GENETICS OF PSORIASIS – SHORT RESUME

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ABSTRACT

Psoriasis is a disease with a genetic background (4). Several psoriasis susceptibility loci (PSORS) have been found on various chromosomes: PSORS1 on 6p21.3, PSORS2 on 17q, PSORS3 on 4q, PSORS4 on 1q21, PSORS5 on 3q21, PSORS6 on 19p, PSORS7 on 1p, PSORS8 on 16q, PSORS9 on 4q31, PSORS10 on 18p11, PSORS11 on 5q31-q33 and PSORS12 on 20q13. (27). However, the exact genes and their functions, or their respective malfunctions, in psoriasis and arthritis have not been unambiguously identified. Recently, it has been argued that PSORS1 may indeed be the HLA-Cw*06 allele encoding the HLA-Cw6 molecule (35).

Psoriasis is a chronic inflammatory disease of skin that also often affects joints and nails. This disorder is characterized by hyperproliferation of keratinocytes, activation of angiogenesis, vasodilatation and mainly by lymphocyte infiltration of dermis and epidermis (45). The process of maturation of keratinocytes is accelerated and thus not quite terminated. Psoriatic lesion appears on skin.

Skin manifestations are typically red bounded areas of different size and shape with characteristic silvery scales (9). Lesions appear mostly on the skin of elbows and knees, scalp including genitals. Individual manifestations differ in size and severity from localized lesions to whole body involvement. Very often psoriasis affects nails of hands and feet. It can also cause inflammatory changes on joints, named as psoriatic arthritis. Similarly to rheumatoid arthritis and sclerosis multiplex, psoriasis is classified as an immune mediated inflammatory disorder. Those disorders are characterized by chronic progression of an inflammatory process and important role of TNF alpha. Because of the role of TNF alpha in pathogenesis, we can use its inhibitors in therapy. It also affects progress of different comorbidities such as diabetes mellitus 2 and cardiovascular problems (21). Patients with psoriasis have often other risk factors for atherosclerosis such as lipid metabolism disorders and overweight (37).

Key words: psoriasis, PSORS, HLA-Cw6

INTRODUCTION

Psoriasis is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, by lymphocytary infiltrate composed mainly of T-cells. Other features are change of endothelium, angiogenesis, dilatation and formation of high endothelial venules (HEV) (29).

Exact pathogenesis of this disorder is unknown, but it is supposed that main role plays an immune system (42, 45).

Theory that psoriasis is primarily keratinocyte proliferation disorder is based on abnormally fast mitotic activity of keratinocytes. T-cell hypothesis imply an abnormal activation of an acquired immunity. Knowing that TNF alpha therapies are very effective, suggests an important role of innate immunity in pathogenesis (5).

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SHORT REVIEW OF LOCI AND CANDIDATE GENES

In the early 1970s psoriasis was placed into associations with the HLA complex on chromosome 6p. Russell *et al.* in 1972 first reported association with allele HLA-B13. After that, were identified strong associations with other two alleles, Cw6 and DR7 (22, 49). These two alleles were estimated to be relative risk factors for the disease.

There are two types of psoriasis (23):
- a familial, early age of onset form (<40 years)
- associated with HLA-Cw6, DR7, B13 and B57
- a non-familial, later age at onset form
- associated with HLA-Cw2 and B27

Psoriasis is a disorder with genetic background and a multifactorial type of heredity. The hypothesis of genetic background is also supported by familial incidence. Chance that a child of nonpsoriatic parents will develop psoriasis is 12 %, if there is a one parent with psoriasis the risk is higher 10-20 % and in a case that both parents are having psoriasis it can be up to 50 % risk. In identical twins the risk that they will develop disease is about 90 %, in nonidentical twins its only 18 % (9). This difference shows a multifactorial type of inheritance and interaction between genetic predisposition and environmental influence (8,14). Based on the study of Bowcock and Barker from 2003 plaque psoriasis can be in small group of patients inherited as an autosomal dominant trait with high penetrance (6).

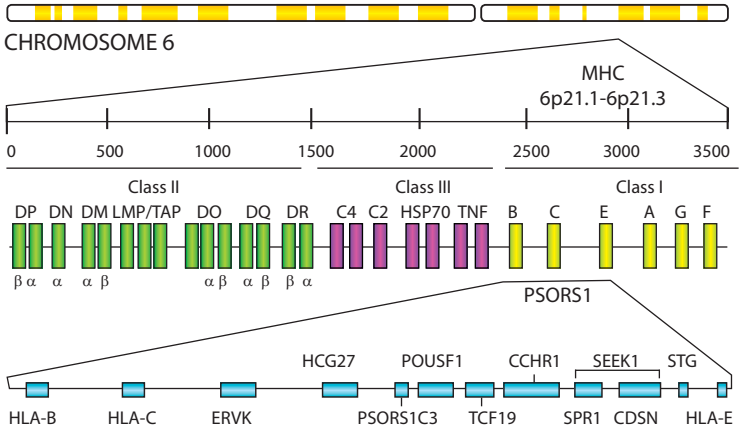

Fig. 1: Localization of locus PSORS1 in MHC locus, and candidate genes in PSORS1 locus (28).

Recently the results of multiple genetic case–control studies have begun to appear providing convincing statistical evidence for six loci (IL12B, IL13, IL23R, STAT2/IL23A, TNFAIP3, and TNIP1) for psoriasis (32).

In these days 10 loci are known named as PSORS1-10 (psoriasis susceptibility 1-9) and one for psoriatic arthritis, PSORAS1 (1; 13). Exact genes and their function are not yet identified (28). There is a possibility, of location PSPRS1 in allele of HLA-Cw6 coding HLA-Cw6 molecule (15, 36).

Using high-density cDNA microarray to identify psoriatic transcriptome and to set down gene expression in psoriatic lesions elevated expression of different molecules was found. Increased expression of certain mRNA associated with the epidermal differentiation complex and hyperproliferation-associated molecules (keratins KRT6A a KRT16) supports hypothesis that psoriasis is keratinocyte disorder, characteristic with their increased proliferation and abnormal differentiation (7, 39, 41, 57).

It is possible that malfunction of CD4+CD25+ regulatory lymphocytes can be partially based on abnormal hematopoietic cells and with genetic background (55).

Table 1: PSORS loci (10)

Locus name	Chromosomal location	Reference
PSORS 1	6p21.3	Zhang *et al.*, 2002
PSORS 2	17q24-25	Samuelsson *et al.*, 1999
PSORS 3	4q34	Samuelsson *et al.*, 1999
PSORS 4	1q21	Capon *et al.*, 1999
PSORS 5	3q21	Enlund *et al.*, 1999
PSORS 6	19p13-q13	Lee *et al.*, 2000
PSORS 7	1p35-p34	Veal *et al.*, 2001
PSORS 8	16q	Karason *et al.*, 2003
PSORS 9	4q31	Zhang *et al.*, 2002
PSORS 10	18p11.23	Asumalahlati *et al.*, 2002
PSORS 11	5q31-q33	www.ncbi.nlm.nih.gov/omim
PSORS 12	20q13	www.ncbi.nlm.nih.gov/omim

PSORS1

The most studied locus is PSORS1 mapped to MHC complex on chromosome 6. This region contains genes coding proteins of immunological pathways and is strongly associated with genes of lymphocyte antigens also situated in this area (1, 11). Main marker of this area is HLA-Cw6 (48). This allele is most frequently mapped in population with early onset psoriasis (36).

Human leukocyte antigen

Psoriasis has signs of an autoimmune disease and there is no surprise that there was found association with certain HLA alleles. Also a role for CD8+ cells is favoured by the observed linkage of psoriasis to certain MHC I alleles, especially HLA Cw6 (20).

Only about 10 % of HLA-Cw6-positive individuals develop psoriasis, suggesting a major role for additional genes and/or environmental triggers (30).

The observation that a large, multiply affected family demonstrated linkage of psoriasis susceptibility to 17q25 (50) and not to HLA suggests that other genes can confer susceptibility. In a study of 23 multiply affected families was observed that 25 % are HLA-Cw6 positive. In one family, all three affected members are HLA-B27 (4, 33, 35).

PSORS2

Locus is situated near telomeres of chromosome 17q (50). Exact localization of risk allele is not known. In this area at least two candidate genes are expected, but last large study eliminated them both (47).

PSO0RS3

Localized is on chromosome 4, in position 4q34. A relation with early onset psoriasis was found in this area (17). Responsible gene is mapped about 50kb from former marker of PSORS3 locus. The newest localization is for PSORS9 locus, mapped closer to centromere (4q31) in PSORS3 area (25, 56). In this region are situated different genes coding immunologically important proteins, including IL-15 gene (53).

PSORS4

Locus PSORS4 mapped to 1q21 of chromosome 4, in area of Epidermal differentiation complex. This region involves 13 genes coding S100 calcium binding proteins. Some of them, S100A7, S100A8 a S100A9 are known to be increased in keratinocytes of psoriatic patients (44). S100 proteins are responsible for chemotaxis of leukocytes.

PSORS5

Localized to 3q21 but his exact position is need to be confirmed by more studies (43).

PSORS6

Mapped to 19p13 and his position is also not exact. In this area is mapped also gene JUNB, which product is member of AP-1 family of transcriptional factors, that control differentiation of keratinocytes (54).

PSORS7

Locus is situated in position 1p. Veal *et al.* (52) referred to fact that gene EPS15 coding intracellular substrate for EGF receptors, highly expressed in psoriatic skin, and is mapped to critical region in position of 1p.

PSORS8

This locus is mapped to 16q. Nair *et al.* (35) referred that PSORS8 area is overlapping with susceptibility locus for Crohn disease. They found that this locus contains NOD2/CARD15 gene. They also found that psoriasis is more often in patients with Crohn disease, in comparison to control group. It shows a possibility that in this region is localized an immunomodulatory locus able to affect both diseases.

PSORS9

Locus is mapped to 4q position.

IL-10

IL-10 plays an important role in the pathophysiology of psoriasis. This disease is characterized by a relative IL-10 deficiency that can in part explain the predominance of a Th1 response. The IL-10 promoter region is very polymorphic and controls transcription of the IL-10 gene (3, 24).

While the concept of an allele that makes an individual susceptible to a disease is easily understood, the concept of a protective allele of a predisposing gene is rather new in the genetics of psoriasis.

Table 3: Frequencies and allele sizes of interleukin (IL)-10.G (a) - Allele nomenclature at the Genome Data Base (http://www.gdb.org) (24).

Size (bp)	Frequency	GDB[a]
132	0.022	Allele 12
134	0.034	Allele 11
136	0.399	Allele 10
138	0.075	Allele 9
140	0.079	Allele 8
142	0.052	Allele 7
144	0.240	Allele 6
146	0.086	Allele 5
148	0.011	Allele 4

Other study analyzed the highly polymorphic IL10.G microsatellite to determine if IL-10 has a role in psoriasis susceptibility. Findings showed a possible role of IL-10 promoter polymorphism in disease susceptibility and the G13 allele at the IL10.G locus was found to be associated with psoriasis (3).

Other allele, allele 3 (IL10.G9) apparently has a small protective effect and is the most frequent allele of this multiallelic polymorphism allele 3 (IL10.G9) was present in 80 % of the families (24).

The effect of the IL10.G9 promoter polymorphism observed by Hensen *et al.* is small compared with the effect of the PSORS1 marker. They also observed a small effect for allele 8 (IL10.14). This allele was present in only 28 % of the families (24).

SPP2 (Secreted phosphoprotein 2)

Bandshift analysis showed that SPP2 is NF-κB dependent gene. High positive regulation of NF-κB dependent gene was detected in samples from affected skin of psoriatic patients (34). NF-κB induces expression of VCAM-1 trough homocysteine. Protein vCAM-1 enables adhesion of lymphocytes, monocytes, eosinophiles and basophiles to endothelium of blood vessels. It also has a function in signal transport between leukocytes and endothelial cell.

VDR

D vitamin receptor is one of the candidate genes in psoriasis. It has immunosuppressive effects and is involved in an antiproliferation and prodifferentiaton cascades in keratinocytes (18). Neutrophils are expressing VDR. Polymorphism in A allele, A-1012G, is linked to negative regulation of TH1 response trough Trans-acting T-cell-specific transcription factor GATA-3. Alleles F and T of Fok1 and Taq1 genes are involved in increased activity of VDR. A-1012G, Fok1 and Taq1 VDR gene polymorphism is linked to with answer to calcipotriol (synthetic vitamin D3). A-1012G and Fok1 have relationship with susceptibility to non-familial psoriasis (18).

ADAM33 and other genes

Polymorphism in locus **ADAM33**, first gene identified in asthma, is in these days given to relation with psoriasis (46).

Li *et al.* have tested 15 SNPs form 7 expected psoriatic risk genes: rs597980 in allele ADAM33, rs6908425 in **CDKAL1** and rs3789604 in **PTPN22**. Results have shown as significant for the same alleles as in previous studies. This data show, that ADAM33, CDKAL1, and PTPN22 are risk genes for psoriasis (32).

Study of Oudota *et al.* in year 2009, confirmed linkage of other six candidate genes to susceptibility to psoriasis: **SCL12A8**, belongs to group of free transposing genes; **FLG** and **TGM5**, involved in epidermal differentiation; **CARD15** and **CYLD**, that modulate transcriptional factor NF-κB and **IL1RN**, coding antagonist receptor of IL-1. It was proved that an association exists between main risk allele HLA-Cw6 and CARD15, CYLD and TMG5 alleles. Together these results show that etiology of psoriasis and other disorders is cooperation of different genetic factors (40).

One region is within the MHC complex on 6p21.3 (51) and includes the non-HLA gene–encoding corneodesmosin (CD) — a protein with homology to keratin-10 (2). The other region includes a cluster of genes on chromosome 1q21 (19, 38). Potential candidate genes encode markers of epidermal differentiation such as corneodesmosin, psoriasin, and CD1d, to name a few (19).

IL-20R

Complex of IL-20 receptor is composed from two chains IL20RA and IL20RB. Its ligands are three members from IL-19 subfamily, IL-19, IL-20 and IL-24. These cytokines are important for manifestation of psoriatic lesions and recently was described also a relation between IL20 gene polymorphism and psoriasis. In last studies the hypothesis is tested, that genetic variants of IL-20-RI influence susceptibility to psoriasis. To these days there isn't proved relationship between SNP in that gene and psoriasis. SNPs in two risk haplotypes influence two transcriptional factors leading to differentiation of immune cells. Other studies are necessary to confirm genetic association of IL-20-RA haplotypes with psoriasis (27).

Conclusion

In the last few years, molecular genetics analyses have permitted novel insights into psoriasis, a disease characterized by uncontrolled proliferation of keratinocytes and recruitment of T cells into the skin. HLA studies revealed an association with certain alleles, notably HLA-Cw6. Despite this HLA component, psoriasis in some families is inherited as an autosomal dominant trait with high penetrance.

Significant progress has been made in the understanding of the genetic, immune and pathogenetic aspects of psoriasis.

Understanding the genetics of psoriasis, and why some people are affected and others are not could lead to more effective treatments. They could work blocking the action of concrete genes, changing their behaviour or by replacing mutated genes with healthy ones via gene therapy.

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