Review paper

Genetic polymorphism in psoriasis and its meaning for the treatment efficacy in the future

Agnieszka Osmola-Mańkowska[1], Ewa Teresiak-Mikołajczak[1], Marzena Skrzypczak-Zielińska[2], Zygmunt Adamski[1]

[1]Department of Dermatology, Psoriasis and Novel Therapies in the Dermatology Unit, Poznan University of Medical Sciences, Poznan, Poland
[2]Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland

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Abstract

The concept of personalized medicine is a new individualized approach which helps application of the targeted therapy. In fact, tailored medicine is mostly present in the field of life-threatening diseases such as oncology. However, skin diseases as such might be regarded as a potential area of implementation of this approach in the future. Stratified medicine in polygenetic and heterogeneous diseases, such as psoriasis, is more complex. Rapid development of science and novel molecular techniques led to better understanding of molecular pathogenetic pathways of many diseases including psoriasis. Identification of the particular immunopathogenetic pathways led to further development of targeted therapies such as biologic drugs. Actually the goal of individualized therapy is to determine the identical homogenous subgroups of patients, according to a biomarker, in which the response to that therapy will be the best and will carry the lowest risk of side effects. This review attempts to analyze the associations between polymorphisms of certain genes and the increased risk of developing psoriasis or psoriatic arthritis. The review of literature has also included the studies investigating the associations between gene polymorphisms and response to biologic therapy in psoriasis and psoriatic arthritis patients.

Key words: psoriasis, psoriatic arthritis, personalized medicine, therapy, biologics.

The concept of personalized medicine

The concept of personalized medicine is a new individualized approach which helps application of the targeted therapy: "the right patient with the right drug at the right dose at the right time". In practice, tailored medicine is mostly present in the field of life-threatening diseases such as clinical oncology, hematology or neurologic disorders.

Actually elements of stratified medicine are also utilized in the management of skin melanoma, non-melanoma skin cancers as well as skin lymphomas. Other skin diseases might also be regarded as a potential area of implementation of this approach in the future. However, stratified medicine in polygenetic and heterogeneous diseases, such as psoriasis, is more complex.

Rapid development of science and novel molecular techniques led to better understanding of molecular pathogenetic pathways of many diseases including psoriasis. In the last two decades, great progress has been made in understanding of the genetic background of psoriasis. Identification of the particular immunopathogenetic pathways led to further development of targeted therapies such as monoclonal antibodies and fusion proteins – the so-called biologicals. This novel group of drugs at the beginning had revolutionized treatment of rheumatic diseases e.g. rheumatoid arthritis (RA), then gastroenterological disorders such as Crohn's disease (CD) or ulcerative colitis and finally skin diseases with psoriasis (Ps) and psoriatic arthritis (PsA). In many cases, when standard drugs were not effective, they allow to obtain remission of the disease during the treatment. In fact, complex pathophysiological mechanisms result in clinical heterogeneity of the disease course. Although at this moment, the range of available antipsoriatic biological drugs is quite wide, we are not able to predict which drug will bring the best results in any particular patient. Moreover, this form of therapy is still very expensive and associated with some relevant side effects.

Address for correspondence: Agnieszka Osmola-Mańkowska, Department of Dermatology, Psoriasis and Novel Therapies in the Dermatology Unit, Poznan University of Medical Sciences, 49 Przybyszewskiego St, 60-355 Poznan, Poland, phone: +48 61 869 12 78, e-mail: agnieszka.osmola@wp.pl
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Actually, the goal of individualized therapy is to determine the identical homogenous subgroups of patients, according to a biomarker, in which the response to that therapy will be the best and will carry the lowest risk of side effects. Implementation of personalized medicine in clinical practice is possible due to biomarkers that are evaluated objectively on the basis of genetic and epigenetic testing together with more conventional analysis (e.g. blood, urine tests). Biomarkers serve as indicators of normal biological and pathogenic processes or pharmacological responses to therapy. Biomarkers are classified as diagnostic biomarkers (early diagnostic of PsA in psoriatic patients) indicating the onset of the disease; prognostic biomarkers (able to predict which patients will develop cardiovascular disorders e.g. the length of tellers or micro-RNAs) and predictive biomarkers (able to predict the response to particular treatment e.g. single nucleotide polymorphisms – SNPs). Detection of biomarkers characteristic of Ps and PsA would be very helpful in choosing the optimal therapeutic approach and predicting the response to a particular treatment (to maximize efficacy and minimize side effects) as well as achieving long-term remissions. The application of biomarkers in clinical practice would increase patient satisfaction and reduce the treatment costs. According to an alternative classification, biomarkers can be distinguished in categories: type 0 – correlating with the severity of the disease (e.g. HLA-Cw*0602 associated with an early onset, more severe course of Ps, but not PsA), type 1 – useful for monitoring the efficacy of therapy in relation to the mechanism of action (e.g. IL-23/IL-17 axis) and the most important type 2 – predicting the treatment efficacy (e.g. SNP in *TNFAIP3* gene and response to anti-TNF therapy or better and quicker response to ustekinumab in HLA-Cw*0602).

Unfortunately, since that time not even one highly specific biomarker has been determined in psoriasis. Such an approach may not only result in cost savings, but also generate some ethical dilemmas [1].

Genetic benefits in dermatology

Intensive development of pharmacogenetics and personalized medicine depends largely on the progress in molecular biology. Especially results from the Human Genome Project in 2003, finding that only near 25 000 human genes exist and characterization of over 3.1 million human SNPs opened a new door to genetic functional studies, improving the disease diagnosis and giving the possibility to explain the background of inter-individual variability in response to treatment [2, 3].

The size of the human genome, meaning the total number of nucleotides in one representative copy of nuclear DNA, is approximately 3 billion bases. Currently, it is possible to read the DNA sequence of the whole genome in 2 days with the already decreased cost of $1000. These opportunities result from the launch in 2005 of high throughput technology, the next generation sequencing (NGS) [4]. The wide analyses of the whole genome (WGA) are so far spread mostly as a scientific tool, but the technology has already started to be used in routine diagnostics. Especially, an economical and useful approach is sequencing a part of a genome, for example the protein-coding regions – whole exome sequencing (WES), which represents only 1.5% of the total genome, but contains approx. 85% of the total DNA changes predisposing to genetic diseases [5]. It is important to note that the NGS allows deep, i.e. multiple, reading of each base that is useful for the analysis of genetic heterogeneous materials and somatic mutation detection in tumor, such as melanoma [6]. The list of rare heredity skin diseases is long. However, in most cases, where genetic factors are well described and characterized, e.g. neurofibromatosis or stiff skin syndrome, in practice for mutation detection, the Sanger sequencing is used as a gold standard. This method is dedicated to analysis of only one specified gene or its region. The final price of DNA Sanger sequencing per sample is about $5–6.

In diseases like psoriasis, where the genetic component of disease is not exactly defined and often shared with different factors e.g. environmental condition, the scientific research using DNA microarrays analysis is carried out. The basis of microarray chips is complementarity of nucleic acid bases and the hybridization process. It allows research on the whole genome level, where hundreds of thousands of SNPs as a target can be analyzed in patient and control groups at the same time and their association with a particular feature can be determined. This analysis is called a genome-wide association study (GWAS) and supports discovering of new genetic correlations as well as study directions. Moreover, microarrays are widely applied in high throughput gene expression analyses. If a gene is expressed in the sample, its messenger RNA (mRNA) will hybridize to complementary DNA probe on the chip. This method enables a simultaneous and parallel indication of the expression level of thousands of genes and is a powerful laboratory tool [7]. The cost of reagents for expression estimation for one sample is $750–800. An older technique, real time PCR, is much cheaper per test, but provides information of only single genes and more genetic material is required.

Looking to the future, the enormous automation in molecular biology and whole genome analyses shows possibilities for the development of new research fields in skin diseases diagnosis and treatment with a focus on the individual patient. Perhaps it is no exaggeration to conclude that the genetics can revolutionize the dermatology.

Personalized therapy in psoriasis

Pathogenesis of Ps involves interaction of genetic, immunological and environmental factors. The complex

etiopathogenesis of the disease is manifested by different clinical variants, a variable and unpredictable course and variable rate of associated diseases such as psoriatic arthritis, cardiovascular disorders (CVD) or metabolic diseases.

There are many treatment options available in Ps from topical to systemic therapies and from standard to innovative targeted therapies. Unfortunately, the successful control of the disease is very difficult because of its clinical heterogeneity, availability of many treatment methods as well as distinct response to treatment, adverse reactions and drug toxicity. Thus, it is of great importance to identify the Ps biomarkers that may allow to predict therapy response or disease prognosis (theranostic biomarkers) and implement a stratified medicine approach in the disease management. Personalized management of Ps patients should involve a multidisciplinary and integrated clinical approach.

To make the most optimal treatment decision, the dermatologist must have a detailed overview of the patient's history and lifestyle relevant information such as demographics, personal and family history as well as drug history, the vaccination status or cardiovascular profile [1].

Genetic background of Ps has been confirmed by population and family studies as well as higher concordance rates in monozygotic twins [8, 9]. Genetic studies of Ps background have also led to the identification of the mutation in the *IL-36RN* gene encoding the anti-inflammatory IL-36 receptor antagonist (IL-36Ra) and have supported the hypothesis that generalized pustular psoriasis (GPP) is a disease of distinct etiology [10]. More advanced GWAS revealed 36 independent psoriasis-associated genetic regions in the European population and 5 more in the Chinese population [11]. Psoriasis susceptibility genes include mainly skin-specific genes and immune-related genes of the innate and adaptive immunity. Psoriasis susceptibility region 1 (*PSORS1* known also as *HLA-C*) within the major histocompatibility complex (MHC) is considered to be the strongest susceptibility locus [12]. In turn, the HLA-Cw*0602 allele of the *HLA-C* gene is associated with an early onset, before the age of 40, and positive family history of Ps [13]. Genome-wide association studies have also identified several psoriasis-related chromosomal regions such as the receptors for interleukin 23 (IL-23) and IL-12B [14, 15]. The results of the Indhumathi study suggest that the variants of *IL-12B* (rs3212227) and *IL-23R* (rs2201841) genes are related to an increased risk of developing Ps in the ethnic South Indian Tamils population [16]. A meta-analysis of 997 Ps cases and 943 control subjects for –238G>A and of 1,156 psoriasis cases and 1,083 control subjects for –308G>A polymorphism of the *TNF* gene showed that a significantly increased risk was associated with the variant –238G>A and GA + AA genotypes, compared with the GG genotype, whereas the GA + AA genotypes in position –308G>A were correlated with a reduced psoriasis risk. These findings suggest that –308G>A and –238G>A polymorphisms of the *TNF* gene might serve as diagnostic biomarkers of psoriasis [17].

The recent genetic data support the important role of the gene's variants engaged in different immunological processes and pathways in psoriasis such as: antigen presentation (*HLA-C*, *ERAP1*, *ERAP2*, *MICA*), T-cell polarization (*RUNX1*, *RUNX*3, *STAT*3, *TAGAP*, *IL-4*, *IL-13*), IL-23/IL-17 axis (*IL12BP40*, *IL23AP19*, *IL23R*, *JAK2*, *TYK2*), negative regulators of immune response (*TNFAIP3*, *TNIP1*, *NFKBIA*, *CARD14, IL36RN*, *SOCS1*, *ZC3H12C*), innate immunity (*TRAF3IP2*, *CARD14*, *c-REL*, *DDX58*, *IFIH1*) and type 1 INF (*IL28RA*, *RNF114*) [1].

Psoriasis may be accompanied in 10–30% of cases by PsA [18]. Moreover, pathophysiological mechanisms of other inflammatory conditions such as RA or CD are at some point similar to Ps and can be treated with the same biological agents that selectively block TNF-α (etanercept, infliximab, adalimumab).

Biologicals, especially anti-TNF drugs have been shown to be one of the most effective forms of therapy in Ps as well as in PsA, RA and CD. However, they are not effective in all patients and response to the drug may diminish during the treatment time and lead to stopping or switching the therapy. The most common reason for discontinuing biological treatment is lack of effectiveness [19]. Moreover, some patients develop severe adverse drug reactions. Therefore, it is necessary to implement the solutions of personalized therapy in order to discover new therapeutic targets that allow the development of more effective drugs and optimize the treatment, reduce the risk of side effects and costs of the therapy [20–22].

Characterization of the pharmacogenetic profile and individual genetic variation associated with susceptibility to certain diseases and response to specific treatment, constitutes the foundation of personalized medicine. Recent studies identified genetic predictors for the clinical response to biologics. Some polymorphisms in genes encoding tumor necrosis factor (*TNF*), *TNF* receptor superfamily 1B (*TNFR1B*) and *TNF* induced protein 3 (*TNFAIP3*) have been associated with response to anti-TNF therapy in patients with Ps [23]. Several studies have also associated polymorphisms at genes encoding cytokines involved in the pathogenesis of Ps with response to treatment (*IL-12B*, *IL-1*, *IL-10*, *IL-13*, *IL-17*, *IL-21*, *IL-23*). Batalla *et al.* established that SNP rs4819554 in the promoter region of *IL-17RA* gene significantly influences the response to anti-TNF drugs at 12-week therapy among Ps patients [24].

Recent studies confirmed associations between genetic markers and response to drug treatment in RA, PsA and Ps. A multicenter study on the Greek population of patients suffering from Ps demonstrated the associations of *TNF* (rs1799124) and TNF receptor II (*TNFRSF1B*) genes polymorphisms (rs1061622) and positive response to treatment with etanercept. None of the studied poly-

Table 1. Associations of gene polymorphisms with susceptibility to Ps, PsA and RA as well as response to treatment

Gene	Gene function	Genetic variant	Associations	References
TNFR1B	TNF receptor superfamily 1B; binds tumor necrosis factor involved in apoptosis and inflammation, proliferation, survival, and differentiation	rs1061622	Positive response to etanercept, poor response to infliximab and adalimumab in Ps	Vasilopoulos 2012 [25]
TNFAIP3	TNF-α induced protein 3 gene; expression rapidly induced by TNF, inhibits NF-κB activation, TNF-mediated apoptosis, critical for limiting inflammation by terminating TNF-induced NF-κB responses	rs2230926	Positive response to anti-TNF in Ps	Tejasvi 2012 [26]
		rs610604	No association with response to ustekinumab in Ps	Talamonti 2013 [30]
IL-12B	Ligand IL23R Differentiation of Th1 cells; stimulation of INF-γ and TNF-α production; expansion and maintenance of Th17 cells	rs3212227	Ps Early onset of Ps PsA PsA, Ps	Cargil 2007 [15], Capon 2007 [14], Indhumanthi 2016 [16], Nair 2008 [31] Smith 2008 [32] Filer 2008 [33] Liu 2008 [34], Li 2009 [35]
		rs6887695	Ps PsA PsA, Ps	Cargil 2007 [15], Capon 2007 [14], Smith 2008 [32], Nair 2008 [31], Filer 2008 [33], Liu 2008 [34] Li 2009 [35]
IL-13	Genetic variations may result in deregulation of the Th1 and Th17 pathways, involved in B-cell differentiation	rs20541	Ps PsA ↑ PsA in Ps PsA	Chang 2008 [36] Duffin 2009 [37]; Eder 2011 [38] Bowes 2011 [39]
		rs848	PsA ↑ PsA in Ps PsA	Duffin 2009 [37] Eder 2011 [38] Bowes 2011 [39]
		rs1800925	Ps, RA ↑ PsA in Ps PsA	Li 2009 [35] Eder 2011 [38] Bowes 2011 [39]
IL-23R	Receptor of IL-23, hyperproliferation of psoriatic skin, expansion and maintenance of Th17 cells, promoter of chronic inflammation in RA, IL-23 inhibits the development of Treg cells, necessary for differentiation of Th17	rs7530511	Early onset of Ps Ps PsA RA, PsA	Smith 2008 [32] Nair 2008 [31] Filer 2008 [33] Li 2009 [35]
		rs11209026	Early onset of Ps Ps PsA	Smith 2008 [32] Nair 2008 [31]; Filer 2008 [33]
		rs2201841	Ps RA	Indhumanthi 2016 [16] Farago 2008 [40]
IL-1B	Mediator of the inflammatory response, inhibits Treg cells, necessary for differentiation of Th17	rs16944	Ps, PsA RA	Reich 2002 [41] Tolusso 2006 [42]
		rs1143634	Ps, PsA RA	Reich 2002 [41] Tolusso 2006 [42]
IL-10	Inhibits Th1 differentiation, promoting Treg differentiation	rs1800896	Ps RA Response to anti-TNF in RA	Baran 2008 [43] Lee 2012 [44] Liu 2008 [45]
		rs1800871	Ps	Baran 2008 [43]
		rs1800872	Ps RA	Baran 2008 [43] Lee 2012 [44]

Table 1. Cont.

Gene	Gene function	Genetic variant	Associations	References
IL-21	Increased hyperproliferation of psoriatic skin, increased mononuclear inflammation	rs6822844	RA Ps, PsA	Zhernakova 2007 [46] Schrodi 2008 [47]
TNF	Mediates numerous inflammatory and immunoregulatory activities	rs1800629 (–308G>A)	Genotype AA – poor response to etanercept in RA Genotype AG – a reduced risk of Ps	Maxwell 2008 [28] Li 2007 [17]
		rs361525 (–238G>A)	Genotype GA – poor response to infliximab in RA and an increased risk of Ps	Maxwell 2008 [28] Li 2007 [17]
		rs1799724	Positive response to etanercept, poor response to infliximab and adalimumab in Ps	Vasilopoulos 2012 [25]
HLA-C	Belongs to the MHC class I receptors, expressed in nearly all cells, and present small peptides to the immune system, *HLA-C* is a locus on chromosome 6, which encodes for a large number of *HLA-C* alleles that are class-I MHC receptors	rs10484554	Positive response to adalimumab in Ps, poor response to ustekinumab in Ps	Masouri 2016 [29]
IL-17R	IL-17 receptor binds interleukin 17A, protects against extracellular pathogens, but conversely promotes inflammatory pathology in autoimmune diseases	rs4819554	Positive response to anti-TNF in Ps	Batalla 2018 [24]
ERAP1	Endoplasmic reticulum aminopeptidase 1, encoded protein is an aminopeptidase involved in trimming HLA class I-binding precursors so that they can be presented on MHC class I molecules	rs151823	Positive response to ustekinumab in Ps	Masouri 2016 [29]
		rs26653	Positive response to ustekinumab in Ps	Masouri 2016 [29]

morphisms influenced the treatment with infliximab or adalimumab [25]. Some polymorphisms in the *TNFAIP3* gene have been associated with Ps, RA, type 1 diabetes mellitus, systemic lupus erythematosus (SLE), and celiac disease. Tejasvi *et al*. have reported the impact of two *TNFAIP3* gene polymorphisms (rs2230926 in exon 7 and rs610604 in intron 3) on positive response to anti-TNFα treatment of Ps [26].

Recently, the influence of the *PDE3A-SLCO1C1* (phosphodiesterase 3A – solute carrier organic anion transporter family member 1C1) locus on the response to anti-TNF agents has been demonstrated in Ps. Interestingly, the allele G of rs3794271 in the *SLCO1C1* gene was previously associated with the lack of response in RA [27]. A number of relatively small studies have also investigated TNF genetic variants as a response marker in the context of anti-TNF therapy in RA. Analyses of the *TNF* gene variant in the position –308 (rs1800629) in RA revealed that genotype AA was associated with a significantly poorer response compared with genotype GG in patients receiving etanercept, but not infliximab. In turn, in locus –238 (rs361525) of the *TNF* gene, the genotype GA was correlated with a poorer response to infliximab, but not etanercept in RA [28].

In the study in a Greek cohort of Ps patients, rs10484554 in the *HLA-C* gene showed a positive correlation with a response to anti-TNF agents (especially to adalimumab) but not to ustekinumab, while rs151823 and rs26653 in the *ERAP1* gene showed associations with an improved response to anti-IL12/23 therapy [29]. Talamonti *et al*. observed an increased and quicker reaction to ustekinumab in HLA-Cw6 positive Ps patients, whereas analysis of *TNFAIP3* rs610604 polymorphism did not show any significant association with response to ustekinumab [30]. Associations between gene variants and Ps, other autoimmune diseases as well as response to treatment that have already been discovered, are presented in Table 1 [31–47].

Although the biological drugs have greatly improved the treatment of Ps, PsA, RA and CD, some percentage of patients fail to respond to the treatment or develop severe adverse drug reactions. Moreover, these medicines are very expensive and do not cure the disease. Characterization of the pharmacogenetic profile associated with response to a specific drug enables to choose the right treatment for the right person without the risk of adverse reactions, increase the efficacy of therapy and reduce costs.

Conclusions

The reliable knowledge of the influence of some gene polymorphisms (e.g. *IL-12B*, *IL-13*, *IL-23R*, *IL-1B*, *IL-10*, *IL-21*, *TNF-α*) on the Ps risk is necessary to identify individuals at high risk of developing Ps or PsA. There are only few studies identifying SNPs (e.g. *TNFR1B*, *TNFAIP3*, *HLA-C*, *IL-17R*, *ERAP1*) related with response to biologic treatment in Ps or PsA (mainly anti-TNF treatment). Large prospective studies are necessary to validate genetic markers associated with various types of therapy used in Ps and PsA before implementation in the daily clinical practice.

That is why this subject might be of interest for further collaborative studies.

Conflict of interest

The authors declare no conflict of interest.

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