THE ROLE OF GENETIC FACTORS IN FAMILIAL CASE OF ACNE

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Acne is one of the most common dermatoses. A prominent genetic component for this disease has been reported and the manifestation in first-line relatives is considered an important risk factor. Here we present a clinical case illustrating the relevance of particular genetic polymorphisms mapped to *NCF1*, *CD3E*, *ORAI1*, *IGHM* and *TAZ* in patients with severe forms and burdened family history of the disease. Genetic examination identified the same allelic variants in five candidate target genes (*NCF1*, *CD3E*, *ORAI1*, *IGHM* and *TAZ*) in two closely related patients (father and son) with severe acne. The identified genetic configuration may interfere with the oxidase activity and promote defects in mitochondrial function along with reduced T cell proliferation and imbalanced immunoglobulin production. The findings may provide an important reference point for further clinical investigation and treatment of severe torpid dermatoses.

Keywords: acne, genetic variant, oxidase system

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Compliance with ethical standards: the study was approved by Ethical Review Board at the Pirogov Russian National Research Medical University (protocol number 138 of 13 October 2014). The participants provided written informed consent for the study including data processing and use for scientific purposes.

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РОЛЬ ГЕНЕТИЧЕСКИХ ФАКТОРОВ ПРИ СЕМЕЙНОМ СЛУЧАЕ АКНЕ

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В настоящее время акне относится к наиболее распространенным дерматозам. Сообщается о роли генетической предрасположенности к развитию заболевания. Показано, что фактором риска развития дерматоза может быть наличие болезни у родственников первой линии родства. Представлен случай идентификации и определения значимости полиморфизма генов *NCF1*, *CD3E*, *ORAI1*, *IGHM*, *TAZ* у больных тяжелыми формами заболевания с отягощенным семейным анамнезом. Проведенные исследования позволили выявить идентичные аллельные варианты в пяти генах: *NCF1*, *CD3E*, *ORAI1*, *IGHM*, *TAZ* у двух близкородственных пациентов (отец и сын) с акне тяжелой степени. Полиморфизмы изученных генов, вероятно, влияют на развитие дисбаланса системы оксидаз, работу митохондрий, сниженной пролиферации Т-клеток, а также формирования дисбаланса секреции иммуноглобулинов. Полученные данные могут быть факторами торпидного течения тяжелой формы дерматоза, что определяет необходимость дальнейших исследований.

Ключевые слова: акне, полиморфизм генов, молекулярно-генетические исследования

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Acne is a prevalent skin disorder with an estimated 35–90% cases arising in adolescents. The age at onset typically spans from 14 years to the beginning of the third decade of life, but clinical symptoms of the disease may persist or develop *de novo* in adulthood. The up-to-date WHO criteria for the definition of chronic diseases classify acne as a chronic dermatosis. Its multifactorial pathogenesis involves the excessive influence of androgens on sebaceous follicles, sebum hypersecretion, abnormal follicular keratinization, *Cutibacterium acnes* colonization and the inflammatory reaction development [1–3]. Gender-based epidemiological studies indicate higher prevalence of acne in women, whereas men in general present with more severe course of the disease [1].

The role of genetic predisposition in acne has been extensively studied. Manifestation of the disease in first-line relatives is considered one of the main risk factors for acne. Familial cases display not only higher incidence of the disease, but also its more severe course. A likely additive effect of maternal and paternal components for this disease has been demonstrated — a history of dermatosis in both parents significantly intensifies the risk of acne in their offspring [4, 5].

The heritable nature of familial acne and its tendency towards aggravated course, especially in boys and men, necessitates the search for molecular markers and putative drug targets in patients with this pathology.

Clinical case description

In 2019–2020, we consulted two patients with severe acne: a father P. 45 years old and his son K. 17 years old. Both patients sought medical attention simultaneously, with similar complaints of skin rashes on face, chest and back.

The first patient (father) had lived with acne for 10 years, i.e. the disease manifested in adulthood without a pubertal history.

The rashes presented as multiple comedones, papules and pustules, initially on the face and spreading to chest and back within 6–7 months. The recurrent and gradually aggravating skin lesions clearly indicated a transition from moderate to severe course: deep pustules and nodules formed confluent conglomerates which resolved to atrophic scars. The patient consulted a local dermatovenerologist and received several treatments including oral antibacterials (doxycycline 100 mg twice a day for 14–21 days; three courses at 1.5–3 month intervals) and external therapy (clindamycin phosphate gel 1%, on clean and dry skin of the affected area in thin layer twice a day for 1 month, in combination with adapalene gel 0.1% on clean and dry skin of the affected area nightly, extended to five months) with a temporary positive effect.

The second patient (son) initially presented with the disease at the age of 14, with multiple comedones, papules, pustules and nodules developing on his face, chest and back. The rashes proceeded to recurrent disease, accompanied by formation of deep nodules that resolved into atrophic scars. The patient also consulted a local doctor and received treatments including oral antibacterials (doxycycline 100 mg twice a day for 14–21 days; four courses at 2–4 month intervals) and external therapy (clindamycin phosphate gel 1%, on clean and dry skin of the affected area in thin layer twice a day for 1 month in combination with adapalene gel 0.1% on clean and dry skin of the affected area nightly, extended to five months, followed by the use of azelaic acid, 15% gel, twice a day mornings and evenings for 6 months). Similarly with the father, the son experienced a temporary curative effect. In addition, the patients had a family burden of cancer: father of the first patient (accordingly, paternal grandfather to the second patient) had rectal cancer.

To assess the contribution of genetic factors to the onset and course of acne in the studied clinical case, we performed molecular genetic examination by high-throughput DNA sequencing (next-generation sequencing, NGS). Genomic DNA was extracted from whole blood samples donated by the patients using CellSep Advanced Kit (DiaSorin Ireland Ltd.; Ireland) in accordance with the manufacturer's protocol. The construction of adapter-ligated DNA libraries was carried out using NebNext Ultra II DNA Library Prep Kit for Illumina (New England Biolabs; USA). The hybridization-based enrichment with coding sequences of target genes was implemented using a custom probe panel (Roche; Switzerland) in accordance with the SeqCap EZ target enrichment protocol for Illumina NGS systems recommended by the manufacturer. The obtained DNA libraries were sequenced on MiSeq platform (Illumina; USA) in a paired-end mode (115×2) with an average depth of 143× and 99% coverage of the target region with a minimal depth of 10×. The sequencing data were processed using a customized automated bioinformatics pipeline.

Population frequencies for the identified variants were estimated using reference datasets of the Genome Aggregation Database (gnomAD) international project — gnomAD Exomes (ExAC) for exonic variants and gnomAD Genomes for intronic variants. Computational assessment of clinical value for the identified missense variants used *SIFT*, *PolyPhen-2*, *PROVEAN* and *UMD Predictor* pathogenicity prediction algorithms for amino acid substitutions. Computational assessment for the identified variants mapping to splice sites or regions adjacent to splice sites used *MutationTaster*, *Human Splicing Finder* and *NNSplice* software.

Discussion

The molecular genetic study identified identical allelic variants in five candidate target genes *NCF1*, *CD3E*, *ORAI1*, *IGHM* and *TAZ* of the two patients (Table). In four of these genes (*NCF1*, *CD3E*, *ORAI1* and *TAZ*), the identified variants mapped to exons. For *IGHM*, two allelic variants were identified, corresponding to single-nucleotide polymorphisms rs1059216 and rs1136534 and mapping to intergenic region: non-synonymous C>T and synonymous A>G, respectively.

The analysis of zygosity status for the identified allelic variants revealed homozygosity for rs707410 in *NCF1*, homozygosity for rs1059216 in *IGHM*, heterozygosity for rs1136534 in *IGHM* and homozygosity for rs62617809 in *TAZ*. The heterozygous *CD3E* (c.353-16A>C) and homozygous *ORAI1* (*GGCCCC>G*) variants have not been previously associated with any disease.

The population frequency analysis for the identified *NCF1*, *CD3E*, *ORAI1*, *IGHM* and *TAZ* allelic variants using the gnomAD Exomes (ExAC) reference datasets also revealed no pathological links.

The representations of identified allelic variants of five candidate genes in two closely related patients were identical. For heterozygous *CD3E* (c.353-16A>C) and homozygous *ORAI1* (GGCCCC>G), no pathological associations have been described prior to this report.

NCF1 (neutrophil cytosolic factor 1) encodes a 47 kDa cytosolic protein subunit of NADPH-oxidase in neutrophils. An important biological indicator of immunity-related significance for these enzymes is their localization in the macrophage plasma membrane and participation in antimicrobial defense. Autosomal-recessive *NCF1* variants have been described in chronic granulomatosis [6]. The rs201802880 polymorphism in *NCF1-339* has been preliminary associated with systemic lupus erythematosus [7].

The identified allelic variant *rs707410* in *NCF1*, homozygous in both patients, may promote imbalance in the oxidase system and interfere with the phagocytic activity of immune cells, thus prolonging the inflammation and contributing to severe clinical symptoms of acne.

CD3E gene encodes ε subunit of T cell co-receptor CD3 (CD3E). Along with γ, δ and ζ subunits of CD3, CD3E forms a complex with T cell receptor and participates in the antigen-specific T cell activation. CD3E is a transmembrane protein that regulates both the clonal T cell development and the adaptive immune response [8]. Mutated *CD3E* has been implicated in the severe combined immunodeficiency [9].

The identified allelic variant *CD3E* (c.353-16A>C), heterozygous in both patients, may interfere with proliferative capacity of T cells and thus mediate a failure of adaptive immunity.

ORAI1 (Orai calcium release-activated calcium modulator 1) encodes a calcium channel activated upon release of calcium ions from internal depots. Such channels provide a principal route for the calcium influx in T cells and their activation [10]. Mutations in *ORAI1* may lead to severe combined immunodeficiency [11]. The ORAI1 calcium channels have been preliminary implicated in allergic dermatoses, albeit by yet unknown mechanism [12]. *De novo* mutations in *ORAI1* have been shown to reduce the counts of NK and T_{reg} cells thus promoting immunodeficiencies and autoimmune inflammatory reactions. Such mutations have been reported in the anhydrotic ectodermal dysplasia [13].

The identified allelic variant *ORAI1* (GGCCCC>G), homozygous in both patients, may contribute to secondary immunodeficiencies.

IGHM (immunoglobulin heavy <constant> mu) encodes a constant region of immunoglobulin heavy chains. During the effector phase of humoral immune response, the antigen-stimulated B cells produce immunoglobulins to ensure the antigen clearance. Mutations in *IGHM* have been implicated in the autosomal recessive agammaglobulinemia [14].

Table. Characterization of *NCF1*, *CD3E*, *ORAI1*, *IGHM* and *TAZ* allelic variants in the patients with severe acne

Locus	*NCF1*	*CD3E*	*ORAI1*	*IGHM*	*TAZ*
Chromosome	7	11	12	14	X
Chromosome coordinates	74777361	118313691	121626865- 121626870	105855558, 105855808	154412069
Allelic variant ID	*rs707410*	previously undescribed	previously undescribed	*rs1059216*, *rs1136534*	*rs62617809*
Location in gene	exon 2, splice site	exon 7, splice site	exon 1, splice site	intergenic region	exon 2
Description	c.153+14T>C	c.353-16A>C	GGCCCC> G	C>T (non-synonymous); A>G (synonymous)	c.110-17T>C
Zygocity	Homozygous	Heterozygous	Homozygous	Homozygous	Homozygous

In addition, both patients presented with identical allelic variants in *IGHM*: homozygous rs1059216 and heterozygous rs1136534. Of these two variants, the homozygous non-synonymous rs1059216 is more likely to interfere with the balanced immunoglobulin synthesis and thus contribute to severe torpid acne.

The X-linked predisposition patterns in dermatoses are of particular clinical interest. *TAZ* gene is located on X chromosome (Xq18) and contains 11 exons; its product, tafazzin, participates in metabolism of cardiolipin incorporated in the inner mitochondrial membrane. The reduced levels of energy metabolism in leukocytes may interfere with their differentiation, with a negative effect on systemic and local immunity. Mutations in *TAZ* are causative for Barth syndrome [15].

The identified allelic variant rs62617809 of *TAZ*, homozygous in both patients, may negatively affect mitochondrial functionalities in multiple cell types including the cellular wing of immunity.

CONCLUSION

Extensive molecular genetic analysis for a selection of candidate genes in two first-line relatives (father and son) with highly similar clinical picture of severe acne identified six allelic variants in five candidate genes. Exonic variants were identified in *NCF1*, *CD3E*, *ORAI1* and *TAZ*; two of them, heterozygous *CD3E* (c.353-16A>C) and homozygous *ORAI1* (GGCCCC>G), are reported for the first time. For the fifth gene, *IGHM*, we identified two previously described allelic variants, rs1059216 and rs1136534, located intergenically and representing single-nucleotide substitutions: C>T (non-synonymous) and A>G (synonymous). All identified genetic variants had the same zygosity status in both patients.

The *NCF1*, *CD3E*, *ORAI1*, *IGHM* and *TAZ* genes participate in the oxidase system activity and play a regulatory role in the rates of T cell proliferation and immunoglobulin production. Specific etiological contributions to severe torpid acne for the identified genetic variants have yet to be determined.

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