxidoreductase gene) is linked to various theories of carcinogenesis, particularly rs1800566, which was found to be demonstrating a strong association with gastric cancer or hepatocellular, renal carcinoma through changes of redox status inside the cells [28]. Rs1800566 is known for the same skin antioxidant capacity along with expressed reduction of enzymatic activity of the corresponding protein [11]. The predominance of the wild-type genotype, in contrast to the heterozygous alleles of this polymorphism, is linked to increased levels of ALT, CRP, MTL, Baso, and CRE, indicating the influence of common pathways affecting cellular membranes and reduced enzyme activity [28]. Conversely, the minor genotype may exhibit an opposing effect, leading to a reduction in enzymatic function.

The cytokine TNF-α is known to play a role in melanocyte apoptosis, and its polymorphism rs1800629 has been found to be associated with immune skin protection. Furthermore, its affected promoter may reduce this ability, therefore correlating with obesity and an increased plasma insulin concentration [29]. We found strong association of heterozygous genotypes with elevated Lymph, Er and CRP levels. Recently its heterozygous genotype has been found to be associated with lymphoblastic leukaemia [30]. Published studies revealed a direct association between rs1800629 and premature aging, due to TNF-α synthesis defect [31], which is probably related to a lack of collagen turnover [32].

Superoxide dismutase 2 (*SOD2)* gene) rs4880 has significant impact on telomere length, *ELN* rs7787362 is found to be related with prolonged age respondents, *SLC45A2* haplotypes rs26722, rs16891982 encode membrane-based proteins, involved in melanin synthesis [33]. We found all these four SNPs, being in different groups for skin features, but all related with elevated TP, Ca, CRE depending on different genotypes and, of course, the different pathways should have been involved affecting the overall outcome. Worth to highlight are their most common protective and supporting functions. Rs26722 and rs16891982 are associated with freckles, eye, hair, and skin pigmentation, playing a protective role for skin, and minor allele of rs16891982 is strongly associated with a black hair colour [34]. *ELN* rs7787362 minor allele was found to be associated with striae formation [35] and *COL1A1* rs1800012 similar studies speculate that minor allele could be associated with skin wrinkles formation, as it was found in relation to soft tissue malfunction [36].

The investigation of other genetic variants, specifically *MMP1* rs1799750 major genotype compared to the heterozygous pair of alleles, revealed an association with increased levels of ALT, Cre, CRP, and IgE. On the other hand, the AHR rs2066853 wild-type genotype was associated with elevated Mono, Total Cholesterol, and MTL levels. These diverse associations within various pathways highlight the extensive involvement of genes and their mutations in multiple functions, particularly related to elasticity, support function, and other physiological processes. Such findings underscore the comprehensive responsibilities of genes in contributing to various biological functions and their potential impact on health outcomes.

Our study involved a stepwise analysis, starting with genotyping of polymorphisms and associations with subsequent blood count and immunochemistry results. Moreover, this study demonstrates an essential approach to each patient's individual combination of multiple tests as it's not enough to get results from a laboratory, further assessment and a comprehensive evaluation by a laboratory medicine doctor, dermatologist, geneticist, or other qualified specialist is required. By compiling information on specific genotypes with results from laboratory testing, a more complete and more accurate picture of overall health is acquired. Further research should be carried out to create an algorithm, which would make an evaluation of large amount data easier and simplified in routine practice.

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It is also important to note that this study has certain limitations. The cross-sectional design limits the ability to prove causal relationships between genotypes and skin aging markers. Additionally, the study population consisted of healthy individuals, which does not represent the entire general population. Further research involving larger and more diverse populations, as well as longitudinal studies, would be valuable in validating and expanding upon these findings, as well as ruling out the effects of any possible unforeseen confounding variables.

5. Conclusions

In conclusion, this cross-sectional study sheds some light on a possible role of genetic polymorphisms in skin aging by revealing possible associations between certain SNPs and routine blood tests within skin properties segment. Answering the questions: what effect for skin aging could have blood changes in particular status, is it possible to modify the weakness of own genetical signature by improving the parameters of related pathogenetic mechanisms, - should help to conduct further analysis and understanding of extended view of one segment example. These findings demonstrate and support the personalized medicine approach for aging and further add onto the growing field of literature. Further investigation is warranted to fully understand the complex interplay between genetic factors, environmental influences, and skin aging.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee (BE-2-53 (2019-06-10) for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Study data are available upon request by email: vaiva.patamsyte@lsmuni.lt

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Appendix

Table A1. Genetic model analysis for complete blood count parameters.

Complete blood count (CBC) parameter	Rs polymorphism	CBC parameter median (min, max)			Genetic model statistical significance (p)			
					C1	C2	D	R
		Wilde type (WT)	Heterozygous (HT)	Minor genotype (MT)	WT vs HT	WT vs MT	WT vs HT+MT	MT vs WT+HT
BASO (%)	rs1800566	0.40 (0.00-2.10)	0.40 (0.00-1.40)	0.60 (0.10-2.00)				0.045
	rs7787362	0.50 (0.00-2.10)	0.40 (0.00-1.80)	0.40 (0.10-2.00)		0.015	0.046	0.035
EOZ (%)	rs1143634	2.40 (0.00-13.20)	2.30 (0.40-7.30)	2.80 (1.00-7.00)				0.046
LYMPH (%)	rs1001179	35.00 (13.90-54.20)	34.10 (17.10-50.90)	38.95 (22.40-65.40)		0.038		0.031

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	rs1143634	35.10 (13.90-65.40)	33.90 (17.70-54.20)	37.20 (27.30-49.90)		0.043	0.026
	rs1800012	34.9 (13.9-65.4)	35.1 (19.9-50.9)	41.6 (35-45.1)		0.042	0.042
	rs1800629	35.4 (13.9-54.2)	33.00 (17.10-65.40)	36.40 (29.40-51.50)	0.029		
	rs4880	34.00 (13.90-65.40)	34.90 (16.00-54.20)	36.30 (17.70-50.90)		0.046	
MONO (%)	rs1050450	8.95 (4.90-23.30)	9.30 (4.50-26.50)	9.80 (4.10-15.10)	0.018	0.014	
	rs2066853	9.20 (4.90-26.50)	8.55 (4.10-14.50)	13.80 (13.80-13.80	0.037		
NEUT (%)	rs1001179	52.20 (23.90-78.20)	52.30 (36.50-73.10)	45.55 (23.50-66.70)		0.027	0.022
	rs1050450	52.65 (23.90-76.90)	49.60 (23.50-78.20)	52.70 (38.50-69.40)	0.049		
	rs1143634	51.80 (23.50-78.20)	53.00 (23.90-70.60)	48.20 (36.50-58.70)		0.009	0.004
LYMPH (N)	rs17553719	1.98 (0.93-3.87)	1.96 (0.96-3.69)	2.21 (1.22-4.25)		0.016	0.019
NEUT (N)	rs1001179	2.89 (1.01-8.27)	3.06 (0.95-7.49)	2.29 (1.32-5.22)		0.017	0.009
	rs1050450	3.12 0.95-8.24)	2.73 (1.29-8.27)	3.18 (1.74-6.21)	0.028		
	rs1800629	2.89 (1.01-8.27)	3.38 0.95-7.49)	2.79 (1.27-3.55)	0.016		
	rs1800795	3.23 (1.01-8.27)	2.90 (0.95-7.05)	2.91 (1.29-7.08)	0.047		
RBC	rs1800629	4.59 (3.66-5.85)	4.63 (3.55-5.74)	4.29 (3.94-4.72)		0.023	
	rs1800795	4.63 (3.55-5.85)	4.59 (3.84-5.61)	4.59 (3.66-5.74)	0.020		0.023
WBC	rs1001179	5.83 (2.54-11.77)	5.92 (2.5-10.75)	5.11 (2.48-8.23)			0.050
	rs1800629	5.69 (2.8-11.77)	6.12 (2.47-10.45)	5.15 (4.08-6.56)	0.044		
MONO (N)	rs1800795	6.06 (2.87-11.78)	5.64 (2.47-10.75)	5.79 (3.41-11.19)	0.048		

RBC – red blood cell, WBC – white blood cell, N – absolute count, % - relative count, LYMPH – lymphocyte, EO – eosinophil, Baso – basophil, MONO – monocyte, NEUT – neutrophil, HT – heterozygous genotype, MT – minor genotype, WT – wild type, C1 and C2 – codominant 1 and 2, D – dominant, R - recessive.

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Table A2. Genetic model analysis for immunohistochemistry parameters.

Immunochemistry parameter	Rs polymorphism	Immunochemistry parameter median (min, max)			Genetic model statistical significance (p)			
					C1	C2	D	R
		Wilde type (WT)	Heterozygous (HT)	Minor genotype (MT)	WT vs HT	WT vs MT	WT vs HT+MT	MT vs WT+HT
ALT	rs1001179	18.10 (4.40-71.90)	17.50 (4.30-116.40)	14.85 (9.10-34.90)		0.05		
	rs1050450	18.00 (4.30-71.90)	16.40 (4.40-116.40)	19.30 (10.30-60.00)				0.046
	rs1799750	16.30 (4.30-48.10)	18.15 (4.40-116.40)	17.10 (4.60-71.90)	0.04		0.049	0.046
	rs1800566	17.80 (4.30-116.40)	17.10 (4.40-66.30)	12.70 (7.80-34.90)		0.036		0.041
	rs1126809	18.30 (4.60-66.30)	16.10 (4.30-71.90)	18.05 (7.80-116.40)	0.03		0.037	
AST	rs1143634	17.90 (10.10-73.10)	18.30 (9.90-124.60)	20.45 (13.40-67.50)		0.011		0.014
	rs16891982	17.95 (9.9-124.6)	21.1 (12.9-34.7)	-	0.01			
	rs26722	18.00 (9.90-124.60)	21.60 (14.10-34.70)	-	0.019			
	rs1799750	17.60 (9.90-45.50)	18.40 (10.20-67.50)	18.10 (10.30-124.60)			0.049	
Chlorine	rs1800012	102.90 (91.90-109.30)	103.65 (98.80-112.40)	101.70 (100.50-105.60)	0.047			
	rs26722	103.15 (91.90-112.40)	101.45 (97.50-106.20)	-	0.01			
	rs16891982	103.2 (91.9-112.4)	101.7 (97.5-106.2)	-	0.006			
	rs26722	71.60 (59.30-81.90)	74.45 (69.60-82.60)	-	0.003			
	rs16891982	71.6 (59.3-81.9)	73.9 (67.3-82.6)		0.005			
Calcium	rs26722	2.39 (1.97-2.67)	2.47 (2.23-2.58)	-	0.003			
	rs16891982	2.39 (1.97-2.67)	2.44 (2.23-2.58)	-	0.031			

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	rs4880	2.41 (2.13-2.63)	2.38 (1.97-2.66)	2.40 (2.15-2.67)			0.06
Calcium^{++}	rs4880	1.25 (1.16-1.35)	1.25 (1.07-1.34)	1.26 (1.18-1.38)			0.036
	krs17553719	1.25 (1.07-1.38)	1.26 (1.16-1.38)	1.25 (1.18-1.29)	0.032		
Potassium	rs17553719	4.5 (3.7-6.06)	4.5 (3.7-5.9)	4.4 (3.9-5.4)		0.041	
	rs26722	4.50 (3.70-6.06)	4.65 (3.90-5.90)	-	0.045		
Creatinine	rs1799750	68.0 (45.0-115.0)	68.0 (45.0-116.0)	71.0 (48.0-124.0)			
	rs1800566	68.0 (45.0-116.0)	71.50 (48.0-124.0)	66.0 (45.0-94.0)	0.022		
Total cholesterol	rs1800795	4.97 (3.07-7.81)	5.29 (2.67-8.63)	5.06 (3.29-8.96)	0.043		
	krs17553719	5.075 (3.07-8.96)	5.08 (2.67-7.63)	5.42 (3.37-7.87)		0.041	0.034
	rs2066853	5.15 (2.67-8.63)	4.78 (3.26-8.96)	5.57 (5.57-5.57)	0.024	0.029	
HDL cholesterol	rs1800795	1.55 (0.76-2.83)	1.71 (0.88-3.00)	1.58 (0.75-2.61)	0.006	0.037	
	rs1126809	1.58 (0.76-3.00)	1.71 (0.75-2.85	1.67 (0.94-2.41)	0.036	0.034	
MTL cholesterol	rs1143634	2.79 (1.04-6.07)	3.05 (1.45-6.15	2.98 (1.47-4.95)	0.040	0.024	
	rs1800566	2.82 (1.04-6.15)	3.17 (1.27-6.07	3.01 (1.54-4.95)	0.043	0.031	
	rs2066853	2.98 (1.04-6.15)	2.59 (1.04-6.07)	3.24 (3.24-3.24)	0.017	0.021	
Triglycerides	rs17553719	1.1 (0.32-5.50)	1 (0.40-7.60)	1.3 (0.5-4.8)		0.049	0.044
Sodium	rs17553719	139.0 (134.0-145.0)	139.0 (135.0-144.0)	138.0 (134.0-143.0)		0.04	0.06
Pancreatic amylase	rs1001179	28.00 (4.00-133.00)	24.50 (10.00-73.00)	32.00 (19.00-63.00)			0.037
	rs1143634	27.00 (10.00-133.00)	27.00 (4.00-73.00)	22.00 (12.00-45.00)		0.015	0.017
	rs2066853	27.00 (4.00-133.00	27.00 (10.00-50.00)	50.00 (50.00-50.00)			
	rs17553719	27.00 (10.0-133.0)	27.00 (4.00-82.00)	33.00 (15.00-58.00)		0.01	0.01
Alkaline phosphatase	rs7787362	55.0 (26.0-175.0)	58.0 (28.0-26.0)	55.0 (13.0-141.0)	0.009	0.032	

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Urea	rs1800012	4.60 (1.70-9.90)	4.60 (2.10-13.20)	3.70 (2.80-4.50)		0.045	0.044
	rs1800795	4.50 (2.10-8.90)	4.60 (1.70-9.90)	4.75 (1.70-13.20)		0.044	0.040
	rs4880	4.55 (2.20-8.50)	4.50 (1.70-9.90)	4.90 (2.10-13.20)			0.048
	rs1800629	4.60 (2.10-10.70)	4.50 (1.70-13.20)	5.00 (3.30-7.30)			0.04
TSH	rs4880	1.39 (0.01-3.67)	1.50 (0.30-52.88)	1.56 (0.10-10.19)		0.020	
	rs1050450	1.47 (0.01-52.88)	1.46 (0.14-7.71)	1.72 (0.59-2.61)		0.02	
CRP	rs1799750	0.54 (0.00-138.89)	0.58 (0.03-21.91)	0.88 (0.06-11.98)			
	rs1800012	0.54 (0.00-138.89)	0.71 (0.01-11.98)	0.27 (0.10-0.35)		0.041	0.031
	rs1800629	0.51 (0.00-138.89)	0.77 (0.08-11.57)	1.27 (0.37-2.58)	0.021		
GGT	rs1143634	13.00 (0.00-218.00)	11.00 (0.00-713.00)	17.00 (5.00-174.00)	0.058	0.022	0.006
	rs26722	12.00 (0.00-2713.00)	18.50 (6.00-56.00)	-	0.039		
IgE	rs1143634	36.00 (0.10-1879.0)	39.80 (0.10-493.0)	16.20 (0.60-398.5)		0.049	0.030

CRP – C reactive protein, LDL – low density lipoprotein, HDL – high density lipoprotein, AST – aspartate aminotransferase, ALT – alanine transaminase, GGT – gamma-glutamyl transferase. HT – heterozygous genotype, MT – minor genotype, WT – wild type, C1 and C2 – codominant 1 and 2, D – dominant, R - recessive.

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