

Disease-oriented Genome Networks

yielded the strongest association (figure 1) are all present in this block.

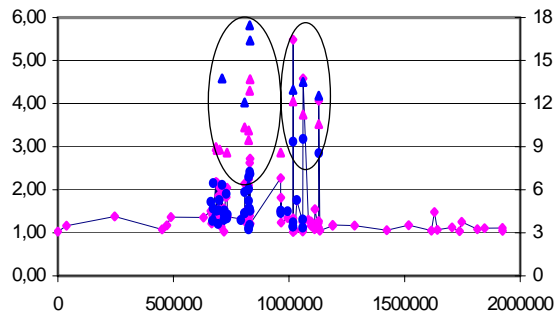


Fig 1: Association and odds ratios for the investigated markers. Connected squares indicate the observed odds ratios for each marker (left), triangles indicate the respective $-\log(p)$ values (right). Magenta: Kiel-, blue: Ann Arbor-cohort. The left circle indicates markers belonging to block I, the right circle markers belonging to block III (see below.)

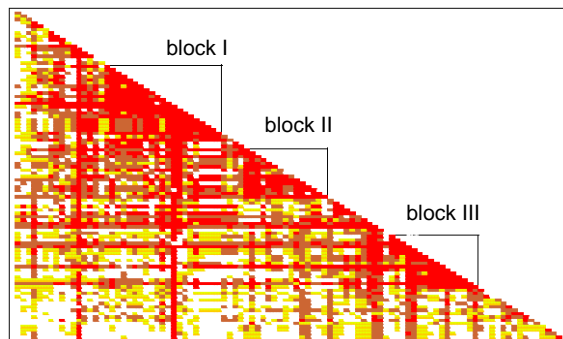


Fig 2: Two point LD as calculated out of 307 deduced haplotypes: Red squares: LD > 95%; orange: LD > 75%, yellow: LD > 50%; white: LD < 50%. The triangles indicate conserved blocks. I: HCR, TCF19, POU5F1, II: NOB4, HCG II, HLA-C, KIA0055hom; III: MICB, IkBL, LTA, TNFa

A further block (block III, Fig. 2) contains the three SNPs which yielded the highest odds ratios. Again, these three SNPs are in almost perfect linkage disequilibrium (LD) and form a well conserved haplotype which in turn is in very close linkage with block I (31 out of 33 chromosomes; 94%). However, block III is less frequent than block I (33 vs 101 chromosomes).

		psoriasis		P	
		block III	Yes		No
Cw6 pos:	Kiel	-	82	62	0,000031
		+	87	20	
	AA	-	27	37	0,003014
		+	44	21	
S	-		109	99	0,000001
	+		131	41	
Cw6 neg:	S	+	6	7	n.s.

Tab 2: Distribution of the P5-1/MICB/TNF-238 risk haplotype (block III) in Cw6 positive and Cw6 negative individuals. Cw6 indicates presence or absence of PSORS1.

Haplotype association: Individuals positive for PSORS1 and Block III were selected and the strength of association was calculated in dependence of the presence or absence of the respective haplotypes. In both cohorts, the frequency of psoriasis was significantly increased when block III was present in individuals positive for block I when compared with

Diseases Due to Environmental Factors

individuals positive only for block I but negative for block III. Block III occurred only very rarely in the absence of PSORS1 (or HLA-Cw6, respectively). Table 2 shows the results of this analysis.

Discussion:

Psoriasis is a common, immunologically-mediated, hyperproliferative skin disease that is influenced by multiple genes, including a major gene in the major histocompatibility complex. Recently discussed candidate genes within the MHC are CDSN, HCR, and HLA-Cw6. However, because the penetrance of the disease allele at this locus is only about 10%, and based on recurrence risk(6) and linkage(1) analysis, it is apparent that additional loci also influence susceptibility to psoriasis. Such additional susceptibility regions might be PSORS2-PSORS6 which have been shown to be in significant linkage with the disorder (1).

We have analysed association and odds ratios of a total of 99 SNP marker located within the MHC I and MHC III. Not surprisingly, markers located within or close to the PSORS1 region as described in the literature yielded the highest significance. The respective marker alleles are very frequent among patients (> 80%, data not shown) but do not carry high relative risks. In contrast, we observed three markers centromeric of PSORS1, which yield much higher odds ratios (fig. 1) but are less frequent in patients. In order to clarify this discrepancy, we deduced the SNP frequencies of the MHC chromosomes present in the investigated families. These investigations demonstrated that the PSORS1 haplotype is in very close linkage with a second haplotype located centromeric of HLA-Cw. The presence of this haplotype significantly increases the risk to develop psoriasis, but only if the PSORS1 haplotype is also present. Without PSORS1, this haplotype does not confer any risk for psoriasis, indicating that there is an interaction of at least two different genes. Genes located in the centromeric region significantly associated with psoriasis are P5.1, TNF α and MICB. Due to their immunological functions, at least TNF α and MICB are well suited psoriasis susceptibility candidates. Taken together, these data indicate that in fact genes additional to the one present in PSORS1 are necessary to develop psoriasis. One of such a gene might also be present in the human MHC, located centromeric of PSORS1 close to the central MHC. Since the psoriasis gene located in PSORS1 is probably involved in the epidermal differentiation dysregulation characteristic for psoriasis, this second gene might be responsible for the immunological dysregulation of psoriasis.

Project Status

The SNP based gene scan of the MHC is now finished. Due to the observed extreme LD within the investigated areas, genotyping probably won't provide further information. Functional analyses now have to show the role of the interacting genes located in that region.

Outlook

To further clarify the role of a second psoriasis gene in the MHC, (i) functional studies will be performed to investigate the role of the identified candidates in the pathogenetics of psoriasis. (ii) The chip based genome wide scan will be used to identify further additional genes in the human genome which interact with PSORS1.

Lit.: 1. Elder JT. Psoriasis clinical registries, genetics, and genomics. *Ann Rheum Dis.* 2005 Mar;64 Suppl 2:ii106-7. 2. Nair RP et al. Localization of psoriasis-susceptibility locus PSORS1 to a 60-kb interval telomeric to HLA-C. *Am J Hum Genet.* 2000 Jun;66(6):1833-44. 3. Oka A et al. Association analysis using refined microsatellite markers localizes a susceptibility locus for psoriasis vulgaris within a 111 kb segment telomeric to the HLA-C gene. *Hum Mol Genet.* 1999 Nov;8(12):2165-70. 4. Welsh K et al. Molecular typing for the MHC with PCR-SSP. *Rev Immunogenet.* 1999;1(2):157-76. 5. Barrett JC et al. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics.* 2005 Jan 15;21(2):263-5. 6. Elder JT et al. The genetics of psoriasis. *Arch Dermatol* 1994;130(2):216-24.