From Genotype to Clinical Phenotype: The Multiple Facets of Psoriasis

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Genetic Loci PsO

- PSORS1 6p21
- PSORS2 17q25
- PSORS3 4q34
- PSORS4 1q21
- PSORS5 3q21
- PSORS6 19p13
- ...TNFAIP3
- PSORS9 IL23R
- IL12B

Stimuli

- Infections
- Drugs
- Trauma
- Stress
- Neuropeptides
- ...

Immunological effectors mechanisms

PsO

Genetic Loci PsA

- 4q27
- 15q21
- IL23R
- IL12B
- ...

Stimuli

- Infections
- Drugs
- Trauma
- Stress
- Neuropeptides
- ...

PsA

Common Variants: Usually Low Effect on Common Diseases

- **Rare alleles causing Mendelian disease**
- **Low-frequency variants with intermediate effect**
- **Common variants implicated in common disease by GWA**

Effect size:
- **High**
- **Intermediate**
- **Modest**
- **Low**

Allele frequency:
- **Very rare**
- **Rare**
- **Low frequency**
- **Common**
Many susceptibility genes in psoriasis are involved in immune responses.

Tissue specific:
- LCE

Innate immunity:
- TNFAIP3
- TNIP1
- DEFB
- Rel/NFKBIA
- IFIH1
- IL28RA
- TRAF3IP3
- TYK2

Acquired immunity:
- IL12B
- IL23R
- IL23A
- HLA-C
- ERAP 1/ZAP 70
- TYK2

Unknown:
- RNF114

Microbes

WTCC2/GAPC Nature Genet, 2010
SNPs in IL23R and IL23p19 coding genes are associated with Psoriasis

Table 1 GWAS signals from loci previously reported to be associated with psoriasis

<table>
<thead>
<tr>
<th>Chr.</th>
<th>SNP</th>
<th>Positiona</th>
<th>Gene or locus</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p31</td>
<td>rs11209026</td>
<td>67,478,546</td>
<td>IL23R</td>
<td>$7.13 \times 10^{-7}$</td>
<td>1.49 (1.27–1.74)</td>
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<td>1q21</td>
<td>rs4112788</td>
<td>150,817,900</td>
<td>LCE3D</td>
<td>$3.32 \times 10^{-10}$</td>
<td>1.29 (1.19–1.40)</td>
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<tr>
<td>5q31</td>
<td>rs20541</td>
<td>132,023,863</td>
<td>IL13</td>
<td>$2.32 \times 10^{-2}$</td>
<td>1.12 (1.02–1.24)</td>
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<tr>
<td>5q33</td>
<td>rs1024995b</td>
<td>150,456,197</td>
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<td>$3.92 \times 10^{-5}$</td>
<td>1.27 (1.14–1.44)</td>
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<td>5q33</td>
<td>rs3213094</td>
<td>158,683,347</td>
<td>IL12B</td>
<td>$4.93 \times 10^{-11}$</td>
<td>1.39 (1.26–1.53)</td>
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<tr>
<td>6p21</td>
<td>rs10484554c</td>
<td>31,382,534</td>
<td>HLA-C</td>
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<td>4.66 (4.23–5.13)</td>
<td>8</td>
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<td>138,241,110</td>
<td>TNFAIP3</td>
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<td>12q13</td>
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<td>1.49 (1.28–1.73)</td>
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<td>20q13</td>
<td>rs2235617d</td>
<td>47,988,384</td>
<td>ZNF313</td>
<td>$1.65 \times 10^{-6}$</td>
<td>1.20 (1.11–1.30)</td>
<td>4</td>
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</tbody>
</table>

SNPs reported in previous studies with robust GWAS and replication evidence. Odds ratios are given for the previously reported risk allele.

*NcBI human genome build 36 coordinates. $^{b}r^2 = 0.48 \ (0.49)$ with the previously published SNP rs17728338 (ref. 8). $^{c}$At the HLA locus, the results are presented for our top SNP. $^{d}r^2 = 1$ with previously published SNP rs495337 (ref. 4). All $r^2$ calculated from 58C and where different, the $r^2$ from HapMap CEU is in brackets. Chr., chromosome.

## IL-17 cytokine family receptors and ligands

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Source</th>
<th>Receptor</th>
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<tbody>
<tr>
<td>IL-17A</td>
<td>• Th17 cells • CD8+ T cells • γδ-T cells • NK cells</td>
<td>IL-17RA</td>
</tr>
<tr>
<td>IL-17F</td>
<td>• NKT cells • LTi cells • Neutrophils</td>
<td>IL-17RC</td>
</tr>
<tr>
<td>IL-17A/IL-17F heterodimer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-17C</td>
<td>• Keratinocytes • Lung epithelial cells</td>
<td>IL-17RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-17RE</td>
</tr>
<tr>
<td>IL-17E (IL-25)</td>
<td>• T cells • Intraepithelial lymphocytes • Lung epithelial cells • Cells of the GI tract and uterus</td>
<td>IL-17RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-17RB</td>
</tr>
<tr>
<td>IL-17B</td>
<td>Expression and function remain under investigation</td>
<td>IL-17RB</td>
</tr>
<tr>
<td>IL-17D</td>
<td></td>
<td>Unknown</td>
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</tbody>
</table>

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**Diagram:**
- IL-17E (IL-25) interacts with IL-17A, IL-17F, and IL-17C.
- IL-17A activates NF-κB pathway with TRAF6 and TRAF5.
- IL-17B and IL-17D have unspecified interactions marked with a question mark.

**Legend:**
- IL-17E (IL-25): Red
- IL-17A: Purple
- IL-17F: Blue
- IL-17C: Green
- IL-17B: Grey
- IL-17D: Black

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Some Variants in IL23R and IL23p19 coding genes protect against psoriasis

Capon F et al. Human Genetics 2007
A Psoriasis Protective Polymorphism (IL23R R381Q) Reduces IL-23-induced IL-17A production

Di Meglio et al, PLoS ONE 2011
IL23R R381Q: from gene-to-function

IL23R R381Q might confer protection against autoimmune diseases by attenuating IL-23-induced Th17 effector response in inflamed tissues.
IL23R R381Q: a gene variant associated with different immune-mediated diseases

Psoriasis

Capon, Di Meglio et al, 2007
Cargill et al., 2007

Crohn's Disease

Duerr et al., 2006

Ankylosing spondylitis

Rueda et al, 2008
Contribution of Studies of Psoriasis Monogenic Variants
Rare Monogenic Variants with High Impact on Disease Susceptibility

- **Rare alleles causing Mendelian disease**
- **Low-frequency variants with intermediate effect**
- **Common variants implicated in common disease by GWA**

### Graph Details
- **X-axis**: Allele frequency
- **Y-axis**: Effect size
- **Legend**:
  - **High**
  - **Intermediate**
  - **Modest**
  - **Low**
- **Very rare**: $0.001$
- **Rare**: $0.005$
- **Low frequency**: $0.05$
- **Common**: $0.05$

- Few examples of high-effect common variants influencing common disease
Psoriasis vulgaris

- Chronic course in severe forms
- Erythematousquamous plaques,
- No fever, fatigue
- Usually no leukocytosis
- Serum level of C reactive protein normal range
- Extracutaneous: osteoarticular (psoriatic arthritis),

Generalised pustular psoriasis

- Repeated, intermittent acute flares
- Erythema and sterile pustules
- High fever, asthenia
- Marked leukocytosis and raised peripheral blood neutrophil count
- Raised serum level of C reactive protein
- Extracutaneous: shock, liver and biliary involvement,..
The Interleukin-1 Family (2013)

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Towne J, Sims JE 2012
Generalised Pustular Psoriasis Following Mendelian Segregation

Autosomal recessive of the generalised pustular psoriasis (GPP) trait

IL36RN mutations Impair function of interleukin-36 receptor antagonist (IL36ra)
Table S1: Summary of clinical features of the sixteen studied patients.

<table>
<thead>
<tr>
<th>Family</th>
<th>Patient</th>
<th>Age (year)/Sex</th>
<th>Age at onset of GPP</th>
<th>Particular mucocutaneous features</th>
<th>Other manifestations</th>
<th>Treatment at the time of study</th>
<th>Triggering factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>V.2</td>
<td>41/M</td>
<td>3 years</td>
<td>GPP, geographic tongue</td>
<td>lingual erythema migrans</td>
<td>Acitretin, oral steroids</td>
<td>Treatment withdrawal, infections</td>
</tr>
<tr>
<td>Family 1</td>
<td>V.3</td>
<td>43/M</td>
<td>unknown</td>
<td>GPP</td>
<td></td>
<td>Acitretin</td>
<td>Treatment withdrawal, infections</td>
</tr>
<tr>
<td>Family 1</td>
<td>V.4</td>
<td>30/M</td>
<td>2 years</td>
<td>GPP, scrotal tongue</td>
<td>oligoarthritis</td>
<td>Acitretin</td>
<td>Treatment withdrawal, infections</td>
</tr>
<tr>
<td>Family 2</td>
<td>IV.2</td>
<td>17/F</td>
<td>1 week</td>
<td>GPP</td>
<td></td>
<td>Acitretin</td>
<td>Menstruation, infections</td>
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<tr>
<td>Family 2</td>
<td>IV.3</td>
<td>35/F</td>
<td>2 weeks</td>
<td>GPP, nail dystrophy</td>
<td></td>
<td>Acitretin</td>
<td>Menstruation, infections</td>
</tr>
<tr>
<td>Family 2</td>
<td>III.4</td>
<td>30/F</td>
<td>11 years</td>
<td>GPP, geographic tongue, nail dystrophy</td>
<td>lingual erythema migrans</td>
<td>Acitretin</td>
<td>Menstruation, infections</td>
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<td>Family 3</td>
<td>V.2</td>
<td>17/M</td>
<td>4 years</td>
<td>GPP, scrotal tongue, nail dystrophy</td>
<td></td>
<td>Treatment withdrawal, infections</td>
<td></td>
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<tr>
<td>Family 4</td>
<td>V.3</td>
<td>6/M</td>
<td>2 months</td>
<td>GPP</td>
<td></td>
<td>Acitretin</td>
<td>Treatment withdrawal, infections</td>
</tr>
<tr>
<td>Family 5</td>
<td>II.1</td>
<td>37/M</td>
<td>5 years</td>
<td>GPP, scrotal tongue</td>
<td>Polyarthritis</td>
<td>Acitretin</td>
<td>Treatment withdrawal</td>
</tr>
<tr>
<td>Family 6</td>
<td>V.1</td>
<td>37/F</td>
<td>2 weeks</td>
<td>GPP, geographic tongue</td>
<td></td>
<td>Topical steroids</td>
<td>Stress, infections, menstruation</td>
</tr>
<tr>
<td>Family 6</td>
<td>V.8</td>
<td>31/F</td>
<td>6 years</td>
<td>GPP</td>
<td>oligoarthritis, cholangitis</td>
<td></td>
<td>infections</td>
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<tr>
<td>Family 6</td>
<td>III.1</td>
<td>72/F</td>
<td>unknown</td>
<td>GPP, scrotal tongue</td>
<td></td>
<td>Topical steroids</td>
<td>Stress</td>
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<tr>
<td>Family 6</td>
<td>IV.3</td>
<td>56/F</td>
<td>3 months</td>
<td>GPP, geographic tongue</td>
<td>cholangitis</td>
<td></td>
<td>stress, infections, menstruation, pregnancy</td>
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<td>Family 7</td>
<td>IV.1</td>
<td>32/F</td>
<td>25 years</td>
<td>GPP</td>
<td>cholangitis</td>
<td>acitretin, adalimumab</td>
<td>nasopharyngeal infection</td>
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<td>Family 8</td>
<td>V.4</td>
<td>35/F</td>
<td>20 years</td>
<td>GPP, impetigo herpetiformis</td>
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<td>Oral steroids</td>
<td>Pregnancy, surgery</td>
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<td>Family 9</td>
<td>V.1</td>
<td>32/F</td>
<td>22 years</td>
<td>GPP, impetigo herpetiformis, nail dystrophy</td>
<td></td>
<td>Topical steroids, phototherapy</td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>
Autoinflammatory Syndromes (AIS)

- Rare, genetically inherited syndromes:
  - Familial mediterranean fever (FMF),
  - Hyper IgD syndrome,
  - TNF receptor associated periodic syndrome (TRAPS),
  - PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, acne),
  - PASH (pyoderma gangrenosum, acne, hidradenitis suppurativa)
  - CAPS (Muckle-Wells syndrome, familial cold autoinflammatory syndrome, NOMID/CINCA syndrome).
  - Deficiency of the IL-1 receptor antagonist (DIRA)
  - Deficiency of the IL-36 receptor antagonist (DITRA)

Farasat S et al. Arch Dermatol 2008; 144:392-402
IL36RN gene status in other populations

- Homozygous or composite heterozygous IL36RN mutations in GPP sporadic cases observed in caucasian individuals from UK with GPP without PV (Onoufriadis A. Am J Hum Gen 2011), in 40% of tested cases in Germany (Körber A. J Invest Dermatol 2013), and in Japanese series (Farooq M. Human Mutation 2012).

- Absence of IL36RN mutations in Chinese GPP patients indicate genetic heterogeneity (Li M. Br J Dermatol 2012).


- In human psoriasis vulgaris, no current evidence for genetic abnormalities targeting the IL-36 pathway, but the receptor, agonists and antagonist are expressed in skin lesions.
CARD14 Mutations in Severe Plaque Psoriasis +/- PsA and in Pityriasis Rubra Pilaris

PSORS2 Is Due to Mutations in CARD14

Catherine T. Jordan, Li Cao, Elisha D.O. Roberson, Katherine C. Pierson, Chi-Fan Yang, Cailin E. Joyce, Caitriona Ryan, Shenghui Duan, Cynthia A. Helms, Yin Liu, Yongqing Chen, Alison A. McBride, Wuh-Liang Hwu, Jer-Yuarn Wu, Yuan-Tsong Chen, Alan Menter, Raphaela Goldbach-Mansky, Michelle A. Lowes, and Anne M. Bowcock

Rare and Common Variants in CARD14, Encoding an Epidermal Regulator of NF-kappaB, in Psoriasis


Familial Pityriasis Rubra Pilaris Is Caused by Mutations in CARD14

Dana Fuchs-Telem, Ofer Sarig, Maurice A.M. van Steensel, Ofer Isakov, Shirli Israeli, Janna Nousbeck, Katharina Richard, Veronique Winnepenninckx, Marigje Vernooij, Noam Shomron, Jouni Uitto, Philip Fleckman, Gabriele Richard, and Eli Sprecher
Heterozygous Gain-of-Function CARD14 Mutations Impact on NFκB and IL-36 Pathways

Plaque-type Psoriasis: Meta-analysis of GWAS Identifies new Susceptibility Loci

<table>
<thead>
<tr>
<th>Locus</th>
<th>Minor Allele</th>
<th>Minor Allele Frequency</th>
<th>LD Score</th>
<th>Risk Allele</th>
<th>Risk Allele Frequency</th>
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<tr>
<td>rs1121129</td>
<td>A</td>
<td>0.308</td>
<td>1.13</td>
<td>G</td>
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Genetic Heterogeneity of Autoinflammatory Diseases Brings Complexity

IL-12/23  IL-1  CARD14  IL-36