International Journal of Biomedicine 13(1) (2023) 134-140
http://dx.doi.org/10.21103/Article13(1)_OA19

ORIGINAL ARTICLE

Dermatology

INTERNATIONAL JOURNAL OF BIOMEDICINE

The Impact of Single-Nucleotide Polymorphisms in Regulatory Genes on the Development of Severe Acne

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Abstract

Background: The pathogenesis of acne is multifactorial, and it was traditionally believed that four different processes play a decisive role in the development of the disease: the increased production of sebum, changes in keratinization processes leading to the formation of comedones, bacterial colonization of hair follicles by *Cutibacterium acnes* (*C. acnes*; formerly called *Propionibacterium acnes*), and synthesis of pro-inflammatory mediators in the pilosebaceous unit.

The role of genetic factors in the development of acne has been repeatedly discussed and continues to be the subject of discussion among scientists. The currently available data from various studies on genetic associations in acne are contradictory, which makes it relevant to address the problem of searching and analyzing the molecular mechanisms of the influence of regulatory genes in the pathogenesis of acne.

The aim of this study was to identify and analyze SNPs in the regulatory genes (*GATA1, GATA2, GATA2-AS1 [GATA2 Antisense RNA 1], NFKB2, NFKBIA*, and *NFKB1*) in patients with severe acne.

Methods and Results: A prospective, open, non-randomized, single-center comparative study was conducted between 2017-2020. The study included 50 (29 men and 21 women) patients (the main group [MG]) with severe acne aged from 15 to 46 years (the median age of 23.2 years) and 20 (13 men and 7 women) apparently healthy individuals (the comparison group [CG]) aged from 16 to 40 years (the median age of 19.4 years). Molecular genetic diagnostics was performed using high-throughput DNA sequencing—next-generation sequencing (NGS). The results of our study made it possible to identify SNPs in regulatory genes (*GATA1*, *GATA2*, *GATA2-AS1* [GATA2 Antisense RNA 1], *NFKB2*, *NFKBIA*, and *NFKB1*) associated with the development of severe acne.

Conclusion: The revealed SNPs within the *GATA1*, *GATA2*, *GATA2-AS1* [GATA2 Antisense RNA 1*]*, *NFKB2*, *NFKBIA*, and *NFKB1* genes in patients with severe acne probably indicate the involvement of regulatory transcription factors in the pathogenesis of acne.**(International Journal of Biomedicine. 2023;13(1):134-140.)**

Keywords: regulatory gene • single nucleotide polymorphism • acne

For citation: Rumyantsev AG, Demina OM. The Impact of Single-Nucleotide Polymorphisms in Regulatory Genes on the Development of Severe Acne. International Journal of Biomedicine. 2023;13(1):134-140. doi:10.21103/Article13(1)_OA19

Abbreviations

IL, interleukin; **IGF-1**, insulin-like growth factor-1; **NGS**, next-generation sequencing; **NF-κB**, nuclear factor kappa B; **SNP**, single nucleotide polymorphism; **TNF**, tumor necrosis factor; **TGF**, transforming growth factor.

Introduction

Currently, acne remains one of the most common dermatoses and, according to the Global Burden of Disease, affects about 85% of people aged 12-25 years. The pathogenesis of acne is multifactorial, and it was traditionally believed that four different processes play a decisive role in the development of the disease:[1-3]

- Androgen-induced increased sebum production
- Altered keratinization with the formation of comedones

- Bacterial colonization of hair follicles by *Cutibacterium acnes* (*C. acnes*; formerly called *Propionibacterium acnes*)
- Inflammation with the synthesis of pro-inflammatory mediators in the pilosebaceous unit

The role of genetic factors in the development of acne has been repeatedly discussed and continues to be the subject of discussion among scientists. An analysis of the risk of developing acne based on family history and in twins showed a significant genetic contribution of susceptibility to acne with a heritability of 78% and 81%, respectively.

According to a genome-wide association analysis performed by Navarini et al.,[4] in the United Kingdom, three genome-wide significant associations were identified: 11q13.1 (rs478304, $P_{combined}=3.23\times10^{-11}$, OR=1.20), 5q11.2 (rs38055, $P_{combined}=4.58\times10^{-9}$, OR=1.17) and 1q41 (rs1159268, $P_{combined}=4.08\times10^{-8}$, OR=1.17) were identified in patients with severe acne. All three loci contain genes linked to the TGFβ cell signaling pathway, namely OVOL1, FST, and TGFβ2. At the same time, the OVOL1 and TFGB2 transcripts had a reduced expression in the affected skin compared to normal. These data support a key role in the dysregulation of TGFβ-mediated signaling in acne susceptibility.

In another study,[5] two new acne susceptibility loci were identified at 11p11.2 (DDB2, rs747650, $P_{combined}=4.41\times10^{-9}$ and rs1060573, $P_{combined}=1.28\times10^{-8}$) and 1q24.2 (SELL, rs7531806, $P_{combined}=1.20\times10^{-8}$) that are involved in androgen metabolism, inflammation processes and scar formation in severe acne.

An analysis of the results of another GWAS study of severe adolescent acne in 928 European Americans found the most significant association with the rs4133274 SNP on chromosome 8q24 ($P=1.7\times10^{-6}$). An allele variant of this SNP (G allele) was associated with an increased risk of severe adolescent acne with OR=4.01 (95% CI: 2.37-6.82).[6]

Combined analysis performed in a meta-analysis by Yang et al. revealed a significant association between the *TNF-α* -308G/A polymorphism and acne vulgaris risk under a recessive model (OR=2.73, 95% CI: 1.37-5.44, *P*=0.004 for AA vs. AG + GG). Subgroup analysis by ethnicity showed that the acne vulgaris risk associated with the *TNF-α* -308G/A polymorphism was significantly elevated among Caucasians under the recessive model (OR=2.34, 95% CI: 1.13-4.86, *P*=0.023).[7]

According to Tasli et al.,[8] the *IGF-1* cytosine-adenine (CA) repeat polymorphism was associated with the development of acne in the Turkish population.

A systematic review of 51 articles covering Asians and Caucasians found 60 genes/loci and their 100 variants implicated in acne. Detailed analysis showed that most of the studied genes/loci were located in the intron, coding region/ missense, and promoter regions. The commonly studied candidate genes/gene families include TNF, IL, and cytochrome P450 (CYP) gene families. As a result, it was shown that most of the analyzed gene variants exhibited insignificant pooled odds ratio (pOR) and significant heterogeneity between studies. The authors found that the *TNF* rs1800629 A allele carriers and the *CYP17A1* rs743572 T allele carriers had significantly reduced mild acne risk [pOR=0.60, 95% CI: 0.33-0.86] and severe acne risk (pOR=0.59, 95% CI: 0.40-0.79), respectively, across populations. Overall, the *FST* (follistatin) rs629725 A allele showed a moderately increased risk for acne (pOR=1.19, 95% CI: 1.14-1.23). At the same time, there was no association of acne development with the *TIMP2* (TIMP 2 metallopeptidase inhibitor*)* rs8179090 and *CYP1A1* rs4646903 (pOR=0.96, 95% CI: 0.80-1.12; OR=0.95, 95% CI: 0.83-1.08, respectively). The authors also discovered 15 new SNPs in the 3'UTR region of the Toll-like receptor 4 (*TLR4*) gene associated with acne.[9]

The currently available data from various studies on genetic associations in acne are contradictory, which makes it relevant to address the problem of searching and analyzing the molecular mechanisms of the influence of regulatory genes in the pathogenesis of acne.

The aim of this study was to identify and analyze the SNPs in the regulatory genes (*GATA1*, *GATA2*, *GATA2-AS1*, *NFKB2*, *NFKBIA*, and *NFKB1*) in patients with severe acne.

Materials and Methods

Our prospective, open, non-randomized, single-center comparative study was conducted between 2017-2020. The study included 50 patients (the main group [MG]) with SA aged between 15 and 46 years (the median age of 23.2 years) and 20 apparently healthy individuals (the comparison group [CG]) aged between 16 and 40 years (the median age of 19.4 years). MG and CG were comparable in age and sex characteristics.

Molecular-genetic diagnostics was carried out by the method of high-throughput DNA sequencing (next-generation sequencing) in the Department of Molecular Genetics at the *NMRC PHOI,* named after Dmitry Rogachev (Moscow, Russia). Genomic DNA was isolated from whole blood samples of examined patients using the CellSep Advanced Kit (DiaSorin Ireland Ltd., Ireland) according to the manufacturer's instructions.

To assess the population frequencies of the identified variants, we used the the international project gnomAD Exomes (ExAC) data for exon variants and the gnomAD Genomes database for intron variants. For computer assessment of the pathogenicity of the missense variants we found, the programs for predicting the pathogenicity of amino acid substitutions (S*IFT, PolyPhen-2, PROVEAN, UMD Predictor*) were used. The *MutationTaster, Human Splicing Finder,* and *NNSplice* programs were used for computer prediction of the effect of changes in the splicing sites or areas adjacent to the splicing site.

The study of the functional significance of the complement system genes in the biological pathways of the body was carried out using an online program (https://www.genecards.org/cgi-bin/carddisp.pl?gene) that employs the STRING database (https://version11.string-db.org/cgi/network.pl?taskId=5WAhRP62DcT8) of known and predicted interactions, including direct and functional associations. The program performs mathematical prediction based on Genomic Context Predictions, High-throughput Lab Experiments, (Conserved) Co-Expression, and Automated Textmining

databases. The STRING database currently covers 24,584,628 proteins from 5,090 organisms.[10,11]

Statistical analysis was performed using the statistical software package XLSTAT 2019. The normality of the distribution of continuous variables was tested by the Shapiro-Wilk test. For descriptive analysis, results are presented as median (Me), first quartile (Q1), and third quartile (Q3). Differences of continuous variables were tested by the Mann-Whitney *U*-test. Group comparisons with respect to categorical variables are performed using the chi-square test. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to determine associations between the SNPs and severe acne. A probability value of $P<0.05$ was considered statistically significant.

This study was approved by the Ethics Committee of the PRNRMU of the Ministry of Healthcare of the Russian Federation and complied with Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 59th WMA General Assembly, Seoul, Republic of Korea, October 2008. All patients gave their written informed consent.

Results

All patients of the MG suffered from a severe form of acne, which was clinically characterized by multiple open and closed comedones, deep inflammatory papules, pustules, and nodules merging into conglomerates, atrophic scars, post-inflammatory stagnant-cyanotic spots with predominant localization on the skin of the face, back and chest. The skin in the lesions had a greasy appearance; subjective sensations were characterized by mild to moderate pain aggravated by movement and palpation.

We stratified the studied SNPs in exons, in introns, in the 3'UTR, 5'UTR, and splicing regions according to their regulatory significance in the genes *GATA1, GATA2, GATA2-AS1, NFKB2, NFKBIA,* and *NFKB1*. Characteristics of SNPs in exons of the *GATA2*, *NFKB1*, and *NFKB2* genes in patients with acne are presented in Table 1. In the GATA1, GATA2-AS1, and NFKBIA genes, we did not identify polymorphic loci in exons.

Four of the 5 SNPs in exons of the studied genes [*GATA2* (rs34799090) (OR=2.055, 95% CI: 0.096-43.775, $P=0.644$), *NFKB2* (rs199577673) (OR=1.221, 95% CI: 0.049-30.606, $P=0.903$), *NFKB1* (rs146936581) (OR=1.221, 95% CI: 0.048-30.6064, $P=0.903$), *NFKB1* (rs4648072) (OR=1.221, 95% CI: 0.049-30.605, $P=0.903$)] probably could be associated with the development of severe acne ($P>0.05$). Whereas one SNP (rs2335052) of the *GATA2* gene (OR=0.705, 95% CI: 0.284-1.748, $P=0.451$) are likely to have a protective effect. Characteristics of SNPs in introns of the *GATA1, GATA2*, and GATA2-AS1 genes in patients with acne are presented in Table 2.

We identified 11 SNPs in the introns of the studied genes for the first time that have not been previously described in any disease. It was found that in one SNP of the *GATA1* gene (.), defined by us for the first time, the frequency of the alternative allele was significantly different between MG and CG ($P=0.009$), and OR=11 (95% CI: 1.189-101.717, $P=0.034$) indicates a significant association with the development of severe acne. For the *NFKB2* (rs4919632) SNP we identified, the frequency of the alternative allele was significantly different between the MG and the CG ($P=0.049$), and OR=18.76 (95% CI: 0.946-371.894, $P=0.049$) indicates a significant association with the risk of acne formation.

The OR results showed that one SNP of the *GATA2* gene, 2 SNPs of the *GATA1* gene, 13 SNPs of the *NFKB2* gene, and 23 SNPs of the *NFKBIA* gene probably could be associated with the development of severe acne ($P>0.05$). At the same time, the remaining SNPs of the studied genes (OR from 0.13 to 0.92) are likely to have a protective effect ($P>0.05$). We identified two SNPs in the GATA2 gene (one in the splicing zone, one in the 5'UTR) and two SNPs in the NFKB2 gene, for the first time in acne patients. Two SNPs in the *NFKB1* gene loci rs386357216 and rs4648143 with ORs>1 indicate a possible association with severe acne. Four SNPs in the *GATA2* gene and 6 SNPs in the *NFKB2* gene are likely to have a protective effect (Table 3).

Discussion

The results of our study made it possible to identify SNPs in regulatory genes (*GATA1*, *GATA2*, *GATA2-AS1* [GATA2 Antisense RNA 1], *NFKB2*, *NFKBIA*, and *NFKB1*) associated with the development of severe acne.

The *GATA1* (GATA Binding Protein 1) gene encodes a protein belonging to the GATA family of transcription factors. The GATA1 protein plays an important role in erythroid development by regulating the switch of fetal hemoglobin into adult hemoglobin. In addition, the *GATA1* gene controls the differentiation of megakaryocytes, platelets, and basophils, and regulates the apoptotic signaling pathway. Mutations in this gene have been associated with X-linked dyserythropoietic anemia. It is important that the *GATA1* gene is located on the X chromosome (p11.23), which leads to X-linked inheritance. Notably, different positions of pathogenic *GATA1* variants result in a wide variety of phenotypes, spanning ineffective erythropoiesis, thrombocytopenia, and thrombocytopathy. A significant association of one SNP (.) in the *GATA1* gene with the risk of developing severe acne (OR=11, 95% CI: 1.189-101.717, $P=0.034$) indicates the involvement of regulatory transcription factors in the pathogenesis of acne.

The *GATA2* (GATA Binding Protein 2) gene encodes a member of the GATA family of zinc-finger transcription factors that are named for the consensus nucleotide sequence they bind in the promoter regions of target genes. The encoded protein plays an essential role in regulating the transcription of genes involved in the development and proliferation of hematopoietic and endocrine cell lineages. The *GATA2* gene also regulates endothelin-1 gene expression in endothelial cells. The *GATA2* SNPs identified in our study showed a probable association with the risk of acne.

The *GATA2-AS1* (GATA2 Antisense RNA 1) gene, an RNA gene, is associated with the lncRNA class. It showed that *GATA2-AS1* positively regulates GATA2 expression at the post-transcriptional level. *GATA2* is combined with the *GATA2-AS1* promoter to enhance GATA2-AS1 expression. Our data regarding the GATA2-AS1 SNPs showed a probable association with the risk of the SA development.

Table 1.

Characteristics of SNPs within exons of the GATA2, NFKB1, NFKB2 genes in acne patients

Gene	Chr: Position (hg19)	SNPid	Exon numbers	Type and position of substitution	*P*-value (Z-test for proportion)	OR (95% CI) *P*-value
GATA2	3:128204951	rs2335052	3	c.G490A: p.A164T (nonsynonymous)	0.449	0.705 (0.284 - 1.748) *P*=0.451
GATA2	3:128204960	rs34799090	3	c.C481G: p.P161A (nonsynonymous)	0.368	2.055 (0.096 - 43.775) *P*=0.644
NFKB2	10:104161032	rs199577673	18	c.G2167A: p.D723N	0.525	1.221 (0.049 - 30.606) *P*=0.903
NFKB1	4:103500158	rs146936581	8	c.G689A: p.R230H	0.526	1.221 (0.048 - 30.606) *P*=0.903
NFKB1	4: 103518700	rs4648072	15	c.A1516G: p.M506V	0.525	1.221 (0.049 - 30.605) *P*=0.903

Table 2.

Characteristics of SNPs within introns of the GATA1, GATA2, GATA2-AS1, NFKB2, NFKBIA, and NFKB1 genes in acne patients.

Gene	SNPid	Chr: Position (hg19)	Type of substitution	P-value (Z-test for proportion)	OR (95% CI) *P*-value
GATA2	rs2713603	3:128200534	G>A	0.406	0.728 (0.344 - 1.542), *P*=0.408
GATA2	rs11708606	3:128200806	G>A	0.665	0.777 (0.248 - 2.438), *P*=0.666
GATA2	rs55914222	3:128202943	G>C	0.139	0.191 (0.017 - 2.179), *P*=0.183
GATA2	rs73862209	3:128207423	C>T	0.367	2.056 (0.096 - 43.775), *P*=0.644
GATA2-AS1	rs559062253	3:128211729	G>A	0.335	0.388 (0.053 - 2.852), *P*=0.352
GATA1	**(.)**	**X:48649428**	**->G**	**0.009**	**11 (1.189 - 101.717), *P*=0.034**
GATA1	rs62600348	X:48649449	T>G	0.650	2.481 (0.048 - 127.204), *P*=0.651
GATA1	rs66717003	X:48649456	T>G	0.650	2.481 (0.048 - 127.204), *P*=0.650
NFKB2	rs76034131	10:104154581	G>A	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB2	rs1572532	10:104154683	C>T	0.651	2.481 (0.048 - 127.204), *P*=0.651
NFKB2	rs36226954	10:104155345	T>C	0.791	0.791 (0.139 - 4.504), *P*=0.792
NFKB2	rs61873662	10:104155823	A>T	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB2	(.)	10:104156392	->T	0.414	1.411 (0.615 - 3.237), *P*=0.415
NFKB2	rs776641137	10:104156856	C>A	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB2	rs12772374	10:104156911	A>G	0.702	1.235 (0.416 - 3.659), *P*=0.702
NFKB2	(.)	10:104157588	C>G	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB2	rs7897947	10:104157711	T>G	0.118	0.488 (0.196 - 1.215), *P*=0.123
NFKB2	**rs4919632**	**10:104157727**	**C>T**	**0.049**	**18.76 (0.946 - 371.894), *P*=0.049**
NFKB2	rs45487496	10:104157947	C>A	0.149	4.664 (0.252 - 86.351), *P*=0.301
NFKB2	rs3740418	10:104158933	C>G	0.414	1.411 (0.615 - 3.237), *P*=0.415
NFKB2	rs11574849	10:104159696	G>A	0.532	1.524 (0.401 - 5.781), *P*=0.535
NFKB2	rs201550645	10:104160934	C>T	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB2	rs72845693	10:104161168	G>A	0.526	1.221 (0.049 - 30.606), *P*=0.903
NFKB2	(.)	10:104161323	G>A	0.112	0.131 (0.005 - 3.284), *P*=0.216
NFKB2	rs11574852	10:104161475	A>C	0.113	0.131 (0.005 - 3.285), *P*=0.216

Table 2 (continued).

Characteristics of SNPs within introns of the GATA1, GATA2, GATA2-AS1, NFKB2, NFKBIA, and NFKB1 genes in acne patients.

Gene	SNPid	Chr: Position (hg19)	Type of substitution	*P*-value (Z-test for proportion)	OR (95% CI) *P*-value
NFKB2	rs11574853	10:104161796	T>A	0.005	0.053 (0.003 - 1.057), *P*=0.054
NFKB2	rs7077329	10:104161967	T>C	0.526	0.770 (0.343 - 1.730), *P*=0.527
NFKBIA	rs149524774	14:35871327	G>A	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKBIA	rs1022714	14:35871407	A>G	0.574	1.269 (0.551 - 2.929), *P*=0.575
NFKBIA	rs5026132	14:35871441	A>G	0.629	1.199 (0.573 - 2.514), *P*=0.629
NFKBIA	rs2233419	14:35871960	G>A	0.101	3.352 (0.730-15.395), *P*=0.119
NFKBIA	rs2233418	14:35872068	G>A	0.564	0.587 (0.094 - 3.656), *P*=0.569
NFKBIA	rs2233417	14:35872094	C>T	0.101	3.352 (0.730 - 15.395), *P*=0.119
NFKBIA	(.)	14:35872170	C>T	0.525	1.221 (0.049 - 30.606), *P*=0.903
NFKBIA	rs3138054	14:35872307	C>T	0.287	2.007 (0.544 - 7.405), *P*=0.295
NFKBIA	rs2233416	14:35872765	G>A	0.231	3.391 (0.410 - 28.038), *P*=0.257
NFKBIA	rs2233415	14:35872792	A>G	0.499	0.761 (0.345 - 1.679), *P*=0.499
NFKBIA	(.)	14:35872837	TC>-	0.113	0.251 (0.040 -1.567), *P*=0.139
NFKB1	rs41477752	4:103446824	T>-	0.872	1.206 (0.121 - 11.953), *P*=0.872
NFKB1	(.)	4:103454926	C>T	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB1	rs230526	4:103458825	A>G	0.445	1.334 (0.635 - 2.804), *P*=0.44
NFKB1	rs230525	4:103458877	G>A	0.345	1.434 (0.676 - 3.041), *P*=0.346
NFKB1	(.)	4:103458890	AC>-	0.445	1.334 (0.635 - 2.804), *P*=0.446
NFKB1	rs2293970	4:103487982	A>T	0.872	1.206 (0.122 - 11.953), *P*=0.872
NFKB1	rs230496	4:103488491	G>A	0.513	1.279 (0.609 - 2.685), *P*=0.514
NFKB1	rs909332	4:103497875	A>T	0.872	1.206 (0.122 - 11.953), *P*=0.872
NFKB1	(.)	4:103501611	A>G	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB1	rs1598858	4:103506095	A>G	0.702	0.864 (0.411 - 1.821), *P*=0.703
NFKB1	rs1020760	4:103514445	C>G	0.829	0.922 (0.441 - 1.928), *P*=0.829
NFKB1	rs4648049	4:103514737	C>T	0.872	1.206 (0.122 - 11.953), *P*=0.873
NFKB1	rs4648050	4:103514741	T>C	0.869	1.065 (0.500 - 2.269), *P*=0.869
NFKB1	rs749750576	4:103516042	G>A	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB1	rs4648073	4:103518843	G>T	0.872	1.206 (0.121 - 11.953), *P*=0.872
NFKB1	(.)	4:103527605	TAAG>_	0.525	1.221 (0.048 - 30.6062), *P*=0.903
NFKB1	rs4648095	4:103527876	T>C	0.872	1.206 (0.122 - 11.953), *P*=0.872
NFKB1	rs4648097	4:103528128	G>A	0.367	2.055 (0.096 - 43.775), *P*=0.644
NFKB1	(.)	4:103528780	G>C	0.112	0.131 (0.005 - 3.284), *P*=0.216
NFKB1	rs4648104	4:103531991	G>C	0.139	0.191 (0.016 - 2.178), *P*=0.183
NFKB1	rs56207297	4:103533052	G>A	0.268	2.907 (0.146 - 7.579), *P*=0.483
NFKB1	rs4648110	4:103533821	T>A	0.118	0.512 (0.219 - 1.195), *P*=0.121
NFKB1	rs4648117	4:103534557	C>T	0.872	1.206 (0.122 - 11.953), *P*=0.873

Table 3.

Characteristics of SNPs within 3'UTR, 5'UTR and splicing area of the GATA2, NFKB2, NFKBIA and NFKB1 genes in acne patients

Gene	SNPid	Chr: Position (hg19)	3'UTR/ 5'UTR/ splice site	Type and position of substitution	*P*-value (Z-test for proportion)	OR (95% CI) *P*-value
GATA2	rs10934857	3:128199662	UTR3	c.*200C>T	0.639	0.807 (0.330 - 1.976), *P*=0.640
GATA2	rs1806462	3:128206618	UTR5	c.-744G>T	0.255	0.642 (0.299 - 1.379), *P*=0.257
GATA2	rs2335237	3:128206710	UTR5	c.-836A>C	0.195	0.607 (0.284 - 1.297), *P*=0.198
GATA2	rs7611275	3:128206759	UTR5	c.-885G>C	0.086	0.278 (0.059 - 1.305), *P*=0.105
GATA2	(.)	3:128206766	splicing	Exon 2:UTR5	0.525	1.221 (0.049 - 30.606), *P*=0.903
GATA2	(.)	3:128207240	UTR5	c.-1366C>G	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB2	rs11574842	10:104154068	UTR5	724:c.-1649C>T	0.525	1.221 (0.048 - 30.606), *P*=0.903
NFKB2	(.)	10:104154327	UTR5	724:c.-1390del-	0.302	0.655 (0.293 - 1.467), *P*=0.304
NFKBIA	rs696	14:35871093	UTR3	c.*126G>A	0.914	0.960 (0.461 - 2.00), *P*=0.914
NFKBIA	(.)	14:35871140	UTR3	c.*79_*77delAGA	0.499	0.393 (0.024 - 6.455), *P*=0.513
NFKBIA	rs8904	14:35871217	UTR3	c.*2C>T	0.914	0.960 (0.461 - 2.00), *P*=0.914
NFKBIA	(.)	14:35873938	UTR5	c.-89_ 88insCGTCCCGC	0.917	0.928 (0.227 - 3.783), *P*=0.917
NFKB1	rs2272676	4:103423326	splicing	Exon 1: UTR5	0.345	0.696 (0.328 - 1.4771), *P*=0.346
NFKB1	rs386357216	4:103534740	splicing	Exon 23:c.2746+2->A	0.665	1.625 (0.176 - 15.00), *P*=0.668
NFKB1	rs4648143	4:103537774	UTR3	c.*23G>A	0.525	1.221 (0.048 - 30.606), *P*=0.903

The *NFKB2* (Nuclear Factor Kappa B Subunit 2) gene encodes a subunit of the transcription factor complex nuclear factor-kappa-B (NF-kB). The NF-kB complex is expressed in numerous cell types and functions as a central activator of genes involved in inflammation and immune function. The protein encoded by this gene can function as both a transcriptional activator and repressor, depending on its dimerization partner. Our data regarding SNP (rs4919632) in the *NFKB2* gene with an increased frequency of the alternative allele in the MG with OR=18.76 (95% CI: 0.946-371.894, *P*=0.049) probably indicates a significant association with the development of severe acne.

The *NFKBIA* (NFKB Inhibitor Alpha) gene encodes a member of the NF-kappa-B inhibitor family, which contains multiple ankyrin repeat domains. The encoded protein interacts with REL dimers to inhibit NF-kappa-B/REL complexes, which are involved in inflammatory responses. The *NFKBIA* SNPs we identified showed a probable association with the risk of developing acne.

The *NFKB1* (Nuclear Factor Kappa B Subunit 1) gene encodes a 105 kD protein, which can undergo cotranslational processing by the 26S proteasome to produce a 50 kD protein. The 105 kD protein is a REL protein-specific transcription inhibitor, and the 50 kD protein is a DNA-binding subunit of the NF-κB protein complex. The *NFKB1* SNPs we identified showed a probable association with the risk of developing acne.

The results of our study made it possible to identify SNPs in regulatory genes (*GATA1*, *GATA2*, *GATA2-AS1* [GATA2 Antisense RNA 1], *NFKB2*, *NFKBIA*, and *NFKB1*) associated with the development of severe acne. The gene-gene interactions are shown in Figure 1.

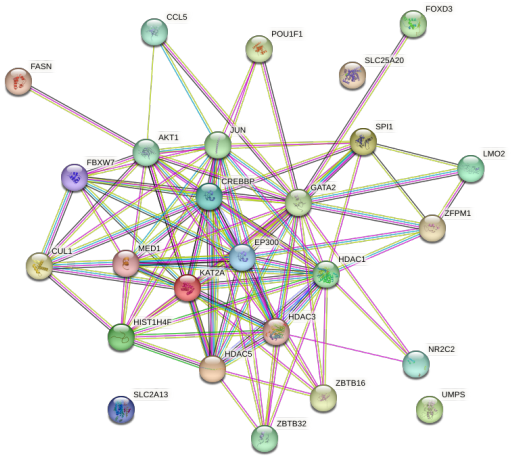

Fig.1. *The gene-gene interactions. https://string-db.org/cgi/network?taskId=bnPlpAHbFXnY&sessionId=b1VYAaiLUmdh*

Conclusion

Transcription factors have previously been defined as "non-drug-responsive" targets, except ligand-inducible nuclear receptors. More excellent knowledge of these

transcription factors, namely their structures and functions, including expression and degradation, as well as their ability to interact with cofactors, has changed this hypothesis.

NF-κB is a pleiotropic transcription factor present in almost all cell types. It is the endpoint of a series of signal transduction events initiated by various stimuli related to many biological processes, such as inflammation, immunity, differentiation, cell growth, tumorigenesis, and apoptosis. NF-κB is a transcriptional regulator activated by various intra- and extracellular stimuli such as cytokines, free radicals, ultraviolet radiation, and bacterial or viral products. Activated NF-κB translocates to the nucleus and stimulates the expression of genes involved in a wide range of biological functions. Impaired NF-κB activation is associated with several inflammatory diseases, while persistent inhibition of NF-κB results in inappropriate immune cell development or stunted growth. The identified polymorphic loci in the regulatory genes are likely to disturb the regulation of the inflammatory response, which can lead to the formation of a prolonged torpid course of acne.

The revealed SNPs within the *GATA1*, *GATA2*, *GATA2-AS1* [GATA2 Antisense RNA 1], *NFKB2*, *NFKBIA*, and *NFKB1* genes in patients with severe acne probably indicate the involvement of regulatory transcription factors in the pathogenesis of acne.

Competing Interests

The authors declare that they have no competing interests.

References

1. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet. 2012 Jan 28;379(9813):361-72. doi: 10.1016/S0140-6736(11)60321-8. Epub 2011 Aug 29. Erratum in: Lancet. 2012 Jan 28;379(9813):314. PMID: 21880356.
2. Tang HY, Xiao B, Liu X, Yang GL. [Signaling Pathways in the Pathogenesis of Acne Vulgaris]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2020 Aug 30;42(4):559-561. doi: 10.3881/j.issn.1000-503X.11470. [Article in Chinese].
3. Hazarika N. Acne vulgaris: new evidence in pathogenesis and future modalities of treatment. J Dermatolog Treat. 2021 May;32(3):277-285. doi: 10.1080/09546634.2019.1654075.
4. Navarini AA, Simpson MA, Weale M, Knight J, Carlavan I, Reiniche P, et al.; Acne Genetic Study Group; Willis C, Déret S, Voegel JJ, Spector T, Smith CH, Trembath RC, Barker JN. Genome-wide association study identifies three novel susceptibility loci for severe Acne vulgaris. Nat Commun. 2014 Jun 13;5:4020. doi: 10.1038/ncomms5020.
5. He L, Wu WJ, Yang JK, Cheng H, Zuo XB, Lai W, et al. Two new susceptibility loci 1q24.2 and 11p11.2 confer risk to severe acne. Nat Commun. 2014;5:2870. doi: 10.1038/ncomms3870.
6. Zhang M, Qureshi AA, Hunter DJ, Han J. A genome-wide association study of severe teenage acne in European Americans. Hum Genet. 2014 Mar;133(3):259-64. doi: 10.1007/s00439-013-1374-4.
7. Yang JK, Wu WJ, Qi J, He L, Zhang YP. TNF-308 G/A polymorphism and risk of acne vulgaris: a meta-analysis. PLoS One. 2014 Feb 3;9(2):e87806. doi: 10.1371/journal.pone.0087806.
8. Tasli L, Turgut S, Kacar N, Ayada C, Coban M, Akcilar R, Ergin S. Insulin-like growth factor-I gene polymorphism in acne vulgaris. J Eur Acad Dermatol Venereol. 2013 Feb;27(2):254-7. doi: 10.1111/j.1468-3083.2011.04299.x.
9. Heng AHS, Say YH, Sio YY, Ng YT, Chew FT. Gene variants associated with acne vulgaris presentation and severity: a systematic review and meta-analysis. BMC Med Genomics. 2021 Apr 13;14(1):103. doi: 10.1186/s12920-021-00953-8.
10. GeneCards: The Human Gene Database. https://www.genecards.org/
11. STRING resource. https://version11.string-db.org/.
12. Freson K, Wijgaerts A, Van Geet C. GATA1 gene variants associated with thrombocytopenia and anemia. Platelets. 2017 Nov;28(7):731-734. doi: 10.1080/09537104.2017.1361525.
13. Huilgol D, Venkataramani P, Nandi S, Bhattacharjee S. Transcription Factors That Govern Development and Disease: An Achilles Heel in Cancer. Genes (Basel). 2019 Oct 12;10(10):794. doi: 10.3390/genes10100794.
14. Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, et al. NF-κB Restricts Inflammasome Activation via Elimination of Damaged Mitochondria. Cell. 2016 Feb 25;164(5):896-910. doi: 10.1016/j.cell.2015.12.057.

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